4. The term *transcytosis* refers to a process where material is transferred right through the thickness of a cell. The process is seen mainly in flat cells (e.g., endothelium). The transport takes place through invaginations of cell membrane called ***caveolae***. A protein ***caveolin*** is associated with caveolae (Fig. 1.8). Caveolae differ from coated pits in that they are not transformed into vesicles. Caveolae also play a role in transport of extracellular molecules to the cytosol (without formation of vesicles) (Fig. 1.9).

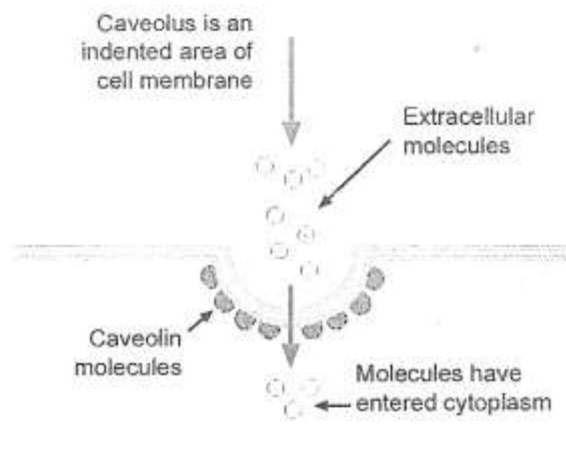

Fig. 1.9. Scheme to show how extracellular molecules enter the cytosol through caveolae. Endocytic vesicles are not formed. The process is called potocytosis.

Contacts between adjoining cells

In tissues in which cells are closely packed the cell membranes of adjoining cells are separated, over most of their extent by a narrow space (about 20 nm). This contact is sufficient to bind cells loosely together, and also allows some degree of movement of individual cells.

In some regions the cell membranes of adjoining cells come into more intimate contact: these areas can be classified as follows.

Classification of Cell Contacts

Unspecialised contacts

These are contacts that do not show any specialised features on EM examination. At such sites adjoining cell membranes are held together as follows.

Some glycoprotein molecules, present in the cell membrane, are called ***cell adhesion molecules*** (CAMs). These molecules occupy the entire thickness of the cell membrane (i.e., they are transmembrane proteins). At its cytosolic end each CAM is in contact with ***an intermediate protein*** (or ***link protein***) (that appears to hold the CAM in place). Fibrous

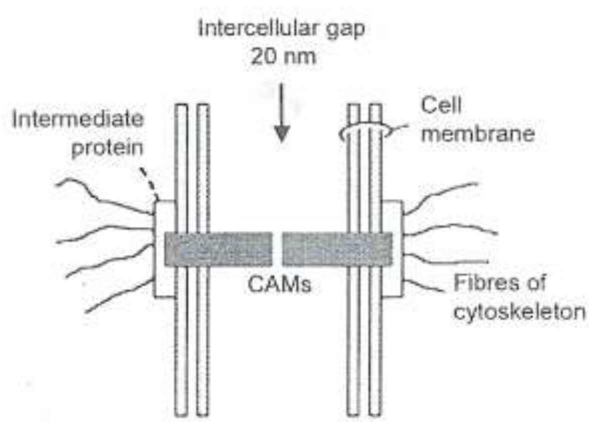

Fig. 1.10. Scheme to show the basic structure of an unspecialised contact between two cells.

elements of the cytoskeleton are attached to this intermediate protein (and thus, indirectly, to CAMs). The other end of the CAM juts into the 20 nm intercellular space, and comes in contact with a similar molecule from the opposite cell membrane. In this way a path is established through which forces can be transmitted from the cytoskeleton of one cell to another (Fig. 1.10).

CAMs and intermediate proteins are of various types. Contacts between cells can be classified on the basis of the type of CAMs proteins present. The adhesion of some CAMs is dependent on the presence of calcium ions; while some others are not dependent on them (Fig. 1.11). Intermediate proteins are also of various types (catenins, vinculin, α actinin).

Specialised junctional structures

These junctions can be recognized by EM. The basic mode of intercellular contact, in them, is similar to that described above and involves, CAMs, intermediate proteins, and cytoskeletal elements. Junctional areas that can be identified can be summarized as follows.

A. ***Anchoring junctions*** or ***adhesive junctions*** bind cells together, They can be of the following types.

1. ***Adhesive spots*** (also called ***desmosomes***, or ***maculae adherens***).
2. ***Adhesive belts*** or ***zona adherens***.
3. ***Adhesive strips*** or ***fascia adherens***.

Modified anchoring junctions attach cells to extracellular material. Such junctions are seen as ***hemidesmosomes***, or as ***focal spots***.

Fig. 1.11. Types of cell adhesion molecules

Type of CAM	Subtypes	Present in
CALCIUM DEPENDENT	Cadherins (of various types)	Most cells including epithelia
	Selectins	Migrating cells e.g., leucocytes
	Integrins	Between cells and intercellular substances. About 20 types of integrins, each attaching to a special extracellular molecule.
CALCIUM INDEPENDENT	Neural cell adhesion molecule (NCAM)	Nerve cells
	Intercellular adhesion molecule (ICAM)	Leucocytes

B. *Occluding junctions* (*zonula occludens* or *tight junctions*). Apart from holding cells together, these junctions form barriers to movement of material through intervals between cells.

C. *Communicating junctions* (or *gap junctions*). Such junctions allow direct transport of some substances from cell to cell.

The various types of cell contacts mentioned above are considered one by one below.

ANCHORING JUNCTIONS

Adhesion spots (Desmosomes, Maculae Adherens)

These are the most common type of junctions between adjoining cells. Desmosomes are present where strong anchorage between cells is needed e.g., between cells of the epidermis. As seen by EM a desmosome is a small circumscribed area of attachment (Fig. 1.12A). At the site of a desmosome the plasma membrane (of each cell) is thickened because of the presence of a dense layer of proteins on its inner surface (i.e., the surface towards the cytoplasm). The thickened areas of the two sides are separated by a gap of 25 nm. The region of the gap is rich in glycoproteins. The thickened areas of the two membranes are held together by fibrils that appear to pass from one membrane to the other across the gap.

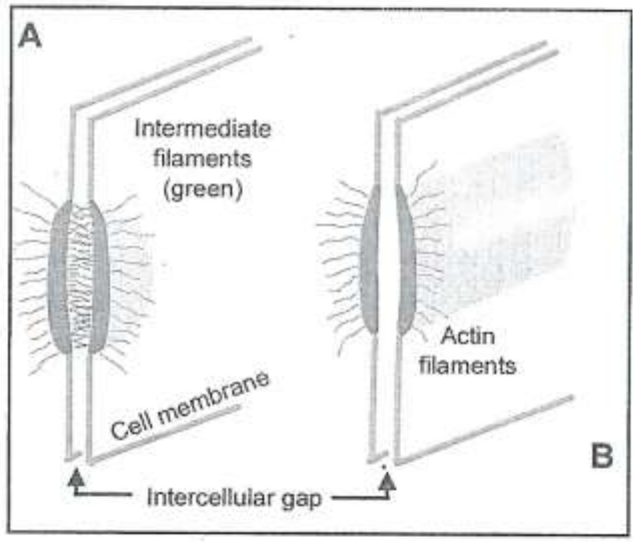

Fig. 1.12. A. EM appearance of a desmosome. B. EM appearance of zonula adherens.

We now know that the fibrils seen in the intercellular space represent CAMs (Fig. 1.13). The thickened area (or plaque) seen on the cytosolic aspect of the cell membrane is produced by the presence of intermediate (link) proteins. Cytoskeletal filaments attached to the thickened area are intermediate filaments (page 22). CAMs seen in desmosomes are integrins (desmogleins I, II). The link proteins are desmoplakins.

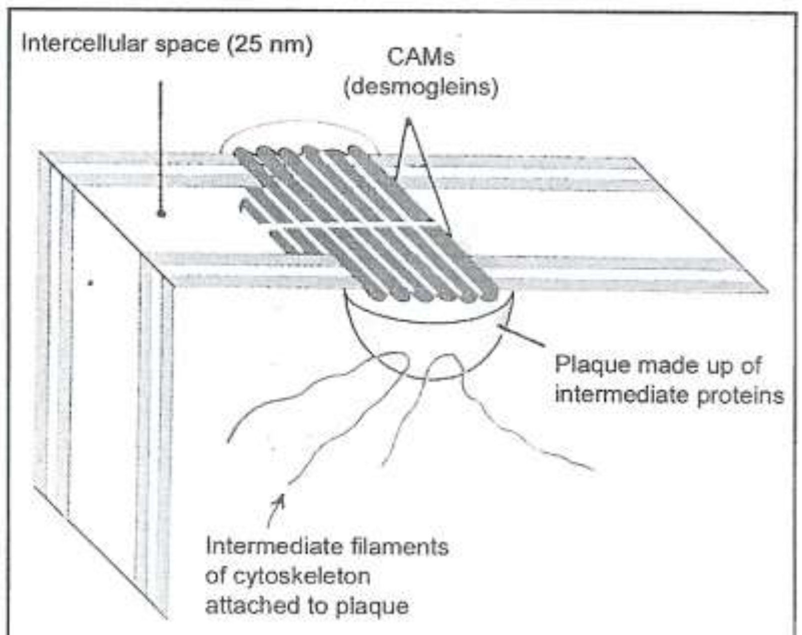

Fig. 1.13. Schematic diagram to show the detailed structure of a desmosome (in the epidermis).

Adhesive Belts (Zonula Adherens)

In some situations, most typically near the apices of epithelial cells, we see a kind of junction called the zonula adherens, or adhesive belt (Fig. 1.12B). This is similar to a desmosome in being marked by thickenings of the two plasma membranes, to the cytoplasmic aspects of which fibrils are attached. However, the junction differs from a desmosome as follows:

(a) Instead of being a small circumscribed area of attachment the junction is in the form of a continuous band passing all around the apical part of the epithelial cell.

(b) The gap between the thickenings of the plasma membranes of the two cells is not traversed by filaments.

The CAMs present are cadherins. In epithelial cells zona adherens are located immediately deep to occluding junctions (Fig. 1.16).

Adhesive Strips (Fascia adherens)

These are similar to adhesive belts. They differ from the latter in that the areas of attachment are in the form of short strips (and do not go all round the cell). These are seen in relation to smooth muscle, intercalated discs of cardiac muscle, and in junctions between glial cells and nerves.

Hemidesmosomes

These are similar to desmosomes, but the thickening of cell membrane is seen only on one side. As such junctions the 'external' ends of CAMs are attached to extracellular structures. Hemidesmosomes are common where basal epidermal cells lie against connective tissue.

The cytoskeletal elements attached to intermediate proteins are keratin filaments (as against intermediate filaments in desmosomes). As in desmosomes, the CAMs are integrins.

Focal spots

These are also called ***focal adhesion plaques***, or ***focal contacts***. They represent areas of local adhesion of a cell to extracellular matrix. Such junctions are of a transient nature (e.g., between a leucocyte and a vessel wall). Such contacts may send signals to the cell and initiate cytoskeletal formation.

The CAMs in focal spots are integrins. The intermediate proteins (that bind integrins to actin filaments) are α-actinin, vinculin and talin.

OCCLUDING JUNCTIONS (ZONULA OCCLUDENS)

Like the zonula adherens the zonula occludens are seen most typically near the apices of epithelial cells. At such a junction the two plasma membranes are in actual contact (Fig. 1.14A).

These junctions act as barriers that prevent the movement of molecules into the intercellular spaces. For example, intestinal contents are

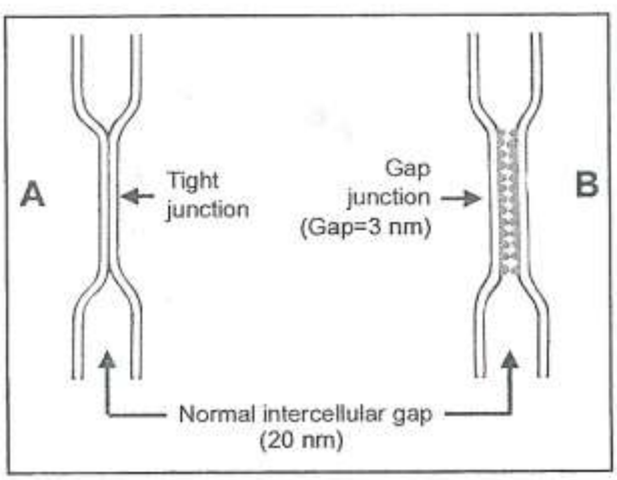

Fig. 1.14. A. Zonula occludens as seen by EM. B. Gap junction as seen by EM.

prevented by them from permeating into the intercellular spaces between the lining cells. Zonulae occludens are, therefore, also called ***tight junctions***.

Recent studies have provided a clearer view of the structure of tight junctions (Fig. 1.15). Adjoining cell membranes are united by CAMs that are arranged in the form of a network that 'stitches' the two membranes together.

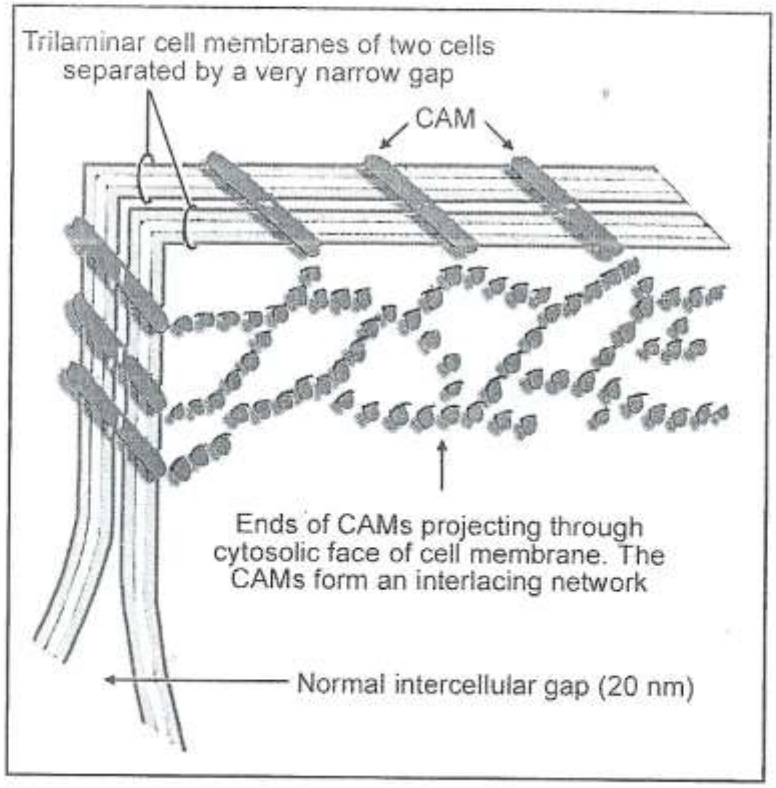

Fig. 1.15. Schematic diagram to show the detailed structure of part of an occluding junction.

Other functions attributed to occluding junctions are as follows.

(a) These junctions separate areas of cell membrane that are specialised for absorption or secretion (and lie on the luminal side of the cell) from the rest of the cell membrane.

(b) Areas of cell membrane performing such functions bear specialised proteins. Occluding junctions prevent lateral migration of such proteins.

(c) In cells involved in active transport against a concentration gradient, occluding junctions prevent back diffusion of transported substances.

Apart from epithelial cells, zonulae occludens are also present between endothelial cells.

In some situations occlusion of the gaps between the adjoining cells may be incomplete and the junction may allow slow diffusion of molecules across it. These are referred to as ***leaky tight junctions***.

Junctional Complex

Near the apices of epithelial cells the three types of junctions described above, namely zonula occludens, zonula adherens and macula adherens are often seen arranged in that order (Fig. 1.16). They collectively form a junctional complex. In some complexes the zonula occludens may be replaced by a leaky tight junction, or a gap junction (see below).

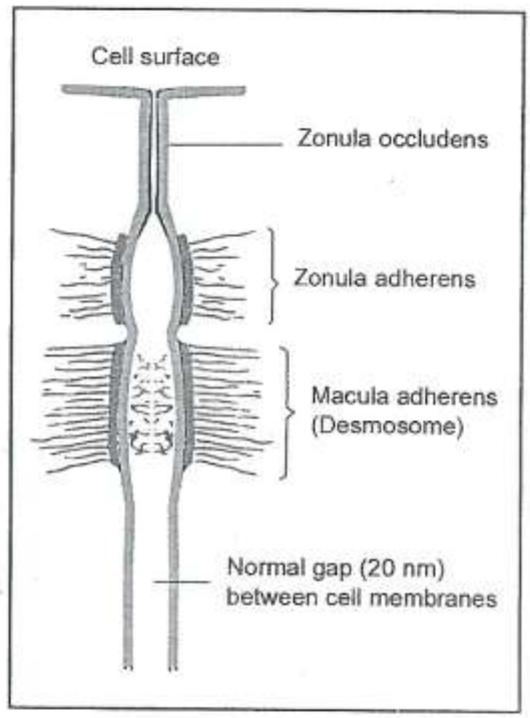

Fig. 1.16. Scheme to show a junctional complex.

COMMUNICATING JUNCTIONS (GAP JUNCTIONS)

At these junctions the plasma membranes are not in actual contact (as in a tight junction), but lie very close to each other, the gap being reduced (from the normal 20 nm) to 3 nm. In transmission electronmicrographs this gap is seen to contain bead-like structures (Fig. 1.14B). A minute canaliculus passing through each 'bead' connects the cytoplasm of the two cells thus allowing the free passage of some substances (sodium, potassium, calcium, metabolites) from one cell to the other (Also see below). Gap junctions are, therefore, also called ***maculae communi-cantes***. They are widely distributed in the body.

Changes in pH or in calcium ion concentration can close the channels of gap junctions. By allowing passing of ions they lower transcellular electrical resistance. Gap junctions form electrical synapses between some neurons.

The number of channels present in a gap junction can vary considerably. Only a few may be present in which case the junctions would be difficult to identify. At the other extreme the junction may consist of an array of thousands of channels. Such channels are arranged in hexagonal groups.

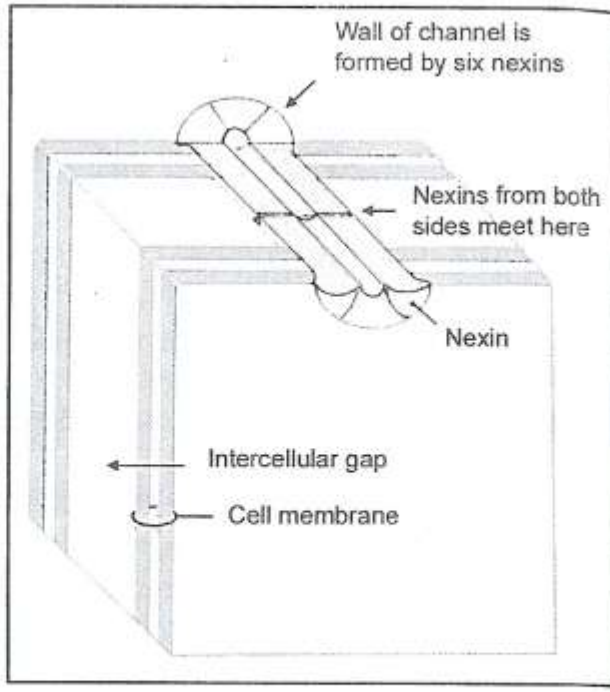

Fig. 1.17. Diagram to show the constitution of one channel of a communicating junction.

The wall of each channel is made up of six protein elements (called ***nexins***, or ***connexons***). The 'inner' ends of these elements are attached to the cytosolic side of the cell membrane while the 'outer' ends project into the gap between the two cell membranes (Fig. 1.17). Here they come in contact with (and align perfectly with) similar nexins projecting into the space from the cell membrane of the opposite cell, to complete the channel.

Cell Organelles

We have seen that (apart from the nucleus) the cytoplasm of a typical cell contains various structures that are referred to as organelles. They include the ER, ribosomes, mitochondria, the Golgi complex, and various types of vesicles (Fig. 1.18). The cytosol also contains a cytoskeleton made up of microtubules, microfilaments, and intermediate filaments. Centrioles are closely connected with microtubules. We shall deal with these entities one by one.