Pharmaceutical Drugs

Chemistry 199L
Pharmaceutical Drugs
(Chapter 19)
Pain relievers and fever reducer: aspirin

- Analgesic (pain reliever)
- Antipyritic (fever reducer)
- Anti-inflammatory
- Anticoagulant: heart attack and stroke prevention

Inhibits production of *prostaglandins* (pain messengers)
Limitation of Aspirin

- Still causes some intestinal bleeding
  (not recommended by people facing surgery, child birth, etc.)
- not effective for severe pain, e.g., migraine headache
- prolonged use can lead gastrointestinal disorders
- overdose
- allergic reactions
- Reye’s syndrome for children with flu or chickenpox
Aspirin substitutes

(Overuse can lead to liver/kidney damage)

Now banned

Tylenol

Advil

Aleve

Orudis KT
Cold remedies: Antihistamines

When allergens bind to surface of certain cells, they trigger release of histamine, which causes redness, swelling and itching.

Antihistamine blocks releases of histamine but some also enter the brains and act on cells controlling sleep, causing drowsiness.

Other cold remedies: Cough suppressants and decongestants
All treat only symptoms, not the cause
Effect of vitamin C has been observed; reason still unknown
Antibacterial drugs: sulfa drugs

Discovered in 1935 by Gerhard Domagk (German chemist)

Chemical mimic-type poison for bacteria
An antibiotic: penicillin

A colony of *Penicillium notatum*, the mold from which penicillin is derived:

1928: first discovered by Alexander Fleming
1941: first tried on human

Antibiotics: soluble substances (often derived from molds or bacteria) that inhibit the growth of other microorganisms

Some bacteria cell walls are made of mucoprotein polymers. Penicillin prevents crosslinking between protein monomers and therefore cell wall synthesis. Cells of higher animals (including human) do not have mucoprotein cell walls.
Antibiotics: penicillins

There are many penicillins
Other antibacterial drugs

- **Tetracycline**
  - Bind to bacterial ribosomes
  - Inhibits bacterial DNA replication

- **Aureomycin (chlorotetracycline)**
- **Terramycin (oxytetracycline)**

- **Fluoroquinolone**
Viruses

- Rabies virus
- Herpes virus
- Bacteriophage
- Measles virus
- Tobacco mosaic plant virus
Viruses

DNA viruses (DNA/proteins)
- enter host cell $\rightarrow$ direct it to make viral proteins

RNA viruses (RNA/proteins)
- enter host cell $\rightarrow$ replicate viral RNA $\rightarrow$ induce synthesis of viral proteins

Retroviruses (RNA/proteins)
- enter host cell $\rightarrow$ synthesize DNA from the RNA (reverse transcriptase) $\rightarrow$ synthesis of viral proteins
Anti-Viral Drugs

HIV drugs:
- Nucleoside analogs (AZT)
- Reverse transcriptase inhibitors
- Protease inhibitors
Anti-cancer drug: Discovery of Cisplatin

- 1845: *cis*-diaminedichloroplatinum(II) (cisplatin) first synthesized
- 1965: Barnett Rosenberg, inhibition of cell growth by cisplatin
- 1970: Cisplatin prevents DNA transcription.
- 1972: Clinical trials of cisplatin.
Anti-Cancer drugs

Problem: How to selectively kill cells

One solution: target rapidly dividing cells (antimetabolites)

\[
\text{Cl} \quad \text{Cl} \\
\text{Pt} \\
\text{NH}_3 \quad \text{NH}_3
\]

Cisplatin
Drug Design

• What is a drug? How do they work?

• What features does a drug need to have?
  • For efficacy?
  • For safety?
  • For cost-effectiveness?

• How do we find/invent/improve drugs?
Terminology

• **Target**: the biomolecule, complex, cell, etc. that the drug is meant to impact

• **Library**: a large collection of substances that may be useable as drugs

• **Hit**: a substance that gives the desired result during screening; a potential drug
Drugs discovery/development

Early 1980’s  Rational drug design or Computer aided design (CAD)

Specificity

• How do we achieve specificity?
• How do we enhance specificity?
• What targets are we good at?
Structure-based CAD

Chemistry

Structure of working drugs

Modeling
Enhancing specificity

- use proteins as drugs
- antisense (nucleic acids)
- structure-based drug design
- SCREENING

Advances in speed, quality, and diversity

- High-throughput techniques
- Combinatorial libraries
Targets

What we’re good at

• enzymes
• dimeric/domain recognition
• antibodies
• nucleic acids
• multimeric complexes
High-throughput screening

Rational design requires lots of supporting data…
Instead, screen EVERYTHING.

Modern advances:
• robotics
• library development
• information systems
• microvolume chemistry
• combinatorial library development

1990: 100 compounds/week
2003: 100,000 compounds/DAY
Modern drug discovery

- Target ID
- Hit generation
- Target validation
- Hit development

Choice of library
- Proteomics
- Bioinformatics
- Verification
- Bioassay

Choice of library
High-throughput screening (HTS)

Applications
- Discovery
- Hit development
- Preliminary assessment of metabolism & toxicity

Components
- Test substance supply
- Bioassay development & implementation
- Informatics
Test substance supply

- Library development
- Combinatorial chemistry
- Natural products
- Structure-based design
Bioassay development

- Whole animals
- Tissue
- Cellular function
- Protein function
- Gene expression
- Genome sequence

Cost

Relevance

Throughput

Specificity

Define target dimensions

Computational analysis

Use relevant libraries

Optimize
Informatics

- Storage
- Retrieval
- Cross-referencing

Define target dimensions → Computational analysis → Use relevant libraries → Optimize
Another big challenge: drug delivery

http://www.pharmj.com/editorial/19990828/pictures/parenteralFig5.gif