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The Underlying Principles of Human Metabolism

Key learning points

- We eat food. We expend energy doing exercise, sleeping, just being. What happens to the food between it entering out mouths and its being used for energy? That's what metabolic regulation (at least, so far as this book is concerned) is all about.
- In order to cover the periods when we are not eating, we need to store metabolic fuels. We store fuel as fat (triacylglycerol) and as carbohydrate (glycogen). Fat provides considerably more energy per gram stored.
- Molecules involved in metabolism differ in an important property: polarity. Polar molecules (those with some degree of electrical charge) mix with water (which is also polar); non-polar molecules, which include most lipids (fatty substances), usually don't mix with water. This has profound implications for the way they are handled in the body.
- Some molecules have both polar and non-polar aspects: they are said to be amphipathic. They can form a bridge between polar and non-polar regions. Amphipathic phospholipid molecules can group together to form membranes, such as cell membranes.
- The different organs in the body have their own characteristic patterns of metabolism. Substrates flow between them in the bloodstream (circulation). Larger blood vessels divide into fine vessels (capillaries) within the tissues, so that the distances that molecules have to diffuse to or from the cells are relatively small.

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1.1 Metabolic Regulation in Perspective

To many students, metabolism sounds a dull subject. It involves learning pathways with intermediates with difficult names and even more difficult formulae. Metabolic regulation may sound even worse. It involves not just remembering the pathways, but remembering what the enzymes are called, what affects them and how. This book is not simply a repetition of the molecular details of metabolic pathways. Rather, it is an attempt to put metabolism and metabolic regulation into a physiological context, to help the reader to see the relevance of these subjects. Once their relevance to everyday life becomes apparent, then the details will become easier, and more interesting, to grasp.

This book is written from a human perspective because, as humans, it is natural for us to find our own metabolism interesting – and very important for understanding human health and disease. Nevertheless, many of the principal regulatory mechanisms that are discussed are common to other mammals. Some mammals, such as ruminants, have rather specialized patterns of digestion and absorption of energy; such aspects will not be covered in this book.

A consideration of metabolic regulation might begin with the question: why is it necessary? An analogy here is with mechanical devices, which require an input of energy, and convert this energy to a different and more useful form. The waterwheel is a simple example. This device takes the potential energy of water in a reservoir – the mill-pond – and converts it into mechanical energy which can be used for turning machinery, for instance, to grind corn. As long as the water flows, its energy is extracted, and useful work is done. If the water stops, the wheel stops. A motor vehicle has a different pattern of energy intake and energy output (Figure 1.1). Energy is taken in very spasmodically – only when the driver stops at a filling station. Energy is converted into useful work (acceleration and motion) with an entirely different pattern. A long journey might be undertaken without any energy intake. Clearly, the difference from the waterwheel lies in the presence of a storage device – the fuel tank. But the fuel tank alone is not sufficient: there must also be a control mechanism to regulate the flow of energy from the store to the useful-work-producing device (i.e., the engine). In this case, the regulator is in part a human brain deciding when to move, and in part a mechanical system controlling the flow of fuel.

What does this have to do with metabolism? The human body is also a device for taking in energy (chemical energy, in the form of food) and converting it to other forms. Most obviously, this is in the form of physical work, such as lifting heavy objects. However, it can also be in more subtle forms, such as producing and nurturing offspring. Any activity requires energy. Again, this is most obvious if we think about performing mechanical work: lifting a heavy object from the floor onto a shelf requires conversion of chemical energy (ultimately derived from food) into potential energy of the object. But even maintaining life involves work: the work of breathing, of pumping blood around the vascular system, of chewing food and digesting it. At a cellular level, there is constant work performed in the pumping of ions across membranes, and the synthesis and breakdown of the chemical constituents of cells.

What is your pattern of energy intake in relation to energy output? For most of us, the majority of energy intake occurs in three relatively short periods during each 24 hours, whereas energy expenditure is largely continuous (the *resting metabolism*)

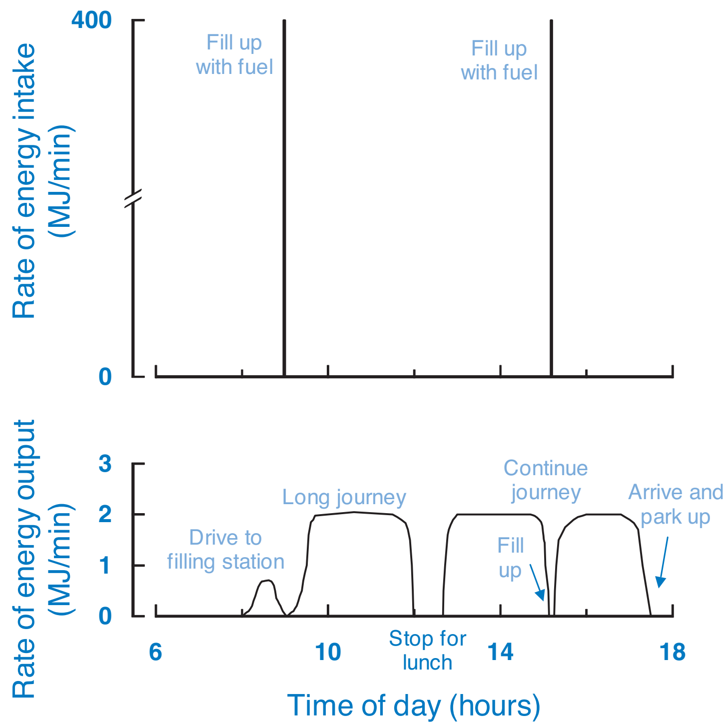

Figure 1.1 Rates of energy intake and output for a motor vehicle. The rate of intake (top panel) is zero except for periods in a filling station, when it is suddenly very high. (Notice that the scales are different for intake and output.) The rate of output is zero while the car is parked with the engine off; it increases as the car is driven to the filling station, and is relatively high during a journey. When totaled up over a long period, the areas under the two curves must be equal (energy intake = energy output) – except for any difference in the amounts of fuel in the tank before and after.

with occasional extra bursts of external work (Figure 1.2). It is clear that we, like the motor vehicle, must have some way of storing food energy and releasing it when required. As with the motor vehicle, the human brain may also be at the beginning of the regulatory mechanism, although it is not the conscious part of the brain: we do not have to think when we need to release some energy from our fat stores, for instance. Some of the important regulatory systems that will be covered in this book lie outside the brain, in organs which secrete hormones, particularly the pancreas. But whatever the internal means for achieving this regulation, we manage to store our excess food energy and to release it just as we need.

This applies to the normal 24-hour period in which we eat meals and go about our daily life. But the body also has to cope with less well-organized situations. In many parts of the world, there are times when food is not that easily available, and yet people are able to continue relatively normal lives. Clearly, the body's regulatory mechanisms must recognize that food is not coming in, and allow an appropriate rate of release of energy from the internal stores. In other situations, the need for energy may be suddenly increased. Strenuous physical exercise may increase the total rate of

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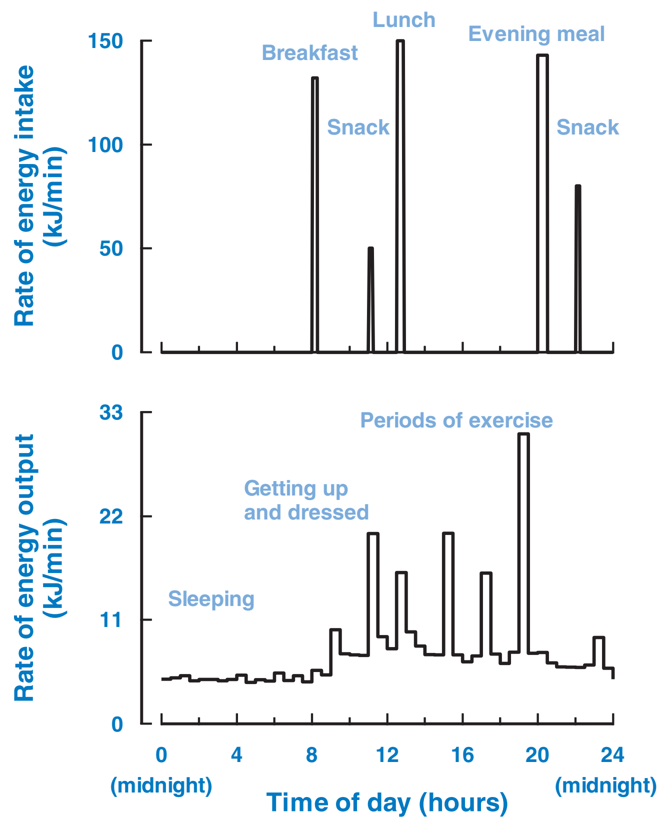

Figure 1.2 Rates of energy intake and output for a person during a typical day. The rate of energy intake (top panel) is zero except when eating or drinking, when it may be very high. The rate of energy output (heat + physical work) (lower panel) is at its lowest during sleep; it increases on waking and even more during physical activity. As with the car, the pattern of energy intake may not resemble that of energy expenditure, but over a long period the areas under the curves will balance – except for any difference in the amounts of energy stored (mainly as body fat) before and after. Data for energy expenditure are for a person measured in a calorimetry chamber and were kindly supplied by Dr Susan Jebb of MRC Human Nutrition Research, Cambridge.

metabolism in the body to twenty times its resting level. Something must recognize the fact that there is a sudden need to release energy at a high rate from the body's stores. During severe illness, such as infections, the rate of metabolism may also be increased; this is manifested in part by the rise in body temperature. Often the sufferer will not feel like eating normally. Once again, the body must have a way of recognizing the situation, and regulating the necessary release of stored energy.

What we are now discussing is, indeed, *metabolic regulation*. Metabolic regulation in human terms covers the means by which we take in nutrients in discrete meals, and deliver energy as required, varying from moment to moment and from tissue to tissue, in a pattern which may have no relationship at all to the pattern of intake. Metabolic regulation works ultimately at a molecular level, mainly by modulation of the activities

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of enzymes. But one should not lose sight of the fact that these molecular mechanisms are there to enable us to lead normal lives despite fluctuations in our intake and our expenditure of energy. In this book, the emphasis will be on the systems within the human body which sense the balance of energy coming in and energy required, particularly the *endocrine* (hormonal) and the *nervous* systems, and which regulate the distribution and storage of nutrients after meals, and their release from stores and delivery to individual tissues as required.

The intention of this preamble is to illustrate that, underlying our everyday lives, there are precise and beautifully coordinated regulatory systems controlling the flow of energy within our bodies. Metabolic regulation is not a dry, academic subject thought up just to make biochemistry examinations difficult; it is at the center of human life and affects each one of us every moment of our daily lives.

1.2 The Chemistry of Food – and of Bodies

Energy is taken into the body in the form of food. The components of food may be classified as *macronutrients* and *micronutrients*. Macronutrients are those components present in a typical serving in amounts of grams rather than milligrams or less. They are the well-known carbohydrate, fat, and protein. Water is another important component of many foods, although it is not usually considered a nutrient. Micronutrients are vitamins, minerals, and nucleic acids. Although these micronutrients play vital roles in the metabolism of the macronutrients, they will not be discussed in any detail in this book, which is concerned with the broader aspects of what is often called *energy metabolism*.

The links between nutrition and energy metabolism are very close. We eat carbohydrates, fats, and proteins. Within the body these are broken down to smaller components, rearranged, stored, released from stores, and further metabolized, but essentially whether we are discussing food or metabolism the same categories of carbohydrate, fat, and protein can be distinguished. This is not surprising since our food itself is of organic origin, whether plant or animal.

In order to understand metabolism and metabolic regulation, it is useful to have a clear idea of some of the major chemical properties of these components. This is not intended as a treatise in physical or organic chemistry but as a starting point for understanding some of the underlying principles of metabolism. The discussion assumes a basic understanding of the meaning of atoms and molecules, of chemical reactions and catalysis, and some understanding of chemical bonds (particularly the distinction between ionic and covalent bonding).

1.2.1 Some Important Chemical Concepts

1.2.1.1 Polarity

Some aspects of metabolism are more easily understood through an appreciation of the nature of polarity of molecules. *Polarity* refers to the distribution of electrical charge over the molecule. A non-polar molecule has a very even distribution of electrical charge over its surface and is electrically neutral overall (the negative charge on the electrons is balanced by the positive charge of the nucleus). A polar molecule has an overall charge, or at least an uneven distribution of charge. The most polar small particles are ions – that is, atoms or molecules which have entirely lost or gained one or more electrons. However, even completely covalently bonded organic molecules may have a sufficiently uneven distribution of electrical charge to affect their behavior. Polarity is not an all-or-none phenomenon; there are gradations, from the polar to the completely non-polar.

Polarity is not difficult to predict in the molecules which are important in biochemistry. We will contrast two simple molecules: water and methane. Their relative molecular masses are similar – 18 for water, 16 for methane – yet their physical properties are very different. Water is a liquid at room temperature, not boiling until 100 °C, whereas methane is a gas ('natural gas') which only liquifies when cooled to – 161 °C. We might imagine that similar molecules of similar size would have the same tendency to move from the liquid to the gas phase, and that they would have similar boiling points. The reason for their different behaviors lies in their relative polarity. The molecule of methane has the three-dimensional structure shown in Figure 1.3a. The outer electron 'cloud' has a very even distribution over the four hydrogen atoms, all of which have an equal tendency to pull electrons their way. The molecule has no distinct electrical poles – it is non-polar. Because of this very even distribution of electrons, molecules near each other have little tendency to interact. In contrast, in the water molecule (Figure 1.3b) the oxygen atom has a distinct tendency to pull electrons its way, shifting the distribution of the outer electron cloud so that it is more dense over the oxygen atom, and correspondingly less dense elsewhere. Therefore, the molecule has a rather negatively charged region around the central oxygen atom, and correspondingly positively charged regions around the hydrogen atoms. Thus, it has distinct electrical poles – it is a relatively polar molecule. It is easy to imagine that water molecules near to each other will interact. Like electrical charges repel each other, unlike charges attract. This gives water molecules a tendency to line up so that the positive regions of one attract the negative region of an adjacent molecule (Figure 1.3b). So water molecules, unlike those of methane, tend to 'stick together': the energy needed to break them apart and form a gas is much greater than for methane, and hence water is a liquid while methane is a gas. The latent heat of evaporation of water is 2.5 kJ/g, whereas that of methane is 0.6 kJ/g. Note that the polarity of the water molecule is not as extreme as that of an ion – it is merely a rather uneven distribution of electrons, but enough to affect its properties considerably.

The contrast between water and methane may be extended to larger molecules. Organic compounds composed solely of carbon and hydrogen – for instance, the alkanes or 'paraffins' – all have the property of extreme non-polarity: the chemical (covalent) bond between carbon and hydrogen atoms leads to a very even distribution of electrons, and the molecules have little interaction with each other. A result is that polar molecules, such as those of water, and non-polar molecules, such as those of alkanes, do not mix well: the water molecules tend to bond to each other and to exclude the non-polar molecules, which can themselves pack together very closely because of the lack of interaction between them. In fact, there is an additional form of direct attraction

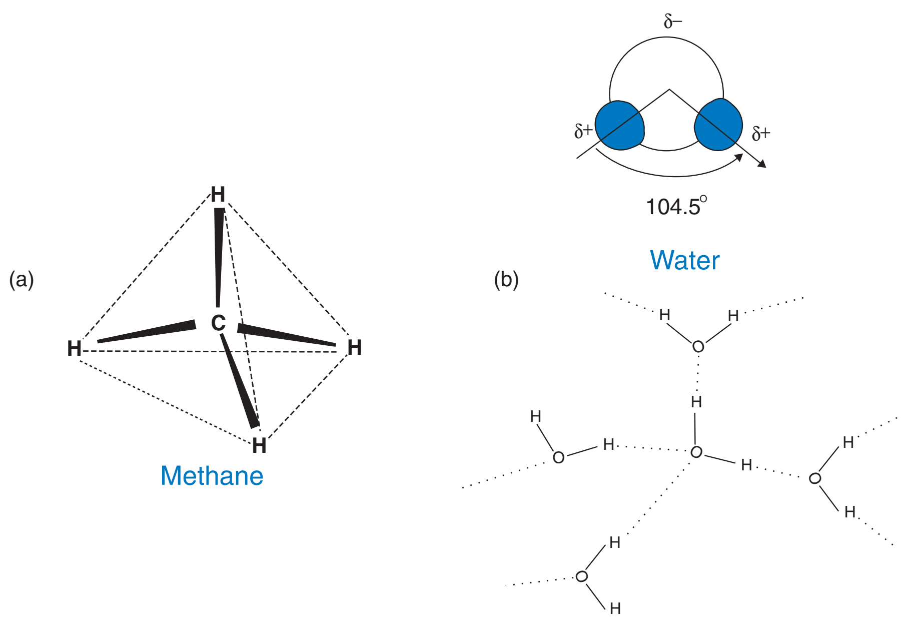

Figure 1.3 (a) Three-dimensional structure of the methane molecule and (b) the molecular structure of water. (a) The hydrogen atoms of methane (CH_4) are arranged symmetrically in space, at the corners of a tetrahedron. (b) The molecular structure of water. Top: view of the 'electron cloud' surrounding the molecule; bottom, interactions between water molecules. The molecule has a degree of *polarity*, and this leads to electrical interactions between neighboring molecules by the formation of *hydrogen bonds*. These bonds are not strong compared with covalent bonds, and are constantly being formed and broken. Nevertheless, they provide sufficient attraction between the molecules to account for the fact that water is a liquid at room temperature whereas the non-polar methane is a gas.

between non-polar molecules, the *van der Waals* forces. Random fluctuations in the density of the electron cloud surrounding a molecule lead to minor, transient degrees of polarity; these induce an opposite change in a neighboring molecule, with the result that there is a transient attraction between them. These are very weak attractions, however, and the effect of the exclusion by water is considerably stronger. The non-polar molecules are said to be *hydrophobic* (water fearing or water hating).

A strong contrast is provided by an inorganic ionic compound such as sodium chloride. The sodium and chlorine atoms in sodium chloride are completely ionized under almost all conditions. They pack very regularly in crystals in a cubic form. The strength of their attraction for each other means that considerable energy is needed to disrupt this regular packing – sodium chloride does not melt until heated above 800 °C. And yet it dissolves very readily in water – that is, the individual ions become separated from their close packing arrangement rather as they would on melting. Why? Because the water molecules, by virtue of their polarity, are able to come between the ions and reduce their attraction for each other. In fact, each of the charged sodium and chloride ions will become surrounded by a 'shell'" of water molecules, shielding it from the attraction or repulsion of other ions. Sodium chloride is said to be *hydrophilic* – water loving. The terms *polar* and *hydrophilic* are for the most part interchangeable. Similarly, the terms *non-polar* and *hydrophobic* are virtually synonymous.

Ionic compounds, the extreme examples of polarity, are not confined to inorganic chemistry. Organic molecules may include ionized groups. These may be almost entirely ionized under normal conditions – for instance, the esters of orthophosphoric acid ('phosphate groups'), as in the compounds AMP, ADP, and ATP, in metabolites such as glucose 6-phosphate, and in phospholipids. Most of the organic acids involved in intermediary metabolism, such as lactic acid, pyruvic acid, and the long-chain carboxylic acids (fatty acids), are also largely ionized at physiological hydrogen ion concentrations (Box 1.1). Thus, generation of lactic acid during exercise raises the hydrogen ion concentration (the acidity) both within the cells where it is produced, and generally within the body, since it is released into the bloodstream.

As stated earlier, polarity is not difficult to predict in organic molecules. It relies upon the fact that certain atoms always have *electronegative* (electron withdrawing) properties in comparison with hydrogen. The most important of these atoms biochemically are those of oxygen, phosphorus, and nitrogen. Therefore, certain functional groups based around these atoms have polar properties. These include the hydroxyl group (—OH), the amino group ($—NH_2$), and the orthophosphate group ($—OPO_3{}^{2-}$). Compounds containing these groups will have polar properties, whereas those containing just carbon and hydrogen will have much less polarity. The presence of an electronegative atom does not always give polarity to a molecule – if it is part of a chain and balanced by a similar atom this property may be lost. For instance, the ester link in a triacylglycerol molecule (discussed below) contains two oxygen atoms but has no polar properties.

Examples of relatively polar (and thus water-soluble) compounds which will be frequent in this book are sugars (with many —OH groups), organic acids such as lactic acid (with a COO^- group), and most other small metabolites. Most amino acids also fall into this category (with their amino and carboxyl groups), although some fall into the *amphipathic* ('mixed') category discussed below.

Another important point about polarity in organic molecules is that within one molecule there may be both polar and non-polar regions. They are called amphipathic compounds. This category includes phospholipids and long-chain fatty acids (Figure 1.4). Cell membranes are made up of a double layer of phospholipids, interspersed with specific proteins such as transporter molecules, ion channels and hormone receptors, and molecules of the sterol, cholesterol (Figure 1.5). The phospholipid bilayer presents its polar faces – the polar 'heads' of the phospholipid molecules – to the aqueous external environment and to the aqueous internal environment; within the thickness of the membrane is a non-polar, hydrophobic region. The physicochemical nature of such a membrane means that, in general, molecules cannot diffuse freely across it: non-polar molecules would not cross the outer, polar face and polar molecules would not cross the inner, hydrophobic region. Means by which molecules move through membranes are discussed in Chapter 2 (Box 2.1, p. 31).

The long-chain fatty acids fall into the amphipathic category – they have a long, non-polar hydrocarbon tail but a more polar carboxylic group head ($—COO^-$).

Box 1.1 Ionization State of Some Acids at Normal Hydrogen Ion Concentrations

The normal pH in blood plasma is around 7.4. (It may be somewhat lower within cells, down to about 6.8.) This corresponds to a hydrogen ion concentration of 3.98×10^{-8} mol/l (since $-\log_{10}$ of 3.98×10^{-8} is 7.4).

The equation for ionization of an acid HA is:

$$HA \Leftrightarrow H^+ + A^-;$$

this equilibrium is described by the equation:

$$\frac{[H^+][A^-]}{[HA]} = K_i$$

where K_i is the dissociation or ionization constant, and is a measure of the strength of the acid: the higher the value of K_i the stronger (i.e., the more dissociated) the acid.

K_i in the equation above relates the concentrations expressed in molar terms (e.g., mol/l). (Strictly, it is not the concentrations but the 'effective ion concentrations' or ion *activities* which are related; these are not quite the same as concentrations because of inter-ion attractions. In most biological systems, however, in which the concentrations are relatively low, it is a close approximation to use concentrations. If activities are used, then the symbol K_a is used for the dissociation constant of an acid.)

Some biological acids and their K_a values are listed in Table 1.1.1, together with a calculation of the proportion ionized at typical pH (7.4).

Table 1.1.1

Acid	K_a	% ionized at pH 7.4
Acetic, CH_3COOH	1.75×10^{-5}	99.8
Lactic, $CH_3CHOHCOOH$	0.38×10^{-4}	99.9
Palmitic acid, $CH_3(CH_2)_{14}COOH$	1.58×10^{-5}	99.8
Glycine, CH_2NH_2COOH (carboxyl group)	3.98×10^{-3}	100

The calculation is done as follows (using acetic acid as an example):

$$K_a = 1.75 \times 10^{-5} = \frac{[H^+][Ac^-]}{[HAc]}$$

(where HAc represents undissociated acetic acid, Ac^- represents the acetate ion). At pH 7.4, $[H^+] = 3.98 \times 10^{-8}$ mol/l. Therefore,

$$\frac{[Ac^-]}{[HAc]} = \frac{1.75 \times 10^{-5}}{3.98 \times 10^{-8}} = 440$$

(i.e., the ratio of ionized to undissociated acid is 440:1; it is almost entirely ionized).

The percentage in the ionized form $= \frac{440}{441} \times 100\% = 99.8\%$.

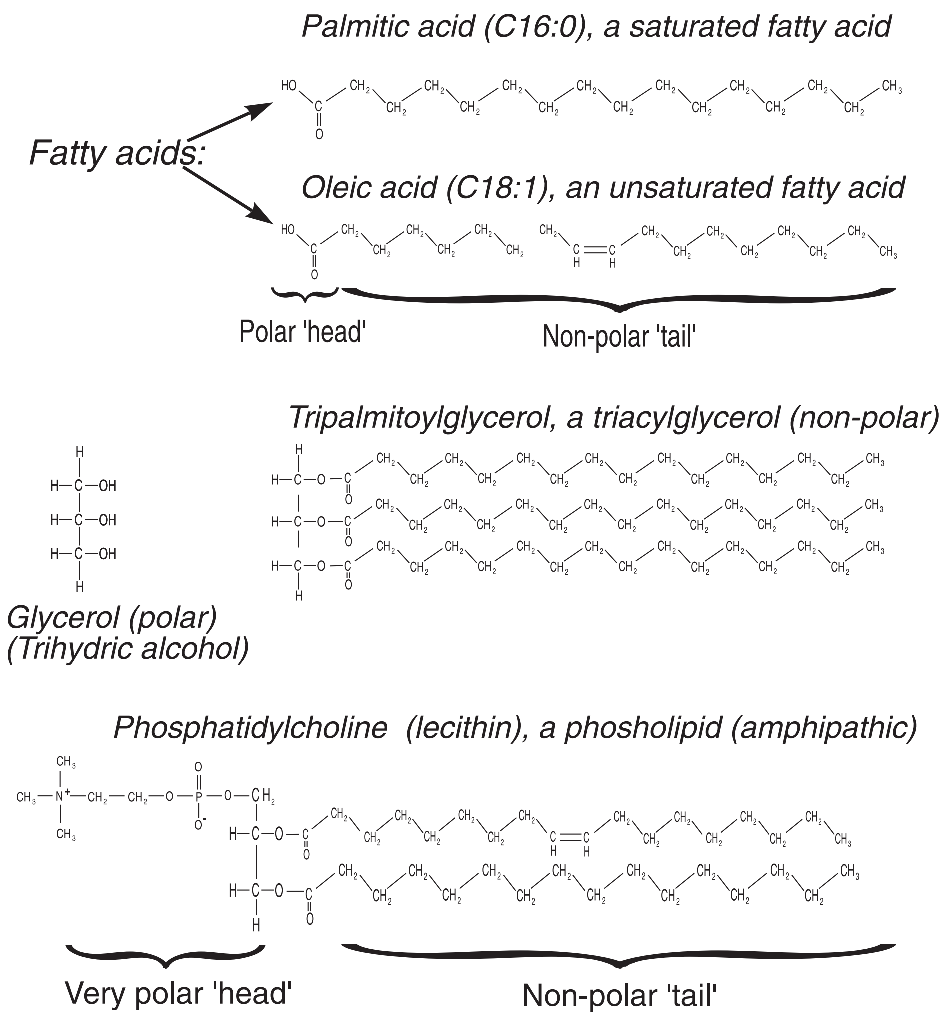

Figure 1.4 Chemical structures of some lipids. A typical saturated fatty acid (palmitic acid) is shown with its polar carboxylic group and non-polar hydrocarbon tail. *Glycerol* is a hydrophilic alcohol. However, it is a component of many lipids as its hydroxyl groups may form ester links with up to three fatty acids, as shown. The resultant *triacylglycerol* has almost no polar qualities. The *phospholipids* are derived from phosphatidic acid (diacylglycerol phosphate) with an additional polar group, usually a nitrogen-containing base such as choline (as shown) or a polyalcohol derivative such as phosphoinositol. Phospholipids commonly have long-chain unsaturated fatty acids on the 2-position; oleic acid (18:1 *n*-9) is shown.

Another compound with mixed properties is cholesterol (Figure 1.6); its ring system is very non-polar, but its hydroxyl group gives it some polar properties. However, the long-chain fatty acids and cholesterol may lose their polar aspects completely when they join in ester links. An ester is a compound formed by the condensation (elimination of a molecule of water) of an alcohol (—OH) and an acid (e.g., a carboxylic

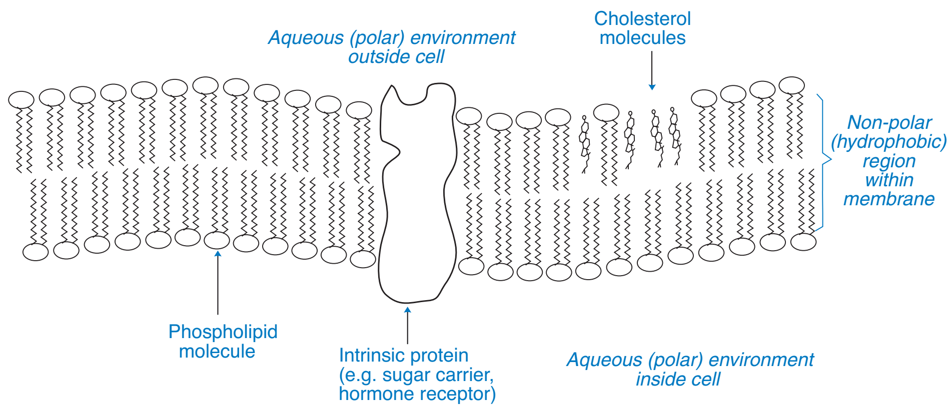

Figure 1.5 Structure of biological membranes in mammalian cells. Cell membranes and intracellular membranes such as the endoplasmic reticulum are composed of bilayers of phospholipid molecules with their polar head-groups facing the aqueous environment on either side and their non-polar 'tails' facing inwards, forming a hydrophobic center to the membrane. The membrane also contains *intrinsic proteins* such as hormone receptors, ion channels, and sugar transporters, and molecules of cholesterol which reduce the 'fluidity' of the membrane. Modern views of cell membrane structure emphasize that there are domains, known as 'rafts,' in which functional proteins co-locate, enabling interactions between them. These lipid rafts are characterized by high concentrations of cholesterol and of certain phospholipids (glycosphingolipids): see Further Reading for more information.

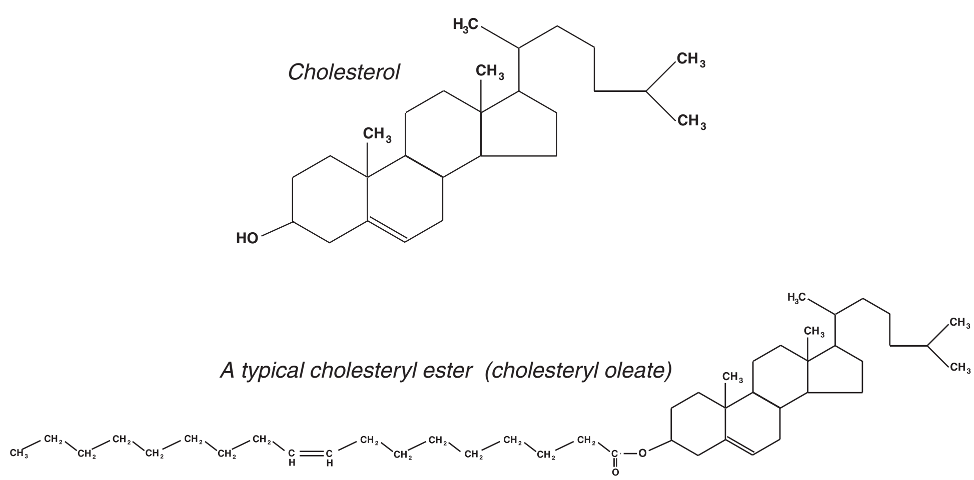

Figure 1.6 Cholesterol and a typical cholesteryl ester (cholesteryl oleate). In the structure of cholesterol, not all atoms are shown (for simplicity); each 'corner' represents a carbon atom, or else –CH or –CH_2. Cholesterol itself has amphipathic properties because of its hydroxyl group, but when esterified to a long-chain fatty acid the molecule is very non-polar.

acid, $-COO^-$). Cholesterol (through its $-OH$ group) may become esterified to a long-chain fatty acid, forming a *cholesteryl ester* (e.g., cholesteryl oleate, Figure 1.6). The cholesteryl esters are extremely non-polar compounds. This fact will be important when we consider the metabolism of cholesterol in Chapter 10. The long-chain fatty acids may also become esterified with glycerol, forming triacylglycerols (Figure 1.4). Again, the polar properties of both partners are lost, and a very non-polar molecule is formed. This fact underlies one of the most fundamental aspects of mammalian metabolism – the use of triacylglycerol as the major form for storage of excess energy.

Among amino acids, the branched-chain amino acids, leucine, isoleucine, and valine, have non-polar side chains and are thus amphipathic. The aromatic amino acids phenylalanine and tyrosine are relatively hydrophobic, and the amino acid tryptophan is so non-polar that it is not carried free in solution in the plasma.

The concept of the polarity or non-polarity of molecules thus has a number of direct consequences for the aspects of metabolism to be considered in later chapters. Some of these consequences are the following:

(1) Lipid fuels – fatty acids and triacylglycerols – are largely hydrophobic and are not soluble in the blood plasma. There are specific routes for their absorption from the intestine and specific mechanisms by which they are transported in blood.
(2) Carbohydrates are hydrophilic. When carbohydrate is stored in cells it is stored in a hydrated form, in association with water. In contrast, fat is stored as a lipid droplet from which water is excluded. Mainly because of this lack of water, fat stores contain considerably more energy per unit weight of store than do carbohydrate stores.
(3) The entry of fats into the circulation must be coordinated with the availability of the specific carrier mechanisms. In the rare situations in which it arises, uncomplexed fat in the bloodstream may have very adverse consequences.

1.2.1.2 Osmosis

The phenomenon of *osmosis* underlies some aspects of metabolic strategy – it can be seen as one reason why certain aspects of metabolism and metabolic regulation have evolved in the way that they have. It is outlined only briefly here to highlight its relevance.

Osmosis is the way in which solutions of different concentrations tend to even out when they are in contact with one another via a *semipermeable membrane*. In solutions, the *solvent* is the substance in which things dissolve (e.g., water) and the *solute* the substance which dissolves. A semipermeable membrane allows molecules of solvent to pass through, but not those of solute. Thus, it may allow molecules of water but not those of sugar to pass through. Cell membranes have specific protein channels (*aquaporins*, discussed in Section 2.2.1.6) to allow water molecules to pass through; they are close approximations to semipermeable membranes.

If solutions of unequal concentration – for instance, a dilute and a concentrated solution of sugar – are separated by a semipermeable membrane, then molecules of solvent (in this case, water) will tend to pass through the membrane until the concentrations of the solutions have become equal. In order to understand this intuitively, it is necessary to remember that the particles (molecules or ions) of solute are not just moving about freely in the solvent: each is surrounded by molecules of solvent, attracted by virtue of the polarity of the solute particles. (In the case of a non-polar solute in a non-polar solvent, we would have to say that the attraction is by virtue of the non-polarity; it occurs through weaker forces such as the van der Waals.) In the more concentrated solution, the proportion of solvent molecules engaged in such attachment to the solute particles is larger, and there is a net attraction for further solvent molecules to join them, in comparison with the more dilute solution. Solvent molecules will tend to move from one solution to the other until the proportion involved in such interactions with the solute particles is equal.

The consequence of this in real situations is not usually simply the dilution of a more concentrated solution, and the concentration of a more dilute one, until their concentrations are equal. Usually there are physical constraints. This is simply seen if we imagine a single cell, which has accumulated within it, for instance, amino acid molecules taken up from the outside fluid by a transport mechanism which has made them more concentrated inside than outside. Water will then tend to move into the cell to even out this concentration difference. If water moves into the cell, the cell will increase in volume. Cells can swell so much that they burst under some conditions (usually not encountered in the body, fortunately). For instance, red blood cells placed in water will burst (*lyse*) from just this effect: the relatively concentrated mixture of dissolved organic molecules within the cell will attract water from outside the cell, increasing the volume of the cell until its membrane can stretch no further and ruptures.

In the laboratory, we can avoid this by handling cells in solutions which contain solute – usually sodium chloride – at a total concentration of solute particles which matches that found within cells. Solutions which match this osmolality are referred to as *isotonic*; a common laboratory example is *isotonic saline* containing 9 g of NaCl per liter of water, with a molar concentration of 154 mmol/l. Since this will be fully ionized into Na^+ and Cl^- ions, its particle concentration is 308 'milliparticles' – sometimes called milliosmoles – per liter. We refer to this as an osmolarity of 308 mmol/l, but it is not 308 mmol NaCl per liter. (Sometimes you may see the term *osmolality*, which is similar to osmolarity, but measured in mmol per kg solvent.)

The phenomenon of osmosis has a number of repercussions in metabolism. Most cells have a number of different 'pumps' or active transporters in their cell membranes which can be used to regulate intracellular osmolarity, and hence cell size. This process requires energy and is one of the components of basal energy expenditure. It may also be important in metabolic regulation; there is increasing evidence that changes in cell volume are part of a signaling mechanism which brings about changes in the activity of intracellular metabolic pathways. The osmolarity of the plasma is maintained within narrow limits by specific mechanisms within the kidney, regulating the loss of water from the body via changes in the concentration of urine. Most importantly, potential problems posed by osmosis can be seen to underlie the metabolic strategy of fuel storage, as will become apparent in later sections.

1.2.2 *The Chemical Characteristics of Macronutrients*

1.2.2.1 Carbohydrates

Simple carbohydrates have the empirical formula $C_n(H_2O)_n$; complex carbohydrates have an empirical formula which is similar to this (e.g., $C_n(H_2O)_{0.8n}$). The name carbohydrate reflects the idea, based on this empirical formula, that these compounds are hydrates of carbon. It is not strictly correct, but illustrates an important point about this group of compounds – the relative abundance of hydrogen and oxygen, in proportions similar to those in water, in their molecules. From the discussion above, it will be apparent that carbohydrates are mostly relatively polar molecules, miscible with, or soluble in, water. Carbohydrates in nature include the plant products starch and cellulose and the mammalian storage carbohydrate glycogen, as well as various simple sugars, of which glucose is the most important from the point of view of human metabolism. The main source of carbohydrate we eat is the starch in vegetables such as potatoes, rice, and grains.

The chemical definition of a sugar is that its molecules consist of carbon atoms, each bearing one hydroxyl group (—OH), except that one carbon bears a carbonyl group (=O) rather than a hydroxyl. In solution, the molecule exists in equilibrium between a ‘straight-chain’ form and a ring structure, but as the ring structure predominates sugars are usually shown in this form (Figure 1.7). Nevertheless, some of the chemical properties of sugars can only be understood by remembering that the straight-chain form exists. The basic carbohydrate unit is known as a monosaccharide. Monosaccharides may have different numbers of carbon atoms, and the terminology reflects this: thus, a hexose has six carbon atoms in its molecule, a pentose five, and so on. Pentoses and hexoses are the most important in terms of mammalian metabolism. These sugars also have ‘common names’ which often reflect their natural occurrence. The most abundant in our diet and in our bodies are the hexoses *glucose* (grape sugar, named from the Greek *glykys* sweet), *fructose* (fruit sugar, from the Latin *fructus* for fruit), and *galactose* (derived from lactose, milk sugar; from the Greek *galaktos*, milk), and the pentose *ribose*, a constituent of nucleic acids (the name comes from the related sugar arabinose, named from *Gum arabic*).

Complex carbohydrates are built up from the monosaccharides by covalent links between sugar molecules. The term *disaccharide* is used for a molecule composed of two monosaccharides (which may or may not be the same), *oligosaccharide* for a short chain of sugar units, and *polysaccharide* for longer chains (>10 units), as found in starch and glycogen. Disaccharides are abundant in the diet, and again their common names often denote their origin: *sucrose* (table sugar, named from the French, *sucre*), which contains glucose and fructose (Figure 1.7); *maltose* (two glucose molecules) from malt; *lactose* (galactose and glucose) from milk. The bonds between individual sugar units are relatively strong at normal hydrogen ion concentrations, and sucrose (for instance) does not break down when it is boiled, although it is steadily broken down in acidic solutions such as cola drinks; but there are specific enzymes in the intestine (described in Chapter 3) which hydrolyze these bonds to liberate the individual monosaccharides.

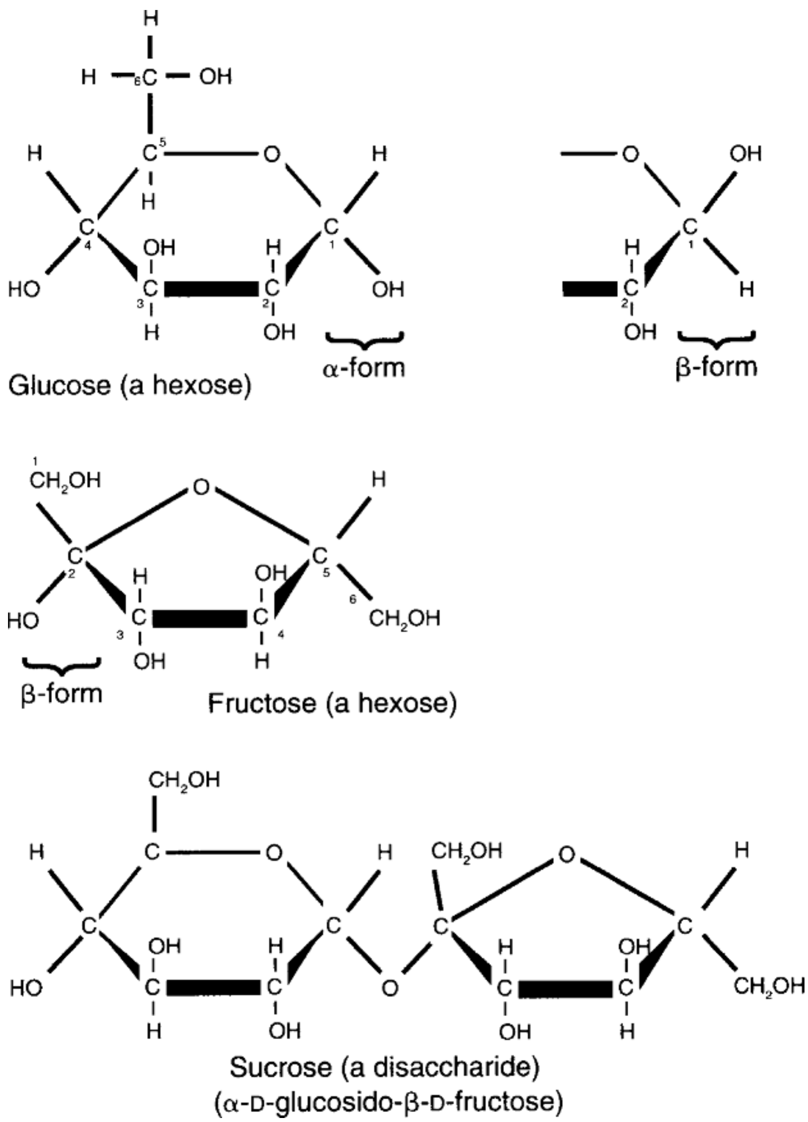

Figure 1.7 **Some simple sugars and disaccharides**. Glucose and fructose are shown in their 'ring' form. Even this representation ignores the true three-dimensional structure, which is 'chair' shaped: if the middle part of the glucose ring is imagined flat, the left-hand end slopes down and the right-hand end up. Glucose forms a six-membered ring and is described as a pyranose; fructose forms a five-membered ring and is described as a furanose. In solution the α- and β- forms are in equilibrium with each other and with a smaller amount of the straight-chain form. The orientation of the oxygen on carbon atom 1 becomes fixed when glucose forms links via this carbon to another sugar, as in sucrose; α- and β-links then have quite different properties (e.g., cellulose vs starch or glycogen).

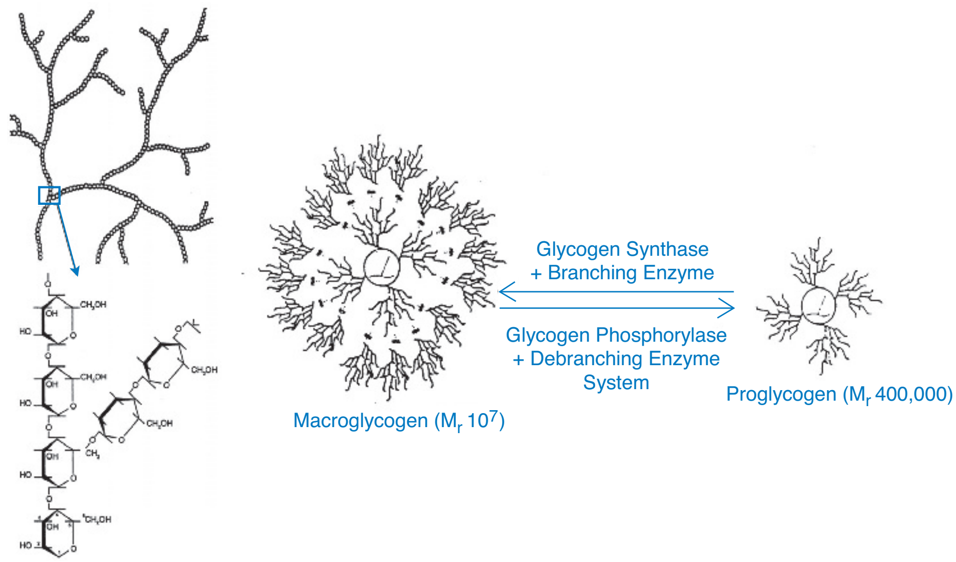

Figure 1.8 Structure of glycogen. Left-hand side: each circle in the upper diagram represents a glucosyl residue. Most of the links are of the α-1,4 variety. One of the branch points, an α-1,6 link, is enlarged below. Amylopectin, a component of starch, has a similar structure. Amylose, the other component of starch, has a linear α-1,4 structure. Right-hand side: glycogen is built upon a protein backbone, glycogenin. The first layer of glycogen chains forms proglycogen, which is enlarged by addition of further glucosyl residues (by glycogen synthase and a specific branching enzyme, that creates the α-1,6 branch-points), to form macroglycogen. When glycogen is referred to in this book, it is the macroglycogen form that is involved. Pictures of proglycogen and macroglycogen taken from Alonso *et al.* (1995), *FASEB Journal*, Copyright 1995 by Fedn of Am Societies for Experimental Bio (FASEB). Reproduced with permission of Fedn of Am Societies for Experimental Bio (FASEB).

Polysaccharides differ from one another in a number of respects: their chain length, and the nature (α- or β-) and position (e.g., ring carbons 1–4, 1–6) of the links between individual sugar units. Cellulose consists mostly of β-1,4 linked glucosyl units; these links give the compound a close-packed structure which is not attacked by mammalian enzymes. In humans, therefore, cellulose largely passes intact through the small intestine where other carbohydrates are digested and absorbed. It is broken down by some bacterial enzymes. Ruminants have complex alimentary tracts in which large quantities of bacteria reside, enabling the host to obtain energy from cellulose, the main constituent of its diet of grass. In humans there is some bacterial digestion in the large intestine (Chapter 3). Starch and the small amount of glycogen in the diet are readily digested (Chapter 3).

The structure of glycogen is illustrated in Figure 1.8. It is a branched polysaccharide. Most of the links between sugar units are of the α-1,4 variety but after every 9–10 residues there is an α-1,6 link, creating a branch. Branching makes the molecules more soluble, and also creates more 'ends' where the enzymes of glycogen synthesis and breakdown operate. Glycogen is stored within cells, not simply free in solution but in organized structures which may be seen as granules on electron microscopy. Each glycogen molecule is synthesized on a protein backbone, or primer, glycogenin. Carbohydrate chains branch out from glycogenin to give a relatively compact molecule called proglycogen. The glycogen molecules that participate in normal cellular metabolism are considerably bigger (Figure 1.8), typically with molecular weights of several million. The enzymes of glycogen metabolism are intimately linked with the glycogen granules.

The carbohydrates share the property of relatively high polarity. Cellulose is not strictly water soluble because of the tight packing between its chains, but even cellulose can be made to mix with water (as in paper pulp or wallpaper paste). The polysaccharides tend to make 'pasty' mixtures with water, whereas the small oligo-, di-, and monosaccharides are completely soluble. These characteristics have important consequences for the metabolism of carbohydrates, some of which are as follows:

(1) Glucose and other monosaccharides circulate freely in the blood and interstitial fluid, but their entry into cells is facilitated by specific carrier proteins.
(2) Perhaps because of the need for a specific transporter for glucose to cross cell membranes (thus making its entry into cells susceptible to regulation), glucose is an important fuel for many tissues, and an obligatory fuel for some. Carbohydrate cannot be synthesized from the more abundant store of fat within the body. The body must therefore maintain a store of carbohydrate.
(3) Because of the water-soluble nature of sugars, this store will be liable to osmotic influences: it cannot, therefore, be in the form of simple sugars or even oligosaccharides, because of the osmotic problem this would cause to the cells. This is overcome by the synthesis of the macromolecule glycogen, so that the osmotic effect is reduced by a factor of many thousand compared with monosaccharides. The synthesis of such a polymer from glucose, and its breakdown, are brought about by enzyme systems which are themselves regulated, thus giving the opportunity for precise control of the availability of glucose.
(4) Glycogen in an aqueous environment (as in cells) is highly hydrated; in fact, it is always associated with about three times its own weight of water. Thus, storage of energy in the form of glycogen carries a large weight penalty (discussed further in Chapter 8).

1.2.2.2 Fats

Just as there are many different sugars and carbohydrates built from them, so there are a variety of types of fat. The term *fat* comes from Anglo-Saxon and is related to the filling of a container or vat. The term *lipid*, from Greek, is more useful in chemical discussions since 'fat' can have so many shades of meaning. Lipid materials are those substances which can be extracted from tissues in organic solvents such as petroleum or chloroform. This immediately distinguishes them from the largely water-soluble carbohydrates.

Among lipids there are a number of groups (Figure 1.4). The most prevalent, in terms of amount, are the *triacylglycerols* or *triglycerides*, referred to in older literature as '*neutral fat*' since they have no acidic or basic properties. These compounds consist of three individual fatty acids, each linked by an ester bond to a molecule of glycerol. As discussed above, the triacylglycerols are very non-polar, hydrophobic compounds. The *phospholipids* are another important group of lipids – constituents of membranes and also of the lipoprotein particles which will be discussed in Chapter 10. *Steroids* – compounds with the same nucleus as cholesterol (Figure 1.6) – form yet another important group and will be considered in later chapters, steroid hormones in Chapter 6 and cholesterol metabolism in Chapter 10.

Fatty acids are the building blocks of lipids, analogous to the monosaccharides. The fatty acids important in metabolism are mostly unbranched, long-chain (12 carbon atoms or more) carboxylic acids with an even number of carbon atoms. They may contain no double bonds, in which case they are referred to as *saturated fatty acids*, one double bond (*mono-unsaturated fatty acids*), or several double bonds – the *polyunsaturated fatty acids*. Many individual fatty acids are named, like monosaccharides, according to the source from which they were first isolated. Thus, *lauric acid* (C12, saturated) comes from the laurel tree, *myristic acid* (C14, saturated) from the *Myristica* or nutmeg genus, *palmitic acid* (C16, saturated) from palm oil, and *stearic acid* (C18, saturated) from suet (Greek *steatos*). *Oleic acid* (C18, mono-unsaturated) comes from the olive (from Latin: *olea*, olive, or *oleum*, oil). *Linoleic acid* (C18 with two double bonds) is a polyunsaturated acid common in certain vegetable oils; it is obtained from linseed (from the Latin *linum* for flax and *oleum* for oil).

The fatty acids mostly found in the diet have some common characteristics. They are composed of even numbers of carbon atoms, and the most abundant have 16 or 18 carbon atoms. There are three major series or families of fatty acids, grouped according to the distribution of their double bonds (Box 1.2).

Differences in the metabolism of the different fatty acids are not very important from the point of view of their roles as fuels for energy metabolism. When considering the release, transport and uptake of fatty acids the term *non-esterified fatty acids* will therefore be used without reference to particular molecular species. In a later section (Box 10.5, p. 298) some differences in their effects on the serum cholesterol concentration and propensity to heart disease will be discussed.

It will be seen from Figures 1.4 and 1.9 that saturated fatty acids, such as palmitic (16:0), have a natural tendency to fit together in nice orderly arrays. The unsaturated fatty acids, on the other hand, have less regular shapes (Figure 1.9). This is reflected in the melting points of the corresponding triacylglycerols – saturated fats, such as beef suet with a high content of stearic acid (18:0), are relatively solid at room temperature, whereas unsaturated fats, such as olive oil, are liquid. This feature may have an important role in metabolic regulation, although its exact significance is not yet clear. We know that cell membranes with a high content of unsaturated fatty acids in their phospholipids are more 'fluid' than those with more saturated fatty acids. This may make them better able to regulate metabolic processes – for instance, muscle cells with a higher content of unsaturated fatty acids in their membranes respond better to the hormone insulin, probably because the response involves the movement of proteins (insulin receptors, glucose transporters) within the plane of the membrane (discussed in Box 2.4, p. 48), and this occurs faster if the membrane is more fluid.

Box 1.2 The Structures and Interrelationships of Fatty Acids

In the orthodox nomenclature, the position of double bonds is counted from the carboxyl end. Thus, α-linolenic acid (18 carbons, three double bonds) may be represented as *cis*-9,12,15-18:3, and its structure is:

$$CH_3{-}CH_2{-}CH{=}C^{15}H{-}CH_2{-}CH{=}C^{12}H{-}CH_2{-}CH{=}C^{9}H{-}(CH_2)_7{-}C^{1}OOH$$

(where the superscripts denote the numbering of carbon atoms from the carboxyl end). However, this is also known as an *n*-3 (or sometimes as an ω-3) fatty acid, since its first double bond counting from the non-carboxyl (ω) end is after the third carbon atom. On the latter basis, unsaturated fatty acids can be split into three main families, *n*-3, *n*-6 and *n*-9 (Table 1.2.1).

Table 1.2.1

Family	Source	Typical member	Simplified structure
Saturated	Diet or synthesis	Myristic	14:0
		Palmitic	16:0
		Stearic	18:0
n-9	Diet or synthesis	Oleic	9-18:1
n-6	Diet	Linoleic	9,12-18:2
n-3	Diet	α-linolenic	9,12,15-18:3

Based on Gurr *et al*. (2002).

The saturated fatty acids can be synthesized within the body. In addition, many tissues possess the *desaturase* enzymes to form *cis*-6 or *cis*-9 double bonds, and to elongate the fatty acid chain (*elongases*) by addition of two-carbon units at the carboxyl end. (These steps are covered in more detail in Box 5.4, p. 112.) But these processes do not alter the position of the double bonds relative to the ω end, so fatty acids cannot be converted from one family to another: an *n*-3 fatty acid (for instance) remains an *n*-3 fatty acid. Oleic acid (*cis*-9-18:1, *n*-9 family) can be synthesized in the human body, but we cannot form *n*-6 or *n*-3 fatty acids. Since the body has a need for fatty acids of these families, they must be supplied in the diet (in small quantities). The parent members of these families that need to be supplied in the diet are linoleic acid for the *n*-6 family and α-linolenic acid for the *n*-3 family. These are known as *essential fatty acids*. They can be converted into other members of the same family, although there seem to be health benefits of consumption of other members of the *n*-3 family, particularly 20:5 *n*-3 (eicosapentaenoic acid) and 22:6 *n*-3 (docosahexaenoic acid), found in high concentrations in fish oils. This is discussed further in Box 10.5. Some patients receiving all their nutrition intravenously have become deficient in essential fatty acids. The problem may be cured by rubbing sunflower oil into the skin!

An important feature of the fatty acids is that, as their name implies, they have within one molecule both a hydrophobic tail and a polar carboxylic acid group. Long-chain fatty acids (12 carbons and more) are almost insoluble in water. They are carried in the plasma loosely bound to the plasma protein albumin. Nevertheless, they are more water miscible than triacylglycerols, which are carried in plasma in the complex structures known as lipoproteins. The simpler transport of non-esterified fatty acids is perhaps why they serve within the body as the immediate carriers of lipid energy from the stores to the sites of utilization and oxidation; they can be released

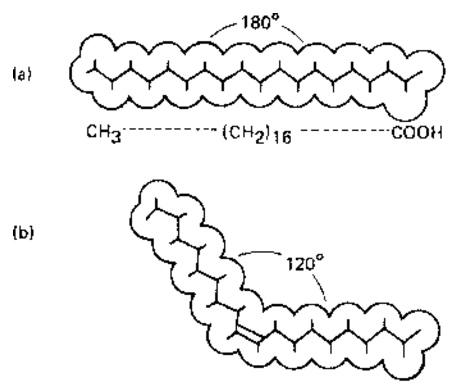

Figure 1.9 Pictures of the molecular shapes of different fatty acids. (a) saturated fatty acid, stearic acid (18:0); (b) mono-unsaturated fatty acid, oleic acid (18:1 n-9). From Gurr *et al.* (2002).

Figure 1.10 Comparison of fat and carbohydrate as fuel sources. Raw potatoes (right) are hydrated to almost exactly the same extent as glycogen in mammalian cells. Olive oil (left) is similar to the fat stored in droplets in mature human adipocytes. The potatoes (1.05 kg) and olive oil (90 g) here each provide 3.3 MJ on oxidation. This emphasizes the advantage of storing most of our energy in the body as triacylglycerol rather than as glycogen. [Please see color plate 1 to see this figure in color.]

very rapidly from stores when required and their delivery to tissues is regulated on a minute-to-minute basis.

But non-esterified fatty acids would not be a good form in which to store lipid fuels in any quantity. Their amphipathic nature means that they aggregate in micelles (small groups of molecules, formed with their tails together and their heads facing the aqueous environment); they would not easily aggregate in a very condensed form for storage. Triacylglycerols, on the other hand, do so readily; these hydrophobic molecules form uniform lipid droplets from which water is completely excluded, and which are an extremely efficient form in which to store energy (in terms of kJ stored per gram weight). This is illustrated in Figure 1.10. Thus, in brief, triacylglycerols are the form in which fat is mostly stored in the human body, and in the bodies of other organisms; hence they are the major form of fat in food. Non-esterified fatty acids, on the other hand, are the form in which lipid energy is transported in a highly regulated manner from storage depots to sites of utilization and oxidation.

1.2.2.3 Proteins

Proteins are chains of amino acids linked through peptide bonds. Individual proteins are distinguished by the number and order of amino acids in the chain – the sequence, or primary structure. Within its normal environment, the chain of amino acids will assume a folded, three-dimensional shape, representing the secondary structure (local folding into α-helix and β-sheet) and tertiary structure (folding of the complete chain on itself). Two or more such folded peptide chains may then aggregate (quaternary structure) to form a complete enzyme or other functional protein.

In terms of energy metabolism, the first aspect we shall consider is not how this beautiful and complex arrangement is brought about; we shall consider how it is destroyed. Protein in food is usually *denatured* (its higher-order structures disrupted) by cooking or other treatment, and then within the intestinal tract the disrupted chains are broken down to short lengths of amino acids before absorption into the bloodstream. Within the bloodstream and within tissues we shall be concerned with the transport and distribution of individual amino acids. These are mostly sufficiently water soluble to circulate freely in the aqueous environment of the plasma. Only tryptophan is sufficiently hydrophobic to require a transporter; it is bound loosely (like the non-esterified fatty acids) to albumin. Amino acids, not surprisingly, do not cross cell membranes by simple diffusion; there are specific transporters, carrying particular groups of amino acids (Chapter 2, Table 2.3, p. 38).

Protein is often considered as the structural material of the body, although it should not be thought of as the *only* structural material; it can only assume this function because of the complex arrangements of other cellular constituents, especially phospholipids forming cell membranes. Nevertheless, apart from water, protein is the largest single component in terms of mass of most tissues.[1] Within the body, the

[1] Two important exceptions are mature white adipose tissue, in which triacylglycerol is the major constituent by weight, and the brain, of which 50–60% of dry weight is lipid (mostly phospholipid).

majority of protein is present in the skeletal muscles, mainly because of their sheer weight (around 40% of the body weight) but also because each muscle cell is well packed with the proteins (actin and myosin) which constitute the contractile apparatus. But it is important to remember that most proteins act in an aqueous environment and are, therefore, associated with water. This is relevant if we consider the body's protein reserves as a form of stored chemical energy. Since protein is associated with water, it suffers the same drawback as a form of energy storage as does glycogen; with every gram of protein are associated about three grams of water. It is not an energy-dense storage medium. Further, although protein undoubtedly represents a large source of energy that is drawn upon during starvation, it should be remembered that there is, in animals, no specific storage form of protein; all proteins have some function other than storage of energy. Thus, utilization of protein as an energy source involves loss of the substance of the body. In evolutionary terms we might expect that this will be minimized (i.e., the use of the specific storage compounds glycogen and triacylglycerol will be favored) and, as we shall see in later chapters, this is exactly the case.

1.3 Some Physiological Concepts

The emphasis of this book on the integration of metabolism in different tissues and organs is more closely related to physiology than to molecular biology. This short section is intended to fill in some physiological concepts for those from more biochemical backgrounds.

1.3.1 Circulation, Capillaries, Interstitial Fluid

Blood is pumped around the body by the heart (Figure 1.11). Strictly, it is pumped by the left ventricle, out into the *aorta* – the main artery – and its various branches, which supply blood to all tissues. Within tissues, the arterial vessels supplying blood divide into smaller and smaller vessels, and eventually into the *capillaries* – small vessels whose interior lumen is approximately 0.01 mm diameter, just large enough for red blood cells to pass through in single file.

The density of capillaries (numbers of capillaries per unit area when the tissue is examined in cross-section under the microscope) varies between different tissues, but in most tissues at least one capillary is in close proximity to each cell. The inner walls of the capillaries are lined with flat endothelial cells, but in most tissues there are gaps between the endothelial cells, and/or 'fenestrations' (passages) through the endothelial cells – not large enough to let red blood cells through, but large enough for proteins and other molecules such as metabolites and hormones to pass. Outside the capillaries, surrounding the cells of the tissue, is an aqueous medium known as the interstitial fluid. For the most part, it is believed that substances diffuse from cells through the interstitial fluid into the capillaries, and from the capillaries through the interstitial fluid to cells, following concentration gradients (Figure 1.12). Thus oxygen, at its highest concentration in the blood supply at the arterial end of the capillary, will diffuse towards cells which are using it, so depleting its local concentration in

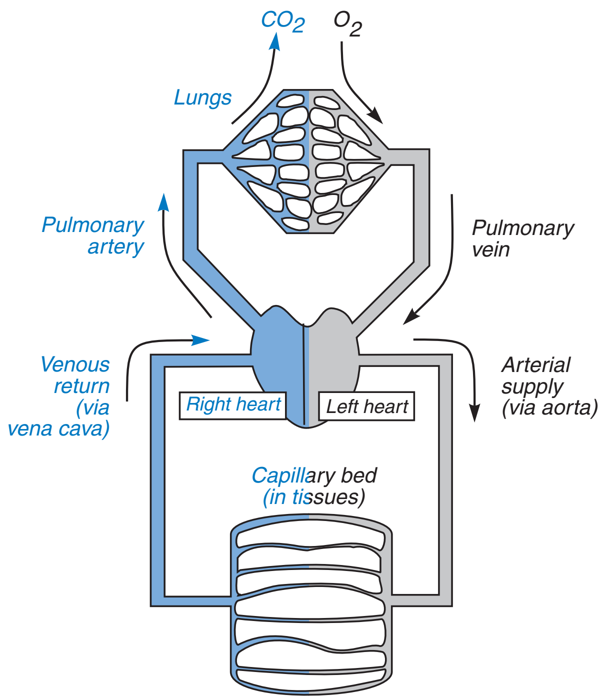

Figure 1.11 The circulatory system. Oxygenated blood from the lungs returns in the pulmonary veins to the left heart, from where it is pumped through the aorta and its various branches (arteries) to the tissues and organs. It returns from the tissues and is pumped to the lungs for reoxygenation and expiration of CO_2. The key feature from the point of view of integration of metabolism is that blood returning from all tissues (and from endocrine glands) is mixed within the heart and lungs, and then redistributed to tissues. Thus, the bloodstream ('the circulation') acts as an efficient means for interchange of nutrients, metabolites and hormones between tissues.

interstitial fluid; carbon dioxide will diffuse from cells which are generating it, and thus creating a high local concentration, into the capillaries where the concentration is lower because it is continuously being removed by the flow of blood. There are some substances for which this cannot be entirely true, especially the non-esterified fatty acids; this will be discussed in more detail later.

There are different types of capillaries: those with abundant fenestrations in the endothelial cells occur in tissues where there are high rates of exchange with the cells, for instance the mucosa (absorptive lining) of the small intestine, where substances are absorbed, and in endocrine tissues where there is rapid secretion of hormones. In the brain the endothelial cells are tightly joined to one another, and this is believed to be the structural basis of the 'blood–brain barrier'; a number of substances, including non-esterified fatty acids and many drugs, are thus denied access to the cells of the brain.

The capillaries in turn lead to larger and larger vessels, merging to form the major veins, through which blood returns to the heart. The returning blood enters the right ventricle, from where it is pumped through the lungs, collecting O_2 and losing CO_2; it then returns to the left heart and starts its journey anew.

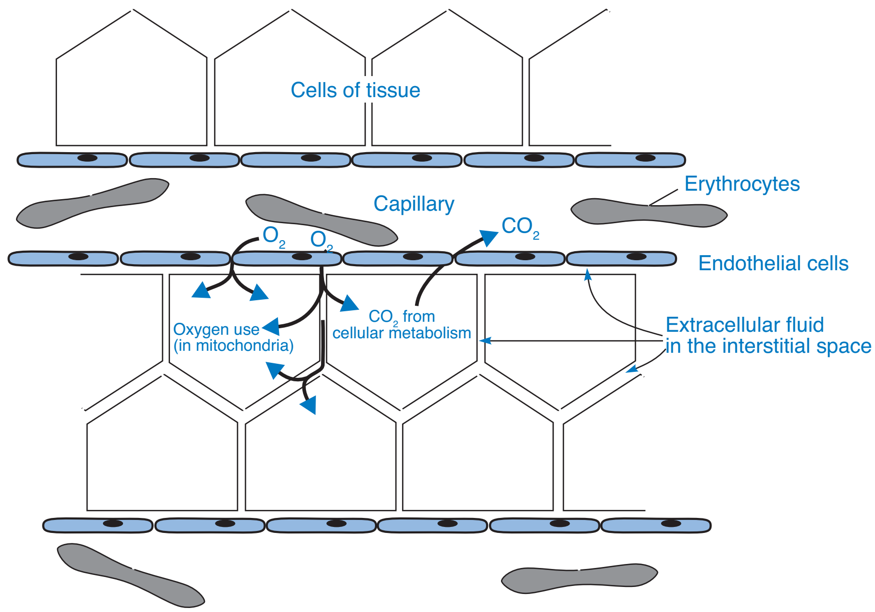

Figure 1.12 Diffusion of chemical substances through the interstitial fluid. A typical tissue is shown (schematically) in cross-section. The diffusion of oxygen from erythrocytes to cells in the tissue is shown as an example. Oxygen diffuses down a concentration gradient, from the erythrocytes, via the plasma and the interstitial fluid, into the cells, where its concentration is depleted as it is used in mitochondrial oxidation. CO_2 diffuses back to the plasma in the same way. The interstitial fluid occupies the space between cells known as the *extracellular space*; this is not a true empty space, but in reality is occupied by glycoproteins and other molecules joining the cells. Nevertheless, it offers a path for diffusion of substances.

The bloodstream is the major means of carrying substances from one tissue to another – for instance, it carries non-esterified fatty acids liberated from adipose tissue to other tissues where they will be oxidized, and it carries hormones from endocrine organs to their target tissues. The term *the circulation* is often used to mean ‘the bloodstream’; we speak of a substance being carried in the circulation, or even of *circulating glucose* (for instance), meaning glucose in the bloodstream. In the metabolic diagrams used extensively later in this book, the clear area in which different organs and tissues sit is meant to represent the bloodstream, and it may be assumed that substances will be efficiently carried across these blank spaces from one tissue to another.

1.3.2 Blood, Blood Plasma and Serum

The blood itself is an aqueous environment, consisting of the liquid *plasma* – a solution of salts, small organic molecules such as glucose and amino acids, and a variety of peptides and proteins – and the blood cells, mostly red blood cells (*erythrocytes*). The erythrocyte membrane is permeable to, or has carriers for, some molecules but not others. Glucose, for instance, partially equilibrates across the erythrocyte membrane. Its concentration is somewhat lower inside the cell than outside, since the erythrocyte uses some for glycolysis and transport across the cell membrane must be somewhat limiting for this process. But nevertheless, glucose and some amino acids are carried around both in blood cells and in the plasma. On the other hand, lipid molecules are excluded from red blood cells and carried in the plasma. On the whole, the term 'in the plasma' will be used for those substances confined to that compartment, and 'in the blood' or 'in the bloodstream' for those which are carried in both compartments.

If blood is allowed to clot and then centrifuged, a yellow fluid can be removed: this is *serum*. It is like plasma but lacks the protein *fibrinogen*, which is used in the clotting process. Serum is often collected from patients for measurement of the concentration of cholesterol or triacylglycerol, mainly because it is convenient to let the blood clot. The term 'serum cholesterol,' for instance, then simply refers to the concentration of cholesterol in the serum; it would be almost exactly the same as the plasma cholesterol concentration.

1.3.3 Lymph and Lymphatics

The interstitial fluid is formed by filtration of the blood plasma through the endothelium (vessel lining), as described earlier. Some of the fluid which leaves the bloodstream in this way will naturally find its way back to the blood vessels, but some is drained away from tissues in another series of vessels, the lymphatics. These are for the most part smaller than blood vessels. The fluid within them, the lymph, resembles an ultrafiltrate of plasma – that is, it is like plasma but without red blood cells and without some of the larger proteins of plasma. The lymphatic vessels merge and form larger vessels and eventually discharge their contents into the bloodstream. We shall be concerned with one particular branch of the lymphatic system – that which drains the walls of the small intestine. The products of fat digestion enter these lymphatic vessels, which collect together and form a duct running up the back of the chest, known as the *thoracic duct*. The thoracic duct discharges its contents into the bloodstream in the upper chest. The lymphatic system also plays an important role in defense against infection, but this immunological role is beyond the scope of this book.

Further Reading

General Metabolic Biochemistry and Nutrition: Other Useful Textbooks

Fell, D. (1997) *Understanding the Control of Metabolism*, Portland Press, London.

Murray, R.K., Granner, D.K., and Rodwell, V.W. (2006) *Harper's Illustrated Biochemistry*, 27th edn, Lange Medical Books, New York.

It may also be necessary to consult one of the 'classical' biochemistry textbooks to give more detail of pathways and structures.

Salway, J.G. (2004) *Metabolism at a Glance*, 3rd edn, Blackwell Publishing, Oxford.

Glycogen

Greenberg, C.C., Jurczak, M.J., Danos, A.M., and Brady, M.J. (2006) Glycogen branches out: new perspectives on the role of glycogen metabolism in the integration of metabolic pathways. *Am. J. Physiol. Endocrinol. Metab.*, **291**, E1–E8.

Roach, P.J. (2002) Glycogen and its metabolism. *Current Molecular Med.*, **2**, 101–120.

Lipids and Membranes

Engelman, D.M. (2005) Membranes are more mosaic than fluid. *Nature*, **438**, 578–580.

Maxfield, F.R., and Tabas, I. (2005) Role of cholesterol and lipid organization in disease. *Nature* **438**, 612–621.

Pike, L.J. (2004) Lipid rafts: heterogeneity on the high seas. *Biochem. J.*, **378**, 281–292.