This chapter is concerned with energy and enzymes. Without them, neither we nor any other organism would be able to function. Indeed, when an enzyme is inactivated, either by the binding of an inhibitor such as hirudin that keeps the enzyme from binding to its target, or by some error leading to an alteration in its three-dimensional structure, its function is destroyed. This can have dire consequences: What if we had hirudin in our blood all the time?

Before considering how enzymes perform their molecular wizardry, let us consider the general principles of energy in biological systems.

Energy and Energy Conversions

Physicists define energy as the capacity to do work, which occurs when a force operates on an object over a distance. In biochemistry, energy represents the capacity for change. All living things must obtain energy from the environment—no cell manufactures energy. Indeed, one of the fundamental physical laws is that energy can neither be created nor destroyed. However, energy can be transformed from one kind into another. Energy transformations are linked to the chemical transformations that occur in cells. Metabolism is the total chemical activity of a living organism; at any instant, metabolism consists of thousands of individual chemical reactions.

Biomedical Medicine from a Natural Source

Leeches are the source of hirudin, a natural clotting factor that prevents blood coagulation by inhibiting the action of an enzyme, thrombin, in mammalian blood.

**Hirudin**

65 a.a. long
Tightly binds to thrombin, a protein present in blood.

Leeches used their sucking mouths and drank blood, released hirudin that prevents coagulation by inhibiting the action of an enzyme, thrombin, in mammalian blood.
3.4 AMINO ACIDS AND THE PRIMARY STRUCTURE OF PROTEINS

Have you ever wondered how permanent waves work (Figure 3.12)? The characteristics of many mammalian body parts—including hair—start with the structure of proteins, just as they do for all other organisms.

Of all the large biological molecules, proteins are the most diverse. Proteins of the class called enzymes make metabolic events proceed much faster than they otherwise would. Structural proteins are the stuff of spider webs, butterfly wings, feathers, cartilage and bone, and a dizzying array of other body parts and products. Transport proteins move molecules and ions across cell membranes and cart them about through body fluids. Nutritious proteins abound in milk, eggs, and many seeds. Protein hormones and other regulatory types are signals for change in cell activities. Many proteins act as weapons against disease-causing bacteria and other invaders. Amazingly, cells build diverse proteins from their pools of only twenty kinds of amino acids!

Amino Acid Structure

Every amino acid is a small organic compound that consists of an amino group, a carboxyl group (an acid), a hydrogen atom, and one or more atoms known as its R group. As you can see from the structural formula in Figure 3.13, these parts generally are covalently bonded to the same carbon atom. Figure 3.14 shows a number of amino acids that we will consider later in the book.

![Figure 3.13 Generalized structural formula for amino acids.](image)

What Is A Protein's Primary Structure?

When a cell synthesizes a protein, amino acids become linked, one after the other, by peptide bonds. As Figure 3.15 shows, this is the type of covalent bond that forms between one amino acid’s amino group (NH₂⁺) and the carboxyl group (–COO⁻) of the next amino acid.

When peptide bonds join two amino acids together, we have a dipeptide. When they join three or more, we have a polypeptide chain. In such chains, the carbon...
Figure 3.18b). As you read this, each of your mature red blood cells is transporting a billion molecules of oxygen, bound to 250 million hemoglobin molecules.

Hemoglobin is at the fourth (quaternary) level of protein structure. In every protein at this level, two or more polypeptide chains are joined by numerous weak interactions (such as hydrogen bonds) and sometimes covalent bonds between sulfur atoms of R groups.

Proteins with quaternary structure are globular or fibrous. Hemoglobin is one of the globular proteins, which have one or more polypeptide chains folded in a sunded shape. Most enzymes are globular proteins, so the fibrous proteins are long strands or sheets of polypeptide chains. Examples are keratin (Figure 3.19) and collagen, the most common animal protein. Skin, bone, corneas, arteries, and many other animal body parts depend on the strength inherent in collagen.

Glycoproteins and Lipoproteins

Some proteins have other organic compounds attached to their polypeptide chains. For example, lipoproteins are when certain proteins circulating in blood combine with cholesterol, triglycerides, and phospholipids that are absorbed from the gut after a meal. Similarly, most glycoproteins have linear or branched oligosaccharides added to them. Nearly all the proteins at the surface of animal cells are glycoproteins. So are most protein cations from cells and many proteins in blood.

Structural Changes by Denaturation

Making weak bonds of a protein or any other large molecule disrupts its three-dimensional shape, an event called denaturation. For example, weak hydrogen bonds are sensitive to increases or decreases in temperature and pH. If the temperature or pH exceeds a protein's range of tolerance, its polypeptide chains will unwind or change shape, and the protein will lose its function. Consider the protein albumin, concentrated in the "egg white" of uncooked chicken eggs. When you cook eggs, the heat does not disrupt the strong covalent bonds of albumin's primary structure. But it destroys weaker bonds contributing to the three-dimensional shape. For some proteins, denaturation might be reversed when normal conditions are restored—but albumin isn't one of them. There is no way to uncook a cooked egg.

Proteins have a primary structure, which is the sequence of different kinds of amino acids along a polypeptide chain. An individual's DNA specifies that sequence.

Proteins have a secondary structure: a coiled pattern or an extended, sheetlike pattern that arises by hydrogen bonding at short, regular intervals along a polypeptide chain. At the third level of protein structure, bonding at certain angles, in certain directions. Interactions among R groups in the chain hold the loops in characteristic positions. At the fourth level of protein structure, numerous hydrogen bonds and other interactions join two or more polypeptide chains. Many proteins are this structurally complex.
Provocative Proteins

- Spider webs and silk fibres are made of the strong protein fibroin. Spider silk is stronger than a steel rod of the same diameter, yet it is much more elastic, so scientists hope to use it for products as diverse as bulletproof vests and artificial joints.

- The light of fireflies (also called lightning bugs!) is made possible by a protein called luciferase. Although most enemies stay away from the bad-tasting insects, some frogs eat so much that they glow.

- The deadly venoms of cobras, scorpions, contain small proteins that act as nerve toxins. Some sea snails stun their prey (an occasionally unlucky humans) with upto 50 such toxins. Incraddibly, scientists are looking for harnessing these toxins to relieve pain that is unresponsive even to morphine!!

  Venom: yilan zamiri

- Snake!!
• Sometimes ships in the northwest Pacific Ocean leave a trail of eerie green light. The light is produced by a protein in jellyfish when the creatures are hit by ships. Because the trail traces the path of ships at night, this green fluorescent protein has interested the Navy for many years. Many cell biologists also use it to fluorescently mark the cellular components they are studying.

• If a recipe calls for rhino horn (perpedan) black feathers or porcupine quills (kirpi), try substituting your own hair or fingernail. It's all the same stuff—alpha-keratin, a tough, water-resistant protein that is also the main component of wool, tortoise shells and outer layer of your skin.

—Jellyfish!!!
—Rhino!!!
Small Errors in Proteins Can Cause Disease

Sometimes, an error in just one amino acid can cause disease. Sickle cell disease, which most often affects those of African descent, is caused by a single error in the gene for hemoglobin, the oxygen-carrying protein in red blood cells.

This error, or mutation, results in an incorrect amino acid at one position in the molecule. Hemoglobin molecules with this incorrect amino acid stick together and distort the normally smooth, lozenge-shaped red blood cells into jagged sickle shapes.

The disease affects about 1 in every 500 African Americans, and 1 in 12 carry the trait and can pass it on to their children, but do not have the disease themselves.

Another disease caused by a defect in one amino acid is cystic fibrosis. This disease is most common in those of northern European descent, affecting about 1 in 9,000 Caucasians in the United States. Another 1 in 20 are carriers.

The disease is caused when a protein called CFTR is incorrectly folded. This misfolding is usually caused by the deletion of a single amino acid in CFTR. The function of CFTR, which stands for cystic fibrosis transmembrane conductance regulator, is to allow chloride ions (a component of table salt) to pass through the outer membranes of cells.

When this function is disrupted in cystic fibrosis, glands that produce sweat and mucus are most affected. A thick, sticky mucus builds up in the lungs and digestive organs, causing malnutrition, poor growth, frequent respiratory infections, and difficulties breathing. Those with the disorder usually die from lung disease around the age of 30.
e. Protein misfolding and aggregation cause diseases

A radical change in conformation usually entails a loss of activity. Such "switch" mutants may be important in causing certain diseases. For example, inherited disorders such as familial Creutzfeldt-Jacob’s disease (CJD) or fatal familial insomnia are putatively linked to mutations in a small protein, prion protein (PrP) (Prusiner 1994 ID: 297) (Prusiner 1997 ID: 301) (Figure I.3.3). The posttranslational modification and consequent accumulation of PrP is also responsible for animal diseases such as bovine spongiform encephalopathy (BSE, also known as mad cow disease) and sheep scrapie (Sc). The normal cellular protein PrP\textsuperscript{c} is proposed (Pan, Baldwin, et al. 1993 ID: 299) (Huang, Gabriel, et al. 1994 ID: 298) to switch in these cases from a predominantly helical structure to a modified isoform (PrP\textsuperscript{sc}) with a high β-sheet content (Figure I.3.3). The latter is relatively insoluble and resistant to digestion by proteases. It forms pathogenic aggregates, or amyloid fibrils, responsible for central nervous system degenerative disorder.

Figure I.3.3. NMR structure of rPrP(90-231), residues 90-231 of the recombinant prion protein rPrP from Syrian hamster, on the left, compared to the structure of the disease-causing form, PrP\textsuperscript{sc} proposed by Huang, Prusiner and Cohen (Huang, Prusiner, et al. 1996 ID: 300), on the right. The NMR structure closely resembles that of the normal cellular protein PrP\textsuperscript{c}. Major structural change occurs at the N-terminal portion, where the relatively disordered structure is organized into a four-stranded antiparallel sheet. (from http://www.cmpharm.ucsf.edu/home/~wallace/public_html/prion/nobel.html)
Structure Explorer - 1A18

Title: Human α-Thrombin Ternary Complex With The Exosite Inhibitor Hirugen and Active Site Inhibitor Pluch2Ocs-D-Dpa-Pro-Benzamido

Classification: Complex (Blood Coagulation/Inhibitors)

Compound: Mol_id: 1; Molecule: α-Thrombin; Chains: H, I; Ext: 3.4.21.5; Biological_Unit: Monomer

Mol_id: 2; Molecule: Hirudin IIb; Chains: I; Ext: 3.4.21.5; Biological_Unit: Monomer

Exp Method: X-ray Diffraction

View Structure

Summary Information
View Structure
Download/Display File
Structural Neighbors
Geometry
Other Sources
Sequence Details

www.rcsb.org/pdb
Rasmol