Introduction

Toxicology, as already described, involves the study of how people and other living organisms interact with drugs and poisons. These interactions can be divided into two main categories – how a drug works on an organism, called pharmacodynamics, and how an organism works on the drug, called pharmacokinetics. The relationship between these two areas is illustrated in Figure 13.2.1.

Pharmacodynamics, the study of changes caused by a drug on a person, deals specifically with how a chemical can affect the internal functioning of an organism. There are many modes of action that allow chemicals to work on the body and each mode specifically determines how a drug or poison can cause an effect. Drugs can bond directly to cells and biomolecules, destroy tissues, replace needed naturally-occurring substances, or reduce the production of unwanted chemicals, among others. For example, some drugs, such as Orinase, can boost the body’s production of insulin, or, in the case of Lipitor, reduce its manufacture of cholesterol. The difficult balance in medicine is to select the right drug in the correct amount to cause only the medically desired effect without doing any harm. Anti-cancer drugs are typically aimed at destroying cancerous cells (a cell poison, called a cytotoxin) without killing other, surrounding healthy cells. The extent to which a drug causes unwanted side effects may limit its usefulness. Cancer drugs are designed to kill the most rapidly growing cells – as are most cancer cells – but also effectively kill other fast growing cells in the body, such as hair follicle and stomach lining cells, leading to hair loss and nausea. Each drug has its own set of side-effects that can range from insignificant to severe – it’s the old axiom to be avoided, that the medicine cured the disease but, unfortunately, killed the patient.

Pharmacokinetics can be described simply as how a body acts upon a chemical, such as a drug or poison, and how the chemical moves through a person and is eventually eliminated from the body. For example, pharmacokinetics follows the path of a drug through a person’s body from the time that it is first administered until it is ultimately excreted, including how it might be metabolized into different molecules, called metabolites, by the body. These metabolites may each have their own separate effects and actions on the body and are frequently employed as chemical “signatures”; when detected they are clear evidence of the use of

Figure 13.2.2. How Valium (diazepam) may be affected by a person body – pharmacokinetics (www.merckmanuals.com/professional/sec20/ch303/ch303a.html).
Drug Names: What Does It All Mean?

The array of names used for drugs is absolutely bewildering! There are so many names and even endless variations of names for each drug that it takes an expert to keep track of them. Why so many names?

Names for a drug arise from the different audiences and uses for the compound. Dr. George Johnson (txtwriter.com) says it reminds him of the T.S. Elliott Poem on The Naming of Cats (the basis of the Broadway play Cats) where every cat needs three names. One name is a “sensible everyday name”, one a “particular name….never belonged to more than one cat”, and one a “private name”. Take, for instance, the abused drug rohypnol. Here’s some of its many names and why there are so many:

• A “Sensible Name” – A name that everyone can remember and that the various drug companies can use to market the drug, such as the name rohypnol.
• A “Particular Name” – A name for pharmacists and doctors to use, one that tells something about the family of drugs it belongs to – sort of like your family name. The “particular name” for rohypnol is flunitrazepam.
• A “Private Name” – just for chemists, who need to be able to put a chemical structure unambiguously to a compound just from the name without ever having seen the compound before. They must be able to figure out the structure from just the name. So rohypnol is called 6-(2-fluorophenyl)-2-methyl-9-nitro-2,5-diazabicyclo[5.4.0]undeca-5,8,10,12-tetraen-3-one [C_{16}H_{12}FN_{3}O_{3}].
• And one more, a “Nickname” (not from Elliot’s characterization, however) – The very familiar or “street names” for rohypnol include "rowies", "rophy", "ruffles", "roachies", "roofies", "ruffies” and dozens of others that seem to change almost daily.

The original drug. Metabolism refers to the chemical processes in our bodies associated with life processes – and drugs, like other chemicals and foods, are metabolized by the body in quite specific ways. How a body breaks down and processes a drug depends both upon the chemical properties of the drug and on factors specific to a person. For instance, many factors including age, gender, diseases present, body impairment and function, tobacco or drug use, exercise, environmental exposures, and others may change the rate and ultimate outcome of how a drug is metabolized in a person’s body. Some of these patient-based variables are shown in Figure 13.2.2 for the drug valium (diazepam). For some people, valium might have the desired effect of anxiety reduction while others may experience unacceptable side effects and reactions from life-threatening reactions to no effect at all. Since the valium taken in each case is chemically identical, any difference...
in the effect it has from person to person must depend upon the genetic and biochemical make-up of each individual; these are pharmacodynamic effects. Ultimately, however, the diazepam (valium) is metabolized in everyone by specific enzymes found in the liver and the predictable metabolites are excreted by the kidneys (Figure 13.3.3).

One useful concept related to pharmacokinetics is the half-life of the drug ($t_{1/2}$) – meaning the time it takes for the body to eliminate $\frac{1}{2}$ of the drug present. This time interval can range from hours to days and weeks and is affected by the same factors that are shown in Figure 13.2.2. For forensic case work, the half-life of a drug limits how long we can detect a drug, or its metabolites, in the body after use – clearly a question of obvious legal importance.

The most common place where drugs and poisons are metabolized by the body is in the liver, where highly specific enzymes reside charged with the task of recognizing, grabbing, and modifying chemicals that are foreign to our bodies (Figure 13.2.3). The presence and action of these enzymes is largely controlled by our DNA and there is great variation among people regarding these enzymes. For example, it has been shown that about 50% of people have DNA modifications that influence how these enzymes metabolize some of the most common drugs. This leads to very different effects from person to person on both the pharmacodynamics and pharmacokinetics of a particular drug. Figure 13.2.4 shows the very large percentage of drugs that are therapeutically ineffective for different people, leading not just to ineffective treatments but to potentially life-threatening adverse drug reactions – estimated at 100,000 deaths and 2.2 million serious drug reactions in the US annually. The fields of genetic toxicology and personalized health care (personalized at the level of each person’s own DNA composition) explore these individual responses to drugs and have the prospect of some day allowing doctors to prescribe drugs tailored for individuals based upon their unique DNA codes – greatly reducing ineffective and adverse drug reactions and maximizing the beneficial effects of a therapy.

Drugs are natural or synthetic chemical compounds that are used for physiological (body) or psychological (mind) medical effects. In common forensic usage today, however, there is unfortunately a distinction made between the terms “drug” and “medicine” by the general public, although in the medical world they are actually very similar, although not identical. Popular use of the term “medicine” refers to those chemicals taken to help

![Figure 13.2.4. Ineffective rate of commonly prescribed medications](www.healthanddna.com/drug-safety-dna-testing/Valium-side-effects).

![Figure 13.2.5. Deadly nightshade (Atropa belladonna)](www.lookoutnow.com/animal/nite_sh.htm) provides a life-saving heart medicine, but a slightly too large or too small a dose can be deadly.
deal with a generally accepted medical condition (e.g., therapy, prevention or diagnosis) while the term “drug” implies chemicals that are taken for originally unintended or uncontrolled uses. In US law, however, a drug, the broader of the two terms, is defined as a “substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, or a substance intended for use as a component of a medicine” while a medicine is defined as a substance used specifically in treating a disease. Nonetheless, the main issues relate to the abusive use of drugs and other chemicals, as legally defined by society.

Poisons, in contrast, are usually defined as compounds designed with the specific purpose of killing cells or organisms - cytotoxins. They act in a variety of ways as will be examined in the following sections. But, as you’ve probably guessed, drugs can behave as poisons and poisons can be used as drugs.

**Medicinal Toxicology**

To paraphrase the 15th century physician Paracelsus, *everything* is a poison – it only depends upon the dose. **Dose** refers to the amount of a substance taken into the body over a short period of time. Actually, Paracelsus was correct in saying that anything can be a poison in the right dosage – even water (too much water dilutes key components of blood, such as potassium and sodium, leading to heart and kidney failure). Often, there can be a fine line between the correct therapeutic dosage to treat a problem and a toxic dosage causing harm. For example, the life-saving, plant-derived heart medicines digitalis (from foxglove) and atropine (from deadly nightshade, Figure 13.2.4) in the right dosages help compromised hearts function better, while just slightly more than the beneficial dosage is fatal.

Toxicity also depends upon how long a person is exposed to the chemical. **Acute** toxicity refers to a single dosage while **chronic** toxicity refers to effects spread over a longer period of time. Effects of an acute exposure are usually seen within the first two to four days after an exposure while chronic effects may take months or even years to become evident. Typically, the doses for acute exposure are higher than those resulting in chronic exposure and the immediate symptoms are much more noticeable and severe. For example, acute toxicity of aspirin occurs at levels above 150 mg per Kg of a person’s body weight (the amount found in about 20 of the 500 mg “extra-strength” tablets for a 150 lb. person; see LD$_{50}$ below). Chronic toxicity for aspirin, however, is usually below 100 mg/Kg taken over many days or weeks. Acute poisoning symptoms frequently include nausea, abdominal pain, organ failure, and may be life-threatening, as shown in Figure 13.2.6, while chronic symptoms may not be immediately

![Figure 13.2.6. Symptoms of acute aspirin toxicity](en.wikipedia.org/wiki/File:Symptoms_of_aspirin_overdose.svg)

![Figure 13.2.7. LD$_{50}$ values for dioxin for different species.](en.wikipedia.org/wiki/File:LD50_Dioxin.svg)
apparent but may include lethargy, dizziness, weakness, and later on, liver and kidney damage. Acute symptoms may be reversible while chronic symptoms typically are not, with much of the damage done before the presence of the toxin is even known. A measure of the toxicity of a substance is its lethal dose, or LD value. Usually, the lethal dose is given as an LD50 value, or the amount of a substance necessary to kill 50% of a population. It is important to note that the LD50 value for a chemical refers to its effect distributed over an entire population and does not give the probability of an individual dying from a particular level of exposure (a person with a sensitivity to a chemical may have a very low tolerance, and a very high chance of death, from even a small exposure). Other LD values are sometimes used

### Using LD50 Values: Body Weight Effects

LD50 values, in mg of chemical per Kg body weight, depend on the size of the person since larger bodies tolerate more of a chemical. It is easy to calculate what the LD50 of a particular sized person is. Here’s an example using ethanol, or drinking alcohol:

**For a 150 lb person (68 Kg):**

$$LD_{50} = (68 \text{ Kg Bodyweight}) \times \left(\frac{1000 \text{ mg EtOH}}{1 \text{ Kg Bodyweight}}\right) = 68,000 \text{ mg} = 68 \text{ grams}$$

**For a 240 lb person (60 Kg):**

$$LD_{50} = (\sim 110 \text{ Kg Bodyweight}) \times \left(\frac{1000 \text{ mg EtOH}}{1 \text{ Kg Bodyweight}}\right) = 110,000 \text{ mg} = 110 \text{ grams}$$

**For a 44 lb child (20 Kg):**

$$LD_{50} = (20 \text{ Kg Bodyweight}) \times \left(\frac{1000 \text{ mg EtOH}}{1 \text{ Kg Bodyweight}}\right) = 20,000 \text{ mg} = 20 \text{ grams}$$

[Note: ~17 grams of alcohol is about what is found in one 12 oz beer (6%)]

### Table 13.2.1. LD50 Values for various common chemical and drugs.

<table>
<thead>
<tr>
<th>Substance</th>
<th>LD50*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>90,000</td>
</tr>
<tr>
<td>Sugar (Sucrose)</td>
<td>29,700</td>
</tr>
<tr>
<td>Table Salt (NaCl)</td>
<td>3,000</td>
</tr>
<tr>
<td>Aspirin</td>
<td>1,750</td>
</tr>
<tr>
<td>Detergent</td>
<td>1,260</td>
</tr>
<tr>
<td>Ethanol</td>
<td>1,000</td>
</tr>
<tr>
<td>Morphine</td>
<td>500</td>
</tr>
<tr>
<td>Caffeine</td>
<td>200</td>
</tr>
<tr>
<td>Heroin</td>
<td>150</td>
</tr>
<tr>
<td>Lead</td>
<td>20</td>
</tr>
<tr>
<td>Cocaine</td>
<td>17.5</td>
</tr>
<tr>
<td>Cyanide</td>
<td>10</td>
</tr>
<tr>
<td>Nicotine</td>
<td>2</td>
</tr>
<tr>
<td>Strychnine</td>
<td>0.8</td>
</tr>
<tr>
<td>Batrachotoxin†</td>
<td>0.002</td>
</tr>
<tr>
<td>Tetanus or Botulina</td>
<td>0.000001</td>
</tr>
</tbody>
</table>

* (in mg of compound/Kg body weight), estimated from animal experiments.
† poison from the pufferfish.

### More LD50 Calculations

- **Cyanide** (for 150 lb human - ~ 68 Kg)
  
  $(70Kg)(10mg/Kg) = 680 mg (0.68g)$

- **Nicotine** (for 150 lb human; e.g.; from Cigarettes)
  
  $(68Kg)(2 mg/Kg) = 136 mg (0.14g)$
  
  (note: 1 cigarette = ~ 2 mg Nicotine)

- **Strychnine** (for 150 lb human - ~ 68 Kg)
  
  $(68Kg)(0.8mg/Kg) = 54 mg (0.05g)$

- **Batrachotoxin** (for 150 lb human - ~ 68 Kg)
  
  $(68Kg)(0.002mg/Kg) = 0.136mg (0.0001g)$

- **Tetanus Toxin** (for 150 lb human - ~ 68 Kg)
  
  $(68Kg)(0.00001mg/Kg) = 0.068mg!$
Instead of LD$_{50}$, in each case the subscript refers to the percentage of the population killed, such as LD$_{90}$ and LD$_{95}$, referring to the dosages needed to kill 90% and 95% of a population, respectively. It is, of course, never ethical to experiment directly on human subjects to determine LD$_{50}$ values, although occasionally these levels are known for humans from accidental exposures. Typically, however, animals are used to determine the LD$_{50}$ values and then estimates are made for humans from these data. It is important to note that LD$_{50}$ values for a particular chemical are very species specific, so the choice of which animal provides the best model for humans is always up for debate, as seen in Figure 13.2.7 for the LD$_{50}$ values for the chemical dioxin in different animals. It is very important to note that LD values refer only to doses that cause death – many chemicals cause varying degrees of harm at much lower than lethal dose levels, such as temporary or permanent biological and psychological impairment, organ damage, drug dependence, and altered biochemical functioning of the body.

Some LD$_{50}$ values for various commonly encountered drugs and toxins are shown in Table 13.2.1. Larger LD$_{50}$ values mean that the chemical is less toxic – a larger dose must be given to reach a toxic level. LD$_{50}$ values are reported in terms of milligrams of the chemical per kilogram of body weight and refer to acute exposures – taken in one dose. These ideas mean that the larger the body, the more of the chemical that must be administered to get the same toxic result (See inset box “Using LD$_{50}$ Values”). From the examples calculated, it’s clear that for drinking alcohol, vastly different amounts are needed to reach life-threatening, toxic levels – 110 g (6 beers taken quickly) for a 240 lb person to just 20 grams (~1 beer) for a 44 lb child to reach lethal levels.

Some surprising results also come out of these calculations by comparing different compounds for the same size person (see box “More LD$_{50}$ Calculations”). For example, nicotine, found in cigarettes, is five times more toxic than cyanide. And the tetanus toxin is ten million times more toxic than cyanide and a grain barely large enough to see could be fatal.

Previous exposure to a chemical can also have a profound effect upon the response a person has to later exposures. In general, there are three ways that a prior exposure can play a role:

- **Sensitization** – Prior exposure may lead to a heightened response the second time someone is exposed to a compound. This often involves an immune-type response on the second exposure to even very small amounts, well below toxic levels. This can lead to an overly strong response, such as Figure 13.2.8. Symptoms of anaphylactic shock – a response to a sensitization to a drug or poison (www.healthcentral.com/allergy/h/anaphylactic-shock-food-allergy.html).

- **Progressive model**
- **Steady-state model**

Figure 13.2.9. Amount of drug needed to maintain the same response over time just to have the same effect (www.jci.org/articles/view/34035/figure/1).
whole body involvement in anaphylactic shock that can lead to rapid death (Figure 13.2.8). This type of allergic response can occur with any type of allergen but is often seen in exposures to food, insect stings, snake bites, poisons, and medication (drugs).

- **Tolerance** – The body may adapt to a chronic exposure to a compound, leading to an increased acceptance (tolerance) of the chemical by the body, Figure 13.2.9. When this happens, an increased dose is needed just to reach the same original effect from the earlier lower dose. Many abused drugs such as heroin, amphetamines, morphine, barbiturates, alcohol, and others follow this pattern of increased tolerance in the user. When coupled with a built up dependence on the compound, this body response creates a vicious circle of the abuser requiring the drug in ever increasing dosages just to have a level effect.

- **Bioaccumulation** – If a compound is not eliminated from the body but is instead stored in tissues, then over time enough of the poison can accumulate to cause significant problems. Heavy metals especially interact with living tissues to result in this type of toxicity.

**Drugs, Poisons and the Human Body**

Drugs and poisons, like all chemicals, follow specific pathways through the body (pharmokinetics) – sometimes causing dramatic changes in the body in the process (pharmacodynamics). A drug’s pathway can be considered to have four distinct steps: absorption – distribution – metabolism – elimination (called “ADME”).

**Absorption:** In order for a chemical to affect a person, it must first make its way into the bloodstream. There are a variety of ways to start this process, including (Figure 13.2.10):

- **Ingestion** – Ingestion means that the compound enters the gastrointestinal system through the mouth (orally). This can happen through contaminated food, drink or in medicinal formulations. Compounds taken in by this route must make it through the formidable battery of digestive chemicals, starting in the mouth and continuing into the stomach and intestines. Eventually, if the drug survives this harsh treatment and makes it into the stomach and small intestine, it can be absorbed into

**Figure 13.2.10.** Methods for drugs to enter the body: ingestion, injection (intravenous), inhalation, and skin contact
(publications.nigms.nih.gov/medbydesign/chapter1.html)

**Figure 13.2.11.** Differences in bioavailability – the amount of a drug in the bloodstream available to do its job – depends on how it is absorbed, with injection being very fast and yielding higher concentrations than oral (ingestion) absorption which results in a slower, more prolonged process with drug lower concentrations
(http://ceaccp.oxfordjournals.org/content/7/1/25/F4.expansion).
the bloodstream – mostly through the small intestines (80-90%). Because of the number of barriers that a chemical must pass through, the bioavailability - the amount of the compound that reaches the bloodstream - is lower and more drawn out over time for oral ingestion than for direct injection (Figure 13.2.11).

- **Injection** – An injection inserts the compound either directly into the bloodstream or into nearby tissue, bypassing most of the complications arising from digestive and other natural barriers designed to keep unwanted foreign chemicals out of our blood. This method can result in a rapid bioavailability of the full dose of the chemical to the body and results in a high concentration of the drug in the bloodstream, especially for when injected directly into a blood vessel. The injection can be directly into a blood vessel (intravenous), into muscle (intramuscular) or into the surface skin layers (subcutaneous), as shown in Figure 13.2.12. Many drugs of abuse are administered by injection since it delivers the maximum dose in the shortest amount of time.

- **Inhalation** - The lungs are organized, of course, to allow for the rapid and easy transport of molecules between the bloodstream and the air – O₂ is transferred into and CO₂ is transferred out of the body. Breathing a compound into the lungs, either a drug (e.g., asthma medicines) or a poison (e.g., carbon monoxide, hydrogen cyanide, etc.), delivers the compound to lung tissue for rapid absorption. The compound is then absorbed through the thin lining of the lungs to enter the bloodstream rather quickly (Figure 13.2.13).

- **Skin or Mucus Membrane Contact** – A compound can be absorbed through the skin or mucus linings (such as lining the nose, under the tongue, or in the rectum). Examples of this type of delivery include transdermal patches (e.g., for sea sickness and assistance in stopping smoking, shown in Figure 13.2.12), suppositories (to deliver antibiotics or analgesics through the rectum), nasal mists (e.g., flu vaccines), and sublingual medications (under the tongue heart drugs).
No matter how a drug or poison is delivered, it must eventually make its way from its point of initial administration into the bloodstream. As mentioned before, the body has a number of protective barriers that limit this from happening. For example, when taken orally, a drug is first transported via a special blood vessel ("portal vein") directly from the intestines to the liver, bypassing entirely the body’s bloodstream loop (Figure 13.2.14). There, it must first go through an initial screening pass in the liver – called the “first-pass effect” – before entering the bloodstream. The amount of a compound that actually makes it into the bloodstream, its bioavailability, is thus regulated by the liver. Other delivery methods bypass the liver, although all but direct injection have hurdles to pass before the chemical can make its way into the blood stream.

**Distribution:** Once in the bloodstream, absorbed chemicals are rapidly carried throughout the body (Figure 13.2.15). On average, red blood cells make a complete circuit of the body in about 60 sec. at speeds of up to ~12 feet per second in the larger vessels, carrying drugs, poisons, and everything else associated with a living organism along with it. This distribution can be affected by circulation problems and the presence of other molecules, such as fats and proteins, that grab onto the drug. In order to cause a desired effect, however, a chemical must make it to the specific “target” cells (organ). If the drug is not specific for a particular target organ, however, it can be taken up by other organs, leading to a variety of unwanted side effects or a decrease in its effectiveness. Some organs have their own “defensive” mechanisms that might slow or prevent a drug or poison from entering it. One such formidable obstacle is the **blood-brain barrier**, a very effective roadblock of tightly packed capillaries that prevents most drugs and poisons from entering the highly sensitive brain. This barrier selectively allows in and out only very small molecules, such as oxygen, glucose, and waste products, while stopping larger molecules from entering, including hormones, viruses, bacteria and drugs. This is usually works well to keep the brain safe and functioning properly but it presents a
significant challenge when designing drugs that target the tissues of the brain.

In general, compounds throughout the body must ultimately make it either into or onto the cells, often through complex mechanisms that cells have developed, to cause an effect.

**Metabolism:** Once at its destination and finished with its “work” on cells and organs, the drug enters into a process where it is transformed into manageable waste products. This operation, called metabolism, forms a variety of products, called metabolites, and actually begins to a limited extent the moment the compound enters the bloodstream. While some of this breakdown may take place in the target organ itself or in the bloodstream, it is the liver where the majority of this decomposition takes place. The liver, the largest organ in the body, continuously screens and removes unwanted chemicals from the body – an enormous but absolutely vital task. This is accomplished by a host of very specialized proteins, called enzymes (Figure 13.3.3), which rip apart, join together, and transform these chemicals into products that can be readily eliminated from the body.

**Elimination** (excretion): The metabolites resulting from a chemical’s transformation in the liver can take several pathways out of the body. Most water soluble compounds travel through the kidneys and are eliminated in the urine, although some move from the liver directly into bile that is eliminated in the intestines (Figure 13.2.16). Fat soluble substances, however, must first be turned into water soluble compounds before they can enter the waste stream and be eliminated. Some compounds may also be eliminated directly either through the skin or into the lungs to be expired while breathing out.

As you can see, a drug or poison has a rather torturous pathway from the outside world, through the body, and then back outside once again, probably transformed into a different compound along the way. Each of these steps, as we shall see later, have very important implication to forensic toxicology.

**Medicinal Chemistry**

Most abused compounds, with the major exceptions of alcohol and plant-based compounds, are usually drugs designed for other purposes that are instead used for unintended “off-label” applications. For this reason, it is helpful when considering any forensic issues involving drugs to have a brief understanding of how pharmaceuticals are developed for medicinal uses. The actual production of the medications available to us today is only the last and probably easiest step in a long path of discovery,

![Figure 13.2.16. Urinary system for eliminating water soluble waste products through the kidneys](www.faqs.org/health/Body-by-Design-V2/The-Urinary-System-Design-parts-of-the-urinary-system.html).

![Figure 13.2.17. Wormwood, an ancient traditional medicine, contains effective agents for stimulating digestive processes](http://drclarkia.com/wormwood.asp).
development, and testing. Drug companies and foundations expend enormous amounts of effort to discover new compounds that are more effective, have fewer side effects, and are easier to make than existing medications.

New drugs typically come from several approaches to drug discovery and design. These include:

- **Ethnopharmacology** – explores traditional folk remedies to identify new drugs (Figure 13.2.17). These cultural and traditional treatments are researched, collected, and attempts made to isolate the active ingredient(s) in the laboratory. Once isolated, it is necessary through stringent testing to learn if the remedy truly works or if it is without true medical validity. Important drugs such as aspirin, digitalis, quinine, and morphine were developed using this approach.

- **Fortuitous** – This method could also be called “accidental” since new drugs arising from this approach are discovered either while looking for something else or are the result of unintended circumstances. The key, of course, is that *someone must realize* what they have actually stumbled into. The classic example of this comes from the discovery of penicillin (see inset box “Fleming’s Vacation”).

### Fleming’s Vacation

In 1928, Alexander Fleming, a researcher studying bacteria, was ready for an extended break. In his rush to leave, he didn’t quite clean up all his experiments as well as he might have, certainly an understandable shortcoming. After his return, just as he was about to dispose of an old petri dish containing some of his bacteria cultures, he grew curious when he observed that a bacterial culture that had accidentally been contaminated with mold grew no bacteria. The key, of course, was that he noticed this oddity rather than just washing the dishes up. But this chance discovery, one that would change modern life, was only one of a number of chance circumstances. If any of these events had been missed, Fleming’s important discovery – Penicillin, the antibiotic that has saved millions of lives – would never have happened.

Some of these chance events leading to the discovery of the antibiotic properties of Penicillin were:

- Fleming left some petri dishes uncleaned when he left for an extended vacation;
- A researcher on the floor below Fleming was studying a rare strain of mold (*penicillium Notatum*);
- Fleming was working on *Staphylococcus* at the time (a bacteria especially sensitive to Penicillin);
- Mold spores drifted from the floor below, into Fleming’s lab, and contaminated some of his unwashed Petri dishes;
- The uncommonly cool weather first slowed the growth of the bacteria but promoted the growth of the mold;
- After a period that was just right, the warm weather returned permitting the growth of the bacteria and slowing the mold’s growth;
- Fleming returned from vacation and noticed antibacterial action.

It still took over a decade after this discovery, and the work of many others, to make Penicillin a drug that could be mass-produced in a safe and effective form. When Fleming accepted the Nobel Prize for medicine, Fleming said “Nature makes penicillin; I just found it.”

![Photo (L) Penicillin and bacterial culture; johnsonherryworldschool.blogspot.com/2011_01_01_archive.html](image-url)
• **Chemical Modification** – an existing drug can be modified to reduce side effects or to improve its effect by systematically changing parts of the molecule and seeing if the properties desired are improved or reduced.

• **Targeted Drug Discovery** – uses a planned approach to finding new drugs. For example, if the underlying biochemistry of a disease is understood, it might be possible to design a drug that interrupts the working of the disease on a molecular level. Additionally, a drug may only need to have a few correct functional groups at the right place in the molecule to be effective. Recognizing what are the active portions of a drug molecule can allow chemists to change the molecule in some places while keeping the active portion of the molecule intact. This can lead to improvements in the action of the drug, as illustrated in Figure 13.2.18.

• **Combinatorial (screening) Methods** –

  Today, vast libraries containing millions of closely related compounds are prepared and screened to see if any of these have medical activity. Once candidates are found that show some activity, new libraries built upon relatives of these “first-generation” compounds are prepared and screened. This approach allows new generations of drugs to be identified and refined rapidly. The new and emerging areas of bioinformatics (Figure 13.2.19), biotechnology and other related approaches are redefining drug discovery with opportunities to develop new drugs in ways never before possible.

  Once a new candidate drug is discovered through one of the methods above, a long process of refinement, testing, testing and more testing begins. It may take ten years and more than a billion dollars to bring a promising new drug to pharmacy shelves and includes the synthesis and purification of the compound, safety and efficacy testing (including toxicity), multi-phased clinical trials, and regulatory evaluations.

![Figure 13.2.18.](image1.png)

**Figure 13.2.18.** The active portion of morphine (left) – the part of the structure of morphine needed to cause its pain-reducing effects – is only part of the molecule. Maintaining this active region (center) and adding other chemical pieces results in a new molecule (Demerol, right) that is more easily produced, keeps much of morphine’s medical properties, and is less addictive.

![Figure 12.2.19.](image2.png)

**Figure 12.2.19.** Bioinformatics – the field combining computer science and statistics with biology – is changing drug discovery by looking for new patterns of drug-DNA interactions modeling and statistical analysis of computer generated data.