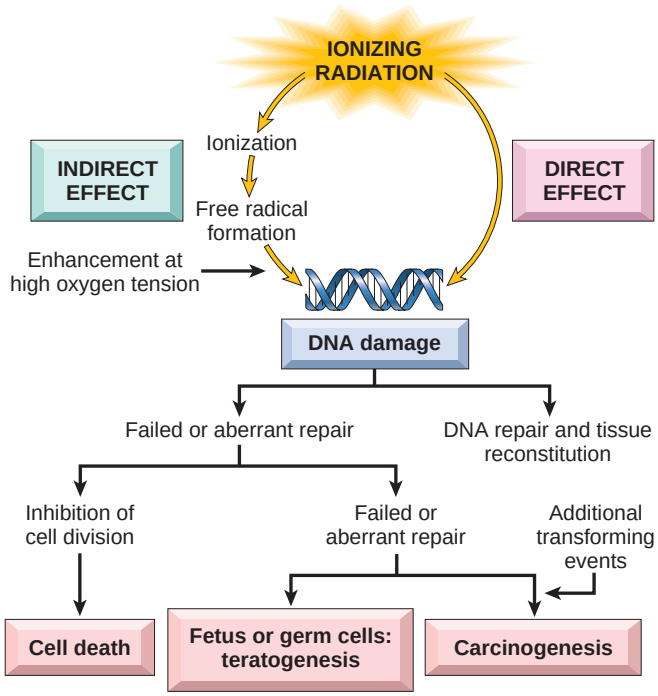


**Figure 9-16** Effects of ionizing radiation on DNA and its consequences. The effects on DNA can be direct, or most importantly, indirect, through free radical formation.

irradiation does not kill nondividing cells, such as neurons and muscle cells. However, as discussed in Chapter 7, in dividing cells DNA damage is detected by sensors that produce signals leading to the upregulation of p53, the "guardian of the genome". p53 in turn upregulates the expression of genes that initially lead to cell cycle arrest and, if the DNA damage is too great to be repair, genes that cause cell death through apoptosis. Understandably, therefore, tissues with a high rate of cell division, such as *gonads, bone marrow, lymphoid tissue*, and the *mucosa of the gastrointestinal tract*, are extremely vulnerable to radiation, and the injury is manifested early after exposure.

- *Oxygen effects and hypoxia*. The production of reactive oxygen species from reactions with free radicals generated by radiolysis of water is the major mechanism by which DNA is damaged by ionizing radiation. Poorly vascularized tissues with low oxygenation, such as the center of rapidly growing tumors, are generally less sensitive to radiation therapy than nonhypoxic tissues.
- *Vascular damage*. Damage to endothelial cells, which are moderately sensitive to radiation, may cause narrowing or occlusion of blood vessels leading to impaired healing, fibrosis, and chronic ischemic atrophy. These changes may appear months or years after exposure (Fig. 9-17). Late effects in tissues with a low rate of cell proliferation, such as the brain, kidney, liver, muscle, and subcutaneous tissue, may include cell death, atrophy, and fibrosis. These effects are associated with vascular damage and the release of proinflammatory mediators in irradiated areas.

Figure 9-18 shows the overall consequences of radiation exposure. These consequences vary according to the dose of radiation and the type of exposure. Table 9-7 lists the estimated threshold doses for acute effects of radiation aimed at specific organs; Table 9-8 lists the syndromes caused by exposure to various doses of total-body radiation.

## MORPHOLOGY

Cells surviving radiant energy damage show a wide range of structural **changes in chromosomes** that are related to double-stranded DNA breaks, including deletions, translocations, and fragmentation. The mitotic spindle often becomes disorderly, and polyploidy and aneuploidy may be encountered. **Nuclear swelling** and condensation and clumping of chromatin may appear; disruption of the nuclear membrane may also be noted. Apoptosis may occur. Several **abnormal nuclear morphologies** may be seen. Giant cells with pleomorphic nuclei or more than one nucleus may appear and persist for years after exposure. At extremely high doses of radiant energy, markers of cell death, such as nuclear pyknosis and lysis, appear quickly.

In addition to affecting DNA and nuclei, radiant energy may induce a variety of **cytoplasmic changes**, including cytoplasmic swelling, mitochondrial distortion, and degeneration of the endoplasmic reticulum. Plasma membrane breaks and focal defects may be seen. The histologic constellation of cellular pleomorphism, giant-cell formation, conformational changes in nuclei, and abnormal mitotic figures creates a more than passing similarity between radiation-injured cells and cancer cells, a problem that plagues the pathologist when evaluating irradiated tissues for the possible persistence of tumor cells.

Vascular changes and interstitial fibrosis are also prominent in irradiated tissues (Fig. 9-19). During the immediate postirradiation period, vessels may show only dilation. With time, or with higher doses, a variety of degenerative changes appear, including endothelial cell swelling and vacuolation, or even necrosis and dissolution of the walls of small vessels such as capillaries and venules. Affected vessels may rupture or thrombose. Still later, endothelial cell proliferation and collagenous hyalinization and thickening of the intima are seen in irradiated vessels, resulting in marked narrowing or even obliteration of the vascular lumens. At this time, an increase in interstitial collagen in the irradiated field usually becomes evident, leading to scarring and contractions.

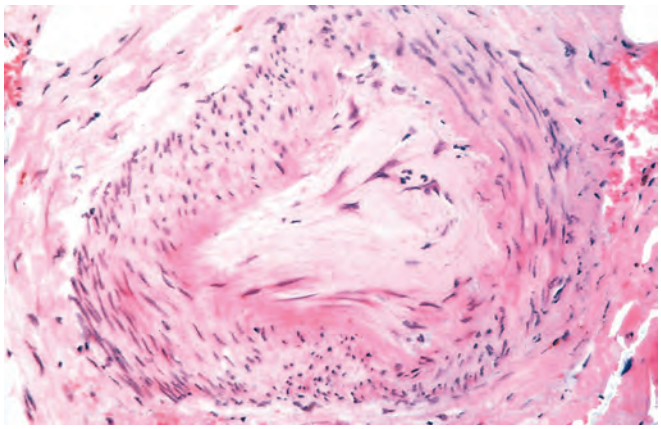

**Figure 9-17** Radiation-induced chronic vascular injury with subintimal fibrosis occluding the lumen. (American Registry of Pathology © 1990.)