

CHEMICAL CARCINOGENESIS

Properties of Chemical Carcinogenesis:

1. Epidemiology studies have showed that aspects of environment or life style such as diet, viruses, chemicals etc., may cause about 70-90% of cancer.
2. The idea that environmental exposure to chemicals might cause cancer has a long history since the 18th century beginning with John Hill.
3. Since then, many other substances have been identified as **carcinogens** as a result of occupational exposure, such as tars, soot's, oils, asbestos.
4. Carcinogens are structurally diverse – there are no common elements.
5. Some carcinogens act directly:
 - Intrinsically electrophilic
 - Cause tumours at or near immediate site of administration (i.e. site of subcutaneous injection)
6. Most carcinogens are unreactive molecules, which are metabolized to generate an active form – “ultimate carcinogen” as a consequence of the body's attempts to eliminate foreign lipophilic substances.
7. This involves oxidation by the cytochrome P450 system of the ER and conjugation to hydrophilic substances such as glucuronate or acetate.
8. Therefore inadvertently generating highly reactive intermediates or unstable conjugates.
9. Differences in tissue specificity and susceptibility of species to carcinogens due to different metabolic mechanisms.
10. Polymorphisms in the cytochrome P450 enzyme system may lead to different susceptibilities to carcinogens on people, e.g. sensitivity to smoking.
11. The significant lag between carcinogen exposure and tumour appearance, e.g. smoking 20-30 years.
 - Experimentally, lag duration is inversely proportional to dose-increased carcinogen shortens delay.
 - Different carcinogens induce different responses.
12. Some strong carcinogens generate tumours after a single dose. However, generally, you need repeated applications over long periods of time.
13. There are multiple independent steps (“genetic hits”) produces a tumour.

Initiation and Promotion:

1. Single, low dose of carcinogen – too low to be effective on its own → **Initiator**
2. Followed by repeated exposure to certain substances that by themselves never cause tumours → **Promoter**
3. The order is very important because:
 - Promoter before initiator gives no tumours
 - Initiator alone gives no tumours
 - Can separate exposure to initiator and promoter by a long interval and still get tumours → the initiation is a stable state.