of mutations that appear to stem from nontemplated error-prone repair of pyrimidine dimers, reinforcing the belief that sun exposure has an important causative role in this potentially lethal cancer.

Ionizing Radiation

Electromagnetic (x-rays, γ rays) and particulate (α particles, β particles, protons, neutrons) radiations are all carcinogenic. The evidence is so voluminous that a few examples suffice. Many individuals pioneering the use of x-rays developed skin cancers. Miners of radioactive elements in central Europe and the Rocky Mountain region of the United States have a tenfold increased incidence of lung cancers compared to the rest of the population. Most telling is the follow-up of survivors of the atomic bombs dropped on Hiroshima and Nagasaki. Initially there was a marked increase in the incidence of certain forms of leukemia after an average latent period of about 7 years. Subsequently the incidence of many solid tumors with longer latent periods (e.g., carcinomas of the breast, colon, thyroid, and lung) increased. Of great concern in the current era of widespread use of computerized tomography (CT scans) are studies that have shown that children who get two or three CT scans have a threefold higher risk of leukemia, and those that received five to 10 such scans have a threefold higher risk of brain tumors. The overall risk in children is very low (roughly one excess leukemia and one excess brain tumor over 10 years per 10,000 CT scans), but nevertheless emphasizes the need to minimize radiation exposure whenever possible.

In humans there is a hierarchy of vulnerability of different tissues to radiation-induced cancers. Most frequent are myeloid leukemias (tumors of granulocytes and their precursors; Chapter 13). Cancer of the thyroid follows closely but only in the young. In the intermediate category are cancers of the breast, lungs, and salivary glands. In contrast, skin, bone, and the gastrointestinal tract are relatively resistant to radiation-induced neoplasia, even though the gastrointestinal epithelial cells are vulnerable to the acute cell-killing effects of radiation, and the skin is "first in line" for all external radiation. Nonetheless, the physician must not forget: practically *any* cell can be transformed into a cancer cell by sufficient exposure to radiant energy.

KEY CONCEPTS

Radiation Carcinogenesis

- Ionizing radiation causes chromosome breakage, translocations, and, less frequently, point mutations, leading to genetic damage and carcinogenesis.
- UV rays induce the formation of pyrimidine dimers within DNA, leading to mutations. Therefore, UV rays can give rise to squamous cell carcinomas and melanomas of the skin. Individuals with defects in the repair of pyrimidine dimers suffer from Xeroderma pigmentosa and are at particularly high risk.
- Exposure to radiation during imaging procedures such as CT scans is linked to a very small, but measurable, increase in cancer risk in children.

Microbial Carcinogenesis

Many RNA and DNA viruses have proved to be oncogenic in animals as disparate as frogs and primates. Despite intense scrutiny, however, only a few viruses have been linked with human cancer. Our discussion focuses on human oncogenic viruses as well as the role of the bacterium *Helicobacter pylori* in gastric cancer.

Oncogenic RNA Viruses

Human T-Cell Leukemia Virus Type 1. Although the study of animal retroviruses has provided spectacular insights into the molecular basis of cancer, only one human retrovirus, human T-cell leukemia virus type 1 (HTLV-1), is firmly implicated in the pathogenesis of cancer in humans.

HTLV-1 causes *adult T-cell leukemia/lymphoma* (ATLL), a tumor that is endemic in certain parts of Japan, the Caribbean basin, South America, and Africa, and found sporadically elsewhere, including the United States. Worldwide, it is estimated that 15 to 20 million people are infected with HTLV-1. Similar to the human immunodeficiency virus, which causes AIDS, HTLV-1 has tropism for CD4+ T cells, and hence this subset of T cells is the major target for neoplastic transformation. Human infection requires transmission of infected T cells via sexual intercourse, blood products, or breastfeeding. Leukemia develops in only 3% to 5% of the infected individuals, typically after a long latent period of 40 to 60 years. A high fraction of the leukemias express the transcription factor FoxP3, a marker of regulatory T cells (Tregs) that act to suppress immune responses. It is hypothesized that the neoplastic expansion of Tregs in ATLL may underlie the susceptibility of affected patients to opportunistic infections, which are a frequent cause of death.

There is little doubt that HTLV-1 infection of T lymphocytes is necessary for leukemogenesis, but the molecular mechanisms of transformation are not certain. In contrast to several murine retroviruses, HTLV-1 does not contain an oncogene, and no consistent integration next to a proto-oncogene has been discovered. In leukemic cells, however, viral integration shows a clonal pattern. In other words, although the site of viral integration in host chromosomes is random (the viral DNA is found at different locations in different cancers), the site of integration is identical within all cells of a given cancer. This would not occur if HTLV-1 were merely a passenger that infects cells after transformation; rather, it means that HTLV-1 must have been present at the moment of transformation, placing it at the "scene of the crime."

The HTLV-1 genome contains the *gag*, *pol*, *env*, and long-terminal-repeat regions typical of all retroviruses, but, in contrast to other leukemia viruses, it contains another gene referred to as *tax*. **Several aspects of HTLV-1's transforming activity are attributable to Tax,** the protein product of this gene. Tax is essential for viral replication, because it stimulates transcription of viral RNA from the 5′ long terminal repeat. However, Tax also alters the transcription of several host cell genes and interacts with certain host cell signaling proteins. By doing so, Tax contributes to the acquisition of several cancer hallmarks, including the following:

- **Increased pro-growth signaling and cell survival.** Tax interacts with PI3K and thereby stimulates AKT; as