The strong association between asbestos exposure and malignant mesothelioma has been widely accepted since 1960 (1,2). Although asbestos is the primary etiologic agent for this tumor, a significant number of patients who develop mesothelioma have no known asbestos exposure. Radiation, nonasbestos mineral fibers, organic chemicals, chronic inflammation (3), and simian virus 40 (SV40) exposure (4,5) have also been suggested as risk factors for mesothelioma in humans.

Because asbestos is ubiquitous, past exposures are often difficult to quantitate. Past asbestos exposure may be assessed by a standardized questionnaire that collects information on occupational, paraoccupational, environmental, and domestic contact with asbestos from insulation, mining, milling, heating trades, shipyard work, and construction (6). However, the long latency period of 20 years or longer from the onset of exposure to the development of malignant mesothelioma likely influences the accuracy of the exposure information obtained (1). More objective evidence of asbestos exposure includes radiologic findings such as bibasilar fibrosis and calcified pleural plaques, the presence of asbestos fibers in sputum or bronchoalveolar lavage samples, and evidence of interstitial fibrosis or ferruginous bodies in lung tissue (7). These criteria have been used to try to exclude asbestos as the causal factor in some cases of mesothelioma.

In published case series, the proportion of mesothelioma cases that have an asbestos exposure history ranges from 16% to 77% (8). Of 668 patients who died of malignant mesothelioma in Canada and the United States from 1960 to 1975, only 50% of men and 5% of women had known asbestos exposure (9). Occupational asbestos exposure in women and children is rare; therefore, most asbestos exposure in these individuals is thought to come from a household member who is employed in an asbestos industry. The occurrence of malignant mesothelioma in children may not be related to asbestos at all. In a report of 13 children diagnosed with mesothelioma in the United States, the short latency period from the time of exposure to tumor development and the absence of geographic clustering argued against an environmental
cause for this malignancy in children (10). Therefore, the disease appears to have a “natural” incidence of undetermined origin. Radiation is a possible etiologic agent for mesothelioma that may act independently or may have a synergistic effect with asbestos (11).

Animal Models of Radiation-Induced Mesothelioma

Animal experiments conducted in the 1970s demonstrated that inhaled or implanted plutonium in rodents and dogs could induce epithelial and mesenchymal tumors in the lungs and thorax (12). When plutonium oxide was injected into the peritoneal cavity of rats, 27% of these animals developed epithelial mesotheliomas and 38% developed sarcomas of various types (13). Both the soft tissue sarcomas and mesotheliomas were frequently seen surrounding “hot spots” of plutonium activity in the omentum. The pattern of PuO₂-induced mesothelioma was similar to that observed following intracavitary administration of asbestos fibers.

However, when animals were given inhaled and intrapleurally injected plutonium dioxide, only a small fraction developed pleural mesotheliomas (14). Only five of 2105 rats given aerosolized ²³⁹PuO₂ developed pleural mesotheliomas, and one of 27 rats given intrapleural injection developed these tumors. The reason for the low incidence appeared to be the rapid clearance of ²³⁹PuO₂ to the thoracic, mediastinal, and hepatic lymph nodes, which limited alpha irradiation of the pleural mesothelium and subsequent mesothelioma formation.

Exposure to cerium-144 dioxide led to the development of mesothelioma in four of 566 study animals (15). Evidence supporting a possible synergistic effect of radiation with asbestos comes from experiments showing an increased incidence of mesothelioma in rats after both irradiation and the administration of asbestos compared with animals that received asbestos alone (16).

Carcinogenic Effect of Radiation in Humans

Evidence that radiation is a human carcinogen comes from a number of epidemiologic studies reported in the literature (17,18). Studies on atomic bomb survivors have shown increased rates of cancers of the lung, breast, thyroid, stomach, urinary tract, and colon, as well as leukemia and multiple myeloma (19). Except for radiation-induced leukemias, which develop a few years after exposure, the average latency period for the development of solid tumors after radiation is more than 15 years (20).

Cancer can also occur as a secondary effect of therapeutic radiation (21). Advances in radiation therapy for cancer have led to increased survival for many patients, but a serious late complication of treatment is the development of second primary malignancies. Radiotherapy-related second primary malignancies usually occur about 10 to 20 years after exposure often within the field of irradiation (22–25) or adjacent