Genetic defects can lead to absence of specific acid hydrolases that are normally present in lysosomes. As a result some molecules cannot be degraded, and accumulate in lysosomes. Examples of such disorders are ***lysosomal glycogen storage disease*** in which there is abnormal accumulation of glycogen, and ***Tay-Sach's disease*** in which lipids accumulate in lysosomes and lead to neuronal degeneration.

Peroxisomes

These are similar to lysosomes in that they are membrane bound vesicles containing enzymes. The enzymes in most of them react with other substances to form hydrogen peroxide which is used to detoxify various substances by oxidising them. The enzymes are involved in oxidation of very long chain fatty acids. Hydrogen peroxide resulting from the reactions is toxic to the cell. Other peroxisomes contain the enzyme catalase which destroys hydrogen peroxide, thus preventing the latter from accumulating in the cell. Peroxisomes are most prominent in cells of the liver and in cells of renal tubules.

Defects in enzymes of peroxisomes can result in metabolic disorders associated with storage of abnormal lipids in some cells (brain, adrenal).

THE CYTOSKELETON

The cytoplasm is permeated by a number of fibrillar elements that collectively form a supporting network. This network is called the cytoskeleton. Apart from maintaining cellular architecture the cytoskeleton facilitates cell motility (e.g., by forming cilia), and helps to divide the cytosol into functionally discrete areas. It also facilitates transport of some constituents through the cytosol, and plays a role in anchoring cells to each other.

The elements that constitute the cytoskeleton consist of the following. **1.** Microfilaments. **2.** Microtubules. **3.** Intermediate filaments. These are considered below.

Microfilaments

These are about 5 nm in diameter. They are made up of the protein ***actin***. Individual molecules of actin are globular (***G-actin***). These join together (polymerise) to form long chains called ***F-actin***, ***actin filaments***, or ***microfilaments***.

Actin filaments form a meshwork just subjacent to the cell membrane. This meshwork is called the ***cell cortex***. (The filaments forming the meshwork are held together by a protein called ***filamin***). The cell cortex helps to maintain the shape of the cell. The meshwork of the cell cortex is labile.

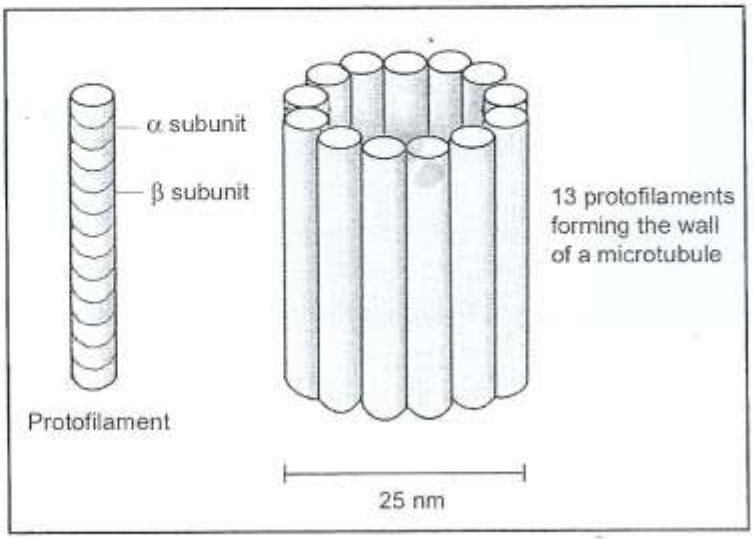

Fig. 1.24. Scheme to show how a microtubule is constituted.

The filaments can separate (under the influence of actin severing proteins), and can reform in a different orientation. That is how the shape of a cell is altered.

Microvilli contain bundles of actin filaments, and that is how they are maintained. Filaments also extend into other protrusions from the cell surface.

Microtubules

Microtubules are about 25 nm in diameter (Fig. 1.24). The basic constituent of microtubules is the protein ***tubulin*** (composed of subunits α and β). Chains of tubulin form ***protofilaments***. The wall of a microtubule is made up of thirteen protofilaments that run longitudinally (Fig. 1.24). The tubulin protofilaments are stabilized by ***microtubule associated proteins*** (MAPs).

Microtubules are formed in centrioles (see below) which constitute a ***microtubule organising centre***.

The roles played by microtubules are as follows.

1. As part of the cytoskeleton, they provide stability to the cell. They prevent tubules of ER from collapsing.
2. Microtubules facilitate transport within the cell. Some proteins (dynein, kinesin) present in membranes of vesicles, and in organelles, attach these to microtubules, and facilitate movement along the tubules. Such transport is specially important in transport along axons.
3. In dividing cells microtubules form the mitotic spindle.
4. Cilia are made up of microtubules (held together by other proteins).

Intermediate filaments

These are so called as their diameter (10 nm) is intermediate between that of microfilaments (5 nm) and of microtubules (25 nm). The proteins constituting these filaments vary in different types of cells.

They include ***cytokeratin*** (in epithelial cells), ***neurofilament protein*** (in neurons), ***desmin*** (in muscle), ***glial fibrillary acidic protein*** (in astrocytes); ***lamin*** (in the nuclear lamina of cells), and ***vimentin*** (in many types of cells).

The role played by intermediate filaments is as follows.

1. Intermediate filaments link cells together. They do so as they are attached to transmembrane proteins at desmosomes. The filaments also facilitate cell attachment to extracellular elements at hemidesmosomes.
2. In the epithelium of the skin the filaments undergo modification to form keratin. They also form the main constituent of hair and of nails.
3. The neurofilaments of neurons are intermediate filaments. Neurofibrils help to maintain the cylindrical shape of axons.
4. The nuclear lamina (page 27) consists of intermediate filaments.

Centrioles

All cells capable of division (and even some which do not divide) contain a pair of structures called centrioles. With the light microscope the two centrioles are seen as dots embedded in a region of dense cytoplasm which is called the ***centrosome***. With the EM the centrioles are seen to be short cylinders that lie at right angles to each other. When we examine a transverse section across a centriole (by EM) it is seen to consist essentially of a series of microtubules arranged in a circle. There are nine groups of tubules, each group consisting of three tubules (Fig. 1.25).

Centrioles play an important role in the formation of various cellular structures that are made up of microtubules. These include the mitotic spindles of dividing cells, cilia, flagella, and some projections of specialized cells (e.g., the axial filaments of spermatozoa). It is of interest to note that cilia, flagella and the tails of spermatozoa all have the 9 + 2 configuration of microtubules that are seen in a centriole.

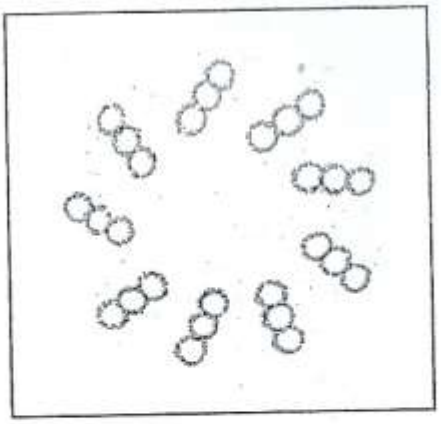

Fig. 1.25. Transverse section across a centriole (near its base). Note nine groups of tubules, each group having three microtubules.

Projections from the Cell Surface

Many cells show projections from the cell surface. The various types of projections are described below.

Cilia

These can be seen, with the light microscope, as minute hair-like projections from the free surfaces of some epithelial cells (Fig. 1.26). In the living animal cilia can be seen to be motile. Details of their structure, described below, can be made out only by EM. A scanning EM view is shown in Fig. 1.27.

The free part of each cilium is called the ***shaft***. The region of attachment of the shaft to the cell surface is called the ***base*** (also called the ***basal body***, ***basal granule***, or ***kinetosome***). The free end of the shaft tapers to a tip.

Each cilium is 0.25 μm in diameter. It consists of (a) an outer covering that is formed by an extension of the cell membrane; and (b) an inner core (***axoneme***) that is formed by microtubules arranged in a definite manner. The arrangement of these tubules, as seen in

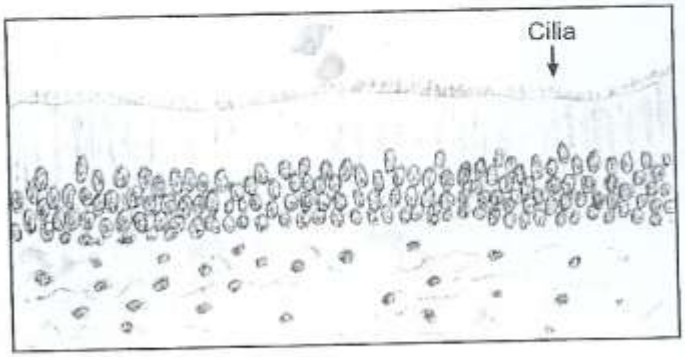

Fig. 1.26. Pseudostratified columnar epithelium showing cilia.

a transverse section across the shaft of a cilium is shown in Fig. 1.28. It has a striking similarity to the structure of a centriole (described above). There is a central pair of tubules that is surrounded by nine pairs of tubules. The outer tubules are connected to the inner pair by radial structures (which are like the spokes of a wheel). Other projections pass outwards from the outer tubules.

As the tubules of the shaft are traced towards the tip of the cilium it is seen that one tubule of each outer pair ends short of the tip so that near the tip each outer pair is represented by one tubule only. Just near the tip, only the central pair of tubules is seen (Fig. 1.29).

At the base of the cilium one additional tubule is added to each outer pair so that here the nine outer groups of tubules have three tubules each, exactly as in the centriole.

Microtubules in cilia are bound with proteins (dynein and nexin). Nexin holds the microtubules together. Dyenin molecules are responsible for bending of tubules, and thereby for movements of cilia.

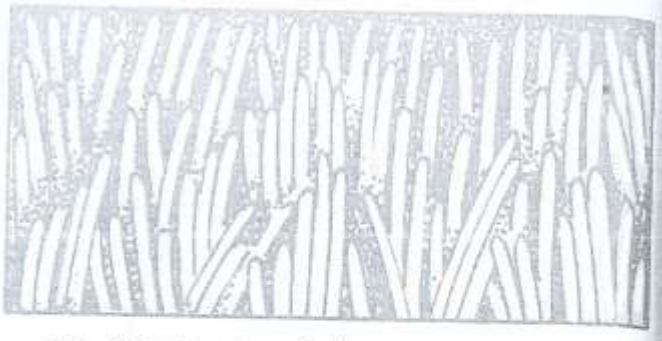

Fig. 1.27. Drawing of cilia as seen by scanning electronmicroscopy.

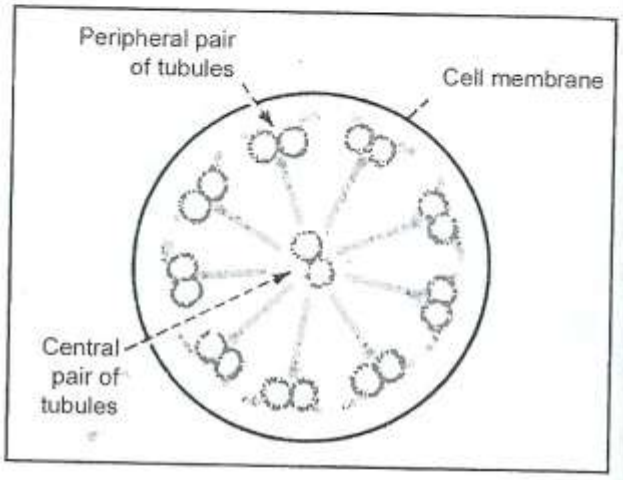

Fig. 1.28. Transverse section across a cilium.

Functional significance of cilia

The cilia lining an epithelial surface move in co-ordination with one another the total effect being that like a wave. As a result fluid, mucous, or small solid objects lying on the epithelium can be caused to move in a specific direction. Movements of cilia lining the respiratory epithelium help to move secretions in the trachea and bronchi towards the pharynx. Ciliary action helps in the movement of ova through the uterine tube, and of spermatozoa through the male genital tract.

In some situations there are cilia-like structures that perform a sensory function. They may be non-motile, but can be bent by external influences. Such 'cilia' present on the cells in the olfactory mucosa of the nose are called ***olfactory cilia***: they are receptors for smell. Similar structures called ***kinocilia*** are present in some parts of the internal ear. In some regions there are hair-like projections called ***stereocilia***: these are not cilia at all, but are large microvilli (see below).

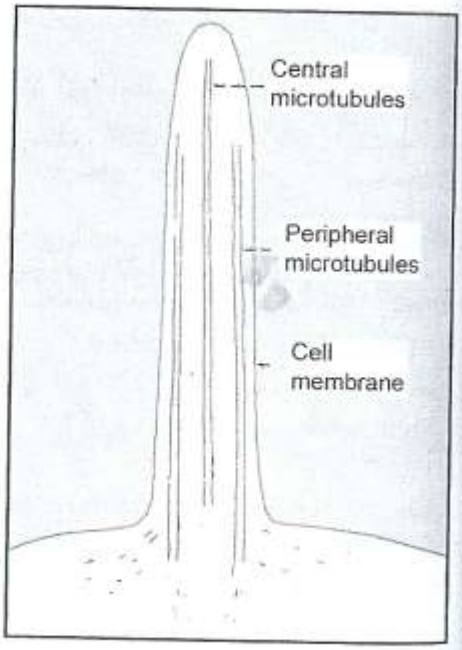

Fig. 1.29. Longitudinal section through a cilium.

Abnormalities of cilia

Cilia can be abnormal in persons with genetic defects that interfere with synthesis of ciliary proteins. This leads to the ***immotile cilia syndrome***. As secretions are not removed from respiratory passages the patient has repeated and severe chest infections. Women affected by the syndrome may be sterile as movement of ova along the uterine tube is affected. Ciliary proteins are present in the tails of spermatozoa, and an affected male may be sterile because of interference with the motility of spermatozoa.

Ciliary action is also necessary for normal development of tissues in embryonic life. Migration of cells during embryogenesis is dependent on ciliary action, and if the cilia are not motile various congenital abnormalities can result.

Flagella

These are somewhat larger processes having the same basic structure as cilia. In the human body the best example of a flagellum is the tail of the spermatozoon. The movements of flagella are different from those of cilia. In a flagellum, movement starts at its base. The segment nearest the base bends in one direction. This is followed by bending of succeeding segments in opposite directions, so that a wave-like motion passes down the flagellum. When a spermatozoon is suspended in a fluid medium this wave of movement propels the spermatozoon forwards (exactly in the way a snake moves forwards by a wavy movement of its body).

Microvilli & Basolateral folds

Microvilli are finger-like projections from the cell surface that can be seen by EM (Fig. 1.30). Each microvillus consists of an outer covering of plasma membrane and a cytoplasmic core in which there are numerous microfilaments (actin filaments). The filaments are continuous with actin filaments of the cell cortex. Numerous enzymes, and glycoproteins, concerned with absorption have been located in microvilli.

With the light microscope the free borders of epithelial cells lining the small intestine appear to be thickened: the thickening has striations perpendicular to the surface. This ***striated border*** of light microscopy (Fig. 1.31) has been shown by EM to be made up of long microvilli arranged parallel to one another.

In some cells the microvilli are not arranged so regularly. With the light microscope the microvilli of such cells give the appearance of a ***brush border*** (Fig. 1.32).

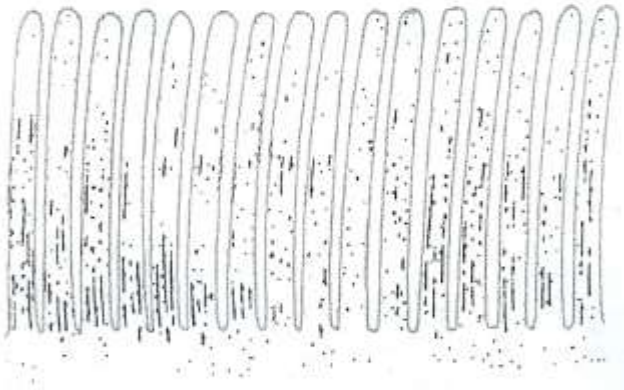

Fig. 1.30. Microvilli as seen in longitudinal section. The regular arrangement of microvilli is characteristic of the striated border of intestinal absorptive cells.

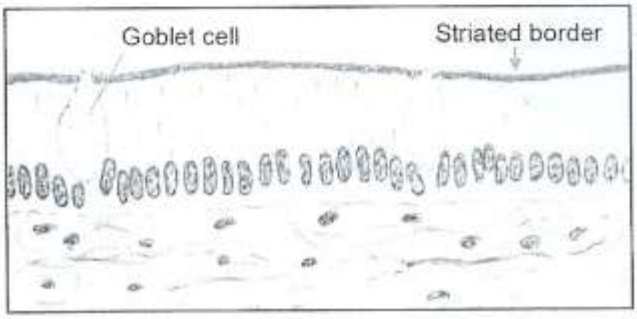

Fig. 1.31. Light microscopic appearance of striated border formed by microvilli.

Microvilli greatly increase the surface area of the cell and are, therefore, seen most typically at sites of active absorption e.g., the intestine, and the proximal and distal convoluted tubules of the kidneys. Modified microvilli called ***stereocilia*** are seen on receptor cells in the internal ear, and on the epithelium of the epididymis.

In some cells the cell membrane over the basal or lateral aspect of the cell shows deep folds (basolateral folds). Like microvilli, basolateral folds are an adaptation to increase cell surface area.

Basal folds are seen in renal tubular cells, and in cells lining the ducts of some glands. Lateral folds are seen in absorptive cells lining the gut.

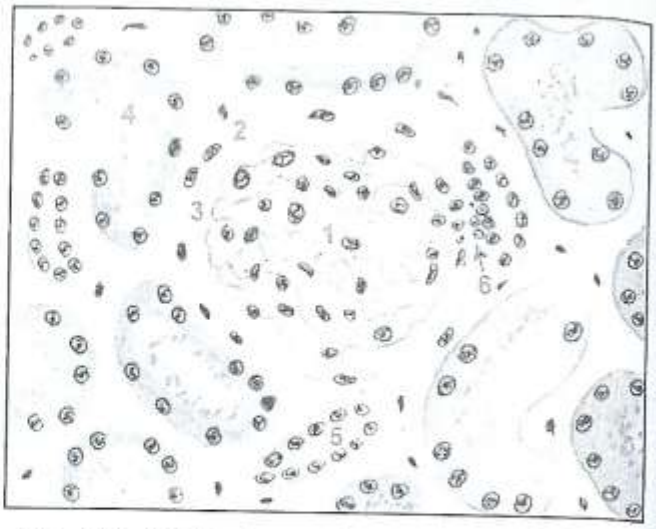

Fig. 1.32. Light microscopic appearance of a brush border (at 4) in epithelium lining renal tubules.

The Nucleus

The nucleus constitutes the central, more dense, part of the cell. It is usually rounded or ellipsoid. Occasionally it may be elongated, indented or lobed. It is usually 4-10 μm in diameter. The nucleus contains inherited information that is necessary for directing the activities of the cell as we shall see below.

In usual class-room slides stained with haematoxylin and eosin, the nucleus stains dark purple or blue while the cytoplasm is usually stained pink. In some cells the nuclei are relatively large and light staining. Such nuclei appear to be made up of a delicate network of fibres: the material making up the fibres of the network is called ***chromatin*** (because of its affinity for dyes). At some places (in the nucleus) the chromatin is seen in the form of irregular dark masses that are called ***heterochromatin***. At other places the network is loose and stains lightly: the chromatin of such areas is referred to as ***euchromatin***. Nuclei which are large and in which relatively large areas of euchromatin can be seen are referred to as ***open-face nuclei.*** Nuclei that are made up mainly of heterochromatin are referred to as ***closed-face nuclei*** (Fig. 1.33).

In addition to the masses of heterochromatin (which are irregular in outline), the nucleus shows one or more rounded, dark staining bodies called ***nucleoli*** (See below). The nucleus also contains

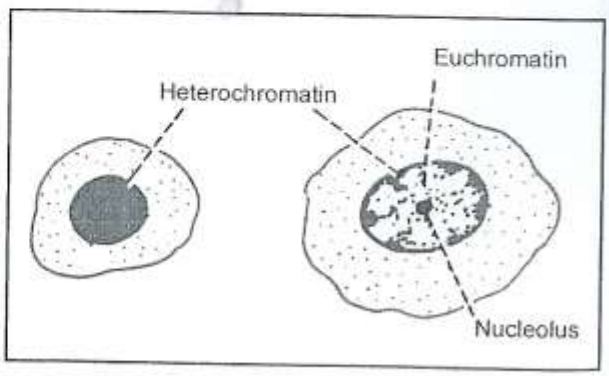

Fig. 1.33. Comparison of a heterochromatic nucleus (left), and a euchromatic nucleus (right).

various small granules, fibres and vesicles (of obscure function). The spaces between the various constituents of the nucleus described above are filled by a base called the *nucleoplasm*.

With the EM the nucleus is seen to be surrounded by a double layered *nuclear membrane* or *nuclear envelope*. The outer nuclear membrane is continuous with endoplasmic reticulum. The space between the inner and outer membranes is the *perinuclear space*. This is continuous with the lumen of rough ER. The inner layer of the nuclear membrane provides attachment to the ends of chromosomes (see below). Deep to the inner membrane there is a layer containing proteins and a network of filaments: this layer is called the *nuclear lamina*. Specific proteins present in the inner nuclear membrane give attachment to filamentous proteins of the nuclear lamina. These proteins (called *lamins*) form a scaffolding that maintains the spherical shape of the nucleus. At several points the inner and outer layers of the nuclear membrane fuse leaving gaps called *nuclear pores*. Each pore is surrounded by dense protein arranged in the form of eight complexes. These proteins and the pore together form the *pore complex*.

Nuclear pores represent sites at which substances can pass from the nucleus to the cytoplasm and vice versa (Fig. 1.19). The nuclear pore is about 80 nm across. It is partly covered by a diaphragm that allows passage only to particles less than 9 nm in diameter. A typical nucleus has 3000 to 4000 pores.

It is believed that pore complexes actively transport some proteins into the nucleus, and ribosomes out of the nucleus.

Nature and Significance of Chromatin

In recent years there has been a considerable advance in our knowledge of the structure and significance of chromatin. It is made up of a substance called *deoxyribonucleic acid* (usually abbreviated to DNA); and of proteins.

The structure of DNA is described on page 31. It is in the form of a long chain of nucleotides. Most of the proteins in chromatin are *histones*. Some non-histone proteins are also present.

Filaments of DNA form coils around histone complexes. The structure formed by a histone complex and the DNA fibre coiled around it is called a *nucleosome*. Nucleosomes are attached to one another forming long chains (Fig. 1.34). These chains are coiled on themselves (in a helical manner) to form filaments 30 nm in diameter. These filaments constitute chromatin.

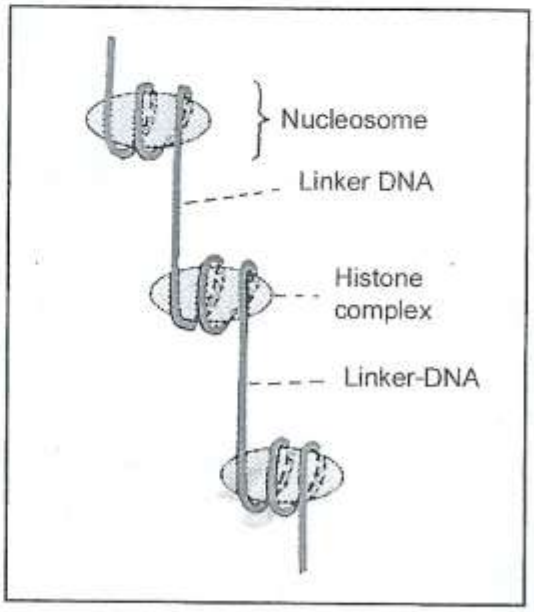

Fig. 1.34. Scheme to show the structure of a chromatin fibre. The DNA fibril makes two turns around a complex formed by histones to form a nucleosome. Nucleosomes give the chromatin fibre the appearance of a beaded string. The portion of the DNA fibre between the nucleosomes is called linker-DNA.