Tobacco & It’s Etiology In Carcinogenesis
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- There are over 19 known carcinogens (proven in humans) in cigarette smoke
- More than 62 proven in animals
- Following are some of the most potent carcinogens
  - **Polynuclear aromatic hydrocarbons (PAH)**
    - E.g. benzopyrene
    - Changes to epoxide $\rightarrow$ attach to nuclear DNA $\rightarrow$ may either kill the cell or cause agenetic mutation $\rightarrow$ If the mutation inhibits programmed cell death, the cell can survive to become a cancer cell
    - Carcinogenity is radiomimetic, i.e. similar to that produced by ionizing nuclear radiation
  - **Acrolein**
    - Gives smoke an acrid smell and an irritating, lacrimary effect
    - Permanently binds to DNA
    - Causes cancers in a manner similar to PAH
    - However, acrolein is 1000 times more abundant than PAHs in cigarette smoke
    - And is able to react as is, without metabolic activation
  - **Nitrosamines**
    - Found in cigarette smoke but not in uncured tobacco leaves
    - Due to combustion effects
  - Aromatic amines
  - Vinyl chloride
  - Ethylene oxide
  - Aldehydes
  - Phenolic compounds
  - Arsenic
  - Nickel
  - Chromium
  - Cadmium
  - **Radioactive carcinogens**
    - In addition to chemical, nonradioactive carcinogens, tobacco and tobacco smoke contain small amounts of lead-$^{210}$Pb and polonium-$^{210}$Po both of which are radioactive carcinogens

Smokeless tobacco products (ie. Chewable forms)

- A variety of carcinogens have been detected in smokeless tobacco products
- The most abundant strong carcinogens are NNK and NNN, which are typically found in total amounts of 1 to 10 ppm in smokeless tobacco products, levels 10 to 1,000 times higher than N-nitrosamines in other products designed for human consumption.
Several other carcinogenic compounds such as formaldehyde, acetaldehyde, hydrazine, cadmium, nickel, and polonium-210 are also present.

- NNK = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
- NNN = N'-nitrosonornicotine

**Nicotine**

- **Is a stimulant** → one of the main factors leading to continued tobacco smoking
- **On average takes only ten seconds to reach the brain**
- **Although nicotine does play a role in acute episodes of some diseases** (including stroke, impotence, and heart disease) by its stimulation of adrenaline release
- **longer term effects are more the result of the products of the smouldering combustion process**
  - **Nicotine** per se, is not carcinogenic or mutagenic
  - **However, it inhibits apoptosis**, therefore accelerating existing cancers
  - **Also, NNK**, a nicotine derivative converted from nicotine, can be carcinogenic.

**Genetic**

- **Cigarette smoke can turn on or off some of the genes, which otherwise would remain inactive or active respectively**
- **Smoking turns off some DNA repair genes that cannot be reversed**
- **It also switches off some genes responsible from protection from cancer growth in the body**

**Particular forms of tobacco use**

- Chewing tobacco
- Cigars
- Hookahs
- Snuff
- Reverse smoking
- Chutta
- Misri
Exhaled mainstream smoke

- More harmful
- Reasons
  - Exists at lower temperatures → chemical compounds undergo changes which can cause them to become more dangerous
  - Smoke undergoes changes as it ages, which causes the transformation of the compound NO into the more toxic NO2
  - Further, volatilization causes smoke particles to become smaller, and thus more easily embedded deep into the lung of anyone who later breathes the air.

Mechanism of Tumor induction by tobacco products

- Central track is major pathway
- Minor pathways
  - Carcinogens directly bind to receptors e.g. EGFR & Cox-2 → decreased apoptosis, increased angiogenesis
  - Enzymatic methylation of promoter regions of genes → gene silencing → Can occur in tumor suppressor genes

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