6.3 Metabolic Pathways and Enzymes

Reactions do not occur haphazardly in cells; they are usually a part of a **metabolic pathway,** a series of linked reactions. Metabolic pathways begin with a particular reactant and terminate with an end product. While it is possible to write an overall equation for a pathway as if the beginning reactant went to the end product in one step, there are actually many specific steps in between. In the pathway, one reaction leads to the next reaction, which leads to the next reaction, and so forth in an organized, highly structured manner. This arrangement makes it possible for one pathway to lead to several others, because various pathways have several molecules in common. Also, metabolic energy is captured and utilized more easily if it is released in small increments rather than all at once.

A metabolic pathway can be represented by the following diagram:

$$A \xrightarrow{E_1} B \xrightarrow{E_2} C \xrightarrow{E_3} D \xrightarrow{E_4} E \xrightarrow{E_5} F \xrightarrow{E_6} G$$

In this diagram, the letters A–F are reactants and letters B–G are products in the various reactions. The letters E_1–E_6 are enzymes.

An **enzyme** is a protein molecule[2] that functions as an organic catalyst to speed a chemical reaction. In a crowded ballroom, a mutual friend can cause particular people to interact. In the cell, an enzyme brings together particular molecules and causes them to react with one another.

The reactants in an enzymatic reaction are called the **substrates** for that enzyme. In the first reaction, A is the substrate for E_1 and B is the product. Now B becomes the substrate for E_2, and C is the product. This process continues until the final product G forms.

Any one of the molecules (A–G) in this linear pathway could also be a substrate for an enzyme in another pathway. A diagram showing all the possibilities would be highly branched.

Energy of Activation

Molecules frequently do not react with one another unless they are activated in some way. In the absence of an enzyme, activation is very often achieved by heating the reaction flask to increase the number of effective collisions between molecules. The energy that must be added to cause molecules to react with one another is called the **energy of activation** (E_a). Figure 6.4 compares E_a when an enzyme is not present to when an enzyme is present, illustrating that enzymes lower the amount of energy required for activation to occur.

In baseball, a home-run hitter must not only hit the ball to the fence, but over the fence. When enzymes lower the energy of activation, it is like removing the fence; then it is possible to get a home run by simply hitting the ball as far as the fence was.

Enzyme-Substrate Complexes

The following equation, which is pictorially shown in Figure 6.5, is often used to indicate that an enzyme forms a complex with its substrate:

[2]Catalytic RNA molecules are called ribozymes and are not enzymes.

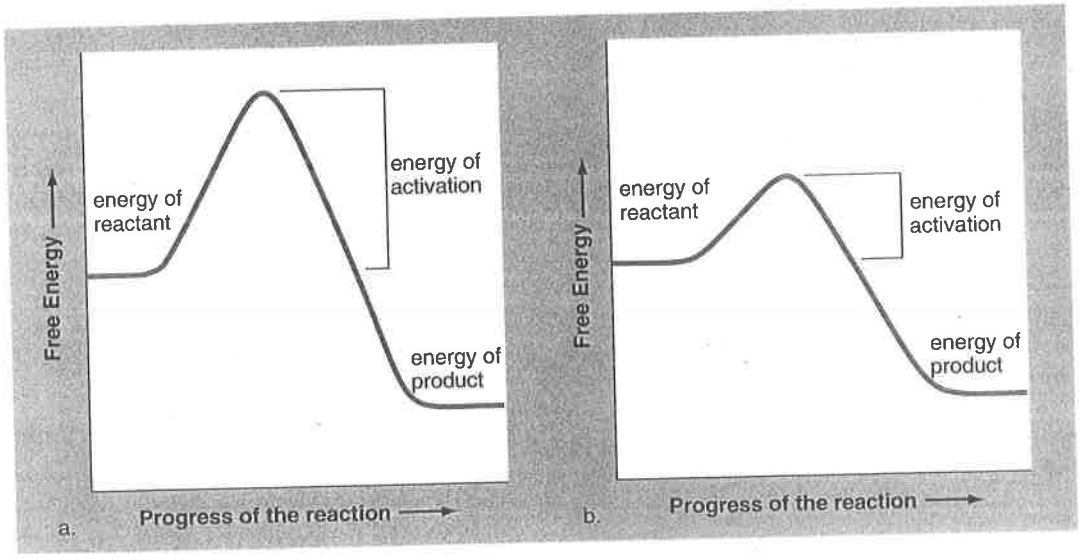


Figure 6.4 Energy of activation (E_a).
Enzymes speed the rate of chemical reactions because they lower the amount of energy required to activate the reactants. **a.** Energy of activation when an enzyme is not present. **b.** Energy of activation when an enzyme is present. Even spontaneous reactions like this one speed up when an enzyme is present.

$$E + S \rightarrow ES \rightarrow E + P$$

enzyme | substrate | enzyme-substrate complex | product

In most instances only one small part of the enzyme, called the **active site,** complexes with the substrate(s). It is here that the enzyme and substrate fit together, seemingly like a key fits a lock; however, it is now known that the active site undergoes a slight change in shape in order to accommodate the substrate(s). This is called the **induced-fit model** because the enzyme is induced to undergo a slight alteration to achieve optimum fit.

The change in shape of the active site facilitates the reaction that now occurs. After the reaction has been completed, the product(s) is released, and the active site returns to its original state, ready to bind to another substrate molecule. Only a small amount of enzyme is actually needed in a cell because enzymes are not used up by the reaction.

Some enzymes do more than simply complex with their substrate(s); they actually participate in the reaction. Trypsin digests protein by breaking peptide bonds. The active site of trypsin contains three amino acids with *R* groups that actually interact with members of the peptide bond—first to break the bond and then to introduce the components of water. This illustrates that the formation of the enzyme-substrate complex is very important in speeding up the reaction.

Sometimes it is possible for a particular reactant(s) to produce more than one type of product(s). The presence or absence of an enzyme determines which reaction takes place. If a substance can react to form more than one product, then the enzyme that is present and active determines which product is produced.

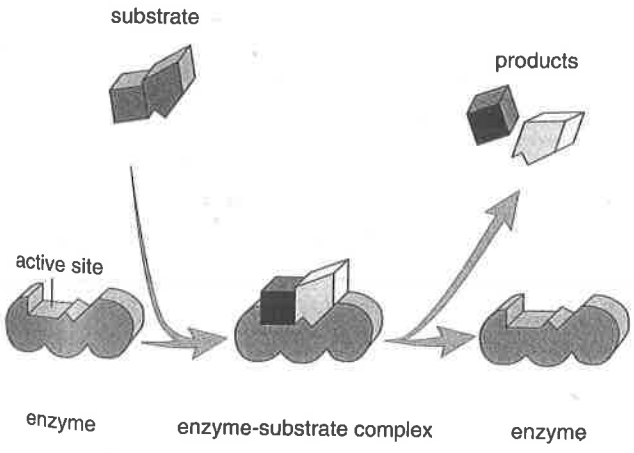
Every reaction in a cell requires its specific enzyme. Because enzymes only complex with their substrates, they are named for their substrates, as in the following examples:

Substrate	Enzyme
Lipid	Lipase
Urea	Urease
Maltose	Maltase
Ribonucleic acid	Ribonuclease
Lactose	Lactase

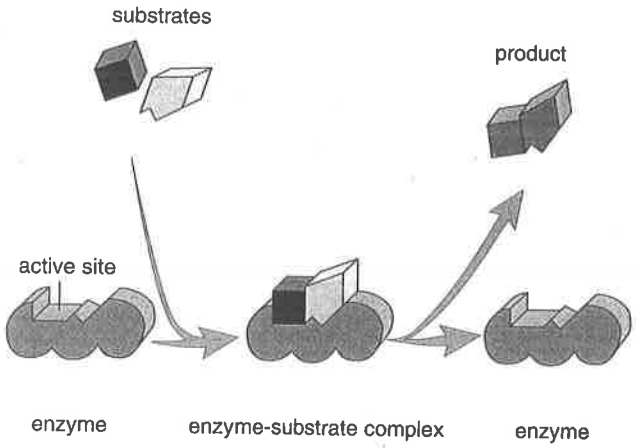
Most enzymes are protein molecules. Enzymes speed chemical reactions by lowering the energy of activation. They do this by forming an enzyme-substrate complex.

Factors Affecting Enzymatic Speed

Enzymatic reactions proceed quite rapidly. Consider, for example, the breakdown of hydrogen peroxide (H_2O_2) as catalyzed by the enzyme catalase: $2\ H_2O_2 \rightarrow 2\ H_2O + O_2$. The breakdown of hydrogen peroxide can occur 600,000 times a second when catalase is present. To achieve maximum product per unit time, there should be enough substrate to fill active sites most of the time. Temperature and optimal pH also increase the rate of an enzymatic reaction.



a. Degradative reaction



b. Synthetic reaction

Figure 6.5 Enzymatic action.
An enzyme has an active site, which is where the substrates and enzyme fit together in such a way that the substrates are oriented to react. Following the reaction, the products are released and the enzyme is free to act again. **a.** Some enzymes carry out degradative reactions in which the substrate is broken down to smaller molecules. **b.** Other enzymes carry out synthetic reactions in which the substrates are joined to form a larger molecule.

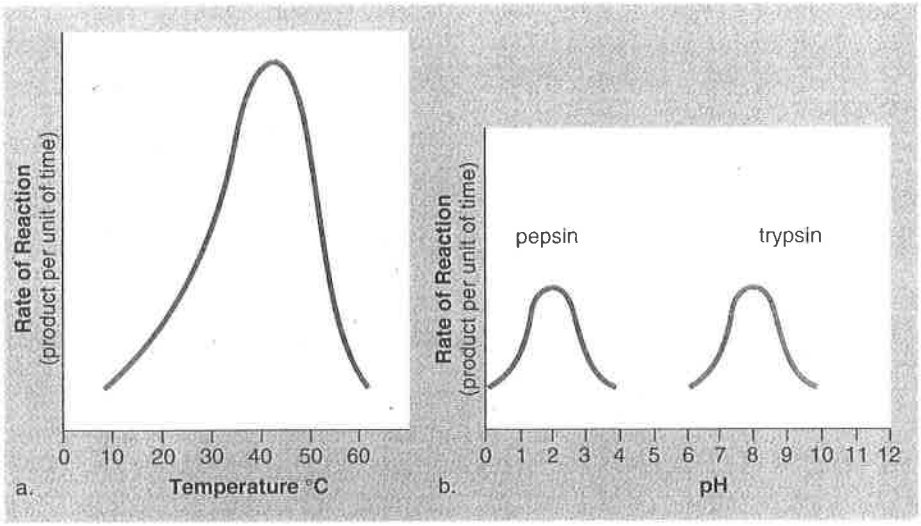


Figure 6.6 Rate of an enzymatic reaction as a function of temperature and pH.
a. At first, as with most chemical reactions, the rate of an enzymatic reaction doubles with every 10°C rise in temperature. In this graph, the rate of reaction is maximum at about 40°C; then it decreases until the reaction stops altogether, because the enzyme has become denatured. **b.** Pepsin, an enzyme found in the stomach, acts best at a pH of about 2, while trypsin, an enzyme found in the small intestine, performs optimally at a pH of about 8. The shape that enables these proteins to bind with their substrates is not properly maintained at other pHs.

Substrate Concentration

Generally, enzyme activity increases as substrate concentration increases because there are more collisions between substrate molecules and the enzyme. As more substrate molecules fill active sites, more product results per unit time. But when the enzyme's active sites are filled almost continuously with substrate, the enzyme's rate of activity cannot increase anymore. Maximum rate has been reached.

Temperature and pH

As the temperature rises, enzyme activity increases (Fig. 6.6*a*). This occurs because as the temperature rises there are more effective collisions between enzyme and substrate. However, if the temperature rises beyond a certain point, enzyme activity eventually levels out and then declines rapidly because the enzyme is **denatured.** An enzyme's shape changes during denaturation, and then it can no longer bind its substrate(s) efficiently.

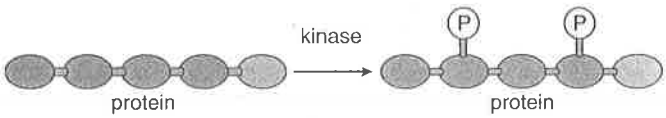
Each enzyme also has an optimal pH at which the rate of the reaction is highest. Figure 6.6*b* shows the optimal pH for the enzymes pepsin and trypsin. At this pH value, these enzymes have their normal configurations. The globular structure of an enzyme is dependent on interactions, such as hydrogen bonding, between *R* groups. A change in pH can alter the ionization of these side chains and disrupt normal interactions, and under extreme conditions of pH, denaturation eventually occurs. Again, the enzyme has an altered shape and is then unable to combine efficiently with its substrate.

Enzyme Concentration

Since enzymes are specific, a cell regulates which enzymes are present and/or active at any one time. Otherwise enzymes may be present that are not needed, or one pathway may negate the work of another pathway.

Genes must be turned on to increase the concentration of an enzyme and must be turned off to decrease the concentration of an enzyme.

Another way to control enzyme activity is to activate or deactivate the enzyme. Phosphorylation is one way to activate an enzyme. Molecules received by membrane receptors often turn on kinases, which then activate enzymes by phosphorylating them:



Enzyme Inhibition

Actually, **enzyme inhibition** is a common means by which cells regulate enzyme activity. In *competitive inhibition*, another molecule is so close in shape to the enzyme's substrate that it can compete with the true substrate for the enzyme's active site. This molecule inhibits the reaction because only the binding of the true substrate results in a product. In *noncompetitive inhibition*, a molecule binds to an enzyme, but not at the active site. The other binding site is called the allosteric site. In this instance, inhibition occurs

when binding of a molecule causes a shift in the three-dimensional structure so that the substrate cannot bind to the active site.

The activity of almost every enzyme in a cell can be regulated by its product. When a product is in abundance, it binds competitively with its enzyme's active site; as the product is used up, inhibition is reduced and more product can be produced. In this way, the concentration of the product is always kept within a certain range. Most metabolic pathways are regulated by **feedback inhibition,** but the end product of the pathway binds at an allosteric site on the first enzyme of the pathway (Fig. 6.7). This binding shuts down the pathway, and no more product is produced.

In inhibition, a product binds to the active site or binds to an allosteric site on an enzyme.

Poisons are often enzyme inhibitors. Cyanide is an inhibitor for an essential enzyme (cytochrome *c* oxidase) in all cells, which accounts for its lethal effect on humans. Penicillin blocks the active site of an enzyme unique to bacteria. When penicillin is taken, bacteria die but humans are unaffected.

Enzyme Cofactors

Many enzymes require an inorganic ion or organic but nonprotein molecule to function properly; these necessary ions or molecules are called **cofactors.** The inorganic ions are metals such as copper, zinc, or iron. The organic, nonprotein molecules are called **coenzymes.** These cofactors assist the enzyme and may even accept or contribute atoms to the reactions.

It is interesting that vitamins are often components of coenzymes. **Vitamins** are relatively small organic molecules that are required in trace amounts in our diet and in the diet of other animals for synthesis of coenzymes that affect health and physical fitness. The vitamin becomes a part of the coenzyme's molecular structure. These vitamins are necessary to formation of the coenzymes listed:

Vitamin	Coenzyme
Niacin	NAD^+
B_2 (riboflavin)	FAD
B_1 (thiamine)	Thiamine pyrophosphate
Pantothenic acid	Coenzyme A (CoA)
B_{12} (cobalamin)	B_{12} coenzymes

A deficiency of any one of these vitamins results in a lack of the coenzyme listed and therefore a lack of certain enzymatic actions. In humans, this eventually results in vitamin-deficiency symptoms: niacin deficiency results in a skin disease called pellagra, and riboflavin deficiency results in cracks at the corners of the mouth.

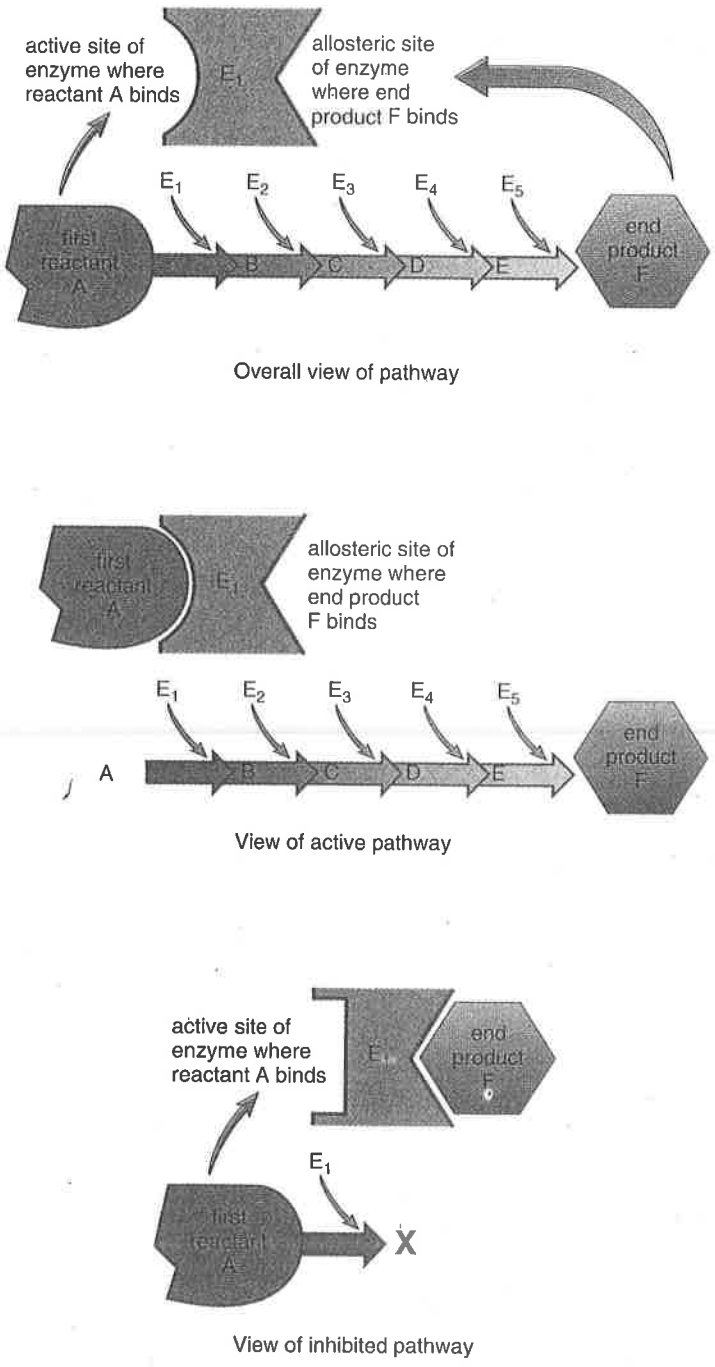


Figure 6.7 Feedback inhibition.
This hypothetical metabolic pathway is regulated by feedback inhibition. When reactant A binds to the active site of E_1, the pathway is active and the end product is produced. Once there is sufficient end product, some binds to the allosteric site of E_1. Now a change of shape prevents reactant A from binding to the active site of E_1 and the end product is no longer produced.

Enzymes speed a reaction by forming a complex with the substrate. Various factors affect enzymatic speed, including substrate concentration, temperature, pH, enzyme concentration, the presence of inhibitors or necessary cofactors.

Endocrine Glands

Endocrine glands can be contrasted with exocrine glands. The latter have ducts and secrete their products into these ducts for transport into body cavities. For example, the salivary glands send saliva into the mouth by way of the salivary ducts. **Endocrine glands** are ductless; they secrete their hormones directly into the bloodstream for distribution throughout the body.

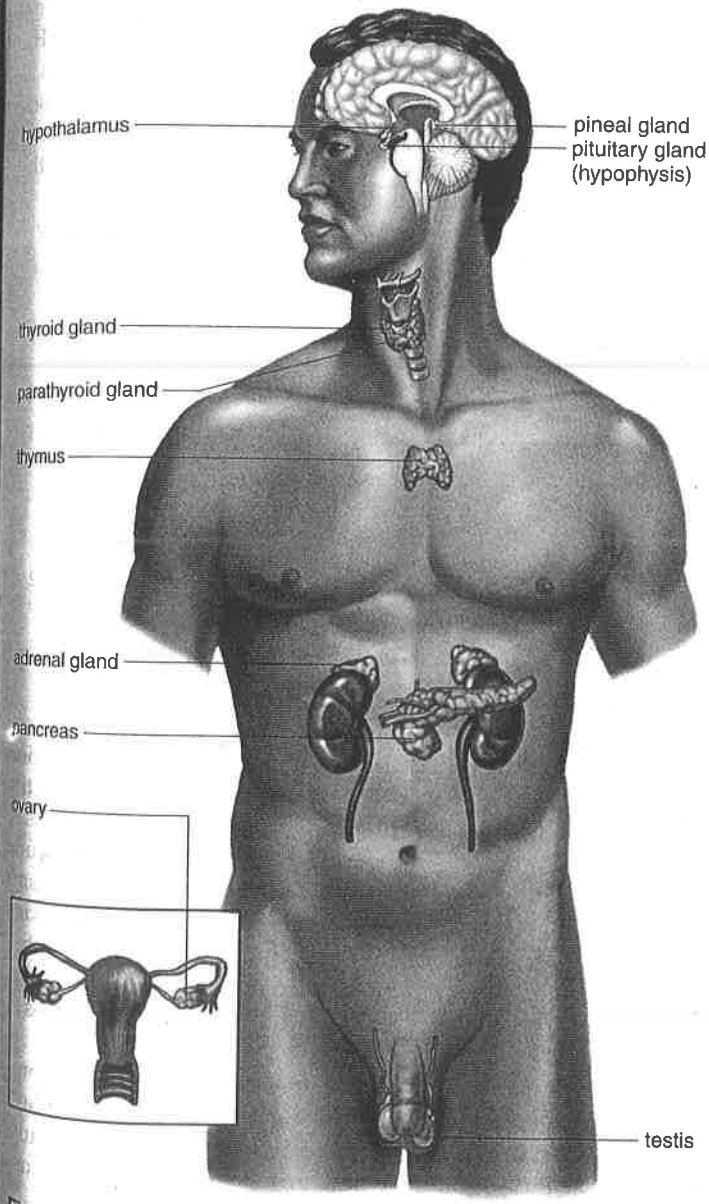


Figure 20.3 The endocrine system.
Anatomical location of major endocrine glands in the body.

Table 20.1 lists the hormones ·rincipal endocrine glands, which are depicted in Figure 20.3. The hypothalamus, a part of the brain, is in close proximity to the pituitary. The hypothalamus controls the pituitary gland and this, too, exemplifies the close association between the nervous and endocrine systems. The pineal gland is also located in the brain. The thyroid and parathyroids are located in the neck, and the thymus lies just beneath the sternum, in the thoracic cavity. The adrenal glands and pancreas are located in the abdominal cavity. The gonads include the ovaries, located in the pelvic cavity, and the testes, located outside this cavity in the scrotum.

Like the nervous system, the endocrine system is especially involved in homeostasis, that is, the dynamic equilibrium of the internal environment. The internal environment is the blood and tissue fluid that surrounds the body's cells. Notice that several hormones directly affect the osmolarity of the blood. Others control the calcium and glucose levels. Several hormones are involved in the maturation and function of the reproductive organs. In fact, many people are most familiar with the effect of hormones on sexual functions.

There are two mechanisms that control the effect of endocrine glands. Quite often a negative feedback mechanism controls the secretion of hormones. An endocrine gland can be sensitive to either the condition it is regulating or to the blood level of the hormone it is producing. For example, when the blood glucose level rises, the pancreas produces insulin, which causes the cells to take up glucose and the liver to store glucose. The stimulus for the production of insulin has thereby been dampened, and therefore the pancreas stops producing insulin. On the other hand, when the blood level of thyroid hormones rises, the anterior pituitary stops producing thyroid-stimulating hormones. We will discuss these examples in more detail later.

The presence of contrary hormonal actions is a way the effect of a hormone is controlled. The action of insulin, for example, is offset by the production of glucagon by the pancreas. Notice there are other examples of contrary hormonal actions in Table 20.1. The thyroid lowers the blood calcium level, but the parathyroids raise the blood calcium level. We will also have the opportunity to point out other instances in which hormones work opposite to one another and thereby bring about the regulation of a substance in the blood.

The secretion of a hormone is often controlled by negative feedback, and the effect of a hormone is often opposed by a contrary hormone. The end result is homeostasis and the normal functioning of body parts.

20.3 Thyroid and Parathyroid Glands

The **thyroid gland** is a large gland located in the neck, where it is attached to the trachea just below the larynx (see Fig. 20.3). The parathyroid glands are imbedded in the posterior surface of the thyroid gland.

Thyroid Gland

The thyroid gland is composed of a large number of follicles, each a small spherical structure made of thyroid cells filled with **thyroxine** (T_4), which contains four iodine atoms and four **triiodothyronine** (T_3), which contains three iodine atoms.

Effects of Thyroid Hormones

To produce thyroxine and triiodothyronine, the thyroid gland actively acquires iodine. The concentration of iodine in the thyroid gland can increase to as much as 25 times that of blood. If iodine is lacking in the diet, the thyroid gland is unable to produce the thyroid hormones. In response to constant stimulation by the anterior pituitary, it enlarges, resulting in a **simple goiter** (Fig. 20.7). Some years ago it was discovered that the use of iodized salt allows the thyroid to produce the thyroid hormones, and therefore helps prevent simple goiter.

Thyroid hormones increase the metabolic rate. They do not have one target organ; instead, they stimulate all organs of the body to metabolize at a faster rate. More glucose is broken down and more energy is utilized.

If the thyroid fails to develop properly, a condition called **cretinism** results (Fig. 20.8). Individuals with this condition are short and stocky and have had extreme hypothyroidism since infancy or childhood. Thyroid hormone therapy can initiate growth, but unless treatment is begun within the first two months, mental retardation results. The occurrence of hypothyroidism in adults produces the condition known as **myxedema,** which is characterized by lethargy, weight gain, loss of hair, slower pulse rate, lowered body temperature, and thickness and puffiness of the skin. The administration of adequate doses of thyroid hormones restores normal function and appearance.

In the case of hyperthyroidism, or *Graves' disease,* the thyroid gland is enlarged and overactive, causing a goiter to form. The eyes protrude because of edema in eye socket tissues and swelling of muscles that move the eyes. This type of goiter is called **exophthalmic goiter.** The patient usually becomes hyperactive, nervous, irritable, and suffers from insomnia. Removal or destruction of a portion of the thyroid by means of radioactive iodine is sometimes effective in curing the condition. Hyperthyroidism can also be caused by a thyroid tumor, which is usually detected as a lump during physical examination. Again, the treatment is surgery in combination with administration of radioactive iodine. The prognosis for most patients is excellent.

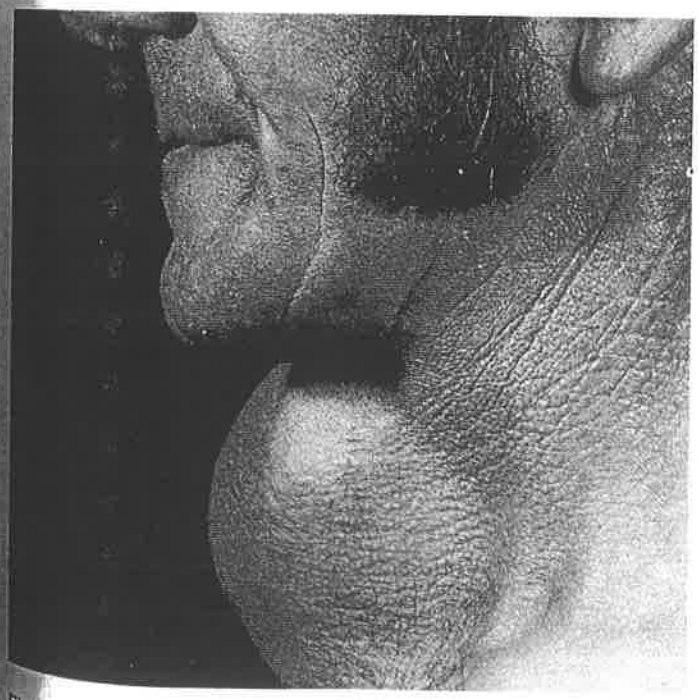


Figure 20.7 Simple goiter.
An enlarged thyroid gland often is caused by a lack of iodine in the diet. Without iodine, the thyroid is unable to produce thyroid hormones, and continued anterior pituitary stimulation causes the gland to enlarge.

Figure 20.8 Cretinism.
Individuals who have hypothyroidism since infancy or childhood do not grow and develop as others do. Unless medical treatment is begun, the body is short and stocky; mental retardation is also likely.