cancer! Subsequently, hundreds of chemicals have been shown to be carcinogenic in animals. Some of the major agents are presented in Table 7-10.

Steps Involved in Chemical Carcinogenesis

As discussed earlier, carcinogenesis is a multistep process. This is readily demonstrated in experimental models of chemical carcinogenesis, in which the stages of initiation and progression during cancer development were first described. The classic experiments that allowed the distinction between initiation and promotion were performed on mouse skin (Fig. 7-43), and revealed the following concepts relating to the initiation-promotion sequence:

- **Initiation** results from exposure of cells to a sufficient dose of a carcinogenic agent; an initiated cell is altered, making it potentially capable of giving rise to a tumor. Initiation alone, however, is not sufficient for tumor formation (Fig. 7-43, treatment group 1).
- **Initiation causes permanent DNA damage (mutations); it is therefore rapid and irreversible and has "memory."** Thus, tumors are produced even if the application of the promoting agent is delayed for several months after a single application of the initiator (Fig. 7-43, treatment group 3).
- **Promoters can induce tumors to arise from initiated cells, but they are nontumorigenic by themselves**. Furthermore, tumors do not result when the promoting agent is applied before, rather than after, the initiating agent (Fig. 7-43, treatment group 4). This indicates that, in contrast to the effects of initiators, the cellular changes resulting from the application of promoters do not affect DNA directly and are reversible. As discussed later, promoters enhance the proliferation of initiated cells, an effect that may contribute to the acquisition of additional mutations.

Although the concepts of initiation and promotion have been derived largely from experiments involving induction of skin cancer in mice, they are also useful concepts when considering the roles of certain factors that contribute to human cancers. With this brief overview, initiation and promotion can be examined in more detail (Fig. 7-44). All initiating chemical carcinogens are highly reactive electrophiles (have electron-deficient atoms) that can react with nucleophilic (electron-rich) sites in the cell. Their targets are DNA, RNA, and proteins, and in some cases these interactions cause cell death. Initiation, obviously, inflicts nonlethal damage to the DNA that cannot be repaired. The mutated cell then passes on the DNA lesions to its daughter cells. Chemicals that can cause initiation of carcinogenesis can be classified into two categories: direct acting and indirect acting.

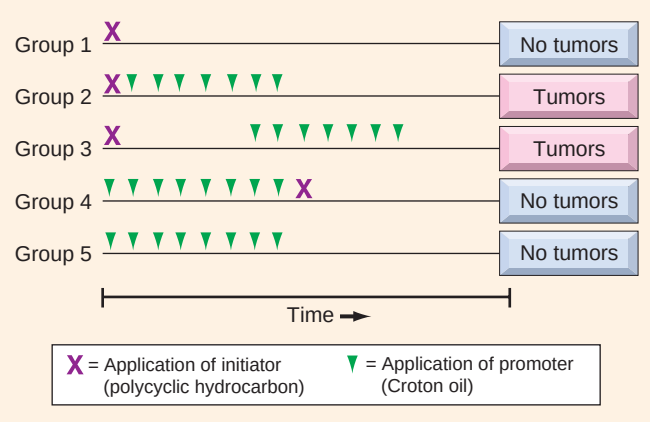

Figure 7-43 Experiments demonstrating the initiation and promotion phases of carcinogenesis in mice. Group 2: application of promoter repeated at twice-weekly intervals for several months. Group 3: application of promoter delayed for several months and then applied twice weekly.

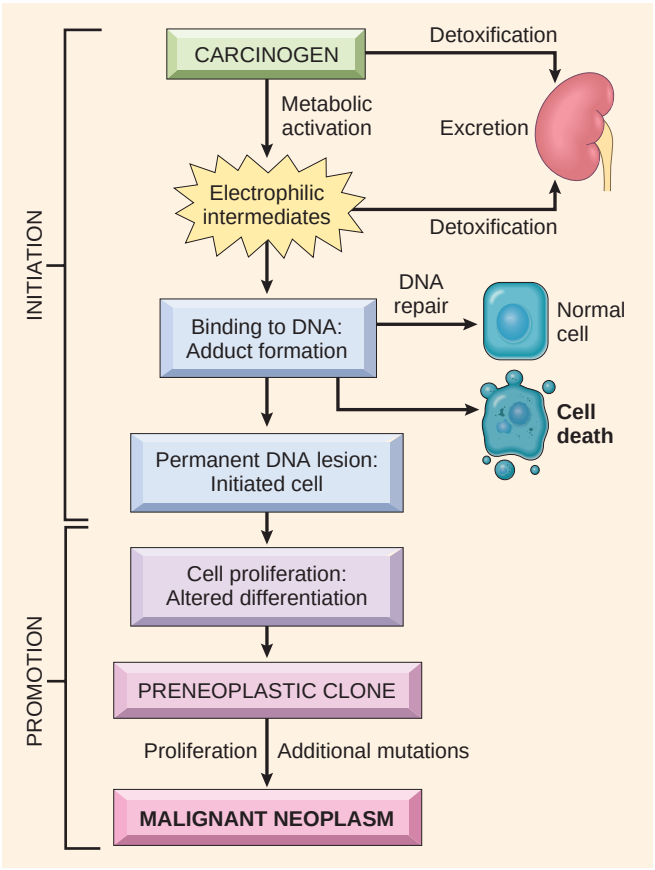

Figure 7-44 General schema of events in chemical carcinogenesis. Note that promoters cause clonal expansion of the initiated cell, thus producing a preneoplastic clone. Further proliferation induced by the promoter or other factors causes accumulation of additional mutations and emergence of a malignant tumor.

Direct-Acting Carcinogens

Direct-acting carcinogens require no metabolic conversion to become carcinogenic. Most are weak carcinogens but some are important because they are cancer chemotherapeutic drugs (e.g., alkylating agents). Tragically, in some instances these agents have successfully cured, controlled, or delayed recurrence of certain types of cancer (e.g., leukemia, lymphoma, and ovarian carcinoma), only to evoke later a second form of cancer, usually acute myeloid leukemia. The risk of induced cancer is low, but its existence dictates judicious use of such agents.