CHAPTER ONE

The Cell as a Unit of Life

The cellular structure of living organisms has been a demonstrable fact for nearly a century and its discovery represents a definite landmark in the history of biology. Hitherto, the only unit of life had been the entire organism and the change in biological thought which is represented in the original Cell Theory[1] is comparable to the change produced in the physical sciences by the concept of the molecule as a unit of chemical structure. In both cases the establishment of a definable unit led automatically to greater precision of observation and of thought.

As a unit of structure the significance of the cell is obvious, for it enables us to define with accuracy the morphological origin and the microscopic structure of most living tissues. Throughout life the cell remains the unit of organisation just as the bricks remain the units of which a house is built. Each cell-unit has a fairly well-defined structure and although this may vary from the normal we can, without much difficulty, form a reasonable conception of a 'typical' cell; it is bounded by a cell membrane and it contains a nucleus embedded in a cytoplasmic matrix of a heterogeneous nature. The problems of classical cytology are largely concerned with intracellular structure and not, primarily, with the parts which individual cells play in the economy of the whole organism; in embryology the significance of the cell is clearly associated with the structure of the whole organism and the facts of cell lineage owe their origin to the conception of the cell as a fundamental unit. For such purposes the cell is essentially a static unit, whose structure we investigate or whose position in the organism can be rigorously determined.

As a physiological unit the rôle of the individual cell is not quite so clear. In the first place the cell is not a fundamental unit in the sense that any process of subdivision leads to a complete disor-

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[1] 'The body is composed entirely of cells and their products, the cell being the unit of structure and function and the primary agent of organisation' (Sharp, 1921, p. 7).

ganisation of its properties. An enucleated fragment of an amoeba, or of a sea urchin's egg is by no means dead, but retains for a considerable time typical properties of living matter; bacteria are alive, yet their structure is by no means similar to that of a typical cell; fungi are also alive, and yet they exhibit no cell structure in the strict sense of the word. Difficulties of this kind have perplexed cytologists for many years and are still real objections to the time-honoured Cell Theory. Further difficulties arise when it is suggested that a metazoön is to be regarded as a colony of cells in which each cell is a fundamental unit of function. Nearly every experimental biologist has declined to accept this view. Driesch's (1907) analysis of the part played by individual cells during the development of echinoderm eggs shows clearly that 'all attempts to depict the organism as an aggregate of cells have proved to be wrong'. The whole organism moulds the cells for its own ends, and its form is not predetermined by the position of the cells. Morgan (1898) showed that when a planarian is cut into fragments, regeneration to form new and complete individuals is effected by a remoulding of the original cells, and that no new cells are produced. Still more striking proof of the inadequacy of the cell as a fundamental unit is derived from Lillie's (1902) work on *Chaetopterus* larvae, where differentiation and development may occur without partition into discrete cells (fig. 1). The significance of these facts was at one time hotly debated (see Dobell, 1911) and although, to-day, our interests in cell-function are concerned with other problems, we must nevertheless be careful to avoid any tacit assumption that the cell is a natural, or even legitimate, unit of life and function.

From a mechanical point of view, cellular structure—or its equivalent—is essential, if life is to assume the forms which we actually find in Nature. Beyond a certain maximum size, a fragment of fluid protoplasm would be mechanically instable unless surrounded by a rigid envelope or endowed with a rigid internal skeleton. Those types of life which exist in the form of small drops or thin films are quite stable in the absence of cell walls—but if life is to exist in three dimensions some means must be found of affording sufficient rigidity to the mass without reducing its flexibility to a very low level. Two alternatives are available: either the protoplasmic mass can be enclosed within a rigid envelope or it must acquire an internal skeleton. The possibilities of a rigid external shell are clearly limited, whereas the existence of flexible and elastic cell walls provides the mechanical properties requisite for life in an almost infinite variety of form. A reasonable analogy is provided by a system of soap bubbles: the form of a single large soap bubble is strictly limited—whereas a large number of small bubbles adhering together can acquire, on the surface of a washtub, sufficient rigidity to endow the whole aggregate with a variety of stable forms. Cellular structure is, teleologically, a mechanical necessity for life in large and varied forms. From this point of view the cell as a unit of life is both unnecessary and unsatisfactory—it is merely the unit of mechanical stability. The real unit of life must be of a protoplasmic nature irrespective of whether it is subdivided to form a mechanically stable system or not: in other words, cellular structure is not in itself of primary significance. If we take a biologically heterogeneous system of growing protoplasm and proceed to a process of internal subdivision there may come a time when each phase of the system will be separated from the others by cell walls. At this stage each cell will represent a natural protoplasmic unit—but before this stage is reached the only real unit available is one which is expressed in terms independent of the process of subdivision. There can be little doubt that the most natural unit of life is the living organism, and

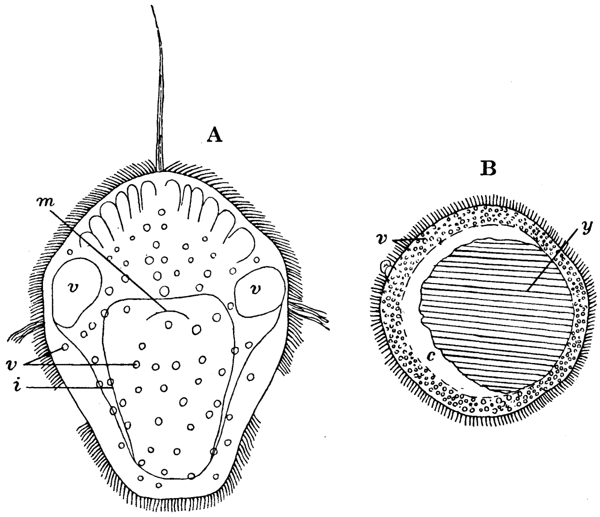

Fig. 1. Differentiation without segmentation. *A*, a normal trochophore of *Chaetopterus*, 24 hours old; *B*, a trochophore from an unfertilised egg treated with potassium chloride, 23 hours old; note the ciliation of the surface. *v*, vacuole; *y*, yolk. (Lillie, 1902.)

when we find, in some cases, that its constituent cells are united by intercellular processes it is impossible to admit the validity of the cell unit without further enquiry.

On the other hand, there can be no doubt that the cell often forms a convenient physiological unit even if its individuality is not so fundamental as is sometimes supposed. Each living cell possesses, structurally, the essential machinery for independent existence; each cell normally has a nucleus and is chemically and physically in equilibrium with its environment by means of its surface membranes. Much of the work on the physiology of the cell has been performed on red blood corpuscles, or egg cells, which are normally isolated units, and some caution is necessary when we attempt to apply these results to the cells which form parts of whole organisms or whole tissues.

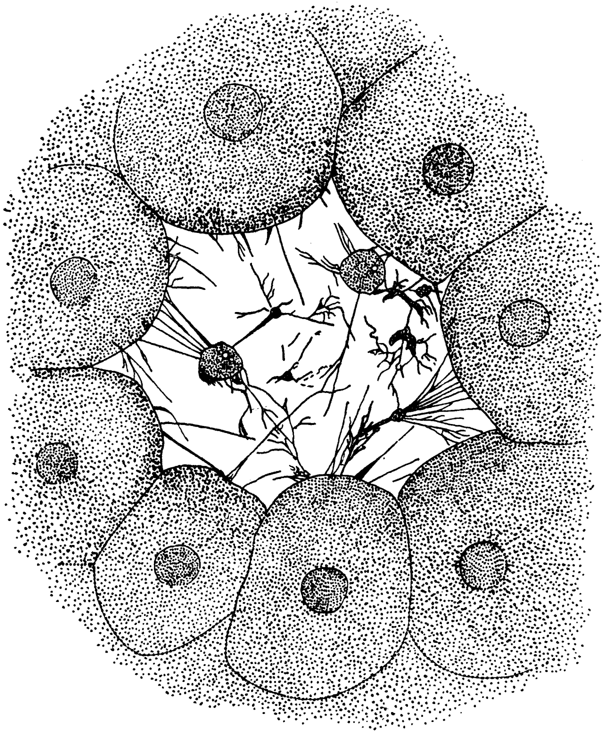

Fig. 2. Protoplasmic bridges between blastomeres of a young *Asterias* blastula (from Andrews).

In other ways the cell is a convenient unit, for by its use we limit the heterogeneity of the material with which we work. A single muscle fibre or a single nerve cell enables us to analyse phenomena which are masked or rendered more complex in a muscle-nerve preparation. In cell physiology we are, in fact, attempting to dissemble the machinery of an organism into its simplest component parts. When we know how each of these works in an isolated state we shall be ready to integrate the data and gain some conception of the whole organism. It is as a convenient unit of functional activity that the cell will be regarded in this book. That we cannot thereby obtain an adequate picture of all vital activities will be only too obvious, but even a cursory summary of recent physiological work will show a growing need for a precise knowledge of intracellular processes. When the organism as a whole establishes with its environment an equilibrium of profound biological significance, it does so by the machinery of its individual cells; these equilibria are seldom detectible by the statical methods of cell morphology—they are, however, detectible by experimental methods. Finally, it is from a study of the cell that we can begin to build up a conception of living matter which can be expressed to some extent in the units which have been found to be applicable to inanimate matter.

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CHAPTER TWO

The Cell as a Physical Unit

A conception of the living cell as a dynamic unit can be reached from two points of view. We may either consider the relationship of cell structures to the phenomena of heredity and development, or we may regard cell structure as a molecular system, whose dynamic properties must be elucidated before we can gain any fundamental knowledge of cell function. As long as we are concerned with the mechanism of development, the units and methods which are employed are essentially biological. If, however, we are primarily interested in the non-reproductive aspects of cell activity we consciously or unconsciously attempt to use the methods and the units which are known to apply with great effectiveness to the study of particular types of inanimate systems. In other words, we attempt to define the structure and behaviour of living cells in terms of physical chemistry. The methods employed in this book frankly involve the validity of this point of view, but, before we proceed to investigate the structure and function of the cell in a mechanistic and material way, it is desirable to consider two fundamental problems which are always present, however carefully they may be disguised. Firstly, how far is it axiomatic that physical and chemical laws will apply to living organisms? Secondly, how far are populations of living units or cells really comparable to molecular systems?

When we regard the cell as a physico-chemical system we imply that the laws which govern physical and chemical systems will apply equally well to matter which is organised into the 'living' state. In one sense this may be true, but it does not follow from the nature of things, and it is a concession which can readily be abused.

Many of the fundamental laws of physical chemistry can be stated as corollaries to the kinetic theory of matter, or at any rate on this foundation they can be expressed in a concrete form. Precise and accurate as these laws appear to be in practice, they are often not statements of infallible truth (see p. 14); they are, on the other hand, expressions whose truth has such a high degree of probability that any other possibility may, for all practical purposes, be ignored. Before we apply these laws to the living cell we ought, so far as is possible, to satisfy ourselves that there is nothing in living matter which is likely to decrease this degree of probability or which may bring other possibilities within the realm of practical observation. For the present purpose, natural laws may be divided into two categories. Firstly, there are laws which define the properties of matter in mass or in systems containing a very large number of molecules. Secondly, there are laws which define the properties of single molecules, and which are not directly concerned with the behaviour of neighbouring molecules.

The application of statistical laws to biological problems assumes that a very large number of participating units are invariably present and that we can safely ignore the behaviour of each unit as such. If these fundamental units are molecules of water or even of proteins the use of statistical laws is almost certainly justified, for even very small cells contain many millions of molecular units (see p. 9). It is, however, by no means certain that biological processes only involve reactions which depend on large numbers of individual molecules and do not involve those which depend upon comparatively small numbers of larger aggregates. Even within inanimate colloidal systems the statistical laws break down when we deal with units which are no larger than typical living cells. Using a suspension of gold particles, whose average radius was 19 $\mu\mu$, Smoluchowski (see Svedberg, 1928) found that within a volume of the suspension equal to 1064 μ^3 (i.e. the approximate volume of many living cells) there was an *average* number of particles equal to 1·545. When this small volume of suspension was examined from time to time, however, the actual number of particles visible varied very considerably—sometimes no particles were visible, at other times as many as seven could be seen. This variation is, of course, due to random Brownian movement. Table I records the results of 518 successive observations. Out of a total of 518 observations, there were 168 occasions when one particle was present, 130 when two particles were present, and only one when seven were present. Instead of expressing these phenomena in terms of the relative frequency of particular states of distribution, we can express them in terms of the average time which elapses before a given state is spontaneously reformed by random movement of the particles. Thus in another case described by Svedberg, seven gold particles occurred on the average every 28 minutes when observations were made at the rate of 39 per

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minute. From these and other data the time interval between two corresponding states can be calculated—thus three particles are present every 2 seconds, or 17 particles once in 50,000 years. During the whole of the observations the *average* number of particles present (in $1064\mu^3$) over a long period of time is unchanged and is identical with that of the mass of the suspension (viz. 1·55).

A similar line of reasoning shows that if we start with a 1 per cent. difference in pressure of a gas on the two sides of a porous partition (see p. 14) and allow equilibrium to be established, we can nevertheless expect to find the original 1 per cent. difference of pressure to be spontaneously regained after an interval of $10^{10^{10}}$ years, if the volume of gas on each side of the partition is 0·5 c.c.

Table I

No. of particles present	No. of observations	Frequency of distribution	
		Obs.	Calc.
0	112	0·216	0·212
1	168	0·324	0·328
2	130	0·251	0·253
3	69	0·133	0·130
4	32	0·062	0·050
5	5	0·010	0·016
6	1	0·002	0·004
7	1	0·002	0·001

Quite clearly the degree of statistical variation which will occur in molecular systems depends largely on the magnitude of the system examined. If we examined 1 c.c. of the gold suspension the amount of variation would be relatively small: if we use a volume of $10\mu^3$ it will be very large indeed. As long as we are dealing with large systems, any significant variation in the distribution of matter or energy occurs for such short periods of time or on so very few occasions, that we are justified in ignoring any state other than the one which is the most probable. In other words, in large systems the statistical possibilities postulated by the kinetic theory of matter are arbitrarily eliminated by assuming the truth of the Second Law of Thermodynamics (see p. 14).

At this point the argument bears directly on biological problems. Are we justified in assuming that the essential events which occur within a living system can be regarded as those which are the most probable from a thermodynamical point of view and which will therefore conform to statistical laws? If our living systems are large, and clearly involve a very large number of molecular or physiological units, we should expect to find that the average states of these systems conform to laws applicable to non-living systems in mass: the second law of thermodynamics would hold good, together with its corollaries the laws of mass action, diffusion, osmotic pressure and the gas laws. Accepting the absolute weight of a single atom of hydrogen as $1{\cdot}63 \times 10^{-24}$ gr., Cameron (1929) gives the following molecular composition for the average mammalian red blood corpuscle. (Table II.)

Table II

Cell constituent	Estimated number of molecules per cell $\times 10^6$
Water	980,000
Haemoglobin ...	300
Phosphatide (*lecithin*)	300
Cholesterol	230
Glucose	295
Urea	295
Glutathione	58
Creatin	26
Uric acid	7
Potassium	6,300
Magnesium	2,800
Chlorine	70

The figures suggest that even within a cell much smaller than the red blood corpuscle (e.g. *Bacillus coli*) there are many thousands of millions of molecules. As long as each molecule is an individual unit the laws of mass action can safely be applied. It is by no means impossible, however, that the essential units of living matter are each composed of a very large number of molecules and under such circumstances the number of units present may be reduced to a figure which will materially affect the validity of statistical laws. The maximum size of an ultrafilterable virus cannot be greater than 20 $\mu\mu$, and the thickness of protoplasmic films is often only a fraction of a micron. If we are to apply physico-chemical laws to the events which occur within these small systems we must be careful not to stress unduly those laws which deal only with the statistically averaged states of much larger populations. In other words, we are probably not justified in assuming the validity of the second law of thermodynamics without careful scrutiny.

The problem arises in a somewhat different form when we are concerned with larger types of living matter. A small sea urchin's egg has an approximate volume of 125,000 μ^3. If the cell is dead, substances in solution distribute themselves within the egg in accordance with those laws which govern inanimate systems in mass, and we have no reason to doubt the validity of the second law of thermodynamics. As long as the cell is alive, however, the protoplasm, although apparently of a liquid nature, must be regarded as the seat of a definite structure (see Chapter V) wherein events which occur after death do not occur during life and *vice versa*. We can look upon the cell system from two points of view. Firstly, we can assume that all the essential units are present in large numbers, and that when left to themselves they will distribute themselves in accordance with the kinetic theory of matter; we may also assume that the 'living' state is definable by the average state of the whole system. If these postulates are reasonable, we should expect the cell to obey the second law of thermodynamics, and we should be justified in applying the laws of mass action to intracellular processes. One way of testing this hypothesis might be to demonstrate that the living cell is unable to absorb heat from surroundings which are at the same temperature as itself, and use this energy for maintaining vital activity. Unfortunately any direct test of this type is technically impossible owing to the intrinsic properties of living matter. As A. V. Hill (1924) remarks, 'What would a student of thermodynamics say if his machine had perforce to have food and drink and oxygen to prevent it from collapsing whilst he put it hurriedly through its Carnot cycle? How pleased would he be with an elastic body which had one set of properties at one moment, another set at another? What accuracy would he attain if his membranes began to leak as soon as he deprived them momentarily of oxygen?' Having failed to find any positive evidence to support the application of the second law to biological systems, we have to consider how far its application is useful as a working hypothesis. Here we are on firmer ground. If we assume the validity of statistical laws, the analysis of living organisms by physico-chemical methods is greatly simplified, since, under these circumstances, the conversion of energy from one form into another within the cell must conform to those limitations which are applicable to inanimate