Textbook of Physiology

1905

Edited by

Donald Emslie-Smith

Colin R. Paterson

Thomas Scratcherd

Nicholas W. Read

ELEVENTH EDITION

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BDS

Edited by

Donald Emslie-Smith

MD (Aberd) FRCP FRCP (Edin)

Reader in Medicine in the University of Dundee; Honorary Consultant Physician, the Royal Infirmary and Ninewells Hospital, Dundee

Colin R. Paterson

MA MSc (Oxon) DM MRCP (Edin) FRCPath

Senior Lecturer in Biochemical Medicine in the University of Dundee; Honorary Consultant to the Tayside Area Health Board

Thomas Scratcherd

MD (Newcastle) FRCP (Edin)

Professor of Physiology in the University of Sheffield

Nicholas W. Read

MA MD (Cantab) FRCP

Reader in Physiology in the University of Sheffield; Honorary Consultant Physician, Royal Hallamshire Hospital, Sheffield

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Preface to the Eleventh Edition

Gratefully we remember George Bell who died in the Spring of 1986. He had edited with us the Tenth Edition of his book and had told us he did not want to edit another. He was, however, delighted that there was to be an Eleventh Edition, and was always interested to hear about its progress. He would not have wanted an obituary notice here but, of course, we miss him greatly, both as a senior colleague and as a friend. His monument is his textbook published in ten editions over thirty years.

Some years ago he told one of us how the late Mr Charles Macmillan of Messrs E. & S. Livingstone approached him originally with the idea of preparing a new Textbook of Physiology and Biochemistry that would be relevant to medical practice. George Bell was then a Senior Lecturer in the University of Glasgow, before he moved to the Chair of Physiology in Dundee. He was fortunate in enlisting the help of two valuable colleagues: the late Professor Norman Davidson, FRS, then a Senior Lecturer in the University of Aberdeen, was a distinguished biochemist; and Professor Harold Scarborough, then a Clinical Tutor in the University of Edinburgh, who later occupied with distinction Chairs of Medicine in Wales and in Africa. The initials of their surnames, B, D and S, soon gave their textbook the affectionate nickname by which it became widely known, and with which we are proud to be associated.

We could not replace George Bell with any single person, so we now welcome Tim Scratcherd and Nick Read. Both are medically qualified physiologists with interests in clinical medicine, as befit editors of a textbook of physiology that still aims primarily to satisfy the needs of medical students, both undergraduate and postgraduate. This edition of BDS has been completely rearranged. Most of the chapters are new, and almost all the rest have been radically re-written. As previously, the editors are also the authors of many chapters.

Dundee
1987

D.E-S.
C.R.P.

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We owe a great debt to our contributors in this as in previous editions of this book. Some were responsible for whole chapters; others made smaller contributions to the chapters associated with their names. We are grateful to them also for their tolerance of our editorial efforts to ensure a uniform style throughout the book.

We thank several colleagues who reviewed and criticised chapters or parts of chapters in draft; these included Dr E. Brookes, Professor P. Howie, Dr T. E. Isles, Dr R. T. Jung and Dr A. S. Todd.

This edition owes much to Miss Mary Benstead who prepared many new and beautiful line drawings, to Mrs M. Lawson and Mrs M. Alexander for their lettering and to Ms Maureen Hughes, Mrs Judith Murant and Mrs Mina Geekie for their skilled secretarial work.

Dundee and Sheffield — D.E-S.
1987 — C.R.P.
T.S.
N.W.R.

Contributors

Professor A. Angel,
Department of Physiology, University of Sheffield (Chapters 32, 35 and 36)
Mr K. Baxby,
Department of Surgery, University of Dundee (Chapter 27)
Miss M. C. K. Browning,
Department of Biochemical Medicine, University of Dundee (Chapters 24–27)
Dr J. Chapman,
Department of Physiology, Sheffield Polytechnic (Chapter 11)
Professor P. Cohen
Department of Biochemistry, University of Dundee (Chapter 23)
Professor M. de Burgh Daly,
Department of Physiology, St Bartholomew's Hospital Medical College (Chapter 10)
Dr P. W. R. Elliott,
Department of Physiology, University of Sheffield (Chapter 11)
Dr C. C. Forsyth,
Department of Child Health, University of Dundee (Chapter 30)
Professor R. Green,
Department of Physiology, University of Manchester (Chapters 12 and 13)
Professor G. R. Hervey,
Department of Physiology, University of Leeds (Chapter 41)
Dr P. Kohn,
Department of Physiology, University of Sheffield (Chapter 2)
Dr D. M. Lewis,
Department of Physiology, University of Bristol (Chapter 40)
Dr D. A. S. G. Mary,
Department of Cardiovascular Studies, University of Leeds (Chapter 7)
Dr J. A. Mills,
Department of Obstetrics and Gynaecology, University of Dundee (Chapters 27 and 28)
Dr R. O'Neil,
Department of Pathology, University of Dundee (Chapter 4)
Professor L. H. Opie,
Department of Medicine, University of Cape Town (Chapter 7)
Dr D. Parratt,
Department of Microbiology, University of Dundee (Chapter 5)
Dr N. Patel,
Department of Obstetrics and Gynaecology, University of Dundee (Chapter 28)
Professor I. C. Roddie,
Department of Physiology, University of Belfast (Chapter 8)
Professor L. B. Strang,
Department of Paediatrics, University College London School of Medicine (Chapter 28)
Dr A. J. Suggett,
Department of Medicine, University of Sheffield (Chapters 9 and 10)

Contents

1

Introduction

Human physiology is concerned with the way the human body works. It is the study of the functions of tissues and organs, and of the way these functions are integrated.

THE CELL

The basic unit of each tissue of the body is the cell. Each organ or tissue consists of many types of cell, held together by supporting structures. A schematic diagram of a 'typical' animal cell is shown in Figure 1.1. The cell consists of a nucleus and other organelles floating in a fluid cytosol or cell sap that is separated from the extracellular fluid by a selectively permeable lipid membrane.

Membranes

The plasma membrane and also the bounding membranes of the nucleus and other organelles have

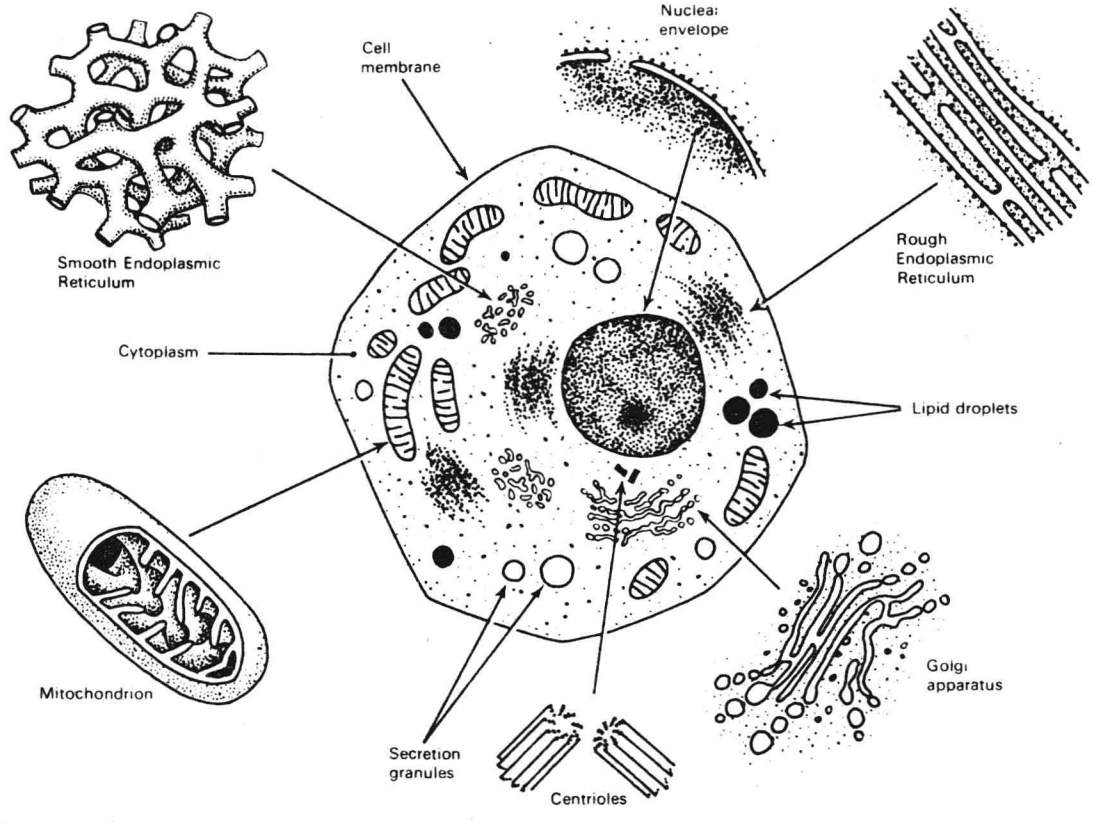

Fig. 1.1 The composition of a typical cell. The organelles, as seen by electron microscopy, are shown in greater detail around the outside.

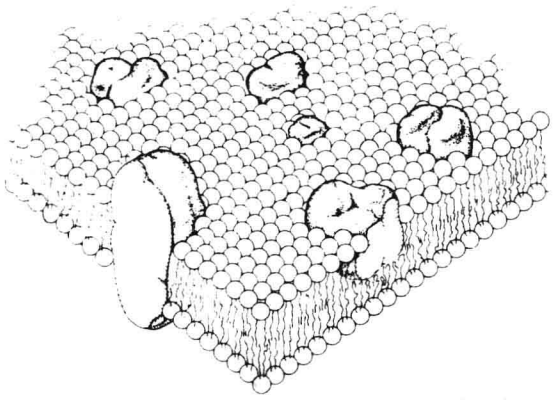

Fig. 1.2 A model to show current views of membrane structure. Irregularly shaped proteins float randomly in a lipid 'sea'. The proportion of protein varies greatly between membranes in different sites.

many features in common. All contain phospholipids and proteins; the lipids exist in a double layer with their hydrophilic 'heads' outermost and their hydrophobic fatty acid chains in the interior of the membrane (Fig. 1.2). The proteins are embedded in the membrane and serve as carriers for the transport of water-soluble substances and as markers to express immunological identity. They may also enclose aqueous channels for the passage of fluid and electrolytes into and out of the cell.

The ease with which a molecule can cross a membrane depends partly on its size but to a greater extent on its solubility in lipids. Thus membranes are usually impermeable to large charged molecules such as proteins but permeable to water and small uncharged molecules like urea. Water-soluble substances such as sugars and amino acids can only cross the cell membrane by combining with specific carrier proteins, bound to the membrane, or by diffusing through aqueous channels bounded by protein.

Because lipids are electrical insulators there may be considerable differences in electrical potential across a membrane; these differences may provide an electrical force for transport of charged particles through aqueous channels.

The organelles

Nucleus

The nucleus contains a mesh-work of densely staining DNA, the *chromatin* of the histologist. Before a cell divides, the chromatin condenses to form the chromosomes, which contain almost all the DNA of the cell. The nucleus is surrounded by a double membrane pierced at intervals by pores. It contains one or more dense, spherical bodies termed nucleoli, which are rich in RNA. The nucleoli are the sites of synthesis of the ribosomal RNA responsible for protein synthesis.

Mitochondria

Surrounding the nucleus is the cytoplasm in which are found various organelles such as secretion granules, lysosomes and mitochondria. Each mitochondrion is bounded by two membranes, each consisting of a lipid bilayer containing proteins. The inner membrane is folded to produce the cristae, which divide the interior into compartments. The mitochondria contain the enzymes responsible for oxidative phosphorylation, and are the sites of production of adenosine triphosphate, ATP. They have been termed the 'power houses of the cell'. The mitochondria also regulate the intracellular calcium concentration by the uptake and release of calcium ions. This property is of considerable importance since calcium serves as an intracellular regulator of many of the metabolic, secretory, and contractile functions of the cell.

Endoplasmic reticulum

The cytoplasm also contains a complex meshwork of canals and vesicles, known as the endoplasmic reticulum (Fig. 1.1), that lead from the exterior of the cell to the nucleus. Two kinds of endoplasmic reticulum can be distinguished under the electron microscope, rough endoplasmic reticulum (RER) and smooth endoplasmic reticulum (SER). The SER contains enzymes responsible for detoxication of foreign substances and for the synthesis of hormones and glycoproteins. The surfaces of RER are studded with small round electron-dense particles (diameter 10–20 nm) known as *ribosomes*. These consist of protein and RNA and are responsible for protein synthesis.

Lysosomes

The cytoplasm of most cells also contains small organelles known as lysosomes, which are essentially little sacks of hydrolytic enzymes that can break down large molecules. These enzymes are discharged into vacuoles containing large molecules, such as proteins and nucleic acids. In white blood cells, lysosomal enzymes play an important part in the digestion of foreign substances such as bacteria (Chap. 5).

Golgi apparatus

Some cells contain a Golgi apparatus, which is concerned with the packaging of proteins produced by the RER before their extrusion from the cell. The Golgi apparatus is particularly important in cells that secrete enzymes.

Microfilaments

Contractile microfilaments and microtubules are concerned with movements of the cell and the movements of organelles within the cell; they form the spindle of the mitotic apparatus, which draws apart the chromosomes during cell division.

INTEGRATION OF ORGAN FUNCTION

The cells are continuously bathed in extracellular fluid which is in constant motion throughout the body, carrying nutrients and oxygen to the cells and taking waste products away. The constancy of this internal environment is essential for cell survival and function, and the ability of the body to maintain this constant internal environment is called *homeostasis*. Cells are only capable of living and performing their special functions if they are well supplied with nutrients and oxygen, and if the concentrations of ions, the pH and the temperature of the fluid in which they are bathed remain constant.

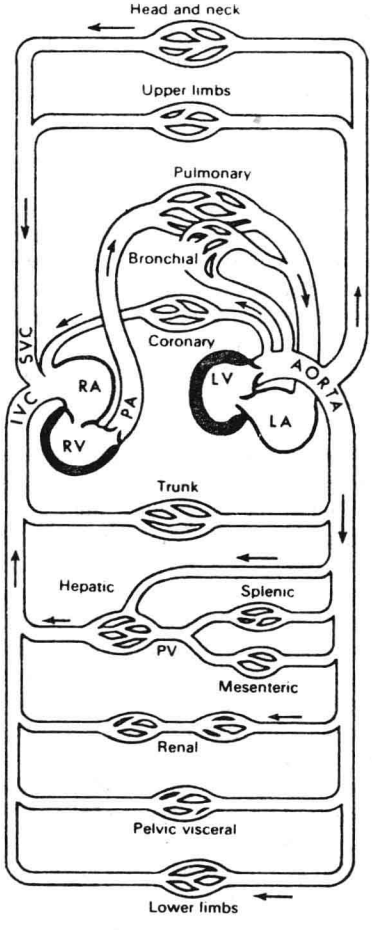

Fig. 1.3 Diagram to show the heart and circulation displayed as two (left and right) hearts and two circulations (systemic and pulmonary) arranged in series. Various important divisions of the systemic circulation are also indicated. Blood flows from arteries through capillary beds to veins. The renal circulation has two capillary beds, glomerular and tubular. PV = portal vein.

Cardiovascular system

Extracellular fluid is circulated around the body by the cardiovascular system, which consists of two circulations (Fig. 1.3). Oxygenated blood returning from the lungs is pumped by the heart to the other organs and tissues where it gives up its oxygen. It then returns to the heart and is pumped to the lungs. Although only about 3 litres of fluid are present in the cardiovascular system, this fluid circulates round the body at least once every minute (up to six times per minute during exercise) and is in equilibrium with the remaining 20 litres of extracellular fluid. The capillaries of most tissues are so permeable that large amounts of water, ions and small molecules can move rapidly between the blood

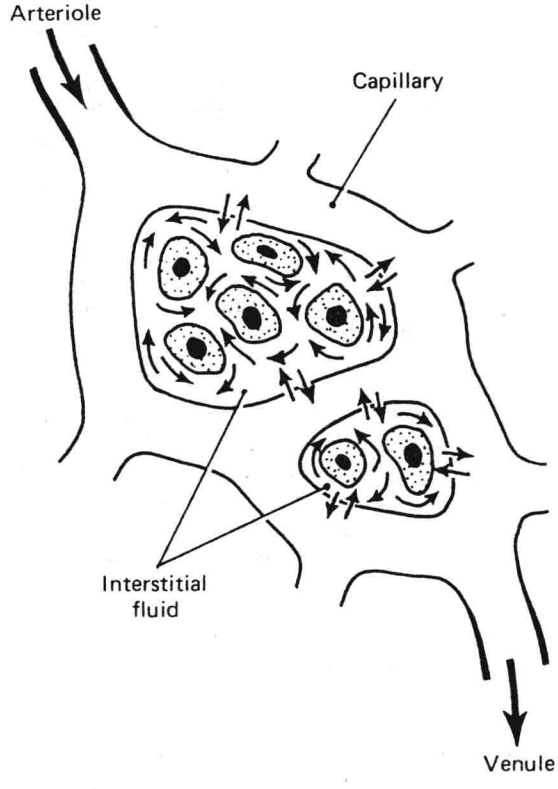

Fig. 1.4 A diagram showing how blood flowing through porous capillaries can mix the extracellular fluid.

and extravascular or interstitial fluid. Thus, circulation of only a proportion of the extracellular fluid by the cardiovascular system is sufficient to maintain the homogeneity of the extracellular fluid (Fig. 1.4).

The cardiovascular system conveys oxygen, which has entered the blood from the lungs, and nutrients, which have entered the blood from the intestine or liver, to the cells. It also transports waste products of metabolism to the lungs and kidneys where they are excreted. Since most cells are located within 50 μm of a capillary, transport between cells and blood is rapid.

The cardiovascular system has the flexibility to adjust flow and increase blood supply to certain organs when their demand for energy is greatest: to the muscles during exercise, to the gut after a meal and to the skin in order to lose heat, while at the same time maintaining the nutrition of other organs.

Respiratory system

Oxygen enters the body through the lungs. During respiration, contraction of the diaphragm and the muscles of the chest wall draws air into the lungs. Oxygen diffuses across the thin walls of the capillaries and combines with the haemoglobin in the red cells. The presence of haemoglobin ensures that the blood can carry sufficient oxygen for the energy requirements of all the cells of the body. Oxygen dissociates from haemoglobin in the tissues and is taken up by the cells. At the same time, carbon dioxide, the principal product of cellular oxidation, is released from the tissues and transported in the blood to the lungs, where it diffuses into the pulmonary air sacs or alveoli and is exhaled.

Gastrointestinal system

Most food consists of complex large molecules derived from plants and animals. After food has been eaten it passes slowly down the gastrointestinal tract where it is serially dismantled by enzymes, first in an acid and then in an alkaline medium, into smaller subunits, ultimately forming products that can be absorbed across the intestinal epithelium and reach the blood. Most nutrients are absorbed in the small intestine, but some of the remainder may undergo bacterial degradation and subsequent absorption in the colon. Any residue that cannot be absorbed is passed out of the anus as faeces.

Liver

Blood from the intestine drains through the liver before reaching the systemic circulation. The liver controls the supply, utilisation and ultimate degradation and excretion of nutrient material. It stores carbohydrate, iron and vitamins, releasing them according to the body's requirements. It possesses the enzymes responsible for the interconversion of protein, fat and carbohydrate in response to the body's requirements and for the synthesis of fats, glycogen, plasma proteins, bile acids and blood clotting factors. The liver breaks down and excretes certain hormones and drugs.

Excretory system

Waste products of cellular metabolism, particularly urea, are excreted in the kidney. Renal excretion involves the filtering of plasma through the glomerulus, followed by the selective reabsorption of certain important substances such as glucose, sodium and amino acids in the tubules, while waste products of metabolism pass out in the urine. This process allows the whole extracellular fluid volume to be 'cleaned' and its composition adjusted at least seven times a day, and provides the means by which the pH, ionic composition and osmolality of body fluids are regulated. The balance between filtration and reabsorption also regulates the normal extracellular fluid volume and plasma volume, and is therefore responsible for maintaining adequate perfusion of all the organs of the body.

Control of visceral functions

The maintenance of an adequate flow of blood to each organ and the regulation of the composition of the extracellular fluid requires a control system sensitive enough to detect and respond to minor changes in the composition of extracellular fluid or in the supply of nutrients or oxygen to an organ. Visceral function is largely controlled by the autonomic nervous system and the endocrine glands. The autonomic nervous system regulates the flow of blood to different organs and maintains a constant body temperature, whereas the endocrine system regulates intermediary metabolism and the composition of the extracellular fluid.

Although both systems of control use chemical transmitters to co-ordinate the function of different organs, they operate in different ways. In the autonomic nervous system, the transmitter is released from nerve endings adjacent to the site of action, interacts with a protein receptor on the cell membrane to alter cell function and is destroyed by nearby enzymes. This ensures a rapidly responsive control system; responses occur as soon as the stimulus commences and end soon after the stimulus ends and can involve different organs according to the site of release of the transmitter.

In the endocrine system transmitters called *hormones* are released into the blood. They circulate in the plasma and affect only those cells that have a specific protein receptor for the hormone. Hormones are not necessarily degraded locally; many are degraded in the liver and excreted in the bile and urine. Thus, in contrast with autonomic control, the control of visceral function exerted by hormones is often slow in response and long in duration.

Regulation of visceral function usually operates on the

principle of *negative feedback*, whereby the response corrects the abnormality providing the stimulus. For example, a rise in arterial pressure stimulates baroreceptors in major arteries and increases the rate of firing in vagal afferent nerve fibres. The increased afferent discharge inhibits the vasomotor centre so that the arterial pressure is reduced.

Control of movement

A person must be able to move purposefully in his environment in order to obtain food, to protect himself and to shelter from adverse environmental conditions. Survival may be severely limited when mobility is impaired.

The contraction of striated muscles alters the position of the bones, and allows respiration and speech. The complex movements of the limbs in walking, and of the tongue, lips and larynx and diaphragm in speech are coordinated by the central nervous system, consisting of the brain and spinal cord. Nerves called efferent or motor nerves leave this system and mediate muscular movement.

Central control is valueless unless the brain has information about events in the body and around it. This information is conveyed to the central nervous system by the sensory or afferent nerves. The special sense organs, such as the eyes, ears and nose receive and transmit information about the environment and allow the body to plan purposeful movements. Sensation from the muscles and joints provide information about the position of the body in space and enable the brain to monitor and adjust the movement according to what is needed.

Although many of the activities occurring in the central nervous system are exceedingly complex, few rise to consciousness. We are quite unaware, for example, of the muscular adjustments needed to maintain balance or to move our eyes so that images are kept fixed on the retinae. These adjustments are called *reflex* and the pathways involved, namely sensory nerves, central nervous system and motor nerves, are called *reflex arcs*.

Reproduction

Reproduction is the process by which new organisms can be generated to replace those that die. Most higher animals reproduce sexually. Sexual reproduction allows infinite combinations of genetic material, creating the adaptability of the species for survival in different or changing environments. Cells, called spermatozoa, carrying the genetic material of the male are produced in the testes. During sexual intercourse they are deposited in the female genital tract, where one of them may combine with and fertilise an ovum, which carries the genetic material of the female. The fertilised ovum divides and implants itself in the uterus, where it grows into an embryo. After implantation, a series of complex changes takes place to ensure provision of nutrients and oxygen to the fetus from the mother via the placenta. At the end of pregnancy the muscular wall of the uterus contracts rhythmically to expel the fetus, which then acquires oxygen directly from its lungs and obtains nutrients by suckling milk produced by the mother's breasts.

2

Biological membranes

The current view of the structure of the cell membrane was indicated in Chapter 1. Membranes are composed mainly of lipids and proteins together with much smaller amounts of carbohydrate.

The lipids of the cell membrane comprise a mixture of polar lipids, mostly phospholipids and cholesterol. All these molecules are amphipathic, that is, they possess one or more charged (polar) groups at one end of the molecule whilst the rest of the molecule is composed of fatty acyl side chains, or the uncharged sterol residue in the case of cholesterol. The polar group exerts an electrostatic attraction for water molecules and is described as *hydrophilic*, whilst the side chains are attracted to one another but exert no attractive forces on the water molecules and are described as *hydrophobic*. The membrane lipids therefore arrange themselves with their polar head groups pointing towards the aqueous regions at the surfaces of the membrane and their hydrophobic side-chains pointing to the middle of the membrane. This bilayer arrangement of the membrane lipids is inherently stable.

The membrane lipids are of three main types. The largest component in most membranes is the phospholipids. These molecules are based on the three-carbon glycerol molecule, which has three hydroxyl groups. At least one, and usually two of these groups are esterified to fatty acids; the third is esterified via a phosphate group to another alcohol, which is most commonly choline, serine, ethanolamine, inositol or a second glycerol molecule (Fig. 2.1). The phosphate group and its associated alcohol comprise the polar head group. The fatty acyl chains constitute the hydrophobic part of the phospholipid. The fatty acyl chains are unbranched, but may contain one or more double bonds (that is, the parent fatty acid is unsaturated).

A second group of membrane lipids is the sphingolipids. These molecules are based on the alcohol sphingosine. One fatty acyl chain is part of the sphingosine molecule and a second is attached via an amino residue (Fig. 2.2). As with a phospholipid, the phosphate–alcohol combination constitutes the polar head group. Together with the phospholipids and sphingolipids, cell membranes also contain various amounts of cholesterol.

Because most membrane lipids contain two fatty acyl chains, the polar head groups are relatively far apart and the stability of the bilayer depends mainly on the side chains. In particular, hydrophobic interactions between the fatty acyl side chains provide the main stabilising force for the membrane and these are reinforced by van der Waal's forces. The polar head groups contribute to the stability of the bilayer, mainly because of electrostatic and hydrogen-bonding interactions with the adjacent water molecules.

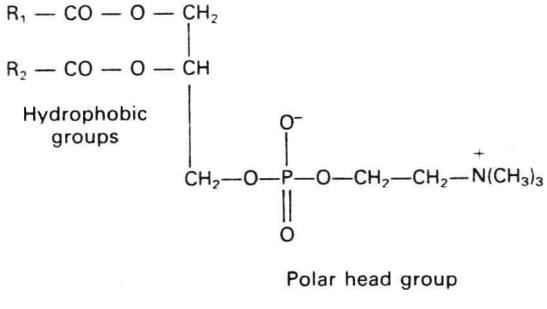

Fig. 2.1 Structures of phosphatidyl choline (lecithin), a typical phospholipid. R_1 and R_2 represent fatty acyl chains.

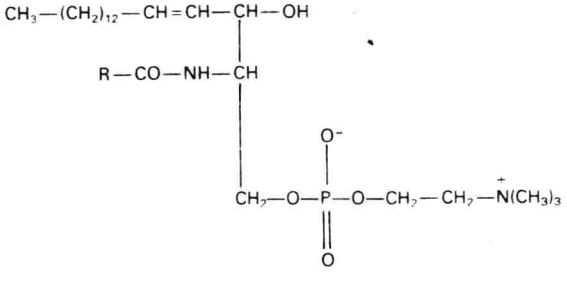

Fig. 2.2 Structure of sphingomyelin, the sphingolipid found in biological membranes in animals. R represents a fatty acyl chain.

Associated with the lipid bilayer are the membrane proteins. Many of these are so firmly attached to the membrane that they can only be removed by complete disruption of its structure. Such proteins are described as *integral*, or *intrinsic*. Other proteins, all of which seem to be associated with the inner face of the membrane, can be removed by changes in the pH or ionic strength of the adjacent aqueous medium, or by the use of chelating agents. These more easily removed proteins are termed *peripheral*, or *extrinsic*.

An examination of the amino acid composition of the membrane proteins shows that whilst peripheral proteins have a similar composition to cytoplasmic proteins, integral proteins contain long sequences of amino acids with hydrophobic side chains. Thus the hydrophobic parts of the integral proteins are associated with the hydrophobic core of the bilayer, whilst the hydrophilic parts are at the membrane surface.

In addition to lipids and proteins, membranes also contain carbohydrate. The amount is quite small, generally less than 10 per cent of the membrane by weight, and all of it is covalently linked to either lipid or protein. The glycolipids and glycoproteins are associated with the outer face of the membrane. They are thought to play a major part in molecular recognition processes; hormone receptors and the sites that confer immunological characteristics on cells include glycoproteins. It is likely that recognition between cells and their organisation into tissues also depends on the carbohydrate components.

The current view of the arrangement of the membrane components is known as the fluid-mosaic model, to emphasise the fluidity of the lipid and the heterogeneity of the structure as a whole (Fig. 2.3).

The main features of the model are the continuous bilayer which is regarded as being fluid in a number of ways. The lipid molecules may move laterally within the membrane by exchange of one molecule with another. At the same time the fatty acyl chains behave almost like a true fluid. Each C–C bond within the fatty acyl chain is a site about which the chain may rotate or vibrate. In addition, the whole chain may rotate or swing about its polar head group. The degree of fluidity increases towards the centre of the bilayer. Peripheral proteins are confined to the surface of the bilayer but integral proteins dip into one leaflet of the bilayer or in some cases span the entire membrane.

Recent studies have emphasised the asymmetry of the membrane in terms of the two leaflets of the bilayer. We have already seen that carbohydrate moieties are confined to the outer leaflet while most peripheral proteins are associated with the inner leaflet. Where it has been possible to separate the two leaflets of the bilayer, it has also been shown that the lipids themselves are distributed asymmetrically.

Similar constraints apply to the proteins. Many integral proteins are firmly anchored to peripheral proteins at the inner surface of the membrane. In the erythrocyte, such peripheral proteins help to define the shape of the cell (p. 24) and constitute what is termed the *cytoskeleton*. Similar cytoskeletons exist in other cells, although less is known about the molecules of which they are formed.

Even those proteins that are not anchored and can diffuse laterally in the plane of the membrane are unable to diffuse from one leaflet of the bilayer to the other. It requires a great deal of energy to move a hydrophilic molecule, or region of a molecule, through a hydro-

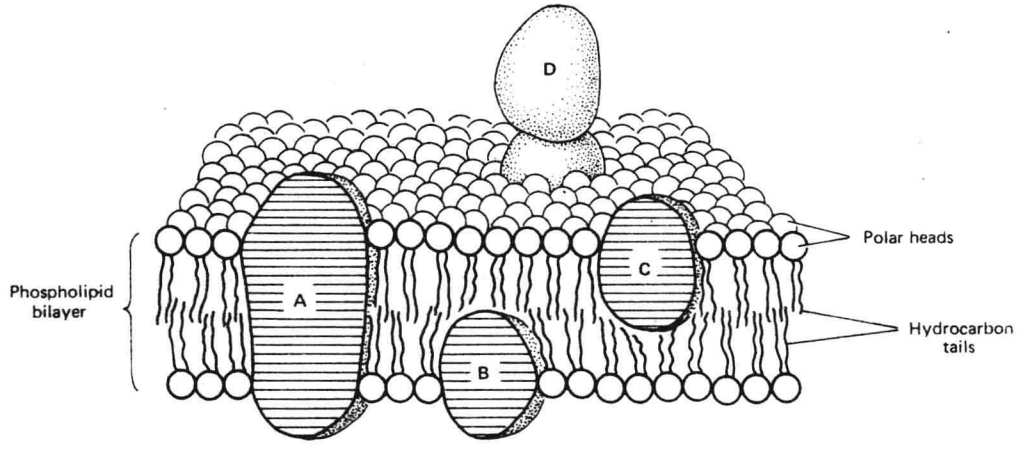

Fig. 2.3 The fluid-mosaic model of the cell membrane. Proteins may be integral (intrinsic; A, B, C), or peripheral (extrinsic; D). The integral proteins have hydrophobic regions that are associated with the hydrophobic parts of the lipid bilayer. (From C R Paterson 1983. Essentials of human biochemistry. Pitman, London).

phobic region of the membrane. Therefore, both lipids and proteins are confined to a single leaflet of the bilayer. Movements from one bilayer to the other are rare, perhaps impossible, for most membrane components.

The discussion so far has emphasised the many features common to all cell membranes. The diversity of membrane function reflects a diversity of composition and structure. At one extreme is nerve myelin, which has a largely structural role and contains around 80 per cent lipid by weight. The erythrocyte membrane contains slightly more protein than lipid, but most of the protein is associated with the inner leaflet of the bilayer. Membranes with a major metabolic role, such as the inner membrane of the mitochondrion, may contain more than 75 per cent protein.

MOVEMENT OF MOLECULES ACROSS THE CELL MEMBRANE

If a lipid bilayer is indeed the basis of plasma membranes, then only those molecules that can readily dissolve in the bilayer would be expected to cross the membrane. In most membranes, lipid-soluble molecules (those that dissolve readily in hydrocarbons) permeate easily. Perhaps surprisingly, such molecules include water itself. This is partly because water is present in extremely high concentrations on each side of the membrane (nearly 56 mol/l) and partly because of the small physical size of the water molecule.

Real biological membranes, however, are much more permeable to a whole range of ions and molecules to which a lipid bilayer might be expected to be relatively impermeable. This suggests that other membrane components, presumably proteins, are able to confer specific permeability properties on the membranes. Since most of these components form only a tiny fraction of the total composition of the membrane, isolating, purifying and studying such components has proved difficult and it has been easier to study their properties *in situ*.

Diffusion

By diffusion is meant the net movement of molecules from regions of higher concentration to regions of lower concentration as a result of the random molecular motion that results from thermal energy. Any molecule that can dissolve in the membrane matrix is able to cross the membrane by diffusion. The rate of diffusion across the membrane is proportional to the concentration of the substrate. It also depends on the partition coefficient of the substance between the aqueous medium and the membrane lipid (that is the relative solubilities in the two media), and on the diffusion coefficient for the substrate within the membrane. Thus the flow of solute across the membrane is linearly dependent on the concentration gradient. This relation is known as Fick's Law. Substances that cross membranes largely or entirely by diffusion include water, oxygen, carbon dioxide, cholesterol and steroid hormones, many lipid-soluble drugs and ethyl alcohol.

Hydrophilic substances, particularly ions, would be expected to have a low permeability through the lipid bilayer and this can be demonstrated with artificial lipid membranes prepared, for example, from pure phospholipids. However, in biological membranes ionic permeability is much higher and often seems to be related to the size of the ion. The highly polar ions exert electrostatic attractions on water molecules, which are also polar, and ions in aqueous solutions move with a more or less tightly associated set of water molecules described as a 'solvation shell'. Small ions, such as Na^+ are more polar and carry a larger solvation shell than larger ions such as K^+. The passive permeability of ions in biological membranes is more related to the 'hydrated ion radius' (the radius of the ion together with its solvation shell) than to the radius of the naked ion.

The permeability to some ions and to other small polar molecules suggests that membranes possess narrow, water-filled channels that provide an alternative route for diffusion through the membrane. The estimated pore diameter of such channels is somewhere between 0.4 and 0.8 nm; it is assumed they are associated with the integral proteins that span the membrane. The postulated dimensions of these channels is at the limit of resolution of the electron microscope and there is no unequivocal evidence for the presence of these pores.

Facilitated diffusion

Although many molecules cross the membrane by diffusion and at a predictable rate, many biologically important molecules cross the membrane much more readily than would be expected from their molecular size or their lipid solubility. Specific mechanisms seem to exist to allow their passage across the membrane and indeed such mechanisms appear to be necessary to allow the entry of very polar molecules such as D-glucose and many of the amino acids that are essential for the metabolism of the cell. Two types of mechanism are known. In one, *facilitated diffusion*, molecules move down their concentration gradients in a manner akin to simple diffusion, but at a greater rate than expected. In the second mechanism, movement is coupled to the movement of sodium ions and is not limited by the concentration gradient.

Facilitated diffusion has a number of characteristic features, many of which are shared by other specialised mechanisms of membrane permeation. First, such