Adverse drug reactions

- Noxious, unintended or undesired response to drug, caused by normal use of normal doses
- Direct causal relationship between the medicine and the occurrence

ADR	Characteristics
Type A (80%)	- Predictable and dose-dependent, usually related to pharmacological actions of drug - Immune system is *not* involved ○ E.g. Toxicity, intolerance, secondary effects, drug interactions, renal failure - Treatment – reduce dose or withhold drug
Type B (15%)	- Unpredictable, not dose-dependent - Unrelated to pharmacological actions of the drug, e.g. penicillin allergy - Treatment – withhold drug and avoid rechallenge

Type B ADR	Antibodies involved	Examples	Timeline
1 – immediate	IgE	Dyspnoea, urticarial, swelling, anaphylaxis	Hours
2 – cytotoxic	IgM, IgG	Haemolytic anaemia, thrombocytopenia	5-14 days
3 – immune complex	IgM, IgG	Small vessels – nephritis, vasculitis, iritis	7-8 days
4 – cell-mediated	None; involves T-cells	Skin rash, eczema, maculopapular, bullous	Weeks

Type 4: delayed-type reactions (most common)

- T_h1 produces TNF-α and IFN-ϒ, activates macrophages
- T_h2 produces interleukins, activates B-cells
- Drugs include – abacavir, allopurinol, azathioprine, NSAIDs, terbinafine, quinolones, sulfonamides, beta-lactam antibiotics

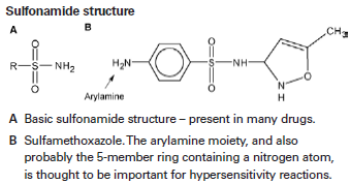
Anaphylaxis

- Combination of immediate-type reactions – usually occurs within 15 minutes to hours
  - Respiratory symptoms – cough, wheeze, hoarseness, cyanosis, upper airway swelling
  - Cardiovascular – tachycardia, severe hypotension, loss of consciousness, palpitations
  - Dermatological – urticarial, erythema, angioedema
  - Nausea, vomiting, abdominal cramps, anxiety, distress
- Treatment – adrenaline IM injection into thigh (blue for the sky, orange for the thigh) + hospital
  - Hold autoinjector in place for 10 seconds, repeat dose every 5 minutes until improvement
    - Lay patient flat, ensure open airways
  - Antihistamines and hydrocortisone are *not* first-line (but may be given later on)
- Causes of anaphylaxis – medicines > insect venom > foods

Haptens

- Antigen too small (insufficient molecular weight) to generate immune response on its own
  - An antigen must be (or attach to) a macromolecule, e.g. large protein, polysaccharide
- Metabolism may produce reactive metabolites haptenate endogenous proteins (increases MW)

Antibiotic allergies



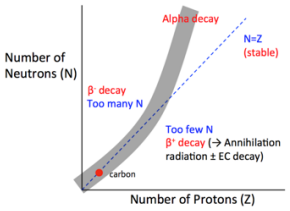
A Basic sulfonamide structure – present in many drugs.
B Sulfamethoxazole. The arylamine moiety, and also probably the 5-member ring containing a nitrogen atom, is thought to be important for hypersensitivity reactions.

- May affect any organ, but most commonly the skin
- Higher rates in HIV and infectious mononucleosis patients
- Patients with history of penicillin allergy who require cephalosporins
  - Possible cross-sensitivity as both are beta-lactam antibiotics
  - Treatment depends on if previous reaction was IgE-mediated, and severity of reaction
- Sulfur allergy – no evidence of cross-reactivity between arylamine and non-arylamine sulfonamides
  - Presence of arylamine ring in sulfonamide structure conveys immunogenicity
  - Arylamine sulfonamides – allergic cross-sensitivity within this groups is possible
    - Many antibiotics, sulfasalazine, sulfamethoxazole, amprenavir, fosampranavir
  - Non-arylamine sulfonamides – no allergic cross-reactivity
    - Acetazolamide, sulfonylureas, loop diuretics, thiazide diuretics, celecoxib
- Allergy to sulfonamides – do *not* need to avoid sulfites/sulfates/sulfur (since low MW)

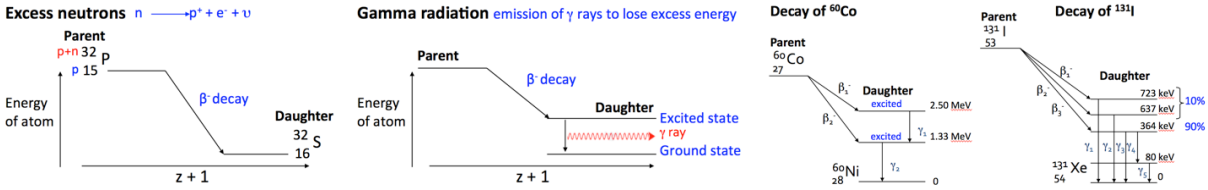
Term	Definition	
Nuclide	Atomic species identified by exact nuclear composition, including mass #A and atomic #Z	
Radionuclide	Unstable or radioactive nuclide	Mass number = # of protons + # of neutrons; Atomic number = # of protons; $^{A}_{Z}X$
Isotopes	Same atomic #Z but different neutron number = different mass #A	
Isomers	Same number of protons and neutrons, but different energy states	

Radioactive decay

- 81 elements with ≥1 isotope = 274 nuclides (most of which are unstable)
- Heavier nuclides tend to have more neutrons than protons
- Unstable nuclides – mostly produced in nuclear reactor or accelerator
- Cyclotron – particle accelerator
    - Used to bombard neutron-deficient target with protons
    - Produces *positron*-emitting radioisotopes

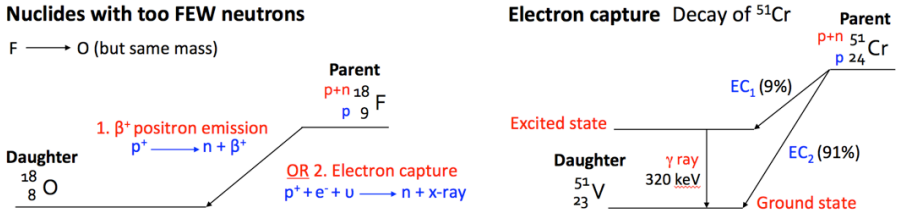


Nuclear instability	Decay mechanism	Mode of decay (i.e. emission)
Excess neutrons	$n \rightarrow p^+ + e^- + \nu$	Electron (β^-) + neutrino (ν)
Excess protons (neutron deficiency)	$p^+ \rightarrow n + e^-$	Positron (β^+) …or…
	$p^+ + e^- \rightarrow n + \nu$	Electron capture
Excess neutrons + protons	$^{A}_{Z}X \rightarrow {}^{A-4}_{Z-2}X + {}^{4}_{2}He$	Alpha ($^{4}_{2}He$)



Excited states

- May be multiple excited states
    - $^{60}_{27}Co$ can decay to 2.50 or 1.33MeV to emit two different energies of γ rays; $^{131}_{53}I$ has four
- More convenient for imaging if there is only one level of gamma ray energy to detect

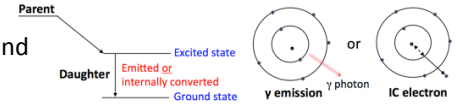


Annihilation (gamma) radiation

- After a positron leaves the nucleus, it loses kinetic energy and is annihilated by combining with an electron to form 2 photons (2 gamma rays)
    - $\beta^+ + \beta^- \rightarrow 2\gamma$
    - I.e. mass of the particles is converted to electromagnetic radiation ($E=mc^2$)
- Both photons have energy of 0.51MeV, but travel in opposite directions (∴ net momentum = 0)
    - Since photons are emitted 180° to each other, they can be used in diagnostic scans

Electron capture (K-capture)

- Proton-rich nuclide absorbs/captures electron from an atomic orbital (usually K-shell)
    - $p^+ + e^- \rightarrow n$ + neutrino emission
- Excited state nuclide will emit gamma rays to return to ground state – two possible ways
    1. Emit energy directly
    2. Internal conversion – energy is transferred to a bound electron, which is then ejected from the atom



Chemotherapy agents

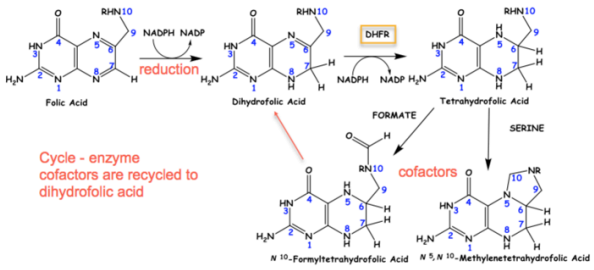
Cell cycle	**G_0 → interphase (G_1 → S → G_2) → M**
G_0	Quiescence – cells can exit cell cycle in G_1 to enter G_0
G_1, G_2	Gap phases – rest, cellular growth and synthesis
S phase	Synthesis – DNA replication - DNA helicase – unwinds and unzips helix - DNA polymerase – inserts new nucleotides - DNA ligase – links sugar-phosphate groups between new nucleotides
M phase	Mitosis – cell division

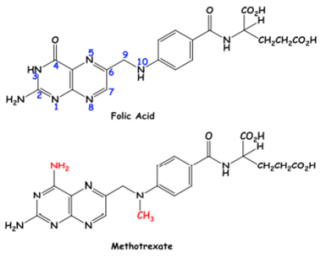
Anti-metabolites (target S-phase)

- Cancer cells – grow rapidly, require more nucleotides than normal cells for DNA synthesis
    - Purine bases (AG) and pyrimidine bases (CTU)
        - Obtained *de novo* and via salvage pathways – all cells use both
        - Cancer cells favour *de novo* synthesis
- Antimetabolites prevent biosynthesis or utilisation of normal cellular metabolites
    1. May be enzyme inhibitor or fraudulent building block
    2. Incorporated into RNA/DNA to inhibit *de novo* synthesis of nucleotides
    3. Affects replication, transcription and translation
- E.g. pyrimidine analogues (5-fluorouracil), purine analogues (6-mercaptopurine), methotrexate
    - Sufficiently similar to essential metabolite – mistaken for, but cannot take its place
    - Usually result from ≥1 bioisosteric changes (similar size but different properties)
        - E.g. H → F, CH_2/O → S, OH → NH_2

<u>Methotrexate (MTX)</u>

- Uses – leukaemia
- Resistance due to up-regulation of DHFR gene → insufficient MTX to inhibit all of DHFR
- MOA – competitive dihydrofolate reductase (DHFR) inhibitor
    - Folic acid – essential metabolite for biosynthesis of DNA
    - DHFR is essential in regeneration of folic acid cofactors required for DNA synthesis
    - DNFR inhibition → absence of cofactor → inhibition of purine and pyrimidine synthesis
- Folic acid → dihydrofolic acid + DHFR → tetrahydrofolic acid → cofactors
- Cofactors – 1 carbon donors (formyl CHO or methyl CH_3) necessary to produce DNA bases
    - N^{10}-formyl-FH_4 – for purine synthesis
    - N^5N^{10}-methyl-FH_4 – for pyrimidine synthesis
        - Thymidylate synthetase normally uses dUMP + cofactor to produce dTMP





<u>5-fluorouracil (5FU)</u>

- Uses – breast and stomach cancers; causes bone marrow toxicity
- Resistance due to down-regulation of cellular enzymes needed to add deoxyribosephosphate unit
- 5FU only inhibits thymidylate synthetase – blocks conversion of uracil (dUMP) to thymine (dTMP)
    - Differs from dUMP by replacing H with F (more electronegative) to become dFUMP
- Thymidylate synthetase binds N^5N^{10}-methyl-FH_4 cofactor + dFUMP
    - Produces irreversibly-bound enzyme-substrate complex with the fluorine
    - Prevents pyrimidine and DNA synthesis