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Cell Biology & Genetics

SECOND EDITION

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Cell Biology and Genetics

SECOND EDITION

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Preface

Genetics and cell biology are subjects that are traditionally unpopular with medical students, possibly because they are rich in jargon and some quite difficult concepts. Recent advances in biology, such as the completion of the first drafts of the human genome project and the development of gene therapy strategies, are predicted to make an understanding of the molecular basis of disease essential for future medical practice. Therefore, genetics and cell biology can no longer be dismissed as the esoteric pursuits of the scientific purist, but rather can be viewed as a fundamental component of the modern medical curriculum.

The Second Edition of this book has been restructured to highlight the concepts that underlie the contemporary study and understanding of hereditary disease, drawing upon the comprehensive clinical content of the First Edition for illustration. We hope that you find it useful, not only for passing the exams that have prompted you to buy the book, but also in formulating an understanding of the mechanics of biology that will serve you throughout your medical career.

Ania L Manson

In the four years since publication of the First Edition of *Crash Course: Cell Biology and Genetics*, advances in the basic sciences and in their application to medicine have gathered pace. The first draft of the human genome sequence has been published, molecular diagnosis has become a practical possibility for a growing number of diseases and a Nobel Prize in Medicine has been awarded for fundamental discoveries on cell cycle regulation. This new edition is therefore timely. It is also, inevitably, a little larger than its predecessor but new discoveries in any field of science ultimately bring clarity and we believe that process is reflected in the style and content of this book.

As with the First Edition, our purpose is not merely to help students prepare for undergraduate examinations but to serve as a ready source of information in clinical practice. We hope that you may actually enjoy reading this book and find that it stimulates your interest in cellular and molecular aspects of medicine.

C Michael Steel
Faculty Advisor

In the six years since the First Editions were published, there have been many changes in medicine, and in the way it is taught. These Second Editions have been largely rewritten to take these changes into account, and keep Crash Course up to date for the twenty-first century. New material has been added to include recent research and all pharmacological and disease management information has been updated in line with current best practice. We have listened to feedback from hundreds of students who have been using Crash Course and have improved the structure and layout of the books accordingly: pathology material has been closely integrated with the relevant basic medical science; there are more multiple-choice questions and the clarity of text and figures is better than ever.

The principles on which we developed the series remain the same, however. Medicine is a huge subject, and the last thing a student needs when exams are looming is to waste time assembling information from different sources, and wading through pages of irrelevant detail. As before, Crash Course brings you all the information you need, in compact, manageable volumes that integrate basic medical science with clinical practice. We still tread the fine line between producing clear, concise text and providing enough detail for those aiming at distinction. The series is still written by medical students with recent exam experience, and checked for accuracy by senior faculty members from across the UK.

I wish you the best of luck in your future careers!

Dr Dan Horton-Szar
Series Editor (Basic Medical Sciences)

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Most of the revision to this title was undertaken while I was recuperating from surgery and I am indebted to my parents who provided for my activities of daily living during this period. I am also grateful to Dr Steve Howe, Dr Amanda McGuigan and especially to Dr Kathy Mann for administering beer, sympathy, figures and MCQs *p.r.n.* As ever, I am thankful to Dr Dan O'Connor for his friendship, but in particular for his rock like qualities in my *annus horribilis*. Finally, I wish to acknowledge the support of the Foulkes Foundation.

Figure acknowledgements

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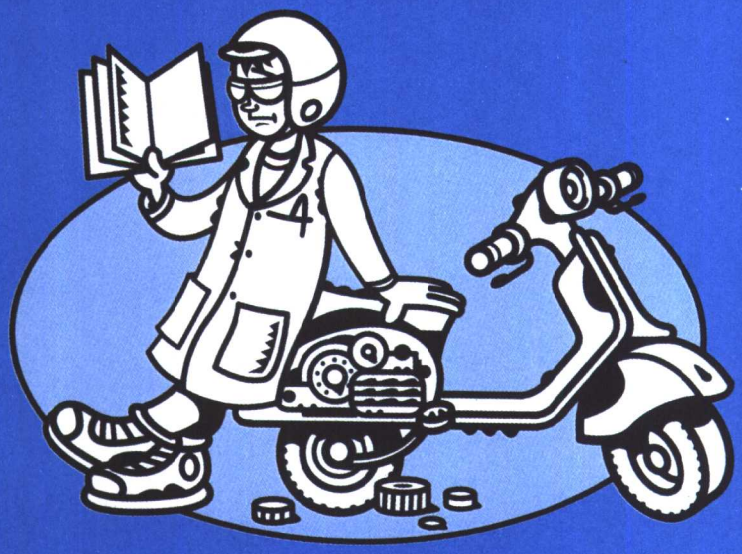
Dedication

To Mum and Dad.
Thanks for the genes.....(And the environment!)

Contents



PRINCIPLES OF CELL BIOLOGY AND MOLECULAR GENETICS

1. General Organization of the Cell

Definitions

Cell

The cell is the basic unit of life. If it is to survive, each cell must maintain an internal environment that supports its essential biochemical reactions, despite changes in the external environment. Therefore, a selectively permeable plasma membrane surrounding a concentrated aqueous solution of chemicals is a feature of all cells.

Organism

An organism is a system capable of self-replication and self-repair, which may be unicellular or multicellular. Unicellular organisms consist of a solitary cell able independently to perform all the functions of life. Multicellular organisms contain several different cell types that are specialized to perform specific functions.

Prokaryotes and eukaryotes

Prokaryotes are the simplest unicellular organisms. It is thought that by a process of mutation and natural selection all living organisms evolved from a common prokaryotic ancestor (Fig. 1.1).

The basic molecular machinery of life has been conserved in all species. The enzymes that perform common reactions such as glycolysis in bacterial and human cells show significant homology at both the DNA and protein level.

The prokaryotic cell

All microorganisms lacking a membrane-bound nucleus (i.e. the various types of bacteria) are classified in the prokaryote superkingdom. The typical prokaryotic cell (Fig. 1.2) shows the following features:

- A single cytoplasmic compartment containing all the cellular components.
- Cell division by binary fission.

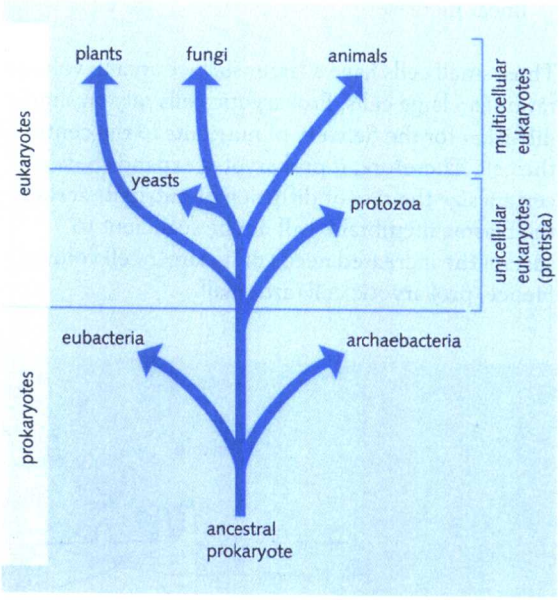


Fig. 1.1 Evolutionary relationships between organisms. Prokaryotes are thought to represent the most primitive life form, with eukaryotic unicellular and multicellular organisms evolving from an ancestral prokaryotic cell by a process involving mutation followed by natural selection. (Adapted from *Molecular Biology of the Cell*, 3rd edn, by B Alberts et al, Garland Publishing Co., 1994. Reproduced by permission of Routledge, Inc., part of The Taylor & Francis Group.)

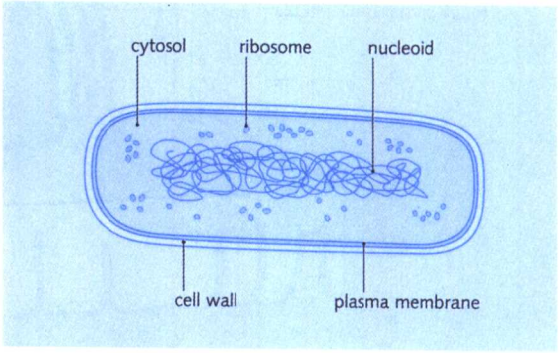


Fig. 1.2 Structure of a typical prokaryotic cell. The DNA molecule is free in the cytoplasm. Bacteria contain some sub-cellular structures such as ribosomes but do not contain membrane bound organelles.

In order for the prokaryotic cell to survive, molecules required for energy and biosynthesis must diffuse into the cell and waste products must diffuse out of the cell across the plasma membrane. The rate of diffusion is related to membrane surface area. When the diameter of a cell increases:

- The cell volume expands to the cube of the linear increase.
- The surface area only expands to the square of the linear increase.

Thus, small cells have a larger surface area to volume ratio than large cells. Prokaryotic cells rely on simple diffusion for the delivery of nutrients to the centre of the cell. Therefore, if prokaryotes expand above a certain size the rate of diffusion of nutrients across the plasma membrane will not be sufficient to sustain the increased needs of its larger cell volume. Hence, prokaryotic cells are small.

The eukaryotic cell

All organisms consisting of cells with a membrane-bound nucleus are classified in the eukaryote superkingdom. The Animalia, Plantae, Protista, and Fungi kingdoms all belong within this group. The typical eukaryotic cell (Fig. 1.3) shows the following features:

- A complex series of inner membranes that separate the cell into distinct compartments which perform specific functions.
- Cell division by mitosis.
- Specialized organelles such as centrioles, mitotic spindles, mitochondria, and microtubules.

Unlike prokaryotes, eukaryotic cells are capable of endocytosis (see Chapter 4). By this means, patches of the plasma membrane pinch off to form membrane-bound vesicles that deliver nutrients from the external environment to compartments

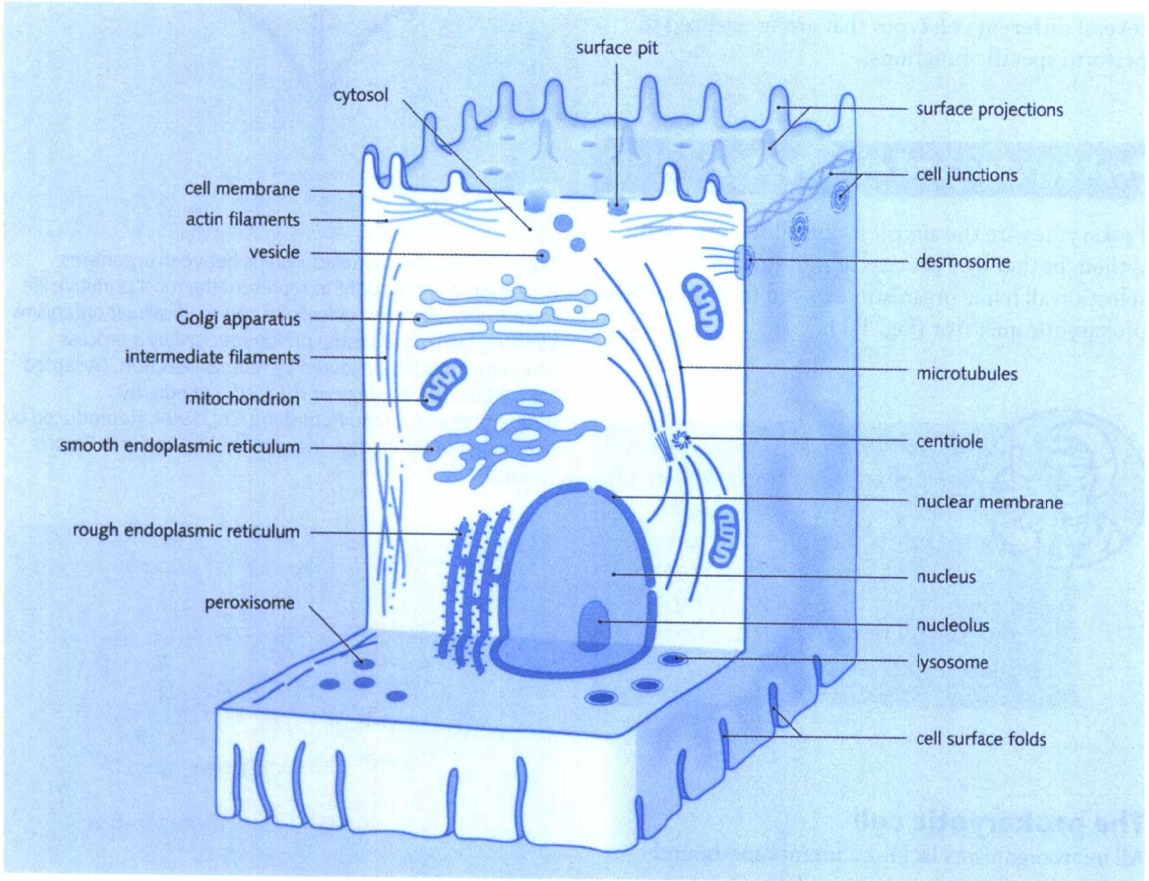


Fig. 1.3 Structure of a typical eukaryotic cell. Genetic material is contained within the nuclear membrane. Membrane bound organelles serve as compartments for specific cellular functions, permitting greater cellular specialization and diversity. Cytoskeletal components maintain cell shape and facilitate dynamic functions such as endocytosis. (Adapted from Stevens and Lowe, 1997.)

deep within the cell. Endocytosis thus liberates eukaryotic cells from the constraints of simple diffusion, allowing them to sustain a relatively small surface area to volume ratio. Eukaryotic cells are, therefore, on average, much larger than prokaryotic cells (Fig. 1.4). In the typical animal cell, the various specialized organelles occupy about half the total cell volume.

Remember: Prokaryotes are primitive. You are a eukaryote.

Structure and function of eukaryotic organelles

The whole cell is surrounded by the plasma membrane, which forms a dynamic interface between the cytosol and the environment. Eukaryotic cells have a complex ultrastructure comprising membranous and non-membranous organelles. These structures serve specific functions within the cell.

Membranous organelles

Membranous organelles are enclosed within a phospholipid bilayer, and they maintain discrete biochemical environments that contain characteristic sets of enzymes.

Plasma membrane

The plasma membrane is a selectively permeable barrier that surrounds cell cytoplasm (Fig. 1.5). Non-polar (lipid soluble) molecules diffuse across the lipid bilayer by passive transport. Proteins embedded within the bilayer are responsible for transport of polar molecules between the cell and extracellular fluid by facilitated diffusion and active transport (see Chapter 3). The ability of the cell to regulate transport protein activity is fundamental to many biological processes, such as muscle contraction generation and conduction of nerve cell action potentials.

Many of the proteins and lipids on the outer surface of the cell membrane have oligosaccharides covalently attached to them. This 'glycocalyx' coat:

- Produces a negative charge, which separates cells within a multicellular layer.
- Acts as a receptor surface that is sensitive to chemical and other changes in the environment.
- Carries chemical signals enabling other cells (e.g. cells of the immune system) to recognize it.

In certain cell types, such as epithelia, the plasma membrane may show specializations that enhance cell function:

- The intercellular surfaces are linked together by cell junctions to form a continuous sheet of cells (see Chapter 4).
- The basal surface is linked to extracellular matrix by hemidesmosomes.

Prokaryotic compared with eukaryotic cells

Prokaryotic cells	Eukaryotic cells
Includes bacteria and blue–green algae	Four major groups: Protista, fungi, plants and animals
No true nucleus	True nucleus
DNA circular and free	DNA linear and within nucleus
No membrane-bound organelles	Internal compartmentalization with organelles, hence division of labour (specialization)
Simple binary reproduction	Mitotic reproduction (and meiotic)
No development of tissues	Tissue and organ systems common
Multicellular types rare	Independent unicellular organism or part of multicellular organism
Size: 1–10 μm	Size: 10–100 μm

Fig. 1.4 Basic features of prokaryotic and eukaryotic cells.

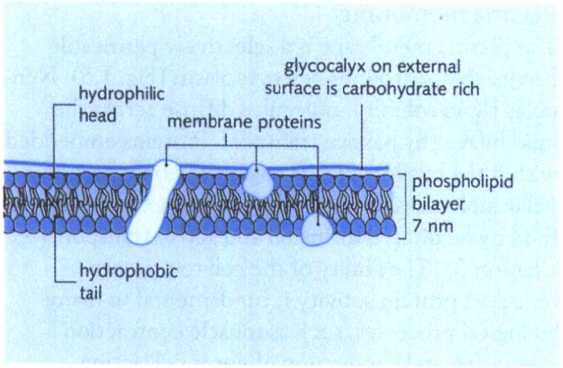


Fig. 1.5 Structure of the plasma membrane. Proteins that penetrate one or both layers interrupt the structural continuity of the phospholipid bilayer. The glycocalyx forms an outer coat to the cell.

- Luminal surfaces may incorporate cilia (motile structures, e.g. lining the fallopian tubes and trachea), microvilli (increase surface area, e.g. in small intestine) or stereocilia (extra long microvilli, e.g. in epididymis).

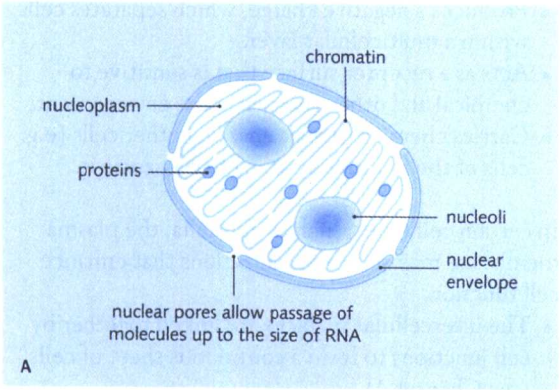
Nucleus

The nucleus (Fig. 1.6):

- Sequesters and replicates DNA.
- Transcribes and splices RNA.
- Allows facilitated selective exchange of molecules such as RNA, e.g. transfer RNA (tRNA), with the cytoplasm.

DNA replication occurs when the genetic code is copied exactly before cell division. In RNA transcription and splicing, genes are copied and adapted to form complementary strands of messenger RNA (mRNA), which can be translated into protein.

Chromosomes are long strands of DNA that carry the genetic code. In eukaryotes, DNA is complexed with histone and non-histone proteins to form chromatin. Histones are DNA binding proteins that are important for DNA packaging. Other DNA-associated proteins function as enzymes for replication and transcription. Nucleoli are dense-staining areas within the nucleus where ribosomal RNA (rRNA) is made.



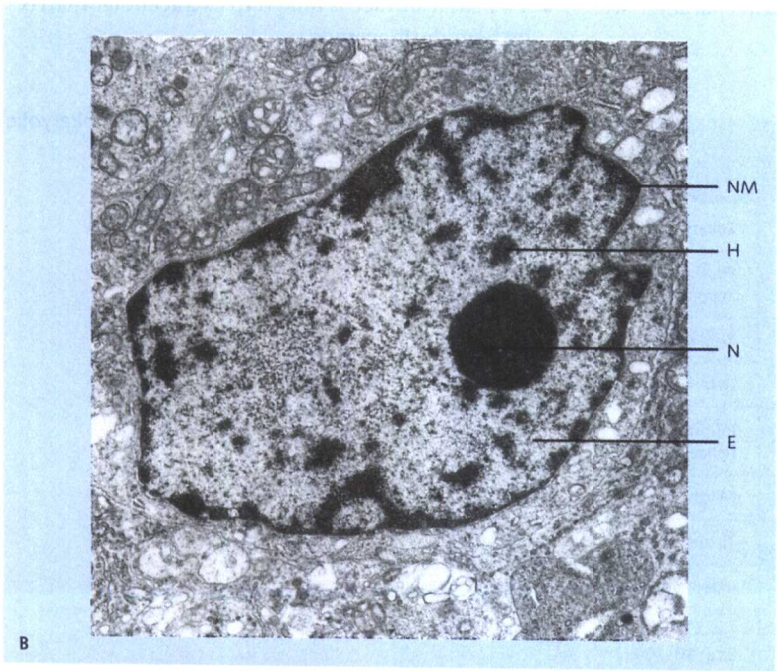


Fig. 1.6 (A) Structure of the nucleus. (B) Electron micrograph showing the double nuclear membrane (**NM**), nucleolus (**N**), heterochromatin (**H**), which is dense staining, and euchromatin (**E**), which is light staining. (Courtesy of Dr Trevor Gray.)

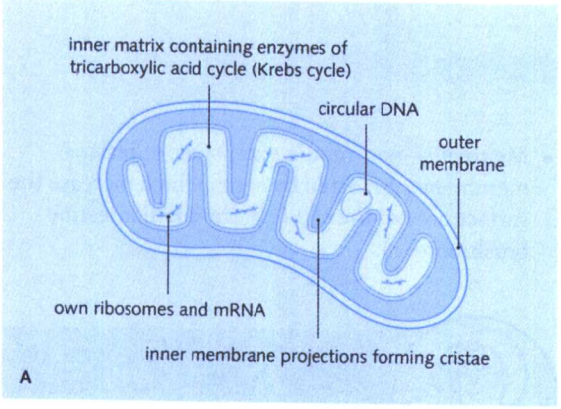
Mitochondria

The structure of a mitochondrion is illustrated in Fig. 1.7. Mitochondria perform aerobic respiration, and they are self-replicating. They have their own DNA, and they are thought to originate from primitive bacteria.

Rough (granular) endoplasmic reticulum

Rough endoplasmic reticulum (RER) is a labyrinth of membranous sacs, called cisternae, to which ribosomes are attached giving a 'rough' appearance on electron microscopy. Enzymes are attached to cisternae membranes or contained within the lumen (Fig. 1.8). Ribosome clusters occur free in the cytoplasm or attached to the outer surface of the cisternae. They make polypeptides, which are then in turn:

- Inserted into the membrane.
- Released into the lumen of the cisternae.
- Transported to the Golgi complex or elsewhere.



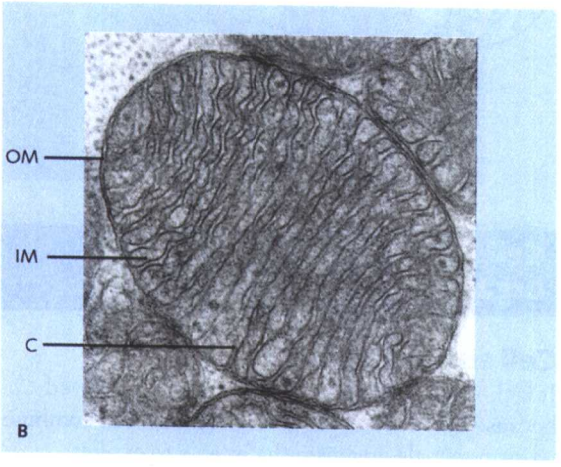


Fig. 1.7 (A) Structure of a mitochondrion. (B) Electron micrograph showing outer membrane (**OM**), inner membrane (**IM**), and cristae (**C**). (Courtesy of Dr Trevor Gray.)

Proteins made within RER are kept within vesicles or secreted. Cells that make large quantities of secretory protein have large amounts of RER (e.g. pancreatic acinar cells, plasma cells).

Free ribosomes synthesize proteins for immediate use in the cytoplasm.

Smooth (agranular) endoplasmic reticulum

Smooth endoplasmic reticulum (SER) is a labyrinth of cisternae with many enzymes attached to its surface or found within its cisternae. SER:

- Makes steroid hormones (e.g. in the ovary).
- Detoxifies body fluids (e.g. in the liver).

Golgi apparatus

The Golgi apparatus (Fig. 1.9) is a system of membranous flattened sacs involved in modifying (e.g. addition of carbohydrate), sorting, and packaging macromolecules for secretion or delivery to other organelles. Cells that produce many secretory products have well-developed Golgi apparatus (e.g. hepatocytes).

Lysosomes

Lysosomes are primary components of intracellular digestion (see Chapter 4). Cells specializing in phagocytosis (e.g. macrophages) have many lysosomes which:

- Are vesicular bodies containing granular amorphous material and about 60 types of hydrolytic enzymes.
- Vary in size from 50 nm to over 1 um.
- Digest material with hydrolases that are active at acid pH.

Peroxisomes

Peroxisomes are vesicular bodies that are smaller than lysosomes, and contain specific enzymes. They perform oxidation and detoxify hydrogen peroxide, which is a product of many metabolic reactions in the cell.

Non-membranous organelles

The cytoskeleton

The cytoskeleton is the internal framework of the cell, consisting of filaments and tubules. Cytoskeletal structures maintain and change cell shape by rearrangement of the cytoskeletal elements. They are thus essential for endocytosis, cell division, amoeboid movements, and contraction of muscle cells. There are several classes of cytoskeletal structural components:

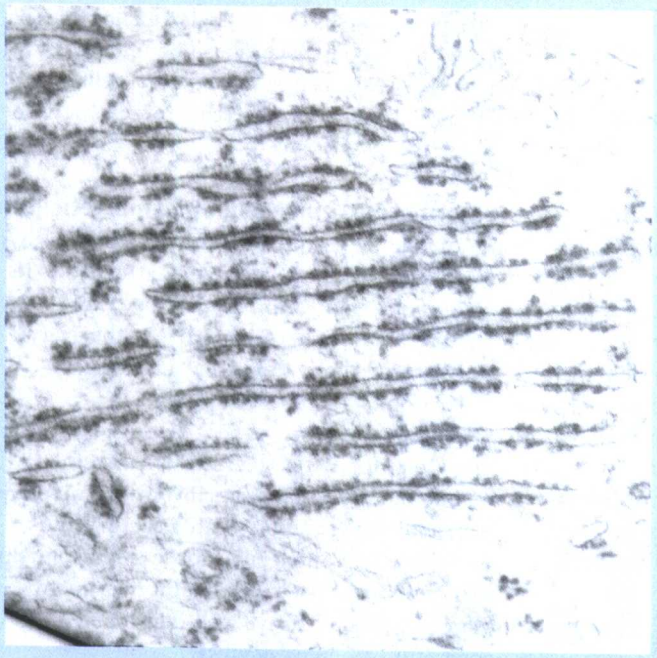


Fig. 1.8 Electron micrograph of rough endoplasmic reticulum (RER). The membranous tubules that make up the ER are studded with ribosomes giving a rough appearance. (Courtesy of Dr Trevor Gray.)

- Microfilaments formed from actin.
- Microtubules formed from tubulin.
- Intermediate filaments formed from intermediate filament proteins such as keratin.

These structures may be cross-linked by other proteins into networks or specialized organelles, the most common of which are:

- Centrioles—these usually occur in pairs and they are the site of spindle assembly in cell division. Each centriole is a short cylinder comprised of nine groups of three fused microtubules arranged around a central cavity.
- Cilia—used by some cells to transport substances (e.g. fallopian cells move ova towards the uterus). Cilia self assembly is seeded at basal bodies on the cell surface, which are identical in structure to centrioles. Microtubules are arranged in a '9+2' arrangement consisting of nine microtubule doublets surrounding two single microtubules (Fig. 1.10). Dynein side arms extend between adjacent doublets and hydrolyse ATP to generate a sliding force between them. This action underlies ciliary beating.
- Flagella—very long cilia used for propulsion by spermatozoa (NB prokaryotic and eukaryotic flagellae have different molecular structures).
- Microvilli—non-motile extensions of plasma membrane supported by actin, which increase the surface area of the cell (e.g. the small intestine brush-border).

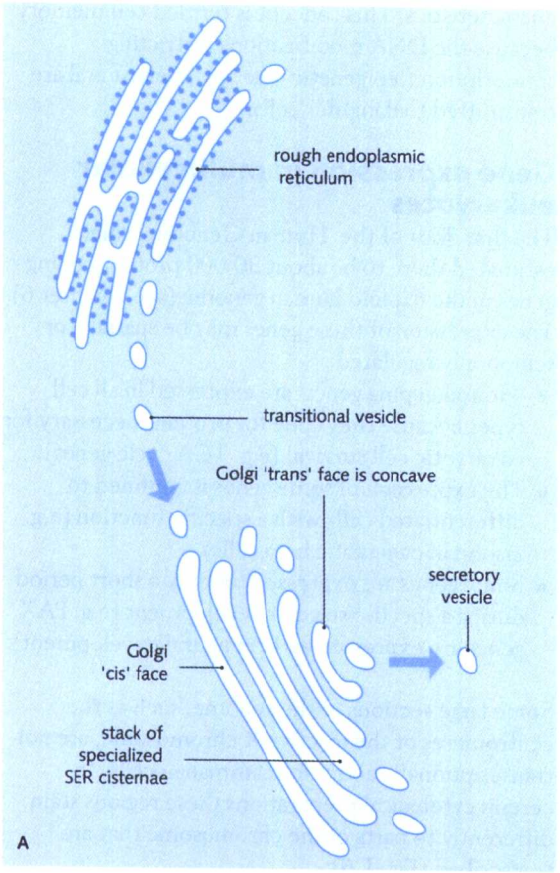
Kartagener's syndrome is an inherited disorder characterized by bronchiectasis, sinusitis, and dextrocardia. It is associated with ultrastructural defects in dynein or microtubule proteins leading to ciliary dyskinesia.

Cell diversity in multicellular organisms

Cell specialization

It is thought that multicellular organisms evolved because specialized cells acting together can combine to form a single organism that is able to exploit ecological niches not available to any of its component cells acting alone.

Similar types of specialized cells combine together to form tissues, of which there are four



main types each adapted to a specific function (Fig 1.11). By definition, specialized cells show structural features that enable them to perform their designated function. In order to cooperate and coordinate their activities in the multicellular animal:

- Cells are bound together by adhesions between their plasma membranes and the extracellular matrix (see Chapter 4).
- Cells interact and communicate with one another (see Chapter 3).

Differentiation

Over 200 types of cell are identifiable in human tissue, differing in terms of their structure, function, and chemical metabolism. All cell types are derived from a single cell (the zygote) following conception. The zygote is described as being totipotent since it is ultimately able to differentiate into all the cell types that make up the adult organism. There is no loss of genetic material from somatic cells during human development (red blood cells are an exception), so different cell types arise as a result of differences in gene expression.

During development, cells differentiate as successive cascades of proteins are expressed that regulate the DNA in each cell, restricting transcription from specific sections of the genome.

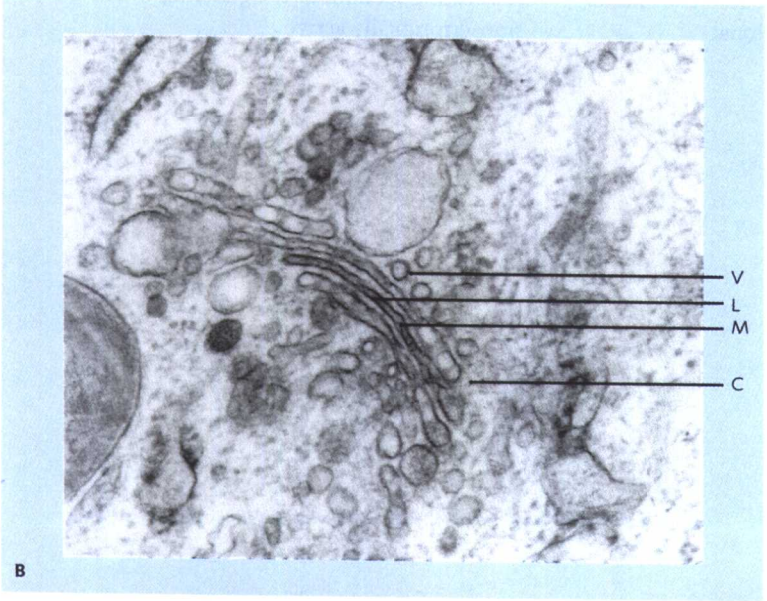


Fig. 1.9 (A) Structure of the Golgi apparatus. (B) Electron micrograph with parallel stacks of membrane (**M**) delineating Golgi lumen (**L**) from the cytosol (**C**). Transport vesicles (**V**) can be seen on their way from endoplasmic reticulum. (Courtesy of Dr Trevor Gray.)