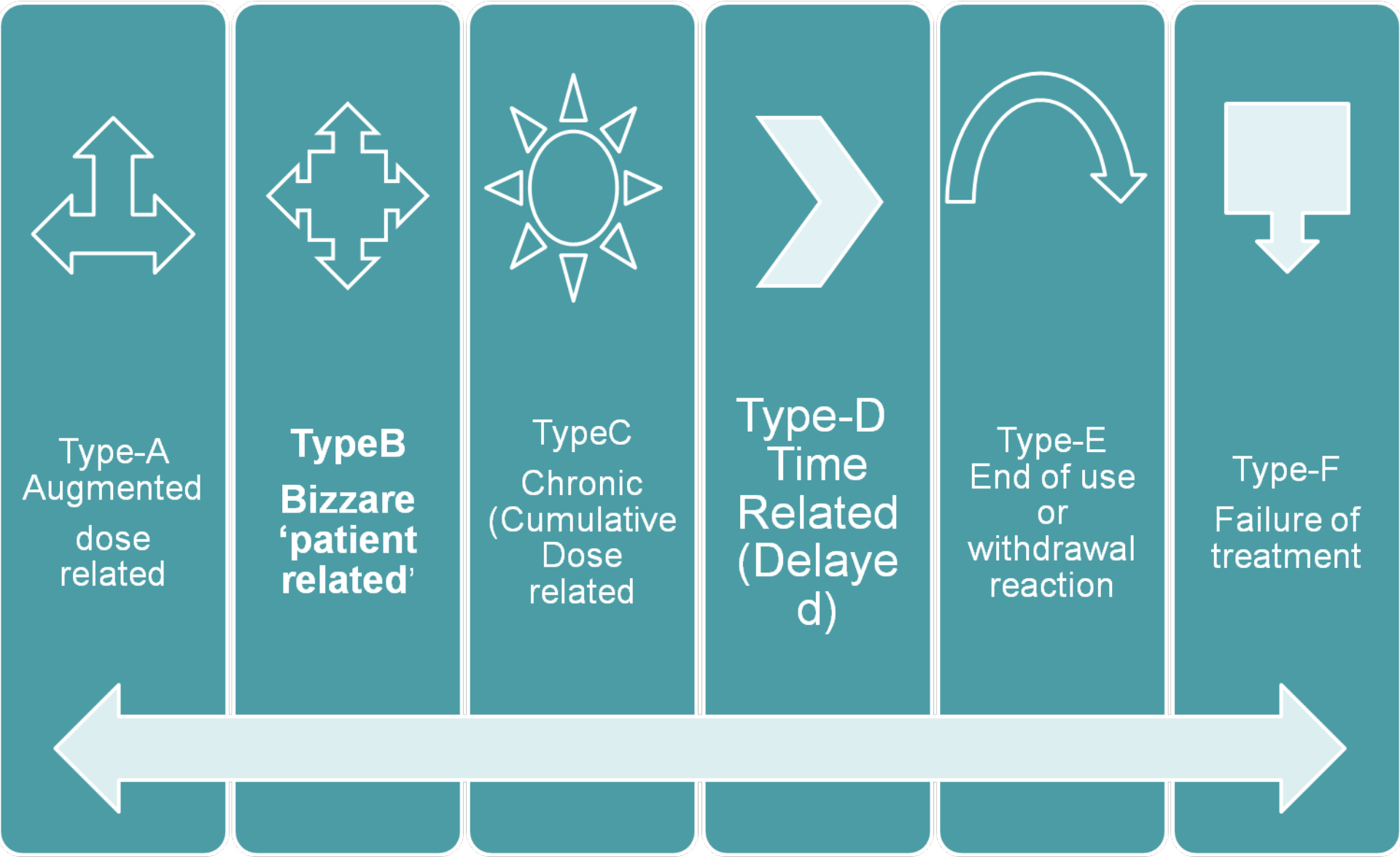
ADVERSE DRUG REACTIONS

- Any noxious and unintended change
- which is suspected to be due to a drug

- occurs at ***normal therapeutic doses*** used in man for the prophylaxis, diagnosis or therapy of disease

- requires treatment or decrease in dose or drug withdrawal or indicates caution in future use of the same drug.

Types of ADRs



TYPE A : EXPECTED UNDESIRABLE EFFECTS

1. SIDE EFFECTS :

-- common, related to pharmacological action of drug

-- mild and manageable

-- predictable , low mortality

Side Effects

Nearly unavoidable secondary drug effect produced by therapeutic doses

- **intensity is dose dependent**
- **Occur immediately after initially taking drug or may not appear until weeks after initiation of drug use**

E.g., e.g. dicyclomine, atropine → dryness of mouth
promethazine →*sedation with antihistamines*

Secondary Effects

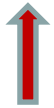
Secondary pharmacological effect

- *E.g., development of diarrhea with antibiotic therapy due to altered GIT bacterial flora*
- *Orthostatic hypotension with a phenothiazine*

Toxic Effects

Toxicity of overdose (Drug overdose)

An adverse drug reaction caused by excessive dosing



e.g. *hepatic failure with* *dose of paracetamol*

Headache with antihypertensives

hypoglycemia with sulfonylurea;

- **Pharmacodynamic –**

  - bleeding due to high dose of heparin
  - coma due to high dose of barbiturates
  - hepatic necrosis from paracetamol overdose

- **Pharmacokinetic :**

  - crystaluria / glomerular nephritis due to precipitation of sulfonamides in acidic urine
  -- nephrotoxicity due to gentamicin

TYPE B – UNEXPECTED UNDESIRABLE EFFECTS:

[Bizarre]

-- drug allergy (hypersensitivity reactions)
on re exposure

-- pharmacogenetic
uncommon, unpredictable, high mortality
not related to pharmacological action of drug

-- immunological

TYPE – I (IMMEDIATE TYPE)

- within minutes (last for 2-3 hrs)

DRUG → ANTIBODY FORMATION (IgE)

↓

fix to mast cells or leucocytes

↓

On ***reexposure*** to drug

↓

Degranulate mast cells and also activation of leucocytes

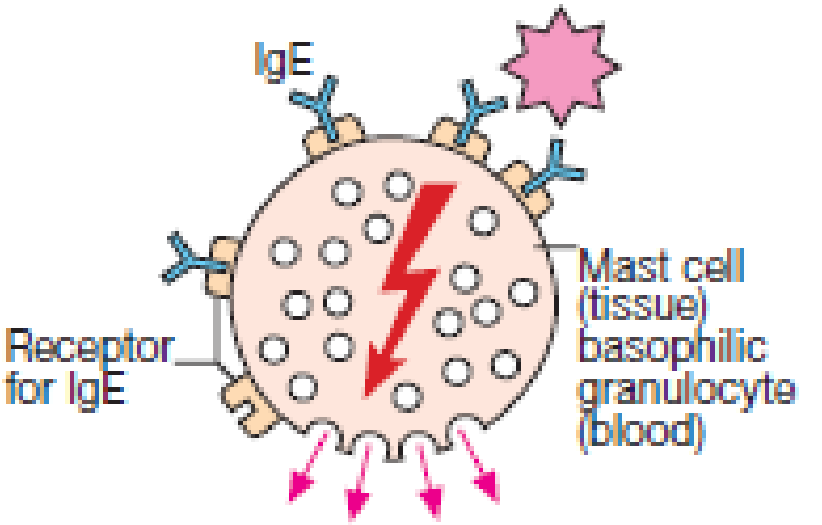
Hypersensitivity /Allergic Reactions
TYPE-1

- Are a result of interaction of drug or metabolite with patient and disease, and subsequent re-exposure.

- most drugs are simple chemicals (mol. wt less than 1000) and act as incomplete antigens or haptens, which become complete antigens in combination with a body protein.

- drug causes formation of tissue-sensitising IgE antibodies that are fixed to mast cells or leucocytes

Immune reaction with repeated drug e



Type 1 reaction:
acute anaphylactic reaction

- **TYPE II (AUTO OR ACCERALATED ALLERGY)**

  -within 72 hrs

drug/metabolite + host protein

↓

Antigen formation

↓

Antibody formation in body (IgG, IgM)

↓

re-exposure

↓

Antigen- antibody reaction

↓

activate complement

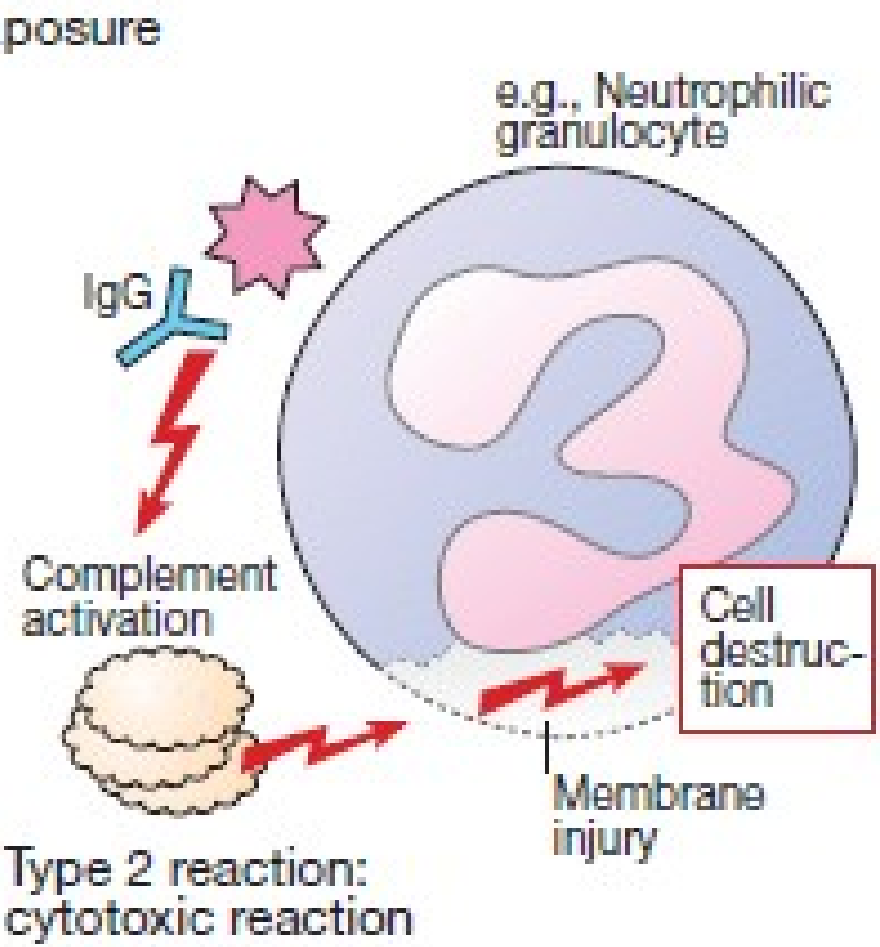
↓

damage cells

↓

fever, SLE, haemolysis, thrombocytopenia

TYPE II HYPERSENSTIVITY



1.Drug antibody (IgG) complexes adhere to the surface of blood cells

2. **These complexes mediate the *Activation of complement***

3. **Activated complement" can *destroy the cell membranes and thereby* cause cell death;**

Methyl dopa induced haemolytic anaemia

Rifampin- thrombocytopenia

Chloroamphenicol-granulocytopenia

- **TYPE III (DELAYED ALLERGY)**

  -- after 72 hrs but within 1-2 weeks

-- Antigen – antibody (IgG) reaction

↓

form complexes which are

↓

Deposited on vascular endothelium and activate complement

↓

characterized by allergic inflammatory reactions in tissue, glomerulonephritis , serum sickness

TYPE III HYPERSENSTIVITY

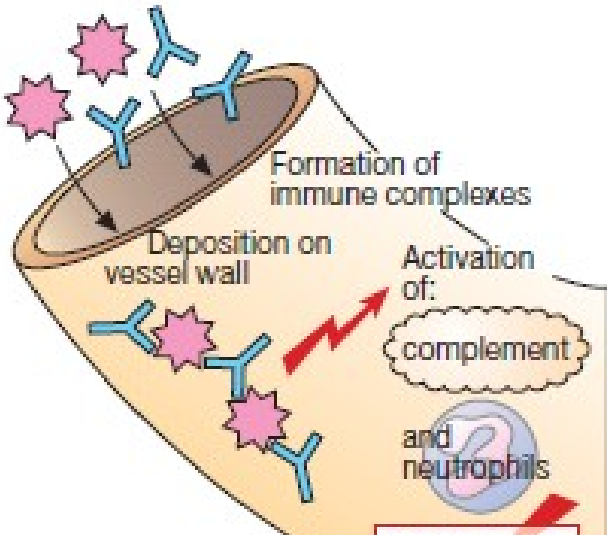
(serum sickness, Arthus reaction).

Drug-antibody complexes precipitate on vascular walls, complement is activated, inflammatory reaction triggered.

Attracted *neutrophils, in a futile* attempt to phagocytose the complexes, liberate lysosomal enzymes that damage the vascular walls (inflammation, vasculitis).

<u>Symptoms may include fever</u>

- swelling of lymph nodes
- arthritis, nephritis, and neuropathy



TYPE IV (CELL MEDIATED ALLERGY)

Antigen specific receptor develop on T - lymphocytes

↓

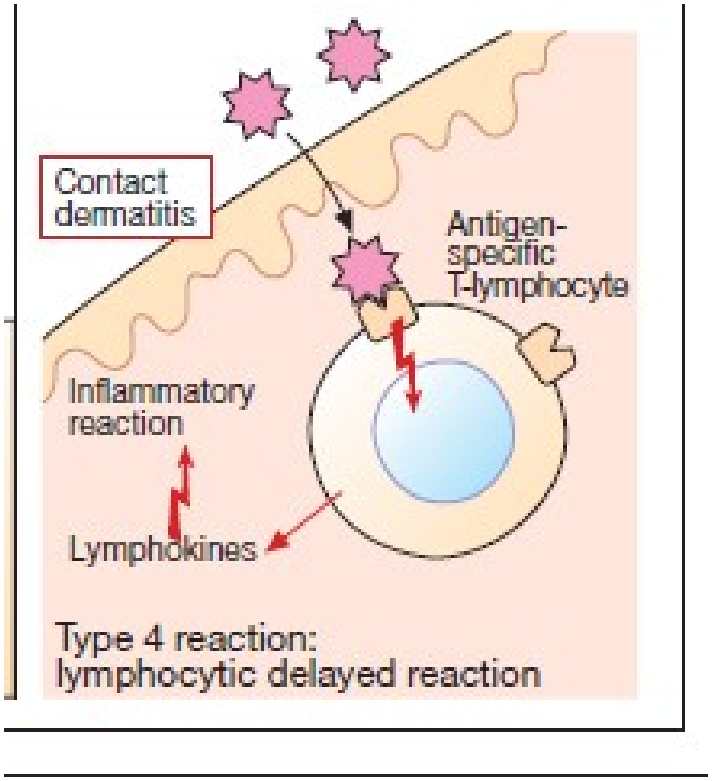
Which when activated after subsequent exposure with drug

↓

- lead to local / tissue allergic reaction

  (photo sensitization and contact dermatitis)

TYPE IV HYPERSENSTIVITY



- ✓Antigen-specific receptors develop on T-lymphocytes.
- ✓Subsequent administration leads to a local or tissue allergic reaction, e.g. contact dermatitis.

GENETICALLY DETERMINED ABNORMAL RESPONSES OF A DRUG

1. Presence of atypical pseudocholine esterase
2. Hydroxylation polymorphism
3. Acetylator status
4. G-6-PD deficiency in RBC
5. Acute intermittant porphyria

IDIOSYNCRATIC DRUG REACTION

1. Malignant hyperpyrexia:

2. Aplastic anaemia : (chloramphenicol)

3. Aspirin induced late onset asthma or chronic renal failure

- **TYPE C (CONTINUOUS DRUG USE)**

--development of tolerance & physical dependence to narcotic analgesics on their continuous use

--tardive dyskinesia in patient receiving antipsychotics

- **TYPE D – DELAYED**

  delayed occurrence of ADR even after stoppage of treatment after long term administration

-- retinopathy by Chloroquine

-- peritoneal fibrosis by methysergide

-- vaginal adenocarcinoma due to stilbesterol

- Renal pelvic carcinoma due to phenacetin abuse

- corticosteroids + azathiorpine

  → Immune responses are supressed

  → develops to lymphomas

TYPE E – END OF DOSE

- Withdrawal reactions occur when drugs are stopped suddenly.
- HT and restlessness on opiate withdrawal
- Seizure with alcohol or BZD withdrawal

- Acute adrenal insufficiency due to corticosteroid withdrawal
- Hypertensive urgency due to clonidine withdrawal
- Worsening of angina pectoris due to stoppage of beta-blockers

- Increase seizure frequency → due to sudden withdrawal of antiepileptic

TYPE F – FAILURE OF THERAPY

-- results from ineffective treatment

-- accelerated Hypertension because of insufficient control

OTHER IMPORTANT ADR

1. **INFERTILITY**

male → cytotoxic drugs, sulfasalazine, MAO inhibitors

female → cytotoxic drugs

2. TERATOGENSIS

- when drug taken in early stage of pregnancy → causes developmental anomalies in fetus

thalidomide → phocomelia (seal limb)

Drug can affect the fetus at 3 stages:

1) ***fertilization and implantation-***

-- conception to 17 days- failure of pregnancy which often unnoticed

2) ***Organogesis***

– 18 to 55 days of gestation- deformities are produced

(3) ***Growth and development*** –

-- 56 days onwards – developmental and functional abnormality

e.g. --ACE inhibitors can cause hypoplasia of organs

--NSAIDS may produce premature closer of ductus arteriosus

- risk category of drugs during pregnancy
  -- category A, B , C, D and X

Category X –

studies in animals or humans have demonstrated fetal abnormalities , and potential risk clearly outweighs possible benefit e.g. estrogens, isotretinoin, ergometrine

DRUG	ABNORAMLITY
Phenytoin	Hypoplastic phalanges, cleft lip/palate, microcephaly
Carbamazepine	Neural tube defects
Sodium valproate	Spina bifida & other neural tube defects
Warfarin	Nose, eye & hand defects, growth retardation

- LATER STAGES OF PREGNANCY

-- sulfonamide → kernicterus

- DURING LACTATION

-- penicillin → hypersensitivity reaction

-- sulfonamide → cause kernicterus and heamolysis in G6PD deficient babies.

(3) ABNORMALITIES OF TASTE AND SMELL –

-- D penicillamine, pyrazinamide,
captopril, metronidazole

(4) HEPATOTOXICITY

-- hepatic cell injury → paracetamol, phenytoin

-- cholestatic jaundice → Chlorpromazine, rifampicin,erythromycin

-- cirrhosis of liver → alcohol, methotrexate

5. NEPHROTOXICITY –

-- tubular necrosis – aminoglycoside

-- interstitial nephritis – cephalosporin, NSAIDs

-- glomerular nephritis – sulfonamides

--nephrotic syndrome – ACE inhibitors

6. PHOTOTOXICITY

- UV – B (290 – 320 nm)
- Erythema, edema, blistering f/b hyperpigmentation & dessquamation
- Acute → Demeclocycline and tar products

- Chronic toxicity

  fluroquinolones, sulfonamides, thiazides, amiodarone

7. PHOTOALLERGIC

-- drug/metabolite → cell mediated immune response

- Papular eczematous contact dermatitis like picture.
- UV –A (320- 400 nm)

- griseofulvin , CHQ , sulfonamides, chlorpromazine

8. **OCULAR TOXICITY** :

--cataract –glucocorticoids

--glaucoma – topical mydriatics

-- pigmented retinopathy → CHQ, CPZ

-- optic neuritis – ethambutol

9. **OTOTOXICITY**

-- deafness -- aminoglycoside, CHQ

-- vestibular disorder – aminoglycoside

10. **BEHAVIORAL TOXICITY**

-- suicidal tendency – reserpine

-- disorientation, confusion -- amphetamine

-- restlessness , psychosis → glucocorticoids

11. **IATROGENIC DISEASE :**

-- parkinsonism – CPZ, reserpine

-- CCF, HTN -- glucocorticoids

-- peptic ulcer – aspirin , indomethacin

12. **ELECTROLYTE DISTURANCES**

-- Decrease Na+ and K+ → thiazide, furosemide

-- Na+ retention → corticosteroids

13. **ENDOCRINE DISTURANCE**

-- menstrual irregularities, galactrorrhea – → chlorpromazine

-- decrease lactation → OC Pills

-- hyperglycaemia → thiazide diuretics

14. **SKIN TOXICITY**

-- acne -- steroids , iodides

-- eczema – captopril, topical antihistaminics

-- SJ syndrome – allopurinol, aminopenicillin, imidazoles

-- urticaria – aspirin, enalapril, penicillins

15. **CVS TOXICITY :**

--torsade de pointes – terfenadine, astimazole, cisapride

--AV block – clonidine, methyl dopa

--thromboembolism – ocpills

--arrhythmias – digitalis (high dose), astemizole, terfenadine

(16) NEUROTOXICITY:

-- peripheral neuropathy → isoniazid

(17) HAEMOPOIETIC TOXICITY

-- haemolytic anaemia → sulfonamide, methyldopa

-- agranulocytosis → clozapine

-- megaloblastic anaemia → chloramphenicol, phenytoin, methotrexate

(18). **DRUG DEPENDENCE**

- **PSYCHOLOGICAL DEPENDENCE :**

-- individual believes that optimal state of wellbeing is achieved only through actions of drug

--opioids, cocaine

- **PHYSICAL DEPENDENCE** :

-- altered physiological state produced by repeated administration of a drug which necessitates continued presence of drug to maintain physiological equilibrium.

-- Discontinuation of drug result in a characteristic withdrawal syndrome.

-- benzodiazepines, alcohol, opiods , barbiturates

DRUG ADDICTION:

it is a pattern of compulsive drug use chararacterized by overwhelming involvement with use of a drug

Amphetamine, cocaine, cannabis , LSD

- **DRUG HABIT** :

-- denotes less intensive involvement with the drug, so that its withdrawal produce only mild discomfort.

-- no physical dependence

tea , coffee, tobacco, social drinking

(19) CARCINOGENICITY :

tobacco, oestrogens, progestogens, radio-isotopes