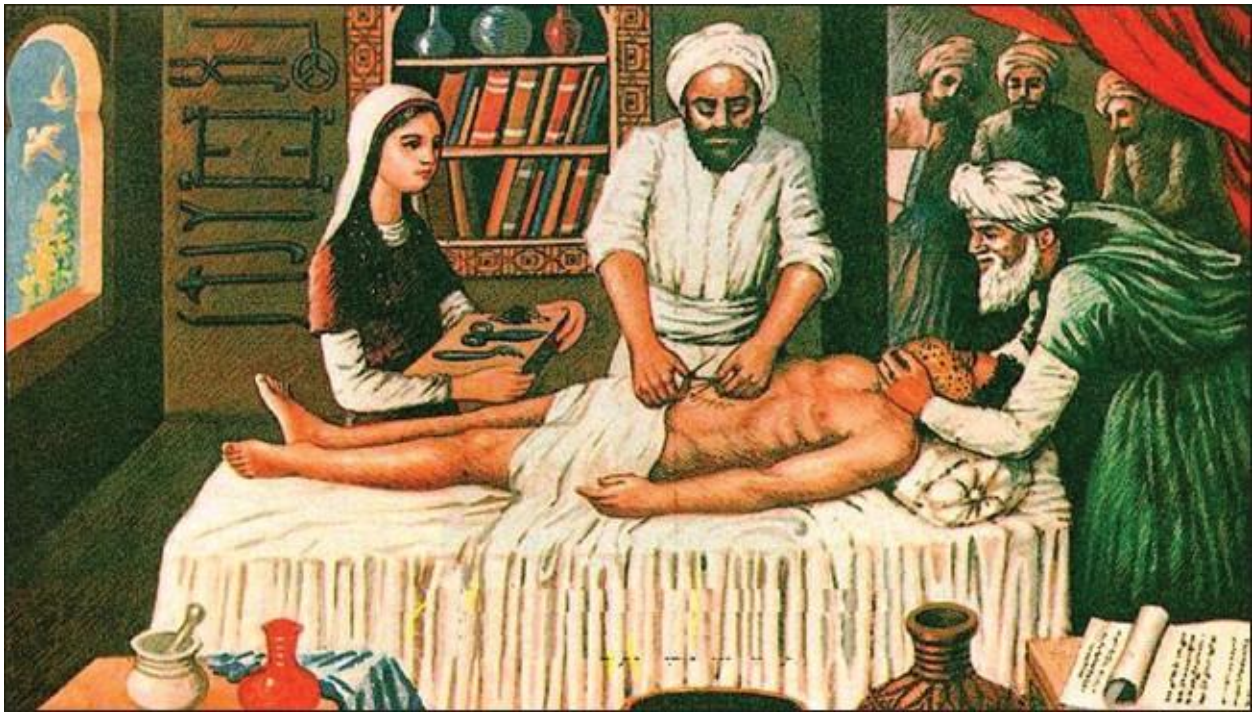
General Anaesthetics

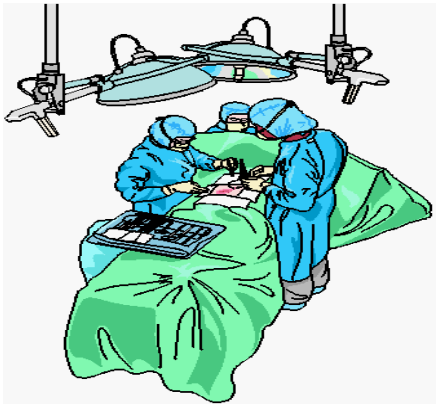


- Ibn al-Quff (1233-1286 AD ; 630 — 685 AH) was an Arab physician and surgeon and author, he was used anesthesia by inhalation, by using anesthetic sponge
- The sponge was soaked in a boiled solution made of water with cannabis (from Arabic hasheesh) opium (from Arabic afiun) and belladonna (from Arabic cit al huscin)
- The anesthetic sponge was placed it over the patient face, the liquid which is absorbed by the mucous membrane of nose and mouth.

General Anaesthetics

Horace Wells

Massachusetts General Hospital, Boston, 1845



General anesthesia is **a reversible** state of central nervous system **(CNS) depression**, causing loss of response to and perception of stimuli.

An ideal General Anaesthetic…….

Rapid smooth loss of consciousness.

Rapid reversible upon discontinuation

Possess a wide margin of safety.

General Anaesthetics

Objectives:

Sedation and reduced anxiety

Lack of awareness and amnesia

Skeletal muscle relaxation

Suppression of undesirable reflexes

Analgesia

The subject is not rousable by external stimuli

No single anesthetic agent currently available when used alone can achieve all of these desired effects.

PATIENT FACTORS IN SELECTION OF ANESTHESIA

Status of organ systems

- Cardiovascular system
- Respiratory system
- Liver and kidney
- Pregnancy

PATIENT FACTORS IN SELECTION OF ANESTHESIA

Concomitant use of drugs

Multiple adjunct agents

H_2 blockers (famotidine, ranitidine)

Benzodiazepines (midazolam, diazepam)

Nonopioids (acetaminophen, celecoxib) or opioids (fentanyl)

Antihistamines (diphenhydramine)

Antiemetics (ondansetron)

Anticholinergics (glycopyrrolate)

Premedications facilitate smooth induction of anesthesia and lower required anesthetic doses.

However, they can also enhance undesirable anesthetic effects (hypoventilation) and, when coadministered, may produce negative effects not observed when given individually.

PATIENT FACTORS IN SELECTION OF ANESTHESIA

Concomitant use of drugs

Concomitant use of other drugs

Patients may take medications for underlying diseases or abuse drugs that alter response to anesthetics.

For example, alcoholics have elevated levels of liver enzymes that metabolize anesthetics, and drug abusers may be tolerant to opioids.

General anesthesia phases (stages):

I) **Induction:** is the time from **administration** of a potent anesthetic (**IV anesthetics**) to **development of effective anesthesia**, depends on **fast effective concentrations** of anesthetic reach the brain.(N.B.) (Child.)

2) **Maintenance:** provides **sustained anesthesia**, is commonly provided with **inhaled anesthetics**. (fent.) (IV drugs)

3) **Recovery:** is the time from **discontinuation** of anesthetic until **consciousness**.

Stages of Anaesthesia [Depth of Anesthesia]

These stages were defined for the original anesthetic **Ether**, which produces **a slow onset** of anesthesia.

With **modern anesthetics**, the stages merge because of the **rapid onset** of stage III.

Stage I (Induction); is the period between the initial administration of the induction agents and loss of consciousness, during this stage:

- **Patient conscious**.
- **Analgesia.**

Stage II (Delirium/Excitement): is the period following loss of consciousness and excited and delirious activity, during this stage:

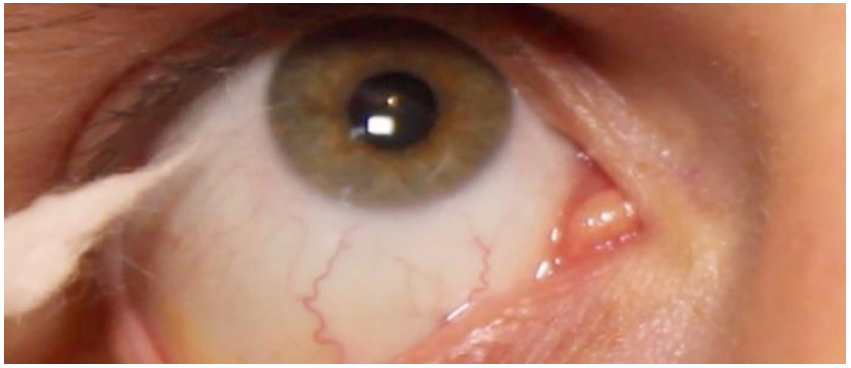
- **Irregular respiration.**
- **Irregular heart rate.**
- **Uncentrolled movements.**
- **Vomiting.**

3) Stage III (Surgical Anaesthesia): is the ideal stage for surgery, during this stage:

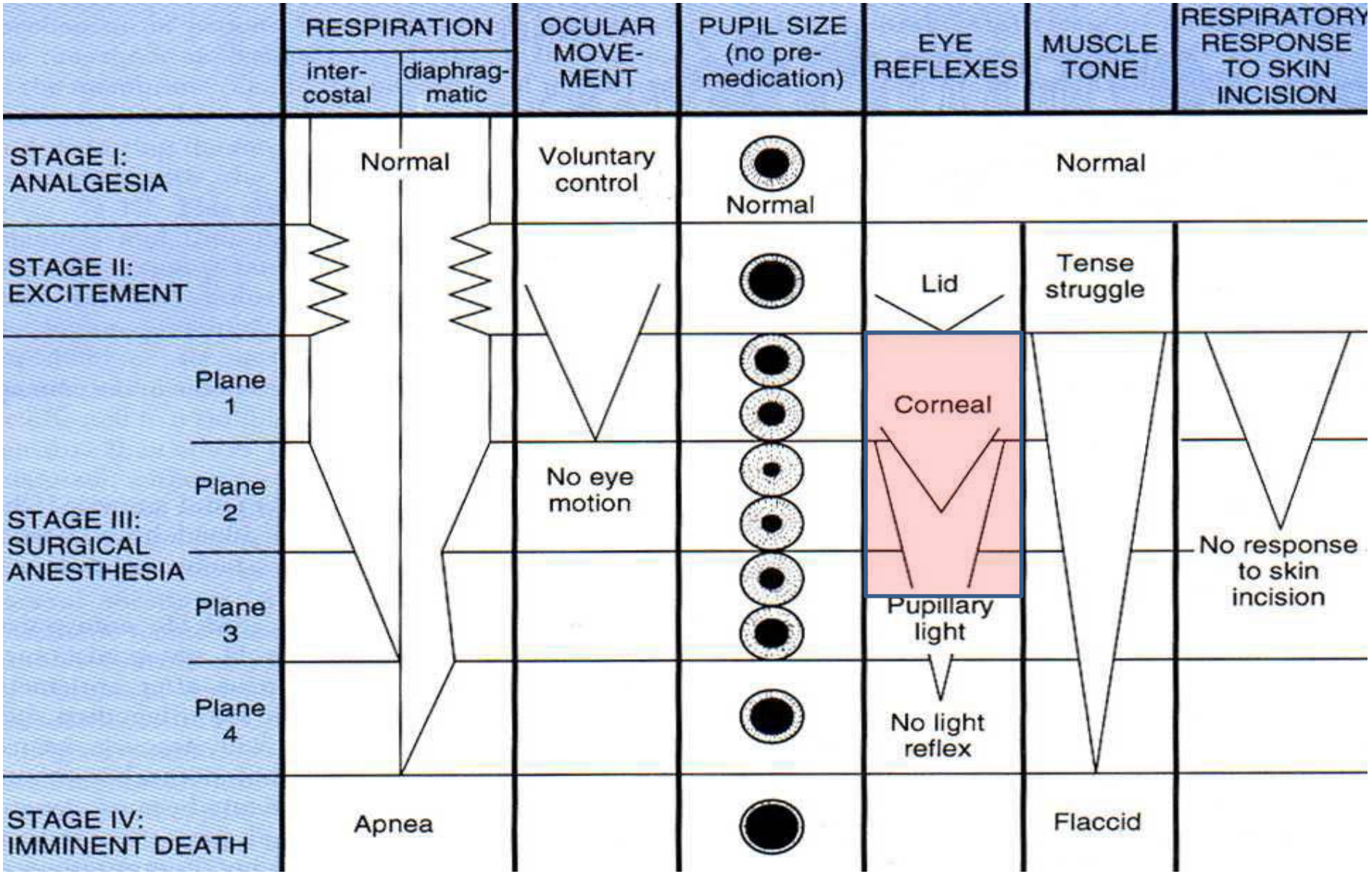
- Patient is unconscious.
- Regular respiration.
- No vomiting.
- No pain.
- No pressure.
- No pupil size.
- Slow eye movements.

Careful monitoring is required during this stage to prevent undesired progression to stage IV.

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.



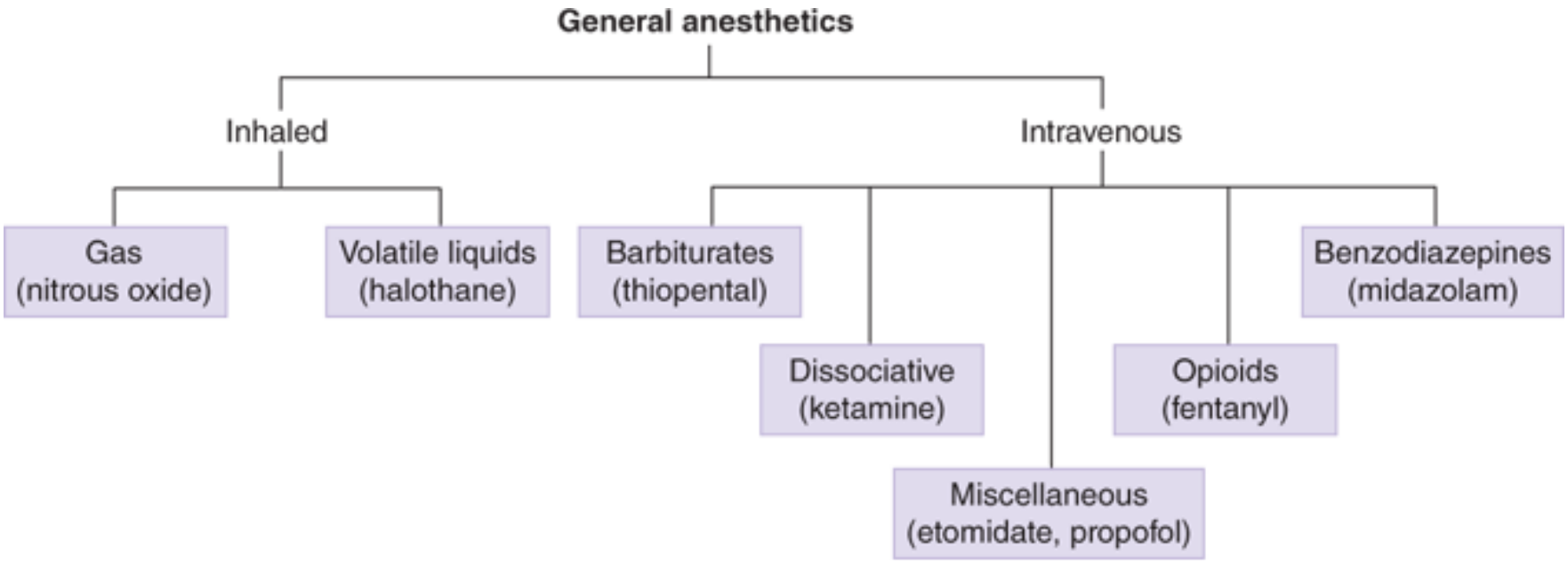
Guedel's Signs and Stages of Anesthesia



Stage IV (Medullary paralysis or overdose): is the stage where t… much medication has been given a… atient has **severe brain ste… medullary depression.**

- Respirat… ession.
- H… ion.
- V…ery weak pulse.
- Death may occur.

Ventilation and circulation must be supported to prevent death.



Source: A.J. Trevor, B.G. Katzung, M. Kruidering-Hall: Katzung & Trevor's Pharmacology: Examination & Board Review, 11th Ed.
www.accesspharmacy.com

INHALATION ANESTHETICS

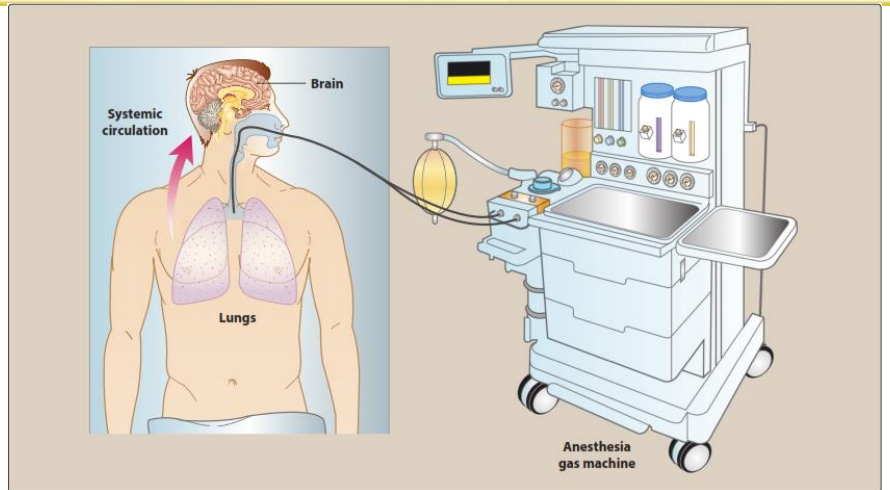
- On October 16, 1846 at the operating theater of the Massachusetts General Hospital, (MGH), in Boston.

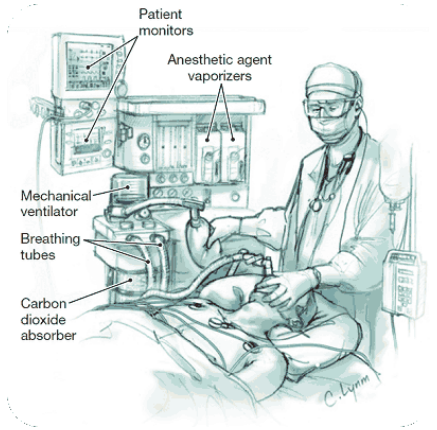
- Dr. John Collins Warren painlessly removed a tumor from the neck of a Mr. Edward Gilbert Abbott.

- Dentist William Morton was used Ether inhaler as a first inhalation anesthetic in surgery (*see photo*).

- This ranks as one of the most significant events in the history of Medicine.

- People around the world annually celebrate **World Anaesthesia Day** on October 16.



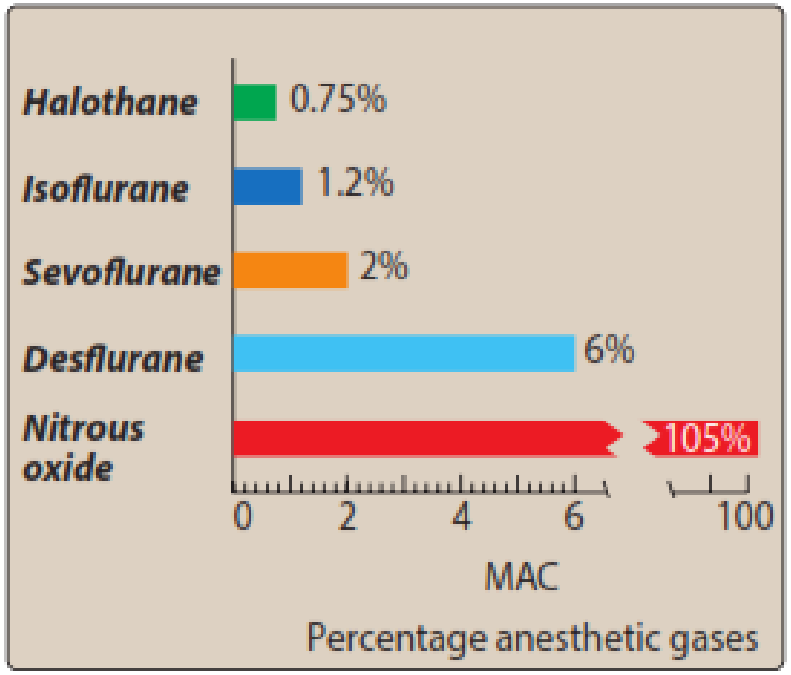


Minimum Alveolar Concentration (MAC) (potncy)

- **MAC**: is the minimum concentration of inhaled anesthetic in the lung needed to produces anesthesia in **50%** of patients.
- MAC used to measures the **potency** of inhaled anesthetics, MAC is **small for potent anesthetics** such as **Halothane** and **large for less potent** agents such as **Nitrous oxide**.
- Factors that can increase MAC: **hyperthermia**, **drugs that increase CNS catecholamines**, and **chronic ethanol abuse**.

Minimum Alveolar Concentration (MAC) (potncy)

- Factors that can **decrease** MAC: **increased age**, **hypothermia**, **pregnancy**, **sepsis**, **acute intoxication**, **concurrent IV anesthetics** and **α_2-adrenergic receptor agonists** (**Clonidine**).



Factors affecting the uptake and distribution of inhalation anesthetics

- Alveolar wash-in

This refers to replacement of normal lung gases with the inspired anesthetic mixture.

↑ the functional residual capacity of the lung → ↑ time

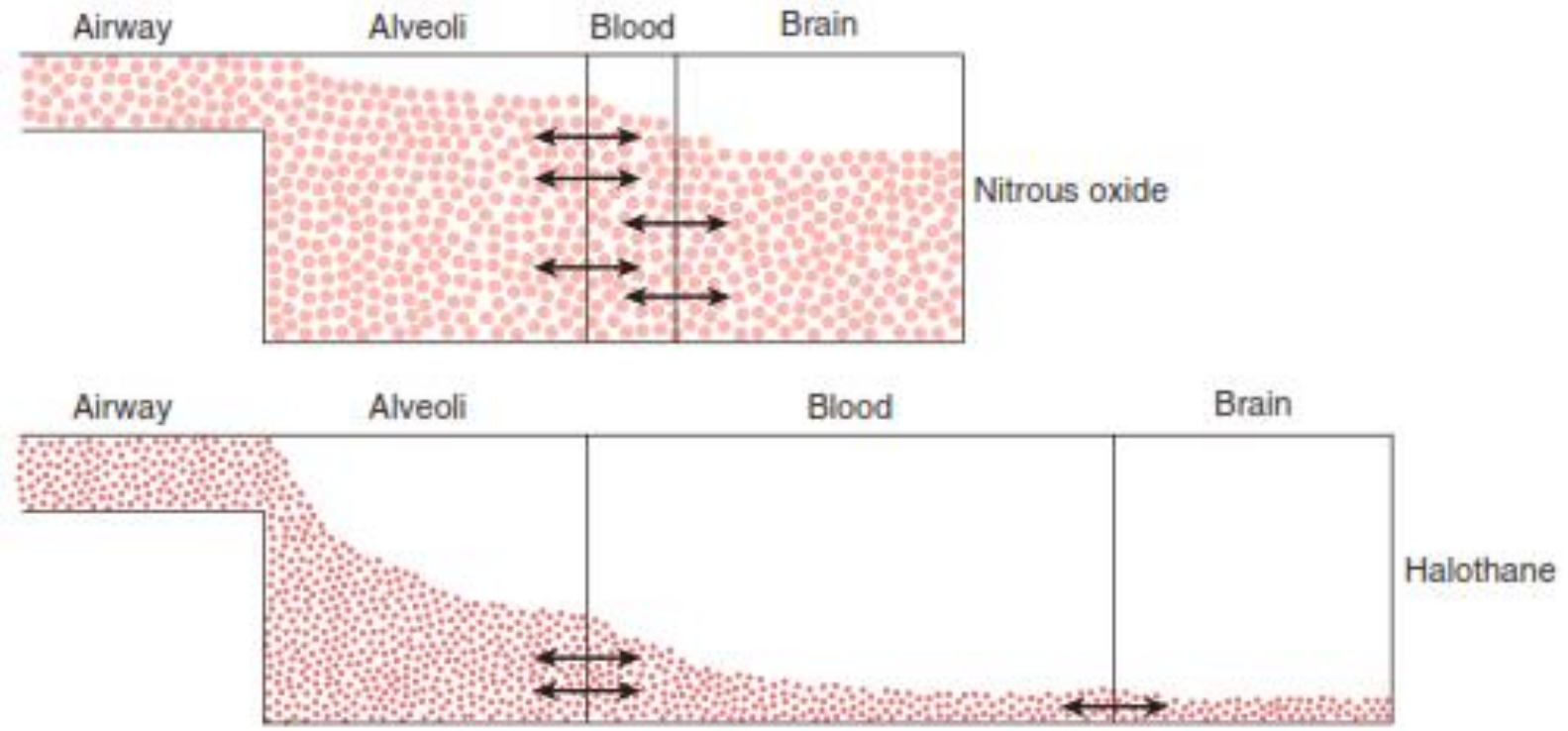
↑ ventilatory rate → ↓ time of wash-in

Solubility

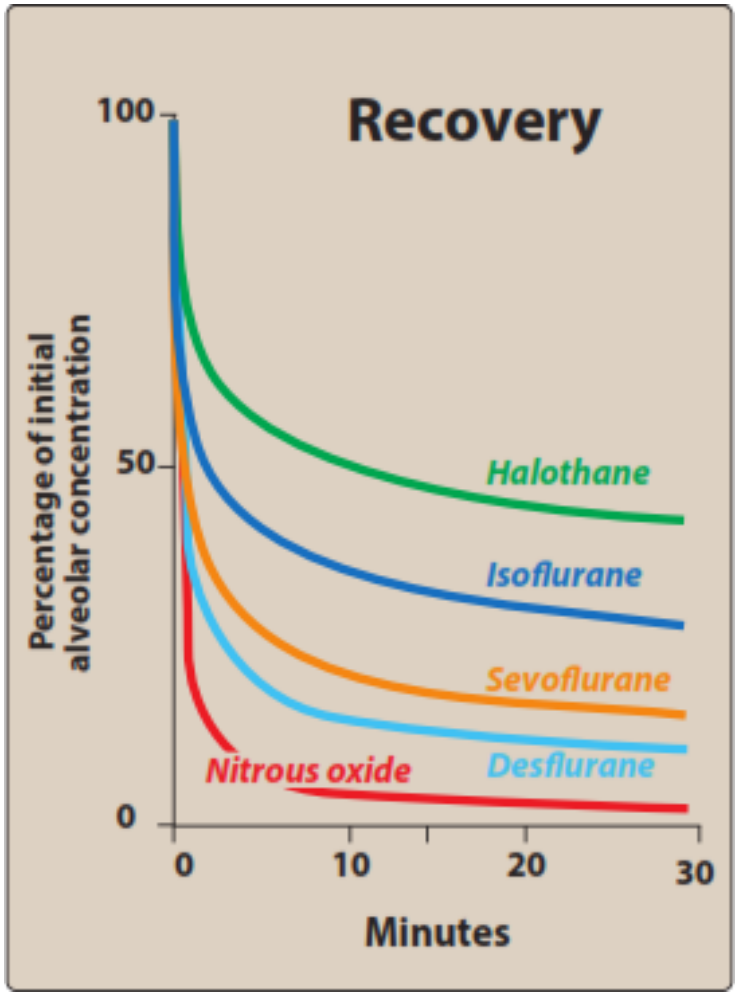
- Expressed as Partition coefficients
- (a ratio of the concentration of the agent in two phases at equilibrium)
- The (blood:gas) partition coefficient, the main factor that determines the rate of induction and recovery
- The (oil:gas) partition coefficient (a measure of fat solubility) determines the potency of an anaesthetic (as well as kinetics in the body)

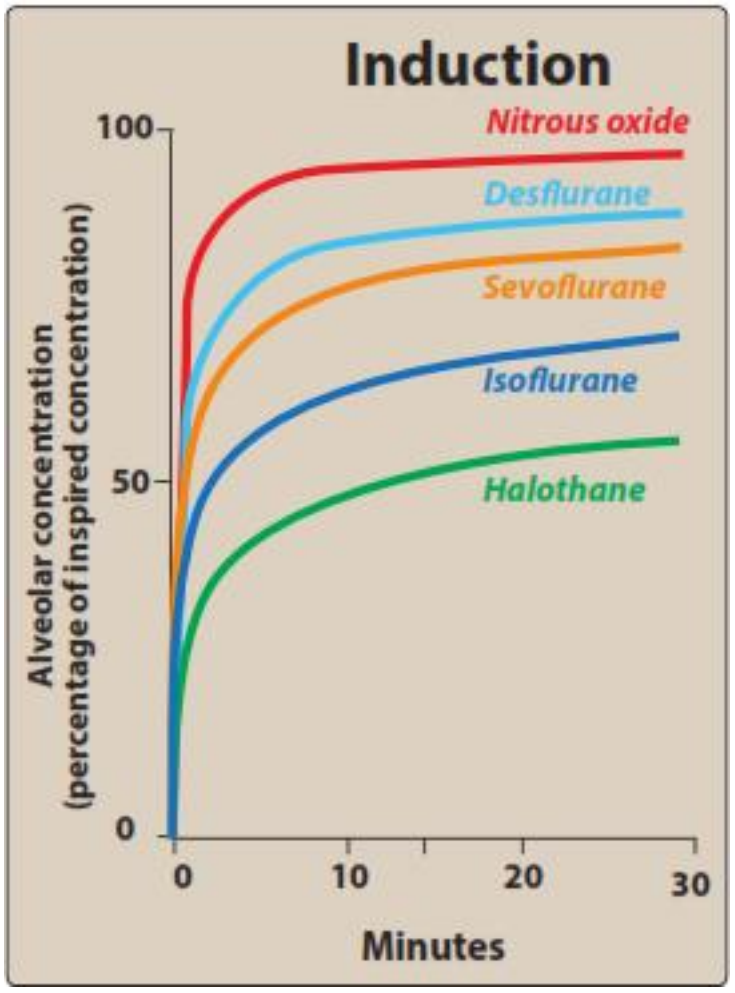
Induction and Recovery

- The lower the (blood:gas) partition coefficient the faster the induction and recovery
- The lower the solubility in blood, the faster the process of equilibration
- Less drug has to be transferred via the lungs to the blood in order to achieve a given partial pressure
- A single lungful of air containing a low-solubility agent will bring the partial pressure in the blood closer to that of the inspired air
- Recovery is the same



Why induction of anesthesia is slower with more soluble anesthetic gases. In this schematic diagram, solubility in blood is represented by the relative size of the blood compartment (the more soluble, the larger the compartment). Relative partial pressures of the agents in the compartments are indicated by the degree of filling of each compartment. For a given concentration or partial pressure of the two anesthetic gases in the inspired air, it will take much longer for the blood partial pressure of the more soluble gas (halothane) to rise to the same partial pressure as in the alveoli. Since the concentration of the anesthetic agent in the brain can rise no faster than the concentration in the blood, the onset of anesthesia will be slower with halothane than with nitrous oxide.


Recovery
100
50
0
Percentage of initial alveolar concentration
Halothane
Isoflurane
Sevoflurane
Desflurane
Nitrous oxide
0
10
20
30
Minutes


Induction
Nitrous oxide
Desflurane
Sevoflurane
Isoflurane
Halothane
100
50
0
Alveolar concentration (percentage of inspired concentration)
0
10
20
30
Minutes

- **Cardiac output**
- For inhaled anesthetics, **higher CO** removes anesthetic from the alveoli **faster** (due to increased blood flow through the lungs) and thus **slows the rate** of rise in alveolar concentration of gas.
- It therefore takes **longer** for the gas to reach **equilibrium** between the alveoli and the site of action in the brain.

higher CO = slower induction

- **Alveolar-to-venous partial pressure gradient of anesthetic**

The **greater the difference** in anesthetic concentration between alveolar (arterial) and venous blood, **the higher the uptake** and the **slower the induction**.

- **Washout:**

When an inhalation anesthetic is discontinued, the body becomes the "**source**" that drives the anesthetic back into the alveolar space.

The same factors that influence attainment of steady state with an inspired anesthetic determine the time course of its clearance from the body.

Mechanism of Action

General anesthetics have been in clinical use for more than 160 years. but their

mechanism of action remains unknown.

- Theories of the possible mechanisms;

A) Lipid Theory; first proposed in 184 7.

They suggested that general anesthetics may act by **dissolving in the fatty fraction of brain cells** and removing fatty constituents from them, thus changing activity of brain cells and inducing anesthesia (In 1899 Hans Horst Meyer published the first experimental evidence of the fact that anesthetic potency is related to lipid solubility; The Meyer—Overton correlation).

B) Ion Channels:

1) Potentiate **$GABA_A$** receptors sensitivity to GABA.

2) **Inhibition** of **NMDA** receptors.

3) **Increase activity** of the inhibitory **glycine receptors**.

Anaesthetic Agent	MAC*	Blood/Gas PC	Brain/Gas PC	Metabolism	Important remarks
Nitrous oxide	**101.0**	**0.47**	0.5	None	Rapid onset & recovery; incomplete anaesthetic
Desflurane	6-7	0.42	1.3	<0.05%	Low volatility; poor induction; rapid recovery
Enflurane	1.7	1.9	3.2	8%	Medium rate of onset & recovery
Isoflurane	1.3	1.4	4.7	<2%	Medium rate of onset & recovery
Halothane	**0.75**	**2.3**	8.2	>40%	Medium rate of onset & recovery
Methoxyflurane	0.16	10.2	31.0	>70% (fluoride)	Slow onset of recovery Nephrotoxic

Note: An inhalational anaesthetic agent with low solubility in blood shows fast induction time and also recovery time (e.g. nitrous oxide), and an agent with relatively high solubility in blood shows slower induction and recovery time (e.g. halothane).

Second Gas Effect

The MAC of an inhalational anaesthetic can be reduced by a concurrent use of another inhalational agent; thus, a concurrent use of nitrous oxide with halothane would reduce the MAC for halothane and also the presence of the latter would reduce the MAC for nitrous oxide. It has been suggested that the presence of agent (gas) facilitates the uptake (transport into the pulmonary blood) of the other agent. Therefore, it is called the **second gas effect**. This effect is utilised for using reduced inspired partial pressure for certain agents, particularly, nitrous oxide which has a high MAC (>100%) which is practically difficult to achieve. Further, a reduction in MAC can also be achieved by the use of adjuvant drugs like **narcotic analgesics** or **sedative-hypnotics**.

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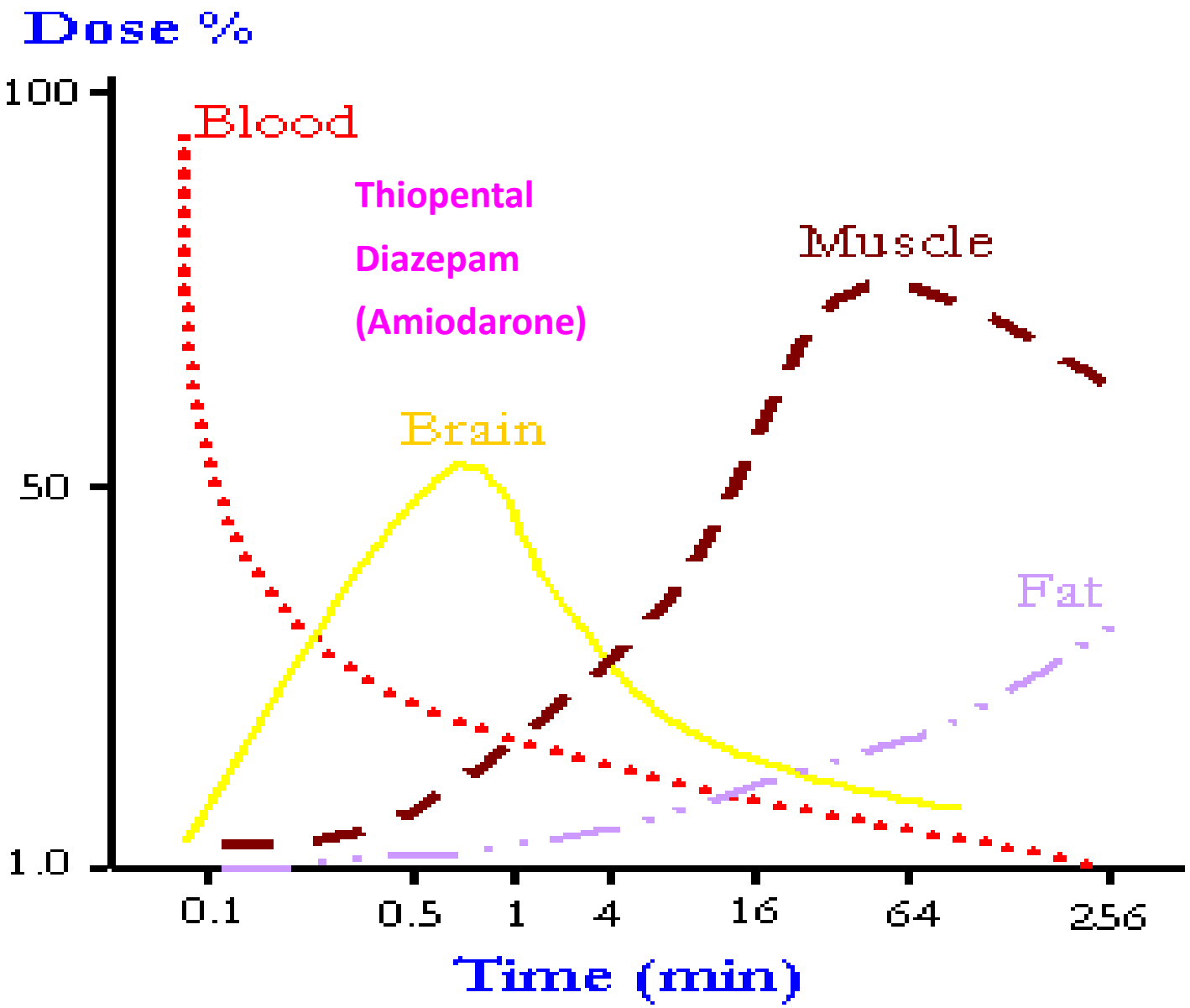
Intravenous Anaesthetics

Thiopental sodium

Thiopental is the most commonly used intravenous anaesthetic in Iraq, usually in combination with inhaled general anaesthetics.


Dose %
100
50
1.0
Blood
Thiopental
Diazepam
(Amiodarone)
Muscle
Brain
Fat
0.1
0.5
1
4
16
64
256
Time (min)

Propofol

The **major advantage of propofol is that it has a useful antiemetic action**. This probably is responsible for the observation that postoperative vomiting is uncommon with propofol.

Etomidate

It is a potent hypnotic (5 minutes) used for induction of anaesthesia. Its major advantages over other agents that it causes **minimal cardiovascular and respiratory depressant effects**.

	Amnesia Hypnosis	Analgesia	Muscle Relaxation	Effect on CVS Res		Adverse Effects and Important Remarks
				Heart rate & Blood pressure	Response to CO_2 & hypoxia	
INDUCTION (i.v.)						
Thiopental	YES	NO	YES	↓	↓	**Contraindicated in porphyria**
Ketamine	YES	YES	NO	↑	NO	**Increases cerebral blood flow. Contraindicated in open eye surgery, neurosurgery (brain), pre-eclampsia (hypertension); hypertensive, hallucinogenic, emergence delirium**

	Amnesia Hypnosis	Analgesia	Muscle Relaxation	Effect on CVS Heart rate & Blood pressure	Effect on Resp Response to CO_2 & hypoxia	Adverse Effects & Important Remarks
MAINTENANE (inhalational)						
Halothane	YES	YES*	YES*	↓	↓	Dysrhythmogenic (sensitises heart), hepatotoxicity (avoid repeated administration in short period, 90 days), malignant hyperthermia; postpartum haemorage, Myocardial depressant properties (bradycardia), Respiratory depression
Nitrous oxide	YES*	YES	NO	Variable	Variable	Megaloblastic anaemia (prolonged exposure →↓ methionine synthase activity)

Neuroleptanaesthesia

When a neuroleptic drug (like **droperidol**) and a narcotic analgesic drug (like **fentanyl** that is 80 times more potent that morphine, shorter onset and duration of action), are administered together to produce a physiological state with somnolence (sleepiness), indifference, analgesia, amnesia, and patients are responsive to commands. This state is called neuroleptanalgesia that is useful for several diagnostic or minor surgical procedures like bronchoscopy, painful dressing, cystoscopy etc. **Neuroleptanalgesia can be converted to neuroleptanaesthesia by the concurrent administration of 65% nitrous oxide in oxygen.**

Thiopental is useful in **abreaction**:

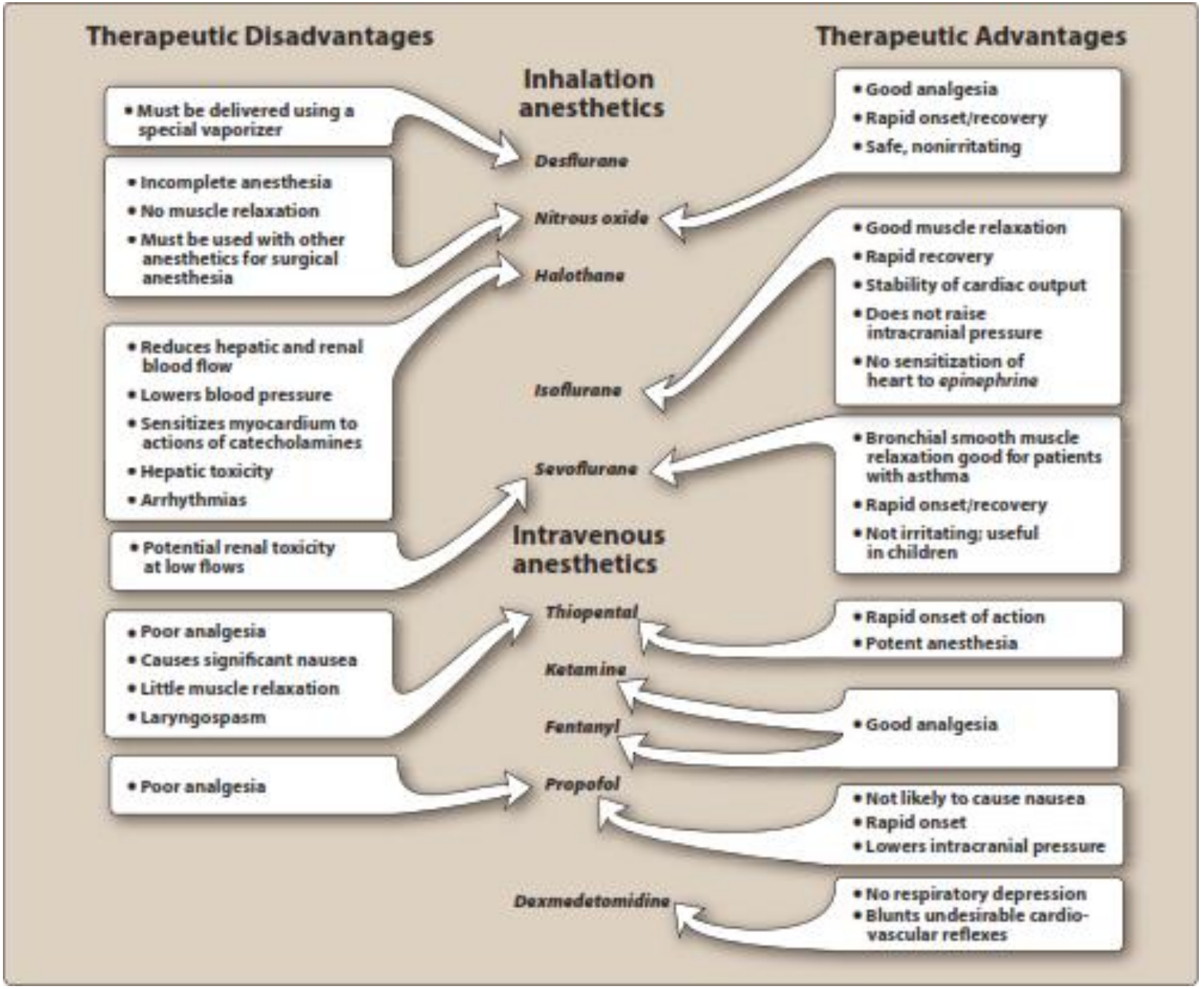
The reliving of an experience in such a way that previously repressed emotions associated with it are released.

Dissociative anaesthesia (the patient seems awake but dissociated from the environment, responds to verbal commands but does not respond to painful stimuli)

Ketamine

Ketamine is a phencyclidine (hallucinogen) derivative and an antagonist of the NMDA-receptor. In anaesthetic doses it produces a trance-like state known as dissociative anaesthesia (sedation, amnesia, dissociation, analgesia).

Bennett & Brown pdf page 351


Therapeutic Disadvantages
Therapeutic Advantages
Inhalation anesthetics
• Must be delivered using a special vaporizer
• Good analgesia
• Rapid onset/recovery
• Safe, nonirritating
Desflurane
• Incomplete anesthesia
• No muscle relaxation
• Must be used with other anesthetics for surgical anesthesia
Nitrous oxide
Halothane
• Good muscle relaxation
• Rapid recovery
• Stability of cardiac output
• Does not raise intracranial pressure
• No sensitization of heart to epinephrine
• Reduces hepatic and renal blood flow
• Lowers blood pressure
• Sensitizes myocardium to actions of catecholamines
• Hepatic toxicity
• Arrhythmias
Isoflurane
Sevoflurane
• Bronchial smooth muscle relaxation good for patients with asthma
• Rapid onset/recovery
• Not irritating; useful in children
• Potential renal toxicity at low flows
Intravenous anesthetics
Thiopental
• Rapid onset of action
• Potent anesthesia
• Poor analgesia
• Causes significant nausea
• Little muscle relaxation
• Laryngospasm
Ketamine
Fentanyl
• Good analgesia
• Poor analgesia
Propofol
• Not likely to cause nausea
• Rapid onset
• Lowers intracranial pressure
Dexmedetomidine
• No respiratory depression
• Blunts undesirable cardiovascular reflexes