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Physiology
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A clinical core text of human physiology with self-assessment

J G McGEOWN

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Contents

Using this book

Philosophy of the book

This section aims to help you:

- understand how self-assessment can make learning easier and more enjoyable
- use the book to increase your understanding as well as knowledge
- plan your learning.

How much do you know about the control of blood pressure? Are they the right things? Can you answer examination problems on physiological control systems? This book aims to help you with these questions. Principles are illustrated and mechanisms explained while essential information is presented in a concise and ordered fashion. Do not think, though, that this book offers a 'syllabus'. It is impossible to draw boundaries around medical knowledge and learning is a continuous process carried out throughout your career. With this in mind, we want you to develop the ability to discriminate material which must be understood from areas which you need to know about, and topics which you might simply be aware of.

You are probably working towards one or more examinations and one aim is to show you how to overcome this barrier. Learning is not simply for the purpose of passing exams, however, so the book aims both to help you to pass and to develop useful knowledge and understanding.

Layout and content of the book

In order to use this book fully, you need to know why it is laid out as it is. The overview to each chapter sets out the scope of material covered. This has been chosen to reflect those things which anyone starting a medical career needs to know and which an examiner expects them to know. If you have already studied a given system, you might start by testing yourself using the self-assessment section at the end of each chapter. This will help to steer you towards areas that you need to work on. Alternatively, you may go straight into the main body of the chapter and check at the end that you have grasped the material; if not, then you will need to do further work and perhaps read about the topics elsewhere.

The main part of the text describes the important physiology for the different systems of the body. Within each section, the essential information is presented. These essentials are summarized at the start of each sub-section in the form of learning objectives, which provide a guide as to what you should know when you have studied that subject. One useful study technique is to check whether you have achieved these objectives or not. Relevant structural information is given first, both anatomical and histological, followed by a description of the main functions carried out. This will generally involve an outline of what a system does and how its performance is measured. Consideration will then be given to the mechanisms which explain these observed functions. Particular emphasis is placed on the controls which regulate function to meet body needs. Finally, important examples will be given of the consequences of abnormal function in each system to provide a link with your clinical study and training.

You have to be sure that you are reaching the required standards, so the final section of each chapter is there to help you to check your knowledge and understanding. The self-assessment is in the form of multiple choice questions, matching items questions, short note questions, modified essay questions, data interpretation and sample viva questions. Some of these formats may be new to you, but all are used in testing aspiring clinicians. Questions are centred around aspects of physiology which are generally regarded as important in clinical practice and so are emphasized in examinations. Detailed answers are given with reference to relevant sections of the text; the answers also contain information and explanations which you will not find elsewhere, so you have to do the assessments to get the most out of this book.

Studying the subject

Use of the self-assessment sections will encourage you to store information and to test your ongoing improvement. You must keep testing your current level of knowledge, both strengths and weaknesses.

Overall, the aim is to help you to learn through the use of interlinked steps. Initially you must decide:

- What do you already know about the subject?
- What do you want to learn about the subject?

Knowledge is acquired more easily if it can be put into a framework, so:

- Ask yourself what things need explaining—what do you not understand?
- Try to expand on these things—explain as much as you can and be as specific as possible about what confuses you.
- Use resources such as textbooks, teachers and your peers to address these confusing issues.
- Check that you are no longer confused using relevant self-assessment materials.

If you can, discuss problems with colleagues/friends. The areas which you understand least well will become apparent when you try to explain them to someone else. You will also benefit from hearing a different perspective on a problem.

Approach to examinations

Your first task is to map out on a sheet of paper an assessment of your strong, reasonable and weak areas. This gives you a rough outline of your revision schedule, which you must then fit in with the time available. Clearly, if your exams are looming large you will have to be ruthless in the time allocated to your strong areas. The discipline of learning is closely linked to preparation for examinations. Many of us opt for a process of superficial learning which is directed towards retention of facts and recall under exam conditions. Ideally, you should acquire a deeper understanding but, recognizing constraints on your time, a pragmatic approach to learning which combines the necessity of passing exams with longer term needs is important.

Next, you need to know how you will be examined. For written examinations you need to know the length of the exam, the types of question (for example, MCQ, modified essay, etc.), the number of questions to be answered and what choice you will have. The hardest step is to determine the likely scope of the exam; medicine does not draw boundaries around knowledge either in breadth or depth and different teachers may have slightly different emphases. Most medical and dental courses now emphasize a core curriculum and this text seeks to identify aspects of physiology which are clinically relevant. The best approach is to combine lecture notes, textbooks (appropriate to the level of study) and past examination papers. The last of these also helps indicate the depth of knowledge expected in a given area. Trying to 'spot' specific questions, however, is a dangerous practice.

The next stage is to map out the time available for preparation. You must be realistic in this, allowing time for breaks and working steadily, not cramming. If you do attempt to cram, you have to realize that if the examination requires understanding you may be in trouble. An approach based on active learning through the use of key steps, learning objectives and self-assessment has much to commend it. For a subject such as cardiovascular physiology, you might set out the topics to be covered and then attempt to summarize your knowledge about each in note form. In this way, prior knowledge will be brought to the front of your mind and gaps in your knowledge/understanding become apparent. It is much more efficient to go to textbooks having been through this exercise as you are then 'looking' for information and explanations.

As the examination draws near, you should start to attempt practice questions and complete papers. It is not sufficient to have the necessary knowledge and understanding; you need to demonstrate these to the examiners. Many people pay insufficient attention to the type of question they are going to encounter. Moving the focus away from books and lecture notes to actual questions helps in identifying where knowledge is still lacking and what work is still to be done. Additionally, attempting complete exams allows concentration to be built up.

Examination methods

Multiple choice questions

Most multiple choice questions test recall of information. The aim is to gain the maximum marks from what you can remember. The common form consists of a stem with several different phrases which complete the statement. Each statement is to be considered in isolation from the rest and you have to decide whether it is 'True' or 'False'. There is no need for 'Trues' and 'Falses' to balance out for statements based on the same stem; they may all be 'True' or all 'False'. The stem must be read with great care and if it is long, with several lines of text or data, then you should try and summarize it by extracting the essential elements. Make sure you look out for the 'little' words in the stem such as 'only', 'rarely', 'usually', 'never' and 'always'. Negatives such as 'not', 'unusual' and 'unsuccessful' often cause marks to be lost. 'May occur' has entirely different connotations to 'characteristic'. The latter generally indicates a feature which is normally observed, and the absence of which would represent an exception to a general rule, e.g. regular elections are a characteristic of a democratic society. Regular (if dubious) elections may occur in a dictatorship, but they are not characteristic.

Remember to check the marking method before starting. Most employ a negative system in which marks are lost for incorrect answers. The temptation is to adopt a cautious approach answering a relatively small number of questions. This can lead to problems, however, as we all make simple mistakes or even disagree vehemently

with the answer favoured by the examiner! Caution may lead you to answer too few questions to pass after the marks have been deducted for incorrect answers.

Distracters are the technical term for parts of questions which sound as though they are correct but are definitely incorrect in the context of the complete statement. A good example would be to take the stem 'Parasympathetic nervous activity' and have as a completion statement 'leads to a rise in heart rate during exercise'. This is false since, although heart rate does rise in exercise, this is not caused by parasympathetic activity, which slows the heart. Another type of distracter is to give what appears to be the numerically correct value for a variable but to change the units, e.g. systemic arterial oxygen tension is normally about 95 mmHg; 95 kPa would be incorrect but could catch out the unwary. This is the commonest area where students lose marks even though they know the answer.

Essays

Although essays are increasingly rare in examinations, you may be asked to write an essay to test your ability to integrate information. Relevant facts will receive marks as will a logical development of the argument or theme. Conversely, good marks will not be obtained for an essay which is a set of unconnected statements. Length matters little if there is no cohesion. Relevant graphs and diagrams should also be included but must be properly labelled.

Most people are aware of the need to 'plan' their answer yet few do this. Make sure that what you put in your plan is relevant to the question asked as irrelevant material is, at best, a waste of valuable time and, at worst, causes the examiner to doubt your understanding. It is especially important in an examination based on essays that time is managed and all questions are given equal weight, unless guided otherwise in the instructions. A brilliant answer in one essay will not compensate for not attempting another because of time. Nobody can get more than 100% (usually 70–80%, tops) on a single answer! It may even be useful to begin with the questions about which you feel you have least to say so that any time left over can be safely devoted to your areas of strength at the end.

Matching item questions

This form of question is a variant of the multiple choice question which is sometimes favoured over the True/False format discussed above because the increased number of options means that negative marking is not required. The main problem that can arise with these questions (other than simply not knowing the answer) is that more than one of the options may seem appropriate to a single statement. All you can do under these circumstances is decide which answer you think is best. Check the instructions carefully to see whether each answer can be used several times (as in my examples) or once only.

Short notes

Short notes are usually marked from a 'marking template' or 'model answer' which gives a mark(s) for each important fact (also called criterion marking). Nothing is gained for style or superfluous information. The aim is to set out your knowledge in an ordered, concise manner. The major faults of students are, firstly, devoting too much time to a single question thereby neglecting the rest and, secondly, not limiting their answer to the question asked. For example, in a question about the control of erythrocyte production, all facts about erythropoiesis should not be listed, only those relevant to its regulation.

Modified essay questions

These provide for the development of a theme using a series of descriptive paragraphs which set the scene interlinked with specific questions which lead the examinee on as the 'story' unfolds. They are widely used in clinical subjects, where they are often known as 'Patient management problems', but they are sometimes used to test knowledge in basic medical sciences as well. MEQs are usually criterion marked so mentioning all the relevant information is vital and a short note format may be used. There is also often a problem solving element which requires application of basic principles to the specific situation described.

One of the main faults in dealing with this sort of question is for students to attempt to use material from near the end of the problem to help them answer earlier questions. The MEQ is commonly designed to suggest a range of equally likely interpretations based on the initial information. Full marks depend on mentioning all of these. Some explanations may then be excluded, and new possibilities introduced, by providing further information. Your answers to a question should reflect the information given up to that point. Using material which comes later may lead you to exclude some of the most relevant responses. Also, you should attempt all sections of the question (unless the exam instructions indicate negative marking). There is usually some degree of independence of the individual sections of the problem so you should be able to attempt later sections even if you cannot answer the initial questions.

Data interpretation

This involves the application of knowledge to solve a problem. In your revision, you should aim for an

understanding of principles since it is impossible to memorize all the different data combinations. In the exam, a helpful approach is often to translate numbers into a description; for example an arterial blood pH below 7.4 represents an acidosis and the ECG tracing of a heart rate of 120 beats min^{-1} shows a tachycardia. Pattern recognition can then be attempted. This type of question is usually not negatively marked so put down an answer even if you are far from sure that it is right. Conversely, there is no point in listing four possibilities, if the question asks for one response. The examiner will not choose from your answers, the first response is likely to be taken!

Vivas

A few points on technique may be useful. The viva examination can be a nerve-wracking experience. You are normally faced with two examiners who may react with irritation, boredom or indifference to what you say. You may feel that the viva has gone well and yet you failed, or more commonly you think that the exam has gone terribly simply because of the apparent attitude of the examiners.

Your main aim during the viva should be to control the questioning of the examiners so that they are constantly asking you about things you know about. It is worth running mock vivas with your colleagues to practise this skill. The 'examiner' also learns much in this situation since asking sensible questions requires deep understanding. Major points relating to any of the systems may be asked but if you are aware of having performed badly in an exam essay make sure you cover related material before a 'pass–fail' viva. Always give the simplest possible answer to the question asked; there are very few intentional traps in vivas but many students confuse themselves by looking for them. The examiners are likely to want to explore the limits of your knowledge so do not be upset if they push you hard. It is all right to say you do not know something and this allows the examiners to change tack to see what you do know about.

Normal values

A student is expected to know the values of certain physiological variables as they are essential to any discussion of normal physiology as well as for making decisions in emergency medicine. Values in the text have been limited to those which you are likely to be expected to know. Make sure you are also clear what the units of measurement are in each case.

Conclusions

I have set out a framework for using this book, but you should amend this according to your own needs and the examinations you are facing. Whatever approach you adopt, your aim should be for an understanding of the principles involved as well as the memorization of facts.

Reference table of normal values Many variables show a considerable range of normal values but mid-values have been quoted in most cases

Variable	Value	Units
Body fluid volumes		
Blood volume	70	ml kg^{-1} body wt.
Plasma volume	40	ml kg^{-1} body wt.
Total body fluid volume	60 (males) 50 (females)	% body wt.
Intracellular fluid volume	2/3 total body fluid volume	—
Extracellular fluid volume	1/3 total body fluid volume	—
Blood cells/platelets		
Haematocrit (packed cell volume)	45% (0.45)	—
Haemoglobin concentration	14	g dl^{-1}
Red cell (erythrocyte) count	5	$\times 10^{12}$ L^{-1}
Reticulocyte count	2	%
Erythrocyte sedimentation rate (ESR)	<5 (males) <7 (females)	mm h^{-1}
White cell (leucocyte) count	6	$\times 10^{9}$ L^{-1}
Neutrophils	3.5	$\times 10^{9}$ L^{-1}
Lymphocytes	2	$\times 10^{9}$ L^{-1}
Eosinophils	0.2	$\times 10^{9}$ L^{-1}
Monocytes	0.5	$\times 10^{9}$ L^{-1}
Basophils	<0.1	$\times 10^{9}$ L^{-1}
Platelet count	250	$\times 10^{9}$ L^{-1}

Reference table (*Cont.*)

Variable	Value	Units
Plasma		
Plasma protein concentration	60	$g\ L^{-1}$
Plasma oncotic (colloid osmotic) pressure	25	mmHg
Plasma osmolality	300	$mosmol\ kg^{-1}$
Na^+	140	$mmol\ L^{-1}$
K^+	4.5	$mmol\ L^{-1}$
Ca^{2+}	2.5	$mmol\ L^{-1}$
Cl^-	105	$mmol\ L^{-1}$
HCO_3^-	25–30	$mmol\ L^{-1}$
Glucose	5	$mmol\ L^{-1}$
Urea	5	$mmol\ L^{-1}$
Cardiovascular function		
Resting cardiac output	5	$L\ min^{-1}$
Resting heart rate	70	min^{-1}
Resting stroke volume	70	ml
Systemic arterial pressure	120/80	mmHg
Pulmonary arterial pressure	25/10	mmHg
Central venous pressure	3–8	cmH_2O
	2–6	mmHg
Respiratory function		
Compliance (lung + chest wall)	100	$ml\ cmH_2O^{-1}$
Intrapleural pressure during quiet breathing	−4 (expiration)	cmH_2O
	−9 (inspiration)	
Tidal volume	500	ml
Respiratory rate	12	min^{-1}
Respiratory minute volume	6	$L\ min^{-1}$
Dead space	150	ml
Alveolar ventilation rate	4.2	$L\ min^{-1}$
FEV_1/FVC	>75	%
Blood gases and acid–base balance (also HCO_3^- above)		
Systemic arterial pH	7.38–7.42	—
Systemic arterial P_{O_2}	13	kPa
	98	mmHg
Systemic arterial P_{CO_2}	5.3	kPa
	40	mmHg
Base excess	−2–+2	$mmol\ L^{-1}$
Renal function		
Renal blood flow	1.2	$L\ min^{-1}$
Glomerular filtration rate	120	$ml\ min^{-1}$
Average urine output (normal hydration)	1	$ml\ min^{-1}$
Renal glucose threshold	11	$mmol\ L^{-1}$
Nutritional status		
Body mass index	20–30	$kg\ m^{-2}$
Hormones		
Thyroxine (T_4)	100	$nmol\ L^{-1}$
Triiodothyronine (T_3)	2	$nmol\ L^{-1}$
TSH	2.5	$mU\ L^{-1}$
Cortisol	400 (peak)	$nmol\ L^{-1}$
	150 (trough)	$nmol\ L^{-1}$
Urinary free cortisol	<300	$nmol\ 24\ h^{-1}$

1 Basic principles and cell physiology

Overview

The physiology of the body is often described in terms of the homeostatic mechanisms which control the cellular environment. Cell function also relies on an adequate energy supply and the appropriate integration of the activities of the different cells within the body through efficient signalling mechanisms, both electrical and chemical. The cell membrane is very important in many of these functions since it forms a barrier between the intracellular and extracellular environments across which important molecules must be transported. The properties of the membranes of excitable cells also account for the generation of action potentials, and many of the receptors which recognize specific chemical messengers are membrane bound.

1.1 Cells, systems and homeostasis

Learning objectives

At the end of this section you should be able to:

- describe the main components of the cell
- identify the main body fluid compartments and estimate their likely volumes
- explain the principles of indicator dilution methods and suggest appropriate indicators for specific compartments
- outline the principles of homeostasis and describe how these apply to temperature regulation.

Physiology is the study of normal biological function. Although the ultimate goal is to understand the intact human, function is often considered in terms of individual physiological systems, each of which consists of different organs and structural elements. The different components of any *system* may be spread widely throughout the body but they serve a *common functional* purpose. Therefore, we talk of the cardiovascular system, consisting of the heart, arteries, capillaries, veins, lymphatics and related control mechanisms, all of which are involved in the circulation of the blood. The fundamental biological unit is the cell, however, and each organ's function reflects the integrated activity of the various specialized cells within it.

Cell structure

Although cells from different organs show considerable differences in shape (morphology) and function, all cells share some general characteristics. Each is bounded by a cell membrane (or *plasma membrane*) which separates the aqueous solution inside the cell (the *cytoplasm* or *intracellular fluid*) from the aqueous solution outside (the *extracellular fluid*). These two fluids have very different ionic compositions (see Section 5.1) and this difference is more easily maintained because ions cannot readily cross the double layer (*bilayer*) of phospholipids in the plasma membrane (Fig. 1). These are oriented with their hydrophilic heads adjacent to the aqueous solutions on either side, while their hydrophobic tails form a fatty core. Membrane proteins move about within the two-dimensional confines of the lipid layer (the fluid mosaic model of the membrane).

Membranes also delimit a number of subcellular units known as *organelles*. These include:

- the *nucleus*, which contains the genetic code for protein synthesis in the form of deoxyribonucleic acid (DNA). Since proteins are key structural and functional molecules in the cell, changes in gene expression regulate how a cell looks and behaves.
- *mitochondria*, which are surrounded by both an outer membrane and a highly folded inner membrane. Mitochondria are responsible for oxidative breakdown of food molecules, providing the cell with usable energy in the form of ATP.

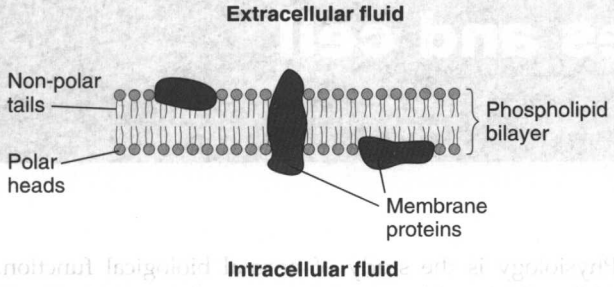

Fig. 1 The plasma membrane. Membrane proteins may be exposed on either side or may cross the whole thickness of the lipid bilayer.

- the *endoplasmic reticulum* (or *sarcoplasmic reticulum* in muscle cells), which is an interconnecting series of membranous channels and vesicles. In some regions this has a large number of *ribosomes* attached to the surface, thus leading to the distinction between rough and smooth endoplasmic reticulum. Ribosomes are involved in protein synthesis.
- the *Golgi apparatus*, a system of stacked vesicles found close to the nucleus. This is involved in the formation of secretory vesicles and lysosomes.

Body fluid compartments

The body contains many different aqueous solutions, which may be classified into a series of fluid compartments depending on their location (Fig. 2). The main subdivision is between intracellular and extracellular fluids. The extracellular compartment represents all fluid not inside cells, including the plasma component of blood, aqueous humour in the eye, synovial fluid in joints and cerebrospinal fluid within the central nervous system. The largest single extracellular subcompartment, however, consists of the *interstitial fluid*, which lies in the connective tissue matrix surrounding most body cells. It is normally this fluid which is in direct contact with the cell membrane and controlling interstitial conditions is vital for normal cell function. Much of this control is achieved by the continuous circulation of blood through the cardiovascular system. The rate of blood flow to any region and the plasma concentrations of different solutes greatly influence the cellular environment since, with the exception of plasma proteins, water and solutes move freely between plasma and the interstitium.

Volume measurement by indicator (dye) dilution methods

The volume of a given fluid compartment, e.g. the extracellular fluid volume, is usually estimated indirectly using an indicator substance. If a known quantity of

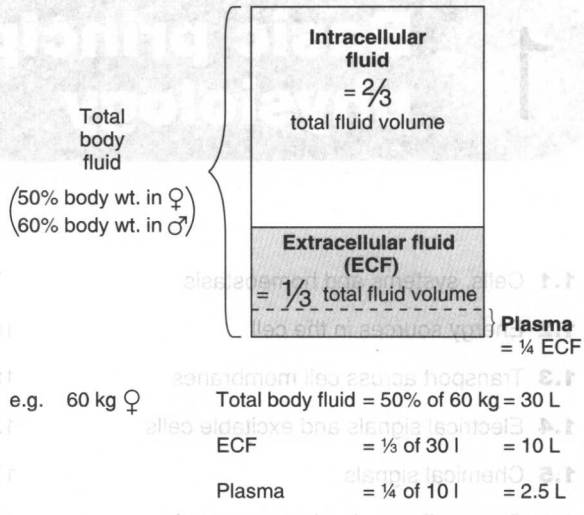

Fig. 2 Fluid compartments within the body showing the relative volumes occupied by intracellular fluid, extracellular fluid and plasma (part of the extracellular space).

indicator becomes evenly distributed through that compartment, measurement of the final concentration of indicator allows the volume of fluid to be calculated using Equation 2 below.

$$\text{Concentration} = \frac{\text{Amount of indicator}}{\text{Fluid Volume}} \qquad \text{(Eq. 1)}$$

$$\therefore \text{Fluid volume} = \frac{\text{Amount of indicator}}{\text{Concentration}} \qquad \text{(Eq. 2)}$$

This technique is called the *indicator*, or *dye dilution method* and it relies on finding an indicator which fulfils two main criteria.

- It should become evenly distributed through the whole of the fluid compartment of interest, otherwise the concentration will be artificially high leading to an underestimate of the volume concerned.
- It should not leak out into other fluid compartments or be rapidly metabolized or cleared from the body, since the concentration of indicator would be reduced under such circumstances, leading to an overestimate of the relevant volume.

For these reasons different indicators are appropriate when estimating the volume of different fluid spaces within the body.

Blood and plasma volume

Blood volume can be measured by taking a sample of an individual's blood and radioactively labelling the red cells, e.g. with chromium-51. These cells are reinjected, given time to mix evenly through the blood volume, and another sample of blood is taken. The radioactivity per

unit volume is used to calculate the total blood volume (normal value is 4–5 L).

Plasma volume is usually estimated using a dye which binds to plasma protein, such as Evans' blue dye. This is restricted to the plasma space because the protein does not readily escape from the circulation. Plasma proteins radiolabelled with iodine-131 can also be used. These indicators do not enter the red cells so the calculated volume is that of plasma only (2.5–3.0 L), and not the total blood volume.

Extracellular fluid volume

Extracellular fluid volume is not easily measured and different indicators give different results in a given subject. Substances which have been used include radioactive sodium, radioactive bromide, the polysaccharide inulin, and sucrose. Mean values are about 10–15 L. The plasma volume represents about 25% of the extracellular space and, since there is free exchange of fluid across the capillary wall, any increase or decrease in extracellular fluid volume will be reflected by a parallel change in plasma volume. This means that mechanisms which affect the total extracellular fluid volume will also alter the plasma and, therefore, blood volumes, e.g. renal fluid reabsorption (Section 5.4).

Homeostasis

Normal cell function relies on appropriate environmental conditions since the temperature, pH, ionic concentrations, O_2 and CO_2 levels in the extracellular fluid all influence biochemical activity inside the cell. The mechanisms which control the body's internal environment are called *homeostatic mechanisms*. These keep conditions inside the body relatively constant despite considerable changes in the external environment.

The following general elements are present in all homeostatic control systems (Fig. 3).

- *Detectors*, or receptors, sensitive to the variable to be controlled.
- A comparator, or *integrating centre*, which receives the afferent signal from the detectors and compares this measured value of the variable with a preferred value, or *set point*, for the system. If the actual value differs from the set point the integrator generates an efferent (outgoing) signal.
- *Effector* systems which can change the measured variable are activated by the signals from the integrator. Their effect is to bring the variable back towards the set point.

In such a system, any deviation of the variable away from its normal (set) value stimulates responses which reduce that deviation. This is referred to as *negative feedback* control and is an important element of homeostasis. The overall effect is to maintain a constant environment but often a phenomenon known as hunting is observed in which the controlled variable oscillates around a fixed mean value rather than remaining exactly at the set point (Fig. 3).

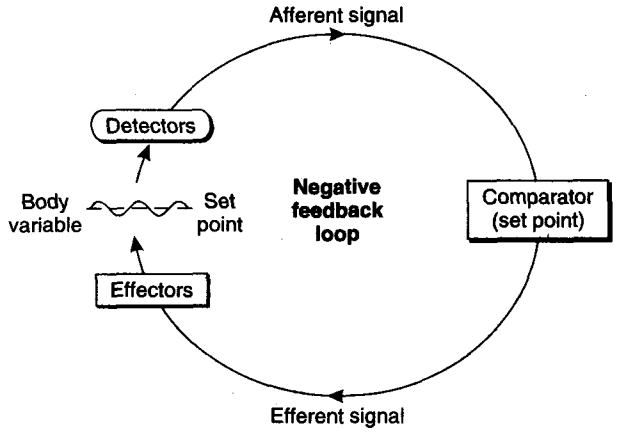

Fig. 3 Elements of a homeostatic control system. The controlled variable may oscillate, or hunt, around a mean value (the set point).

Biological systems may also demonstrate *positive feedback* in which deviations from the steady state are actually amplified, rather than diminished, by a feedback loop. Such mechanisms, however, have no part to play in homeostasis.

Homeostatic regulation of body temperature

Regulation of body temperature provides a good example of homeostasis. The body core is normally held close to 37°C, even though the environmental temperature (which affects the rate of heat loss from the body) and rate of metabolic heat production may vary widely.

Temperature detectors (*thermoreceptors*) monitor both the core temperature (the regulated variable) and the peripheral temperature (a separate but relevant variable). The afferent inputs go to an integrating centre (the *thermoregulatory centre*) in the *hypothalamus* of the brain, which compares core temperature with the set point of 37°C. If these differ, outgoing nerve signals activate a number of effector systems which alter the rates of heat production and heat loss.

In cold conditions:

- reflex increases in muscle tone and shivering liberate metabolic energy as heat
- in infants, there may also be increased heat production in brown fat (Section 9.6)
- heat loss is reduced by sympathetic constriction of peripheral blood vessels, which decreases skin blood

flow; erection of skin hair (piloerection) also occurs but has limited significance in humans.

In hot conditions the rate of heat loss can be greatly accelerated by:

- increased sweating stimulated by sympathetic nerves which in this specific case release the neurotransmitter acetylcholine
- dilatation of cutaneous blood vessels caused by reduced activity in vasoconstrictor sympathetic nerves releasing the more typical sympathetic neurotransmitter noradrenaline (norepinephrine). There may also be active dilatation of arterioles (Section 3.7).

Behavioural aspects are important too, e.g. we dress up, warmly, exercise and eat hot food when we are cold, while preferring light clothes and cool drinks in hot weather.

Box 1
Clinical note: Pyrexia

Pyrexia or fever is a temporary elevation of the core temperature commonly caused by infection. It is not due to any breakdown of the detector or effector systems responsible for temperature control but results from a change in the set point. Toxins released from bacteria and immune cells cause the hypothalamus to respond to a core temperature of 37°C as if it were abnormally low and so it increases heat production, e.g. through shivering (rigors). This raises body temperature.

1.2 Energy sources in the cell

Learning objectives

At the end of this section you should be able to:

- outline the main steps in cellular energy exchange.

Body cells require energy to carry out mechanical work (e.g. in muscle cells), to transport ions or molecules against concentration gradients (e.g. ion pumps) and for the synthesis of complex molecules. These active processes are ultimately fuelled by the energy released through the breakdown of carbohydrate, fat and protein from our diet. The initial series of reactions in the breakdown of glucose is referred to as glycolysis and does not require O_2 (anaerobic metabolism). This leads to the formation of lactic acid and produces small amounts of *adenosine triphosphate* (*ATP*), the main source of usable energy within the cell. In the presence of O_2 (aerobic conditions), however, intramitochondrial enzymes catalyse the complete catabolism of the products of glycolysis, releasing much greater amounts of ATP and generating CO_2 and water as byproducts (Section 4.7). Whereas glycolysis leads to a net production of 2 molecules of ATP per glucose molecule, oxidative metabolism can produce an additional 34–36 ATP molecules. Subsequent hydrolysis of the high-energy phosphate bonds in ATP by *ATPase enzymes* makes energy available for the active processes of the cell.

1.3 Transport across cell membranes

Learning objectives

At the end of this section you should be able to:

- list the factors affecting solute diffusion across cell membranes
- identify the conditions necessary for osmosis and understand the differences between osmolality, tonicity and osmotic pressure
- describe the characteristics of carrier-mediated transport and differentiate between facilitated diffusion, primary active transport and secondary active transport
- describe what is meant by endocytosis and exocytosis.

There is a constant traffic across cell membranes, supplying O_2 and substrate molecules for intracellular metabolism and removing CO_2, waste substances and active products. A variety of transport mechanisms are involved.

Diffusion

Diffusion can occur whenever a substance is present at a higher concentration on one side of the cell membrane than the other. It results in net movement from high to low concentration, i.e. a net flux of the ion or molecule. No energy source is required so this is referred to as a *passive transport* mechanism. Diffusion is affected by the following factors.

Solute concentration gradients, i.e. not the absolute concentrations but the difference in concentration.

Membrane permeability to the solute. The plasma membrane is selectively permeable to fatty and small nonpolar molecules which dissolve in the membrane lipid. Thus, fatty acids, steroid hormones, O_2 and CO_2 all diffuse readily into cells. The permeability to water-soluble (lipid-insoluble) ions and large polar molecules

such as proteins, however, is generally low. Certain ions can diffuse across the cell membrane much more readily (i.e. they are more permeant) than their lipid solubility would predict. This is because of membrane proteins which bridge the lipid barrier and provide an easier route for ion diffusion. These may take the form of carrier molecules, which bind to the ion and then move it across the membrane by changing conformation, or they may provide fluid-filled channels through which the ions can pass (Section 1.4). The roles of both these types of molecule are considered in more detail later in the chapter. Specific carriers and channels are selective for different kinds of ion and so membrane permeability to a given ion may differ widely from cell to cell, depending on which proteins are present.

Transmembrane voltage gradients affect the movement of ions. If the inside of the membrane is negative with respect to the outside, cations (positively charged) will be electrostatically attracted into the cell and anions (negatively charged) will be repelled outwards. The net transmembrane flux of an ion is proportional to the combined effect of the electrical and concentration gradients acting on it, i.e. on the *electrochemical gradient* for that ion.

Molecular weight of the diffusing substance. Small molecules diffuse more rapidly.

Diffusion distance. Diffusion is too slow to allow effective exchange over distances of more than about 100 μm.

Membrane surface area. For a given set of conditions rate of diffusion is proportional to the surface area of membrane.

Osmosis

Osmosis depends on the passive diffusion of water across a membrane from a region of low solute concentration (effectively high water concentration) to a region of high solute concentration (low water concentration). Osmosis requires:

- a solute concentration gradient across a membrane
- a *semipermeable membrane*, i.e. permeable to the solvent (water) but not the solute. If the membrane is highly permeable to the solute, conditions on either side of the membrane will rapidly equilibrate by solute diffusion, thus removing the osmotic driving force.

Cell membranes are permeable to water molecules (because of their small size), so any solute which cannot cross the membrane (an impermeant solute) can generate an osmotic gradient. Normally cells exist in osmotic equilibrium, the osmotically active particles inside the cell being balanced by those in the extracellular fluid. Any disturbance of this balance will lead to a net movement of water across the cell membrane and a change in cell volume.

The osmotic properties of a solution can be described in several ways.

Osmolality is defined as the total number of dissolved particles per kg of solvent (H_2O), and has units of mosmol kg^{-1}. Osmolality will be used throughout this text since this determines osmotic effects and is usually reported in biochemistry tests. Since H_2O has a density of 1 kg L^{-1}, however, osmolality for dilute solutions is very similar to *osmolarity* which refers to the number of particles per litre of solution (mosmol L^{-1}), and physiology and medical texts often use osmolarity and osmolality interchangeably. Substances which dissociate in solution increase the number of dissolved particles, and this raises the osmolality above the concentration of solute. For example, 1 mmol L^{-1} of glucose has an osmolality of 1 mosmol kg^{-1} but a 1 mmol L^{-1} NaCl solution has an osmolality of 2 mosmol kg^{-1} since each NaCl molecule dissociates to produce two ions.

Tonicity is a biological term relating to the actual effect of a solution on living cells, specifically erythrocytes. A solution may be:

- *Isotonic*, i.e. in osmotic equilibrium with the intracellular fluid. Plasma and interstitial fluid are normally isotonic and intravenous fluid supplements should generally be isotonic to avoid red cell damage.
- *Hypertonic*, i.e. contains a higher concentration of osmotically active particles than the intracellular fluid, leading to osmotic water loss and cell shrinking (crenation).
- *Hypotonic*, i.e. contains a lower concentration of osmotically active particles than the intracellular fluid, leading to osmotic cell swelling and possibly cell lysis.

Tonicity depends both on the osmolality of a solution and the ease with which the solute in question can pass through the cell membrane. Readily diffusible substances have no osmotic effect on a cell even at high osmolality. Thus a 300 mosmol kg^{-1} solution of NaCl (an effectively impermeant solute) is isotonic while a 300 mosmol kg^{-1} solution of urea (which crosses cell membranes readily) is extremely hypotonic, leading to water absorption and almost immediate cell lysis resulting from the unbalanced osmotic effect of trapped intracellular solutes (mainly K^+ and inorganic anions).

Osmotic pressure is the hydrostatic pressure that would be necessary to exactly oppose the osmotic effect of a solution and prevent any net water movement. It is usually expressed in mmHg or kPa (kPa = mmHg × 0.133). The osmotic pressure exerted on the cell membrane by isotonic fluids is over 770 kPa, i.e. over 7.5 × atmospheric pressure. Normally this is exactly balanced

by the osmotic pressure resulting from impermeant intracellular solutes, i.e. the osmotic pressure gradient across the cell membrane is zero.

Carrier-mediated transport

Carrier proteins in the cell membrane bind to a specific substrate and then undergo some conformational change. As a result, the substrate is transported across the membrane and released on the other side. The maximum rate of transport (V_{max}) is dependent on the density of carriers in a given cell, since all transport sites will be occupied above a certain substrate concentration (Fig. 4). This is referred to as saturation. *Substrate specificity* and *saturation* are two hallmarks of carrier-mediated transport, whether it is passive (facilitated diffusion) or active.

Facilitated diffusion

The energy driving facilitated diffusion is the substrate concentration gradient, so this is a passive process, i.e. no additional energy input is required. Movement across the membrane is, nevertheless, dependent on the availability of transport or carrier proteins (Fig. 5). Cellular absorption of glucose from the extracellular fluid is one example.

Active transport

In active transport systems carrier molecules transport molecules or ions against concentration or electrical gradients. Such carriers must use energy from some other source to do the necessary work. The energy can be provided in two ways.

Primary active transport uses the energy released by hydrolysis of ATP, e.g. to transport Na^+ out of the cell and K^+ into the cell against their electrochemical gradients (the Na^+/K^+ ATPase, or Na^+/K^+ pump: Fig. 5).

Secondary active transport uses the energy released during the passive movement of one substance down its electrochemical gradient to transport another substance against a concentration gradient (Fig. 5). For example, sodium cotransport systems couple Na^+ diffusion into intestinal cells with the absorption of glucose from the gut lumen (Section 7.4). Absorption can continue even if the concentration of glucose is higher inside the cell than outside. Although the cotransport step itself does not require an external energy source, such systems ultimately depend on active pumping of Na^+ back into the extracellular space by Na^+/K^+ ATPase so as to maintain the Na^+ diffusion gradient into the cell.

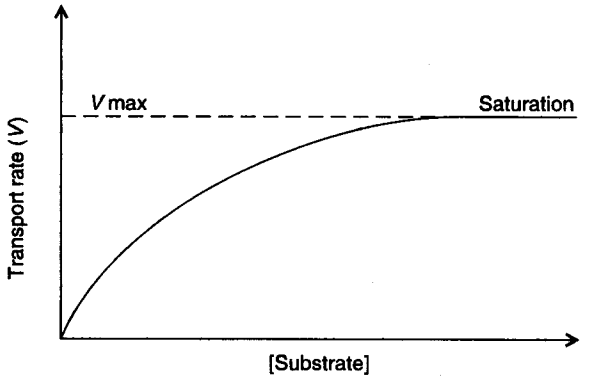

Fig. 4 The rate of transport as a function of substrate concentration for carrier-mediated transport.

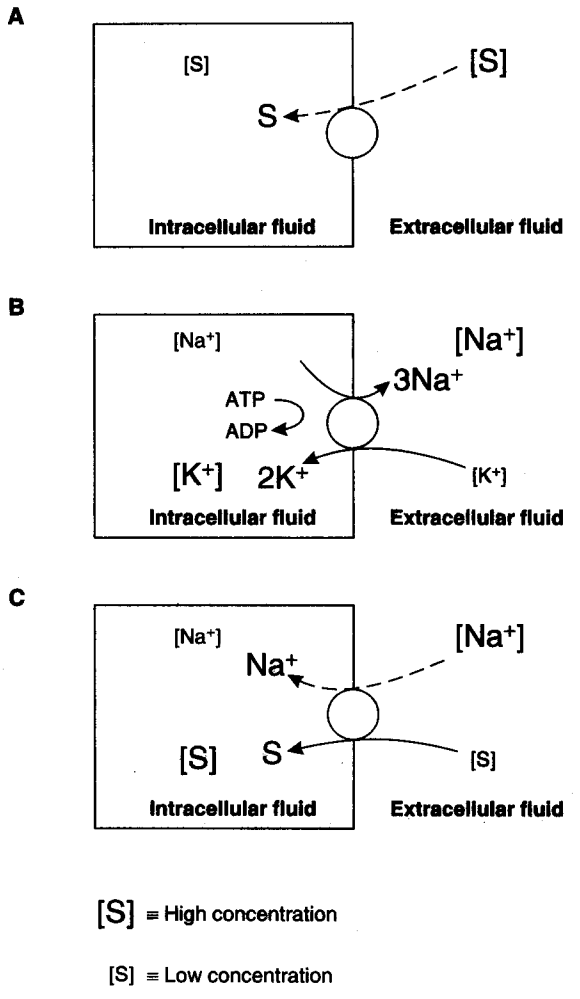

Fig. 5 Carrier-mediated transport mechanisms. (A) In facilitated diffusion the substrate (S) moves down a concentration gradient. (B) Primary active transport links ATP breakdown to the transport of a substrate against a concentration gradient. (C) Secondary active transport uses passive movement of one substance to drive a substrate against a concentration gradient.

Vesicular transport

Vesicular transport depends on the transport of substances within membrane-bound vesicles. Limitations

on transport resulting from large molecular size and low membrane permeability can be circumvented since the vesicle contents never physically cross the membrane. *Endocytosis* involves the invagination of a portion of plasma membrane into the cell, which forms a vesicle containing extracellular fluid and near membrane molecules. In *exocytosis* a vesicle from within the cell fuses with the membrane, releasing its contents to the extracellular fluid (Fig. 6). Exocytosis is particularly important in the release of glandular secretions and chemical transmitters.

1.4 Electrical signals and excitable cells

Learning objectives

At the end of this section you should be able to:

- explain the term resting membrane potential (RMP)
- outline the role of diffusion potentials and electrogenic pumps in generating the RMP
- draw the typical membrane potential changes during a nerve action potential (AP) and list the main AP properties
- describe how changes in cell ionic conductances produce an AP
- explain how voltage controlled ion channels regulate ionic conductance
- explain how local circuits lead to unidirectional AP propagation.

Electrical signalling within the nerves and muscles of the body is a vital aspect of body function. These cells are said to be *excitable* because they are capable of generating self-propagating electrical signals known as action potentials.

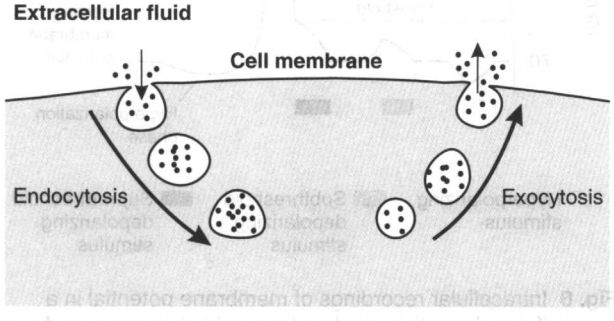

Fig. 6 Fluid and large, membrane-impermeant molecules can be moved in and out of cells using vesicular transport.

Resting membrane potential

Electrical recordings from nerves show that there is a potential difference of about 70 mV across the cell membrane with the inside negative with respect to the outside. We say that the resting membrane potential is –70 mV. This can be explained by the fact that the cell membrane separates two solutions with different ionic concentrations and is not equally permeable to all the ions involved. As a result, a diffusion potential is generated across the membrane.

Diffusion potentials and equilibrium potentials

Suppose we start with zero electrical potential across the cell membrane (Fig. 7). The concentration of K^+ is higher inside the cell than outside and the membrane is permeable to K^+, so K^+ diffuses outwards. Permeability is selective, however, and the large intracellular anions cannot follow K^+. Consequently, an imbalance of charge builds up across the membrane producing a potential difference, with the inside negative with respect to the outside. This is a diffusion potential. The voltage gradient opposes further diffusion of the positive K^+, making it more and more difficult for them to leave the cell. The diffusion potential will increase until an equilibrium state is achieved in which the concentration gradient is exactly balanced by the opposing voltage gradient. The potential difference under these conditions is known as the equilibrium potential for K^+ (E_K). This depends on

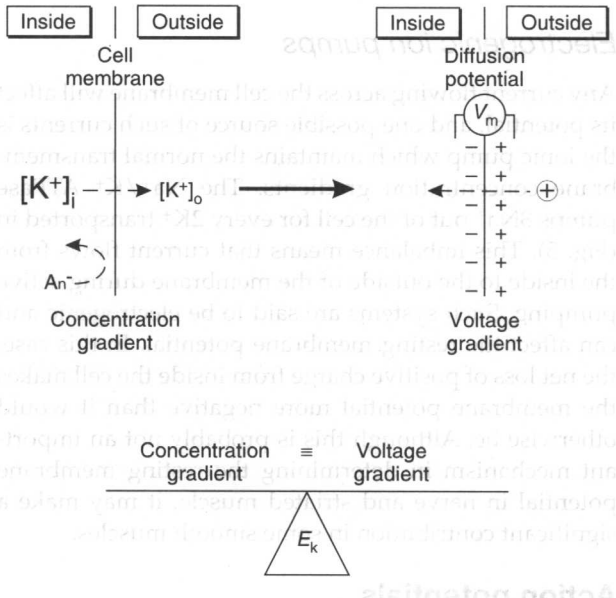

Fig. 7 A diffusion potential results from movement of K^+ down its concentration gradient across a membrane that is impermeable to anions. At E_K, there is no net movement of K^+.

the ratio of $[K^+]$ on either side of the membrane and can be calculated using the *Nernst equation*:

$$E_K \frac{RT}{zF} \log_e \frac{[K^+]_o}{[K^+]_i} \quad \text{(Eq. 3)}$$

where R = ideal gas constant, T = absolute (or thermodynamic) temperature (°C +273 K), F = Faraday's constant and z = ionic valency (+1 for K^+)

If we apply this equation to a nerve cell, the concentration of K^+ is much higher inside the cell than outside and the calculated value for E_K is approximately −90 mV. The measured value of the resting membrane potential (−70 mV) is more positive than this, so it cannot be explained solely in terms of the diffusion potential generated by K^+. In fact other ions can also cross the membrane, particularly Na^+. The concentration gradient for Na^+ is in the opposite direction to K^+ (Fig. 9, below) and the calculated value for E_{Na} is approximately +65 mV. The Na^+ gradient tends to make the membrane potential more positive than it would otherwise be, but because the resting membrane is much more permeable to K^+ than Na^+, the resting potential is much closer to E_K than E_{Na}. One equation which takes account of the involvement of both K^+ and Na^+ in determining the resting membrane potential (RMP) is:

$$\text{RMP} = \frac{RT}{F} \log_e \frac{[K^+]_o + \alpha[Na^+]_o}{[K^+]_i + \alpha[Na^+]_i} \quad \text{(Eq. 4)}$$

$$\text{where } \alpha = \frac{\text{Permeability to } Na^+}{\text{Permeability to } K^+}$$

This equation works well using $\alpha = 0.01$, i.e. assuming the membrane permeability to K^+ is 100 × permeability to Na^+ at rest.

Electrogenic ion pumps

Any current flowing across the cell membrane will affect its potential, and one possible source of such currents is the ionic pump which maintains the normal transmembrane concentration gradients. The Na^+/K^+ ATPase pumps $3Na^+$ out of the cell for every $2K^+$ transported in (Fig. 5). This imbalance means that current flows from the inside to the outside of the membrane during active pumping. Such systems are said to be electrogenic and can affect the resting membrane potential. In this case, the net loss of positive charge from inside the cell makes the membrane potential more negative than it would otherwise be. Although this is probably not an important mechanism in determining the resting membrane potential in nerve and striated muscle, it may make a significant contribution in some smooth muscles.

Action potentials

If a nerve cell is stimulated by injecting electric current, the membrane potential becomes less negative (Fig. 8). We say the membrane potential has reduced (because the magnitude of the potential difference is reduced even though it is less negative) or that the membrane has been *depolarized*. With small stimuli (subthreshold), the membrane potential simply returns to normal after the stimulus ceases. If, however, the membrane is depolarized to a certain level, known as the *threshold potential*, the nerve itself generates a series of changes in the potential, known as an action potential. Action potentials are a feature of nerves and muscles, and it is the ability to generate these characteristic electrical signals which typifies excitable tissues.

The action potential in nerve has an initial phase of *rapid depolarization* which reverses the potential difference across the membrane, reaching a peak at about +50 mV within a few tenths of a millisecond. The membrane then begins to *repolarize*, falling back to the normal resting potential about 1 ms after initiation of the action potential. The potential may actually become more negative than normal for a time (*hyperpolarization*), but eventually returns to the resting potential after a further 2–3 ms.

Action potential properties

Action potentials demonstrate a number of important properties.

- Action potentials obey an *all-or-none law*. Subthreshold stimuli do not elicit any active voltage changes, while any stimulus which exceeds threshold (suprathreshold stimuli) will lead to a full action potential (Fig. 8). Increasing the stimulus

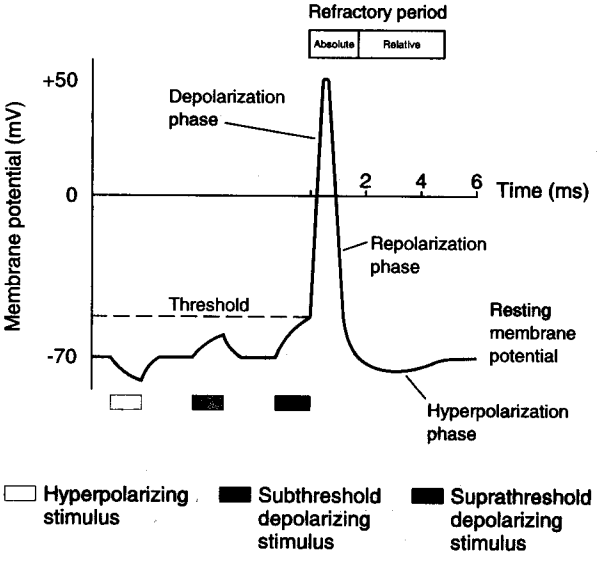

Fig. 8 Intracellular recordings of membrane potential in a nerve. If depolarization reaches threshold, the nerve produces an action potential. Further stimulation is inhibited during the refractory period.