

Pharmaceutical Biotechnology

(Introduction)

Biotechnology encompasses any **techniques** that use **living organisms** like micro-organisms, isolated mammalian cells in the production or modification of products having beneficial use.

The **classic example** of biotechnologic drugs was **proteins** obtained from **recombinant DNA** (rDNA) technology.

Biotechnology now encompasses the use of tissue culture, living cells or cell enzymes to make a defined product.

rDNA and **monoclonal antibody** (mAb) technologies have provided exciting opportunities for the development of more pharmaceuticals and approaches to the **diagnosis, treatment, and prevention** of a disease.

Also, it is:

Any technique that uses living organisms or substances from those organisms to make or modify a product, to improve plants or animals or to develop microorganisms for specific uses (**Organismic Biotechnology**).

Cloning is an example of organismic biotech, which is a process of producing a new organism from cells or tissues of existing organism.



In 1997 cloned sheep – “Dolly”

Molecular Biotechnology

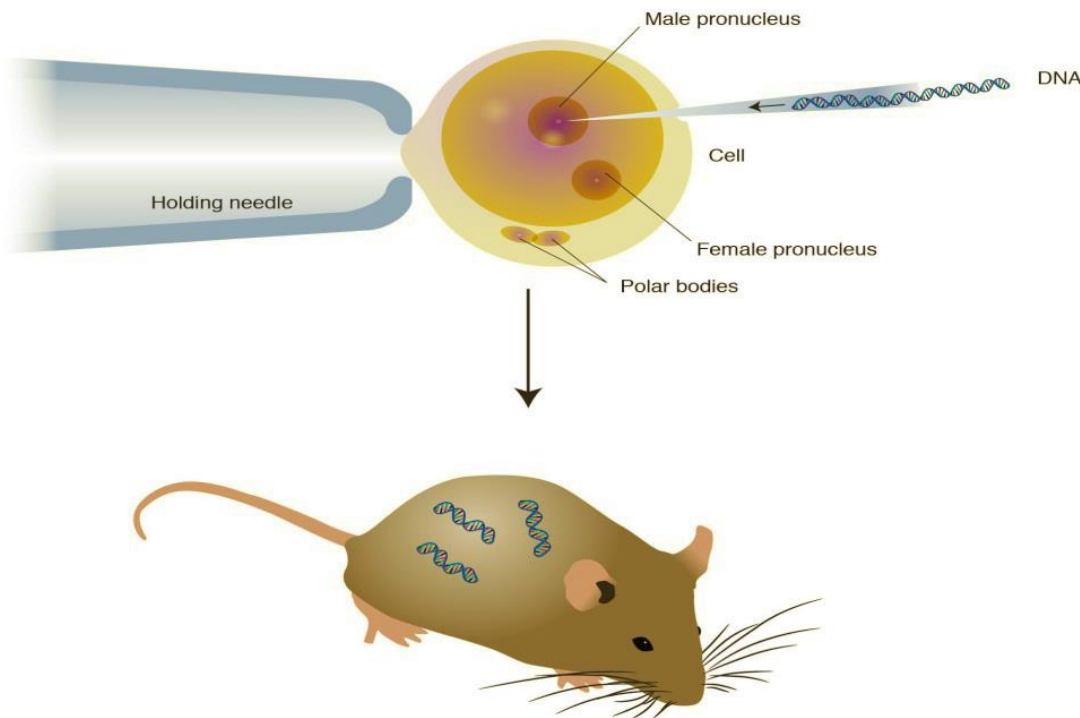
Changing the genetic makeup of an organism or altering the structure or parts of cells.

The **genetic engineering** is an example.

Transgenic

Results of Genetic Engineering are said to be “transgenic”.

Genetic material in an organism has been altered.



Applications

- Medicine
- Agriculture
- Environment
- Food

Medicine

Some new developments delve into the hereditary material of humans known as **gene therapy**.

Biopharmaceutical drug or vaccine developed through biotechnology.

The first of the novel biotechnologic pharmaceuticals were **proteins**, but eventually an increasing number will be **smaller molecules**, discovered through biotechnology-based methods that will determine just how proteins work.

Biosimilars, also known as follow-on biologics, are biologic medical products whose active drug substances are made by a living organism or derived from a living organism by means of recombinant DNA or controlled gene expression methods.

Biotechnology Products are **different** from others?

Synthetic drugs are **small molecules** with relatively easy synthesis like Aspirin.

Extraction Biologics are complex and **large molecules**, may obtained from animal source like Insulin, Heparin and Calcitonin or human source like HGH, Coagulation Factors and Albumin.

Biotechnologic drugs or **Biopharmaceuticals** are complex and large molecules, may be obtained using different techniques with better yield & more safe.

By use of micro-organisms (procaryotic or eucaryotic) genetically modified for production of these complex molecules.

After purification, the products are used in human or animal therapeutics.



Formulation of Biotech Products **(Biopharmaceutical Considerations)**

Dr. Ahmed Faisal

MICROBIOLOGICAL CONSIDERATIONS

Sterility

Most proteins are administered **parenterally** and have to be sterile.

In general, proteins are **sensitive** to heat and other regularly used sterilization treatments; they cannot withstand autoclaving, gas sterilization, or sterilization by ionizing radiation.

Consequently, sterilization of the end product is not possible.

Therefore, protein pharmaceuticals have to be assembled under **aseptic conditions**, following the established and evolving rules in the pharmaceutical industry for aseptic manufacture.

Equipment and **excipients** are treated separately and autoclaved or sterilized by dry heat ($>160\text{ }^{\circ}\text{C}$), chemical treatment, or gamma radiation to minimize the bioburden.

Pre-filters remove the bulk of the bioburden and other particulate materials.

The final “sterilizing” step before filling the vials is **filtration** through 0.2 or 0.22 μm membrane filters.

Assembly of the product is done in rooms that contain **laminar airflow** that is filtered through **HEPA** (high efficiency particulate air) filters.

The **human factor** is a major source of contamination.

Well-trained operators wearing **protective cloths** (face masks, hats, gowns, gloves, or head-to-toe overall garments) should operate the facility.

Regular exchange of filters, regular validation of HEPA equipment, and thorough cleaning of the room plus equipment are **critical factors** for success.

Viral Decontamination

As **recombinant DNA products** are grown in microorganisms, these organisms **should be tested for viral contaminants**, and appropriate measures should be taken if viral contamination occurs.

In the rest of the manufacturing process, no (unwanted) viral material should be introduced.

Excipients with a certain risk factor such as blood-derived human serum albumin should be carefully tested before use, and their presence in the formulation process should be minimized.

Pyrogen Removal

Pyrogens are compounds that induce **fever**.

Exogenous pyrogens (pyrogens introduced into the body, not generated by the body itself) can be derived from bacterial, viral, or fungal sources.

Bacterial pyrogens are mainly endotoxins shed from **gram-negative bacteria**.

They are **lipopolysaccharides**.

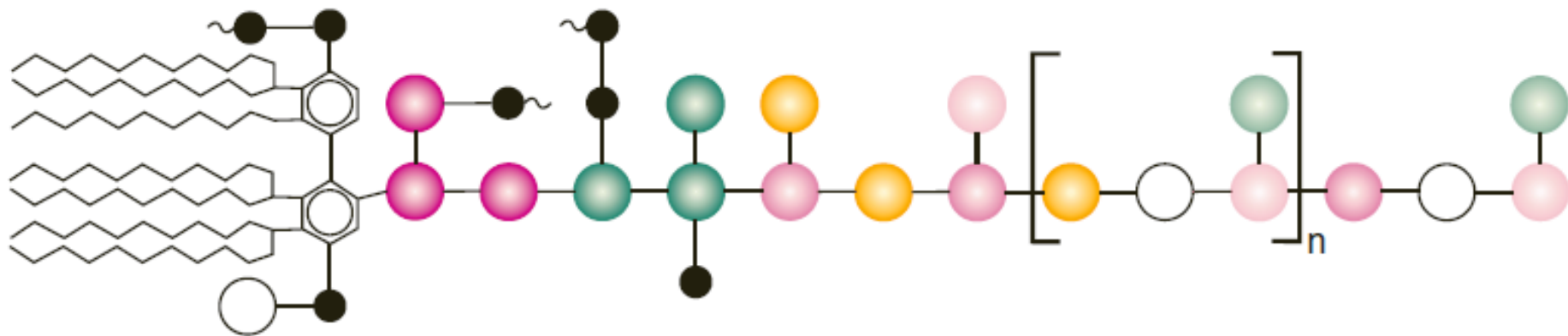
This conserved structure in the full array of thousands of different endotoxins is the **lipid-A** moiety.

Another general property shared by endotoxins is their high, **negative electrical charge**.

Their tendency to aggregate and to form large units with MW of over 10^6 in water and their tendency to adsorb to surfaces indicate that these compounds are **amphipathic** in nature.

They are **stable under standard autoclaving** conditions but break down when heated in the dry state.

For this reason equipment and container are treated at temperatures above $160\text{ }^{\circ}\text{C}$ for prolonged periods (e.g., **30 min dry heat at $250\text{ }^{\circ}\text{C}$**).



| Lipid a | Core | O-specific antigen chain |
|--------------------|------|--------------------------|
| Lipopolysaccharide | | |

Generalized structure of endotoxins

Pyrogen removal of recombinant products derived from bacterial sources should be an **integral** part of the preparation process.

Ion exchange chromatographic procedures (utilizing its negative charge) can effectively reduce endotoxin levels in solution.

Excipients used in the protein formulation should be essentially endotoxin-free.

For solutions (**water for injection**) should be “freshly” distilled or produced by reverse osmosis.

The **aggregated endotoxins** cannot pass through the reverse osmosis membrane.

Removal of endotoxins immediately before filling the final container can be accomplished by using **activated charcoal** or other materials with large surfaces offering hydrophobic interactions.

Endotoxins can also be inactivated on **utensil surfaces** by **oxidation** (e.g., peroxide) or dry heating (e.g., 30 min dry heat at 250 °C).



EXCIPIENTS

USED IN PARENTERAL FORMULATIONS OF BIOTECH PRODUCTS

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TYPES OF EXIPIENTS

- Solubility enhancers
- Anti-adsorption and anti-aggregation agents
- Buffer components
- Preservatives and Antioxidants
- Osmotic agents

Solubility Enhancers

Proteins, in particular those that are **non-glycosylated**, may have a tendency to **aggregate** and **precipitate**.

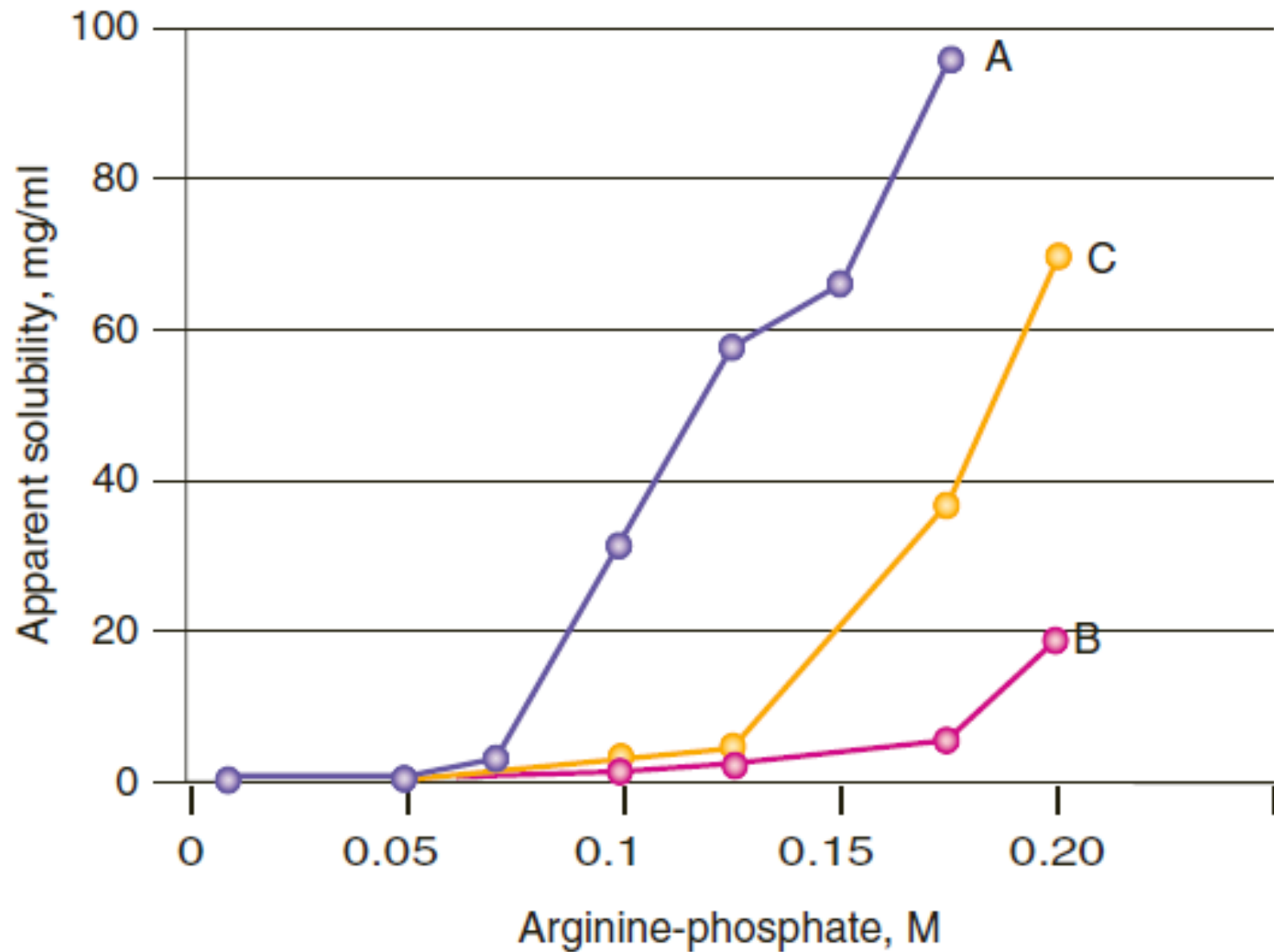
Approaches that can be used to **enhance solubility** include selection of the proper **pH** and **ionic strength** conditions.

Addition of **amino acids** such as **lysine** or **arginine** used to solubilize tissue plasminogen activator, **t-PA** (alteplase) or **surfactants** such as **sodium dodecyl sulfate** to solubilize non-glycosylated **IL-2** can also help to increase the solubility.

Aggregation is physical in nature, based on hydrophobic and/or electrostatic interactions between molecules.

However, aggregation based on the formation of covalent bridges between molecules through disulfide bonds and ester or amide linkages.

In those cases, proper conditions should be found to **avoid** these chemical reactions.



Effect of arginine on type I and type II alteplase at pH 7.2 and 25 °C.
(A) type I alteplase, (B) type II alteplase, (C) 50:50 mixture of type I and type II alteplase

Anti-adsorption and Anti-aggregation Agents

Anti-adsorption agents are added to reduce adsorption of the active protein to interfaces.

Some proteins tend to expose hydrophobic sites, normally present in the core of the native protein structure when an interface is present.

These interfaces formed between the aqueous phase and utensils used to administer the drug (e.g., catheter, needle).

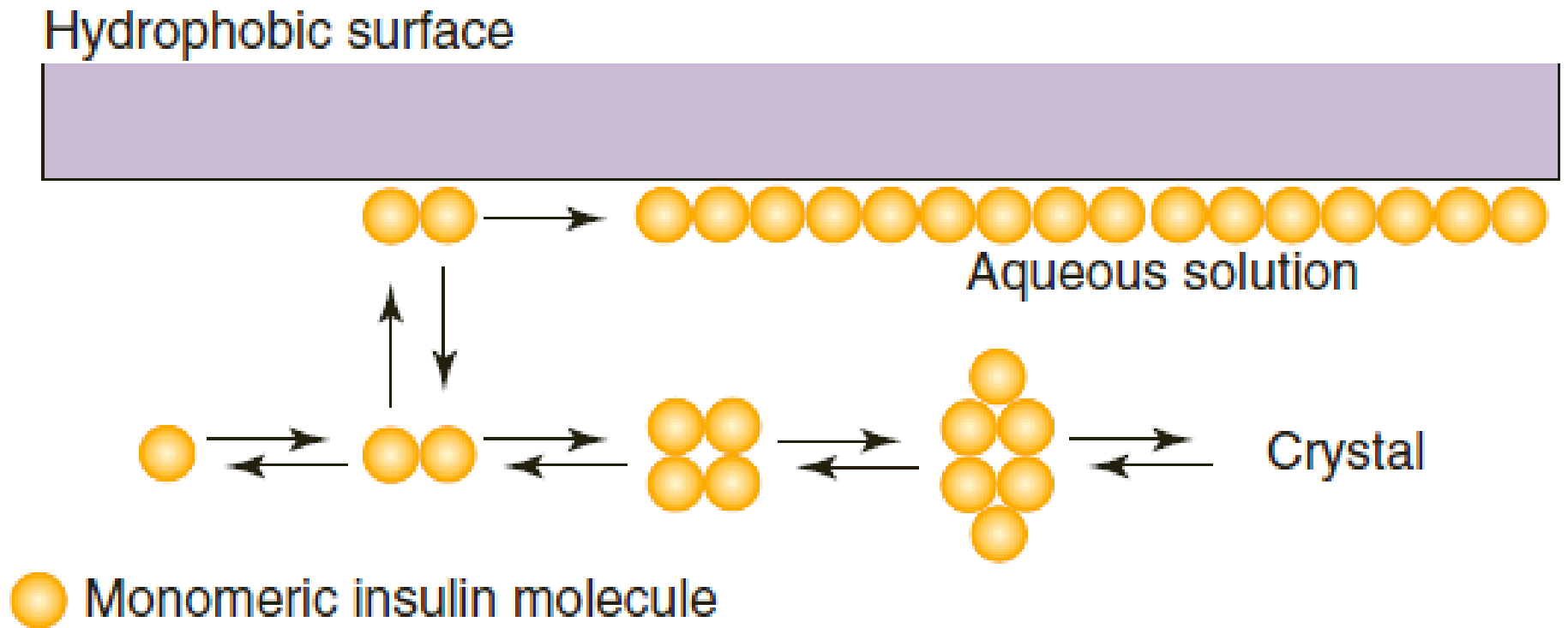
These adsorbed, partially unfolded protein molecules form aggregates, leave the surface, return to the aqueous phase, form larger aggregates, and precipitate.

Native insulin in solution is monomeric, dimeric, tetrameric, and hexameric forms.

The relative abundance of the different **aggregation states** depends on the **pH, insulin concentration, ionic strength**, and specific **excipients** (e.g., Zn^{2+} and phenol).

It has been suggested that the **dimeric** form of insulin **adsorbs** to **hydrophobic interfaces** and subsequently forms larger aggregates at the interface.

This explains why anti-adhesion agents can also act as anti-aggregation agents.



Reversible self-association of insulin, its adsorption to the hydrophobic interface, and irreversible aggregation in the adsorbed protein film.

Albumin has a strong tendency to adsorb to surfaces and is therefore added in relatively high concentrations (e.g., 1 %) to protein formulations as an **anti-adhesion** agent.

Albumin **competes** with the therapeutic protein for binding sites and supposedly **prevents adhesion** of the therapeutically active agent by a combination of its binding tendency and abundant presence.

Insulin is one of the many proteins that can form fibrillar precipitates (long rod-shaped structures).

Low concentrations of **phospholipids** and **surfactants** have been shown to exert a **fibrillation-inhibitory** effect.

Apart from albumin, **surfactants** can also prevent adhesion to interfaces and precipitation.

These molecules readily adsorb to hydrophobic interfaces with their own hydrophobic groups and render this interface hydrophilic by exposing their hydrophilic groups to the aqueous phase.

Buffer Components

Buffer selection is an important part of the formulation process, because of the pH dependence of **protein solubility** and physical and chemical **stability**.

Buffer systems regularly encountered in biotech formulations are **phosphate**, **citrate**, and **acetate**.

Even short, temporary **pH changes** can cause **aggregation**, for example, during the freezing step in a freeze-drying process, when one of the buffer components is crystallizing and the other is not.

In a phosphate buffer, Na_2HPO_4 **crystallizes faster** than NaH_2PO_4 , this causes a pronounced drop in pH during the freezing step.

Preservatives and Antioxidants

Methionine, cysteine, tryptophan, tyrosine, and histidine are amino acids that are readily **oxidized**.

Proteins rich in these amino acids are liable to oxidative degradation.

Replacement of oxygen by inert **gases** in the vials helps to **reduce oxidative stress**.

Moreover, the addition of antioxidants such as **ascorbic acid** or **acetylcysteine** can be considered.

However, ascorbic acid can act as an **oxidant** in the presence of a number of heavy metals.

Certain proteins are formulated in containers designed for multiple injection schemes.

After administering the first dose, contamination with microorganisms may occur, and **preservatives** are needed to **minimize growth**.

Usually, these preservatives are present in concentrations that are **bacteriostatic** rather than bactericidal in nature.

Antimicrobial agents mentioned in the USP are phenylmercuric nitrate, phenol, benzyl alcohol, and chlorobutanol.

Osmotic Agents

Saline and mono- or di- saccharide solutions are commonly used.

These excipients may not be inert; they may **influence** protein structural **stability**.

For example, **sugars** and **polyhydric alcohols** can stabilize the protein structure through the principle of “preferential exclusion”.

These additives (water structure promoters) enhance the interaction of the solvent with the protein and are themselves excluded from the protein surface layer; the protein is **preferentially hydrated**.

This phenomenon can be monitored through an **increased thermal stability** of the protein.

Unfortunately, a **strong** “preferential exclusion” effect enhances the tendency of proteins to **self-associate**.



DELIVERY OF PROTEINS

(ROUTES OF ADMINISTRATION)

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The Parenteral Route of Administration

Parenteral administration is here defined as administration via those routes where a **needle** is used, including intravenous (IV), intramuscular (IM), subcutaneous (SC), and intraperitoneal (IP) injections.

It suffices here to state 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.

Obviously, one reason to develop modified proteins through site-directed mutagenesis is to **enhance circulation half-life**.

A simple way to **expand the mean residence time** for short half-life proteins is to switch from IV to IM or SC administration.

One should realize that by doing that, changes in **disposition** may occur, with a significant impact on the therapeutic performance of the drug.

These changes are related to (1) the prolonged residence time at the IM or SC site of injection compared to IV administration and the enhanced exposure to degradation reactions (peptidases) and (2) differences in disposition.

Regarding point 1: Prolonged residence time at the IM or SC site of injection and the enhanced exposure to degradation reactions.

For instance, diabetics can become “insulin resistant” through high tissue peptidase activity.

Other factors that can contribute to absorption variation are related to differences in **exercise** level of the muscle at the injection site and also **massage** and **heat** at the injection site.

The state of the tissue, for instance, the occurrence of **pathological conditions**, may be important as well.

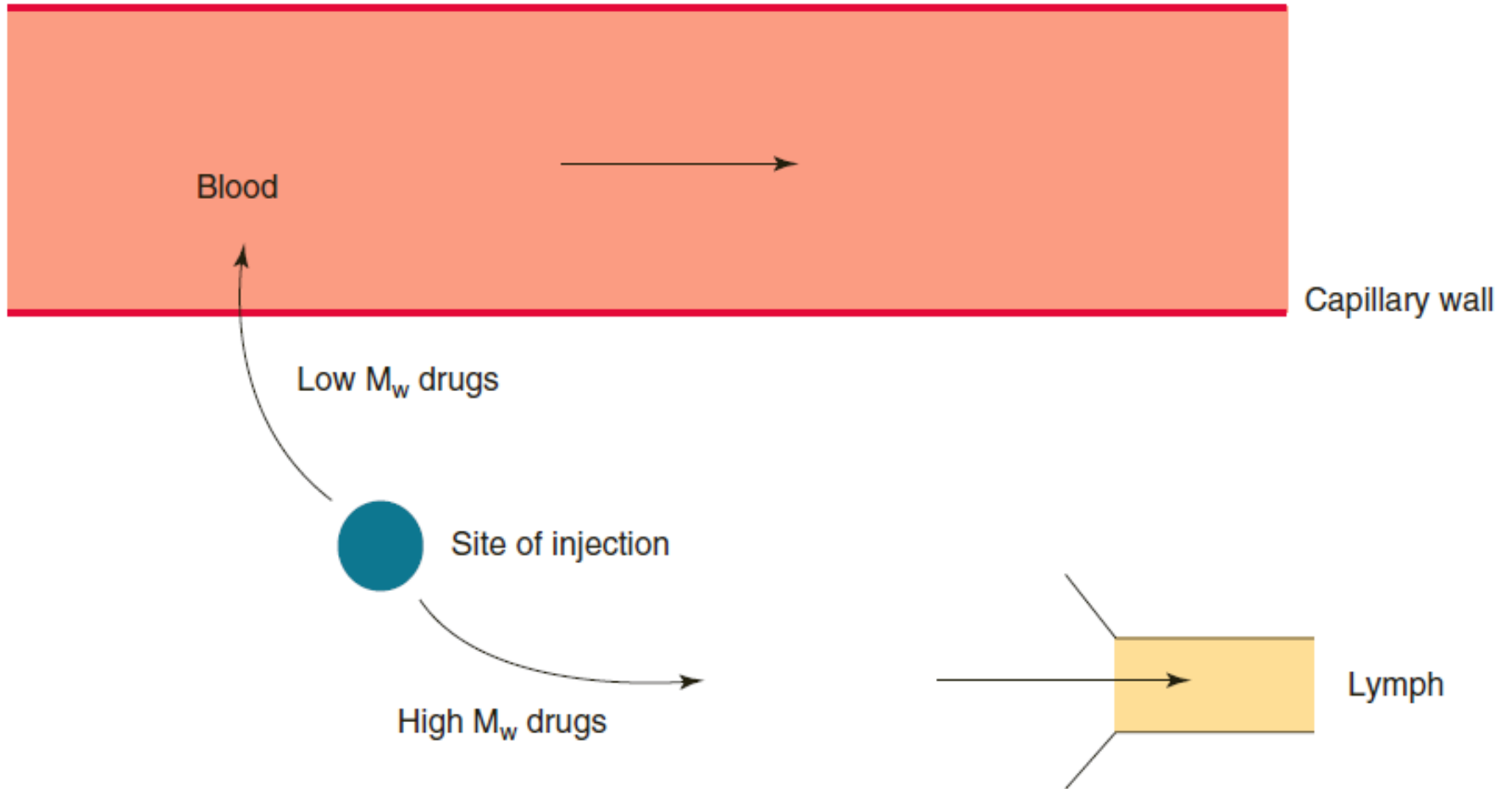
Regarding point 2: Differences in disposition.

Upon administration, the protein may be transported to the blood through the **lymphatics** or may enter the blood circulation through the **capillary wall** at the site of injection.

The fraction of the administered dose taking this lymphatic route is **molecular weight** dependent.

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.



Routes of uptake of SC- or IM-injected drugs.

The Oral Route of Administration

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.

The two main reasons for this failure of uptake are:

- (1) Protein degradation in the gastrointestinal (GI) tract.**
- (2) Poor permeability of the wall of the GI tract in case of a passive transport process.**

Regarding point 1: Protein degradation in the GI tract.

The human body has developed a very efficient system to break down proteins in our food to amino acids or di- or tri-peptides.

These building stones for body proteins are actively absorbed for use wherever necessary in the body.

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 **endopeptidases** capable of cleaving peptide bonds **distant from the ends** of the peptide chain.

They preferentially cleave peptide bonds **between two hydrophobic amino acids**.

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

They have different peptide bond cleavage characteristics that more or less complement each other.

Exopeptidases, proteases degrading peptide chains from their **ends**, are present as well. Examples are **carboxypeptidase A** and **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.

Regarding point 2: Permeability.

High molecular weight molecules do not readily penetrate the intact and mature epithelial barrier if diffusion is the sole driving force for mass transfer.

Their diffusion coefficient decreases with increasing molecule size.

Active transport of intact therapeutic recombinant proteins over the GI-epithelium has not been described yet.

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.

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

The target cells are **lymphocytes** and **antigen presenting** accessory cells located in Peyer's patches.

The B-lymphocyte population includes cells that produce secretory **IgA antibodies**.

These Peyer's patches are macroscopically identifiable follicular structures located in the wall of the gastrointestinal tract.

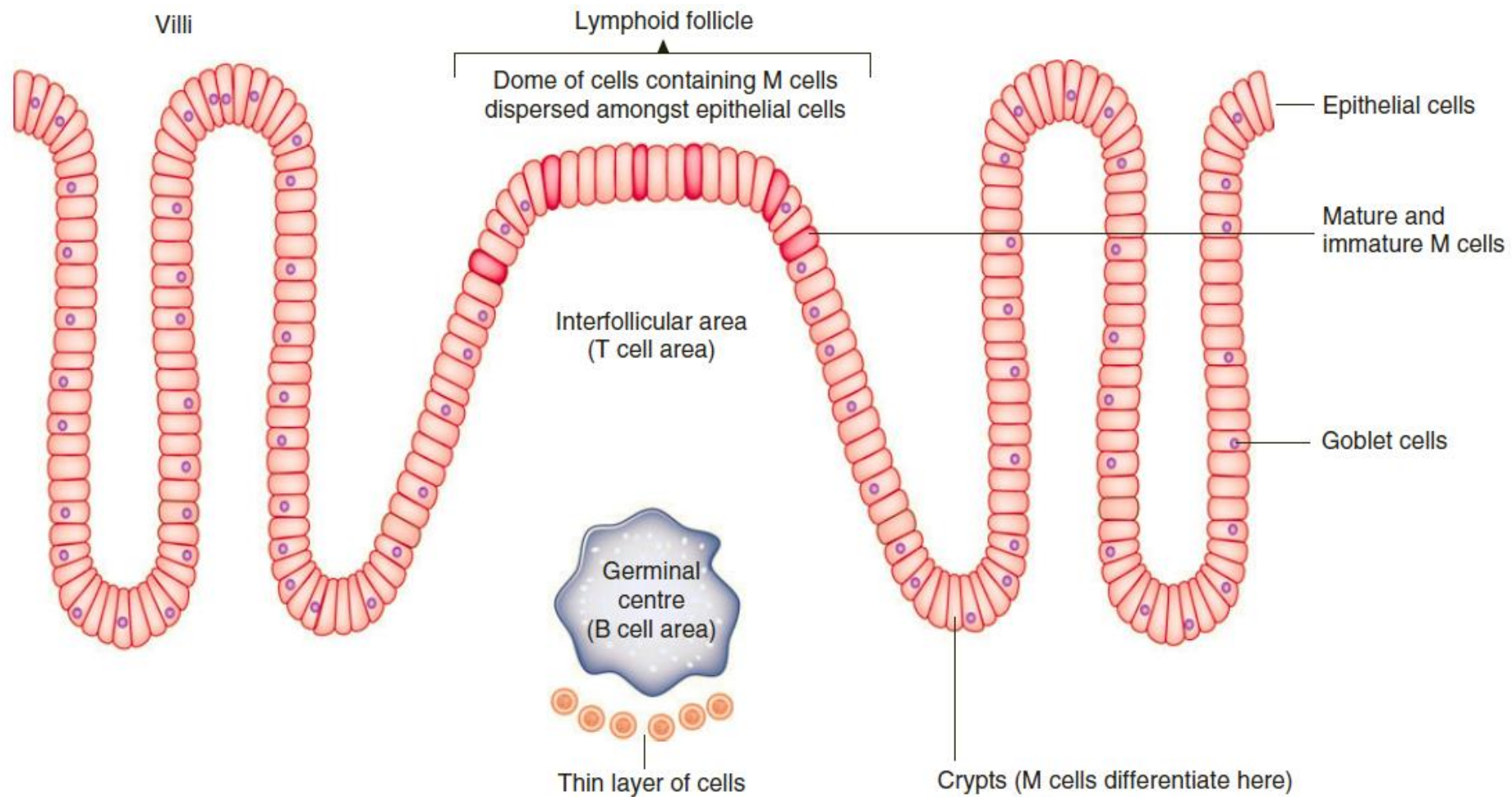
Peyer's patches are overlaid with microfold (M) cells that separate the luminal contents from the lymphocytes.

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.

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.



Question

DELIVERY OF PROTEINS

(ALTERNATIVE ROUTES OF ADMINISTRATION)

Dr. Ahmed Faisal

Parenteral administration has disadvantages (needles, sterility, injection skills) compared to other possible routes.

Therefore, systemic delivery of recombinant proteins by alternative routes of administration (apart from the GI tract), has been studied extensively.

The nose, lungs, rectum, oral cavity, and skin have been selected as potential sites of application.

The nasal, buccal, rectal, and transdermal routes all have been shown to be of little clinical relevance if systemic action is required and if simple protein formulations without an absorption-enhancing technology are used.

In general, bioavailability is too low and varies too much! The pulmonary route may be the exception to this rule.

The first pulmonary insulin formulation was approved by FDA in January 2006 (Exubera®) but taken off the market in 2008 because of poor market penetration.

Pulmonary inhalation of insulin is specifically indicated for mealtime glucose control.

Uptake of insulin is faster than after a regular SC insulin injection (peak 5–60 min vs. 60–180 min).

Inhalation technology plays a critical role when considering the prospects of the pulmonary route for the systemic delivery of therapeutic proteins.

Dry powder inhalers and nebulizers are being tested.

The fraction of insulin that is ultimately absorbed depends on **(1)** the fraction of the inhaled/nebulized dose that is actually leaving the device, **(2)** the fraction that is actually deposited in the lung, and **(3)** the fraction that is being absorbed, i.e.,

Total relative uptake (TO %) = % uptake from device × % deposited in the lungs × % actually absorbed from the lungs.

TO % for insulin is estimated to be about 10 %.

The fraction of insulin that is absorbed from the lung is around 20 %.

These figures demonstrate that insulin absorption via the lung may be a promising route, but the fraction absorbed is small and with the Exubera technology, the patient/medical community preferred parenteral administration.

Therefore, different approaches have been evaluated to increase bioavailability of the pulmonary and other non-parenteral routes of administration.

The goal is to develop a system that temporarily decreases the absorption barrier resistance with minimum and acceptable safety concerns.

Until now, no products utilizing one of these approaches have successfully passed clinical test programs.

Nasal

Advantages

Easily accessible, fast uptake, proven track record with a number of “conventional” drugs, probably lower proteolytic activity than in the GI tract, avoidance of first pass effect, spatial containment of absorption enhancers is possible.

Disadvantages

Reproducibility (in particular under pathological conditions), safety (e.g., ciliary movement), low bioavailability for proteins.

Pulmonary

Advantages

relatively easy to access, fast uptake, proven track record with “conventional” drugs, substantial fractions of insulin are absorbed, lower proteolytic activity than in the GI tract, avoidance of hepatic first pass effect, spatial containment of absorption enhancers is possible.

Disadvantages

reproducibility (in particular under pathological conditions, smokers/nonsmokers), safety (e.g., immunogenicity), presence of macrophages in the lung with high affinity for particulates.

Rectal

Advantages

easily accessible, partial avoidance of hepatic first pass, probably lower proteolytic activity than in the upper parts of the GI tract, spatial containment of absorption enhancers is possible, proven track record with a number of “conventional” drugs.

Disadvantages

low bioavailability for proteins.

Buccal

Advantages

easily accessible, avoidance of hepatic first pass, probably lower proteolytic activity than in the lower parts of the GI tract, spatial containment of absorption enhancers is possible.

Disadvantages

low bioavailability of proteins.

Transdermal

Advantages

easily accessible, avoidance of hepatic first pass effect, removal of formulation if necessary is possible, spatial containment of absorption enhancers, proven track record with “conventional” drugs, sustained/controlled release possible.

Disadvantages

low bioavailability of proteins.

Approaches to enhance bioavailability of proteins

Classified according to proposed mechanism of action

Increase the permeability of the absorption barrier:

Addition of fatty acids/phospholipids, bile salts, enamine derivatives of phenylglycine, ester and ether type (non)-ionic detergents, saponins, salicylate derivatives, derivatives of fusidic acid or glycyrrhizinic acid, or methylated β -cyclodextrins.

Through iontophoresis By using liposomes.

Decrease peptidase activity at the site of absorption and along the “absorption route”: aprotinin, bacitracin, soybean tyrosine inhibitor, boroleucin, borovaline.

Enhance resistance against degradation by modification of the molecular structure.

Prolongation of exposure time (e.g., bio-adhesion technologies).

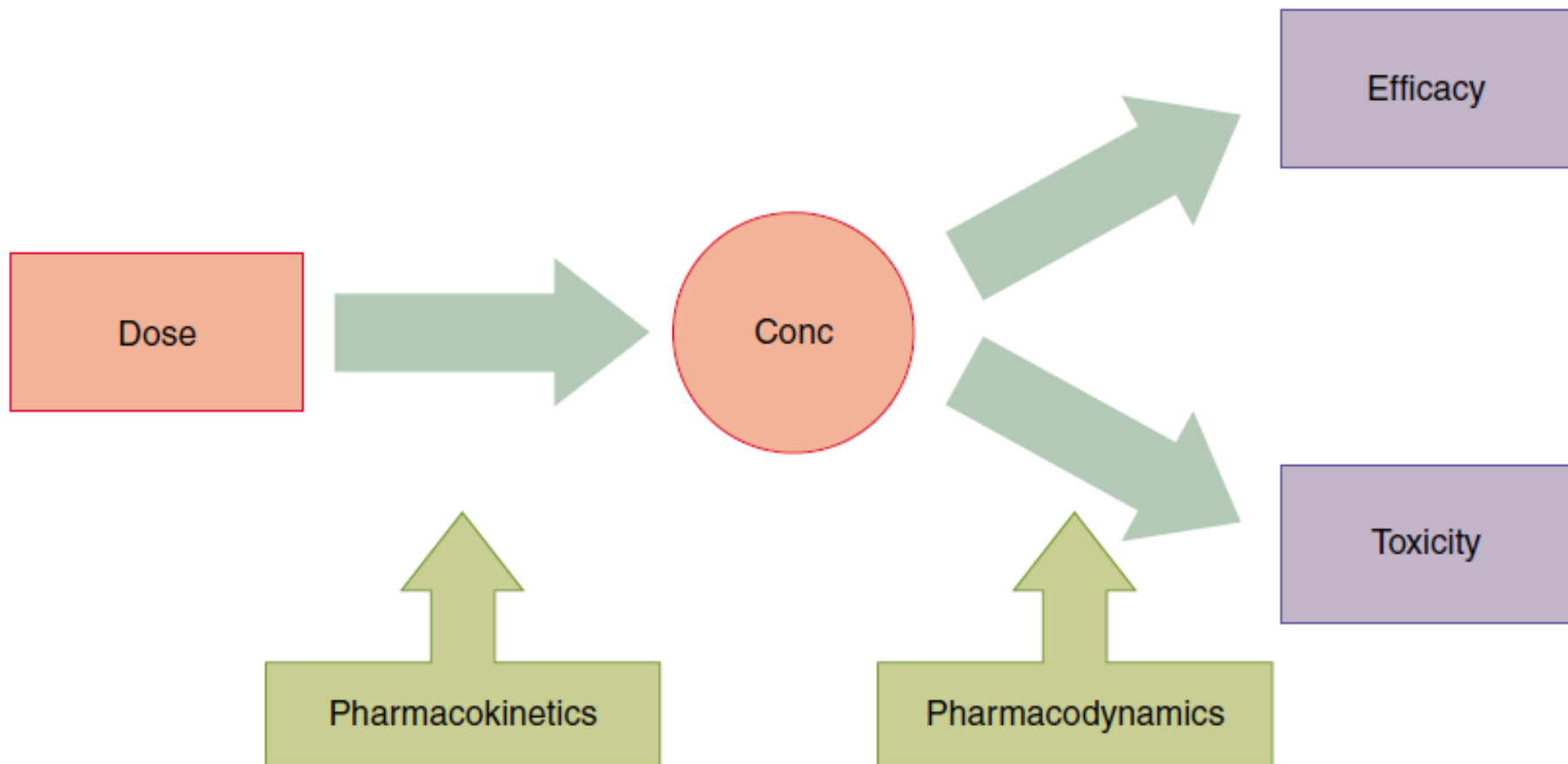


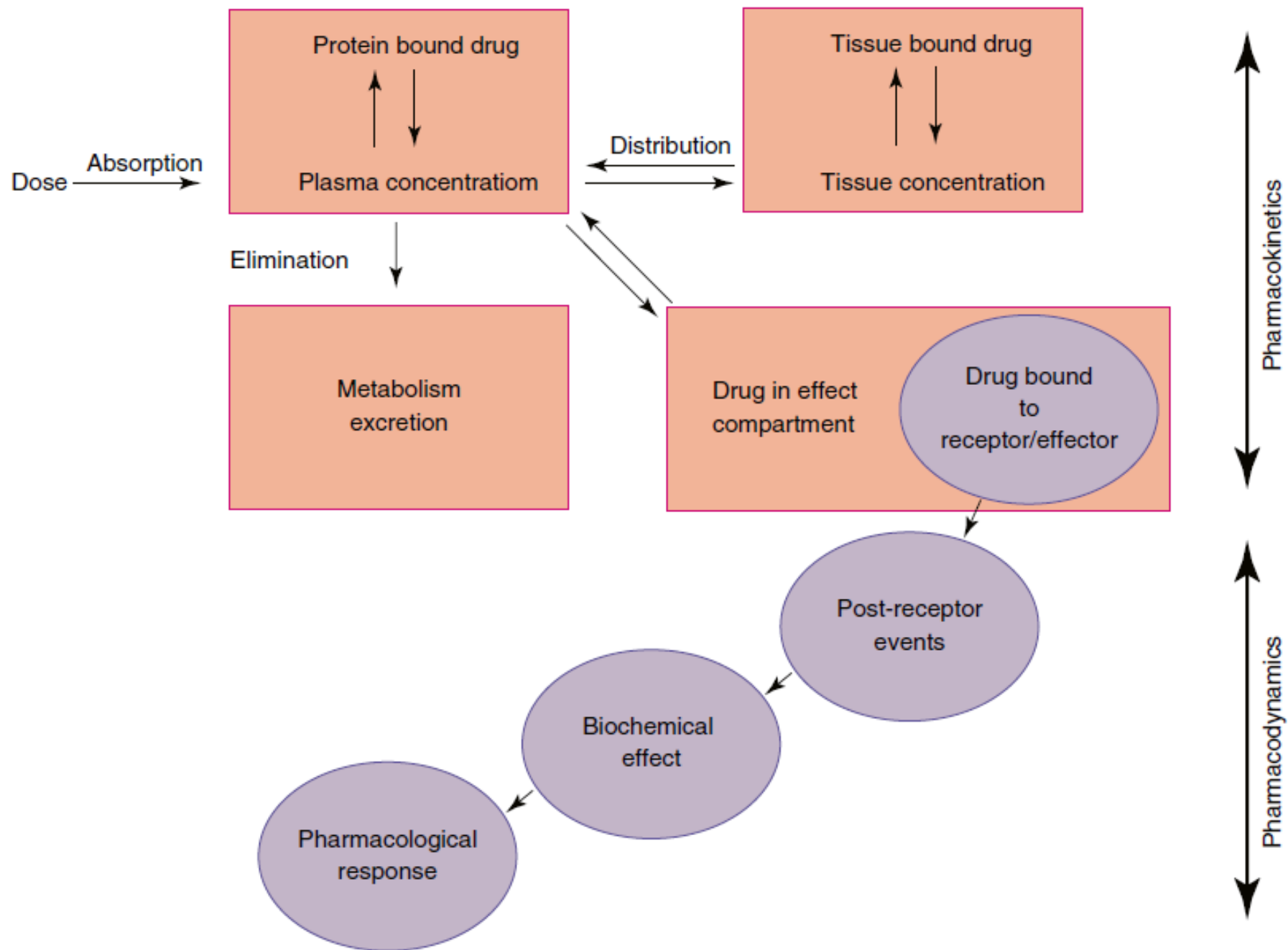
Pharmacokinetics of peptides and proteins

Pharmacokinetics describes the time course of the concentration of a drug in body fluid that results from the administration of a certain dosage regimen.

It comprises all processes affecting drug **absorption**, **distribution**, **metabolism** and **excretion**.

It has the property of “**what does the body do to the drug**”.





Pharmacokinetics for proteins may be different from that for conventional drugs. (Why?)

This is related to:

- 1) The structural similarity to some endogenous compounds.
- 2) With regulatory feedback mechanisms.
- 3) Difficulties in analysis (interferences).
- 4) Their large molecular weights.

Absorption of protein therapeutics

Poorly absorbed orally.

Mainly administered parenterally (I.V, I.M, and S.C.) depending on type of protein.

One of the potential limitations of SC and IM administrations, however, are the pre-systemic degradation processes, local blood flow, injection trauma and the capillaries sizes.

Then **$K_a = F \cdot K_{app}$**

K_a = the true absorption rate constant.

F = The bioavailability compared to IV administration.

K_{app} = apparent absorption rate constant for IM, SC.

Distribution of protein therapeutics

The rate and extent of protein distribution are largely determined by their size and **MW, physicochemical properties** (like charge, lipophilicity), **protein binding**, and their **dependency on active transport**.

The lymphatic system play important role in distribution of proteins depending on size.

Protein charge is important for electrostatic attraction of +vely charged proteins with –vely charged cell membranes (containing glycoaminoglycans).

Then for **distribution characterization** :

- 1) Biopsy or necropsy for determination of actual proteins concentrations in the tissue.
- 2) Bio-distribution studies with radiolabeled compound and/or imaging techniques.

The binding to endogenous protein structures (specific) can affect the distribution, pharmacodynamics (PD) and disposition properties of proteins.

The binding may be non specific to plasma proteins (albumin and lipoproteins).

Site-specific receptor mediated uptake can also substantially influence and contribute to the distribution, elimination and PD of proteins.

Elimination of protein therapeutics

The exogenous proteins are subjected to the same catabolic pathways as endogenous ones.

The end products of protein metabolism are thus amino acids that are reutilized in the endogenous amino acids pool for synthesis of endogenous proteins.

The elimination pathways includes:

- 1) Proteolysis**
- 2) GIT protein metabolism**
- 3) Renal protein metabolism and excretion**
- 4) Hepatic protein metabolism**
- 5) Receptor-mediated protein metabolism**

Molecular weight as major determinant of the elimination mechanisms of peptides and proteins

| Molecular weight | Elimination site | Predominant elimination mechanisms | Major determinant |
|------------------|------------------|--|--------------------------------|
| <500 | Blood, liver | Extracellular hydrolysis Passive lipoid diffusion | Structure, lipophilicity |
| 500–1,000 | Liver | Carrier-mediated uptake Passive lipoid diffusion | Structure, lipophilicity |
| 1,000–50,000 | Kidney | Glomerular filtration and subsequent degradation processes | Molecular weight |
| 50,000–200,000 | Kidney, liver | Receptor-mediated endocytosis | Sugar, charge |
| 200,000–400,000 | | Opsonization | α_2 -macroglobulin, IgG |
| >400,000 | | Phagocytosis | Particle aggregation |

Proteolysis:

The metabolic rate for protein degradation generally increases with decreasing MW from large to small proteins to peptides, but is also dependent on other factors such as size, charge, lipophilicity, functional groups and molecular properties (glycosylation, 2° or 3° structures).

The clearance may include metabolism and cellular uptake.

Proteolytic degradation can occur unspecifically nearly everywhere in the body (within blood) or can be limited to a specific organ or tissue.

As enzymes, proteases and peptidases are found extra- and intra-cellularly.

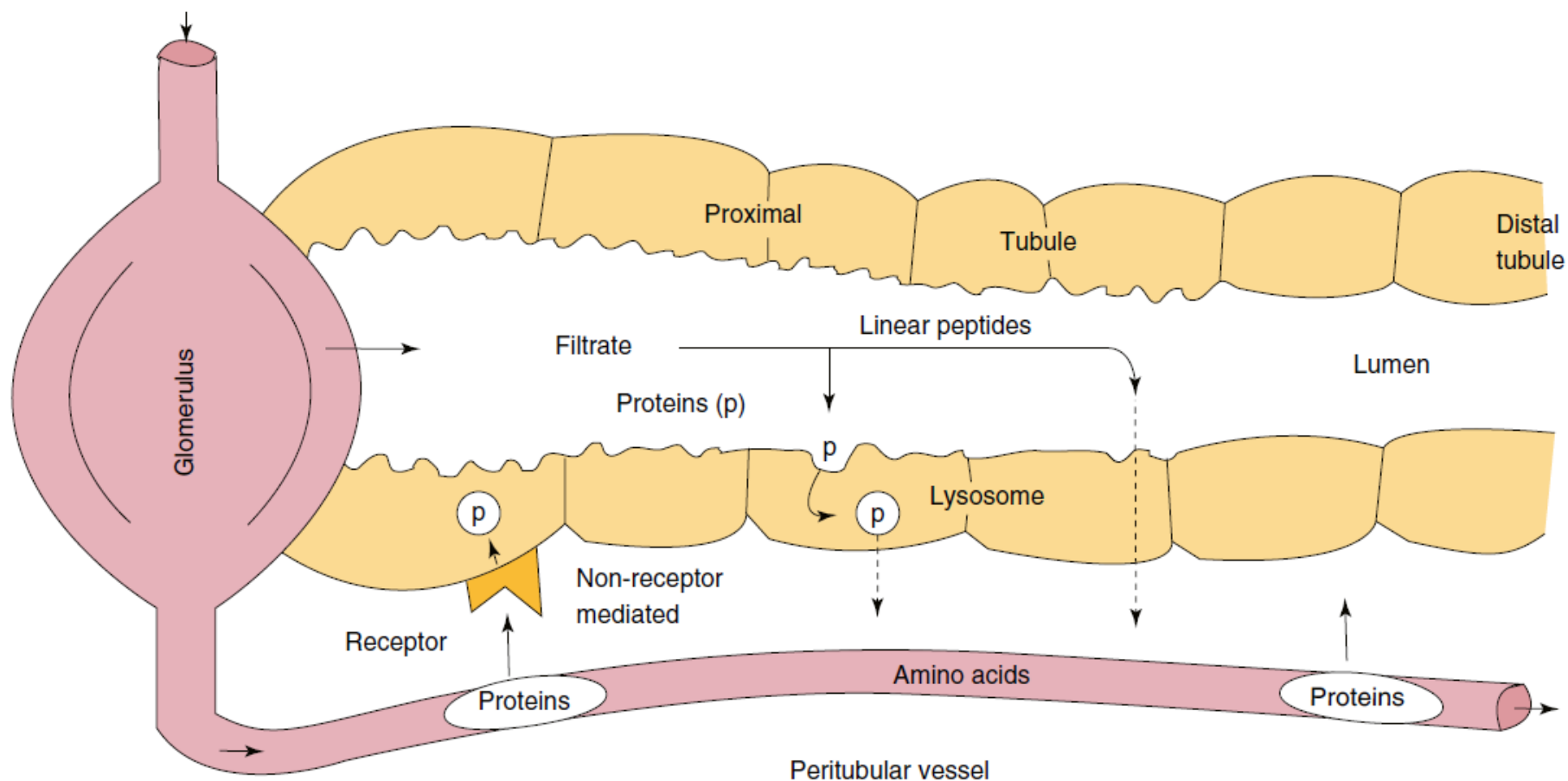
GIT protein metabolism:

As before, mainly for orally administered proteins and some parenterally administered proteins in the intestinal mucosa following intestinal secretion (as for endogenous albumin).

Renal protein metabolism and excretion:

The kidneys are a major site of protein metabolism for smaller sized proteins that undergo glomerular filtration (GF).

It is most efficient for proteins smaller than 30kD and the rate falls off sharply for larger than 30kD.



Pathways of renal metabolism of peptides and proteins: glomerular filtration followed by either (I) intraluminal metabolism or (II) tubular reabsorption with intracellular lysosomal metabolism and (III) peritubular extraction with intracellular lysosomal metabolism

Hepatic protein metabolism:

The rate of hepatic metabolism is largely dependent on the specific a.a. sequence of the protein (endopeptidases or exopeptidases action).

Mechanisms of hepatic uptake for proteins depend on the size and hydrophobicity.

There are different hepatic cells for this uptake mechanisms like:

- 1) Hepatocytes
- 2) Kupffer cells (specialized macrophages)
- 3) Endothelial cells
- 4) Fat-storing cells

Receptor-mediated protein metabolism

Occurred for proteins that bind with high affinity to membrane-associated receptors on the cell surface.

Includes endocytosis and subsequent intracellular lysosomal metabolism.

It is not constant (dose-dependent), decreases with increasing the dose.

It is not limited for a specific organ or tissue type, but depend on number of protein drug receptors.



GOOD LUCK
FOR YOUR

EXAM A
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DO THE BEST

