

# **Applied Toxicology**

**NURS 735**

## **Carcinogenesis**

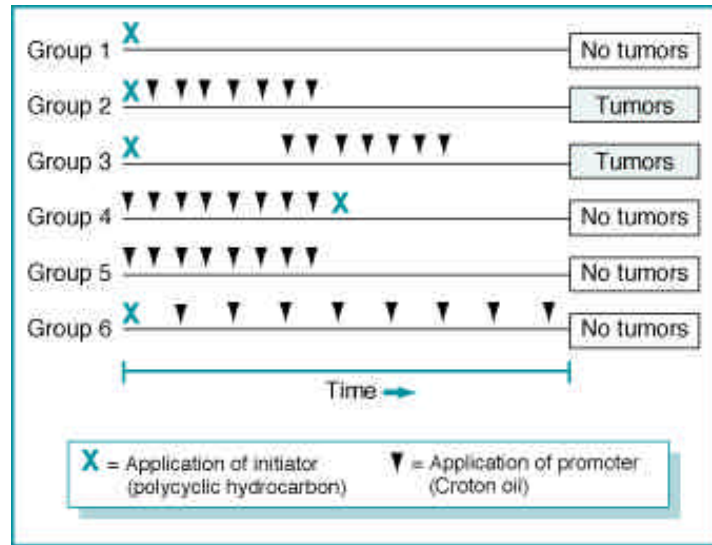
### **• Section 5: Initiation and Promotion**

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### **Etiology and Pathogenesis of Neoplasia Initiation and Promotion**

- Carcinogenesis is a multi-step process
- The initiation of carcinogenesis involves the induction of an altered but non-neoplastic cell which is capable of participating in the neoplastic process.
- This altered cell is commonly referred to as an "initiated cell". These cells can be differentially stimulated to produce focal proliferations

## Etiology and Pathogenesis of Neoplasia Initiation and Promotion



Slide 8.45

## Etiology and Pathogenesis of Neoplasia Initiation and Promotion

- Cancer development with chemicals can begin with a brief exposure (hours or days) to an activated form and the chemical need not be present ever again.
- Initiated cells display altered characteristics which may include an increased life span, selective resistance to cell toxins, apoptotic stimuli and inhibitors of cell proliferation, alterations in the programming or control of normal cell progression and differentiation.
- The existence of the initiated state can not be detected *per se* but is evident only when some selection environment is created; promoting the subsequent focal proliferations.

### **Etiology and Pathogenesis of Neoplasia Initiation and Promotion**

- Initiation - point at which an irreversible alteration, usually genetic, is introduced into a target cell.
  - (1) is essentially irreversible
  - (2) caused only by carcinogenic compounds
  - (3) occurs rapidly after carcinogen exposure
  - (4) alone does not result in tumor formation

### **Etiology and Pathogenesis of Neoplasia Initiation and Promotion**

- **Biological nature of initiated cells.** - Available evidence is that these cells are not neoplastic, i.e., do not have an autonomous growth capability. They may have an increased life span when compared to normal cells of the same tissue. This may in part be determined by resistance to apoptotic stimuli.
  - b. In skin and colon systems initiated cells apparently have a disturbance in the programming or control of the normal progression of differentiated properties.
  - c. In the liver, enzyme deficiencies or the reappearance of fetal enzymes occur in presumed initiated cells.
  - d. Initiated cells seem to be resistant to the inhibitory effects of carcinogens on normal cell division; or the initiated cells retain a response to selective mitogens.

**Etiology and Pathogenesis of Neoplasia  
Initiation and Promotion**

- Promotion
  - (1) reversible
  - (2) acts only after exposure to an initiating agent
  - (3) requires repeated administration of a promotor
  - (4) is not carcinogenic in itself

**Etiology and Pathogenesis of Neoplasia  
Initiation and Promotion**

- Promotion is the process whereby an initiated tissue or organ develop focal proliferations, one or more of which may act as precursors for subsequent steps in the carcinogenic process.
- An essential feature of promotion is the creation of a mitogenic environment.
- Promotion requires the presence of continuous stimulation which may enhance the possibility for the acquisition of additional genetic alterations

### **Etiology and Pathogenesis of Neoplasia Initiation and Promotion**

- The diagram on the next slide depicts the theoretical framework for carcinogenesis. It introduces the concepts of oncogenes and tumor suppressor genes as critical targets for carcinogen action. It implies that alterations in these genes are critical for initiation and the subsequent promotion of cells towards malignancy. We will develop this concept in the next sections on neoplasia. This diagram demonstrates that irrespective of the initial etiologic agent, carcinogenic changes is set into gear by critical alterations in DNA at the site of a few classes of genes that are important to cell growth, death and the regulation of these processes. This diagram is the starting point for the remainder of our discussions on neoplasia.

### **Etiology and Pathogenesis of Neoplasia Overall Hypothesis**

**The diagram on the final slide depicts the theoretical framework for carcinogenesis. It introduces the concepts of oncogenes and tumor suppressor genes as critical targets for carcinogen action. It implies that alterations in these genes are critical for initiation and the subsequent promotion of cells towards malignancy. We will develop this concept in the next sections on neoplasia. This diagram demonstrates that, irrespective of the initial etiologic agent, carcinogenic changes are set into gear by critical alterations in DNA at the site of a few classes of genes that are important to cell growth, death and the regulation of these processes. This diagram is the starting point for the remainder of our discussions on neoplasia.**

## Etiology and Pathogenesis of Neoplasia Overall Hypothesis

