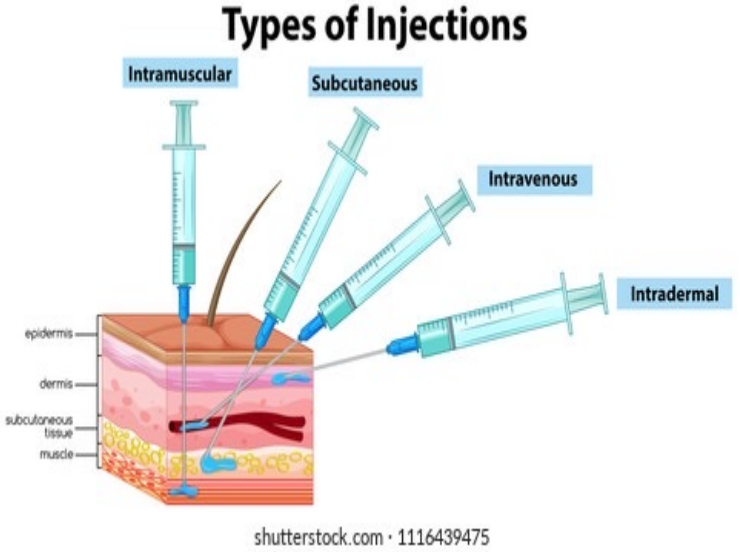

Routes of Administration and
Absorption Enhancement

Handling of Pharmaceutical Proteins Post-Production

- Protein formulations undergo extensive testing during development and formulation to **ensure their maximus stability and effectiveness**.
- In spite of all these efforts, pharmaceutical proteins **remain sensitive** to 'real life' handling and may readily show degradation reactions that obviously affect both efficacy and safety. →
- Set of instruction is generated for health professionals and patients about the conditions that should be maintained for the product, e.g., **storage temperature** window, **avoidance of shaking/shear**, **exposure to light.**
- As an example, the package insert of trastuzumab states: 'Swirl the vial gently to aid reconstitution. Trastuzumab may be sensitive to shear-induced stress, e.g., agitation or rapid expulsion from a syringe. DO NOT SHAKE' (FDA web site).

Routes of Administration
The Parenteral Route of Administration

- Parenteral administration is defined as administration via those routes **where a needle is used**, including intravenous (IV), intramuscular (IM), subcutaneous (SC), and intraperitoneal (IP) injections.
- It is Important to understand that the blood half-life of biotech products can vary over a wide range.
- **For example**, the circulation half-life of tissue plasminogen activator (t-PA) is a few minutes, while monoclonal antibodies reportedly have half- lives of a few days to weeks.



Routes of Administration
The Parenteral Route of Administration

- A simple way **to expand the mean residence** time for short half-life proteins is to switch from IV to IM or SC administration.
- But this may result in **slow uptake to blood compartment** and lower extent of absorption → this mean lower bioavailability.
- This may be due to:

1. **Increase in the residence time at the IM or SC** → increase in the exposure to inactivation reaction such as **peptidase**.
   - For instance, diabetics can become "insulin resistant" through high tissue peptidase activity.
   - The state of the tissue, for instance, the occurrence of pathological conditions, may be important as well.

2. **Differences in disposition**: Upon administration, the protein may reach the blood through the **lymphatics** or enter the blood circulation through **the capillary** wall at the site of injection.
   - **Lymphatic transport** takes time (**hours**), and uptake in the blood circulation is highly dependent on the injection site.
   - On its way to the blood, the lymph passes through draining lymph nodes, and contact is possible between lymph contents and cells of the immune system such as macrophages and B and T lymphocytes residing in the lymph nodes.

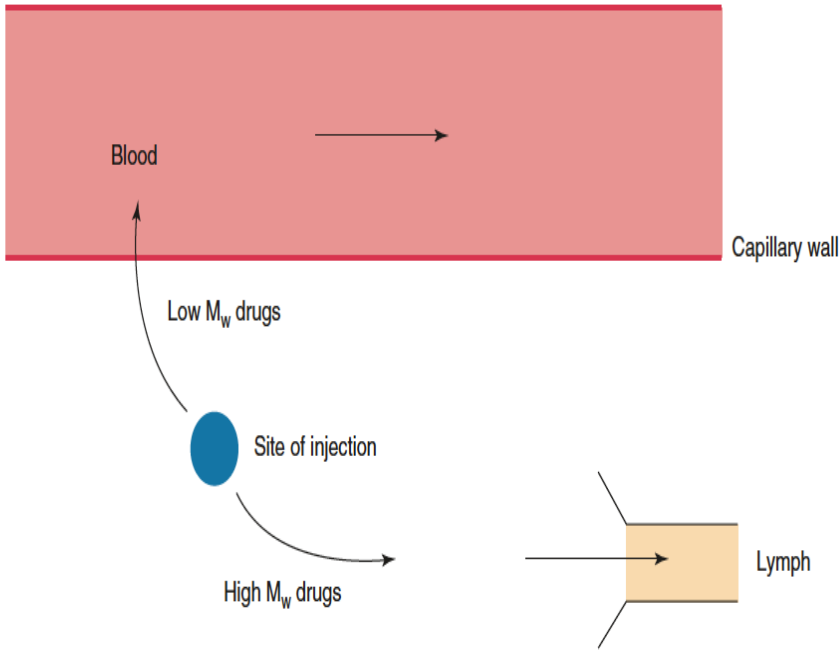


Figure 5.12 Routes of uptake of SC- or IM-injected drugs

Other Rout of Administration
The Oral Route of Administration

- For several reasons, e.g., ease of administration, patient friendliness and cost, alternative administration routes to the parenteral route would be welcome for the successful systemic delivery of recombinant proteins.
- **Oral Route:**
- Oral delivery of protein drugs would be preferable, because it is patient friendly and no intervention by a healthcare professional is necessary to administer the drug.
- Oral bioavailability, however, is usually **very low for proteins**.

The Oral Route of Administration

- The **two main reasons** for this failure of uptake are (why oral bioavailability is low):

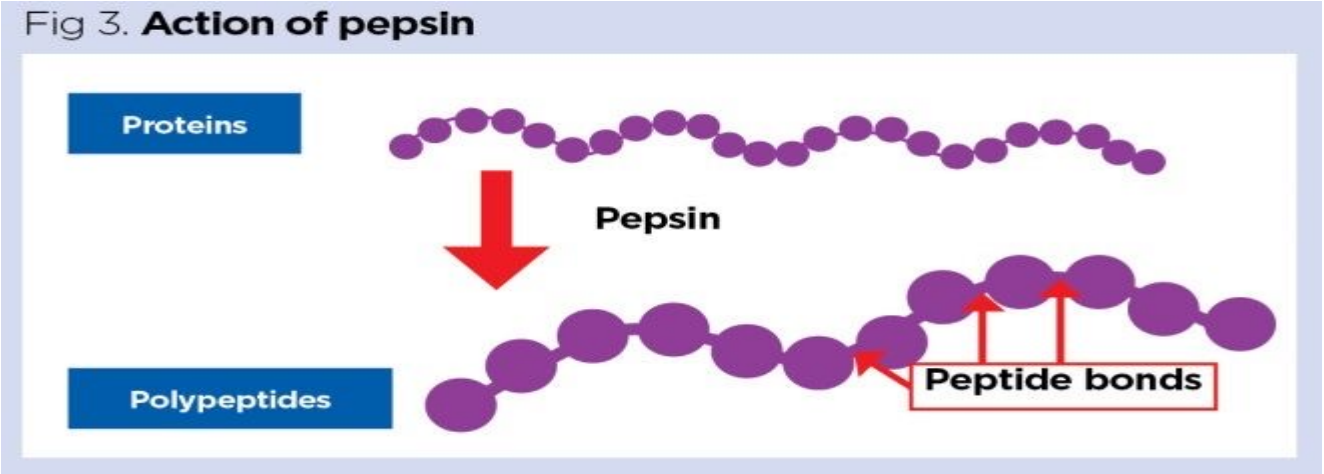
1. The **efficient enzymatic system** that breakdown the protein:
   - The human body has developed a very efficient system to break down proteins in our food to amino acids or di- or tripeptides.
   - These building stones for body proteins are **actively** absorbed for use wherever necessary in the body.
   - Enzymes such as pepsin, trypsin and other are found in the GI tract.

The Oral Route of Administration

I. In the **stomach**, **pepsins,** a family of aspartic proteases, are secreted.

- They are particularly active between **pH 3 and 5** and **lose activity** at higher pH values.
- Pepsins are endo-peptidases capable of **cleaving peptide bonds distant from the ends** of the peptide chain.
- They preferentially cleave peptide bonds between two hydrophobic amino acids (such as glycine (Gly), alanine (Ala), valine (Val)).

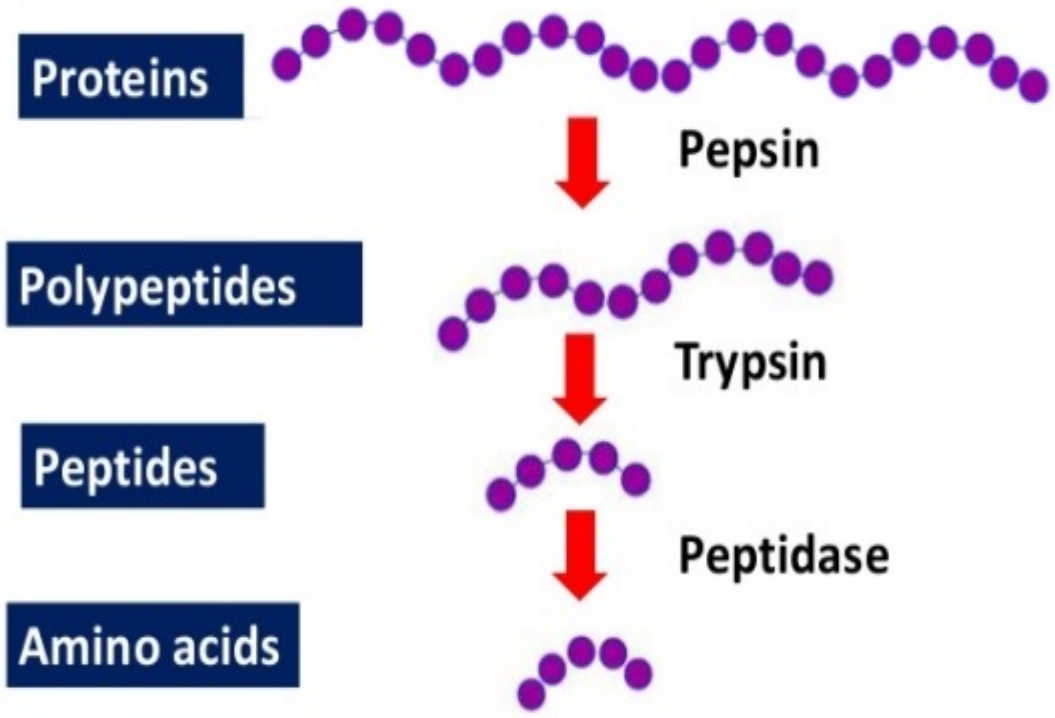
Fig 3. **Action of pepsin**



II. **Other endopeptidases** are active in the gastrointestinal tract at **neutral pH** values, e.g., trypsin, chymotrypsin, and elastase.

III. **Exopeptidases**, proteases degrading peptide chains from their ends, are present as well.

- Examples are carboxypeptidase A & B.
- In the GI lumen the proteins are cut into fragments that effectively further break down to **amino acids**, di and tripeptides by brush border, and cytoplasmic **proteases of the enterocytes**.



The Oral Route of Administration

- Second Reason for low oral bioavailability:

2. Permeability:

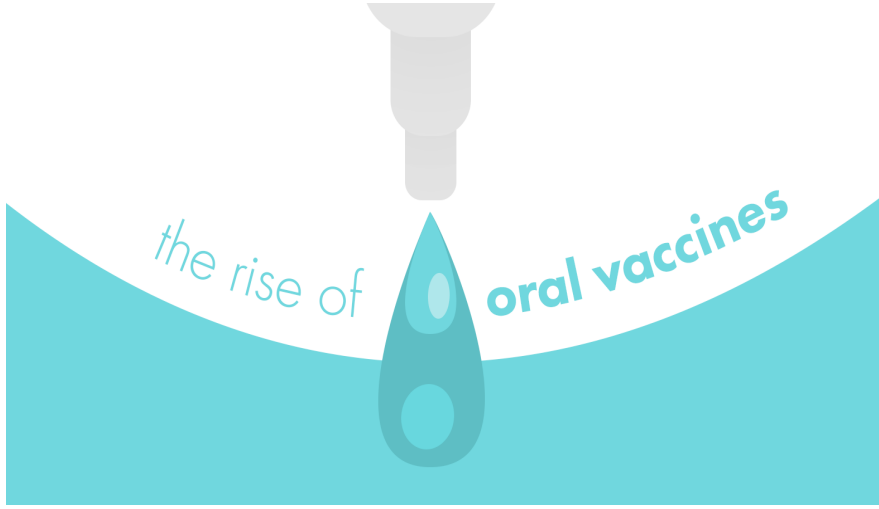
  - **High molecular** weight molecules **do not readily penetrate** the intact and mature epithelial barrier.
  - **Active transport** of **<u>intact</u>** therapeutic recombinant proteins over the GI-epithelium has **not been described yet**.

- This leaves **paracellular transfer** and **intracellular endocytosis** into the enterocyte membrane as the sole pathway for mass transfer.

The Oral Route of Administration

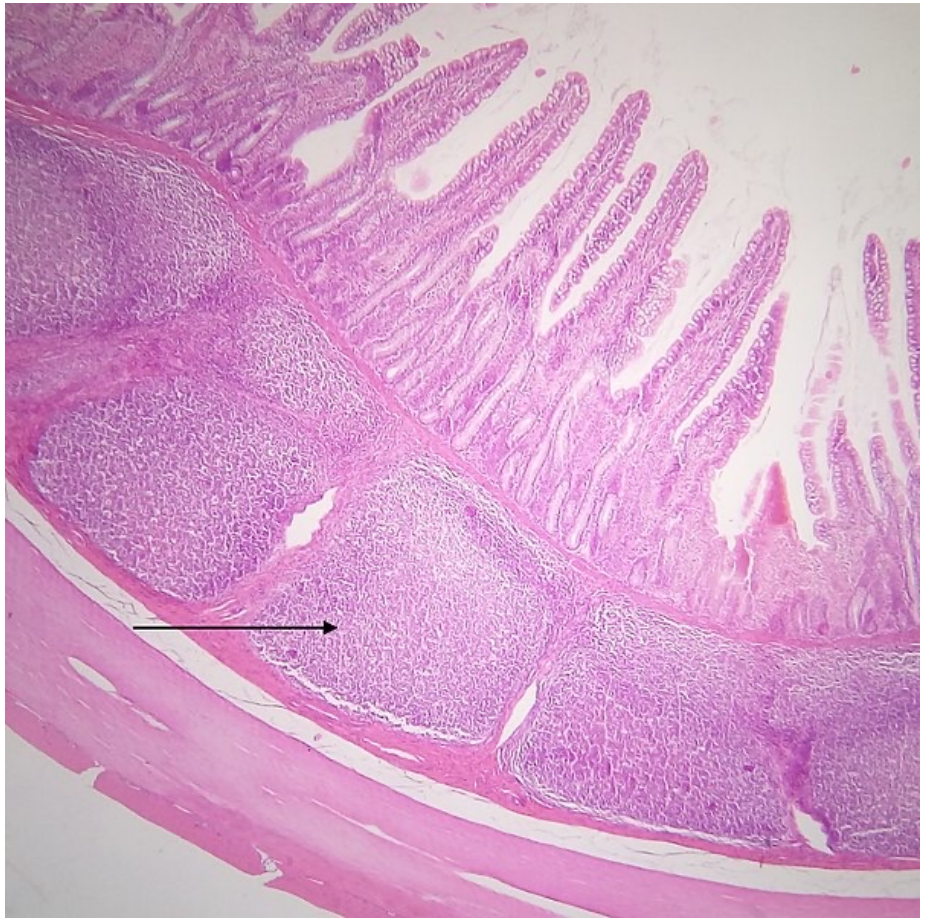
- The above analysis leads to the conclusion that nature, unfortunately, does not allow us to use the oral route of administration for therapeutic proteins if high (or at least constant) bioavailability is required.
- However, for the category of **oral vaccines**, the above - mentioned hurdles of degradation and permeation are not necessarily prohibitive. Because:→

1. For oral immunization, **only a (small)** fraction of the antigen (protein) has to reach its target site to illicit an immune response.



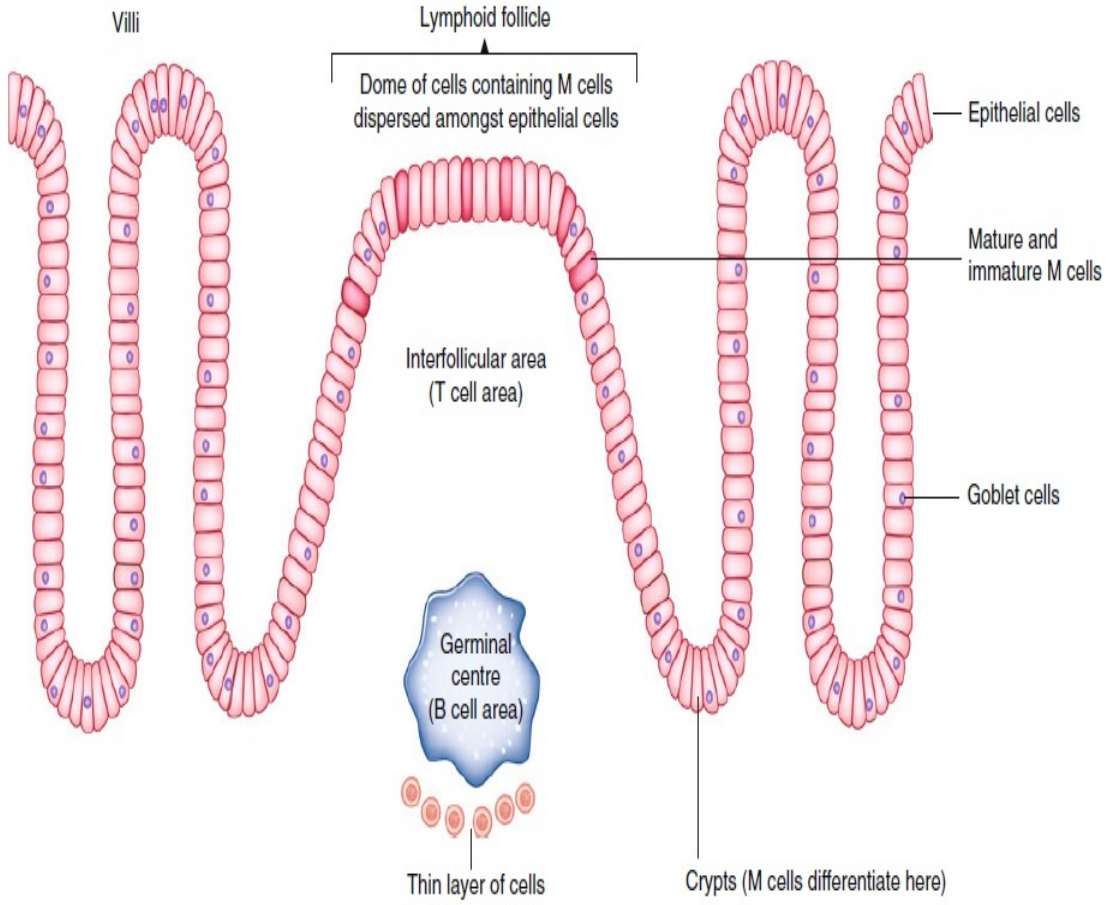
The Oral Route of Administration

2. The target cells are lymphocytes and antigen presenting accessory cells located in **Peyer's patch.**
   - These Peyer's patches are macroscopic identifiable follicular structures located in the wall of the GI tract.
   - Peyer's patches are overlaid with microfold (M) cells that separate the luminal contents from the lymphocytes.



The Oral Route of Administration

- These M cells have little lysosomal degradation capacity and allow for **antigen sampling by the underlying lymphocytes**.
- Moreover, mucus-producing goblet cell density is reduced over Peyer's patches. This reduces mucus production and facilitates access to the M cell surface for luminal contents.



The Oral Route of Administration

- Attempts to improve antigen delivery via the Peyer's patches and to enhance the immune response are made by using microspheres, liposomes or modified live vectors, such as attenuated bacteria and viruses.