• **Anesthesia** defined as the abolition of sensation

• **Analgesia** defined as the abolition of pain

• “Triad of General Anesthesia”
  – need for unconsciousness
  – need for analgesia
  – Need for amnesia
  – (±) need for muscle relaxation
**Signs and Stages of Anesthesia**

**Sedation.** *Mild CNS depression.* Suitable for surgical procedures not requiring muscle relaxation. Most anesthetics do not produce analgesia.

**D elirium:** An excited state resulting from *cortical motor depression.* This can be avoided with rapidly acting, potent anesthetics. This stage extends from the loss of consciousness in stage 1 to surgical anesthesia in stage 3.

**Surgical Anesthesia:** Further subdivided into stages representative of increasing *muscle relaxation,* the final stage is disappearance of muscle tone.

**Deep anesthesia and Respiratory paralysis:** Generally not desirable.
Inhalational anesthesia refers to the delivery of gases or vapors from the respiratory system to produce or maintain anesthesia.

Exposure to the pulmonary circulation allows a more rapid appearance in arterial blood than intravenous administration.
Advantages of inhalational anesthesia

• Completely painless induction
• No IV (intravenous) access needed
• Rapid appearance of drug in arterial blood
• Safe: as long as patient is breathing satisfactorily, elimination of agent and emergence from anesthesia is essentially guaranteed.
1840, William Morton publically administered ether
1847, James Simpson introduced chloroform
   It was more potent but could have severe side effects such as sudden death and late onset severe liver damage
1877, introduction of local anesthesia
1920's intravenous induction agents were introduced
1940’s Muscle relaxants were introduced
Minimum Alveolar Concentration

• Minimal alveolar concentration of inhalational agent that prevent movement in 50% of the patients in response to surgical stimulation (skin incision)

• Equivalent to ED$_{50}$
Minimum Alveolar Concentration

- The rationale for this measure of anesthetic potency is,
  a. alveolar concentration can be easily measured
  b. near equilibrium, alveolar and brain tensions are virtually equal
  c. the high cerebral blood flow produces rapid equilibration

- Factors which support the use of this measure are,
  a. MAC is invariant with a variety of noxious stimuli
  b. individual variability is small
  c. sex, height, weight & anaesthetic duration do not alter MAC
  d. doses of anaesthetics in MAC's are additive
Factors affecting MAC

PHYSIOLOGIC & PHARMACOLOGIC
FACTORS AFFECTING MAC

Increase in MAC:-

- Hyperthermia
- Hypernatraemia
- Drug induced elevation of CNS catecholamine stores
- Chronic alcohol abuse & chronic opioid abuse
- Increases in ambient pressure (experimental)
- Cyclosporine
- Excess pheomelanin production (red hair)

Decrease in MAC:-

- Hypothermia & Hyperthermia (if >42°C)
- Hyponatraemia
- Drug induced decrease in CNS catecholamine level
- Increasing age (6% decrease/decade)
- Preoperative medication
- Hypoxaemia (PaO2 < 38 mmHg)
- Hypotension (<40 mm hg - MAP)
- Anaemia (Haematocrit < 10%)
- Pregnancy (progesterone)
- Postpartum (returns to normal in 24-72 hrs)
- CNS depressant drugs – Opioids, Benzodiazepines TCA’s etc.
- Other drugs – Lithium, Lidocaine, Magnesium
- Acute alcohol abuse
- Cardiopulmonary bypass
Ideal Characteristics

1. Be **pleasant** to inhale, permitting a smooth induction and emergence.
2. Be **potent** to allow the concomitant administration of high oxygen.
3. **Rapid** induction and emergence (low solubility).
4. Be **easy to administer** and analyze
5. Be easily and cheaply prepared in pure form.
6. Be **stable** in storage and with soda-lime, not flammable, not metabolized.
7. Act at specific CNS sites to cause unconsciousness.
8. No CV or respiratory effects, **non-toxic** to organ systems.
9. Provide **postop pain relief**.
The depth of general anesthesia depends on the partial pressure (or gas fraction) exerted by the inhalational agent in the patient brain (b).

This brain partial pressure depends on arterial (a) blood partial pressure which depends on alveolar (A) partial pressure which depends on partial pressure of agent in the inspired gas (I):

\[ p_I -> p_A -> p_a -> p_b \]
Halothane

- Halogen substituted ethane
- Volatile liquid easily vaporized, stable, and nonflammable
- **Most potent** inhalational anesthetic
- **MAC** of 0.75%
- Efficacious in depressing consciousness
- Very soluble in blood and adipose
- Prolonged emergence
Halothane Systemic Effects

**Cardiovascular**

- Direct myocardial depression → dose-dependent reduction of arterial BP
- Systemic vascular resistance: unchanged
- Coronary artery vasodilator, but coronary blood flow ↓ due to systemic BP ↓
- **Blunt the reflex**: hypotension inhibits baroreceptors in aortic arch and carotid bifurcation → vagal stimulation ↓ → compensatory rise in HR
- Sensitizes the heart to the **arrhythmogenic** effects of epinephrine
Halothane Systemic Effects

**Respiratory**
- Rapid, shallow breathing
- Alveolar ventilation: ↓
- Resting PaCO2: ↑
- Hypoxic drive: severely depressed
- A potent *bronchodilator*, reverses asthma-induced bronchospasm
- Depress clearance of mucus → promoting postoperative hypoxia and atelectasis
Halothane Systemic Effects

**Cerebral**
- Dilating cerebral vessels $\rightarrow$ cerebral vascular resistance $\downarrow$ $\rightarrow$ CBF $\uparrow$
- Blunt autoregulation (the maintenance of constant CBF during changes in arterial BP)
- ICP: $\uparrow$, prevented by hyperventilation prior to administration of halothane
- Metabolic oxygen requirement: $\downarrow$

**Neuromuscular**
- Relaxes skeletal muscle
- A triggering agent of malignant hyperthermia
Halothane Systemic Effects

Renal
- Renal blood flow, GFR, U/O: ↓
- Part of this can be explained by a fall in arterial BP and CO, preoperative hydration limits these changes

Hepatic
- Hepatic blood flow: ↓
Halothane Side Effects

**Halothane Hepatitis** — 1/35,000 cases

- oxidized in liver by cytochrome P-450 2E1 to trifluoroacetic acid
- fever, jaundice, hepatic necrosis, death
- immunologically mediated assault
- exposure dependent
Halothane Side Effects

Malignant Hyperthermia-- 1/60,000

- **Classic** -- rapid rise in body temperature, muscle rigidity, tachycardia, rhabdomyolysis, acidosis, hyperkalemia, DIC
- **physiology**--hypermetabolic state by inhibition of calcium reuptake in sarcoplasmic reticulum
- **Diagnosis** -- previous symptoms, increase CO$_2$, rise in CPK levels, myoglobinuria
- **autosomal dominant** inheritance
- **Treatment** -- early detection, d/c agents, hyperventilate, bicarb, IV dantrolene (2.5 mg/kg), ice packs/cooling blankets, lasix/mannitol/ fluids.
- **ICU monitoring**
Halothane

Contraindications
- Unexplained liver dysfunction following previous exposure
- Intracranial mass lesion, hypovolemic, severe cardiac disease...

Drug interactions
- Myocardial depression is exacerbation by β-blockers and CCB
- With aminophylline → serious ventricular arrhythmia
• Developed in 1963 by Terrell, released for use in 1972
• Stable, nonflammable liquid
• **MAC** 1.68%
• Haloginated methyl ethyl ether.
Enflurane Systemic Effects

**Cardiovascular:**
- Inhibits sympathetic baroreflex response
- Sensitizes myocardium to effects of exogenous catecholamines – arrhythmias
- Potent *inotropic and chronotropic depressant* and decreases systemic vascular resistance-- lowers blood pressure and conduction dramatically
Enflurane Systemic Effects

**Respiratory**
- drive is greatly depressed -- central and peripheral responses
- increases dead space
- widens A-a gradient
- produces hypercarbia in spontaneously breathing patient
- bronchodilator
Enflurane Side Effects

- Metabolism one-tenth that of halothane-- does not release quantity of hepatotoxic metabolites
- Metabolism releases fluoride ion-- renal toxicity
- Epileptiform EEG patterns
Nonflammable, pungent

MAC of 1.20 %

Haloginated methyl ethyl ether

A chemical isomer of enflurane
Isoflurane Systemic Effects

**Cardiovascular**

- Minimal cardiac depression
- Systemic vascular resistance: ↓ (Produces most significant reduction in systemic vascular resistance) → BP: ↓
- Dilates coronary arteries → **coronary steal syndrome** or drop in perfusion pressure → regional myocardial ischemia → avoided in patients with CAD
- Sensitizes myocardium to catecholamines -- less than halothane or enflurane
Isoflurane Systemic Effects

**Respiratory**
- Respiratory depression, minute ventilation: ↓
- Blunt the normal ventilatory response to hypoxia and hypercapnia
  - Irritate upper airway reflex
  - A good bronchodilator

**Cerebral**
- CBF, ICP: ↑, reversed by hyperventilation
- Cerebral metabolic oxygen requirement: ↓

**Neuromuscular**
- Relaxes skeletal muscle
Isoflurane Systemic Effects

Renal
  – Renal blood flow, GFR, U/O: ↓

Hepatic
  – Total hepatic blood flow: ↓
Desflurane

• Structure is similar to isoflurane
• **High vapor pressure**
• requires special vaporizer
• Low solubility → *ultrashort duration of action*
• Moderate potency
• **MAC 6%**
Desflurane systemic effects

Cardiovascular

- Systemic vascular resistance: ↓ → BP: ↓
- CO: unchanged or slightly depressed
- Rapid increases in concentration lead to transient elevation in HR, BP, catecholamine levels
Desflurane systemic effects

**Respiratory**
- Tidal volume: ↓, respiratory rate: ↑
- Alveolar ventilation: ↓, resting PaCO2: ↑
- Depress the ventilatory response to ↑PaCO2
- **Pungency and airway irritation**

**Cerebral**
- Vasodilate cerebral vasculature → CBF, ICP: ↑, lowered by hyperventilation
- Cerebral metabolic rate of oxygen: ↓
Desflurane systemic effects

**Neuromuscular**
- Dose-dependent decrease in the response to train-of-four and tetanic peripheral nerve stimulation

**Renal**
- No evidence of any nephrotoxic effects

**Hepatic**
- No evidence of hepatic injury
Desflurane side effects

Degraded by desiccated CO2 absorbent into carbon monoxide
Contraindications
  – Severe hypovolemia, malignant hyperthermia, intracranial hypertension

Drug interactions
  – Potentiate nondepolarizing NMBAs
• Nonpungency
• Rapid increase in alveolar anesthetic concentration
• Smooth and rapid inhalation inductions in pediatric and adult patients
• MAC 2%
Sevoflurane systemic effects

**Cardiovascular**
- Mildly depress myocardial contractility
- Systemic vascular resistance, arterial BP: ↓
- CO: not maintained well due to little rise in HR

**Respiratory**
- Depress respiration
- Reverse bronchospasm
Sevoflurane systemic effects

**Cerebral**
- CBF, ICP: slight ↑
- Cerebral metabolic oxygen requirement: ↓

**Neuromuscular**
- Adequate muscle relaxation for intubation of children

**Renal**
- Renal blood flow: slightly ↓
- Associated with impaired renal tubule function

**Hepatic**
- Portal vein blood flow: ↓
Sevoflurane side effects

**Biotransformation & toxicity**
- Liver microsomal enzyme P-450
- Degraded by alkali (barium hydroxide lime, soda lime), producing nephrotoxic end products (**compound A**)


Contraindications

- Severe hypovolemia, susceptibility to malignant hyperthermia, intracranial hypertension
The only inorganic anesthetic gas in clinical use.
- Characterized by inert nature with minimal metabolism.
- Colorless, odorless, tasteless, and does not burn.
- Weak anesthetic good analgesic agent.
- Major difference is low potency.
- MAC value is 104%.
- Needs other agents for surgical anesthesia.
- Low blood solubility.
Nitrous Oxide Systemic Effects

**Cardiovascular**

- Depress myocardial contractility
- Arterial BP, CO, HR: unchanged or slightly ↑ due to stimulation of catecholamines
- Constriction of pulmonary vascular smooth muscle → increase pulmonary vascular resistance
- Peripheral vascular resistance: not altered
Nitrous Oxide

Nitrous Oxide Systemic Effects

Respiratory
- Respiratory rate: ↑
- Tidal volume: ↓
- Minute ventilation, resting arterial CO2: minimal change
- Hypoxic drive (ventilatory response to arterial hypoxia): ↓

Cerebral
- CBF, cerebral blood volume, ICP: ↑
- Cerebral oxygen consumption (CMRO2): ↑
Nitrous Oxide Systemic Effects

**Neuromuscular**
- Not provide significant muscle relaxation
- Not a triggering agent of malignant hyperthermia

**Renal**
- Increase renal vascular resistance
- Renal blood flow, glomerular filtration rate, U/O: ↓

**Hepatic**
- Hepatic blood flow: ↓

**Gastrointestinal**
- Postoperative nausea and vomiting
Nitrous Oxide Side Effects

• Beginning of case: second gas effect
• Diffusion into closed spaces
• Inhibits vitamin B-12 metabolism
Contraindications

- N2O diffuse into the cavity more rapidly than air (principally N2) diffuse out

  *Pneumothorax, air embolism, acute intestinal obstruction, intracranial air, pulmonary air cysts, intraocular air bubbles, tympanic membrane grafting*

- Avoided in pulmonary hypertension
Xenon

- Nonexplosive, nonpungent, odorless and chemically inert
- No metabolism and low toxicity
- High cost
- **MAC 71%**
- It has some **analgesic effect**.
- Reduces anesthesia-emergent nausea and vomiting
- Very close to the ‘ideal agent’
- Minimal haemodynamic effects.
- Seems not to trigger malignant hyperthermia.
<table>
<thead>
<tr>
<th>MAC</th>
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</thead>
<tbody>
<tr>
<td>Halothane</td>
<td>0.75%</td>
</tr>
<tr>
<td>Enflurane</td>
<td>1.6%</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>1.2%</td>
</tr>
<tr>
<td>Desflurane</td>
<td>6%</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>2%</td>
</tr>
<tr>
<td>Nitrous Oxide</td>
<td>104%</td>
</tr>
<tr>
<td>Xenon</td>
<td>71%</td>
</tr>
</tbody>
</table>
Respiratory Effects

Type of breathing
- Rapid shallow breathing
- Decrease minute ventilation
- Increase PaCO2

Hypoxic drive
- 0.1 MAC produce 50% depression
- 1.1 MAC produce 100% depression

Airway resistance
- They cause bronchodilation
- They can cause airway irritation
Cardiovascular Effects

- All caused decrease in BP (ex. N2O)
- Isoflurane and desflurane cause increased heart rate which may mask depression

Systemic vascular resistance
- Isoflurane and desflurane cause most decrease
- Halothane and nitrous oxide do not change
- Steal phenomena
Cardiovascular Effects

**MAP**

- N2O cause no or modest increase
- Halothane cause decrease by cardiac depression
- Others causes decrease by causing decrease SVR

**HR**

- Halothane does not cause tachycardia.
- Others increase HR
CNS Effects

CBF:
  – >0.6 MAC in normocapnic pt. produce cerebral vasodilation and results in dose dependent increase in CBF.

O2 requirements:
  – All decrease (except N2O)

ICP
  – All increase
Renal Effects

- All decrease arterial pressure
- They cause a dose related decrease in renal blood flow, glomerular filtration rate and urine output.
- RBF and GFR will be maintained until threshold of autoregulation
- Enflurane ........ nephrotoxic
Hepatic effects

Circulation
– Hepatic blood flow is maintained or decreased

Hepatic function
– Transient increase in liver enzymes
Skeletal muscle effects

NMJ
- They cause dose dependent potentiation of NMBD (except for N2O)

Malignant hyperthermia
Obstetric effects

- Produce dose dependent decrease in uterine contractility and blood flow
- may cause uterine atony and PPH
- They rapidly cross the placenta and reach the fetus