INTRODUCTION

The modern anesthetist expeditiously develops and then sustains anesthetic concentrations in the central nervous system that are sufficient for surgery with agents and techniques that usually permit rapid recovery from anesthesia. Understanding the factors that govern the relationship between the delivered anesthetic and brain concentrations enhances the optimum conduct of anesthesia.

I. UPTAKE OF INHALED ANESTHETICS.

A. Factors raising the alveolar concentration, assuming a constant inspired anesthetic concentration, and no uptake by blood:

1. The inspired concentration (Fi).
   a. The rate of rise is directly proportional to the inspired concentration.

2. The alveolar ventilation (V_{alveolar})
   a. The larger the minute alveolar ventilation (V_{alveolar}), the more rapid the rise in alveolar concentration (F_A).
   b. Inspired gas is diluted by the FRC, so the larger the FRC, as a fraction of V_{alveolar}, the slower the alveolar rise in anesthetic concentration.
   c. For ventilatory rates over 4 breaths, the ventilatory rate does not make any difference at the same V_{alveolar}.

3. The time constant
   The time required for flow through a container to equal the capacity of the container.

   \[
   \text{Time Constant} = \frac{\text{volume (capacity)}}{\text{flow}}
   \]

<table>
<thead>
<tr>
<th>Time Constant</th>
<th>% washin/washout</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>63%</td>
</tr>
<tr>
<td>2</td>
<td>86%</td>
</tr>
<tr>
<td>3</td>
<td>95%</td>
</tr>
<tr>
<td>4</td>
<td>98%</td>
</tr>
</tbody>
</table>

   For example;
   If 10 liter box is initially filled with oxygen and 5 l/min of nitrogen flow into box then, the TC is volume (capacity)/flow.
   \[
   \text{TC} = \frac{10}{5} = 2 \text{ minutes.}
   \]
   So, the nitrogen concentration at end of 2 minutes is 63%.

   The time constant for the lungs is FRC/V_{alveolar}.
The time constant for the anesthesia circuit is circuit capacity/FGF.
4. The larger the FRC, the slower the washin of a new gas.
5. The rate of rise of the alveolar concentration (FA/Fi) is greatly slowed by anesthetic uptake by the blood.

Factors that Increase or Decrease the Rate of Rise of FA/Fi

<table>
<thead>
<tr>
<th>Increase</th>
<th>Decrease</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low blood solubility</td>
<td>High blood solubility</td>
<td>As the blood solubility decreases, the rate of rise in FA/Fi increases.</td>
</tr>
<tr>
<td>Low cardiac output</td>
<td>High cardiac output</td>
<td>The lower the cardiac output, the faster the rate of rise in FA/Fi</td>
</tr>
<tr>
<td>High minute ventilation</td>
<td>Low minute ventilation</td>
<td>The higher the minute ventilation, the faster the rate of rise in FA/Fi</td>
</tr>
<tr>
<td>High pulmonary arterial to venous partial</td>
<td>Low pulmonary arterial to venous partial</td>
<td>&quot;At the beginning of induction, PV is zero but increases rapidly (thus [PA-PV] falls rapidly) and FA/Fi increase rapidly. Later during induction and maintenance, PV rises more slowly so FA/Fi rises more slowly.&quot;</td>
</tr>
</tbody>
</table>

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B. Factors determining uptake by blood.

1. Solubility in blood:
   a. The blood/gas partition coefficient.
   b. The relative capacity per unit volume of two solvents (e.g. gas and blood) to hold the anesthetic gas. (i.e. blood-gas partition coefficient of 1.4 means that each milliliter of blood holds 1.4 times as much isoflurane as a milliliter of alveolar gas does)
   c. The relative molar amount in equal volumes of blood and gas when the partial pressures are equal. ("Equilibrium" means that no difference in partial pressure exists)

<table>
<thead>
<tr>
<th>Gas</th>
<th>Blood/Gas</th>
<th>Brain/Bld.</th>
<th>Muscle/bld</th>
<th>Fat/Bld</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrous Oxide</td>
<td>0.47</td>
<td>1.1</td>
<td>1.2</td>
<td>2.3</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>1.4</td>
<td>1.6</td>
<td>2.9</td>
<td>45</td>
</tr>
<tr>
<td>Enflurane</td>
<td>1.8</td>
<td>1.4</td>
<td>1.7</td>
<td>36</td>
</tr>
<tr>
<td>Halothane</td>
<td>2.5</td>
<td>1.9</td>
<td>3.4</td>
<td>51</td>
</tr>
<tr>
<td>Desflurane</td>
<td>0.45</td>
<td>1.3</td>
<td>2.0</td>
<td>27</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>0.65</td>
<td>1.7</td>
<td>3.1</td>
<td>48</td>
</tr>
<tr>
<td>Diethyl Ether</td>
<td>12</td>
<td>2.0</td>
<td>1.3</td>
<td>5</td>
</tr>
<tr>
<td>Methoxyflurane</td>
<td>15</td>
<td>1.4</td>
<td>1.6</td>
<td>38</td>
</tr>
</tbody>
</table>

References: Eger El II, Uptake and Distribution in Miller
d. Other things equal, the more soluble the anesthetic, the more drug will be taken up by the blood, and the slower the rise in alveolar concentration.

2. Cardiac Output:
   a. The flow of blood through the lungs determines the amount of blood available to remove anesthetic gas.
   b. The greater the cardiac output, the slower the rise in alveolar concentration.
   c. Mathematically, changes in cardiac output have exactly the same influence on anesthetic uptake from the lungs as changes in solubility, since both influence exactly the same process: the size of the storage capacity of the blood for anesthetic agent over a given time interval.

3. The mixed venous anesthetic concentration:
   a. The higher the mixed venous concentration, the slower the anesthetic uptake.
   b. Initially 0.
   c. At equilibrium, the venous partial pressure = arterial partial pressure = alveolar partial pressure (e.g. uptake = 0).
   d. The uptake from the lung, in liters of gas/minute:

   \[
   \text{uptake from lung} = \frac{\text{blood solubility} \times \text{cardiac output} \times (P_{\text{alveolar}} - P_{\text{venous}})}{\text{atmospheric pressure}}
   \]

   e. The rate of rise of the mixed venous concentration depends on the tissue uptake of the anesthetic.

4. Tissue uptake of anesthetic:
   a. The tissue uptake (including blood) equals the uptake from the lungs.
   b. The same factors which govern uptake by the blood from the lungs govern uptake by the tissues from the blood:
      1. The tissue/blood partition coefficient (tissue solubility)
      2. The tissue blood flow.
      3. The tissue anesthetic concentration (analogous to the mixed venous tissue concentration).
   c. Tissue uptake, in liters of gas/minute =

   \[
   \text{tissue uptake} = \frac{\text{tissue solubility} \times \text{tissue blood flow} \times (P_{\text{arterial}} - P_{\text{tissue}})}{\text{atmospheric pressure}}
   \]

   d. The rate of rise in tissue anesthetic concentration is proportional to tissue blood flow.
   e. The rate of rise in tissue anesthetic concentration is inversely proportional to the tissue capacity.
      1. The tissue capacity is: \text{tissue volume} \times \text{tissue solubility}
   f. Just as discussed for the lungs, the tissues have a time constant:
      1. \text{time constant} = \frac{\text{solubility} \times \text{volume}}{\text{flow}}
Thus, eventually fat governs the uptake of all anesthetics, until equilibrium is reached (at several days)

g. The contribution of each tissue to the mixed venous partial pressure is the tissue anesthetic partial pressure * the flow to that tissue.

h. The body can be roughly divided into 4 tissue groups, vessel rich group (brain, heart, lungs, kidney, splanchnic bed, glands), the muscle group, the fat group, and the vessel poor group (bones, cartilage, ligaments):

<table>
<thead>
<tr>
<th>Gas</th>
<th>Group</th>
<th>% MASS</th>
<th>% CO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrous Oxide</td>
<td>VRG</td>
<td>10</td>
<td>75</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>MG</td>
<td>50</td>
<td>18</td>
</tr>
<tr>
<td>Enflurane</td>
<td>FG</td>
<td>20</td>
<td>5.5</td>
</tr>
<tr>
<td>Halothane</td>
<td>VPG</td>
<td>20</td>
<td>1.5</td>
</tr>
<tr>
<td>Desflurane</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sevoflurane</td>
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<td></td>
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<tr>
<td>Diethyl Ether</td>
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</tr>
<tr>
<td>Methoxyflurane</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

C. Unifying the above concepts:

1. Wash in of gas to the FRC occurs very fast (within 1 minute), so we will ignore it.
2. The alveolar/inspired partial pressure ratio approaches 1 with time.
3. \[ \frac{F_{alveolar}}{F_{inspired}} = 1 - \frac{U_{Lang}}{F_{inspired} \times V_{alveolar}} \]

Where \( U_{Lang} \) = uptake from lung and
\( F_{inspired} \times V_{alveolar} \) is the rate of drug delivery to the lungs.

while \( U_{Lang} = \frac{\lambda_B \times Q \times (P_A - P_{venous})}{\text{Barometric pressure}} \)

- is the rate of drug leaving the lung.

D. Metabolism

a. About 10-20% of halothane is eliminated through metabolism.
   i. May be related to halothane hepatotoxicity
b. About 2.5% of enflurane is metabolized.
c. No significant metabolism of isoflurane, nitrous oxide, or desflurane.
d. Sevoflurane is broken down into Compound A by CO$_2$ absorbants (baralyme and soda lime).
   i. Most studies to date suggest that this is NOT a clinical issue with sevoflurane, even at low flow.

II. Hydraulic Model (intuitive model)

A. The model consists of 5 upright cylinders.
   1. The cylinders represent the inspired reservoir (mouth), the alveolar gas, vessel rich group, the muscle group, and the fat group.
   2. The arrangement of the cylinders is as follows: (Fig 1)

(Fig 1) Mapleson Hydraulic Model

3. The cross sectional surface of each cylinder corresponds to its capacity (volume * tissue solubility)
4. The four peripheral cylinders are connected to the alveolar gas cylinder by pipes at their bases. The diameter of the pipes correlates to the blood/gas partition coefficient times the cardiac output to each group, (except for the connection between the inspired reservoir (mouth), where the diameter of the pipe represents alveolar ventilation.)
5. The height of the column of fluid in each cylinder corresponds to the partial pressure of the anesthetic in that cylinder.

B. Mapleson’s analogy for inhaled anaesthetics of varying solubility:

1. The cross-sectional area of the vessels must be proportional, not only to the volume of the tissues but also to the solubility of the anaesthetic concerned in the tissues.
2. If two anaesthetics of different solubility are to be represented, two versions of model are needed.
3. For a low solubility anaesthetic (Fig 2)
   * All the compartments are small
   * The pipes are represented as small because the low solubility of anaesthetic is less carried by given blood flow
   * To achieve equilibrium for least soluble of anaesthetic small quantity of anaesthetic has to go in to the system

(Fig 2)

4. For a high solubility anaesthetic (Fig 3)
   * All the compartments are large
   * The pipes are represented as larger because the high solubility of anaesthetic is more carried by given blood flow
   * To achieve equilibrium for high solubility of anaesthetic large quantity of anaesthetic has to go in to the system through the same sized ventilation pipe and therefore it takes longer time.
III. The concentration and second gas effects:

A. The concentration effect

1. The higher the inspired concentration, the more rapid the rise in alveolar concentration.

   Explanations:
   
   a. The concentrating effect: As gas is taken up by the blood, the remaining gas is present in a smaller volume, which diminishes the change in partial pressure that might otherwise be expected.

   b. The ventilation effect: As gas is taken up, more gas is brought in to the lungs to replace the lost volume, which both increases $V_{alveolar}$ and lowers the influence of uptake on reducing $F_{alveolar}$

2. Examples:

   Example 1: We instantaneously fill a 4 liter box (the lungs) with 50% nitrous oxide. The concentrating effect tells us that if half of the nitrous oxide is taken up (1 liter), we will have 1 liter of nitrous in a 3 liter box, for a concentration of 33%, not 25% as might be expected. If we consider the ventilation effect: the 1 liter of nitrous taken up will be replaced with another liter of 50% nitrous (the inspired gas), which will add another .5 liters of nitrous to the box. This results in 1.5 liters of nitrous in a 4 liter box, for a final concentration of 38%. (Fig 4)
Example 2: We start with a 4 liter box the lungs filled with 100% nitrous oxide (don’t try this), connected to gas supply that is also 100% nitrous oxide. No matter how much nitrous is taken up, the concentration cannot fall below 100%.

3. The concentration effect is only significant for gases present in high concentrations (e.g. nitrous). It is negligible for the potent agents.

B. The second gas effect (applies to the effects of nitrous oxide on the uptake of another gas):

1. Analogous to the concentration effect, but relates instead to the use of a potent agent concurrently with a second gas present in large quantity, usually nitrous oxide.
2. The higher the inspired concentration of the second gas (nitrous), the more rapid the rise in alveolar concentration. Explanations:
   a. The concentrating effect: As the second gas (nitrous) is taken up in significant volumes, all remaining gases (including the potent agent, which is the "first" gas) are concentrated in the remaining volume.
   b. The ventilation effect: As the second gas is taken up in significant volumes, additional fresh gas in brought into the lungs. This increases $V_{alveolar}$, which increases the rate of rise of anesthetic concentration.
3. Example:
   We instantaneously fill a 4 liter box with 50% nitrous oxide and 40 cc (1%) of isoflurane. The concentration effect tells us that if half of the nitrous oxide is taken up, the concentration of isoflurane will increase from 1% to 1.33% (40cc / 3 liters). The ventilation effect tells us that another liter of fresh gas, containing 500 mls of nitrous, and 10mls of isoflurane will be brought into the lungs, resulting in a concentration of 1.25%. Although the ventilation effect has lowered the concentration of isoflurane slightly, it has increased $V_{alveolar}$, which will more than offset the change. (Fig 5)
IV. Changes in Ventilation and Circulation
   A. Changes in Ventilation
      1. Increasing ventilation increases the rate of rise of alveolar concentration.
      2. The change is greatest for more soluble anesthetics:
         A doubling of ventilation increases the methoxyflurane concentration at 10 minutes of
         anesthetic administration by 75%, increases the isoflurane concentration by 18%, and
         increases the desflurane concentration by only 6%. (Fig 6)
3. Anesthetics depress $V_{\text{alveolar}}$, which slows the rate of rise of the alveolar concentration. However, the concentration only stops rising towards the inspired concentration when the patient stops breathing entirely.
   a. This depression is sets an upper limit on the alveolar concentration which can be obtained in a spontaneously breathing patient. For halothane, patients stop breathing entirely when the concentration in the brain reaches 2.5%.
   b. There is a delay caused by the time required for transport of the anesthetic from the lungs to the brain, and so in the first few minutes, patients may breath spontaneously with alveolar concentrations higher than 2.5%.

4. Hyperventilation reduces cerebral blood flow.
   The effect on induction time is function of solubility:
   a. For nitrous oxide, the reduction in cerebral blood flow more then compensates for the increased rate of rise of the alveolar concentration with hyperventilation, so induction time is actually slower in the hyperventilating patient (remember hyperventilation didn't help that much in the first place).
   b. For halothane, the reduction in cerebral blood flow almost exactly balances the effect of the increased rate of rise of alveolar concentration.
   c. For ether, the increased rate of rise of alveolar concentration more than compensates for the reduction in cerebral blood flow, so induction is faster.

B. Changes in Cardiac Output
   1. Increasing cardiac output lowers the alveolar anesthetic concentration, and slows the rate of rise of alveolar anesthetic concentration.
   2. The change is greatest for more soluble anesthetics (as was the influence of changes in ventilation)
      a. Nitrous rises quite fast, regardless of cardiac output.
      b. The potent agents are highly affected by cardiac output, with halothane the most affected, desflurane the least.
   3. If the cardiac output is lowered, the effect depends on the distribution of cardiac output.
      a. If the cerebral circulation is less, then induction will be slower, even though the alveolar concentration will rise more quickly.
      b. If the cardiac output is reduced, but cerebral circulation is maintained (the usual situation), then the alveolar concentration will rise more rapidly, and this rapid rise will be quickly reflected in the brain anesthetic concentration.
      c. Thus, patients in hypovolemic shock will have very rapid rises in cerebral anesthetic concentration.
      d. Patients in septic shock may have fairly slow rises in cerebral anesthetic concentration.
   4. Anesthetics may reduce cardiac output, which will increase the rate of rise of anesthetic concentration.
V. Recovery from an inhalational anesthetic

A. Overall, it is the reverse process of the anesthetic induction:
   1. The rate of fall in alveolar concentration determines anesthetic recovery.
   2. Increased solubility slows recovery
   3. Increased cardiac output slows recovery
   4. Increasing ventilation may help the recovery from potent agents, but with hyperventilation, the increased rate of fall in alveolar concentration is nearly balanced by the reduced cerebral blood flow.
   5. Hyperventilation probably delays recovery from nitrous oxide, because there is little improvement in pulmonary wash-out, while wash-out from the brain is delayed from the reduced cerebral blood flow.
   6. There is no concentration effect on emergence, as there was on induction, because the gas in high concentrations (nitrous oxide) is not being drawn from an infinite reservoir, as it was on induction.

B. Diffusion Hypoxia
   1. Related to the large outpouring of nitrous oxide diluting the inspired oxygen at the conclusion of a case.
   2. Only a risk for the first 3-5 minutes after terminating the nitrous oxide.
   3. Easily managed (and now almost never seen) with supplemental oxygen for a few minutes following termination of the nitrous.

C. The low partial pressure of anesthetics in most peripheral tissues (especially fat) means that during the initial recovery from anesthesia, anesthetic is continuing to pass into these tissues, rather than being released from these tissues. Thus, recovery is enhanced by redistribution of the inhalational anesthetic into fat and muscle, just like it is for most intravenous anesthetics.

References:
2. Read Eger's The Pharmacology of Inhaled Anesthetics.