Essentials of Physiology

J. F. LAMB C. G. INGRAM

I. A. JOHNSTON R. M. PITMAN

Second Edition

Essentials of Physiology

J. F. LAMB
MB, PhD, FRCP(E)
Chandos Professor

C. G. INGRAM
MB, ChB
Senior Lecturer

I. A. JOHNSTON
BSc, PhD
Reader

R. M. PITMAN
BSc, PhD
Lecturer

All of the Department of Physiology and Pharmacology
University of St Andrews, Fife

BLACKWELL
SCIENTIFIC PUBLICATIONS
OXFORD · LONDON · EDINBURGH
BOSTON · PALO ALTO · MELBOURNE

Preface

This book is aimed at those students of science, medicine, dentistry and allied professions who are studying a first year course of Physiology at University or equivalent level.

We have kept the book short so as to encourage the student to feel that he can grasp and understand the whole subject; a point especially important at a time when other subjects are making large demands on his time. We have chosen those aspects of the subject which we think are essential for the student to understand, and arranged them in such a way that students can use them in future as pegs to hang more information on. In order to achieve this, we have predigested most of the usual information given to students in larger text books, and then used graphs and diagrams to present it as simply and concisely as possible. This book is, however, concerned more with current ideas in Physiology than with a list of the currently known facts of the subject; for we feel that this approach is more likely to interest students who are starting the subject and, in consequence, is more likely to lead to their remembering the subject. Historically it is also true that the importance, and sometimes even the validity of 'facts', varies with the current theories about the subject.

A major difficulty in teaching physiology is to give a simple explanation of the complex mechanisms involved in the control of various bodily functions. Part of this difficulty is due to the problem of showing dynamic feedback loops in static diagrams. In our teaching, therefore, we have started to adopt a convention devised by Allweis for constructing such diagrams; in the book we have included some examples of these diagrams which our own students have found useful. (The convention is illustrated in Fig. 5.48.)

In choosing the material to be included in the book we have been guided by a set of Objectives for a course on Physiology produced by the Physiology Department of the University of Aarhus in Denmark (translated and published by the Physiological Society), and by *Learning Objectives in Medical Physiology* (1976) published by the University of London Board of Studies in Physiology. The reference list included is generally that which we found useful, and usually consists of other secondary references, i.e. larger texts, monographs, etc. We have occasionally referred to recent original papers where these are relevant.

We are grateful to Mr N. W. Palmer of Blackwell Scientific Publications who gave us a detailed specification for the book, and to colleagues who read various sections.

J.F.L., C.G.I.,
I.A.J., R.M.P.

Preface to the Second Edition

Our objectives in this edition are as before: to present an account of modern ideas about Physiology as clearly and as concisely as possible. For the former we have relied on the articles listed later, on seminars and particularily on colleagues familiar with fields foreign to us. For the latter we have tried to follow the adage that 'if a thing can be described it can be described simply'.

Those unfamiliar with this book will find that the text is generally simpler to understand than some of the illustrations. We often use the illustrations, particularly the captions, to 'amplify' rather than 'illustrate' the text. We suggest that on a first reading you read the text by itself, leaving the more conceptual Figures outlined in boxes for a second reading.

The chapters on the Gastrointestinal tract, Nutrition, and Kidney have been extensively revised, a short chapter on Circadian Rhythms and a section on Homeostasis added. Most of the other sections have been updated. Those familiar with the First Edition will find that the book has moved slightly 'up market', it has also become a little longer and acquired a second colour.

Many people were kind enough to send us helpful comments on the First Edition; we hope that readers will continue to point out our errors, stupidities and misconceptions in this Edition.

We are most indebted to Bridget Cook, of Blackwell Scientific Publications for much skilful, dedicated help in the preparation of this Edition.

Contents

Preface, vii

Preface to Second Edition, ix

PART 1 · BASIC PROPERTIES

1 Introduction and Cells, 3

2 Nerve and Synapse, 27

3 Muscle, 41

PART 2 · MAINTENANCE SYSTEMS

4 Blood and Body Fluids, 65

5 The Cardiovascular System, 88

6 · Gastrointestinal System and Nutrition, 141

7 Respiratory system, 178

8 The Kidney and Micturition, 205

PART 3 · COMMUNICATIONS AND CENTRAL CONTROL

9 The Nervous System, 229

10 Special Senses, 291

11 Endocrinology and Metabolism, 326

PART 4 · REPRODUCTION

12 Reproductive Physiology, 379

PART 5 · INTEGRATION

13 Hydrogen Ion Regulation, 407

14 Regulation of Body Fluids and Electrolytes, 413

15 Temperature Regulation, 422

16 Exercise, 430

17 Circadian Rhythms, 438

Appendix—Useful Data, 441

Reference Material, 447

Source of Figures, 450

Index, 453

Part 1
Basic Properties

Chapter 1
Introduction and Cells

INTRODUCTORY IDEAS

The structure and function of cells

There are three generalisations in biology:

1 The theory of evolution—all species living at present are a subset of all those which have lived and all are related to each other.

2 The cell theory—all living organisms are composed of cells: other life forms may have existed once but they have died out. Cells are a closed domain, this allows the concentrations of essential materials to be kept high enough so that the chemical reactions needed for life can proceed at fast rates. This is possible because there are membranes round and within cells and these act as selective barriers.

3 The unity of biochemical and physiological processes—all organisms now living share certain basic biochemical reactions. The two main things in common are:

a The chemistry of the tape, i.e. the genetic code is the same, and always based on nucleic acids.

b The machinery—proteins and devices for making proteins—are generally the same.

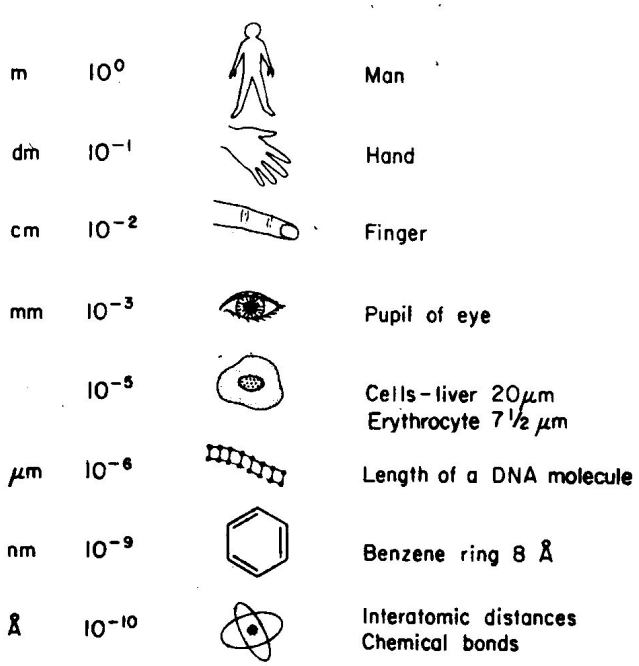

Fig. 1.1. Relative scales of the component parts of a man (after D'Arcy Thomson, see Source of Figures).

Because of this common basis we can study certain processes of life in whichever animal is convenient, e.g. the process of nerve conduction was worked out on the squid giant axon, that of blood pressure control in dogs, reflexes in cats and dogs and the genetic code in bacteria and so on. The data on which any 'human' course is based has been obtained largely from other animals.

Cells could not be seen until microscopes were invented in the 17th century, for they are small on our scale, although large compared to the atoms of the chemist. In size they lie about half way (on a logarithmic scale) between ourselves and the atoms (Fig. 1.1) and contain about as many atoms as we contain cells (10^{14}). In the evolution of multicellular

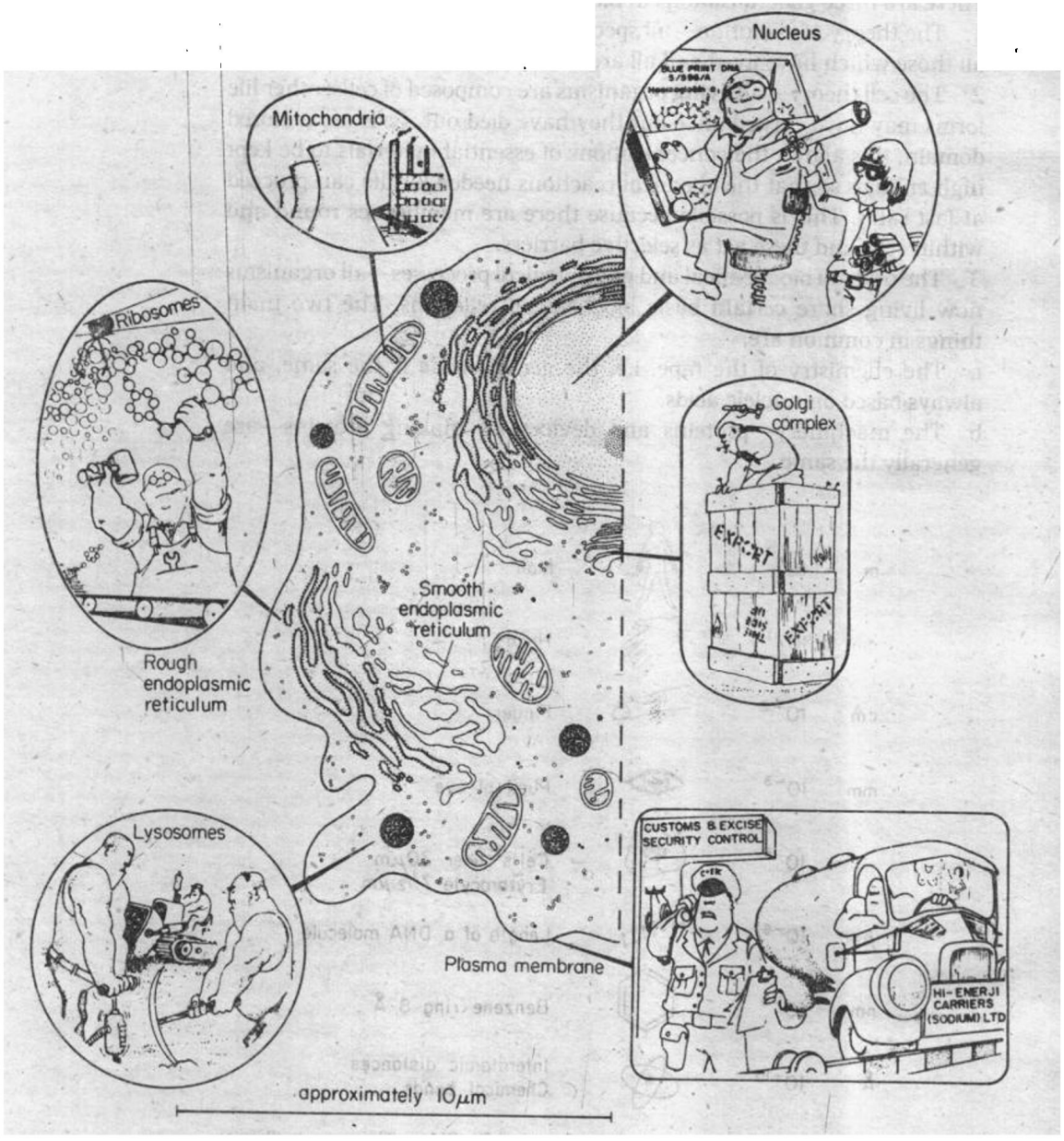

Fig. 1.2. Cellular components with an indication of their function (after Finean).

organisms, cells became specialised and organised into different systems, cardiovascular, muscle, kidney and so on, but generally retained common features (Fig. 1.2) and indeed have the same genetic information (in any one organism).

Such diagrams tend to give you the misleading impression that cells are static and fixed, whereas in life all parts of each cell are wearing out, being replaced or modified so that our cells of today do not contain the same molecules as our cells of yesterday. 'P'ological structure is not like that of a rock or a crystal, but rather like that of a flame or a waterfall' (Robinson). The rate of molecular replacement varies from minutes to months; that of cells from the few hours of the alimentary tract to the years of our bones.

Membranes in cells. The membranes of animal cells make up some 40–90 percent of the total dry mass in various cell types. They are of major importance in biological systems, because they divide cells into various compartments; this allows high concentrations of substrates to be created in parts of the cell with the possibility of high reaction rates, and allows control to be exercised by altering the rates of movement between compartments. Although their detailed structure varies from one location in the cell to another, all membranes have certain features in common. The present view is of a double layer of phospholipid some 10 nm thick (1 nm = 10 Å) with proteins studded in and on each side of it (Fig. 1.3). The phospholipid molecules can be thought of as a clothes-pin (Ganong) with a water-soluble, charged phosphate head and a water-insoluble, non-charged, lipid tail; these are arranged in a double layer with the heads in the water at each side of the membrane, and the tails in the centre. Proteins in globular form are embedded in the inner or outer membranes; in a more elongated form they span the membrane. There are both lipoproteins (lipid containing) and glycoproteins (carbohydrate containing) in the membrane. Some of the proteins which span the outer cell membrane perhaps act as receptors for hormones or neurotransmitters, and others may act as ion channels. It is now clear that membrane constituents (proteins and some lipids) can move laterally within the membrane at quite fast rates. So the membrane can be thought of as a fluid mosaic, largely composed of phospholipids but with many embedded proteins.

The nucleus. The individual active units of heredity—the genes—are strung together along the chromosomes, which are thread-like bodies in the nucleus of each cell. These genes contain all the information needed by the cell to reproduce itself; they do this by bearing within themselves, in coded form, the detailed specifications for the many thousands of protein molecules required by the cell for its moment-to-moment existence. The information in the gene is stored as a one-dimensional message, which is translated by the cellular machinery into the one-dimensional sequence of amino acids in the final protein molecule.

The genetic material in all cells is the giant chain-like molecule of deoxyribonucleic acid (DNA); in mammals dozens of these are clustered

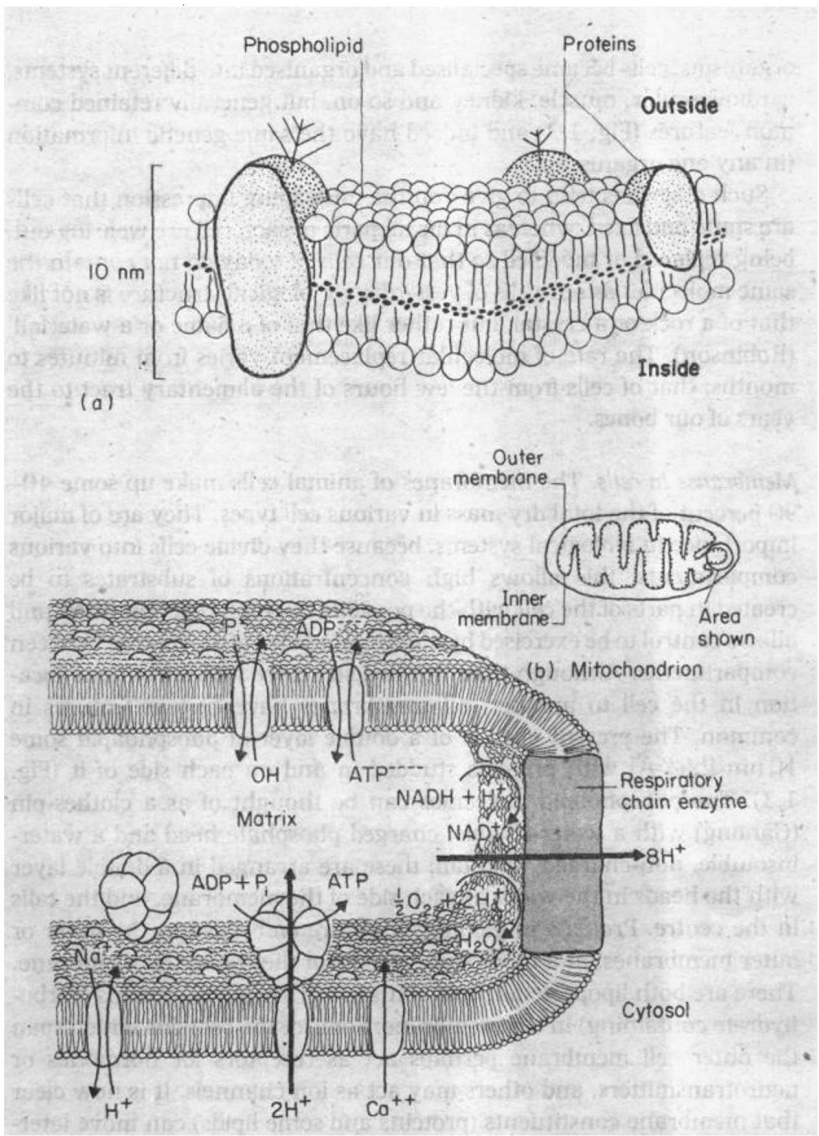

Fig. 1.3. Detailed structures of membranes. (a) Plasma membrane. (b) Mitochondrial membrane. Electrons and protons from carbohydrates and fats are carried by molecules of the hydrogen carrier, NADH, to a system of enzymes embedded in the mitochondrial membrane. These enzymes convey protons across the mitochondrial membrane to the cell cytoplasm. The gradient of proton and electrical potential so formed forces protons back through the membrane driving the process of ATP synthesis and the various carrier systems in the mitochondrial membrane (after Hinkle and McCarty).

together in the chromosomes. The DNA molecules are arranged like a ladder that has been twisted into a helix; the sides of the ladder are formed by alternating units of 5-carbon sugar and phosphate groups. The rungs, which join two sugar units, are made of pairs of bases; either adenine (A) paired with thymine (T) or guanine (G) paired with cytosine (C). These are the four 'letters' which spell out the genetic message; the exact sequence of bases along the sides of the 'ladder' determines the particular protein molecule.

Proteins are made from a standard set of 20 amino acids, uniform throughout nature, which are joined end to end to form the long polypeptide chains of protein molecules. Each protein has its own characteristic sequence of amino acids. Each polypeptide may have from 100 to more than 300 amino acids in it.

The genetic code is the 'dictionary' used by the cell to translate from the four-letter language of the nucleic acid to the twenty-letter language of the proteins. In doing so the cell uses a variety of intermediate molecules and mechanisms. The DNA message is first transcribed into a similar molecule called messenger RNA (ribonucleic acid), which has the bases adenine, guanine, cytosine, and uracil (U) instead of thymine. This moves out into the cytoplasm of the cell where the ribosomes travel along it, 'reading' the code contained in its base sequence and synthesising the polypeptide chain of the protein, starting at the amino end (NH_2). Each amino acid is recognised by a transfer RNA, which carries it to the growing polypeptide chain to which it is added.

The genetic code is a triplet code, i.e. the bases on the DNA are read three at a time rather than singly, and each group—called a codon—corresponds to a particular amino acid. Mathematically, the four letters of the DNA code can be combined into 64 distinct triplets so that there are more codons available than amino acids; it appears that some amino acids are represented by several codons.

The endoplasmic reticulum is a series of tubules in the cytoplasm of the cell. They are either smooth or rough in appearance. The roughness comes from the presence of ribosomes; globules some 10 nm in diameter made up of two subunits, a larger 50S and a smaller 30S (called after their rate of sedimentation in the centrifuge). Ribosomes may also be found in clumps of three to five as polysomes (polyribosomes) or free in the cytoplasm. Ribosomes manufacture protein on templates (messenger RNA) produced by the cell nucleus, using amino acids free in the cytoplasm. Cells which export* protein (pancreas, etc.) have their ribosomes organised on the endoplasmic reticulum; those which produce protein for replacement purposes within the cell have free ribosomes. Ribosomes are attached to membranes in pairs, probably with a pore present in the centre of the four subunits through which proteins are exported.

Smooth endoplasmic reticulum in muscle (= sarcoplasmic reticulum) is important in contraction; in steroid secretory cells it is the place where steroid hormones are made and in other cells is a site for detoxification.

The Golgi complex is a filamentous or plate-like collection of smooth membranes. Although present in the cytoplasm of all cells it is largest and most important in exporting cells and is believed to be responsible for 'packaging' the protein (for export). The most characteristic enzymes found here are those responsible for linking sugars with proteins to form glycoproteins.

* Manufacture protein for use outside the producing cell

The lysosomes are made in the Golgi apparatus, and are large and irregular membrane-bound structures. They contain a variety of enzymes which can break down proteins, carbohydrates, phosphate esters and RNA and DNA. They can be thought of as the digestive system of the cell, whose function is to break down unwanted parts of the cell, release hormones by breaking down precursors (for example, thyroid), kill engulfed bacteria, etc. Several of these functions are brought about by the lysosome merging with another vesicle containing the 'substrate' material. The resultant products are either excreted to the exterior of the cell or absorbed into the cell.

Microfilaments and microtubules are elongated structures present in many cells; the microfilaments are solid rods some 4–6 nm in diameter, whereas the microtubules are hollow cylinders some 25 nm in diameter with walls 5 nm thick. Microfilaments are made up of the same filaments—actin and myosin—that give muscles their contractile properties; if they contain much tropomyosin they are readily seen in electron micrographs (EM), if not they are not easily seen. Microtubules are made up of various proteins—the main one being tubulin—sometimes with side arms. Various drugs—for example, vinblastin and colchicine—and cold break up the labile variety of microtubules.

These filamentous structures are thought to be involved in cellular functions such as movement, ingestion of food, spindle formation during cell division, controlling the shape of cells, sensory transduction and perhaps the organisation of proteins in the cell membrane. The precise way in which this occurs is, at present, unclear; one view is that the microfilaments are the 'muscles' of the cell whereas the microtubules provide a framework for the organisation and co-ordination of the power so produced. The microtubules are the railway lines, the microfilaments the railway engine.

The mitochondria are sausage-shaped structures in the cytoplasm of cells. They have an outer membrane and an inner membrane folded into a variable number of cristae. The mitochondria are the 'power-house' of the cell where ATP* is made by a process called oxidative phosphorylation. It is found that the number of mitochondria and the number of cristae per mitochondrion are related to the energy requirements of the cell.

The current view is that mitochondria make ATP by a 'chemi-osmotic' method. It is thought that oxidation drives protons from the inside of the mitochondrion (the matrix) out into the cytoplasm; as the protons flow back the complex enzymes in the mitochondrial membrane form ATP (Fig. 1.3b).

The mitochondria may have originated as independent bodies which progressed through a symbiotic relationship with primeval cells to their present state. They have their own DNA and can make protein. Their DNA, however, is unlike that in the nucleus in that it is ring-shaped and attached to the mitochondrial boundary membrane and the coding is also different in mitochondria from that in the nucleus.

* Adenosine triphosphate—the universal energy currency of cells

This section contains a summary of those aspects of physiology 'that show some immediate prospect of being described in terms of the known laws of physics and chemistry' (Davson).

Water is important in the body, for our cells are largely composed of it, are suspended in it, our food is dissolved in it and we excrete into it.

The three atoms of the water molecule are arranged at an angle of about 104°, with the central oxygen electronegative and the hydrogen positive (Fig. 1.4). The properties of water which are important for our present purpose follow from this structure.

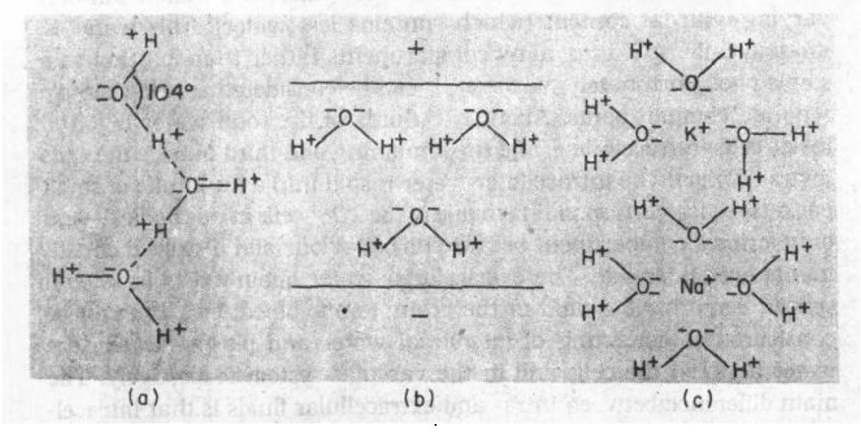

Fig. 1.4. (a) The clusters of dipolar molecules in liquid water; (b) its dielectric effect on electric forces between charged plates; and (c) the formation of hydration shells around Na^+ and K^+ ions.

Na^+ and K^+ have the same charge but the atomic radius of Na^+ is smaller and so it has a more intense field at its surface, leading to a greater hydration shell. The molecules of water in free clusters (a) or in shells (c) exchange rapidly with other water molecules, perhaps at rates of 10^{11} and 10^9 times per second.

1 Liquid water is formed of clusters or chains of molecules held together by hydrogen bonds between the oxygen of one molecule and the hydrogen of another. When water freezes, a regular structure of water molecules is formed with each molecule bound to four others by hydrogen bonds. On melting, some bonds are broken; further increases in temperature lead to more and more bonds being broken until only single molecules are left in water vapour. So, change in temperature is associated with chemical as well as physical changes in the structure of water, and requires much more heat than would be expected on simple grounds. Water, compared to say chloroform, has a very high specific heat and a high latent heat of evaporation. This means that water can readily absorb local heat produced by chemical reactions and that sweating in the tropics is a very effective way of losing heat. If we used chloroform instead of water as the solvent in our bodies, we would need to sweat 200 litres/day instead of the 10–15 litres of water we can sweat in the tropics to lose the same heat.

2 Water molecules, because of their charge, become orientated in an electric field. This means (a) that if an electric field exists across a membrane then the water molecules all line up and so reduce the electrostatic forces across this membrane (water is said to have a large dielectric* property, due to its dipolar nature); and (b) water molecules 'cluster' like a shell around a charged particle. These hydration shells (Fig. 1.4c) increase the size of the ions and partly obscure the chemical nature of the central ion, which only has direct access to its surroundings when the water molecules surrounding it exchange with those in free solution.

Water distribution in the body

Some two-thirds of our body consists of water, the actual amount varying with fat content (which contains less water). This water is, anatomically, split into many compartments rather than existing as a single pool. Fortunately, however, it can be considered as a few simple separate compartments. About two-thirds of the total water is found inside cells (intracellular), and the remaining one-third outside the cells (extracellular). The intracellular water is split into a multitude of small packets—each corresponding to one of the 10^{14} cells in our bodies—and only forms a compartment because its behaviour and dissolved constituents are all similar. The extracellular water again exists in several spaces: cerebrospinal fluid in the brain; joints; blood; etc., but can be considered as consisting of interstitial water and plasma water, the water between the cells and in the vascular system respectively. The main difference between intra- and extracellular fluids is that intracellular fluid contains potassium and organic anions (mainly organic phosphate) whereas extracellular fluid contains sodium chloride (Fig. 1.5). The extracellular fluid can be considered as the descendant of the seas our ancestral cells inhabited, although compared to the present-day sea it is only one-third as concentrated. Thus even though our remote ancestors left the sea to colonise the land, our cells are still tiny aquatic organisms floating in their own sea.

Homeostasis and control system theory

Claude Bernard introduced the idea that our lives are free and independent because our internal sea is fixed and constant: most of our cells do not have to share the same rigours that our whole body has to. Much of physiology is concerned with the homeostatic mechanisms which keep this internal sea constant. The magnitude of the problem can be appreciated by reflecting that our cellular mass has to live in a fluid environment of roughly one-quarter of its own volume† (Fig. 1.5). A real pond with this proportion of organisms to pond water would have a consistency like porridge and would soon become desperately polluted. Our bodies remain in a constant state because our extracellular space is very well mixed, has its gases replenished, is supplied with food and has its waste products removed.

* Transmitting electric effects without conducting

† About a 'legful' of water for our bodies

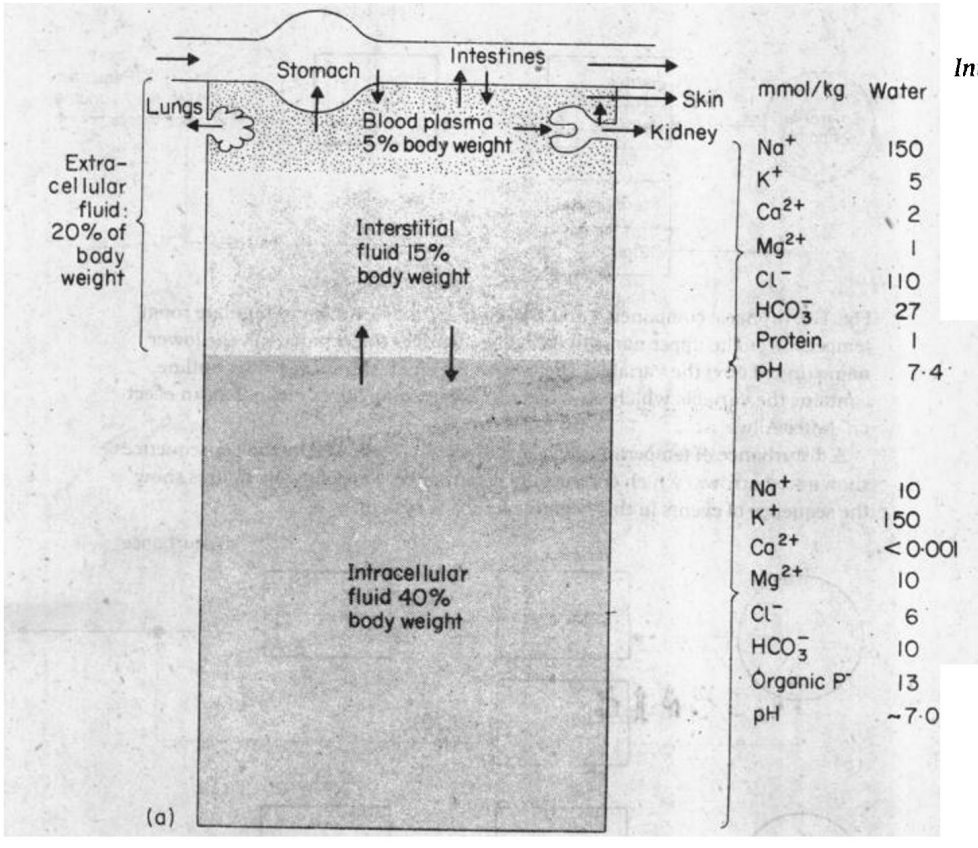

Fig. 1.5. The sizes and dissolved substances in the body fluid compartments. The arrows represent fluid exchanges.

The intracellular compartment can be considered as 'the discontinuous dispersed phase of an emulsion in the continuous extracellular fluid' (Robinson). All compartments have the same osmotic pressure, i.e. are isosmotic. (after Gamble)

Many conditions in the body are in fact so constant that minor departures from the normal can be used in the diagnosis of disease, if they persist. Thus, in man, the body temperature, and in the blood, the amount of sugar, the slight alkalinity, the concentration of various salts, the number of red or white cells etc., are constant or vary only within narrow limits.

In order to keep the output of a system constant (or to vary it in some controlled way) the inputs need to be manipulated. We will describe this by using a system familiar to you; keeping a room heated to a constant temperature. The essentials of such a control system consist of a heater, a sensor, i.e. thermometer, a controller and connections between them (Fig. 1.6). The temperature of the room is measured, compared with a desired temperature (set point) and the heater switched on or off. The sensor therefore detects the effects of the applied disturbance on the regulated variable, and *feeds back* a signal to the controller.

Additional points on the more complex arrangements present in physiological systems:

1 Most feedback systems are *negative*, i.e. the output of the sensor is subtracted from the set point in the controller to give an 'error' signal.