activated in the liver, have cleavage products (acrolein) that can produce hemorrhagic cystitis. This can be prevented with the free radical scavenger MESNA (mercaptoethane sulfonate), which is required for ifosfamide administration. Hemorrhagic cystitis caused by these agents may predispose to bladder cancer.

## REPRODUCTIVE AND ENDOCRINE DYSFUNCTION

### CHEMOTHERAPEUTIC AGENTS

Alkylating agents are associated with the highest rates of male and female infertility, which is directly dependent on age, dose, and duration of treatment. The age at treatment is an important determinant of fertility outcome, with prepubertal patients having the highest tolerance. Ovarian failure is age related, and females who resume menses after treatment are still at increased risk for premature menopause. Males generally have reversible azoospermia during lower intensity alkylator chemotherapy, and long-term infertility is associated with doses of cyclophosphamide >9 g/m$^2$ and with high-intensity therapy, such as that used in hematopoietic stem cell transplantation. Males undergoing potentially sterilizing chemotherapy should be offered sperm banking. Gonadotropin-releasing hormone (GnRH) analogs remain experimental to preserve ovarian function. Assisted reproductive technologies can be helpful to couples with chemotherapy-induced infertility.

### RADIATION THERAPY

Testicles and ovaries in prepubertal patients are less sensitive to radiation damage; spermatogenesis is affected by low doses of radiation, and complete azoospermia occurs at 600–700 cGy. Leydig cell dysfunction, in contrast, occurs at <2000 cGy, and hence, endocrine function is lost at much higher radiation doses than spermatogenesis. Erectile dysfunction occurs in up to 80% of men treated with external-beam radiation therapy for prostate cancer. Sildenafil may be useful in reversing erectile dysfunction. Ovarian function damage with radiation is age related and occurs at doses of 150–500 cGy. Premature induction of menopause can have serious medical and psychological sequelae. Hormone replacement therapy is often contraindicated (as in estrogen receptor–positive breast cancer). Attention must be paid to maintenance of bone mass with calcium and vitamin D supplements and oral bisphosphonates, and bone mass should be monitored using bone density determinations. Paroxetine, clonidine, pregabalin, and other drugs may be useful in symptomatically controlling hot flashes.

Long-term survivors of childhood cancer (e.g., ALL) who have received cranial radiation may have altered leptin biology and growth hormone deficiency, leading to obesity and reduced strength, exercise tolerance, and bone density.

Radiation therapy to the neck (e.g., in Hodgkin's lymphoma) may lead to hypothyroidism, Graves' disease, thyroiditis, and thyroid malignancies. Thyroid-stimulating hormone (TSH) is followed routinely in such patients to prevent hypothyroidism, and to suppress persistently elevated levels of TSH which may cause or drive thyroid cancer.

## OCULAR COMPLICATIONS

Cataracts may be caused by glucocorticoids, depending on duration and dose; radiation therapy; and uncommonly tamoxifen. Orbital radiation therapy may cause blindness.

## ORAL COMPLICATIONS

Radiation therapy can produce xerostomia (dry mouth), with an attendant increase in caries and poor dentition. Taste and appetite may be suppressed. Bisphosphonate use may result in osteonecrosis of the jaw.

## RAYNAUD'S PHENOMENON

Up to 40% of patients treated with bleomycin may develop Raynaud's phenomenon as a result of an unknown mechanism.

## SECOND MALIGNANCIES

Second malignancies in patients cured of cancer are a major cause of death, and treated cancer patients must be monitored for their occurrence. The induction of second malignancies is governed by the complex interplay of a number of factors including age, gender, environmental exposures, genetic susceptibility, and cancer treatment itself. In a number of settings, the events leading to the primary cancer themselves increase the risk of second malignancies. Patients with lung cancer are at increased risk of esophageal and head and neck cancers, and vice versa, due to shared risk factors including alcohol and tobacco abuse. Indeed, the risk of developing a second primary head and neck, esophageal, or lung cancer is also increased in these patients. Patients with breast cancer are at increased risk of breast cancer in the opposite breast. Patients with Hodgkin's lymphoma are at risk for non-Hodgkin's lymphomas. Genetic cancer syndromes (e.g., multiple endocrine neoplasia or Li-Fraumeni, Lynch's, Cowden's, and Gardner's syndromes) are examples of genetically based second malignancies of specific types. Cancer treatment itself does not appear to be responsible for the risk of these secondary malignancies. Deficient DNA repair can greatly increase the risk of cancers from DNA-damaging agents, as in ataxia-telangiectasia. Importantly, the risk of treatment-related second malignancies is at least additive and often synergistic with combined chemotherapy and radiation therapy, and hence for such combined-therapy treatment approaches, it is important to establish the necessity of each in the treatment program. All of these patients require special surveillance or, in some cases, prophylactic surgery as part of appropriate treatment and follow-up.

### CHEMOTHERAPEUTIC AGENTS

Chemotherapy is significantly associated with two fatal second malignancies, acute leukemia and myelodysplastic syndromes. Two types of leukemia have been described; in patients treated with alkylating agents, acute myeloid leukemia is associated with deletions in chromosome 5 or 7. The lifetime risk is about 1–5%, is increased by radiation therapy, and increases with age. The incidence of these leukemias peaks at 4–6 years, with risk returning close to baseline at 10 years. The other type of acute myeloid leukemia is related to therapy with topoisomerase inhibitors, is associated with chromosome 10q23 translocations, has an incidence of <1%, and generally occurs 1.5–3 years after treatment. Both of these acute myeloid leukemias are refractory to treatment and have a high mortality. The development of myelodysplastic syndromes is increased following chemotherapy, and these are often associated with leukemic progression and a dismal prognosis.

### RADIATION THERAPY

Patients receiving radiation have an increasing and lifelong risk of second malignancies that is 1–2% in the second decade following treatment but increases to >25% after 25 years. These malignancies include cancers of the thyroid and breast, sarcomas, and CNS cancers, which often tend to be aggressive and have a poor prognosis. An example of organ-, age-, and sex-dependent radiation-induced secondary malignancy is breast cancer, in which the risk is small with radiation in women under age 30 but increases about 20-fold over baseline in women over 30. A 25-year-old woman treated with mantle radiation for Hodgkin's lymphoma has a 29% actuarial risk of developing breast cancer by age 55.

### HORMONAL THERAPY

Treatment of breast cancer with tamoxifen for 5 years or longer is associated with a 1–2% risk of endometrial cancer. Surveillance is generally effective at finding these cancers at an early stage. The risk of mortality from tamoxifen-induced endometrial cancer is low compared to the benefit of tamoxifen as adjuvant therapy for breast cancer.

### IMMUNOSUPPRESSIVE THERAPY

Immunosuppressive therapy, as used in allogeneic bone marrow transplantation, particularly with T cell depletion using antithymocyte globulin or other means, increases the risk of Epstein Barr virus–associated