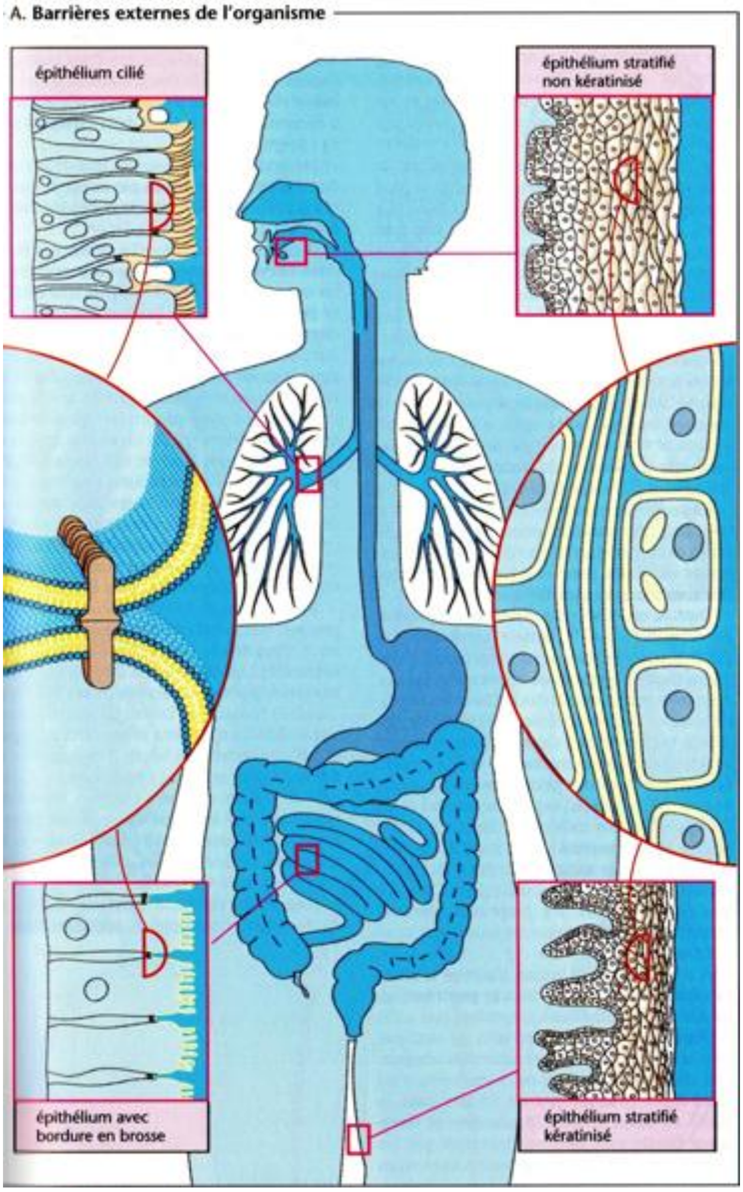
PK phase

While Liberation was about the drug leaving its physical form, Pharmacokinetics (PK) is about the body taking control. It can be framed as the ADME process. It's essentially a story of how a molecule survives the body's defense systems to reach its target.

1. Absorption: The Membrane Hurdle

Absorption is the passage of the drug from the site of administration into the general circulation.

- The Biological Challenge: To be absorbed, the drug must cross cell membranes (remember the lipid bilayer).



- Mechanisms:
  - Passive Diffusion: The most common (moves down the concentration gradient).
  - Active Transport: Requires ATP and a carrier protein (crucial for some large biotech molecules).
  - Facilitated Diffusion: Uses a carrier but no energy.

1.1. The Chemistry of "The Crossing": Weak Acids and Bases

Most drugs are not neutral; they are either **weak acids** or **weak bases**. The body's various compartments have different pH levels (Stomach ≈1–2, Intestine ≈ 6–7, Blood ≈ 7.4). A drug can only cross the membrane if it is in its **non-ionized (uncharged)** form, as charged molecules are too polar to dissolve in the lipid bilayer.

We use the **Henderson-Hasselbalch equation** to calculate the ratio of ionized to non-ionized drug:

- **For a Weak Acid (HA):**

$$pH = pK_a + \log \frac{[A^-] \text{ (Ionized)}}{[HA] \text{ (Non-ionized)}}$$

- **For a Weak Base (B):**

$$pH = pK_a + \log \frac{[B] \text{ (Non-ionized)}}{[BH^+] \text{ (Ionized)}}$$

- **The "Biology" Logic:** If you have a weak acid like **Aspirin** (pKa ≈3.5) in the highly acidic stomach (pH ≈1.5), the equation shows that [HA] (the neutral form) will dominate. Because it is neutral, it passes easily through the gastric lining. Conversely, a weak base will become "trapped" in the stomach because it becomes heavily ionized (BH^+) in acidic conditions.

1.2. The Absorption of Biologics: A Different Strategy

The rules of simple diffusion often do not apply. **Biologics** (monoclonal antibodies, growth factors, enzymes) are "giants" compared to chemical drugs.

- **The Oral Impossibility:** Biologics are almost never given orally. Why? The stomach's **proteases** (like pepsin) digest them into amino acids. Furthermore, their high molecular weight makes crossing the intestinal epithelium via diffusion impossible.

- **The Lymphatic Route:** When a biologic is injected subcutaneously (SC), it is often too large to enter the blood capillaries directly. Instead, these molecules are absorbed into the **lymphatic system**. They travel through lymph nodes before eventually emptying into the blood via the thoracic duct.

- **Transcytosis:** In some cases, large proteins cross cell barriers via **vesicular transport** (endocytosis on one side, exocytosis on the other). This is a slow, energy-consuming process compared to the rapid diffusion of small molecules.

➢ **The concept of Bioavailability (F)**. If we give 100mg of a drug orally, but only 70mg reaches the blood, F = 0.7 (or 70%).

To assess Absolute Bioavailability (F), we compare the amount of drug that reaches the systemic circulation after a specific route of administration (like oral) to the amount that reaches the circulation after Intravenous (IV) injection. Since an IV dose bypasses all absorption barriers and the first-pass effect, its bioavailability is by definition 100% (F = 1).

Experimentally, we measure the drug's plasma concentration over time for both routes and plot them on a graph. The total exposure of the body to the drug is represented by the **Area Under the Curve (AUC)**. By calculating the ratio of the AUCs, adjusted for the dose given, we determine the fraction of the drug that actually reach the general blood stream. Mathematically, it is expressed as:

$$F = \frac{AUC_{oral} \times Dose_{IV}}{AUC_{IV} \times Dose_{oral}}$$

If the doses are identical, the formula simplifies to $F = \frac{AUC_{oral}}{AUC_{IV}}$.

F's values span between **0 and 1** (or 0% to 100%). A low F value usually indicates poor absorption in the gut or high degradation by the liver before the drug can reach its target.

💊 Application Example: Calculating F for "Drug X"

Scenario:

A pharmaceutical lab is testing a new analgesic, **Drug X**. To determine its bioavailability, they conduct two trials on the same group of volunteers:

1. **Trial A:** They administer **100 mg** of Drug X **orally**.
2. **Trial B:** They administer **50 mg** of Drug X via **IV injection**.

Experimental Results (Measured Data):

- The Area Under the Curve for the oral dose AUC_{oral} is **200 mg·h/L**.
- The Area Under the Curve for the IV dose AUC_{IV} is **400 mg·h/L**.

Biological Interpretation

After showing the math, ask your students: **"What happened to the other 75%?"**

This allows you to recap the previous concepts:

- **Incomplete Liberation:** Maybe the tablet didn't dissolve fully in the stomach.
- **Poor Absorption:** The molecule might be too hydrophilic or have an unfavorable pKa for the intestinal pH.
- **The First-Pass Effect:** Most likely, the liver "intercepted" and metabolized 75% of the drug before it ever reached the heart and the rest of the body.

➢ **Bioavailibilty of biologics**

1. The Oral Route: F≈ 0%

For biologics, the oral route is a "death trap."

- **Enzymatic Digestion:** The stomach and small intestine are designed to break down proteins into amino acids. Proteases like pepsin and trypsin destroy the drug before it's absorbed.
- **Size Constraint:** Even if a protein survived the acid, it is a "giant" (>150,000 Daltons for an IgG).

2. The SC/IM Route: The Lymphatic "Detour"

Since we can't give them orally, we inject them (Subcutaneous or Intramuscular). But even here, F is rarely 100%.

- **The Capillary Barrier:** Blood capillaries have tiny pores (fenestrae). Small molecules slip right in. Biologics are too large to fit.
- **The Lymphatic "Back Door":** Instead of entering the blood directly, biologics are picked up by the **Lymphatic Vessels**. These vessels have much larger openings.
- **The Consequence:** Because lymph moves much slower than blood, the **Tmax** (time to reach peak concentration) for biologics can be **days** (3–8 days for some antibodies) rather than minutes or hours.

3. Presystemic Degradation (The "Shadow" First-Pass)

Just as the liver has a "first-pass effect" for oral drugs, the injection site has a "presystemic" effect for biologics.

- **Tissue Peptidases:** While the biologic is sitting in the subcutaneous tissue waiting for a lymph vessel to pick it up, local enzymes can begin breaking it down.
- **Result:** This lowers the F value. For most monoclonal antibodies, F via the SC route is typically between **50% and 80%**.

4. Comparison Table for the Lecture

Route	**Bioavailability (F)**	**Why?**
Oral	**≈ 0%**	Proteolysis and massive molecular size.
Intravenous (IV)	**100%**	Bypasses all barriers; direct entry.
Subcutaneous (SC)	**50-80%**	Slow lymphatic transport + local degradation.
Inhalation	**Variable**	Large surface area but risk of alveolar macrophage "eating" the drug.

A High-Level Note for Biology Students: Immunogenicity

Mention that the "bioavailability" of a biologic can decrease over time in the *same* patient. If the body’s immune system recognizes the biologic as foreign, it creates **Anti-Drug Antibodies (ADAs)**. These ADAs bind to the drug and clear it from the system, effectively dropping the F and the Vd to zero.

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