Veterinary Physiology

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Preface

THE objective of this book is to present an account of the fundamental principles of physiology, in particular as these pertain to the health of domestic animals. The text has been written bearing in mind the constraints imposed by the recent trend towards shorter curricula in the preclinical or basic sciences in Veterinary Schools and it should also be suitable for animal physiology courses in Colleges of Agriculture and Animal Science. The level of presentation is intended for undergraduate rather than graduate students and the depth of coverage in some sections has been related to the practical relevance of that section to the animal industry. In all sections, however, the aim has been to present the reader with a clear but concise account of the functioning of the various body systems of domestic animals.

In order to provide the reader with sections written by experts in the various branches of physiology and yet still have a consistency of style and continuity within the various sections, the editor has limited the number of contributors to the book. Each section or independent chapter has therefore been prepared by one individual. The editor would like to express his appreciation of the time and effort that these contributors have spent on the preparation of their chapters.

The order in which the material is presented has been selected to provide the information necessary for an understanding of the successive chapters. The book commences with an analysis of basic cellular physiology and the properties of nerve and muscle cells. The functioning of the peripheral and central nervous systems is then discussed in some detail, followed by an account of the regulation of the body's second co-ordinating system, the endocrine glands. Circulation, respiration, and gastro-intestinal and renal systems are discussed in sequence, followed by the sections on metabolism and bioenergetics, reproduction, and lactation. The book concludes with a section on biostatistics, which should be of especial significance to future specialists in the various fields of animal management and science.

Each chapter or section includes a short list of references. These have of necessity been limited in number and the emphasis has been placed on monographs, chapters in books, or review articles and particularly significant research articles. The reference lists are not intended to be comprehensive but rather to provide ready access to the literature.

The editor is grateful for the assistance and co-operation of his colleagues in the preparation of the manuscript. Drs. N. Lake, G. G. Yarbrough, and R. M. Jell read and commented on various sections of the manuscript. The

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Finally, the editor would like to acknowledge with especial gratitude the sympathetic support received from his wife, Shane, during the many trials encountered in the preparation of this textbook.

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Section 1: Introduction to Cell Physiology

Chapter 1

The Living Cell

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For a hundred years or so it has been accepted by biologists that the higher animals and plants are composed of large numbers of subunits or cells. Of course the individual cells communicate and influence each other in a variety of ways (with which most of this book is concerned), but in principle each cell *can* exist and function independently of the others. In the process of *tissue culture* for example, cells are removed and kept alive in an artificial medium, often surviving for many years. The number of cells in an organism is staggering. For example, the red blood-cell or erythrocyte is not a particularly small cell but in a single teaspoon of blood there are about 10,000,000,000 of them. Why are there so many cells? One possible answer is that all cells have to exchange foodstuffs, oxygen, waste products, and so on with their environment, and that this can only be done quickly enough if the cells are very small (*see* p. 23).

All cells have the ability to obtain energy for life processes from simple foodstuffs which they take up from their fluid environment. For example, almost all vertebrate cells can oxidize glucose to water and carbon dioxide, reversing a reaction which occurs in the opposite direction in the green leaves of plants:

$$C_6H_{12}O_6 + 6\,O_2 \rightleftharpoons 6\,CO_2 + 6\,H_2O + 700 \text{ kcal/mole} \qquad (1)$$

The energy required to drive this reaction to the left during photosynthesis comes from sunlight, so it can be said that it is the continuous flow of energy from the sun which maintains the flows of energy-consuming processes which we call animals and plants.

What is this energy used for? The most obvious use is for *movement*, and much is known of the way that muscle cells are able to convert chemical energy into mechanical energy (Chapter 2). Another important function is *growth*. Energy is required to put together the complex structures which make up living cells, whether these are being made in new tissue in young, growing animals or in the process of replacing old cells in an adult. This process should not be underestimated. To return to the example of the erythrocyte, it can be

calculated that in an adult man over ten million erythrocytes are destroyed and replaced by new ones each minute. Some cells, however, are not renewed, such as the cells of the central nervous system. When these cells die they are not replaced and the number of nerve cells gradually falls during an animal's lifetime. The third vital role of energy metabolism is in the *maintenance* of living cells. A complex structure such as an organism or a cell constantly tends to break down into simpler components. It is unstable. If the structure of an organism remains constant over a period of time it is due to the continuous application of energy to reverse this breakdown as it occurs. If the supply of energy is cut off even for a very short time then the changes become irreversible and the cell or organism dies. In the language of thermodynamics it may be said that living organisms are structures of very low *entropy* which are maintained in a *steady state* which is far from equilibrium by the continuous flow of *free energy* from outside. This energy flux is not of course a one-way flow. In the steady state an equal quantity of heat flows out from the organism to its surroundings. In a resting, adult (not growing), animal this flow of heat is called the *basal heat production* and is equal to the rate of energy supply needed to keep the body in its basal, or resting, state. To illustrate this cycle let us consider the heart. The heart is a pump; its cells convert chemical energy into mechanical work on the blood which passes through it, establishing the circulation. Where does this energy go? As blood leaves the left ventricle it has a high velocity (kinetic energy) and a high pressure (potential energy). Then as it goes round the body this energy is gradually used in overcoming the viscosity and frictional forces opposing blood-flow and an equivalent amount of heat is produced. When the blood reaches the heart again it has returned to the same energy status as it had before: all the work done by the heart has been converted into heat. The same process occurs at all levels. Thus while it is possible for ions to move across cell membranes, the concentration of any given ion species is almost always different in the intracellular fluid inside the cell and in the extracellular fluid outside. This results in a slow drift of the ion down its concentration gradient which has to be balanced by an equal rate of ion 'pumping' in the opposite (uphill) direction to maintain the steady state. The work done by this ion pump is dissipated as heat of mixing as the ions drift back down their concentration gradients.

CELL STRUCTURE AND FUNCTION

All the cells in the body are ultimately derived from the single fertilized egg. However, during development such specialization of the different groups of cells occurs that it is doubtful if there is any cell type in the adult mammal which can be thought of as truly unspecialized. If we can imagine a 'typical cell' then something like *Fig. 1:1* might be a schematic diagram of it.

Membrane Systems

The cell membrane at the boundary divides the extracellular from the intracellular phases. The intracellular phase or cytoplasm is usually considered

by physiologists to be a simple aqueous solution of the many charged and uncharged soluble substances contained in the cell. The cell membrane has the job of maintaining the many differences in composition which exist between the extracellular fluid (ECF) and the intracellular fluid (ICF) and, as we shall see,

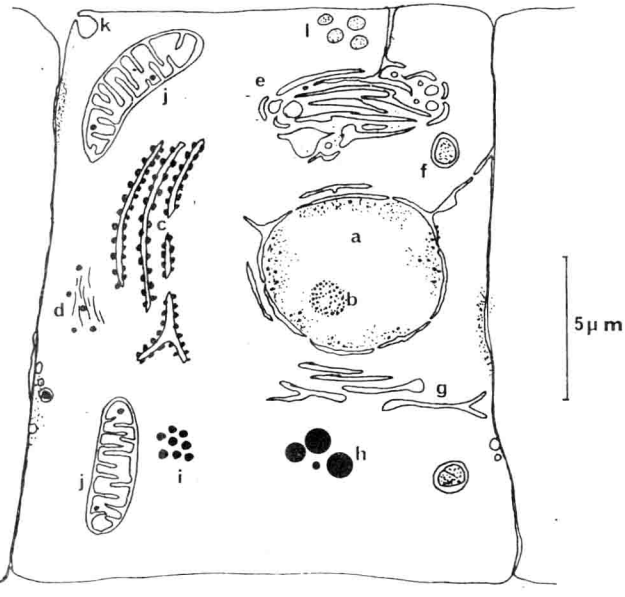

Fig. 1:1. Diagram of the components of a 'typical' mammalian cell. **a,** The cell nucleus bounded by the nuclear membrane system with gaps or 'nuclear pores'; **b,** Nucleolus; **c,** Rough endoplasmic reticulum (with ribosomes); **d,** Free ribosomes and cytoplasmic filaments, **e,** Golgi apparatus; **f,** Lysosome; **g,** Smooth endoplasmic reticulum; **h,** Fat droplets; **i,** Glycogen granules; **j,** Mitochondrion; **k,** Pinocytotic vesicle; **l,** Secretion granules.

much of cell physiology is concerned with finding out how this is done. In fact the peculiar properties of this osmotically active surface membrane or *plasma membrane* made physiologists aware of its existence long before electron microscopy was developed enough to obtain pictures of its appearance. Details of the structure and behaviour of the plasma membrane will be given later. In the electron microscope it appears as a relatively simple uniform structure about 100 A (10^{-5} mm) thick. In most cells there is an additional outermost layer known as the 'basement membrane', a somewhat ill-defined layer of mucopolysaccharide material which seems to be involved in the immunologic reactions by means of which cells 'recognize' each other. In some single-celled organisms, and notably in bacteria, this outer coat may be very elaborate. In any case these outer layers of material may be considered as

extracellular since they are products of cellular activity which have been secreted through the plasma membrane.

Although its fundamental structure may be uniform from cell to cell and from place to place on the cell's surface, the plasma membrane should not be thought of as a smooth skin stretched tightly over the cell's contents. This is so in the erythrocyte for example, but in muscle the plasma membrane appears slack and wrinkled, and in many cells the surface area of the membrane is increased by the formation of fingerlike projections or *microvilli*. These are found in cells actively involved in absorptive and transport functions. In addition to these relatively stable structures, it seems that the membranes of most cells are able to form transient invaginations and evaginations which may be involved in the transmembrane movement of macromolecules too big to cross the membrane by simple diffusion. This process is known as *pinocytosis* (p. 31).

Membranes similar to the plasma membrane are known to surround some of the cell's organelles such as the mitochondria and the nucleus. Careful analysis has shown, however, that differences in fine structure do exist between these different membranes. For example, although plasma and mitochondrial membranes both contain much lipid material, the mitochondrial membrane contains relatively more cholesterol and less phospholipid than the plasma membrane. Presumably these differences reflect differences in the membrane's functions. Despite these differences, it has become clear in the last decade that there is a membrane system within the cell which connects the various organelles and the surface membrane. This is the rather variable system of tubules and vesicles known as *endoplasmic reticulum*. The function of the endoplasmic reticulum is not really known, though it often seems that it is involved in the movement of substances from place to place inside the cell. One of its most intriguing features is its variability from one type of cell to another. Its most highly developed arrangement is found in striated muscle cells, where it forms a regular and complex array called the *sarcoplasmic reticulum* which plays an essential role in the contractile process (p. 67). A yet less understood membrane system is the *Golgi apparatus*. This is a characteristic parallel arrangement of tightly packed, smooth, vesicles which is often found close to the nucleus. In secretory cells, the products of secretion accumulate here. However, non-secretory cells also have a Golgi complex, so presumably this also has a metabolic function not related to storage. There is evidence that some polymerization processes occur here.

In general it may be said that most of the cell's enzyme-catalysed reactions probably occur at membrane sites. This is not surprising since the local microenvironment close to a membrane interface will be comparatively highly structured in terms of composition and energy distribution. This is because of the tendency for solutes to accumulate near, and be adsorbed onto, the membrane, and the consequent appearance of local but intense electric fields known as 'Helmholtz double layers'.

Another suggested function of the Golgi apparatus is the production of *lysosomes*. These are small (0·2–0·8 μ) membrane-bounded vesicles which

contain enzymes (hydrolases and aldolases) capable of breaking down complex molecules. In fact when the cell dies, the lysosomal membrane breaks down and releases these enzymes which then destroy the cell (autolysis). During life the lysosomes are used to digest damaged or redundant parts of the cell such as old mitochondria (autogenous digestion), and for the breakdown of material brought into the cell by phagocytosis. The phagocytic vesicle fuses with the lysosome to form what is known as a 'phagosome' inside which the digestive function is carried out. In short, the lysosomal system is the cellular equivalent of the digestive system of the whole animal.

The Nucleus

The cell nucleus contains the blueprints for the animal in the form of the information contained on the *chromosomes*. It is the nucleus in each cell which is responsible for controlling and co-ordinating the production of *proteins*. The way in which this is done is a fascinating story which is outside the realm of cell physiology. It is sufficient to note here that most of the chemical reactions which are essential for life will not go on in cells unless the right organic catalyst or *enzyme* is present. Now these enzymes are proteins and furthermore they do get used up slowly so that continual replacement is necessary. Also the cell's structural proteins slowly break down and have to be replaced. For this reason an enucleated cell (one without a nucleus) soon dies as it cannot put proteins together—it certainly will not be able to divide and reproduce itself. Such a cell is the erythrocyte or red blood-cell which is formed from nucleated precursor cells in the bone-marrow. The erythrocyte is highly specialized for efficiently transporting oxygen to the tissues, and contains little but the respiratory pigment haemoglobin. The average erythrocyte survives in the blood for about 100 days. Presumably it survives for even this length of time because there is so little in it to go wrong.

Proteins, however, are not actually *made* in the nucleus. This process is associated with the *ribosomes*, which are small dense bodies found on the surface of the endoplasmic reticulum (*Fig. 1:1*). Reticulum with ribosomal granules on it is called *rough endoplasmic reticulum*; the other sort is called *smooth endoplasmic reticulum*. This is not the place to go into the details of protein synthesis, but it is such an important topic that a brief outline of the elements will be given here. *Proteins* are substances of large molecular weight (10^4–10^7 mol. wt.) which are composed of large numbers of simple 'building blocks'—the *amino-acids*. The 21 different amino-acids are all either absorbed from food in the gut or synthesized from other amino-acids in the liver. Thus the necessary amino-acids reach the cell via the blood. Now the properties of a protein molecule are determined by the *number* of amino-acid subunits it contains and the *sequence* in which the individual different amino-acids are joined together. The function of the cell nucleus is to store and if necessary provide the information which is needed about the amino-acid sequences in all the different proteins which may be made in the cell. This enormous amount of information is contained in the base sequences in the DNA molecules

(deoxyribose nucleic acid). The way in which this huge library functions is now largely understood; in particular the way in which the base sequences in the long DNA helix code for specific amino-acids in proteins (*the genetic code*) is known. The length of the chromosomal DNA which contains the blueprint for an individual protein is known as a *gene*. During the process of cell division the DNA replicates, i.e., the mother cell's DNA makes an exact copy or replica of itself which is then included in the daughter cell. This means that, barring accidents, every cell nucleus in an animal's body contains exactly the same DNA since all cells ultimately come from division of the single fertilized germ cell. So it follows that in an individual cell much of the DNA library is never read, since the different types of cell differ markedly in their protein make-up. This process of 'regulation of genetic activity' is not at present fully understood. Now, to come back to protein synthesis, the DNA always stays in the nucleus. It influences the ribosomes through a smaller but similar molecule called RNA (ribose nucleic acid). Actually there are several kinds of RNA in the cell—the one we are concerned with here is called 'messenger RNA' or mRNA. It carries the genetic message about amino-acid sequence from the nuclear DNA to the assembly site on the ribosomes where the amino-acids are put together. This process involves another, smaller, RNA molecule, 'soluble RNA' or sRNA. Finally in order to put the simple amino-acids together to make protein, *energy* is required. Since amino-acids do not spontaneously self-assemble into enormous molecules, the ribosomal machinery has to be driven by a steady supply of metabolic energy. Thus protein synthesis needs:

1. Raw materials—amino-acids;
2. Information—mRNA;
3. Energy.

There are substances such as actomycin and puromycin, which can be used experimentally to stop protein synthesis in cells. Instances of the use of this technique, which is becoming common in experimental physiology, will be found later in this book. These substances interfere with protein synthesis by preventing information transfer from DNA to mRNA.

Energy Utilization and Production

The energy supply for protein synthesis comes from a chemical reaction that seems to be used everywhere in the cell when energy is required*; the dephosphorylation of adenosine triphosphate, ATP.

$$\text{ATP} \rightleftharpoons \text{ADP} + \text{P} + \text{energy} \qquad (2)$$

This reaction is so ubiquitous and important that it seems worthwhile to give the structure of ATP (*Fig. 1:2*).

* A little more energy can be derived from the further dephosphorylation of ADP to AMP (adenosine monophosphate), a reaction which is catalysed by the enzyme myokinase, present in all cells. Also a few cell reactions obtain energy by splitting molecules similar to ATP but with the bases inosine (ITP), guanine (GTP), and uracil (UTP). These reactions, though interesting, are not quantitatively important in the overall energy balance of the cell.

As you might expect, the dephosphorylation of ATP never occurs spontaneously in the cell, or at any rate the reaction proceeds extremely slowly in the absence of an enzyme (an *ATPase*) which will catalyse it. Now if the reaction (2) occurs as it is written, then the energy released by the reaction simply appears as useless heat—as it would if we mixed ATP solution and ATPase in a test-tube. The splitting of ATP *in vivo* only occurs when energy is needed by one of the special mechanisms in the cell. In practice the process is always

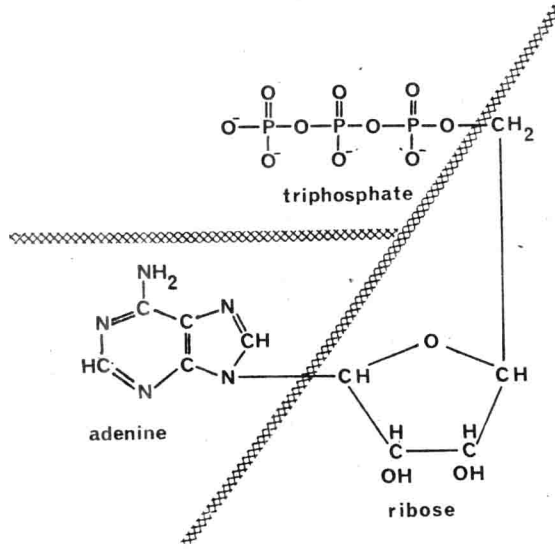

Fig. 1:2. The structure of ATP.

complex and usually seems to involve the intermediate transfer of the terminal phosphate group of ATP to another molecule before its release as inorganic phosphate.

$$\text{ATP} + \text{a} \rightarrow \text{aP} + \text{ADP}$$
$$\text{aP} \rightarrow \text{b} + \text{P}$$

ATP can not normally cross cell membranes (the molecule is large and electrically charged—*see* p. 19) so if cellular processes are to continue, reaction (2) must be reversed in each cell as fast as it occurs. The necessary energy is supplied by the oxidation of fats and carbohydrate molecules which can pass relatively easily from blood to the intracellular fluid. Carbohydrate may be stored within the cell in the form of granules of glycogen, a form of polymerized glucose. These granules can be seen in *Fig. 1:1*. On breakdown the glycogen granules yield glucose, which in turn is broken down in a number of steps to yield pyruvate. Each 6-carbon glucose molecule gives rise to two 3-carbon pyruvate molecules. This process, known as 'glycolysis', occurs in the cytoplasm. Two of the steps are coupled to the phosphorylation of ADP and