

CELLS AND CELL STRUCTURE

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Preface

This book describes the results of recent work on the structure of cells and something of current theories about cell function. The post-war years have been fruitful for cell biology; the last decade alone has brought an immense enlargement of our knowledge of cytology through the development of new methods of microscopy. It is just to say that, as the first golden age of cytology was ushered in by the perfection of the compound light microscope, so a second has been made possible by the invention of the electron microscope.

In this same period new ways of regarding biology problems have appeared, bringing with them new words—such as *molecular biology* and *cybernetics*. Molecular biology is the name given to the synthesis of biochemistry, cell physiology and structure in terms of molecular interaction, which, following the determination of the molecular structure of key macromolecules, now seems possible.

The viewpoint of cybernetics and information theory is more novel; with its conception of organisms as self-controlling and self-replicating machines, integrated largely by information transfer between their parts, it promises a way out of the impasse engendered by earlier thinking about the remarkable integration and goal-seeking activities of living matter.

These developments have as yet found little expression in books available for classroom use or general reading; yet, since an appreciation of the biology of the immediate future will be impossible without them, it seems to me they should figure largely, even in an introductory work, simply because of the new and necessary points of view they introduce. I do not believe that the student, who for some years may not be able to appraise the experimental data on which these advances are based, should be shielded from the viewpoints of the men who make them. In fact this would be impossible, for the basic working concepts of modern biology—such as self-duplicating mechanisms and control by information transfer—which might have been cautiously regarded twenty years ago, are now 'in the air'; they are understood readily and accepted by a generation whose intellectual fare has included guided missiles, recording tapes and self-controlled mechanisms.

Further, I see no reason why young readers should not be introduced to current speculation which may prove to be wrong or at least incomplete in a very short time. I believe it is the correct procedure; for, by an acquaintance with contemporary experimental activity and speculation, we participate in, experience and understand science as an evolving organic growth rather than a static completed body of knowledge.

Primarily we are concerned in this book to describe the structures which form the material bases of the working parts of cells. The fine cytology of a number of cell types will be outlined, but a systematic account of particular organisms and tissues is not attempted. Emphasis is placed throughout on the principal problem of biology: the transfer of genetic information from cell to cell and the nature of its control over the cell's synthetic processes.

A current event of some significance is the closing of the attack on the problem of multicellular organization and its integration. We may anticipate that, whereas the great triumphs of the medicine of the immediate past have been based on the control of pathogenic invaders, those of the future will concern the control of disorders arising from failures at the level of cellular organization: cancer, diseases of cellular incompatibility, congenital defects and mental disorders. Thus, as an introduction to these developments, it seemed proper to include some account of current views concerning the cellular basis of multicellular integration.

I should like to acknowledge my debt to my many colleagues of the Chester Beatty Research Institute with whom I have discussed this book and particularly to those who have read and criticized portions. I am grateful to Mr M. S. C. Birbeck and Mr D. T. Hughes for permission to reproduce certain micrographs (Plates 1 and 3), to Mr Michael Docherty who prepared the prints and to Dr K. Simkiss who drew many of the illustrations.

London, 1961

E.H.M.

Cell, Plasma Membrane and Nucleus

Cells and microscopes

THE structural and functional unit of most living matter is the cell. This constructional habit is not the unique way in which organisms can be formed—some, such as the slime moulds, are not subdivided in this way; but unquestionably the cell has certain advantages of construction and maintenance which have led to its almost universal occurrence.

It is a matter of observation that all cells are produced by other cells, and that in the daughter cells the same structures are reproduced as were found in the parent cells. A mere description of these structures is not satisfying; we wish to know how they come about. What is it that parent cells pass on to their progeny and how is it translated into structure? The tentative answers we are able to give to these questions and a description of intracellular structure, as revealed by light and electron microscopy, will form the subject matter of this book.

Most cells are very small, usually of the order of 10 to 100 μ in diameter.¹ There are larger cells, for example the relatively enormous birds' eggs and the many specialized cells in plants, but both in plants and animals the growing and multiplying cells are small and similar in size (20–30 μ).

Since these units are so small, the study of their structure and behaviour demands the use of microscopes. Of these there are two kinds: the light and the electron microscope. We are not too much here concerned with how these work, but something must be said of their uses. The *light microscope* is comparatively familiar. It makes use of the absorption of light by the cell in order to form an image of it; dyes are commonly used to stain the cell or its parts to reveal the structure more clearly. A more recent development, called the *phase microscope*, is invaluable for the study of living cells without resort to stains; its image-forming properties depend simply on differences in refractive indices between the several parts of the cell. By means of

¹ Two units which will recur frequently throughout this book are the micron (μ) = 1/1000 mm and the Ångstrom (Å) = 1/10,000,000 mm. A hydrogen atom is about 1 Å in diameter.

the light microscope, objects which are separated by a distance as small as $0.3\ \mu$ can be seen as two; when closer they fuse into one. This distance is therefore called the *resolving power* of the microscope. It is determined largely by the wavelength of the light which is used, e.g. sodium light $0.6\ \mu$. Thus, in a cell of a diameter of $20\ \mu$, a microscope of this resolving power will enable us to distinguish numerous smaller intracellular objects of varying sizes down to about $1/3\ \mu$ in diameter.

The electron microscope was more recently developed and, being more expensive and complicated, is less common. It makes use of a beam of electrons instead of a light beam but is not in principle very different from the light microscope. Since the wavelength of the electrons in a microscope using an accelerating voltage of 50,000 V is $0.05\ \text{\AA}$ (or $0.00005\ \mu$), the electron microscope has a vastly greater resolving power than a light microscope. The actual instruments in use today have a resolving power of about $10\ \text{\AA}$ or $1/1000\ \mu$; since a H atom is about $1\ \text{\AA}$ in diameter, objects separated by a distance of the order of 10 H atoms (assuming they are sufficiently dense to stop enough electrons) can be resolved by modern instruments. This has in the last ten years revolutionized the outlook for cytology (the study of cells) because it means that we are potentially able to visualize everything to be found in cells except the smaller mobile molecules such as water and salts.

Unfortunately, since an electron microscope operates in a vacuum, it is very difficult to examine living material. In practice, cells are fixed by means of osmium tetroxide or formaldehyde solutions, dehydrated, embedded and sectioned for use on these instruments. The microscope forms an enlarged image (up to $\times 200,000$) on a fluorescent screen resembling that of a television tube. Photographs (electron micrographs) are made for further enlargement and closer study.

Intracellular specialization

When a number of different kinds of cells are examined in the microscope we see that, although they vary greatly in shape and internal contents (Figure 1.1), two compartments can always be distinguished¹: an inner rounded *nuclear space*, enclosed by a distinct nuclear membrane, and an outer, the *cytoplasm*, enclosed by a second membrane, the *plasma membrane* or cell membrane (Figure 1.2). The function of this plasma membrane is, in the first place, the simple mechanical one of keeping the bits and pieces together and, secondly, by its peculiar permeability, to help in maintaining the special environment in which these intracellular organelles work best. This subdivision of the cell corresponds to the two distinct basic activities which it must carry on if it is to persist and leave progeny. In what might be called a primary division of labour, the outer part—the cytoplasm, nearer the external world—is concerned with day-to-day activities, the procuring of raw materials, food and energy; the inner chamber enshrines

¹ The familiar red blood cell is exceptional; it lacks a nucleus.

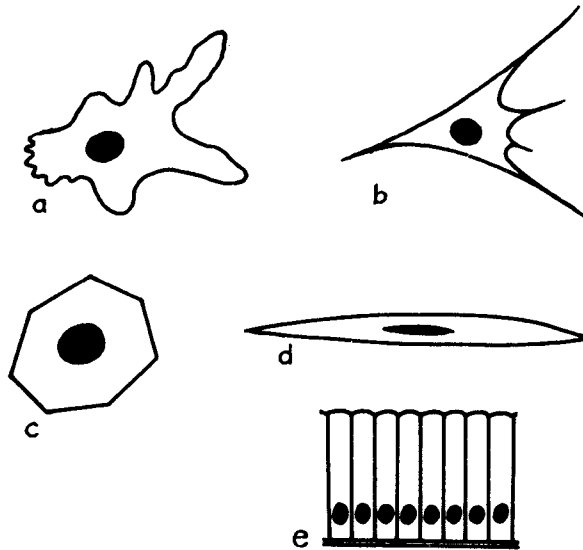


FIG. 1.1

Shapes of cells (a) and (b) free cells. (a) an amoeba (b) a fibrocyte; (c), (d) and (e) tissue cells which owe their shape largely to their adhesion to other cells. See also other diagrams to follow. (c) cell in lower layers of epidermis (d) smooth muscle cell (e) an epithelium

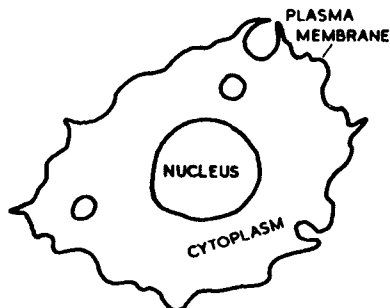


FIG. 1.2

The primary divisions of the cell:
nucleus, cytoplasm and plasma membrane

the *genetic apparatus*, concerned with the passing on of the 'know-how' of the parent to the offspring. Without this latter provision the species would become extinct.

The genetic apparatus in the nucleus, which in all existing cells is derived from that of antecedent cells, not only ensures the formation of a copy of itself to pass on to daughter cells. It also guides and controls the formation of the materials within the cell and is thus largely responsible for the cell's character, its structure and activity.

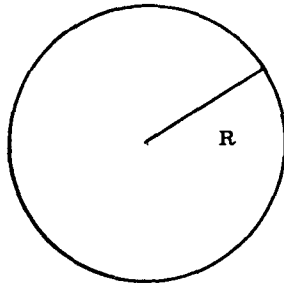
Cells are in no way immune from the basic physical laws; they must find both raw materials and energy from which to construct their parts and keep them working. Some have emphasized that living matter creates order and complexity, and this is true; but it succeeds in doing so only at the cost of its surroundings. That is, cells are able to build up their elaborate and ordered structures only by consuming matter and energy from outside. The total result of their activity, when the overall balance is struck, is an increase in the total disorder. Thermodynamically speaking, cells effect a *local* decrease in entropy at the cost of a larger overall increase.

The size of cells

Most cells are between 10 and 100 μ in diameter; the exceptions to this are special cases and there is usually some good reason for their size. Eggs are as a rule large, those of selachian fishes, reptiles and birds being veritable giants among cells; but they are stocked with food by accessory cells and are poised ready to divide and restore the norm. Protozoa have special internal organelles developed to overcome the limitations imposed by size, and many zoologists regard them as having a distinct acellular organization. Bacteria are peculiar, too, in their exceptional smallness, and are best considered apart (Chapter VI). Since all other cells are so much of a size, and since if they greatly exceed this size they divide in two, we conclude that there is something particularly satisfactory about it. We are not concerned for the moment with the mechanism of cell division, nor with what triggers off division at any particular instant, but rather with considerations of a general character which would lead us to expect cells to have sizes of the order of magnitude actually found.

A first reason for this size is that, in the absence of internal organs of circulation, cells must rely on molecular diffusion for the transport of the molecules of food-stuffs and oxygen and for the removal of the products of metabolism (CO_2 , NH_3 etc.). If this is to be efficient, granted the rates of diffusion of these molecules, the paths must be short or the inner parts of a cell will be starved or choked. Consider for a moment the growth of a spherical cell of radius R : the demands for food and for removal of excreta increase as the *volume*, i.e. the amount of material present, which is proportional to R^3 . The *surface*, through which substances enter or leave, increases as R^2 . For instance, when the cell's radius has increased three times, the volume is 27 (3^3) times as

large and the surface only 9 (3^2). It is clear that with such a disparity between the rate of growth of volume and surface a growing cell quickly runs into trouble and must do something or starve and suffocate. Among the great variety of cell shapes to be observed in organisms many are clearly solutions to this dilemma. The simplest solution is a change in shape, bringing all parts nearer to the surface. Cells may flatten, elongate, fold or adopt a convoluted outer surface as illustrated in Figure 1.3. The largest plant



$$\text{Volume} = \frac{4}{3} \pi R^3$$

$$\text{Surface area} = 4\pi R^2$$

Relation of volume and surface of a sphere

cells, as will be described in Chapter VI, develop a very large vacuole in the centre of the cell and press a thin layer of cytoplasm against the cell wall (see Figure 6.5, p. 92). Among Protozoa and the large plant-cells, means exist actually for stirring up

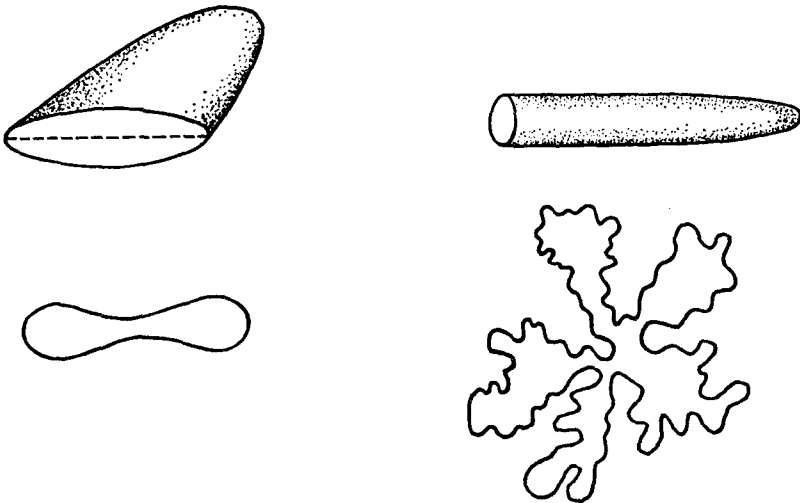


FIG. 1.3

Non-spherical cell shapes by means of which the diffusion path between the environment and the cell's interior may be shortened

the cytoplasm; and some large acellular fungi produce an intermittent mass flow of their contents. The adoption of such devices has led in some instances to the development of very large cells, so large indeed that the term 'non-cellular' may be preferred to emphasize the very different organization created.

Large size also raises difficulties over the strength required of the retaining membrane. The plasma membrane (thickness $\sim 70 \text{ \AA}$) may not be strong enough and is often strengthened by the secretion of a cuticle, pellicle or capsule.

Clearly, when we contemplate some of the forms shown in Figure 1.3, an easy way out is to continue the subdivision until separate smaller cells result, and so satisfactory is this solution that it is all but universally adopted. For the complex organism of many cells (Chapter III), a cellular organization also simplifies construction and maintenance. It offers a simple means of differentiation and of organ-construction; repair after damage is simplified too, since cells on the spot simply divide until the damage is made good, and processes involving the actual sacrifice of cellular units may be introduced.

A second reason for limiting size arises from the balanced relationship existing between nucleus and cytoplasm. As we shall see later, the nucleus supplies certain necessities to the cytoplasm, and conversely the nutritional and energy needs of the nucleus are supplied by the surrounding cytoplasm. Thus a balanced ratio of nucleocytoplasmic ratio is to be expected; once again the distance between the parts of the two partners must be such that diffusion is adequate to maintain communication. Growth throws this balance out.

The difficulty is met in some cells by introducing nuclear shapes like those shown in Figure 1.3 for whole cells; in others, by nuclear division; or again the whole may be stirred by cytoplasmic movements. Nevertheless, simultaneous nuclear and cytoplasmic division is the easiest way to restore the nucleocytoplasmic ratio.

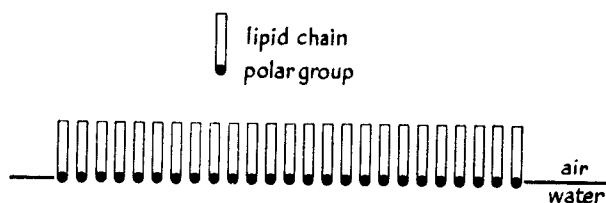
The cell membrane or plasma membrane

An important organelle of the cell is the plasma membrane, for without this retaining sheath, keeping its organelles together, the cell would not exist. Its strength may be supplemented by a cell wall or pellicle secreted *outside* the plasma membrane. Such coverings may also serve to give the cell a definite, non-spherical shape, whereas in their absence it would tend to a spherical shape like a drop of water. One of the primary distinctions between plant and animal cells rests on the nature and elaboration of the cell wall.

Chemical analysis of the cell sap of free cells reveals that it is of a fairly constant composition and different from the surrounding natural liquids; the cell membrane keeps these fluids of different composition from mixing. The intracellular fluid may differ markedly in the amounts of its several salts (salts of Na, Ca, Mg and K); usually there is much more potassium relative to sodium in cell sap than in sea water or pond water, for example. This suggests that the chemical reactions going on within the cell

function best in a medium of different salt composition from the usual surroundings of free cells, and shows that there must exist some special mechanism in cells whose function it is to maintain this difference against the tendency to diffusion. Here we have come upon one of the most fundamental characteristics of biological systems, the tendency to maintain a stable state. In general, cells and organisms composed of cells are found to have means of maintaining a constant composition and a constant internal environment in which their parts function best. This is the phenomenon of *homeostasis*. Cell division itself may be regarded as a homeostatic mechanism, the effect of which is to restore the nucleo/cytoplasmic balance thrown out by growth.

The first step towards the controlled environment begins, very logically, with the outside boundary of the cell, the cell membrane. This, experiment shows, is in effect a relatively watertight barrier, not unlike a thin film of oil, which water and substances easily soluble in water do not readily pass. Chemical analysis shows that the plasma membrane contains large amounts of *phospholipids*, complicated organic compounds containing phosphate and called lipids because they dissolve in fatty-type solvents (benzene, chloroform and the like) and not in water. Phospholipid molecules are long, and consist of a part with lipid properties and a group at one end with polar properties, i.e. with a tendency to dissolve in water. Molecules of this type tend to be absorbed at an air-water or water-oil interface because the polar end enters the water, and the lipid end the oil or air.



Such a preferred orientation favours the formation of surface films and, therefore, molecules of this kind are said to be *surface active*. In the absence of an air or oil phase, the molecules form swarms or micelles with their lipid groups turned inwards and their polar group in the water.

