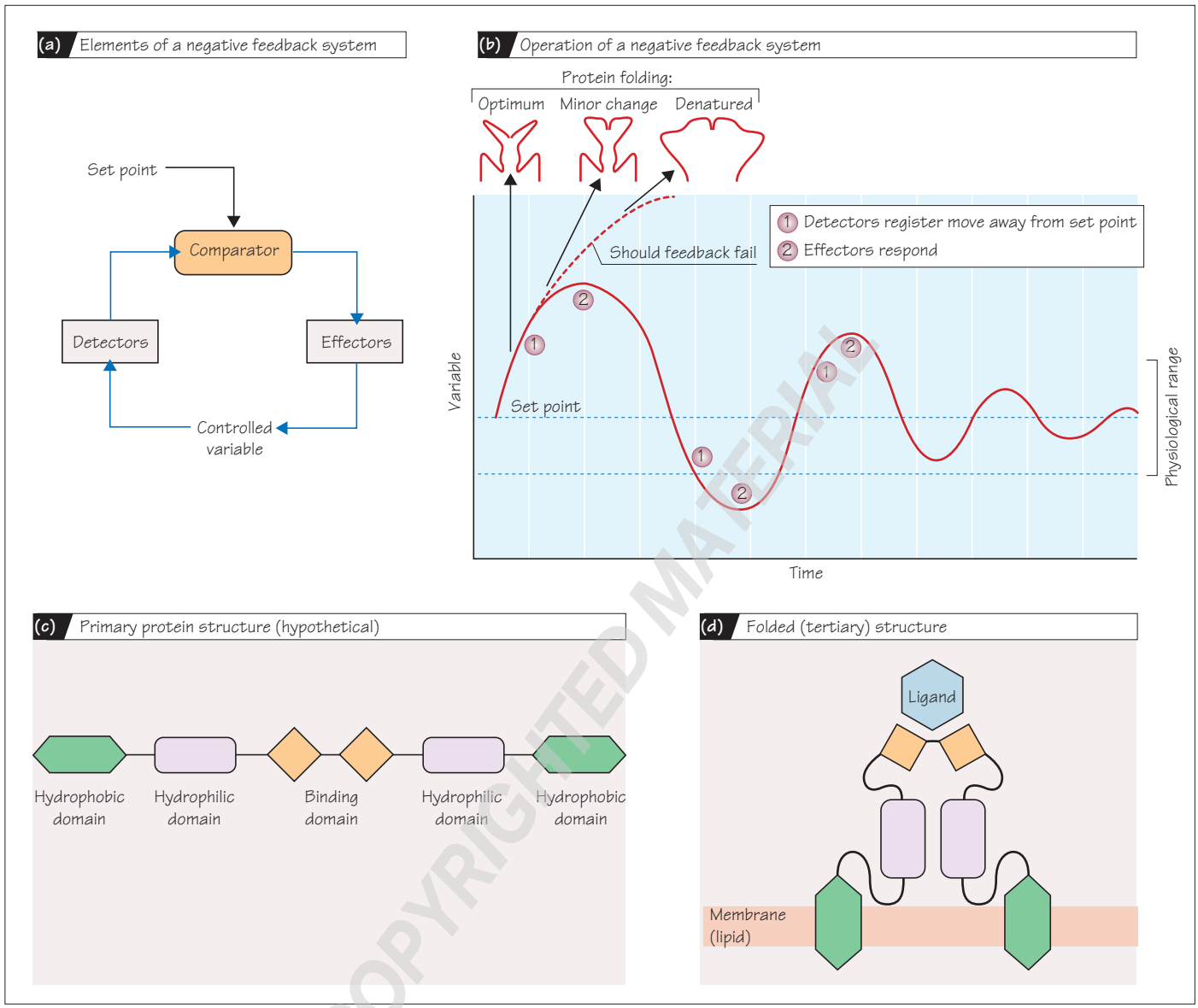
1 Homeostasis and the physiology of proteins



Claude Bernard (1813–1878) first described 'le mileau intérieur' and observed that the internal environment of the body remained remarkably constant (or in equilibrium) despite the ever changing external environment. The term **homeostasis** was not used until 1929 when **Walter Cannon** first used it to describe this ability of physiological systems to maintain conditions within the body in a relatively constant state of equilibrium. It is arguably the most important concept in physiology.

Homeostasis is Greek for 'staying the same'. However, this so-called **equilibrium** is not an unchanging state but is a dynamic state of equilibrium causing a **dynamic constancy** of the internal environment. This **dynamic constancy** arises from the variable responses caused by changes in the external environment. Homeostasis maintains most physiological systems and examples are seen throughout this book. The way in which the body maintains the H^+ ion concentration of body fluids within narrow limits, the control of blood glucose

Physiology at a Glance, Third Edition. Jeremy P.T. Ward and Roger W.A. Linden.

by the release of insulin, and the control of body temperature, heart rate and blood pressure are all examples of homeostasis. The human body has literally thousands of control systems. The most intricate are genetic control systems that operate in all cells to control intracellular function as well as all extracellular functions. Many others operate within organs to control their function; others operate throughout the body to control interaction between organs. As long as conditions are maintained within the normal physiological range within the internal environment, the cells of the body continue to live and function properly. Each cell benefits from homeostasis and in turn, each cell contributes its share towards the maintenance of homeostasis. This reciprocal interplay provides continuity of life until one or more functional systems lose their ability to contribute their share. Moderate dysfunction of homeostasis leads to sickness and disease, and extreme dysfunction of homeostasis leads to death.

Negative feedback control

Most physiological control mechanisms have a common basic structure. The factor that is being controlled is called the **variable.** Homeostatic mechanisms provide the tight regulation of *all* physiological variables and the most common type of regulation is by ***negative* feedback**. A negative feedback system (Fig. 1a) comprises: **detectors** (often neural **receptor cells**) to measure the variable in question; a **comparator** (usually a neural assembly in the central nervous system) to receive input from the detectors and compare the size of the signal against the desired level of the variable (the **set point**); and **effectors** (muscular and/or glandular tissue) that are activated by the comparator to restore the variable to its set point. The term 'negative feedback' comes from the fact that the effectors always act to move the variable in the opposite direction to the change that was originally detected. Thus, when the partial pressure of CO_2 in blood increases above 40 mmHg, brain stem mechanisms increase the rate of ventilation to clear the excess gas, and vice versa when CO_2 levels fall below 40 mmHg (Chapter 29). The term 'set point' implies that there is a single optimum value for each physiological variable; however, there is some tolerance in all physiological systems and the set point is actually a narrow *range* of values within which physiological processes will work normally (Fig. 1b). Not only is the set point not a point, but it can be reset in some systems according to physiological requirements. For instance, at high altitude, the low partial pressure of O_2 in inspired air causes the ventilation rate to increase. Initially, this effect is limited due to the loss of CO_2, but, after 2–3 days, the brain stem lowers the set point for CO_2 control and allows ventilation to increase further, a process known as **acclimatization**.

A common operational feature of all negative feedback systems is that they induce oscillations in the variable that they control (Fig. 1b). The reason for this is that it takes time for a system to detect and respond to a change in a variable. This delay means that feedback control always causes the variable to overshoot the set point slightly, activating the opposite restorative mechanism to induce a smaller overshoot in that direction, until the oscillations fall within the range of values that are optimal for physiological function. Normally, such oscillations have little visible effect. However, if unusually long delays are introduced into a system, the oscillations can become extreme. Patients with congestive heart failure sometimes show a condition known as **Cheyne–Stokes' breathing**, in which the patient undergoes periods of deep breathing interspersed with periods of no breathing at all (**apnoea**). This is partly due to the slow flow of blood from the lungs to the brain, which causes a large delay in the detection of blood levels of CO_2.

Some physiological responses use ***positive* feedback**, causing rapid amplification. Examples include initiation of an action potential, where sodium entry causes depolarization which further increases sodium entry and thus more depolarization (Chapter 5), and certain hormonal changes, particularly in reproduction (Chapter 50). Positive feedback is inherently unstable, and requires some mechanism to break the feedback loop and stop the process, such as time-dependent inactivation of sodium channels in the first example and the birth of the child in the second.

Protein form and function are protected by homeostatic mechanisms

The homeostatic mechanisms that are described in detail throughout this book have evolved to protect the integrity of the protein products of gene translation. Normal functioning of proteins is essential for life, and usually requires binding to other molecules, including other proteins. The specificity of this binding is determined by the three-dimensional shape of the protein. The **primary structure** of a protein is determined by the sequence of amino acids (Fig. 1c). Genetic mutations that alter this sequence can have profound effects on the functionality of the final molecule. Such gene **polymorphisms** are the basis of many genetically based disorders. The final shape of the molecule (the **tertiary structure**), however, results from a process of **folding** of the amino acid chain (Fig. 1d). Folding is a complex process by which a protein achieves its lowest energy conformation. It is determined by electrochemical interactions between amino acid side-chains (e.g. hydrogen bonds, van der Waals' forces), and is so vital that it is overseen by **molecular chaperones**, such as the **heat shock proteins**, which provide a quiet space within which the protein acquires its final shape. In healthy tissue, cells can detect and destroy misfolded proteins, the accumulation of which damages cells and is responsible for various pathological conditions, including **Alzheimer's disease** and **Creutzfeldt–Jakob disease**. Folding ensures that the functional sequences of amino acids (**domains**) that form, e.g. binding sites for other molecules or hydrophobic segments for insertion into a membrane, are properly orientated to allow the protein to serve its function.

The relatively weak nature of the forces that cause folding renders them sensitive to changes in the environment surrounding the protein. Thus, alterations in acidity, osmotic potential, concentrations of specific molecules/ions, temperature or even hydrostatic pressure can modify the tertiary shape of a protein and change its interactions with other molecules. These modifications are usually reversible and are exploited by some proteins to detect alterations in the internal or external environments. For instance, nerve cells that respond to changes in CO_2 (chemoreceptors; Chapter 29) possess **ion channel** proteins (Chapter 4) that open or close to generate electrical signals (Chapter 5) when the acidity of the medium surrounding the receptor (CO_2 forms an acid in solution) alters by more than a certain amount. However, there are limits to the degree of fluctuation in the internal environment that can be tolerated by proteins before their shape alters so much that they become non-functional or irreversibly damaged, a process known as **denaturation** (this is what happens to egg-white proteins in cooking). Homeostatic systems prevent such conditions from arising within the body, and thus preserve protein functionality.