Section One: Chapter 5: Cell Boundaries, Membranes and Transport

Now that we have some background in the fundamental building blocks such as atoms and molecules, we can look more closely at the cellular aspects of the body. In our studies, the cell is considered the functional unit of living systems, therefore, understanding what creates the boundaries around a cell, and the consequences of those characteristics are crucial to understanding cell transport mechanisms. The concept of a cell boundary, like a plasma membrane, is the primary orchestrator of any cell's interaction with its external surroundings, as well as being a regulator of its internal activities.

There are about **200** different cell types in the Human Body. Below are just a few examples of some names of well-known cells. Keeping etymology in mind and the meaningfulness of names, there is plenty of information in each of these descriptive names to indicate where they are and what they do.

- **Hepatocytes** – liver (hepato-) cells (cytes).
- **Osteocytes** – mature bone (osteo-) cells (cytes).
- **Osteoblasts** – cells that make (-blast) bone (osteo-) matrix.
- **Chondroblasts** – cartilage (chondro-) cells that make (-blast) cartilage matrix.
- **Erythrocytes** – red (erythro) blood cells (cytes).

All of the cell types in the human body combine to make only four (4) different tissues. They are:

- **Epithelial Tissue**
- **Connective Tissue**
- **Muscle Tissue**
- **Nervous Tissue**

The Various Cell Membrane Models

An important concept is that there are many different models that attempt to explain the cell membrane. For example, there are several 'Lipid Bilayer models'; there is the Unit Membrane model (Protein-Lipid Bilayer-Protein); the Fluid Mosaic model, the Dannelli model (organized droplets of lipids and layers of protein); and even an Exclusions Zone charged water plasma membrane model.

The roles of a cell membrane are many, almost regardless of the model, but perhaps the first thing we notice about it is that it is a **physical barrier** – it creates the **boundary** of any cell. Taking a look at the diagram in **Fig. 5.1**, the theoretical contents and arrangement are much like a container with a boundary.

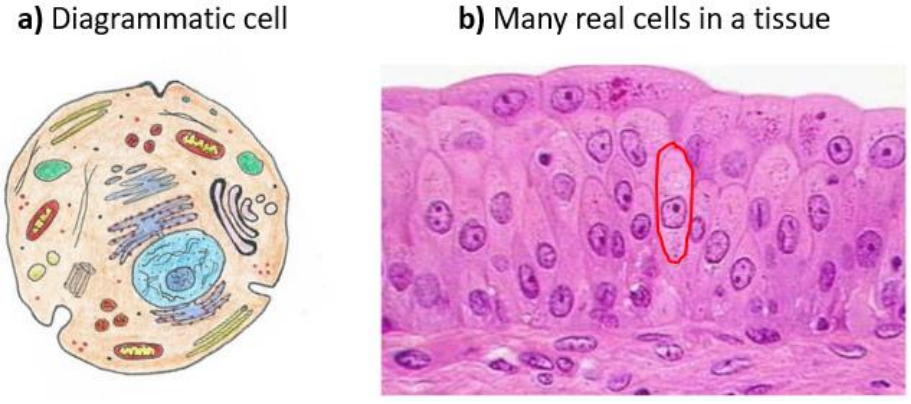


Figure 5.1 Comparison of **a)** a typical diagrammatic representation of a single eukaryotic cell with organelles, and **b)** a photograph of a histological preparation of many cells side by side in real epithelial tissue. Notice how one of the cells in **b)** is outlined in red to show where the membrane boundary is likely to be on that one cell.

Similar to a fence that outlines the yard contained within it, what we call the plasma membrane is the functional indicator of a separate structure. At the same time, many cells are closely connected to each other (as seen in **Fig. 5.1 b**) and will have considerable communications with each other. Therefore, this physical barrier must also facilitate exchange, recognition and communication.

Quick Review of the Organelles of our Cells

The leading popular theory regarding the plasma membrane structure is that it is created from a **phospholipid bilayer** which has proteins and other structures suspended in it. The cell membrane is described as **semipermeable** or **selectively permeable**, because it does not just let any old thing go through it! The plasma membrane regulates the transport of materials entering and exiting the cell.

Below in **Fig. 5.2** is a drawing of a single hypothetical human cell showing the relationship between the plasma membrane encompassing the cell, and the many other organelles within the cell. In the preceding section we went through all of the major organelles, and reviewed their functions and basic structure.

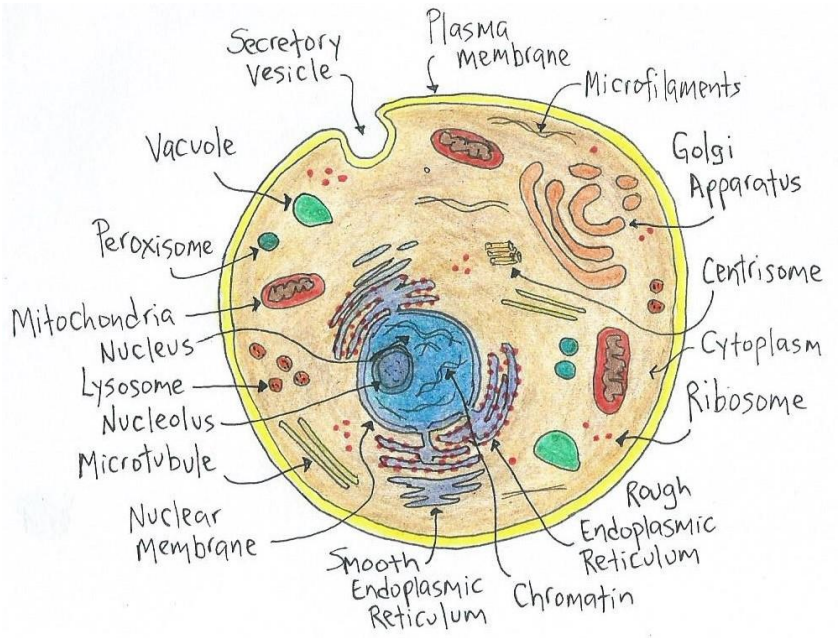


Figure 5.2 This shows a typical diagrammatic representation of a human (eukaryotic) cell, including the organelles that are encased by the plasma or cell membrane. The outside of the cell is surrounded by extracellular fluid (ECF) which is physically separated from the intracellular fluid (ICF) contained within the cell.

Extracellular and Intracellular Fluid of the Plasma Membrane

As we have seen in the 'Levels of Organization' and from our quick review above, cells are made from organelles that are bound and contained within a plasma membrane. The plasma membrane (PM) is the structure that determines the boundary that differentiates the inside of the cell from the outside.

Like other sections in physiology, it is very important at the start of any new material to be pedantic about the terminology used so that we know what these terms mean. The fluid on the outside of the cell is called the **extracellular fluid** (**ECF**). The fluid in the internal portion of a cell (the cytoplasm) is called the **intracellular fluid** (**ICF**). Thus, the plasma membrane sits in between these two different types of fluid.

It is imperative that there be adequate exchange and communication between the inside and outside of cells, and we will cover this aspect in great detail in cell transport. It is also important to know that the

fluid bathing the outside of the cell is substantially different from the composition of the internal fluid of a cell. We will discover that **this difference is harnessed and used by the cell to do work**.

Plasma Membrane Theory: Lipids and Proteins arranged in a Fluid Mosaic Model

What are the components of the plasma membrane of cells and how do they all function? Interestingly, like most things in science, there is still much to know about the exact nature of the plasma membrane. However, what is clear is that the membrane is constructed in such a way as to make a perfect regulator and insulator. This membrane must both prevent passage and flow of electrical currents, and yet also allow for transport, exchange and signaling across the cell, all rapidly and continually.

Described and shown below (**Fig. 5.3**) are the basic concepts of what the plasma membranes may be composed of, and the likely role and functions of these various components. The functions of the plasma membrane are reminiscent of the concepts of homeostasis in that there is always a stable baseline both in cell shape and activity, which is maintained for the very purpose of being able to change it and then bringing it back to baseline.

A Typical Theoretical Cell Membrane

The plasma membrane of any cell will have a general composition that is much like any other cell, although the percentages (%) that are described are based on a ***hypothetical plasma membrane***, like a conglomerate of the various types. Keep in mind that these percentages can vary significantly depending on the specific type of cell in the body. The general compositions is as follows:

- **Lipids**: 40-60% - arranged in a double lipid bilayer.
- **Protein**: 30-50% - proteins which are inserted either partly or completely through the bilayer.
- **Carbohydrate**: 5-10% - carbohydrates which attach to extracellular fluid (ECF) side.

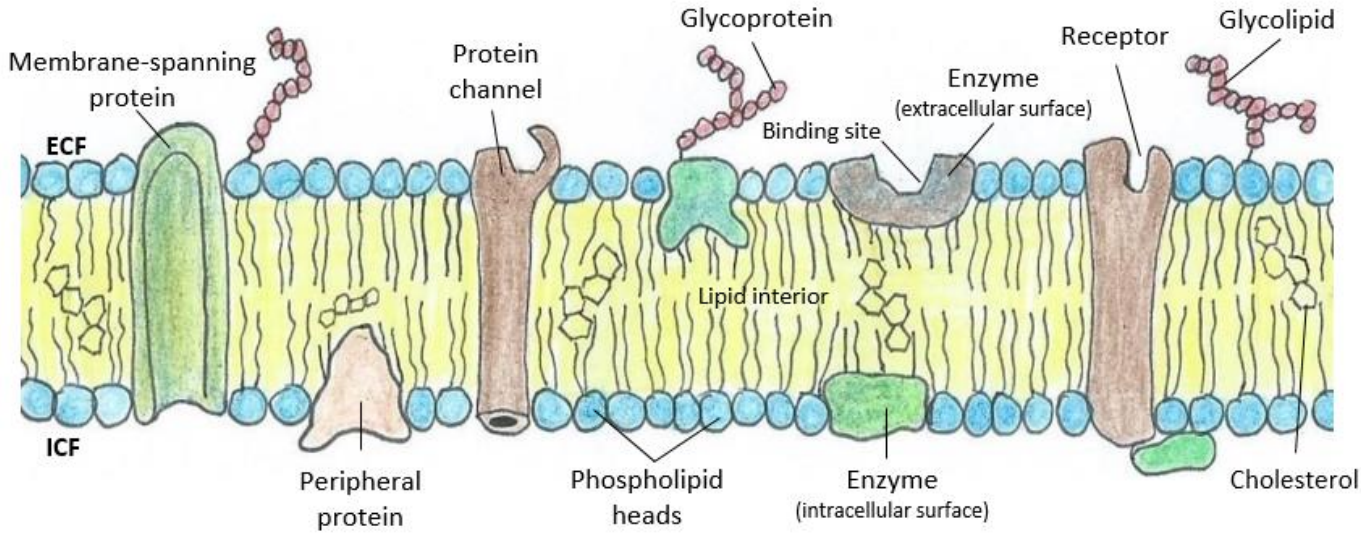


Figure 5.3 Above is a diagrammatic representation of a theoretical plasma membrane, showing a phospholipid bilayer creating by an insulated lipid area in between the extracellular surface (outside of cell) and the intracellular surface (inside of cell). Various proteins are embedded in the bilayer, some stretching completely across the entire membrane (membrane-spanning) can act as transporters, while others are located on one side or the other only (peripheral proteins) and do not span the entire membrane. The arrangement of the phospholipids make a lipid interior of the plasma membrane with their fatty acid tails and cholesterol molecules, but also a hydrophilic interface with the phospholipid heads in contact with the watery internal and external environment.

The General Idea and Roles of the Plasma Membrane

When contemplating the plasma membrane, it has many important facets and we can organize them into four (4) basic categories outlined below. As an exercise, it may be helpful to think of a plasma membrane as the fence that encloses a yard within it, as shown in **Figure 5.4** below. With this in mind, read the four roles below and start to assign aspects of the drawing to them.

1. **Physical Barrier**
2. **Regulation of Exchange**
3. **Structural Support**
4. **Communication and Cellular ID**

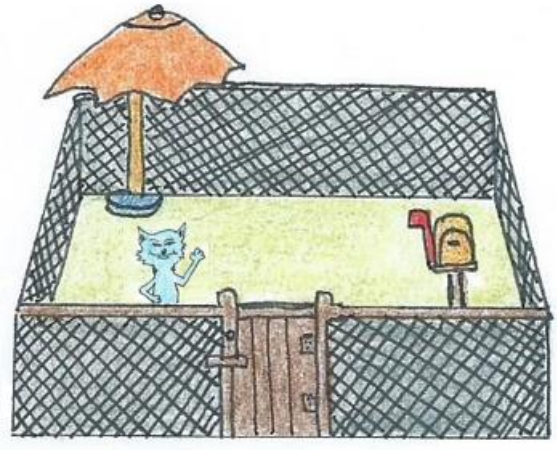


Figure 5.4 The plasma membrane of a cell can be compared to a fence around a yard. It acts as a physical separator, controls what comes in and out, offers support and a means of communication.

The physical perimeter of the yard is marked out by the fence as a barrier, though there are small openings in the fence. There is a gate in the front to allow larger structures in or out. That nice umbrella in the back can be supported by the fence. And there is a mailbox attached to the fence which can send and receive information (see **Fig. 5.4**).

Much of physiology is **centered on the concept of a membrane** of the cell, since it is so fundamental to cell responses and function. Notice, we don't even need to talk about the nucleus of a cell at all right now, which many text will say is the 'brain' of the cell. In the scheme of things, the nucleus may be a sort of library with plenty of important information and instructions, but it is the plasma membrane that is interacting all the time with both the internal and external environments of the cell. This is why we need to explore this structure in order to gain insight and better understand how, in the macro sense, the entire body functions.

The 4 General Functions of Plasma Membranes

1. Physical Barrier

The plasma membrane (PM) acts as a physical barrier as it physically separates the inside of the cell, containing intracellular fluid (**ICF**), from the outside of the cell, containing extracellular fluid (**ECF**). It creates the boundary of the cell and isolates it, allowing it to be distinct from other cells and structures.

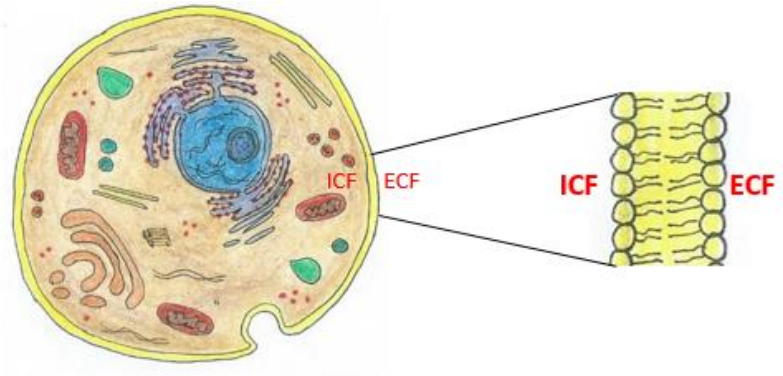


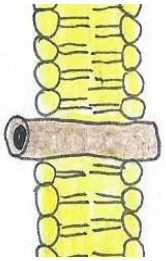
Figure 5.5 It is the model of the phospholipid bilayer shown here that creates the partition and provides the physical barrier distinguishing the contents inside the cell (ICF), and those outside the cell (ECF).

As a quick Example

As we will see shortly, the contents of the ICF and the ECF are *very* different. The concentration of potassium ions (K^+) under normal resting conditions is very high on the inside and very low on the outside of the cell. Part of the role of the plasma membrane is to ensure that these two regions (the inside and outside of the cell) stay separate and distinct. We will also see that this can change, but for now we will appreciate that the plasma membrane is a great physical barrier.

2. Regulation of Exchange into and out of Cell

Anything that goes into or out of a cell must do so by crossing the plasma membrane. Therefore, **regulation of exchange is a key role of the plasma membrane**. Exchange with the environment occurs across the plasma membrane, either by slipping through the lipid bilayer of the membrane by diffusion, or by being transported across the membrane by protein channels, protein carriers, or vesicles that are embedded within or can fuse into the plasma membrane.



Example:

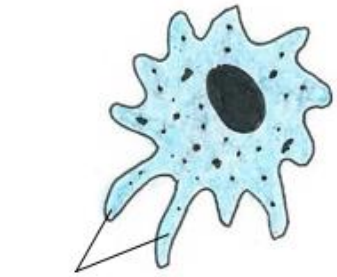
If a water molecule, **H_2O**, wanted to go from one side of the membrane to the other, shown in the drawing to the left, it could squeeze through the phospholipid bilayer (yellow part), or it could go through the very nice little tunnel created by the protein embedded in the phospholipid bilayer. It is because water is so small that it can move across almost any membrane in the body. The moment of water to where it is less will always naturally occur. As we shall see shortly, the net movement of water down its concentration gradient across a semi-permeable membrane is called **osmosis**. There are many mechanisms of transport we shall cover shortly.

3. Structural Support

Structural proteins are tethered to the internal (intracellular) aspect of the plasma membrane in order to create the internal structural support for the cell. This internal framework is referred to as the ***cytoskeleton*** of the cell. Structural proteins attached to the plasma membrane helps to create the **shape** of cells.

Examples:

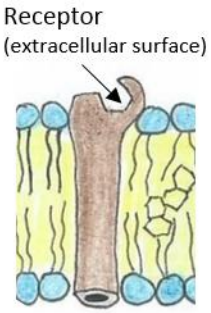
The cytoskeleton interacts with the plasma membrane and helps to create the distinctive **biconcave disc** shape of **red blood cells** (left). This unique shape is critical to their function, as the biconcave disc increases the surface area to volume ratio and increases their ability to exchange the gases oxygen (O_2) and carbon dioxide (CO_2). The **macrophage** ('big eater') to the right, is a cleaning defense cell with foot like extensions called **pseudopods** (false feet). These are created and extended by actions and movements generated from the cytoskeleton.



4. Communication and Cellular ID

a) Communication signals from the external environment of the cell are transferred into the internal compartment across the plasma membrane. This often involves **receptors** that sit on the external aspect of the plasma membrane to receive the signal. Signal molecules called 'ligands' bind to receptors associated with the cells, much like substrates bind to enzymes. As a result, the activity of the cell changes.

Example:
Signal molecules, like hormones or neurotransmitters, can bind to receptors located on the extracellular (outer) surface of the cell membrane – as shown in the drawing to the right. Depending on what these receptors are linked to (such as an ion channel in this case), there will be a change in the cell's activity as information is communicated.



b) There are also molecules which attach to the external surface of the plasma membrane and act to identify the cell as self, for example ***glycoproteins*** and ***glycolipids***. These molecules act as **'flags'** or **cell markers** for **cell identification** (ID), and for example, are responsible for the blood typing (A, B, AB or O) of a red blood cell.

Examples:
The molecules acting as cell markers are called **glycoconjugates** (glyco is sugar, con is together, and jugum is yolk) which are carbohydrates covalently linked to another molecule with a polysaccharide called a **glycan**. In the drawing below at right are two important examples: **a)** **glycoproteins** are composed of the glycan attached to a protein; and **b)** **glycolipids** are composed of the glycan attached to a lipid. These both function as cell identification, with the glycan portion acting as a cell marker or flag. They also help to stabilize the membrane and facilitate cell–cell communication.

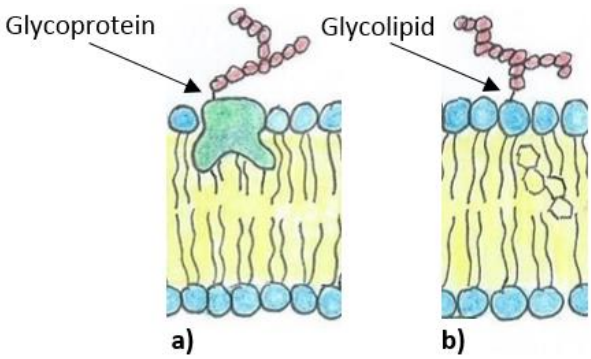


Figure 5.6 Shown above are **a)** a glycoprotein, with a sugar attached to an embedded protein, and **b)** a glycolipid, with a sugar attached to a lipid on the outer surface of the plasma membrane of a cell.

For those terms above, the suffix (ending) is usually in abundance to the prefix (beginning) in this naming system, meaning that a glycoprotein has a lot of protein and a smaller amount of sugar. However, if it is a proteoglycan, then there is more sugar and less protein.

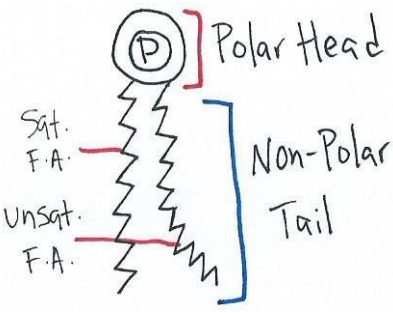
The Constituents of the Plasma Membrane

What is the cell membrane composed of? What are its main constituents?

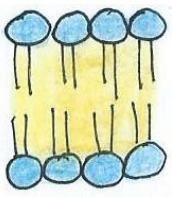
Membrane Lipids

1. Phospholipids - usually about 75% of the lipid content.

The head of a phospholipid is a polar glycerol-phosphate that is **hydrophilic** and has a non-polar fatty acid (FA) tail as the **hydrophobic** end (see drawing at left). Typically, one fatty acid is saturated and the other is unsaturated.

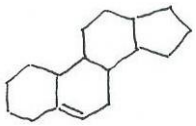


The entire molecule is ***amphiphilic***, meaning it can mix with both water and lipid environments. The phospholipids are thought to be arranged in two rows (as shown diagrammatically to the right) called the *phospholipid bilayer* and this acts as a barrier that only lipid-soluble molecules can easily penetrate. Anything else that wants to get through the membrane must have assistance via a **protein channel**, a **protein carrier** or from **vesicular transport**. The phospholipid bilayer also provides a framework for membrane proteins to be embedded in. Whatever it is that makes up the cell membrane, it is also an excellent insulator.

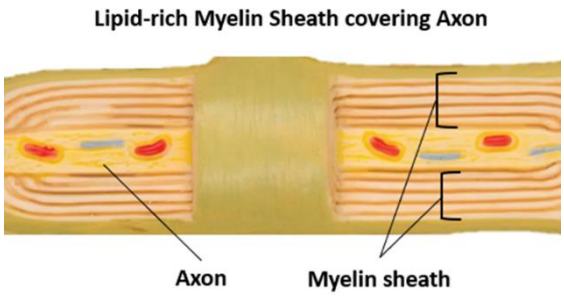


2. Cholesterol - usually about 20 - 30% of lipid content.

Cholesterol is a 4 ringed lipid structure that inserts into the hydrophobic center with the nonpolar fatty acid tails. Cholesterol helps to stabilize the plasma membrane. It functions to keep membranes as **impermeable** and **flexible** as possible. Membranes with higher cholesterol concentrations are less permeable to ions, water, and other small molecules. The more cholesterol in the plasma membrane the more **insulative** the membrane will be. The cholesterol in the membrane helps to fill any voids in the lipid insulator and presumably cholesterol blocks the openings between phospholipid tails through which small molecules could otherwise pass.



Lipids provide great insulation, and in terms of body temperature (T_b) the "plasticizing" (meaning flexible) effect of cholesterol in mammals to maintain a relatively constant T_b is not as important as it is in poikilothermic (cold blooded) animals, whose internal temperature varies considerably.

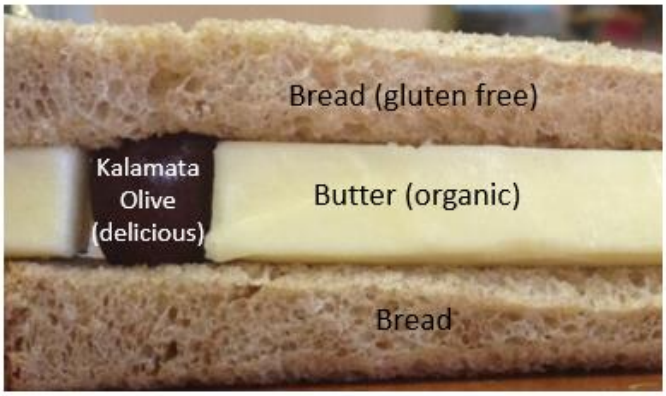


The **myelin sheath** insulates the axons of neurons (see above right) and is **80%** lipids, with **cholesterol** its major lipid. It acts as an insulating layer around axons in the brain and spinal cord and allows the electrical impulses to be transmitted extremely quickly and efficiently throughout the nervous system.

A Butter Sandwich

The "Butter sandwich with olives" analogy for the plasma membrane may be a useful one to share at this juncture (see **Fig. 5.7**). The lipid nature of our body is striking, and it is vital to recognize and appreciate the nature of lipids and the special qualities they provide to the entire body, and the cell membrane.

In terms of permeability (the way a substance moves across the plasma membrane), cells are referred to as **semi-permeable** or **selectively permeable**. This means that not everything can get across the membrane with ease. The cell membrane is restrictive for two main reasons: To control the types and quantity of molecules that are in the ICF and the ECF; and to keep the two sides of the membrane electrically insulated! For these reasons, the bulk of the plasma membrane is made up of **phospholipids** and **cholesterol**, which are **non-polar (lipid) molecules**.



This means that non-polar molecules usually have a very easy time passing through the membrane because they are lipid soluble, but polar molecules (ones that dissolve in water) do not have such an easy time crossing. However, the **membrane spanning proteins** embedded in the lipids can transport polar molecules across the cell quite effectively. The other very important quality of fats (lipids) is that they are very good insulators as they **resist conducting electrical charges**.

Figure 5.7 The butter sandwich analogy for the cell membrane structure creating a selectively permeable barrier.

Knowing this information, we can now think of the plasma membrane as a butter sandwich with olives embedded in it, stay with me (**Fig. 5.7**). The bread is the polar region of the phospholipids, the butter is

the lipid-rich inner region of the membrane and the Kalamata olives are the delicious membrane spanning protein transporters. This arrangement provides a nimble yet rigid interface that is restrictive yet allows passage and can also provide insulation to electrical charges across the plasma membrane, and also allows the current flow.

3. Glycolipids – usually about 5% of the lipid content.
As discussed briefly above, the prefix glycol- means 'glucose' or 'sugar', and a glycolipid is a small amount of a sugar attached to a large amount of lipid. Glycolipids on the external surface of the plasma membrane act as **cell markers**, helping to identify the cell as 'self' to defense cells of the body. Glycolipids are glycol-conjugates of polysaccharides (many sugars) that are covalently linker via glycosylation with lipids that are generally found on the **extracellular** face of cell membranes. Since the lipid portion of the glycolipids is typically buried within the membrane, it is the carbohydrates on glycolipids are the most exposed structures on the extracellular surface of the cell. They are flexible with numerous binding sites, and this makes them optimal for **cell signaling** and **cell identification**. They also function to maintain stability of the membrane and to facilitate cell to cell interactions.

Other Phospholipid Arrangements

1. Micelles are small droplets with the hydrophobic tails forming the interior and the hydrophilic heads form the exposed boundary. These are important in digestion and absorption of fats in digestive tract.

2. Liposomes are larger hollow spheres with phospholipid bilayer walls. Their hollow core can be loaded with water-soluble molecules.

Membrane Carbohydrates

Plasma membrane **carbohydrates** attach to both lipids and proteins. As such they are included in the section for both the lipids and the proteins of the plasma membrane. Primarily, the carbohydrates are polysaccharides that are covalently bonded to lipids and protein on the external surface of the cell.

The **Glycocalyx** is a protective layer on cell surface formed by **Glycoproteins** (when glucose attaches to membrane proteins), and **Glycolipids** (when glucose attaches to membrane lipids). Again, the carbohydrates of the glycocalyx play a critical role in identifying cells; for example, the carbohydrates of the glycocalyx in human blood cells differentiate the main ABO blood groups from one another.

Membrane Proteins

1. Associated Proteins
These are the proteins that are attached loosely to membrane-spanning proteins or to polar regions of phospholipids and **they do not span the plasma membrane**. They are also termed ***peripheral*** or ***extrinsic*** **proteins**. They cannot function as membrane transporters because they do not span the entire membrane. They typically function as **enzymes**, **receptors** or **structural components** of the membrane.

2. Integral and Membrane-Spanning Proteins
These proteins are tightly bound within the phospholipid bilayer and are also termed ***intrinsic proteins***. While a few integral proteins only extend partway into the membrane, **most are membrane-spanning proteins**. Membrane-spanning proteins have segments that cross the membrane multiple times, looping in and out of regions. Carbohydrates attach to the extracellular loops and phosphates attach to the intracellular loops.

It is still not well understood how proteins may or may not be held in place within the lipid layer of the plasma membrane, some are immobile, held in place by **cytoskeleton** proteins. Other protein have amino acids links to form an α-helix, and this ties the protein firmly to the membrane and it can only be freed by disrupting the phospholipid bilayer with detergents. Other proteins are mobile and move under the direction of cytoskeleton.

Lastly, with regard to **membrane-spanning proteins**, these are the proteins that act as **cell membrane transporters**. If a substance is going through the plasma membrane using a protein transporter, then the protein must span across the entire membrane. The detailed discussions ahead about protein channels and carriers (both membrane-spanning) will elaborate on this important point.

3. Glycoproteins

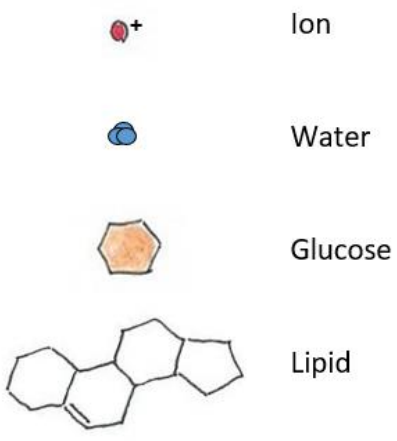
As briefly mentioned earlier, glycoproteins are found on the external surface of the lipid bilayer. Again, the prefix glyco means 'glucose', so a **glycoprotein** is a small amount of a carbohydrate (sugar) attached to a large amount of protein. Recall the convention is that the prefix is less abundant and the suffix is in greater abundance in the molecule. If the molecule is called a **proteoglycan**, then there is more sugar (glyco) than protein (proteo). The glycoproteins act as cell markers for identification and communication, but also have a protective function for cells and other structures.

Some Examples: There are glycoproteins that have important functions for defense, molecules such as **antibodies** (immunoglobulins) interact directly with antigens in a type of antibody dependent response. These molecules are also a part of the **major histocompatibility complex** (MHC), which are expressed on the surface of cells as a "self" identifier flag molecule and interact with defense cells.

Movement of Molecules across Membranes

It bears repeating that the membrane has been described as ***selectively*** or ***semi-permeable***. Again, this means that some molecules can get across, and some molecules cannot. More importantly is the reality that although some molecules may be 'prevented' from moving across that lipid-rich buttery membrane, if the cell needs that substance it will find a way of getting that molecule across the membrane if the cell needs that to happen!

This next discussion examines the common **characteristics** of molecules that will determine their basic permeability across a typical membrane. The range of different types of cells will have different needs, and the main strategy of any cell is how to get across the material they need (in or out), whilst at the same time continuing to maintain the integrity of the cell, via the membrane.



It will become more and more clear that knowing certain properties of a molecule, together with the general properties of the plasma membrane, will enable a very good understanding of what substances can get through a cell membrane easily and which will meet barriers.

As a quick introduction to this idea, the **4** categories of molecules shown diagrammatically above give a good representation of this concept. The relative issues of charge, size, polarity (or lipid solubility) of any given molecule will have a very important impact on how it gets through a membrane. In this chapter we will match and pair certain molecules with specific transport methods, and that is a very useful practice.

General Factors Influencing Molecule Permeability

The membrane composition determines which molecules move across. Permeable molecules can cross a membrane by any method. Impermeable molecules cannot cross cell membrane without assistance. Although the components of a plasma membrane can vary for different cells, the properties of a given molecule will have a large effect on whether is passes through the plasma membrane easily, or if it needs assistance or if it cannot pass at all. Below are the 3 main factors that determine whether a molecule can pass easily directly through the plasma membrane or not.

1. Size of molecule – ***smaller*** molecules can more easily pass through than larger molecules.

2. Polarity (lipid solubility) – ***lipid soluble*** molecules pass through more easily than polar molecules.

3. Charge of molecule – ***uncharged*** molecules pass through more easily than charged molecules.

The permeability of a molecule can be influenced by all three of these factors, not just one.

Let's take the molecule **water** (H_2O) for example.

- Size: Water is very **small**. The molecular weight (MW) of H_2O is only **18**, thus it is considered very small molecule and for this reason can easily pass through most cell membranes in the human body.
- Polarity: Water is a **polar** molecule, that is, it is insoluble (does not mix) in lipids. This would tend to make it less permeable, since the phospholipid bilayer creates a significant barrier to polar substances crossing the membrane.
- Charge: Water is not charged and therefore is less restricted than molecules with charge.
- In summary, water is highly permeable to cells, mostly due to its small size.

As another example, let's examine **ions**.

- Size: Ions are **small**. The MW of Na^+ is 23.5, so this tends to favor permeability.
- Polarity: Ions form electrolytes in solution with water and are not lipid soluble.
- Charge: by definition, ions are charged particles, this significantly limits permeability.
- In summary, ions are normally not very permeable to cells (unless ion channels open).

One more example, a **large lipid**.

- Size: Large, the high MW would tend to hamper permeability.
- Polarity: Lipids are **lipid soluble** and this is the most critical element for ease of passage.
- Charge: Most lipids are essentially neutral, this also makes passage much easier.
- In summary, lipids are extremely permeable to cells.

Function of Plasma Membrane Proteins

Proteins are considered the most versatile of the organic molecules, meaning that they are able to play many different roles, not only in the plasma membrane but throughout human physiology. As such, they also play a critical role in the all of fundamental functions of the plasma membrane.

The proteins that are associated with the plasma membrane have an expansive range of roles. They include:

1. Structural Elements
2. Cell Adhesion Molecules
3. Enzymes
4. Receptors
5. Transporters

Here is a quick review of the roles of the proteins in the cell membrane.

1. Structural Proteins – These link the **cytoskeleton** to the plasma membrane to maintain cell shape, e.g., the microvilli, or the bi-concave shape of red blood cells. The characteristic shape of the red blood cell is due to an extensive cytoskeleton that pulls the cell membrane into a biconcave disc shape. In diseases such as *spherocytosis* (sphere = round like a ball), problems in cytoskeletal proteins produce abnormally sphere-shaped red blood cells that are unable to move normally through the circulatory system.

2. Cell Adhesion Molecules – These form part of the cell-to-cell connections holding tissues together. Membrane-spanning proteins link the cytoskeleton to the extracellular matrix. The most common fibrous protein that attaches a cell to adjacent cells is **collagen**!

3. Enzymes – When have seen how important enzymes are in an earlier chapter. Plasma membrane associated enzymes act as any other enzymes do but they are **fixed** to the plasma membrane. Chemical reactions can take place on either membrane face, i.e., on the extracellular or intracellular surface. For example, enzymes on luminal (exposed) surface in small intestine cells can digest peptides and carbohydrates on the extracellular surface. Enzymes on the intracellular surface, such as adenylyl cyclase, play an important role in signal transduction for cells.

4. Receptors – These act as receivers for the body's chemical signaling system, with each receptor being specific for a certain type or family of signal molecule. A **ligand** is any molecule binding to a receptor. Ligand binding usually triggers other membrane events. For example, if hormone binds a receptor on the plasma membrane, it may directly lead to an ion channel in the membrane opening or closing.

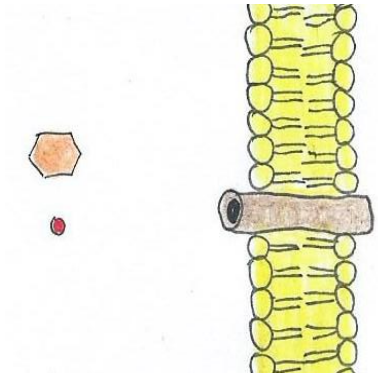
5. Transporters - Many molecules require the use of transporters **to cross cell membranes**. Most hydrophilic (lipophobic) molecules, such as smaller carbohydrates, amino acids, peptides, proteins, and charged particles such as ions, need some assistance in the form of membrane-spanning proteins in order to get into or out of cells.

All of the functions listed above for proteins of the plasma membrane are very important and critical in maintaining homeostasis in the body. In the next section that follows however, we are going to concentrate mostly on **#5** on the list above, that is, their role as proteins ***transporters*** across the plasma membrane. We will spend some time understanding the various mechanisms by which they move molecules from one side of the cell membrane to the other.

Protein Transporters

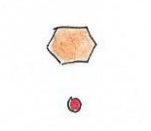
There are two categories of protein that act as transporters across the plasma membrane. They are: **Protein Channels** and **Protein Carriers**. We will examine each in detail.

1. Protein Channels



Protein channels are well named; they are very much like little water-filled channels, **forming a passageway that directly links the ECF to ICF**. The narrow diameter of protein channels restricts passage through them to small sized molecules, mostly **water** (H_2O) and **ions** (**K^+**, **Na^+**, **Cl^-** and **Ca^{2+}**). Electrical charges lining the inner channel may restrict the movement of some molecules; therefore they can be very specific as to what they allow to travel through them. This mode of transport is very fast, much faster than protein carriers because there is no need for the binding of any substrate as in protein carriers, thus the substrate can flow right through.

Looking at the two molecules in the drawing above to the left we see a protein channel in the membrane. This type of channel is always open, so which of the two molecules shown do you think will get through this protein channel and why?



- This one is a larger molecule, let's say it could be **glucose**.
- This one is a very small molecule, let's say it could be a sodium ion (**Na^+**).

Since protein channels are **small water filled pores**, they can only let small substances through them. The glucose-looking molecule is **too big** to fit through that pore, or any pore! However, **small**, **charged** particles, such as Na^+ or K^+, or Cl^- or Ca^{2+} ions could easily fit through these pores. For this reason, the small molecule above (which could be Na^+), would be the one likely to move through this protein channel.

Many protein channels are open and spend most of their time in the open configuration and are also called **pores**. When we begin to see how different the environments of the two sides of the cell membrane can be (inside versus outside), we will appreciate the power of a simple protein channel.

Keep in mind these main concepts about any **Protein Channel**:

- They only allow passage of **small things**, e.g., **water**, which is **H_2O**, with a molecular weight of 18.
- They also allow **small**, **charged particles**, or **ions** through them, e.g., K^+, Na^+, Cl^- and Ca^{2+}, etc.
- They move ions **extremely fast** in terms of the time it takes to go from one side to the other.
- They can be **non-specific**, in that anything that can fit through will be transported.
- They can also be **very specific** and only allow one type of ion through it.
- They can be **always open**, or they can be **gated** and therefore require triggers to open and close.
- They are **passive transporters**, never using ATP, just the gradients that already exist.

Note: **Non-gated protein channels** are ion channels that are **always open**. For this reason these channels are sometimes called '**leak**' or '**leaky**' ion channels. These are the simplest type of ion channel in that their permeability is more or less constant without any impedance, and this means that ions can constantly flow through them down their electrochemical gradients. This is important in many cells, but particularly important in nerve cells, or **neurons**.

For example, potassium ion (K^+) leak channels allow K^+ to move out of the cell freely according to the electrochemical gradients for K^+ that are maintained by pumps (as we will see in the active transport mechanisms section just ahead). Theoretically, if for some reason there were a greater concentration of K^+ outside the cell, for example in **hyperkalemia**, this could allow K^+ to move into the cell using these channels. However, this would not normally occur – because if it did, and this K^+ gradient inside our cells were eliminated or reversed, this would lead to death! This aspect of the vital importance of maintaining the resting cell membrane will be discussed in significant detail, because it is so important.

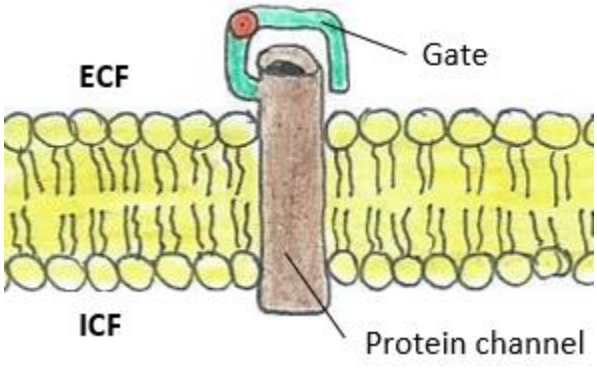
Other protein channels are ***gated***, and hence can be open or closed, and spend most of the time in a closed state. Let's take a look at those now.

Gated Protein Channels

Some protein channels are "**Gated**" and need to be "**Opened**" before allowing ions to travels through them. The protein channels that have gates that can open or close are called **gated ion channels**.

Types of Gated Ion Channels

There are three (3) types of gated ion channels we will explore, and they differ with regard to the 'trigger' that opens or closes the gate. In any drawing of the plasma membrane, the orientation is not important but knowing which side is the ECF and which is the ICF is very important as we will soon understand.



In the diagram to the left (**Fig. 5.8**), the protein channel embedded in the plasma membrane now has a gate on it! In the closed configuration, nothing is going to get through that channel. However, when it is triggered to open, it will allow passage through it. This is a very powerful way to regulate transport across a cell membrane and these gated channels are found everywhere!

Figure 5.8 The gated protein channel is embedded within the lipid rich barrier which keeps the extracellular fluid (ECF) and the intracellular fluid (ICF) separate, yet allows for passage from one side to the other via this channel.

The three types of Gated Channels are:

1. **Chemically Gated Channels**: These are triggered by specific ligands (chemicals) that bind to a receptor associated with the channel and can open or close the channel.

Examples in the Body: Commonly present in all cells that communicate with hormones, neurotransmitters or other signal molecules.

2. **Voltage-Gated Channels**: These are triggered by changes in the electrical charge across the cell membrane, and can open or close channels in response to variations in membrane voltage.

Examples in the Body: Neurons (a type of cell in the nervous system) and myocardiocytes (cells of the heart) have many different types of voltage gated channels for responding to electrical signals.

3. **Mechanically Gated Channels**: These are triggered by distention or physical force applied to the membrane to open or close the channel.

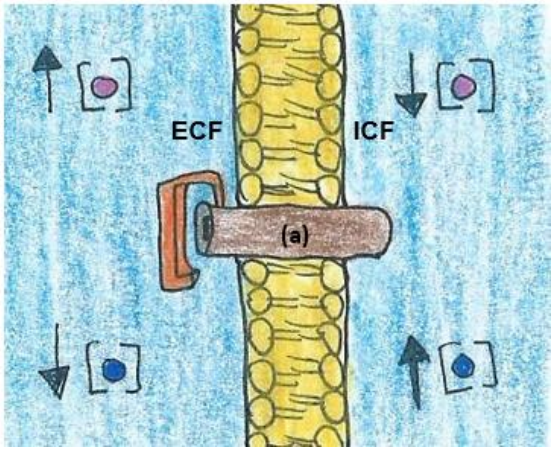
Examples in the Body: Cells in the skin, in lung tissue, and in the heart are very sensitive to changes is physical distention, such as stretching and applied pressure, and these channels respond to mechanical (physical) deformation (changes) in the membranes of cells.

How is the direction of flow through a protein channel determined?
Basically, the direction of flow through a protein channel is determined by the *gradients* present for the given substance. As we shall see more fully, there is an **electrical and chemical gradient** (difference) that exists across the plasma membrane. When no ATP is involved, substances will move down their electrical and chemical gradients - more on this soon in the transport mechanism section ahead.

For now, we can say it is the concentration and electrical gradients of a molecule on either side of the plasma membrane that will determine which direction a substance travels through an open protein channel. For instance, if a molecule has a high concentration in the ECF and a low concentration in the ICF, spontaneously that molecule will move from high to low concentration, or in other words, *down its concentration gradient*, thus it will move from the outside (ECF) to the inside (ICF) of the cell.

Exercise: In the diagram below (**Fig. 5.9**), both molecules are shown with concentration brackets ([o]) and both could fit through the gated protein channel. Now think about which molecules would travel which direction through the gated ion channel if the closed gate were opened and why.

Even if we do not know what the types of ions are, or the values of their concentrations, we can just work from the concentration gradients shown and predict the direction they would move. Also, even though the gate appears on the extracellular surface, a molecule can travel into or out of the cell via this channel.



(b) Analysis for each substance:

This substance would move from high to low concentration, and go from the ECF where it is high and move into the ICF where it is lower.

This substance would move from high to low concentration, and go from the ICF where it is high and move out into the ECF where it is lower.

Figure 5.9 Here is a gated protein channel **(a)** and there are two different types of molecules in the ECF and the ICF. Relatively speaking, the arrow up means high and the arrow down means low, with the square brackets [ ] are shorthand for 'concentration' of the mystery substances. The analysis **(b)** for each is discussed.

In the next chapter, which is **neurophysiology**, we will need to be familiar with how **gated ion channels** play an incredibly important role in cell signaling. Recall that protein channels are for the transport of water and small charged particles, or ions, such as K^+, Na^+, and Cl^-, etc.

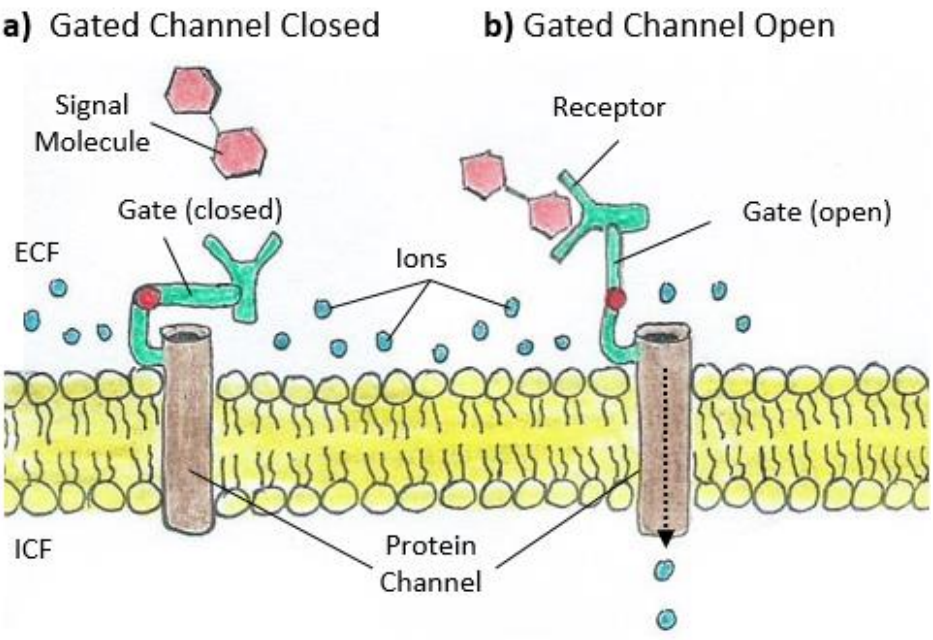


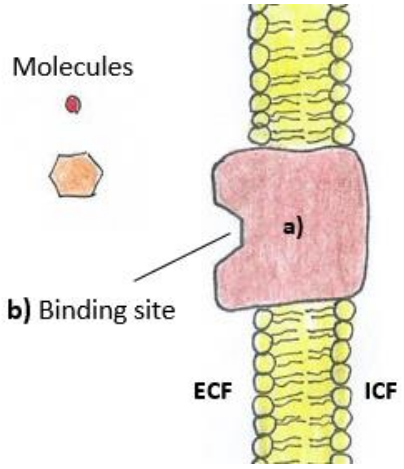
Figure 5.10 Shown diagrammatically embedded in the membrane is a ligand gated ion channel, which is **a)** closed, and in this configuration nothing can pass through it. When the signal molecule binds to the receptors linked to the gated channel, it triggers a conformational change and **b)** the gate is swung open, allowing the small ions (whatever they may be will vary) through the protein channel down their gradients. This will cause a change in the cell.

From **Figure 5.10** above we can see an example of a theoretical **ligand-gated** protein channel. On the left the ion channel is in the closed configuration and no current is flowing because when gated ion channels are closed nothing can travel through them! The key to opening a ligand gated ion channel is that a **ligand** or **signal molecule** (in this instance they both mean the same thing) binds to the receptor portion of it. When the signal molecule binds the receptor, it triggers the opening of the gate. This now allows the inward (**influx**) or outward (**efflux**) movement of ions, this will depend on whatever the channel is specific for. The signal molecule is most often a **neurotransmitter** or a **hormone**.

2. Protein Carriers

The second type of protein transporters are called protein carriers. These never form a direct or continuous passage between the ECF and the ICF, as seen **in Fig. 5.11**. It is not a tunnel like channels are. Protein carriers have a ***binding site*** (like enzymes) and will only transport specific molecules that match this site. Once the molecule binds to the site, the protein carrier undergoes a conformation (shape) change. It can rotate, or close at one end while it opens at the opposite end, in this way carrying the molecule across membrane. This mode of transportation is slower than protein channels, as it requires a little more time to bind the substrate and then change shape in order to move the substrate.

Question: What types of molecules will get through the membrane with this transporter?



A protein carrier is typically used for transporting **larger**, **polar** molecules across a plasma membrane. A perfect example is **glucose** ($C_6H_{12}O_6$) which has a MW of 180, so it is a **larger molecule**, but it's not massive like starch or albumin. It is also a **polar molecule**, meaning it is soluble (mixes) in water. **Amino acids** are another good example of molecules moved by protein carriers. As seen in the illustration to the left (**Fig. 5.11**) a carrier is not a direct tube between ECF and ICF (like channels are), they need for their substrates to bind first in order to cause the conformation changes required to transport molecules from one side of the membrane to the other.

Figure 5.11 Here is a protein carrier **a)** with two different types of molecules in the ECF trying to get into the cell. Protein carries have highly specific binding sites **b)** for the substances they transport, and binding them will trigger conformation changes that will move the molecules to the other side of the membrane.

Keep in mind these main concepts about any **Protein Carrier**:

- They allow passage of **larger molecules**, e.g., **Glucose**, with a molecular weight of 180.
- They have very specific **binding sites** for their substrates.
- They are **not direct conduits** between ECF and ICF, but instead must experience **conformation changes** in order to transport any molecules.
- They move substances **more slowly** that channels, due to the time it takes to bind and change shape or spin around.
- They are **very specific** and on carrier often only transports one type of substance through it.

There are three general types of Protein Carriers:

1) Uniport: Moves only one kind of molecule in one direction.

2) Symport: Moves at least two molecules in the same direction.

3) Antiport: Moves at least two molecules in the opposite directions.

See all of these in **Fig. 5.12** below. Note that "co-transport" is when a protein transporter moves more than one molecule at a time, so both **symport** and **antiport** are types of co-transport.

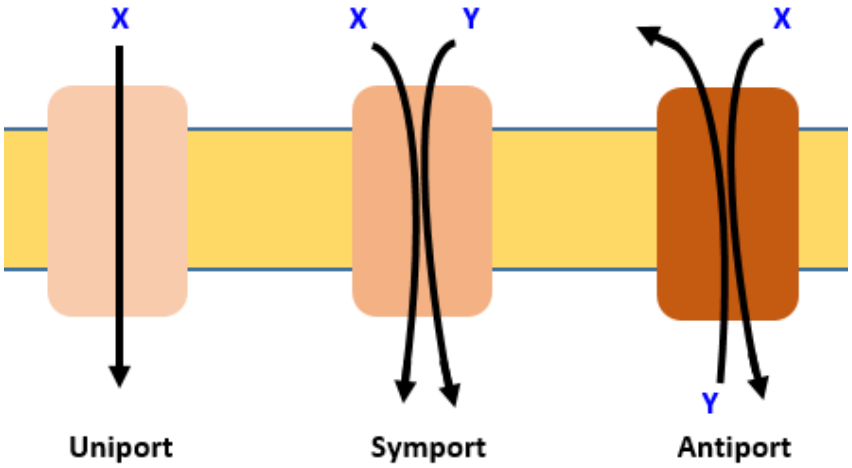


Figure 5.12 Shows the three general types of protein carriers. Uniport, which here moves only one molecule X at a time in one direction. Symport moves both X and Y in the same direction (into or out of the cell). Antiport moves X and Y in opposite directions at the same time.

Properties of Protein Carrier Mediated Transport

Because of the way that protein carriers work, their transport exhibits these three characteristics: specificity, competition and saturation.

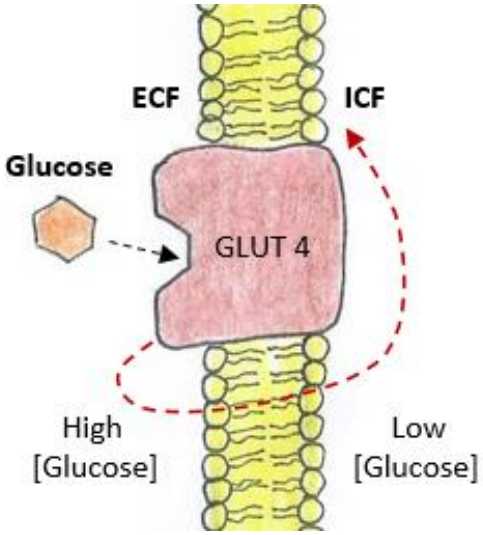


Figure 5.13 The GLUT 4 transporter is a protein carrier that specifically moves glucose across the membrane after conformational changes.

1. Specificity

Protein carriers are usually *very specific* regarding what they move, as the molecule being transported must match or fit the **binding site** on the carrier in a specific way that triggers the conformational change that will spin the carrier around, or open the opposite end, whatever the alteration might be, to get the molecule to the other side of the membrane.

For example, some carriers move **glucose**, and they are called **GLUT transporters** (see **Fig. 5.13** to the left). Like all protein carriers, the binding of the ligand glucose causes conformational (shape) changes in the carrier that stimulates transport of the glucose from one side of the plasma membrane to the other, from high to low concentration.

Other carriers may move a family of closely related molecules, such as glucose, mannose, galactose, and fructose across membranes. Those ones are specific for naturally occurring *6-carbon monosaccharides*. Still other carriers will transport amino acids, with up to 20 different types of protein carriers for this, each type specific for the 20 different amino acids the human body uses.

2. Competition

Carriers have a preference (or affinity) for certain molecules. This can result in *competition* for the binding site between various similar molecules. If another substance that is not the *true ligand* can bind to the carrier protein, this is a form of **inhibition** of transport of the true ligand (see **Fig. 5.14**).

For example, **maltose** is a **disaccharide** made of **2 glucose molecules**, so one end of the maltose is very much like glucose, and it could try to occupy the binding site for a glucose specific transporter. Although it can bind to the transporter, typically it will not be transported in the process, as it is not the right shape overall. That extra bit will be too clunky! Thus, in this case, maltose would be a **competitive inhibitor** to glucose transport because it 'took a seat' that glucose would normally occupy, and by doing so prevented the glucose from being transported. Even if the maltose could be transported across the cell, it has still competitively inhibited glucose from being transported.

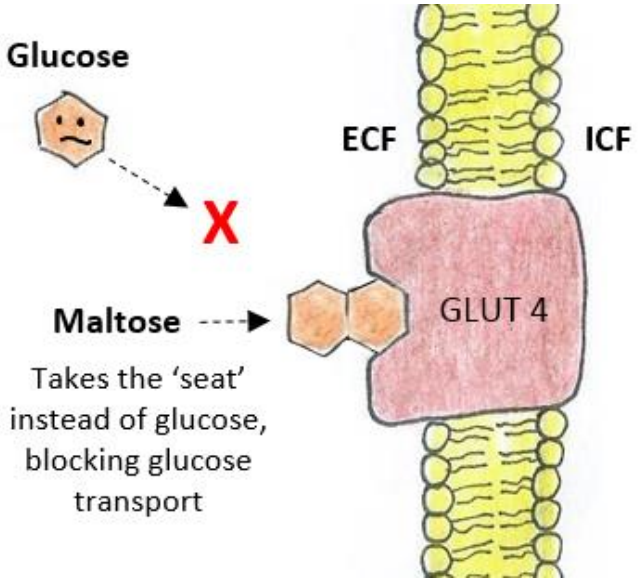


Figure 5.14 The transport of glucose is unfairly inhibited by another molecule that is able to occupy the binding site and sadly therefore prevent the glucose from binding and being transported.

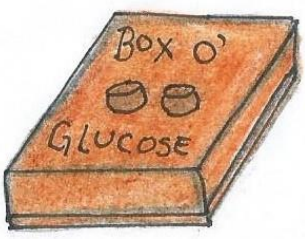
3. Saturation

Saturation occurs when a group of protein carriers are transporting their substrate at its **maximum rate**, with all carriers occupied. In other words, it's like they are at full capacity. Saturation will depend on the number of available carriers and substrate concentration. Cells can sometimes increase or decrease the number of available carriers to control substrate movement. As the substrate (molecule) concentration increases, **transport rate increases until the carriers become saturated**. At this stage, called saturation, they are at their maximum transport capacity and cannot move things across the membrane any faster.

Day-to-day Example

An interesting consequence of carrier saturation can be seen in the transport of **glucose** in the **kidney**.

Question: Normally, should not find any glucose in your urine? Answer: No. As we will see in detail in the renal section, any glucose that is filtered by the kidneys is *reabsorbed* by the body so that normally no glucose is eliminated in the urine. If there is glucose in the urine it is called **glucosuria** and can be a sign of **diabetes mellitus**. However, if a person were to consume large quantities of glucose, say by eating too many chocolates from a thoughtful giant gift, the glucose carriers in your kidney tubules can become **saturated** due to the abnormally high amounts of glucose being filtered by your renal system. If the carriers reach their maximum rate and more glucose remains in the filtrate, glucose will end up in the urine due to protein carrier saturation, because the amount of substrate (in this case glucose) is too high for the carriers to transport all of it fast enough. As a consequence, a person may have glucose in their urine that is not due to diabetes mellitus, but more likely due to chocolitis maximitis.



Molecule Transported Across a Cell: Passive and Active Transport

There are many ways that molecules can get from one side of a plasma membrane to the other, but there are only two categorical ways a molecule can be transported across a cell membrane, and they are **Passive Transport** and **Active Transport**. Simply stated, passive transport is the movement of substances across the membrane *without energy* required and, in contrast, active transport is the movement of substances across the membrane *using energy.* Cellular energy is traded with adenosine triphosphate (ATP).

① **Passive Transport: Does not require energy** (ATP). This only involves movement of a substance down its gradient. This can be an electrochemical gradient, a pressure gradient, a thermal gradient, etc. Most commonly in our studies, the concentration (chemical) gradient is the driving force for passive moment of molecules in the body. There are 3 basic categories of Passive Transport in the body:

1) Diffusion

2) Facilitated diffusion

3) Filtration

Let's examine each of these three types of passive transport in detail.

1. Diffusion

Diffusion is the net movement of molecules from an area of higher concentration of that molecule to an area of lower concentration of that same molecule. In other words, it is the movement of the molecule ***down its concentration gradient***. It is going from High to Low, like rolling a ball downhill. This is a passive transport mechanism. For example, getting in a kayak and going down stream (in the same direction as the flow of the river) is an example of passive transport because no energy expenditure is required to be moved; you can just sit there enjoying the scenery and be moved down stream without any effort. In the body, the net movement of molecules continues down its concentration gradient until **equilibrium** is reached (see **Fig. 5.15**). Diffusion can occur in open regions or across a partition such as a membrane.

Factors that Influence the Rate of Diffusion

Diffusion is a very common and important mode of transport in the human body. The oxygen (O_2) that enters our blood stream from our lungs does so by simple diffusion. A useful thing to understand in human physiology is what factors affect the rate of diffusion of a molecule from one side of a plasma membrane to the other. Listed below are some of the important factors that affect the rate (how quickly) diffusion takes place.

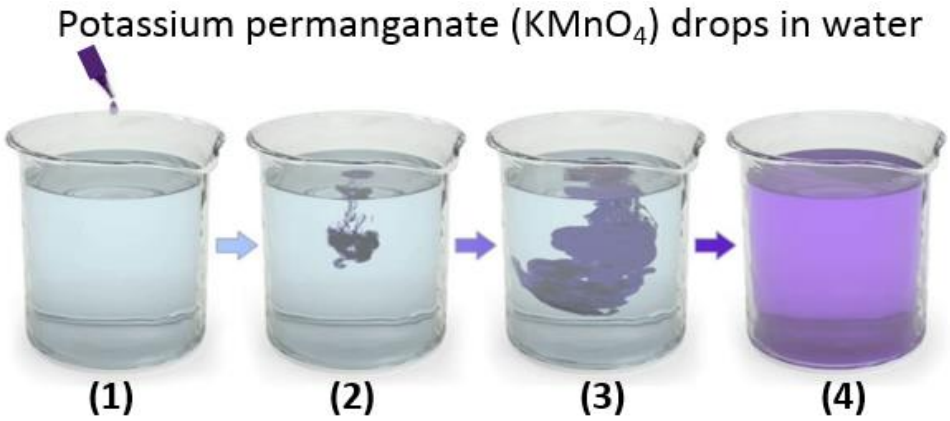


Figure 5.15 Diffusion is seen with the very colorful chemical potassium permanganate ($KMnO_4$) as it is dropped into a beaker of room temperature distilled water **(1)**. Over a period of time, the crystals in solution move to where they are less **(2)** and **(3)**, displaying various degrees of diffusion until reaching equilibrium, shown at **(4)**.

Factors that have an effect on the Rate of Diffusion:

1) Size of the molecule (as indicated by its MW) – smaller = faster.
2) Distance to travel – shorter = faster.
3) Temperature of surroundings – warmer = faster.
4) Surface area of membrane – greater = faster.
5) Thickness of barrier – thinner = faster.
6) Steepness of concentration gradient – greater = faster.

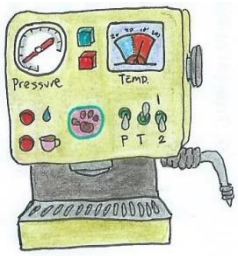
As we continue in physiology, all of these factors listed above about diffusion will be revisited in the various organ systems we will encounter. The movement of substances in the body and what causes them to move more slowly or more quickly is such an important concept in physiology that it is worth taking a little bit of time to be familiar with these factors now.

2. Facilitated Diffusion

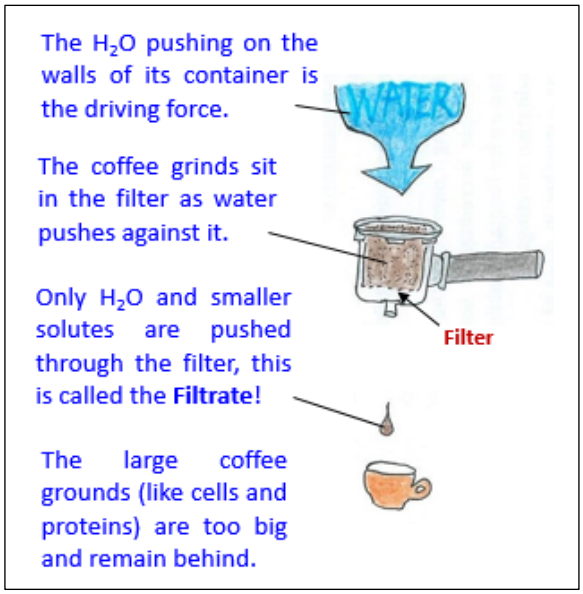
Some molecules that are polar or too big to use simple diffusion to get across a membrane can get the **assistance of a protein carrier** to move ***down their concentration gradient***. This requires no energy. This is different from simple diffusion because the molecules must bind to the membrane carrier (as discussed above and seen in **Figure 5.9**), in this way it needs the 'help' of a protein carrier to move down its gradient across the membrane. As long as it is going down its concentration gradient, it is still diffusion, but the term 'facilitated diffusion' indicates that the molecule is getting some assistance from a protein carrier. As we have seen, this process is also prone to *specificity*, *competition* and *saturation*.

3. Filtration

Filtration is the net movement of water and solutes across a membrane due to the force of hydrostatic pressure (HP). Think of making coffee…



Hydrostatic pressure can be defined as the force of a fluid on the walls of its container. Any fluid in any container exhibits hydrostatic pressure. The water in a cup has hydrostatic pressure, as the water exerts a force on the cup containing it. A useful analogy for **filtration** is making coffee (see the boxed example to the right). If you place ground coffee in a filter (a container with pores) and pour water over the top of it, the filter allows water and small solutes to pass through the pores, but not the bigger coffee grinds. What you get on the other side of the filter is a 'filtrate' of what was above, that is, anything small enough to pass through the holes of the filter, and in this case a nice cup of coffee. The **filtrate** comes from the process of 'filtration'.



In human physiology, a perfect example of **filtration** is what occurs across every capillary blood vessel in the body. As shown in **Figure 5.16** below, the **hydrostatic pressure** of blood in a blood vessel pushes the fluid portion of blood, called plasma (which is mostly water and small solutes) across the blood vessel wall into the interstitium. This is a normal function of most blood vessels, as we shall see later.

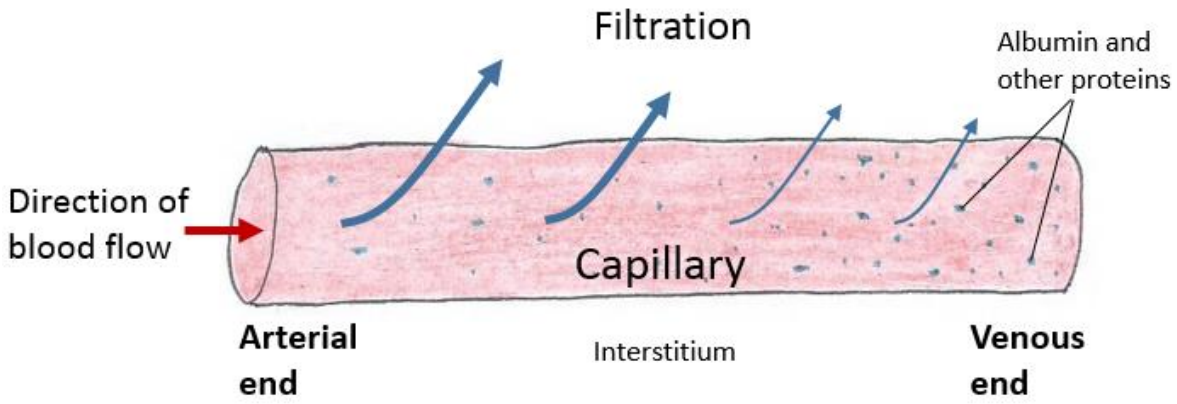


Figure 5.16 The capillary has higher hydrostatic pressure at its arterial end than at its venous end, this is why blood flows in that direction down its pressure gradient, from arterial to venous end. Fluid and solutes are filtered out into the interstitium along the way, with less and less force (as shown by the diminishing strength of the arrows) toward the venous end. The larger plasma proteins, like albumin, are too large to be pushed across the capillary wall and remain inside the blood vessel.

② **Active Transport: Requires energy input** (ATP). If energy is required, it means that something is being moved up a concentration gradient. There are three (3) basic categories of Active Transport in the body:

1) Primary (direct) active
2) Secondary (indirect) active
3) Vesicular transport

In biology, the active transport of a substance requires the input of energy from ATP. This ATP is required because molecules are being moved ***up or against their concentration gradients***. It is the transporter proteins that move these molecules *against* their concentration gradients. In any living system, it is important to understand that creating and maintaining a state of ***disequilibrium*** across a membrane in the body is very important and useful. Creating and maintaining disequilibrium requires the input of energy. Active transport can be the movement of one or more substances across a membrane. The three (3) categories of active transport are now explored in detail below.

1. Primary Active Transport (Direct)
In primary active transport, energy from ATP is *directly* used to transport molecules *against* their concentration gradient.

The best example of this is the Na^+/K^+-ATPase, also referred to as the '**Na^+/K^+ pump**'. This is thought to be a membrane spanning protein carrier. Please note the *–ase* ending on its official name. This indicates that it is also an **enzyme** that ***hydrolyzes*** (breaks bonds with water) ATP to get its energy.

This transporter works non-stop to continuously **expel 3 Na^+ ions** out of the cell and at the same time **import 2 K^+ ions** into the cell per cycle. In the body, both Na^+ and K^+ ions constantly leak down their concertation gradients, therefore this Na^+/K^+-ATPase acts much like a pump that is *bailing out a leaky ship*. This transporter is moving both ions, Na^+ and K^+, against their concentration gradients, therefore we know that ATP must be required because this movement requires energy and that is defined as active transport. Each cycle of the pump requires 1 ATP molecule, which is hydrolyzed to ADP + P_i + Energy and heat!

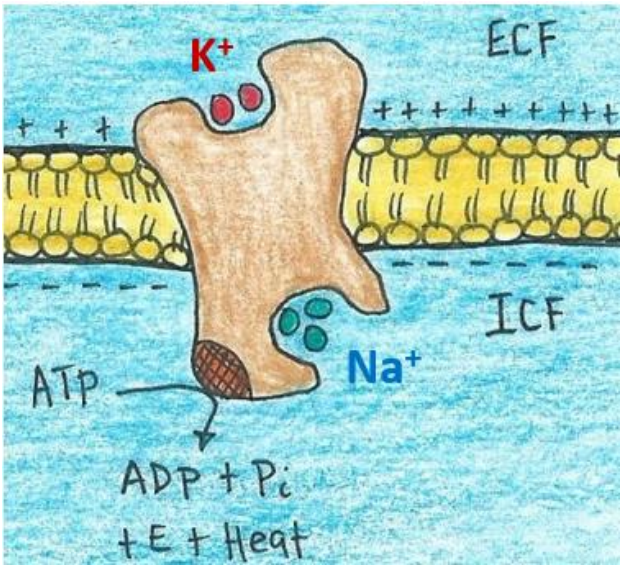


Figure 5.17 The Na^+/K^+ is shown embedded in the plasma membrane where it actively transports 2 K^+ ions (red circles) into the cell, and 3 Na^+ ions (green circles) out of the cell at the cost of 1 ATP per cycle.

The diagrammatic Na^+/K^+ pump to the left (**Fig. 5.17**) shows a membrane spanning protein carrier with binding sites for the $2K^+$ ions on the ECF aspect, and for the $3Na^+$ ions on the internal ICF aspect of the plasma membrane. The hydrolysis of 1 ATP molecules powers 1 'spin' of the transporter and delivers $2K^+$ ions into the cell and ejects $3Na^+$ ions to the outside of the cell.

This constant action of the Na^+/K^+ pump causes a slight electrical imbalance across the membrane, such that it is slightly positive on the outside and slightly negative on the inside of the cell (see the + and – charges in drawing). This makes sense since the constant ejection of 3 positive ions compared to the import of only 2 positive ions results is a small positive charge on the outside and negative on the inside of the cell.

This is an **antiport** mechanism because the molecules are being transported in **opposite** directions. The Na^+/K^+ pump helps to maintain the **resting membrane potential** (**RMP**) across the plasma membrane of all living cells.

2. Secondary Active Transport (Indirect)

In secondary active transport, the ATP is used *indirectly* to move molecules across membranes. Essentially what this means is the potential energy that is stored in a concentration gradient is used to help move molecules across a membrane (see **Fig. 5.18**).

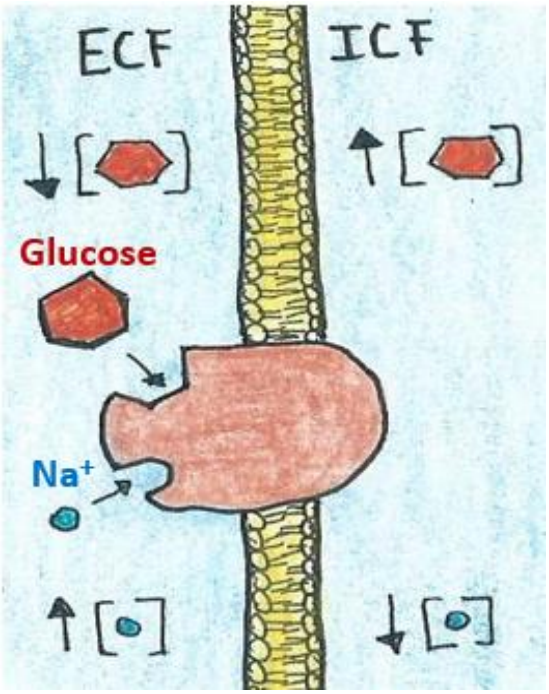


Figure 5.18 The Na^+/glucose carrier is shown in the plasma membrane where it passively transports a Na^+ ion (green circle) into the cell, while at the same time actively moving glucose (red pentagonal) into the cell.

An excellent illustration of how this is done can be seen in the **Na^+/glucose transporter**. The relative concentration of Na^+ is low on the inside of the cell and high on the outside of the cell. When Na^+ moves down its concentration gradient (into the cell) this force is harnessed to move glucose *against* its concentration gradient by pulling it into the cell along with it.

While the Na^+ goes down its gradient, the glucose can be dragged along with it, even though it is being pulled up hill, so to speak, against its concentration gradient.

The original source of ATP that allows this to occur is the ATP used in the Na^+/K^+ pump described above, because it is that Na^+/K^+ pump that maintains the low Na^+ concentration inside the cell.

This mechanism described in the Na^+/glucose transporter is a **symport** transport because both molecules are being transported in the **same** direction.

3. Vesicular Transport

Vesicular transport is used to move large macromolecules or large quantities of a molecule across the plasma membrane with vesicles. **Vesicles** are like mini lipid bilayer bubbles that bud off from the plasma membrane and encapsulate large molecules within them (see **Fig. 5.19** below). This is an active form of transport that directly requires energy in the form of ATP for the maneuvering of the cytoskeleton which causes the formation, movement and invagination of the vesicles.

The Two main Types of Vesicular Transport

There are two main forms of vesicular transport, they are **1) endocytosis** - the process of capturing a substance or particle from outside the cell by engulfing it within a vesicle and pulling it into the cell, and **2) exocytosis** - the process of vesicular fusion with the plasma membrane and releasing contents of vesicle outside of the cell.

1. Endocytosis - bringing material into the cell, inward vesicular transport. The prefix 'endo' means in and 'cyto' means cell. There are three general kinds of endocytosis (see **Figures 5.19** and **5.20**).

A) Pinocytosis (cell drinking): Relatively unselective whereby ECF is transported into the cell.

B) Phagocytosis (cell eating): Which is a process whereby cells engulf a particle or another cell into a much larger vesicle, e.g., certain types of WBC (**macrophages**) engulf bacteria this way.

C) Receptor-Mediated Endocytosis: This is a very selective process, and it is shown in detail in **Fig. 5.20** (below). The receptors on the external surface of the plasma membrane bind specific ligands.

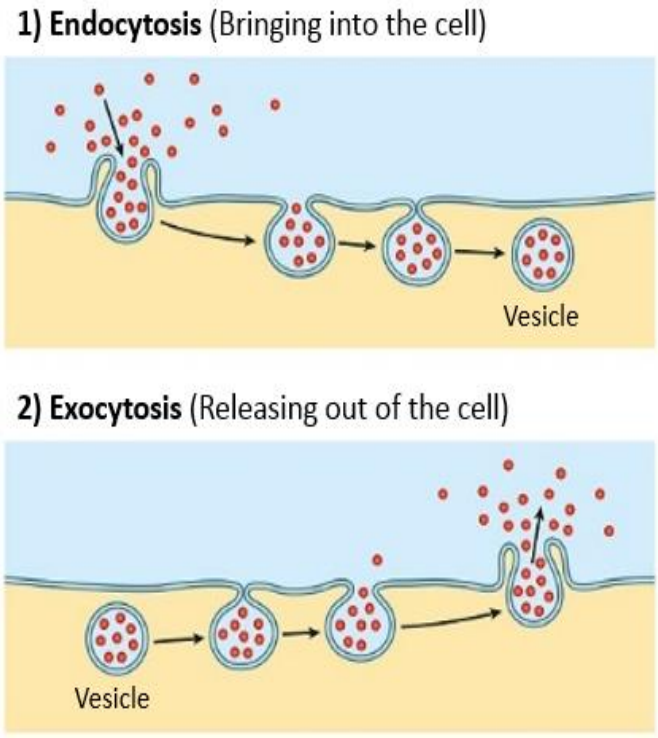


Figure 5.19 Above is **1)** endocytosis, and below is the opposite of that, **2)** exocytosis, both of which occur across the cell membrane.

This ligand-receptor complex creates a coated pit (also called a 'clathrin-coated' pit). It is a type of invagination of the membrane that is triggered by the binding of the ligand (the substance that the cell wants to bring in). The membrane then pinches this off and becomes a cytoplasmic **vesicle**, ingesting the ligand-receptor complexes. After the contents are harvested by the cell, the vesicle membrane and receptors are recycled to the surface plasma membrane and used again.

All three of the vesicular mechanisms discussed above are forms of endocytosis, that is, bringing materials into the cell. Keep in mind that vesicular transport is always for the movement of large macromolecules or large amounts of a substance.

2. Exocytosis – id the releasing material from the cell, this is the outward transport of cell contents via vesicles. The prefix 'exo' means out and 'cyto' means cell. This type of transport is used by many cells to secrete or release *large molecules* or *large amounts* of a molecule. Intracellular vesicles fuse with the plasma membrane, then releases its contents into ECF.

This process, like endocytosis, requires energy (ATP) and Ca^{2+} and also involves other proteins. An excellent example of how this process of exocytosis is commonly used in the body is the proposed release of **neurotransmitters** from **neurons** into the synaptic cleft. This process is also used to secrete large lipophobic molecules, such as hormones, protein fibers and mucus across cell membranes. Exocytosis is also thought to be used to insert proteins, such as receptors and GLUT transporters, into membranes.

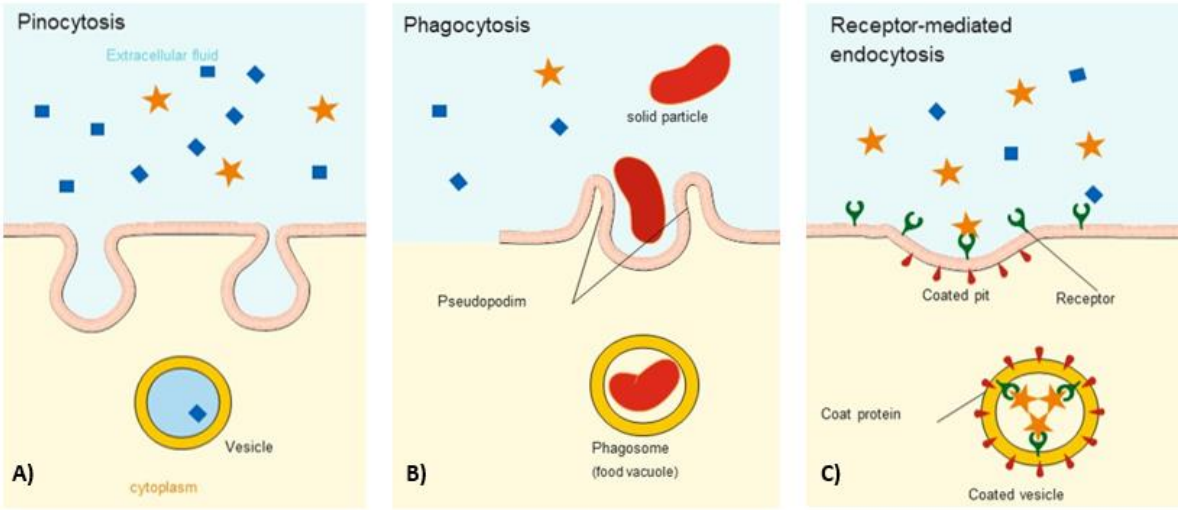


Figure 5.20 Shows **A)** pinocytosis which is non-specific 'cell drinking'. In **B)** it shows phagocytosis which is ingestion of large solids or cells, a type of 'cell eating'. Finally in **C)** it shows receptor-mediated endocytosis, the most selective process of bringing large materials into the cell within vesicles.

Transcytosis and Vesicular Transport

Transcytosis means movement across (trans) a cell (cytosis); it can involve endocytosis, vesicular transport across cell, and exocytosis out of the cell at the other end. So the substance has moved completely ***across*** the entire cell. This transcytosis provides for movement of large proteins intact, e.g., the absorption of maternal antibodies through breast milk, or the movement of proteins across the capillary endothelium.

Transport across Epithelial Linings

Now that we have covered all of the important types of transport across a cell membrane, it will be useful to put things into context by exploring an example of how all of these modes work together in the body. In **Fig. 5.21** below is a drawing of two epithelial cells that cover or line the innermost surface of the gastrointestinal (GI) tract. These epithelial cells are part of a mucous membrane and they exhibit 'polarity; the term in this sense means there is a 'sidedness' to the cell. That is, there is a top (exposed) side and a bottom (anchored to the tissue below) side. The exposed top side it called the **apical end**, this faces the lumen of a tube or canal. The anchored side is called the **basal end**, this faces the underling connective tissue of the membrane. The cell will have different transport proteins embedded in different regions of the cell, for reasons that will become obvious. As you can see, the two adjacent cells are attached together along their lateral borders.

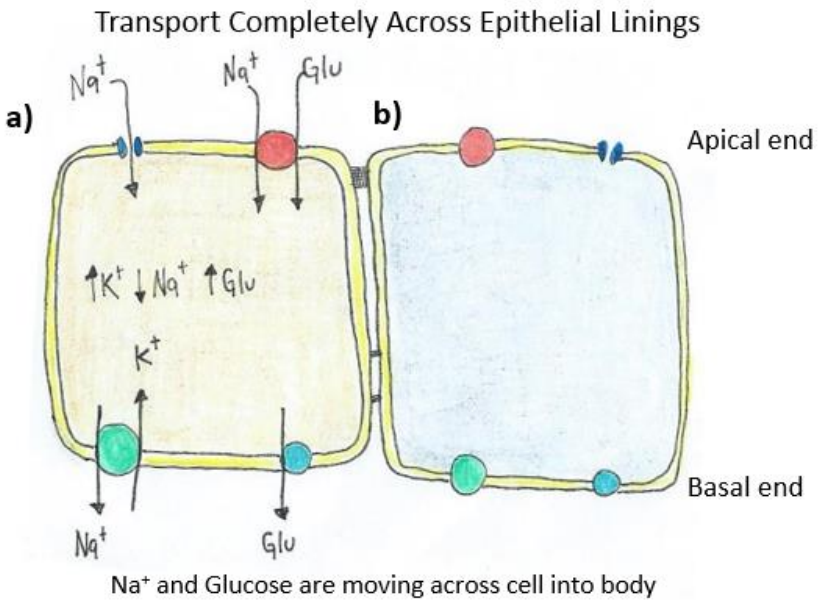


Figure 5.21 The two cells **a)** and **b)** above are good examples of the type of epithelial cells that line the gastrointestinal (GI) tract. They have the various protein transporters in their plasma membrane, usually with specific transporters at the apical (top) and basal (bottom) ends, to achieve transcytosis of many substances. Cell **a)** displays the various concentration gradients that promote the importation of Na+ and glucose from one end of the cell, and the export of these same substances at the basal end of the cell.

As a good summary example of the various types of transport discussed so far, and exemplified in **Fig. 5.21** above, is the transport of molecules across epithelial linings and it is called **transepithelial** movement. These cells have the various protein transporters in their plasma membrane, usually with specific apical (top) transporters and basal (bottom) transporters to achieve ***transcytosis*** of many substances.

Walking through the example in **Fig. 5.21** above, cell **a)** has various concentration gradients set up by the body between the outside and the inside of the cell, and this plays a significant role in how a substance will travel across a cell. Looking at the Na^+-glucose symport, it is on the apical aspect of the membrane, and the Na^+/K^+-ATPase is only on basal end (bottom side) of the membrane. Thus, this cell is set up to transport glucose across it. Furthermore, epithelial cells engaged in actively transporting materials can alter their permeability by inserting or withdrawing various membrane proteins.

Transport of Glucose

Although glucose is a large polar molecule (thus it has 2 strikes against it for an easy passage across a cell), there are two different transport systems to move glucose across epithelial cells (see **Fig. 5.22**):

1. Secondary active transport. The Na^+/glucose symport from the lumen of the gut into the cell through the apical membrane. This is made possible by the continuous active transport of Na^+, constantly being ejected across the basolateral membrane of the cell via Na^+-K^+-ATPase.

2. Glucose can also move across a membrane down its concentration gradient by facilitated diffusion, as seen in in the glucose carrier protein across basolateral membrane of the cell.

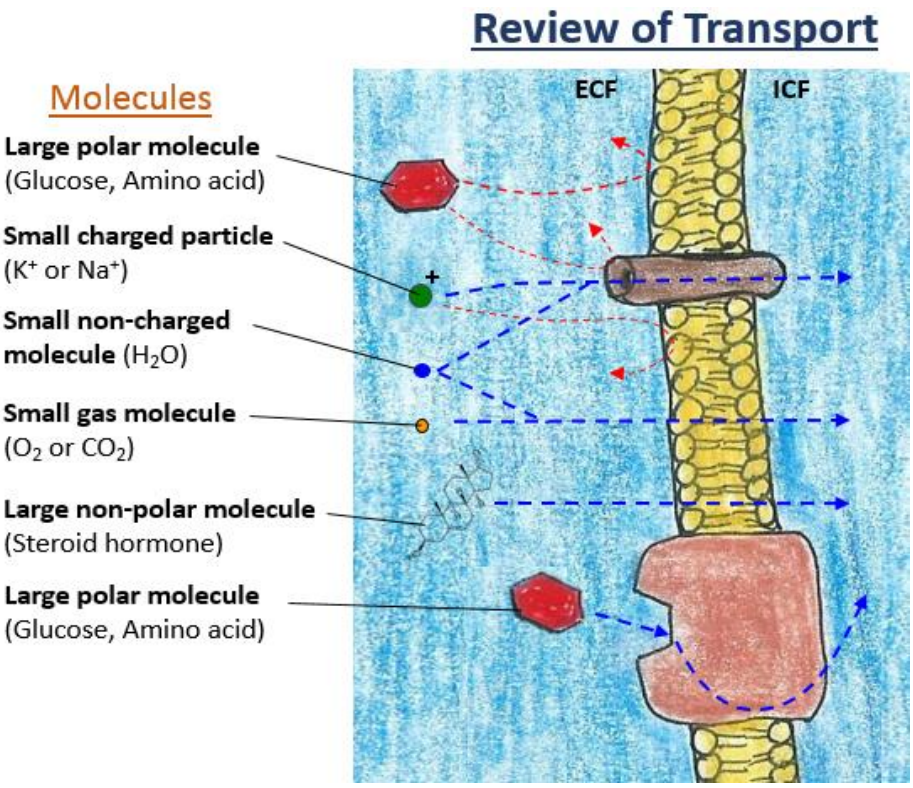


Figure 5.22 Shows a drawing of a hypothetical membrane. As a review, the list of molecules on the left (with their characteristics) is put into action in the diagram to the right, in terms of examining their permeabilities. A dashed blue arrow going all the way across the membrane indicates successful crossing of the molecule with that mode of transport – via a protein channel, carrier or directly through the plasma membrane. The dashed red line indicates impermeability of molecule in that route indicated.

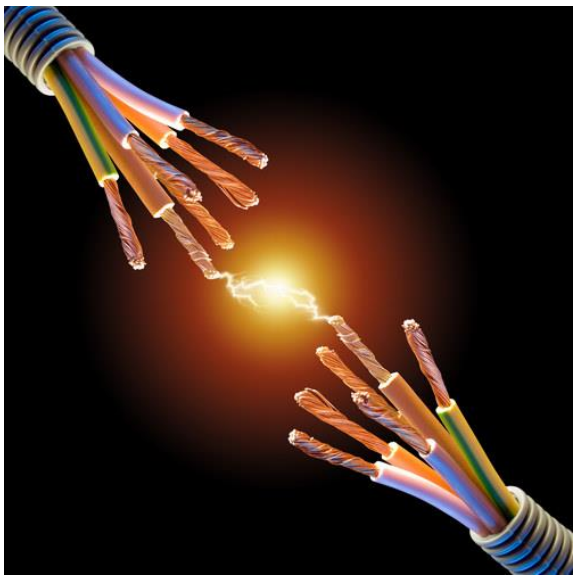
Electrochemical Disequilibrium

It is pivotal to understand that the body's cells are in a state of electrical and chemical disequilibrium, and this is a useful state as it provides power to the cells, like a battery, for them to be able to do things!

There is a difference in the electrical charge between the two sides of the plasma membrane. In living cells, it is slightly negative inside the cell and slightly positive on the outside. This is termed the **electrical disequilibrium**, since they are not at equilibrium. The major intracellular ions are K^+, phosphate (PO_4^{3-}) and to some degree proteins, and the major extracellular ions are Na^+, Cl^- and Ca^{2+}. Thus, there is a difference in the concentrations of chemical between the two sides of the plasma membrane. This is termed the **chemical disequilibrium**. Together, this is referred to as the **electrochemical disequilibrium** and this creates the Resting Membrane Potential (RMP) of all living cells.

Electricity and Electrical Signals

Atoms are electrically neutral. Ions are created as electrons are added or removed from an atom, making a cation (+) or an anion (-). The flow of charged particles is an electric current, and as we will see, the human body is super charged with flowing electrical currents everywhere!



There are important principles for electricity in physiological systems. For example, opposite charges attract, like charges repel and energy is required to separate opposite charges or bring together like charges. Conductors of electrical charge allow free movement of positive and negative charges whereas **insulators** prevent movement of charged particles, and as it turns out, cell membranes are insulators.

Insulated Plasma Membrane

The plasma membrane is a crazy insulator that is not fully understood, but a key element is that it **allows work to occur across it**. Recall from chapter 2 that energy is the potential to do work, and work is moving things. In a way, the cell membrane turns out to be the most central important component of the cell.

In healthy organisms, the plasma membrane is set up to have electrical and chemical gradients across it. The separation of electrical charges and chemical concentrations across the lipid bilayer creates these gradients and this is a very powerful arrangement.

This electrochemical disequilibrium is also referred to as the **Electrochemical Gradient** and allows for work (moving things) to occur across the plasm membrane. This electrochemical gradient is created and maintained constantly by active transport mechanisms and selective membrane permeability to certain ions.

In the next chapter some good solid information about Physiological Solutions will be introduced (Chapter 6) and hopefully this relates back to some lab exercises. This groundwork will provide an excellent basis for delving into the physiology of the two control systems, the **nervous system** and the **endocrine system**, focusing initially on **neurophysiology** (Chapter 7), which is the way that it is thought nerve cells (neurons) communicate. These next areas will rely on the knowledge of the plasma membrane and the transport mechanisms presented in this chapter.

Review Questions for the Chapter 5: Plasma Membrane

1. A chondrocyte is a cell in _____ tissue; and hepatocytes are found in the _____.

a) Bone; kidneys.
b) Liver; cartilage.
c) Cartilage; liver.
d) Blood; gallbladder.
e) Cartilage; kidney.

2. Which of these is **not** a function or role of the plasma membrane?

a) It acts as a regulator of exchange into and out of the cell.
b) It provides structural support connecting to an internal framework of the cell.
c) It acts as a physical barrier giving protection to the cell from the outside environment.
d) It enables the cell to communicate, to send and received information.
e) It secretes hormones and other molecules to protect the exterior of the cell.

3. Compared to active transport, passive transport involves _____; and a specific example is _____.

a) movement up a concertation gradient; filtration
b) diffusion; vesicular transport
c) movement down a concertation gradient; Na^+/glucose symport
d) movement down a concertation gradient; facilitated diffusion
e) pumping molecules into a cell; Na^+/K^+ pump

4. For these molecules, which ones are properly paired with a transport mechanism that would get it across a normal plasma membrane? Select **all** that are valid and accurate. _____.

1) Large protein: Vesicle
2) O_2: Protein channel
3) Cl-: Simple diffusion through membrane
4) Fatty acid: Vesicle
5) Glucose: Protein carrier
6) CO_2: Simple diffusion through membrane
7) Amino acids: Vesicles
8) H_2O: Protein channel

5. Which of the statements about the role of cholesterol in the plasma membrane is true?

a) it acts as a chemical messenger
b) it gives stability to membrane
c) it acts as a lipophobic barrier
d) it attaches to the extracellular side for cell identity
e) it provides pores in membrane for ion transport

6. What force is responsible for **filtration** of water and solutes from the capillary into the interstitium?

a) the hydrostatic pressure of the blood
b) the amount of proteins in solution
c) the plasma colloid osmotic pressure
d) the continual action of the Na^+/K^+ pump

7. The Na^+/K^+ pump is
- **a)** a peripheral protein
- **b)** a structural protein
- **c)** an integral (spanning) protein
- **d)** non-specific
- **e)** a protein channel

8. The plasma membrane is normally <u>freely permeable</u> to all of the following substances **except**:
1. glucose **2.** fatty acids **3.** CO_2 **4.** K^+ **5.** water **6.** amino acids
- **a)** 6, 1 and 4
- **b)** 2, 5 and 3
- **c)** 1, 4 and 3
- **d)** 5 and 1
- **e)** 1 and 4

9. For **protein carriers** in the plasma membrane, which of these statements is most accurate?
- **a)** They do not always need to be membrane spanning proteins.
- **b)** They change conformation when they bind their transport molecules.
- **c)** Not all protein carriers have binding sites.
- **d)** Very small ions are constantly transported across the membrane with protein carriers.
- **e)** Some protein carriers are gated, requiring a trigger to move their ligands across the membrane.

10. Which of the following factors will <u>increase</u> the rate of diffusion of a substance?
1. a thinner barrier **2.** a decreased temperature **3.** a larger molecule weight **4.** a shorter distance
- **a)** 2 and 3
- **b)** 1, 2 and 4
- **c)** 4 only
- **d)** 2, 1 and 4
- **e)** 4 and 1

Answers in Appendix B