PRINCIPLES OF PHARMACOLOGY

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Principles of Pharmacology

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CHAPTER OVERVIEW

1: Chapters

1.1: Immunosuppression for Solid Organ Transplantation

The success of solid organ and bone marrow transplantation (BMT) has correlated with improvements in selective immunosuppression. Immunosuppression decreases both the incidence of acute and chronic organ graft and bone marrow rejection, and a potentially life threatening complication of BMT known as graft-vs-host disease (GVHD). Selective immunosuppression targets specific pathways of immune signaling and activation, and minimizes the incidence of deleterious side effects.

History

- 1954: First successful human kidney transplant
- 1960s: Introduction of effective immunosuppressive drugs. Steroids, ATG, azathioprine
- 1968: Successful bone marrow transplants for congenital immunodeficiency syndromes
- 1970s: Cyclosporine introduced
- 1980s: OKT3, tacrolimus, mycophenolate mofetil introduced
- In 1988 1 year renal cadaver graft survival was 76% and 1 year renal living donor graft survival was 89%
- ▫ By 1995, graft survival rates improved to 87% and 93% respectively
- 1980s: The addition of cyclosporine to GVHD prophylaxis regimens halved the incidence of severe disease and improved survival post -transplant
- 1990s: Leflunomide, TNF antagonists, and selective mAbs introduced; additional mAb therapies expected in future

Balancing Benefits and Risks of Immunosuppression

Benefits: Immunosuppression decreases risks of both acute and chronic organ graft and bone marrow rejection, and GVHD

Risks: Immunosuppression poses risk of several types of side effects to the patient:

- Acute effects: gastrointestinal upset
- Opportunistic infection because patient is immunocompromised: CMV, Candida,Pneumocystis carinii, etc.
- Malignancies (lymphomas, skin cancer, etc.)
- Toxicities specific to particular immunosuppressive agent: steroids, etc.

Types of Organ Graft Rejection

- Hyperacute: Occurs within minutes after transplant. Mediated by preformed anti- donor antibodies in recipient. Involves small vessel thrombosis and graft infarction.
- Acute: Occurs weeks after transplant. Delayed-type hypersensitivity / Cell mediated response of cytotoxic T lymphocytes reacting against the foreign MHC molecules of the graft. Histologically characterized by mononuclear infiltrate, hemorrhage, and edema in graft. Reversible with immunosuppressive therapy.
- Chronic: Occurs months to years post transplant. Results from antibody mediated vascular damage (fibrinoid necrosis) and is irreversible. Vascular damage results in vascular cell wall proliferation which may occlude vessel lumen resulting in graft ischemia and fibrosis. Can progress insidiously despite increased immunosuppressive therapy.

Graft Rejection and GVHD Following Bone Marrow Transplantation

- Graft rejection occurs uncommonly (<1%) after conventional myeloablative bone marrow/stem cell transplantation, with increased incidence (1-15%) after HLA- mismatched BMT/cord blood transplantation.
- The rate of graft rejection is higher after nonmyeloablative preparative therapy for BMT
- Acute GVHD, which is usually evident before day 100 post-transplant, occurs in 1/3 of HLA matched transplants and 2/3 of HLA-mismatched transplants.
- Chronic GVHD (>day 100) occurs in approximately 1⁄2 of transplants
- Acute GVHD affects predominantly skin, the GI tract, and liver. Tissue injury involves effector cells (initiated by T-cells), particularly of the TH1 subset, and cytokines (e.g. TNF-alpha, interferon-gamma, and interleukin-1).
- Chronic GVHD may affect almost any organ/tissue and often mimics a collagen vascular disease in its clinical presentation.

Molecular Basis of Immune Response and Immunosuppression

The immune response involves both humoral and cellular responses: *Humoral:* The humoral response involves recognition of foreign antigens which causes the differentiation of B-cells into memory cells and plasma cells. Plasma cells secrete antibodies into circulation. *Cellular:* Macrophages ingest and present antigen via the major histocompatibility (MHC) II molecule. The

macrophage is a type of antigen presenting cell which binds to CD4 T lymphocytes cells via the MHC II – T cell receptor (TCR) interaction. CD3 is a necessary accessory molecule to the MHC II – TCR interaction. The interaction induces proliferation of the CD4 T-cell (see diagram page 4), and release of IL-2, which promotes activation of cytotoxic CD8 T-cells. CD8 T cells bind to MHC I molecules. When CD8 cells recognize an antigen presented on an MHC I molecule (which indicates the presenting cell is foreign, or, for example, a tumor cell or virally infected cell) the CD8 cell induces the death of the target.

In the context of an MHC mismatched organ or bone marrow transplant, the MHC molecules of the cells of the organ (or bone marrow) graft are recognized by the host

TCR not as self-MHC molecules, but rather in the same manner as a self-MHC plus the foreign peptide it is presenting. The immunologic response to the foreign MHC molecules is a major cause of most graft rejection. Conversely the donor immune system may recognize disparate MHC antigens in the host and initiate an immunologic response in the form of GVHD.

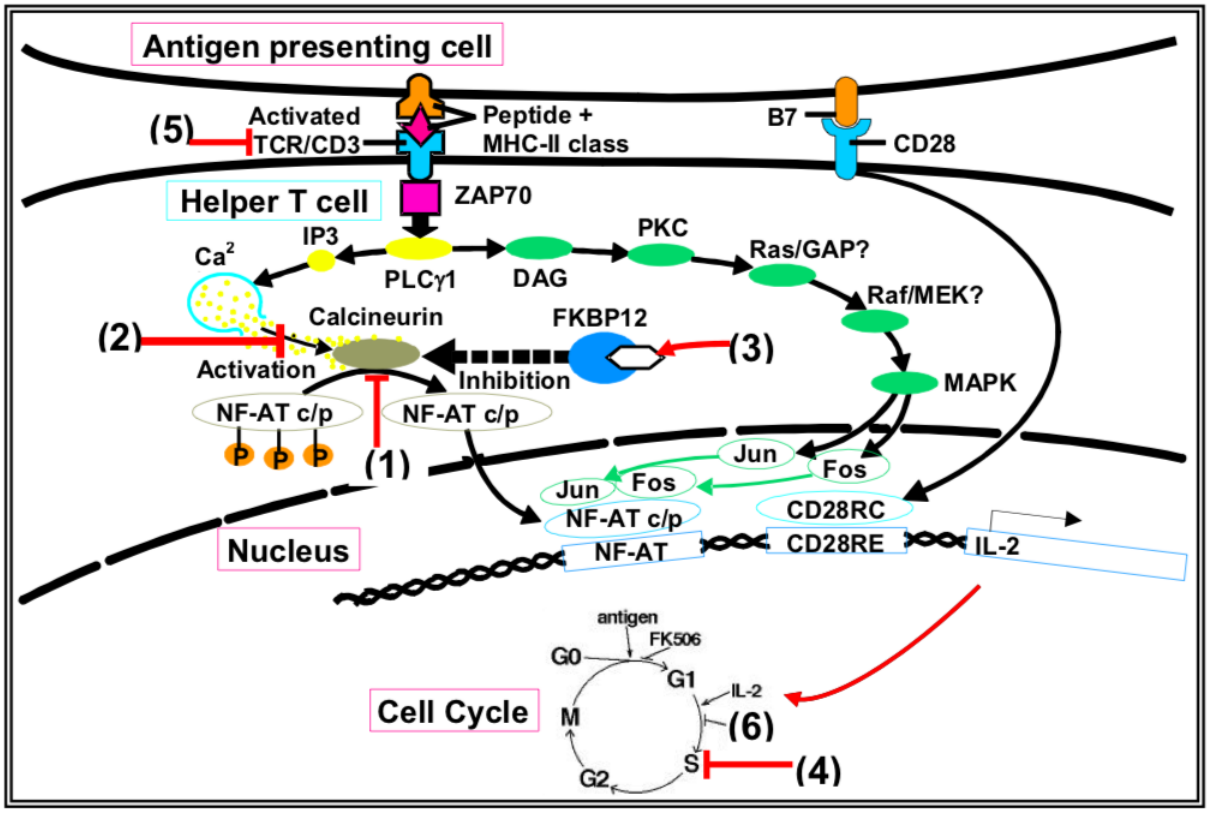
MHC molecules are divided into class I and class II antigens; inheritance involves multiple alleles, and all loci are found on chromosome 6. Class I antigens include HLA A, HLA-B, and HLA-C alleles . Class II antigens include HLA-DR, HLA-DQ, and HLA-DP alleles. Minimization of the antigenic differences between donor and recipient, by matching their MHC alleles, has decreased rejection and GVHD and improved graft survival. Identical twins have identical MHC genes (6/6 loci), siblings have half similarity (3/6), and the match of unrelated persons must be determined by tissue typing.

As most bone marrow/stem cell transplants are from HLA matched (or only minor mismatched) related or unrelated donors, minor histocompatibility antigens play a large role in eliciting an immune response (GVHD). Polymorphisms of minor histompatibility antigens have been identified as risk factors for GVHD in the HLA-matched setting.

Types of Immunosuppressive Agents and Sites of Action

The schematic on page 4 shows the molecular pathways that are activated in a helper T cell after it contacts an antigen presenting cell which presents an antigen on its MHC II molecule. Superimposed on the pathways are sites of pharmacologic intervention which will inhibit signaling and thus can be used as immunosuppressive agents.

- Affect NFAT pathway: Steroids (1)
- Affect Calcineurin: Cyclosporine (2); Tacrolimus (3)
- Affect Cell Cycle by inhibiting DNA synthesis (4): azathioprine, MMF, leflunomide, cyclophosphamide
- Anti-TCR/CD3 antibody agents (5): Polyclonal agents are ATG, ALG. OKT3 is a monoclonal agent.
- Inhibit IL-2 dependent signaling: Sirolimus (6)



(1) Steroids (corticosteroids):

Biochemical Mechanism: Affect NF-AT mediated pathway of signal transduction, which results in ultimate blockade of IL-1 and IL-6 production in macrophages at the earliest stage of immune response.

Physiological Effects: Inhibits leukocyte proliferation, reduce leukocyte migration into bloodstream (by decreasing production of endothelial adhesion molecules). Steroids are non-specific and broad spectrum anti-inflammatory agents used in a large number of medical conditions.

Side Effects: Cushing's Syndrome [hypertension, hyperglycemia, insulin resistance, weight gain, moon facies, osteoporosis, impaired wound healing, ulcers], hyperlipidemia, adrenal suppression which may result in crisis if withdrawn abruptly

(2) Cyclosporine

Biochemical Mechanism: Cyclosporine complexes with immunophilin protein in T cell. The complex blocks the phosphatase calcineurin. Without calcineurin activity, NF-AT is not dephosphorylated, is not translocated to the nucleus, and cannot activate transcription.

Physiological Effects: Transcription of cytokines, including IL-2, is blunted. Consequently, T cell proliferation is inhibited, secretion of gamma interferon declines, and macrophage activation is limited.

Nephrotoxicity (preventable with mannitol diuresis; chronic cyclosporine nephrotoxicity may produce irreversible interstitial fibrosis), **N**eurotoxicity (tremor, headache, tinnitus),

Neoplasms (lymphoproliferative malignancy);

Hypertension, **H**yperkalemia, **H**epatotoxicity, **H**irsutism, **H**ypertrophy of gingiva,

Hyperglycemia, **H**yperlipidemia

(3) Tacrolimus (similar to cyclosporine)

Biochemical Mechanism: Binds to FK506 Binding Protein (FKBP). The Tacrolimus- FKBP complex inhibits calcineurin. The mechanism is therefore the same as that of cyclosporine.

Physiological Effects: 10-100 times more potent than cyclosporine, but similar mechanism: decreased production of IL-2

Side Effects: Similar to cyclosporine. Do not use with cyclosporine!

(4) Cell Cycle Inhibitors

Azathioprine: Azathioprine is metabolized in vivo to 6-mercaptopurine (6MP). 6MP is a purine anti-metabolite that prevents DNA and RNA synthesis which inhibits proliferation of lymphocytes. Side effects include pancytopenias, gastrointestinal symptoms, and hepatic dysfunction (hepatitis).

Mycophenolate mofetil (MMF): MMF is a prodrug of mycophenolic acid (MPA), which is an inhibitor of inosine monophosphate dehydrogenase (IMPDH). Inhibition of IMPDH limits production of guanosine nucleotides required for nucleic acid synthesis, and thus exerts a potent, selective cytostatic effect on B- and T- lymphocytes (decreased antibody production and generation of cytotoxic T-cells). Side effects include pancytopenias, infections and malignancies, and gastrointestinal symptoms.

Leflunomide: Leflunomide inhibits dihydroorotate dehydrogenase (an enzyme involved in de novo pyrimidine synthesis); as a result, nucleic acid synthesis and lymphocyte proliferation are inhibited. Side effects include pancytopenias, hepatotoxicity, risk of lymphoproliferative disorders, and rare cases of Stevens- Johnson syndrome and toxic epidermal necrolysis.

Cyclophosphamide: Cyclophosphamide is an extremely potent alkylating agent which destroys proliferating lymphoid cells. Cyclophosphamide causes pancytopenias, hemorrhagic cystitis, alopecia, and infertility.

(5) Anti-TCR/CD3 antibody agents:

anti-lymphocyte globulin (ALG) and anti-thymocyte globulin (ATG) both inactivate peripheral lymphocytes and impair cellular immunity. These antibodies are used for induction of immunosuppression, treating initial rejection, and treating steroid resistant rejection. Side effects include anaphylactic response (because these antibodies are foreign proteins), serum sickness, antigen-antibody induced glomerulonephritis, reactivation of latent viral infections, post transplant lymphoproliferative disease, and development of human anti(mouse) antibodies.

OKT3: OKT3 is a murine monoclonal antibody that blocks the binding of the TCR to antigen, thus downregulating the activity of the entire TCR/CD3 receptor complex. Compared to ALG and ATG, there are fewer serum proteins associated with OKT3 preparations than with those polyclonal antibody preparations (which may result in a more specific effect and fewer side effects). Side effects of OKT3 include fever, myalgias, arthralgias, CNS symptoms, GI irritation, and B-cell lymphoproliferative disorders.

(6) Sirolimus (rapamycin, a macrolide antbiotic)

Biochemical Mechanism: Inhibits IL-2 mediated signaling by inhibiting Target of Rapamycin (TOR), an enzyme active in IL-2 cascades in proliferating lymphocytes.

Physiological Effects: Cell cycle progression from G1 to S is blocked; T- cell and B- cell proliferation is limited, and B-cell antibody production is inhibited.

Side Effects: Hyperlipidemia, Hypertension, Hypokalemia, Pancytopenias, decreased GFR / increased Serum Creatinine, metallic taste in mouth

Newer agents:

Anti-TNF agents include etanercept and infliximab (see Dr. Weinblatt's lecture).Etanercept is a form of soluble TNF receptor. Infliximab is a chimeric IgG1 monoclonal with a human Fc and murine Fab. By limiting TNF activity, the generation of pro-inflammatory cytokines IL-1 and IL-6 are diminished. In addition, anakinra is recombinant version of the human IL-1 receptor antagonist that inhibits IL-1 by blocking its receptor. Soluble IL-1 receptor antagonists are being developed.

Daclizumab is a humanized monoclonal murine IgG1 antibody that binds to a subunit of the IL-2 (CD25) receptor on the surface of activated lymphocytes. Daclizumab thereby functions as an IL-2 inhibitor. Side effects include hypersensitivity, cellulitis, and wound infection.

Basiliximab is a chimeric murine/human monoclonal IgG1 antibody that blocks the alpha chain of the IL-2 (CD25) receptor on the surface of activated T-cell lymphocytes. Basiliximab is indicated for the prophylaxis of acute organ rejection in renal transplantation. Side effects include hypersensitivity and gastrointestinal disorders.

ALG/ATG can deplete the lymphocyte population. Since daclizumab and basiliximab preferentially affect activated T cells, they are less apt to cause lymphocyte depletion.

Relationship Between Immunosuppressive and Cancer Chemotherapy.

Many cytotoxic drugs are used for both immunotherapy and cancer chemotherapy, but the therapeutic goals are tied to important differences in the cellular targets.

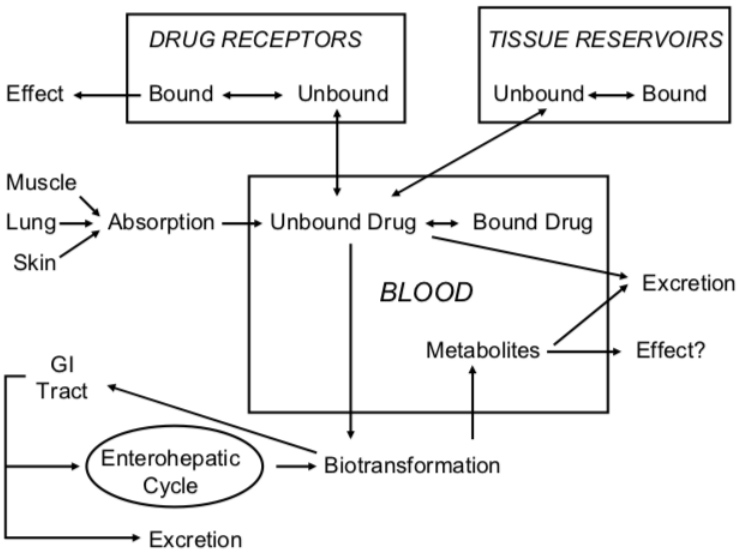
1. Cancer cells undergo largely unregulated, asynchronous proliferation, while immune cells proliferate in a burst of activity when antigen (i.e. transplant) is presented. This means immunosuppressant therapy can be timed for maximal effect on the smallest population of immune cells.
2. An antigen stimulates proliferation by specific clones of precursor cells, so a cytotoxic drug will have greatly enhanced effects on those clones (i.e. the drug will be relatively selective for rapidly dividing cells). In cancer chemotherapy, selectivity of cell cycle active drugs depends upon the innate growth characteristics of the tumor relative to normal tissue (see Dr. Kufe's lecture) and is much harder to achieve.
3. Immunosuppressants are usually given in low, continuous dose regimens in order to maintain suppression of cellular and inflammatory responses to a persistent antigenic stimulus. In cancer chemotherapy high-dose pulse administration is more common because it allows for recovery of immune function and re-growth of normal cell populations.

1.2: Introduction to Pharmacology

A drug is a chemical agent which can affect living processes. For purposes of this course we will mainly be talking about small molecules which affect cellular processes. Most of these are Xenobiotics (Gr. xenos - stranger) chemicals that are not synthesized by the body, but introduced into it from outside. There is inevitably a certain amount of ambiguity in this definition: Is oxygen or water a drug? How about Vitamin C in a glass of orange juice? How about an injection of Vitamin C to treat scurvy?

Pharmacology (Gr. pharmakon - a drug or poison, logos - word or discourse) is the science dealing with actions of drugs on the body (pharmacodynamics) and the fate of drugs in the body (pharmacokinetics). It overlaps with pharmacy, the science of preparation of drugs; much of it deals with therapeutics, the treatment of disease (by whatever means). Toxicology is the branch of pharmacology dealing with the "undesirable" effects of drugs on biological processes (in the case of a nerve gas the bad effect may be a desired one).

In order for a drug to work, it must enter the body and somehow be distributed in such a way that it gets to its site of action. In most cases the site of action is a macromolecular "receptor" located in the target tissue. Most drug effects are temporary, because the body has systems for drug detoxification and elimination. We will consider these issues broadly for now and go into more depth in individual lectures. As you read, refer to the figure below:



Overview of Pharmacokinetics - "What the body does to the drug"

1. The drug may enter the body in a variety of ways: as an oral liquid, pill, or capsule; as an inhaled vapor or aerosol; absorbed through intact skin or a mucous membrane; injected into muscle, subcutaneous tissue, spinal fluid, or directly into the bloodstream. As we shall see, the physical properties of the drug and the specific way it is prepared greatly influence the speed of absorption.
2. If the drug is given orally and swallowed, it must be absorbed from the GI tract into the portal circulation. If it is absorbed from the skin, mouth, lungs or muscle it will go directly into the systemic circulation. If drug is injected directly into the bloodstream (e.g., intravenous injection), 100% of it is available for distribution to tissues. This is not usually the case for other modes of administration. For example, drug which is absorbed via the portal circulation must first pass through the liver which is the primary site of drug metabolism (biotransformation). Some of the drug may therefore be metabolized before it ever reaches the systemic blood. In this case,"**first-pass**" **metabolism** reduces the **bioavailability** to less than 100%.
3. Once the drug is in the bloodstream a portion of it may exist as free drug, dissolved in plasma water. Some drug will be reversibly taken up by red cells and some will be reversibly bound to plasma proteins. For many drugs, the bound forms can account for 95-98% of the total. This is important because it is the free drug which traverses cell membranes and produces the effect. It is also important because protein-bound drug can act as a reservoir which releases drug slowly and thus prolongs its action.
4. The unbound drug may then follow its concentration gradient and distribute into peripheral tissues. In some cases, the tissue contains the target site and in others the tissue is not affected by the drug. Sites of non-specific binding act as further reservoirs

for the drug. This total **volume of distribution** determines the equilibrium concentration of drug after a specified dose.

5. Tissue-bound drug eventually reenters the bloodstream where it perfuses the liver and kidneys. The liver metabolizes most drugs into inactive or less active compounds which are more readily excreted. These metabolites and some of the parent compound may be excreted in the bile and eventually may pass out of the body in the feces. Alternatively, some of the drug may be reabsorbed again, farther down the GI tract (the so-called enterohepatic cycle). Any biotransformed drug which is not excreted in bile passes back into the systemic circulation.
6. Parent drug and metabolites in the bloodstream may then be excreted: most are filtered by the kidney, where a portion undergoes reabsorption, and the remainder is excreted in the urine. Some drugs are actively secreted into the renal tubule. Another route of excretion is the lung: Drugs like alcohol and the anesthetic gases are eliminated by this route. Smaller amounts of drug are eliminated in the sweat, tears and breast milk.
7. Biotransformation may sometimes produce metabolites with a great deal of activity. Occasionally, we administer a parent drug which is inactive (a pro-drug) and only the metabolite has activity. [How might this be useful?]

Overview of Pharmacodynamics - "What the drug does to the body"

As stated above, the majority of drugs bind to specific receptors on the surface or interior of cells, but there are many other cellular components and non-specific sites which can serve as sites of drug action.

1. **Water** can be a target. Osmotic diuretics like mannitol are not reabsorbed by the kidney, and the osmotic load they create in the renal tubule obligates the loss of water. Laxatives like magnesium sulfate work in the intestine by the same principle.
2. **Hydrogen** ions can be targets. Ammonium chloride is sometimes used to acidify the urine. When it is taken orally, the liver metabolizes ammonium ion to urea, while the chloride is excreted in the urine. The loss of Cl- obligates the loss of H+ in the urine, thus the pH is lowered.
3. **Metal** ions can be targets. Chelating agents like EDTA may be used to bind divalent cations like Pb++. Metal ions are most frequently drug targets in cases of poisoning.
4. **Enzymes** are targets of many therapeutically useful drugs. Drugs may inhibit enzymes by competitive, non-competitive, or irreversible blockade at a substrate or cofactor binding site. Digitalis glycosides increase myocardial contractility by inhibiting the membrane enzyme, Na+-K+ - ATPase. Antimicrobial and antineoplastic drugs commonly work by inhibiting enzymes which are critical to the functioning of the cell. In order to be effective, these drugs must have at least **someselective toxicity** toward bacterial or tumor cells. This usually means that there is a unique metabolic pathway in these cells or some difference in enzyme selectivity for a common metabolic pathway. An example of this is the inhibition of folate synthesis by sulfonamides. These drugs are effective antibacterial agents because the bacteria depend upon folate synthesis, while the host doesn't. This example will be covered in detail in one of our case discussions.
5. **Nucleic acids** are targets for antimetabolites and some antibiotics. In the case of 5- fluorouracil, the compound acts as a counterfeit substitute for uracil and becomes incorporated into a faulty mRNA. Antisense oligonucleotides are another very specific way to interfere with a restricted part of the genome.
6. Some drugs, like general anesthetics, appear to act by non-specific **binding to a macromolecular receptor** target. These drugs are thought to alter the function of membrane proteins, in part, by disordering the structure of the surrounding lipid membranes. Their lack of specificity is reflected in very low chemical structural requirements. The general anesthetics include compounds as chemically diverse as nitrogen, xenon, halogenated ethers, and steroids. They exhibit very little stereoselectivity, that is, there are not marked differences in anesthetic activity between enantiomers.
7. Finally, we have the drugs which act by binding to **specific receptors**. As you will see in lectures 2 and 6, these drugs have both high structural specificity and stereoselectivity, i.e. relatively small changes in chemical structure can radically alter the activity of these drugs.

Let us finish with some important definitions. These are concepts which we will return to repeatedly throughout the course.

- **Agonist** is a drug which binds to its "receptor" and produces its characteristic effect. A drug may be a **full agonist** or **partial agonist**, depending on the maximal effect it produces. An antagonist binds to the receptor without causing an effect, thereby preventing an active substance from gaining access. Antagonists, like enzyme inhibitors, may be competitive, non-competitive or irreversible.
- **Dose-Response**. The sine qua non of drug effect. Simply put, as the dose of drug increases, the response should increase. [What if the response increases, then decreases as the dose is raised?] The curve generated is usually sigmoidal when effect is plotted against log dose (Dr. Strichartz will discuss the theoretical basis for this). Effect may be measured as a graded variable (change in blood pressure, force of contraction) or as a quantal variable (number dead/alive). The slope of the curve is characteristic of

the particular drug-receptor interaction. When two drugs act by the same receptor mechanism, we expect to see two parallel log-dose response curves.

- **ED_{50}**. The median effective dose, or the dose which produces a response in 50% of subjects. If the response is death (lethality) we call it the **LD_{50}**. The EC50 refers to concentration rather than dose. Similar abbreviations are used for other response levels: ED_{99}, LD_1, etc.
- **Potency**. A terribly misused word – the lay public uses it to mean "effectiveness." The potency of a drug refers to the dose (actually the molar concentration) required to produce a specific intensity of effect. [We usually specify the ED50, why?] If the ED50of drug A and B are 5 and 10 mg, respectively, the Relative Potency of A is twice that of B. Relative potency specifically applies to the comparison of drugs which act by the same mechanism, and therefore have parallel dose-response curves.
- **Efficacy**. Also called **Maximal Efficacy** or **Intrinsic Activity**. This is the maximum effect of which the drug is capable. A potent drug may have a low efficacy, and a highly efficacious drug may have a low potency. For the clinician, efficacy is much more important than potency (within limits). Who cares if the pill contains 5 or 10 mg of drug?
- **Affinity**. This refers to the strength of binding between drug and receptor. It is quantified by the dissociation constant kD (covered in the next lecture).
- **Selectivity**. This refers to the separation between desired and undesired effects of a drug. In the ideal case, a drug is completely **specific**, and an effective dose does not elicit any undesired effect. Penicillin is an example of a highly selective drug, since it works specifically by inhibiting cell wall synthesis, and (other than allergic responses) it has very little effect on human cells at normal doses. Unfortunately, many therapeutic agents, like digoxin and theophylline, produce dose-related side effects near their therapeutic dose range. For some drugs like cancer chemotherapeutic agents, their selectivity is their dose-limiting property, i.e., they are given to kill tumor cells until they produce toxicity in normal cells as well.
- **Therapeutic Window**. For every drug, there exists some concentration which is just barely effective (the **Effective Concentration**) and some dose which is just barely toxic (the **Toxic Concentration**). Between them is the therapeutic window where most safe and effective treatment will occur.
- **Therapeutic Index**. This is the ratio of toxic to effective doses at the level of 50% response: TD_{50}/ED_{50}. In animal toxicology studies, it is usually the LD_{50}/ED_{50}. Another measure sometimes utilized is the **Certain Safety Factor**, which is TD_1/ED_{99}.

1.3: Pharmacokinetics I

Learning Objectives

- Describe the physicochemical and physiological factors that influence the absorption of drugs from enteral and parenteral routes of administration, their distribution within the body, and their routes and mechanisms of elimination.
- Explain how dose, bioavailability, rate of absorption, apparent volume of distribution, total clearance, and elimination half-life affect the plasma concentrations of a drug after administration of a single dose.
- Describe the factors which determine the time-course of systemic accumulation of a drug administered by infusion or multiple doses.

Absorption of Drugs

A. **Transport Across Cell Membranes**

1. **Passive diffusion**
   a. Passage through lipid cell membrane by dissolution in membrane; rate dependent on concentration gradient and lipid:water partition coefficient of drug; rate markedly higher for unionized form of weak electrolyte because of its higher lipophilicity than the ionized form; obeys first-order kinetics (rate of transport is proportional to concentration gradient at transport site).
   2. Filtration through aqueous channels within membranes and between cells.
2. **Active transport**
   a. Passage facilitated by an energy-dependent membrane carrier mechanism such that transport can occur against a concentration gradient; transporters include the family of ATP-dependent proteins, such as
      - the multidrug resistance p-glycoprotein (amphipathic cationic and neutral substrates, 170 kD, mdr gene product, verapamil sensitive)
      - the multidrug resistance-associated proteins (MRP1-6, organic anion substrates, 190 kD, probenecid sensitive).
   b. Exhibits structural selectivity, saturability, competition between structural analogues and genetic variants.
   3. Sites for drugs in intestinal mucosa (cell to lumen), capillary endothelium of brain and testis (cell to blood), choroid plexus (CSF to blood), proximal renal tubular cell (blood to urine), hepatocyte (blood to bile), tumor cells (efflux pump).
   4. Obeys Michaelis-Menten kinetics: if drug concentration is high enough to saturate carrier mechanism, kinetics are zero-order (rate of transport is constant).
3. **Endocytosis**
   a. Passage into cell within membrane invagination.
   b. Important mechanism for particulates and high molecule weight compounds, such as proteins.

B. **Routes of Drug Administration**

1. **General determinants of absorption rate**
   a. Dissolution into aqueous fluids at absorption site, lipid solubility, concentration gradient, blood flow at absorption site, surface area of absorption site.
   2. Importance of rate-limiting process
2. **Oral (p.o.) Ingestion**
   a. Convenient route for administration of solid as well as liquid formulations.
   2. Additional variables which may influence rate and extent of absorption include disintegration and dissolution of solids, acidity of gastric contents, gastric emptying rate, intraluminal and mucosal biotransformation by host or bacterial enzymes, dietary contents, and presence of other drugs.
   3. First-pass effect: absorbed drug passes via portal circulation through liver which may clear substantial fraction and thus decrease bioavailability (percent of dose which reaches the systemic circulation).
3. **Parenteral Injection**
   1. Subcutaneous (s.c.) and intramuscular (i.m.) administration: more extensive absorption of high molecular weight, polar molecules than by oral route, via lymphatic circulation; absorption rate can be manipulated by formulation, e.g. rapid from aqueous solution, slow from suspension or solid pellet.

2. Intravenous (i.v.) injection: complete bioavailability; drugs only given in sterile solution; important when immediate effect required; increased risk of toxicity.

4. **Pulmonary Inhalation**
    1. Rapid absorption of drugs in gaseous, vaporized or aerosol form.
    2. Absorption of particulates/aerosols depends on particle/droplet size which influences depth of entry in pulmonary tree; 1-5 uM particles reach alveolus
5. **Topical Application**
    1. Usually for local effect; patch formulations for systemic effect
    2. Absorption through mucous membrane may be rapid.
    3. Absorption through skin generally slow; enhanced by increased lipophilicity, by damage to stratum corneum, and by increased blood flow.

C. **Distribution of Drugs**

A. **Tissue differences in rates of uptake of drugs.**

1. **Blood flow:** distribution occurs most rapidly into tissues with high blood flow (lungs, kidneys, liver, brain) and least rapidly in tissues with low flow (fat).
2. **Capillary permeability:** permeability of capillaries is tissue dependent;distribution rates relatively slower into CNS because of tight junction between capillary endothelial cells, insignificant aqueous membrane pores, juxtaposed glial cells around endothelium and efflux transporters in vascular endothelium ("blood-brain barrier"); capillaries of liver and kidney more porous.

B. **Differences in tissue/blood ratios at equilibrium**

1. Dissolution of lipid-soluble drugs in adipose tissue
2. Binding of drugs to intracellular sites
3. Plasma protein binding; many drugs reversibly bind to albumin, α1-acidglycoprotein or other proteins in plasma; extent of binding dependent on affinity, number of binding sites, and drug concentrations; drug bound to albumin is not filtered by renal glomerulus but may be cleared by proximal renal tubule and liver; binding reduces free drug available for distribution into tissue; many drug interactions based on displacement from binding sites.

C. **Apparent Volume of Distribution (V_d)**

1. Fluid compartments of 70-kg subject in liters and as percent of body weight: plasma 3 l (4%), extracellular water 12 l (17%), total body water 41 l (58%).
2. Estimation of Vd from extrapolated plasma concentration at "zero-time" (Co) after intravenous administration:

$$\mathbf{V}_d = \frac{Dose}{\mathbf{C}_o} \tag{1.3.1}$$

3. Prediction of Vd from chemical characteristics of drug, e.g. high lipid solubility, high V_d
4. The plasma half-life of a drug (the time to reduce the concentration by one- half) is directly proportional to Vd, and inversely proportional to total clearance (Cl_T); for a given Cl_T, the higher the V_d, the longer the $t_{1/2}$:

$$\mathbf{t}_{\frac{1}{2}} = \frac{ln2(\mathbf{V}_d)}{\mathbf{Cl}_T} \tag{1.3.2}$$

Elimination of Drugs

A. **Total Clearance (Cl_T)**

1. Volume of plasma completely cleared of drug per unit time by all routes and mechanisms.
2. Summation of clearance values for each route, generally:

$$\mathbf{CL}_T = \mathbf{Cl}_{renal} + \mathbf{Cl}_{hepatic} \tag{1.3.3}$$

3. If intrinsic capacity of an organ to clear drug is high and exceeds plasma flow to that organ, then the clearance equals plasma flow and is altered by changes in plasma flow.
4. The plasma half-life of a drug is inversely proportional to total clearance, and directly proportional to Vd; for a given Vd, the higher the total clearance, the shorter the half-life.

B. **Biotransformation**

1. Elimination of drug by chemical modification of the molecule by spontaneous or (more usually) enzymatically catalyzed reaction. Drug may be biotransformed by reactions at several sites on the molecule.
2. Product(s) may have greater, lesser or qualitatively different pharmacologic activity from parent compound. A prodrug is inactive and is biotransformed to a therapeutic agent. Highly reactive products such as quinones or epoxides may cause tissue necrosis or DNA damage.
3. Reaction rate dependent on chemical structure and obeys Michaelis-Menten kinetics (usually first-order at therapeutic drug concentrations).
4. Enzymatic activity generally highest in liver; enzymes in target organ may be responsible for conversion of drug to therapeutic or toxic metabolite; enzymes in intestinal bacteria may facilitate enterohepatic circulation of drug conjugates excreted in bile.
5. Sources of individual variation in rates of biotransformation: chemical exposures (drugs, dietary constituents and supplements, smoke); genetics; age; disease
6. Major pathways of hepatic biotransformation
    a. Phase I: often first step in biotransformation with formation of product susceptible to phase II conjugative reaction
    b. Phase II: Coupling of drug or its oxidized metabolite to endogenous conjugating agent derived form carbohydrate, protein or sulfur sources; generally products more water-soluble and more readily excreted in urine or bile.

C. **Excretion**

1. Elimination of drug by excretion unchanged in body fluid or breath.
2. Routes of excretion
    a. Urine: quantitatively most important excretory route for nonvolatile drugs and their metabolites; excretion rate depends on rate of glomerular filtration (drug not bound to plasma proteins), proximal tubular active secretion, and passive reabsorption

    1) Determination of renal clearance (ClR), the volume of plasma completely cleared of drug per unit time (ml/min).

$$Cl_R = \frac{excreation\ rate\ iurine}{plasma\ concentration} \tag{1.3.4}$$

    Measure the amount of drug excreted in the urine during a time interval t_1 to t2. Find the plasma concentration of the drug at the midpoint of the time interval, $(t_1 + t_2)/2$, by interpolating on the ln C_p vs. t plot.

$$Cl_R = \frac{\left[\frac{amount\ excreted\ from\ t_1\ to\ t_2}{(t_2 - t_1)}\right]}{C_p\ at\ \frac{(t_1+t_2)}{2}} \tag{1.3.5}$$

    2) Mechanism of renal excretion can be inferred by comparison of Cl_R to that of an indicator of glomerular filtration (creatinine), i.e., greater than 120 ml/min in 70-kg subject indicates tubular secretion and less than that indicates net reabsorption (if no plasma binding); maximum renal clearance = renal plasma flow (e.g. para-aminohippuric acid, 650 ml/min in 70-kg subject).

    3) Factors modifying Cl_R: extent of plasma protein binding (displacement enhances glomerular filtration), urinary pH (reabsorption of drugs with ionizable group is dependent on urinary pH; raising the pH promotes excretion of acids, impairs excretion of bases), renal disease (creatinine clearance or its estimate from serum creatinine provides a useful clinical indicator of impaired renal function and is approximately proportional to drug renal clearance; the effect of renal impairment on the total clearance of a drug can be estimated from the Cl_{CR} and the nonrenal clearance).

    b. Bile: quantitatively important excretory route for drugs and their metabolites which are actively transported by hepatocyte; once in small intestine, compounds with sufficient lipophilicity are reabsorbed and cleared again by liver (enterohepatic circulation), more polar substances may be biotransformed by bacteria (e.g. hydrolysis of drug conjugates) and products reabsorbed; unabsorbed drugs and metabolites are excreted in feces.
    c. Minor routes: sweat, tears, reproductive fluids, milk; generally pH- dependent passive diffusion of lipophilic drugs; can be of toxicologic significance e.g. exposure of infants to drugs in milk.

Time Course of Plasma Concentrations

A. Relationship between plasma concentration and drug effect: minimum effective concentration, latency, duration of effect, time and magnitude of peak effect

B. Time-course of plasma concentrations for a single dose

1. Case with Highly Rapid Absorption Relative to Elimination

a. Single compartment model

1) First -order elimination: drug assumed to rapidly equilibrate into volume of distribution; plasma concentrations decline according to first-order kinetics; elimination rate from plasma is proportional to plasma concentration, fraction eliminated per unit time is elimination rate constant (k_{el}).

$$\frac{dC_p}{dt} = -k_{el}C_p \tag{1.3.6}$$

$$C_p = C_0 e^{-k_{el}t} \tag{1.3.7}$$

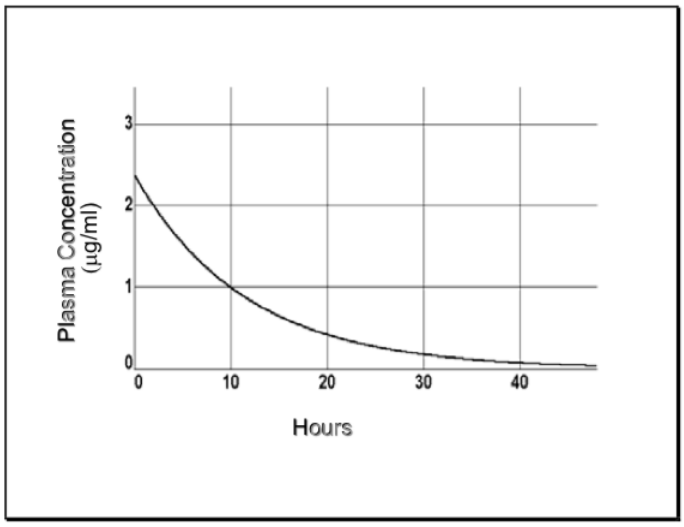


Figure 1

Determination of elimination rate constant and elimination half-life:

$$lnC_p = lnC_0 - k_{el}t \tag{1.3.8}$$

Plot of ln C_p vs. t is a straight line with slope of -k_{el}. Plasma half-life ($t_{1/2}$ =.693/k_{el}) is constant and independent of dose.

Determination of apparent volume of distribution:

Extrapolation to time zero of the line of best fit for ln C_p vs t data; antilog of drug concentration at time 0 designated as C_0. Then,

$$V_d(in\ mls\ or\ liters) = \frac{Total\ Dose}{C_0} \tag{1.3.9}$$

Determination of total clearance:

According to definitions above, total clearance is the mass of drug (Cp Vd) eliminated per unit time divided by the plasma concentration; therefore,

$$Cl_T = \frac{(k_{el})(C_p \cdot V_d)}{C_p} = (k_{el})(V_d) = [\frac{0.693}{t_{1/2}}](V_d) \tag{1.3.10}$$

Determination of nonrenal clearance (ClNR):

If total clearance and renal clearance are determined from plasma and urine samples as described above, then clearance by nonrenal routes (which includes biotransformation) can be estimated from

$$Cl_{NR} = Cl_T - Cl_R \tag{1.3.11}$$

2) Kinetics of zero-order elimination: elimination rate is constant, $t_{1/2}$ is dose-dependent (example: ethanol).

3)

$$C_p = C_0 - k_0 t \tag{1.3.12}$$

b. Multicompartment model

Non-instantaneous distribution from blood to tissue resulting in multiexponential plasma concentration curve, initial phase reflects distribution out of central compartment into total Vd, terminal phase reflects elimination.

$$C_p = Ae^{-\alpha t} + Be^{-\beta t} \tag{1.3.13}$$

Where α and β are hybrid rate constants describing the 2 slopes.

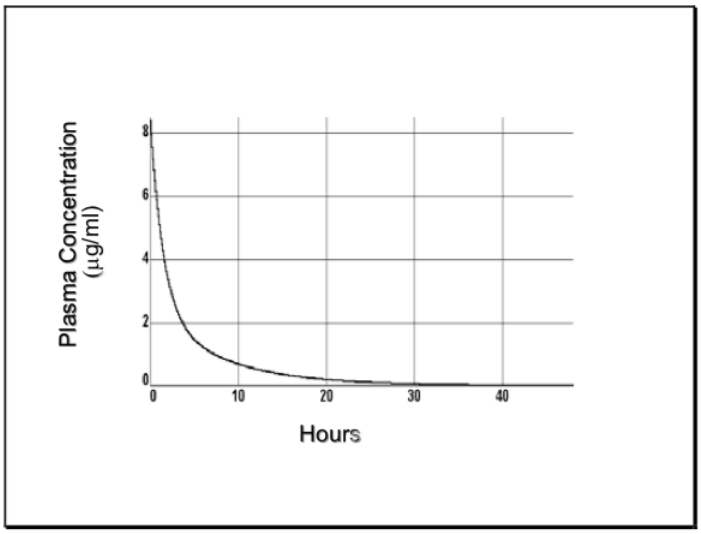


Figure 2

2. Case with Non-Instantaneous Absorption

a. Kinetics of first-order absorption and elimination: determination of absorption and elimination half-lives

$$C_p = \frac{k_a F D}{V_d(k_a - k_{el})}[e^{-k_{el}t} - e^{-k_a t}] \tag{1.3.14}$$

Note that the terminal slope may be either the elimination rate constant, the absorption rate constant, or a hybrid

See Katzung, *Basic & Clinical Pharmacology*, 2001, p. 42

b. Peak plasma concentration is dependent on absorption and elimination half-lives, volume of distribution, dose (D), and fraction of dose absorbed (F)

c.

$$AUC = \frac{F \cdot D}{Cl_T} \tag{1.3.15}$$

Fraction of dose absorbed into systemic circulation (F) is the bioavailability of the drug product; determined experimentally by measuring AUC of dosage form of drug given by one route and comparing it to AUC of same dose of drug under conditions of complete absorption, i.e. given i.v.

C. Effect of infusions or multiple dosing on time-course of plasma concentrations

1. Infusion Kinetics

One approach to maintaining a desired therapeutic level of a drug is to administer the agent by intravenous infusion. Drug delivery may be controlled by gravity- regulated drip of the agent into i.v. tubing or by use of an infusion pump.

a. When a drug is administered at a constant dosing rate (DR) and its elimination follows first-order kinetics, the concentration of drug in the plasma rises exponentially and reaches a steady-state or plateau level (C_{ss}).

$$C_p(t) = C_{ss}(1 - e^{-k_{el}t}) \tag{1.3.16}$$

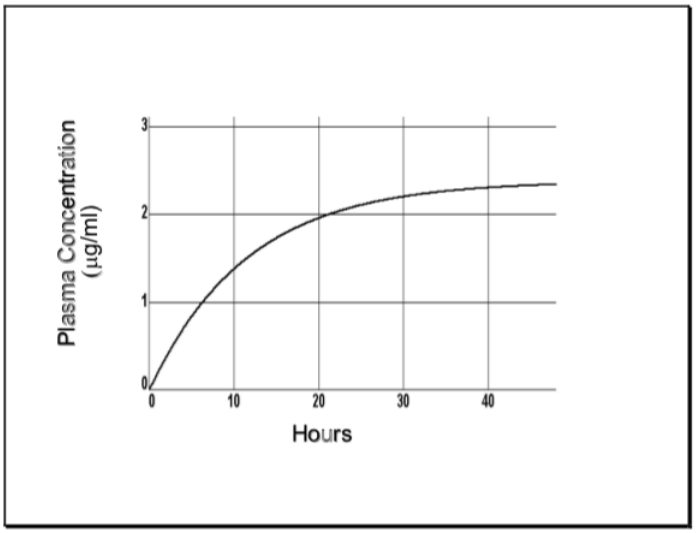


Figure 4

b. At steady-state the INPUT RATE = OUTPUT RATE. The input rate is DR, which may be expressed as the total dose (D) divided by the length of the infusion (T). The output rate in the case of first-order elimination is the total amount of drug in the body (C_{ss} Vd) times the elimination rate constant (k_{el}).

$$DR = C_{ss} \cdot V_d \cdot k_{el} \tag{1.3.17}$$

Therefore, the plasma concentration at steady-state can be predicted as follows:

$$\frac{C_{ss} = DR}{V_d k_{el}} \tag{1.3.18}$$

Remember that total clearance equals the elimination rate constant (k_{el}) times the volume of distribution. Therefore, the plasma concentration at steady-state (C_{ss}) is directly proportional to the input rate (DR) of the drug and inversely proportional to its total plasma clearance (Cl_T).

$$C_{ss} = \frac{DR}{Cl_T} \tag{1.3.19}$$

c. The rate of achieving steady-state is dependent only on the elimination half-life of the drug. Half the C_{ss} level is achieved in one $t_{1/2}$, and about 94% of C_{ss} in four $t_{1/2}$.

d. Because of the lag in achieving steady-state when a constant infusion rate is administered, a loading dose may be given to achieve the desired therapeutic effect more quickly. The loading dose may be chosen to produce the amount of drug in the body that would eventually be reached by the infusion alone.

$$Loading\ dose = C_{ss} \cdot V_d \tag{1.3.20}$$

At least on a theoretical basis, the plasma concentration will instantaneously reach the therapeutic level and that level will be maintained. Note that the steady-state level achieved with a continuous infusion is determined by the infusion rate and is not affected by the size of the loading dose.

2. Multiple Dosing Kinetics

a. Commonly, drugs are administered repeatedly in order to maintain their therapeutic effects. In the simplest case, a maintenance dose (D) is given at a constant dosing interval (τ) – [note that this is not the same as the time constant, τ]. Since the route of administration may not be i.v., the amount of drug which reaches the systemic circulation may be some fraction (F) of the dose. If elimination is by first-order kinetics, a steady-state is eventually reached. The “average”

Css at steady-state equals the fraction absorbed times dosing rate divided by total clearance, analogous to the C_{ss} from an infusion (see above).

\[{C}_ss\ average={({F\cdot D\over\tau})\over {Cl}_T}$

b. However, in the case of repetitive dosing, unlike an infusion, plasma concentrations of drug fluctuate during the dosing interval, depending on the kinetics of absorption and elimination. The degree of fluctuation in the plasma concentration during a dosing interval increases with increasing dose, dosing interval, clearance, and absorption rate.

c. If a drug is administered i.v. (or where absorption is rapid and complete), the peak plasma concentration at steady-state (C_{maxss}) relative to the peak after

the first dose (C_0) depends on the ratio of the elimination half-life and the dosing interval ($t_{1/2/\tau}$).

d.

$$C_{mass_{ss}} = \frac{C_0}{1-f} \tag{1.3.21}$$

f is the fraction of drug remaining at the end of a dosing interval.

$$f = e^{-k_{el}\cdot\tau} = e^{(\frac{-0.693}{t_{t/2}})\cdot\tau} = 0.5^{\frac{\tau}{t_{1/2}}} \tag{1.3.22}$$

Each time that the maintenance dose D is administered, the plasma concentration increases from C_{min} to C_{max}.. The decline from Cmax to Cmin is governed by the $t_{1/2}$, just as in single dosing. These relationships are described mathematically as:

$$C_{min_{ss}} + \frac{D}{V_d} = C_{max_{ss}} \tag{1.3.23}$$

$$\frac{D}{V_d} = C_0 \tag{1.3.24}$$

$$C_{min_{ss}} + C_0 = C_{max_{ss}} \tag{1.3.25}$$

$$lnC_{min_{ss}} = lnC_{max_{ss}} - (\frac{0.693}{t_{t/2}}\tau) \tag{1.3.26}$$

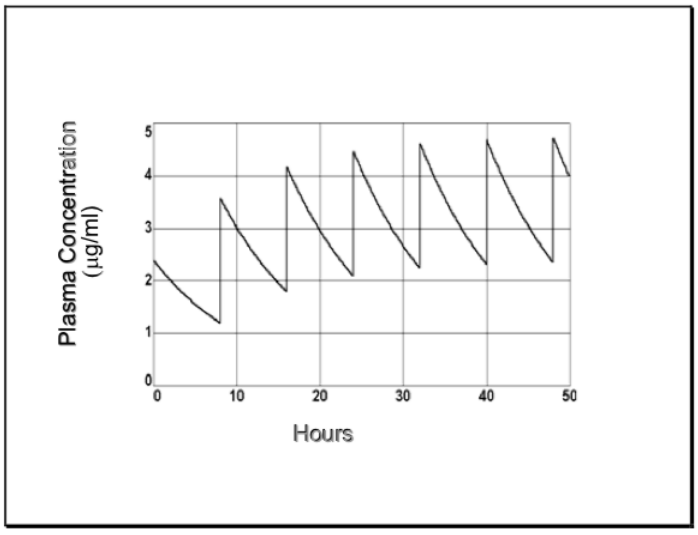


Figure 5

e. Prediction of Cmax and Cmin at steady-state can be of great importance in cases where therapeutic efficacy is to be maintained while minimizing the risk of toxic side effects. (Note that the Css “average” described above lies between Cmaxss and Cminss, but it is not mathematically equivalent to their arithmetic or geometric mean.) The therapeutic window in a dosing regimen is the range of efficacious, non-toxic plasma concentrations lying between $Cmax_{ss}$ and $Cmin_{ss}$. If these are known, then the dosing regimen is determined as follows:

$$Maintenance\ Dose = (C_{max_{ss}} - C_{min_{ss}}) \cdot V_d \tag{1.3.27}$$

$$Dosing\ interval\ (\tau) = [ln\frac{C_{max_{ss}}}{C_{min_{ss}}}][\frac{t_{t/2}}{0.693}] \tag{1.3.28}$$

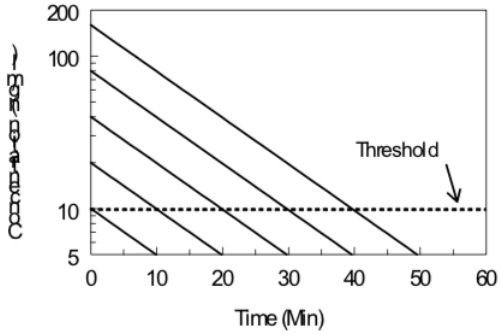
f. The rate of achieving steady-state is determined by the elimination half-life (as with an infusion). A loading dose may be used to rapidly achieve steady-state concentrations; especially important for drugs with long half-lives since attainment of steady-state is slow.

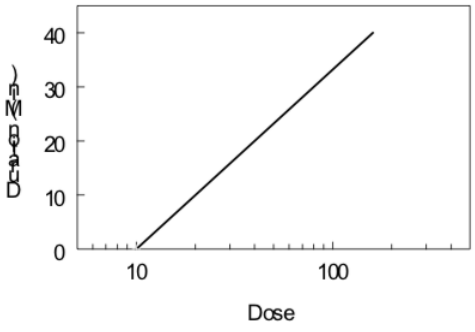
$$Loading\ dose = C_{max_{ss}} \cdot V_d \tag{1.3.29}$$

Time-Course of Drug Effect

Under certain conditions (first-order kinetics, reversible effect, single compartment kinetics, iv administration), the elimination half-life of a drug and its threshold dose for a particular effect can be estimated by monitoring the effect of the drug as a function of time after drug administration. Data obtained from several doses can then be evaluated by examining the duration of a given level of effect as a function of the logarithm of the dose, as illustrated below. The slope is directly proportional to the elimination half-life; the steeper the slope (i.e., increase in duration with an increase in dose), the longer the elimination half-life. The x-intercept indicates the log of the threshold dose; the smaller the x-intercept the greater the potency of the drug.

$$Duration\ of\ Action = \frac{t_{1/2}}{0.301}(Log\ Dose\ - Log\ Threshold\ Dose) \tag{1.3.30}$$





1.4: Pharmacokinetics II - Dosing

USE OF PHARMACOKINETIC PARAMETERS TO ESTIMATE DOSING REGIMENS

You have decided to prescribe a new drug GOOD-4U® to your patient, Ms. H.S.T., who weighs 70 kg and has normal renal function. The population average pharmacokinetic parameters for GOOD-4U are: Vd = 0.6 l/kg (about total body water), ClT = 60.6 ml/min. Therapeutic efficacy generally occurs at Cp of 2.38 µg/ml; side effects begin to occur with Cp of 5.0 µg/ml.

You decide to administer a single dose of 100 mg by iv injection.

1. Assuming rapid distribution in the Vd, are you expecting to produce side effects (hint: what is the initial C0)?

   No, assuming a single compartment system, the 100 mg will distribute in 42 liters to achieve an initial Cp of 2.38 µg/ml. See Fig. 1.

2. How long before 94% of the dose is eliminated (hint: what is the half-life)?

   The half-life computed from the total clearance and Vd is 8 hours; 94% of the dose is eliminated in about 4 half-lives, 32 hours.

3. A complete urine collection from the time of dosing until 16 hr later contains 37.5 mg of the drug. To what extent is the renal function of Ms. H.S.T. of importance to the total clearance of this drug?

   Computation of the renal clearance indicates that it is about 50% of the total clearance. At 16 hr, which is 2 half-lives, 75 mg should have been eliminated by all clearance mechanisms. Half of that is appearing in the urine suggesting the renal clearance is 30 ml/min. The drug must be extensively bound to plasma proteins and/or is substantially reabsorbed after glomerular filtration. It is reasonable to predict that reduction of the patient's creatinine clearance by 50% will reduce total clearance by at least 25%.

   One week later you decide to administer GOOD-4U® by constant iv infusion to achieve the therapeutic effect.

4. What loading dose would you administer?

   The minimum loading dose would be (2.38.µg/ml)(42 liters) or 100 mg.

5. What infusion rate would you prescribe?

   To achieve a Css of 2.38 µg/ml, given a total clearance of 60.6 ml/min, the infusion rate should be 144.2 µg/min. See Fig. 4.

   If instead you had administered 100 mg by iv injection every 8 hours:

6. At steady-state what would be the Cmax?

   The drug is given repeatedly at a dosing interval which in this case equals the elimination half-life. The drug will accumulate to twice the initial C0, ie. 4.76

   µg/ml. You can prove that from the equation provided (cf. Figure 5).

$$\mathbf{C_{max_{ss}} = \frac{C_0}{1 - f}} \tag{1.4.1}$$

7. At steady-state would the Cmin be sufficient to achieve continuous therapeutic efficacy throughout the regimen?

   Yes, since Cmin will be 2.38 µg/ml. At steady-state the input from each dose equals the output over the dosing interval. Since each dose adds 2.38 µg/ml, the Cmax,ss drops by 2.38 µg/ml to a Cmin of 2.38 µg/ml. Or approached another way, the dosing interval equals one half-life so Cmin will be 50% of Cmax! See Fig. 5.

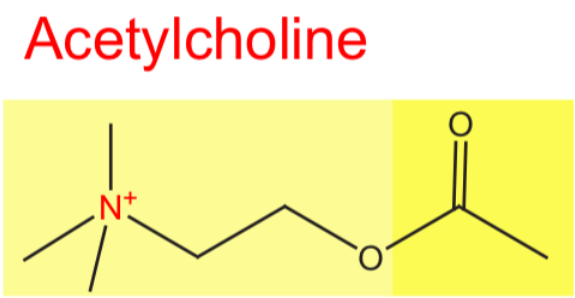
1.5: Case Study - Anticholinesterase

Case 1: AnticholinesteraseFebruary 3, 2005

1. Cholinergic Pharmacology
2. Anticholinesterase inhibitors
3. Therapeutic use
4. Managing toxicity

Case: Organophosphate Poisoning

A 55 yr old crop duster calls because he has lost control over his chronic twitch, and he is now beginning to have problems with blurry vision andcontrol of his bowels and bladder. He wants to go back to the airfield to finish his crop dusting, but his supervisor makes him call you first.



Synthesized from acetyl-CoA and choline by choline acetyltransferase (ChAT).

Poor absorption and low lipophilicity due to charge on quaternary ammonium.

Multiple systemic effects, esp autonomic pathways and at the neuromuscular junction (NMJ).

Acetylcholinesterase (AChE)

Clears Ach from site of action (also degraded by plasma butyrylcholinesterase)

Receptor class	*Locations*
Muscarinic M_1	Post-synaptic ANS ganglia, CNS
Muscarinic M_2	Heart, smooth muscle
Muscarinic M_3	Vessels (smooth muscle), exocrine glands
Muscarinic M_4	CNS
Muscarinic M_5	CNS
Nicotinic N_M	NMJ
Nicotinic N_N	Pre-synaptic ANS ganglia, adrenal medulla, CNS

Bound on post-synaptic membrane

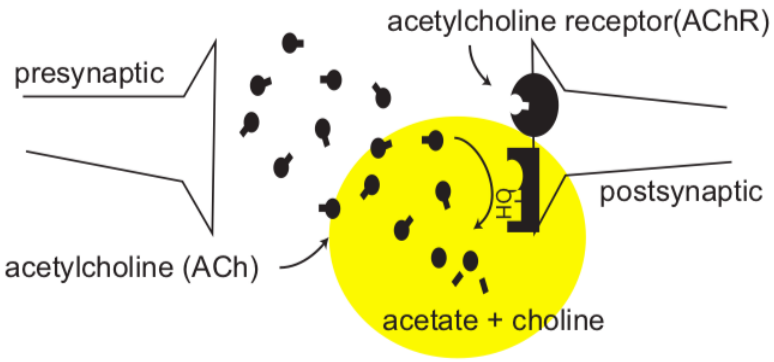
Rate = 400,000 per min

Inhibition of AchE results in build up of Ach at muscarinic and nicotinic synapses!

Step 1: Binding

Step 2: Formation of covalent intermediate and release choline

Step 3: Hydrolysis of acyl-enzyme intermediate



Direct-acting agonists

Mimics acetylcholine by binding Ach receptor and activating downstream signaling

Examples: methacholine, carbachol, bethanechol, pilocarpine

Indirect agonists

Inhibits AchE from breaking down acetylcholine at synapse

Quaternary alcohols

- competes w/ ACh for binding to AChE (step 1)

Examples: edrophonium

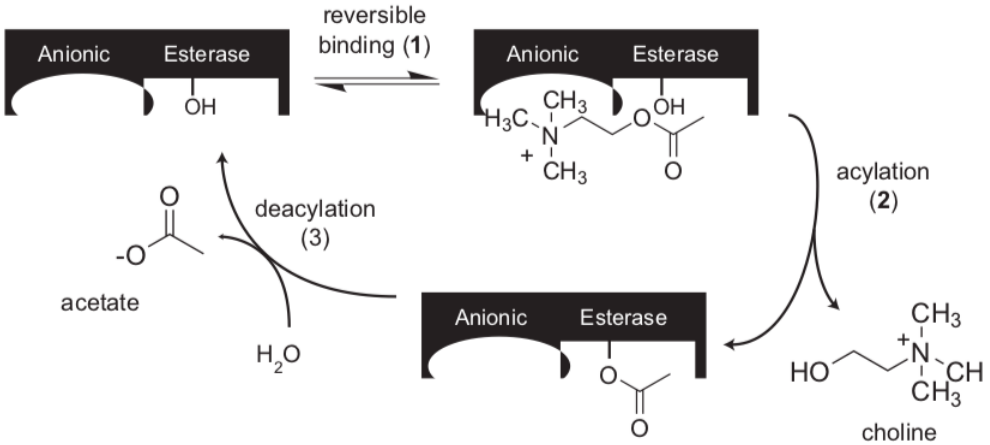
Carbamate esters

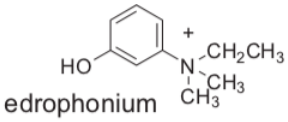
- formation of carbamylated enzyme intermediate (step 2)

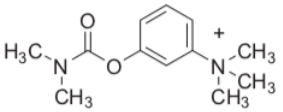
Examples: neostigmine, pryidostigmine

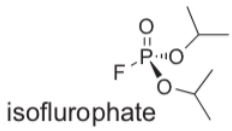
Organophosphates

- formation of phosphorylated enzyme intermediate (step 2)



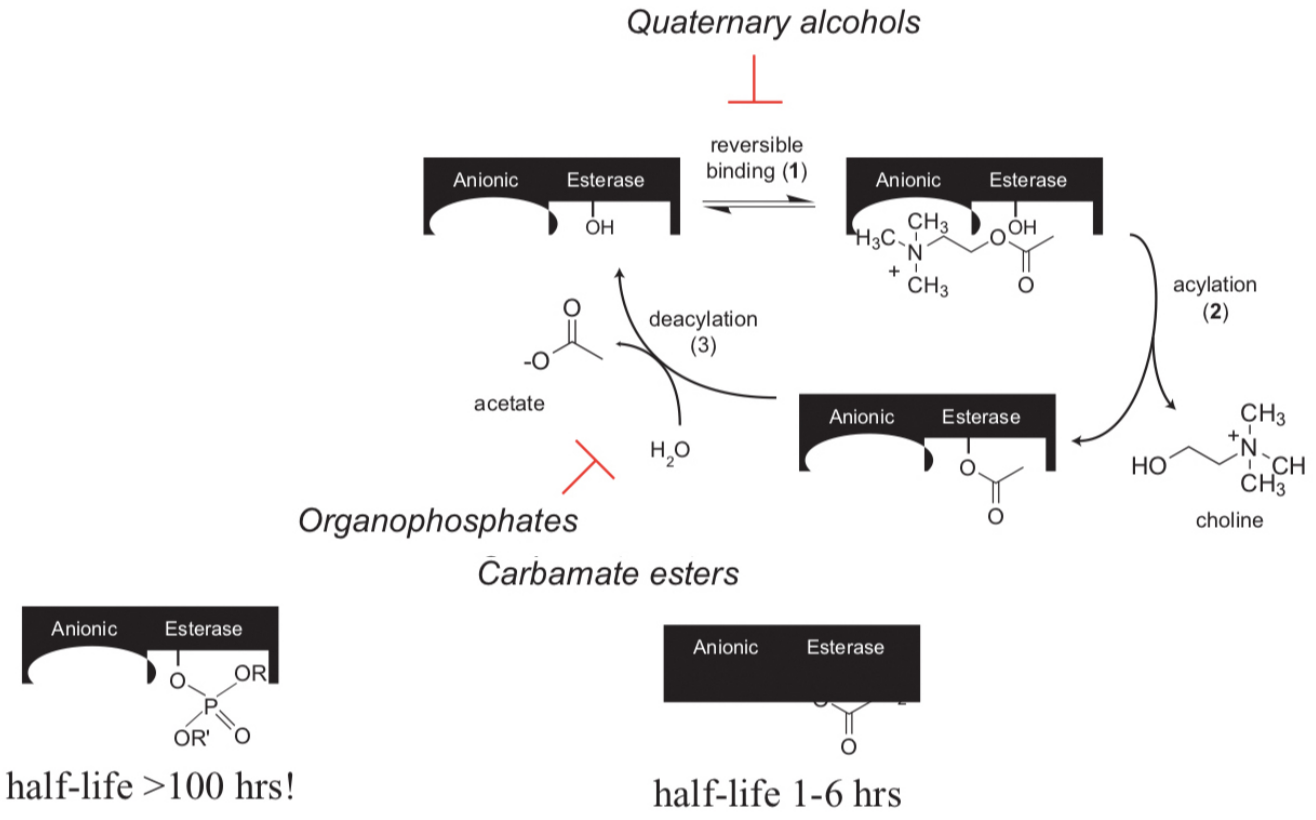




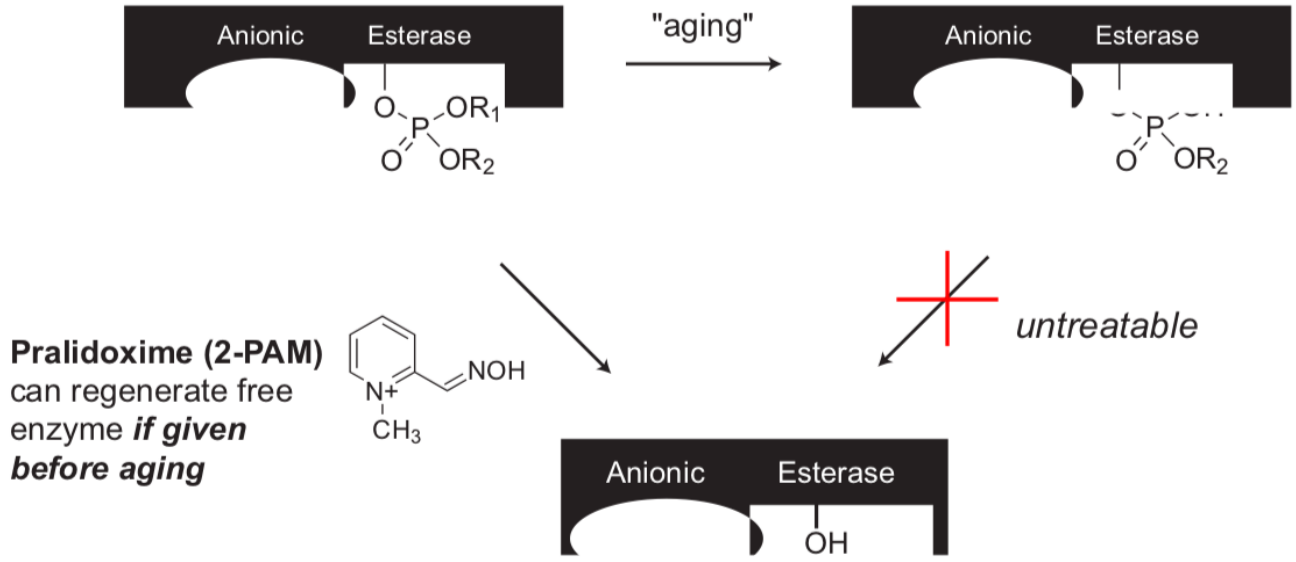


Examples: parathion, malathion are insecticides soman, sarin are nerve agents

AchE inhibitors: reversible versus irreversible



Inhibition by organophosphate: "Aging"



Pharmacokinetics of organophosphates

Parathion and malathion are biotransformed in the liver to become active (insects perform this process more efficiently)

Highly lipid soluble, widely distributed and penetrates CNS

When used as insecticides, can be dispersed as aerosols or dusts and absorbed by all possible routes: GI, skin, mucous membranes, lungs

Slow hepatic metabolism; urine excretion of hydrolysis products Lipid-soluble drug can remain in systems for weeks to months!

Effects of acute O/P overdose

Muscarinic	Nicotinic	CNS
Ciliary spasm, Miosis	Weakness	Confusion
Bronchoconstriction	Fasciculation	Anxiety, Agitation
Bronchosecretion	Twitching	Restlessness, Tremor
Diaphoresis	Flaccid Paralysis (resp.)	Ataxia
Salivation, Lacrimation		Convulsions
Bradycardia, Hypotension		Respiratory depression
Incontinence, Diarrhea	Severe Cases: also include conduction block, pulmonary edema	CV collapse
GI spasms (cramping)		Coma
Emesis, Nausea		

DUMBBELLS: Diarrhea (Diaphoresis), Urination, Miosis, Bronchospasm (secretion) Bradycardia, Excite skeletal muscle and CNS (Emesis), Lacrimation, Lethargy, Salivate

Mode of death: respiratory failure via flaccid muscular paralysis exacerbated by bronchosecretion and bronchoconstriction

Chronic Exposure to Low Doses: blurred vision, incontinence, twitching*** neuropathy associated with axonal demyelination

Treatment

Lethal Dose
Remove contaminated clothing; remove from exposure site Wash skin with soap, bleach (alkaline hydrolysis) Respiratory support (O2, ventilatory assistance, treat Sz)

Atropine – anti-muscarinic agent

- reverses dangerous parasympathetic effects (respiratory)
- 0.5-2 mg IV q15min until respiratory secretions dry (days!)

Pralidoxime (2-PAM) - specific for organophosphate poisoning

Therapeutic use of AchE inhibitors

Myasthenia gravis (edrophonium, pyridostigmine, neostigmine)

Alzheimer's Disease (tacrine and donepezil)

Reversal of neuromuscular blockers (neostigmine, physostigmine)

Glaucoma (physostigmine, echothiophate)

Summary of Key Points

Reversible versus irreversible inhibition of AchE causes build up of Ach at synapse

Toxicity associated with AchE inhibitors (patient case!) include global nicotinic, muscarinic, & CNS effects (*DUMBBELLS*)

Treatment for Exposure to Irreversible Inhibitors Atropine – counteract ACh agonism 2-Pralidoxime – prevent aging

1.6: Autonomic Pharmacology

As you will see throughout the course, the autonomic nervous system (ANS) is a very important topic for two reasons: First, manipulation of ANS function is the basis for treating a great deal of cardiovascular, pulmonary, gastrointestinal and renal disease; second, there is hardly a drug worth mentioning without some major autonomic side effects (cf. antihistamines). You have already heard something about the ANS and its wiring diagram in the lecture by Dr. Strichartz on cholinergic receptors, and it is certainly not my intent to reproduce these pictures or the various diagrams in your text. I hope to give you a slightly different presentation which highlights the important points in this rather long textbook assignment.

You have already heard about nicotinic cholinergic receptors and the somatic nervous system (SNS) control of voluntary striated muscle. The ANS, simply put, controls everything else: smooth muscle, cardiac muscle, glands, and other involuntary functions. We usually think about the ANS as a motor system -- although it does have sensory nerves, there is nothing particularly distinctive about them.

Anatomy

The sympathetic division of the ANS is called THORACOLUMBAR, but it has input from higher brain centers like hypothalamus, limbic cortex, etc. The preganglionic sympathetic nerves have cell bodies in the intermediolateral column of the spinal cord from about T1 to L3. The efferent fibers exit with the ventral roots of the spinal nerves and then leave in a white ramus which leads to a GANGLION (i.e., a collection of cell bodies of postganglionic neurons). The preganglionic nerves may stimulate several postganglionic nerves which rejoin the spinal nerve by way of a grey ramus. The ganglia are located in several places:

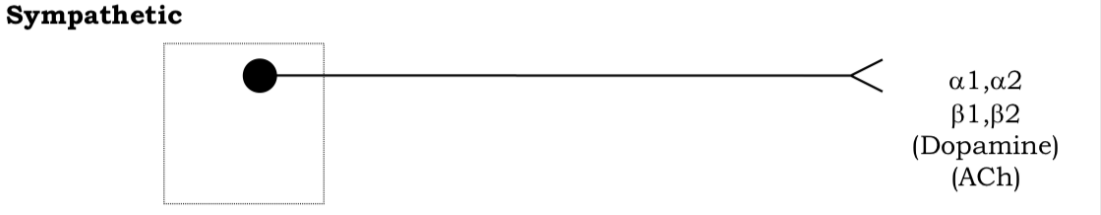
1. Paravertebral: 22 pairs located on either side of the vertebral column. The uppermost ganglia are fused to form the superior and middle cervical ganglia and the stellate ganglion, which is located at about C6. The preganglionic neuron may travel up or down several dermatomal levels before synapsing with one or more postganglionic neurons.
2. Prevertebral: The celiac, superior mesenteric and inferior mesenteric ganglia. Sometimes called collateral ganglia.
3. Adrenal Medulla: This is also derived from neural crest tissue and functions in much the same way as a ganglion, although the output is circulating epinephrine and norepinephrine.

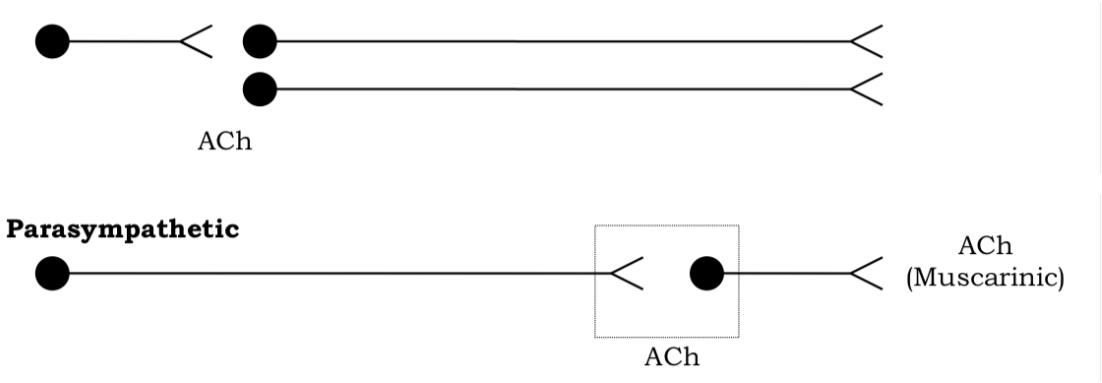
The parasympathetic or CRANIOSACRAL division has its origin in the nuclei of cranial nerves III, VII, IX, and X as well as the S2-4 nerve roots. The preganglionic fibers travel almost to the end-organ before synapsing in the ganglion:

1. III goes from the Edinger Westphal nucleus to the ciliary ganglion, and the postganglionic nerves continue to the eye.
2. VII innervates the pterygopalatine and submandibular ganglia which control lacrimal and salivary glands, respectively.
3. IX innervates the otic ganglion which controls the parotid
4. X innervates the heart, lung, GI tract, and other splanchnic viscera. The postganglionic cell bodies are contained in specialized tissue within the heart (e.g. AV nodal tissue), GI tract (e.g. Auerbach's plexus).
5. S2-4 preganglionic nerves originate in the sacral parasympathetic nucleus and leave the cord by way of the pelvic splanchnic and pudendal nerves. They innervate the distal GI tract, bladder, and genitalia.

We will not specifically discuss the enteric nervous system – often treated as a third division of the ANS. It consists of complex networks of interconnected ganglia and nerve fibers, largely contained with the myenteric (Auerbach's) and submucosal (Meissner's) plexuses. This system exerts local control over GI secretion, motility, blood vessel tone,, and fluid transport. It is subject to control by sympathetic, parasympathetic, and CNS iinputs.

If we look at the sympathetic and parasympathetic divisions schematically, it is easy to see how the sympathetic division is suited to "flight or fright" responses. The stimulation of one preganglionic neuron can lead to widespread activation of postganglionic neurons and to the liberation of stress hormones like epinephrine. The parasympathetic division is often called a "vegetative" system, and it is well suited to controlling discrete parts of the body.





There are some differences between the somatic and autonomic systems that are worth remembering.

AUTONOMIC	SOMATIC
• Synapses in periphery • Nerve plexuses • Organs, glands, sm. muscle have activity without nerves • Symp and Parasymp afferent and efferent nerves overlap in terminal retinaculum • Sm. muscle has protoplasmic bridges, so stimulating one can depolarize 100 others.	• Synapses in CNS • No plexuses • Skeletal muscle atrophies without nerve • Nerves end in discrete motor end plates on muscle fibers • Muscle fiber depolarized discretely

Cholinergic neurotransmission

Fig 6-3 and 6-4 in Katzung schematize the cholinergic and adrenergic nerve terminals. Cholinergic receptors are generally categorized as follows:

Nicotinic motor end plate autonomic ganglia

Muscarinic autonomic ganglia parasympathetic postganglionic

All nicotinic receptors are, by definition, stimulated by the alkaloid nicotine. We know that the two types of nicotinic receptor differ because they are differentially affected by various agonists and antagonists

	Agonists	Antagonists
Motor End Plate	phenyltrimethylammonium (PTMA)	decamethonium bungarotoxin
Ganglion	dimethylphenylpiperazinium (DMPP)	hexamethonium

Muscarinic receptors are those stimulated by the alkaloid muscarine, which comes from the mushroom Amanita muscaria. At this writing there are 5 postulated subtypes of muscarinic receptors (see table) although not much is known about the last two.

Muscarinic Receptor Subtypes

	M1	M2	M3	M4	M5
Antagonists					
atropine	+	+	+	+	+
pirenzipine	M1>M3>>M2				
AFDX-116		M2>M1>>M3			
4-DAMP			M3>>M1>M2		
Location	Neural	Heart Sm. Musc. Neural	Endocrine Sm Musc. Neural	Striatum	
Amino Acids	460	466	589/590	478/479	531/532

Cholinergic Signal Transduction

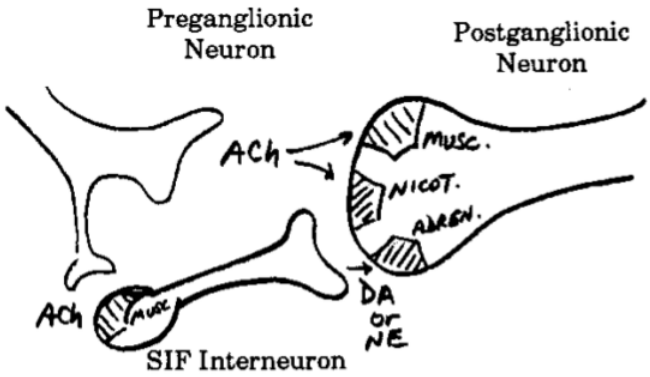
The nicotinic response of skeletal muscle has been discussed in detail. ACh causes depolarization by a sudden increase in Na+ conductance. Repolarization depends upon the outward flow of K+.

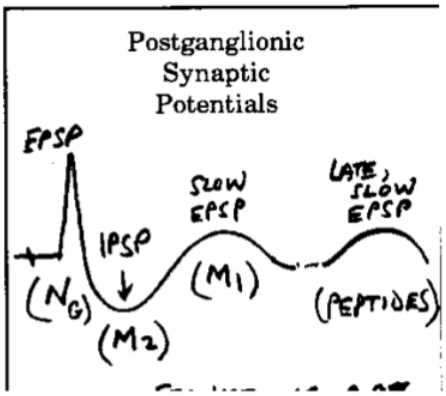
The transduction of muscarinic responses depends upon the tissue. For example ACh causes hyperpolarization of cardiac conducting tissue by increasing K+ conductance (M2). In G.I. smooth muscle it causes partial depolarization by increasing Na+ and Ca2+ conductance (M3).

Muscarinic Responses

Receptor	M2	M1 + M3
G-Protein	G_k, G_i	G_q, G_s
Second Messenger	↓cAMP ↑arachidonic acid	↑cAMP ↑DAG ↑IP_3
Ionic Conductance	↑K^+, ↓Ca^{2+} (heart) ↓K^+ (sm. muscle)	↓K^+, ↑Na^+ ↑or ↓Ca^{2+}
Responses	hyperpolarization (heart) depolarization (sm. muscle) presynaptic inhibition	myosin phosphorylation depolarization hyperpolarization presynaptic inhibition glandular secretion

Ganglionic transmission is a very complex system (cf. Strichartz lecture). An initial nicotinic effect leads to an increase in Na+ conductance and a fast excitatory post-synaptic potential (EPSP). This is modulated by a muscarinic (M1) slow EPSP, and an inhibitory postsynaptic potential (IPSP) which may be muscarinic (M2) or may involve adrenergic transmission from a SIF (small, intensely fluorescent) interneuron.





(see Katzung, p.87)

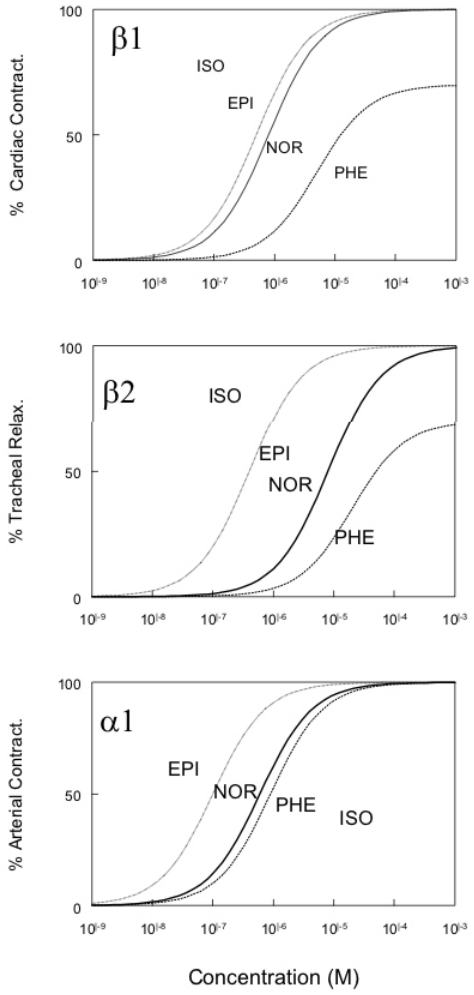
Adrenergic Neurotransmission

Neurotransmission from almost all sympathetic postganglionic nerves is adrenergic, that is, it involves noradrenaline (NE, norepinephrine, levarterenol). Adrenergic receptors were first divided into α and β by Ahlquist in 1948. The pattern of responses he defined was based on the relative potencies of agonists:

α-- epinephrine > norepinephrine > phenylephrine >> isoproterenol

β -- isoproterenol > epinephrine ≥ norepinephrine >> phenylephrine

More subtle potency differences and selective antagonists allowed us to subtype these receptors.



Selective Adrenergic Agonists and Antagonists

Receptor Subtype	Selective Agonist	Selective Antagonist
α-1	methoxamine	prazosin
α-2	clonidine dexmedetomidine	yohimbine idazoxan atipamezole
β-1	dobutamine	metoprolol
β-2	albuterol terbutaline	butoxamine

Subtypes of α receptors (α1a, α1b, α1d; α2a, α2b, α2c) have been cloned and localized in different tissues, but their physiologic functions are not known. A β-3 response has been described which mediates lipolysis in adipocytes. There are no truly selective agonists/antagonists for the β-3 receptor, and the response is not blocked by most β antagonists. The selectivity of the drugs in the table is only relative.

Signal transduction of adrenergic receptors has been studied extensively. The α-2 and β receptors depend on G-protein mediated inhibition or activation of adenylyl cyclase, while α-1 works by activating phospholipases to hydrolyze phosphoinositides.

Receptor	G Proteins	Effector Mechanisms
α1	G_q, G_iG_o	↑Phospholipase C,D,A_2
α2	G_i, G_o	↓ cAMP.
β1	G_s	↑ cAMP, ↑ L-type Ca Channels
β2	G_s	↑ cAMP
β3	G_s	↑ cAMP

How can we use drugs to promote or inhibit cholinergic or noradrenergic neurotransmission? I recommend that each of you draw a schematic of the two types of nerve terminals (cf Katzung 6-3 and 6-4) and try to incorporate the information from Table 6-5. We'll go through this briefly in class. In both cases, there are toxins or approved/experimental drugs which can affect

1. The synthesis, transport or storage of transmitter
2. The release of transmitter
3. The effect of transmitter at receptor sites
4. The inactivation or metabolism of transmitter

[It is also possible to modify sympathetic neurotransmission at the level of signal transduction--Can you think of an example?]

It is important to realize that the responses to most autonomic drugs are not static over time. The magnitude of the response depends enormously on baseline tone, and responses may change with repeated drug administration or alterations in patient physiology. When a drug loses its effect we say that the patient becomes **tolerant** -- i.e. the same dose produces less effect (or it takes a lot more to produce the same effect). This phenomenon is best described in the case of adrenergic drugs:

- "Tachyphylaxis" Certain drugs like ephedrine act by releasing intraneuronal stores of preformed norepinephrine. After repeated dosing, the supply of neurotransmitter may be temporarily exhausted.
- Receptor Down Regulation This may be a decrease in the number of available receptors or a decrease in ligand affinity for the receptor. A good example is the decrease in β1 receptors in the myocardium of patients with congestive failure.
- Desensitization Reversible uncoupling of receptor occupancy and cellular response by receptor phosphorylation and internalization. This is best worked out for the β adrenergic receptor.

Effects on End-Organs

Table 6-3 in Katzung (or Table 5-1 in G & G) lists the effects of stimulating α and β or muscarinic cholinergic receptors. In most cases you will notice that parasympathetic stimulation produces effects which promote normal "vegetative" functions like urination, defecation, production of saliva, accommodation of the eye for near vision, etc. Sympathetic activation does those things deemed necessary for "fight or flight" like increasing cardiac output, increasing metabolic rate, relaxing the ciliary muscle for distance vision, etc. Often the two systems function in opposition, but this is not always the case. In the case of blood vessels, the predominant tone is α−adrenergic, and there is relatively little β or muscarinic tone. [Why does this make sense?]

In a healthy, young individual at rest the predominant tone in most tissues is parasympathetic: for example, there is predominant vagal tone in the heart, peristalsis in the GI and GU tract, and the pupils are small. In a subject under physical stress (or a critically ill patient) there may be maximal sympathetic tone. This is important for two reasons:

1. A drug which acts by blocking any autonomic activity will have much more effect if there is a great deal of activity to begin with.
2. It follows that a drug which blocks ganglionic transmission (i.e., both sympathetic and parasympathetic function) will have its greatest effect on the system which predominates. [So, are the predominant effects of ganglionic blockers sympatholytic or parasympatholytic? What are they used for?]

Clinical Applications of the Various Drug Classes

Cholinergic Agonists

The use of these agents is rather limited, in part because they have such widespread effects. Nicotinic agonists occupy a small but important place in therapeutics and toxicology. We cannot use acetylcholine itself effectively [why?].

> Nicotine and succinylcholine are the two most commonly used nicotinic "agonists," but paradoxically both of these drugs cause such persistent membrane depolarization that they inactivate Na channels and *block* neuromuscular transmission (cf. Dr. Strichartz comments on "depolarizing" muscle relaxants). Nicotine is used as an insecticide and self-administered (in low doses) by those who smoke and those who are trying to quit. Succinylcholine is used clinically to produce neuromuscular blockade.

The most common “agonists” are those that act indirectly by inhibiting acetylcholinesterase (ChE). The reversible inhibitors like neostigmine and pyridostigmine are used by anesthesiologists to reverse the effects of nicotinic antagonists like curare. They are also given to patients who suffer from myasthenia gravis and have circulating antibody to their own nicotinic receptors. In both cases, the drugs are working by increasing the concentration of acetylcholine available at the motor end-plate. Centrally acting ChE inhibitors are also being used in Alzheimer’s dementia.

The irreversible ChE inhibitors like the organophosphates permanently inactivate the enzyme. These drugs were presented in Case Discussion 1 --they are used as insecticides and as "nerve gases." One of them, echothiophate, is used clinically to produce long-lasting miosis (pupil constriction) for refractory glaucoma.

Muscarinic agonists like methacholine, pilocarpine, bethanecol and carbachol are used to produce miosis (in cases of glaucoma or eye surgery) and to increase the activity of GI and GU smooth muscle. The latter effects are sometimes useful in cases of diabetic gastroparesis or bladder dysfunction.

Cholinergic Antagonists

Nicotinic Antagonists like d-tubocurarine (curare) and pancuronium are used to produce muscle relaxation for surgery and sometimes to facilitate ventilation in critically ill patients. These so-called "non-depolarizing" relaxants act as competitive antagonists at the nicotinic receptor. The selectivity of these older relaxants is not very good: curare is a weak ganglionic blocker, and pancuronium can produce substantial muscarinic block. [What will their side effects be, when used for muscle relaxation?]

Botulinum toxin is a bacterial toxin which blocks acetylcholine release by binding to docking proteins and inhibiting exocytosis. It is now used in some focal dystonias, movement disorders and strabismus (crossed eyes). The drug is given by direct injection into the muscle and produces partial denervation for 3-5 months.

Muscarinic antagonists are still fairly widely used. The prototypes are the belladonna alkaloids, atropine and scopolamine. There are also a fairly large number of synthetic atropine-like drugs. These are all competitive, reversible antagonists which produce mydriasis (pupil dilation), dry mouth, tachycardia, sedation, and decreased tone of bronchial, GI and GU smooth muscle. Logically enough, they are used to treat bradycardia, diarrhea and bladder spasms. Atropinics are also used as sedatives, to dilate the pupils, to reduce secretions, and to produce bronchodilation. Frequently, atropine is used to counteract the muscarinic effects of drugs like the ChE inhibitors.

It is very important to remember that many useful drugs from completely different categories have pronounced anticholinergic side-effects-- examples of these include antihistamines (Benadryl), tricyclic antidepressants (Elavil), phenothiazines (Mellaril). All of these drugs can produce sedation, rapid heartbeat, constipation and urinary retention.

Adrenergic Agonists

This class includes the endogenous agonists norepinephrine (NE), epinephrine (E), and dopamine (DA). These drugs are not terribly selective for the various receptors, and their relative α vs β (or δ, in the case of DA) activity depends a great deal on the dose administered. Most of the agonists act directly at pre- or postsynaptic receptors, but a few (ephedrine, amphetamine, tyramine) act by releasing NE from terminals.

Please review Table 9-4 and Figure 9-6 in Katzung which describe the different cardiovascular responses to phenylephrine, isoproterenol, and epinephrine (an α, β, and mixed sympathomimetic drug, respectively). Epinephrine (in low doses) and isoproterenol stimulate β1 and β2 receptors to increase heart rate and contractility but decrease peripheral vascular resistance. Norepinephrine has very little effect on vascular β2 receptors, so it produces peripheral constriction (G & G p. 205):

α-1 agonists like phenylephrine are primarily used for their effects on vascular tone. By local vasoconstriction they can act as nasal decongestants and retard the absorption of other drugs like local anesthetics. Of course, they are used to treat hypotension or shock,

especially when there is inappropriate vasodilation (e.g. gram-negative sepsis). These drugs are also used frequently as mydriatics

α-2 agonists. Clonidine, methyldopa, guanfacine, and guanabenz reduce blood pressure through a central reduction in sympathetic tone. All are used for the outpatient treatment of hypertension. Stimulation of postsynaptic α-2 receptors can initially cause vasoconstriction and increase peripheral resistance. The antihypertensive effects of clonidine and other imidazolines are thought to be mediated, in part, by non- adrenergic "imidazoline" receptors (cf. Katzung, p. 159). Clonidine and dexmedetomidine are also used in man for their sedative and analgesic properties.

β-1 agonists like dobutamine or non-selective β agonists like isoproterenol are used to increase myocardial contractility, and sometimes to increase heart rate or automaticity. The fact that these agents may actually decrease afterload is an advantage in patients with congestive failure; the propensity of β agonists to cause tachyarrhythmias is not.

β-2 agonists like albuterol, metaproterenol or terbutaline are extremely useful for their bronchodilator properties. Asthmatics commonly take them by inhalation. β-2 agonists can also stabilize mast cell membranes and abort acute hypersensitivity reactions like anaphylaxis. The drug of choice for this indication is epinephrine. β-2 agonists can relax uterine smooth muscle, and drugs like ritodrine are sometimes used to delay premature labor.

Adrenergic Antagonists

α-1 antagonists like prazosin are used for the outpatient treatment of hypertension. The older non-selective a blockers like phentolamine were much more likely to cause tachycardia [why?]. Phenoxybenzamine, a non-competitive α blocker, has been used for the therapy of pheochromocytoma.

α-2 antagonists like atipamezole are not marketed, but have been tested in man. Theoretically, they could be useful to reverse the effects of drugs like clonidine and dexmedetomidine.

β antagonists like propranolol, nadolol, and timolol are non-selective drugs which are widely used. Metoprolol, esmolol and atenolol are relatively selective for β-1 receptors. [What is the theoretical advantage of this?] Labetalol has both α and β antagonist activity. These drugs are of major importance for the treatment of hypertension, ischemic heart disease, obstructive cardiomyopathy, and tachyarrhythmias. They may increase survival after myocardial infarction. Propranol has also been used to treat thyroid storm. Unlike some β blockers, propranolol has substantial CNS activity and has proven useful for migraine headache and benign essential tremor. [How might the metabolic effects of β-blockers pose a problem?]

Miscellaneous sympathoplegic drugs. These drugs are older treatments for hypertension and have largely been superceded by drugs like angiotensin converting enzyme inhibitors, calcium channel blockers, as well as α and β blockers. Reserpine, which depletes nerve terminals of NE, is described (Katzung, p.163) as an acceptable treatment for hypertension. In my opinion, the drug is of mainly historical interest. Guanethidine, prevents the release of NE -- another kind of chemical sympathectomy. Its side effects, especially postural hypotension and diarrhea, can be severe, so it has traditionally been reserved for cases of hypertension refractory to other treatments. Metyrosine (α-methyl p- tyrosine) inhibits tyrosine hydroxylase, the rate limiting step in the biosynthesis of catecholamines. It has had some use in the adjunctive treatment of pheochromocytoma.

Questions to be covered in Autonomic Nervous System lectures

1. What are the important differences between the somatic and autonomic nervous systems?
2. How is the anatomy of the sympathetic/parasympathetic system suited to its physiologic role?
3. How can we distinguish nicotinic receptors at the motor end-plate from those in autonomic ganglia?
4. What is the basis for subtyping α and β adrenergic receptors? What are the supposed advantages of therapeutic agents which are specific for one subtype of receptor?
5. By what mechanisms may drugs modify adrenergic and cholinergic transmisssion?

Problem Set -- Autonomic Nervous System

Pindolol is a partial agonist at β receptors. How can it act as an antagonist? What is the putative advantage of this drug?

What are the possible reasons for the development of tolerance to a βagonist drug (in general terms, please)? If we suspect that there has been receptor down-regulation, how might we investigate it? How could we determine whether there are fewer receptors or the receptor has decreased affinity for the agonist? Hint: See Scatchard Plot in notes by Dr. Strichartz.

We have accepted the fact that NE and ACh are neurotransmitters for postganglionic sympathetic and parasympathetic neurons, respectively. What kind of evidence was necessary to come to this conclusion?

A patient receiving the MAO inhibitor, pargyline, can have a hypertensive crisis after eating cheese or drinking Chianti, yet this drug was originally marketed to *lower* blood pressure. How can we explain these apparently opposite effects?

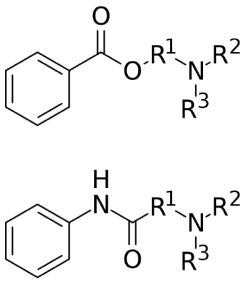
1.7: Local Anesthetics

Learning Objectives

- To describe the mechanisms of local anesthesia as well as some relevant clinical pharmacology of local anesthetics.

Local anesthesia is the selective numbing of a particular, circumscribed region of the body by a controlled, reversible procedure. Drugs called local anesthetics (LA) are usually employed for these procedures, although directly applied pressure, cooling, or even heating will also produce numbness. The general strategy is to inhibit the propagation or generation of impulses in nerves from a defined anatomical region.

Knowledge of the structure of local anesthetic drugs is essential for an understanding of their mechanism of action, potencies and pharmacokinetics. The general structure of a local anesthetic is:



The aim of this lecture is to describe the mechanisms of local anesthesia as well as some relevant clinical pharmacology of local anesthetics. (Public Domain; User:Edgar181)

Structures and properties of drugs used clinically are listed in Table 1, along with one experimental derivative, QX-314.

The aromatic group sometimes contains a para-amino group (-NH_2) at R3 (procaine) and additional alkyl groups attached to this amino (tetracaine), or at R_1, R_2 (lidocaine, and other amides).

Amide or ester bonds connect the aromatic moiety to a tertiary (3°-) amine which can have alkyl groups of lengths from -CH_3 to -C_4H_9 attached to it. The absolute potency of LA increases with increasing alkyl length substituents on both aromatic and 3°-amine groups. Physico-chemical analysis reveals a monotonic increase of absolute potency with increasing hydrophobicity for all compounds. Since the mechanisms of action are complex (see below), the exact relationships between structure, pKa, and membrane distribution are still not known.

Mechanism of Action

LAs block nerve impulses by interfering with the sodium permeability increase (PNa) which subserves the depolarizing phase of action potentials. The mechanistic details depend on the LA molecule being used.

A. Active species: (3°)-amine local anesthetics (pKa = 7.8-10) exist as equilibrium mixtures of protonated cation and neutral base at physiological pH.

   The ionization reactions at neutral pH are quite rapid (-10^{-3} sec).

   Evidence to answer these questions comes from:

   Conclusion: Both neutral and protonated species of LA can inhibit Na channels and block impulses. In general, however, the protonated form appears to be more potent.

   1. Which form of the LA module blocks P_{Na}?
   2. Where does it act: inside or outside the cell or on the membrane?
   3. Quaternary (4^o)-amine derivatives (permanent cations, e.g., QX-314 which do not permeate the membrane, block sodium channels (P_{Na}), but only when applied in the cytoplasm.
   4. The observed impulse-blocking potency of benzocaine and of lidocaine derivatives where -OH replaces -NR_2 (both permanently neutral molecules). These drugs act identically whether applied externally or cytoplasmically.

Molecular Mechanisms

1. The block of sodium current (I_{Na}) or of impulses by 4^o -amine LAs increases in extent with repetitive opening of sodium channels ("use-dependent" block) (Figure 2). Use-dependent block is reversed when stimulation stops.
2. With benzocaine (and some alcohols) and with 3^o-amine anesthetics at alkaline pH, resting nerve block reveals more "inactivated" sodium channels (Fig. 3) but use-dependent block is very weak. 3o-amine LAs show much more use-dependent block at neutral or slightly acid pH than at alkaline pH (external). Internal pH has surprisingly little effect.
3. Inhibition of ionic Na+ current by benzocaine is paralleled by a proportional reduction of "gating current", the movement of charge which results directly from conformational changes of Na channels during activation (Figure 4).

   The sodium channel itself appears to be a receptor for local anesthetics. Intentional mutation of part of the channel's inner pore region changes resting and use- dependent pharmacology of various local anesthetic molecules. In addition, in normal channels the membrane potential changes the channel conformations, which in turn have different anesthetic affinities. This is collectively referred to as the "modulated receptor hypothesis" (Figure 5). In addition, there is a non-receptor mediated action of local anesthetic agents, which may occur through a disruption of normal membrane structure.

4. Calcium ions may antagonize the blocking action of some local anesthetics, but this probably is mediated through changes in channel structure and is not necessarily evidence for direct steric competition between Ca^{2+} and LA binding.
5. LAs also have been shown to inhibit K+ channels, Ca^{2+} channels, and the nicotinic acetylcholine-activated conductance, the substance P receptor and even the G-protein modulation of certain channels. These alternative actions may contribute to spinal (intrathecal) anesthesia and to some aspects of toxicity.
6. Modes of Administration and Pharmacokinetics

   A. A. Injection--minor, to block small regions via peripheral nerve; major (includes iv), to block whole limbs via peripheral nerve.

      Clinically, local anesthetics are usually injected as 0.25-1 % (w:v) solutions, equivalent to 10-40 mM, where 1/40-1/100 of those concentrations provide a 50% absolute block of impulses in an isolated, desheathed nerve. Interestingly, less than 10% of the dose of injected drug actually reaches the nerve to provide complete functional block.

   B. Infiltration--usually at skin or other superficial surfaces, e.g. scalp, oral mucosa.
   C. Topical--superficial application, on skin, tracheal (pre-intubation) to reduce irritation and gag reflex.
   D. Central injections--at spinal cord:
      1. epidural--blocks roots, but LA also enters cord, CSF.
      2. intrathecal--"spinal":
         a. potent block of many dermatomes
         b. drug is often dissolved in a hypo- or hyperbaric solution to control spread.
         c. positioning of patient may also be adjusted to control anatomical distribution of block.
   E. Removal--LAs are removed from site of injection by local tissue uptake and local circulation.
      1. removal by circulation is often reduced by co- injection of epinephrine, but this in not true for all LAs at all locations.
      2. complications arising:
         a. epinephrine itself may have subliminal blocking action.
         b. epinephrine is usually packaged with anti- oxidant and at acid pH. Antioxidant can be neurotoxic, and low pH renders LA less penetrating, therefore less effective.
   F. Metabolism--little intact LA is eliminated from the body.
      1. esters--hydrolyzed by tissue and serum cholinesterases (non-specific).
      2. amides--oxidized by mixed-function oxidase system, of hepatic ER.

7. Differential Fiber Blockade: Early papers and most pharmacology texts report that smaller nerve fibers are blocked "before" larger diameter fibers by LA drugs. "Before" almost certainly means earlier during the development of the block, but when a steady- state (absolute) block has been achieved, single impulses in the larger fibers are often more inhibited than those in the smaller ones (Figure 6).

   It is unlikely that an absolute differential block, short of a total one, is ever reached under these "clinical" conditions. `During onset of block of a nerve containing many fiber types, we observe functional activities being lost in a consistent sequence: pain, temperature, touch, proprioception, and skeletal muscle tone and voluntary tension. Since both sensory and motor functions are

dependent on frequencies of trains of impulses, the modulation of AP frequency rather than the absolute loss of impulses may correspond to the functional deficits observed clinically.

Sensations from more proximal regions are blocked earlier and recover later than those from more distal segments. This reflects the diffusion of anesthetic through the somatotopically organized peripheral nerve.

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1.8: Antiinflammatory Drugs

Inflammation is mediated in part by prostaglandins produced by the cyclooxygenase pathway. NSAIDs inhibit this pathway and serve as combined anti-inflammatory, anti pyretics, and analgesics. Because NSAIDs are generally nonspecific and exert numerous side effects, there is great interest in more specific therapeutics such as selective COX-2 inhibitors and anti-cytokine agents.

Prostaglandins: Physiologic and Pathologic Functions

All cells in the body have the capacity to synthesize prostaglandins. In response to inflammatory stimuli arachidonic acid (AA) is separated from plasma phospholipids by phospholipase A2. Cyclooxygenase metabolizes AA to the cycloendoperoxide prostaglandin H2 (PGH2), which is then converted to either PGD2, PGE2, PGF2α, PGI2(prostacyclin) or TXA2 (thromboxane) by appropriate enzymes (i.e. thromboxane synthase in platelets, prostacyclin synthase in endothelial cells).

The prostaglandins exert numerous physiologic and pathophysiologic functions :

- Physiologic: temperature homeostasis, bronchial tone, cytoprotection (gastric and renal mucosa), intestinal mobility, myometrial tone, semen viability (some prostaglandins like PGE1 have anti-inflammatory effects), renin secretion
- ƒ Pathologic: fever (aberrant hypothalamic thermoregulation), asthma (airway responsiveness and immune hyperreactivity), ulcers (loss of cytoprotection), diarrhea (intestinal mobility), dysmenorrhea (myometrial tone), inflammation, bone erosion, pain (thought to be caused by PGD2)

Specific functions of prostaglandins in the context of inflammation include:

- ƒ PGI2: inhibits platelet aggregation, vasodilatation, vascular permeability (edema)
- ƒ PGE2: pain, hyperalgesia, heat, vasodilatation, bronchoconstriction, synergistically act with other pro-inflammatory mediators (histamine, complement, LTB4)
- ƒ TXA2: promotes platelet aggregation, vasoconstriction, bronchoconstriction

Cyclooxygenase

There are two forms of cyclooxygenase (COX) enzymes: COX-1 and COX-2. Though COX-1 and COX-2 catalyze the same reaction, their expression, functions, and properties are markedly different.

	COX-1	COX-2
Expression	Constitutive (activated by physiologic stimuli)	Inducible by pro-inflammatory stimuli (LPS, TNFα, IL-2, IFNγ, etc)
Tissue Localization	Ubiquitous	Inflammatory and neoplastic sites (small amounts in kidney, uterus, ovary, CNS [neocortex, hippocampus])
Role	"**Housekeeping**" and Maintenance	Pro-inflammatory and mitogenic functions (? Neuronal plasticity)

COX-1 produces PGE2, PGI2, and TXA2 in platelets, GI mucosa, vascular endothelium, and the kidney. The housekeeping functions of these prostaglandins include maintaining renal and gastrointestinal blood flow (cytoprotection), regulation of vascular homeostasis, renal function, intestinal mucosal proliferation, and platelet function.

Pro-inflammatory functions of COX-2 produced prostaglandins include pain, fever, leukocyte proliferation, and inflammation. COX-2 produces prostaglandins at sites of inflammation (in macrophages, in synovial tissue of rheumatoid arthritis joint). Mitogenic functions of COX-2 produced prostaglandin include renal genesis and reproduction.

The goal of pharmacologic anti-inflammatory therapy has been to inhibit COX-2 produced prostaglandins. Non-specific inhibition of COX-1 results in gastrointestinal and platelet side effects. Recent data on the toxicity of COX-2 selective nsaids illustrate that this is an overly simplistic view. The magnitude of the COX-2 problem is still unclear at this writing, but it will be considered at various points in this discussion.

lipoxygenases

There is an entire additional pathway of arachidonic acid metabolism by enzymes called lipoxygenases. 5-lipoxygenase is not present in all tissues but is limited to neutrophils, eosinophils, monocytes, and certain mast cell populations. Lipoxygenases produce leukotrienes (e.g. LTB4, LTD4), which are potent bronchoconstrictors and chemotactic agents. Leukotrienes have important roles in asthma, glomerulonephritis and inflammatory bowel disease. (Refer to the Asthma case.

NSAIDs (Non-steroidal anti-inflammatory drugs)

Most NSAIDs are polycyclic carboxylic acid derivatives with relatively low pKa values. NSAIDs are often classified on the basis of their chemical structure (see Figure 1).

- ƒ Salicylates: aspirin; diflunisal, 5-aminosalicylate, sodium salicylate, magnesium salicylate, sulfasalazine, olasalzine
- ƒ Acetic acids: indomethacin, diclofenac, sulindac, etodolac, ketorolac, tolmetin
- ƒ Propionic acids: ibuprofen, naproxen, fenoprofen, ketoprofen, flurbiprofen, oxaprozin
- ƒ Fenamic acids: meclofenamate, mefenamate
- ƒ Enolic acids (oxicam class): piroxicam
- ƒ Ketones: nabumetone (converted to 6-naphthylacetic acid in liver)

NSAID General Pharmacodynamics

All NSAIDs (except aspirin) act as reversible, competitive cyclooxygenase inhibitors. They block the hydrophobic channel by which the substrate arachidonic acid accesses the enzyme active site. Aspirin covalently modifies and destroys the cyclooxygenase enzyme.

The ultimate function of the NSAID is to inhibit COX-2, preventing generation of proinflammatory eicosanoids, and thus limiting the extent of inflammation and adverse signs and symptoms.

- ƒ All NSAIDs have a ratio of inhibition of COX-2 / inhibition of COX-1. The higher the ratio, the more specific the therapeutic effect and fewer GI or platelet effects.
  - NSAIDs with high ratio (100:1 to 1000:1) are COX-2 Selective (Coxib)ƒ
- Despite the benefits of NSAIDs, they only provide symptomatic relief, as the underlying pathophysiology or injury generally is unaffected.

NSAIDs have three primary therapeutic effects:

- ƒ **Analgesia**
- ƒ **Anti-pyrexia** (decreasing hypothalamic PGE2)ƒ
- **Anti-inflammatory**

NSAIDs are also used as anti-thrombotics. Since they impair platelet aggregation, they prolong bleeding time, and function as anticoagulants. The COX-2 specific inhibitors do not exert anti-thrombotic effects. Other functions of NSAIDs include inhibition of:

- Superoxide generation
- ƒ Lysosomal enzyme release
- ƒ Neutrophil aggregation / adhesion
- Lymphocyte function
- ƒ Cytokine release (IL-6)

Indications for Specific NSAIDs

Please refer to Table 1 to find indications common to each structural class of NSAID. See below for COX-2 selective drugs.

Non-selective NSAIDs are used as analgesics for moderate pain of musculoskeletal and inflammatory origin (headaches, dysmenorrhea, osteoarthritis, rheumatoid arthritis, gout, surgical pain, tendonitis, and bursitis). NSAIDs also function as anti-inflammatory agents in many of these conditions and ulcerative colitis. Aspirin anti-platelet effects are used for MI and stroke prophylaxis. Acetaminophen (technically not an NSAID) has no anti-inflammatory activity but is widely used as an analgesic and anti-pyretic.

NSAID Pharmacokinetics

As stated previously, NSAIDs are weak organic acids. They generally have

- Efficient GI absorption (nearly complete)
- Low first pass hepatic metabolism
- Small volumes of distribution but extensive protein binding (>95%) which slows the rate at which these drugs cross the capillary wall and penetrate tissue.
- Accumulation in cells at sites of inflammation (acidic NSAIDs are preferentially sequestered in inflamed synovial tissues)
- Efficient enterohepatic and renal excretion
- Variable half lives (the lower the pKa generally the shorter the half-life)

Plasma Elimination Half Lives: Another method to classify NSAIDs (besides structure)

- Short Half Life (< 6 hours): more rapid effect and clearance Aspirin (0.25-0.33 hrs), Diclofenac (1.1 ± 0.2 hrs), Ketoprofen (1.8 ± 0.4 hrs), Ibuprofen (2.1 ± 0.3 hrs), Indomethacin (4.6 ± 0.7 hrs)
- Long Half Life (> 10 hours): slower onset of effect and slower clearance Naproxen (14 ± 2 hrs), Sulindac (14 ± 8hrs), Namebutone (26 ± 5 hrs), Piroxicam (57 ± 22 hrs) (also COX-2 Selective Inhibitors)

Important Drug Interactions:

- Displace other drugs from plasma protein binding sites:
  - Anti-coagulants (warfarin): Bleeding risk greatly increased
  - Phenytoin: (increased CNS toxicity, difficulty dosing)
  - Oral Hypoglycemics: (increased hypoglycemic risk)
  - Methotrexate: (increased toxicity)
- Anti-Hypertensives (diuretics, beta blockers, ACE inhibitors): NSAIDs may blunt the anti-hypertensive effects and cause renal decompensation or renal failure in patients receiving these drugs
- Methotrexate, digoxin, aminoglycosides, lithium: NSAIDs inhibit clearance
- Probenecid: renal clearance of NSAIDs reduced by probenecid
- Antacids: absorption of some NSAIDs inhibited by antacids
- Aspirin: may lower levels of other NSAIDs, but side effects are additive

NSAID Toxicity

NSAIDs affect the gastrointestinal, CNS, hepatic, renal, hematologic, and skin systems. NSAIDs also cause allergic phenomena.

Gastrointestinal Toxicity of NSAIDs

Prostaglandins suppress gastric acid secretion and help maintain gastric mucosal barrier, thus providing gastrointestinal protection. Because of their suppression of prostaglandin synthesis NSAIDs tend to cause gastric irritation, exacerbate peptic ulcer disease, cause mucosal lesions (superficial to penetrating ulcers), and may induce bleeding.

NSAID induced gastropathy typically includes gastritis, gastric bleeding, mucosal and subepithelial damage, and erosions, which may progress to ulcerations and perforations.

- Occult blood loss may occur and massive GI bleeding may also develop.
- Symptoms including pain, dyspepsia, nausea, vomiting are frequent
- Overall, there is poor correlation of these symptoms with endoscopic findings.
- NSAID induced gastric toxicity causes great morbidity, requiring annual care expenditures of $4 billion, and causes 7500 deaths per year.
- FDA estimates that ulcers, bleeding or perforation occur in 1 to 2 % of patients using NSAIDs for three months and 2 to 5% of those using them for one year.
- Specific risk factors for NSAID induced GI toxicity include: higher NSAID doses, older age, concurrent steroid use, history of peptic ulcer disease

Treatment of NSAID Induced GI Toxicity

- Discontinuation / Avoidance of NSAIDs / Use “Gastroprotective” NSAIDs
- Take medication with meal
- Pharmacologic

- H2 Receptor Antagonists (high doses of ranitidine)
- Proton Pump Inhibitors (omeprazole)
- Misoprostol (PGE1 analog which restores cytoprotective effects)
- Sucralfate

- COX-2 Specific NSAIDs – use now called into question (see discussion below)
  - Reduce risks of ulceration, bleeding, perforation vs. nonselective NSAIDs

CNS Toxicity:

CNS toxicity includes headache, confusion, tinnitus (aspirin), dizziness, mood alteration and depression, and aseptic meningitis (particularly in SLE patients). Aspirin is linked toReye's Syndrome (below).

Hepatic Toxicity:

NSAIDs may cause asymptomatic elevations of liver enzyme, or transaminitis (most common with diclofenac. Acute idiosyncratic hepatitis has also been reported. Reye's Syndrome is an often fatal combination of microvesicular steatosis and hepatic encephalopathy thought to be caused by the administration of aspirin to children post febrile viral infection (VZV, influenza B). For this reason, aspirin is generally not given to children.

Nephrotoxicity:

In healthy individuals with normal kidneys PGE2 and PGI2 play no role in controlling renal function. Under certain conditions of localized circulatory stress often associated

with elevated levels of angiotensin II and catecholamines, locally produced vasodilating prostaglandins become essential to the maintenance of adequate renal function.
Inhibition of these vasodilating prostaglandins decreases renal renal blood flow and GFR and may cause tissue injury. Patients at most risk include those with congestive heart failure, volume depletion, chronic renal disease, liver disease and those patients receiving diuretics. Nephrotoxic effects of NSAIDs include edema, high blood pressure, increased creatinine, and hyperkalemia. Hypertension and edema have been seen with both selective and non-selective NSAIDs. NSAIDs may ultimately cause renal ischemia or failure, nephrotic syndrome, interstitial nephritis (most commonly with fenoprofen), renal papillary necrosis, and calculi.

Hematologic Effects:

An effect on platelet aggregation persists for as long as the NSAIDs are present. They should be discontinued for a long enough period before surgery to permit complete excretion (i.e., 4 to 5 times the half-life). Aspirin should be discontinued 7-10 days prior in order to give sufficient time to make new platelets. NSAIDs can interfere with the therapeutic antiplatelet effect of aspirin if the drugs are taken together.

Blood dyscrasias such as agranulocytosis, thrombocytopenia and aplastic anemia are rarely associated with NSAIDs.

Cutaneous and Hypersensitivity Effects:

NSAIDs can cause urticaria, bronchospasm, anaphylaxis, and erythema multiforme. A wide variety of skin reactions most frequently reported with piroxicam and benoxaprofen (withdrawn from market) include photosensitivity reactions, exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

NSAID-induced hyperreactivity: In patients with aspirin allergy, NSAID exposure is more likely to cause ocular and nasal congestion, severe bronchospasm, and possible anaphylactic reaction. Possible etiology is shunting of arachadonic acid to lipoxygenase pathway leading to increased synthesis of bronchoconstrictor leukotrienes.

- ƒ Samter's triad: aspirin allergy / hypersensitivity higher in patients with nasal polyps, bronchial asthma, and rhinitis (sinusitis).
- ƒ Occurs in 10% of asthmatics.

Other Toxicities Unique to Aspirin:

Aspirin overdose can cause metabolic acidosis but also stimulates the medullary respiratory center, causing respiratory alkalosis.

Salicylism refers to a syndrome of chronic, excessive aspirin dosing characterized by nausea, vomiting, diarrhea, and dehydration, hyperventilation, headache, tinnitus, visual and auditory disturbances, confusion, stupor, and delirium.

COX-2 Selective Inhibitors: The Coxibs

The coxibs represent a subset of NSAIDs that preferentially block the hydrophobic substrate channel in COX-2. Currently approved coxibs include celecoxib and valdecoxib. These drugs are approved for rheumatoid arthritis, osteoarthritis, pain, primary dysmenorrhea, and familial adenomatous polyposis (they decrease the number and size of adenomas in patients with history of FAP).

- The potential therapeutic role of coxibs in Alzheimer's disease is being studied (COX-2 is the predominant isoform in the neocortex and hippocampus).
- ƒ COX-2 is induced by LH prior to ovulation and at delivery. COX-2 selective inhibitors may have a role in preventing preterm labor and delivery.

Effects and Toxicities of COX-2 Selective Drugs:

Rofecoxib was recently withdrawn from the market when an increased rate of myocardial infarction and stroke was seen in a placebo-controlled trial for FAP. There is now concern that all COX-2 inhibitors may increase the risk of thrombotic events during chronic therapy. Evidence for this has now appeared in one trial of valdecoxib and one study of celecoxib. A possible explanation may be that coxibs can inhibit endothelial prostaglandin synthesis but lack a compensatory effect on platelet thromboxane synthesis. The situation is currently unsettled, but it seems prudent to restrict the use of these drugs to patients for whom the potential benefits are clearly worth the risk. The risk vs. benefit may be difficult to characterize: COX-2 inhibitors were designed in part to limit the gastrotoxicity associated with NSAIDs. Although the rate is lower, events still occur and symptoms are similar. However, events are less serious (i.e. less perforation) vs. conventional NSAIDs.

Platelets only express COX-1, so COX-2 has no effect on platelet function or the production of TXA2. The implications of this are:

- ƒPatients on MI prophylaxis still need aspirin even if they are on a COX-2 selective inhibitor
- ƒCoxibs unlike NSAIDs may be administered safely with warfarin.

COX-2 is present in the kidney and knock out mice show kidney inflammation and papillary changes. This suggests that chronic treatment with coxibs may impair normal renal development and function. Some evidence suggests that inhibition of COX-2 may generate problems with wound healing and angiogenesis.

Glucocorticoids

Glucocorticoids are 21-carbon steroid molecules with a variety of physiologic and metabolic effects. Cortisol (hydrocortisone) is the principal circulating glucocorticoid in humans. Glucocorticoid activity depends on presence of a hydroxyl group at carbon number 11 in the steroid molecule. Cortisone and prednisone lack glucocorticoid activity until converted to cortisol and prednisolone in the liver (by reducing the C=O at carbon 11 to a hydroxyl). All glucocorticoid preparations marketed for topical use are 11 beta hydroxyl compounds, thus eliminating the need for hepatic transformation.

Commonly used glucocorticoids are characterized short, medium, and long acting on the basis of ACTH suppression after a single dose (of equivalent anti-inflammatory activity to 50 mg of prednisone). The relative potency of the glucocorticoids correlates with their affinity for the glucocorticoid receptor. The observed potency of a glucocorticoid is a measure not only of the intrinsic biological potency but also the duration of action. However, relationships between the circulating half-life and duration of action, and between circulating half-life and glucocorticoid potency are imprecise.

Drug	Plasma Half Life	Biologic Half Life	Glucocorticoid Potency	Equivalent Dose (mg)	Mineralocorticoid Activity
Cortisol	80–115 min	8-12 hrs	1	20	Yes
Prednisone	3.4–3.8 hrs	18-36 hrs	4	5	No
Methylprednisolone	2.3–4.0 hrs	18-36 hrs	5	4	No
Dexamethasone	1.8–4.7 hrs	36-54 hrs	30	0.75	No

It has been suggested that the duration of action of a glucocorticoid is not determined by its presence in the circulation. Steroids pass through the cell membrane and enter the cytoplasm where they bind to a specific cytoplasmic receptor protein. These glucocorticoid receptors belong to a superfamily of DNA binding proteins that affect gene regulation. Glucocorticoids alter transcriptional regulation of specific cytokine genes. Therefore, the effects of glucocorticoids continue to act within the cell after glucocorticoids have disappeared from the circulation (note disparities in plasma and biologic half lives).

Therapeutic Effects of Glucocorticoids

Glucocorticoids are anti-inflammatory and immunosuppressive agents. Glucocorticoids administered at pharmacologic doses inhibit the action of COX-2 by decreasing the expression of COX-2 and the cytokines that activate it. They limit the available pool of arachidonic acid substrate by inhibiting phospholipase A2 (via the lipocortin pathway). These combined actions create a powerful anti-inflammatory effect because virtually all eicosanoid pathways are inhibited. Because of this profound and global suppression, glucocorticoids are indicated for a number of autoimmune and inflammatory conditions.

Effects of Glucocorticoids on Humoral Factors

- ƒMild decrease in immunoglobulin levels
- ƒDecreased RE clearance
- ƒDecreased synthesis of prostaglandins and leukotrienes

Type of Leukocyte	Effect of Glucocorticoids on Leukocyte: Movement	Function
Lymphocyte	▪ Circulating lymphocytopenia ▪ Depletion of recirculating lymphocytes ▪ Selective depletion of T lymphocytes	▪ Suppression of delayed hypersensitivity skin testing ▪ Suppression of lymphocyte proliferation to antigen ▪ Suppression of mixed lymphocyte reaction ▪ Suppression of natural cytotoxicity
Monocyte	▪ Circulating monocytopenia ▪ Inhibition of accumulation at inflammatory sites	▪ Blockade of Fc receptor binding ▪ Inhibition of IL1 production
Neutrophil	▪ Circulating neutrophils ▪ Accelerated release of neutrophils from bone marrow ▪ Blockade of accumulation at inflammatory sites	▪ Increase in antibody dependent cellular cytotoxicity
Eosinophil	▪ Circulating eosinopenia ▪ Decreased eosinophil migration	

Glucocorticoid Toxicities

Glucocorticoids exhibit a diverse array of toxicities (see Table). Recall that a condition of glucocorticoid excess is a Cushingoid syndrome.

System	Side Effect of Glucocorticoids
Endocrine	Hyperglycemia, hypokalemia, growth suppression, truncal obesity, hirsutism, impotence, menstrual irregularities
Cardiovascular	HBP, CHF
Musculoskeletal	fatigue, weakness, myopathy, osteoporosis, avascular necrosis
Immunologic	immunosuppression
Ophthalmic	cataracts, glaucoma
Gastrointestinal	PUD, pancreatitis
Neuropsychiatric	pseudotumor cerebri, alterations in mood, psychosis
Dermatologic	fragile skin, ecchymoses, impaired wound healing, acne

Steroid Withdrawal and Glucocorticoid Replacement

Because of suppression of the pituitary-adrenal axis by chronic glucocorticoid therapy, patients that undergo surgical procedures or acute medical illness should receive stress dose steroids generally equivalent to 300 mg of hydrocortisone administered as a split dose over a 24 hour period. Patients may require very slow and low reductions of steroids back to baseline to minimize the symptoms of steroid withdrawal, which include joint and muscle pain, nausea, lethargy, weight loss, and fever.

Anti-Cytokine Agents

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune and inflammatory disease that primarily attacks the joints. Autoimmune targeting of normal joint proteins results in inflammation with local release of cytokines, especially TNFα, growth factors, and interleukins, all of which induce COX-2 expression. Levels of TNFα, COX-2, and PGE2are markedly elevated in the

synovial fluid of affected joints. PGE2 binds to synovial cell receptors on and stimulates release of matrix metalloproteinases (MMPs) which directly damage joint tissue. TNFα also stimulates production of IL-1 and IL-6; these pro- inflammatory mediators along with COX-2 derived prostaglandins activate the surrounding endothelial tissue to recruit inflammatory cells.

The newest therapeutic agents inhibit the pro-inflammatory effects of the cytokines TNFα and IL-1. By limiting TNF activity, the generation of pro-inflammatory cytokines IL-1 and IL-6 is diminished. Three strategies have emerged: 1) creating monoclonal antibodies to the TNFα and IL-1 proteins, 2) solubilizing forms of the endogenous receptors of TNFα, and 3) making recombinant versions of endogenous receptor antagonist.

Agent	Target	Strategy	Comments	Indications
Etanercept	TNFα	Soluble TNF receptor	Fusion protein: the extracellular domain of TNFαR and Fc of human IgG1	RA Juvenile RA Psoriatic arthritis Ankylosing spondylitis Psoriasis
Infliximab	TNFα	mAb	chimeric IgG1 mAb with human Fc and murine Fab	RA (with MTX) Crohn's Disease Ank spondylitis
Adalimumab (D2E7)	TNFα	mAb	Human mAb	RA
Anakinra	IL-1	Block IL-1R	Recombinant IL-1R antagonist	RA

Comparison of Infliximab, Etanercept, and Adalimumab in rheumatoid arthritis:

- ƒInfliximab administered IV (by doctor); etanercept and adalimumab given subcutaneously (by patient)
- ƒInfliximab 3 mg/kg loading dose with similar doses at 2 weeks, 6 weeks, and then every 8 weeks thereafter. Etanercept 25 mg twice weekly or 50 mg weekly. Adalimumab 40 mg every other week.
- ƒInfliximab must be administered in combination with methotrexate. Etanercept and adalimumab may be monotherapy or may be combined with methotrexate.
- ƒAll reduce signs, symptoms, and structural damage (joint erosion on radiograph).

Anti-Cytokine Agent Toxicities:

The anti-cytokine agents blunt the immune response, and thus cause many side effects that result from immunosuppression (infections, and loss of tumor surveillance). The body's response to the foreign protein also poses risk of development of antibodies.

- Injection site reactions
- ƒHypersensitivity reactions (i.e. to murine protein)ƒ
- Opportunistic Infections
  - Tuberculosis
  - Fungi (Aspergillus)
  - Pneumocystiis carinii
  - Listeria
  - Bacterial Sepsis
- Lymphoproliferative Disorders
- Lupus like Syndrome
- Autoantibodies and Antibodies to drug
- Rare aplastic anemia, demyelinating syndrome

Future Applications of Anti-Cytokine Therapies

Because of the broad role of TNFα in disease, there is interest in applying these drugs to conditions as varied as vasculitis, myositis, GVHD, uveitis, CHF, sarcoidosis, psoriasis, ARDS, Still's disease, Wegener's syndrome, etc.

Pharmacology of the Eicosanoids –Summary of Important Drugs

Excerpted from Dudzinski, D. M. and Serhan, C.N. Eicosanoids: An Update on Biosynthesis, Actions, and Current Pharmacopoeia. *Inflammation* (in press).

Drug	Clinical Uses	Side Effects/Toxicities	Interactions/Contraind.	Notes
NSAIDS				
Aspirin (salicylate class)	Pain, headaches, platelet inhibition for stroke / MI prophylaxis	Aspirin hypersensitivity, aspirin-triggered asthma, Reye's syndrome, and NSAID effects below.	Increased absorption in presence of metoclopramide or caffeine; inhibition of valproate absorption	
Sulfasalazine; olsalazine; 5-aminosalicylate	Ulcerative colitis (mild to moderate, and maintenance of remission)	Salicylate hypersensitivity; diarrhea, nausea; headache; rash; blood dyscrasias; oligospermia; nephritis		Low bioavailability (2-15%) so compound remains in gastrointestinal tract and exerts topical activity.
Ibuprofen, naproxen, ketoprofen, flurbiprofen, oxaprozin, and fenoprofen (proprionic acid class)	Osteoarthritis, rheumatoid arthritis, dysmenorrhea, gout, moderate or surgical pain	NSAID allergies or hypersensitivity NSAID-induced gastropathy: risk of GI bleeding, ulceration, perforation, dyspepsia, abdominal pain, nausea, diarrhea Renal events: edema, risk of renal papillary necrosis, acute interstitial nephritis (with hematuria and proteinuria), reduced renal blood flow; Headache, tinnitus, dizziness, rash Borderline elevations of liver function tests	Contraindicated in patients with NSAID allergies, peptic ulcer disease, inflammatory gastrointestinal diseases, history of gastrointestinal disease, or GI bleeding; do not use in pregnant or nursing women. Caution in patients with heart failure, hypertension, renal disease, or severe edema. Risk of renal decompensation and/or abatement of anti-hypertensive/natriuretic effects in patients taking beta blockers, diuretics, and ACE inhibitors: monitor BP and fluid retention, consider using sulindac or raising dose of anti-hypertensive Absorption of some NSAIDs inhibited by antacids. Elevated risk of bleeding with warfarin. Aspirin administered concomitantly with other NSAIDs may lower levels of NSAID and cause additive side effects.	
Namebutone (ketone class)	Osteoarthritis and rheumatoid arthritis			Greatest selectivity for COX-2 of all NSAIDs. Hepatic transformation to 6-methoxynaphthylacetic acid. Hepatic metabolism route results in less risk of renal effects.
Meclofenamate, mefenamate (fenamate class)	Osteoarthritis, rheumatoid arthritis, primary dysmenorrhea			
Piroxicam (oxicam class)	Rheumatoid arthritis, osteoarthritis			Long half life, only single daily doses required
Indomethacin, sulindac, diclofenac, etodolac, (acetic acid class)	Rheumatoid arthritis, gouty arthritis, osteoarthritis, ankylosing spondylitis, tendonitis, bursitis			Indomethacin used to close patent ductus arteriosus (compared to use of prostanoid mimetics to maintain ductus arteriosus). Sulindac may be used safely in patients with renal disease
Ketorolac, tolmetin, (acetic acid derivative)	Short term (≤ 5 days) management of moderate acute or post-operative pain requiring analgesia at opioid level			May be administered parenterally. Concomitant use of ketorolac and probenecid is contraindicated.
	Seasonal allergic conjunctivitis, post-cataract extraction surgery anti-inflammatory agent	Burning and stinging, allergic reaction, corneal edema, ocular inflammation irritation, infections, xerophthalmia, headache.	Contraindicated in patients with evidence of corneal epithelial breakdown.	Risk of adverse corneal events in patients with complicated or repeated surgeries, diabetes, rheumatoid arthritis, or other ocular surface disease.

1.9: Vasoactive Drugs I

Hypertension & its Pharmacological Management

What constitutes "hypertension?"

	Systolic (mmHg)		Diastolic (mmHg)
Normal	<120	AND	<80
Pre-hypertension	120-139	OR	80-89
Stage I (moderate)	140-159	OR	90-99
Stage II (severe)	>160	OR	>100

Hypertensive emergencies (malignant hypertension) are defined as severe hypertension coupled with acute end-stage organ damage.

How common is hypertension?

Hypertension effects approximately 25% of the adult American population.

What are signs or symptoms of hypertension?

There are usually no symptoms or signs of hypertension, and thus it is called the "silent killer". Since humans are completely unaware of excessive blood pressure, it is only through measurements that it becomes detected. The exception is malignant hypertension, which can cause headache, congestive heart failure, stroke, seizure, papilledema, renal failure and anuria.

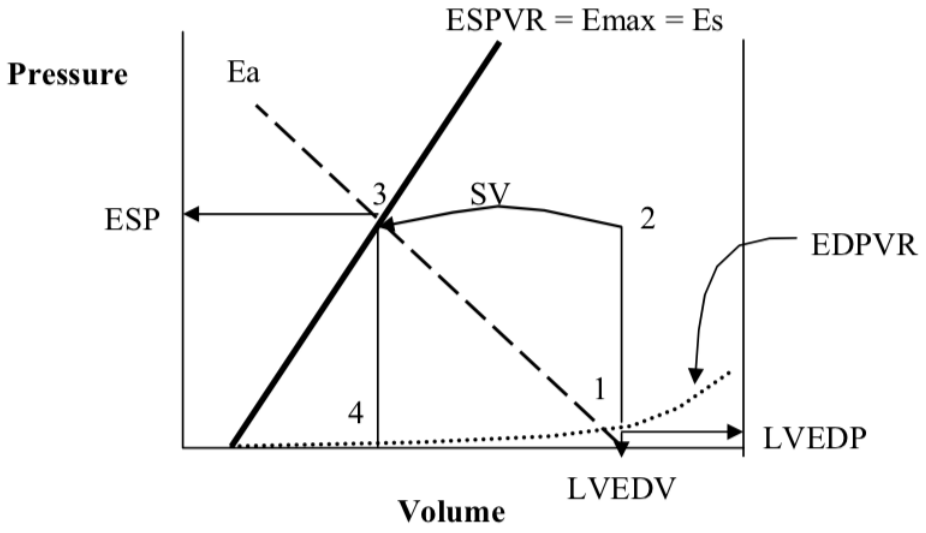
What are consequences of long-standing hypertension?

Long-standing hypertension causes accelerated atherosclerosis, which in turns leads to all of the biological fallout of this disease. Some consequences include: stroke, coronary artery disease, myocardial infarction, aneurysmal and occlusive aortic disease. Long-standing hypertension also causes the heart to remodel and undergo a process of hypertrophy (left ventricular hypertrophy or LVH). Hypertrophy can lead to diastolic dysfunction, which can lead to congestive heart failure (CHF) since the heart is too stiff to relax properly. (This will be covered in more detail in the next lecture.) The stiffened heart requires elevated filling pressures, and this can worsen the dysfunction. Long-standing hypertension can also cause the heart to dilate and lose its ability to pump during systole (systolic congestive heart failure). Lastly, the kidneys are injured by long-standing hypertension and this is a significant cause of renal failure in the U.S.

What causes hypertension?

Over 90% of hypertension in the U.S. is "essential" or idiopathic hypertension, i.e., without an identifiable cause. About 10% of hypertension is secondary to some identifiable cause such as steroids, renal vascular disease, renal parenchymal disease, pregnancy related, pheochromocytoma, Cushing's syndrome, coarctation of the aorta or primary hyperaldosteronism to name a few.

The physiological framework for understanding hypertension: Ventriculo-arterial coupling



Key:
1 = End diastole, just prior to LV contraction. The pressure at 1 is the left ventricular end diastolic pressure (LVEDP) and the volume is the left ventricular end diastolic volume (LVEDV)
(1 to 2 = isovolemic contraction)

2 = Opening of the aortic valve and beginning of ejection into the aorta
(2 to 3 is the volume ejected from the LV into the aorta which is the stroke volume (SV))

3 = End systole. The pressure at 3 is known as the end-systolic pressure (ESP). The aortic valve shuts just after 3.
(3 to 4 is isovolumic relaxation)

4 = Beginning of passive diastolic filling.
4 to 1 is diastolic filling along the dotted curve. This dotted curve is the end-diastolic pressure volume relation (EDPVR).

ESPVR = End-systolic pressure volume relation. This also called Emax or Es which stand for maximal elastance or elastance at end-systole, respectively. This characterizes the strength of the LV irrespective of the systolic load it faces.

Ea = Effective arterial elastance. This is characterizes the arterial tree and the load it presents to the LV during systole. Ea is primarily determined by arterial resistance but arterial compliance effects it too.

Ea and ESPVR “Couple” to exactly determine the stroke volume. In essence, the volume lost by one chamber is exactly equal to the volume gained by the other. The elastance of each chamber (heart and vascular tree) determines the pressure. The exact systolic and diastolic pressures that obtain are dependent on arterial properties (Ea), ventricular properties (ESPVR) and the filling state (LVEDV).

There are FOUR possible mechanisms for hypertension

1. The volume ejected from the LV can be too high. This could result from an excessive contraction during systole (a very high ESPVR). This mechanism is described in the medical literature but is not typical. A hyperdynamic circulation is thought to play a role in the hypertension seen in some young, otherwise fit African-American males.
2. The intravascular volume may be too high causing an excess of venous return, leading to an elevated LVEDV. The very full heart would then eject a large volume into the arterial tree thus leading to hypertension. The high intravascular volume could be caused by renal dysfunction with subsequent fluid retention, or it could be due to exogenous administration. There does seem to be a subset of patients that has an elevated intravascular volume Nevertheless, the excessive intravascular volume mechanism appears to occur infrequently since many newly diagnosed hypertensive patients actually have a contracted intravascular volume. The excessive intravascular volume mechanism also implies that the cardiac output would be elevated, but it is usually normal.
3. Excess venous return could also occur even with a reduced intravascular volume if thevenous tone were significantly elevated. This would cause a rise in the LVEDV even with a normal or low actual blood volume. Whether this occurs as a regular feature of hypertension is not known.

4. The effective arterial elastance (Ea) can be too high. This can occur either because the resistance is too high or because the compliance is too low. Many forms of hypertension are associated with an elevated arterial resistance. Furthermore, in older humans, the arterial tree becomes stiffer and less compliant. Thus, for a given stroke volume delivered into the arterial tree, the pressure goes up, especially the systolic pressure.

Rational pharmacotherapy of hypertension is based on the four mechanisms outlined above.

1. Reduce LV systolic performance (reduce the ESPVR): negative inotropes (beta-blockers (metoprolol, atenolol, propranolol) and calcium channel blockers (verapamil,diltiazem)).
2. Reduce blood volume and thus drop LVEDV: diuretics (thiazide – hydrochlorothiazide, loop diuretics – furosemide, bumetanide and potassium sparing diuretics – spironolactone, amiloride, triamterene).
3. Reduce venous tone and thus venous return: Central sympatholytics such as clonidine act to reduce overall sympathetic tone.
4. Reduce arterial tone (i.e. resistance) and thus reduce Ea: Effective arterial dilators include angiotensin converting enzyme inhibitors (ACE inhibitors – lisinopril, captopril), angiotensin receptor blockers (ARB's – valsartan, losartan), calcium channel blockers (nifedipine, amlodipine), potassium channel openers (minoxidil), nitric oxide donors (nitroprusside), alpha1 blockers (prazosin, terazosin, doxazosin), and mixed alpha and beta-blockers (labetalol)

Major Antihypertensive Drug Classes

(These descriptions are intended as a supplement to the more complete discussions in the text.)

Diuretics (thiazide, loop, and potassium-sparing diuretics).

- **Thiazide** diuretics such as hydrochlorothiazide and chlorthalidone are among the most commonly used drugs for treating hypertension. They inhibit reabsorption of Na and Cl in the distal tubule and lose effectiveness when GFR is low. Their initial effects are said to be mediated by decreasing intravascular volume, however (as mentioned above) most untreated hypertensives have contracted intravascular volume. Diuretics cause peripheral vascular resistance to fall through an unknown mechanism. Unfortunately thiazide diuretics have a number of undesirable metabolic effects such as hypercalcemia, hypokalemia, hyponatremia, hyperglycemia, hyperlipidemia, and hyperuricemia. These side effects often dictate which drugs to use. When thiazide diuretics are used in low doses, their side effects seem to be minimized.
- **Loop** diuretics such as furosemide inhibit the Na/K/Cl cotransporter in the ascending limb of the loop of Henle. They cause a very brisk diuresis, but their anti-hypertensive effects are actually not that strong. Acute intravenous administration of furosemide can cause venodilation by an unknown mechanism. Loop diuretics are often part of treatment for malignant hypertension and hypertension with hypervolemia (e.g., renal insufficiency). The metabolic derangements produced by these drugs (particularly hypokalemia, and hypocalcemia) can be profound. This class is not recommended as initial monotherapy for hypertension.
- **Potassium-sparing** diuretics such as spironolactone, amiloride, and triamterene are not as efficacious as thiazides or loop diuretics in reducing blood pressure, however, they do correct the potassium loss associated with thiazide and loop diuretics. Amiloride and triamterene inhibit the Na/proton exchanger in the distal and collecting tubules. Spironolactone inhibits the Na/K exchanger affected by aldosterone, and it is particularly effective in the face of hyperaldosteronism. If potassium-sparing diuretics are given to patients on ACE inhibitors, particular care must be taken since both classes cause elevations in serum potassium.

Sympatholytics (beta-blockers, mixed alpha and beta-blockers, alpha-blockers and central sympatholytics).

- **Beta adrenergic blockers** such as propranolol, metoprolol or atenolol are typical first-line agents for treating hypertension. They have negative chronotropic and negative inotropic effects. The acute effect of blocking beta-2 receptors is an increase in SVR, however chronic administration can decrease peripheral resistance, probably by decreasing plasma renin and angiotensin II. Unfortunately beta-blockers can elevate triglycerides and reduce HDL. In addition, they can produce glucose intolerance, impotence, and depression. In patients prone to bronchospasm (i,e., asthmatics), non-selective beta-blockers can theoretically worsen the problem, although the risks are somewhat overplayed. These side effects often dictate drug choices for the hypertensive patient.
- **Alpha-1 adrenergic blockers** such as prazosin, terazosin and doxazosin are effective at reducing sympathetic vasoconstriction and thereby reducing vascular resistance. These drugs are also useful for men who have benign prostatic hypertrophy because they can reduce bladder outlet obstruction. Unlike the beta blockers and thiazide diuretics, the alpha blockers have not been shown to decrease mortality. In fact, doxazosin caused an increase in congestive failure in the ALLHAT trial. Thus, the indications for these drugs in hypertension are currently unclear, and they are not considered first line treatments. Non-selective

alpha blockers such as phenoxybenzamine and phentolamine are not used for hypertension because they produce an excessive amount of reflex tachycardia. However, the profound alpha blockade possible with the non-competitive antagonist, phenoxybenzamine, has proven very useful in the treatment of pheochromocytoma. These patients are usually given alpha-blockade first and then beta-blockade to control the reflex tachycardia.

- **Central sympatholytics** such as clonidine stimulate central alpha-2 receptors and thereby reduce sympathetic outflow. These drugs are effective in decreasing heart rate, contractility and vasomotor tone, however, they cause sedation and are usually not first line therapies.
- **Mixed alpha and beta antagonists** such as labetalol.and carvedilol block both alpha receptors and beta receptors, so the reduction in blood pressure is usually not associated with reflex tachycardia. Labetalol is a very effective intravenous antihypertensive, but it is less frequently used chronically in its oral form. Carvedilol has had its primary use in the treatment of chronic congestive heart failure.

Vasodilators (calcium-channel blockers, direct arterial vasodilators, and sodium nitroprusside).

- **Calcium channel blockers** such as verapamil, diltiazem, nifedipine and amlodipine block L- type calcium channels and are effective arterial vasodilators. The dihydropyridine agents nifedipine and amlodipine act primarily as vasodilators and have minimal direct effects on the heart. In contrast, verapamil and diltiazem act principally as negative inotropes and negative chronotropes, and thus decrease heart rate, contractility and cardiac conduction speed. In addition, they reduce vascular resistance. There is controversy over the use of short-acting dihydropyridines in patients with angina because they can cause reflex sympathetic activation and worsen ischemia. When using verapamil or diltiazem one has to expect a reduction in LV systolic function as well as a reduction in cardiac conduction. Thus, in patients with congestive heart failure of the systolic type or in those with a significant conduction defect, these drugs should be avoided. Verapamil and diltiazem are synergistic with beta-blockers and the combination can cause severe bradycardia, heart block or pump dysfunction.
- **Direct arterial vasodilators** such as minoxidil and hydralazine have relatively limited use. Neither has much effect on venous tone. The mechanism of action of hydralazine is not known. Minoxidil appears to increase potassium conductance in vascular smooth muscle, and the resultant hyperpolarization reduces calcium entry. Both drugs can cause reflex tachycardia (particularly minoxidil) and fluid retention. These side effects can be managed with the addition of a beta-blocker and/or a diuretic. Neither drug is effective for sustained periods. They are usually reserved for the short-term treatment of refractory hypertension, especially in patients with renal failure. Each of these drugs has a unique side effect: hydralazine can cause a lupus-like syndrome (cf. Drug Allergy case), and minoxidil can produce hair growth (and is sold for the purpose!).
- **Sodium nitroprusside** breaks down non-enzymatically to form nitric oxide. It is an extremely potent arteriolar and venous dilator that is used intravenously for rapid control of hypertensive crises and for blood pressure control during operations. Reflex increases in heart rate and contractility usually require treatment with beta blockers.

Renin-angiotensin system (RAS) blockers comprise two broad categories: angiotensin converting enzyme inhibitors (ACE inhibitors) and angiotensin type 1 receptor blockers (ARB's).

- **ACE inhibitors** like captopril, enalapril, and lisinopril decrease the conversion of angiotension I to angiotensin II (ATII). This reduces peripheral vascular resistance and promotes both natriuresis and hyperkalemia, since a reduction in ATII leads to a reduction in aldosterone. ACE also breaks down bradykinin, so inhibiting this enzyme can increase bradykinin levels and cause more vasodilation. ACE inhibitors have been shown to reduce morbidity (and possibly mortality – see below), and their relatively benign side-effect profile makes them frequent choices for first-line or monotherapy. Of note, ACE inhibitors are associated with a definite improvement in renal function in patients with diabetes and it has been shown that renal injury due to long-standing diabetes is reduced. Diabetics who do not have a contraindication for this class of drugs should be taking them for renal protective purposes. ACE inhibitors are associated with a 5-10% incidence of dry cough, probably caused by the elevated bradykinin levels. For patients who have reduced renal perfusion pressure (e.g., renal artery stenosis), ACE inhibitors can cause renal dysfunction or renal failure. (Patients with bilateral renal artery stenosis have high levels of endogeneous angiotensin II which is used to maintain glomerular filtration and ACE inhibitors disrupt that compensatory process.) Finally, ACE inhibitors are associated with a rare, but potentially fatal, angioedema of the airway. .
- **Angiotensin receptor blockers (ARB's)** like losartan and valsartan cause arteriolar vasodilation by blocking the effects of angiotensin II at the angiotensin Type I receptor. Since the mechanism is essentially the same as for the ACE inhibitors, the indications and contraindications are the same. The blockade is downstream, so bradykinin is not elevated, and this class of drugs is not associated with a cough.

Treating Hypertension

As a first principle, one should always couple any chemical therapy with lifestyle modifications (maintaining ideal body weight, engaging in aerobic physical exercise, eating a healthy diet low in saturated and total fats, limiting sodium intake and reducing alcohol intake). Each of these lifestyle modifications has been shown to reduce blood pressure modestly. These modifications are inexpensive and pose very little risk. Compliance remains the primary trouble with these methodologies. As a second principle, additional risk factors for coronary artery disease and stroke should be aggressively managed in all patients with hypertension. In particular, patients should be counseled on smoking cessation, lipid reduction and diabetic management. When these diseases occur in combination, the probability of end-organ damage goes up significantly and careful management of each of the co-morbidities is all the more important.

Does treating hypertension ameliorate the long-standing negative consequences of having hypertension?

There is overwhelming evidence that normalization of the blood pressure (using a variety of therapies) is very effective in reducing end-organ damage such as left ventricular hypertrophy (LVH), myocardial infarction, stroke and renal failure. There are studies addressing each particular end-organ and its responsiveness to reductions in blood pressure.

Have certain drugs been shown to reduce the morbidity and mortality due to hypertension?

Thiazide diuretics and beta-blockers have been shown to reduce the risk of stroke, coronary disease and overall mortality from cardiovascular disease in patients with hypertension. Other drugs used to treat hypertension are being studied at the present time and the mortality benefit they offer is being clarified. For example, ACE inhibitors likely reduce the risk of stroke, coronary disease and major cardiac events and death from cardiovascular causes.

Do physicians do a good job treating hypertension in the United States?

Not usually. On the whole, physicians are adequately treating less than 50% of patients with hypertension in the United States today. Despite being “easy to treat”, significant numbers of patients do not have their hypertension under adequate control.

What is the best initial therapy for the newly diagnosed hypertensive patient?

Therapeutic interventions usually begin with lifestyle modifications for the first six months to one year. If this does not rectify the situation, then one moves to diuretics – particularly thiazide diuretics. If the diuretic is not fully successful, then one can add a sympatholytic such as a beta-blocker. Thereafter, vasodilators such as calcium-channel blockers, ACE inhibitors, or ARB’s are instituted. Thiazide diuretics or beta-blockers are considered by many to be first line agents in the treatment of hypertension because they are inexpensive and have proven efficacy in reducing overall mortality. Unfortunately, the side effects of these drugs are troubling to some patients, and this may decrease compliance. For this reason, many patients are started early on more expensive drugs like ACE inhibitors. The long-term effects on morbidity and mortality are still being determined, and what is considered “first- line therapy” is likely to be a moving target in the coming years. The concept of stepped care is very important in the treatment of hypertension. If one therapy fails to achieve the targeted blood pressure, one adds an additional therapy. In general, giving small doses of two or more antihypertensives from different classes can cause additive or synergistic effects on blood pressure while minimizing side effects. In most cases this is preferable to giving a larger dose of a single drug.

Demographic factors

Patients of African descent are more responsive to diuretics and calcium-channel blockers than to beta-blockers or ACE inhibitors. A notable exception is the previously mentioned young African-American who may do well on beta-blocker therapy due to a “hyperdynamic circulation”.

Elderly Patients are said to respond quite favorably to diuretics and calcium-channel blockers. However, due to their frequent conduction system disease, many of these patients need to be watched carefully when they are introduced to beta-blockers. Beta-blockers and diuretics reduce mortality in patients with isolated systolic hypertension (very common in the elderly).

Hypertensive crisis (malignant hypertension).

This is an uncommon form of acute severe hypertension that can rapidly progress to stroke, MI, renal failure, or encephalopathy. These patients are admitted to the Intensive Care Unit for invasive hemodynamic monitoring and careful reduction of their blood pressure with fast- acting potent vasodilators such as sodium nitroprusside.

Disease processes which are affected by anti-hypertensive drugs:

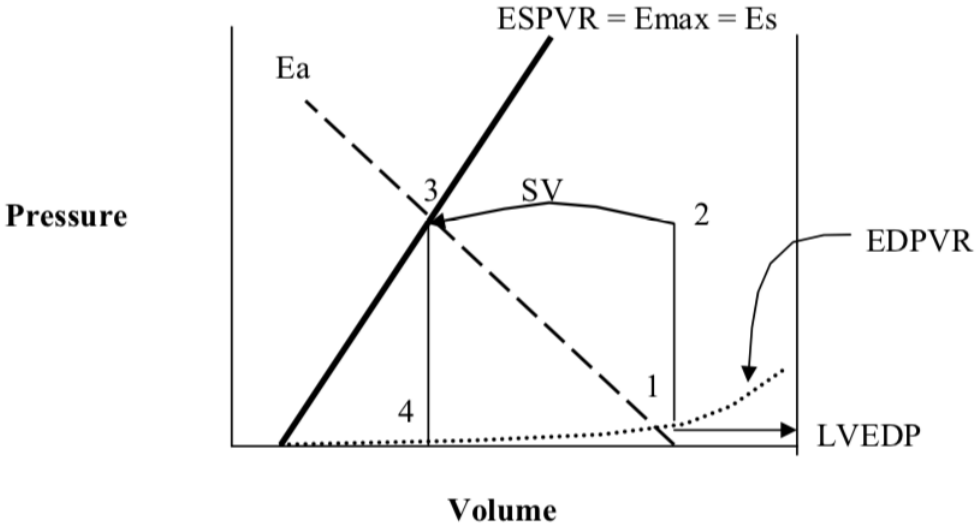
- Diabetes – Beta-blockers and thiazide diuretics may make glycemic control difficult. ACE inhibitors can protect the kidney.

- Coronary Artery Disease – Beta-blockers offer a mortality benefit (in general). Short-acting calcium channel blockers can worsen ischemia.
- Congestive Heart Failure (compensated vs. un-compensated) – Beta-blockers offer a mortality benefit as do ACE inhibitors. Beta-blockers should not be used in uncompensated CHF.
- Hyperlipidemia – Beta-blockers and thiazide diuretics may affect lipid profile unfavorably.
- COPD/Asthma – Beta-blockers need to be used with caution.
- Peripheral Vascular Disease (with Symptoms) – Beta-blockers need to be used with discretion.
- Renal Artery Stenosis (bilateral vs. unilateral) – ACE inhibitor or ARB's are relatively contraindicated.
- Cardiac Conduction Defects – Beta-blockers, diltiazem and verapamil can exacerbate conduction defects.
- Benign Prostatic Hypertrophy – Alpha-1 blockers can provide symptomatic improvement.
- Depression – Beta-blockers may exacerbate.
- Raynaud's Syndrome – Beta-blockers may exacerbate.
- Renal Failure – ACE inhibitors may cause a reduction in renal performance
- Pregnancy – ACE inhibitors and ARB's are contraindicated.
- Aortic Stenosis – Vasodilators need to be introduced with caution.
- Hyperuricemia (Gout) – Thiazide diuretics may increase uric acid levels.

1.10: Vasoactive Drugs II - Heart Failure

Congestive Heart Failure& its Pharmacological Management

The physiological framework for understanding CHF: The Pressure-Volume Loop of the LV



Key:

1 = End diastole, just prior to LV contraction. The pressure at 1 is known as the left ventricular end diastolic pressure (LVEDP)
(1 to 2 = isovolemic contraction)

2 = Opening of the aortic valve and beginning of ejection into the aorta
(2 to 3 is the volume ejected from the LV into the aorta which is the stroke volume (SV))

3 = End systole. The pressure at 3 is known as the end-systolic pressure (ESP). The aortic valve shuts just after 3.
(3 to 4 is isovolumic relaxation)

4 = Beginning of passive diastolic filling.
4 to 1 is diastolic filling along the dotted curve. This dotted curve is the end-diastolic pressure volume relation (EDPVR).

ESPVR = End-systolic pressure volume relation. This also called Emax or Es which stand for maximal elastance or elastance at end-systole, respectively. This characterizes the strength of the LV irrespective of the systolic load it faces.

Ea = Effective arterial elastance. This is characterizes the arterial tree and the load it presents to the LV during systole. Ea is primarily determined by arterial resistance but arterial compliance effects it too.

Ea and ESPVR "Couple" to exactly determine the stroke volume.

What is meant by "congestive heart failure" (CHF)?

Congestive heart failure simply means that the pulmonary blood volume is expanded and, therefore, the pulmonary circulation is congested with blood. The congestion arises because of elevated left ventricular end-diastolic pressure (LVEDP). An elevated LVEDP is a hallmark of uncompensated congestive heart failure. Common symptoms include shortness of breath, fatigue, orthopnea and paroxysmal nocturnal dyspnea (PND). Once a patient is treated for CHF they may become asymptomatic. This is termed compensated CHF and does NOT imply that the underlying disease process has gone away! It is entirely reasonable and even common for patients who are well medically managed to have a markedly reduced ejection fraction (EF) yet be capable of most normal activities. This handout pertains primarily to LEFT ventricular failure. Although RIGHT ventricular failure occurs, it is less common and not the focus of this handout.

How long do people live if they have congestive heart failure?

For all comers, the mortality is 50% in five years. However, if a patient is symptomatic, despite treatment, one-year mortality can approach 50%. Approximately five million people have congestive heart failure (CHF) in the United States at any given time. The great majority of these patients have primarily left ventricular failure.

There are FIVE main physiologic ways to get CHF

1. Decrease the strength of the LV and thereby decrease its ejection – this causes the LVEDP to rise (CHF). This is characterized by a reduction in the slope of the ESPVR line.
   Acute causes include: myocardial ischemia, myocardial infarction, sepsis syndrome, myocardial contusions, excess beta blockers or excess calcium channel blockers.
   Chronic causes include: dilated cardiomyopathy due to certain viral illnesses, multiple myocardial infarctions or large territory myocardial infarctions, excessive alcohol consumption and certain chemotherapeutic agents such as adriamycin. Prolonged pressure overload (hypertension and aortic stenosis) also causes a weak heart after initially causing hypertrophy. With continued overload, the compensation of hypertrophy progresses to a failing myocardium (a low ESPVR)
2. Provide much too much venous return (and hence filling) to the LV– this causes the LVEDP to rise (CHF).
   Acute causes include: excessive volume administration or large increased in venous tone as with some vasoconstrictors. Exercise causes a large increase in venous return and if the LV cannot eject all that it receives, there is an elevation in the LVEDP (CHF).
   Chronic causes include profound chronic anemia, longstanding mitral regurgitation or aortic regurgitation. Poor compliance with diuretic therapy or with high salt intake can cause a rise in the plasma volume which in turn elevates the venous return.
3. Alter the passive filling characteristics of the LV such that a normal filling volume is associated with a high pressure – this causes the LVEDP to rise (CHF). This is calleddiastolic CHF.
   Acute causes include: myocardial ischemia
   Chronic causes include: prolonged pressure overload (hypertension and aortic stenosis) which cause this problem by initially causing hypertrophy of the cardiac muscle. The thickened myocardium does not relax well. Certain infiltrative diseases like amyloidosis cause diastolic CHF.
4. Present an enormous load to the LV such that it cannot eject well – this causes the LVEDP to rise (CHF). This is characterized by having a severe increase in the arterial load and is shown by a steep increase in the slope of Ea, the effective arterial elastance.
   Acute causes include: pheochromocytoma and catechol release, very poorly controlled hypertension.
   Chronic causes include: pressure overload with aortic stenosis or long term severe hypertension

5. Reduce the function of the heart with other problems:
   Acute causes include: severe tachycardia or bradycardia, pericardial tamponade, acute ventricular septal defect, acute mitral regurgitation.

Regardless of the cause of CHF, certain management strategies pertain to all patients.

Salt restriction and fluid restriction are regular features of any congestive heart failure management program. Secondly, any underlying cause should be treated aggressively.
For example, hypertension is a very frequent precipitator of congestive heart failure and should be managed aggressively. Similarly, coronary artery disease should be managed with the full armamentarium available for that disease. Patients having profound anemia and who suffer from high output congestive heart failure should have their anemia and underlying pathology managed. For patients who are drinking excessive alcohol and have alcohol- induced cardiomyopathy, treating the underlying alcoholic behaviors are essential. Additional risk factor management clearly includes smoking cessation, lipid optimization, optimizing diabetes management and so on.

We will now consider how to treat CHF for the first four mechanisms outlined above.

In almost all cases of symptomatic CHF, the LVEDP is too high. This is responsible for the symptom of shortness of breath. When the pulmonary blood volume is congested with blood, the lungs become stiff and the work of breathing goes way up. There are multiple acute ways to reduce the LVEDP:

- **Improve LV systolic performance (improve the ESPVR):** inotropes (digoxin, milrinone, dobutamine). Digoxin is the hallmark drug for augmenting systolic performance. Although digoxin certainly helps in the symptomatic management of systolic heart failure, it does not confirm a mortality benefit.

- **Improve arterial loading conditions (reduce Ea):** arterial dilators such as angiotensin converting enzyme inhibitors (ACE inhibitors – lisinopril, captopril), and angiotensin receptor blockers (ARB's – valsartan, losartan). An important feature of ACE inhibitors is their mortality benefit. All patients with CHF who do not have contraindications should be taking ACE inhibitors. For patients who cannot tolerate ACE inhibitors, angiotensin receptor blockers are very likely to be an adequate substitute and their mortality benefit is being studied presently. Other drugs that reduce Ea include hydralazine, minoxidil and nitroprusside. These drugs do not confer a mortality benefit.
- **Improve the diastolic filling characteristics of the LV:** All underlying causes such as myocardial ischemia should be treated.
- **Reduce the blood volume and thus drop the LVEDP:** diuretics (loop diuretics – furosemide, bumetanide and potassium sparing diuretics – spironolactone). Of the diuretic therapies, only spironolactone has been shown to have a mortality benefit in treating patients with CHF.

The Secondary Physiologic Response to LV Failure.

The failing LV precipitates a host of secondary neuroendocrine events which are well described in figure 23-10 from Golan.

Image removed for copyright reasons. See Fig. 23-10 in Golan.

Management of secondary neuroendocine effects.

It is the correction of neuroendocrine abnormalities (elevated renin, angiotensin II, and aldosterone) that is most likely responsible for prolonging the lives of patients with CHF. Remodeling is the process that the left ventricle undergoes when it is insulted either by chronic unfavorable loading conditions or chronic neuroendocrine "siege." It involves a change in ventricular mass or dimension without a corresponding change in the number of ventricular myocytes. The functional left ventricle first begins to hypertrophy, then begins to dilate, and finally becomes fibrotic. The exact mechanisms that cause remodeling are unclear but the neuroendocrine effects seem to be responsible. It is currently thought that reducing the neuroendocrine effects of CHF is what leads to longer lives for those patients having CHF. This may explain why ACE inhibitors, ARB's, spironolactone (blocks aldosterone) and beta-blockers (block renin production) all confer a mortality benefit.

The use of beta-blockers is, paradoxically, one of the fundamental treatments for systolic congestive heart failure. These drugs offer a definite mortality benefit.

Beta-blockers are well known to depress LV systolic function (i.e. reduce ESPVR) and thus appear counterintuitive in managing congestive heart failure. However, beta-blockers have been found to offer an important mortality benefit to patients with congestive heart failureincluding those with severely decreased LV function. It is most likely that beta-blockers interfere with the secondary neuroendocrine events (such as an activated sympathetic nervous system and elevated renin) associated with congestive heart failure. The beta-blockade should be started in all patients who do not have significant contraindications to these drugs. Presently metoprolol and carvedilol are the two drugs with a proven mortality benefit. Patients with symptomatic congestive heart failure (uncompensated CHF) are poor candidates for these drugs. However, once their symptoms are resolved (with diuretics and ACE inhibitors along with other management strategies), the introduction of beta-blockers is reasonable. Initial doses are usually low and titrated upwards, as tolerated.

Knowing that Beta-Blockers offer a mortality benefit, do physicians use beta-blockers as the data suggest?

No. For reasons that are not entirely clear, physicians often deny patients beta-blockers.

Severe Decompensated CHF.

In the case of severe, Class IV/Stage D CHF (see appendix), patients are often admitted to the hospital for IV therapy using inotropes such as Digoxin, Dobutamine or inodilators such asMilrinone or Amrinone These drugs treat symptoms of CHF, but do not offer a mortality benefit. In fact, chronic therapy with some of these drugs can actually increase mortality. They are only used as a "bridge" to more definitive therapy or until resolution of the precipitating event can be accomplished. In patients with acute severe decompensated CHF, a number of highly invasive therapies exist. Intra-aortic balloon pumping (IABP) offers a bridge to cardiac transplantation. Many patients with dilated cardiomyopathies die due to malignant dysrhythmias. Patients with dilated hearts and severely reduced ejection fraction have a survival benefit with automatic implantable cardiac defibrillators (AICD's).
Lastly, with severely reduced ejection fractions and cardiac conduction defects, cardiac resynchronizing pacemakers offer symptomatic relief of CHF.

Appendix

The Clinical Characterization of CHF follows two schemes. One is older and based on symptoms (NYHC), the other is newer and based on disease progression (Stages A, B, C, D).

New York Heart Classifications of symptoms (NYHC I, II, III, IV)

- Class I: Patients with no limitation of activities and no symptoms from ordinary activities.
- Class II: Patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.
- Class III: Patients with marked limitation of activity; they are comfortable only at rest.
- Class IV: Patients who should be at complete rest; confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

The current Staging system deals with progression of the underlying disease.

Stage A: Patients at high risk for developing heart failure are those with:

  - Hypertension
  - Diabetes mellitus
  - Coronary artery disease (including being S/P myocardial infarction)
  - History of cardiotoxic drug therapy
  - History of alcohol abuse
  - History of rheumatic fever
  - Family history of cardiomyopathy

- **Stage B:** Pateints with known heart disease but who have never had symptoms of heart failure.
- **Stage C:** Patients with known heart disease with current or prior symptoms. Symptoms include:

  - Shortness of breath
  - Fatigue
  - Reduced exercise tolerance

- **Stage D:** Presence of advanced symptoms even with optimized medical care.

Appendix

All types of CHF start with an elevated LVEDP. There are multiple ways to get an elevated LVEDP. In each case below, the dotted line shows the circumstance prior to developing symptoms of CHF. Examples are from Suga and Sagawa.

Type I is from too much venous return from any cause
Type II is from too much ‘afterload’ (Ea is too high)
Type III is from diastolic dysfunction from any cause (unfavorable EDPVR)Type IV is from a weak LV (ESPVR is too low) from any cause

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1.11: Lipid Lowering Drugs - Hyperlipidemia and Atherosclerosis

Atherosclerosis: A chronic inflammatory disease characterized by enzymatic destruction of the normal arterial skeleton (largely elastin, collagen and smooth muscle), and replacement by disorganized collagen and elastin, cholesterol, and foam cells.

1. Afflicts all long-lived mammals.
2. Major risk factors:
   - Longevity
   - Hypertension
   - Diabetes – glycosylation of plasma proteins and arterial wall proteins
   - Dyslipoproteinemia
   - Cigarette Smoking
3. Homocysteinemia
   - Plasma homocysteine levels controlled by 3 genes related to methionine metabolism
   - High homocysteine is toxic to the endothelium and eventually atherogenic
4. Lp(a) lipoprotein
   - Levels variable and genetically determined
   - Inhibits tissue plasminogen activator and allows thrombus formation, which may be atherogenic
   - Increases likelihood of thrombosis and clinical catastrophe when atherosclerosis is present
5. Chronic bacterial infection
6. **Transmembrane Receptors on Mammalian Cells – Three Broad Classes**
   1. Receptors mediating transmembrane signaling (e.g. β receptor)
      - Serve to amplify the effect of a tiny concentration of ligand
   2. Receptors regulating intracellular substrate concentration (e.g., LDL receptor)
      - Bind tiny fraction of substrate
      - Rapid cholesterol turnover involves translocation into the cell
      - Receptors supply cholesterol, when needed, to rapidly growing cells
      - Normally strongly down-regulated except in liver
   3. Scavenger receptors (e.g., asialoglycoprotein receptor)
      - Receptors of normal catabolism
      - Remove certain “worn out” proteins from the plasma or extracellular fluid.
      - Oldest of these, the asialoglycoprotein receptor, was described more than 30 years ago. Removes liver proteins which have become desialated over time from the plasma.
      - Recently, more scavenger receptors described which scavenge oxidized albumin, oxidized LDL, and many others
      - SR-B1 is the HDL scavenger receptor
7. **Apolipoproteins**
   1. Proteins involved in the solubilization of fat for transport into and out of cells, from one place in the body to another.
   2. Many types, but most important are A1, B, and E
      - All three involved in cholesterol transport
      - A1 and B in triglyceride as well
      - ApoE has 3 common variants. Plays a critical role in cholesterol absorption, reverse cholesterol transport, and in inhibiting the accumulation in cells of certain hydrophobic proteins.
8. **Sterols**
   1. Distinguishing feature between plants and animals is not the presence or absence of chlorophyll, but rather the sterols they synthesize.
      - Major plant sterol is sitosterol
      - Major animal sterol is cholesterol
   2. Animals differ widely in how they absorb and excrete sterols.
   3. Disease sitosterolemia highlights importance to human health of sterol absorption and excretion.

4. Multiple sterol pumps regulate cellular and body sterol concentrations. These are energy-requiring ATP-dependent pumps.
   - ABC (ATP Binding Cassette) transporter family (recently discovered)
   - ABCA1 is a reverse cholesterol transporter in all cells. Defect causes Tangier disease (inherited HDL deficiency)
   - ABC5 and 8 are proteins which mediate sterol absorption by gut and sterol secretion by liver cells.

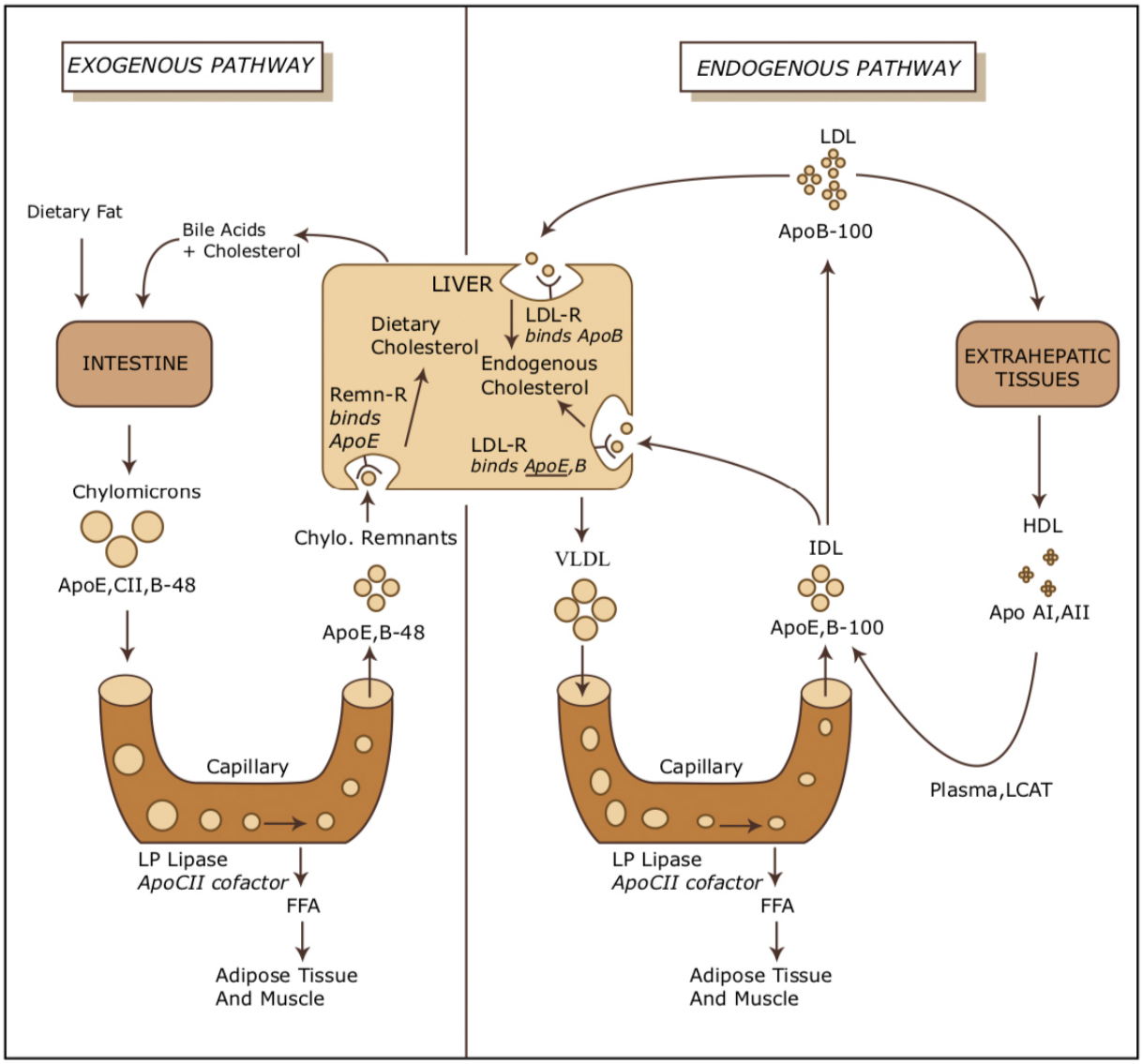


Figure by MIT OCW.

9.

A. **Exogenous Lipid Transport**

1. Cholesterol is variably absorbed in the small intestine and incorporated into **chylomicrons** by the gut mucosal cells.
   - Hydrophobic core = triglyceride (95%) + esterified cholesterol.
   - Amphipathic surface = Phospholipids, non-esterified cholesterol, and apolipoproteins (B48, C, E, A-I, A-II).
2. Chylomicrons travel via the lacteals and the thoracic duct to the venous circulation.
3. In muscle and adipose cells the triglyceride core is progressively hydrolyzed by **hormone sensitive lipase (HSL)** to form free fatty acids. This leaves a so-called **chylomicron remnant**. (Apo C obtained from circulating HDL is required for this step.)
4. Apo A and C are then removed and recycled to HDL, and the chylomicron remnants are taken up by hepatocytes. This process involves **LDL receptor-mediated endocytosis** and requires Apo E.

5. The liver may now excrete the cholesterol into bile (either unchanged or as bile acids), incorporate it into membranes, or resecrete it into plasma as lipoprotein cholesterol.

B. **Endogenous Lipid Transport: The VLDL-LDL Cycle (Apo B100 System)**

1. This cycle allows the hepatocyte to export triglycerides and cholesterol to peripheral tissues as VLDL. VLDL synthesis requires microsomal triglyceride transfer protein (MTP).
   - Hydrophobic core = triglycerides (55-80%) + esterified cholesterol (5- 15%)
   - Surface = phospholipids (10-20%), Apo B100, C, E
2. The triglycerides in hepatocytes come from two sources:
   - FFA synthesized de novo in liver
   - FFA and glycerol taken up from plasma and re-esterified. These are produced in adipose tissue and muscle by the action of HSL. HSL activity is regulated by adrenergic nerves and circulating catecholamines.
3. The cholesterol in hepatocytes also comes from two sources
   - Uptake of chylomicron remnants
   - Synthesized de novo by HMG CoA-reductase
4. Once the VLDL are circulating, the triglycerides may be hydrolyzed by HSL in plasma, and the fatty acids may be used to provide fuel for muscle cells, or re- esterified and stored in adipocytes. When the VLDL particle has been depleted of triglycerides it becomes a smaller, denser particle called a VLDL remnant orIDL.
5. Like chylomicron remnants, the triglyceride-poor VLDL remnants may reenter the liver. Unlike chylomicrons, the VLDL remnants may be further metabolized to become LDL.
6. The major determinant of LDL concentration in plasma is the number/activity of LDL receptors.
   - Present on nearly all cells and account for 70-80% of LDL catabolism.
   - Most LDL taken up by liver and the rest by peripheral tissues, adrenals and gonads (the latter need cholesterol for steroid synthesis).
   - Apo E is critical ligand for binding of lipid particles to LDL receptor

C. **Endogenous Lipid Transport: The HDL Cycle (Apo A-I System)**

1. This “antiatherogenic” cycle allows cholesterol to be scavenged from chylomicrons, VLDL and peripheral tissues by HDL particles.
   - Core = triglycerides (5-10%) + esterified cholesterol (15-25%)
   - Surface = phospholipids, + Apo A-I, A-II, C, E
2. Transport of cholesterol from tissue stores to HDL is mediated by ABCA1transporter. It is then esterified by lecithin-cholesterol acyltransferase (LCAT)to make bigger HDL particles. Esterified cholesterol is then disposed of by three primary mechanisms:
   - Transfer to VLDL, LDL, IDL, and chylomicron remnants by cholesteryl ester transfer protein (CETP) and subsequent endocytosis by hepatocytes.
   - Direct uptake in liver, adrenals, and gonads by the scavenger HDL receptor called SR-BI.
   - Hydrolysis by hepatic lipase

10. **Lipid Lowering Drugs**

1. **HMG-CoA Reductase Inhibitors: Statins**
   - **Mechanism of Action:** Structural analogs of 3-hydroxy-3-methylglutaric acid (HMG) that competitively inhibit HMG-CoA reductase, the rate-limiting step in cholesterol synthesis.
   - **Endogenous Regulation:** Hepatocytes maintain critical intracellular sterol pools. The genes for HMG-CoA reductase and the LDL receptor are under the transcriptional control of an SRE (sterol responsive element). When enough sterol is present in the cell, a repressor binds to the SRE inhibiting the transcription of enzyme and receptor and thus the production and recycling of more cholesterol.
   - **Physiologic Response to HMG-CoA Reductase Inhibitors:** By inhibiting cholesterol production, statins deplete sterol pools, “activating” the production of HMG-CoA reductase and the LDL receptor. The increase in LDL receptor levels results in the uptake of more IDL and LDL from the plasma. The net effect is that a new steady state is established with lower levels of plasma LDL. The most effective statins, such as atorvastatin and rosuvastatin can lower LDL by 60-70%.

- It is thought that apoB-100 synthesis (requisite for VLDL) may also be inhibited resulting in decreased VLDL production. This may be one factor that explains the fall in triglycerides from 10% to 30%.
- **Usage:** Statins are useful agents in all hyperlipidemias (except for homozygous LDL-R deficiency)
- **Adverse Effects:**
  1. Co-administration with triazole antifungals, and certain other drugs can virtually arrest cholesterol synthesis, but produces severe toxicity.
  2. As a group, the statins are quite tolerable with rare serious adverse effects. Some of those effects can include rhabdomyolysis and liver abnormalities.

2. **Bile Acid Binding Resins: Cholestyramine, Colestipol,**
   - **Mechanism of Action:** These are anion exchange resins that are not absorbed by the intestine. They exchange chloride anions for negatively charged bile acids. This results in increased excretion of bile acids.
   - **Physiologic Response to Bile Acid Binding Resins:** Since fewer bile acids are recycled, hepatocytes increase conversion of cholesterol to the production of bile acid. Again this depletes the intracellular sterol pool leading to upregulation of cholesterol synthesis enzymes and LDL receptor. Thus, hepatocyte pools are replenished as a result of increased production of cholesterol as well as enhanced uptake of LDL from plasma. A new steady state is reached with 10-25% less plasma LDL.
   - **Usage:** Resins are useful generally in hyperlipidemia (again except for homozygous LDL-R deficiency).
   - **Adverse Effects:** Since these agents are not absorbed, they are very safe. Gastrointestinal side effects include bloating, constipation, and abdominal discomfort. They also interfere with the absorption of many other drugs, although this problem can be minimized by appropriate timing of drug administration.
3. **Cholesterol absorption inhibitors: Sitostanol-ester margarine, Colesevelam, Ezetimibe**
   - **Mechanism of Action:** Sitostanol-ester margarine is created by saturating the B-ring of sitosterol to produce sitostanol and then esterifying it. Colesevelam is a non-absorbed synthetic soluble fiber. These agents inhibit cholesterol absorption by unknown mechanisms. Ezetimibe is thought to inhibit ABC sterol pumps in gut and liver, reducing the absorption of cholesterol and increasing its secretion into bile. It is absorbed and glucuronidated and undergoes enterohepatic recirculation.
   - **Physiologic response:** All of these drugs lower LDL by 10-15%. None has much effect on HDL or triglycerides.
   - **Usage:** The margarine is available over the counter. The other drugs are prescribed most often as adjunctive therapy. Ezetimibe is marketed in a combination product with simvastatin. The combination has additive effects, so a large decrease in LDL occurs with a lower dose of statin.
   - **Adverse effects:** Almost none.
4. **Niacin (Nicotinic Acid, Vitamin B3)**
   - **Mechanism of Action and Physiologic Response:** Niacin inhibits HSL in adipose tissue. This decreases the levels of free fatty acids in the plasma and the amount delivered to hepatocytes. As a result, less VLDL and triglycerides are synthesized. The reduction in plasma VLDL leads to a 10-15% decrease in LDL. Niacin also produces substantial increases in HDL, probably by decreasing the clearance of its major apolipoprotein, apoAI. Niacin is the only known lipid-lowering agent that has been reported to decrease Lp(a) levels.
   - **Usage:** This drug can produce a long-term improvement in both cardiovascular and total death rate. Niacin is very inexpensive and extremely useful for many patients. A multitude of annoying and occasionally dangerous side effects keep it from being a first-line agent for many.
   - **Adverse Effects:** Cutaneous flushing, headaches, pruritis, dermatitis. Some effects can be decreased by pretreatment with NSAIDs or use of sustained- release preparations. Niacin can cause hyperglycemia (and sometimes overt diabetes), hyperuricemia or gout, gastritis and GI bleeding. Serious liver abnormalities can occur when the drug is taken in large doses.
5. **Fibric Acid Derivatives: Gemfibrozil and fenofibrate**
   - **Mechanisms of Action and Physiologic Response:** These agents stimulate the nuclear receptor peroxisome proliferator-activated receptor α, increasing the expression of many proteins involved in lipid metabolism. They stimulate HSL in muscle and thus, catabolism of triglyceride rich lipoproteins such as VLDL. This can lower the level of triglycerides in the plasma by as much as 35%. Fibrates have also been reported to decrease production of VLDL in hepatocytes by inhibiting fatty acid synthesis. The decrease in VLDL usually leads to some decrease in LDL.

- Fibrates can increase increase HDL levels by 15-25%. This is due to both an increase in HDL production and an increase in reverse cholesterol transport.
- **Usage:** These drugs are used for hypertriglyceridemia, especially when HDL is low. They are also used in familial dysbetalipoproteinemia.
- **Adverse Effects:** GI distress, cholelithiasis, myositis, and interaction with warfarin and other albumin bound drugs.

11. **Non-drug Treatment: LDL apheresis**
    - Two systems for selective removal of LDL from plasma by vein to vein apheresis in U.S. market
    - Highly effective in lowering LDL, even with homozygous LDL receptor deficiency.
    - Produces arrest and regression of both xanthomas and atherosclerosis
    - Limited by cost and inconvenience
12. **Investigational Treatments**
    1. **ACAT (acyl cholesterol acyl transferase) inhibitors**
        - **Mechanism of Action:** Inhibits the enzyme that esterifies cholesterol for storage in tissues and prevents cholesterol absorption and its storage in arterial foam cells.
        - **Adverse effects:** Unfortunately, it also prevents storage in the adrenals and gonads
        - Research to identify selective ACAT inhibitors – an arterial selective inhibitor may appear soon
    2. **MTP (microsomal triglyceride transfer protein) inhibitors**
        - **Mechanism of Action:** Inhibits VLDL production by the liver and lowers cholesterol by preventing its exit from the liver in VLDL and LDL.
        - **Adverse Effects:** Produces fatty liver and threat of cirrhosis.
    3. **CETP (cholesterol ester transfer protein) inhibitors**
        - **Mechanism of Action:** Decreases reverse cholesterol transport from HDL to VLDL or IDL, thereby increasing HDL while decreasing LDL production.
    4. **Gene Therapy** – still far off

1.12: Neuropharmacology I - Drugs for Movement Disorders

Neuropharmacology I Parkinson's Disease and Movement Disorders

What are movement disorders?

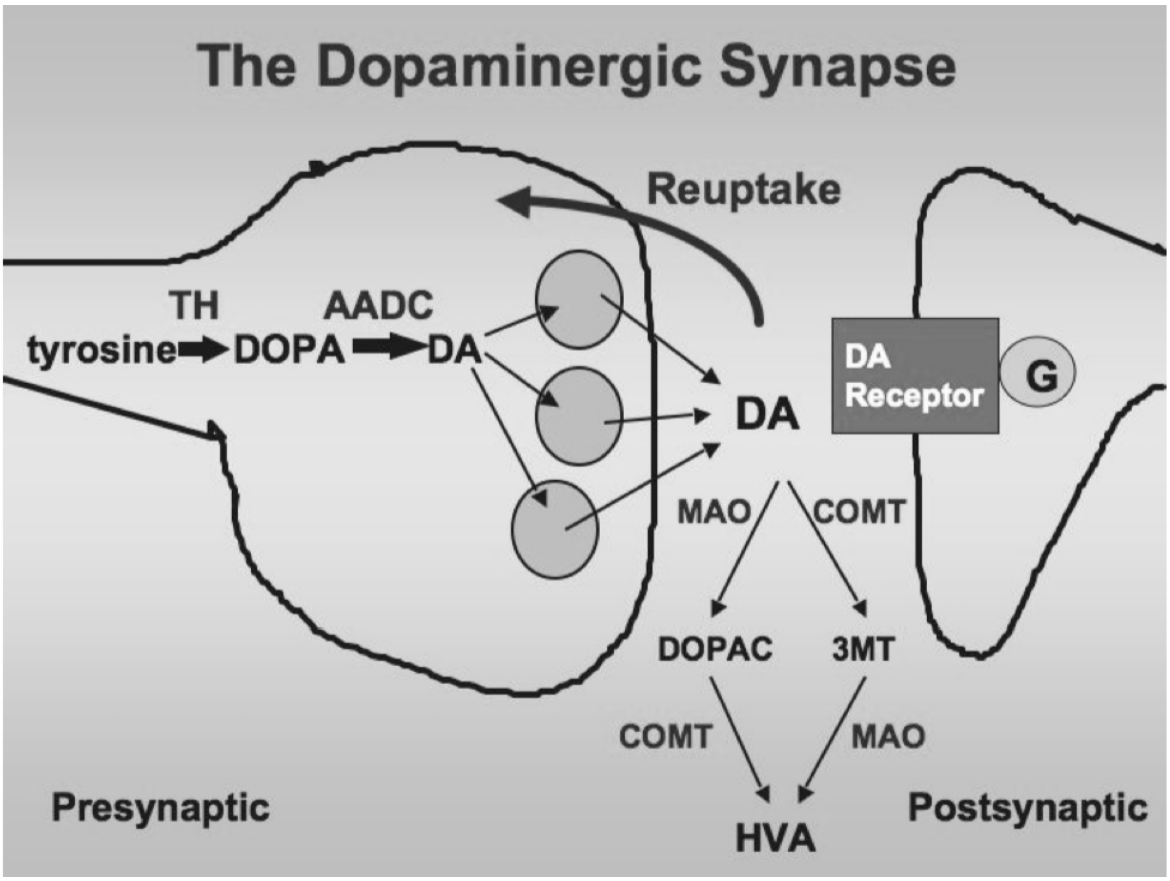
- These are a diverse group of neurologic disorders in which the normal functions of the motor system are impaired.
- Parkinson's disease is by far the most common disorder of movement, affecting >3% of individuals over the age of 65.
- Other common movement disorders include:
  - Tremor - rest, postural or intention
  - Chorea - typified by Huntington's chorea, an autosomal dominant disorder
  - Dystonia
  - Tic disorders - Tourette's syndrome

Pharmacological Approaches to Treatment of Parkinson's Disease

- Symptomatic treatments
  - most are based on dopamine augmentation
- "Neuroprotective" treatments
  - none presently proven
  - most current studies are based on "oxidative stress hypothesis"

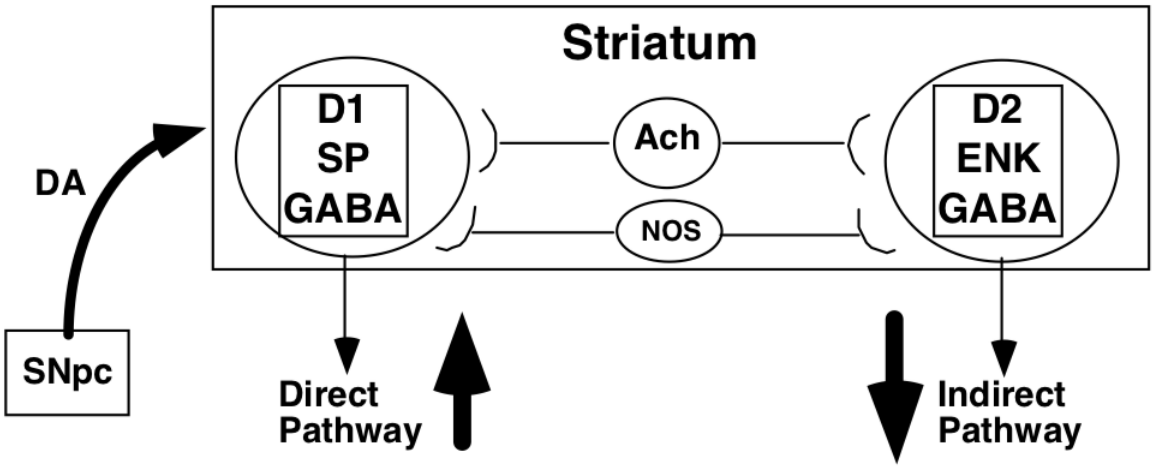
Parkinson's disease

- Cardinal signs of PD are:rest tremor
  - bradykinesia
  - rigidity
  - impairment of postural reflexes.
- Pathologically, PD is characterized by a loss of dopaminergic neurons from the substantia pars compacta (SNpc) in the midbrain, with the presence of Lewy bodies. This results in a loss of dopaminergic innervation of the striatum (caudate and putamen).
- The cause of most cases of Parkinson's disease is unknown. Rare families with genetic mutations causing Parkinson's have been identified, but most cases are sporadic. Increasing evidence implicates a) the protein alpha-synuclein and b) the role of environmental exposures, including pesticides.
- Some other, relatively rare disorders may give rise to similar clinical features - examples include striatonigral degeneration, progressive supranuclear palsy, and multiple cerebral infarcts. In general, these do not respond as well to medication as idiopathic PD



Biochemistry of Dopamine:

- Synthesis, storage and release
  - synthesized from tyrosine by tyrosine hydroxylase
  - stored in presynaptic vesicles by active transport mechanism (blocked by reserpine)
  - Released by calcium ion-dependent exocytosis
- Termination of action and catabolism
  - reuptake (blocked by cocaine, amphetamine)
  - catabolism - COMT and MAO
  - catabolic process may lead to the production of toxic free radicals
- Dopamine receptors
  - Pharmacological classification - based on effect on intracellular cAMP - D1 stimulates, D2 inhibits
  - Molecular cloning has revealed that there are 5 DA receptor proteins. These each have 7 transmembrane domains, and are part of the superfamily of G-protein coupled receptors
  - d1 and d2 are abundant in striatum
  - d5 (D1 type) and d3, d4 (D2 type) are primarily extrastriatal
- Dopamine and the etiology of Parkinsonism: (see Reference Section at the end of the handout).
  - Essential feature is the differential effect of DA on the output of striatal neurons
  - Cholinergic interneurons have an important regulatory role



The "Oxidative Stress" hypothesis

$$\text{Dopamine} + O_2 + H_2O \xrightarrow{MAO} \text{DOPAC} + NH_2 + H_2O_2$$

- Proposes that dopamine cell death is caused by the reactive free radicals produced by the catabolism of dopamine
- Suggests that treatments which reduce catabolism of dopamine should slow the progress of the disease

Treatment of Parkinson's disease

Levodopa

- Most effective agent for the treatment of the symptoms of PD
- Metabolic precursor of dopamine - acts by augmenting the effectiveness of remaining nigrostriatal neurons.
- Converted to dopamine by L-aromatic acid decarboxylase
- Almost always administered in combination with carbidopa, an inhibitor of the decarboxylase which does not cross the blood-brain barrier
- Onset of action is rapid - 30 - 60 min - but affected by gastric pH and emptying. Uptake from GI system and transport into brain by active mechanism - other aromatic amino acids compete
- Duration of action is variable, and is greatly affected by extent of disease. Declining duration of effect is the primary limitation of long-term levodopa therapy.
- Available in both standard (e.g., Sinemet® 10/100, 25/100, 25/250) and controlled-release formulation (e.g., Sinemet CR® 50/200)
- Adverse effects:
  - peripheral:
    - nausea and vomiting
    - hypotension
    - reduced by carbidopa
  - central:
    - psychosis
- Major limitation of long term use is the induction of "motor complications" – wearing off and dyskinesia.

Dopamine agonists

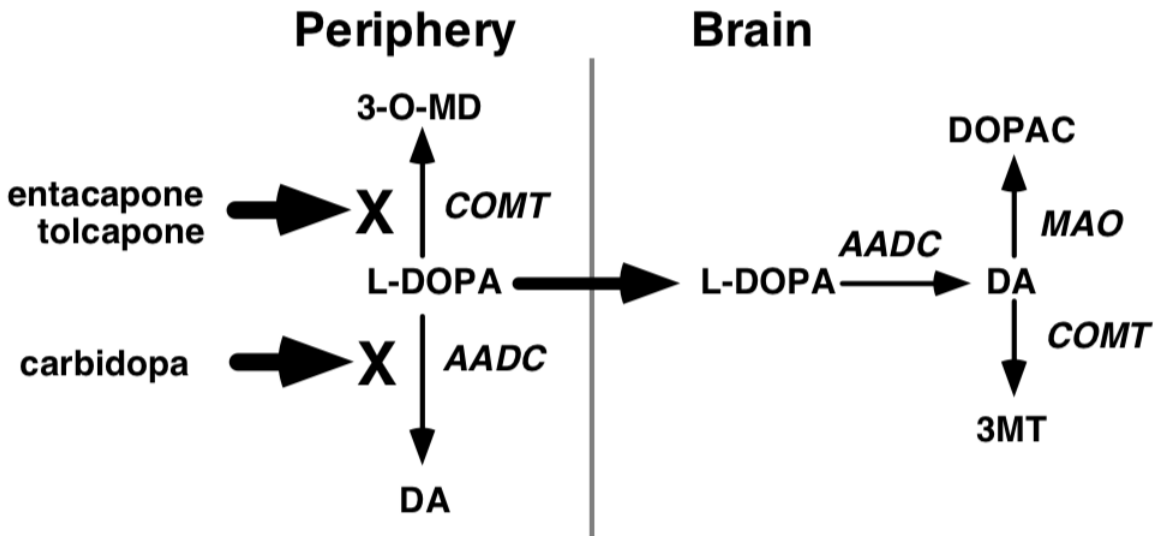
- Act directly at dopamine receptors. Four currently available:
  - older drugs: ergot derivatives
    - bromocriptine - d2,3,4 agonist, partial d1/d5 antagonist
    - pergolide - d1-d5 agonist

- newer drugs: non-ergots
  - pramipexole - selective d2/d3 agonist
  - ropinerol - selective d2/d3 agonist
- Newer drugs are much better tolerated than older agents, and have expanded the use of this category of medications

- Adverse effects
  - Most adverse effects related to dopaminergic actions and similar to levodopa
  - Pramipexole and Ropinirole produce less nausea
  - Both ergot and non-ergot drugs can lower blood pressure and cause peripheral edema.
  - Pergolide recently linked to cardiac valve fibrosis.
  - All of the agonists, as well as levodopa, can cause somnolence.
- Dopamine agonists vs. levodopa/carbidopa – which to use?
  - Recent evidence suggests that use of an agonist rather than levodopa leads to a reduced incidence of wearing off and dyskinesias
  - But this comes at a price – increased side effects (somnolence, hallucinations, peripheral edema).
  - There is also some recent evidence to suggest that the choice of drug may have an effect on the rate of progression of the disease – although interpretation of these studies remains controversial.

COMT inhibitors

- New class of drugs which act by inhibiting the breakdown of levodopa.
- When given alone have no effect on PD, but when combined with levodopa increase the duration of action



- Tolcapone
  - First agent released
  - Favorable kinetics – relatively long half life, both central and peripheral inhibition of COMT
  - After released to market, associated with 3 fatal cases of fulminant hepatic failure – use now limited to patients not responding to other treatments.
- Entacapone
  - No effect unless administered together with levodopa
  - Less favorable kinetics- short half life, does not cross blood brain barrier
  - A useful and relatively safe treatment for levodopa-associated wearing off.

Other Agents

- Selegiline: Irreversible inhibitor of the enzyme MAO-B, the subtype of MAO responsible for most central metabolism of dopamine. Symptomatic benefit arises from reduction in the rate of dopamine breakdown; magnitude of this effect is modest. Has been proposed that selegiline might have neuroprotective properties, slowing the death of dopaminergic neurons by

inhibiting the generation of toxic free radicals which are a byproduct of dopamine catabolism. Despite initial enthusiasm, a recent multicenter trial (the DATATOP study) did not demonstrate any protective effect of selegiline. Metabolized to amphetamine and methamphetamine - may cause insomnia. At doses used for PD (10 mg/day) does not inhibit MAO-A, and thus does not require dietary restrictions.

- Anticholinergics: Trihexyphenidyl is the most widely used agent in this class; all have similar profile of actions and adverse effects. Rarely satisfactory as primary therapy for PD, except in mild cases. Used most often as adjunct to levodopa. Side effects reflect antimuscarinic actions. Most significant are drowsiness and confusion, which are particularly prominent in the elderly and those with pre-existing cognitive impairment
- Amantadine: Developed as an antiviral; Mechanism uncertain, although has both anticholinergic and dopamimetic actions

Approach to the treatment of Parkinson's disease

- The treatment of early PD is changing rapidly with the availability of new drugs
- Levodopa/carbidopa is very effective, but there is increasing interest in delaying the use of this drug as long as possible in order to reduce later complications (wearing off and dyskinesias)
- New DA agonists are now used as primary therapy in many patients, especially younger onset.
- When wearing off and dyskinesias develop, both COMT inhibitors and dopamine agonists are useful

Dopamine receptor antagonists

- Several drugs which are antagonists of central dopamine receptors are widely used clinically. These are often grouped together as "antipsychotics" since their principle application is in the treatment of psychiatric illness.
- These drugs may be used to treat some types of movement disorders; in addition, their use may induce temporary or permanent abnormalities of movement.
  - More than a dozen members of this family are marketed.
  - They are distinguished by their potency at dopaminergic blockade, and the degree of sedation which they produce.

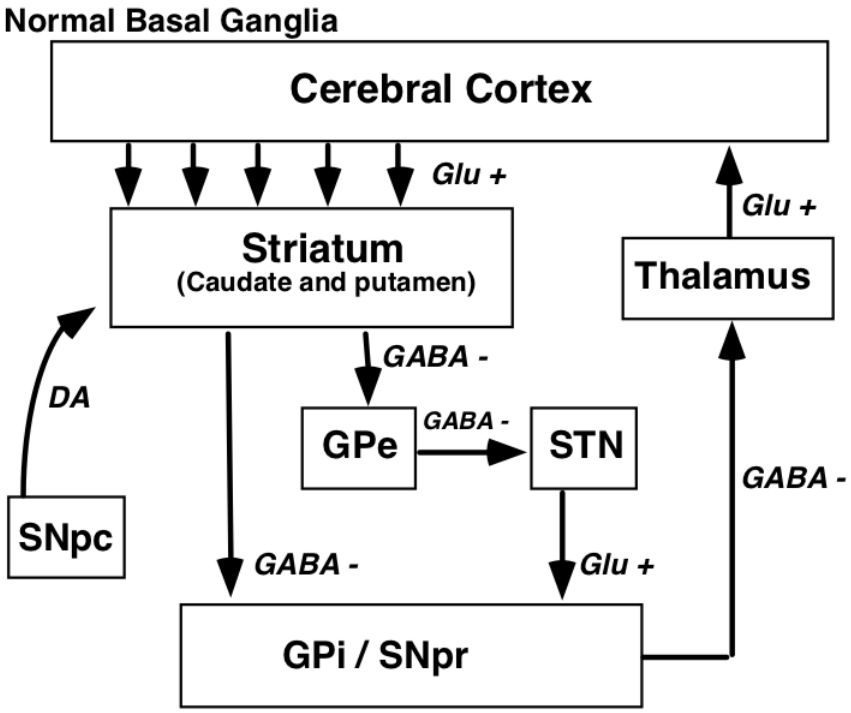
Examples of antipsychotics				
	trade name	typical daily dose	extrapyramidal effects	sedation
chlorpromazine	Thorazine	200-800	+	+++
thioridizine	Mellaril	150-600	+	+++
thiothixine	Navane	5-30	++	++
haloperidol	Haldol	2-20	+++	+

  - Primary clinical use is treatment of psychotic illness.
  - Also used for nausea, GI disorders (metaclopramide, prochlorperazine).
  - They can produce a variety of movement disorders:
  - All are capable of producing Parkinsonism or akathisia (a feeling of restlessness)
  - Each of them may cause dystonia (abnormal postures of the face neck, trunk, or limbs. This effect is usually sudden in onset and short-lived (hours to days). It often responds to anticholinergic treatments.
  - All may also produce tardive dyskinesia, a choreiform disorder that most often affects the face and mouth and may persist for years even if the medication is discontinued. This effect is difficult to treat.
  - Rarely, they may also cause "neuroleptic malignant syndrome" - rigidity, hyperthermia, obtundation, elevated serum CK. This most often occurs most often with high-potency, long acting phenothiazines. This may be fatal if untreated - dantrolene, bromocriptine useful

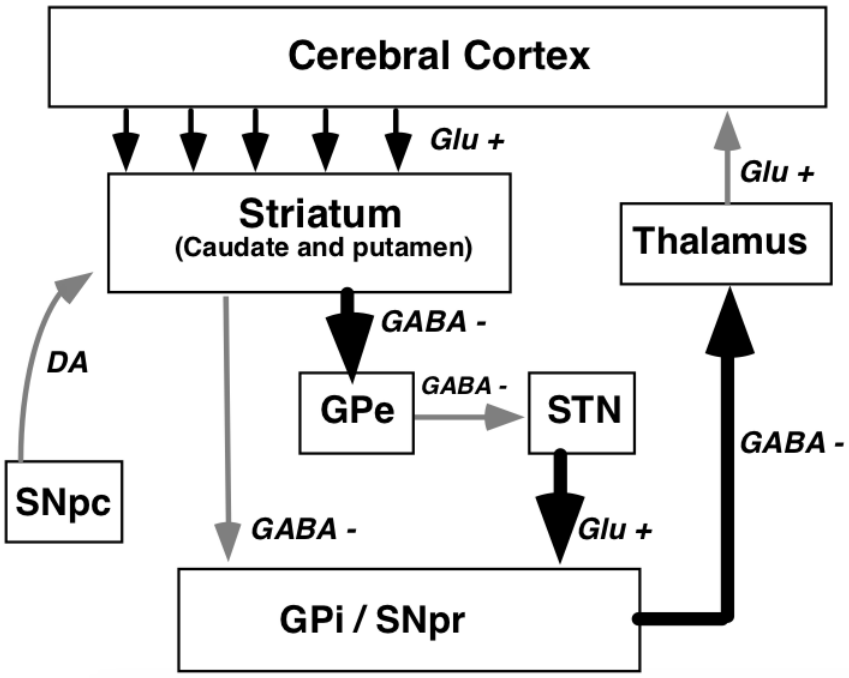
"Atypical" antipsychotics-

- New class of drugs which are dopamine antagonists but do not produce extrapyramidal side effects
- clozapine - d4 antagonist, effective in treatment of refractory psychosis. Numerous adverse effects, including neutropenia (which may be fatal) and seizures (1-2%). Requires intensive monitoring.
- Risperidone, olazepine, quetiapine - newer, less selective, but more favorable adverse effect profile.

Reference section: A model of the basal ganglia. For more information about these models, see Albin RL, Young AB, Penney JB (1989) The functional anatomy of basal ganglia disorders. Trends Neurosci 12:366-375.



Basal Ganglia in Parkinson's Disease. Dark lines reflect increased activity, while grey lines reflect decreased activity.



1.13: Nitric Oxide

The major objective of this lecture is to describe the effects of inhaling low levels of nitric oxide (NO) on the hemodynamic and gas exchange function of both the normal and diseased lung. Considerable attention will be paid to safety and hazards of inhaled NO therapy. During the past few years remarkable progress has been made in understanding the NO guanylate cyclase signal transduction system. NO has been given considerable clinical investigation in pulmonary artery hypertension and adult respiratory distress syndrome (ARDS) patients. This lecture concentrates on this area of clinical research.

Pulmonary hypertension with severe hypoxemia may complicate the care of patients with diseases such as chronic pulmonary hypertension, ARDS, chronic respiratory failure, congenital heart disease, and after cardiopulmonary bypass.

Numerous vasodilator therapies aimed at reducing pulmonary hypertension have been tested in these patients. Systemic vasodilation and hypotension occur with all the currently available intravenous vasodilators tested in dosages sufficient to reduce the pulmonary artery pressure. In addition, intravenous infusions of systemic vasodilators such as nitroprusside or prostacyclin (PGI2) markedly increase the venous admixture (1,2).

NITRIC OXIDE

In 1987, the gaseous molecule NO was identified as an endothelium derived relaxing factor (EDRF) (3,4). NO is an ideal local transcellular messenger because of its small size, lipophilic nature, and short duration of action (5) and its numerous functions in various tissues have been reviewed (6). In vascular endothelial cells, NO is synthesized from the terminal guanidine nitrogen of L-arginine and diffuses rapidly into subjacent vascular smooth muscle (7). There, NO binds to the heme iron complex of soluble guanylate cyclase. The resulting nitrosylheme activates guanylate cyclase, stimulating the production of cyclic guanosine 3',5'-monophosphate (cGMP) and subsequently relaxing vascular smooth muscle (7,8). When NO diffuses into the intravascular space, its biologic activity is limited by avid binding to hemoglobin. Interestingly, the nitroso vasodilators we have used for decades, such as nitroglycerin and nitroprusside, act by releasing NO (9).

Endothelium-dependent relaxation in pulmonary arteries occurs in response to a variety of physical and pharmacologic stimuli (10). Endogenous NO can be measured in the exhalation of rabbits, guinea pigs, and humans (11). In normal lungs, however, baseline pulmonary vascular tone is very low and the administration of acetylcholine or the addition of exogenous NO has little effect on pulmonary vascular resistance (12 - 14). In patients with pulmonary hypertension, on the other hand, acetylcholine infusion or NO inhalation can reduce pulmonary vascular resistance (12,13). It is possible that in some acute and chronic pulmonary hypertensive states, such as ARDS, or chronic pulmonary hypertension, the production of endogenous NO is impaired (15,16). This might produce further vasoconstriction and foster platelet aggregation (17). Evidence supporting this hypothesis is indirect at this time. Such patients may have an intact response to inhaled NO even though their response to intravenous acetylcholine is impaired (18).

NO Inhalation in ARDS

We hypothesized that inhaled NO should diffuse into the pulmonary vasculature of ventilated lung regions and cause relaxation of pulmonary vascular smooth muscle, thereby decreasing pulmonary hypertension in ARDS (19,20). Since the NO is inhaled, the gas should be distributed predominantly to well-ventilated alveoli and not to collapsed or fluid-filled areas of the lung. In the presence of increased vasomotor tone, selective vasodilation of well-ventilated lung regions should cause a "steal" or diversion of pulmonary artery blood flow towards well-ventilated alveoli, improving the matching of ventilation to perfusion and improving arterial oxygenation during ARDS. Such an effect would be in marked contrast to the effects of intravenously administered conventional vasodilators (such as nitroprusside, nitroglycerin, or prostacyclin). These intravenous agents also decrease PA pressure, but by nonselectively dilating the pulmonary vasculature, they augment blood flow to nonventilated areas, thereby increasing right-to-left shunting and reducing the PaO_2. Also unlike available intravenous vasodilators, inhaled NO, because it is avidly bound to hemoglobin and rapidly inactivated, should not produce systemic vasodilation.

Rossaint and coworkers compared the effects of NO inhalation (18 and 36 parts per million (ppm)) to intravenously infused prostacyclin in nine patients with ARDS (21). NO selectively reduced mean pulmonary artery pressure from 37 + 3 to 30 + 2 mmHg (mean + SE). Oxygenation improved due to a decreased venous admixture (QVA/Qt). During NO breathing, the PaO_2/FIO2 ratio increased from 152 + 15 mmHg to 199 + 23 mmHg. While the intravenous infusion of prostacyclin also reduced pulmonary artery pressure, mean arterial pressure and PaO_2 decreased as QVA/Qt increased. Subsequent reports documented that inhalation of lower concentrations of NO (< 20 ppm) effectively reduced pulmonary artery pressure and improved PaO2 (22 - 25). Even very

small inhaled concentrations (as low as 250 parts per billion NO) may be effective in some patients (26). Right ventricular ejection fraction may increase in some patients responding to inhaled NO, suggesting that the observed decreases of pulmonary artery pressure may be hemodynamically important (24,25).

A marked variation has been reported for the hemodynamic and respiratory effects of NO inhalation, both among patients and within the same patient at different times in their illness (22,27,28). It is possible that preexisting pulmonary disease as well as the concomitant administration of other vasoactive drugs may contribute to the observed variability. In general, the baseline level of pulmonary vascular resistance appears to predict the degree of pulmonary vasoconstriction reversible by NO inhalation. Those with the greatest degree of pulmonary hypertension appear to respond best to NO inhalation (22,28). Dellinger recently reported a dose-response analysis of a randomized trial of NO in 177 ARDS patients (29), a trial which was too small to obtain significant outcome data.

Tachyphylaxis has not been observed even when NO inhalation was continued for up to 53 days (21). Pulmonary artery pressure and PaO2quickly return to baseline values, however, after discontinuation of the gas. Occasionally, sudden discontinuation of inhaled NO can produce problematic pulmonary vasoconstriction and possibly bronchoconstriction (22,30,31). The reason for this is unclear. Possibly, the addition of exogenous NO may decrease NO synthase activity (32) or increase tissue cGMP phosphodiesterase activity.

The vasoconstrictor almitrine besylate has been given intravenously to enhance pulmonary vasoconstriction during NO breathing. This agent has further reduced Qs/Qt in ARDS in combination with NO inhalation (33).

NO Inhalation in Neonatal Respiratory Failure

At birth, there is a sustained decrease of pulmonary vascular resistance and an increase of pulmonary blood flow, in part due to increasing oxygen tensions. If this does not occur, persistent pulmonary hypertension of the newborn (PPHN) may result. Persistent pulmonary hypertension of the newborn is a syndrome characterized by an increased pulmonary vascular resistance, increased right-to-left shunting across the ductus arteriosus and foramen ovale, and severe hypoxemia. Extracorporeal membrane oxygenation (ECMO) is often used to support these infants, because conventional vasodilator therapy is limited by severe systemic hypotension and may reduce PaO_2 by increasing right-to-left shunting. It has been hypothesized that endogenous production of NO by the pulmonary vasculature might be decreased in PPHN. If so, then inhaled NO might provide an effective therapy for these severely ill infants (34, 35). Multiple small clinical studies of NO inhalation have been performed in neonates, infants, and children with various types of acute respiratory failure. In general, pulmonary hypertension is reduced and systemic arterial oxygenation is improved with inhalation of less than 20 ppm NO. Nitric oxide inhalation in babies with PPHN and hypoxic respiratory failure has been studied in randomized multicenter trials(36,37). As in adults, however, the response is variable. In the neonatal lung, the degree of improvement with NO appears to depend upon the presence of mature surfactant.

Laboratory studies of the neonatal pulmonary circulation have also documented that inhaled nitric oxide is an effective pulmonary vasodilator (38). Additionally, important experimental evidence is accumulating that the inhalation of nitric oxide attenuates chronic hypoxic pulmonary vascular remodeling of the pulmonary circulation (39,40). Conceivably, inhaled nitric oxide therapy might be used to limit the chronic pulmonary vascular changes which accompany neonatal acute respiratory failure.

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1.14: Neuropharmacology II - Anxiolytics and Antidepressants

Depression is a frequent problem, affecting up to 5% of the population. Common presentations include low mood, loss of energy, disinterest in activities. May also include weight loss, sleep disturbance, or psychosis. Should be considered in patients with atypical dementia and chronic pain

Diagnosis of Depression - DSM-IV

- Five of the following present during the same 2-week period and represent a change from previous functioning:
  - depressed mood
  - markedly diminished interest or pleasure in all, or almost all, activities
  - significant weight loss when not dieting or weight gain
  - insomnia or hypersomnia
  - psychomotor agitation or retardation
  - fatigue or loss of energy
  - feelings of worthlessness or excessive or inappropriate guilt
  - diminished ability to think or concentrate, or indecisiveness
  - recurrent thoughts of death, recurrent suicidal ideation or a suicide attempt
- The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).
- The symptoms are not better accounted for by Bereavement

Pathophysiology of depression

- At present, mechanism is unknown - may be more than one mechanism.
- No useful biomarkers or imaging abnormality during life
- Study of postmortem brain has not revealed any consistent structural or neurochemical abnormality
- Majority of the currently available medications were discovered empirically
- Most current theories are based on “amine hypothesis”

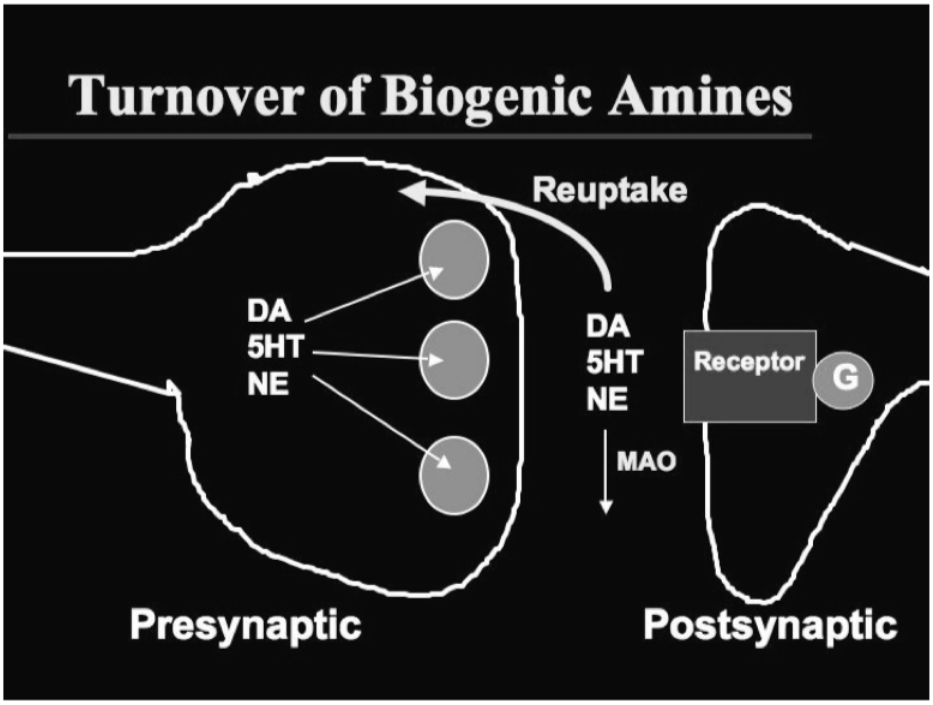
Biogenic amines

◆ **Dopamine**
- Synthesis: tyrosine $\xrightarrow{TH}$ L-DOPA $\xrightarrow{AADC}$ dopamine
- Origin: substantia nigra, ventral tegmental area
- Targets: basal ganglia, cerebral cortex

u **Norepinephrine**
- Synthesis: dopamine $\xrightarrow{D\beta H}$ Norepinephrine
- Origin: locus ceruleus
- Targets: cerebral cortex

u **Serotonin**
- Synthesis: tryptophan $\xrightarrow{TPH}$ 5-HTP $\xrightarrow{AADC}$ serotonin
- Origin: raphe nuclei
- Targets: cortex, basal ganglia, hippocampus, brainstem

Turnover of Biogenic Amines



Classes of Antidepressants

- Tricyclics and heterocyclics
- Selective serotonin reuptake inhibitors (SSRI's)
- Bupropion
- Nonselective MAO inhibitors
- Non-pharmacological therapy
  - ECT
  - Psychotherapy

Tricyclics and heterocyclics - Clinical pharmacology

- Large family of structurally related compounds
- Multiple pharmacological actions
- Therapeutic effect probably due to ability to block reuptake of serotonin and/or norepinephrine
- All may be sedating, although some much more than others
- Many of these drugs have anticholinergic (anti-muscarinic) actions - leads to somnolence, dry mouth, urinary retention

Tricylics and heterocyclics - pharmacokinetics and toxicity

- All are primarily metabolized by the liver, and undergo first pass metabolism
- Biochemical half-lives range from 4 to more than 24 hours, but clinical response is much slower - typically several weeks of therapy is required to observe any clinical improvement
- Overdose of tricylics (more than 1 gram) is often lethal due to cardiac conduction disturbances. Great care must be taken when these drugs are prescribed for potentially suicidal patients.

Some commonly used tricylics and heterocyclics

- Amitriptiline (Elavil®)
  - Inhibits serotonin & NE reuptake
  - Prominent anticholinergic effects
  - Metabolite is nortriptyline
- Desipramine (Norpramine®)
  - Inhibits NE reuptake
  - Mild anticholinergic effects
- Trazodone (Desyrel®)
  - Heterocyclic
  - Inhibits serotonin reuptake
  - Minimal anticholinergic effects
  - Sedating

Selective Serotonin Reuptake Inhibitors (SSRI's)

- Act by inhibition of presynaptic reuptake of serotonin in central synapses.
- Not as sedating as many of the tricylic compounds
- Also do not have the anticholinergic side effects of the tricyclics
- Some are potent inhibitors of P450 enzyme systems, and may lead to drug interactions

Some commonly used SSRI's

- Fluoxetine (Prozac®)
- Sertaline (Zoloft®)
- Citalopam (Celexa®)
- Paroxetine (Paxil®)
  - All are potent inhibitors of serotonin reuptake
  - Adverse effects: anxiety, tremor
  - Overdose of SSRI alone is rarely lethal
  - Should not be administered with nonselective MAO inhibitors
  - Suicide as an adverse effect?

Bupropion

- Structurally related to the tricyclics, but seems to have a different therapeutic mechanism, related to altered release of NE
- Not sedating or anticholinergic, but does sometime induce hallucinations or seizures
- Also effective in treating tobacco addiction

MAO Inhibitors

- Non-selective, irreversible enzyme inhibitors - long duration of action

- Therapeutic effect is due to is enhancement of CNS amine levels
- Major adverse effects are due to excessive accumulation of amines in the circulation
  - Tyramine: the “cheese effect.”
  - Drug interactions: SSRI’s, sympathomimetics
- Safe in carefully controlled circumstances, but “real world” use may lead to serious adverse effects.

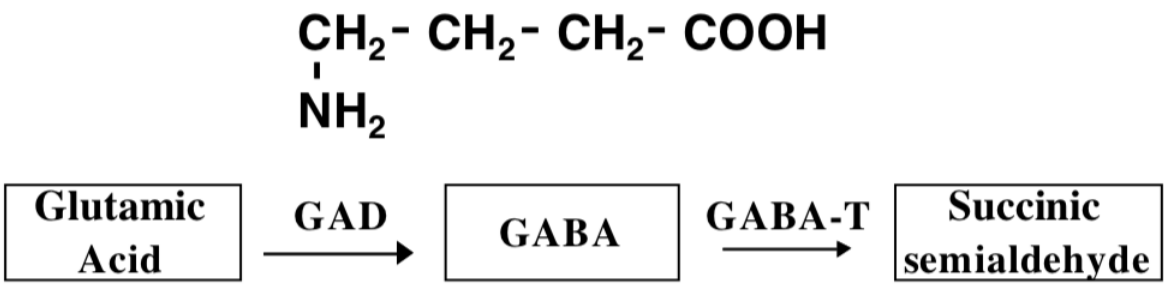
Treatment of depression

- Many patients will not report symptoms of depression unless asked specifically
- Patients who are depressed may be suicidal - it is essential to inquiry about their intentions
- The response of an individual patient to a particular antidepressant cannot be predicted, and treatment often requires sequential trials of several drugs
- In severely depressed patients, ECT often produces a rapid improvement and may be the best initial treatment

Sedatives and hypnotics

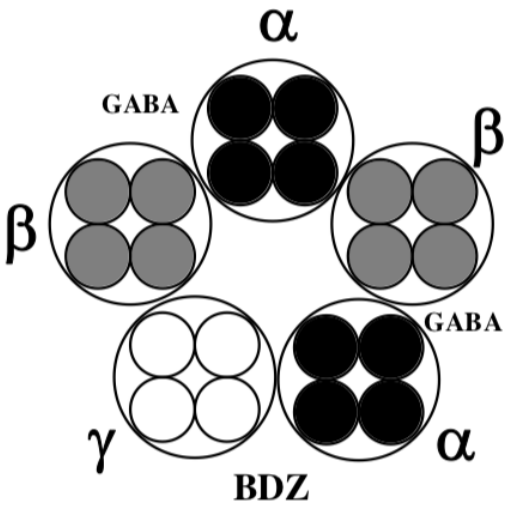
- Used to reduce anxiety, or induce sleep
- Very commonly prescribed
- Two principal chemical classes:
  - Benzodiazepines
  - Barbiturates
- Both work by enhancing activity of the inhibitory neurotransmitter, GABA

GABA (γ-aminobutyric acid)



- Principal inhibitory transmitter of the mammalian brain
- Receptors:
  - $GABA_A$: ligand gated ion channels, regulate chloride ion, at least 15 different subunit proteins
  - $GABA_B$: G-protein coupled receptors

Effects of benzodiazepines and barbiturates on GABA Receptors



- Both drugs bind to GABAA receptor subunits, but at different sites.
- Neither one binds to the agonist site
- Benzodiazepines increase the frequency of channel opening, but do not alter conductance or duration of opening
- Barbiturates prolong the duration of channel opening

Benzodiazepines

- More than a dozen benzodiazepines are marketed in the US
- They are distinguished primarily by their profiles of distribution and half-life.

Examples of some benzodiazepines			
	trade name	**t1/2 - hours**	**typical application**
midazolam	*Versed*	1 - 3	IV - brief sedation for procedure
triazolam	*Halcion*	2 - 4	hypnotic - may produce amnestic syndrome
temazepam	*Restoril*	10 - 17	hypnotic
lorazepam	*Ativan*	10 - 20	hypnotic, sedative
diazepam	*Valium*	30 - 60	hypnotic, sedative
flurazepam	*Dalmane*	50 - 100	old hypnotic - not recommended

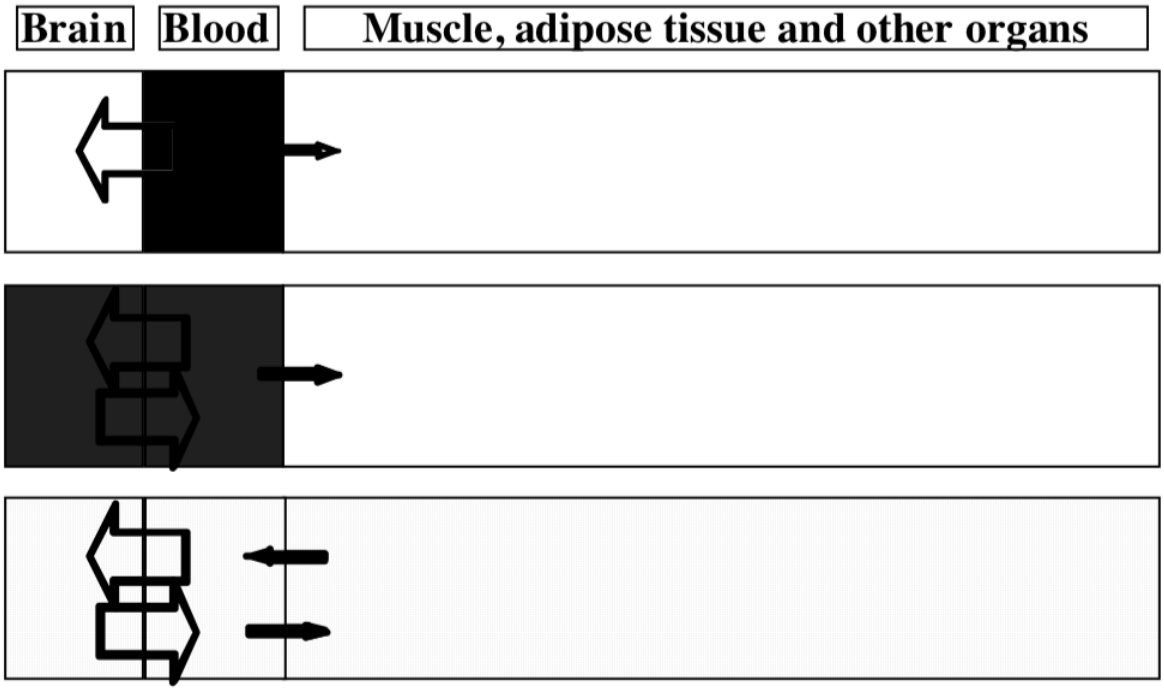
- Toxicity is mainly excessive sedation.
- After chronic use, withdrawal seizures may occur, especially with short half-life agents
- Flumazenil: a benzodiazepine antagonist, blocks effects of other benzodiazepines

Barbiturates

- Also distinguished largely by half-life and duration of action.
- Toxicity is excessive sedation, but unlike benzodiazepines, often leads to respiratory depression which may be fatal.
- Biochemical half lives range from 3 hours (methohexital) to 100 hours (phenobarbital)
- Redistribution is a key mechanism regulating duration of the biological effect of barbiturates (and benzodiazepines) when administered rapidly.

Redistribution

- Redistribution is a mechanism which limits the duration of action



- Effect is greatest when:
  - Agent is administered rapidly (e.g., intravenous)
  - Agent is highly lipophilic
- Can lead to very short duration of action (minutes) even though biochemical half life is longer (hours).

Clinical use of sedatives

- Anxiolytic use
  - Usually a medium to long acting benzodiazepine, such as diazepam, administered orally.
- Hypnotic use
  - Usually a short to medium acting benzodiazepine, such as temazepam, administered orally - but note that all hypnotics lose efficacy if taken daily.
- Sedative use (for surgical procedures)
  - A short acting benzodiazepine, such as midazolam
  - A short acting barbiturate, such as thiopental
  - Administered intravenously, and action terminated by redistribution.

Tolerance, cross-tolerance, and addiction

- Chronic use of sedatives of either class (benzodiazepine or barbiturate) induces tolerance to all members of the class, and cross-tolerance to members of the other class.
- Both also induce tolerance to ethanol, which acts in part through GABA receptors.
- Both benzodiazepines and barbiturates may produce dependence and are susceptible to abuse. Potentially lethal actions of the barbiturates makes them particularly problematic when abused.
- Rapid withdrawal from either class of sedatives may lead to anxiety, agitation, and seizures

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1.15: Neuropharmacology III - Anticonvulsants

Neuropharmacology IIIAnticonvulsants

What are seizures?

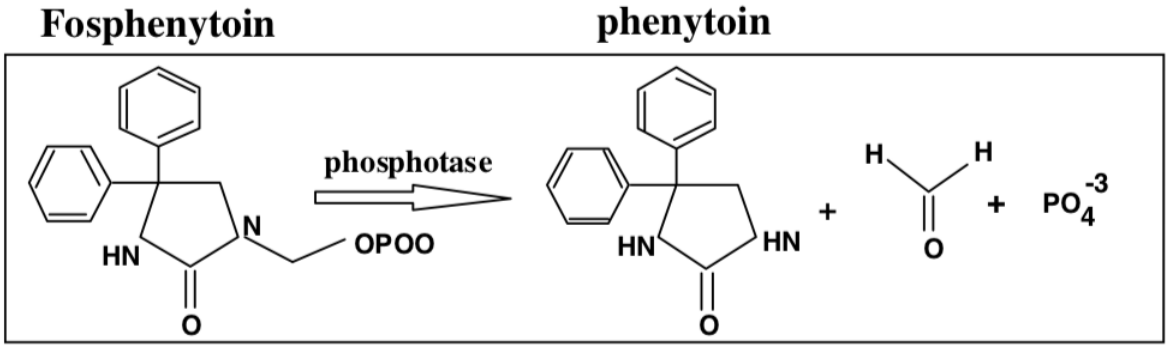
- Seizures are episodes of neurologic dysfunction arising from abnormal synchronous activity of neurons.
- Alterations of consciousness and abnormal motor activity are the most common manifestations
- Epilepsy (recurring seizures without a clear precipitant) is common, affecting about 1% of the population
- Pharmacological treatment is very successful in the majority of cases, but requires accurate diagnosis and classification of seizures

Classification of seizures:

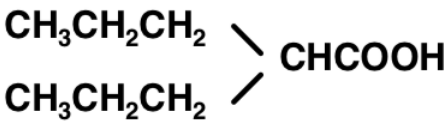
- Partial seizures (focal onset)
  - Simple partial seizures most common; “Jacksonian march” sometimes observed. May also affect sensory and autonomic systems
  - Complex partial: impairment of consciousness, with or without motor or other signs
  - Either simple or complex partial seizures may become secondarily generalized, producing a tonic-clonic seizure.
- Primary generalized seizures - bilateral onset
  - Typified by absence (“petit mal”) seizures, which can be recognized by clinical characteristics as well as interictal EEG abnormalities (3Hz spike and wave).
- Strategies for the discovery of anticonvulsant drugs:
  - “Traditional” – screening of compounds in animals models of epilepsy
  - “Rational” – based on presumed mechanism of seizure initiation or propagation
    - Inhibit repetitive activity – e.g., blockade of voltage-dependent Na^+ channels
    - Increase inhibitory input – e.g., GABA enhancers
    - Reduce excitatory input – e.g., glutamate antagonists

Drugs for treatment of partial seizures or generalized tonic-clonic seizures:

- **phenytoin**
  - One of the oldest and most widely used anticonvulsants.
  - Mechanism uncertain, but probably related to effect on Na+ channels.
  - May be administered orally or IV.
  - Pharmacokinetics are complex:
    - oral absorption is good but rate is variable.
    - highly protein-bound - important to note that usual laboratory test measures total, not free phenytoin
    - metabolism is primarily hepatic. Exhibits saturation kinetics, so that small increment in dose can produce an abrupt rise in equilibrium concentration.
    - half-life averages 22 hours but highly variable; bid dosing usually satisfactory
    - induces hepatic metabolism of other anticonvulsants as well as anticoagulants
    - Acute toxicity of oral form is usually nystagmus, ataxia and diplopia; sedation may also occur.
    - Chronic administration causes hirsuitism, gingival hyperplasia, cerebellar dysfunction, and peripheral neuropathy
    - Hypersensitivity with fever, rash which may progress to exfoliation (Stevens-Johnson syndrome) is relatively infrequent, but requires discontinuation of the drug in most cases.
- **Fosphenytoin (Cerebyx) a “prodrug”**
  - fosphenytoin is rapidly metabolized to phenytoin
  - fosphenytoin is water soluble; allows IM administration, and eliminates toxicity of propylene glycol vehicle required for phenytoin
  - 1200 mg phenytoin = $1.50; fosphenytoin = $119.00



- **Carbamazepine**
  - Structural features similar to phenytoin; mechanism of action likely similar as well.
  - Available in oral form only; rate of absorption variable.
  - Protein binding less than that of phenytoin.
  - Metabolism is primarily hepatic; induces own metabolism, as well as that of other drugs (OCP's, warfarin, other anticonvulsants particularly problematic).
  - Half-life is 10-20 hours; tid dosing usually satisfactory, although qid sometimes required
  - Several active metabolites, including a 10,11 epoxide, contribute to both anticonvulsant activity and toxicity
  - Most common effects of toxicity are ataxia and diplopia, sedation also observed. May also cause hyponatremia.
  - Aplastic anemia may occur and can be fatal. This is rare (6-8/million patients/year) but requires monitoring of CBC.
  - Oxcarbazepine – a derivative, does not form epoxide metabolites and may have lower incidence of adverse effects.
- **Barbiturates**
  - Family of drugs used for hypnotic, anesthetic and anticonvulsant applications
  - Mechanism probably related to increased GABA-mediated chloride conductance
  - Two members of class commonly used as anticonvulsants:
    - Phenobarbital
      - May be administered PO, IM or IV
      - Long half-life (about 100 hours), hepatic metabolism. Strong inducer of microsomal system.
      - Frequently used in infants; less commonly used in adults because of dose-related sedation.
    - Primidone
      - Parent drug has anticonvulsant properties, but is metabolized rapidly by the liver to phenobarbital and PEMA.
      - Toxicity similar to that of phenobarbital



  - Carboxylic acid, structurally distinct from other current classes of anticonvulsants.
  - Mechanism uncertain - effective against both partial and primary generalized seizures; drug of choice for myoclonic epilepsy
  - Oral or IV administration
  - Hepatic metabolism, with half life 8-12 hours. Induces metabolism of other anticonvulsants
  - Common adverse effects are tremor, weight gain, nausea.
  - Most significant risk is hepatotoxicity, which may be fatal. Occurs most often in infants under 2 years when taking multiple anticonvulsants.
- **Drugs for primary generalized epilepsy**
  - Ethosuccimide
    - drug of choice for treatment of absence seizure. Also effective in other forms of primary generalized epilepsy, but not usually effective in partial seizures.

    - Valproic acid
        - effective in generalized as well as focal epilepsy; particularly useful when several seizure types are present.
- **New anticonvulsants**
    - Because they are new, the clinical indications for these agents are not yet completely defined, and none are currently used as the first treatment for epilepsy.
    - Felbamate was approved by the FDA in early 1994 and was the first new drug for epilepsy to be approved in 15 years. Although there was great initial enthusiasm for this agent, in less than a year post- marketing surveillance revealed an unacceptably high rate of drug- related aplastic anemia.
    - Lamotrigine was approved in late 1994. It is thought to act by blockade of sodium channels; useful in partial seizures and possibly also in primary generalized seizures.
    - Gabapentin is approved for use as an “add-on” medication for treatment of partial seizures. Mechanism is uncertain; toxicity is low and does not induce or inhibit metabolism of other anticonvulsants.
    - Topiramate approved in 1997; unknown mechanism, possibly acts on voltage-gated Na+ channels.
    - Tiagabin - an inhibitor of GABA reuptake, approved in 1997 as “add- on” for treatment of partial seizures.
    - Levetiracetam – analog of piracetam, mechanism uncertain, approved as “add-on” for refractory partial seizures
    - Vigabatrin - an inhibitor of GABA transaminase, the degradative enzyme for GABA; approved as an “add-on” agent in refractory epilepsy
    - Zonisamide, a sulfonamide derivative approved for partial seizures; acts on Na^+ channels
- **Benzodiazepines:**
    - An important anticonvulsant use of benzodiazepines is in setting of urgent treatment of status epilepticus (see below). Two agents are frequently used, diazepam and lorazepam. These are particularly suitable because of rapid action after intravenous injection
    - Note that although biological half-life of diazepam is long, duration of action when used IV is short, because activity is terminated by redistribution
    - Oral benzodiazepines are not frequently used alone in primary treatment of epilepsy, although sometimes a useful adjunct in both focal and generalized seizures

Principles for the Management of epilepsy

- Attempt to classify, localize and investigate underlying etiology
- Not every seizure is an indication for anticonvulsant therapy
- In general, monotherapy is preferred to the use of multiple drugs
- Serum drug levels are a guide to therapy, but you should treat the patient, not the numbers
- Roughly 80% of patients with epilepsy can achieve good control with one agent; >90% with two or more.
- In refractory epilepsy, surgical treatment may be appropriate

Pregnancy and the use of anticonvulsant drugs

- All of the anticonvulsant drugs have been reported to have teratogenic effects
- Also important to recognize that uncontrolled seizures have an adverse effect on the fetus. Most important period is first 12 weeks
- In general, the best approach is to keep the number of drugs low (monotherapy if possible) and use the lowest dose which provides adequate control.
- Valproic acid should probably be avoided if at all possible, as the increased incidence of neural tube defects with this drug is well documented.
- Abrupt discontinuation of anticonvulsants during pregnancy is not advisable

Emergency medicine: treatment of status epilepticus

- **Definition and identification**
    - Status epilepticus is a state of repeated or continuous seizures.
    - Often defined operationally as a single seizure lasting more than 20 minutes, or repeated seizures without recovery of consciousness
    - Prolonged status epilepticus leads to irreversible brain injury and has a very high rate of mortality. Goal of therapy should be to achieve control of seizure within 60 minutes or less

- **Management**
  - ABC's - Airway, Breathing, Circulation
  - IV access - obtain initial labs (electrolytes, ABG, CBC, tox screen, anticonvulsant levels). History and examination should be performed concurrently
  - Administer glucose (50g IV) and thiamin (100mg IV)
  - Initial treatment: - lorazepam, 1-2 mg IV, repeat at 3-5 min intervals to 10 mg total
  - Administer a long acting agent - phenytoin or fosphenytoin - 15-20 mg/kg IV. With phenytoin, do not exceed 50 mg/min. Not compatible with IV fluids containing glucose. Often causes hypotension, and may provoke arrhythmia - continual monitoring required. Fosphenytoin much safer - but also more expensive !
  - If seizures persist, next agent is phenobarbital. Initial dose is 5 mg/kg IV. May be repeated to 10-15 mg/kg total. These large doses of phenobarbital often produce respiratory depression or arrest, as well as hypotension; intubation, respiratory support, and pressors may be required.
  - Seizures which are refractory to these measures require urgent expert consultation. Barbiturate coma induced by high doses of pentobarbital, a short half-life barbiturate, is used in many centers.

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1.16: Antimicrobials I and II

Pharmacologic Principles of Antimicrobial Therapy

A. Successful antimicrobial therapy occurs when an effective concentration of drug is delivered to the site of infection for a sufficient period of time. Minimum effective concentrations are those needed to inhibit growth (bacteriostatic concentration, MIC) or kill (bacteriocidal concentration,MBC) the pathogen in question.

Bacteriocidal therapy required in the following conditions

a. Bacterial infection in the neutropenic host
b. Endocarditis (and other intravascular infections)
c. Meningitis and brain abscess d. Staphylococcal (and probably other forms of) osteomylitis
e. Prosthetic device infection

B. Drug Absorption

1. The determinants of drug absorption are poorly understood and can only be determined by clinical studies.
2. Must determine effects of food, gastric pH, and antacids on drug absorption.
   a. Food absorption usually decreases, may increase
   b. Ketoconazole requires acid pH
   c. Chelation of tetracyclines and fluoroquinolones by cations in antacids may block absorption.

C. Drug Elimination

Three major routes of elimination:

1. Kidneys– renal elimination may occur either by glomerular filtration or tubular secretion; in general, tubular secretion (seen with penicillins and many cephalosporins) is more efficient than glomerular filtration, and results in shorter serum half-lives. Probenicid blocks active secretion.
2. Hepatobiliary – if significant hepatobiliary elimination occurs, then little dosage adjustment is needed in renal failure.
3. Metabolism – generally occurs in the liver, and can lead to drug interactions, because of effects on liver enzyme systems.

D. Distribution of Antimicrobial Agents in Tissues

There are three major determinants of distribution of drugs between the plasma (central compartment) and extravascular space (peripheral compartment)

1. Nature of the Capillary Bed – In most tissues and organs the capillary bed is fenestrated by small pores that permit the ready diffusion of substances with molecular weights up to 1000 daltons (most antimicrobial agents). A few locations in the body, termed specialized sites, have unfenestrated capillaries. As drugs must pass through the endothelial cells of the capillaries to reach extravascular space in these specialized sites, the rate of diffusion is limited by the degree of lipid solubility of the drug.
   a. The most clinically important specialized sites, are the central nervous system, the retina and the prostate gland.
   b. Such drugs as the β-lactams, aminoglycosides, mosttetracyclines and vancomycin are weakly lipid soluble and penetrate specialized site poorly.
2. Degrees of Serum Binding – only free drug is available for diffusion and is active. The major binding protein for most drugs is albumin.
3. Active Transport Pumps – The best studied of these pumps act on organic anions and are located in the choroid plexus of the brain, the retina and the proximal tubule of the kidney. These pump out β-lactam drugs and are completely inhibited by probenicid.

E. Site of Infection –

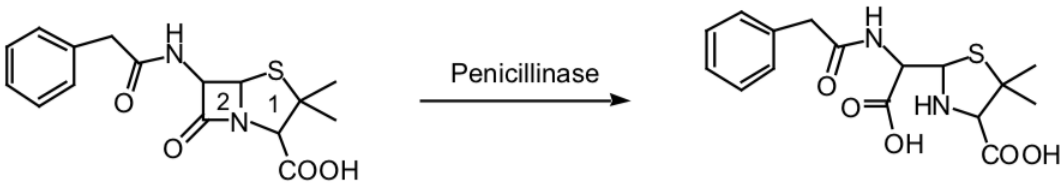
The site of infection determines not only the choice of the agent, but also its dose and the route by which it is administered.

1. In general, we wish to exceed to MIC.
2. Effects of subinhibitory concentrations
   a. Alter the bacterial morphology and adherence properties
   b. Decrease opsonic requirements
   c. Enhance phagocytosis

d. Aid in intracellular killing

Penicillins

A. Structure



1 Thiazolidine ring
2 β-lactam ring

Three components: A **thiazolidine** ring, the **β-lactam** ring, and a side chain. The **side chain** determines in large part to antibacterial spectrum and pharmacologic properties of a particular penicillin.

B. Mechanism of Action – surprisingly incompletely understood.

1. Penicillin inhibits bacterial growth by interfering with the synthesis of the bacterial cell wall after binding to penicillin binding proteins (many of these are enzymes are involved in cell wall biosynthesis).
2. Although penicillins are bacteriocidal drugs, the mechanisms by which they kill bacteria vary for different species. For pneumococcus and E. coli, killing is by lysis resulting from deregulation of the autolytic enzyme system (i.e., peptidoglycan hydrolases). Penicillin may also directly enhance autolytic activity. In the case of streptococcus, penicillin induces hydrolysis of cellular RNA.
3. Post-antibiotic effects are observed with gram-positive, but not gram negative bacteria.

C. Spectrum of Activity

see appendix for details generally active against cocci, many bacilli and anaerobes. activity against enterobacteriaceae and pseudomonas seen with aminopenicillins.

D. Resistance (see XII A for more details)

1. The most important mechanism of bacterial resistance to penicillin is enzymatic hydrolysis of the β-lactam bond by **β-lactamases.**
   a. S. aureus – plasmid encoded and inducible. This plasmid is increasingly found in enterococcus.
   b. In gram negatives, β-lactamases can be chromosomally or plasmid mediated, constitutive or inducible, and active against only certain β-lactams or broad spectrum.

      The ability of penicillin to inhibit growth of gram negative bacilli is dependent on the rate of influx across the outer membrane being greater than the rate of hydrolysis by β-lactamases. Alteration in the penicillin side chain governs gram negative activity, generally by enhancing penetration across the outer membrane rather than reducing the rate of hydrolysis.
2. Alteration in penicillin binding site.
   a. Penicillin resistant pneumococci
   b. Methicillin resistant staphylococci
3. Tolerance – MBC > 16 x MIC. Organisms exhibiting tolerance appear to have realigned or altered autolytic action with exposure to penicillin.
   a. Enterococci are naturally resistant
   b. Some S. aureus and streptococci.
4. Altered permeability of the outer membrane of gram negative bacilli provides another mechanism for resistance to the penicillins. Mutants with reduced or altered porion channels show 2-16 fold higher MICs to the broad spectrum penicillins. This mechanism often occurs jointly with altered PBPs or inducible β-lactamases.

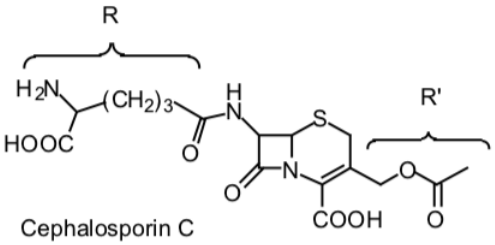
E. Adverse Reactions

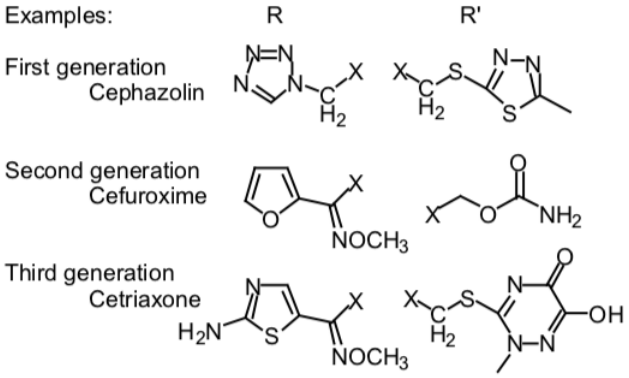
1. Hypersensitivity

2. CNS—seizures (primarily penicillin G and in patients with renal failure).
3. Gastrointestinal—C. difficile, and nonspecific GI upset—diarrhea, nausea, and vomiting.

Cephalosporins

A. Structure





B. Mechanism of Action—essentially the same as penicillin.

C. Spectrum of Activity—The cephalosporins are broad spectrum agents. As a rule, gram positive activity diminishes while gram negative activity increases as one progresses from first to third generation agents. None of the cephalosporins is active against enterococci, Listeria monocytogenes, or methicillin-resistant S. aureus.

see appendix for details.

D. Mechanism of Resistance (see XII A)

1. β-lactamase production
2. Alterations in target penicillin binding proteins.
3. Inability of the drug to reach its binding site: In order to reach its target PBP, a cephalosporin must penetrate an organism's cell envelope. This is done relatively easily in the case of gram-positive organisms, as the peptidoglycan structure that comprises the cell wall routinely allows the passage of cephalosporin-sized particles. Gram-negative organisms possess a more formidable barrier, a complex structure composed of polysaccharides, lipids, and proteins. Materials penetrate this outer cell envelope through water-filled channels, or porions, produced by various outer membrane proteins. Passage by a cephalosporin depends on channel size, charge, and hydrophilic properties.

E. Adverse Reactions

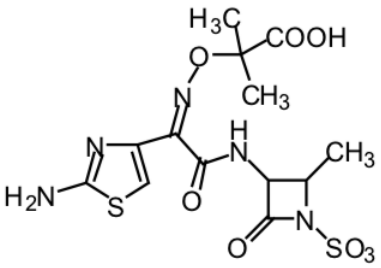
1. Hypersensitivity
2. Gastrointestinal, including hepatitis.

F. Other Beta-Lactam Strategies

A. β-lactamase Inhibition

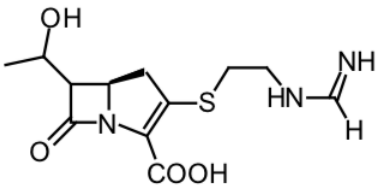
1. Sulbactam (ampicillin-sulbactam, Unasyn).
2. Clavulanic acid (amoxicillin-clavulanate, Augmentin; ticarcillin- clavulanate, Timentin).
3. Tazobactam (pipercillin-tazobactam, Zosyn).

B. Aztreonam—a monocyclic β−lactam relatively resistant to β−lactamases. Spectrum similar to gentamycin.



Aztreonam

C. Imipenem—broadest spectrum β−lactam. A carbapenem.



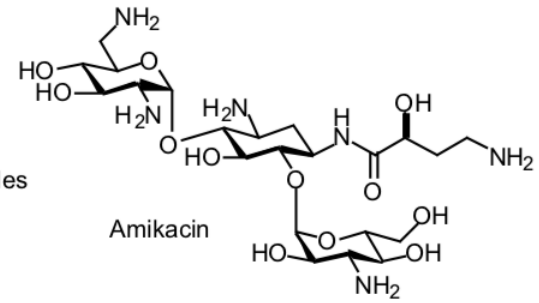
Imipenem
(N-formimidoyl thienamycin)

1. Unique pharmacologic problem: After imipenem is removed from the circulation by glomerular filtration and secreted, it is metabolized by a renal peptidase which is located on the brush border of the proximal renal tubules. The metabolites are nephrotoxic.
2. To overcome this problem, a specific peptidase inhibitor, cilastin, was synthesized, which totally blocks the metabolism of imipenem in the kidney, thus blocking toxicity. Cilastin has no antimicrobial activity.
3. Compound drug is imipenem-cilastin combination (Primaxin).
4. Particular toxicity is seizures, primarily in renal failure or in the face of ongoing or preceding brain injury.

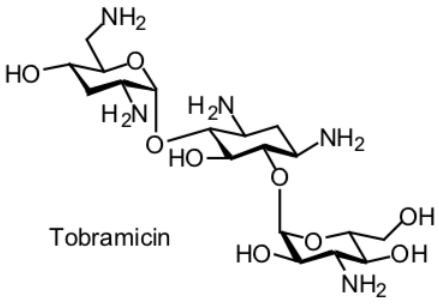
Aminoglycosides

A. Structure—All aminoglycosides consist of central six-memberedaminocyclitol ring linked to two or more aminosugar residues by glycosidic bonds. The aminoclycitol of streptomycin is streptidine, whereas that of all other available aminoclycosides is 2-deoxystreptamine.

Aminoglycosides



Amikacin



Tobramicin

B. Mechanism of Action—incompletely understood

1. Aminoglycosides bind to ribosomes, with the different aminoglycosides binding to different sites (streptomycin to the 30S subunit, the others at other sites; streptomycin binding does not compete with binding of the other aminoglycosides).
2. The consequences of the interaction of aminoglycosides are numerous. The two best-documented consequences are the inhibition of protein synthesis and an infidelity in correctly reading the genetic code.
3. These, however, don't explain the bactericidal effect of aminoglycosides. Aminoglycoside transport across the cell membrane, with accumulation in the cytosol is central to this effect. The transport process is energy-dependent and pH dependent (thus, aminoglycosides don't work well in situations of low pH and anaerobiosis; i.e., an abscess).

C. Spectrum of Activity

1. Aerobic and facultative gram negative bacilli. Especially useful against enteric organisms.
2. Partner in synergetic killing with β-lactam
   a. Absolutely required for Enterococci.
   b. In vitro, (in vivo?) for Staphylococcus aureus, Streptococcus pneumonia, other streptococci.
   c. Pseudomonas (one of a handful of useful drugs).

D. Mechanisms of Resistance

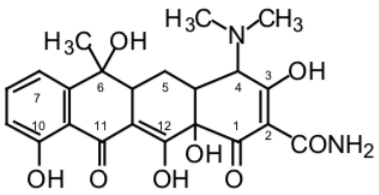
1. Aminoglycoside-modifying enzymes—diverse array; carried on plasmid and transposons; Ex: acetylation of an amino group, adenylation of a hydroxyl group, phosphorylation of a hydroxyl group. The resulting compound binds poorly to ribosomes. This is the major form of resistance.
2. Mitochondrial alterations of ribosomes—binding sites modified due to chromosomal interaction; as yet, rare.
3. Mutations interfering with aminoglycoside uptake—results in resistance to all aminoglycosides.

E. Adverse Reactions

1. Renal toxicity.
2. VIII cranial nerve toxicity.

Tetracycline

A. Structure



Tetracycline

Variants: Short acting	Intermediate acting	Long acting
Chlorotetracycline 7-chloro	**Demeclocycline** 7-chloro, 6-desmethyl	**Doxycycline** 6-desmethyl, 5-hydroxy

B. Mechanism of Action

Tetracyclines are bacteriostatic drugs and act on the bacterial ribosome. Penetration of the bacterial wall by tetracycline probably occurs as a result of both passive diffusion and an active transport system. Once the drug is within the bacterial cell, inhibition of protein synthesis occurs by binding to the 30S ribosomal subunit, so as to block the binding of the aminoacyl-tRNA to the acceptor site of the mRNA ribosome complex. This prevents the addition of new amino acids to the growing peptide chain.

C. Spectrum of Activity

1. First of the broad spectrum antibacterial agents; now superceded by other agents for conventional bacteria.
2. Major use now is in the treatment of
    a. Chlamydia
    b. Mycoplasma species
    c. Rickettsiae
    d. Spirochetes (including Lyme Disease agent)
3. Also useful as part of combination therapy for
    a. Plague (with streptomycin).
    b. Melioidosis (with chloramphenicol).
    c. Brucellosis (with streptomycin).
    d. Tularemia (with streptomycin).

D. Mechanisms of Resistance

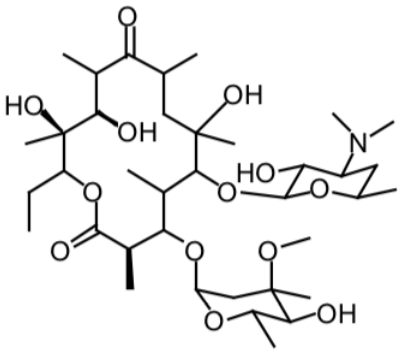
1. Primarily related to plasmid encoded decrease in the influx transport system and/or increasing the ability of the cell to export the antibiotic.
2. Also can be on a transposon (tetm).

E. Adverse Effects

1. Skin—photosensitivity.
2. Teeth and bones.
3. Gastrointestinal—fatty liver; diarrhea, nausea and vomiting.

Erythromycin

A. Structure—Erythromycin is one of the 14-membered macrolides consisting of a macrocyclic lactone ring attached to two sugar moieties.



Erythromycin

B. Mechanism of Action

1. An inhibitor of protein synthesis in susceptible organisms, erythromycin binds reversibly to a single high-affinity site on the 50S subunit of the 70S bacterial ribosome. It does not bind to mammalian 80S ribosomes, thus explaining its lack of toxicity.
2. Generally bacteriostatic; under special conditions bactericidal.

C. Spectrum of Activity

1. First line drug against Legionella, Chlamydia, Mycoplasma pneumonia.
2. Second line drug against the others.

D. Mechanism of Resistance (see XII B)

1. Impermeability of the bacterial cell wall -- in some gram negatives.
2. Plasmid mediated methylation of RNA adenosine of ribosome.
3. Plasmid mediated inactivation of erythromycin by an esterase.

E. Adverse Reactions

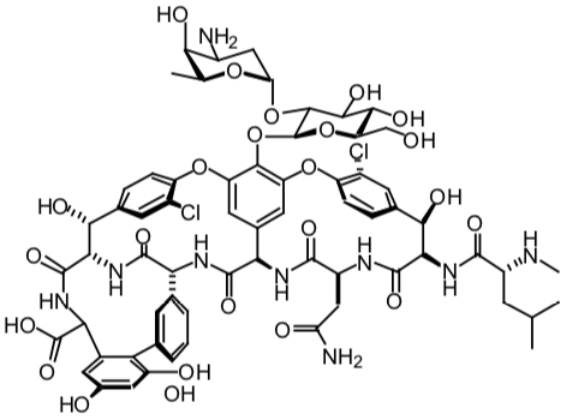
1. Gastrointestinal—hepatic plus gut.
2. Temporary sensorineural hearing loss with large doses.

F. New Macrolides—Clarithromycin, azithromycin

1. Broad spectrum of activity: H. influenza, tuberculosis.
2. Better GI tolerance.
3. Unusual pharmacokinetics of azithromycin.

Vancomycin

A. Structure—a bactericidal glycopeptide antibiotic



Vancomycin

B. Mechanism of Action

1. Inhibits cell wall synthesis by binding to D-Ala-D-Ala dipeptide intermediate in cell wall biosynthesis.
2. Injures protoplasts by altering the permeability of their cytoplasmic membrane.

3. Impairs RNA synthesis.

C. Spectrum of Activity

1. Gram positive.
2. Particularly useful against methicillin-resistant compounds.
3. NB: CNS penetration unreliable.

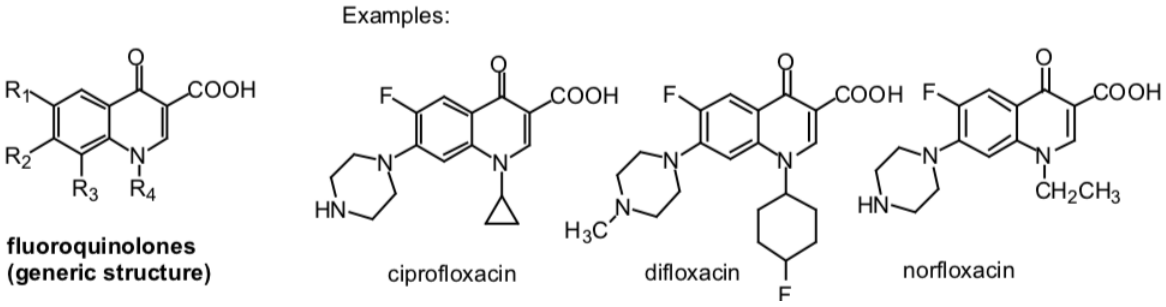
D. Mechanisms of Resistance (see XII, A, 1c and 2b)

E. Adverse Effects

1. VIIIth nerve.
2. “Red man syndrome.”
3. Nephrotoxicity.

Fluoroquinolones

A. Structure



B. Mechanism of Action

Bactericidal effect due to inhibition of DNA topoisomerases (gyrases), which are required to supercoil strands of bacterial DNA into the bacterial cell.

C. Spectrum of Activity

1. Broad gram negative action. Most do not cover anaerobes. see appendix for details.
2. Particularly useful because of high concentration in tissue interstitium intracellularly.
3. Do not penetrate the CNS.

D. Mechanism of Resistance

1. Mutations in the gene encoding DNA gyrase so that there is reduced quinolone binding to its target.
2. Mutations that change the outer membrane porions.

E. Adverse Effects

1. CNS toxicity.
2. Gastrointestinal.
3. NB: cartilage abnormalities in beagle puppies. Therefore, contraindicated in children & pregnancy.

General Principles of Antimicrobial Use

A. Factors to be considered in the initial choice of antibiotics

1. The identity of the infecting organism must be known, or at the very least, it must be possible to make a probability assessment of the most likely culprit(s)
2. The likely antimicrobial susceptibility pattern of the invading organisms must be estimated.
3. Individual Hospital and ICU Variation
    a. Particular issues today: Methicillin-resistant Staphylococcus aureus(“MRSA”); antibiotic resistant gram negative bacilli; Vancomycin, ampicillin, gentamycin-resistant enterococci (“VRE”)
    b. Possible issues tomorrow: penicillin-resistant pneumococci
4. The presence or absence of host factors that can modify the choice of antimicrobial agents

a. History of previous adverse reactions - must be specific as to nature of reaction. (e.g., nausea, vomiting, diarrhea not a major contraindication to repeat use of a drug; history of anaphylaxis or Stevens-Johnson syndrome is a major contraindication)

b. Age of patient

- Neonates - chloramphenicol normally conjugated to glucuronide by liver; hepatic glucuronyl transferase levels in neonate very low, toxicity is very common
  sulfonamides compete with bilirubin for binding sites on serum albumin, can contribute to kernicterus
- Children - quinolones cause cartilage damage and arthropathy in young animals, therefore contraindicated in prepubescent children.tetracyclines - bind to developing bone and tooth structures, causing purplish brown discoloration of teeth, and even enamel hypoplasia.
- Elderly - isoniazid - above age 50, incidence of hepatotoxicity is 2.3%, under age 30 it is 0.3%
  increased nephrotoxicity with aminoglycosides and other similar drugs, likely secondary to decreased GFR associated with aging

c. Pregnancy - As a general rule, the published data are totally inadequate for making recommendations. The following statements at present appear reasonable

1. Penicillins (with the exception of ticarcillin), cephalosporins, and erythromycin are unlikely to be teratogenic and appear to be safe for use in pregnancy.
2. Metronidazole and ticarcillin are teratogenic in rodents and should never be used
3. Rifampin and trimethoprim should be avoided on theoretical grounds
4. Tetracyclines (in addition to effects on teeth of infant) are associated with fatty necrosis of the liver, pancreatitis, and probably renal damage in the pregnant woman
5. Aminoglycosides cross the placenta, ?effects on VIIIth nerve function of fetus. Ex: streptomycin
6. Isoniazid - ? associated with psychomotor retardation, myoclonus, and seizures in infant.

- Pharmacokinetics are altered in pregnancy - larger volume of distribution and more rapid clearance from blood, therefore lower serum levels.
- Essentially all antimicrobial agents appear in breast milk. Therefore, need to consider potential effects on infant

d. Genetic or metabolic abnormalities - This is an area that will expand rapidly in the next decade.

- Slow acetylators of INH (45-64% of Americans) - at risk for polyneuritis. Therefore give everyone pyridoxine.
- G6PD deficiency - sulfonamides, sulfones, nitrofurantoin, chloramphenicol will precipitate hemolysis

e. Renal and Hepatic function

- Dosage adjustment in renal dysfunction or failure is highly variable.
- As a general rule, the amount of dosage manipulation necessary in renal failure depends upon the extent to which nonrenal routes of clearance (primarily hepatobiliary) can compensate.
- Erythromycin, chloramphenicol, lincomycin, and clindamycin should be used with caution in patients with impaired hepatic function.

5. Site of Infection - the site of infection determines not only the choice of the agent but also its dose and the route by which it should be administered.

a. ability to achieve effective concentration at sites of interest: e.g., CSF

b. local factors that may modify drug efficacy

1. Pus

- Aminoglycosides and polymixins bind to (and are inactivated by) pus.
- Beta-lactamases produced by such organisms as Bacteroides fragilis can cause local inactivation of beta-lactam antibiotics at the site of mixed infection.

c. pH – e.g. aminoglycosides have low activity at low pH.

d. presence of foreign body.

B. Rational Use of Antimicrobial Combinations in Infectious Disease process

1. For preventing emergence of resistant organisms
2. High probability of a polymicrobial infection
3. Provision of broad antimicrobial spectrum as initial therapy when patient seriously ill and etiology unclear.
4. Combination therapy to permit lower doses and decrease toxicity.

5. To achieve antimicrobial synergy
   - only examples to be clinically proven to be of importance: penicillin + aminoglycoside for serious enterococcal infection; anti-pseudomonal beta-lactam + tobramycin for Pseudomonasamphotericin + flucytosine for Cryptococcus neoformans
   - many examples of test tube synergy with questionable clinical importance.
6. Disadvantages of antimicrobial combinations:
   - Antagonism
   - Cost
   - Side-effects.

C. ChoiceofRouteofAdministration.

In addition to issues related to the intrinsic pharmacokinetic properties of a drug, the major reasons for utilizing parenteral therapy (usually IV) are:

1. Serious illness that requires immediately achieving high blood and tissue concentrations
2. Inadequate GI tract function - i.e., the presence of ileus, nausea and vomiting, etc.

D. First Two Commandments of Antimicrobial Therapy

1. Buy Time. The first concern is to keep the patient alive until you know the etiology and antimicrobial susceptibility of the invading pathogen and thereby precisely target treatment. Up until that point, you need to make this important distinction:
   a. therapeutic emergency -- "front load" antibiotics
   b. diagnostic dilemma -- "after load" antibiotics.
2. Look for abnormality. The second question is whether the patient has an abnormality that increases the risk from an inadequately treated bacteremia.

   Ex: abnormal heart valve, prosthetic joint, prosthetic vascular graft. If yes, "front load" with bactericidal therapy.

Antimicrobial Resistance in the New Millennium

A. Particular problems in Antimicrobial Resistance that are Emerging

“We are about to enter the post-antibiotic era.”

"We are constantly heading towards antimicrobial resistance."

- The Second Law of Thermodynamics states that the world is constantly heading to Chaos; the application of the Second Law to infectious disease practice is to state,

1. Antimicrobial Resistance of Staphylococci - Penicillin and other beta-lactams act by binding to enzymes called penicillin-binding proteins (PBPs) that, in staphylococci, mediate transpeptidation and carboxypeptidation reactions, important for the cross- linking of the peptidoglycan backbone in the bacterial cell wall. The normal substrate of the PBPs is acyl D-alanyl-D-alanine; penicillin acts as its analog. Therefore, penicillin disrupts peptidoglycan synthesis and causes eventual death and lysis of the bacterium. Susceptible isolates of S. aureus produce four PBPs: PBP1, PBP2, PBP3, and PBP4. PBPs 1, 2, 3 are considered the major targets for beta-lactams.
   a. Penicillin resistance - Initially, in the early 1940's, staphylococci were universally penicillin sensitive. Penicillin-resistance, first recognized in 1942; by 1949, -75% of hospital isolates were penicillin resistance; by 1967 >85% of both community-acquired and hospital-acquired strains resistant.
      1. Mechanism of Resistance: beta-lactamase production by the organism; usually encoded for on a plasmid; can be part of a transposon that is now integrated into the chromosome; beta-lactamase production is usually inducible, with rare strains exhibiting constitutive production of the enzyme.
      2. Strategy to Control Problem: the isolation of the penicillin precursor, 6-amino-penicillanic acid in 1959 made the production of semisynthetic penicillins possible. Modifications of the acyl side chain resulted in steric protection of the beta-lactam ring, which prevented hydrolysis by beta- lactamase. Such drugs as methicillin, oxacillin, nafcillin, cloxacillin, etc., became widely used, and effectively dealt with this problem.
   b. Methicillin resistance - Both S. aureus (“methicillin resistant S. aureus, MRSA”) and S. epidermidis strains resistant to the semisynthetic penicillins emerged, again first in the hospital (particularly ICUs) then spreading into nursing homes,

and, finally, the community. In addition, many of the MRSA also produced beta-lactamase and seemed to be a reservoir for resistance determinants for a variety of other antimicrobials, including quinolones, streptomycin, tetracycline, sulfonamides, chloramphenicol, erythromycin, clindamycin, fusidic acid, gentamicin, and neomycin.

1. Mechanism of Resistance: Methicillin-resistant staphylococci, both S. aureus and S. epidermidis, produce a unique PBP called PBP 2' or 2a, a 78 kDa protein with low binding affinity for beta-lactam antimicrobial agents. The gene encoding this novel PBP is called mecA and is present on the chromosome of MRSA isolates.
2. Strategy to Control Problem: vancomycin. or teicoplanin

c. Vancomycin Resistance: In 1997, outbreak in a Japanese hospital of partial vancomycin resistance (as well as methicillin resistance and beta-lactamase production) of an epidemic strain of S. aureus. Mechanism is as yet unknown, but increased production of PBP2 may be involved.

2. Antibiotic Resistance of Enterococci- Enterococci-, like penicillin-sensitive strains of staphylococci, are inhibited by low concentrations of penicillin. However, with staphylococci, binding to the PBPs also triggers the activation of autolytic enzymes present in the bacterial cell wall, "a suicide mechanism," so that the concentration of drug necessary to kill (bactericidal effect) is essentially identical to the concentration necessary to inhibit growth (bacteriostatic effect). With enterococci, this signal transduction does not occur, and for a bactericidal effect, a cell wall active agent (e.g., penicillin, ampicillin, or vancomycin) needs to be combined with an aminoglycoside (this is of critical importance in the treatment of bacterial endocarditis). In recent years, this inherent problem with enterococci. has been compounded by:

a. Penicillin resistance -- some enterococci- produce beta-lactamases, which render them resistant to penicillin and ampicillin, and some are inherently resistant.
b. Vancomycin-resistant enterococci (VRE) - an epidemic throughout the developed world.

1. Mechanism of resistance: Under normal conditions of peptidoglycan synthesis in enterococci, two molecules of D-alanine are joined by a ligase enzyme to form D-ala-D-ala, which is then added to UDP-N- acetylmuramyl-tripeptide to form the UDP-N-acetylmuramyl-pentapeptide that, when incorporated into the nascent peptidoglycan (transglycosylation), permits the formation of cross-bridges (transpeptidation) that contribute to the strength of the peptidoglycan layer. Vancomycin binds with high affinity to the D-ala-D-ala termini of the pentapeptide precursor units, blocking their addition to the growing peptidoglycan chain and preventing subsequent cross-linking. Resistance is mediated by a variety of genes that favor the production of D-ala-D- lactate or D-ala-D-serine which is not susceptible to vancomycin effect.
2. Strategy to Control: Linezolid or quinupristin-dalfopristin are last ditch treatments for VRE colonization or invasive infection. Otherwise, the only strategies available are surgical ablation and quarantine.

B. Mechanisms of Antimicrobial Resistance

1. Inactivation of antimicrobial agent
   - Examples of enzymes that inactivate antimicrobial agents include beta- lactamase, chloramphenicol acetyltransferase, aminoglycoside-modifying enzymes, esterases that inactivate macrolide antibiotics, etc.
2. Permeability Alterations
   a. Natural Characteristics. Virtually all gram negative bacilli are intrinsically resistant to penicillin G because of its inability to easily traverse the outer cell envelope of these organisms. Likewise, lack of permeability also plays a role in relative resistance of enterococci to aminoglycosides, and of gram negatives to macrolides.
   b. Acquired Characteristics
      - Chromosomal mutations that alter porin proteins in gram-negative bacilli can lead to increased resistance to cephalosporins and carbapenems.
      - Mutations that alter the membrane transport system for aminoglycosides can lead to resistance to S. aureus and a variety of gram negatives.
      - Efflux systems can result in resistance to tetracyclines, macrolides,- chloramphenicol, and the quinolones.
3. Alterations in Target Sites
   a. Alterations in penicillin-binding proteins (PBPs) leading to methicillin resistance in S. aureus, penicillin resistance in pneumococci, and relative resistance to penicillin in enterococci.
   b. Some bacteria are able to produce alternative resistant targets. For example, plasmid-mediated resistance to trimethoprim-sulfamethoxazole may be due to plasmid-mediated production of a second set of enzymes in the folic acid synthesis pathway that are resistant to the effects of these agents.

Specific Examples of Resistance to Antimicrobial Drugs

A. Resistance to Beta-Lactam Antibiotics

May result from any previously described mechanisms, either alone or in combination:

1. Alterations in penicillin-binding protein (PBPs) decrease affinity for penicillin (or produce increased resistance to inactivation by beta-lactams).
2. Beta-lactam resistance due to permeability barriers:
   a. In general, most gram-positive cocci have no permeability barriers to beta-lactams.
   b. The outer cell envelope of gram-negative bacteria, however, is a natural permeability barrier to beta-lactam antibiotics, which must penetrate this (usually via porin proteins) in order to reach their target sites.
      - Alterations in porin proteins caused by chromosomal mutation can lead to striking decreases in permeability and resistance to a variety of penicillins, cephalosporins, and even carbapenems.
3. Beta-lactam resistance due to elaboration of beta-lactamases, enzymes capable of hydrolyzing the beta-lactam ring

   Chromosomally-mediated beta-lactams are inducible and are primarily active against the cephalosporins.

   - Genes for these enzymes are found in Enterobacter cloacae, Citrobacter freundii, Serratia marcescens, Pseudomonas aeruginosa, and indole- positive Proteus species. Because these enzymes are inducible, in vitro testing may suggest false susceptibility to cephalosporins under certain test conditions.
   - Moreover, the use of cephalosporins (including “third generation” cephalosporins) has resulted in therapeutic failure in infections caused by organisms with these genes, primarily associated with the selection of “stable derepressed” mutants. These mutants are usually resistant to all present beta-lactams except amdinocillin, the penems and carbapenems. The recent description of plasmid-mediated, transferable Group 1 enzymes in Klebsiella pneumonia is a particularly disturbing development!
   - Finally, certain metalloenzymes may inactivate even imipenem and other carbapenems. Although these enzymes are chromosomally located in most instances, and their occurrence has been rare thus far (limited primarily to Xanthomonas maltophilia and rare isolates of B. fragilis, Aeromonas hydrophilia, Flavorobacter odoratum, Serratia marcescens, Legionella gormaniae, Bacillus cereus, and Pseudomonas aeruginosa), the recent description of plasma-mediated, transferable metalloenzymes conferring resistance to imipenem in Pseudomonas aeruginosa in Japan is most worrisome.

B. Resistance to Macrolide Antibiotics

Many macrolide antibiotics have pharmacokinetic or toxicologic advantages overerythromycin, and some have enhanced spectra of activity as well. Extensive use of these antibiotics, as well as cross-resistance with erythromycin, is highly likely; hence the importance of understanding the potential for development of resistance. Examples of new macrolides are azithromycin and clarithromycin.

Under circumstances of heavy utilization, resistance to erythromycin in gram-positive organisms, such as staphylococci and Group A streptococci, has emerged with almost explosive rapidity, and in hospital settings, over 50% of S. aureus have become resistant to erythromycin when it has been utilized exclusively for treating hospital-acquired staphylococcal infections. In Japan and Finland, outbreaks of erythromycin- resistant Group A streptococci have been described, and in the late 1970s, over 60% of Group A streptococci in Japan were erythromycin-resistant.

Mechanism of macrolide antibiotic resistance:

1. Major mechanism of resistance to macrolides in gram-positive cocci is due to alterations of the ribosomal target, which results in decreased affinity for macrolides and lincosamides.
2. Other mechanisms: Resistance may occur by any of the major mechanisms previously described in this outline.
   - Intrinsic resistance to macrolides in most gram-negative bacilli is almost certainly due to inability of the macrolide to penetrate these organisms.
   - In addition, coagulase-negative staphylococci with the "MS" phenotype have been shown to have an ATP-binding transport protein that causes efflux of macrolides.
   - Novel macrolides capable of binding to methylated ribosomes have been developed recently. Although present analogs have only modest antimicrobial activity, this technology may become more important if extensive use of these agents turns the possibility of resistance among gram-positive organisms into reality.

1.17: Chemotherapy

Principles of Clinical Cancer Chemotherapy and Drug Resistance

Cancer Mortality: 2000 = 553,091; Est.2003 = 556,500
Cancer Chemotherapy -- Effectiveness by Disease

Curative

- Acute Lymphocytic Leukemia, Hodgkin's Disease, Diffuse Histiocytic Lymphoma, Burkitt's Lymphoma
- Testicular Cancer, Choriocarcinoma
- Wilms' Tumor,* Ewing's Sarcoma,* Embryonal Rhabdomyosarcoma*

Probably Curative

- Acute Myelogenous Leukemia
- Small Cell Lung Cancer, Breast Cancer,* Osteogenic Sarcoma*

Major Therapeutic Benefit (Short of Cure)

- Head and Neck Cancer, Cervical Cancer, Metastatic Breast Cancer, Ovarian Cancer
- Soft Tissue Sarcoma
- Nodular Lymphomas, Chronic Leukemias
- Insulinomas

Limited Effectiveness

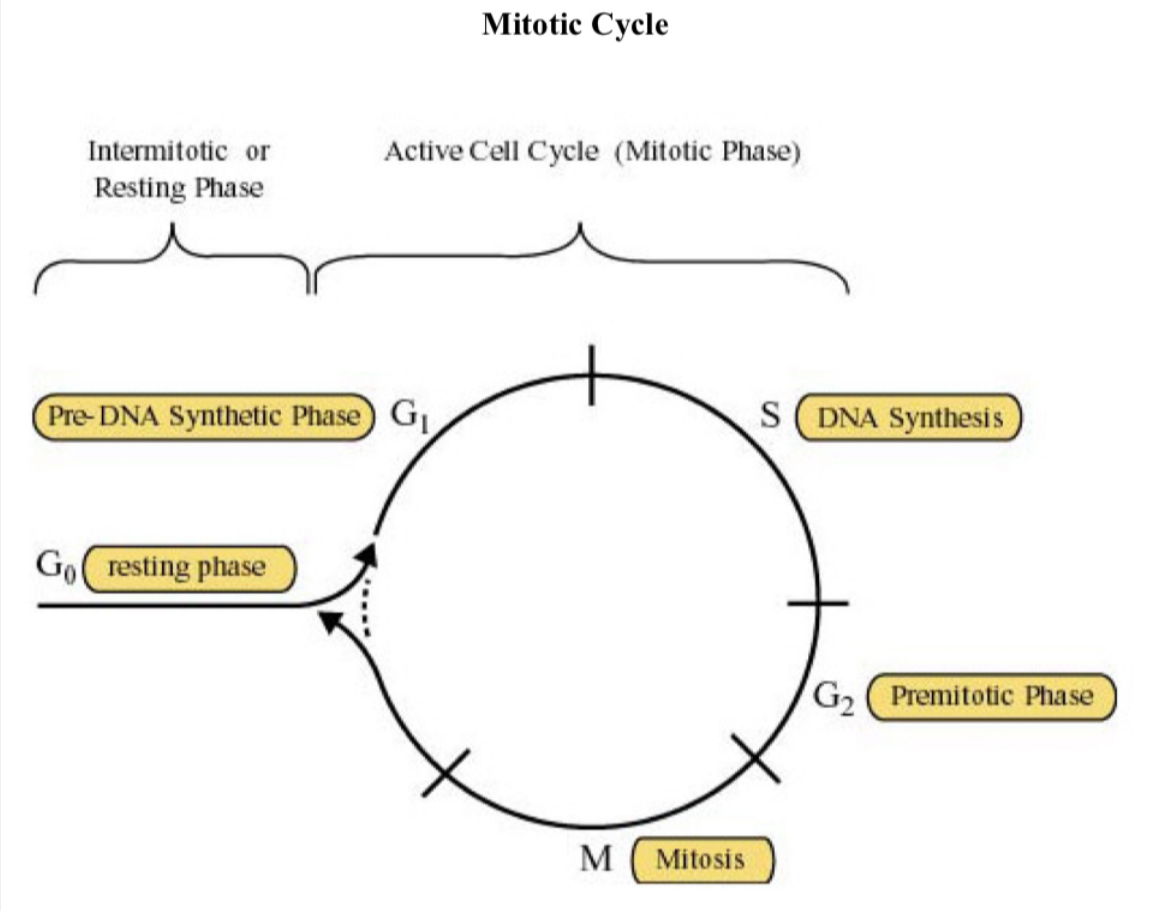
- Lung Cancer
- GI Cancer
- Prostate Cancer
- Melanoma

* Adjuvant chemotherapy: Drugs administered after removal of all detectable disease.

Acute Lymphocytic Leukemia: Induction of Chemotherapy

First Order Kinetics

A given dose/unit time of chemotherapy will kill a constant percentage of cells, not a constant number. This means that the same dose which decreases the tumor burden from 10^6 to 10^3 cells will be needed to decrease the burden from 10^3 to 100 cells.



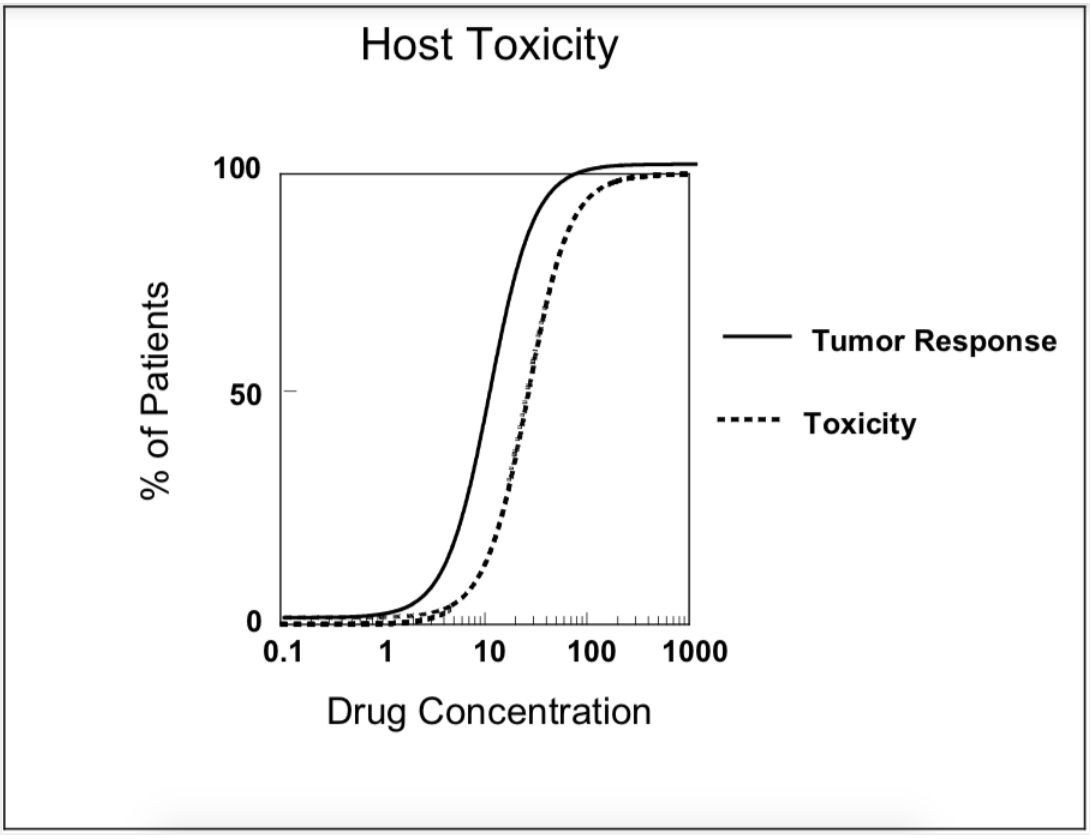
Assuming an initial tumor burden of 106 cells, a treatment which is 99.9% effective will still leave 103 cells untouched. Thus, treatment may eliminate clinical symptoms, but the tumor can recur. Treatment should aim for 10-1 cells or less remaining to ensure a high percentage of cures.

"Log-kill hypothesis"

- Dashed line = no treatment.
- Top solid line = moderate, infrequent dosing of chemotherapy which prolongs survival but results in recurrent symptoms and eventual death.
- Middle line = aggressive treatment. Cell kill exceeds regrowth and treatment is sufficiently long to sterilize tumor (patient is cured).
- Bottom line = primary tumor is surgically removed or debulked, and adjuvant chemotherapy is used to kill remaining occult tumor.

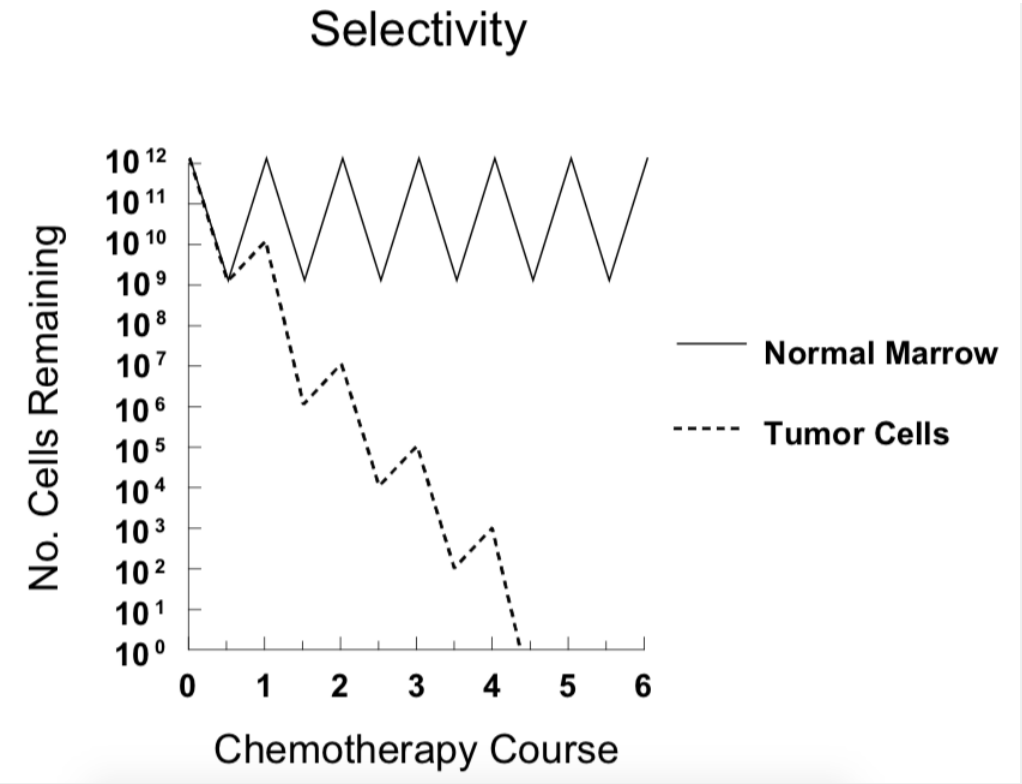
Host Toxicity

Therapeutic effects on tumor (solid line) and toxicity (broken line) are related to drug dose. Both curves are steep, and displacem ent of the toxicity curve to the right reflects the therapeutic index (median toxic dose/median effective dose) which is usually low for antitumor agents.



Selectivity

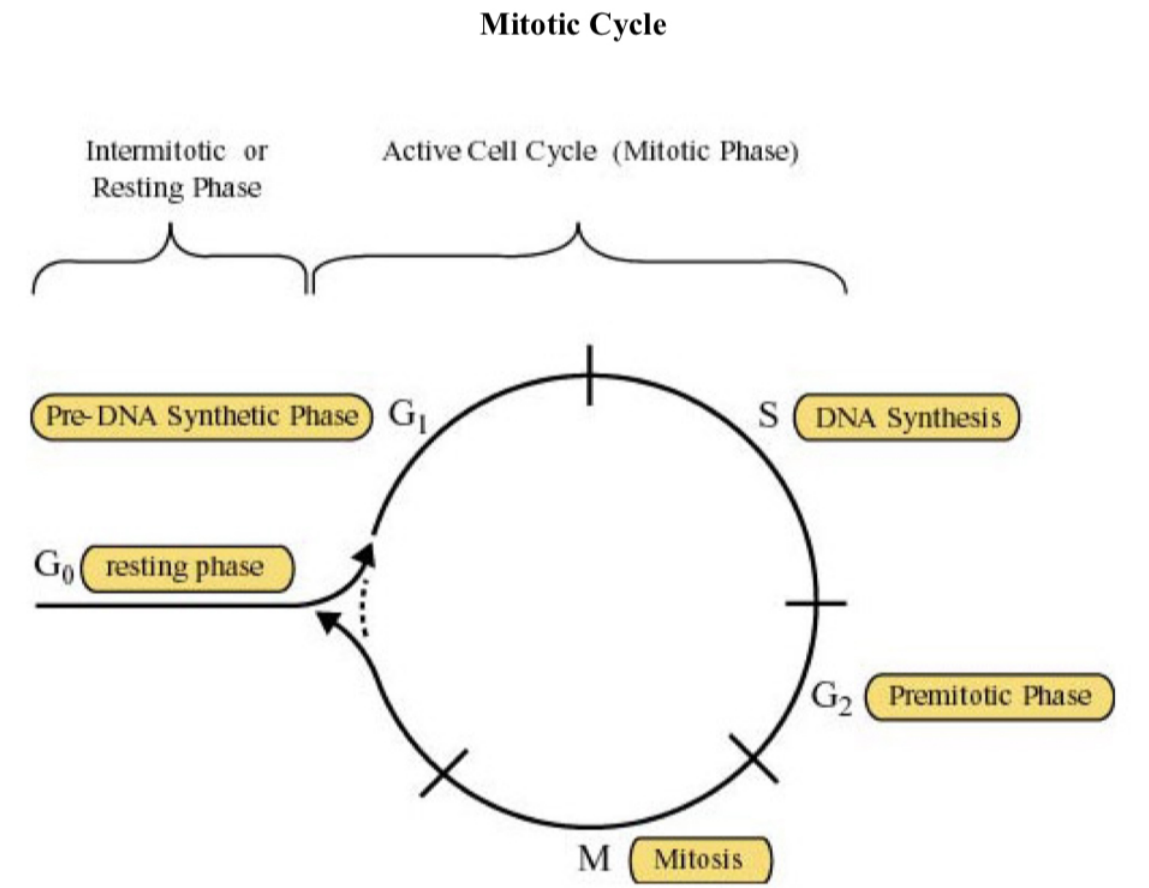
Normal bone marrow cell kill and recovery (solid line) are compared to tumor cell kill and recovery (broken line). Each chemotherapy course causes a similar destruction of normal bone marrow and tumor cells, Rate of recovery of normal bone marrow, however, is greater than that of tumor cells. Number of normal bone marrow progenitors does eventually decrease with continued therapy.



Combination Chemotherapy

Combining drugs with different mechanisms of action and different dose-limiting toxicities can produce a bigger therapeutic effect at maximally tolerated doses of all drugs. Antitumor drugs may be placed into one of three classes based on the relationship of the effect to the mitotic cycle of the cell:

1. Cell cycle active, phase specific
2. Cell cycle active, phase non-specific
3. Non-cell cycle active



Cell Cycle Active, S Phase Specific

ANTIMETABOLITES

Mechanisms

- incorporation of nucleotide analog in DNA or RNA, resulting in abnormal nucleic acids
- inhibition of certain enzymes involved in nucleotide biosynthesis

Examples:

- Pyrimidines

  Uracil: 5-fluorouracil (5-fluoro-2'-deoxyuridine)

  Thymine: 3'-azido-3'-deoxythymidine

  Cytosine: Cytosine arabinoside; 5-azacytidine

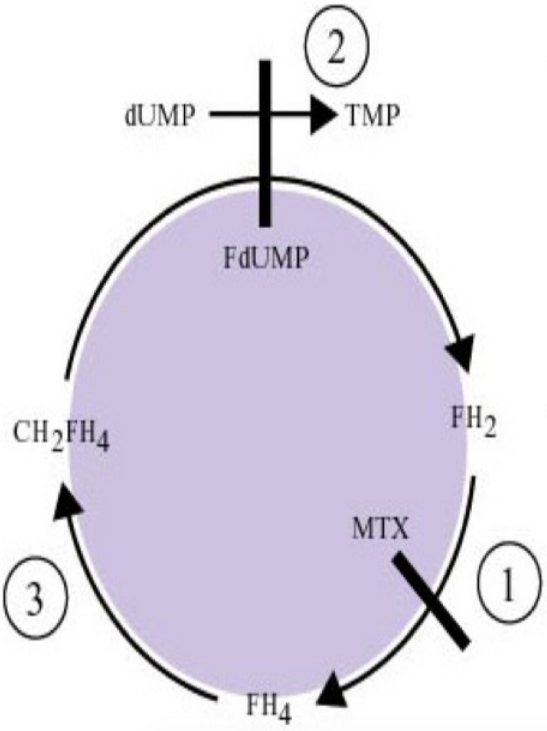
- Purines

  Adenine: 6-mercaptopurine

  Guanine: 6-thioguanine

ANTIFOLS (METHOTREXATE)

Mechanism: competitive inhibition of dihydrofolate reductase, necessary for generation of methyl donors required for thymidine synthesis.



Sites of action of methotrexate (MTX) and the fluoropyrimidine antimetabolite, fluorodeoxyuridylate (FdUMP): (1) DHFR, dihydrofolate reductase; (2) TS, thymidylate synthase; (3) SHM, serine hydroxymethylate; FH_2, dihydrofolate; FH_4, tetrahydrofolate; CH_2FH_4, N^5, N^{10} -methylene- tetrahydrofolate.

Toxicity (general)

- interfere with replication of all rapidly proliferating cells
- bone marrow --- myelosuppression
- GI mucosa ---- diarrhea, stomatitis

Toxicity (specific)

- 6-mercaptopurine --- cholestatic jaundice
- Methotrexate

  renal – high doses may block tubules and cause acute renal failure
  hepatic – usually seen with chronic daily administration of low doses (i.e., psoriasis treatment)
  CNS – encephalopathy in patients given prior irradiation

Cell Cycle Active, G2/M Phase Specific

BLEOMYCIN

Mechanisms

- induces single-strand and double-strand DNA breaks
- selectivity for G2 phase, but cells in G1 can also be killed

Toxicity

- subacute or chronic pneumonitis
- little myelosuppression

PLANT ALKALOIDS: VINCRISTINE (VCR), VINBLASTINE (VBL), TAXOL, EPIDOPHYLLOTOXINS (VP-16, VM-26), CAMPTOTHECINS

Mechanisms

- Tubulin Binders
  VCR, VBL inhibit polymerization of tubulin
  Taxol blocks depolymerization; stabilizes microtubule

- VP-16, VM-26 target topoisomerase II; non-intercalating
- Camptothecins (topotecan, irinotecan) inhibit topoisomerase I

Toxicity

- neurotoxicity
- paresthesias
- constipation
- decreased deep tendon reflexes
- myelosuppression
- SIADH (VCR, VBL)

Cell Cycle Active, Phase Non-Specific

ALKYLATING AGENTS

Mechanisms

- base alkylation resulting in DNA cross-linking
- single strand breaks
- double strand breaks and strand misreading

Examples:

- Nitrogen Mustard
- Cyclophosphamide
- Nitrosoureas
- Cis-platinum
- Busulfan

Toxicities (general)

- myelosuppression
- stomatitis
- nausea/vomiting
- alopecia
- impaired ovulation and spermatogenesis
- mutagenesis and carcinogenesis

Toxicities (specific)

- Cyclosphosphamide: hemorrhagic cystitis, bladder fibrosis, cardiotoxicity (reversible), SIADH
- Busulfan: interstitial pulmonary fibrosis
- Nitrosoureas: cumulative myelosuppression
- Platinum: acute tubular necrosis, ototoxicity

ANTHRACYCLINES

Mechanisms

- intercalate between strands of DNA double helix
- formation of drug free radicals
- inhibition of topoisomerase II

Examples:

- daunorubicin
- doxorubicin (Adriamycin)

Toxicities

- myelosuppression
- stomatitis
- cardiotoxicity (irreversible, dose-related)

Non Cell Cycle Active

CORTICOSTEROIDS

Mechanisms

- unclear –induce apoptosis of lymphoblasts and effective in lymphoid malignancies
- work via nuclear receptors

Examples

- prednisone
- dexamethasone

Toxicity

- typical steroid toxicity –relatively modest in this context

L-ASPARAGINASE (E. COLI, ERWINIA)

Mechanisms

- l-asparaginase converts asparagine to aspartate and NH3. Normal cells can reverse this process to form asparagine.
- Drug has activity in acute lymphocytic leukemia. Lymphoblasts lack asparagine synthetase and die without preformed asparagine in plasma.

Toxicity

- Hypersensitivity (urticaria, anaphylaxis)
- Pancreatitis
- Hepatotoxicity

Classification by Important Toxicity

1. Renal - Acute Tubular Necrosis
    - Platinum
    - Streptozotocin
    - Methotrexate
2. Hepatic
    - 6-Mercaptopurine (cholestatic jaundice)
    - L-asparaginase (abnormal liver function tests)
    - Anthracyclines (dependence on biliary excretion)
3. Bladder (hemorrhagic cystitis)
    - Cyclophosphamide
4. Neurotoxicity (paresthesias)
    - Plant alkaloids
5. Pulmonary (interstitial fibrosis)
    - Bleomycin
    - Busulfan
    - Nitrosoureas (high doses)
6. Cardiac
    - Anthracyclines (chronic cardiomyopathy)
    - Cyclophosphamide (acute arrhythmias)
7. Carcinogenesis
    - Alkylating agents
    - Procarbazine
8. SIADH
    - Vincristine

- Cyclophosphamide

Requirements for Combination Chemotherapy

1. Several different drugs, each independently active against a given disease
2. Each drug should have
   - A different mechanism of action
   - A different dose-limiting toxicity
3. As a result:
   - Each drug is given at full dose
   - The rate of cell kill increases
   - The chance of emergence of a drug-resistant clone decreases

Examples:

Combination Chemotherapy – ALL

Drug(s)	Dose-limiting toxicity	% Full Dose	% Complete Remission
Methotrexate (MTX)	Marrow	100	21
Mercaptopurine (MP)	Marrow	100	27
Vincristine (VCR)	Neuropathy	100	47
Prednisone (Pred)	Steroid	100	57
MTX + MP		50 + 50	45
PRED + MP		100 + 100	86
PRED + VCR		100 + 100	92

Combination Chemotherapy: Other Curative Regimens

MOPP – Hodgkin's Disease

Drug(s)	Toxicity	% Full Dose	% Remission
Nitrog. Mustard	Marrow	100	10
VCR	Neuropathy	100	5
PRED	Steroid	100	5
Procarbazine	Marrow	100	15
MOPP		60/100/100/60	70 (50% cure)

M-BACOP – Diffuse Lymphoma

Drug(s)	Toxicity	% Full Dose	% Remission
MTX-CF		100	10
Bleo	Lung	100	0
Adriamycin	Marrow	100	20
Cyclophosph.	Marrow	100	15
VCR	Neuropathy	100	10
PRED	Steroid	100	0
M-BACOP		100/100/60/60/100/100	80 (50% cure)

VBP – Testis

Drug(s)	Toxicity	% Full Dose	% Remission
VBL	Marrow	100	20
Bleo	Lung	100	0
Cis-Platinum	Kidney	100	20
VBP		100/100/100	90 (70% cure)

Adriamycin®= doxorubicin Oncovin®= vincristine

Tumor Host Resistance

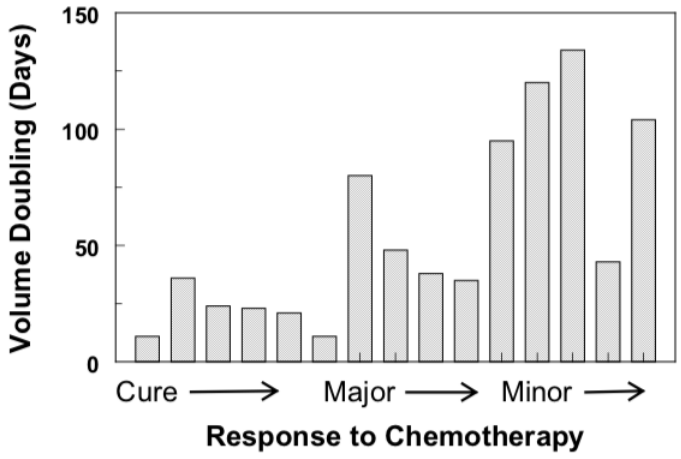
A. Changes in the tumor

1. Location of tumor cells
   - Pharmacologic sanctuary
   - Blood supply to the anatomical region
   - Extravascular distance for drug diffusion
   - Drug metabolism by extracellular enzymes and normal cells that surround the tumor
2. Effect of tumor size
   - First order kinetics
   - Penetration of drug
   - Gradients of oxygen, nutrients
3. Growth Characteristics

Mean volume doubling times for certain human tumors

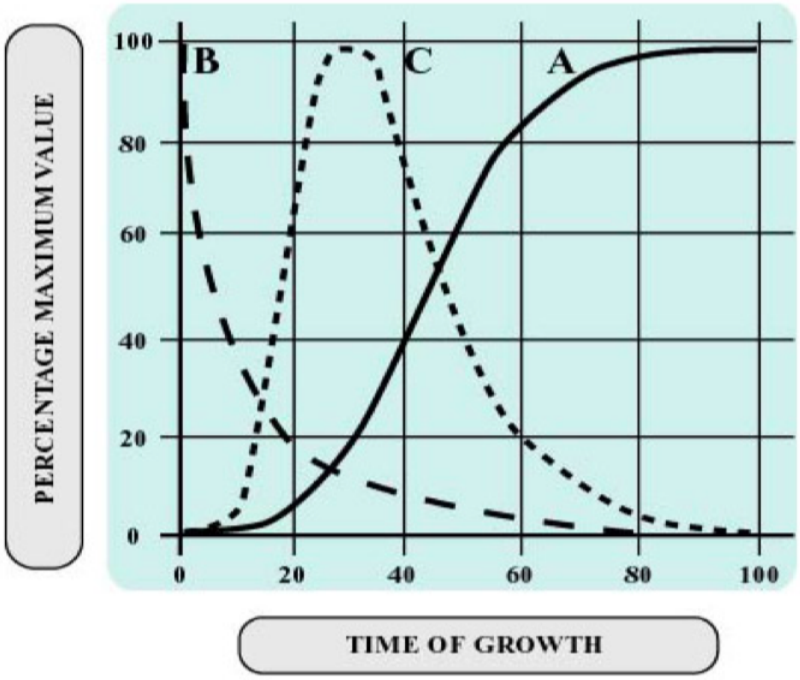
Tumor	Doubling Time (Days)
Testicular Carcinoma	21
Ewing's Sarcoma	22
Non-Hodgkin's Lymphoma	25
Osteogenic Sarcoma	34
Hodgkin's Disease	36
Fibrosarcoma	48
Colonic Adenocarcinoma	95
Pulmonary Adenocarcinoma	154

There is an inverse correlation between volume doubling time and response to chemotherapy (slower growth = worse response). Each bar in the graph below represents the average doubling time of a different human metastatic tumor:



Gompertzian growth

Relationship between tumor size (A), growth fraction (B), and growth rate (C)



Although growth fraction is maximal at time of initiation of growth, the growth rate is maximal when the tumor is about 37% of its limiting size.

B. Changes in the Host

1. Altered absorption, distribution or excretion of a drug so that less reaches the tumor.
2. Increased synthesis of enzymes from non-malignant cells which inactivate the drug.
3. Increased sensitivity of normal tissues to the effect of a drug.

Cellular Resistance

A. Natural Drug Resistance – lack of sensitivity of a tumor cell to drugs prior to therapy.

B. Acquired Drug Resistance – genotypic and phenotypic changes during therapy that render a tumor cell insensitive to the lethal effects of a drug.

1. Goldie-Coldman Hypothesis: the probability of selecting a single cell with resistance to a specific drug is related to both population size and mutation frequency. Drug exposure provides the pressure for selection of a resistant cell population.
2. The frequency of drug resistant mutants is increased by antitumor agents which are also mutagens. Heidelberger et al. demonstrated that treatment with chemical mutagens and single-step selection results in the emergence of tumor cells resistant to fluoropyrimidines. The one-step selection following exposure to a mutagen may be relevant to the clinical use of combinations such as CMF.

C. Mechanisms of Acquired Drug Resistance

- Decreased Expression of a gene product

Defective transport

Drug	Alteration
MTX	Decreased carrier-mediated uptake (5-methyltetrahydrofolate)
Melphalan	Decreased carrier-mediated uptake (leucine)
Cytosine arabinoside	Decreased membrane nucleoside binding (deoxycytidine)

Decrease in activating enzyme

Drug	Alteration
MTX	Defective polyglutamylation
Cytosine arabinoside	Decreased deoxycytidine kinase
6-MP, 6-TG	Decreased HGPRT
5-FU	Decreased uridine kinase, uridine phosphorylase

- Increased expression of a gene product

Increased drug inactivation

Drug	Alteration
Cytosine arabinoside	Increased cytidine deaminase
Bleomycin	Increased bleomycin hydrolase
Alkylating agents	Increased intracellular glutathione, metallothionein

Gene amplification of target enzyme

Drug	Alteration
MTX	Increased DHFR copy number
FUdR	Increased thymidylate synthase copy number

- Expression of an altered gene product

Drug	Alteration
MTX	DHFR
VCR	Tubulin
5-FU	Thymidylate synthase

D. Acquired Methotrexate Resistance

Acquired MTX resistance has been attributed to a variety of mechanisms. For example, the following have been identified in MTX-resistant sublines of a human squamous cell carcinoma (SCC15) established in culture by progressive dose escalation:

1. Altered transport
2. Defective polyglutamylation

- Polyglutamate derivatives (MTX-PGs) with 2 to 5 γ-linked glutamyl moieties (MTX-Glu2 to MTX-Glu5) are selectively retained by cells.
- MTX-PGs have a higher affinity for DHFR, cause prolonged inhibition of DNA synthesis and increase cytotoxicity.

3. Increased production of DHFR (gene amplification)
   - Abnormal homogeneous staining regions (HSRs): sites identified in MTX resistant cells which represent amplified DHFR genes on chromosome 2 (mouse) and 5 (human). HSRs are associated with stable resistance.
   - Double minute chromosomes (DMs): small chromosomes of varying size without centromeres, usually occurring in pairs. These chromosomes do not segregate and therefore are lost during the process of cell division. Gene amplification on the double minute chromosome is thus unstable in the absence of selecting agents.
4. Altered DHFR
   - DHFRs in some resistant cells have a low affinity for MTX.
   - An altered DHFR gene has a mutation in the codon for amino acid 22. This mutation (arginine for leucine) decreases both binding of MTX and function of the enzyme.

E. Multidrug or Pleotropic Resistance

1. Tumor cells exposed to a single drug develop cross-resistance to structurally unrelated compounds with different mechanisms of action. The affected drugs include a wide spectrum: anthracyclines, vinca alkaloids, actinomycin, podophyllotoxins.
2. Resistant cells have an impaired ability to accumulate and retain drug. Drug efflux is probably more efficient.
3. An over-expressed plasma membrane glycoprotein, designated the P- or permeability glycoprotein, with a MW of 170,000 daltons, is consistently found in multidrug- resistant human and animal cell lines, and in transplantable tumors.
   - Drug resistance is related to the amount of P-glycoprotein
   - Cells which regain drug sensitivity no longer express the membrane alteration.
   - Transfer of DNA from drug-resistant cells confers multidrug resistance and plasma membrane glycoprotein expression.
   - Transfer of multidrug resistance with a cDNA coding for the P-glycoprotein demonstrates that overexpression of this single gene is sufficient to confer the resistance phenotype.
4. The P-glycoprotein or MDR1 gene is a member of a small family of genes. Not all members of this family confer the multidrug-resistant phenotype, thus suggesting that there may be functionally distinct classes of P-glycoprotein isoforms.
5. Double minute chromosomes (DMs) and homogeneous staining regions (HSRs) are found in multidrug resistant lines. The degree of amplified DNA fragments correlates with the degree of drug resistance. The HSRs represent amplified P-glycoprotein genes and are reversible.
6. The P-glycoprotein is comprised of 1280 amino acids with 12 hydrophobic segments that act as transmembrane domains. There are two similar domains with cytoplasmic sites that bind ATP. Both domains appear to be required for function. P-glycoprotein is primarily expressed on plasma membranes while smaller amounts have been detected in the ER and Golgi membranes.
7. Vinblastine photoaffinity analogs bind to the P-glycoprotein, and binding is competitively antagonized by unlabeled vinblastine and anthracycline. The vinblastine protein complex is precipitated by a monclonal antibody to the P-glycoprotein. Moreover, vinblastine is transported by an ATP-dependent process through membranes that contain P-glycoprotein. These findings have established that the P-glycoprotein is a transporter molecule.

   The P-glycoprotein is also homologous to bacterial transport proteins which are involved in ATP-dependent transport of specific molecules, particularly hemolysin, through the bacterial inner cell membrane.
8. High levels of MDR1 gene expression have been found in liver, colon, small intestine, kidney, adrenal cortex and adrenal medulla. The P-glycoprotein is localized in a highly polar fashion on the bile canalicular surface of hepatocytes, the lumenal surface of the proximal tubule cells of the kidney, and on the lumenal mucosal surface of intestinal columnar cells. MDR1 RNA levels are usually high in those cancers derived from normal tissues which themselves have high MDR1 expression.
9. Intrinsic multidrug resistance appears to be related to persistent expression of a gene involved in normal cellular function. Similar biochemical changes occur in multidrug resistant human breast cancer cells and in rat hyperplastic liver nodules that develop resistance to a wide variety of hepatotoxins (Solt Farber model). Mechanisms of de novo resistance to therapy in tumors associated with increased carcinogen exposure (colon, lung cancer) may therefore be similar to those associated with acquired resistance to anti-neoplastic agents.

10. Drugs such as verapamil, diltiazem and quinidine have been found to overcome multidrug resistance in cell culture and in some animal experiments. For example, verapamil has been used to reverse adriamycin resistance in human ovarian cancer cells. Verapamil competes with vinblastine for binding, suggesting that drug binding to the P-glycoprotein is a necessary step in the process of drug resistance.

    Other agents that reverse P-glycoprotein-mediated multidrug resistance include steroids and steroid antagonists (progesterone and tamoxifen) and reserpine. The most potent chemosensitizers are hydrophobic molecules with a basic nitrogen atom and two planar aromatic rings (termed the “pharmacophore”).

11. Verapamil has been used clinically in an attempt to reverse multidrug resistance. A Phase I-II study failed to demonstrate a potentiation of doxorubicin therapy with verapamil in eight drug-resistant ovarian cancer patients. However, a more recent study has shown a therapeutic benefit for three of eight patients with multiple myeloma and non-Hodgkin’s lymphoma by adding a continuous infusion of verapamil to the VAD regimen. The three responding patients had P-glycoprotein positive tumors. Dose-limiting toxicity of verapamil was hypotension and cardiac arrhythmias. Myelosuppression was not increased in this trial. In this regard, in vitrostudies have demonstrated that doxorubicin cytotoxicity is not increased by verapamil in normal human marrow cells. Other clinical studies are underway using amiodarone and quinidine as inhibitors of P-glycoprotein mediated resistance.

F. Acquired Resistance to Alkylating Agents

Prolonged exposure of human cells to alkylating agents has resulted in a maximum of 10- 15 fold resistance. This finding for alkylating agents is distinct from patterns of resistance seen with other chemotherapeutic agents. Alkylating agents therefore more closely resemble X-irradiation where significant resistance has not been demonstrated with repetitive treatment.

Reference

- Bast Fr. RC, Kufe DW, Pollack RE, Weichselbaum RR, Holland JF, Frei III E.: Cancer Medicine, 5th Edition. BC Decker, Inc., 2000

1.18: Opioid Pharmacology

Opium – a mixture of alkaloids from *Papaver somniferum*. An opiate is a naturally occurring alkaloid, i.e., morphine or codeine, and an opioid is any natural or synthetic compound, which has morphine-like properties. Hundreds of opioid alkaloids and peptides have been synthesized, but all clinically available opioid analgesics are alkaloids.

Structure-Activity Relationships

Most opioid analgesics are related to morphine (Figure 16.1). Distinctive features of morphine include 5 rings, 3- and 6-hydroxyl groups (phenolic and alcoholic), piperidine ring with an N-methyl group, and a quaternary carbon at position 13. Morphine is optically active, and only the levorotatory isomer is an analgesic.

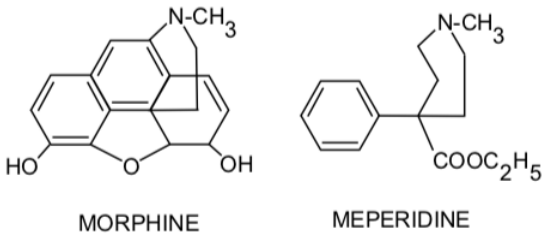


Figure 16.1

Simple modifications of morphine make active analgesics, e.g., Codeine is morphine O-methylated at position 3 and geroin is morphine O-acetylated at positions 3 and 6. Replacing the N-methyl with something larger (allyl, cyclopropyl, cyclobutyl) usually produces a compound with opioid antagonist properties. N-allyl substitution of morphine and oxymorphone produces the antagonists nalorphine and naloxone, respectively. Morphine may be modified extensively, but still have agonist activity. Meperidine (Demerol) is a synthetic opioid with only fragments of the morphine structure (Figure 16.1).

Opioid Classification

1. Based on intrinsic activity
   - Agonists (morphine, fentanyl)
   - Pure antagonists (naloxone, naltrexone)
   - Mixed agonist-antagonists (nalbuphine, butorphanol)
2. Based on interaction with μ, κ, or δ opioid receptor subtypes
   - All three receptors have been cloned, and knockout mice created.
   - Each receptor thought to have 2-3 (or more) subtypes, but no distinct gene products have been identified. All belong to the superfamily of G-protein coupled receptors.
   - Most opioid analgesics are relatively selective μ opioid agonists. The various μ effects are discussed below.
   - A few analgesics (pentazocine, nalbuphine, butorphanol) are κ agonists, although they are not highly selective. Experimental selective κ drugs produce analgesia, but also unique effects like diuresis and dysphoria.
   - The selective δ agonists are mainly peptides. Receptor may function permissively with μ receptor (allosteric interaction?).

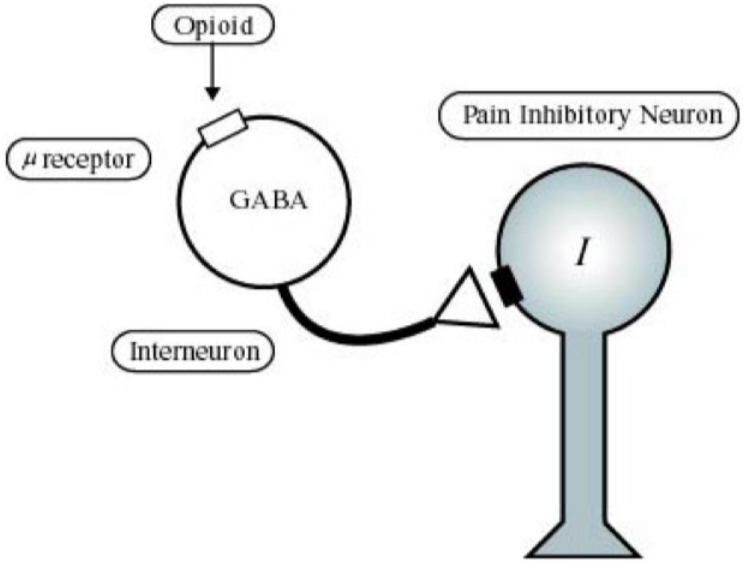
Endogenous Opioid Peptides

1. Enkephalins include several compounds derived from a large proenkephalin molecule (also called proenkephalin A).
   - Most important compounds are pentapeptides, methionine- and leucine- enkephalin. Relatively selective δ ligands.
   - Widely distributed in CNS
   - Act like morphine to modulate neurotransmitter release (see p. 3)
   - Found with catecholamines in sympathetic terminals and adrenal.
2. Endorphins (chiefly β-endorphin) are derived from the large precursor molecule pro opiomelanocortin (POMC).
   - POMC also the precursor for ACTH and MSH, which are found together withβ-endorphin.
   - β-endorphin is a 31 amino acid peptide which has analgesic activity in man and animals. It binds preferentially to μ receptors.
   - Localized primarily in pituitary and hypothalamus.

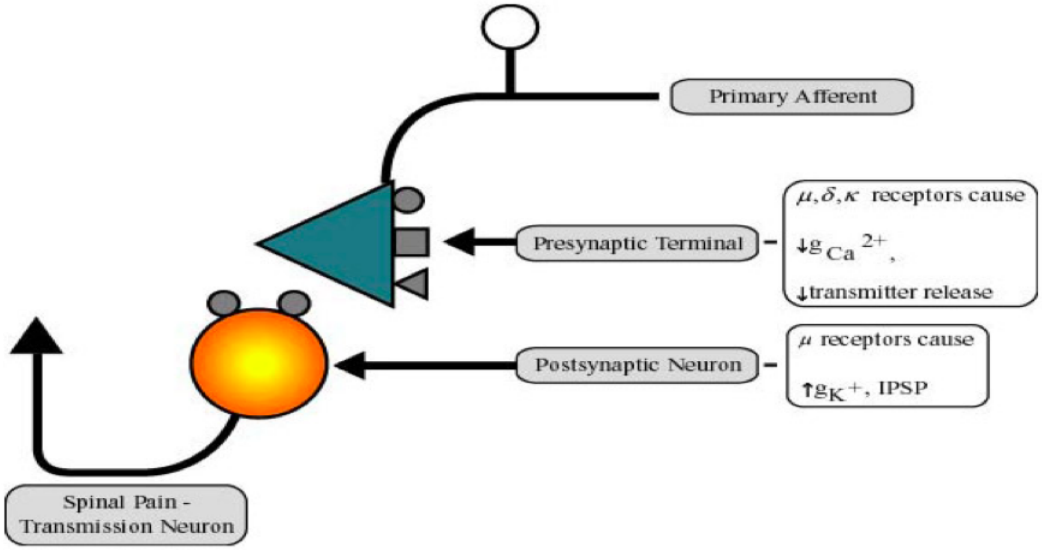
3. Dynorphins are derived from a prodynorphin molecule (also called proenkephalin B).
    - Dynorphin A is a 17 amino-acid peptide which is a potent and highly selective agonist at κ receptors.
    - Similar distribution to the enkephalins.
4. Opioid peptides are located in places which allow them to function as neurotransmitters or neuromodulators.
5. Probably modulate pain transmission in the cord and alter acetylcholine release in the myenteric plexus.
6. Postulated to play fundamental roles in areas as diverse as hormonal secretion, thermoregulation, and cardiovascular control.

Opioid Agonists -Pharmacodynamics

1. General Mechanisms



- Opioids inhibit adenylyl cyclase via interaction with G_i/G_0.



- Hyperpolarize postsynaptic neurons by increasing outward K+ currents
- Act presynaptically to block Ca++ uptake and consequently inhibit neurotransmitter release. Opioids have been shown to inhibit the release of many neurotransmitters, including substance P, acetylcholine, norepinephrine, glutamate, and serotonin.

- Opioids produce highly specific depressant and stimulant effects by acting at discrete CNS sites. For example, morphine stimulates the vagal nuclei in the medulla while depressing respiratory centers only a few millimeters away.
- The mechanism for neuronal stimulation is often the depression of an inhibitory interneuron .

2. General Clinical Properties

Acute and Chronic Effects of Opioids

Acute	
Analgesia	Miosis
Respiratory Depression	Nausea and vomiting
Sedation	Skeletal muscle hypertonus
Euphoria	Constipation
Vasodilatation	Urinary retention
Bradycardia	Biliary Spasm
Cough suppression	
Chronic	
Tolerance	Physical Dependence

- All of the clinically-used μ opioid agonists produce these effects.
- The few qualitative differences between drugs (e.g. histamine release) usually do not involve specific opioid receptor mechanisms.
- Opioids differ greatly in physicochemical properties as well as speed of onset and duration of action, so clinical selection is frequently based on pharmacokinetic considerations.

3. CNS Effects

a. Analgesia and Mood

Mechanisms:

Clinical characteristics:

- Processing of pain information is inhibited by a direct spinal effect at the dorsal horn. Probably involves presynaptic inhibition of the release of tachykinins like substance P.
- Rostrad transmission of pain signals decreased by activation of descending inhibitory pathways in the brainstem.
- Emotional response to pain altered by opioid actions on the limbic cortex.
- Opioids may act at receptors located peripherally on sensory neurons. Possibly important in painful conditions accompanied by tissue inflammation.
- Selective relief of pain at doses which do not produce hypnosis or impair sensation.
- Typically, patients report that pain is still present, but the intensity is decreased and it no longer bothers them as much.
- Mood elevation, sometimes frank euphoria can occur. Sense of well-being and cloudy detachment thought to be an important reason for opioid abuse.
- Some types of pain more responsive to opioids than others. More effect in prolonged, burning pain than sharp pain of an incision. Neuropathic pain (e.g. pain of nerve root compression) can be very resistant.
- Relative potencies (see text) usually determined in postoperative pain. Similar data for other pain states generally not available. Actual dose administered will vary greatly from patient to patient.

b. Sedation-Hypnosis

- Drowsiness, feelings of heaviness, and difficulty concentrating are common.
- Sleep may occur with relief of pain, although these drugs are not hypnotics.

  Most likely to occur in elderly or debilitated patients and in those taking other CNS depressants (EtOH, benzodiazepines).

c. CNS Toxicity

- Dysphoria and agitation occur infrequently (incidence higher with meperidine and codeine).
- Seizures can be produced by meperidine—major metabolite, normeperidine, is a convulsant.

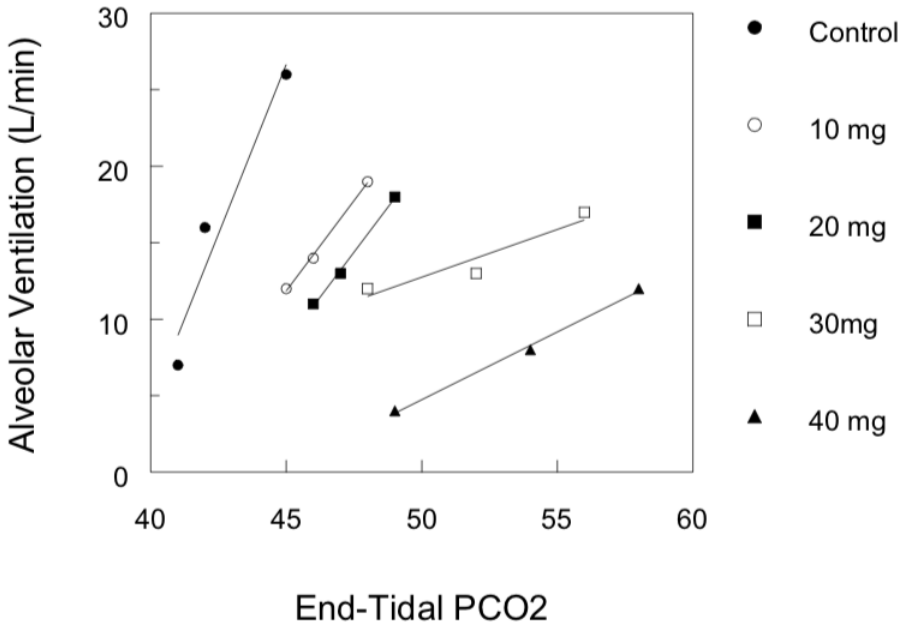
- Opioids generally avoided in head injury or when elevated intracranial pressure (ICP) is suspected.
  1. ↓ ventilation can ↑ PaCO2 and raise ICP further.
  2. Pupil effects may mask changing neurologic signs.

d. Respiratory Depression

Mechanisms:

Clinical Characteristics:

- Direct effects on respiratory centers in the medulla.
- Dose-related depression of ventilatory response to hypercarbia and hypoxia. This shifts CO2 response curve to the right (see figure).
- May involve a distinct subset of μ2 receptors.
- With usual analgesic doses, arterial O2 saturation often decreases.
- Drive to breathe may be abnormal despite an apparently normal respiratory rate and state of consciousness.
- Effects are dose related. First CO2 and hypoxic response are depressed, then respiratory rate slows. Very large doses may cause irregular or periodic breathing and eventually apnea.
- Trouble most likely to occur with pre-existing pathology (such as hypothyroidism, pulmonary or CNS disease) or previous drug administration (alcohol, general anesthetics, benzodiazepines).
- Sleep depresses the response to CO2 and potentiates the opioid effect.
- Respiratory depression is the major toxicity of opioids and nearly always the cause of death from overdose.
- Equianalgesic doses of all opioids produce equivalent amounts of respiratory depression. There is no convincing evidence than any analgesic is more or less dangerous than morphine in this regard.



- Both analgesia and respiratory depression are reduced by administration of an opioid antagonist or by the development of tolerance. This has two important clinical implications:
  1. Tolerant individuals who require large amounts of opioid for relief of pain are not at proportionately increased risk for respiratory depression
  2. Respiratory depression is difficult to reverse without reversing some analgesia (see "Naloxone").

e. Cough Suppression

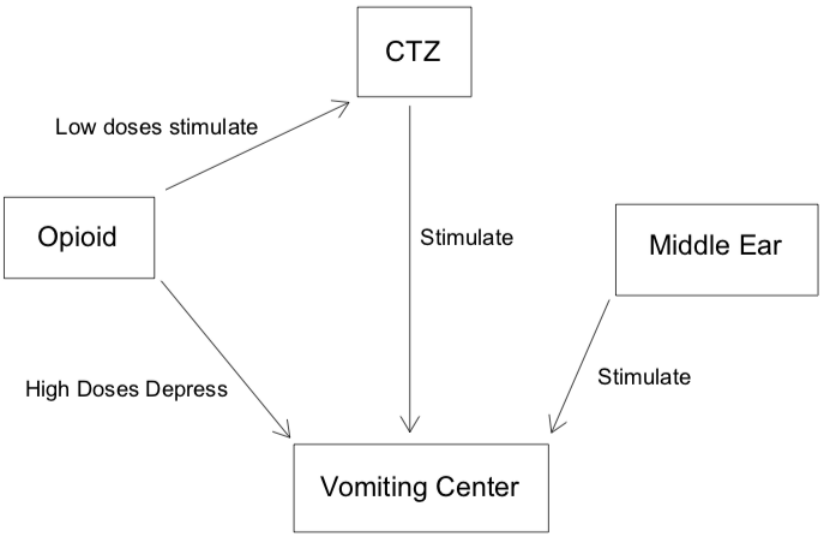
- Depression of cough centers in the medulla (and possibly, the periphery).
- Different molecular mechanism than analgesia or respiratory depression— cough suppressed by dextro-isomers of opioids (e.g. dextromethorphan), compounds which have no analgesic activity.

f. Pupillary Constriction

- Stimulation of Edinger-Westphal (parasympathetic) nucleus of the oculomotor nerve to produce miosis.
- Pinpoint pupil is a pathognomonic sign of opioid overdose.
- Antagonized by naloxone, atropine or ganglionic blockers.

g. Nausea and Vomiting

- Complex effects on vomiting centers in the medulla.



- Direct stimulation of the chemoreceptor trigger zone (CTZ) in the area postrema on the floor of the fourth ventricle. This activates the vomiting center proper
- Emetic effects markedly potentiated by stimulation of the vestibular apparatus, so ambulatory patients are much more likely to vomit than those lying quietly.
- In animals (and man?), very high doses can depress the vomiting center

h. Muscle Rigidity

- Large i.v. doses can cause generalized stiffness of skeletal muscle. Thought due to μ-mediated increase in striatal dopamine synthesis and inhibition of striatal GABA release.
- Most common with fentanyl and congeners.
- May play a role in some overdose fatalities.

4. Cardiovascular Effects

- Decrease in central sympathetic tone causes vasodilation and orthostatic hypotension.
- Effects on both capacitance and resistance vessels.
- Bradycardia by stimulating central vagal nuclei
- Little or no myocardial depression.

5. Histamine Release

- Morphine, codeine, meperidine cause non-immunologic displacement of histamine from tissue mast cells.
- Occasionally redness, hives, itching near injection site. Rarely, hypotension, generalized flushing.
- Not an allergy—true allergic responses to opioids are very rare.
- Facial itching and warmth are common after opioids—probably a dysesthesia which has nothing to do with histamine.

6. Smooth Muscle Effects

a. Intestine and Stomach

- Spasm of smooth muscle all along the GI tract. Both small and large bowel become hypertonic, but rhythmic propulsive activity is diminished. Delay in intestinal transit time and spasm of the anal sphincter cause constipation.
- Delayed gastric emptying. Important because it may slow absorption of oral medications.
- Mechanism involves both CNS effects and peripheral actions on opioid receptors in the enteric plexus. Smooth muscle effects of morphine > meperidine > agonist-antagonist opioids.

- Chronic administration of opioids frequently necessitates the administration of laxatives and stool softeners to treat constipation. Recent evidence that poorly-absorbed quaternary opioid antagonists are also effective in reversing this local effect.
- Constipating effect is used therapeutically for treatment of diarrhea. Diphenoxylate (in Lomotil) and loperamide (Imodium) are poorly-absorbed opioids that do not produce central effects.

b. Biliary System

- Contraction of smooth muscle along the biliary tree and spasm of the sphincter of Oddi.
- Can precipitate biliary colic on rare occasions.
- Effect antagonized by naloxone and partially reversed by glucagon, nitroglycerin, or atropine.

c. Urinary Tract

- Increase contractions of the ureter and tone of the urinary sphincter, but decrease force of detrusor muscle contraction. Decreased attention to full bladder. Can cause urinary retention.
- Probably both central and peripheral mechanisms involved.

7. Effects on Pregnancy and the Neonate
   - All cross the placenta.
   - No teratogenic effects, but chronic use may cause physical dependence in utero. Neonatal withdrawal after delivery can be life-threatening.
   - Opioids given during labor can cause respiratory depression in baby.
8. Tolerance
   - Reduction in effect with repeated dosing (or higher dose to produce same effect). First indication usually decreased duration of analgesia, then decreased intensity. Can be profound.
   - Cross-tolerance to other opioids.
   - Mechanism not known precisely. Involves adaptive response of adenylyl cyclase and/or G protein coupling. Not a pharmacokinetic effect.
   - Develops most rapidly to depressant effects like analgesia, respiratory depression, euphoria, but much less tolerance to stimulatory effects like constipation or miosis. This has some important clinical consequences:
     1. Heroin addicts or methadone maintenance patients may have little euphoria from high doses but continue to experience constipation and miosis.
     2. Terminal cancer patients and others requiring high doses for analgesia are also tolerant to respiratory depression (cf. p. 6), but they frequently require treatment for constipation.
9. Physical Dependence
   - Adaptation which produces stereotyped withdrawal syndrome (abstinence) when drug is stopped. Symptoms stop when small dose of opioid is given.
   - Giving antagonist (naloxone) to physically dependent person causes rapid onset of more severe precipitated abstinence.
   - Withdrawal symptoms include runny nose, vomiting, diarrhea, gooseflesh, mydriasis, shaking chills, drug seeking behavior.
   - Physical dependence not the same as psychological dependence or addiction. Mild physical dependence may be common.
   - Addiction produced by appropriate medical treatment is a very unusual event. Irrational fear of addicting patients cited as a frequent cause for inadequate pain treatment.
10. Use of Methadone in Opioid Physical Dependence:
    - Opioid Detoxification—patient switched from short-acting opioid to methadone ($T_{1/2}$ = 35 hr) and tapered slowly. Withdrawal symptoms protracted, though mild. Adjuvants like clonidine and sedatives may be helpful.
    - Maintenance—chronic methadone to maintain a state of tolerance and physical dependence. Several putative benefits:
      1. ↓ withdrawal symptoms, so drug seeking (& illegal activity) decreased.
      2. Tolerance develops to opioid euphoria, so injection of illegal heroin is not reinforcing. (Behavior may or may not decrease.)
      3. Methadone given orally, so risk of needles reduced.
      4. Obtaining methadone requires regular contact with caregivers and access to counseling and other treatment.

Onset and duration most often the basis for selection of an opioid. Huge variation in physicochemical properties and therefore absorption and distribution throughout the body.

Physicochemical Properties of Some Opioid Agonists

Physicochemical Properties of Some Opioid Agonists

Drug	pK_a	% Ionized[1]	Partition Coefficient[2]
Morphine	7.9/9.4	76	1.4
Meperidine	8.5	95	38.8
Fentanyl	8.4	91	860

[1] At pH 7.4

[2] A measure of lipid solubility, this is the n-octanol/water partition coefficient corrected for the percentage of drug unionized at pH 7.4.

Opioid Pharmacokinetic Parameters

Drug	$T_{1/2\alpha(\beta)}$ (min)	$T_{1/2(\gamma)}$ (hrs)	Vol_{dist} (L/kg)	Clearance (ml/kg/min)	% Bound
Morphine	1.7 (19.8)[1]	3-4	3.2-4.7	12.4-15.2	30
Meperidine	7-11	3-4	2.8-4.2	10.1-16.4	64
Fentanyl	1.8 (13.2)[1]	4-7	3.2-4.2	11.2-13.3	84

[1] The data are best described by a three compartment model.

A. Pharmacokinetics of Morphine

1. Rapid absorption, wide distribution, and rapid clearance from plasma.
2. Clearance mainly by hepatic biotransformation (70% first pass).
   - Primarily 3-glucuronide (inactive)
   - 6-glucuronide. A highly active metabolite, but role in clinical effects is uncertain. May account for opioid depression reported in renal failure. May also be important with chronic dosing.
   - N-demethylation to normorphine
3. Polar metabolites cleared by kidney.
4. Relatively hydrophilic drug, so CNS penetration and exit are slow. This accounts for slow onset and long duration. Effects lag behind changes in plasma concentrations.

B. Pharmacokinetics of Meperidine

1. Rapid absorption, wide distribution, and rapid clearance from plasma.
2. Clearance mainly by hepatic biotransformation (48-56% first pass).
   - N-demethylation to normeperidine, oxidation to meperidinic acid or normeperidinic acid.
   - Normeperidine is a CNS stimulant and can produce convulsions in man. Metabolite has T1⁄2 of 8-12 hr so significant amounts may accumulate. Toxicity most likely with high doses in renal failure.

C. Pharmacokinetics of Fentanyl

1. Rapid absorption, wide distribution, moderately rapid hepatic clearance
2. More than 60% first-pass metabolism to inactive metabolites.
3. Extremely lipophilic. Rapidly crosses BBB and other membrane barriers so effects parallel changes in plasma concentrations.

4. Fat solubility means that drug may be administered by multiple routes: useful analgesic effects by transdermal patch, intranasal spray, and buccal mucosa (fentanyl “lollipop”).

Opioid Agonists – Individualization of Dosage

1. Analgesic requirements are enormously variable. Usual adult morphine dose (10 mg) only 70% effective in acute pain.
2. Range of effective concentrations (the “therapeutic window”) is narrow for each patient but varies widely between patients. Implication: “cookbook” analgesia likely to be inadequate or excessive much of the time.
3. Lower starting doses for elderly, hypovolemic, debilitated, hypothyroid or those given other CNS depressants.
4. Do not be afraid to give adequate treatment to patients who have become highly tolerant.
5. Watch for accumulation of parent drug and/or metabolites in hepatic or renal failure.

Opioid Antagonists

1. Naloxone
   - Pure, competitive antagonist at μ, κ, and δ receptors (highest affinity at μ)
   - Given alone, almost no effect. Some behavioral effects in animals.
   - Rapidly reverses opioid overdose, but effect short due to redistribution. Patient may become renarcotized.
2. Naltrexone
   - Used orally in high doses to treat detoxified heroin addicts (blocks euphoria from injected heroin).
   - Effects primarily from active metabolite, 6-β-naltrexol.

Opioid Agonist-Antagonists

1. Developed in search for less abusable potent analgesics.
2. All have analgesic (agonist) properties as well as ability to antagonize morphine effects.
3. Two basic mechanisms:

- Partial agonists at μ receptor. Buprenorphine has high affinity, but limited efficacy at μ receptor. Given alone, it has morphine-like effects. Competes effectively with agonists like morphine and may reduce effect.
- Agonists/Partial agonists at κ receptor. Nalorphine, pentazocine, nalbuphine, butorphanol act as κ agonists (probably κ3) to produce analgesia. Also act as competitive antagonists at μ receptors (high affinity but no efficacy at this receptor).

1. Clinical properties:

- Potent analgesics effective in moderate to severe pain.
- Relatively limited toxicity (respiratory dep., smooth muscle)
- Decreased abuse potential, but also decreased patient acceptance (mood elevation may be clinically important!).
- Occasional dysphoria or hallucination with κ agonists
- Antagonist properties mean they can precipitate withdrawal in patients already receiving chronic treatment with opioid agonists.

1. Neither agonist vs. antagonist potency nor μ/κ selectivity seem to predict clinical utility or patient acceptance.

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Glossary

Sample Word 1 | Sample Definition 1

Glossary

Sample Word 1 | Sample Definition 1

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