EVE 491/591
Toxicology
Lecture #10
1. On to Chile…
2. Chemicals and Cancer
3. Case Study: DDT and Malaria

Chile Earthquake
• Feb. 27, 2010; 3:30 AM local time
• 8.8 on Richter scale (“great” category)
• 773 dead
• Some collapsed buildings and power outages
• $10-ish million in humanitarian aid pledged so far
  – Differences between Haiti and Chile?

Chemicals and Cancer
• The etiology (i.e., causation) of cancer is extremely complex
  – Cancer is a collection of diseases that share common aspects of abnormal cellular behavior
    • These cells lose the normal regulatory control mechanisms that keep growth and replication in check
Chemicals and Cancer, cont.

- **Hyperplasia** results in the production of more cells than one would expect to see in a particular tissue
  - It is a normal response to certain stimuli
  - Exp: Pregnancy → breast hyperplasia
    - The end of gestation and cessation of lactation return the tissue to its normal state.

- **Metaplasia** results in the replacement of one cell type for another due to an abnormal stimulus
  - Original cells have trouble adapting to “new” conditions; more adaptable cells replace them
  - It can be induced environmentally.
  - Exp: The respiratory tissue of new smokers becomes “squamous” (scaly)
    - The tissue may revert back to normal if smoking ceases in a timely manner.

- **Neoplasia** is the abnormal growth and proliferation of cells (initiated by a stimulus)
  - Growth exceeds and is uncoordinated with that of the surrounding tissue
  - Growth persists even after stimulus removed
  - Causes a neoplasm (tumor) that may be
    - Benign
    - Pre-malignant
    - Malignant
Neoplasms/Tumors: Definitions

- **Benign tumor**: A noncancerous tumor or growth that remains confined to the growth site and may increase in size over time but does not invade into distant tissues.

- **Malignant tumor**: Any cancerous tumor that may, depending on the type of cancer, spread from its primary growth site to potentially distant sites (metastasis).

- **Cancer**: The general term to designate any tumor or cells that have departed far from what is recognized as normal with respect to structure, growth, and replication.

Mestastasis

Mutations & Cancer Development
Our Genes May Help

- **Tumor suppressor genes** play an important role in maintaining a balance in the response of the cell to positive and negative regulators of cellular growth.
  - The importance of the tumor suppressor gene is to limit the proliferation of mutated cells.
  - Although these genes may also mutate
    - This leads to an increased risk for cancer development
    - People with a family history of certain cancers have often inherited a mutated tumor suppressor gene

History of Chemical Carcinogenesis

- The area of chemical carcinogenesis today is one of intense research
  - Many new understandings and breakthroughs
- Early recognition of a relationship between chemicals and an increased incidence of cancer include the observations of:
  - **John Hill**, who in 1761 observed a causal relationship between nasal cancer in snuff users
  - **Sir Percival Pott**, who in 1775 recognized that soot and coal tar were the likely causal agents of scrotal cancer.
  - Other names: T. Bovari, F. Khan, J. and E. Miller

History of Chemical Carcinogenesis

- Researcher:
  - **Theodore Bovari** in 1914 hypothesized that alterations in the genetic material of the cells of the body are somehow involved in the process that produces cancer. This idea has been referred to as the *somatic mutation theory*. 
History of Chemical Carcinogenesis

• Researcher:
  – **Furthand Kahn** in 1934 experimentally used animal tumors to test cells for their ability to produce tumors in a tumor-free animal. It was observed that when the cells were introduced into a tumor-free host animal, similar tumors could be produced.

History of Chemical Carcinogenesis

• Researchers:
  – **James and Elizabeth Miller** in the 1950s recognized the relationship between metabolism and the bioactivation of carcinogens to produce metabolites that could bind to the macromolecules of the cell. The process of metabolism was recognized to produce electrophilic products, more reactive than the unmetabolized parent chemicals, thus establishing what has been referred to as the **electrophilic theory of carcinogenesis**.

Tumor Metastasis and Staging

• A pathologist can assign the tumor a grade from 1 to 4 that corresponds to its degree of malignancy, with 4 being the most malignant and 1 being benign.
  • The more malignant the tumor, the less organized the cells of the tissue are
  • The prognosis worsens as cells become less organized
Benign Tumors

- The normal tissues that make up the organs of our body consist of numerous cell types
  - Parenchymal cells are the functional cells that are recognized as being unique to that organ.
  - Stromal cells, which are important to the tissue, may be viewed as supportive in nature.
- Similarly, a neoplasm consists of both parenchymal and stromal components
  - In benign neoplasms, the parenchymal and stromal cells may closely resemble those of the normal surrounding tissue.

Naming of Benign Neoplasms

<table>
<thead>
<tr>
<th>Prefix</th>
<th>Tissue</th>
<th>Benign Tumor Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adeno-</td>
<td>Gland</td>
<td>Adenoma</td>
</tr>
<tr>
<td>Chondro-</td>
<td>Cartilage</td>
<td>Chondroma</td>
</tr>
<tr>
<td>Hernangio-</td>
<td>Blood vessels</td>
<td>Hemangioma</td>
</tr>
<tr>
<td>Hepato-</td>
<td>Liver</td>
<td>Hepatoma</td>
</tr>
<tr>
<td>Lipo-</td>
<td>Fat</td>
<td>Lipoma</td>
</tr>
<tr>
<td>Myo-</td>
<td>Muscle</td>
<td>Myoma</td>
</tr>
<tr>
<td>Osteo-</td>
<td>Bone</td>
<td>Osteoma</td>
</tr>
<tr>
<td>Fibro-</td>
<td>Fibrous connective tissue</td>
<td>Fibroma</td>
</tr>
<tr>
<td>Neuro-</td>
<td>Neural tissue</td>
<td>Neuroma</td>
</tr>
</tbody>
</table>

Malignancies Graded on the Basis of Differentiation

Differentiation = organization
Dysplasia = abnormal maturation
Malignant Tumors

- The **malignant** tumor grows within its tissue of origin; however, it may spread beyond these local confines
  - These cells can invade into deeper layers of tissue (invasion) and are capable of metastasis
  - These cells have requirements for adequate levels of oxygen, the removal of metabolic wastes, and a supply of nutrients and other factors

Malignant Tumors

- Malignant tumors are similarly named for the tissue from which the tumor is derived; one of three suffixes is generally attached to create the name of the cancer:
  - **Carcinomas**: epithelia tissue origin and the most common of all human malignancies (approximately 90%). This cancer spreads primarily through the lymphatic system.
  - **Sarcomas**: connective tissue origin.
  - **Blastomas**: derived from (or resembling) embryonic tissue

Naming of Malignant Tumors

<table>
<thead>
<tr>
<th>Malignant Tumor Name</th>
<th>Tissue of Origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinomas</td>
<td>Glandular epithelium</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>Squamous epithelium</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>Bone</td>
</tr>
<tr>
<td>Chondrosarcoma</td>
<td>Cartilage</td>
</tr>
<tr>
<td>Lymphosarcoma</td>
<td>Lymph node</td>
</tr>
<tr>
<td>Liposarcoma</td>
<td>Adipose tissue</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>Retinal tissue</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>Neural tissue</td>
</tr>
<tr>
<td>Nephroblastoma</td>
<td>Renal tissue</td>
</tr>
</tbody>
</table>
Carcinogen Classification

• **Based on Chemistry**
  – Thousands of suspected carcinogens have already been tested for their ability to produce mutations and cancer in laboratory animals and *in vitro* systems.
  – These chemicals fall into many different categories of chemical agents based on shared structural similarities.

Carcinogen Classification

• **Based on Mechanism of Action**
  – **Genotoxic**
    • Genotoxic carcinogens are DNA reactive or DNA-reactive metabolites capable of altering the integrity DNA through direct interaction.
  – **Nongenotoxic**
    • Nongenotoxic carcinogens do not directly cause DNA mutation. The mechanism of action is poorly understood.

Exposure to Carcinogens

• The U.S. governmental regulatory definition of a carcinogen is "any substance at any dose, administered by any route, that increases tumor incidence in rats."
• The word *tumor*, as used in the regulatory definition, is not synonymous with cancer because we know that tumors can be either benign or malignant.
Chemical-Induced Carcinogenesis Is a Multistep Process

- **Initiation** - the genotoxic event that leads to mutations of the DNA and places the affected cells at a greater risk for tumor formation.

- **Promotion** - the second step in the carcinogenesis process, which moves initiated cells further along their transformation process. Exposure of initiated cells to chemicals that stimulate cell proliferation, such as irritating substances, results in the production of a clone of proliferating cells within the tissue.

- **Progression** - Progression is the next step toward the transformation of cells into a tumor that is malignant. At this stage in the process, and depending on the particular tissue of origin of the cell, a high growth rate and invasion into surrounding tissue may occur.

Cancer is a Multistep Process

Case Study #3: Dark and Lovely?

Refer to the handout provided (Part 1).

- Questions:
  - What are some differences between Judy and Mariah that might make Judy more "at risk" for skin cancer than Mariah?
  - What observations did Judy make concerning her mole?