

# ***General anesthetics***

# Surgery Before Anesthesia



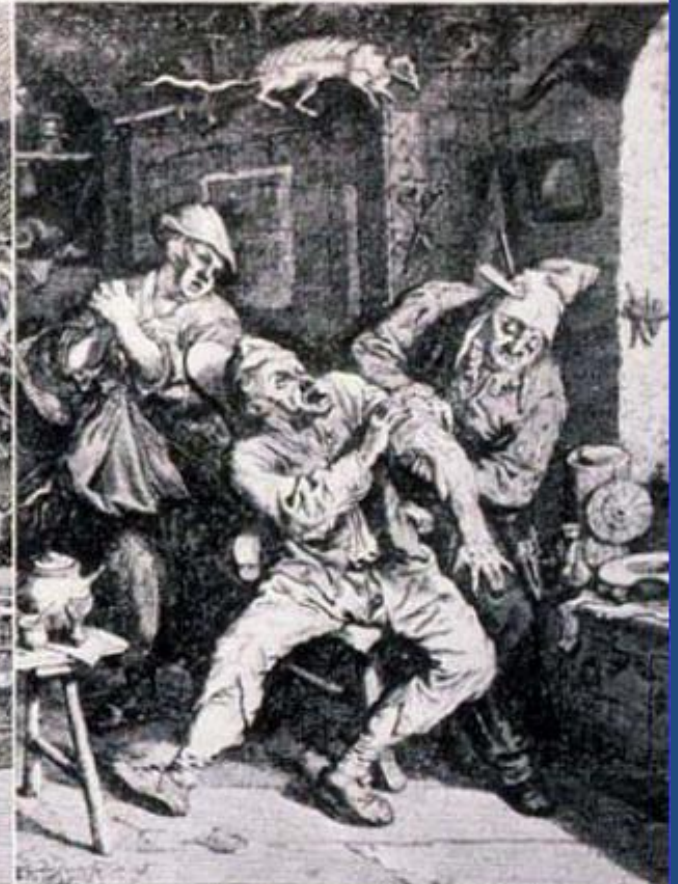
Mural of Dr. Villander, Hôtel de Dieu, Paris.

A



From *Behind the Doctor*, by Logan Clendenning, published by Alfred A. Knopf.

B



From *Devils, Drugs and Doctors*, by Howard W. Haggard, M.D., published by Harper and Brothers.

C

## PICTORIAL RECORDS OF THE AGONY ENDURED IN OPERATIONS BEFORE THE ADVENT OF ANESTHESIA

- A. A surgeon cutting with his big saw.
- B. A very painful operation of the seventeenth century.
- C. A surgeon torturing his patient.



# Fun and Frolics led to Early Anesthesia



[FIG. 1] Early use of alcohol for anesthetic purposes in a monastic hospital. From Diebold Schilling's *Swiss Chronicle*, 1513.

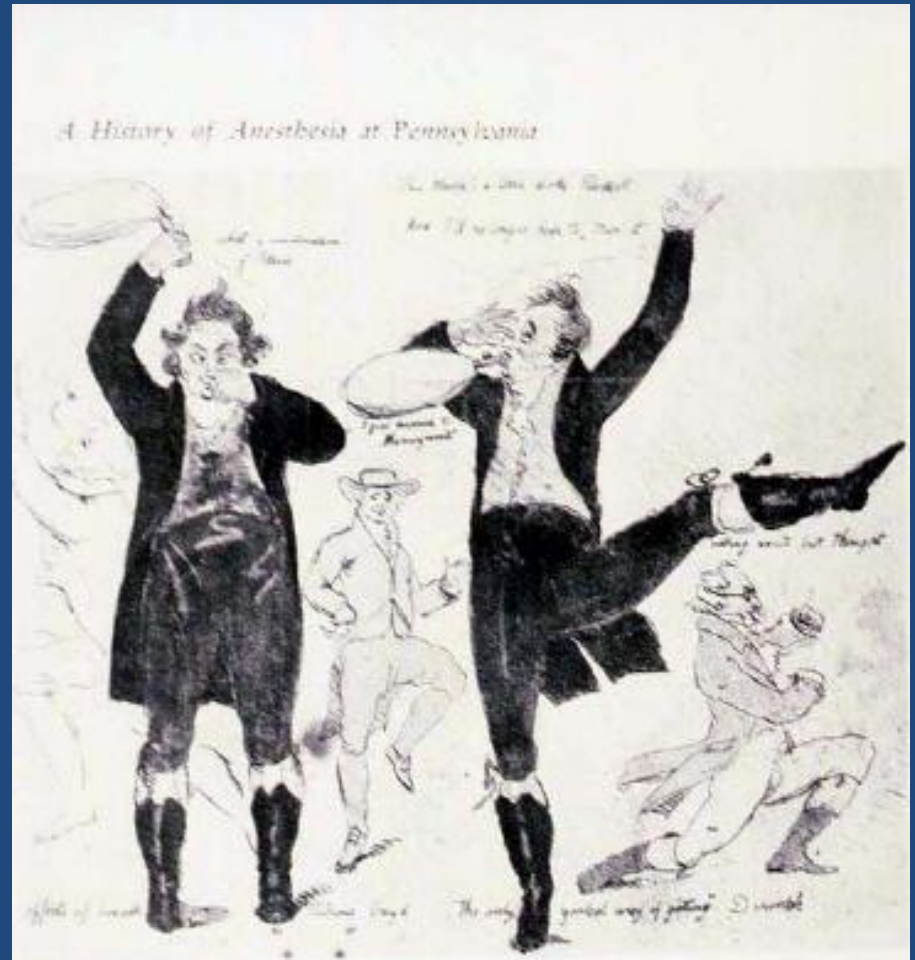
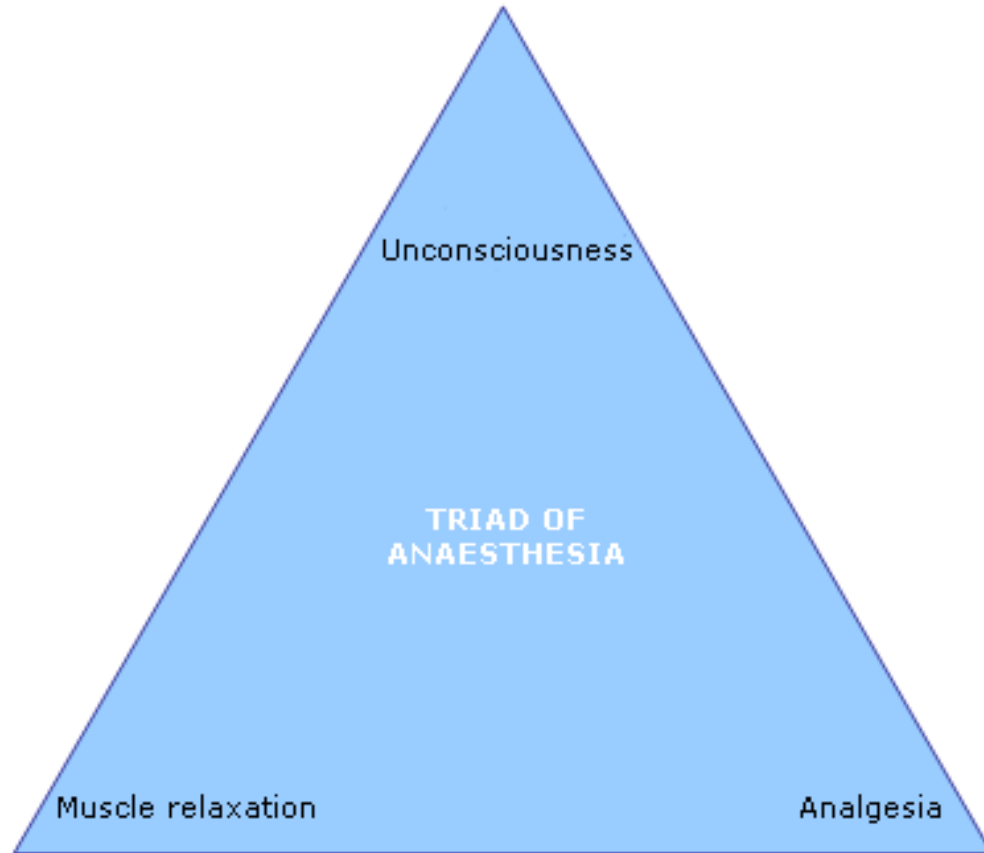


FIGURE 3. Caricature published in 1898 satirizing the work and thoughts of W. P. C. Barton on Nitrous Oxide. (Reproduced with the permission of the Edgar Faby Smith Memorial Collection, University of Pennsylvania.)

# AIMS OF ANAESTHESIA

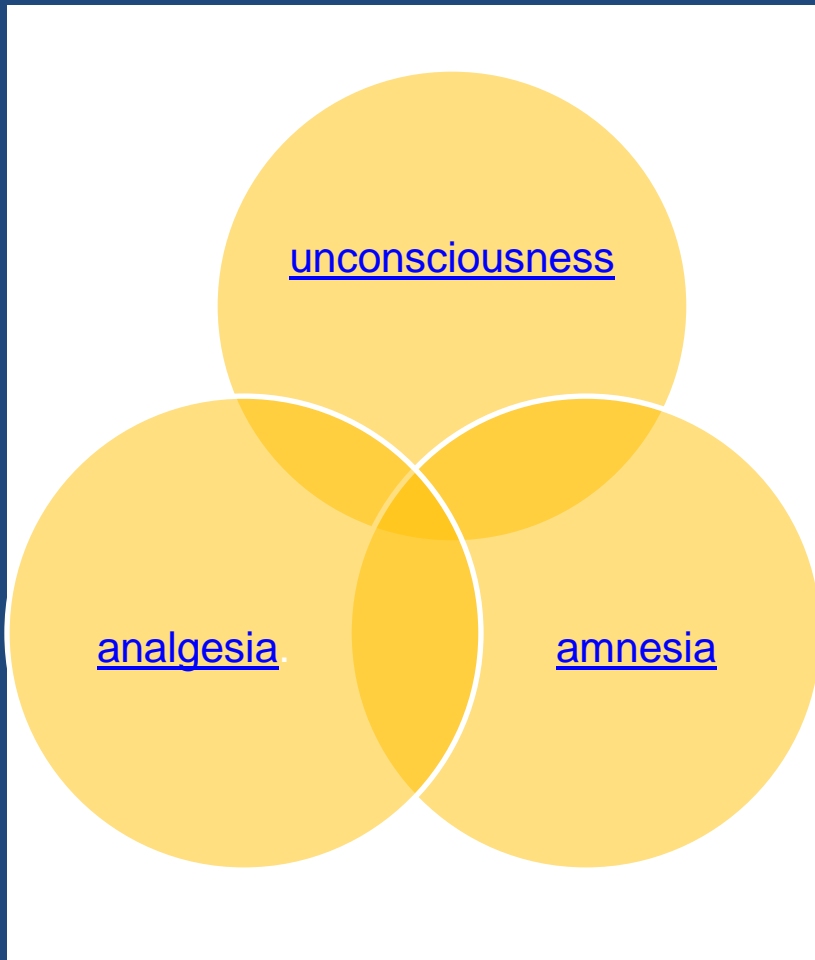


# Triad of anaesthesia

- **Neuromuscular blocking agents** for muscle relaxation
- **Analgesics/regional anaesthesia** for analgesia
- **Anaesthetic agents** to produce unconsciousness

# General Anaesthesia (GA)

- A variety of drugs are given to the patient that have different effects with the overall aim of ensuring unconsciousness, amnesia and analgesia.



# General anaesthetic-how do they work

- **TASK – EXPLAIN**

1. Loss of conscious awareness
2. Loss of response to noxious stimuli
3. Reversibility

- Anatomical site of action

- Brain : thalamus, cortex
- Spinal cord

# Stages of anaesthetics

- **Pre-medication**
- **Induction** – putting asleep
- **Muscle relaxation and intubation**
- **Maintenance** – keeping the patient asleep
- **Analgesia**
- **Reversal** – waking up the patient



# What are General Anesthetics?

- A drug that brings about a reversible loss of consciousness
- generally administered by an anesthesiologist in order to induce or maintain general anesthesia to facilitate surgery.

**Stage I: Disorientation, altered consciousness**

**Stage II: Excitatory stage, delirium, uncontrolled movement, irregular breathing. Goal is to move through this stage as rapidly as possible (i.v. *anesthetic*).**

**Stage III: Surgical anesthesia; return of regular respiration.**

**Plane 1: “light” anesthesia**

**Plane 2: Loss of blink reflex, regular respiration . Surgical procedures can be performed at this stage.**

**Plane 3: Deep anesthesia. Shallow breathing, assisted ventilation needed. Level of anesthesia for painful surgeries**

**Plane 4: Diaphragmatic respiration only, assisted ventilation is required. Cardiovascular impairment.**

**Stage IV: Too deep; essentially an overdose and represents anesthetic crisis. This is the stage between respiratory arrest and death due to circulatory collapse (Depressione bulbare)**

# Anesthetics divide into 2 classes

## Inhalation Anesthetics

- Gasses or Vapors
- Usually Halogenated

## Intravenous Anesthetics

- Injections
- Anesthetics or induction agents

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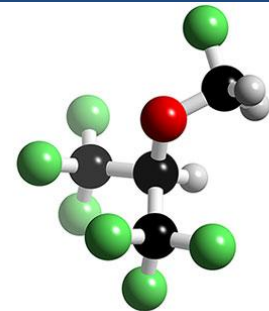
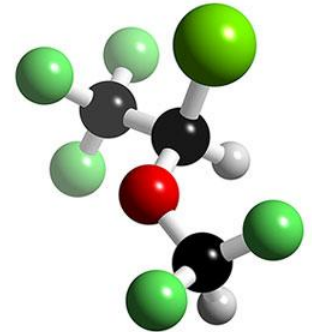
# Inhalation Anesthetics

Nitrous oxide



Halogenated anaes:

- Halothane
- Isoflurane
- Sevoflurane
- Enflurane



# Mechanism of Action

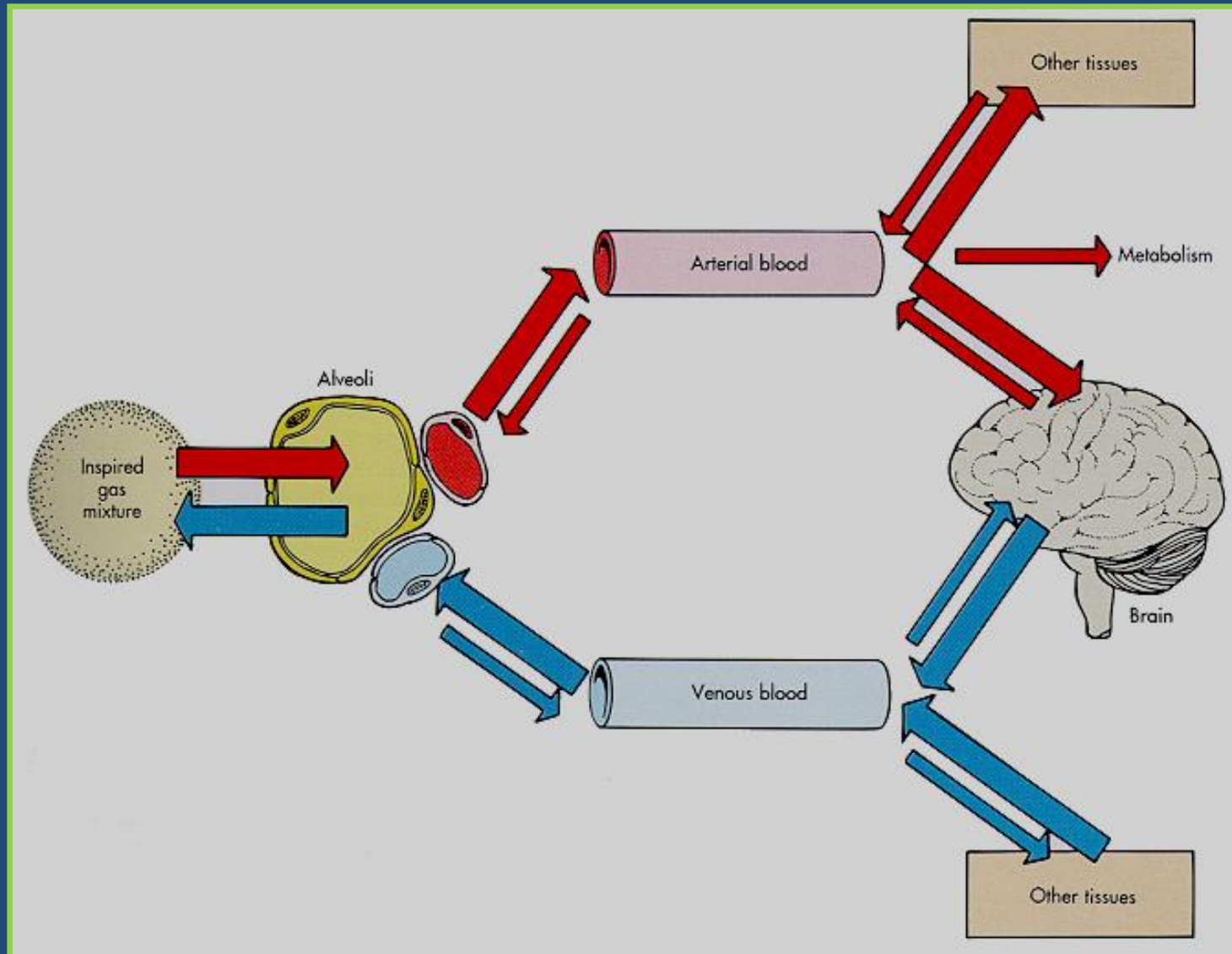
- lipid bilayer **expansion**
- Interaction with lipoprotein like channels and receptors
- Modification of membrane fluidity
- Increase of GABA and Glycine (inhibitory neurotransmitters) signals



# Molecular theories

- Critical volume hypothesis
  - Disruption of the function of ionic channels
- Perturbation theory
  - Disruption of annular lipids assoc. with ionic channels
- **Receptors**
  - **Inhibitory** – GABA<sub>A</sub>, glycin ← enhance
  - **Excitatory** - nACh, NMDA ← inhibit

# Pathway for General Anesthetics



# MAC

(minimum alveolar concentration)

- A measure of potency of inhaled anesthetics
- MAC is the concentration required to prevent 50 % of patients moving when subjected to standard midline incision

- Sevoflurane MAC 1.8 %
- Isoflurane MAC 1.17 %



# Pharmacokinetics of Inhaled Anesthetics

## 1. Amount that reaches the brain

Indicated by oil:gas ratio (lipid solubility) -  
***potency***

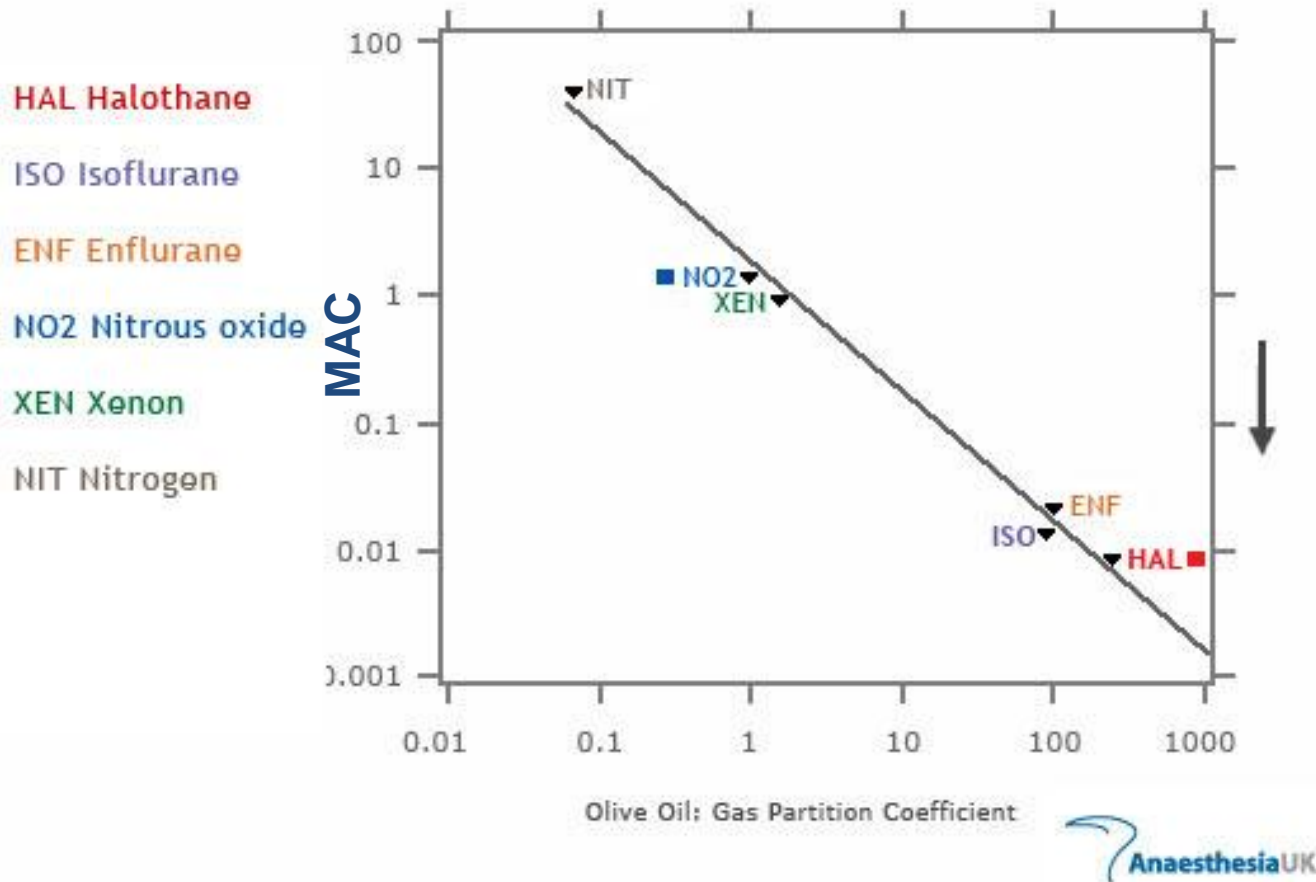
## 2. Solubility of gas into blood

The lower blood:gas ratio, more anesthetics  
will arrive to the brain

***rapid induction and recovery***

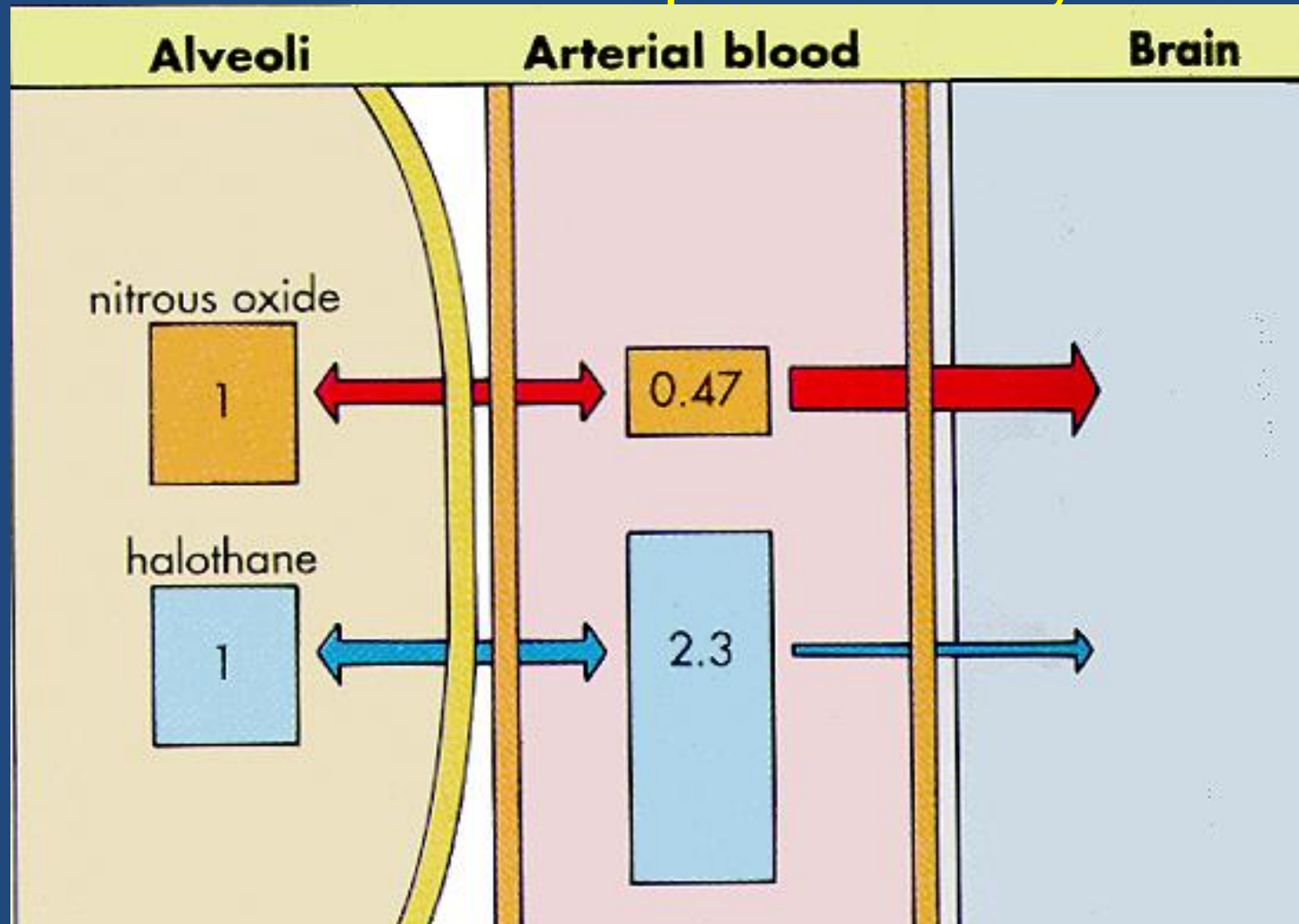
# Molecular theories

## Meyer Overton Correlation



- Linear correlation between the lipid solubility and potency

# Rate of Entry into the Brain: Influence of Blood and Lipid Solubility



**Halothane, oil/gas 224 – blood/gas 2.3 – MAC 0.8**

**Nitrous oxide, oil/gas 1.4 – blood/gas 0.47 – MAC > 100**



# General Actions of Inhaled Anesthetics

- Respiration
  - Depressed respiration and response to CO<sub>2</sub>
- Kidney
  - Depression of renal blood flow and urine output
- Muscle
  - High enough concentrations will relax skeletal muscle

# Cont'

- Cardiovascular System

- Generalized reduction in arterial pressure and peripheral vascular resistance.
- Isoflurane maintains CO and coronary function better than other agents

- Central Nervous System

- Increased cerebral blood flow and decreased cerebral metabolism

# Inhaled Anesthetics

## Nitrous Oxide

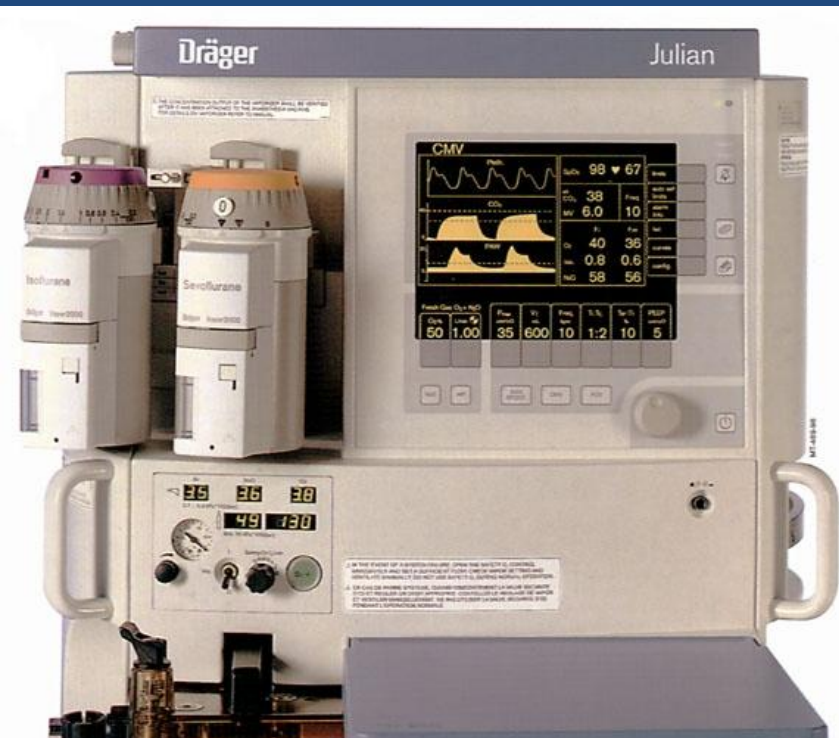
- widely used
- potent analgesic
- produce a light anesthesia
- does not depress the respiration/vasomotor center
- used as adjunct to supplement other inhalationals



# Inhaled Anesthetics

## Halothane

- non-flammable
- 20% metabolism by P450
- induction of hepatic microsomal enzymes
- myocardial depressant (SA node), sensitization of myocardium to catecholamines - arrhythmia



## Inhaled Anesthetics

# Halothane

- Transient hepatic damage
- Liver necrosis
- In repeated exposure
- Immunosensititation

# Malignant Hyperthermia

- Malignant hyperthermia (MH) is a pharmacogenetic hypermetabolic state of skeletal muscle induced *in susceptible individuals* by inhalational anesthetics and/or succinylcholine (and maybe by stress or exercise).



- Genetic susceptibility-Ca<sup>+</sup> channel defect (CACNA1S) or RYR1 (ryanodine receptor)
- Excess calcium ion leads to excessive ATP breakdown/depletion

## Malignant Hyperthermia

- Signs: tachycardia, tachypnea, metabolic acidosis, hyperthermia, muscle rigidity, sweating, arrhythmia
- May be fatal
- Treated with dantrolene

# Inhaled Anesthetics

## Enflurane

- Rapid, smooth induction and maintenance
  - 2-10% metabolized in liver
  - Introduced as replacement for halothane

# Isoflurane

- smooth and rapid induction and recovery
- very little metabolism (0.2%)
- no reports of hepatotoxicity or renotoxicity
- most widely employed

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## Intravenous Anesthetics

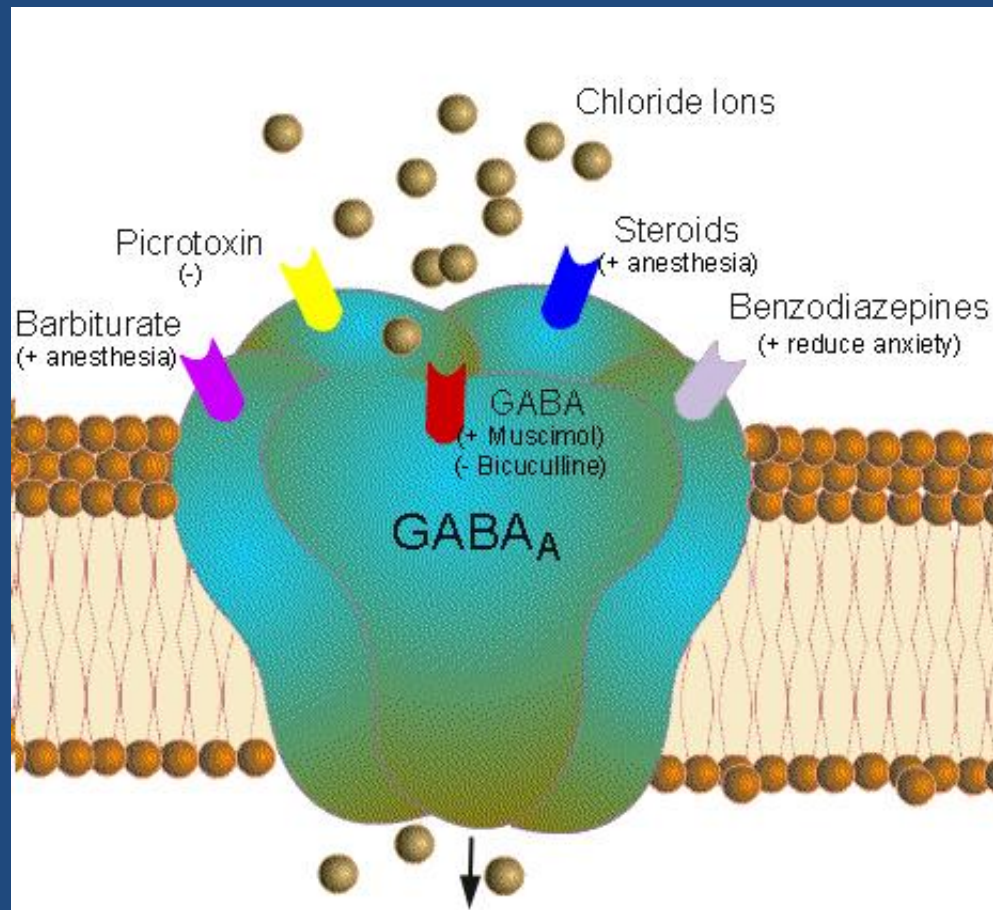
- Injections
- Anesthetics or induction agents

# Intravenous anaesthetics

- Onset of anaesthesia within one arm – brain circulation time – 30 sec
- Effect site → brain
  - Propofol
  - Thiopentale
  - Etomidate
  - Ketamine



# GABA<sub>A</sub> receptor



# Intravenous Anesthetics

- Most exert their actions by potentiating GABA<sub>A</sub> receptor
- GABAergic actions may be similar to those of volatile anesthetics, but act at different sites on receptor



# Organ Effects

- Most decrease cerebral metabolism and intracranial pressure
- Most cause respiratory depression
- May cause apnea after induction of anesthesia

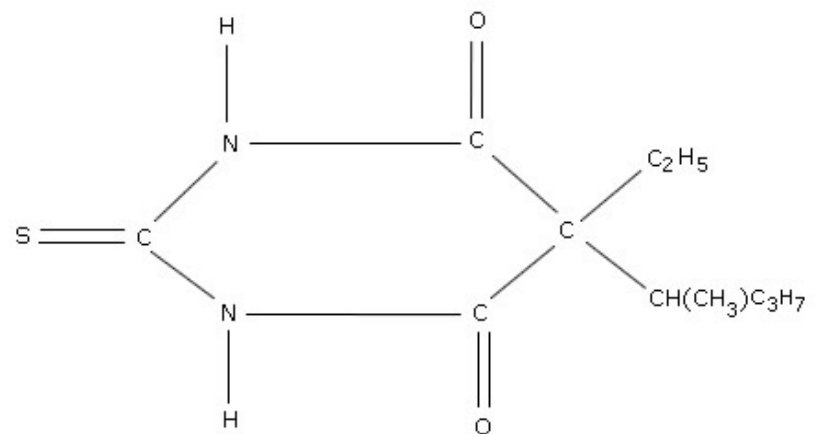
# Cardiovascular Effects

- Barbiturates, benzodiazepines and propofol cause cardiovascular depression.

# Thiopental sodium

- Barbiturate
- **Dose** 3-7 mg/kg
- **Effects** : hypnosis, anti-epileptic, analgesic
- rapid onset (20 sec)

- short-acting



- effect terminated not by metabolism but by redistribution
- repeated administration or prolonged infusion approached equilibrium at redistribution sites
- build-up in adipose tissue = very long emergence from anesthesia

## Side effects

- hypotension
- apnoea
- airway obstruction



# Thiopentale

- **Problems with use**
  - Extremely painful and limb-threatening when given intra-arterially
  - Hypersensitivity reactions 1: 15 000
- **Contraindications**
  - Porphyria

# Propofol

Phenolic derivative

**Dose** 1- 2.5 mg/kg

**Effects** : hypnosis

- short-acting agent used for the induction
- maintenance of GA and sedation
- onset within one minute of injection



- It is highly protein bound *in vivo* and is metabolised by conjugation in the liver

## Side-effect

- pain on injection
- hypotension
- transient apnoea following induction



# Etomidate

- Ester
- Dose 0.3 mg/kg
- Effects : hypnosis
- Side effects
  - CVS: very little effect on HR, CO, SVR
  - minimal respiratory depression



# Etomidate

- **Problems with use**
  - Pain on injection
  - Nausea and vomiting
  - Adrenocortical suppression
  - Hypersensitivity reaction 1: 75 000
- **Relative Contraindications**
  - Porphyria

# Ketamine

Phencyclidine derivative

- NMDA Receptor Antagonist
- usually stimulate rather than depress the circulatory system.

Use – analgesic in Emerg. Med



- Analgesic
- dissociative anesthesia

Cataleptic appearance, eyes open,  
reflexes intact, purposeless but  
coordinated movements

- Stimulates sympathetic nervous system
- Psychomimetic – “emergence reactions”
  - vivid dreaming extracorporeal (floating "out-of-body") experience misperceptions, misinterpretations, illusions
  - may be associated with euphoria, excitement, confusion, fear

# General anesthesia

- Induction
- Maintenance

# Induction

intravenous

Faster onset

avoiding the  
excitatory  
phase of  
anaesthesia

inhalational

where IV  
access is  
difficult

Anticipated  
difficult  
intubation

patient  
preference  
(children)

# Maintenance

- In order to prolong anaesthesia for the required duration
- breathe to a carefully controlled mixture of oxygen, nitrous oxide, and a volatile anaesthetic agent
- transferred to the patient's brain via the lungs and the bloodstream, and the patient remains unconscious



# Maintenance

- Inhaled agents are supplemented by intravenous anaesthetics, such as opioids (usually fentanyl or morphine)

# What is Balanced Anesthesia?

- Use specific drugs for each component
  - 1. Sensory**
    - N<sub>2</sub>O, opioids, ketamine for analgesia
  - 2. Cognitive**
    - Produce amnesia, and preferably unconsciousness
    - inhaled agent
    - IV hypnotic (propofol, midazolam, diazepam, thiopental)
  - 3. Motor**
    - Muscle relaxants

# Simple Combinations

- Morphine
- Propofol
- N<sub>2</sub>O
- Sevoflurane
- Relaxant of choice

# Simple Combinations

- Fentanyl
- Thiopental sodium
- N<sub>2</sub>O
- Halothane
- Relaxant of choice

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