Synthesis and Release of Thyroid Hormones

The thyroid gland is composed of a large number of follicles. Each follicle is surrounded by a single layer of cells and filled with a proteinaceous material called colloid.The primary constituent of colloid is the large glycoprotein thyroglobulin, which contains the thyroid hormones in its molecule. The following steps are required for the synthesis and secretion of thyroid hormones into the blood (Figs. 76–1 and 76–2):

• **Iodide trapping (iodide pump) or sodium-iodide symporter(NIS)**. Iodine is essential to thyroid hormone synthesis. Ingested iodine is converted to iodide and absorbed from the gut. Most circulating iodide is excreted by the kidneys; much of the remainder is taken up and concentrated by the thyroid gland. To achieve this, the thyroid follicular cells actively transport iodide from the circulation across their basal membrane into the cell by the NIS. In a normal thyroid gland, the NIS concentrates the iodide many times over the concentration in the blood. Several anions, such as thiocyanate and perchlorate, decrease iodide transport by competitive inhibition. In so doing, they decrease the synthesis of thyroid hormones and are used to treat hyperthyroidism.

• **Oxidation of iodide**. Once in the thyroid gland, iodide is rapidly oxidized to iodine by thyroid peroxidase; this occurs at the apical membrane of the follicular cells.

• **Synthesis of thyroglobulin**. This glycoprotein is synthesized by the follicular cells and secreted into the colloid through exocytosis of secretion granules that also contain thyroid peroxidase. Each thyroglobulin molecule contains many tyrosyl groups, but only a fraction become iodinated.

• **Iodination (organification) and coupling**. Once iodide is oxidized to iodine, it is rapidly attached to the 3 position of tyrosine molecules of thyroglobulin to generate monoiodotyrosine (MIT). MIT is next iodinated in the 5 position to give diiodotyrosine (DIT). Thereafter, two DIT molecules are coupled to form thyroxine (T4), the major product of the coupling reaction; or one MIT and one DIT molecule are coupled to form triiodothyronine (T3). A small amount of reverse T3 (RT3) is formed by condensation of DIT with MIT. These reactions are catalyzed by thyroid peroxidase and blocked by antithyroid drugs such as propylthiouracil. Approximately two thirds of the iodinated compounds bound to

thyroglobulin are MIT or DIT; most of the remainder are the active hormones T3 and, especially, T4. Thyroglobulin is stored in the lumen of the follicle as colloid until the gland is stimulated to secrete thyroid hormones.

• **Proteolysis, deiodination, and secretion.** The release of T3, T4 and RT3 into the blood requires proteolysis of the thyroglobulin. At the apical surface of the follicular cells, colloid is taken up from the lumen of the follicles through endocytosis. Colloid vesicles then migrate from the apical to the basal cell membrane and fuse with lysosomes. Lysosomal proteases release free RT3, T3, and T4, which then leave the cell. Free MIT and DIT are not secreted into the blood but, instead, deiodinated within the follicular cell by the enzyme deiodinase; the free iodine is reused in the gland for hormone synthesis. More than 90% of the thyroid hormone released from the gland is T4. The remaining secretion products are T3 and very small amounts of the inactive compound reverse T3.