T_3, DIT, and MIT are released into the cytoplasm of the follicular cell. T_4 and T_3 diffuse into the systemic circulation after their liberation from Tg. DIT and MIT are deiodinated by an intracellular microsomal iodotyrosine dehalogenase. The freed iodide is then reused for thyroid hormone synthesis.

Each step in the synthesis of thyroid hormones is regulated by pituitary **thyroid-stimulating hormone (TSH)**. TSH stimulates (1) the "iodide pump," (2) Tg synthesis, and (3) colloidal uptake by follicular cells. TSH also regulates the rate of proteolysis of Tg for the liberation of T_4 and T_3. In addition, TSH induces an increase in the size and number of the thyroid follicular cells. Prolonged TSH stimulation leads to increased vascularity and eventual hypertrophic enlargement of the thyroid gland (**goiter**).

Metabolism

Free (unbound) T_4 (FT_4) is the primary secretory product of the normal thyroid gland. T_4 undergoes peripheral deiodination of the outer ring at the 5′ position to yield T_3. This deiodination occurs in a number of tissues but primarily in the liver. Reverse T_3, produced by removal of one iodine from the inner ring of T_4, is metabolically inactive and is an end-product of T_4 metabolism (see Figure 41-1). Peripheral deiodination is a rapidly responsive mechanism of control for thyroid hormone balance. Acute or chronic stress or illness causes a shift in the direction of this deiodination, favoring formation of rT_3 rather than T_3. Various medications also shift peripheral deiodination toward the inactive product rT_3.

T_4 and T_3 in the circulation are bound reversibly and almost completely to carrier proteins. These carrier proteins are (1) thyroxine-binding globulin (TBG), (2) thyroxine-binding prealbumin (TBPA), and (3) albumin. Collectively, they bind 99.97% of T_4 and 99.7% of T_3. Thus only a very small fraction of each of these hormones is unbound and free for biological activity. Because a wide variation exists in the concentration of T_4-binding proteins, even under normal circumstances, a wide variation also exists in total T_4 concentrations among individuals with normal (euthyroid) thyroid function. Total T_3 concentrations also vary with alterations in binding proteins, although usually to a lesser degree than T_4 concentrations. Circumstances in which thyroid hormone–binding protein concentrations are increased or decreased are shown in Box 41-1.

BOX 41-1 | Alterations in the Concentration or Affinity of Thyroid Hormone–Binding Proteins

INCREASES IN:

A. TBG concentration (or affinity)
   1. Genetic (inherited) causes
   2. Nonthyroidal illness (HIV infection, infectious and chronic active hepatitis, estrogen-producing tumors, acute intermittent porphyria)
   3. Normal physiology (pregnancy, newborn)
   4. Drug use (oral contraceptives, estrogens, tamoxifen, methadone)
B. Prealbumin concentration
C. Albumin binding (familial dysalbuminemic hyperthyroxinemia)
D. T_4 binding by antibodies (autoimmune thyroid disease, hepatocellular carcinoma)

DECREASES IN:

A. TBG concentration
   1. Genetic (inherited) determination
   2. Nonthyroidal illness (major illness or surgical stress, nephrotic syndrome)
   3. Drug use (androgens, anabolic steroids, large doses of glucocorticoids)
B. TBG binding capacity (drugs bound to TBG, such as salicylates and phenytoin)
C. Prealbumin concentration

ANALYTICAL METHODOLOGY

Table 41-1 is a review of the nomenclature for tests of thyroid hormones and thyroid-related proteins in serum. Guidelines for the classification of various thyroid tests have been further described in a special report from the American Thyroid Association.[8] Almost all laboratory tests for thyroid function are commercially available in either kit form or on automated immunoassay instruments. The following is a brief description of tests that are considered useful for the evaluation of thyroid status. More detailed descriptions of methods are discussed in an expanded version of this chapter.[3] Package inserts that accompany commercial products also are a source of additional information. Reference intervals for the analytes discussed below are found in Table 45-1 in Chapter 45.

Determination of Thyroid-Stimulating Hormone in Blood

Immunoassay is the method of choice for the measurement of serum TSH in the clinical laboratory. High sensitivity assays for TSH have become available that employ various detection signals, including chemiluminescence and assays with low end detection limits in the 0.01 to 0.05 mIU/L range.[12,13] Clinically, these assays are capable of measuring TSH at concentrations required to accurately differentiate the low concentrations of serum TSH found in patients with true hyperthyroidism from the suppressed concentrations found in patients with nonthyroidal illnesses.

Secretion of TSH occurs in a circadian fashion: highest concentrations prevail at night between 200 and 400, and lowest concentrations occur between 1700 and 1800. Low-amplitude oscillations also occur throughout the day.[9] The nocturnal increase in TSH is lost in critical illness and after surgery. TSH surges immediately after birth, peaking at 30 minutes at 25 to 160 mIU/L; values decline back to cord blood concentrations by 3 days and reach adult values in the first weeks of life. There are no significant sex or race differences. Euthyroid serum TSH concentrations are log-gaussian or log-normal in distribution; reference intervals should be evaluated logarithmically to achieve accurate estimates of the lower limit of normal.

Determination of Thyroxine in Serum

Typically, clinical laboratories measure total T_4 with competitive immunoassays performed on automated instruments. Many T_4 immunoassays use high-affinity antibodies produced against an albumin-T_4 conjugate. These polyclonal antisera are quite specific and are able to distinguish among molecules differing by only one atom (e.g., T_3 and T_4).

Immunoassays of total T_4 measure both free and protein-bound thyroxine. Accurate measurement of total endogenous hormone therefore requires dissociation of T_4 from its serum transport proteins because 99.97% of T_4 circulates tightly bound to TBG, albumin, and TBPA. Binding of T_4 to albumin is usually not a concern because the association constant of T_4