Toxicogenomics

It is a new scientific field that elucidates how the entire genome is involved in biological responses of organisms exposed to environmental toxicants/stressors

or

Is the study of the response of a genome to environmental stressors and toxicants (Waters, et al 2003).

or

"The study of the relationship between the structure and activity of the genome (the cellular complement of genes) and the adverse biological effects of exogenous agents" (Aardema and MacGregor 2002).

Toxicogenomics was first described as a term to illustrate the integration of toxicological research with the emerging new technologies designed to broadly interrogate the functional genome (that is RNA, protein, metabolite profiling, and polymorphisms/functional DNA mutations).

The application of toxicogenomics provides an exceptional opportunity to identify the biological pathways and processes affected by exposure to pharmaceutical compounds and/or xenobiotics (exogenous agents)

Toxicogenomics combines toxicology with information-dense genomic technologies to integrate toxicant-specific alterations in **gene**, **protein**, and **metabolite** expression patterns with phenotypic responses of cells, tissues, and organisms.

Genomics: the study of genes in the aggregate - DNA, the primary transcript and mRNA.

If we assume there is some change in gene expression in response to toxicity, then expression profiling is an extremely powerful tool to assess a specific response to environmental exposures.

Proteomics: the study of protein products in aggregate - it applies to the translation from the mRNA to the primary protein products, and their maturation and modification to yield active proteins.

Metabonomics/Metabolomics

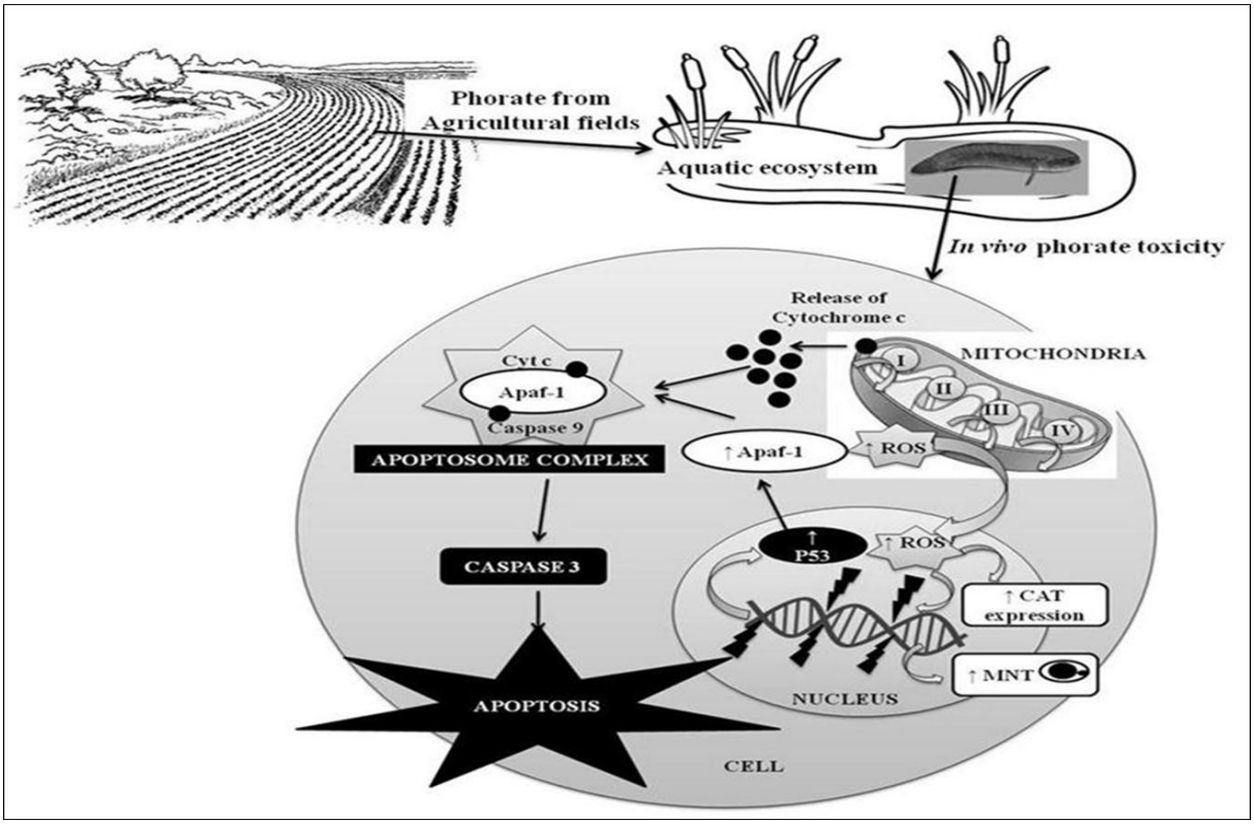
Furthermore, metabolites are the last step in the molecular response to a toxicants

Toxicogenomics has three principal goals:

*****Understand the relationship between environmental stress and human disease susceptibility.

*****Identify useful biomarkers of disease and exposure to toxic substances.

*****Elucidate the molecular mechanisms of toxicity.



Challenges for Toxicogenomics Applications

• Gene annotation.(Identify the gene location and its function) Example: Public genome projects

• Cross-species extrapolation. Example: Public genome projects

• Technical standards for evolving platforms. Example: National Institute of Standards, MIAME and MAQC consortiums

• Standards for data sharing. Example: NCBI, MIAME, and MAQC consortiums

• Signature/biomarker qualification. Example: Critical Path Institute, FDA, Environment Protection Agency and European Regulatory Groups

• Translation of assays for regulatory purposes. Example: FDA Critical Path Initiative, ICH

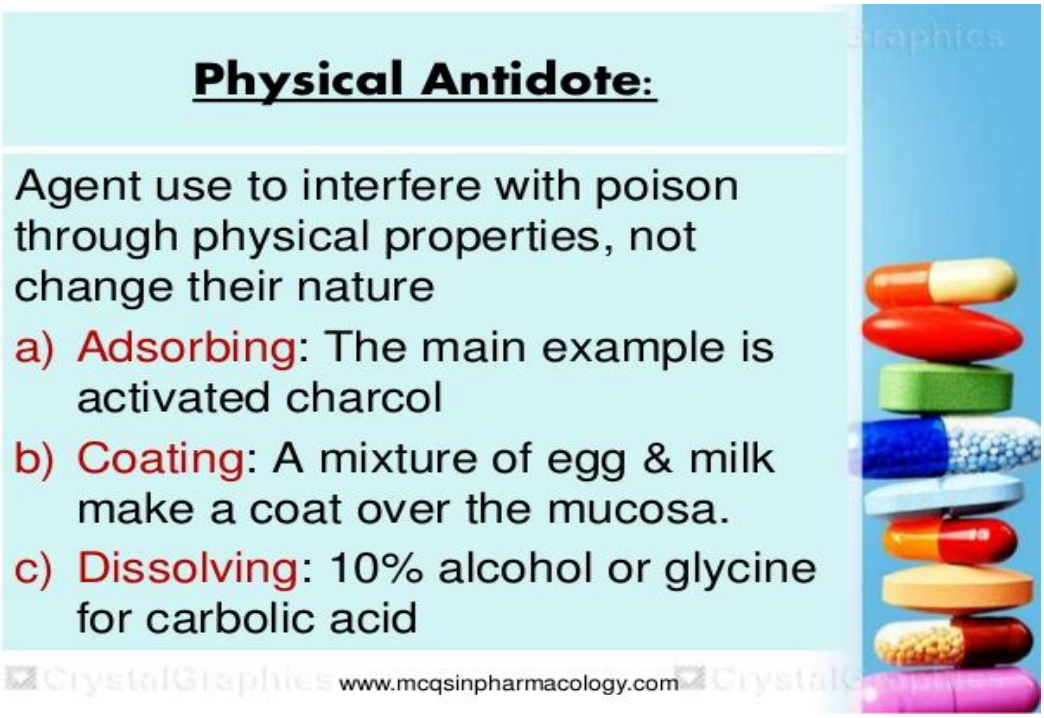
• Ethical, Legal, Social Issues. Example: National Institutes of Health, NHGRI

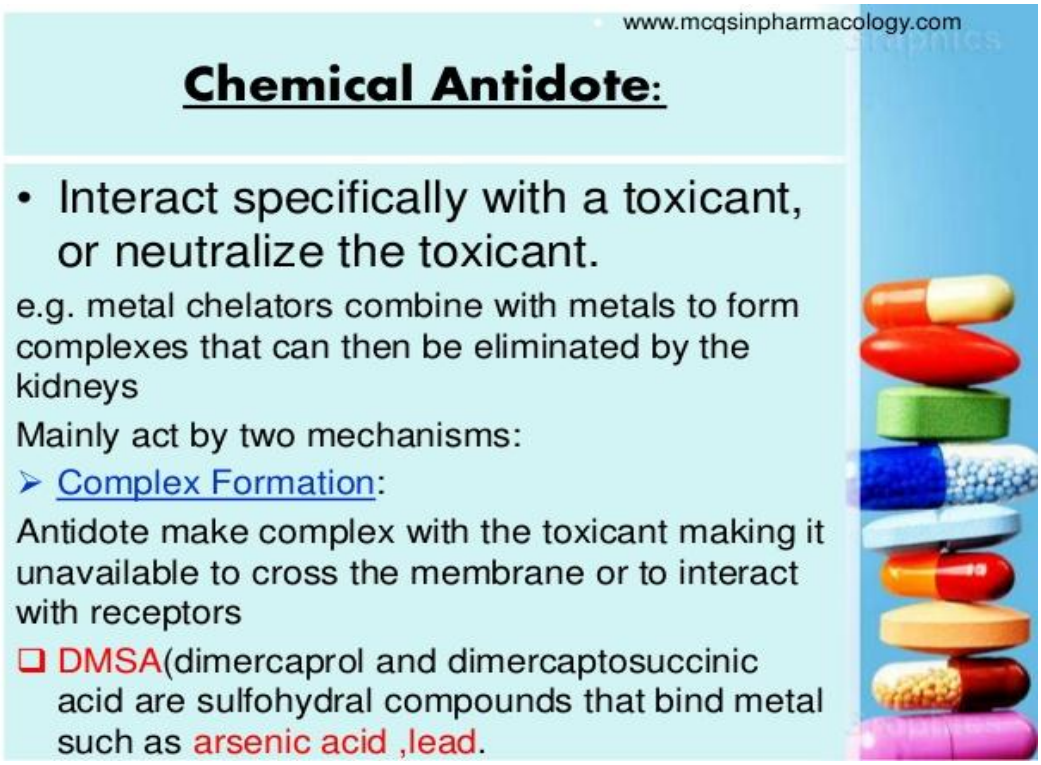
Antidotal Therapy

Antidotes: Antidote can be defined as therapeutic substance used to counter act the toxic actions of a specified xenobiotics.

According to mode of action antidotes can be classifide in three types

1. Physical
2. Chemical
3. Pharmacological/Physiological





➢ **Metabolic Conversion**: Detoxification to less toxic product

Common modes of action of antidotes are as follows:

- **1. Inert complex formation** - Some antidotes interact with the poison to form an inert complex which is then excreted from the body e.g., chelating agents for heavy metals, Prussian Blue for thallium, specific antibody fragments for digoxin, dicobalt edetate for cyanide, etc.
- **2. Accelerated detoxification** - Some antidotes accelerate the detoxification of a poison, e.g., thiosulfate accelerates the conversion of cyanide to non-toxic thiocyanate, acetylcysteine acts as a glutathione substitute which combines with hepatotoxic paracetamol metabolites and detoxifies them.
- **3. Reduced toxic conversion** - The best example of this mode of action is provided by ethanol which inhibits the metabolism of

methanol to toxic metabolites by competing for the same enzyme (alcohol dehydrogenase).

- **4. Receptor site competition** - Some antidotes displace the poison from specific receptor sites, thereby antagonizing the effects completely. The best example is provided by naloxone, which antagonizes the effects of opiates at stereo-specific opioid receptor sites.
- **5. Receptor site blockade** - This mode of action is best exemplified by atropine which blocks the effects of anticholinesterase agents such as organophosphates at muscarinic receptor sites.
- **6. Toxic effect bypass** - An example of this type of antidotal action is provided by the use of 100% oxygen in cyanide poisoning.