Thyroid dysfunction or deregulation is a clinically significant sequela of cancer therapy due to the spectrum of physiologic consequences. Primary hypothyroidism or hyperthyroidism may result from direct irradiation of the thyroid gland incidental to the treatment of malignancies such as Hodgkin’s disease and head and neck rhabdomyosarcoma. Primary hypothyroidism may also result from central nervous system (CNS) tumors that require spinal axis irradiation [7, 11, 32]. Central hypothyroidism may develop in children with brain tumors treated with cranial irradiation or chemotherapy that includes the hypothalamic-pituitary axis [25]. The development of benign thyroid nodules and malignancy after thyroid radiation therapy (RT) is also a sequela with potential adverse consequences [12, 13, 16, 18, 23, 44].

9.1 Pathophysiology

The hypothyroidism that follows direct thyroid irradiation manifests as an elevated serum thyroid stimulating hormone concentration, with or without a concomitant decreased serum thyroxine concentration. The pathophysiology is not clearly understood, but it is possible that it results from direct radiation damage to the thyroid follicular cells, the thyroid vasculature or the supporting stroma. The endocrine parenchymal cells of the thyroid are fully differentiated cells with a low turnover rate (reverting postmitotic cells) that may have relatively low radiation sensitivity. Conversely, the endothelial cells (EC) of the thyroid may have proliferation cycles shorter than those of endocrine cells. As a result, damage to the EC of the extensive thyroid capillary network may
be an important mechanism for both early and late radiation injury [15]. Less likely mechanisms that could contribute include radiation-induced immunologic cascades or damage from the iodine load administered during lymphangiography (LAG). Support for the latter theory is based on the observation that radioiodine treatment will induce hypothyroidism in patients with autoimmune thyroiditis [3]. Histopathologic changes in an irradiated thyroid gland include progressive obliteration of the fine vasculature, degeneration of follicular cells and follicles and atrophy of the stroma [29]. Because radiation damage is dependant on the degree of the mitotic activity and because the thyroid of a developing child grows in parallel with the body [14], this gland might be expected to show an age-related degree of injury and repair.

9.2 Clinical Manifestations

The common clinical manifestations of hypothyroidism include cold intolerance, constipation, inordinate weight gain, dry skin and slowed mentation. Specific signs include a round puffy face, slow speech, hoarseness, hypokinesia, generalized muscle weakness, delayed relaxation of deep tendon reflexes, cold and dry skin, brittle hair and periorbital edema. The most common clinical picture of hyperthyroidism is similar to that of Graves’ disease and usually characterized by a diffusely enlarged thyroid gland, ophthalmopathy and dermopathy.

9.2.1 Hypothyroidism

The incidence of hypothyroidism noted following therapeutic irradiation for Hodgkin’s disease (HD) varies, depending on the report. If an elevated serum TSH concentration is the determinant, then 4–79% of patients become affected. This large range exists because parameters relevant to the induction of hypothyroidism – such as radiation dose, technique and the frequency and types of follow-up testing – differ in the various reports. A recent study by Hancock and colleagues [16] of 1677 children and adults with Hodgkin’s disease in whom the thyroid had been irradiated showed that the actuarial risk at 26 years for overt or subclinical hypothyroidism was 47% (Table 9.1), with the peak incidence occurring 2–3 years after treatment. There are few reports specifically addressing the incidence of hypothyroidism in children as a function of radiation dose. Constine and colleagues [7] noted thyroid abnormalities in four of 24 children (17%) who received mantle irradiation of 26 Gy or less, and in 74 of 95 children (78%) who received greater than 26 Gy. The abnormality in all but three children (one with hypothyroidism and two with thyroid nodules) included an elevated serum TSH concentration with or without low serum T4 concentration. The spontaneous return of TSH to normal limits was observed in 20 of the 75 patients (27%).

A recent report by Sklar [37] from the Childhood Cancer Study Group showed that the relative risk of hypothyroidism in HD survivors was 17.1, with 28%
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The Thyroid Gland

of the cohort affected. The average time to developing hypothyroidism was five years. In a multivariate analysis, the major risk factors associated with the future development of hypothyroidism were the dose of radiation, female sex and older age at diagnosis. In fact, the actuarial risk of developing hypothyroidism 20 years after a diagnosis of HD was 30% for patients whose thyroid received 35–44.99 Gy and 50% for patients whose thyroid received 45 Gy or more (Fig. 9.1). In patients who were treated with chemotherapy alone, the incidence of hypothyroidism was 7.6%.

Although patients may develop an abnormal thyroid function test within six months of RT, most patients become abnormal between 1–5 years after treatment; however, rare and unexpected new cases can occur more than 20 years after diagnosis of HD [16, 37]. Uncompensated hypothyroidism (decreased serum T4 and elevated serum TSH concentration) occurs in 6–27% of children receiving radiation to the thyroid. In the thyroid dysfunction study by Constine and colleagues, age did not affect the incidence of hypothyroidism but was weakly correlated with the degree of abnormality, as suggested by higher serum TSH concentrations in adolescents compared with younger children [7]. In both Hancock's and Sklar's reports, older age at treatment of HD was a major risk factor for future development of an underactive thyroid. This may reflect the greater sensitivity of the thyroid gland in rapidly growing puber-

### Table 9.1. Thyroid disease after treatment of Hodgkin's disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>No. of patients/total no.</th>
<th>Actuarial risk (%)</th>
<th>Time to occurrence (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>20 years</td>
<td>26 years</td>
</tr>
<tr>
<td>At least one thyroid disease</td>
<td>573/1787</td>
<td>50</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>570/1677</td>
<td>52</td>
<td>67</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>513/1787</td>
<td>41</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>512/1677</td>
<td>43</td>
<td>47</td>
</tr>
<tr>
<td>Graves' disease b</td>
<td>34/1787</td>
<td>3.1</td>
<td>3.1</td>
</tr>
<tr>
<td></td>
<td>32/1677</td>
<td>3.3</td>
<td>3.3</td>
</tr>
<tr>
<td>Graves' ophthalmopathy B</td>
<td>21/1677</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Silent thyroiditis</td>
<td>6/1677</td>
<td>1.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Hashimoto's thyroiditis</td>
<td>4/1677</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Thyroidectomy</td>
<td>26/1677</td>
<td>6.6</td>
<td>26.6</td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>6/1677</td>
<td>1.7</td>
<td>1.7</td>
</tr>
<tr>
<td>Benign adenoma</td>
<td>10/1677</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Adenomatous nodule</td>
<td>6/1677</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Multinodular goiter</td>
<td>4/1677</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Clinically benign nodule</td>
<td>12/1677</td>
<td>3.3</td>
<td>5.1</td>
</tr>
<tr>
<td>Clinically benign cyst</td>
<td>4/1677</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Multinodular goiter c</td>
<td>2/1677</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

* a The total refers either to all 1787 patients at risk or to the 1677 patients who underwent irradiation of the thyroid region.

* b Thirty of the 34 patients who had been given a diagnosis of Graves' disease had hyperthyroidism; ophthalmopathy developed in three during a period of hypothyroidism and in one during a period of euthyroidism.

* c Identified by clinical examination.

(From [16], with permission.)
tal children, compared with preadolescents; or, it may reflect the fact that the older children generally received a higher radiation dose than the younger children. The iodine load from LAG may be a causal factor in the hypothyroidism observed in patients who are irradiated for Hodgkin’s disease. In fact, there is a low, but greater than expected incidence, of hypothyroidism in patients having LAG without neck irradiation. Some recent reviews found that thyroid function was more likely to be abnormal in patients irradiated soon after LAG and mantle irradiation. However, no influence of LAG on thyroid dysfunction was noted in other studies [32, 38, 43]. The role of chemotherapy in producing thyroid abnormalities is less understood. The influence of chemotherapy on the development of thyroid dysfunction among Hodgkin’s patients appears to be negligible in most reports [7, 11, 42], although data from England suggest that chemotherapy may add to the frequency of compensated hypothyroidism [25].

Primary hypothyroidism following irradiation of the spinal axis in the course of treating children with CNS tumors is also well documented. Ogilvy-Stuart [25] evaluated 85 such children and found a 32% incidence of compensated hypothyroidism. Constine [6] evaluated eight children treated with 4–10MV photon radiation to the spinal axis (mean dose: 30 Gy). Three demonstrated primary thyroid injury with low serum free-T4 concentration and an exaggerated TSH response to provocative testing with thyrotropin releasing hormone (TRH). Other reports indicate an incidence for compensated hypothyroidism of 20–68%, with overt hypothyroidism being rare [19, 24].

A recent study by Paulino [26] reviewed the incidence of hypothyroidism in children with medulloblastoma treated with lower dose CSI (23.4 Gy) plus chemotherapy (CT), compared with higher dose CSI (36 Gy) alone or in combination with CT. Paulino found that 56% patients developed hypothyroidism (38% primary and 19% central) at a median of 41 months after CSI. Hypothyroidism was more common in patients treated with combined chemotherapy and radiation than in those treated with radiation therapy alone, suggesting that chemotherapy did augment the effects of RT. A recent analysis by the Childhood Cancer Survivor Study (CCSS) [17] showed that the risk of adult survivors of childhood brain tumors developing hypothyroidism was more than twice as great for patients who had received a thyroid radiation dose >25 Gy, compared with the risk of patients who received a radiation dose of <25 Gy, with an RR of 2.7. Another study by Schmiegelow et al. [33] compared CSI with cranial irradiation (CIR) in causing hypothyroidism among survivors of childhood brain tumors. The overall incidence of primary hypothyroidism was 24%, of whom 71% had been treated with CSI, versus 29% who had been treated with CIR. In the CIR cohort, primary hypothyroidism was more common than central hypothyroidism, suggesting that the thyroid was directly affected by scattered radiation from the cranial RT field.

Overall, the role of chemotherapy in causing thyroid dysfunction in survivors of brain tumors remains controversial. The study by Paulino suggests that chemotherapy might be more causative in the induction of hypothyroidism than was previously recognized, but the number of patients was small. Nevertheless, Paulino concluded that the benefit of lowering RT dose was negated by the addition of chemotherapy. Two other reports supported his conclusion [19, 25], but two more studies did not find an association [4, 33].

Patients undergoing a bone-marrow transplant who receive total body irradiation (TBI) are also at risk for thyroid injury due to direct injury to the thyroid gland, rather than to the pituitary-hypothalamic axis. Sklar [36] found that a single dose of 7.5 Gy caused a decrease in serum T4 concentration in 9% patients and an elevated serum TSH concentration in 35%. The frequency of overt hypothyroidism following transplantation is highly variable and depends largely on the conditioning regimen. It was found to be nearly 90% with a 10 Gy, single-dose of TBI [18], but only 15% with fractionated TBI. The frequency of overt hypothyroidism was even less common after conditioning with Bu-Cy [40].

Thyroid abnormalities have been observed among long-term survivors of acute lymphoblastic leukemia (ALL). Robibson [28] collected data on 175 survivors first evaluated seven years after diagnosis. Seventeen
(10%) had thyroid function abnormalities, including five with uncompensated primary hypothyroidism and 11 with compensated hypothyroidism. Eight in the latter group reverted to normal without replacement therapy. No significant association was observed between hypothyroidism and the radiation dose (18 Gy versus 24 Gy), duration of chemotherapy (3 years versus 5 years), or age at the time of irradiation.

### 9.2.2 Hyperthyroidism

The potential for Graves’ disease also appears to be increased after RT for Hodgkin’s disease, with a risk that is 7.2–20.4 times the expected risk [16]. In the same childhood cancer survivors study described by Sklar et al., the RR of developing a hyperactive thyroid gland among HD survivors was found to be 8, with 5% of patients diagnosed with hyperthyroidism. The mean time between diagnosis of HD and development of hyperthyroidism was 8 years. A radiation dose of ≥35 Gy was an independent predictor of hyperthyroidism [37]. An immunologic basis has been suggested as an explanation for the apparent higher frequency observed after treatment for Hodgkin’s disease, compared with other malignancies in which the neck is incidentally irradiated.

### 9.2.3 Thyroid Nodules

Extensive data exist on the development of benign thyroid nodules and malignancy after thyroid RT. Representative incidences for thyroid nodules are 6% for malignant and 8–12% for benign lesions following lower dose (less than 15 Gy) external beam RT [8]. The latency period for the development of thyroid cancer following thyroid RT varies from 5–26 years [37]. A recent report from the Late Effects Study Group [44] found that, of 9170 patients who had survived two or more years after the diagnosis of a cancer in childhood, the risk for thyroid cancer was 53 times as great. This risk was associated with both increasing radiation dose and the time from treatment. Sixty-eight percent of the cancers occurred in areas directly within the radiation field, and the thyroid glands of all patients had received at least 1 Gy (via scatter for some patients).

Hancock et al. [16] observed nodularity in 44 of 1677 patients treated for Hodgkin’s disease 1.5–25 years after RT. Six patients were diagnosed with malignant nodules, with an RR of 15.6 (95% CI, 6.3–32.5). The other two reports found an RR for developing thyroid cancer among childhood Hodgkin’s disease survivors following RT almost identical at 32.7 (95% CI, 15.3–55.3) and 33 (95% CI, 15–62), suggesting that children are at greater risk [2, 31]. Patients treated for neuroblastoma and Wilms’ tumor were affected more commonly than those treated for HD; however, patients with the former two cancers were generally younger in age, which may be associated with an increase in risk for thyroid cancer as a second malignancy when data from children are compared with those from adults.

In the recent report by Sklar et al. [37], the incidence of thyroid nodules in HD survivor patients was 9%, with an RR of 27, compared with sibling controls, and 7.5% of these nodules were malignant. There were nine cases of thyroid cancer without any known associated thyroid nodule. The RR of developing thyroid cancer was 18.3, compared with the general population. Their multivariate analysis revealed that an interval ≥10 years since diagnosis, female sex and radiation dose ≥ 25 Gy were independently associated with future development of thyroid nodules.

In Hancock’s data [16], the risk for developing thyroid cancer nine to 18 years after RT was 15.6%. In a study by Schneider and colleagues [34], 318 of 5379 patients who had received RT for benign conditions of the head and neck developed thyroid cancer 3–42 years later. Overall, in this setting (low dose RT, generally 2–5 Gy, for benign conditions) new nodules develop at a rate about 2% per year, with a peak incidence at 15 to 25 years [10]. It is crucial to review the pathology of any biopsied nodule carefully, because an adenomatous nodule with cytologic atypia can be difficult to distinguish from thyroid carcinoma [5]. The most common type of cancer in this study was papillary carcinoma, which, fortunately, has a high cure rate if detected early [30]. The course of the cancer in these patients was the same as that of thyroid cancer found in other settings [34]. It is important to note that thyroid nodules have been found during surgery or autopsy in as many as 35–50% of a non-
irradiated population, and that clinically palpable nodules are found in 4–7% of normal adults [22, 27, 39, 41].

9.3 Detection and Screening

It is clearly important to obtain a comprehensive history and perform a thorough physical examination in all patients who received direct or scattered RT to the neck. Laboratory screening evaluations for asymptomatic patients should include serum concentrations of TSH and thyroxine (usually, free T4) tests. The measurement of free T4 rather than other tests (usually, total T4 by radioimmunoassay) is recommended because the former is not affected by changes in binding proteins [46]. Although some patients with normal serum-free T4 and TSH concentrations might show an exaggerated TSH response to provocative testing with TRH, the clinical significance of this finding is unclear. Screening for immunologic abnormalities can be performed by examining serum concentrations of antimicrosomal and antithyroglobulin antibodies, but abnormalities in asymptomatic patients are, again, of uncertain clinical significance. Patients with palpable abnormalities of the thyroid gland should undergo ultrasonography (USG) to evaluate the number, location and density of nodules and 99mTc scanning to evaluate the functional status of the nodules. Whether all patients who have received radiation to the thyroid gland should undergo periodic screening with one or the other of these techniques is controversial. Stewart and colleagues performed USG on 30 patients treated with mantle radiation for Hodgkin’s disease who did not have palpable abnormalities and found unilateral or bilateral atrophy in eight patients, multiple hypoechogenic lesions smaller than 0.75 cm in 18 and dominant cystic solid or complex lesions larger than 0.75 cm in seven patients [41]. Biopsies were not performed. Soberman [39] performed USG on 18 long-term survivors of Hodgkin’s disease who had received a mean dose of 34 Gy to the neck 1–16 years (mean 6.4) previously; 16 patients (89%) had abnormalities, including diffuse atrophy (nine cases), solitary nodules (five cases), multiple nodules (six cases) and gland heterogeneity (one case). Only two patients had palpable nodules. Biopsies in four patients revealed multifocal papillary carcinoma in one patient and adenomas in three patients.

We have performed 99mTc scanning in 34 patients who were irradiated to the cervical region for Hodgkin’s disease or other malignancy. All patients had an interval of at least five years since radiation treatment, all were euthyroid and all were without palpable thyroid abnormalities. Seven patients (21%) had abnormal scans, and two of these patients were diagnosed with thyroid cancer [30]. Patient numbers are currently too small to make firm recommendations. Although 99mTc scanning is less sensitive than USG, its specificity for detecting clinically-significant nodules is greater.

9.4 Management

The functions regulated by the thyroid gland are particularly important in a growing child. Therefore, early diagnosis and treatment of hypothyroidism, even when subclinical, is required to optimize growth, cognition and progression to puberty [35].

Patients with uncompensated hypothyroidism (low serum concentration of thyroxine) clearly require thyroid replacement therapy. In most institutions, patients with compensated hypothyroidism (elevated serum concentrations of TSH but normal thyroxine) also are treated with thyroid replacement therapy. The rationale for this approach is based on animal studies, which have demonstrated that elevated levels of TSH in the presence of irradiated thyroid tissue can lead to the development of thyroid carcinoma. The observation of thyroid cancer following neck irradiation in humans and the high frequency of elevated serum TSH concentrations in children who have received radiation for Hodgkin’s disease have prompted us to institute thyroid replacement therapy in this population. Approaches to decrease the risk of thyroid injury in the setting of RT for Hodgkin’s disease have included shielding the gland from irradiation [20] and administering thyroxine during irradiation [1]. The former approach was found to place patients at risk for the inadvertent shielding of dis-
eased cervical lymph nodes, and the latter approach did not prevent subsequent hypothyroidism. Therefore, these approaches are not recommended. Thyroid tissue is routinely protected from the radio-iodides used in MIBG scanning by administering a large dose of cold iodide, but this approach is successful in only 36% of patients. A recent study by van Santen et al. [45] found that administering thyroxine, methimazole (a drug to treat hyperthyroidism) and potassium iodide protects the thyroid gland effectively against radiation damage from Iodine-123/131 during diagnostic and therapeutic MIBG administration in children with neuroblastoma. At 2.6 years follow-up, this combination had successfully protected the thyroid in 85.6% of children. In contrast, the protection afforded by potassium iodide alone was 60%.

Patients with palpable thyroid abnormalities should undergo USG or 99mTc scanning and be evaluated by an endocrinologist and surgeon. If nodules are discovered, then biopsy is necessary. Depending on the results, further therapy may be necessary. The treatment approaches vary in different centers, as recently reviewed by Mazzaferri [21]. For papillary thyroid carcinoma, treatment will generally involve near total thyroidectomy, radioactive iodine and TSH suppression with thyroxine [9]. It remains unclear how best to treat patients who are not receiving replacement hormone and have clinically normal thyroid glands, but who also have nodules detected by USG or 99mTc scanning. Multiple small 2–3 mm carcinomas have been found in irradiated thyroid glands [18]. Because autopsies have shown a high incidence of occult (less than 1 mm) papillary carcinomas, the significance of cancer found in clinically occult lesions is arguable. However, it would seem appropriate to biopsy nodules that are detectable until additional information is available for more definite guidelines.

References