In the world's organisms are divided into five groups:

1-Prokaryota a----Eubacteria

b----Archaebacteria

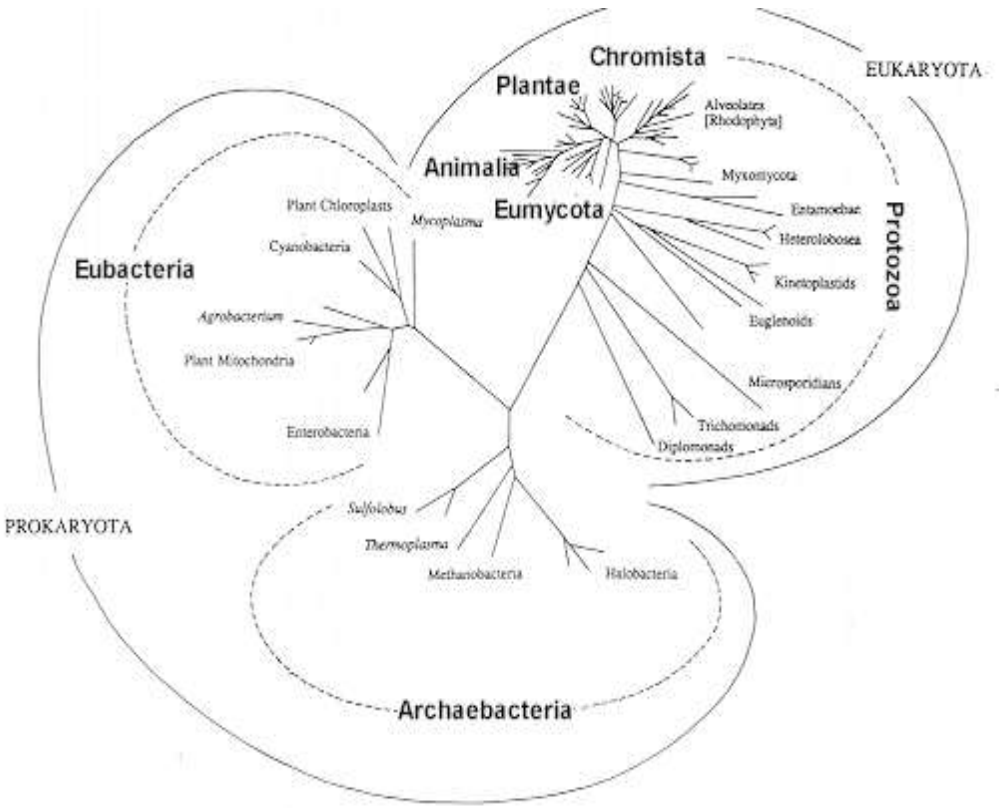
2-Eukaryota a----Protozoa

b----Chromista(Straminipila)

c---- Eumycota

d----Plantae

E---- Animalia



The general characteristics of fungi:

1- Organisms lacking chlorophyll.
2-Nutrition by absorption (saprophyte or parasite).

3- Fungi body consists of a single cell, such as a yeast or a multi celular-such as molds (mycelium).
4- Fungal cell is surrounded by a cell wall, except Myxomycetes. .
5- Fungi reproduce by forming spores (sexual or asexual) .

Defined fungi as eukaryotic,spore bearing, lacking chlorophyll that may reproduce sexual or asexual and whose filamentous,branched and somatic structures are typically surrounded by cell walls containing chitin,cellulose or both of these substances with many other complex carbohydrates.

With photosynthetic pigments being absent, fungi have a heterotrophic mode of nutrition. In contrast to animals which typically feed by ingestion, fungi obtain their nutrients by extracellular digestion due to the activity of secreted enzymes, followed by absorption of the solubilized breakdown products. The combination of extracellular digestion and absorption can be seen as the ultimate determinant of the fungal lifestyle. often patchy resources is greatly facilitated by the production of numerous small spores .growth as a system of branching tubes(, the hyphae) which together make up the mycelium. Hyphae are generally quite uniform in different taxonomic groups of fungi. One of the few features of distinction that they do offer is the presence or absence of cross-walls or septa. The **Oomycota and Zygomycota** generally have aseptate hyphae in which the nuclei lie in a common mass of cytoplasm. Such a condition is described as coenocytic . . In contrast**, Asco- and Basidiomycota** and their associated asexual states generally have septate hyphae in which each segment contains one, two or more nuclei. If the nuclei are genetically identical, as in a mycelium derived from a single uninucleate spore, the mycelium is said to be **homokaryotic,** but where a cell or mycelium contains nuclei of different genotype, e.g. as a result of fusion (anastomosis) of genetically different hyphae, it is said to be **heterokaryotic.** A special condition is found in the mycelium of many Basidiomycota in which each cell contains two genetically distinct nuclei. This condition is dikaryotic, to distinguish it from mycelia which are monokaryotic. It should be noted that septa, where present, are usually perforated and allow for the exchange of cytoplasm or organelles. Not all fungi grow as hyphae. Some grow as discrete **yeast cells** which divide by fission or, more frequently, budding Yeasts are common, especially in situations where efficient penetration of the substratum is not required, on plant surfaces or in the digestive tracts of animals . A few species, including certain pathogens of humans and animals, are dimorphic (capable of switching between hyphal and yeast-like growth forms) Intermediate stages between yeast cells and true hyphae also occur and are termed pseudohyphae . Some lower fungi grow as a thallus. a walled structure in which the protoplasm is concentrated in one or more centres from which root-like branches **(rhizoids**) ramify Certain obligately plant-pathogenic fungi and fungus-like

organisms grow as a naked **plasmodium** a uni- or multinucleate mass of protoplasm not surrounded by a cell wall of its own, or as a pseudoplasmodium of amoeboid cells which retain their individual plasma membranes.

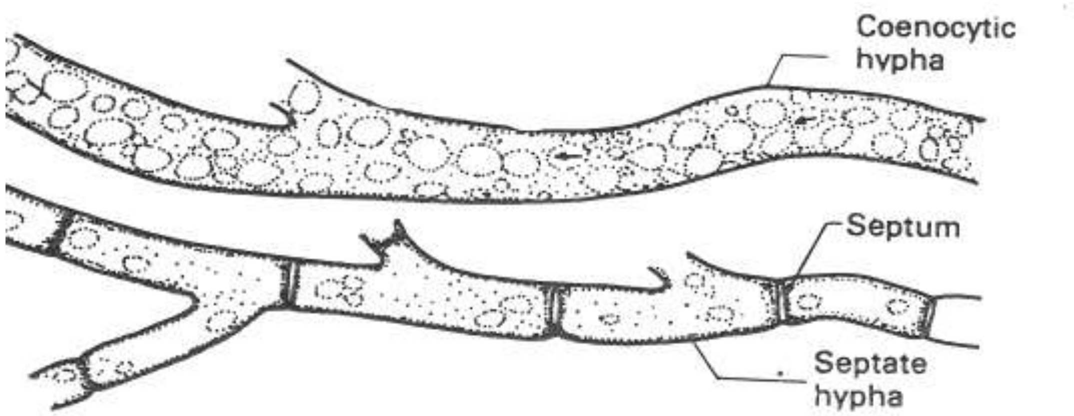


Fig. 1.1: Two types of somatic hyphae.

The fungal cell:

1-fungal cell wall :

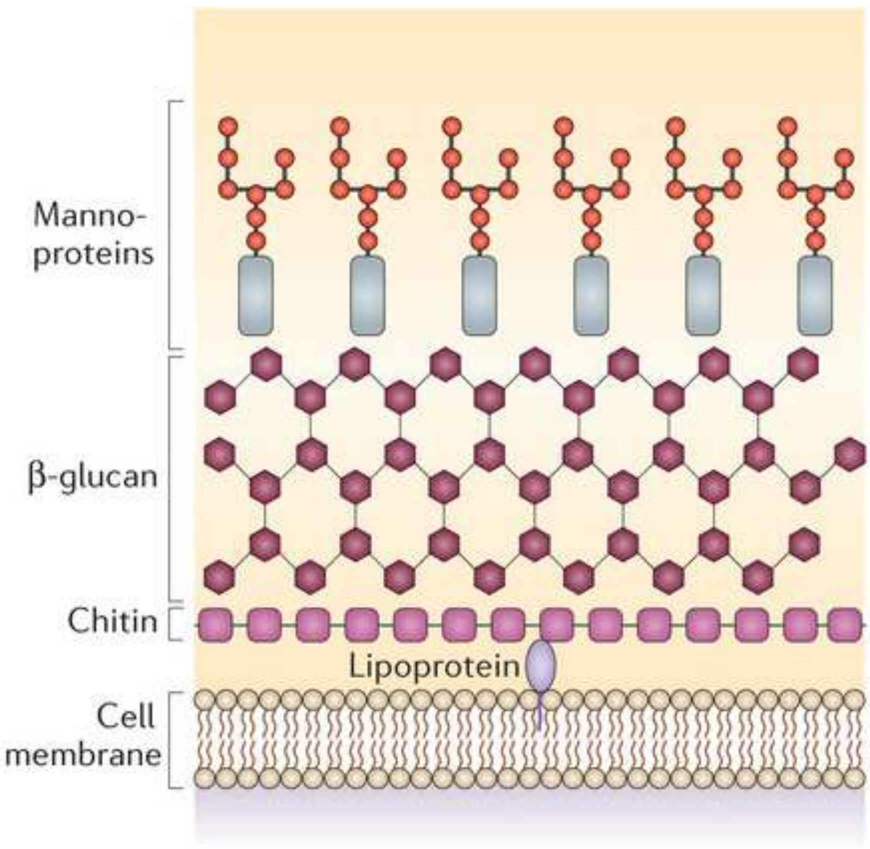
a—Microfibrils.(consist of Chitine or Chitosan / Cellulose / Glucans / Protein/ Lipid .(cellulose microfibrils in the Oomycota only but not contane chitine).

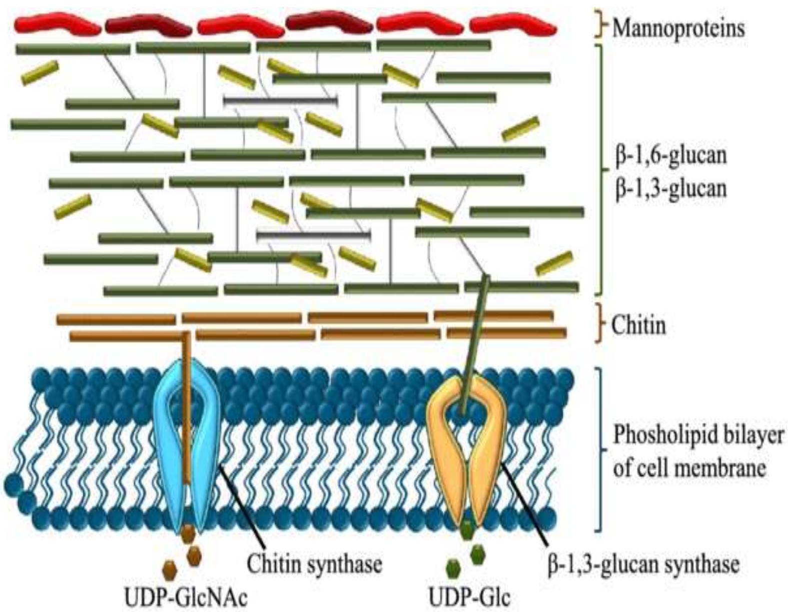
b—Matrix.

Cell wall components are different depending on Each cell fungal solid wall gives the cell shape and keeps the components from external effects and consists of the cell wall in fungi, mainly from multiple sugars and relatively small amounts of proteins and fats, and inorganic ions. Although the chemical composition of cell walls can vary considerably between and within different groups of fungi ,the basic design seems to be universal. It consists of a structural scaffold of **fibres** which are crosslinked, and a **matrix** of gel-like or crystalline material ,The degree of cross-linking will determine the plasticity (extensibility) of the wall, whereas the pore size (permeability) is a property of the wall matrix.

The scaffold forms the inner layer of the wall and the matrix is found predominantly in the outer layer In **the Ascomycota and Basidiomycota, the fibres are chitin microfibrils, i.e. bundles of linear b-(1,4)-linked N-acetylglucosamine chains** , In **the Zygomycota, the chitin fibres are modified after their synthesis by partial or complete deacetylation to produce poly-b-(1,4)-glucosamine, which is called chitosan fibres are cross-linked by polysaccharides containing glucuronic acid and various neutral sugars ,The cell wall matrix comprises glucans and proteins**,
Oomycota from the 'true fungi' (Eumycota) has been the absence of chitin from their cell walls even though chitin is now known to be produced by certain species of Oomycota under certain conditions , the structural is filled by

cellulose, As in many other fungi, the fibres thus produced
are cross-linked by an alkali-insoluble glucan
containing b-(1,3)- and b-(1,6)-linkages. In addition
to proteins, the main matrix component
appears to be an alkali-soluble b-(1,3)-glucan .
fungi, as well as different stages of growth, as well as different environmental factors surrounding it .
the cell wall is composed of several layers as follows :





(Schematic of fungal cell wall component)

ig. 1. Schematic overview of fungal cell wall composition. The fungal cell wall mainly consists of chitin (brown) located close to the cell membrane, β-1,3- and β-1,6-glucan (green) adjacent to the chitin fibers and mannoproteins (red) as the outermost part of the cell wall. Chitin is synthesized by transferring N-acetylglucosamine residues from uridine diphosphate-N-acetylglucosamine (UDPGlcNAc; brown hexagon) to a growing fiber that is shuttled through the cell membrane by the transmembrane chitin synthase (light blue). β-1,3-glucan is synthesized by a β-1,3-glucan synthase (yellow) that uses uridine diphosphate-N-glucose (UDPGlc; green hexagon) as a donor to transfer glucose to the extruded β-1,3-glucan fiber.

Group	Example	Chitin	Cellulose	Glucans	Protein	Lipid
Oomycota	*Phytophthora*	0	25	65	4	2
Chytridiomycota	*Allomyces*	58	0	16	10	?
Zygomycota	*Mucor*	9*	0	44	6	8
Ascomycota	*Saccharomyces*	1	0	60	13	8
	Fusarium	39	0	29	7	6
Basidiomycota	*Schizophyllum*	5	0	81	2	?
	Coprinus	33	0	50	10	?

*Mainly chitosan.

Structural formulae of the principal fibrous components of fungal :

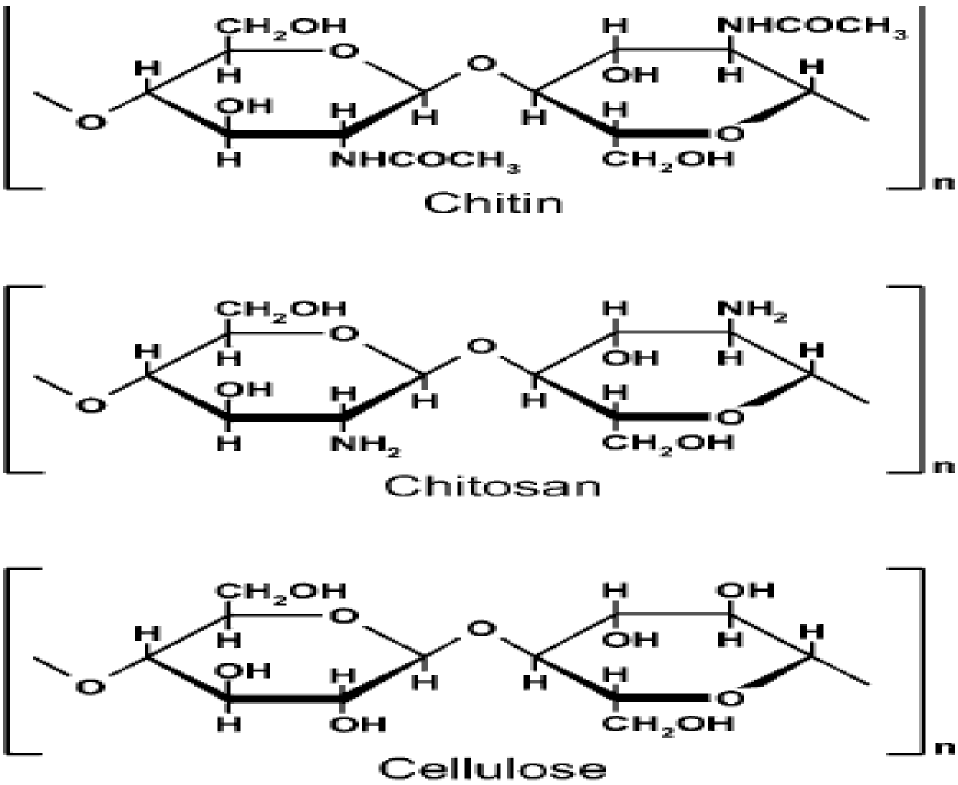
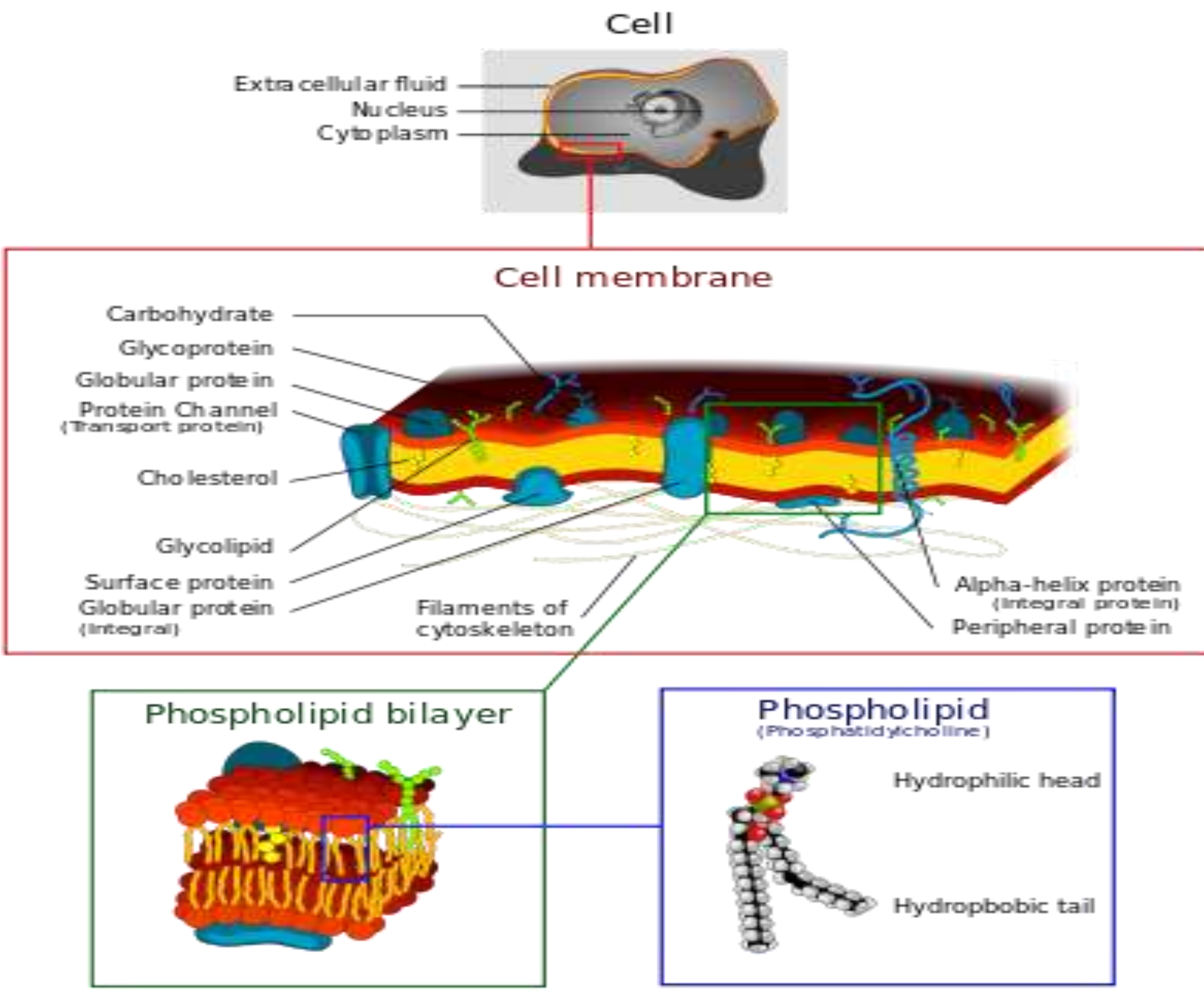


Fig 1.5 Structural formulae of the principal fibrous components of fungal cell walls.

The cell membrane is a biological membrane that separates the interior of all cells from the outside environment.[1] The cell membrane is selectively permeable to ions and organic molecules and controls the movement of substances in and out of cells.(A **semipermeable membrane**, also termed a **selectively permeable membrane**, a **partially permeable membrane** or a **differentially permeable membrane**, is a membrane that will allow certain molecules or ions to pass through it by diffusion and occasionally specialized "facilitated diffusion").[1] The basic function of the cell membrane is to protect the cell from its surroundings. It consists of the lipid bilayer with embedded proteins. Cell membranes are involved in a variety of cellular processes such as cell adhesion, ion conductivity and cell signaling and serve as the attachment surface for several extracellular structures, including the cell wall, glycocalyx, and intracellular cytoskeleton. Cell membranes can be artificially reassembled.



The endoplasmic reticulum (ER)

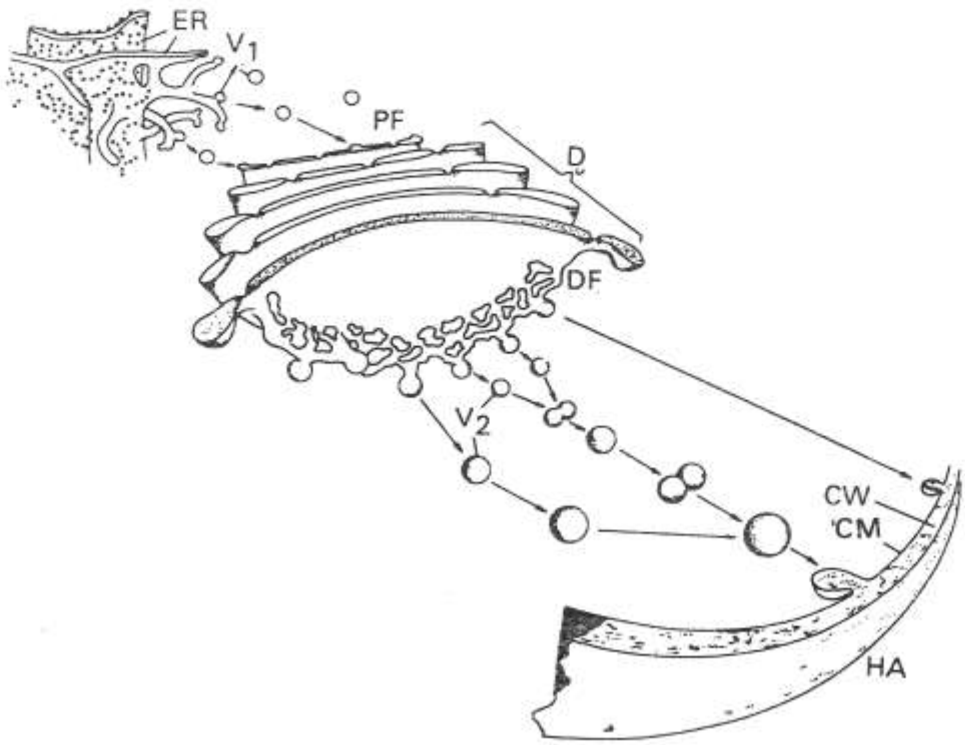
is an organelle of cells in eukaryotic organisms that forms an interconnected network of membrane vesicles. According to the structure the endoplasmic reticulum is classified into two types, that is, **rough endoplasmic reticulum**[**(RER)** and **smooth endoplasmic reticulum (SER)**.

The rough endoplasmic reticulum is studded with *ribosomes* on the *cytosolic* face. These are the sites of *protein synthesis*

The smooth endoplasmic reticulum is concerned with *lipid metabolism*, *carbohydrate metabolism* and *detoxification*

The Golgi apparatus

Part of the cellular endomembrane system, the Golgi apparatus packages proteins inside the cell before they are sent to their destination; it is particularly important in the processing of proteins for secretion.



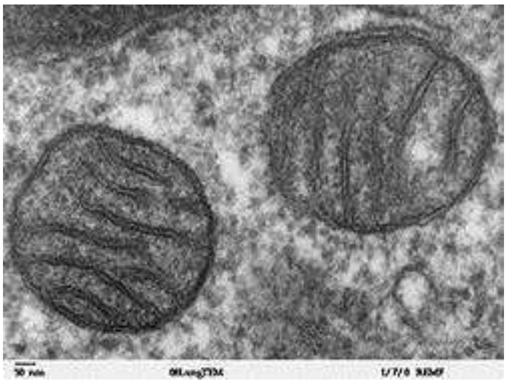
The material is transferred from the endoplasmic reticulum (E R) to the dictyosome(D) by blebbing of the endoplasmic reticulum and coalescene of vesicles (V) to forma cisterna at the proximal face (P F) of the dictyosome. The contents of the cisterna and membranes are then transformed as the cisterna is moved to the distal face (D F) of the dictyosome.Secretory vesicle (V) released from the cisterna enlarge and / or fuse with one another , migrate to the apex of the hypha and fuse with cell membrane (C M) liberating their contents to the cell wall (C W) .

Nucleus

The nucleus is a highly specialized organelle that serves as the information and administrative center of the cell. This organelle has two major functions. It stores the cell's hereditary material, or DNA, and it coordinates the cell's activities, which include intermediary metabolism, growth, protein synthesis, and reproduction (cell division).

Mitochondrion

" cellular power plants" because they generate most of the cell's supply of adenosine triphosphate (ATP), used as a source of chemical energy In addition to supplying cellular energy

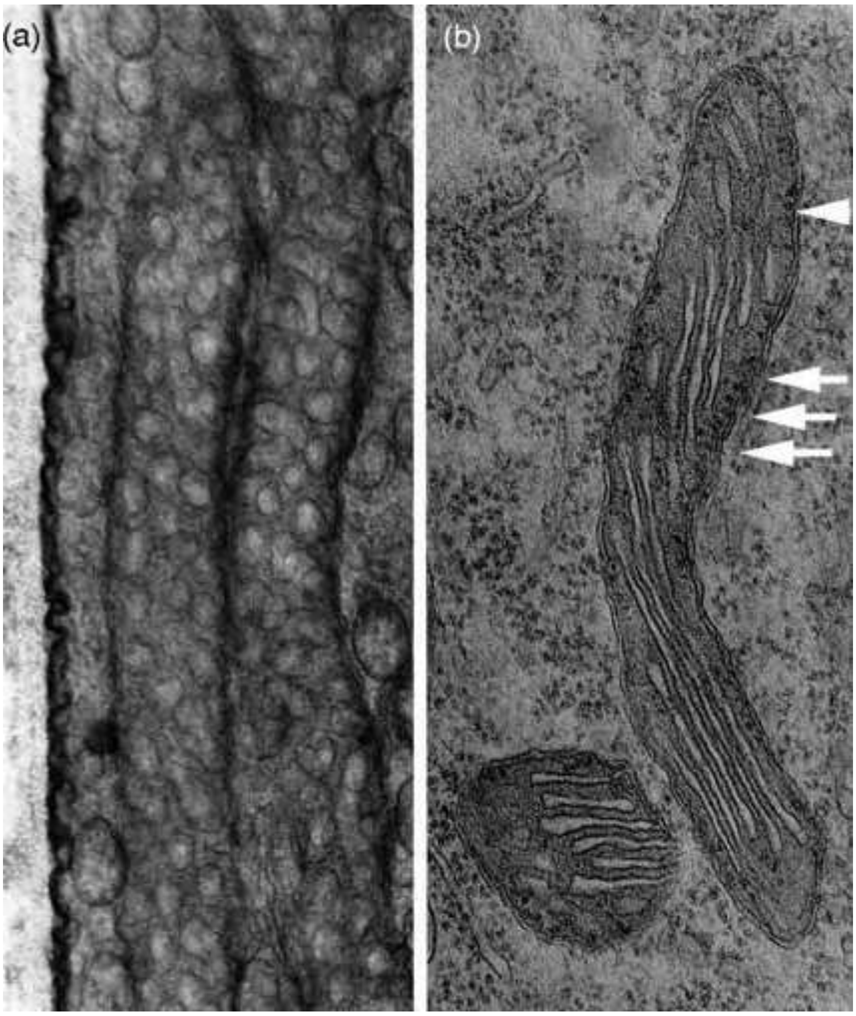


The number of mitochondria in a cell varies widely by organism and tissue type. Many cells have only a single mitochondrion, whereas others can contain several thousand mitochondria. The organelle is composed of compartments that carry out specialized functions. These compartments or regions include the outer membrane, the intermembrane space, the inner membrane, and the cristae and matrix.

Mitochondrial ultrastructure observed by transmission electronmicroscopy.

(a) Mitochondrion of *Phytophthora erythroseptica* (Oomycota) (all Straminipilla).The inner Mitochondrial membrane is folded into a complex tubular network.

(b) Mitochondrion of *Sordaria fimicola* (Ascomycota) (all Eumycota) with the inner membrane appearing lamellate.Mitochondrial .



Types of fungal septa

The hyphae in Ascomycetes,Basidiomycetes and fungi Imperfecti are regularly septate, in some species septa occur close together ,in other they are widely separated . in contrast to those of lower fungi,the septa of other groups are incomplete, and have a minute central pore through which protoplasmic continuity is maintained throughout the length of the hypha.

The various types of fungal septa .
(A) Septum showing Micropores (Geotrichum) .
(B) Septum with simple pores (most of the Ascomycetes , Uredinales and Deuteromycetes).
(C) Septum of Trichomycetes .
(D) Dolipore septum most of the
Basidi – Oomycete (excepting rusts and smuts) .

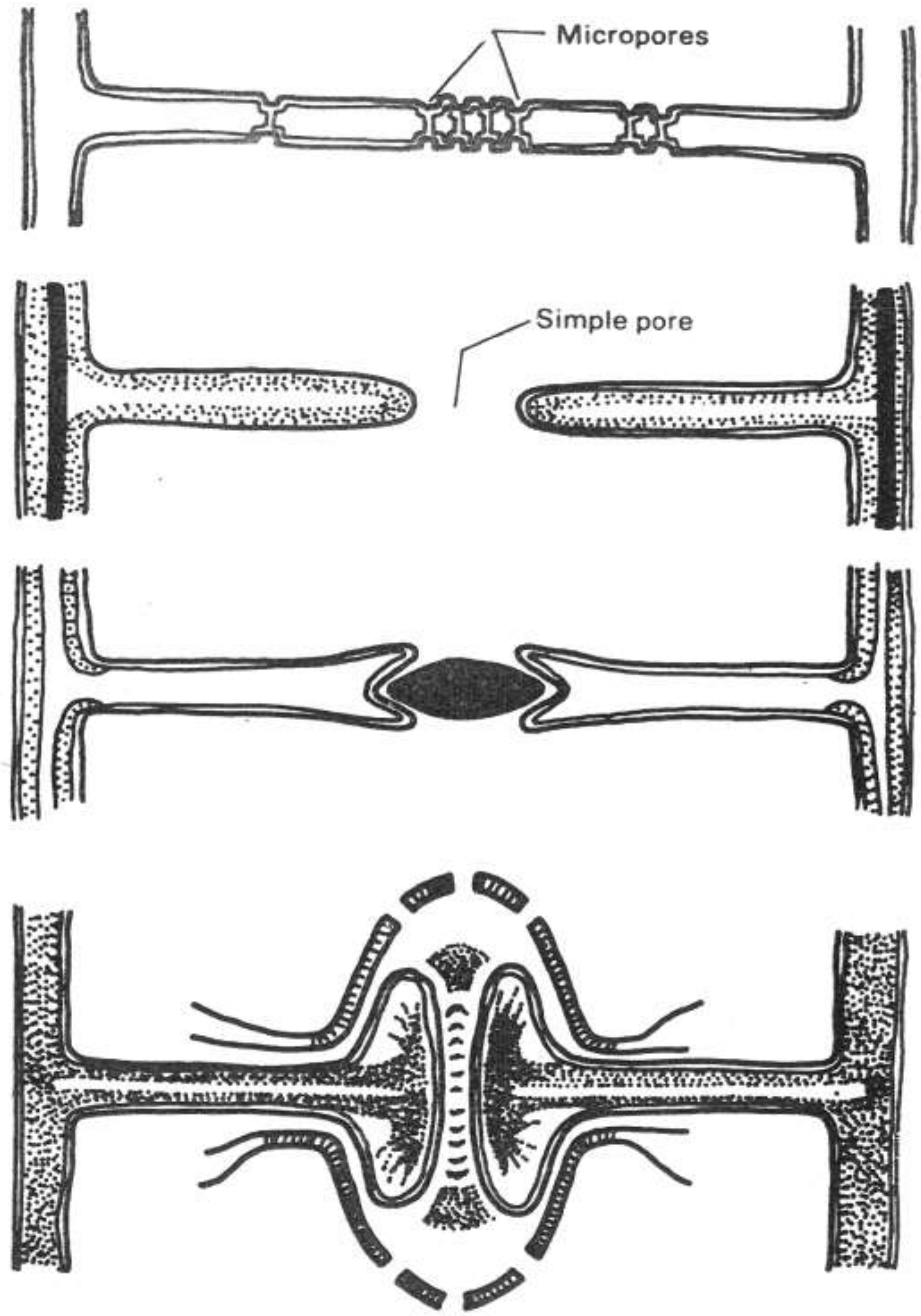


Fig. 1.2: Diagrammatic representation of the various types of fungal septa. (A) Septum showing micropores (*Geotrichum*). (B) Septum with simple pores (most of the Ascomycetes and Deuteromycetes). (C) Septum of Trichomycetes. (D) Dolipore septum (most of the Basidiomycetes excepting rusts and smuts) (After Barnett, 1976).

Biochemical targets for antifungal agents :

•Antifungal chemotherapy depends on biochemical differences between fungi and mammal cells. Such differences are few since both type of cells are eukarytoics. Example of such differneces

1.Fungal cells have both cell membrane and outer cell wall, where as mammalian cells only have cell membrane

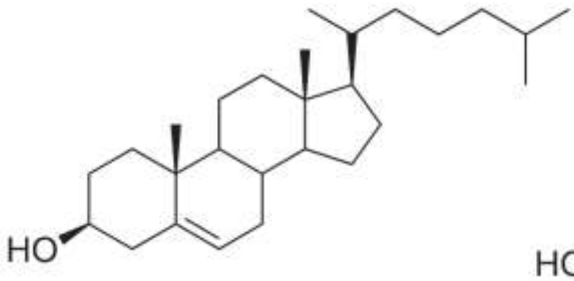
2.The membranes of fungal and mammalian cells have different types of sterols (i.e. Ergosterol and cholesterol, respectively).

β-glucan component of the fungal cell wall

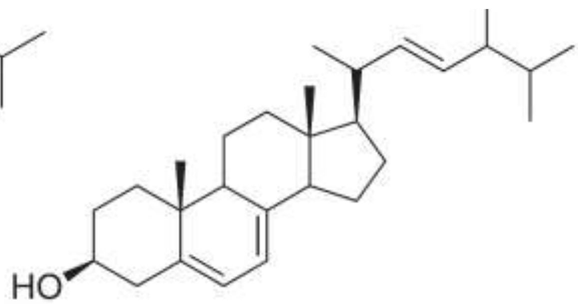
The structural carbohydrate polymers glucan and chitin compliment and reinforce each other in a dynamic process to maintain the integrity and physical strength of the fungal cell wall. The assembly of chitin and glucan in the cell wall of the budding yeast Saccharomyces cerevisiae and the polymorphic human pathogen Candida albicans are essential processes that involve a range of fungal-specific enzymes and regulatory networks. The fungal cell wall is, therefore, an attractive target for novel therapies as host cells lack many cell wall-related proteins. The most recent class of antifungal drug approved for clinical use, the echinocandins, targets the synthesis of cell wall β(1-3)glucan. The echinocandins are effective at treating invasive and bloodstream Candida infections and are now widely used in the clinic. However, there have been sporadic reports of breakthrough infections in patients undergoing echinocandin therapy. The acquisition of point mutations in the FKS genes that encode the catalytic β(1-3)glucan synthase subunits. Ergosterol:is sterol found in cell membranes of fungi and protozoa ,serving many of the cell functions that cholesterol seres in animal cells.

Because many fungi and protozoa cannot survive without ergosterol ,the enzymes that create it have become important targets for drug discovery .

Biochemical targets for antifungal agents (Ergosterol) :



Cholesterol



Ergosterol

•Although the ergosterol and cholesterol are quite similar, the side chains are slightly different, and when three-dimensional models are constructed, the ring system of ergosterolis slightly flatter because of the additional double bonds in the B ring.

•This difference in sterol components provides the biochemical basis of selective toxicity for most of the currently available antifungal drugs.

•The antifungal agents can be divided into the following classes, based on their chemical structure, mechanism of action, and source:

I.Antibiotics: Amphotericin B, Nystatin, Griseofulvin

II.Azoles(imidazole, triazole derivates)
•Imidazoles—Clotrimazole, Ketoconazole, Miconazole, Bifonazole, Butoconazole, and Zinoconazole
•Triazoles—Fluconazole, Itraconzole, Terconazole
III.Allylamines Tolnaftate, Naftifine, and Terbinafine

IV.Fluorinated pyrimidines: Flucytosine

V.Chitin synthetase inhibitors: NikomycinZ

VI.Peptides/proteins: Cispentacin

VII.Fatty and other acids: propionic acid, undecylenic acid,

Polyene membrane disrupters:

•The polyenes have an affinity to sterol-containing membranes, thus being inserted into the membrane, causes leakage and disruption of function.

•The polyenes have higher affinity for ergosterol over cholesterol-containing membrane.

•**NYSTATIN** Nystatin, the first clinically useful polyene antifungal antibiotic, is a conjugated tetraene isolated from cultures of the bacterium *Streptomyces noursei S. nodosus* in 1951. It is too toxic for systematic use and can be used orally to treat yeast infections.

•**AMPHOTERICIN B** Amphotericin B, which as a heptaene has low enough toxicity to mammalian cells to permit intravenous (IV) administration, was discovered in 1956. It can not cross blood-brain barrier. Formulated as water-soluble complex with deoxycholic acid for IV administration.

•Azole antifungal are the largest class of antimycotics available today.

•Some azoles are used topically, for dermatophytic infections others are used orally to treat systematic infections.

•Unlike amphotericin B, azoles are orally bio available and have broader spectrum of activity.

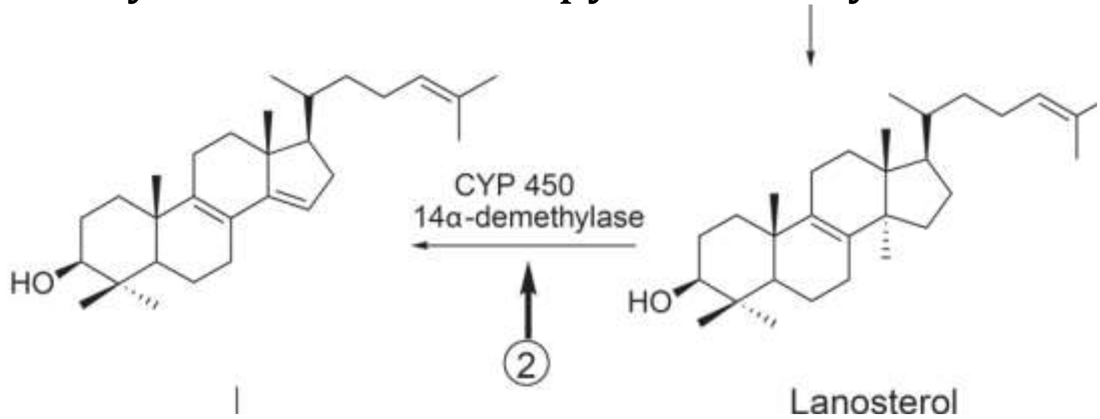
•All azoles inhibit 14α-demethylase of ergosterol biosynthesis

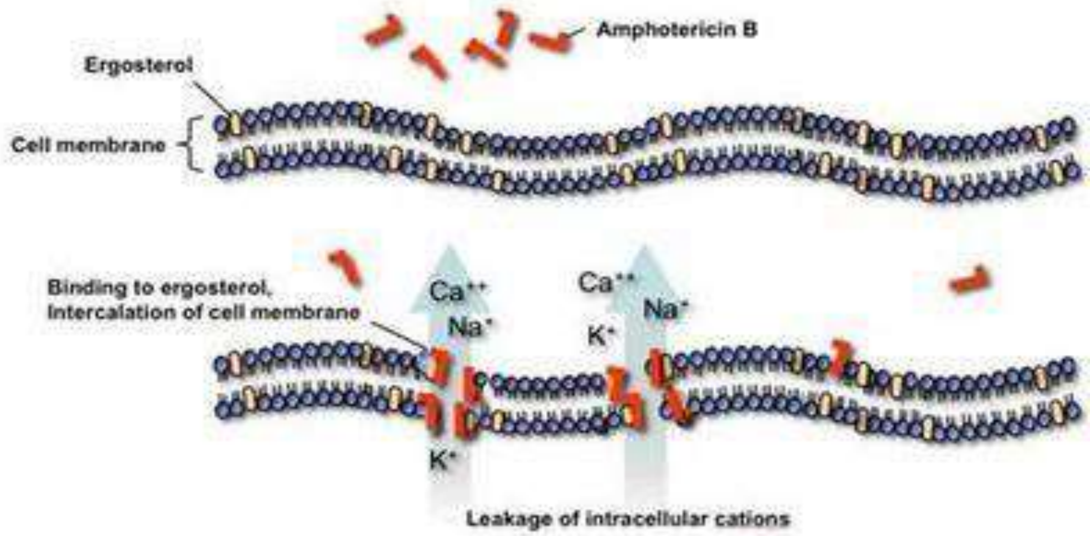
•At high in vitro concentrations (micromolar), the azoles are fungicidal; at low in vitro concentrations (nanomolar), they are fungistatic.

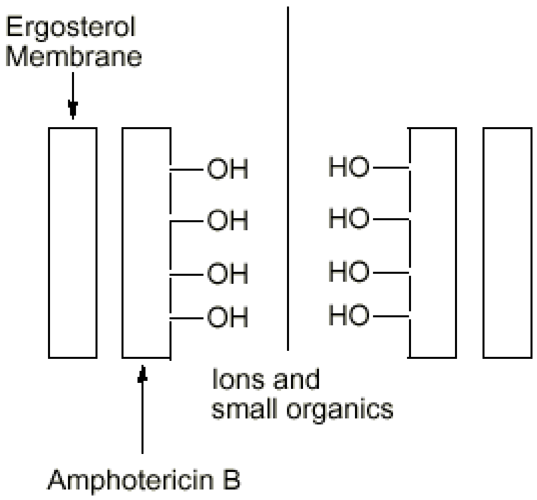
Ergosterol Biosynthesis Inhibitors :

- The function of lanosterol14α-demethylase is to oxidatively remove a methyl group from lanosterol during ergosterol biosynthesis.
- The enzyme is membrane-bound of the class cytochrome P450.
- The enzyme possesses a heme moiety as part of its structure, and the basic electron pairs of the azole rings can occupy a binding site and prevent the enzyme from turning over
- The enzyme is also present in mammalian biosynthesis of cholesterol, and the azoles are known to inhibit cholesterol biosynthesis also (e.g. biosynthesis of adernocorticoids)
- The mammalian copy of the enzyme is much sensitive and binds azoles with lower affinity than fungal copy (which explains the selective fungal toxicity).
- The 1,2,4-triazoles appear to cause a lower incidence of endocrine effects and hepatotoxicity than the corresponding

imidazoles, possibly because of even lower affinity to mammalian copy of the enzyme.







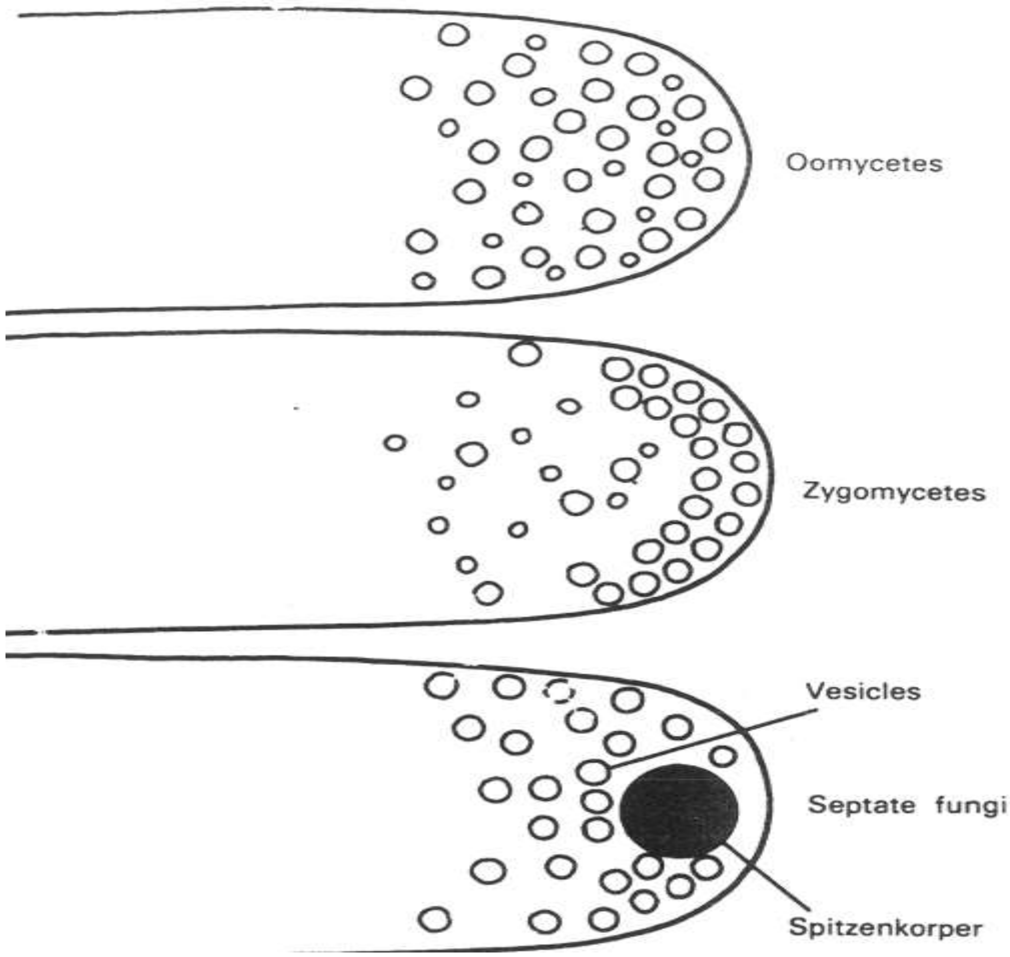
Amphotericin

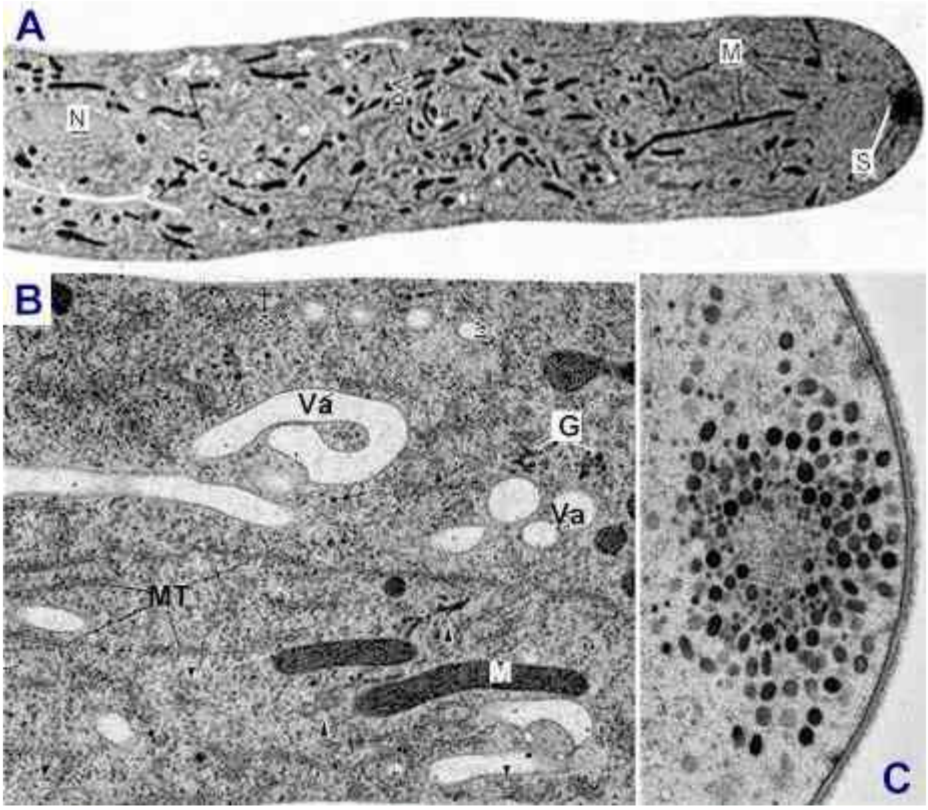
Growth and elongation of the hyphal top .

Fungal hypha have the ability to grow in the suitable conditions and formation of a tube germination and trying to grow in all directions from the center point.the hyphal top is divided into three main areas which are as follows :

1-Apical Zone ./
2-Subapical Zone .
3-Zone of Vaculation.

1- The first area contains cytoplasemic vesicles Which are spread according to the following patterns :





Ultrastructure of the hyphae of *Sclerotium rolfsii*, prepared for electron microscopy by freeze substitution. From photographs supplied by Dr Robby Roberson (see Roberson & Fuller, 1988).

Fig. A. Young region of a hypha, showing progressive changes in ultrastructural organisation behind the hyphal apex. The apex contains a **Spitzenko**

rper (**S**). Behind this is a zone rich in mitochondria (**M**, the dark tubular structures), then a zone containing tubular vacuoles (light coloured) and nuclei (**N**).

Fig. B. Part of a mature region of a hypha (the apex, not shown, is towards the right of the image) showing mitochondria (M), vacuoles (Va), Golgi bodies (G, seen as dark, ring-like structures) and longitudinally running microtubules (MT).

2-The second zone containing organelles fungal and be free of vesicles.

3-The third area where there vesicles food Which is increasing in size as we move away from the top area of hypha .

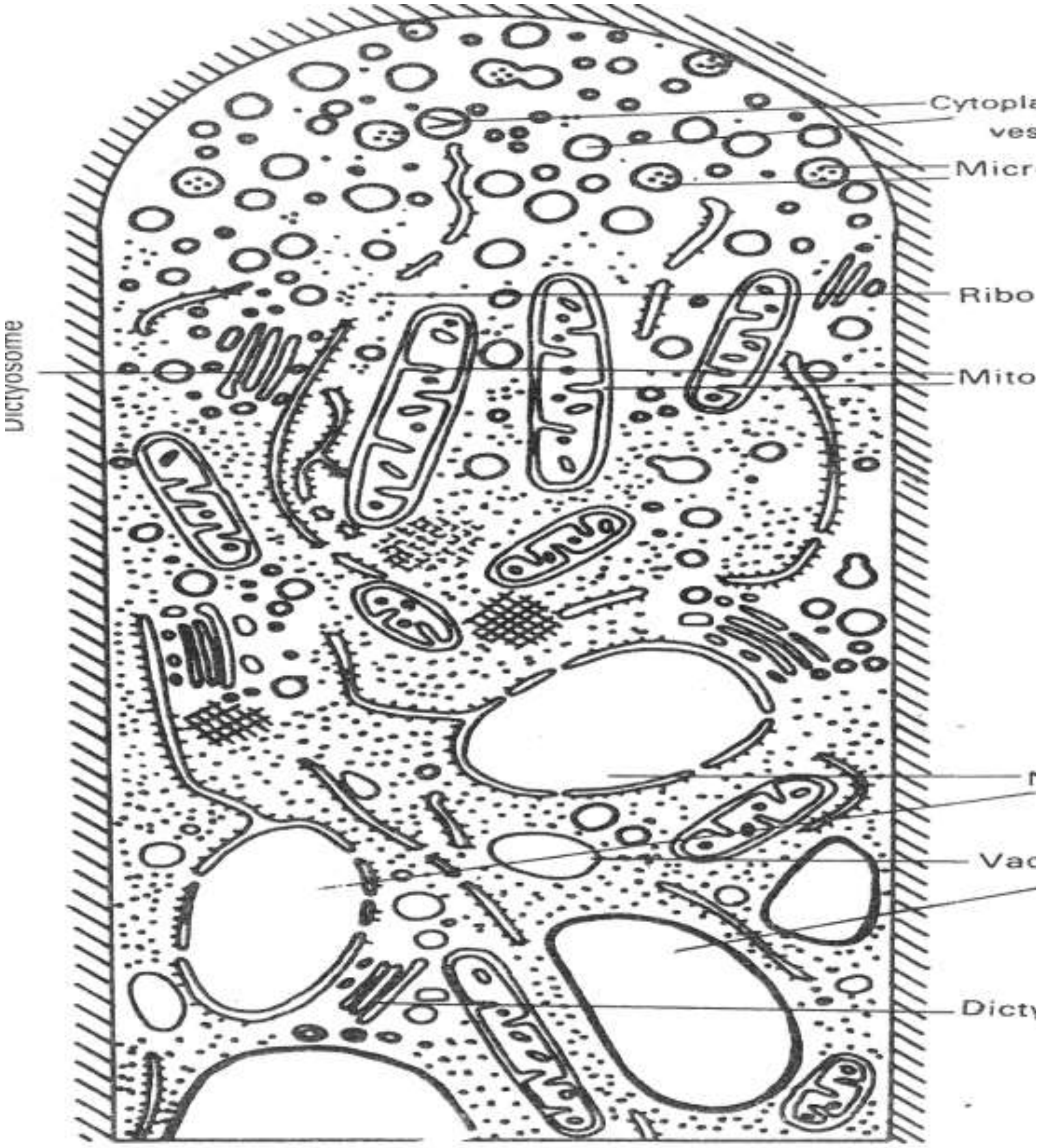


Fig. 1.19: Organelles distribution in a hypha of *Pythium ultimum.*

The life cycle of fungi

There are great variations in the life cycles of fungi. Raper (1954, 1966) recognizes seven basic types. These are represented graphically in Fig. 1.33.

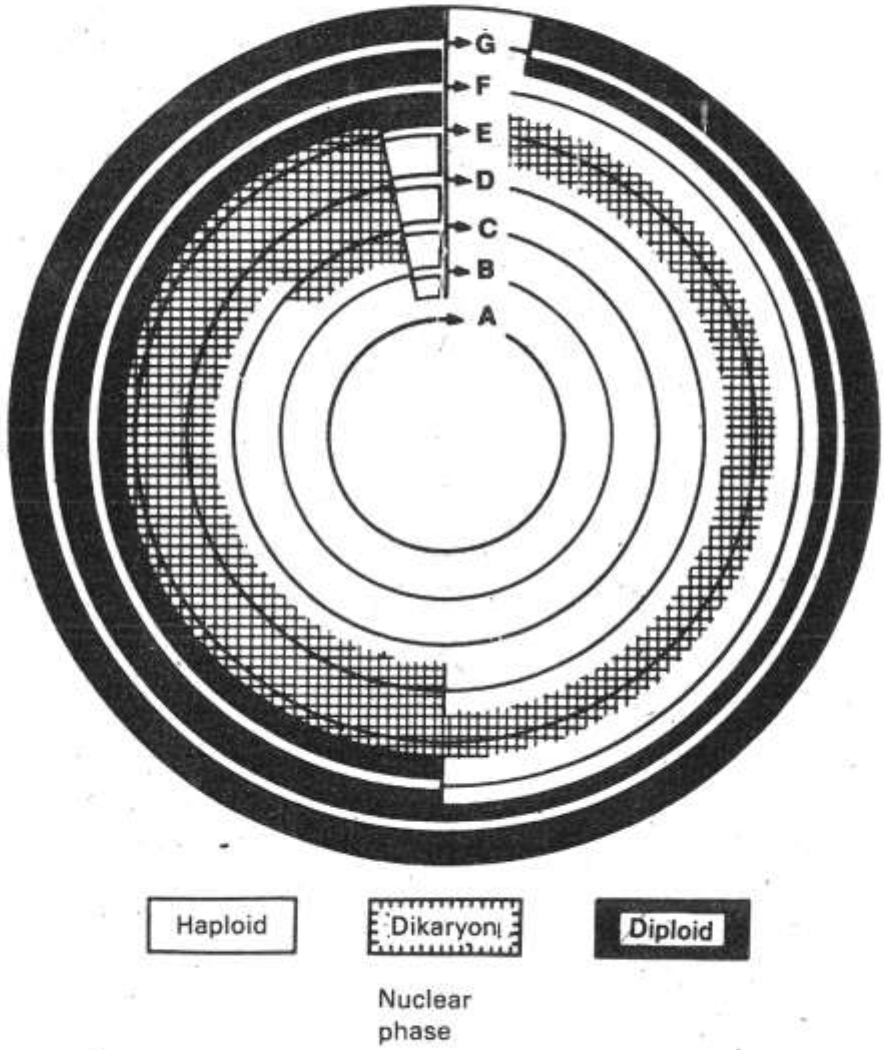


Fig. 1.33: Various types of life cycle in fungi (From Raper, 1954).

1. **Asexual cycle;** in which sexual reproduction apparently lacks and diploidy is restricted to somatic diploids. The entire group known as Fungi Imperfecti and numerous other species which clearly belong to various groups of the perfect fungi, such as *Penicillium notatum* have this life cycle. Certain benefits of sexuality are provided here in many of the sterile forms by parasexual recombination.

2. **Haploid cycle;** in which meiosis follows immediately after nuclear fusion. This type of life cycle is the simplest possible and is seen in many lower fungi and some Ascomycetes. Here the diploid phase is confined to the zygote nucleus only.

3. **Haploid cycle with restricted dikaryon;** is similar to the haploid cycle excepting that paired, potentially conjugant kinds of nuclei lie in close association in some hyphal segment (hence dikaryon) and divide synchronously for a greater or lesser period. Such a life cycle is characteristic of the higher Ascomycetes e.g. *Neurospora.*

4. **Haploid dikaryotic cycle;** which differs from the previous cycle because of the unrestricted and independent growth of the dikaryotic phase. Here the mycelium derived from germination of a meiospore may persist in the haploid condition, as a monokaryon. But once a dikaryon is formed, it shows potentially unrestricted and independent growth and may well comprise the longest phase of the life cycle. This type of life cycle is characteristic of many Basidiomycetes except many of the smut fungi (Ustilaginales).

5. **Dikaryotic cycle;** in which the immediate products of meiosis, ascospores or basidiospores, fuse immediately to reform a dikaryon so that fungus is dikaryotic throughout its life cycle. This type of life cycle is occasionally seen in yeasts and occurs among the smut fungi.

6. **Haploid-Diploid cycle;** in which the haploid and diploid phases alternate regularly. Such a life cycle is common in algae and higher plants, and occurs rarely in fungi, and has been described only in two groups. The better known of these is the chytridiomycetous order Blastocladiales, especially in the section *Eu-Allomyces* of the genus *Allomyces* as well as in *Ascocybe grovesii* (Endomycetales).

7. **Diploid cycle;** in which the haploid phase is restricted to the gametes. It seems likely that the majority of oomycetous fungi conform to this pattern (Sansome, 1961, 1963, 1965, 1966, 1976; Brasier and Sansome, 1975; Win-Tin and Dick, 1975). This type of life cycle is also known to occur in a number of yeasts such as *Saccharomyces cerevisiae* (Winge, 1935; Guilliermond, 1940), in the Myxomycetes, or true slime molds (Alexopoulos, 1962) and also in some members of the Blastocladiales (Couch and Whiffen, 1942; McCranie, 1942).