INTRODUCTORY MEDICINAL CHEMISTRY

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CHAPTER 3

The Pharmacokinetic Phase

The passage of a drug from its point of entry into the body until it reaches its site of action is covered by the pharmacokinetic phase. During this journey the drug will encounter many tissues which need to be entered and numerous membranes which need to be traversed. It is thus necessary to consider the structures of these membranes which are ubiquitous in tissues and, further, the structure of the fundamental building block of the body, the cell. From the structural features of the cell, and its means of assimilating materials, can be derived the physico-chemical properties of a drug desirable for passage through membranes. This knowledge can then be used to attempt to quantitatively relate the biological activity of a series of molecules to their chemical structures. Such relationships, especially their predictive uses, have occupied the dreams and ambitions of all medicinal chemists who desire to change the reliance of their art on serendipity to that of a logical science.

3.1 THE CELL

The cell is the fundamental building block of all independently viable forms of life. The cell may be described as being a unit of biological activity contained within a semi-permeable membrane and capable of self-reproduction in a medium free from other living systems. Thus the lowest forms of life on this earth consist of simple cells, which are capable of performing all essential functions, for example, ingestion of food, excretion of waste materials and reproduction, necessary to maintain their viability. Whilst numerous unicellular organisms thrive, such systems are very much at the mercy of the external environment, particularly its pH, temperature and ionic strength, over which they can have little control.

Grouping together individual cells to produce a multi-cellular organism has a number of advantages. It is no longer necessary for all cells to be able to constituent cells can be more easily controlled and maintained separately from the external environment. A major disadvantage of co-operative units is that damage in a section of the organism can affect the whole organism, but despite this, multi-cellular organisms have reached some very sophisticated levels.

An idea of the complexity achieved can be envisaged in the human body which contains an estimated 10^{14} different types of cell ranging in size from that of nerve cells which can be 0.5–1 m in length to the red blood cell which has a diameter of 7 μm.

It is perhaps useful at this stage, especially for organic chemists accustomed to thinking in molecular terms, to give an approximate idea of the scales involved (Fig. 3.1). A simple amino-acid with a molecular weight of approximately 200 has a radius of 0.5 nm, whilst a small macromolecule, for example, egg albumin,

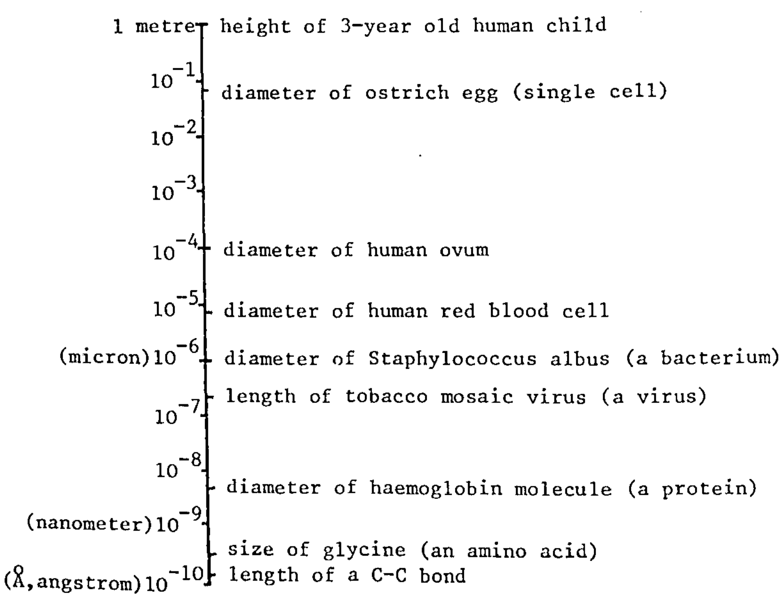

Fig. 3.1 – Scale of sizes in the biological world.

has a radius of 4 nm. A large macromolecule, the haemoglobin molecule, has a radius of 12 nm, whilst the smallest unicellular bacteria are some ten times larger than this. As seen in the table, some viruses are even smaller than this but as viruses can only reproduce inside a host cell, they are differentiated from cells.

Using one of the smallest bacteria, Dialester pneumosintes, which has the dimensions 0.5 × 0.5 × 1.0 μm, it is possible to calculate from its material average molecular weight of 40,000. Thus, ignoring the presence of any non-enzymatic proteins, this would mean that the cell is capable of performing some 800 enzymatic reactions. It seems that a basic minimum of reactions necessary to maintain a functioning living cell is between 500 and 1000. The lower limit to cell size is therefore set by the physical requirement of the volume needed to contain sufficient enzymes to catalyse these reactions.

At the other end of the scale the upper limit to cell size is set by other considerations. A bird or reptile egg just after being laid is essentially a very large single cell. This is because the egg has to contain all the food necessary to maintain the developing embryo, but once the embryo starts to develop the cell is no longer unicellular. Within the body the upper size limit is controlled by the fact that, somehow, by processes not yet understood, the nucleus of the cell controls the whole activity of the cell. When the cell becomes too big this process becomes very inefficient. Cells exist because they exchange nutrients and waste materials with their environment through their membrane. As a cell gets bigger the ratio of surface area to volume falls rapidly and it becomes more difficult for the cell to obtain its nutrient supplies. In some cells this difficulty is overcome by the cell surface becoming deeply invaginated, essentially to increase the area, and in others by the cells becoming very long and thin.

Thus the size of the cell needs to be sufficient to contain all the elements required to maintain viability, but not so large that its functioning becomes inefficient. The balance between these two considerations results in most cells having sizes in the range 1–20 μm.

It was stated earlier that an advantage for multi-cellular organisms is that certain cells can become specialised. A result of this specialisation is that the overall shapes and sizes of the cells can vary and this is certainly the case in the human body (Fig. 3.2). The cells of the gut, kidney and liver all have deeply invaginated surfaces, called microvilli, which give the cells enormous surface areas. One of the major functions of these cells is to absorb materials from their surrounding media, notably blood or intracellular fluids, and a large surface area will greatly facilitate this process. Muscle cells, on the other hand, spend their lives expanding and contracting and are, therefore, long, relatively thin, and packed with fibrils which govern their change in length. Nerve cells control the activity of the body in the transmission of electric messages. Thus, they consist of a central body with extremely long arms known as axons, which are covered with a myelin sheath to insulate them, rather as the rubber covering insulates electrical cables. The myelin sheath is designed to be highly impenetrable to ions and other materials but to facilitate rapid electrical conduction. The arteries and veins of the body are made up of tough smooth muscle cells which facilitate the blood circulation, but the walls of the capillaries are only a single cell thick to allow ready transfer of gases, nutrients and drugs between the blood and the body tissues. Thus the shape and sizes of the millions of cells in the body vary

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