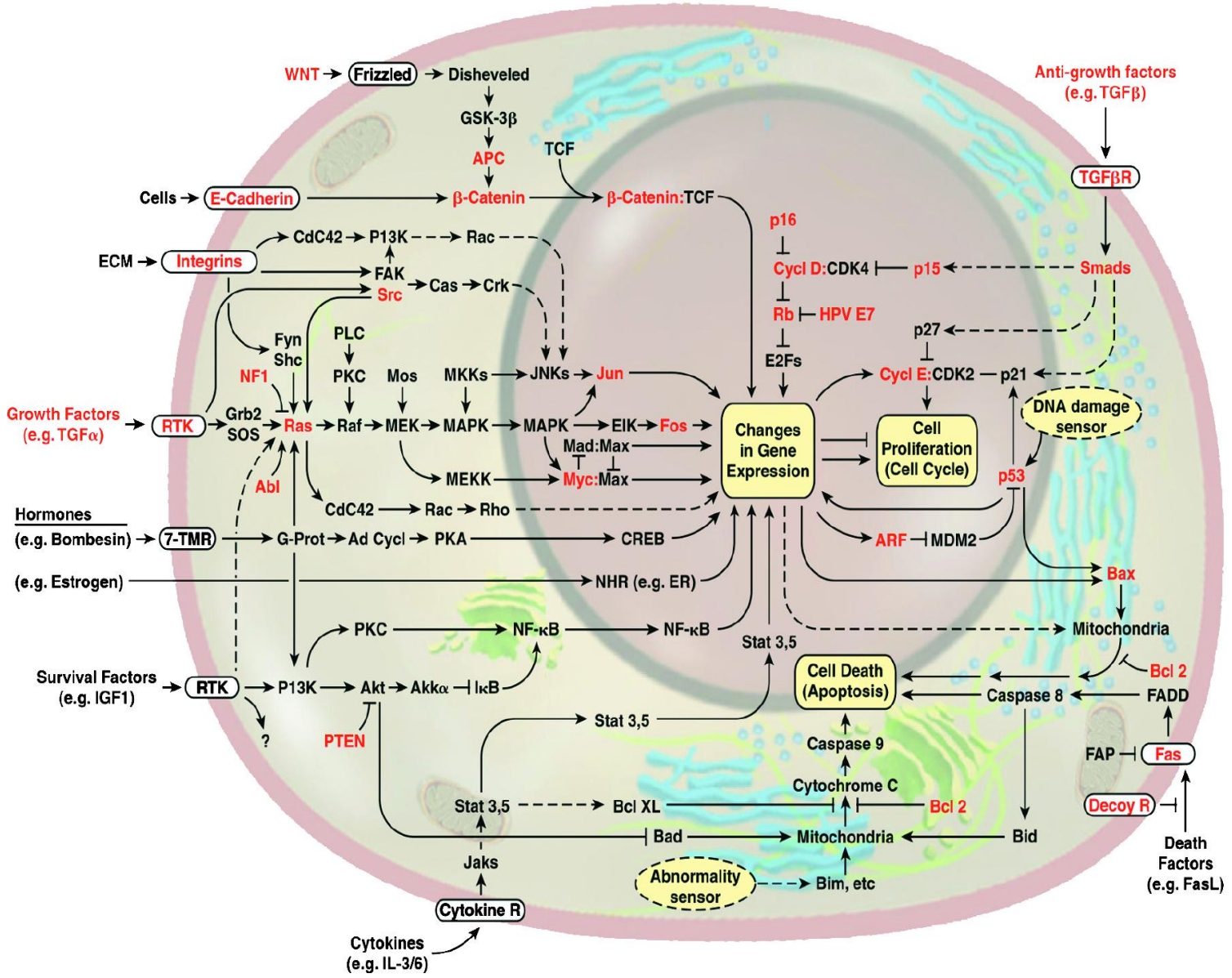
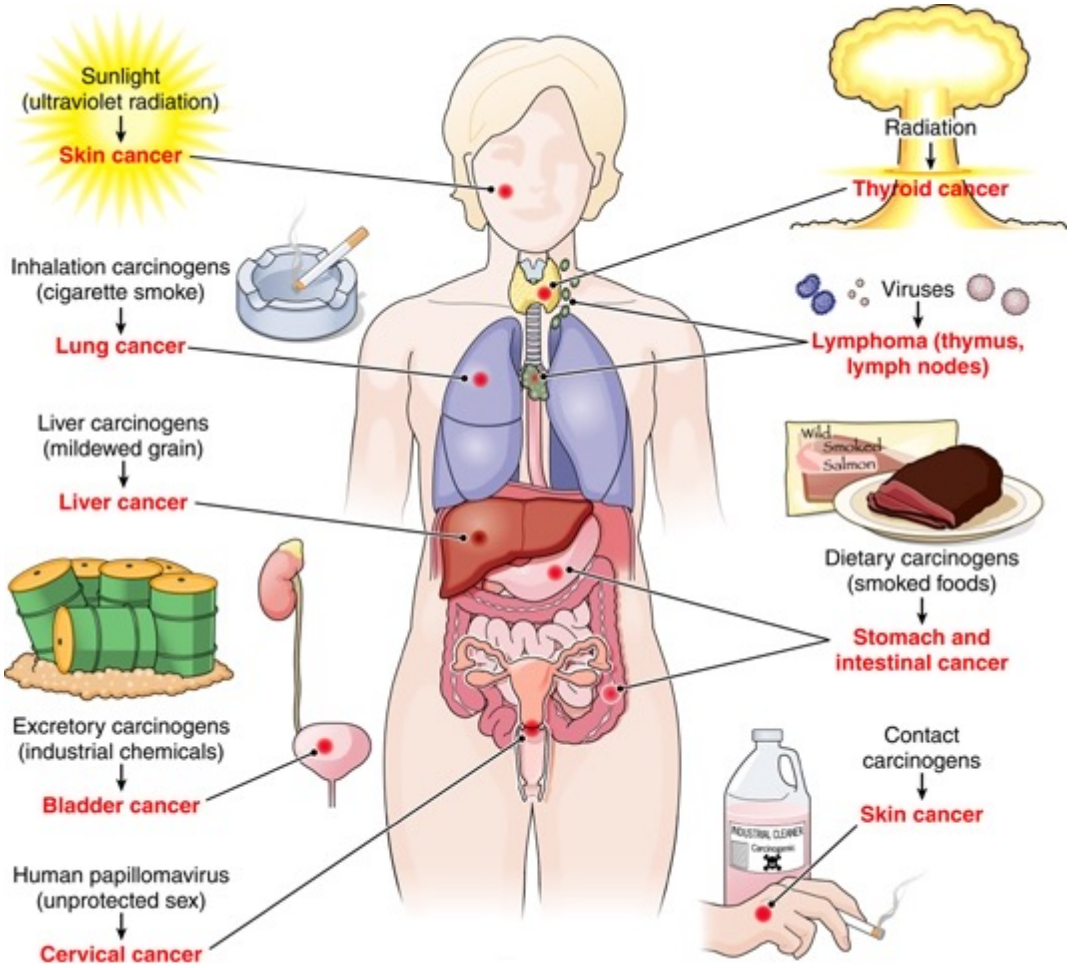
Carcinogens

October 18, 2016

Carcinogenesis can be a complex process…



…and a lot of research focuses on agents that can cause cancer.



Cancer development

- Cancer is the abnormal or uncontrolled growth of new cells in any part of the body, characterized by cells that tend to invade surrounding tissue and metastasize to new body sites.

- Cancer development is a **multistep process**: For cancer growth to occur, several factors must work together, and different steps are necessary:
    1. Initiation
    2. Promotion
    3. Progression

What are carcinogens?

- Carcinogens are chronic toxins. They cause damage after repeated or long-duration exposure. They may have not immediate apparent harmful effects, with cancer developing only after a long latency period.

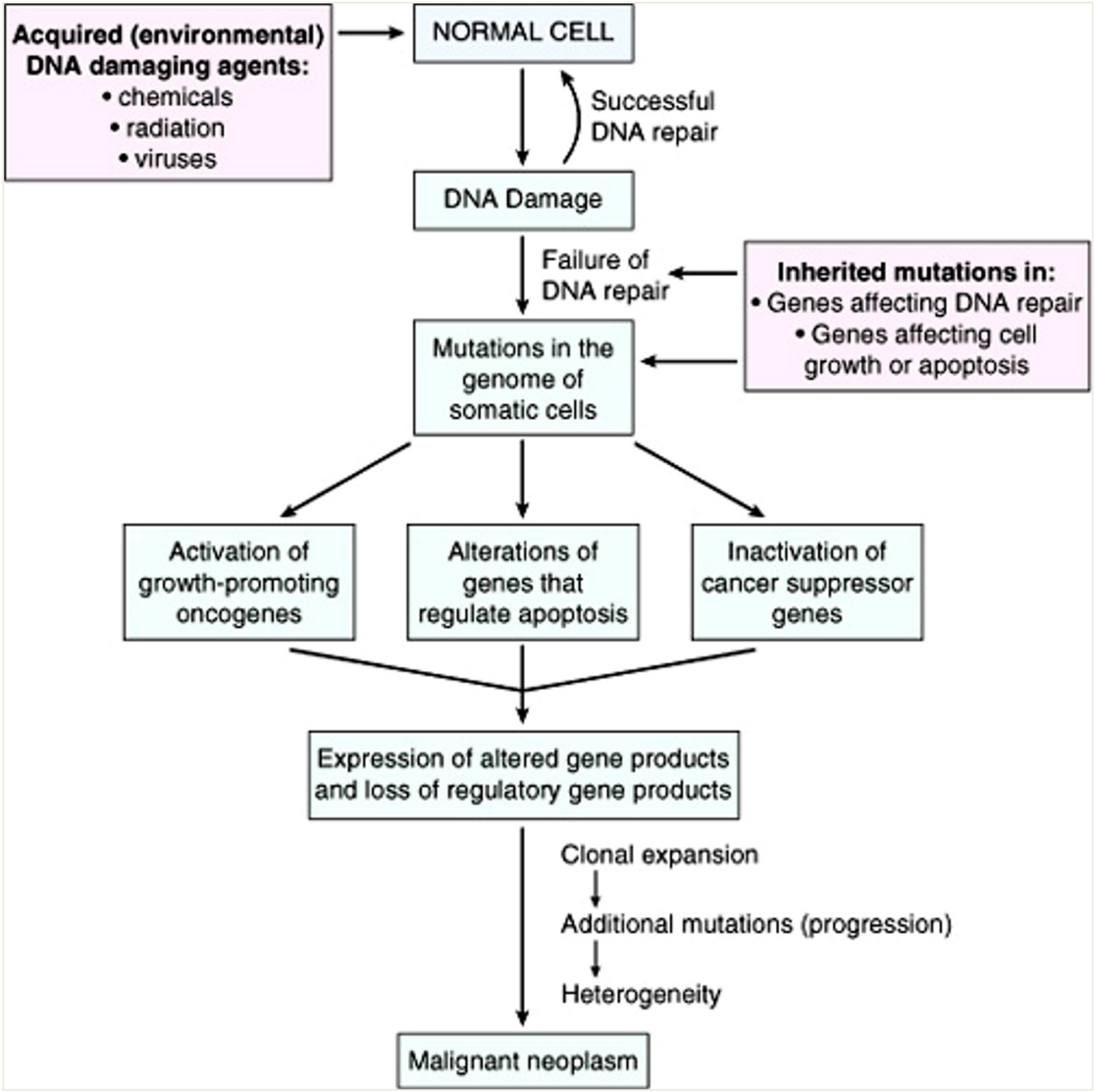
  - Dose: amount and length of exposure. The lower the dose the least likely you are to develop cancer or related diseases.

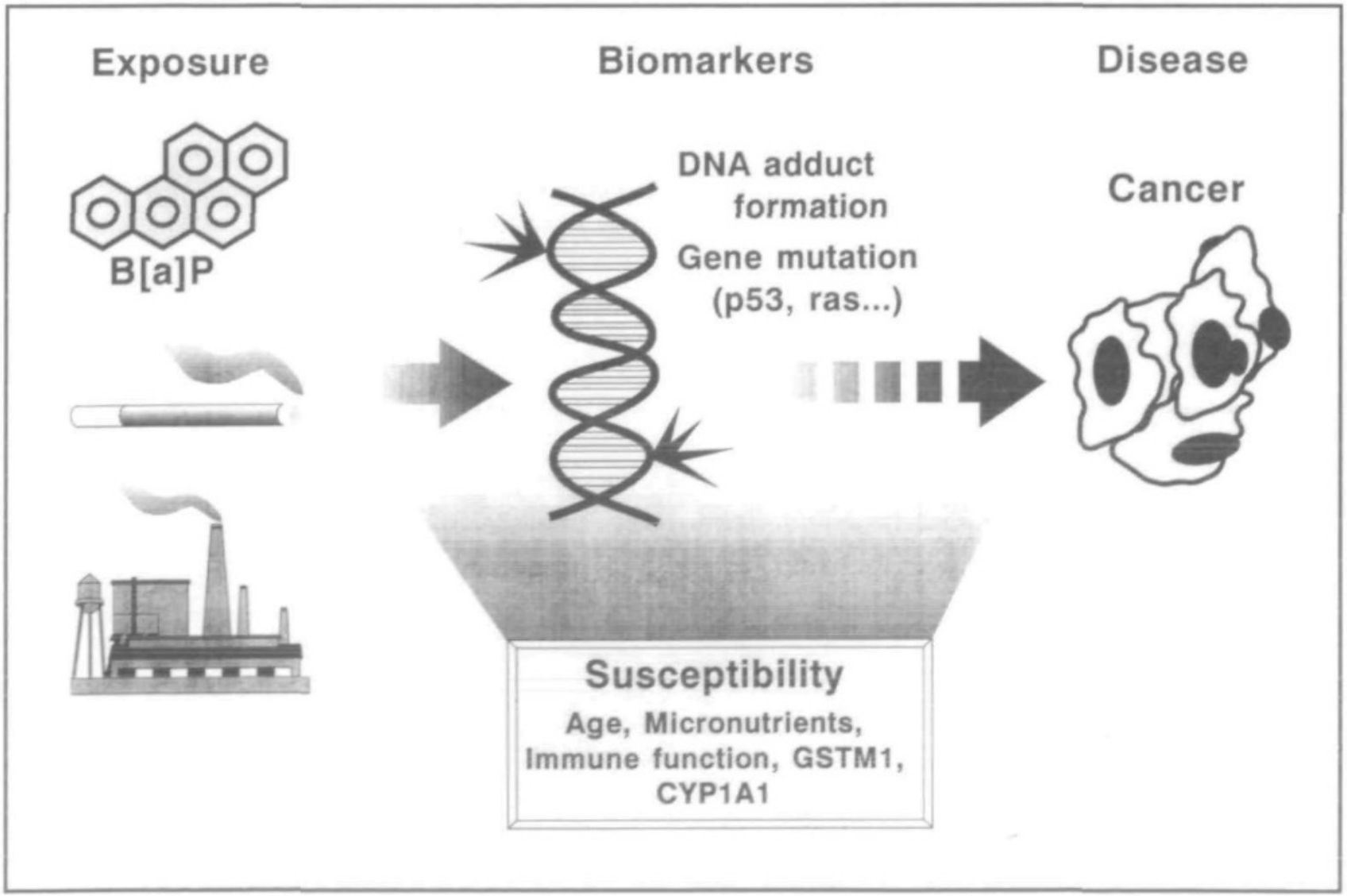
How do Carcinogenic Agents Produce their Effects?

- Genetic damage and mutation are the essential features of carcinogenesis.
- Carcinogenic agents are classified based on how they inflict cell damage and produce their effects.

1. Chemical agents
2. Radiation
3. Oncogenic viruses
4. Carcinogenic bacteria

Cancer: General Etiology and Pathogenesis




Exposure
Biomarkers
Disease
B[a]P
DNA adduct formation
Gene mutation (p53, ras...)
Cancer
Susceptibility
Age, Micronutrients, Immune function, GSTM1, CYP1A1

How do carcinogens enter the body?

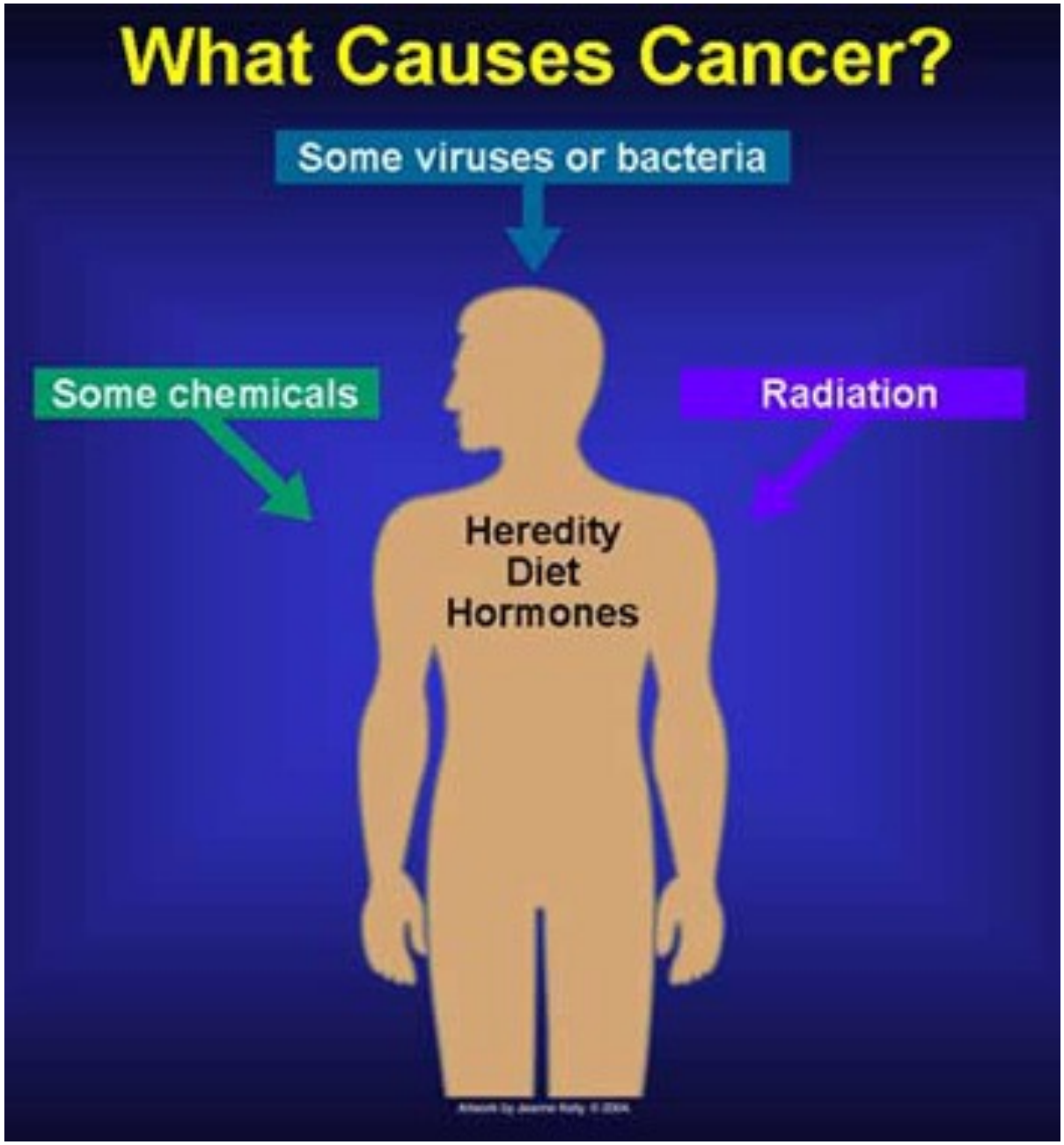
- Skin absorption: Many solvents and other chemicals go directly through the skin.
- Ingestion: Swallowing of a carcinogen.
- Inhalation: Breathing gases, fumes and vapors is the most common form of exposure.

IARC - International Agency for Research on Cancer

- The International Agency for Research on Cancer (IARC) is a branch of the World Health Organization that monitors cancer occurrence worldwide and performs epidemiological and laboratory investigations to understand the causes of cancer.

- More than 400 chemical agents have been listed as carcinogenic, probably carcinogenic, or possibly carcinogenic by

- Has done extensive work to examine a complete range of studies necessary to classify a substance as carcinogenic e.g.:
  - bacterial mutagenese e.g. Ames test
  - study at molecular level (DNA)
  - animal tests



International Agency for Research on Cancer (IARC),

1. Chemical Agents

- Asbestos (Mesothelioma)
- Nitrosamines and polycyclic hydrocarbons found in tobacco smoke (lung, pancreatic, bladder cancer)
- Polycyclic and heterocyclic hydrocarbons formed during smoking and broiling of meats (bladder, lung, pancreatic colorectal cancer)
- Nitrates used in the preservation of meats (stomach cancer)
- Aflatoxin B_1 is formed in moldy foods, especially peanuts (liver cancer).
- Aniline dyes and food colors (bladder cancer)
- Cyclophosphamide –immunosuppressive drugs (AML, bladder cancer)
- Vinyl chloride in the manufacture of plastics (liver cancer)

Activation of Chemical Carcinogens

- We are exposed to hundreds of potentially carcinogenic chemicals, both natural and synthetic, on a yearly *(daily)* basis.

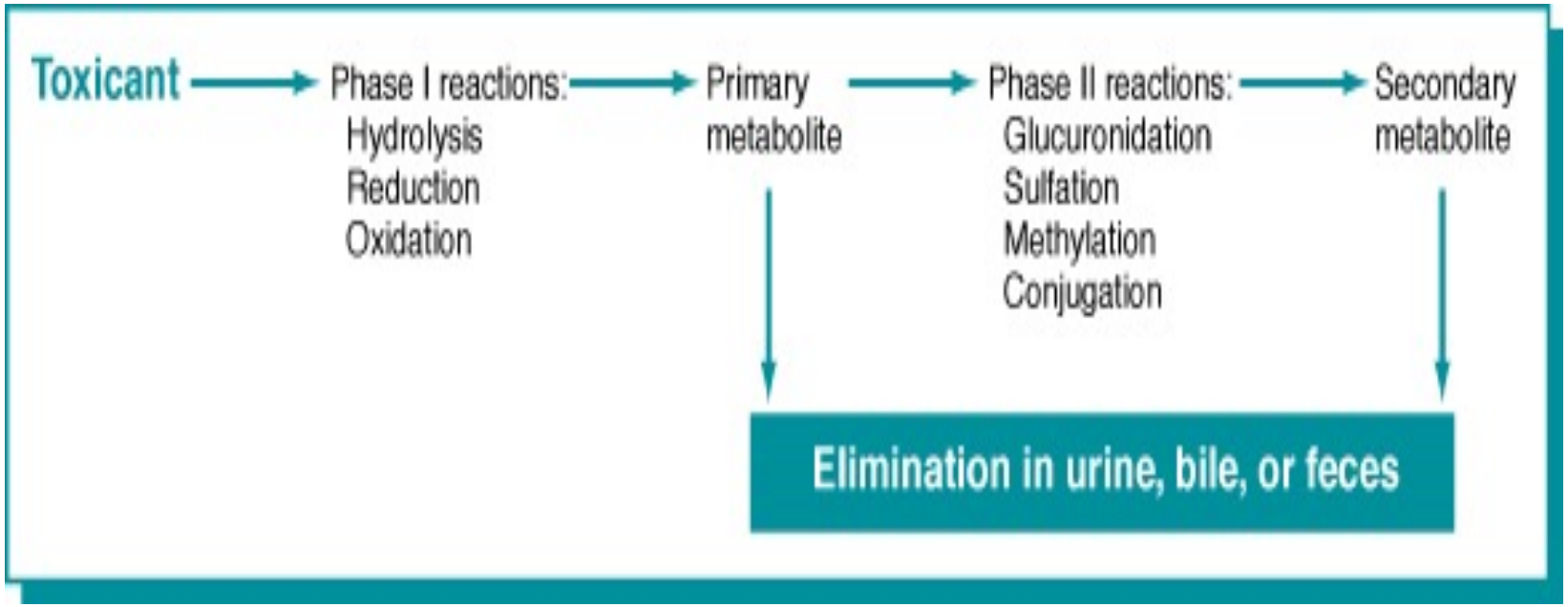
- Most carcinogens require metabolic activation for conversion into an ultimate carcinogens

Detoxification of chemical carcinogens

- The body has developed an elaborate system for the detoxification of most chemicals.

- The carcinogenic potency of a chemical is determined by the balance between activation reactions and metabolic detoxification in the body.

Chemical Carcinogen Detoxification



Examples:
Phase 1: Cytochrome P450 enzyme group (P450)
Phase 2: Glutathione-S-transferase

2. Radiation

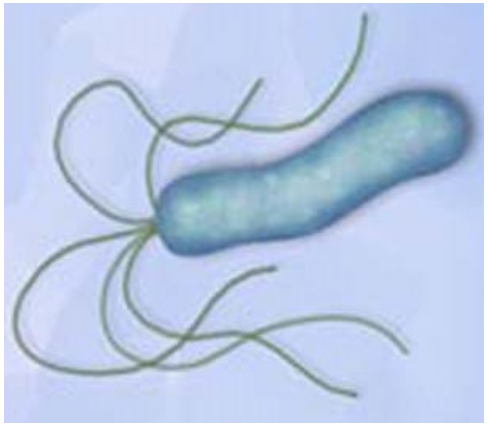
- **Ultraviolet** (UV-B light 280-320 nm) from the sun can increase the risk of squamous carcinoma, basal cell carcinoma and malignant melanoma of the skin.

- **Ionizing** X-rays in high dosage & gamma rays, alpha- and beta-particles and radiation from thermonuclear devices.

3. Oncogenic Viruses

- Numerous viruses are carcinogenic in animal models
- Only a few viruses are carcinogenic in humans.
- The viruses are from two classes:
  - **DNA viruses** (HPV/cervical cancer, EBV/B-cell lymphoma)
  - Slowly transforming **RNA viruses** (HTLV-1/T-cell lymphoma)
- Most viruses have several types or strains, a subset of which are important in disease causation.

4. Carcinogenic bacteria



- *H. pylori* is acquired by a fecal-oral route or an oral-oral route.
- *H. pylori* colonizes mucosa layer of the stomach.
- Evades stomach acid and immune system response.
- DNA damage accumulates over time and is passed onto daughter cells.
- Cells become cancerous

Immune Response to *H. pylori*

- Concurrent infection with other pathogens may modify the immune response to *H. pylori*
  - Concurrent helminth infection could shift the T-helper cell immune response from a predominantly Th1-type to a Th2-type
  - Some research shows that helicobacter-associated gastric atrophy was considerably reduced in mice who were co-infected with an enteric helminth.

H. pylori Eradication

- A potential strategy for high-risk regions-screening
- Several considerations to be made:
  - Access to healthcare may be limited
  - Who/when to treat?
  - Higher reinfection rates after effective eradication therapy
  - The development of antibiotic-resistant strains of *H. pylori*
  - Is it even effective?

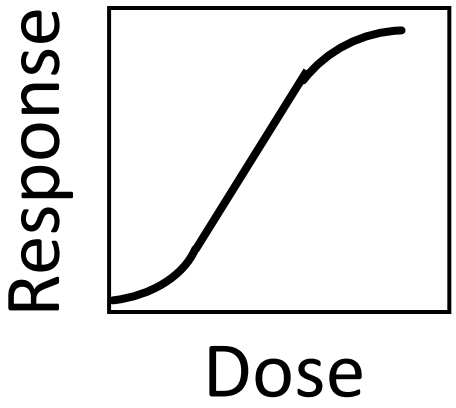
What killed Napoleon?

Napoleon: it wasn't poison after all…

Challenges to carcinogen ascertainment

'All substances are poisons, there is none which is not a poison. The right dose differentiates a poison and a remedy.'

Paracelsus (1493-1541)



Any chemical may be toxic if the dose is high enough

Challenges to carcinogen ascertainment

- The effect may not occur at time of exposure
  - By the time it occurs the person may not be working with the substance (latency time)
- People vary in susceptibility (react differently)
  - Variations may be due to age, gender, health status, ...
- Complications of combined effects
  - Exposure to different substances
  - Exposure to alcohol, tobacco or prescribed drugs (e.g. synergistic effects asbestos and tobacco)
- Impact of life style
- Detailed toxicological or exposure information is often not available for many substances