**TABLE 63-1 PHYSIOLOGIC EFFECTS OF THYROID HORMONE**

| SYSTEM | EFFECTS |
|---|---|
| Cardiovascular | Increased heart rate and cardiac output |
| Gastrointestinal | Increased gut motility |
| Skeletal | Increased bone turnover and resorption |
| Pulmonary | Maintenance of normal hypoxic and hypercapnic drive in the respiratory center |
| Neuromuscular | Increased muscle protein turnover and increased speed of muscle contraction and relaxation |
| Metabolism of lipids and carbohydrates | Increased hepatic gluconeogenesis and glycogenolysis, as well as intestinal glucose absorption<br>Increased cholesterol synthesis and degradation<br>Increased lipolysis |
| Sympathetic nervous system | Increased numbers of β-adrenergic receptors in the heart, skeletal muscle, lymphocytes, and adipose cells<br>Decreased cardiac α-adrenergic receptors<br>Increased catecholamine sensitivity |
| Hematopoietic | Increased red blood cell 2,3-diphosphoglycerate, facilitating oxygen dissociation from hemoglobin with increased oxygen available to tissues |

## Tests of Serum Thyroid Hormone Levels

Measurements of total serum $T_4$ and total $T_3$ indicate the total amount of hormone bound to thyroid-binding proteins by radioimmunoassay. Total $T_4$ and $T_3$ levels are elevated in hyperthyroidism and low in hypothyroidism. Increased production of TBG (as with pregnancy or estrogen therapy) increases the total $T_4$ and $T_3$ levels without actual hyperthyroidism. Similarly, total $T_4$ and $T_3$ are low despite euthyroidism in conditions associated with low levels of thyroid-binding proteins (e.g., congenital decrease, protein-losing enteropathy, cirrhosis, nephrotic syndrome). Therefore, further tests to assess the free hormone levels, which reflect biologic activity, must be performed. Free $T_4$ and free $T_3$ levels can be measured directly or by dialysis or ultrafiltration.

Serum TSH is measured by a third-generation immunometric assay that accurately discriminates between normal TSH levels and levels below the normal range. Thus, the TSH assay can diagnose clinical hyperthyroidism (elevated free $T_4$ and free $T_3$ and suppressed TSH) and subclinical hyperthyroidism (normal free $T_4$ and free $T_3$ and suppressed TSH). In hyperthyroidism, the free $T_3$ may be elevated in the presence of a normal free $T_4$. In primary (thyroidal) hypothyroidism, serum TSH is supranormal because of diminished feedback inhibition. The TSH is usually low but may be normal in secondary (pituitary) or tertiary (hypothalamic) hypothyroidism.

Serum thyroglobulin measurements are useful in the follow-up of patients with papillary or follicular carcinoma. After thyroidectomy and iodine-131 ($^{131}I$) ablation therapy, thyroglobulin levels should be less than 0.5 µg/L while the patient is on suppressive levothyroxine treatment. Levels in excess of this value indicate the possibility of persistent or metastatic disease.

Calcitonin is produced by the C cells of the thyroid and has a minor role in calcium homeostasis. Calcitonin measurements are invaluable in the diagnosis of medullary carcinoma of the thyroid and for monitoring the effects of therapy for this entity.

**TABLE 63-2 HIGH-RISK FACTORS FOR MALIGNANCY IN A THYROID NODULE**

| |
|---|
| **HISTORY** |
| Head and neck irradiation |
| Exposure to nuclear radiation |
| Rapid growth |
| Recent onset |
| Young age |
| Male sex |
| Familial incidence (medullary and about 5% of papillary carcinomas) |
| **PHYSICAL EXAMINATION** |
| Hard consistency of nodule |
| Fixation of nodule |
| Lymphadenopathy |
| Vocal cord paralysis |
| Distant metastasis |
| **LABORATORY AND IMAGING STUDIES** |
| Elevated serum calcitonin |
| Cold nodule on technetium scan |
| Ultrasonography: |
| Presence of microcalcifications |
| Presence of nodule hypoechogenicity compared with the normal thyroid parenchyma |
| Presence of increased nodular vascularity |
| Presence of irregular infiltrative margins |
| Nodule taller than wide on transverse view |
| Absent halo |
| Suspicious cervical lymphadenopathy |
| Partially cystic nodule |
| Spongiform appearance, defined as an aggregation of multiple microcystic components in >50% of the nodule volume |

## Thyroid Imaging

Technetium-99m ($^{99m}Tc$) pertechnetate is concentrated in the thyroid gland and can be scanned with a gamma camera, yielding information about the size and shape of the gland and the location of the functional activity in the gland (thyroid scan). The thyroid scan is often performed in conjunction with a quantitative assessment of radioactive iodine ($^{123}I$) uptake by the thyroid. Functioning thyroid nodules are called *warm* or *hot* nodules; *cold* nodules are nonfunctioning. Malignancy is usually associated with a cold nodule; 16% of surgically removed cold nodules are malignant.

Thyroid ultrasound evaluation is useful in the differentiation of solid nodules from cystic nodules. It also may be used to guide the clinician during FNA of a nodule (E-Fig. 63-3), and ultrasound characteristics of thyroid nodules may be helpful to distinguish those that are more likely to be malignant (Table 63-2).

## Thyroid Antibodies

Autoantibodies to several different antigenic components in the thyroid gland, including thyroglobulin (TgAb), thyroid peroxidase (TPO Ab, formerly called *antimicrosomal antibodies*), and the TSH receptor, can be measured in the serum. A strongly positive test for TPO Ab indicates autoimmune thyroid disease. Elevated TSH receptor antibody occurs in Graves' disease (see later discussion).

## Thyroid Biopsy

FNA of a nodule to obtain thyroid cells for cytologic evaluation is the best way to differentiate benign from malignant disease.