

**Drugs acting on CNS**

# **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.

## Definitions

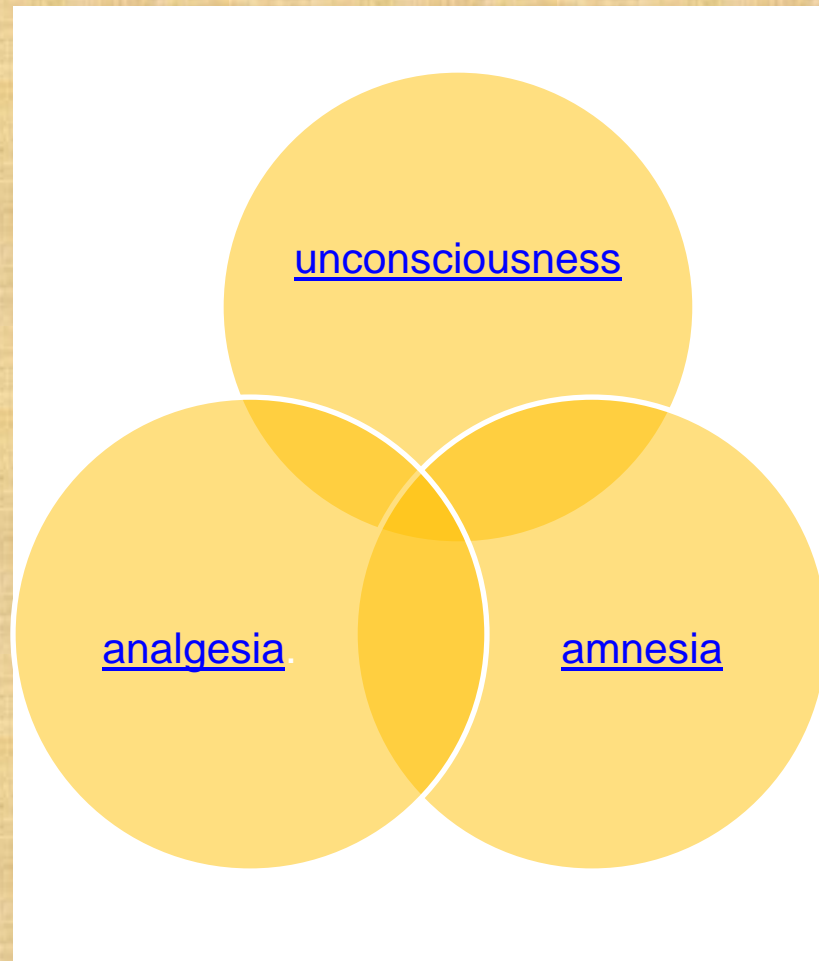
- **Sleep:** A condition of body and mind which typically recurs for several hours every night, in which the nervous system is inactive, the eyes closed, the postural muscles relaxed, and consciousness practically suspended.
- **Amnesia:** A medical condition that makes you unable to remember things or loss of the ability to remember.
- **Analgesia:** Insensibility to pain without loss of consciousness.



## Definitions

- **Delirium:** an acutely disturbed state of mind characterized by restlessness, illusions, and incoherence, occurring in intoxication, fever, and other disorders.
- **General anaesthesia:** A reversible loss of consciousness and analgesia due to administration of general anaesthetics in order for surgeons to operate on a patient.

# General Anaesthesia (GA)



- An induced state of unconsciousness, amnesia and analgesia in combination.

# Phases/planes of General Anaesthesia

- **Stage I:** Stage of analgesia; Disorientation, altered consciousness
- **Stage II:** Stage of delirium; excitatory stage, delirium, uncontrolled movement, irregular breathing. Goal is to move through this stage as rapidly as possible.
- **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.

## Phases/planes of General Anaesthesia

- **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:** Medullary paralysis; too deep, essentially an overdose and represents anesthetic crisis. This is the stage between respiratory arrest and death due to circulatory collapse.



STAGE		Respiration		Ocular movem.	Pupil size	Reflexes	SK.mus. tone	B. P.	H. R.	USES
		Thor.	Abd.							
I ANALGESIA				NORMAL		<div>EYE LID</div> <div>PHARYNGEAL</div> <div>CORNEAL</div> <div>LIGHT</div>				Labour, Incisions and Minor ops.
II DELIRIUM				<div>ROVING EYE BALLS</div>						NIL
SURGICAL ANAESTHESIA III	1									<div>Most of the surgical operations</div> <div>Occasionally reached now</div> <div>Never attempted</div>
	2									
	3									
	4									
IV MEDULLARY PARALYSIS										

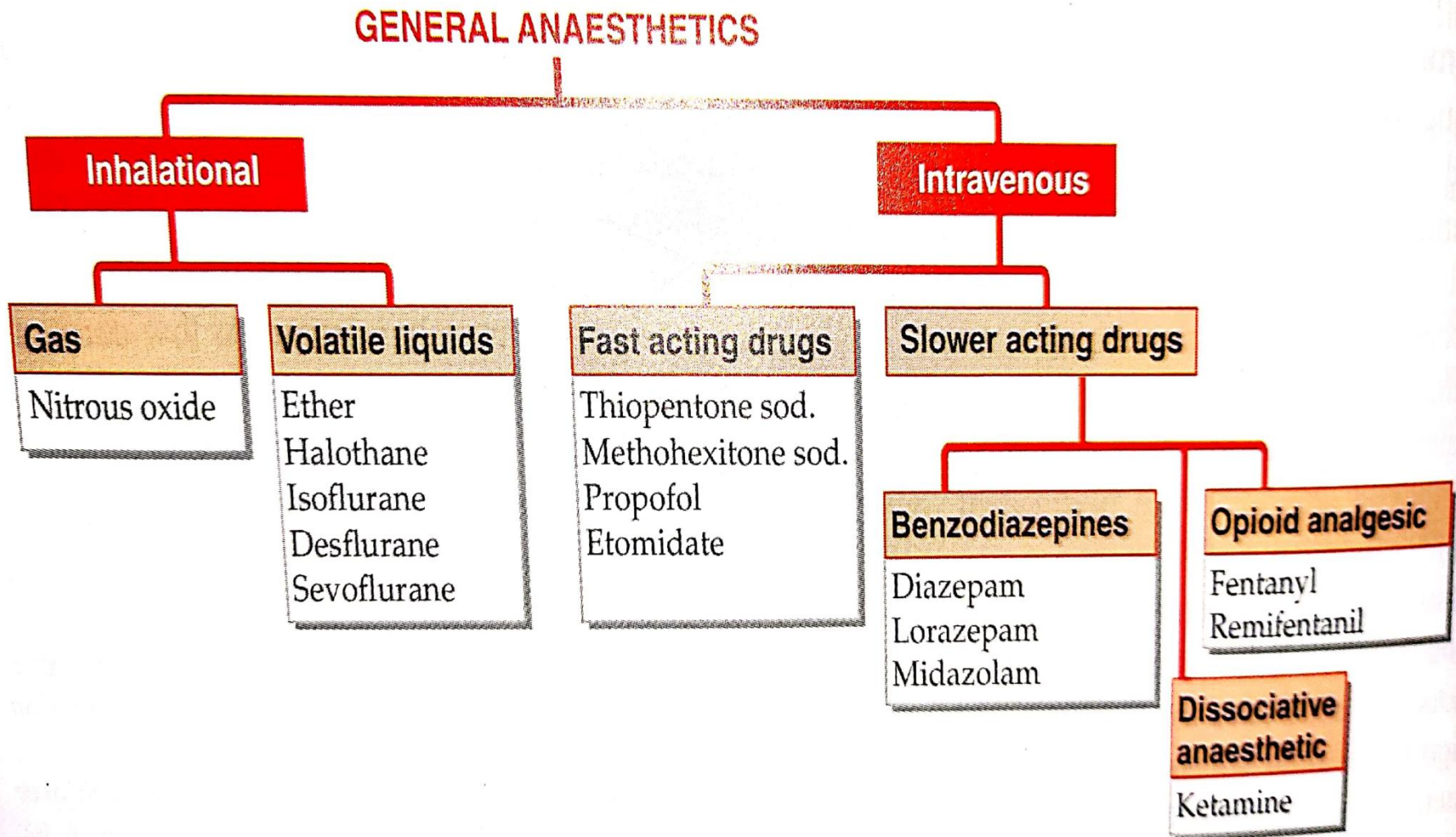
**Fig. 27.1:** Physiological changes during stages of general anaesthesia (with ether)



# What are General Anaesthetics?

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

# Anaesthetics classes



Cyclopropane, trichloroethylene, methoxyflurane and enflurane are no longer used.

# Anesthetics divide into Two classes

## Inhalation Anesthetics

- Gasses or Vapors
- Usually Halogenated

## Intravenous Anesthetics

- Injections
- Anesthetics or induction agents



# Inhalation Anesthetics

Nitrous oxide

GAS

Halogenated  
anaes:

- Halothane
- Isoflurane
- Sevoflurane
- Enflurane

LIQUID  
VAPOUR

## Mechanism of Action

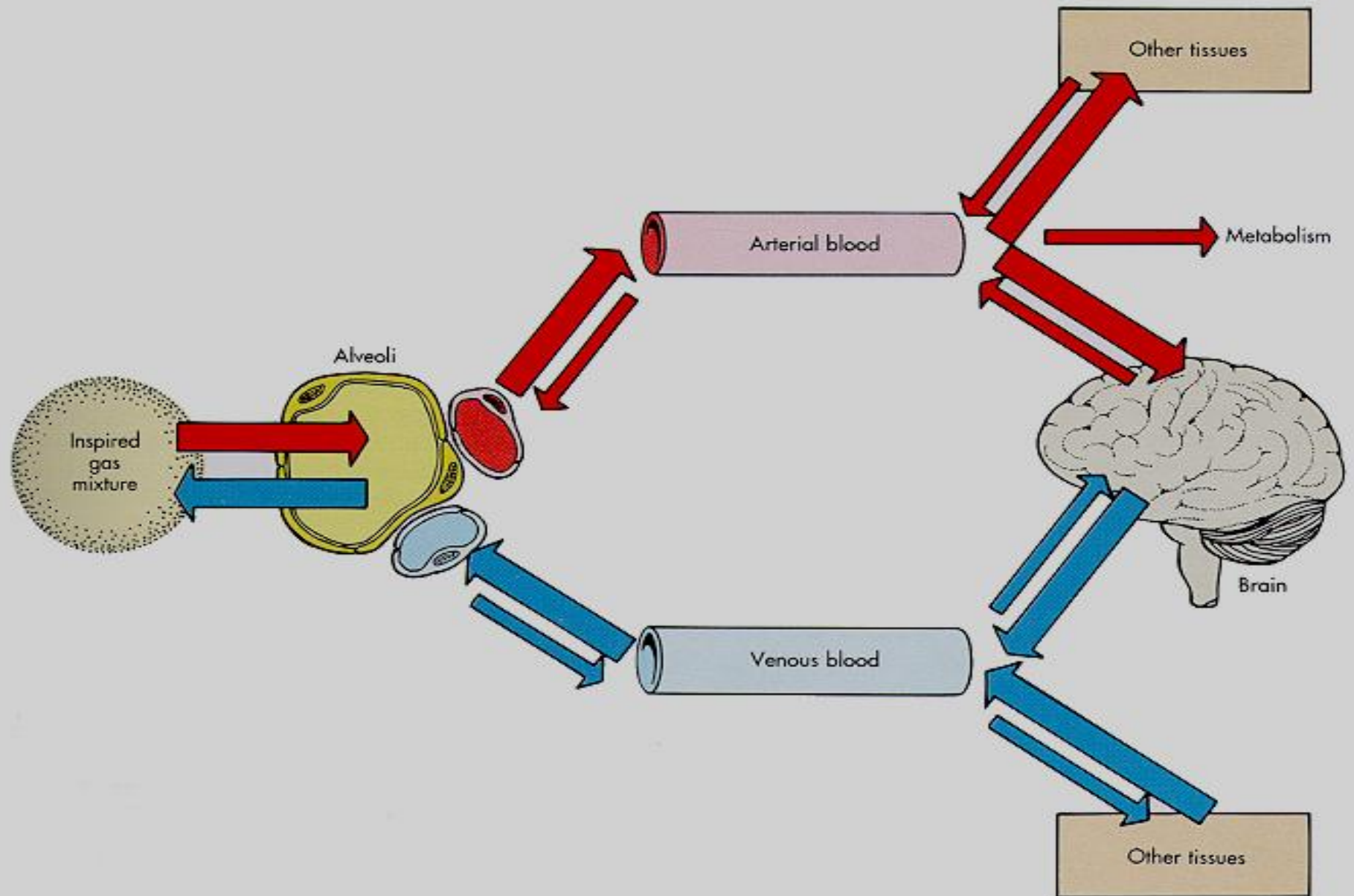
- Interaction with membrane protein receptors or the lipid protein interface at CNS.
- Volatile Anaesthetics – increase GABA / Glycine ( inhibitory neurotransmitters) to open Cl(-) channels in the spinal cord and medulla.

## MAC(minimum alveolar concentration)

- A measure of potency of inhaled anesthetics
- MAC is the concentration necessary to prevent responding in 50% of population.



# Pathway for General Anesthetics



# Pharmacokinetics of Inhaled Anesthetics

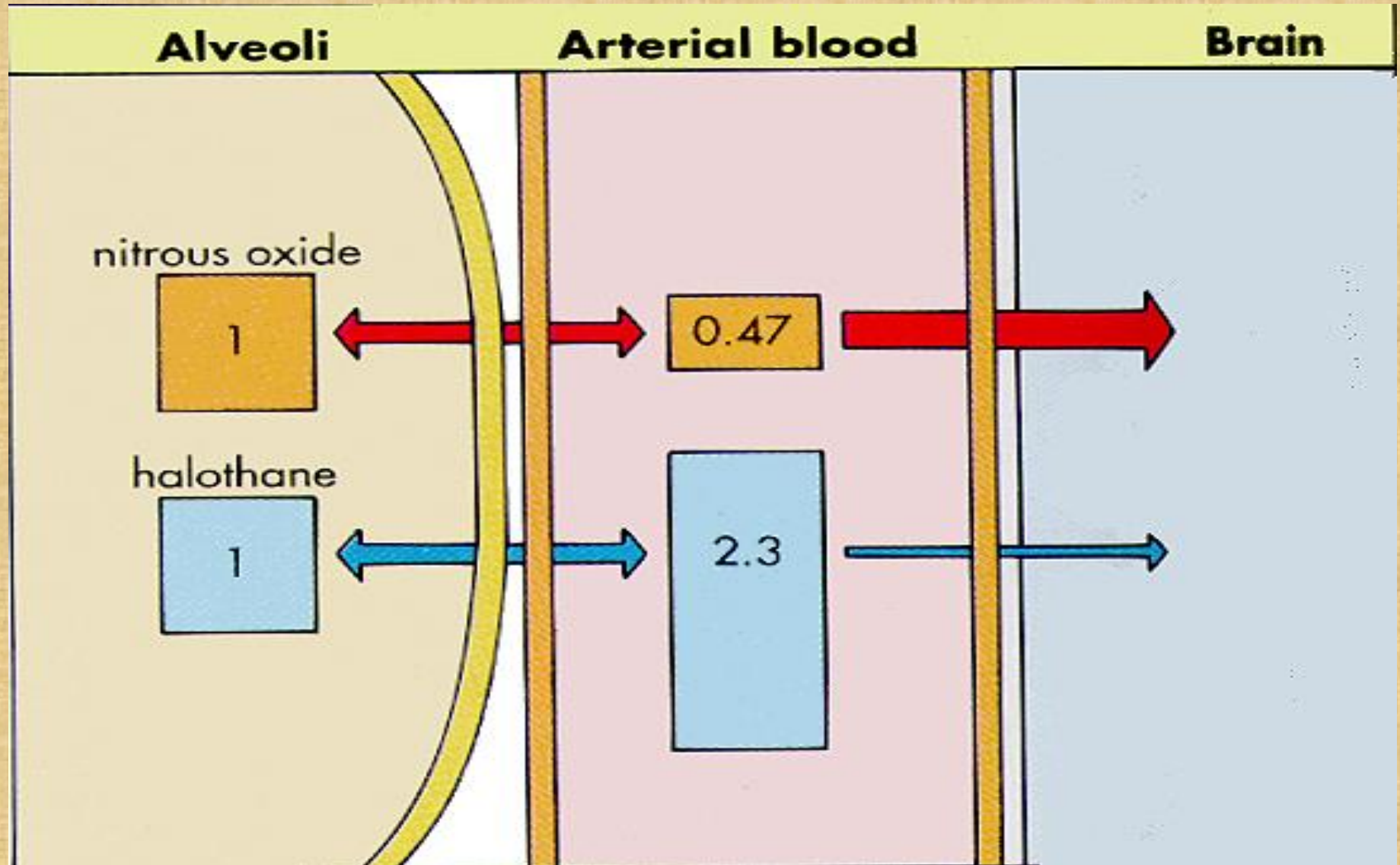
## 1. Amount that reaches the brain

Indicated by oil:gas partition coefficient (ratio)  
(lipid solubility)

## 2. Solubility of gas into blood

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

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





# 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

# General Actions of Inhaled Anesthetics

- 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

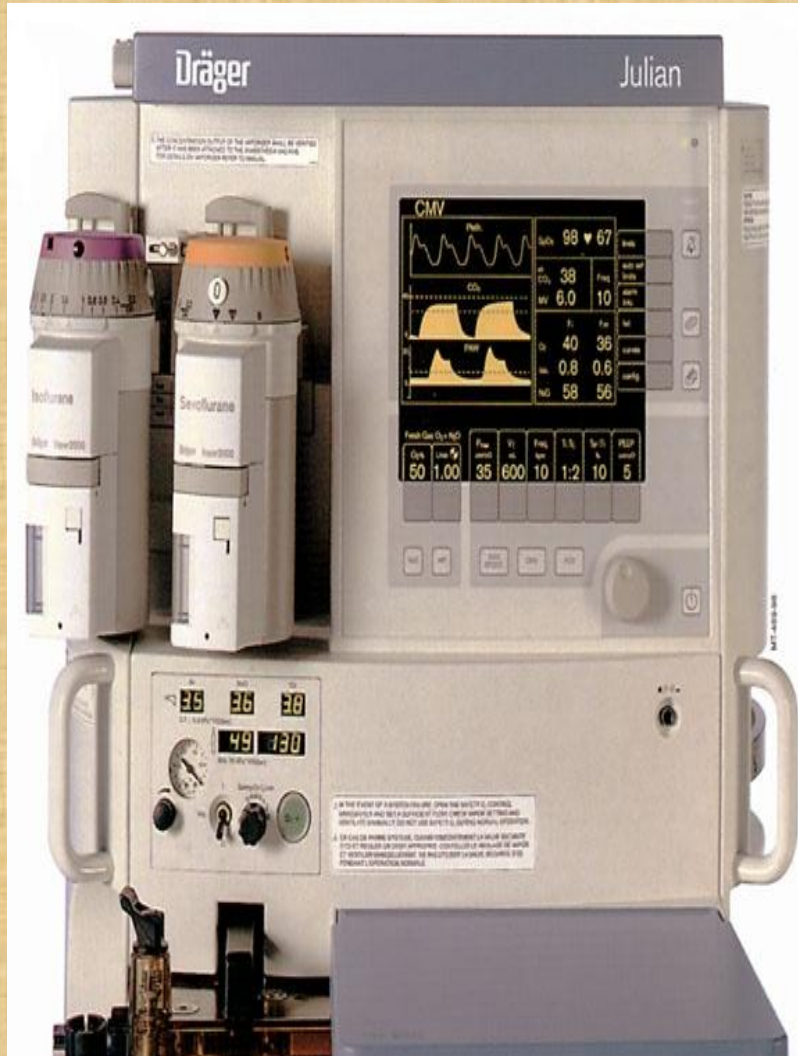
- widely used
- Potent analgesic
- Produce a light anesthesia
- Do not depress the respiration/vasomotor center
- Used adjunct to supplement other inhalationals





# 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 side effects

- 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 neurotoxicity
- most widely employed

# Anesthetics divide into Two classes

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# Intravenous Induction Agents

- Commonly used IV induction agents:
  - Propofol
  - Thiopental sodium
  - Ketamine

## MOA of 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

- **CNS effect:** Most of the intra venous GAs decrease cerebral metabolism and intracranial pressure
- **Respiratory effect:** Most cause respiratory depression
- May cause apnea after induction of anesthesia
- **Cardiovascular Effects:** Barbiturates, benzodiazepines and propofol cause cardiovascular depression.

# Thiopental sodium

- 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 for anesthesia



## Side effects

- Hypotension
- apnoea
- airway obstruction



# Propofol

- 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



# Ketamine

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



- Analgesic
- Dissociative anesthesia

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

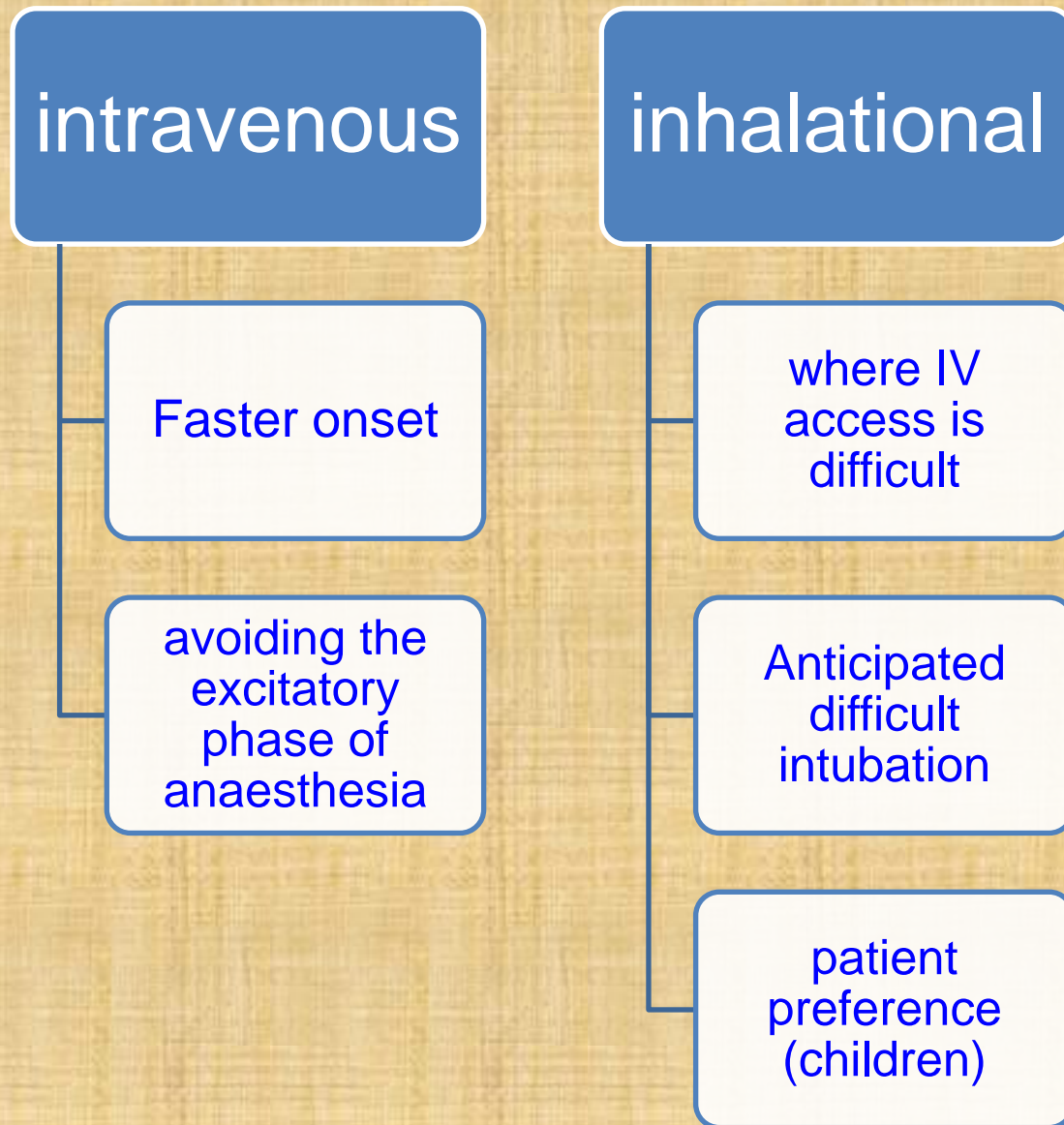
- Stimulates sympathetic nervous system
- Psychomimetic – “emergence reactions”
  - vivid dreaming extracorporeal (floating "out-of-body") experience misperceptions, misinterpretations, illusions
  - may be associated with euphoria, excitement, confusion, fear



# General Anaesthesia Management

- Induction
- Maintenance

# Induction



## 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
- 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

**THANK YOU**