GENERAL ANAESTHESIA

Dr.H.K.Singh
Professor & Head
Department of Pharmacology

What is Anaesthesia ???

- **Anesthesia** – is a reversible condition of comfort, quiescence and physiological stability in a patient before, during and after performance of a procedure
- **General anesthesia** – for surgical procedure to render the patient unaware / unresponsive to the painful stimuli
  - Drugs producing G. Anaesthesia – are called General Anaesthetics
- **Local anesthesia** - reversible inhibition impulse generation and propagation in nerves. In sensory nerves, such an effect is desired when painful procedures must be performed, e.g., surgical or dental operations
  - Drugs producing Local Anaesthesia – are called Local Anaesthetics e.g. Procaine, Lidocaine and Bupivacaine etc.

General anaesthetics (Defn.)

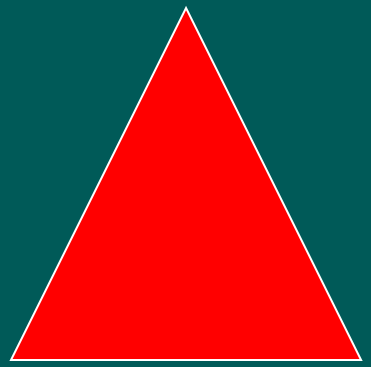
- **General Anaesthetics** are the drugs which produce reversible loss of all sensation and consciousness, or simply, a drug that brings about a reversible loss of consciousness

- **Remember !!!** These drugs are generally administered by an anesthesiologist in order to induce or maintain general anesthesia to facilitate surgery
- **General anaesthetics** are – mainly ***inhalation or intravenous***

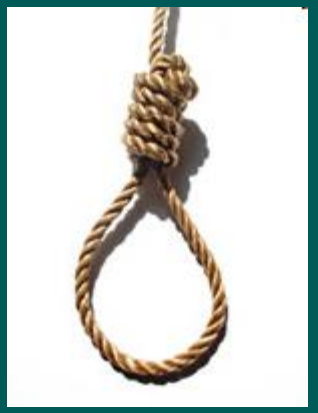
Essential components of GA:

- **Cardinal Features:**
  - Loss of all sensations
  - Sleep and Amnesia
  - Immobility or Muscle relaxation
  - Abolition of reflexes – somatic and autonomic

- **Clinically – What an Anaesthetist wants ???**
  - **Triad of GA**
    - need for unconsciousness
    - need for analgesia
    - need for muscle relaxation



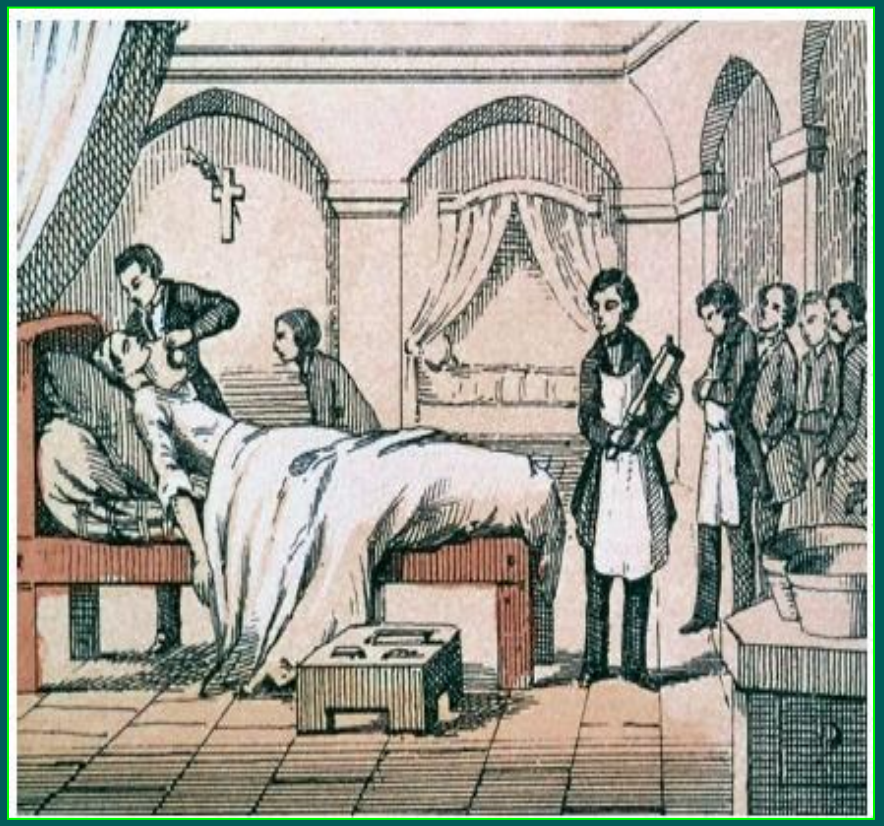
History - The Primitive techniques



- Club
- Strangulation
- Alcohol
- Mesmerism
- Plants

History – contd.

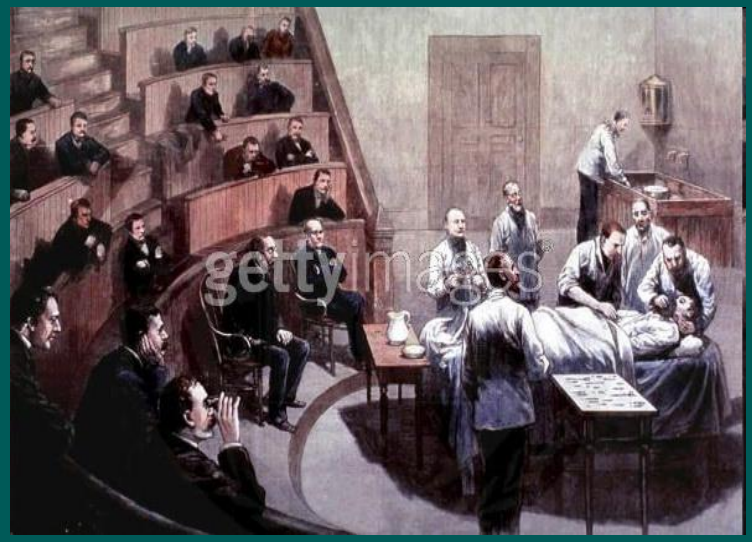
- General anesthesia was absent until the mid-1800's
- Original discoverer of general anesthetics
  - Crawford Long, Physician from Georgia: 1842, ether anesthesia
- Chloroform introduced
  - James Simpson: 1847
- Nitrous oxide
  - Horace Wells in 1845



19th Century physician administering Chloroform

History – contd.

- William T. G. Morton, a Boston Dentist and medical student - October 16, 1846 - **Gaseous ether**
  - Public demonstration gained world-wide attention
  - Public demonstration consisted of an operating room, "**the ether dome,**" where Gilbert Abbot underwent surgery for removal of a neck tumour in an unconscious state at the Massachusetts General Hospital
- But, no longer used in modern practice, yet considered to be the first "ideal" anesthetic



They did it for a better tomorrow!

What are the Drugs used as GA ? (Classification)

- **Inhalation:**
  1. **Gas:** Nitrous Oxide
  2. **Volatile liquids:**
     - Ether
     - Halothane
     - Enflurane
     - Isoflurane
     - Desflurane
     - Sevoflurane

- **Intravenous:**
  1. **Inducing agents:**
     - Thiopentone, Methohexitone sodium, propofol and etomidate
  2. **Benzodiazepines (slower acting):**
     - Diazepam, Lorazepam, Midazolam
  3. **Dissociative anaesthesia:**
     - Ketamine
  4. **Neurolept analgesia:**
     - Fentanyl

Mechanisms of GA

- The unitary theory of anesthesia – *Meyer-Overton rule (1901)*
- Lipid : water partition coefficient
  - GA (gases) are highly lipid soluble and therefore can easily enter in neurones
  - After entry causes disturbances in physical chemistry of neuronal membranes – fluidization theory
  - Finally, obliteration of Na+ channel and refusal of depolarization

- Potency of a gas correlated with its solubility in olive oil (olive oil : water) – lipid bilayer as the only target for anesthetic action
- Clear exceptions have been found out now
- The unitary theory has been discarded now!

Mechanisms of GA

- **For inhalation anesthetics –** Minimum Alveolar Concentration (MAC) – 1 (one) MAC is defined as the minimum alveolar concentration that prevents movement in response to surgical stimulation in 50% of subjects. Correlates with oil/gas partition coefficient
- **Practically –**
    - Alveolar concentrations can be monitored continuously by measuring end-tidal anesthetic concentration using spectrometry
    - End point (immobilization) – can me measured.
    - Other end points – Verbal commands or memory etc.

- **For Intravenous agents –** Potency of IV agent is defined as the free plasma concentration (at equilibrium) that produces loss of response to surgical incision in 50% of subjects.
- Difficult to measure:
    - no available method to measure blood or plasma concentration continuously
    - Free concentration at site of action cannot be determined

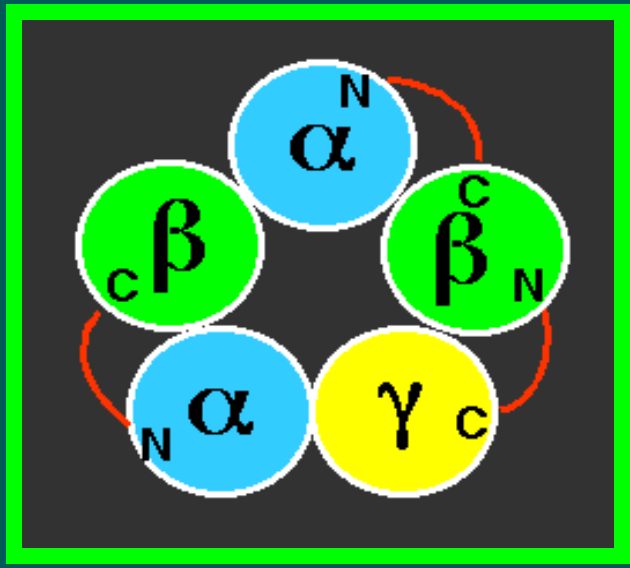
(MAC explains only capacity of anaesthetics to enter in CNS and attain sufficient concentration, but not actual MOA)

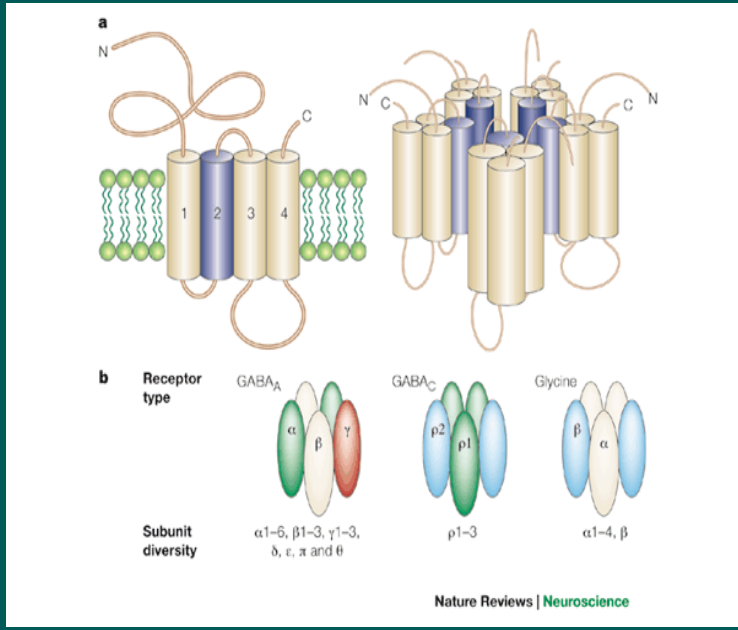
Modern theory on Mechanism of General Anesthesia

- **Major targets –** ligand gated ion channels
- **Important one –** $GABA_A$ receptor gated Cl^- channel
  - Examples – Many inhalation anesthetics, barbiturates, benzodiazepines and propofol
  - Potentiate the GABA to open the Cl^- channels

Structure of $GABA_A$?

- $GABA_A$ receptors - 4 transmembrane (4-TM) ion channel
  - 5 subunits arranged around a central pore: 2 alpha, 2 beta, 1 gamma
  - Each subunit has N-terminal extracellular chain which contains the ligand-binding site
  - 4 hydrophobic sections cross the membrane 4 times: one extracellular and two intracellular loops connecting these regions, plus an extracellular C-terminal chain

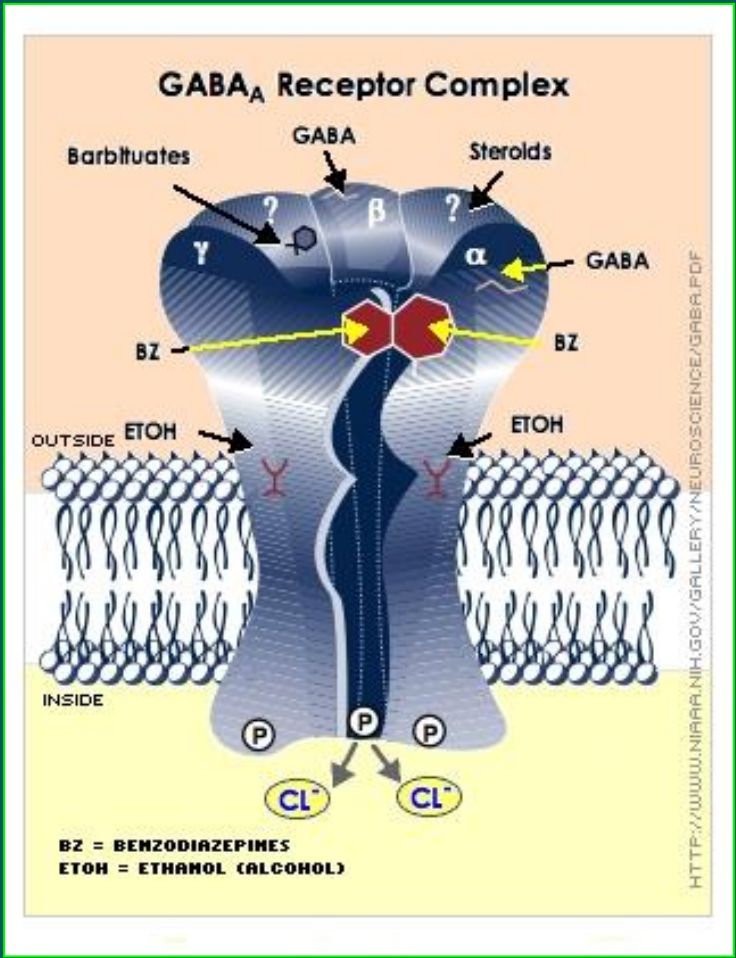




$GABA_A$ Receptor gated Cl^- Channel

- Normally, $GABA_A$ receptor mediates the effects of gamma-amino butyric acid (GABA), the major inhibitory neurotransmitter in the brain
  - $GABA_A$ receptor found throughout the CNS
    - most abundant, fast inhibitory, ligand-gated ion channel in the mammalian brain
    - located in the post-synaptic membrane
    - Ligand binding causes conformational changes leading to opening of central pore and passing down of Cl- along concentration gradient
    - Net inhibitory effect reducing activity of Neurones
  - General Anaesthetics bind with these channels and cause opening and potentiation of these inhibitory channels – leading to inhibition and anaesthesia

GABA Receptors – contd.



- Receptor sits on the membrane of its neuron at the synapse
- GABA, endogenous compound, causes GABA to open
- Drugs (GA) don't bind at the same side with GABA
- GA receptors are located between an alpha and beta subunit

Mechanism of GA – contd.

Other Mechanisms:

- Glycine – Barbiturates, propofol and others can activate in spinal cord and medulla
- N – methyl D- aspartate (NMDA) type of glutamate receptors - Nitrous oxide and ketamine selectively inhibit

4 (Four) Stages and signs !!!

- Traditional Description of signs and stages of GA - Also called Guedel`s sign
  - Typically seen in case of Ether
  - Slow action as very much lipid soluble
  - Descending depression of CNS
  - Higher to lower areas of brain are involve
  - Vital centers located in medulla are paralyzed last

Stages of GA

Stage I: Stage of Analgesia

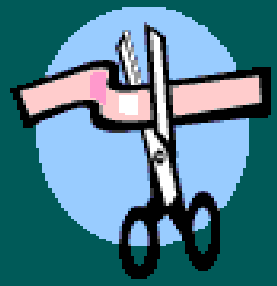
- Starts from beginning of anaesthetic inhalation and lasts upto the loss of consciousness
- Pain is progressively abolished during this stage
- Patient remains conscious, can hear and see, and feels a dream like state
- Reflexes and respiration remain normal
- It is difficult to maintain - use is limited to short procedures only

stages of GA – contd.

Stage II: Stage of Delirium and Excitement:

- From loss of consciousness to beginning of regular respiration
- Excitement - patient may shout, struggle and hold his breath
- Muscle tone increases, jaws are tightly closed.
- Breathing is jerky; vomiting, involuntary micturition or defecation may occur.
- Heart rate and BP may rise and pupils dilate due to sympathetic stimulation.
- No stimulus or operative procedure carried out during this stage.
- Breatholding are commonly seen. Potentially dangerous responses can occur during this stage including vomiting, laryngospasm and uncontrolled movement.
- **This stage is not found with modern anaesthesia – preanaesthetic medication, rapid induction etc.**

stages of GA – contd.

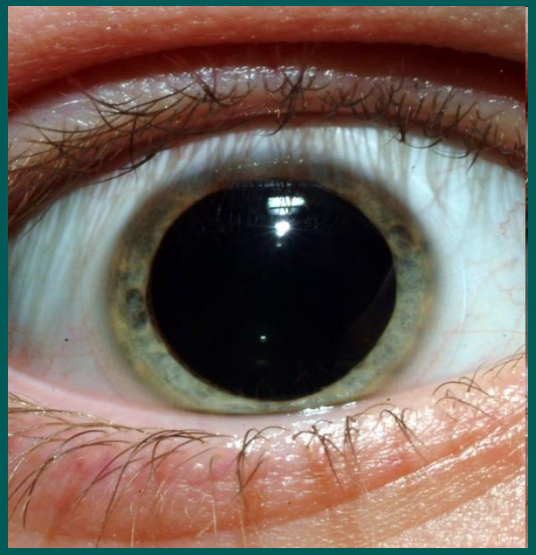


- **Stage III: Stage of Surgical anaesthesia**
  - Extends from onset of regular respiration to cessation of spontaneous breathing. This has been divided into 4 planes:
  - Plane 1: Roving eye balls. This plane ends when eyes become fixed.
  - Plane 2: Loss of corneal and laryngeal reflexes.
  - Plane 3: Pupil starts dilating and light reflex is lost.
  - Plane 4: Intercostal paralysis, shallow abdominal respiration, dilated pupil.

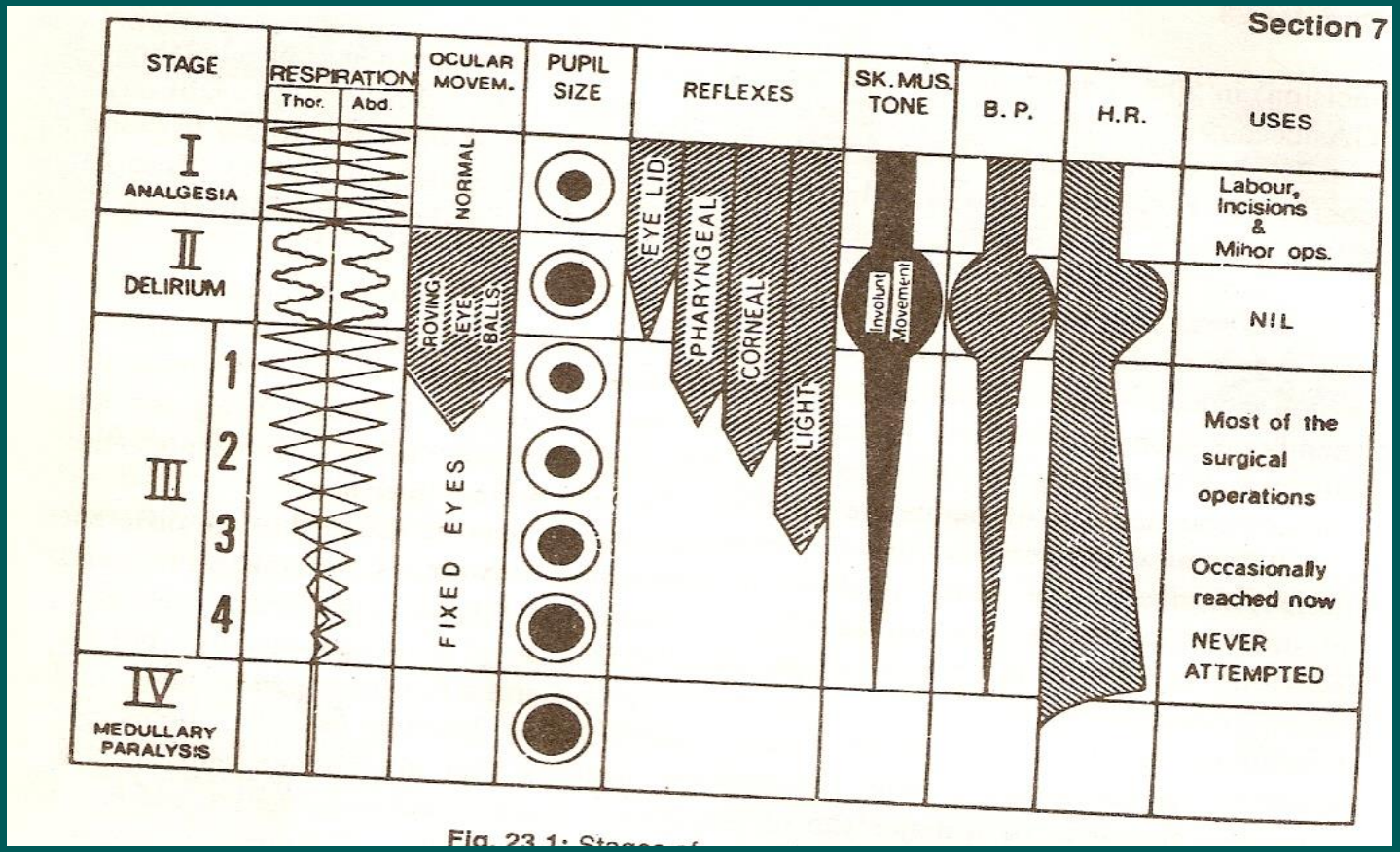
stages of GA – contd.

Stage IV: Medullary / respiratory paralysis

- Cessation of breathing ⟶ failure of circulation ⟶ death
- Pupils: widely dilated
- Muscles are totally flabby
- Pulse is imperceptible
- BP is very low.



signs & stages of GA – contd.



But not seen these days, because!

- Availability of rapidly acting agents – IV as well as Inhalation
- Mechanical control of Respiration
- Pre-operative and post operative Drugs
  - Atropine – dilate pupil, Opioid – depressing of respiration and SMRs
- Important signs observed by anaesthetists:
  - If no response to Painful stimulus - stage III
  - On Incision - rise in BP, respiration etc. – light anaesthesia
  - Fall in BP, respiratory depression – deep anaesthesia

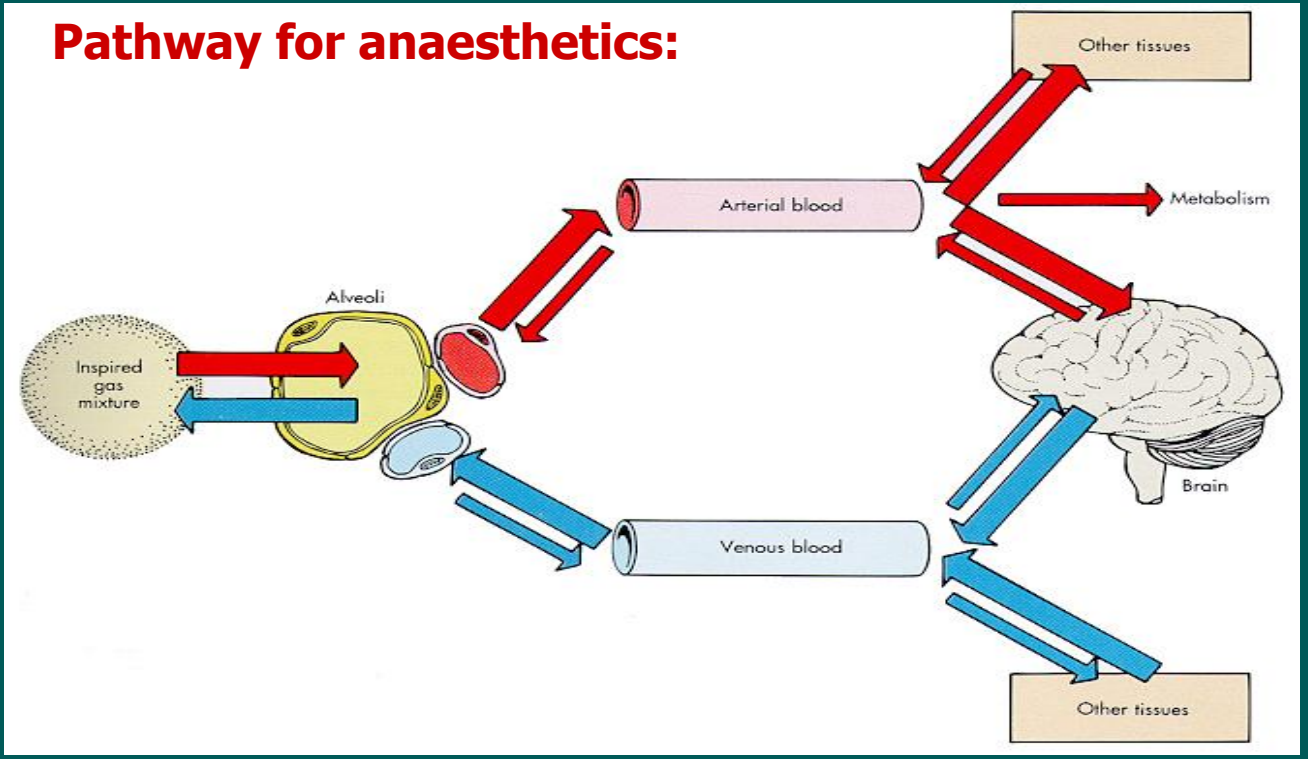
- Modern methods: Monitoring of Vital signs by CAM **(computer assisted monitoring)**

Practically what is done in OT ???

- There are 3 (three) phases:
  - **Induction, Maintenance and Recovery**
- **Induction (Induction time):** It is the period of time which begins with the beginning of administration of anaesthesia to the development of surgical anaesthesia (Induction time).
  - Induction is generally done with IV anaesthetics like Thiopentone Sodium and Propofol
- **Maintenance:** Sustaining the state of anaesthesia. Usually done with an admixture of Nitrous oxide and halogenated hydrocarbons
- **Recovery:** At the end of surgical procedure administration of anaesthetic is stopped and consciousness regains (recovery time)

Pharmacokinetics of inhalation anaesthetics:

- Inhalation anaesthetics: Depth of anaesthesia depend on MAC and Partial Pressure of the gas in Brain
- Passes through a series of tension gradients



Factors affecting Pharmacokinetics of inhalation GA

Factors affecting PP of anaesthetics in Brain:

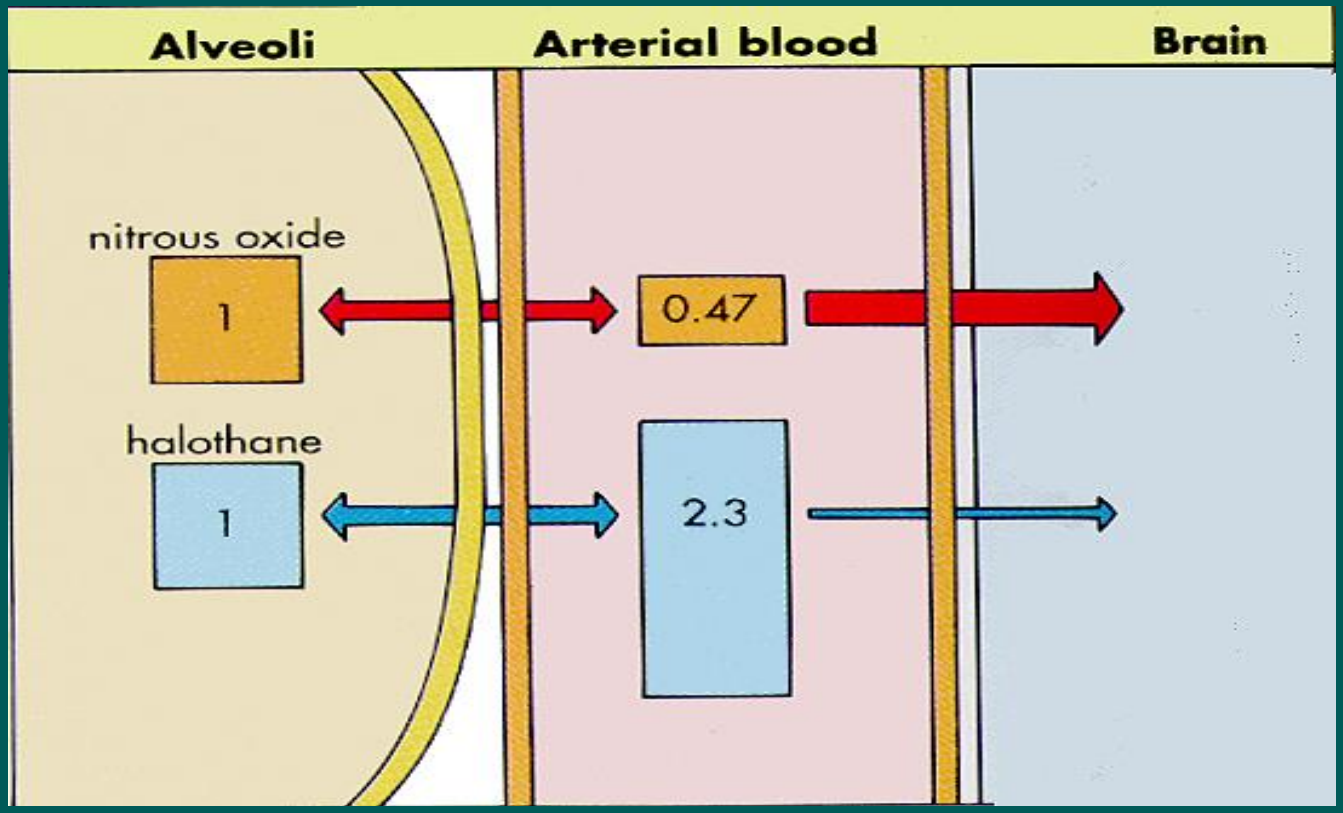
1. PP of anaesthetic in the inspired gas
2. Pulmonary ventilation – can be manipulated
3. Alveolar exchange - perfusion
4. Solubility of anaesthetic in blood - Blood: gas partition coefficient - important
5. Solubility in tissues – Halothane
6. Cerebral blood flow – CO_2 inhalation

Blood : Gas partition coefficient

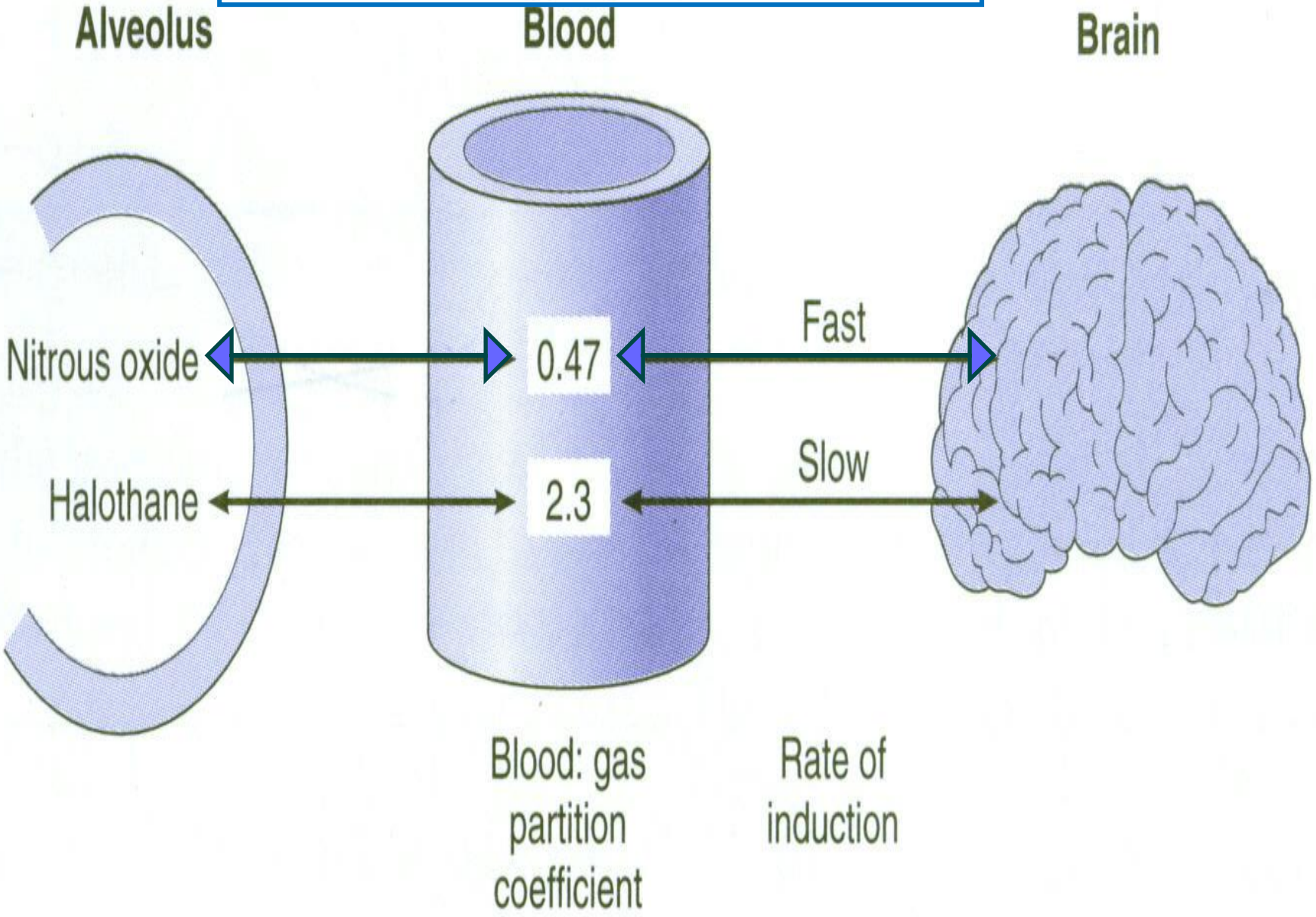
- Solubility of an anesthetic agent in blood is quantified as the blood : gas partition coefficient
- It is defined as the ratio of the concentration of an anesthetic in the blood phase to the concentration of the anesthetic in the gas phase when the anesthetic is in equilibrium between the two phases
- **Lower the blood : gas co-efficient** – faster the induction and recovery – Nitrous oxide
- **Higher the blood : gas co-efficient** – slower induction and recovery – Halothane

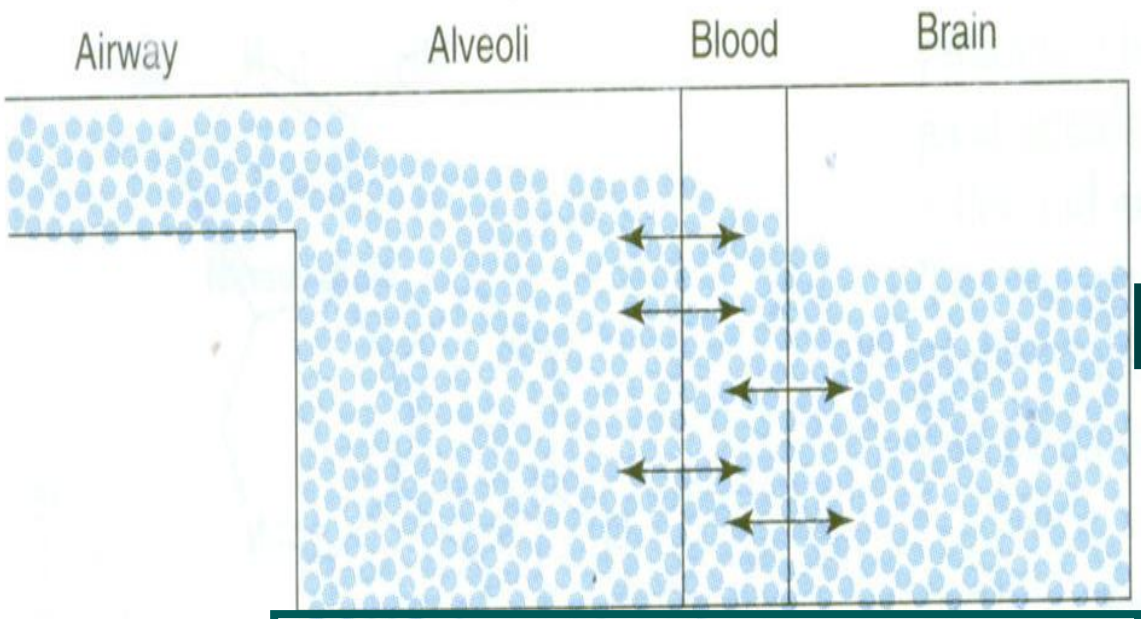
Rate of Entry into the Brain:

- Influence of Blood and Lipid Solubility



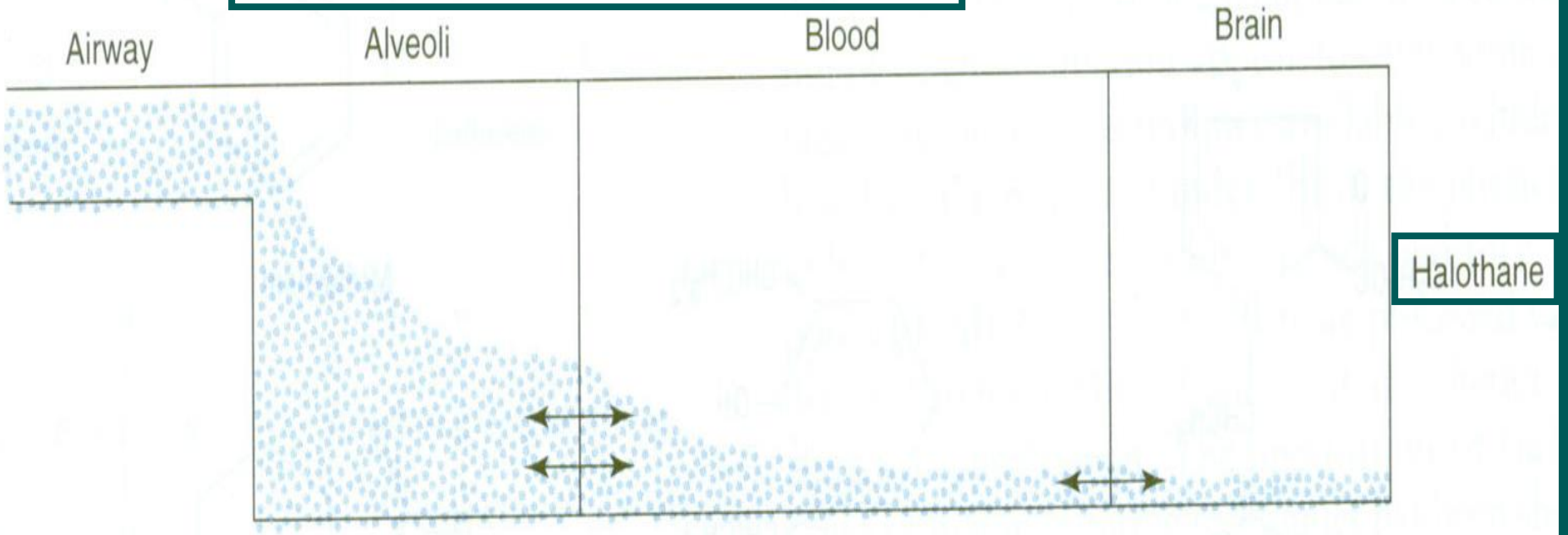
BLOOD GAS PARTITION CO-EFFICIENT





Agents with low solubility in blood quickly saturate the blood. The additional anesthetic molecules are then readily transferred to the brain.

BLOOD GAS PARTITION COEFFICIENT



Elimination of GA

- Mostly through lungs in unchanged form
- Channel of absorption (lungs) become channel of elimination
- Generally, Enter and persists in adipose tissue for long periods – high lipid solubility and low blood flow
- Muscles become intermediates in that process
- Excreted unchanged except Halothane
- Recovery may be delayed in prolonged anaesthesia

Elimination of GA – contd.

- Second gas effect: Seen only wit N_2O
  - Initially, more and more gas will go to blood irrespective of tidal volume or minute volume (because patient is ventilated)
  - For Example, N_2O and Halothane are given as mixture (commonly)
    - N_2O will be sucked in fast in a few minutes carrying along Halothane at the same rate
    - Induction becomes faster
- Diffusion hypoxia:
  - Reverse happens during recovery: discontinue N_2O
  - Diffuses to alveoli and dilutes air in alveoli (otherwise being maintained)
  - Oxygen is reduced – **hypoxia occurs** in low cardiopulmonary patients
  - **Treatment: Oxygen Inhalation**

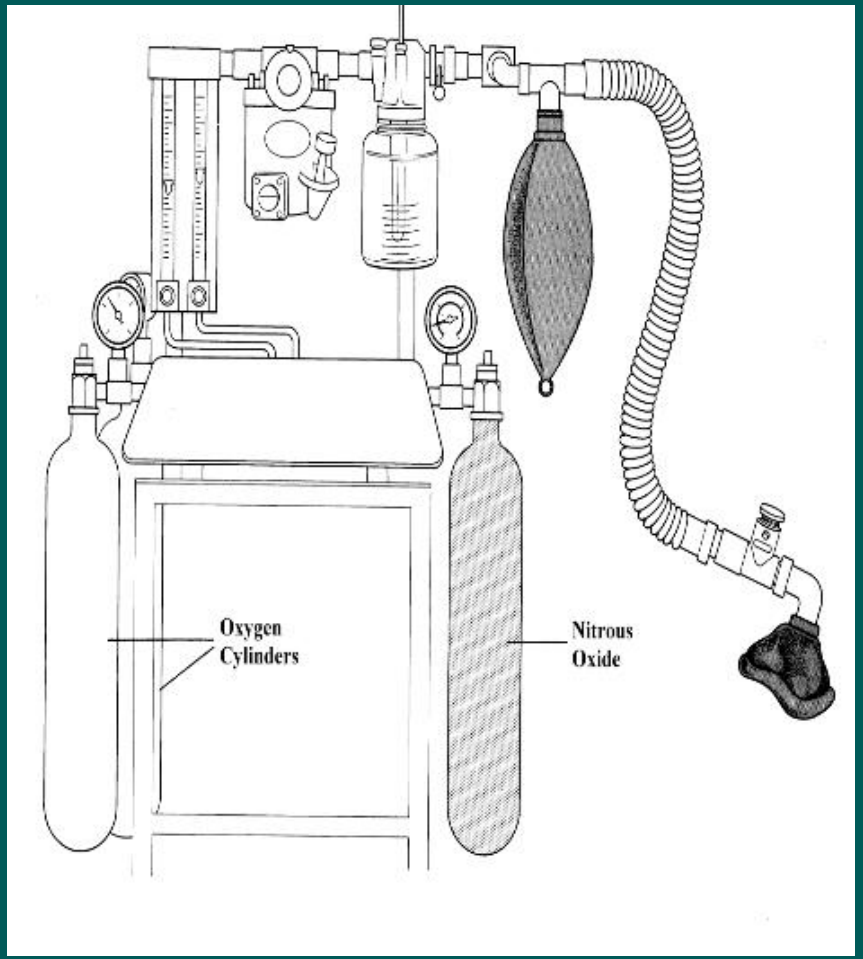
Techniques of inhalation GA

- Open drop method
- Through anaesthetic machines
  - Open system
  - Closed system
  - Semi-closed system

Continuous flow (Boyle's) anaesthetic machine

Anaesthetic Machine (Boyle's equipment)

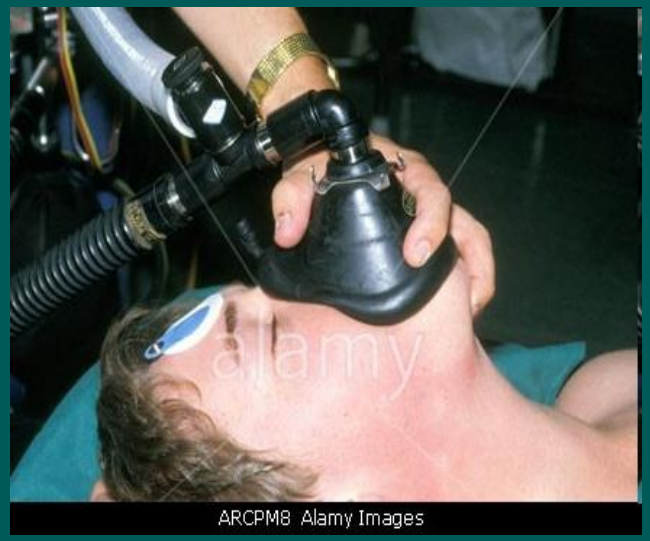
- The anaesthetic machine
- Gas source- either piped gas or supplied in cylinders
- Flow meter
- Vaporisers
- Delivery System or circuit



Properties of GA – contd.

- **For Patient:**
  - Pleasant, non-irritating and should not cause nausea or vomiting
  - Induction and recovery should be fast
- **For Surgeon:**
  - analgesia, immobility and muscle relaxation
  - nonexplosive and noninflammable
- **For the anaesthetist:**
  1. Margin of safety: No fall in BP
  2. Heart, liver and other organs: No affect
  3. Potent
  4. Cheap, stable and easily stored
  5. Should not react with rubber tubing or soda lime
  6. Rapid adjustment of depth of anaesthesia should be possible

Individual **Inhalation** anaesthetic agents



1. Diethyl ether ($C_2H_5 – O – C_2H_5$)

- Colourless, highly volatile liquid with a pungent odour. Boiling point – 35ºC
- Produces irritating vapours and are inflammable and explosive
- Pharmacokinetics:
  - 85 to 90 percent is eliminated through lung and remainder through skin, urine, milk and sweat
  - Can cross the placental barrier

Ether – contd.

- Advantages
  - Can be used without complicated apparatus
  - Potent anaesthetic and good analgesic
  - Muscle relaxation
  - Wide safety of margin
  - Respiratory stimulation and bronchodilatation
  - Does not sensitize the heart to adrenaline
  - No cardiac arrythmias
  - Can be used in delivery
  - Less likely hepato or nephrotoxicity

- Disadvantages
  - Inflammable and explosive
  - Slow induction and unpleasant - atropine
  - Slow recovery – nausea & vomiting
  - Cardiac arrest
  - Convulsion in children
  - Cross tolerance – ethyl alcohol

2. Nitrous oxide/laughing gas (N_2O)

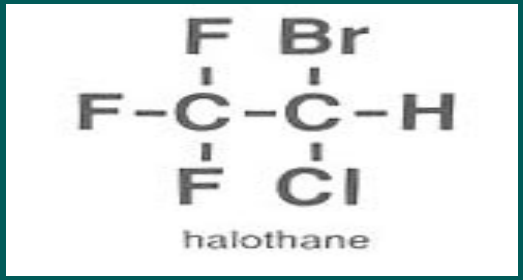
- NH_4NO_3 (s) → 2 H_2O (g) + N_2O (g)
- Colourless, odourless inorganic gas with sweet taste
- Noninflammable and nonirritating, but of low potency
- Very potent analgesic
- Carrier and adjuvant to other anaesthetics – 70% + 25-30% + 0.2-2%
- As a single agent used wit O_2 in dental extraction and in obstetrics

Nitrous oxide – contd.

- Advantages:
  - Non-inflammable and nonirritant
  - Rapid induction and recovery
  - Very potent analgesic (low concentration)
  - No nausea and vomiting
  - Nontoxic to liver, kidney and brain

- Disadvantages:
  - Not potent alone (supplementation)
  - Hypoxia
  - Inhibits methionine synthetase (precursor to DNA synthesis)
  - Inhibits vitamin B-12 metabolism
  - Dentists, OR personnel, abusers at risk
  - Gas filled spaces - dangerous

3. Halothane

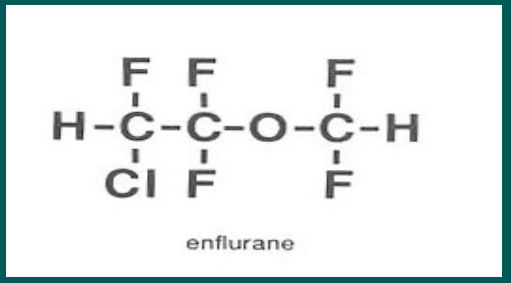


- Fluorinated volatile liquid with sweet odour, non-irritant non-inflammable and supplied in amber coloured bottle
- Potent anaesthetic, 2-4% for induction and 0.5-1% for maintenance
- Boiling point - 50ºC
- Pharmacokinetics: 60 to 80% eliminated unchanged. 20% retained in body for 24 hours and metabolized

Halothane – contd.

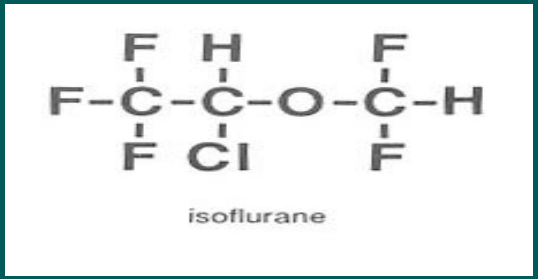
- Advantages:
  - Non-inflammable and non-irritant
  - Pharyngeal and laryngeal reflexes – bronchodilatation
  - Potent and speedy induction & recovery
  - Controlled hypotension
  - Inhibits intestinal and uterine contractions
- Disadvantages:
  - Special apparatus
  - Poor analgesic and muscle relaxation
  - Hypotension and – direct action (Ca++) and failure of sympathetic activity
  - Arrythmia
    - Direct vagal stimulation, direct depression of SA node and lack of baroreceptor action
  - Respiratory depression
  - Decreased urine formation – due to decreased gfr
  - Hepatitis: 1 in 10,000
  - Malignant hyperthermia: Ryanodine receptor
  - Prolong labour

4. Enflurane:



- Non-inflammable, with mild sweet odour and boils at 57ºC
- Similar to halothane in action, except better muscular relaxation
- Depresses myocardial force of contraction and sensitize heart to adrenaline
- Induces seizure in deep anaesthesia and therefore not used now - Epileptiform EEG
- Metabolism one-tenth that of halothane-- does not release quantity of hepatotoxic metabolites
- Metabolism releases fluoride ion-- renal toxicity

5. Isoflurane:



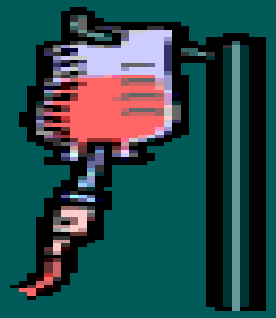
- Isomer of enflurane and have simmilar properties but slightly more potent
- Induction dose is 1.5 – 3% and maintenance dose is 1 – 2%
- By special vapourizer

Isoflurane – contd.

- Advantages:
  - Rapid induction and recovery
  - Good muscle relaxation
  - Good coronary vasodilatation
  - Less Myocardial depression than no myocardial sensitization to adrenaline
  - No renal or hepatotoxicity
  - Low nausea and vomiting
  - No dilatation of pupil and no loss of light reflex in deep anaesthesia
  - No seizure and preferred in neurosurgery
  - Uterine muscle relaxation
- Disadvantages:
  - Pungent and respiratory irritant
  - Special apparatus required
  - Respiratory depression
  - Maintenance only, no induction
  - ß adrenergic receptor stimulation
  - Costly

Intravenous Anaesthetics:

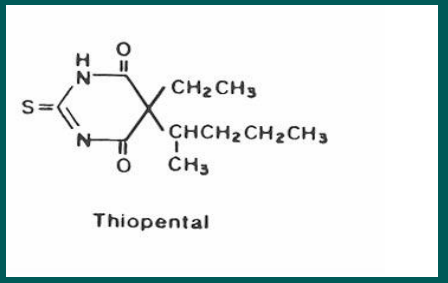
- For induction only
- Rapid induction (one arm-brain circulation time
- For maintenance not used
- Alone – supplemented with analgesic and muscle relaxants



Intravenous:

- Inducing agents:
  - Thiopentone, Methohexitone sodium, propofol and etomidate
  - Benzodiazepines (slower acting):
    Diazepam, Lorazepam, Midazolam
- Dissociative anaesthesia:
  Ketamine
- Neurolept analgesia:
  Fentanyl

Thiopentone sodium:

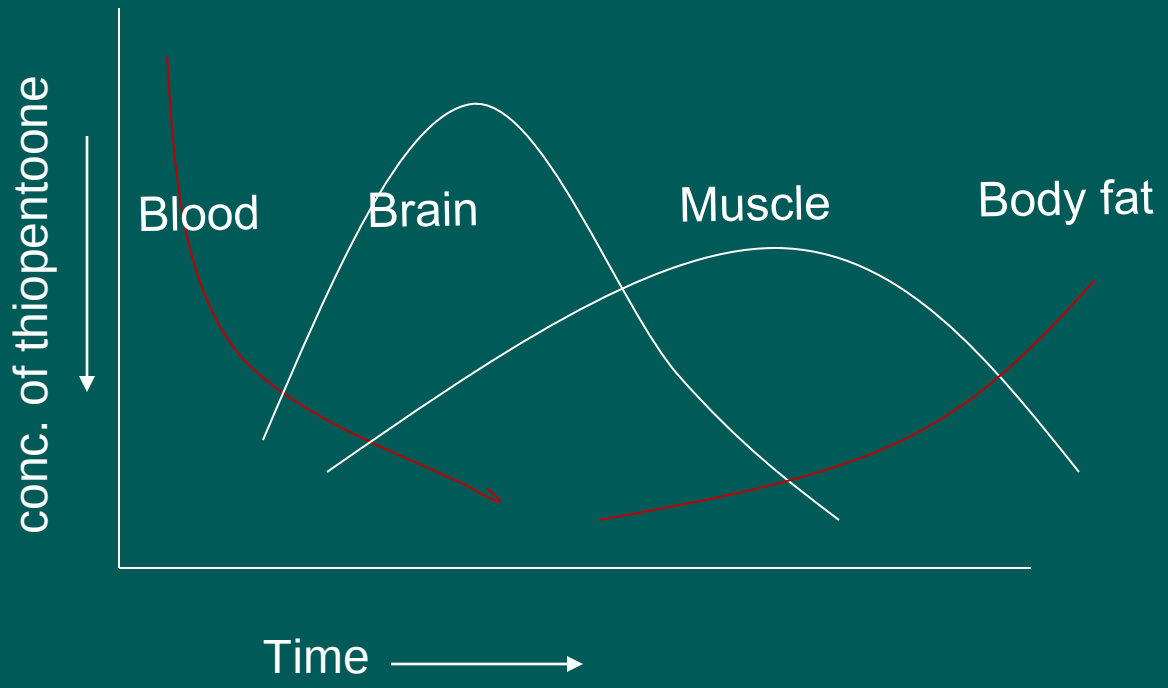


Thiopental

- Barbiturate: Ultra short acting
  - Water soluble
  - Alkaline
  - Dose-dependent suppression of CNS activity
  - Dose: 3-5mg/kg iv (2.5%) solution – 15 to 20 seconds
- Pharmacokinetics:
  - Redistribution
  - Hepatic metabolism (elimination half-life 7-12 hrs)
- CNS depression persists for long (>12 hr)

Tiopentone – contd,.

Redistribution:



Side effects of Thiopentone:

- Pre-anaesthetic course - laryngospasm
- Noncompatibility - succinylcholine
- Tissue necrosis--gangrene
- Post-anaesthetic course - analgesic

Thiopentone – contd.

- Advantages:
  - Rapid induction
  - Does not sensitize myocardium to adrenaline
  - No nausea and vomiting
  - Non-explosive and non-irritant\
  - Short operations (alone)
  - Other uses: convulsion, psychiatric patients and narcoanalysis of criminals

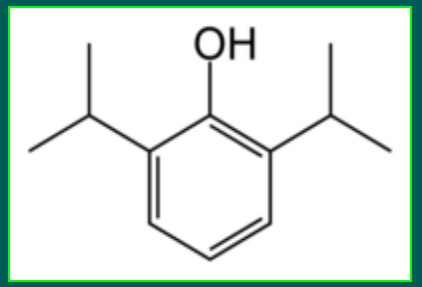
- Disadvantages:
  - Depth of anaesthesia difficult to judge
  - Pharyngeal and laryngeal reflexes persists - apnoea – controlled ventilation
  - Respiratory depression
  - Hypotension (rapid) – shock and hypovolemia
  - Poor analgesic and muscle relaxant
  - Gangrene and necrosis
  - Shivering and delirium

Thiopentone – contd.

- Advantages:
  - Rapid induction
  - Does not sensitize myocardium to adrenaline
  - No nausea and vomiting
  - Non-explosive and non-irritant
  - Short operations (alone)
- Other uses: convulsion, psychiatric patients and narcoanalysis of criminals

- Disadvantages:
  - Depth of anaesthesia difficult to judge
  - Pharyngeal and laryngeal reflexes persists - apnoea – controlled ventilation
  - Respiratory depression
  - Hypotension (rapid) – shock and hypovolemia
  - Poor analgesic and muscle relaxant
  - Gangrene and necrosis
  - Shivering and delirium

2. Propofol



- Replacing thiopentone now
- Oily liquid used as 1% emulsion
- Rapid induction (one arm-brain circulation time): 15 – 45 seconds and lasts for 5–10 minutes
- Rapid distribution – distribution half-life (2-4 min)
- Short elimination half-life (100 min)
- Dose: Induction - 2mg/kg bolus i.v.
  Maintenance - 9 mg/kg/hr i.v.
- Propofol is extensively metabolized
  - 88% of an administered dose appears in the urine
- Metabolized by hepatic conjugation of the inactive glucuronide metabolites

Propofol – contd.

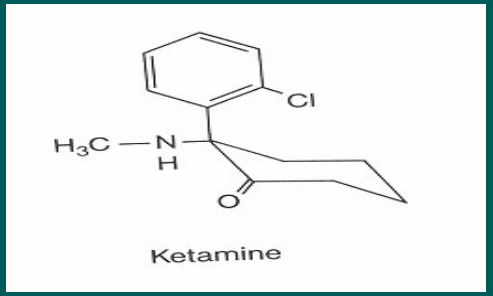
Advantages:

- Rapid induction
- Does not sensitize myocardium to adrenaline
- No nausea and vomiting
- Non-explosive and non-irritant
- Total i.v. anaesthesia
- Short operations (alone)

Disadvantages:

- Induction apnoea
- Hypotension
- Braddycardia
- Dose dependent respiratory depression
- Pain during injection: local anaesthetic combination

3. Ketamine:



Ketamine

- Phencyclidine derivative
- Dissociative anaesthesia: a state characterized by immobility, amnesia and analgesia with light sleep and feeling of dissociation from ones own body and mind and the surroundings.
- Site of action – cortex and subcortical areas – NMDA receptors
- Dose: 5-10mg/kg im or 1-2mg i.v.

Ketamine – contd.

- Disadvantages:
  - Limb movements and nystagmus
  - Emergence phenomenon – 50% patients
  - Hypertensives
  - Increase in IOT and ICP
  - Uterine stimulation
  - Psychosis and shizophrenia
  - Rare laryngospasm
  - Poor muscle relaxation

Ketamine – contd.

Uses:

1. Characteristics of sympathetic nervous system stimulation (increase HR, BP & CO) – hypovolumic shock
2. In head and neck surgery
3. In asthmatics
4. Short surgical procedures – burn dressing, forceps delivery, breech extraction manual removal of placenta and dentistry
5. Combination with diazepam - angiography, cardiac catheterization
6. OPD surgical procedures

4. Fentanyl

- Neurolept analgesia: droperidol
- 4-acylanilino derivative
- Opioid analgesic
- Duration of action: 30-50 min.
- Uses:

- in combination with diazepam used in diagnostic, endoscopic and angiographic procedures
- Adjunct to spinal and nerve block anaesthesia

Fentanyl – contd.

Advantages:

- Smooth onset and rapid recovery
- Suppression of vomiting and coughing
- Commanded operation
- Less fall in BP and no sensitization to adrenaline

Disadvantages:

- Respiratory depression
- Increase tone of chest muscle
- Nausea, vomiting and itching during recovery

Complications of anaesthesia:

During anaesthesia:

- Respiratory depression
- Salivation, respiratory secretions
- Cardiac arrhythmias
- Fall in BP
- Aspiration
- Laryngospasm and asphyxia
- Awareness
- Delirium and convulsion
- Fire and explosion

After anaesthesia:

- Nausea and vomiting
- Persisting sedation
- Pneumonia
- Organ damage – liver, kidney
- Nerve palsies
- Emergence delirium
- Cognitive defects

Preanesthetic medication:

- Definition:

It is the term applied to the use of drugs prior to the administration of an anaesthetic agent to make anaesthesia safer and more agreeable to the patient.

- Aim:

➢ Relief of anxiety
➢ Amnesia for pre and post operative events
➢ Analgesia
➢ Decrease secretions
➢ Antiemetic effects
➢ Decrease acidity and volume of gastric juice

Preanaesthetic medication – contd.

- Drugs used:
  - Sedative-anxiolytics – diazepam or lorazepam, midazolam, promethazine etc.
  - Opioids – Morphine and its congeners
  - Anticholinergics – Atropine
  - H_2 blockers – ranitidine, famotidine etc.
  - Antiemetics – Metoclopramide, domperidone etc.

The Practical approach: Protocol

Preoperative assessment →

Preanaesthetic medication → Induction by thiopentone or Propofol → Muscle relaxants → Intubation → Nitrous oxide + halogenated hydrocarbon →

Withdraw and recovery

Important

- Drugs used in General Anaesthesia
- Stages of General Anaesthesia with important points in each stage
- Details of Inhalation agents, mainly Ether, Halothane and Isoflurane
- Details of Inducing agents – Thiopentone and Propofol
- Dissociative anaesthesia
- Complications of Anaesthesia
- Preanaesthetic medication and examples of Drugs
- Second gas effect, diffusion hypoxia, malignant hyperthermia and Fentanyl
-

Thank you