Adaptation and homeostasis are the two fundamental features of living organisms. Simple forms of life (e.g. bacteria) can survive over a wide range of temperature and can adapt themselves to the changes in the environment and to food stuffs available. Adaptation of man to environments varying from a desert to arctic conditions or adaptation of pupil to varying degree of illumination (Fig. 2.2) are some of such examples. However, most of the physiological responses are directed towards preservation of constant physical and chemical internal environment (milieu interieur). Maintenance of a stable internal environment is called homeostasis. The subject of physiology is devoted to the mechanisms which help in homeostasis. Failure of homeostatic mechanism results in disturbed body function known as disease.

HOMEOSTATIC MECHANISMS

As mentioned above, various physiological or pathological processes tend to disturb one or more components of extracellular fluid. The disturbance sets into motion a series of physiological responses that eliminate the disturbing factor and normalize the composition of extracellular fluid (Fig. 2.3). The homeostatic mechanisms allow an organism to function effectively in a broad range of environmental conditions.

All homeostatic mechanisms have at least three components (Fig. 2.4):

1. Receptor that detects a change in the internal environment and sends information to the control center.
2. Control center is the structure that evaluates the disturbance and activates the correcting mechanisms.
3. Effector is the structure that carries out the corrective responses as directed by the control center.

For example, exposure to cold tends to lower the body temperature. The change in body temperature is detected by cold thermal receptors (receptor). The information is communicated to the temperature-regulating areas of hypothalamus in the brain (center). The body responds by involuntary contractions of skeletal muscle called shivering (effector). Shivering generates heat and prevents a fall in body temperature. Exposure to hot environment tends to raise body temperature. The change in body temperature is detected by warmth thermal receptors (receptor). The information is communicated to the temperature-regulating areas of hypothalamus in the brain (center). The body responds by sweating that results in heat loss by evaporation (effector). This is an example of body temperature homeostasis.

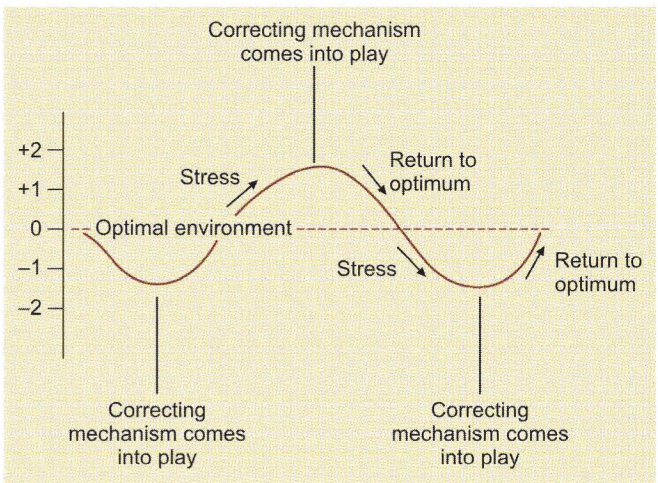

Fig. 2.3: Basic homeostatic mechanism.

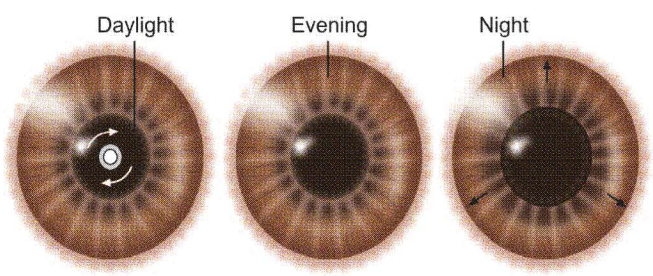

Fig. 2.2: Pupillary adaptation to varying degree of illumination.

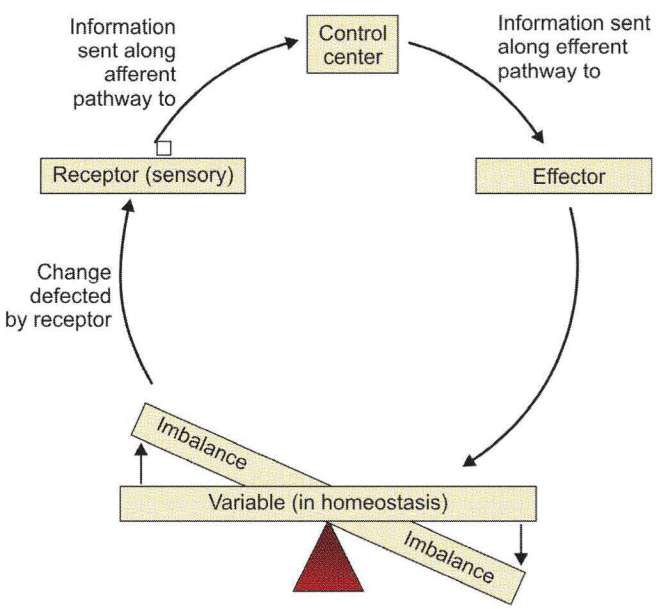

Fig. 2.4: Components of homeostatic mechanisms.

3

to enter the cell, i.e. into ICF, whereas molecule D remains within ECF.

Although individual molecules move at very high velocity, the number of collisions they undergo prevents them from travelling very far. If the concentration of the solute molecules on the two sides of the cell membrane is similar, some molecules would enter the cell and a similar number is likely to leave it at any given moment, i.e. the net flux of the molecules is zero. Net movement of the solute molecules would occur only if concentration of molecules on one side of the membrane is greater than the concentration on the other side. In Fig. 3.4, the net movement of molecules of solute occurs from the left to the right chamber till equilibrium is reached. Thus diffusion always occurs down the electrochemical gradient, i.e. from an area of high concentration to an area of low concentration of the molecules (downhill transport). This phenomenon is called *simple diffusion*. In *carrier-mediated diffusion*, though diffusion occurs down the gradient, it occurs with the help of a protein molecule located in the cell membrane called a carrier or a carrier protein (Fig. 3.5.).

Simple Diffusion

As explained above, simple diffusion means diffusion of molecules or ions through a membrane without the help of any carrier protein. The rate of diffusion is proportionate to (i) the difference in the concentration of the substance across the membrane (concentration gradient or chemical gradient), (ii) cross-sectional area of the membrane through which diffusion takes place, and (iii) inversely proportionate to the thickness of diffusion membrane. Electrical gradient causes diffusion of ions. Positively charged ions move towards an area with negative charge. Besides the physical factors mentioned above, diffusion across biological membranes is affected by permeability of the membrane to a particular substance, depending upon its lipid solubility, as well as, specific and selective permeability of the membrane for different molecules. These factors shall now be discussed.

Diffusion of Lipid-soluble Substances

The extracellular and intracellular fluids are composed of water and water-soluble substances. The lipid bilayer of the cell membrane forms a barrier for the diffusion of water-soluble substances. However, lipids and lipid-soluble substances, such as O_2, N_2, *alcohol* and *steroids*, can diffuse across the membrane with great ease. Lipid solubility of a substance is, therefore, one of the determinants of the rate of diffusion across the biological membranes.

Diffusion of Water and Water-soluble Substances

In spite of the presence of lipid bilayer, water and many water-soluble substances diffuse across the cell membrane relatively easily, though not as fast as lipid-soluble substances. The diffusion of water is extremely rapid. The diffusion of water-soluble substances, like urea, glucose, Na^+, K^+, etc., is inversely proportionate to their molecular size. From these observations, it was postulated that the cell membrane contains pores of approximately 0.8 nm diameter. However, recent investigations have revealed that there are no such pores in the cell membrane. Instead, there are large *protein* molecules dispersed among the lipid molecules of the cell membrane which act as *channels* for the diffusion of water and water-soluble substances. The size of the molecules or ions is not the only factor determining their diffusion through these protein channels. Selective permeability and "gating" of these channels further regulate the rate of diffusion.

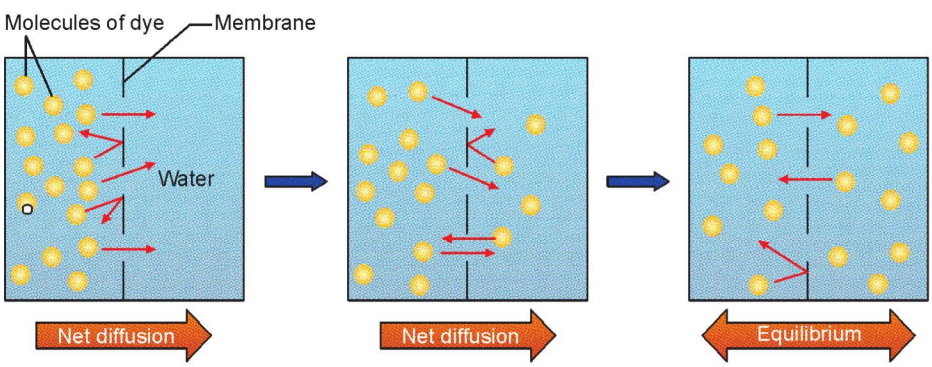

Fig. 3.4: Direction of net movement in diffusion is always down the gradient.

for secondary active transport of molecules such as glucose, amino acids, etc. (see below)

3. The sodium/potassium gradient across the membrane is partially responsible for the resting membrane potential across nerve and muscle membranes.
4. In excitable tissues, such as neuron, skeletal muscle and cardiac muscle, the sodium pump reestablishes the electrical potential across the plasma membrane following excitation-induced depolarization (action potential).
5. It has an important role in regulating cytoplasmic pH and Ca^{2+} levels through the Na^+/H^+ and Na^+/Ca^{2+}exchangers, respectively.
6. The extrusion of sodium is important to reduce the osmotic inflow of water into the cell and regulation of cell volume.
7. The function of the pump in absorption of Na^+ in the intestine or reabsorption in the kidney requires tight regulation of the enzyme in the respective organs to maintain normal levels of Na^+ and K^+ during altered salt intake.
8. Because water and Na^+ transport across epithelia are invariably linked, the work of the sodium pump is also critical to water absorption in the intestine and reabsorption in the kidney.

Secondary Active Transport of Molecules

The uphill transport (against the gradient) of many substances occurs without direct utilization of ATP by the transport protein. This phenomenon is called secondary active transport. Glucose and amino acids are transported across the luminal membrane of the intestinal mucosal cells by secondary active transport (Fig. 3.14). In the mucosal epithelial cell, the Na^+–K^+ pump operates at the *basolateral border* of the cell and maintains intracellular concentration of Na^+ very low (a primary active transport phenomenon). *Luminal border* of the cell contains cotransport protein for facilitated diffusion of Na^+ as well as glucose. Since the intracellular Na^+ concentration is low, the facilitated diffusion of Na^+ is so powerful that glucose can be transported even when intracellular glucose concentration is higher than the intraluminal glucose concentration. In other words, downhill Na^+ transport at the luminal border of the cell leads to uphill glucose transport because both the molecules share a common transport system. The Na^+–K^+ cotransporter does not use ATP. Since glucose transport is secondary to the active Na^+–K^+ transport, it is named secondary active transport (Fig. 3.14).

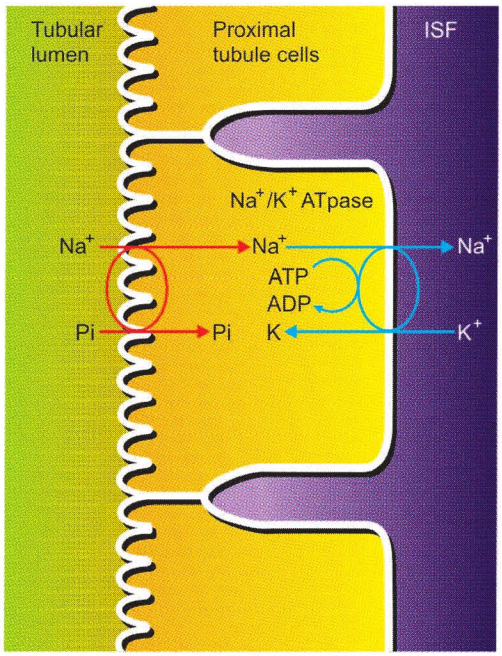

Fig. 3.14: Absorption of glucose molecule (Pi) in the renal tubules by secondary active transport. ISF = interstitial fluid.

Transport of amino acids in the intestine, or renal tubular cells is also by secondary active transport. Of course, different transport proteins are involved in this case. Secondary active transport proteins may act as antiport. For example, Na^+ is exchanged for K^+ or H^+ in the renal tubular cells or for calcium ion in the myocardial cells.

The Calcium Pump

The intracellular Ca^{2+} concentration is about 10,000 times less than that of extracellular fluid. Such low Ca^{2+} concentration is maintained by two calcium pumps. One of the calcium pumps extrudes Ca^{2+} out of the cell, whereas the other pumps cytoplasmic calcium into one or more of the cellular organelles like cytoplasmic reticulum of the muscle cells or mitochondria in all other cells. The carrier protein of both these Ca^{2+} pumps has ATPase activity. But the difference from the Na^+–K^+ pump is that the carrier protein binds Na^+ and Ca^{2+} rather than Na^+ and K^+.

Transport of Macromolecules—Vesicular Transport: Endocytosis and Exocytosis

Macromolecules, such as large protein molecules, cannot pass through the cell membrane by diffusion or active transport mechanism. They are transported into or out of the cells by a different *energy-consuming*

the NADH-methemoglobin reductase present in the red cells. Methemoglobinemia occurs only when this enzyme system is overwhelmed by oxidizing drugs.

iii. *Carboxyhemoglobin*

Inhalation of carbon monoxide (CO) causes attachment of CO at the sixth covalent bond, (where O_2 is normally attached). The product is called carboxyhemoglobin. Since the affinity of Fe^{2+} to CO is 200 times stronger than that for O_2, carboxyhemoglobin cannot take part in O_2 transport leading to hypoxia. (For further details *see* Chapter 20)

Methemoglobin and carboxyhemoglobin are formed by alterations in the heme component and can be reconverted to normal hemoglobin by administration of reducing agents, like methylene blue (or ascorbic acid) and inhalation of pure oxygen, respectively. The presence of carboxyhemoglobin or methemoglobin can be easily detected by spectroscopic examination of blood.

GENETIC (INHERITED) DEFECTS OF HEMOGLOBIN SYNTHESIS

The red cells of certain individuals contain abnormal types of hemoglobin due to *genetically determined abnormalities* in the polypeptide chains of the globin component. These disorders include:

a. Thalassemia

In this genetic disorder, there is a *decrease or absence of α or β chains* of hemoglobin A. β thalassemia is characterized by deficiency of β chain synthesis, whereas α thalassemia is characterized by deficiency of α chain synthesis. Consequently, the red cells contain excess of the other type of globin chains. Such red cells have a shorter lifespan than the normal red cells that lead to severe anemia. In β-thalassemia, the concentration of HbA2 is greater than normal.

b. Hemoglobinopathies

Hemoglobinopathy is a kind of genetic defect that results in *abnormal structure* of one of the globin chains of the hemoglobin molecule.

Hemoglobin S

This type of hemoglobinopathy is caused by the presence of amino acid valine instead of glutamic acid at position 6 in the β chain. Such hemoglobin is known as hemoglobin S (HbS), because, in deoxygenated form it becomes much less soluble making the red cells sickle-shaped (Fig. 4.6). Sickle-shaped cells are more prone to rapid destruction (hemolysis) resulting in (hemolytic) anemia.

Hemoglobin S is highly prevalent in black population of Africa. *Sickle cell anemia* occurs only in those individuals who are homozygous for hemoglobin S gene, that is, whose red cells contain only hemoglobin S. Children with sickle cell anemia die young. *Sickle cell trait* is far more common disorder. In certain areas, as much as 40% of the population has sickle cells trait. These individuals are heterozygous for hemoglobins gene, that is, their red cells contain hemoglobin S (50%) as well as hemoglobin A (50%). Persons with sickle cell trait do not suffer from excessive hemolysis of red cell. On the other hand, they are highly resistant to a very dangerous type of malaria (falciparum type) prevalent in those areas.

There are some other types of congenitally defective hemoglobins, e.g. HbC, HbE, HbG, etc. Hemoglobinopathies can be diagnosed accurately by electrophoresis.

HEMOPOIESIS

In the early fetal life, hemopoiesis (formation of blood cells) occurs intravascularly by proliferation of endothelial cells of the capillaries. Next, hemopoiesis occurs in the liver and spleen of the fetus. By the end of 4th month of fetal life, the bone marrow takes over the function of hemopoiesis. In children, blood formation occurs in the marrow cavities of most of

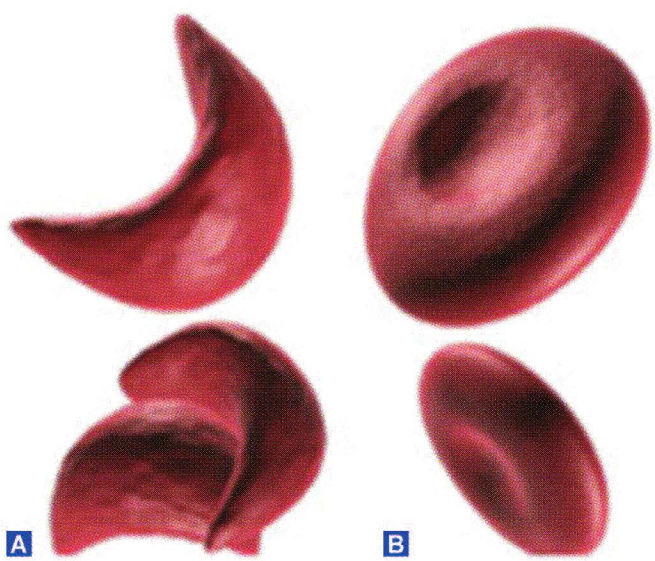

Fig. 4.6: Sickled cells **A**, as compared to normal red cells **B**.