may prove useful in epidemiologic studies of chemical carcinogenesis.

Additional potential carcinogens in the workplace and at home include vinyl chloride, arsenic, nickel, chromium, insecticides, fungicides, and polychlorinated biphenyls. Finally, nitrites used as food preservatives have caused concern, in that they cause nitrosylation of amines contained in the food. The nitrosoamines so formed are suspected to be carcinogenic.

Promotion of Chemical Carcinogenesis

Promoters are chemical agents that are not mutagenic, but which instead stimulate cellular proliferation. It is self-evident that in the absence of proliferation, tumors cannot arise. In tissues that are normally quiescent, such as the liver, the mitogenic stimulus may be provided by the initiating agent. This occurs if the carcinogenic initiator is toxic and kills a large number of cells, thereby stimulating regeneration of the surviving cells. In classic experimental systems, however, the carcinogenic potential of initiators is only revealed upon the subsequent administration of promoters (e.g., phorbol esters, hormones, phenols, and drugs), which by definition are nontumorigenic. Application of promoters leads to proliferation and clonal expansion of initiated (mutated) cells. Driven to proliferate, subclones of the initiated cells suffer various additional mutations, and eventually a cancerous clone with all the necessary hallmark characteristics may emerge. It is likely that many factors contributing to oncogenesis in humans also act by stimulating proliferation and thus can be thought of conceptually as tumor promoters; examples include unopposed estrogenic stimulation of the endometrium and breast, and chronic inflammatory processes associated with tissue repair (e.g., inflammatory bowel disease, chronic hepatitis, and Barrett esophagus).

KEY CONCEPTS

Chemical Carcinogenesis

- Chemical carcinogens have highly reactive electrophile groups that directly damage DNA, leading to mutations and eventually cancer.
- Direct-acting agents do not require metabolic conversion to become carcinogenic, while indirect-acting agents are not active until converted to an ultimate carcinogen by endogenous metabolic pathways. Hence, polymorphisms of endogenous enzymes such as cytochrome P-450 may influence carcinogenesis.
- After exposure of a cell to a mutagen or an initiator, tumorigenesis can be enhanced by exposure to promoters, which stimulate proliferation of the mutated cells.
- Examples of human carcinogens are direct-acting agents (e.g., alkylating agents used for chemotherapy), indirect acting agents (e.g., benzo[a]pyrene, azo dyes, aflatoxin), and promoters or agents that cause pathologic hyperplasias of the endometrium or regenerative activity in the liver.

Radiation Carcinogenesis

Radiant energy, in the form of the UV rays of sunlight or as ionizing electromagnetic and particulate radiation, is carcinogenic. UV light is clearly implicated in the causation of skin cancers, and ionizing radiation exposure from medical or occupational exposure, nuclear plant accidents, and atomic bomb detonations has produced a variety of cancers. Although the contribution of radiation to the total human burden of cancer is probably small, the well-known latency of damage caused by radiant energy and its cumulative effect require extremely long periods of observation and make it difficult to ascertain its full significance. An increased incidence of breast cancer has become apparent decades later among women exposed during childhood to atomic bomb tests. The incidence peaked during 1988-1992 and then declined. Moreover, possible additive or synergistic effects of radiation with other potentially carcinogenic factors add another dimension to the picture.

Ultraviolet Rays

Exposure to UV rays derived from the sun, particularly in fair-skinned individuals, is associated with an increased incidence of squamous cell carcinoma, basal cell carcinoma, and melanoma of the skin. The degree of risk depends on the type of UV rays, the intensity of exposure, and the quantity of the light-absorbing "protective mantle" of melanin in the skin. Persons of European origin who have fair skin that repeatedly becomes sunburned but stalwartly refuses to tan and who live in locales receiving a great deal of sunlight (e.g., Queensland, Australia, close to the equator) have among the highest incidence of skin cancers (melanomas, squamous cell carcinomas, and basal cell carcinomas) in the world. Nonmelanoma skin cancers are associated with total cumulative exposure to UV radiation, whereas melanomas are associated with intense intermittent exposure—as occurs with sunbathing. The UV portion of the solar spectrum can be divided into three wavelength ranges: UVA (320-400 nm), UVB (280-320 nm), and UVC (200-280 nm). Of these, UVB is believed to be responsible for the induction of cutaneous cancers. UVC, although a potent mutagen, is not considered significant because it is filtered out by the ozone layer surrounding the earth (hence the concern about ozone depletion).

The carcinogenicity of UVB light is due to formation of pyrimidine dimers in DNA. If the energy in a photon of UV light is absorbed by DNA, the result is a chemical reaction that leads to covalent crosslinking of pyrimidine bases, particularly adjacent thymidine residues in the same strand of DNA. This distorts the DNA helix and prevents proper pairing of the dimer with bases in the opposite DNA strand. Pyrimidine dimers are repaired by the nucleotide excision repair pathway. There are five steps in nucleotide excision repair, and in mammalian cells the process may involve 30 or more proteins. It is postulated that with excessive sun exposure, the capacity of the nucleotide excision repair pathway is overwhelmed, and error-prone nontemplated DNA-repair mechanisms become operative that provide for the survival of the cell at the cost of genomic mutations that, in some instances, lead to cancer. The importance of the nucleotide excision repair pathway of DNA repair is most graphically illustrated by the high frequency of cancers in individuals with the hereditary disorder *xeroderma pigmentosum* (discussed previously). The role of UV exposure in the etiology of melanoma has been somewhat controversial. However, recent sequencing of melanoma genomes has revealed a very large number