DRUG ACTING ON CNS

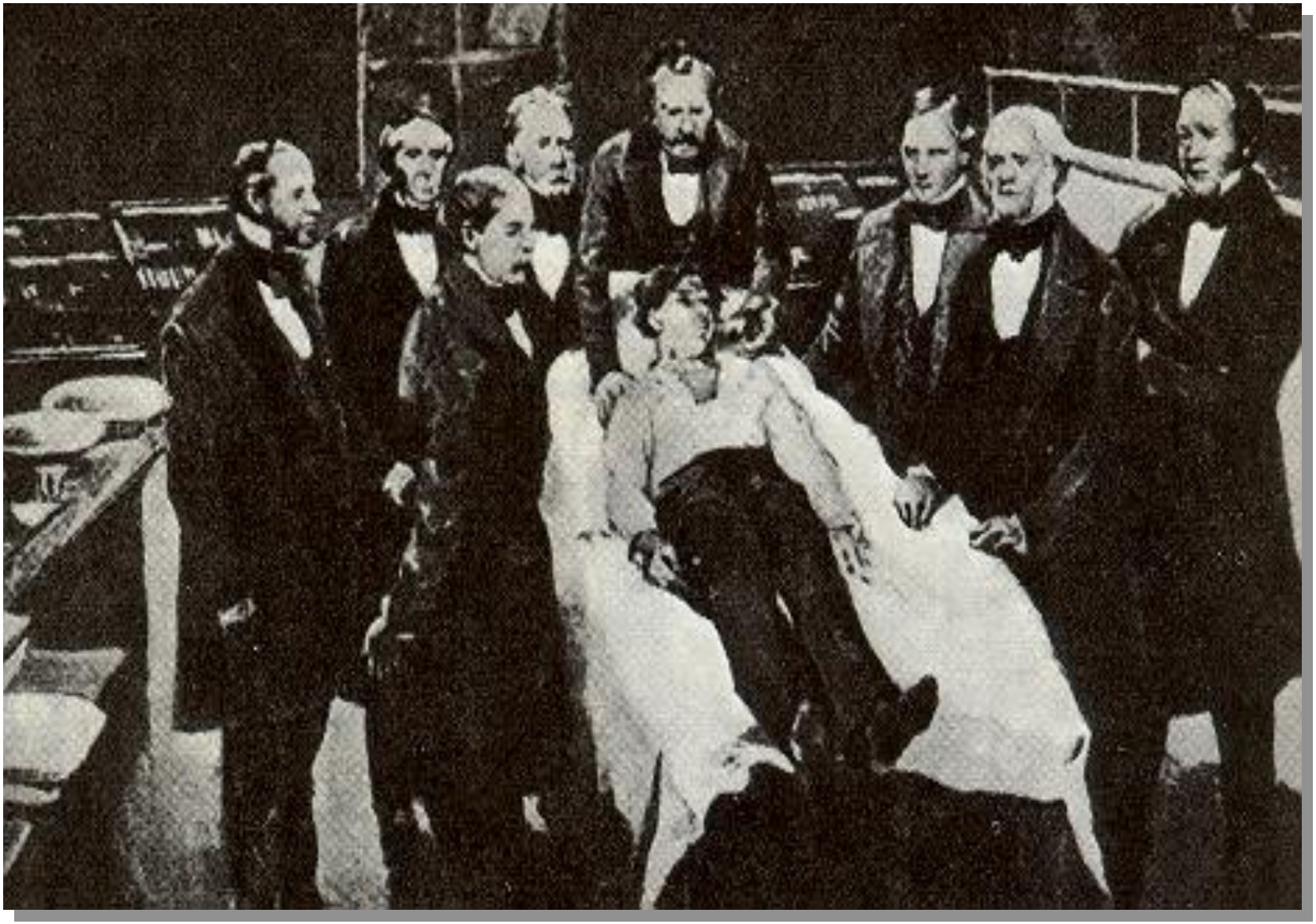
ANESTHATICS
(Pharmacology)

General anesthetics (GAs)

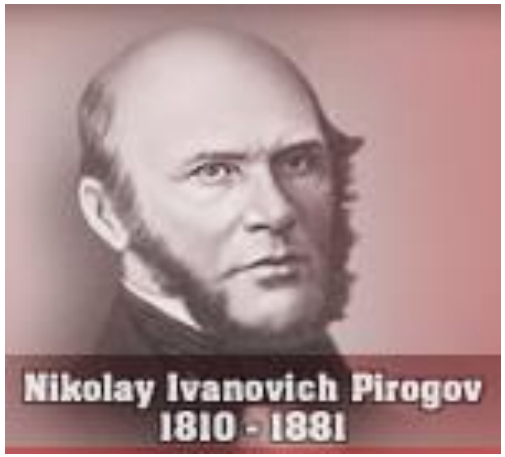
History

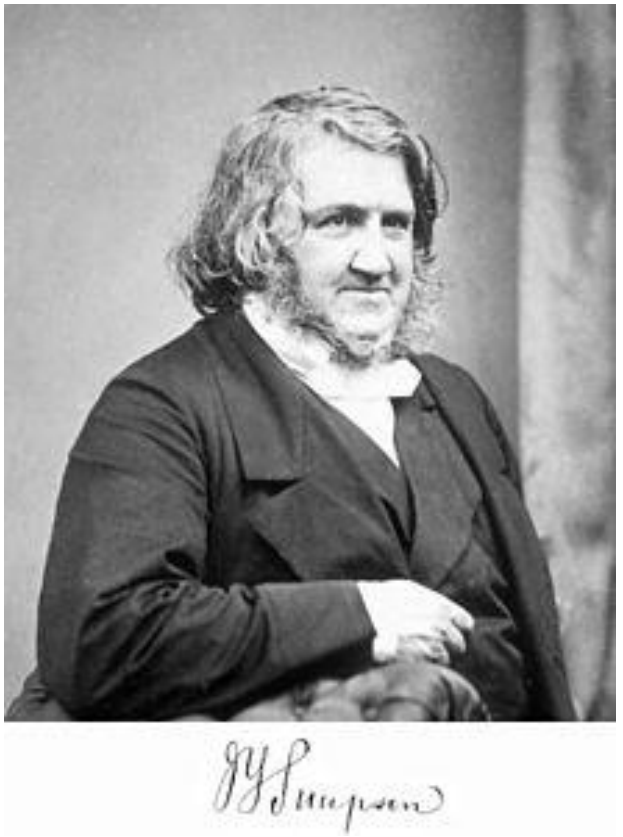
General anesthesia was introduced into clinical practice in the 19th century with the use of volatile liquids such as diethyl ether and chloroform.

Cardiac and hepatic toxicity limited the usefulness of *chloroform (out of date!)*.



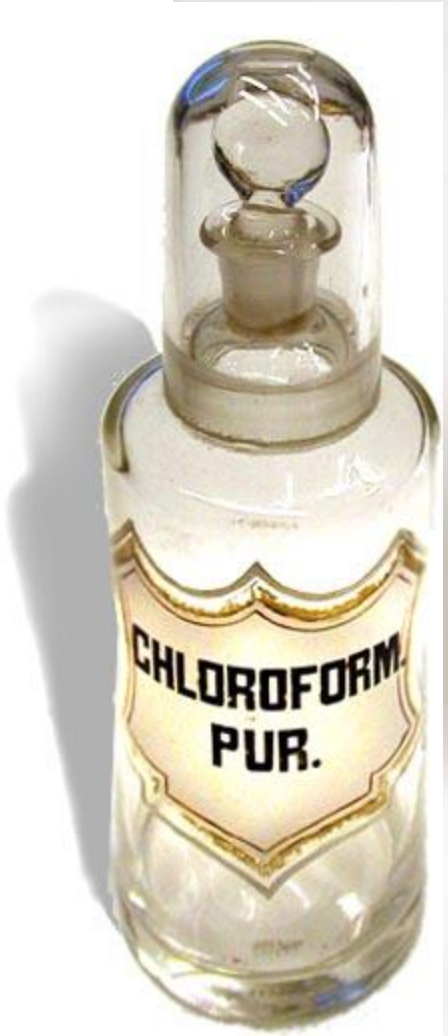
William Morton (Boston, 1846) used ether successfully to extract a tooth.

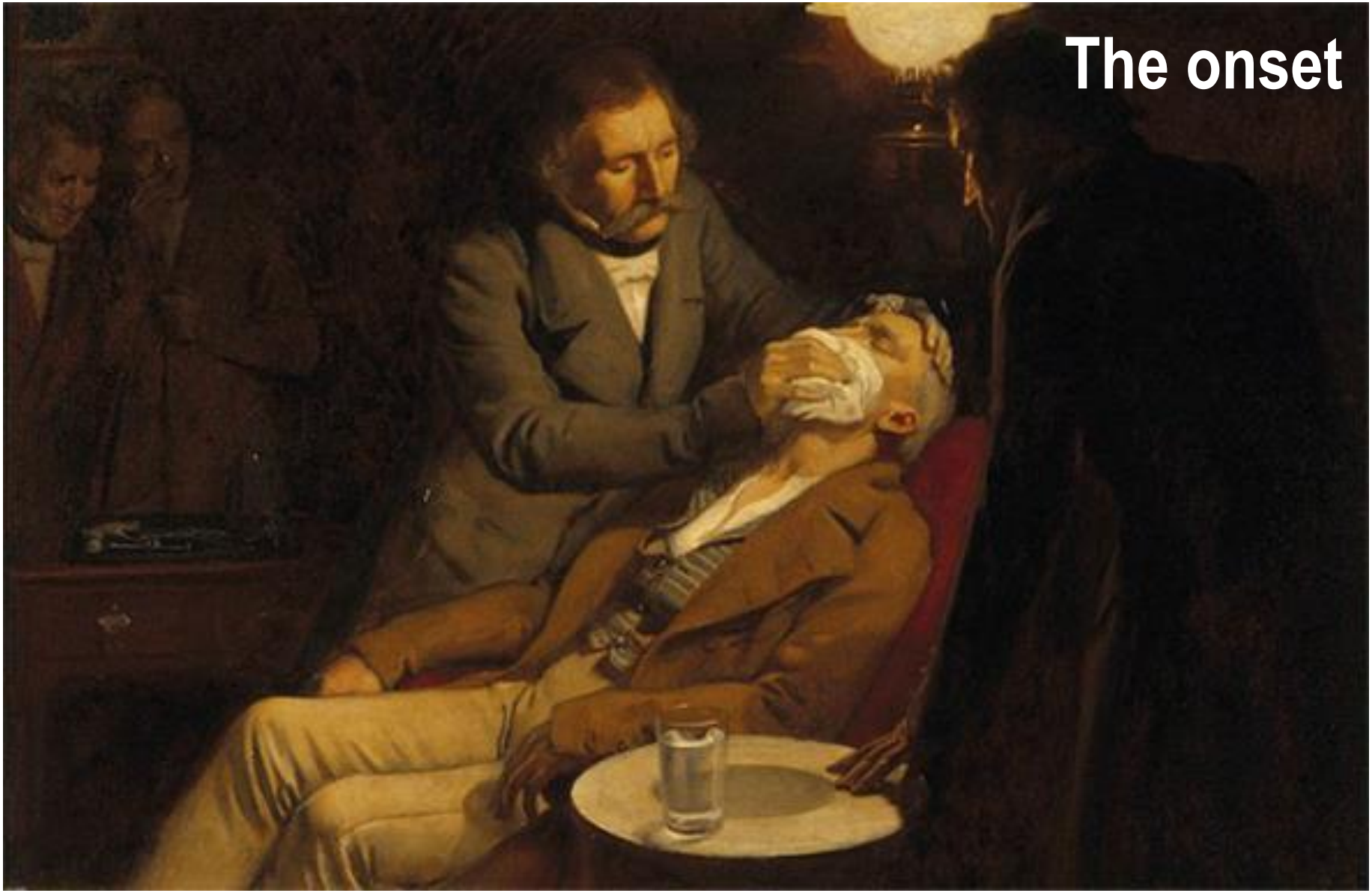




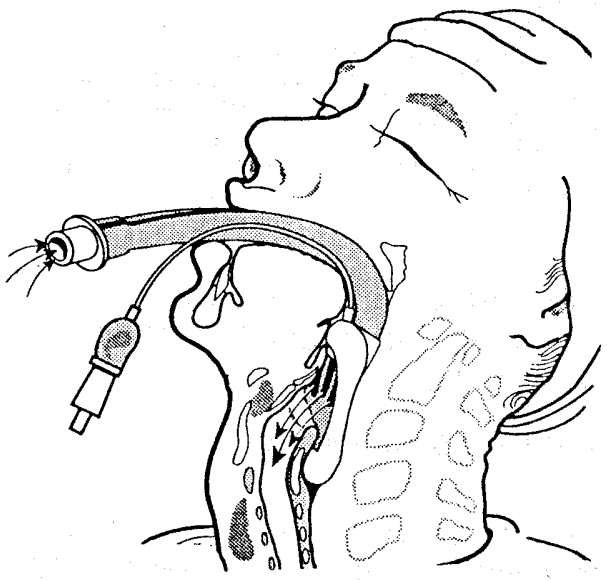
Pirogoff (Russia, 1847)
used ether.
Simpson (Glasgow, 1847)
used chloroform in obstetrics.
Queen Victoria **gave**
birth to her children
under chloroform anesthesia.

The onset

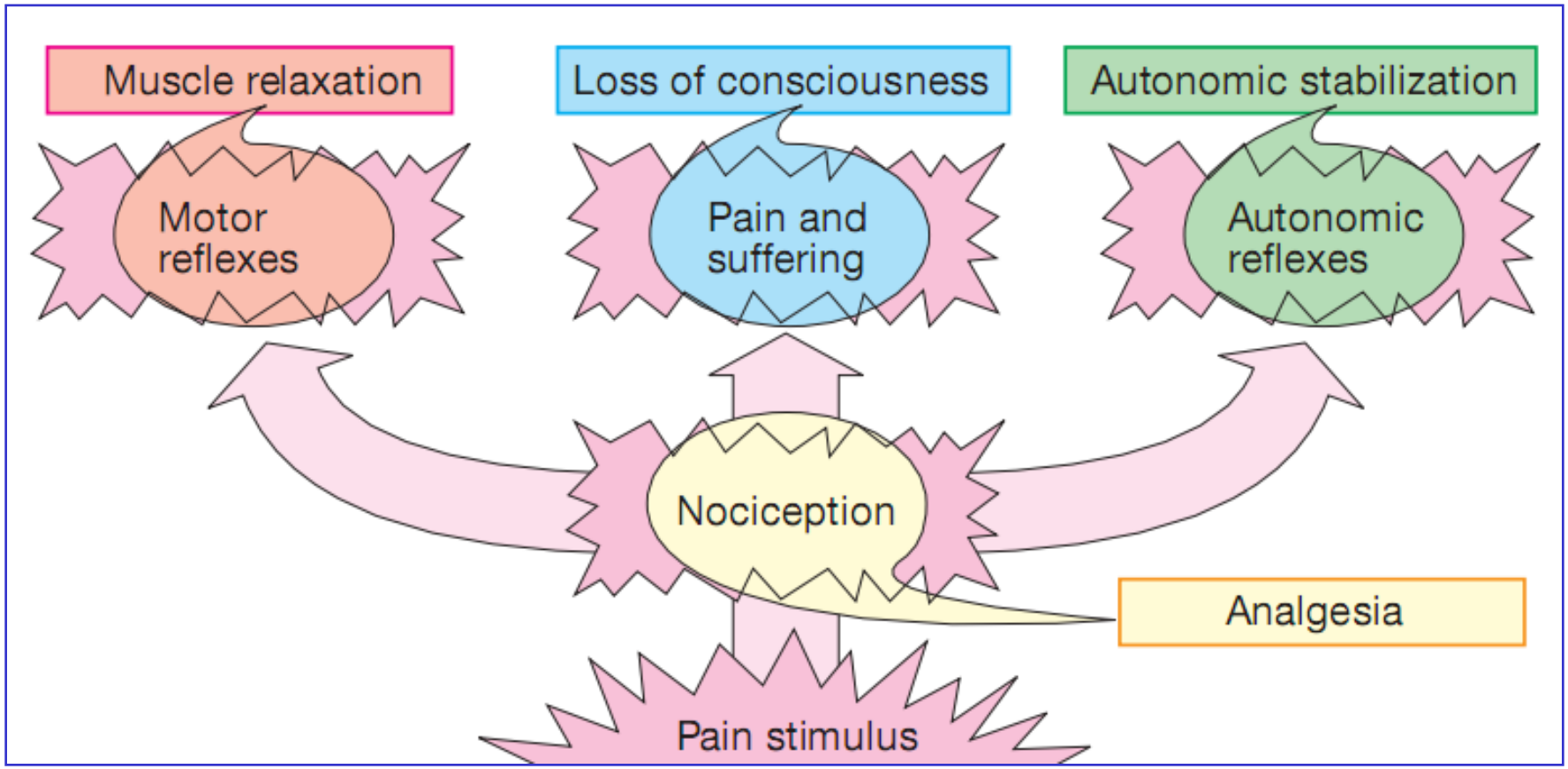



The onset

General anesthesia causes:



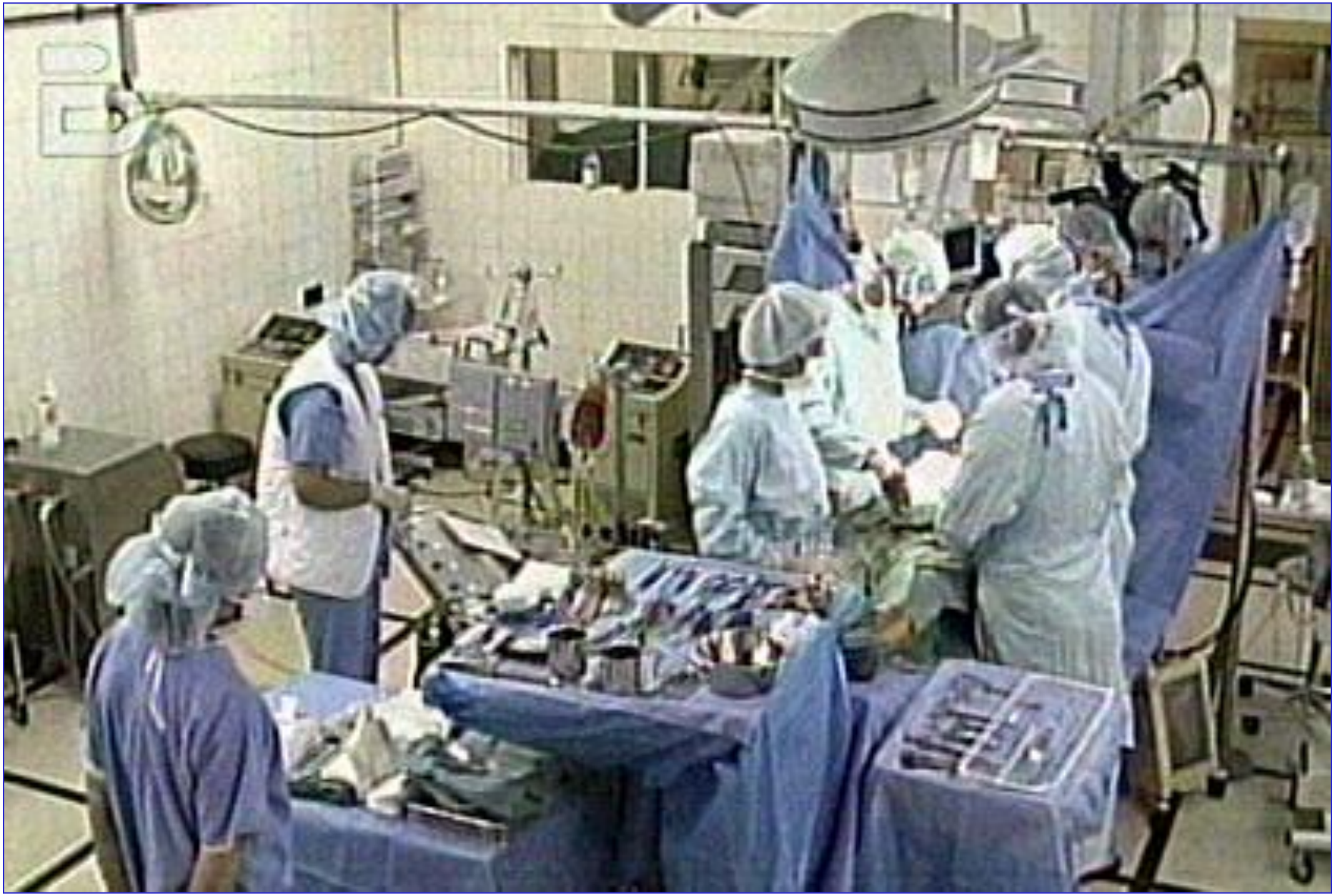
- loss of consciousness
- analgesia
- amnesia
- muscle relaxation (expressed in different extent)
- loss of homeostatic control of respiration and cardiovascular function



Goals of surgical anesthesia

Lüllmann, Color Atlas of Pharmacology – 2nd Ed. (2000)

Now




Now

The mode of action of GAs is still debated.

- All GAs act on the mid-brain reticular activating system and cerebral cortex to produce complete but reversible loss of consciousness.
- The principle site of their action is probably the neuronal lipid membrane or hydrophobic domains of membrane proteins.

According to the new

polysynaptolytic theory

general anesthetics

inhibit reversible

neurotransmission

in many synapses of CNS.

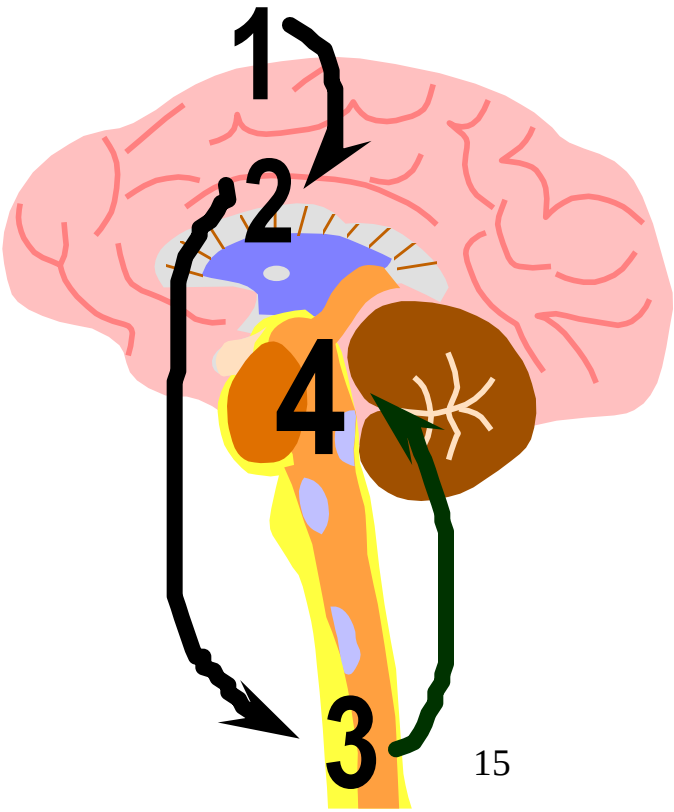
GAs depress the CNS in the following order:

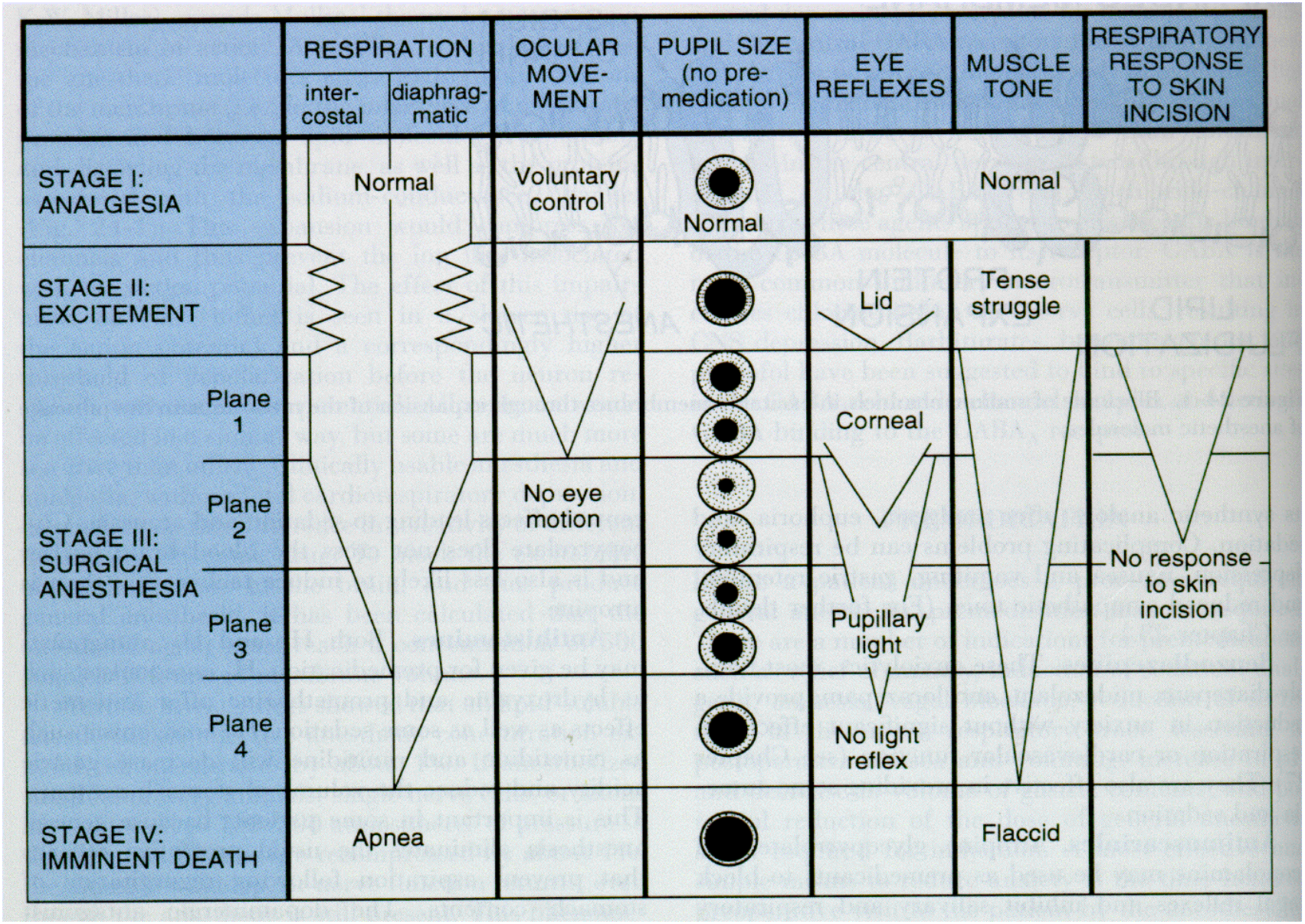
1st – cerebral cortex

2nd – subcortex

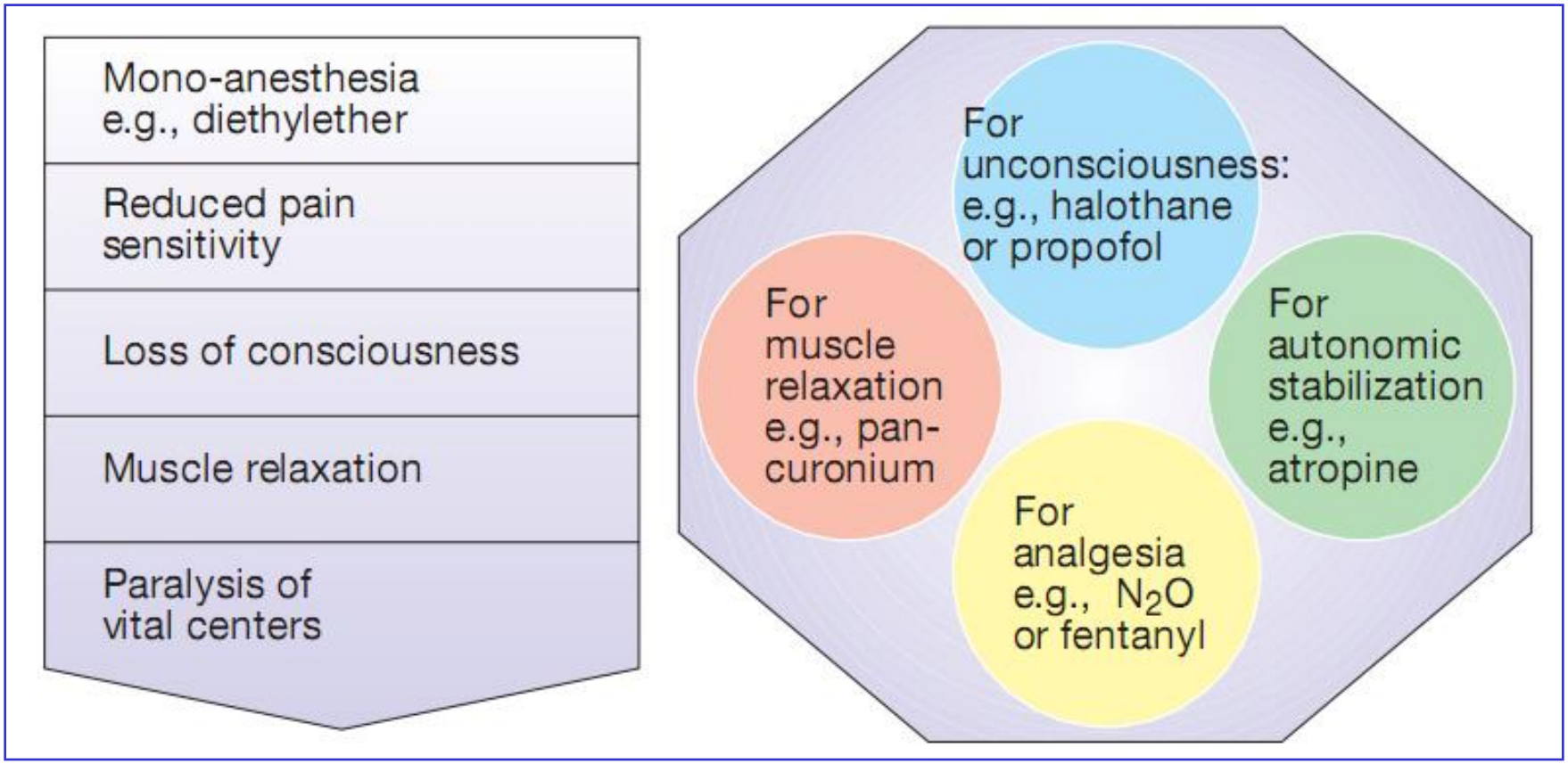
3rd – spinal cord

4th – medulla oblongata





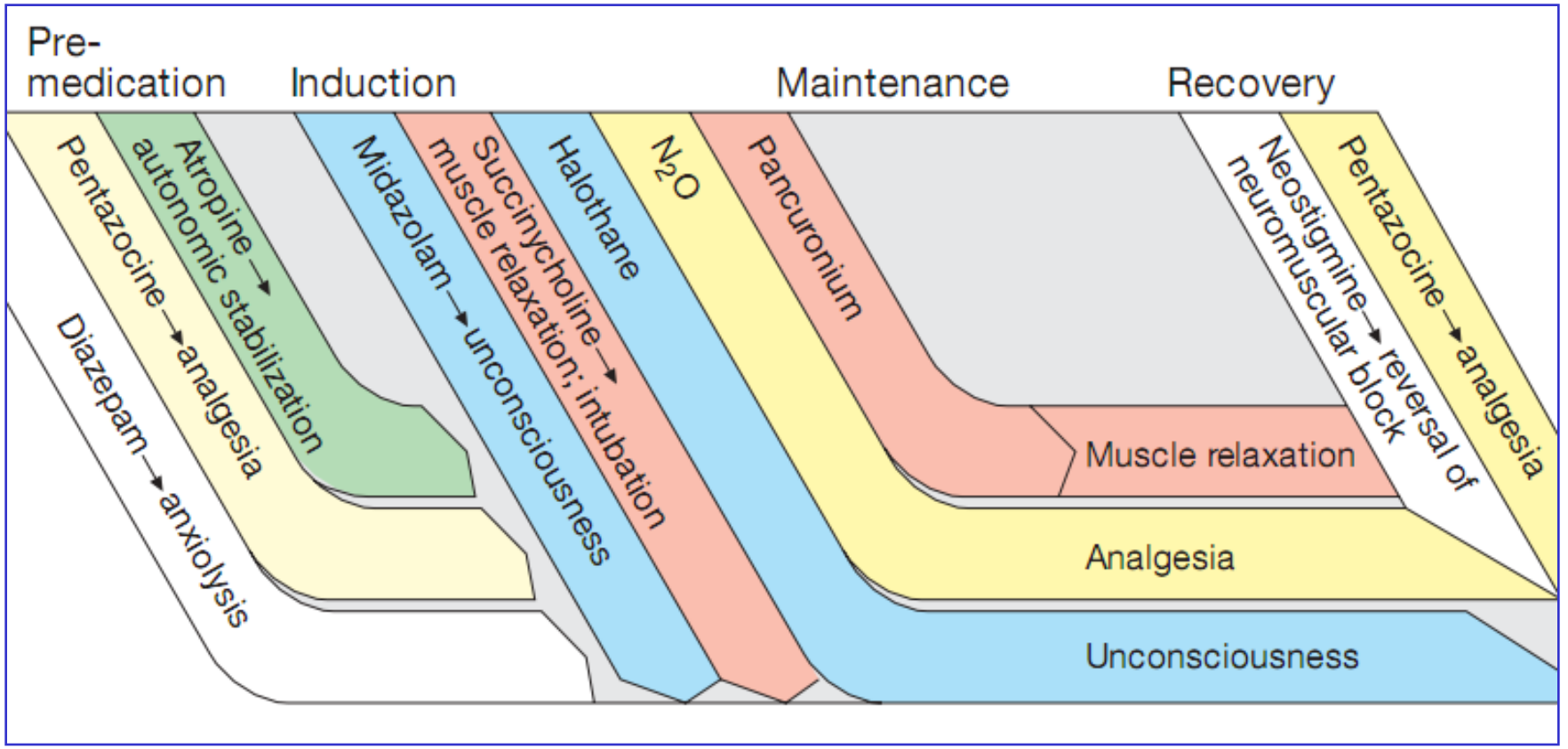
***Principles of Medical Pharmacology* – 6th Ed (1998)**



Traditional monoanesthesia vs. modern balanced anesthesia

Lüllmann, Color Atlas of Pharmacology – 2nd Ed. (2000)

Inhalation anesthetics are not particularly effective analgesics and vary in their ability to produce muscle relaxation; hence if they are used alone to produce general anesthesia, high concentrations are necessary. If inhalation anesthetics are used in combination **with specific analgesic or muscle-relaxant** drugs the inspired concentration of inhalation agent can be reduced, with an associated decrease in adverse effects. The use of such drug combinations has been termed balanced anesthesia.



Regimen for balanced anesthesia

Lüllmann, Color Atlas of Pharmacology – 2nd Ed. (2000)

1. Inhalational GAs

- **Volatile liquids**

  Desflurane
  Isoflurane
  Enflurane
  Halothane
  Methoxyflurane
  Sevoflurane

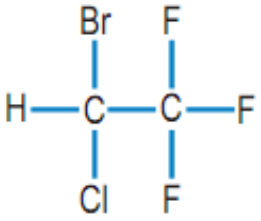
  halogenated anesthetics

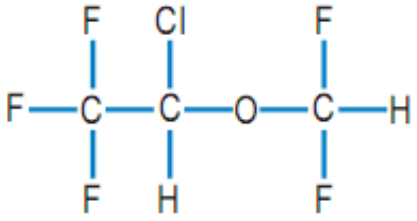
  Diethyl ether (out of date)

- **Gases**

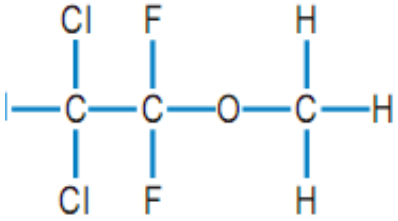
  Nitrous oxide



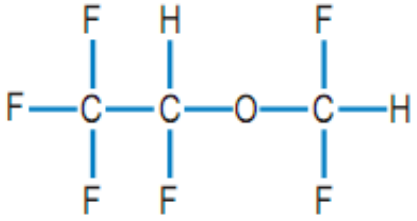
Halothane



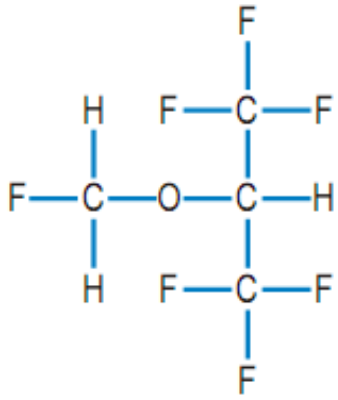
Isoflurane



Methoxyflurane



Desflurane



Sevoflurane

Chemical structure of the volatile halogenated anesthetics

General pharmacokinetics

The vapor pressure gives an indication of the ease with which a volatile anesthetic evaporates. The higher the vapor pressure, the more volatile the anesthetic. The saturated vapor pressure also dictates the maximum concentration of vapor that can exist at a given temperature. The higher the saturated vapor pressure, the greater the concentration of volatile agent that can be delivered to the patient. To determine the maximum concentration, vapor pressure is expressed as a percentage of barometric pressure at sea level, i.e. 760 mmHg. For example, halothane has a saturated vapor pressure of 244 mmHg at 20°C; therefore the maximum concentration of halothane that can be delivered at this temperature is 32% (244/760 × 100 = 32%).

The aim in using inhalation anesthetics is to achieve a partial pressure of anesthetic in the brain sufficient to depress CNS function and induce **general anesthesia**. Thus, anesthetic depth is determined by the partial pressure of anesthetic in the brain. To reach the brain, molecules of anesthetic gas or vapor must diffuse down a series of partial pressure gradients, from inspired air to alveolar air, from alveolar air to blood and from blood to brain:

Inspired air → Alveolar air → Blood → Brain

The rate of change of anesthetic depth

Factors that produce a rapid change in alveolar partial pressure of anesthetic will produce a rapid change in anesthetic depth, appreciated clinically as a rapid induction and recovery. The most important factors are listed below and can be broadly divided into those that affect delivery of anesthetic to the alveoli and those that affect removal of anesthetic from the alveoli:

- inspired concentration;
- alveolar ventilation;
- solubility of anesthetic in blood;
- solubility of anesthetic in tissues;
- cardiac output.

Metabolism and elimination

Inhalation anesthetics are eliminated primarily through the lungs, i.e. **they are exhaled**. Nonetheless, these agents are not totally inert and undergo biotransformation, primarily in the liver, to a variable degree. Metabolism might be expected to promote recovery from anesthesia. However, for the newer inhalation agents any contribution to recovery is slight. Of more direct importance is the potential production of toxic metabolites.

Anesthetic potency: minimum alveolar concentration (MAC)

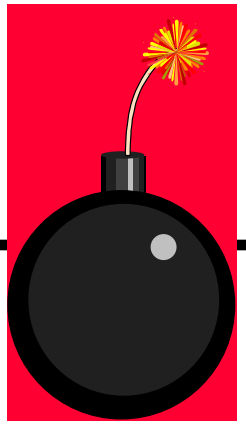
The potency of a drug is a measure of the quantity of that drug that must be administered to achieve a given effect. In the case of inhalation anesthetics potency is described by the minimum alveolar concentration **(MAC)**. The MAC value is the minimum alveolar concentration of anesthetic that produces immobility in 50% of patients exposed to a standard noxious stimulus.

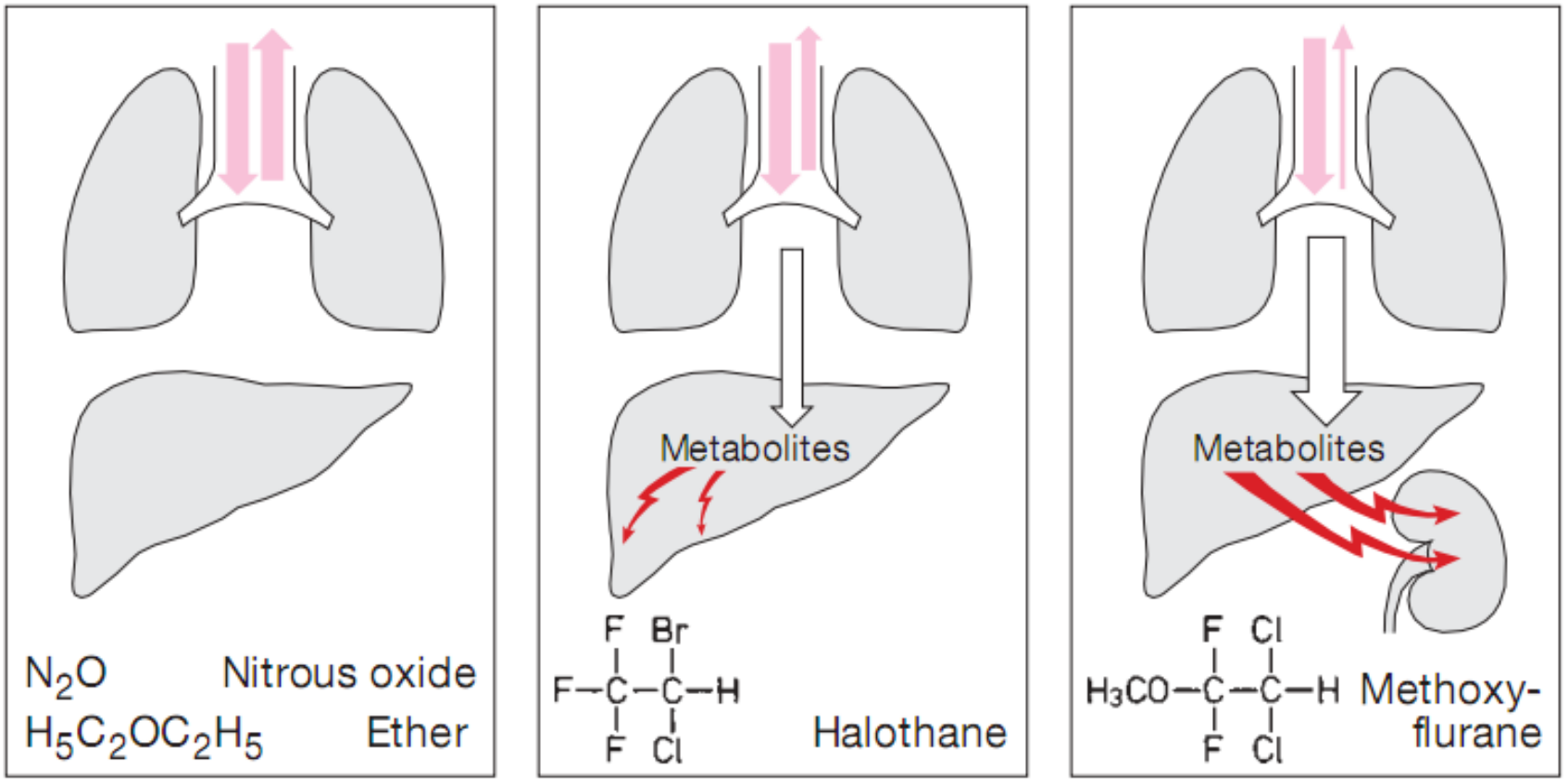
Factor that decrease MAC	Factor that increase MAC
Hypothermia Hyponatremia Pregnancy Old age CNS depressants (sedatives, analgesics, injectable anesthetics) Severe anemia Severe hypotensia Extreme respiratory acidosis (P_{CO2} > 95 mmHg)	Hyperthermia Hypernatremia CNS stimulants (e.g. amphetamine, coffeinum)

For practical purposes GAs can be regarded physicochemicaly as ideal gases: their solubility in different media can be expressed as *partition coefficients (PC)*, defined as the ratio of the concentration of the agent in two phases at equilibrium.

Drug	Blood/gas PC	Oil/gas PC	Induction time (min)
N_2O	0.5	1.4	2–3
Isoflurane	1.4	91	–
Enflurane	1.9	96	–
Halothane	2.3	224	4–5
Ether	12.1	65	10–20

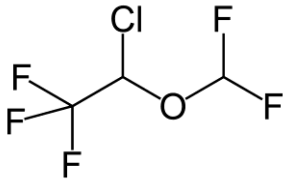
Drug	MAC (%)	Metabolism (%)	Flammability
N_2O	>100	0	–
Isoflurane	1.2	0.2	–
Enflurane	1.7	2–10	–
Halothane	0.8	15	–
Ether	2	5–10	++





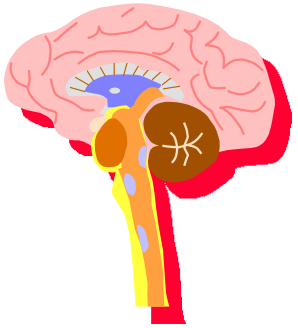
Elimination routes of different volatile anesthetics

Lüllmann, Color Atlas of Pharmacology – 2nd Ed. (2000)



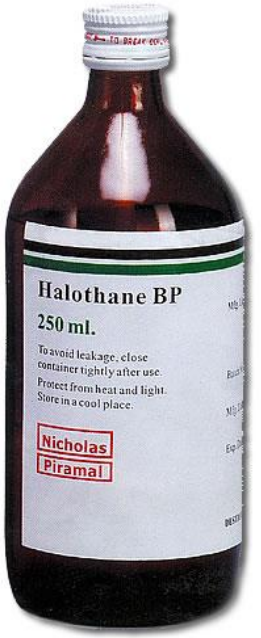
Isoflurane is a less soluble isomer of enflurane, and is widely use. It *potentiates the action of neuromuscular blockers*. It produces dose-dependent peripheral vasodilatation and hypotension but with *less myocardial depression* than enflurane and halothane.

- **Cerebral blood flow is little affected by isoflurane which makes it an agent of choice during neurosurgery.**

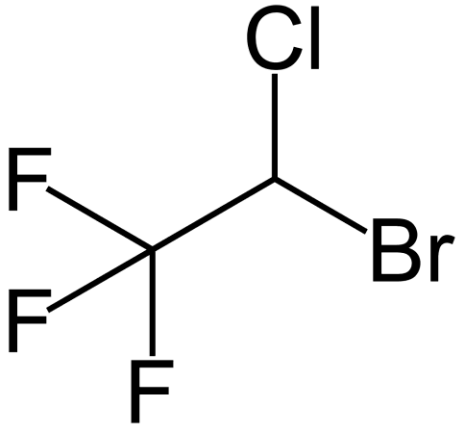


- **Uterine tone is well maintained as compared with halothane or enflurane, and thereby isoflurane reduces postpartum hemorrhage.**

Particular aspects of the use of **Halothane** relate to the following:

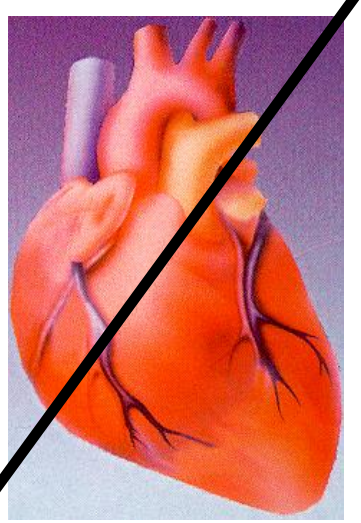


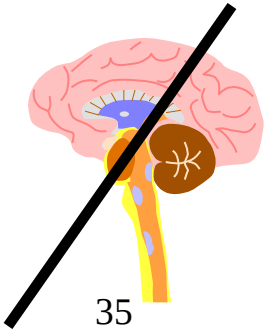
- Moderate muscular relaxation is produced, but is rarely sufficient for major abdominal surgery. It *potentiates the action of neuromuscular blockers*.
- Heat loss is accelerated.
- It is useful in bronchitic and asthmatic patients.



Adverse effects of halothane

- Increased myocardial excitability (ventricular exstrasystoles, tachycardia, and fibrillation). Extrasystoles can be controlled by beta-blockers.
- Blood pressure usually falls, due to central vasomotor depression and myocardial depression.
- Cerebral blood flow is increased which is an contraindication for use in head injury and intracranial tumors.





- **Halothane is not good analgesic and also may lead to convulsions.**
- **It can produce massive hepatic necrosis or subclinical hepatitis following anesthesia. The *liver damage* appears to be a hypersensitivity type of hepatitis which is independent of dose.**
- **Halothane can cause malignant hyperthermia (which needs treatment with *Dantrolene i.v.*), uterine atony and postpartum hemorrhage. It has a teratogenic activity.**

- N_2O uses to reduce pain during childbirth.
- Concomitant administration of N_2O with one of the volatile GAs reduces the MAC value of the volatile drug by up to 75%.
- Risk of *bone marrow depression* occurs with prolonged administration of N_2O.

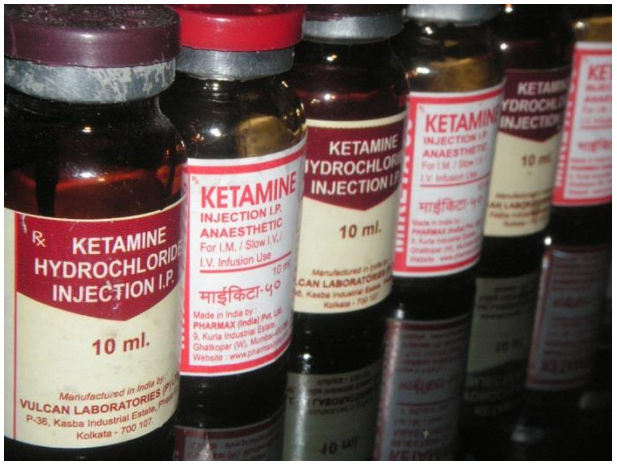
2. Injcectable GAs

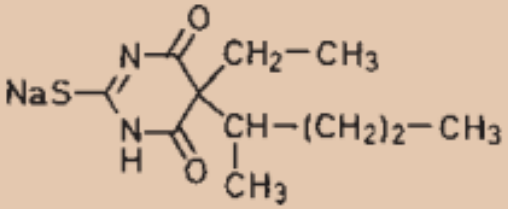
Barbiturates and thiobarbiturates

- **Methohexital i.v.**
- **Thiopental (Pentothal, Thiopenthone) i.v.**

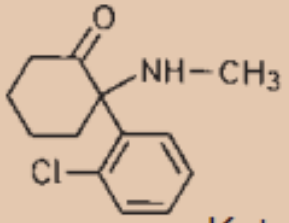
Other preparations

- **Ketamine i.v./i.m.**
- **Propofol i.v.**
- **Etomidate i.v.**
- **Brbiturates (Midazolam, Triazolam)**

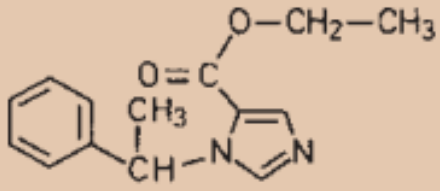




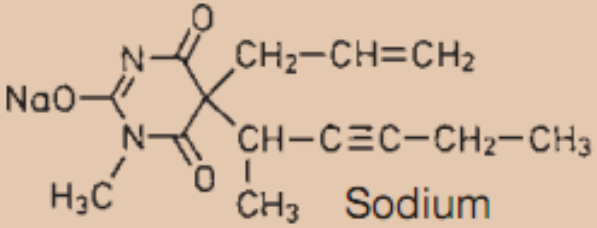
Sodium thiopental



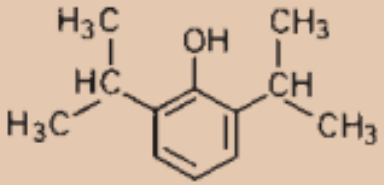
Ketamine



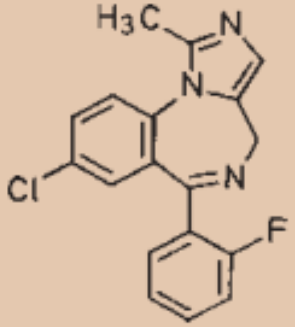
Etomidate



Sodium methohexital

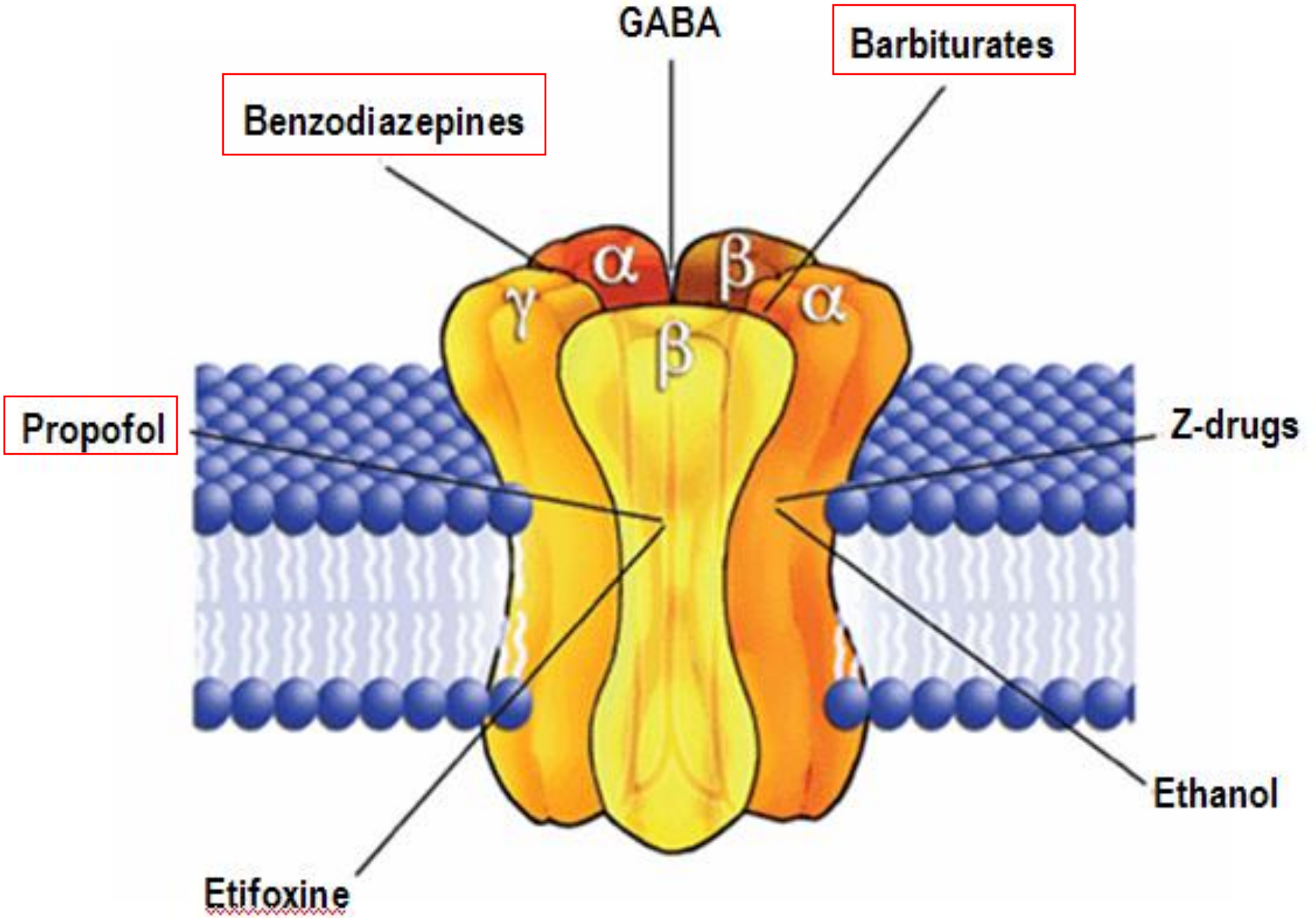


Propofol

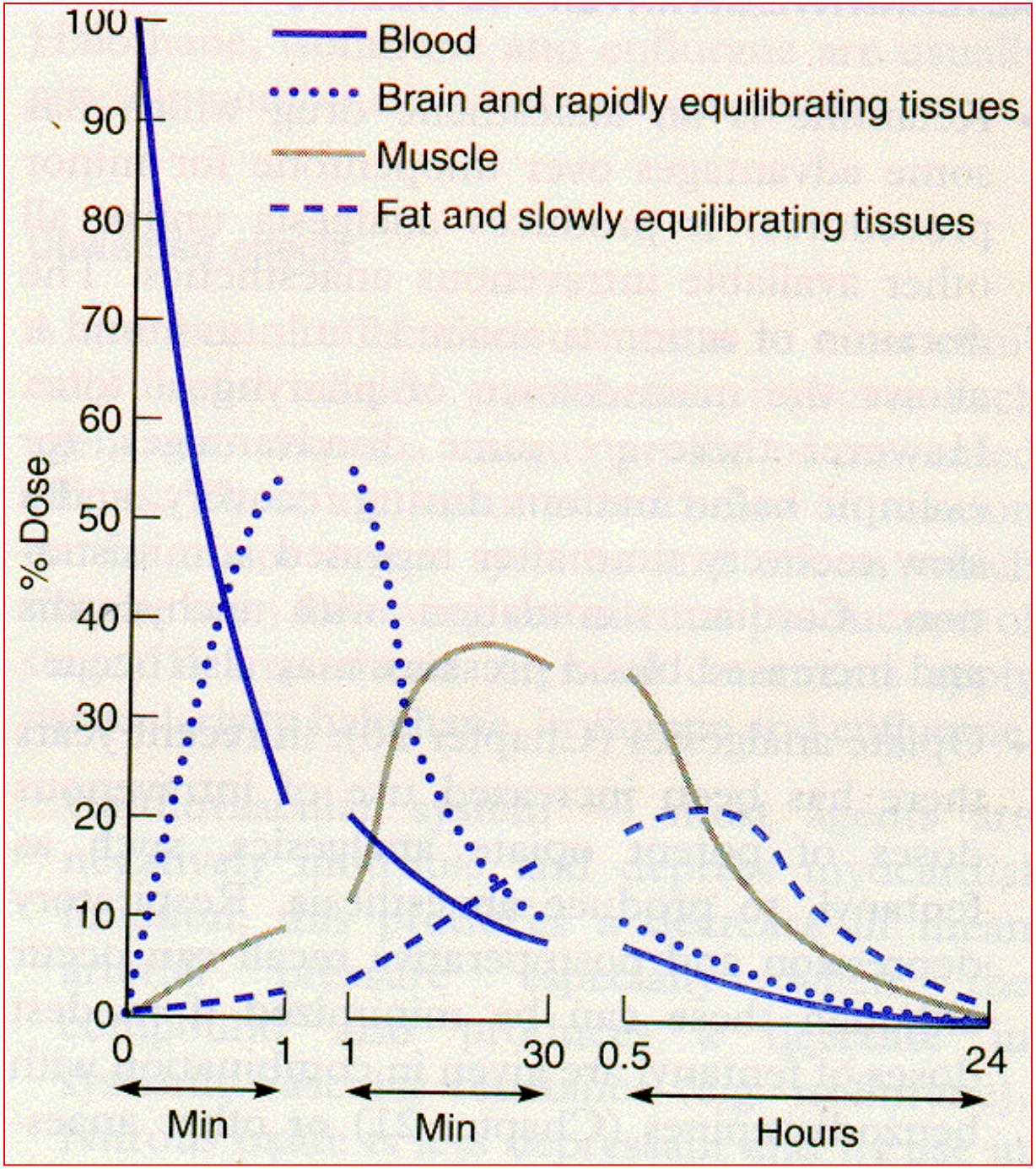


Midazolam

Studies have demonstrated that most injectable anesthetic agents produce anesthesia by enhancing GABA-mediated neuronal transmission, primarily at $GABA_A$ receptors. GABA is an inhibitory neurotransmitter found throughout the CNS.


GABA
Barbiturates
Benzodiazepines
α
β
γ
β
α
Propofol
Z-drugs
Ethanol
Etifoxine

Thiopental (thiopentone) -redistri- bution in muscle and fat (long post- narcotic sleep)



Principles of Medical Pharmacology (1994)

Thiopental use i.v. for induction of anaesthesia, which is maintained with an inhalation agents.

Propofol. The onset of its action begins after 30 s. After a single dose patient recovers after 5 min with a clear head and no hangover.

Propofol is a donor of NO with amnesic and antiemetic action.

Indications:

- i.v. induction (2–2.5 mg/kg)
- maintenance of anaesthesia in doses of 6–12 mg/kg
- sedation (2–3 mg/kg) in intensive care or during intensive procedures.

Ketamine is an antagonist of NMDA-receptor.

- It produces *dissociative anaesthesia* (sedation, amnesia, dissociation, analgesia).
- Ketamine can cause *hallucinations* and unpleasant, brightly *coloured dreams* in 15% of patients during recovery, which are very often accompanied by *delirium*.
- Its use is widespread in countrie where there are few skilled specialists.
- Usually it is applied mainly for minor procedures in children (10 mg/kg i.m.).

Ketamine

- **Calypsol**

amp. 500 mg/10 ml

Children: 10 mg/kg i.m.

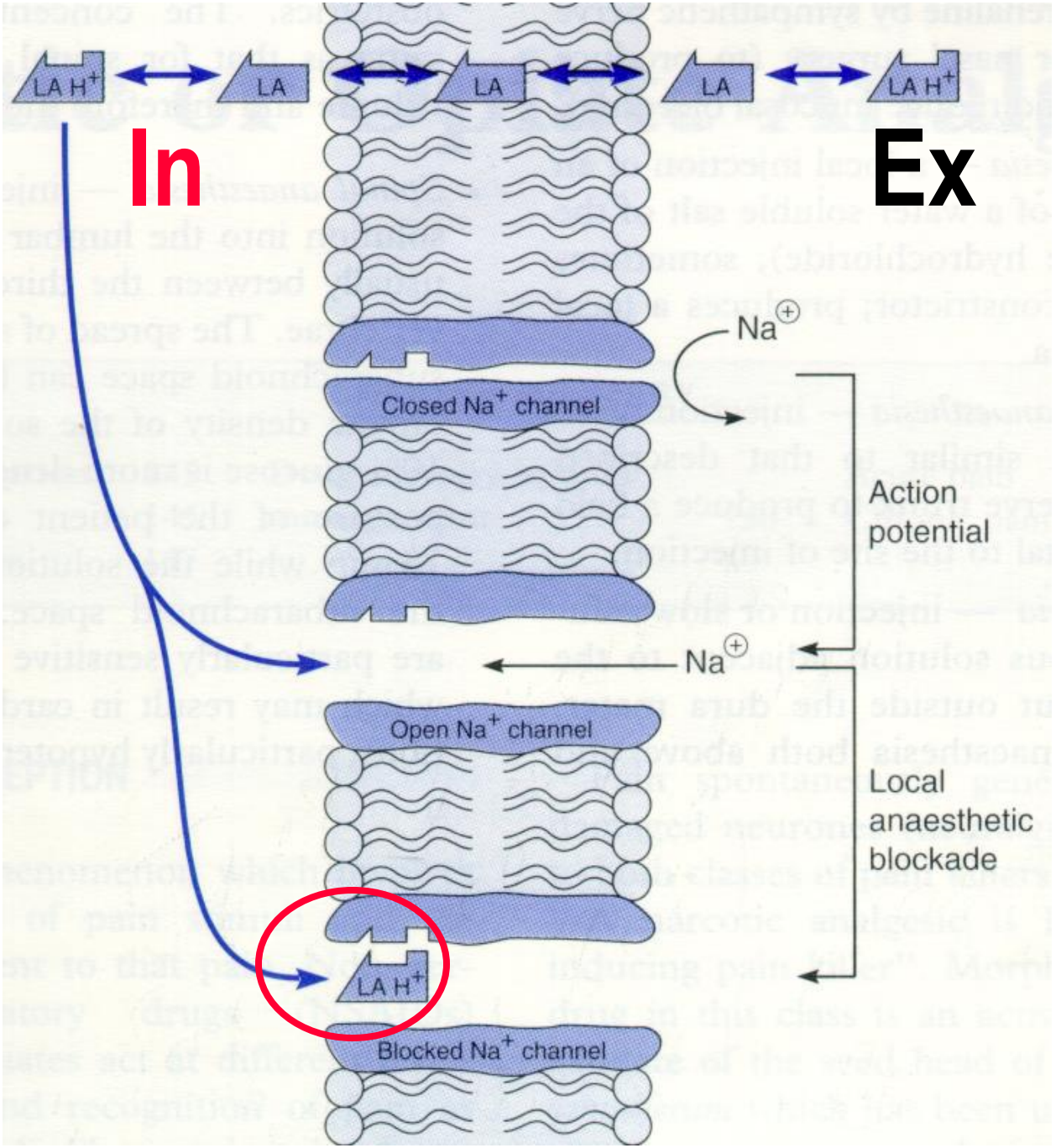
Local anesthetics (LAs)

- **LAs are drugs which reversibly prevent the transmission of pain stimuli locally at their site of administration.**
- **The clinical uses and responses of LAs depend both on the drug selected and the site of administration.**

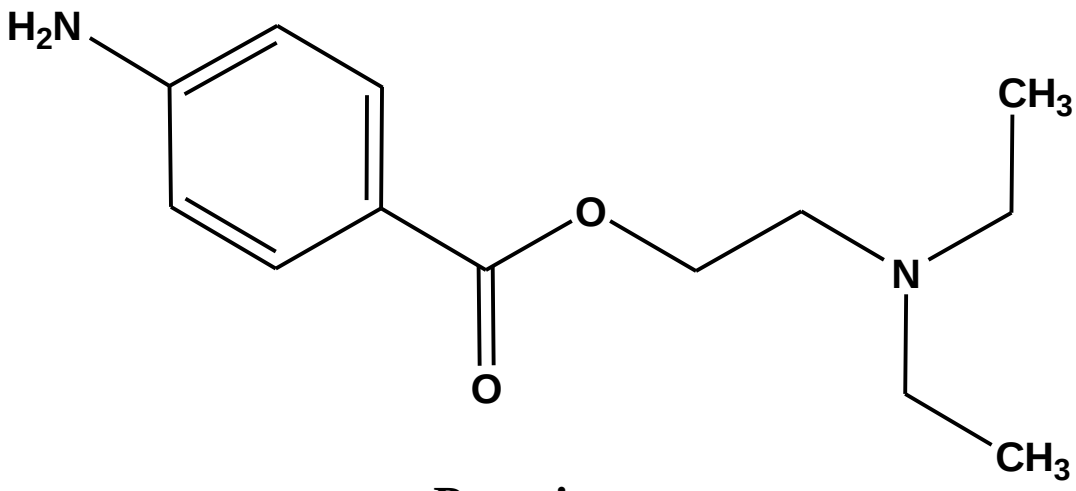
LAs are weak bases (pK_b 7–8).

They exist as an equilibrium between ionized (LAH^+) and unionized (LA) forms. The unionized forms are lipid soluble and cross the axonal membranes. After that the part of the unionized forms *protonates intracellulary* into the ionized forms. The ionized forms bind to the intracellular receptors, obstruct, and block Na^+ channel (see figure).

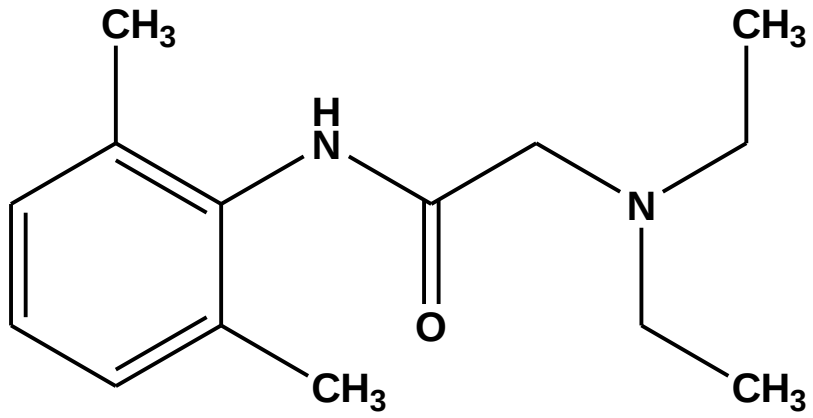
LAH^+ (local anaes-thetics) block Na^+ channels.



Principles of Medical Pharmacology (1994)



Procaine



Lidocaine

Anaesthetic potency

Lidocaine	4
Bupivacaine	16
Procaine	1
Articaine	4

LAs from the group of *ester* (procaine, tetracaine, benzocaine) in plasma and liver hydrolyze to the para-amino-benzoic acid, which is a competitive antagonist of the *sulfonamides*. Thus, the *co-administration* of esters and sulfonamides *is not rational*.

Unwanted effects

Local effects **at the site of administration: irritation and inflammation; local hypoxia (if co-administered with vasoconstrictor); tissue damage (sometimes necrosis) following inappropriate administration (e.g. accidental intra-arterial administration or spinal administration of an epidural dose).**

***Systemic effects*. High systemic doses may affect other excitable membranes such as the heart (e.g. lidocaine can cause AV block and cardiovascular collapse; bupivacaine can cause serious arrhythmias) or the CNS (tetracaine can cause convulsions and eye disturbances; cocaine – euphoria, hallucinations, and drug abuse).**

Procaine **sometimes causes *urticaria*.**

Some systemic unwanted effects due to the vasoconstrictors - NA or adrenaline. They include hypertension and tachycardia.

Clinical uses

The extent of local anesthesia depends largely on the technique of administrations:

Surface administration (anesthesia)

- high concentrations (2–5%) of the LAs can slowly penetrate the skin and mucous membranes to give a small localized anesthesia.

Benzocaine and tetracaine are suitable for these purposes. They produce useful anesthesia of the mucous membranes of the throat.

Cocaine and tetracaine are used before painful ophthalmological procedures.

***Propipocaine* widely used in dentistry, dermatology, and obstetrics to produce surface anesthesia.**

Infiltration anesthesia

can produce with 0.25–0.5% aqueous solution of lidocaine or procaine (usually with co-administration of adrenaline).

The other main types of local anesthesia are:

- ***nerve trunk block anesthesia;***
- ***epidural anesthesia* (injection of the LAs to the spinal column but outside the dura mater), used *in obstetrics*;**
- ***spinal anesthesia* (injection of the LAs into the lumbar subarachnoid space, usually between the 3rd and 4th lumbar vertebrae).**

1. Esters

Erythroxylum coca Lam.

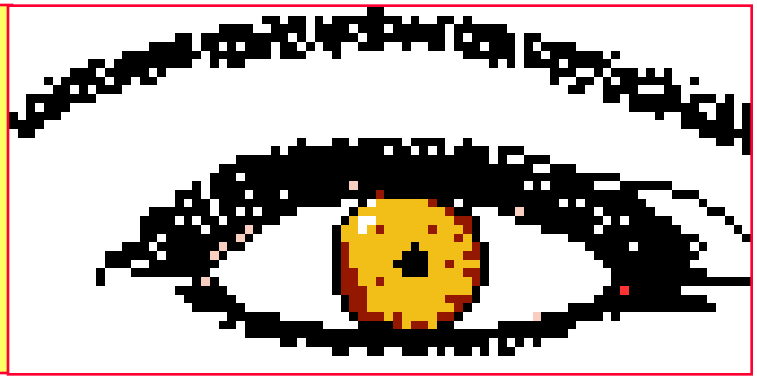
1.1. Esters of benzoic acid

- Cocaine (out of date)

1.2. Ester of para-aminobenzoic acid

- Benzocaine (in Almagel A®)
- Chloroprocaine, Procaine

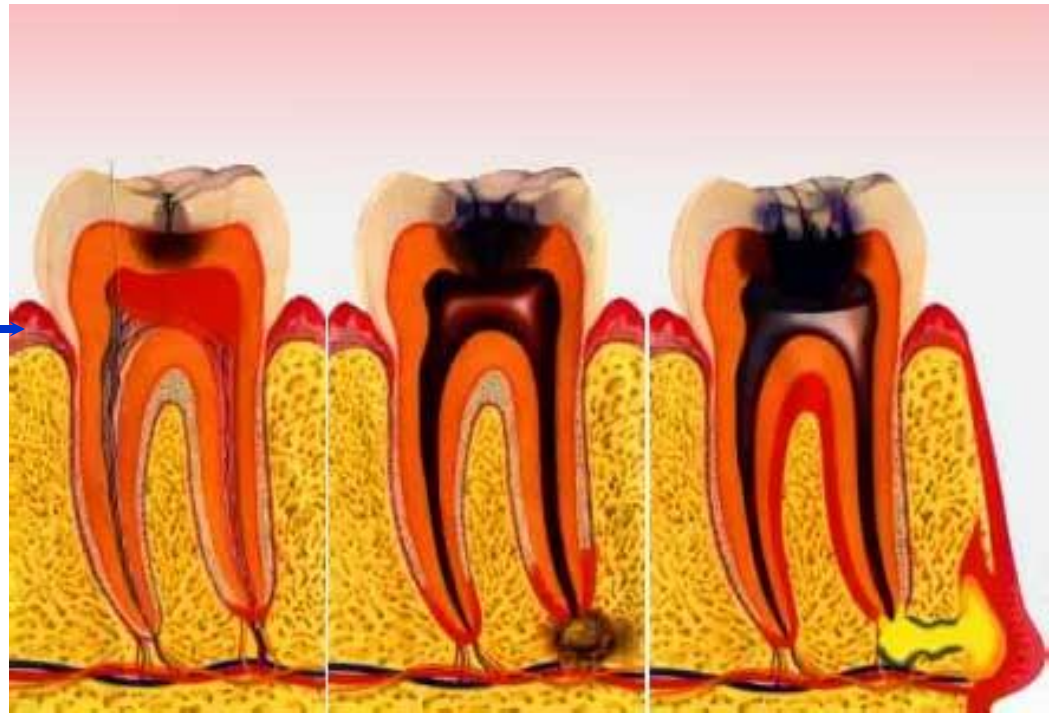
- Oxybuprocaine
- Proxymetacaine
- Tetracine (Dicain®)



2. Amides

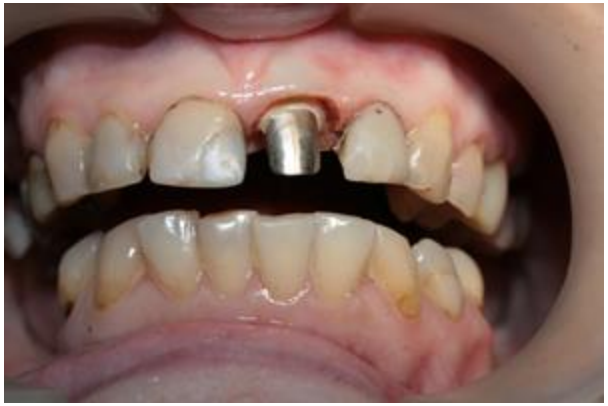
- **Lidocaine** (PRC: B)
- **Bupivacaine**
- **Cinchocaine**
- **Mepivacaine**
- **Prilocaine**
- **Articaine & Epinephrine**
  - **Ubistesine®**
  - **Ultracaine®**

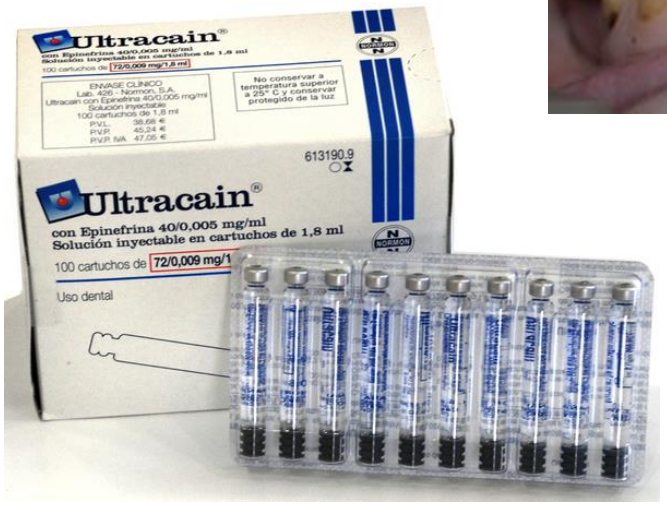
Emla (lidocaine + prilocaine) crème 5% 5 g

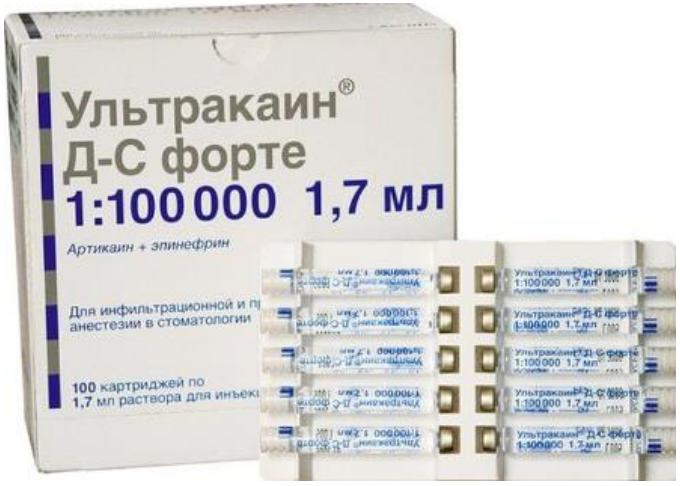



3M ESPE
Ubistesin
4%


3M ESPE
Ubistesin™ forte
40 mg/ml + 10 Mikrogramm/ml
Injektionslösung
Wirkstoffe: Articainhydrochlorid und Epinephrin (Adrenalin)
Lokalanästhetikum für die Zahnheilkunde
Anwendung in der Mundhöhle




Ultracain
con Epinefrina 40/0,005 mg/ml
Solución inyectable en cartuchos de 1,8 ml
613190.9
Ultracain
con Epinefrina 40/0,005 mg/ml
Solución inyectable en cartuchos de 1,8 ml
100 cartuchos de 72/0,009 mg/1
Uso dental

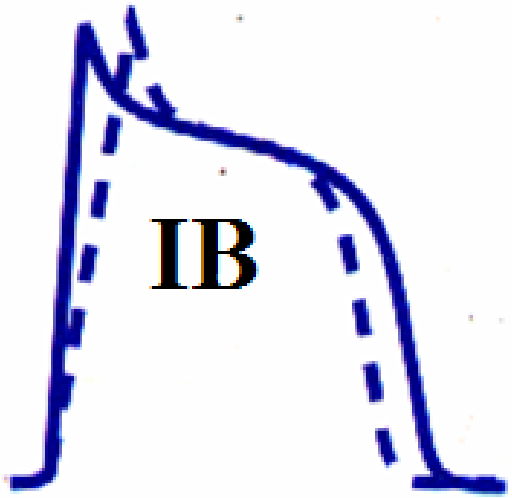

Ультракаин®
Д-С форте
1:100 000 1,7 мл
Артикаин + эпинефрин
Для инфильтрационной и
анестезии в стоматологии
100 картриджей по
1,7 мл раствора для

Different syringes (CITOJECT and others) in dental medicine for local anaesthesia

Lidocaine (Lignocaine)

has also antiarrhythmic action.

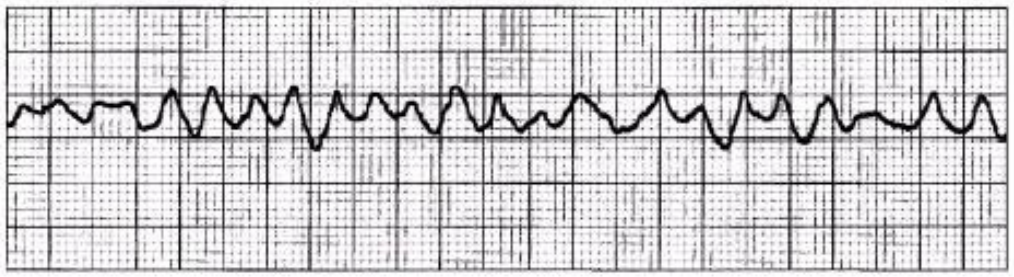
It is an antidysrhythmic agent from class IB, used for the treatment of ventricular tachyarrhythmia from myocardial infarction, ventricular tachycardia, and ventricular fibrillation.



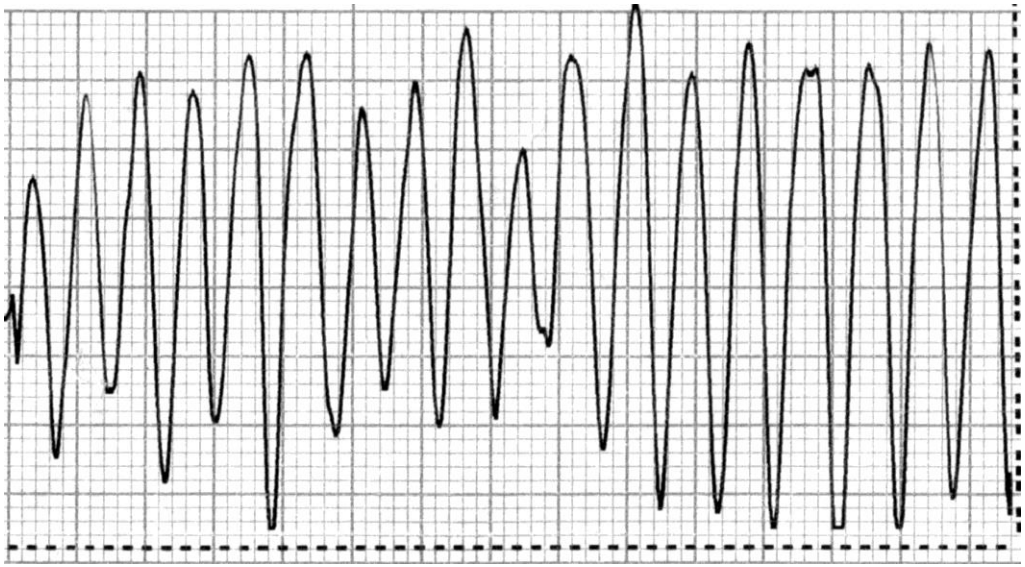
Lidocaine

Class IB: Decreases the duration of AP

ADRs: Bradycardia, AV block, (-) inotropic effect, disturbances of GIT, rashes



***Ventricular fibrillation*, characterized by irregular undulations without clear ventricular complexes**



Ventricular flutter

Dorland's Illustrated Medical Dictionary (2003/2004)