



## Medicines and other poisons

Mitzi Glover, PhD, MT(ASCP)

### Objectives

- Describe some historical cases of unexpected toxicity of drugs or other substances.
- Discuss current uses for substances previously found to be toxic.
- Briefly describe the evolution of toxicity testing in the U.S.

### Methods of toxicity

- Overdose
- Off-target effects
- Adulteration
- Drug interactions



Poison is in everything, and no thing is without poison. The dosage makes it either a poison or a remedy.

(Paracelsus)

In other words,

Too much of a  
**GOOD THING** is a **BAD THING**



**POISON # 1**

## POISON # 1

Some of you may remember this news story.

### Jury Rules Against Radio Station After Contest Kills Calif. Mom

By SUZAN CLARKE and RICH MCHUGH via GMA  
Nov. 2, 2009



- 28-year old mother of 3
- 2<sup>nd</sup> place in a radio contest
- Afterward, called in sick to work, crying, with a bad headache
- Died within hours of the contest



- Coroner's report stated that she was severely hyponatremic

Do you know what her poison was?

### Jury Rules Against Radio Station After Water-Drinking Contest Kills Calif. Mom

By SUZAN CLARKE and RICH MCHUGH via GMA  
Nov. 2, 2009



Family awarded \$16 million in wrongful death lawsuit.

- "Hold Your Wee for a Wii" contest
- Drank nearly 2 gallons of water in just over 3 hours
- Listeners (including a nurse) called in to the radio show warning of the danger



Jennifer Strange

## KDND-FM

"Can you get water poisoning and, like, die?" - female disc jockey.

"Not with water. Your body is 98 percent water. Why can't you take in as much water as you want?" – male disc jockey

"Maybe we should have researched this before," - female disc jockey

Ten employees were fired following the incident.

## Body water content

Water accounts for approximately 60% of body weight

- Higher in males (65%) than females (55%)
- Higher in infants than adults

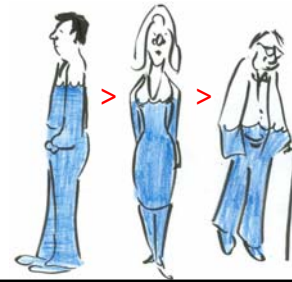
Why would that be?



Babies are born full of fluid, so they could survive, even if not fed right away.



What about adults?



### Water content in different tissues

Different tissues have different amounts of water in them

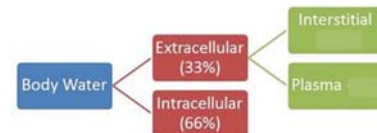
- Skeletal muscle
- Bone
- Fat-least hydrated tissue



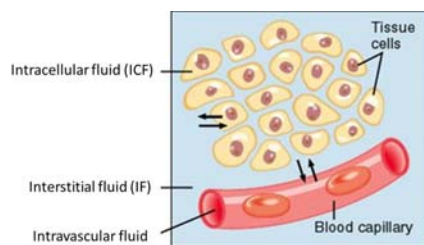
Robert Krulwich/NPR

### Distribution of water

- 2/3 in intracellular fluid (ICF)
- 1/3 in extracellular fluid (ECF)
  - interstitial fluid (approx. 2/3)
  - plasma, or intravascular (approx. 1/3)



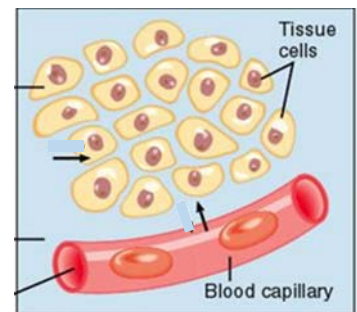
### Fluid movement between compartments

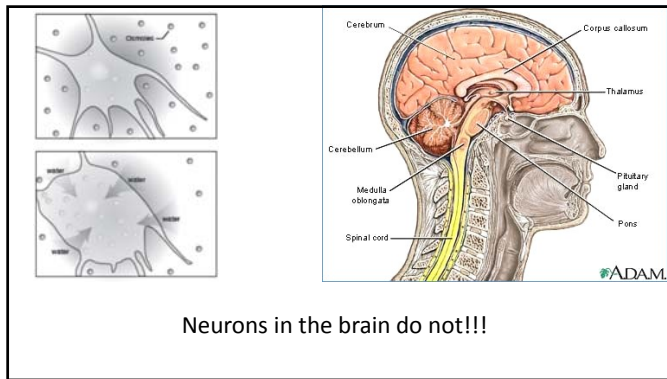


(b) Exchange of water among body fluid compartments

### Water movement in water intoxication

- Low osmolality of blood (diluted)
- Water moves out of blood into interstitium to balance this out
- This makes the interstitium more dilute, so water moves into cells
- Many cells in the body have the space to deal with this...





### Water intoxication

- **Acute dilutional hyponatremia**
- Dilute extracellular fluid causes water to move into cells
- Swelling of the brain → death

a) Normonatremia

b) Acute hyponatremia

Hyponatremia –  $[Na^+] < 135$  meq/L

## POISON # 2

## POISON # 2

69 year old woman with chronic headaches taking prescribed Percocet and OTC products developed drowsiness, poor appetite, nausea, vomiting and mild diarrhea. She was brought to the emergency room by her daughter who found her mother to be confused and not her usual highly functioning self.

Serum bilirubin 4.8 mg/dL (0.2-1.2 mg/dL)  
 ALT 5,945 U/L (20-60 U/L)  
 AST 12,476 U/L (10-40 U/L)  
 Alkaline phosphatase normal  
 Tests for hepatitis A and B were negative as were autoantibodies.  
 Positive for antibody to hepatitis C; HCV RNA testing was not performed.  
 Abdominal ultrasound showed no evidence of biliary obstruction.

## POISON # 2



No history of liver disease or alcohol use. The patient and her daughter denied that she was suicidal. She had no signs of chronic liver disease.

Doctors felt chronic hepatitis C may have contributed to elevated AST and ALT, but pattern of serum enzyme elevations were not likely due to acute hepatitis.

Do you know what her poison was?

## POISON # 2

Severe acetaminophen hepatotoxicity after unintentional overdose.



Serum acetaminophen at toxic levels.  
 Treated with N-acetyl cysteine. Made a full recovery.

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## Is Tylenol 'By Far The Most Dangerous Drug Ever Made?'

By Josh Bloom — September 11, 2017

Which OTC Painkillers Can You Take Together?

Pain In The Time Of opioid crisis: An Interview With Amy Hausknecht, M.D.

Tylenol Isn't So Safe, But At Least It Works, Right?

Adult Works As Well As Opioids: For Acute Pain? Not So Fast.

It's Drug Use Out There: Doping The Iditarod With Tramadol

If you own Johnson and Johnson stock you probably have enough problems on your hands. The company keeps getting hammered by lawsuits alleging that talc in baby powder has given women cancer (1). So you sure don't need me unpacking down Tylenol, which had worldwide sales of almost \$2 billion in 2016. But, don't blame me. This is not my quote. It's part of a written interview I did back in July with Amy Hausknecht, M.D., "Pain In The Time Of Opioid Crisis: An Interview With Amy Hausknecht, M.D."

TYLENOL EXTRA STRENGTH

You damn well better

hauknecht@stanford.edu

OF Opioid Crisis: An Interview With Amy Hausknecht, M.D.

**\* DID YOU KNOW?**

## Acetaminophen overdose is the leading cause of liver failure in the U.S.

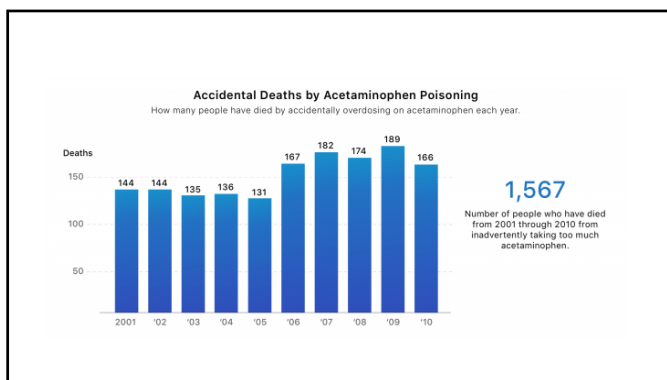
Many over-the-counter and prescription medications contain acetaminophen.

Nearly half of overdoses are unintentional.

Check the medication's label and do not exceed **4,000 mg** of acetaminophen daily, or less if you drink alcohol.

healthfeed.uclahealth.org

UNIVERSITY OF CALIFORNIA HEALTH CARE



## TYLENOL LIVER DAMAGING RESULTS

**Serious Side Effects:**  
Acute liver toxicity  
Neurosis  
Hepatic Steatosis or Steatosis  
Death  
Allergic Reaction

**Allergic Reactions Include:**  
Swelling  
Difficulty Breathing  
Closing of Throat and more  
discomforts

**Landmark Lawsuit**  
Tylenol's failure to Warn Consumers

In 1994, a Virginia federal court awarded \$8.8 million in damages to a patient who ended up in a coma after having liver damage brought on by the use of Tylenol.

**Reported Adverse Events for Tylenol:**

Hospitalization (prior or prolonged)	48,401
Other	38,727
Death	17,816
Required Intervention (all-cause procedure, hospitalization)	4,094
Life-Threatening	7,884
Disability	3,300
Congenital Anomaly	541

**Liver Damage**

acetaminophen liver damage is one of the leading causes of liver failure in the United States. It is attributed to almost 40,000 emergency room visits, 10,000 hospitalizations, and over 100 deaths each year.

As early as 1971, the FDA had recommended an advisory of the drug warning label against combining liver damage but it was not heeded until 2011, nearly 40 years later.

Call d'Oliveira & Associates at 1-800-992-6878 for a free Consultation

SECTIONS HOME SEARCH

ARCHIVES 1994

## Liver Patient Wins Suit Against Maker of Tylenol

By PHILIP J. HILTS OCT. 21, 1994

Lawsuit claimed patient had been in good health until he began taking Tylenol Extra Strength in the recommended doses to treat the flu.

Patient slipped into a coma after taking the drug for several days. Doctors found that he was suffering from liver failure. He received a liver transplant several days later.

## Alcohol and Tylenol

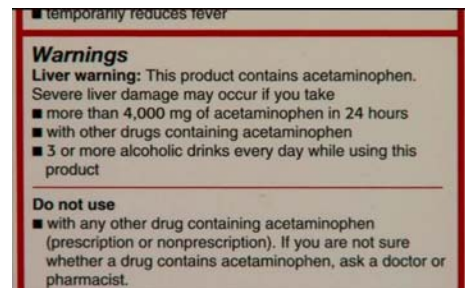
Patient regularly had wine with dinner.

Won lawsuit (\$8.8 million), because when this occurred, doctors had known for some time that repeatedly mixing alcohol with acetaminophen, could cause liver damage.

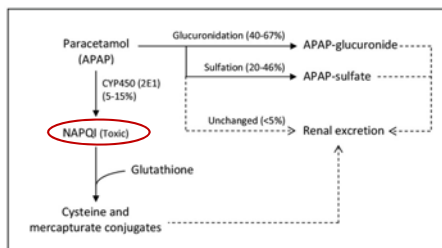
The severity seen in this case is rare.

## Alcohol and Tylenol (drug interaction)

- 1994- Patient won lawsuit (injuries had occurred in 1993).
- June 1993- advisers to FDA recommended the agency require warning on acetaminophen packaging -- heavy drinking while taking the drug can cause serious liver damage.
- 2009 (effective 2010)- changes in warning labels were made mandatory

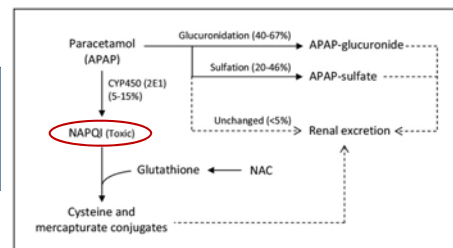


## Metabolism of acetaminophen (paracetamol)



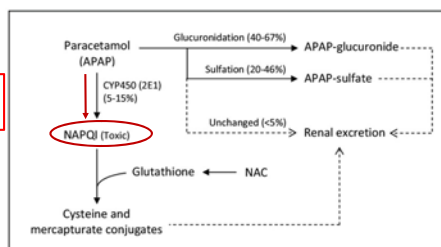
## Overdose of acetaminophen (paracetamol)/antidote

NAC (N-acetylcysteine, Mucomyst) protects the liver by maintaining or increasing glutathione levels, but must be given early (within 16 hours).



## Metabolism of acetaminophen (paracetamol) with alcohol- drug interaction

Alcohol induces cytochrome P450 (2E1), so more of this pathway.




## Mucomyst – selects for targets by route into body

- Inhaled- to break up thick mucus  
 (e.g., cystic fibrosis, pneumonia)
- Oral ingestion – acetaminophen overdose







<b>600</b>	medications with acetaminophen currently approved for sale in the U.S.
<b>27</b>	acetaminophen doses sold in the U.S. in 2009
<b>1,567</b>	Americans who died from 2000-2010 from accidental acetaminophen poisoning
<b>1,400</b>	Americans who committed suicide by taking acetaminophen from 2000-2010

## POISON # 3

1982 – Do you remember? Were you born?

- Early on the morning of Sept. 29, 1982, Mary Kellerman, a 12-year-old girl from a suburb of Chicago, took one extra-strength Tylenol capsule. She was dead by 7 a.m.

On the same day

- 27-year-old Adam Janus, also from Illinois, died of what was initially thought to be a massive heart attack.
- His brother and sister-in-law took extra-strength Tylenol from the same bottle Adam had used
- Stanley died that day and Theresa died 2 days later.

Do you know what their poison was?



**THE DAILY HERALD**

**5 dead after taking Tylenol capsules filled with cyanide**

A different kind of poisoning- adulteration

- Extra-strength Tylenol had been laced with **potassium cyanide**.
- Perpetrators have never been found.
- Changed the way we purchase and consume OTC medications.



## Cyanide

- Has been used in pesticides; some industrial uses
- Found in cigarette smoke, exhaust fumes, and some foods (small amounts)
- In larger doses – blocks cells from utilizing oxygen (cyanide ions bind irreversibly to iron)

### HISTORY

Cyanide has been used for centuries as a poison, but was first identified in 1782 by the Swedish chemist Scheele; in fact, it's thought Scheele's death may have been contributed to by cyanide exposure.

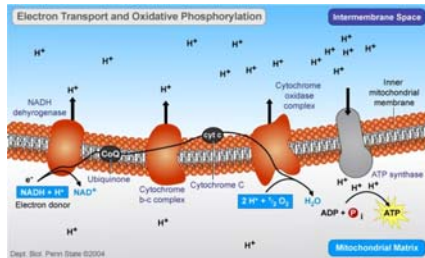
During WWI, the French attempted to use hydrocyanic acid, then cyanogen chloride, in chemical warfare. In WWII, The Nazis used hydrogen cyanide in the form of Zyklon B to kill millions in their concentration camps.

Hydrogen cyanide gas has previously been used for pest control, which sometimes led to accidental deaths. Today, cyanides are still used in the mining of gold and silver, and in organic synthesis reactions.

## Cyanide mechanism of toxicity

Prevents cells from utilizing oxygen effectively:

- Binds mitochondrial cytochrome oxidase of the electron transport chain, uncoupling oxidative phosphorylation → depletion of ATP



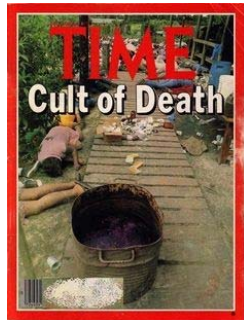
## Cyanide poisonings

- In 1945, a number of Nazi officials committed suicide using cyanide capsules
- Ironic- cyanide gas had been used in gas chambers of concentration camps



## Jonestown, Guyana, 1978

- 909 Americans died on orders from the leader of the People's Temple, Jim Jones
- Victims voluntarily or forcefully ingested grape drink with cyanide
- 33 people escaped



## Famous cyanide poisonings

- Grigori Rasputin (The Mad Monk), spiritual advisor to Czar Nicholas of Russia
- Rumors spread that he was poisoned with cyanide, but was unaffected





## Famous cyanide poisonings

- In fact, he was shot in the head and dumped in a lake, 1916
- Murderers spread the poison rumor to portray Rasputin as some sort of devil



CBC | MENU

AS IT HAPPENS

## Man treated for poisoning from apricot kernels says, 'Selling them like nuts is nuts'



CBC Radio - November 24, 2017

## \_\_\_\_\_ in apricot pits

- Brendan Brogan treated for \_\_\_\_\_ poisoning after eating apricot pits from health food store
- California man visiting a friend in Montreal
- Friend warned him to be careful, because they were poisonous.
- Brendan thought that couldn't be the case, because they were marked as "superfood"
- Then he saw the warning on the back of the package.

Do you know what his poison was?



## Cyanide in apricot pits

- Called poison control, who advised him to head to ER.
- "I had to drink a huge glass of charcoal soup, which was like eating seven or eight charcoal bricks from a barbecue, and then they tested my blood every couple hours while keeping me under observation."
- Released the next day with a pounding headache

radio

Man treated for cyanide poisoning from apricot kernels says, 'Selling them like nuts is nuts'



Brendan Brogan had already eaten about 40 dried apricot kernels when he saw the label on the back of the bag that eating more than a couple can result in cyanide poisoning. (Submitted by Brendan Brogan)

## Off-target effects of drugs

**POISON #4****POISON #4**

1959- London, England

- Young woman delivers her third child, a beautiful baby girl with severely malformed limbs
- Uneventful pregnancy, but with some pretty bad morning sickness



Do you know what poison her mother took?

Call the Midwife- PBS

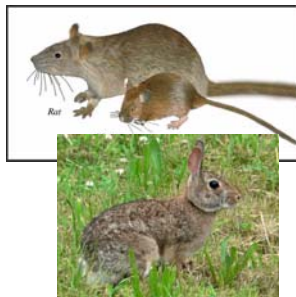
## Thalidomide – off target effect

- Drug developed in Germany in the 1950s
- Sedative used to treat morning sickness
- > 10,000 babies born with deformities around the world
- Withdrawn from the market in 1961



## Thalidomide – what went wrong?

- Birth defects not demonstrated in rat, mouse, or rabbit testing of the drug
- Rodents and rabbits have different metabolism rates, antioxidant capacities, etc.
- Demonstrated problems in animal testing



## Thalidomide – an early clue?

- Some patients taking the drug developed neuritis (neuropathy)
  - Neuritis = inflammation of nerves. May manifest as paresthesia (pins and needles), weakness, paralysis, pain



## Thalidomide babies in US?

- FDA never approved the drug in the US
- **Frances Oldham Kelsey** at the FDA rejected thalidomide application
- She didn't think a sedative should cause neuritis; she also worried about possible effects on fetuses



Receiving the President's Award for Distinguished Federal Civilian Service

## POISON #5

ARCHIVES | Anticholesterol Drug Pulled After Link With 31 Deaths

ARCHIVES | 2001

## Anticholesterol Drug Pulled After Link With 31 Deaths

By GINA KOLATA and EDMUND L. ANDREWS AUG. 9, 2001

I did not remember hearing about this.  
Do you know what this poison was?

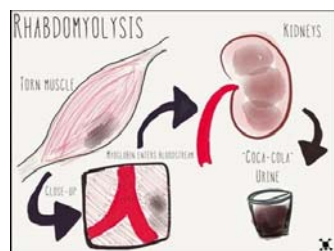
## Anticholesterol Drug Pulled After Link With 31 Deaths

By GINA KOLATA and EDMUND L. ANDREWS AUG. 9, 2001

Bayer A.G., the German pharmaceutical and chemical conglomerate, voluntarily withdrew **Baycol**, its highly profitable cholesterol-lowering drug, from the world market yesterday. Thirty-one patients have died while taking it, the company reported, because the drug caused an unusual condition in which muscle tissue broke down.

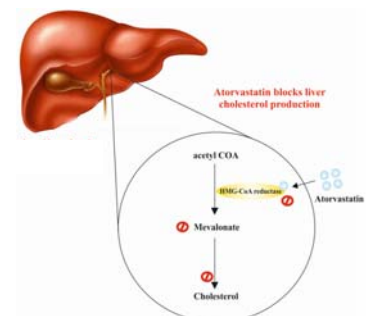
## Baycol (Lipobay)

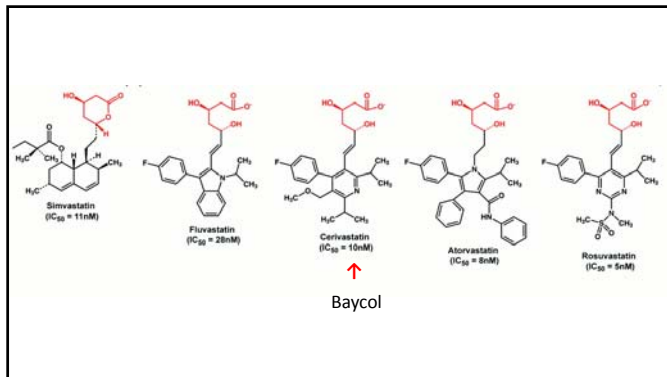
- Withdrawn 2001
- Deaths primarily due to rhabdomyolysis leading to **renal failure**



## Statins

- Cholesterol lowering drugs
- HMG CoA Reductase inhibitors





## Statins

I take Lipitor.



## Atorvastatin (my labs)

Began taking atorvastatin  
after 10/15/17 testing

Name	5/8/15	4/28/17	10/5/17	4/3/18
Standard Range				
Cholesterol, Total 140 - 200 mg/dL	223	254	270	186
HDL Cholesterol >50 mg/dL	64	64	70	67
LDL Calculated 60 - 135	143	170	185	103
Total Chol / HDL Ratio 0.00 - 4.45	3.48	3.97	3.86	2.78
Triglycerides 35 - 150 mg/dL	81	100	77	79

## Atorvastatin (Lipitor)

- I take this one
- My mother could not

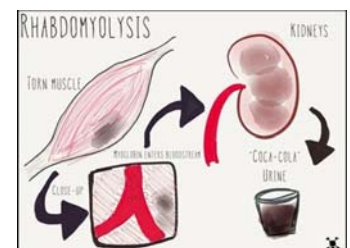


## Statins and muscle damage

- Other statins linked to muscle cell damage (rare cases)
- Problem 10X more common with Baycol

## Rhabdomyolysis

- Characterized by muscle necrosis and release of intracellular muscle constituents into the circulation.



### Symptoms

- Muscle pain, weakness, and dark urine (more than half of patients may not report muscular symptoms)
- Muscle pain - thighs, calves, shoulders, and lower back

### Laboratory findings

↑↑↑ CK (almost entirely CK-MM)

↑ serum and urine myoglobin

Reddish-brown urine (due to myoglobinuria)

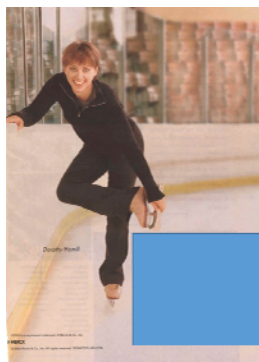


### Other laboratory findings

- Hyperkalemia, Hyperphosphatemia
- Hypocalcemia
- Hyperuricemia (release of purines from damaged muscle cells)
- Metabolic acidosis
- Increased anion gap may be present



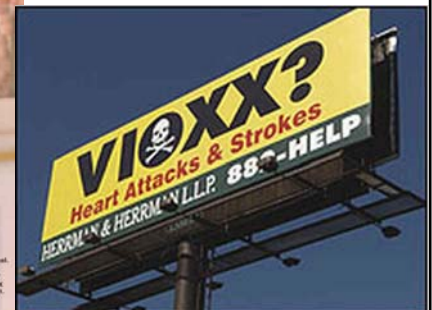
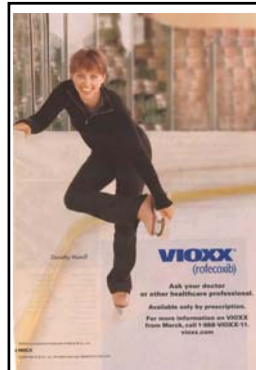
## POISON #6



Pain reliever advertised here by Dorothy Hamill, was one of a relatively new group of NSAIDs called COX-2 inhibitors

Used by many arthritis sufferers, this drug was pulled from the market in 2004, for causing increased risk of cardiac events

Do you know what this poison is?



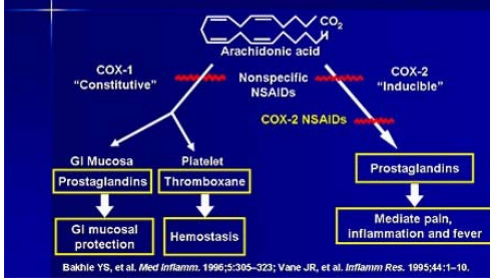
## COX-2 inhibitors

- **Vioxx (rofecoxib)** received FDA approval in 1999; COX-2 inhibitor
- These drugs caused **fewer GI side effects** than older nonselective NSAIDs like ibuprofen.



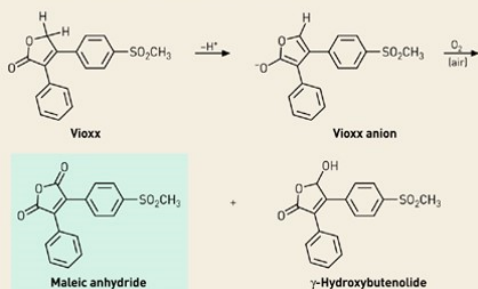
## COX inhibitors

- **Nonselective** NSAIDs (e.g., aspirin and ibuprofen) – work by blocking production of two enzymes, COX-1 and COX-2.
- **COX-2 inhibitors** only block the type of enzyme directly responsible for pain and inflammation (COX-2).
- COX-1 is thought to help protect the stomach from ulcers.

Mechanism of Action of NSAIDs:  
New Concept

## Vioxx

- Widely prescribed; used by millions
- Manufacturer thought it may contribute to prevention of colon cancer
- Launched clinical trial called Adenomatous Polyp Prevention on Vioxx (APPROVe) to test this.
- Results showed increased risk of cardiovascular events, including heart attacks and strokes, in patients taking Vioxx

UNIQUE REACTIVITY  
Air oxidation leads to potentially toxic compound**POISON #7**



## POISON #7

- 1932 - German pathologist Gerhard Domagk discovered new antibacterial drug
- Used in battlefield in World War II to prevent infections
- Several pharmaceutical companies sold as pills and powders
- S.E. Massengill Company decided that to produce a liquid form
- At the time, no formal government approval was required to begin marketing new drugs

## POISON #7

- Massengill's chief chemist formulated a solution
- Company's internal control lab approved the solution's appearance, taste, and fragrance— raspberry flavored
- By September 1937, Massengill had distributed 240 gallons of the liquid, called Elixir \_\_\_\_\_, across the country.

## POISON #7

71 adults and 34 children died in the Fall of 1937 after taking Elixir \_\_\_\_\_

No deaths had occurred in taking the antibiotic in powder or pill form

Do you know what their poison was?



## Sulfanilimide 'Elixir'

- Deaths caused by renal failure after taking the elixir
- Investigators identified the medicine's solvent, **diethylene glycol**, as the cause of the deaths.



## Lack of regulation

- At the time, Massengill had only broken the law by calling the medicine an "elixir,"
- Drugs had to contain ethanol to be called elixirs

## Diethylene glycol scandals

### Toxic Toothpaste Made in China Is Found in U.S.

By WALT BORDENHORN JUNE 2, 2007



1980s- Wines from Austria

## Diethylene glycol

- Over the years, DEG has been incorporated into all varieties of medicine — (e.g., cough syrup, fever medication)
- Sweet-tasting solvent used in place of more expensive one (e.g., glycerin)
- “Toxic syrup” has played a role in multiple mass poisonings around the world.
- Researchers estimate that thousands have died.
- In many cases, the precise origin of the poison has never been determined.

## From China to Panama, a Trail of Poisoned Medicine

By WALT BOGDANICH and JAKE HOOKER MAY 6, 2007



## 2007

- Panama - government officials unwittingly mixed diethylene glycol into 260,000 bottles of cold medicine
- 365 deaths reported
- Chinese companies made and exported it as 99.5% pure glycerin.
- The counterfeit glycerin passed through multiple trading companies on three continents; none tested the syrup to confirm what was on the label.

## 2007 - Another issue with China

- Accused by U.S. authorities of exporting wheat gluten containing an industrial chemical, melamine, that ended up in pet food and livestock feed.
- F.D.A. banned imports of Chinese-made wheat gluten after it was linked to pet deaths



Poisons used for good

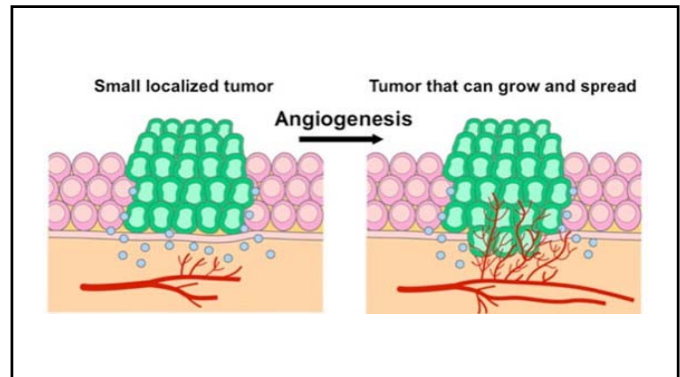


Example A

### Example A



- Taken off market for causing birth defects
- In recent years made available again for other uses
- Mechanisms of action include **anti-angiogenic** and **anti-inflammatory** properties (Birth defects not likely due to only one mechanism)



### Example A

- 2004 – made available for uses such as certain complications of leprosy (WHO does not recommend)
- Now also used to treat multiple myeloma and some other cancers

Do you know what this 'good poison' is?

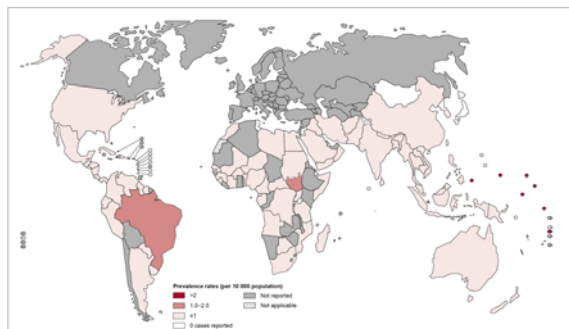


### Thalidomide and leprosy in Brazil

- Leprosy (Hansen's disease) - still a public health problem in Brazil
- Affects skin, peripheral nerves, mucosal surfaces of respiratory tract and eyes
- Caused by *Mycobacterium leprae*
- WHO recommends multidrug therapy – NOT thalidomide!



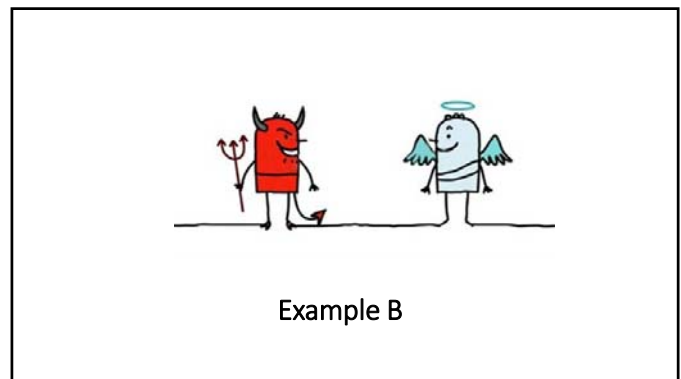
Leprosy prevalence rates, data reported to WHO as of January 2013



### Thalidomide use in Brazil today (Hansen's disease)

- Most cases in poor areas - patients not educated
- Used for skin lesions; supposed to be strictly regulated
- Can only be prescribed to a woman on 2 types of birth control
- Clear warnings on packets





Bacterium that produces this toxin

- Can be foodborne due to improperly canned foods
- Spores can be found in honey, so children < 1 year old should not eat honey
- Can cause a wound illness in heroin addicts or after trauma such as motorcycle accidents

Example B

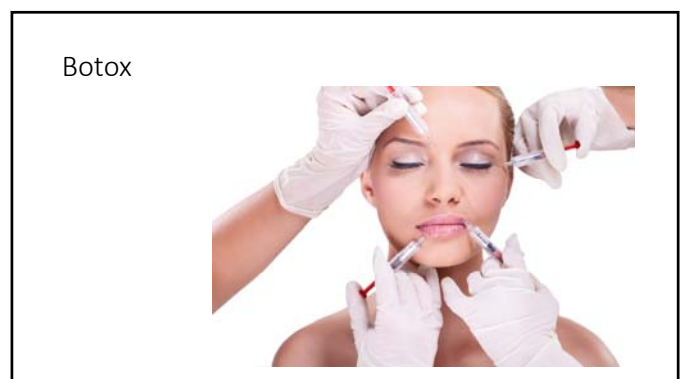
Neurotoxin (attacks nerves)

- Early symptoms due to weakness of muscles of the eyes, face, mouth, and throat (double or blurry vision, droopy eyelids, difficulty swallowing, muscle weakness)
- Can progress to paralysis of muscles including respiratory muscles; can cause death

Example B

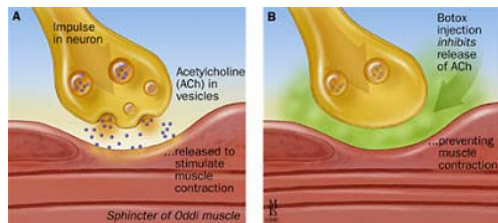
Currently in use for cosmetic procedures as well as some clinical therapies

Do you know what this 'good poison' is?

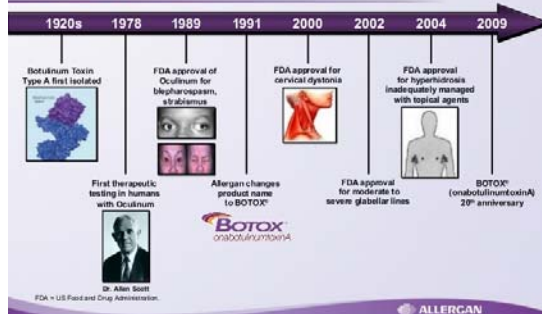


## Botulinum toxin

Binds nerve endings, blocking release of acetylcholine into neuromuscular junction → prevents muscle contraction



## History of Development, FDA Approvals, and Clinical Trials



## Botox other uses – FDA approvals

- 2010 – chronic migraines  
upper limb spasticity
- 2013 – overactive bladder
- 2016 – lower limb spasticity

In all cases, mechanism is essentially the same



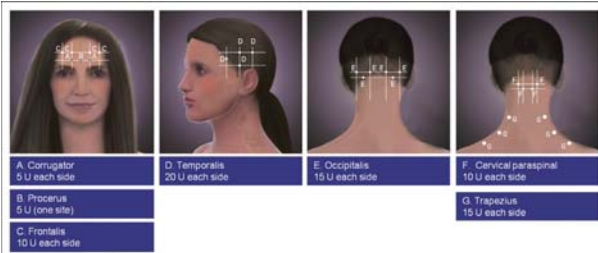
## Spasticity

Continuous contraction of certain muscles due to damage caused to the parts of brain or spinal cord controlling voluntary movements

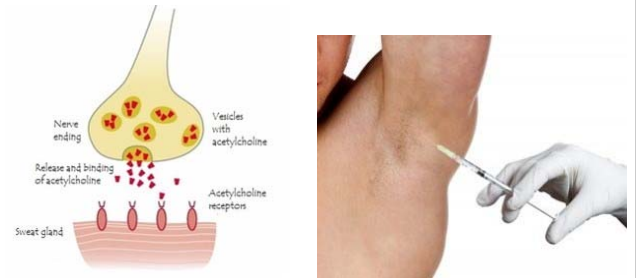
- Muscle tightness
- Joint stiffness
- Involuntary jerking movements
- Unusual posture
- Muscle spasms and fatigue



## Chronic migraines



## Hyperhidrosis



Example C

## Example C



- This element was discovered in 1898 by a now famous married couple
- It was used to treat a number of varied diseases (e.g., cancer, gout, constipation)
- Its healing and revitalizing reputation led to its use in healing waters, spas
- Its luminous properties led to use in watch and clock faces and other dials (It made things glow!)

## The Radium Girls — still glowing in their coffins

Kate Moore pays tribute to last century's tragic factory workers, who suffered grotesque poisoning from luminous paint — to aid the war effort  
Maggie Ferguson



Do you know what this 'good poison' is?

## The Radium Girls — still glowing in their coffins

Kate Moore pays tribute to last century's tragic factory workers, who suffered grotesque poisoning from luminous paint — to aid the war effort  
Maggie Ferguson





## The girls became ill

- Chronic exhaustion.
- Stillborn babies.
- Severe tooth decay. When teeth were removed, gums wouldn't heal
- Skin so thin it would split open easily
- Death was usually accompanied by violent hemorrhaging.



## Radium

- Associated with cancers, anemias
- Particularly associated with bone destruction

Periodic Table of the Elements

Radium behaves like calcium in the body; ends up in bones and teeth

## Marie Curie

- Died, 1934, of aplastic anemia, believed to be caused by prolonged exposure to radiation.
- Known to carry test tubes of radium around in the pocket of her lab coat

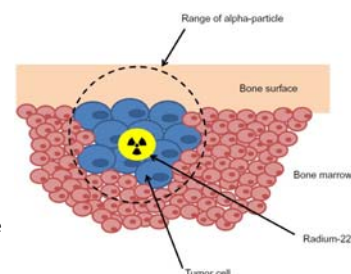


## Radium – early treatments

- First used in early 1900s to treat cancer
- Radium 'points' were stitched to tumors
- Sometimes the cancer died; sometimes the patient died

## Radium 223 today

- Alpha particle-emitting radiopharmaceutical approved for treatment of bone metastases in prostate cancer.
- Administered I.V.
- No requirement for complex shielding
- Specifically targets areas of bone metastasis.





Other examples

Yew tree (*Taxus baccata*)

- Leaves, bark, berries all very poisonous, but
- The chemotherapy drugs docetaxel and paclitaxel have been derived from extracts of yew trees



## Brazilian pit viper

Venom used to produce ACE inhibitors, used to lower blood pressure



## Brief history of food and drug testing in US

1883

- Dr. Harvey W. Wiley is made chief chemist at the Bureau of Chemistry's food adulteration studies
- He took his position very seriously



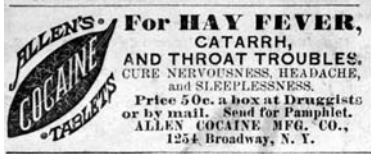
## 1880s through 1890s - Food and drug industries

Very different from today

- Chemical preservatives and colorings (untested, uncontrolled)
- Ice for refrigeration
- Sanitation poor
- Milk still unpasteurized
- Medicines and labels uncontrolled



- In the late 1800s cocaine was found in Coca Cola among other things.



### Late 1800s

- People were leaving farms and taking industrial jobs in cities
- Food had to be brought in from distant places
- Additives and adulterants used to prevent spoilage, improve appearance, and lower overhead
- Dr. Wiley worried that these tactics were unsafe



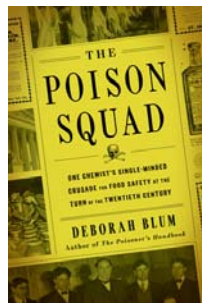
### Milk

- Watered down (not always with clean water)
- Additives for color, consistency – chalk or plaster powder
- Preservative - formaldehyde



### The poison squad

- Dr. Wiley lined up volunteers for his experiments- The Hygienic Table Trials
- Young, male government workers
- Volunteers ate meals prepared by chefs
- Foods contained chemicals that were being used as food additives



### Poison Squad (1902-1907)



### Preservatives included:

- Borax
- Formaldehyde
- Sulfuric acid
- Copper sulfate



### The Poison Squad

- Motto was "Only the Brave Dare Eat The Fare"
- Had its own catchy rhyme, courtesy of poet S.W. Gillian:

On prussic acid we break our fast  
We lunch on morphine stew  
We dine with a matchhead consommé  
Drink carbolic acid brew

### In the end

- Of course they became ill
- Helped pave the way for legislation to protect from these additives
- Harvey W. Wiley often referred to as the 'Father of the FDA'



### 1905 – Samuel Hopkins Adams

- Wrote a series of articles about medicines of his day
- Exposed false claims made by medicine manufacturers
- The series was published as a book in 1906, "The Great American Fraud"



#### AN ACETANILID DEATH RECORD.

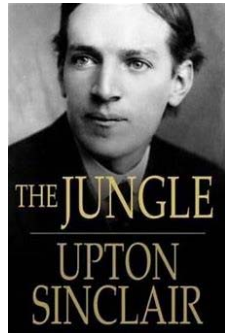
This list of fatalities is made up from statements published in the newspapers. In every case the person who died had taken to relieve a headache or as a brace a patent medicine containing acetanilid, without a doctor's prescription. This list does not include the case of a dog in Utmost, Pa., which died immediately on eating some sample headache powder. The dog did not know any better.

Mrs. Minnie Bishop, Louisville, Ky.; Oct. 16, 1903.  
Mrs. Mary Cook and Mrs. Julia Ward, of 172 Perry Street, New York City; Nov. 27, 1903.  
Fred P. Smith, Scranton, Pa.; Dec. 5, 1903.  
C. Frank Henderson, Toledo, O.; Dec. 15, 1903.  
Joseph E. Shady, St. Paul, Mich.; Feb. 18, 1904.  
Charles M. Swift, New Albany, Ind.; March 15, 1904.  
Oscar McKinley, Pittsburgh, Pa.; April 15, 1904.  
Otis Strainer, student at Wabash College; April 15, 1904.  
Mrs. Florence Ramsey, Clinton, Ia.; April 15, 1904.  
Jenny McGee, Philadelphia, Pa.; May 27, 1904.  
Mrs. William Maher, Lehigh, Mich.; Sept. 5, 1904.  
Mrs. Jacob Friedman, of South Bend, Ind.; Oct. 19, 1904.  
Miss Libbie North, Rockdale, N. Y.; Oct. 26, 1904.  
Margaret Haskins, Dayton, O.; Oct. 26, 1904.  
Samuel Williamson, New York City; Nov. 21, 1904.  
George Kolisch, St. Louis, Mo.; Nov. 24, 1904.  
Robert Brock, St. Louis, Mo.; Nov. 27, 1904.  
Mrs. Harry Haven, Oakdale, Pa.; Nov. 27, 1904.  
Mrs. Jennie Whyler, Akron, O.; April 5, 1905.  
Mrs. Augusta Strickman, St. Louis, Mo.; June 20, 1905.  
Mrs. Mary A. Hughes, Philadelphia, Pa.; July 2, 1905.  
Mrs. Theo. Patterson, Huntington, W. Va.; Aug. 15, 1905.

Some of these victims died from an alleged overdose; others from the prescribed dose. In almost every instance the local papers suppressed the name of the fatal remedy.

## 1905- Upton Sinclair

- Wrote a series of articles exposing conditions in the meat-packing industry that were later published as book, "The Jungle"



## 1906 – Pure Food and Drug Act and Meat Inspection Act

- Signed by Theodore Roosevelt
- Pure Food and Drug Act- outlaws selling food or drugs that are adulterated, misbranded
- Meat Inspection Act – U.S. FDA inspections, cleanliness standards



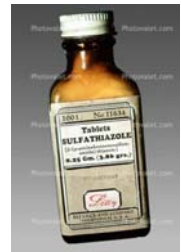
## 1937 – Sulfanilimide elixir disaster

- Public outcry led to the **1938 Food, Drug, and Cosmetics Act**, which gave the FDA power to monitor the **safety** of new drugs.



## 1941- Sulfathiazole tragedy

- Winthrop Chemical Company sold sulfathiazole (antibiotic) tablets
- Nearly 300 deaths.



## Sulfathiazole tragedy- adulteration

- Tablets were contaminated with phenobarbital.
- FDA's investigation revealed numerous control deficiencies in the plant
- The incident became the basis for the future production control standards for all pharmaceuticals.



## 1950s to 1961- Thalidomide debacle

- **1962**, prompted passage of the **Kefauver-Harris Drug Amendments**, requiring companies to provide evidence of **efficacy** in addition to **safety**.





## 1982-Tylenol murders Tamper-proof packaging

- Introduced by Johnson & Johnson
- Foil seals and other features that made it obvious if tampered with.
- November 1982 - FDA requirement
- 1989, the FDA established guidelines for manufacturers.



Future worries

## A serious new hurdle for CRISPR: Edited cells might cause cancer, two studies find

By SHARON BEGLEY *Outlook* / JUNE 15, 2019



## ACE inhibitors linked to increased risk for lung cancer

"The silver lining of our findings is that while we found an association, the risk at the individual patient level is likely low, even after 10 years of use," said researcher Laurent Azoulay.

By Steven Reinberg, HealthDay News



It just goes to show you ...

