Dosage Form Design

Lecture 2

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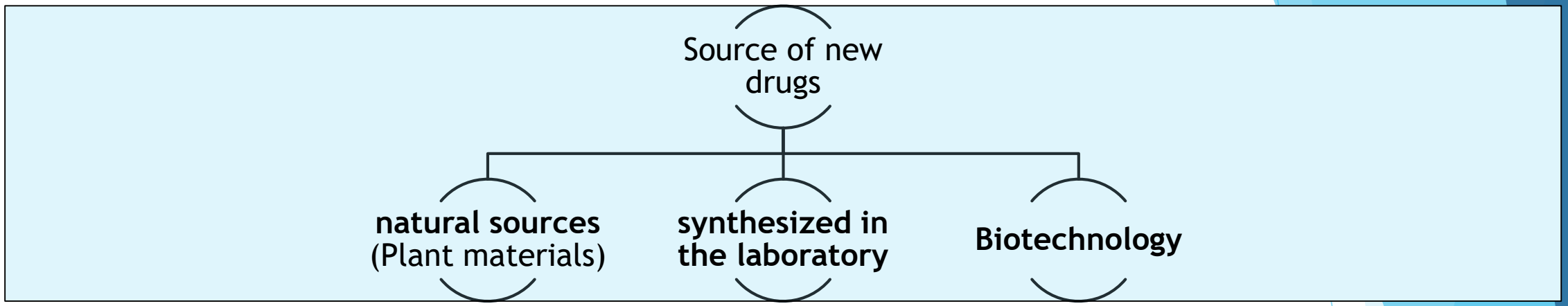
Drug discovery and drug design

- The discovery of new drugs and their development into commercial products take place across the broad scope of pharmaceutical industry.
- The basic underpinning for this effort is the cumulative body of scientific and biomedical information generated worldwide in research institutes, academic centers, and industry. (The combined efforts of **chemists**, **biologists**, **molecular biologists**, **pharmacologists**, **toxicologists**, **statisticians**, **physicians**, **pharmacists** and **pharmaceutical scientists**, **engineers**, and many others participate in drug discovery and development.)
- Some pharmaceutical firms focus their research and development (R&D) activity on new prescription drugs for human use
- Many of the large pharmaceutical companies develop and manufacture products of various types, with some firms having subsidiary companies for specialized functions and products.
- The pharmaceutical industry in the United States grew rapidly during World War II and in the years immediately following the upsurge in production is due to wartime hazards and consequent undependability of overseas shipping, the unavailability of drugs from previous sources and the increased need of drugs of all kinds.
- **Penicillin,** antibiotic that became commercially available in **1944, 15 years after its discovery in England by Sir Alexander Fleming** and 1 year before the end of the war.

- The post war boom in drug discovery continued with the development of many new agents, such as vaccines to protect against poliomyelitis, measles, and influenza, and new pharmacologic categories of drugs including oral hypoglycaemic drugs effective against certain types of diabetes mellitus, antineoplastic or anticancer drugs, immunosuppressive agents to assist the body's acceptance of organ transplants. Oral contraceptives to prevent pregnancy, and a host of tranquilizers and antidepressant drugs to treat the emotionally distressed.
- Annually, approximately 40 new molecular entities receive FDA approval for marketing. In addition, many new dosage strength and dosage forms of previously approved drugs, new generic products, and new biologics are approved each year.
- Not all drugs are discovered, developed, and first approved in the United States



1. **natural sources** (Plant materials) Plant extracts from *V. rosea* yield two potent drugs. These two materials, vinblastine and vincristine, since have been used successfully in the treatment of certain types of cancer, including acute leukemia, Hodgkin disease, lymphocytic lymphoma, and other malignancies

After the isolation and structural identification of active plant constituents, organic chemists may recreate them by

- total synthesis in the laboratory
- use the natural chemical as the starting material in the creation of slightly different chemical structures through molecular manipulation (semisynthetic drugs)

semisynthetic drugs, may have a slightly or vastly different pharmacologic activity from that of the starting substance, depending on the nature and extent of chemical alteration.

Source of new drugs

2- synthesized in the laboratory (some by accident, mostly by many years of work).

3- Biotechnology (engineered biologic material resulting from research that is more targeted; that is, directed specifically toward the identified physiologic/metabolic process or biomolecular target of a disease)

- Example on Monoclonal antibodies application (home pregnancy testing products). Their use ensures that a women can perform the test easily in a short period with high reproducibility and in an inexpensive manner.
- In these tests, the mAb is highly sensitive to binding on one site on the human chorionic gonadotropin (HCG) molecule, a specific marker to pregnancy because in healthy women, HCG is synthesized exclusively by the placenta.
- The first FDA-approved therapeutic mAb was muromonab, a transplant rejection drug, approved in 1986.

A Goal Drug

- In theory, a goal drug

1. Would produce the specifically desired effect
2. Be administered by the most desired route (generally oral) at minimal dosage and dosing frequency
3. Have optimal onset and duration of activity
4. Exhibit no side effects
5. Following its desired effect would be eliminated from the body efficiently and completely and without residual effect
6. It would be easily produced at low cost
7. Be pharmaceutically elegant
8. Physically and chemically stable under various conditions of use and storage.

Methods of Drug Discovery

1. **Random or untargeted screening:** involves the testing of large numbers of synthetic organic compounds or substances of natural origin for biologic activity

- Purposes: random screens may be use initially
  1. to detect an unknown activity of the test compound or substance
  2. to identify the most promising compounds to be studied by more sophisticated non-random targeted screens to determine a specific activity
- sometimes promising compounds may be overlooked if the screening models are not sensitive enough to reflect accurately the specific disease against which the agent or its metabolites may be useful.

The initial bioassays may be performed in vitro using cell cultures to test the new agent's effect against enzyme systems or tumor cells
whereas subsequent bioassays may be performed in vivo and may use more expensive and disease-specific animal models.
Newer methods, such as high-throughput screening, are capable of examining 15,000 chemical compounds a week using 10 to 20 biologic assays.

Methods of Drug Discovery

2. **Molecular modification:** is chemical alteration of a known and previously characterized organic compound (frequently a **lead compound**) for the purpose of enhancing its useful as a drug.

Purpose: this could mean

1. Enhancing its specificity for a particular body target site
2. Increasing its potency
3. Improving its rate and extent of absorption
4. Modifying to the advantage its time-course in the body
5. Reducing its toxicity
6. Changing its physical and chemical properties (e.g., solubility) to provide desired features.

- The molecular modifications may be slight or substantial

Lead compound

is a prototype chemical compound that has a fundamental desired biologic or pharmacologic activity. Although active, the lead compound may not possess all of the features desired, such as potency, absorbability, solubility, low toxicity, and so forth.

- the medicinal chemist ma seek to modify the lead compound's chemical structure to achieve the desired feature while reducing the undesired ones.
- The synthesis of derivatives of the prototype chemical may ultimately lead to successive generations of new compounds of the same pharmacologic type. Ex The development of new generations of cephalosporin antibiotics,

Most drugs exhibit activities secondary to their primary pharmacologic action. It is common to take advantage of a secondary activity by using molecular modification to develop new compounds

. **Example:** Finasteride (Proscar) was originally developed and approved to treat benign prostatic hyperplasia. Later, the same drug as (Propecia) was approved at lower recommended dosage to treat male pattern baldness.

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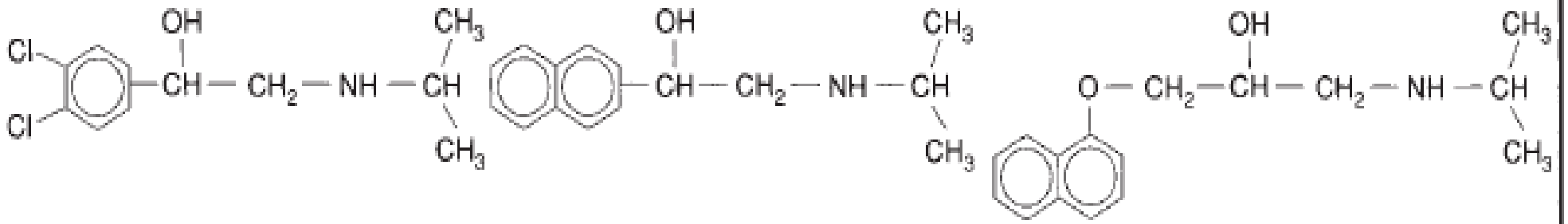
BETA-BLOCKERS



Dichloroisoproterenol
1957

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Pronethalol
1962

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Propranolol*
1964

Progress leading to the first commercial beta-blocker. Dichloroisoproterenol—first compound with beta-adrenoceptor blocking action; had partial agonist (sympathomimetic) activity. Pronethalol—beta-adrenoceptor blocking agent, relatively free from sympathomimetic activity. Clinical use limited by side effects, including light-headedness, incoordination, nausea and vomiting. Propranolol—beta-adrenoceptor blocking agent, free of sympathomimetic activity, and lacking side effects of pronethalol in humans.

The molecular modifications that led to the discoveries of the first commercial beta-blocker, propranolol

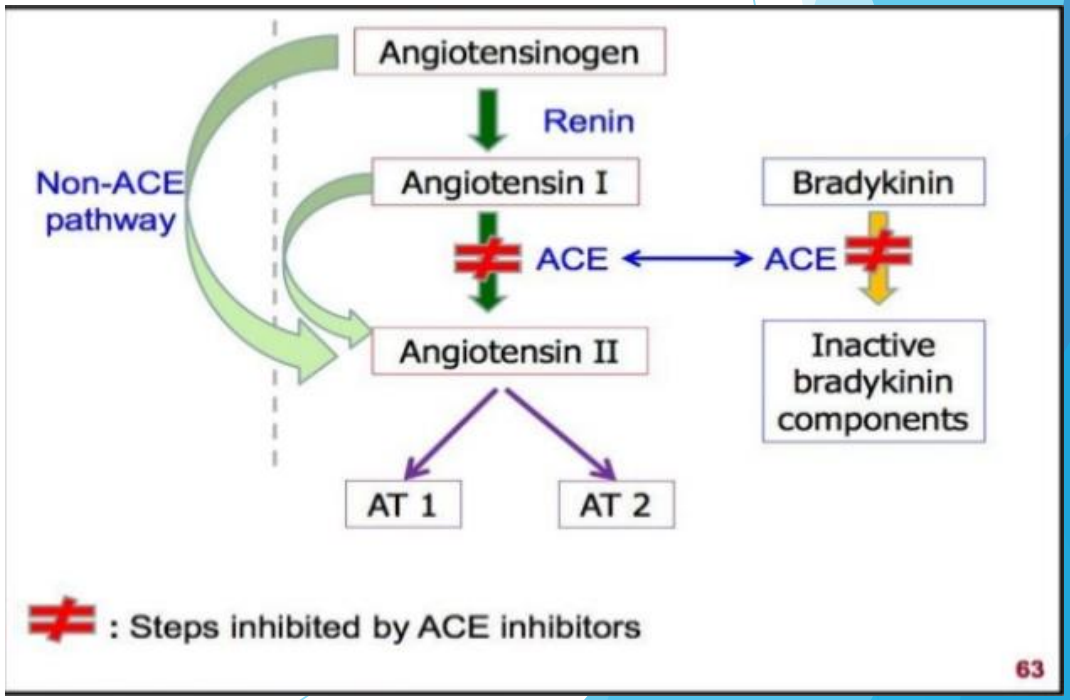
Methods of Drug Discovery

3. **Mechanism-based drug design:** is a molecular modification to design a drug that interferes specifically with the known or suspected biochemical pathway or mechanism of a disease process

Purpose: The intention is the interaction of the drug with specific cell receptors, enzymes systems, or metabolic process of pathogens or tumor cells, resulting in blocking, disruption, or reversal of the disease process.

Example of Mechanism-based drug design

Enalapril (Enalaprilat, Vasotec), which inhibits the angiotensin-converting enzyme (ACE) that catalyzes the conversion of angiotensin I to the vasoconstrictor substance angiotensin II. Inhibition of the enzyme results in decreased plasma angiotensin II, leading to decrease vasopressor effects and lower blood pressure.



FDA's Definition of a New Drug

- A New Molecular Entity (NME) is defined by the FDA as an active ingredient that has never before been marketed in the United States in any form
- According to the FDA, a new drug is any drug that is not recognized as being safe and effective in the conditions recommended for its use in the labeling among experts who are qualified by scientific training and experience.
- **Note: A drug need not be a new chemical entity to be considered new.**

1. A change in a previously approved drug product's formulation or method of manufacture constitutes newness under the law since such changes can alter the therapeutic efficacy and/or safety of a product.
2. A combination of two or more old drugs or a change in the usual proportions of drugs in an established combination product.
3. A proposed new use for an established drug, a new dosage schedule or regimen, a new route of administration, or new dosage form makes a drug or a drug product's status new and triggers reconsideration for safety and efficacy.

Drug Nomenclature

- When first synthesized or identified from a natural source, an organic compound is represented by an empirical formula, for example, $C_{16}H_{19}N_3O_5S.3H_2O$ for amoxicillin, which indicates the number and relationship of the atoms in the molecule.
- To be adequate and fully specific, name must reveal every part of the compound's molecular structure, so that it describes only that compound and no other.
- The systematic name is soon replaced in scientific communication by a shortened name, which, although less descriptive chemically, is understood to refer only to that chemical compound.
- This shortened name is the chemical's **non-proprietary (or generic or official or public)** name (e.g., amoxicillin). It is different from **Brand name** which is given by the company to the product
- The task of designating appropriate **non-proprietary names** for newly found chemical agents rests primarily with the **USAN** Council (U.S. Adopted Names (USAN) Council).
- paracetamol/acetaminophen is the non-proprietary name (generic name) while Crocin/Metacin/Meftal/Tylenol etc. are brand names or proprietary name

- Note: Nonproprietary names are issued only for single agents, whereas proprietary names may be associated with a single chemical entity or with a mixture of chemicals constituting a specific proprietary product.

Biologic Characterization

- Drug substances undergo preclinical testing for biologic activity to assess their therapeutic activity.
- These studies, fall into areas of **pharmacology, drug metabolism,** and **toxicology** and leads to the determination of whether a chemical agent possesses adequate features of safety and sufficient promise of usefulness to pursue as a prospective new drug.
- To judge whether a drug is safe and effective, information must be gained on how it is absorbed, distributed throughout the body, stored, metabolized, and excreted and how it affects the action of body's cells, tissues, and organs.

Pharmacology

- Within its broad definition, pharmacology is the science concerned with drugs, their sources, appearance, chemistry, actions, and uses.From this basic field of study come subareas as
- **Pharmacodynamics**, **Pharmacokinetics**, **Clinical Pharmacology**, **Molecular Pharmacology**
- **Molecular Pharmacology** study of drugs at the molecular level such as receptors, enzymes and membrane transport proteins

General steps for pharmacologic studies

1. Among the early studies are the determination of compound's selectivity for various receptors and its activity against select enzyme systems.
2. Studies of the compound's effect on cell function are then performed to detect evidence of efficacy and to determine whether the compound is an agonist or antagonist.
3. studies with isolated animal tissues to define further the compound activity and selectivity.
4. Whole-animal studies are used to evaluate the pharmacologic effects of the agent on specific organ systems.
5. Studies are undertaken using animal models of human disease for which the compound is considered a drug candidate.

Animal testing

- The primary objective of the animal studies is to obtain basic information on the drug's effects that may be used to predict safe and effective use in humans. This is a difficult task because of species variation and the fact that animals are not absolute predictors of human response.
- Most animal testing is done on small animals, usually rodents **(mouse, rats)** for a number of reasons including

1. cost,
2. availability
3. the small amount of drug required for a study,
4. the ease of administration by various routes (oral, inhalation, intravenous)
5. experience with drug testing in these species.

- However, in final pharmacologic and toxicologic studies, two or more animal species are used as required by the FDA, including a rodent and an animal from another order.
- Drug are studied at various dose levels to determine the effect, potency, and toxicity.

- However, a number of animal models have been developed to mimic certain human diseases, and these are used effectively.
- For instance, there are animal models for type I diabetes and hypertension, using genetically diabetic and hypertensive animals, respectively, and for tumor growth, using tumor transplants in various species.
- Certain animal species have been determined to be the best for certain studies of organ systems, or as human disease models, including

1. dogs or rats for hypertension,
2. dogs and guinea pigs for respiratory effects
3. dogs for diuretic activity;
4. rabbits for blood coagulation;
5. mice and rats for CNS studies.

- Unfortunately, useful animal models are not available for every human disease.
- **As a drug candidate progresses in its preclinical pharmacologic evaluation, drug metabolism and toxicity tests are initiated.**

Drug metabolism

- A series of animal studies of a proposed drug's ADME are undertaken to

1. The extent and rate of drug absorption from various routes of administration, including the one intended for human use
2. The rate of distribution of the drug through the body and the site or sites and duration of the drug's residence.
3. The rate, primary and secondary sites, and mechanism of the drug's metabolism in the body and the chemistry and pharmacology of any metabolites
4. The proportion of administered dose eliminated from the body and its rate and route of elimination. In these studies, a minimum of two animal species are employed (generally the same as used in the pharmacologic and toxicologic studies), rodent and one other, usually a dog.

- Determine whether a drug's metabolic products are toxic or nontoxic to the animal and later to the human.

Toxicology

- Deals with the adverse or undesired effects of drugs.
- Initial toxicology studies are conducted on rodents. Another animal, dog is added
- Not all side effects of new drugs to be tested in animals will be detected but the greater the likelihood the effect will also be seen in humans **Example:** headache

Purpose of Safety Evaluation and Toxicity Studies

1. The substance's potential for toxicity with short-term (acute effects) or long- term use (chronic effects)
2. The substance's potential for specific organ toxicity
3. The mode, site, and degree of toxicity.
4. Dose-response relationships for low, high, and intermediate doses over a specified time
5. Gender, reproductive, or teratogenic toxicities
6. The substance's carcinogenic and genotoxic potential

Acute or Short-Term Toxicity Studies

- These studies are designed to determine the toxic effects of a test compound when administered in a **single dose and/or in multiple doses over a short period, usually a single day.**
- Test compound administered at **various dose levels**, with toxic signs observed for **Onset, Progression, Severity, Mortality, Rates of incidence.**
- **Doses are ranged to find;**

1. **Largest single dose** of test compound that will not produce toxic effect.
2. **Dose** level at which **severe toxicity occurs**.
3. **Intermediate toxicity** levels.

- Animals are observed and compared with the controls for eating and drinking habits, weight changes, toxic effects, psychomotor changes, and any other sign of untoward effects, usually over a **30-day postdose period**.

- feces and urine are collected and clinical laboratory test performed to detect changes in clinical chemistry and other changes that could indicate toxicity.

- Animal death: recorded; study on histology; pathology and statistically evaluated on the basis of dose response **gender, age, intra species and interspecies findings**, and against laboratory controls.

Subacute or Subchronic Studies

- Animal toxicity studies of a minimum of **2 weeks of daily drug administration at three or more dosage levels to two animal species** are required to support the initial administration of a single dose in human clinical testing.

Chronic toxicity studies

- The initial human dose is usually one-tenth of the highest nontoxic dose (in milligrams per kilogram of subject's weight) shown during the animal studies.
- For drugs intended to be given to humans for a week or more, animal studies of 90 to 180 days must demonstrate safety.
- If the drug is to be used for a chronic human illness, animal studies 1 year or longer must be undertaken to support human use.

Carcinogenicity Studies

- Carcinogenicity testing is usually component of chronic testing and is undertaken when compound has shown sufficient promise as a drug to enter human clinical trials.
- Carcinogenicity studies carried out in limited number of rat and mouse strains when there is information on spontaneous tumor incidence.
- Carcinogenicity studies are long term (18-24 months), with surviving animals killed and studied at defined weeks during the test period.
- Data on the causes of animal death, tumor incidence, type and site, and necropsy findings are collected and evaluated.
- Any preneoplastic lesions and/or tissue-specific proliferation effects are important findings

Dose-ranging studies

- Dose-ranging studies are done with female and male animals using high, intermediate, and low doses over a 90-day period.

Reproduction Studies

- Reproduction studies are undertaken to reveal any effect of an active ingredient on mammalian reproduction. Included in these studies are fertility and mating behavior; early embryonic, prenatal, and postnatal development, multigenerational effects, and teratology.
- In these studies, the maternal parent, fetus, neonates, and weaning offspring are evaluated for anatomic abnormalities, growth, and development.
- The animal used in other toxicity studies in reproductive studies, usually the rats.
- In embryotoxicity studies only, a second mammalian species traditionally has been required. The **rabbit** is the preferred choice for practically and the extensive background knowledge accumulated on this species.

Genotoxicity or Mutagenicity Studies

- Performed to determine whether the test compound can affect gene mutation or cause chromosome or DNA damage.

Reference

Ansel’s pharmaceutical dosage forms and drug delivery systems , tenth edition