“One of the features which is thought to distinguish man from other animals is his desire to take medicines”

(Sir William Osler, 1849-1919)
Definitions

- **Pharmacology** is the science of the interaction of chemicals with living systems at all levels.

- **Pharmacokinetics** investigates the effects of the biological system on drugs (absorption, distribution, elimination…).

- **Pharmacodynamics** describes the fundamental action of a drug on a physiological, biochemical or molecular level.

- **Pharmacogenetics** examines the effects of genetic factors to variations in the drug response (“Asian Flush”, Codeine “resistance”).

- **Toxicology** studies the undesirable effects of chemicals on living systems (includes poisons, antidotes and unwanted side effects of drugs).

- **Pharmacy** is the art of preparing, compounding and dispensing chemicals for medicinal use.
Definitions

• **Prophylactic** refers to a drug or procedure aimed to **prevent** disease

• **Palliative** refers to a drug or procedure aimed to **relieve symptoms**

• **Therapeutic** refers to a drug or procedure aimed to **cure** disease

• **Tolerance** is the increased resistance to the usual effects of an established dose of a particular drug

• **Effective dose (ED50)** is the concentration at which 50% of the subject show a predefined response

• **Efficacy** refers to the inherent capability of a drug to produce a desired effect

• **Potency** compares the relative effectiveness of drugs to produce a desired effect

  e.g. Drug A requires fewer milligrams than Drug B to achieve the same pharmacological response

  --> Drug A has the **higher potency**, yet, both drugs have the **same efficacy**.
History of Pharmacology

- Initially most medicines were of botanical or zoological origin

- Since 1950’s, large increase in synthetic organic chemicals

- Recent introduction of recombinant DNA technology has extended synthesis to molecules of human origin
History of Pharmacology

• Early agents were naturally occurring inorganic salts and plant alkaloids
  – Opium
  – Foxglove
  – Mercury, arsenic or lead compounds
• Most ineffective or actually dangerous
• Standardization of dose very difficult
  – Narrow therapeutic index with foxglove
Homeopathy

- **1790-96: Dr. Samuel Hahnemann:**
  
  To discover the true mode of action by which cinchona bark cured malaria, he ingested cinchona juice twice daily for a few days. To his great astonishment, he very soon developed symptoms very similar to malarial fever.

  – Postulated a new principle of treatment: “Likes cure likes”

  – Drug is called the remedy, obtained through serial dilutions of the chemical

  The remedy is mainly extracted from the plants, animals and minerals. The medicinal extract is diluted and potentiated to such an extent that not even an atom of the mother material can be detected in the remedy by the time it reaches the 12th potency. Dilutions are done in steps. For example: In the centi scale, one drop of mother tincture is mixed with 99 drops of alcohol and shaken rigorously using pre-determined strokes. This is termed as 1c. From this, one drop is mixed with 99 drops of alcohol and is termed as 2c and so on. The higher the dilution, the more powerful the remedy. It was proposed recently that the magnetic aura of the remedy increases with potency (supposedly, this had been proven with Kirlian photography).

  Since the remedies are used after diluting several times, it cannot have chemical effects on the body to create a long standing side effect.
History of Pharmacology

• Major advance in safe use of naturally derived agents was the isolation, purification and chemical characterization of the active compound:

  – Allowed administration of a controlled dose
  – Allowed administration of the active component of herbal mixtures to be given alone
  – Identification and characterization of active component allowed definition of mechanism of action, leading to synthesis of improved agents with greater selectivity, potency, altered duration of action, etc.
History of Pharmacology

- **Aspirin®** - first synthetic drug

  - **Hippocrates**: pain relief treatments with powder made from the bark and leaves of the willow tree (Salix sp.)

  - **Johann Buchner** (1829): isolated Salicin as the active ingredient in Meadowsweet (Spiraea ulmaria)
    (hydrolyzed into glucose and Salicyl-aldehyde -> oxidized to Salicylic Acid)
    Salicylic Acid is very tough on the stomach->

  - **Felix Hoffman** (1898-9): Chemist at Bayer synthezised Acetyl-Salicylic Acid, (process discovered originally by Charles Gerhardt in 1853) and tested it on his arthritis-suffering father!

  - **March 6, 1899**: Bayer receives patent for Aspirin®

  - **Sales today exceed 50 billion pills per year**
History of Pharmacology

- 20\textsuperscript{th} Century: Dramatic change in antimicrobial therapy
  - Survival of patients with severe infections with historically high mortality
  - Introduction of sulfonamides (Gelmo 1908: Sulfanilamide) and arsenic compounds (Ehrlich 1908/10: arsephenamine = Salvarsan) and subsequently penicillins (Fleming 1928/29)
New Drug Discovery

• Analogues to existing drugs
  – Usually shows only minor changes in potency, absorption, duration of action

• New applications for existing drugs
  – Occasionally unexpected additional properties may become evident when the compounds are tested in humans
    • Sulfanilamide --> thiazide diuretics
    • Sulfanilamide --> sulfonylurea hypoglycemics
    • Aspirin® --> Anti-aggregatory --> Cardioprotective
New Drug Discovery

• Synthesis and screening of new chemical entities
  
  • Subject new chemicals to a battery of tests designed to detect a particular type of biological activity ("Drug screening")

  • Chemicals produced by direct synthesis, or isolation from biological sources (or combination of both: semi-synthetic)

  • Apparently not an efficient method since huge numbers of chemicals may need to be screened, however, new robotic instruments are now screening millions of compounds against defined receptors or enzymes
New Drug Discovery

• Design of compounds for a specific biological function
  (“Rational drug design”)
  – Synthesis of naturally occurring compounds or structural analogues
    • Examples:
      – Levodopa, H2 receptor antagonists, omeprazole
  – Use of structural information (receptor, enzyme) to develop interacting compounds
    • Examples:
      – STI571 (Glevec®): Bcr-Abl specific inhibitor, but high pK, also resistance =>
        2nd generation Bcr-Abl inhibitors are being designed based on the structure of the Bcr-Abl/STI571 complex
  – Cloning of genes to produce large biologically active peptides
    • Examples:
      – Rec. hormones, cytokines; soluble receptor; antibodies
New Drug Discovery

- Extremely high cost of new drug development in general restricts it to the province of large pharmaceutical companies
- Cost of new drug development is in the $100 to $500 million range
- Cost of initial marketing is also very high
- Incentives are very high with important new drugs having greater than $1 Billion in yearly sales
Patent Protection of new Drugs

• Patent life in the US is 20 years

• Drug is frequently patented five years or more before marketing begins

• After patents expire, other manufacturers may produce and sell bioequivalent “generic” products (usually much cheaper, as these companies had very little “development” cost)
Orphan Drugs

- Drugs for conditions affecting less than 200,000 individuals in the US

- Orphan Drug Act of 1983 provides incentives for the development of drugs for this small market segment (tax breaks, exclusive marketing rights, grant funding)

- 890 Orphan drugs in the US for the treatment of 6.5 million people
Drug Nomenclature

• Brand Name
  – Prevacid®, Zoton® (New Zealand), Keval® (Mexico), Lanzor® (France), etc.

• Generic Name
  – Lansoprazole

• Chemical Name
  – 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-benzimidazole
Drug Approval

Historically, manufacturers or sellers had no responsibility

--> Regulatory systems have arisen to protect patients from toxicity and
more recently to ensure benefit (efficacy)

1938 - Federal Food, Drug and Cosmetic Act
Drug Approval

• Safety
  – Introduction of new drugs has sometimes been bought at the price of significant toxicity
    • 1937: >100 deaths due to diethylene glycol in Sulfanilamide elixir
    • 1960’s: Thalidomide (Contergan®) disaster:
      – developed by the company Grünenthal as a sleep-inducing drug and to combat symptoms associated with morning sickness of pregnant women
Drug Approval

• Safety
  – Bacterial, isolated cellular, and intact animal toxicity testing
  – Testing for toxicities including
    • Teratogenicity
    • Mutagenicity
    • Reproductive toxicity
Drug Quality

- Regulatory bodies (FDA)
  - ensure quality of prescribed drugs

- Defined criteria for:
  - Purity
  - Stability and sterility
  - Limits of potentially toxic impurities
  - Defined, approved amount of drug, released at a specified rate (United States Pharmacopoeia, British Pharmacopoeia, European Pharmacopoeia)
Drug Efficacy

- Efficacy must be established in patients for whom the medicine is intended

- All medicines, except dietary supplements, must have evidence of efficacy for their licensed indications.
Drug Efficacy - Dietary Supplements?

- **Leptoprin®** (30 pills = $153):
  - Calcium (amino acid chelate) 264mg
  - Vitamin B6 25mg
  - Acetylsalicylic acid 324mg
  - Caffeine 200mg
  - Green Tea Extract (no amount listed)
  - L-Tyrosine (no amount listed)
  - Kelp 100mg
  - Ephedrine 20mg
  - Cayenne (no amount listed)

The FDA had previously issued a policy that ephedrine products must be labeled with possible adverse effects, contain no more than 8 milligrams of ephedrine per serving, and be used for no longer than seven days, because of the significant dangers associated with ephedra or ephedrine use. Since April 2004, ephedrine has been banned in dietary supplements!

**Conclusion:** The only ingredient in Leptoprin that might assist in weight loss is calcium. If you do not get enough calcium in your diet, you can buy cheap supplements at any drugstore.
Drug Efficacy - Dietary Supplements?

• CortiSlim® (30 pills = $78):
  
  – “Dr”. Greg Cynaumon?
    Ph.D. from “Sierra University” in Psychology - School was shut down by the State of California!
  
  – September 2004 : Greg Cynaumon forced to admit that he is not a psychologist or a marriage and family therapist. The California Board of Psychology issues a citation and fines Greg Cynaumon $1,500 for continuing to impersonate a psychologist.
  
  – The California Board of Behavioral Sciences issued a citation and fined Greg Cynaumon $1,000 for continuing to impersonate a marriage/family therapist.
  
  – “FTC Targets Products Claiming to Affect the Stress Hormone Cortisol”
    Agency Alleges That Marketers of CortiSlim and CortiStress Made False or Unsubstantiated Claims
Cosmetics

• Cosmetics:
  – “Articles intended to be applied to the human body for cleansing, beautifying, promoting attractiveness, or altering the appearance without affecting the body’s structure or functions”
  – Some cosmetics are also drugs
    (usually list an “Active Ingredient”: e.g. Dandruff shampoo, Fluoride Toothpaste)
  – **Soap**: Exempted from the Food, Drug and Cosmetic Act as long as no “Cosmetic Claim” (e.g. Deodorant Soap) is being made: Pure Soap (alkali salt of fatty acids)

• Regulated by the FDA, but less stringent
  – Cosmetics and their ingredients are **not required** to undergo approval **before** they are sold to the public (only monitored **after** release !)
  – Cosmetics require declaration of ingredients in descending quantity (note: no ACTIVE ingredients)
  – **No required performance substantiation** !
  – **No safety testing required**
    (product must then be labeled “WARNING: The safety of this product has non been determined”)
  – **FDA acts only when a product is proven unsafe !!**
Establishing Safety and Efficacy

- Preclinical studies
- Phase I clinical studies
- Phase II clinical studies
- Phase III clinical studies
- Phase IV post-marketing surveillance
Preclinical Studies

• Pharmacological effects or pharmacological profile
  – In-vitro effects using isolated cells/organs
  – Receptor-binding characteristics
  – In-vivo effects in animals/animal models of human disease
    • Drugs are lacking where a good animal model of a human disease does not exist
  – Prediction of potential therapeutic use
Preclinical Studies

• Pharmacokinetics
  – Identification of metabolites (since these may be the active form of the compound)
  – Evidence of bioavailability (to assist in design of clinical trials and assess toxicity)
  – Establishment of principal route of administration and rate of elimination
Preclinical Studies

• Toxicological effects
  – In vitro and in vivo batteries of tests to identify toxic compounds and metabolites prior to extensive exposure of animals and subsequently humans

  – Toxicity testing has two primary goals:
    • Recognition of hazards
    • Prediction of that hazard occurring in humans at therapeutic doses
      – A wide range of doses is tested
        » High doses to detect acute toxicity
        » Low doses to predict risk at long-term therapeutic doses
Toxicity Testing

- **Mutagenicity**
  - A variety of in vitro tests using bacteria and mammalian cell lines are employed at an early stage to define any potential effect on DNA that may be linked to carcinogenicity or teratogenicity

- **Carcinogenicity**
  - Repeated doses given throughout lifetime of an animal (usually two year rodent assay)
  - Especially important in drugs intended for chronic administration (greater than one year)

- **Reproductive toxicity**
  - Repeated doses given prior to mating and throughout gestation
  - Assesses effect on fertility, implantation, fetal growth, production of fetal abnormalities and neonatal growth
Toxicity Testing

• **Acute Toxicity**
  - Animal model - single dose given by proposed route for humans
  - Defines dose range associated with toxicity
  - Defines dose range for initial human trials

• **Subacute Toxicity**
  - Repeated doses given for 14 or 28 days
  - Reveals target for toxic effects
  - Comparison with single-dose studies indicate potential for accumulation

• **Chronic Toxicity**
  - Repeated doses given up to six months
  - Reveals target(s) for toxicity (except cancer)
  - Aim is to define doses associated with adverse effects and “no observed adverse effect level” associated with “safe” dose
Toxicity Testing

• Animal Studies:
  – Remain an important part of toxicological testing
  – Essential to investigate both interference with integrative function and complex homeostatic mechanisms
  – Necessary to prevent extensive toxicity in subsequent human trials
  – Extensive research underway to reduce the need for animal studies by using in vitro methodology
Toxicity Testing

- Animal Studies:
  - Methodology is not perfect, but animal studies do provide an effective predictive screen
  - Not all hazards detected at very high doses in experimental animals are relevant to human health
  - FDA has to judge if there is clinical relevance of data in animals at doses that may be two orders of magnitude above those intended for human use
Premarketing Clinical Studies: Phase I-III Trials

• Notice of Claimed Investigational New Drug (IND) is filed with the FDA
  – Information on composition and source of drug
  – Manufacturing information
  – Data from animal studies
  – Clinical plans and protocols
  – Names and credentials of physicians conducting the trials
Phase I Studies

- Studies carried out in healthy volunteers
- Carried out by pharmaceutical companies or major hospitals
- In some cases patients with the disease in question may be enrolled (cancer chemotherapy)
- Initially small doses (as little as one fiftieth of intended dose)
- Toxicity evaluated with routine hematology and biochemical monitoring of liver and renal function
- Dose is escalated until pharmacologic effect is observed or toxicity occurs
Phase I Studies

- Used to study the disposition, metabolism and main pathways of elimination of the new drug in humans
- Identify the most suitable dose and route of administration for further clinical studies
- Use of isotope-labeled (usually beta-emitting) compounds to investigate pharmacokinetics and metabolism
Phase II Studies

- Pharmacology of the new drug is determined in patients with the intended clinical condition
- Principal aim is to define relationship between dose and pharmacological and/or therapeutic response in humans
- During phase II some evidence of beneficial effect may emerge
- Address subjective element in human illness (placebo effect)
- Additional studies:
  - Special populations (elderly, etc.)
  - Tests for potential interactions with other drugs
  - Optimum dosage established for use in phase III trials
Phase III Studies

• Main clinical trial
  – Drug is compared to placebo, or if this would be unethical (effective treatment for the disease in question already exists), an established drug in use for this disease
  – Comparison to other established treatments
  – Addition to established treatment with placebo control
Phase III Studies

- Random placebo-controlled studies
  - Randomization of patient population
  - Sometimes there is double-blinding of the study
  - Between patient population studies
    - Separate patient population arms
    - Requires greater number of patients
  - Within patient population studies ("crossover")
    - Alternate treatment with new drug and standard therapy or placebo
      => each patient gets both treatments sequentially
    - Takes longer
Phase III Studies

• Measurements of adverse effects and possible benefit made at regular intervals

• Attention to detecting likely occurring side effects (type A reactions), and unpredictable, rarer complications (type B reactions)
  – Majority of type B reactions may not be seen until post marketing because during the Phase III trial usually only 2000-3000 people will take the drug, usually for short periods
  – Type B reactions typically occur in one in 1000 to 10,000 patients
Phase IV studies:

• Postmarketing Surveillance
  – Ongoing monitoring of drug safety under actual conditions of use in large numbers of patients. (Pharmacovigilance)
  – Physician and pharmacist reporting of adverse drug events
  – No fixed duration
  – Picks up adverse events occurring in less than one in 1000 subjects
Adverse Reactions to Drugs

• Severe adverse effects:
  – Uncommon, but explainable extensions of known pharmacologic effects
  – Unexpected, may not be recognized until a drug has been marketed for years, sometimes unexplainable (Thalidomide)
    • Often represent immunological reactions
      – Urticaria, angioedema,
      – Lupus-like, serum sickness, cell mediated allergies
      – Severest form --> Anaphylactic shock!