Anesthesia and Anesthetic Agents

C. B. Smith, M.D., Ph.D.

A323 MSRB III
734-763-9825
cbsmith@umich.edu
Anesthesia

- a reversible, drug-induced absence of perception of all sensation
- five features: unconsciousness, analgesia, amnesia, skeletal muscle relaxation, reduced autonomic responses
Consciousness

an awareness of one’s feelings and surroundings
Types of anesthetics

I. Inhalation anesthetics

II. Intravenous anesthetics

III. Local anesthetics
General Anesthesia

- Sleep induction
- Loss of pain responses
- Amnesia
- Skeletal muscle relaxation
- Loss of reflexes
5. From consciousness to death

MANIA

CONSCIOUSNESS

Intoxication

Analgesia

Amnesia

Increasing depth of anaesthesia

Loss of responsiveness

Loss of motor response

Respiratory depression

Loss of vasomotor control

Cardiac dysrhythmias

Arrest

DEATH

Increasing concentration of anaesthetic
General Anesthesia

Stages of Anesthesia

- **Stage I**
  - Analgesia

- **Stage II**
  - Disinhibition

- **Stage III**
  - Surgical anesthesia

- **Stage IV**
  - Medullary depression
Usage of Anesthetics in the USA

- 40 million anesthetics administered per year
- At least 90% provided by anesthesiologists
- Deaths due to anesthesia are 1 in 250,000 (= 0.0004%)

Source: American Society of Anesthesiologists (ASA)
January, 2000
General Anesthesia
I. Inhalation anesthetics

Mecanisms of Action

• Activate K⁺ channels
• Block Na⁺ channels
• Disrupt membrane lipids
• In general, all general anesthetics increase the cellular threshold for firing, thus decreasing neuronal activity.
Short History of Inhalation Anesthesia
Nitrous oxide, \( \text{N}_2\text{O} \), is a colorless, almost odorless gas, that was first discovered in 1793 by the English scientist and clergyman Joseph Priestley (who was also famous for being the first to isolate other important gases such as oxygen, carbon monoxide, carbon dioxide, ammonia, and sulfur dioxide). Priestley made \( \text{N}_2\text{O} \) by heating ammonium nitrate in the presence of iron filings, and then passing the gas that came off (NO) through water to remove toxic by-products.
On 17th April 1799, Humphrey Davy performed an experiment to test the effects of breathing in nitrous oxide. Davy continued his experiments in this manner between May and July of the same year.

"The objects around me became dazzling and my hearing more acute. Towards the last inspirations, the thrilling increased, the sense of muscular power became greater."

"appears capable of destroying physical pain"
13. Nitrous oxide for recreation

LIVING MADE EASY

PRESCRIPTION FOR SCOLDING WIVES.

London 1837 by J. M. Low, 60, Holborn. June 1, 1837
Diethyl Ether

The colorless liquid ether was first synthesized about 1540 by Valerius Cordus (1515-1544), a German physician and botanist, who called his discovery "sweet oil of vitriol" and described its medicinal properties. Paracelsus (1493-1541), a contemporary of Valerius, noted that the "oil" induced sleep in chickens when added to their feed. Frobenius (Froben) named the liquid "ethereal spirits" or "ether" in 1730.
In the 1790s, doctors at the Pneumatic Institution in Bristol, England used ether inhalation to treat patients with consumption (tuberculosis). The Institution's director Humphrey Davy then discovered the pain-alleviating and exhilarating effects of inhaling nitrous oxide. Davy's student Michael Faraday noted the same results from inhaling ether in 1818. "Ether frolics" soon became popular, especially among medical students in the United States.
1842 - On March 30, Dr. Crawford W. Long administered the first anesthetic using ether in Jefferson, Georgia, a small community 60 miles northeast of Atlanta. However, this event was not publicized.
1844 - On December 11, Dr. Horace Wells, a dentist, inhaled nitrous oxide while a fellow dentist painlessly extracted one of Dr. Well's teeth. However, Dr. Wells' attempt to produce anesthesia using nitrous oxide at Massachusetts General Hospital in 1845 failed and the use of nitrous oxide for medical purposes fell into disrepute.
1846 - On Friday, October 16, Dr. William Thomas Green Morton, a dentist from Harford, Connecticut, and Dr. Well's partner, administered ether to Mr. Gilbert Abbott for the removal of a tumor by the well-known surgeon Dr. John C. Warren at Massachusetts General Hospital. An account of this event appeared in the *Boston Daily Journal* the next day.
1853 – When Dr. John Snow, an English physician, administered chloroform to Queen Victoria during the birth of Prince Leopold in 1853 obstetrical anesthesia gained public acceptance. Dr. Snow was the first physician to devote his medical practice to the administration of anesthetics, making him the first anesthesiologist.
I. Inhalation anesthetics

Ether (diethyl ether)

- Spontaneously explosive
- Irritant to respiratory tract
- High incidence of nausea and vomiting during induction and post-surgical emergence
I. Inhalation anesthetics

Nitrous Oxide

\[ \begin{align*}
\text{N≡N–O}^- & \leftrightarrow \text{N≡N=O}^+ \\
\end{align*} \]

- Rapid onset
- Good analgesia
- Used for short procedures and in combination with other anesthetics
- Supplied in blue cylinders
I. Inhalation anesthetics

Halothane (Fluothane)
- Volatile liquid
- Narrow margin of safety
- Less analgesia and muscle relaxation
- Hepatotoxic
- Reduced cardiac output leads to decrease in mean arterial pressure
- Increased sensitization of myocardium to catecholamines
I. Inhalation anesthetics

**Enflurane (Ethrane)**
- Similar to Halothane
- Less toxicity

**Isoflurane (Forane)**
- Volatile liquid
- Decrease mean arterial pressure resulting from a decrease in systemic vascular resistance
23. Inhalation anesthetics

Snow, 1858

Isoflurane

\[
\begin{array}{c}
\text{F} \\
\text{C} \\
\text{C} \\
\text{O} \\
\text{C} \\
\text{H} \\
\text{F} \\
\text{F} \\
\text{F} \\
\text{Cl} \\
\text{F} \\
\end{array}
\]

Sevoflurane

\[
\begin{array}{c}
\text{F} \\
\text{C} \\
\text{C} \\
\text{O} \\
\text{C} \\
\text{F} \\
\text{F} \\
\text{F} \\
\text{F} \\
\end{array}
\]

Nitrous oxide

\[
\begin{array}{c}
\text{O} \\
\text{N} \equiv \text{N} \\
\end{array}
\]
General Anesthetics

• Introduction: States of Consciousness;
  Defining Anesthesia; Historical Overview

• Uptake and Distribution

• Elimination and Recovery

• Dosage and Potency: MAC

• Depth of Anesthesia

• Intravenous Anesthetics

• Mechanisms of Anesthetic Action
In a mixture of ideal gases, each gas has a **partial pressure** which is the pressure which the gas would have if it alone occupied the volume. The total pressure of a gas mixture is the sum of the partial pressures of each individual gas in the mixture. In chemistry, the partial pressure of a gas in a mixture of gases is defined as above. The partial pressure of a gas dissolved in a liquid is the partial pressure of that gas which would be generated in a gas phase in equilibrium with the liquid at the same temperature. The partial pressure of a gas is a measure of thermodynamic activity of the gas's molecules. Gases will always flow from a region of higher partial pressure to one of lower pressure; the larger this difference, the faster the flow. Gases dissolve, diffuse, and react according to their partial pressures, and not necessarily according to their concentrations in a gas mixture.
Uptake and Distribution of Inhalation Anesthetics

1. Depth of anesthesia is determined by the tension or partial pressure of the anesthetic agent in the brain. The terms tension and partial pressure are synonymous.

2. Rate of anesthetic induction and rate of recovery from anesthesia depend upon the rate of change of anesthetic tension in brain.
Uptake and Distribution of Inhalation Anesthetics

3. Anesthetic tension in brain equilibrates with tension in arterial blood, which equilibrates with alveolar tension. Thus, alveolar partial pressure of the anesthetic is very important.

4. The rate of rise of alveolar tension is determined by: anesthetic input to lung and uptake from lung by blood and tissues.
Factors that Determine Anesthetic Tension

Input to the lungs

1. Anesthetic concentration in the inspired gas
2. Minute ventilation

Uptake from the lungs to the blood and tissues

3. Transfer of anesthetic from alveoli to blood
4. Transfer of anesthetic from blood to tissues
Increasing Anesthetic Concentration Increases Rate of Rise of Alveolar Tension

Eger EI. Anesthetic Uptake and Action, Williams & Wilkins, Baltimore, 1974, p. 116
Increasing Minute Ventilation Increases the Rate of Rise of Alveolar Tension

Eger EI. Anesthetic Uptake and Action, Williams & Wilkins, Baltimore, 1974, p. 123
Factors that Determine Anesthetic Tension

Uptake from the lungs to the blood and tissues

3. Transfer of anesthetic from alveoli to blood
   a. anesthetic solubility in blood
   b. pulmonary blood flow (cardiac output)
   c. alveolar-to-venous anesthetic partial pressure difference
Anesthetic Solubility in Blood

\[
\frac{\text{BLOOD}}{\text{GAS}} \quad \text{PARTITION COEFFICIENT} = \frac{40}{80} = 0.5
\]

Eger EI. *Anesthetic Uptake and Action*, Williams & Wilkins, Baltimore, 1974, p. 80
### Blood/Gas Partition Coefficients

<table>
<thead>
<tr>
<th>Anesthetic</th>
<th>( \lambda )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desflurane</td>
<td>0.45</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>0.65</td>
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<tr>
<td>Nitrous Oxide</td>
<td>0.47</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>1.41</td>
</tr>
<tr>
<td>Enflurane</td>
<td>1.78</td>
</tr>
<tr>
<td>Haloflurane</td>
<td>2.3</td>
</tr>
<tr>
<td>Diethyl ether</td>
<td>12.1</td>
</tr>
</tbody>
</table>

Eger et al., *Anesthesiology* 80:906-922, 1994

Eger El. *Anesthetic Uptake and Action, Williams & Wilkins, Baltimore, 1974, p. 82
Increasing Anesthetic Solubility Decreases the Rate of Rise of Alveolar Tension

Eger et al., Anesthesiology 80:906-922, 1994
Increasing Cardiac Output Decreases the Rate of Rise of Alveolar Tension

Eger EI. Anesthetic Uptake and Action, Williams & Wilkins, Baltimore, 1974, p. 131
Alveolar-to-Venous Anesthetic Partial Pressure Difference

• results from the uptake of anesthetics from blood by the tissue during anesthetic induction

• at the onset of anesthetic administration, mixed venous blood returning to lungs will have a much lower tension than the alveoli (i.e., arterial blood); this difference will diminish with time
Summary

Anesthetic uptake from alveoli to blood =

(Solubility)(Cardiac Output)(A-V PP Difference)
Factors that Determine Anesthetic Tension

Uptake from the lungs to the blood and tissues

4. Transfer of anesthetic from blood to tissues
   a. anesthetic solubility in tissues
   b. tissue blood flow
   c. alveolar-to-tissue anesthetic partial pressure difference
<table>
<thead>
<tr>
<th>Anesthetic</th>
<th>Blood Gas</th>
<th>Brain Blood</th>
<th>Liver Blood</th>
<th>Muscle Blood</th>
<th>Fat Blood</th>
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<tbody>
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<td>Enflurane</td>
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<td>1.7</td>
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<tr>
<td>Halothane</td>
<td>2.3</td>
<td>2.9</td>
<td>2.6</td>
<td>3.5</td>
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<td>Methoxyflurane</td>
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<td>2.0</td>
<td>1.9</td>
<td>1.3</td>
<td>49</td>
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</tbody>
</table>

Eger EL. *Anesthetic Uptake and Action*, Williams & Wilkins, Baltimore, 1974, p. 82
### Table of Partition Coefficients

<table>
<thead>
<tr>
<th>Anesthetic</th>
<th>Blood Gas</th>
<th>brain Blood</th>
<th>Muscle Blood</th>
<th>Fat Blood</th>
<th>MAC</th>
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</thead>
<tbody>
<tr>
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<tr>
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<td>1.1</td>
<td>1.0</td>
<td>3.7</td>
<td>1.92</td>
</tr>
</tbody>
</table>

Eger El. *Anesthetic Uptake and Action*, Williams & Wilkins, Baltimore, 1974, p. 82
Factors that Determine Anesthetic Tension

Tissue blood flow

- the faster the blood flow to a given tissue, the more rapidly anesthetic tension will rise in that tissue

- brain has a high perfusion rate, thus anesthetic will equilibrate rapidly in brain
Factors that Determine Anesthetic Tension

Tissue blood flow

- fat is poorly perfused, thus anesthetic gases are delivered to and taken up by adipose tissue more slowly
Factors that Determine Anesthetic Tension

Alveolar-to-tissue partial pressure difference

- at the onset of anesthetic administration, tissue partial pressure increases rapidly
- as tissue tension approaches arterial tension, tissue uptake of anesthetic gas slows
### Summary of Uptake

<table>
<thead>
<tr>
<th>Factor</th>
<th>$\frac{F_A}{F_I}$</th>
<th>Induction Time</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Input to lung</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Concentration of inspired gas</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>• Minute ventilation</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Uptake from lung</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• solubility</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>• cardiac output</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>• alveolar-to-venous partial pressure difference</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

The table above summarizes the factors affecting the uptake of substances into the body. The arrows indicate the direction of change:
- ↑ Increase
- ↓ Decrease
General Anesthetics

- Introduction: States of Consciousness;
  Defining Anesthesia; Historical Overview
- Uptake and Distribution
- **Elimination and Recovery**
- Dosage and Potency: MAC
- Depth of Anesthesia
- Intravenous Anesthetics
- Mechanisms of Anesthetic Action
Factors that Determine Elimination and Recovery

• The rate of elimination of inhaled anesthetics from the brain determines the rate of recovery from general anesthesia.

• The main route of elimination is clearance by the lungs into the expired air.

• The rate of fall of alveolar tension depends on three main factors: removal from lungs, output to lungs, and duration of anesthesia.
Factors that Determine Elimination and Recovery

*Anesthetic removal from the lung*

1. Minute ventilation

*Anesthetic output from blood and tissues to lung*

2. Transfer of anesthetic gas from blood and tissues to lung
   a. anesthetic solubility in blood and tissue
   b. pulmonary blood flow (cardiac output)
   c. venous-to-alveolar pp difference

*Duration of anesthesia*
Increasing Minute Ventilation Increases the Rate of Fall of Alveolar Tension

Eger EI. Anesthetic Uptake and Action, Williams & Wilkins, Baltimore, 1974, p. 235
Increasing Anesthetic Solubility Decreases the Rate of Fall of Alveolar Tension

Eger EI. Anesthetic Uptake and Action, Williams & Wilkins, Baltimore, 1974, p. 241
Graph for various agents Minutes of Administration

Eger et al., Anesthesiology 80:906-922, 1994
Increasing Anesthetic Solubility Increases Recovery Time

Eger et al., Anesthesiology 80:906-922, 1994
Factors that Determine Elimination and Recovery

pulmonary blood flow (cardiac output)

• increasing cardiac output will deliver more anesthetic to the alveoli

• this will slow the rate of fall of alveolar tension
Factors that Determine Elimination and Recovery

venous-to-alveolar partial pressure difference

• this difference develops after alveolar concentration decreases due to ventilation

• this difference contributes to a reduction in the rate of fall of alveolar tension
Increasing Anesthesia Duration Decreases the Rate of Fall of Alveolar Tension

Eger EI. Anesthetic Uptake and Action, Williams & Wilkins, Baltimore, 1974, p. 241
## Summary of Elimination

<table>
<thead>
<tr>
<th>Factor</th>
<th>$F_E/F_{EO}$</th>
<th>Recovery Time</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Removal from lung</strong></td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>• Minute ventilation</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Output to lung</strong></td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>• solubility</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>• cardiac output</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>• venous-to-venous partial pressure difference</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Duration of anesthesia</strong></td>
<td>↑</td>
<td>↓</td>
</tr>
</tbody>
</table>