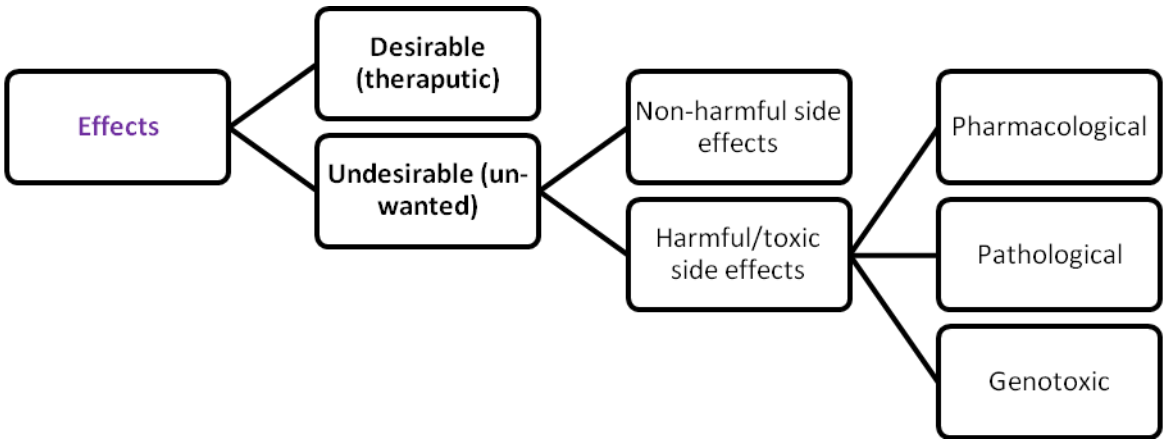

- **What is an adverse effect?**
  - It is a response to a drug which is noxious (ضار ومؤذٍ) and un-wanted and which occurs at doses normally used for prophylaxis, diagnosis or treatment of a disease or for a modification of a physiologic function (example: contraceptives which are given to alter something physiological – there is no disease!).
- "There is no difference between a medicine and a poison… it is the dose which determines this issue" – Paracelsus (father of toxicology which is concerned with studying harmful/ toxic effects of drugs).
  - Notice that every drug is toxic in some individuals at some dose.
- **What are the factors which affect toxicity of a drug?**
  - **Dose**: with increased dose, there is an increased risk in producing adverse effects.
  - **Route**: IV route of administration has more potential in causing harmful effects to the body because the drug will be introduced very rapidly to the systemic circulation.
  - **Species**.
  - **Age**: especially in extremes of age (e.g. newborns and elderly).
  - **Gender.**
  - **Health.**
  - **Environment.**
  - **Individual characteristics** (such as genetic makeup).
- **Classification of adverse effects (based on the cause):**

Type A (Augmented)	It is dose-dependent and there is an extension of the normal effect of a drug (e.g. insulin normally lowers blood sugar level but in a high dose it leads to hypoglycemia and coma)
Type B (Bizarre)	Represented by allergic reactions which are unpredictable (at the first time) and dose-independent (e.g. allergy to penicillin)
Type C (Continuous)	e.g. osteoporosis resulting from prolonged use of steroids.
Type D (Delayed)	Effect appears after a long time of stopping the drug
Type E (End of dose)	Which means something happens when stopping the drug (e.g. stopping steroids after a long time of using them results in acute adrenal crisis).

- **Classification of adverse effects (according to seriousness):**
  - Death!
  - Life-threatening effect.
  - Congenital anomaly (تشوه خلقي).
  - Hospitalization (يتسبب في إقامة المريض في المستشفى لتلقي العلاج).
  - Disability: which is defined as significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/ structure, physical activities or quality of life.

- **Drug toxicity can be:**
  - **Dose-dependent**: which is further classified to the following:
    - ✓ Pharmacological (changes/effects cannot be seen under the microscope):
      - ❖ *Example*: barbiturates have the potential to cause dose-dependent CNS depression which might result in coma!
    - ✓ Pathological (these type of changes can be observed= there is a damage to the structure of a tissue):
      - ❖ *Example*: liver toxicity which is seen with overdose of paracetamol
        - ➢ Acetaminophen is metabolized to: (non-toxic glucuronide and sulfate conjugates) and (a highly reactive metabolite NAPQI which leads to pathologic hepatic necrosis when there is acetaminophen overdose).
    - ✓ Genotoxic (seen by special techniques):
      - ❖ *These changes take place at the level of DNA due to:*
        - ➢ Ionizing radiation.
        - ➢ Anti-cancer drugs.
        - ➢ Certain chemicals.
  - **Dose-independent** (allergic reaction):
    - ✓ Type-I hypersensitivity (immediate hypersensitivity):
      - ❖ Mediated by IgE antibodies with different mediators (prostaglandins, leukotrienes and histamine).
      - ❖ There will be vasodilation, edema and inflammatory response.
      - ❖ Main targets for this type of reaction are:
        - ➢ GIT (represented by food allergies).
        - ➢ Skin (urticaria: skin rash due to allergy to food, atopic dermatitis).
        - ➢ Respiratory system (rhinitis and asthma).
        - ➢ Vasculature (anaphylactic shock: صدمة ناتجة عن حساسية مفرطة تجاه مادة معينة)
    - ✓ Type-II hypersensitivity (autoantibody-mediated):
      - ❖ Mediated by both: IgG and IgM antibodies with activation of the complement system.
      - ❖ Target tissues are cells in the circulatory system.
      - ❖ Examples include:
        - ➢ Penicillin-induced hemolytic anemia.
        - ➢ Quinidine-induced thrombocytopenic purpura.
        - ➢ Sulfonamide-induced granulocytopenia.
    - ✓ Type-III hypersensitivity (immune complex):
      - ❖ Mediated by IgG antibody (there is an antigen-antibody complex which will get deposited in vascular endothelium and fix complement).
      - ❖ Serum sickness: an extensive allergic response which can mimic SLE thus producing confusion in the diagnosis.
    - ✓ Type-IV hypersensitivity (delayed hypersensitivity):
      - ❖ Mediated by sensitizied T-lymphocytes and macrophages:
        - ➢ When sensitized cells come in contact with the antigen, an inflammatory reaction is generated by the production of lymphokines and the subsequent influx of neutrophils and macrophages.
      - ❖ Example: contact dermatitis caused by poison ivy
  - **Idiosyncratic (related to the individual himself):** means that there is a strange unpredictable reaction in some persons who are genetically predisposed. Examples:
    - ✓ A patient who has acetylation deficiency will have an increased incidence of peripheral neuropathy when treated with isoniazid.

- ✓ A black male with G6PD deficiency will develop hemolytic anemia when treated with primaquine.
- ✓ A patient with alteration in vitamin K epoxide reductase will have resistance to the anticoagulant action when treated with warfarin.

- **Therapeutic index (ratio):**
  - **In humans**: median toxic dose (TD_{50}) divided by the median effective dose (ED_{50}).
    - ✓ Therapeutic index = $\frac{TD_{50}}{ED_{50}}$
  - **In animals**: median lethal dose (LD_{50}) divided by the median effective dose (ED_{50}).
    - ✓ Therapeutic index = $\frac{LD_{50}}{ED_{50}}$
  - **Therapeutic index has to be higher than (1) for the drug to be considered as being safe:**
    - ✓ A drug with high therapeutic index is safe: penicillin.
    - ✓ A drug with low therapeutic index is dangerous: digoxin.
- **Margin of safety:**
  - It is a measure of how close the lowest lethal dose is to the highest effective dose.
  - It is mainly applied with humans because the median lethal dose cannot be calculated.
  - **Margin of safety** = $\frac{LD_1 \text{ (lethal dose observed in one patient)}}{ED_{99}}$
- **Pharmacolovigilance (to keep watching the drug):** it is concerned in dealing with adverse effects and then coming up with recommendations to reduce them. These adverse effects can be classified according to their causality:
  - **Certain**: you are 100% sure that the adverse reaction cannot be explained by a disease or another drug.
  - **Probable/ likely**: there is an event or laboratory test abnormality with reasonable time relationship to drug intake. It is unlikely to be attributed to a disease or other drugs.
  - **Possible**: the adverse reaction can also be explained by a disease or other drugs.
  - **Unlikely**: event or laboratory test abnormality with a time to drug intake that makes a relationship improbable (but not impossible).
  - **Conditional/ unclassified**: more data are needed to comment on the effect.
  - **Unassessable/ unclassifiable**: data cannot be supplemented or verified.
- **Reporting adverse effects:**
  - **Yellow-card system (in UK):** an adverse effect must be reported so a necessary action can be taken.
  - **This is known as adverse reaction monitoring (ARM):**
    - ✓ Patients reporting adverse effects to their doctors.
    - ✓ Doctors reporting adverse reactions to regulating authorities.