Radiation is known to be a universal carcinogen, capable of causing cancer in most mammalian tissues (1). The specific type of radiation injury which leads to cancer, however, is still unknown; many hypotheses for the mechanism of radiation induced cancer are discussed elsewhere (1).

It is widely believed that it is a change in the cellular DNA which gives rise to the malignant transformation of a cell. Radiation is known to produce several different types of characteristic DNA lesions, such as single and double-strand breaks (at the phosphodiester bond) in the DNA, apurinic and apyrimidinic sites, and specific products such as 5,6 dihydroxydihydrothymine (from ionizing radiation) or pyrimidine dimers (from UV light), etc. The biologic consequences of these DNA lesions are unknown.

It is generally recognized that carcinogenesis is a multi-step process which involves two or more intracellular events to transform a normal cell into a cancer cell. There are three major hypotheses concerning the mechanism(s) by which radiation induces these changes: a) mutations, including changes in single genes or alterations in chromosome structure, b) changes in the gene expression patterns of cells and c) induction of an oncogenic virus which in turn causes cancer. Although there continues to be controversy among investigators as to which of these mechanisms plays the major role in radiation carcinogenesis, the hypotheses are not mutually exclusive; carcinogenesis may involve different mechanisms at different stages in the multi-step process.

The somatic mutation theory of carcinogenesis, originally proposed by Theodor Boveri in 1914 (2), still receives widespread support, as has been discussed in detail elsewhere (1). According to this theory, a change in the DNA sequence results in cancer. Specific mutations which have been observed in DNA in radiation induced carcinogenesis are shown in Figure 1 (3-10).

The major alternative to the somatic mutation theory is the "epigenetic" theory of carcinogenesis, i.e., that malignant cells do not result from changes in the genetic code, but instead result from changes in the expression patterns of the cellular genes. According to this theory, a carcinogen alters the expression pattern of a normal cell and thereby changes it into a pre-neoplastic or a cancer cell. Of importance to this theory is the fact that nuclei transplanted from cancer cells to enucleated cells or ova can produce normal cells and even complete normal organisms of several species, including mice (reviewed in ref.11). Evidence that an epigenetic change is involved in radiation carcinogenesis is discussed below.
1. **Ras Alterations**

   Mouse Lymphomas [Guerrero et al. (3,4)]
   Dog lung tumors and leukemia cells [Frazier et al.(5)]
   Rat skin tumors [Sawey et al. (6)]

2. **Alterations in c-myc**

   Rat skin tumors [Sawey et al. (6)]
   In vitro-Mouse C3H10T1/2 cells [Sawey and Kennedy (7)]

3. **Non-ras Genes Which Cause Transformation in the NIH3T3 Transfection Assay System**

   In vitro-mouse C3H10T1/2 cells [Borek et al. (8)]
   In vitro-mouse C3H10T1/2 cells [Sawey and Kennedy(7)]
   In vitro-human W1-38 cells. [Mizuki et al. (9)]
   Mouse skin tumors [Jaffe and Bowden (10)]

The theory that radiation induces a virus which ultimately causes cancer has been discussed at length in radiation biology. In one strain of mouse, radiation induces the "radiation leukemia virus," which has been thought to play a role in the induction of thymic lymphoma/leukemia (12). The evidence for the virus playing a causative role in the genesis of this disease has recently been challenged, however (13, 14).

It is now widely accepted that initiation, the first step in malignant transformation, begins the carcinogenic process, while promotion is often required to complete it (15). The "two-stage" model of carcinogenesis was originally developed from studies on mouse skin which involved administration of a low dose of an initiating carcinogen followed by repeated treatment with a promoting agent (16,17). The concept of two-stage carcinogenesis is now widely believed to be applicable to many different organ systems in vivo and many in vitro transformation systems. Many different initiating and promoting agents have been studied in both in vivo (18,19) and in vitro systems (20). At high doses, most initiating agents are carcinogenic by themselves, with only one exposure being necessary for carcinogenesis to occur (21). Promoting agents, however, must be given over a long period of time (22). Several different phases of promotion can be distinguished in in vivo promotion systems, with different compounds being able to promote or suppress the various specific stages involved in promotion (19). Promoting agents often shorten the latent period for cancer development (22). Another stage in carcinogenesis is referred to as tumor progression, which refers to the conversion of a benign tumor into a malignant tumor.

Radiation is likely to play a role in all of the phases of carcinogenesis which have been studied experimentally. Radiation has been shown to work as an "initiating agent" for several types of carcinogenesis in vivo (23), including two-stage carcinogenesis with croton oil (24) or TPA (25,26) as the