Medicines and other poisons

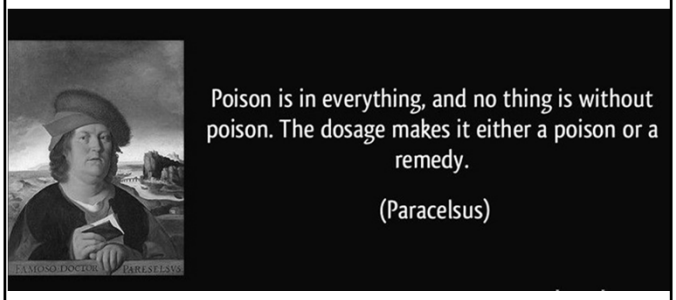
Mitzi Glover, PhD, MT(ASCP)

Objectives

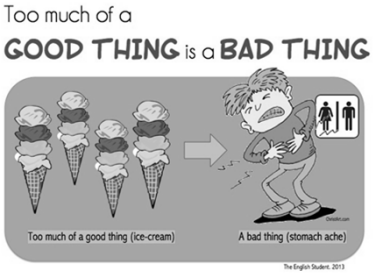
- Describe some historical cases of unexpected toxicity of drugs or other substances.
- Discuss current uses for substances previously found to be toxic.
- Briefly describe the evolution of toxicity testing in the U.S.

Methods of toxicity

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



In other words,



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
- 2nd 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

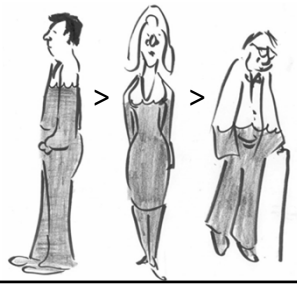
Water accounts for approximately 60% of body weight

- 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.

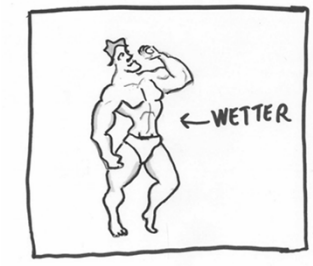
What about adults?



Water content in different tissues

Different tissues have different amounts of water in them

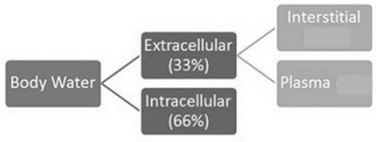
- Skeletal muscle
- Bone
- Fat-least hydrated tissue



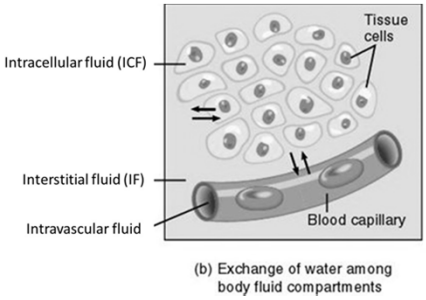
Robert Krulwich/NPR

Distribution of water

- 2/3 in intracellular fluid (ICF)
- 1/3 in extracellular fluid (ECF)
  - interstitial fluid (approx. ¾)
  - plasma, or intravascular (approx. ¼)



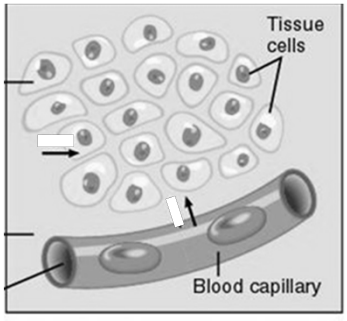
Fluid movement between compartments

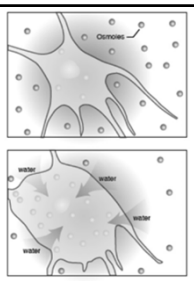


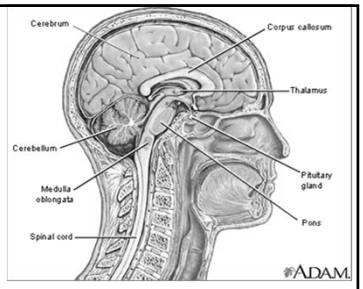
(b) Exchange of water among body fluid compartments

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…



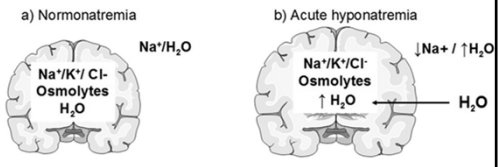




Neurons in the brain do not!!!

Water intoxication

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



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.

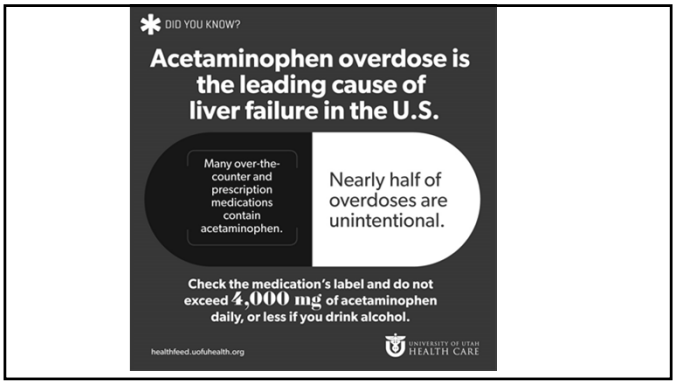
Doctors felt chronic hepatitis C may have contributed to elevated AST and ALT, but pattern of serum enzyme elevations were not likely due to acute hepatitis.

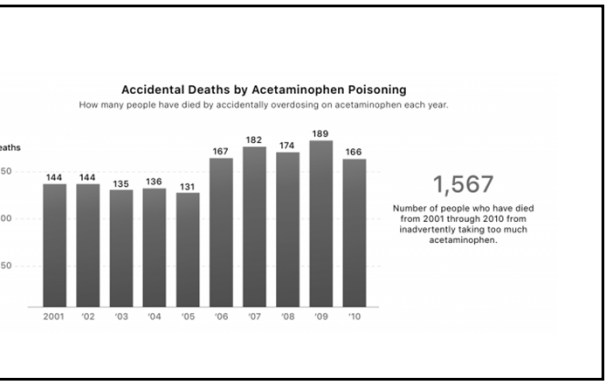
Do you know what her poison was?

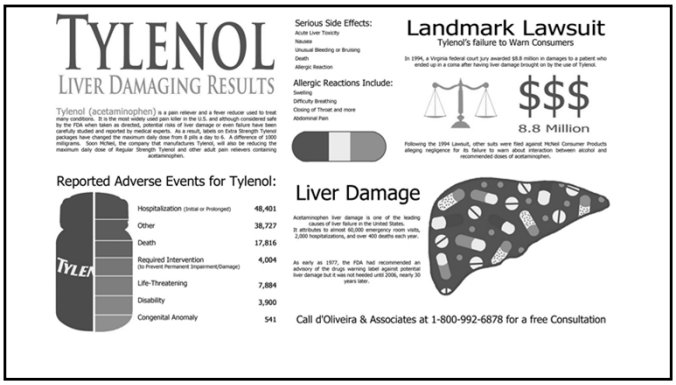
POISON # 2

Severe acetaminophen hepatotoxicity after unintentional overdose.

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







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

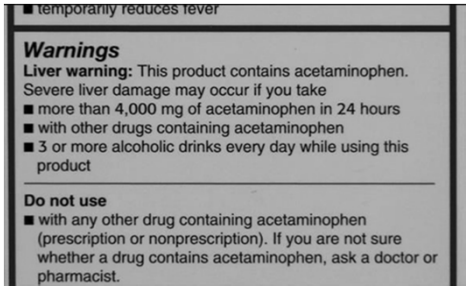
Patient regularly had wine with dinner.

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



■ temporarily reduces fever

Warnings

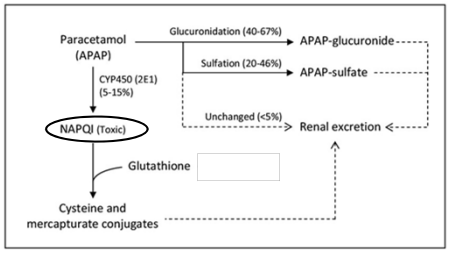
Liver warning: This product contains acetaminophen. Severe liver damage may occur if you take

- more than 4,000 mg of acetaminophen in 24 hours
- with other drugs containing acetaminophen
- 3 or more alcoholic drinks every day while using this product

Do not use

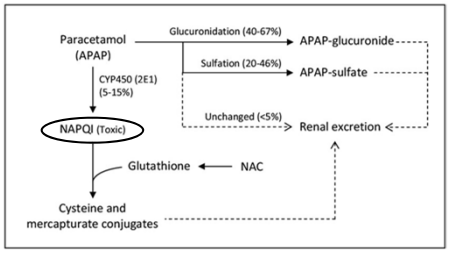
- with any other drug containing acetaminophen (prescription or nonprescription). If you are not sure whether a drug contains acetaminophen, ask a doctor or pharmacist.

Metabolism of acetaminophen (paracetamol)



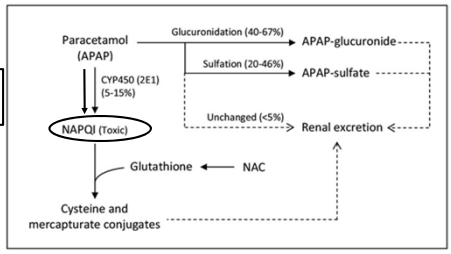
Overdose of acetaminophen (paracetamol)/antidote

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

600 medications with acetaminophen currently approved for sale in the U.S.

27 acetaminophen doses sold in the U.S. in 2009

1,567 Americans who died from 2000-2010 from accidental acetaminophen poisoning

1,400 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

Arlington Heights Edition

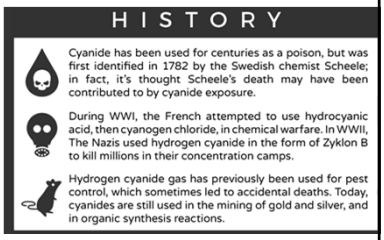
5 dead after taking Tylenol capsules filled with cyanide

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

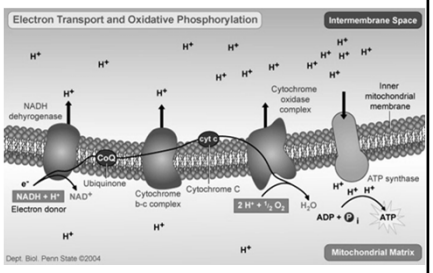
- Has been used in pesticides; some industrial uses
- Found in cigarette smoke, exhaust fumes, and some foods (small amounts)
- In larger doses – blocks cells from utilizing oxygen (cyanide ions bind irreversibly to iron)



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

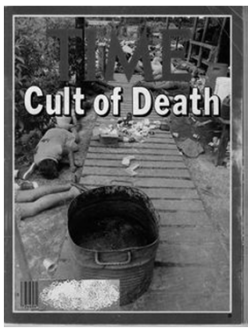


Cyanide poisonings

- 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

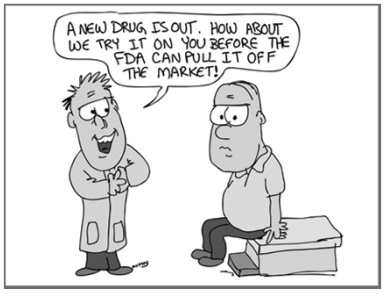
- Brendan Brogan treated for _____ poisoning after eating apricot pits from health food store
- California man visiting a friend in Montreal
- Friend warned him to be careful, because they were poisonous.
- Brendan thought that couldn't be the case, because they were marked as "superfood"
- Then he saw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

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?

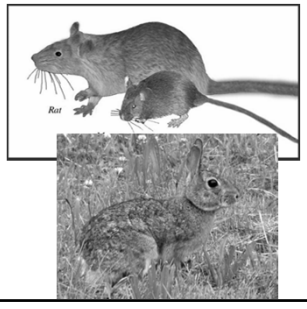
Call the Midwife- PBS

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?

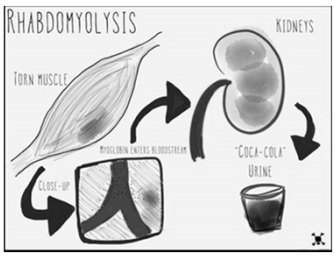
Anticholesterol Drug Pulled After Link With 31 Deaths

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.

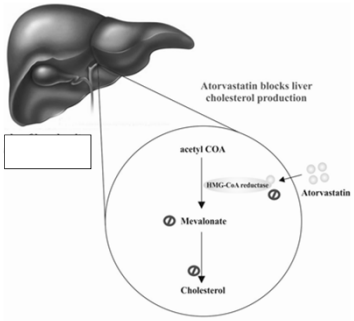
Baycol (Lipobay)

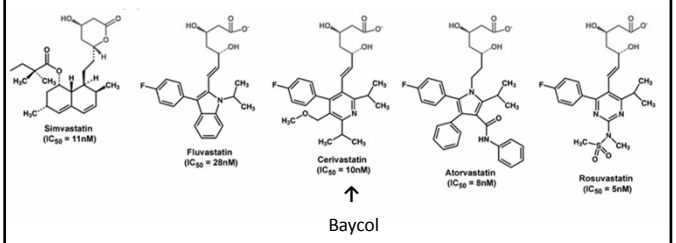
- Withdrawn 2001
- Deaths primarily due to rhabdomyolysis leading to **renal failure**



Statins

- Cholesterol lowering drugs
- HMG CoA Reductase inhibitors





↑ Baycol

Statins

I take Lipitor.

Atorvastatin (my labs)

Began taking atorvastatin after 10/15/17 testing

Name *Standard Range*	5/8/15	4/28/17	10/5/17 ↓	4/3/18
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)

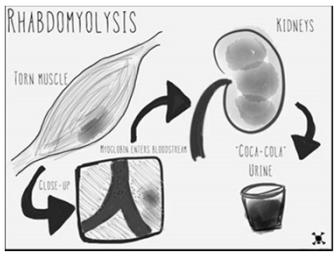
- I take this one
- My mother could not

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

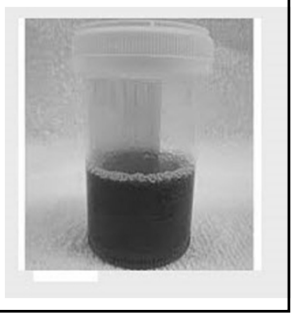
↑↑↑ CK (almost entirely CK-MM)

↑ serum and urine myoglobin

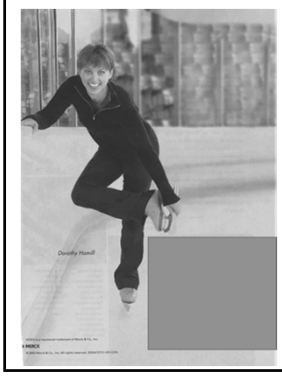
Reddish-brown urine (due to myoglobinuria)

Other laboratory findings

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



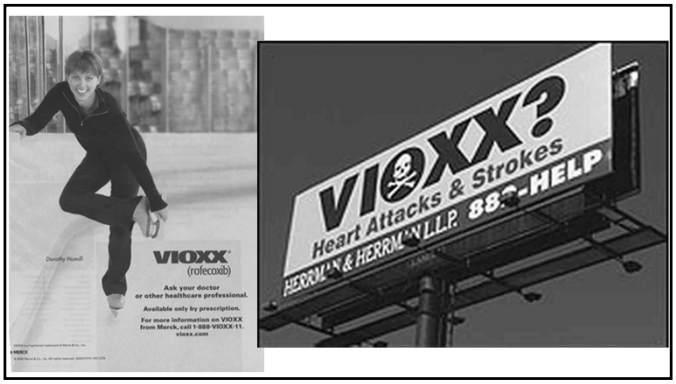
POISON #6



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?

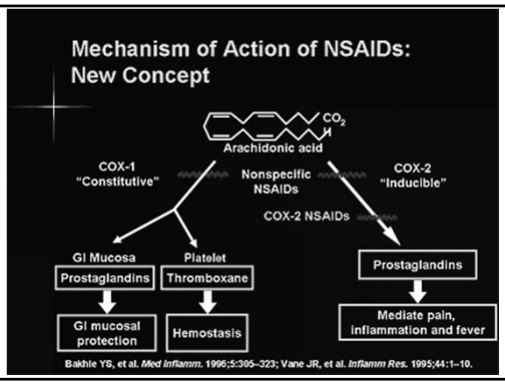


COX-2 inhibitors

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

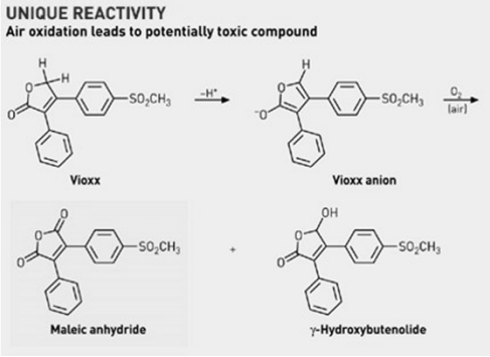
COX inhibitors

- ***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.



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



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

U. S. Races Death to Save 700 From Elixir

Recovery of Pint Bottles Sold to Patients Goal as Deaths From Poison Reach 36

By Associated Press.

CHICAGO, Ill., October 24.—A nation-wide race with death, to obtain recovery of more than 700 bottles, mostly pints, of a new liquid medicine, named Elixir of Sulfanilamide, which has already caused 36 verified deaths, was described today at the headquarters here of the American Medical Association.

Every agent of the United States Food and Drug Association, said Dr. Morris Fishbein, spokesman of the Medical Association, is scouring the country to recover the bottles. By some time on Monday said J. G. Clarke of the Food and Drug Administration, it is hoped that all of the "outstanding" shipments will be recovered.

lies in the fact that large dosages are customary with sulfanilamide preparations.

The medicine stops the kidneys. At Medical Association headquarters its effects were said to be like those of bichloride of mercury. No antidote is known yet. The "Elixir" is made of sulfanilamide and diethylene glycol, a near relative of auto antifreeze fluid. The diethylene glycol is blamed for the lethal effect, although not itself classed as a poison.

The principal shipments, said Mr. Clarke, went to the South and Midwest. But in addition consignments have been traced to the Northern Peninsula of Michigan, to a distributing house in New York City and to another in San Francisco. An

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 BOGDANICH 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

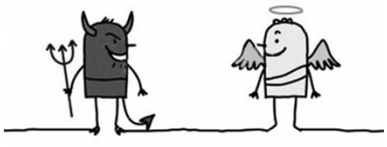
By WALT BOGDANICH and JAKE HOOKER MAY 6, 2007

2007

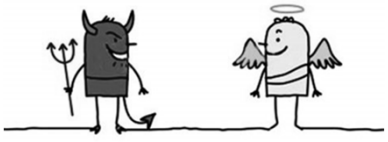
- Panama - government officials unwittingly mixed diethylene glycol into 260,000 bottles of cold medicine
- 365 deaths reported
- Chinese companies made and exported it as 99.5% pure glycerin.
- The counterfeit glycerin passed through multiple trading companies on three continents; none tested the syrup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



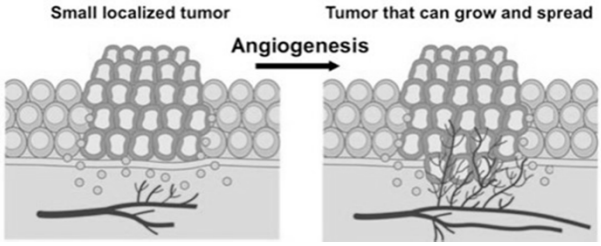
Poisons used for good



Example A

Example A

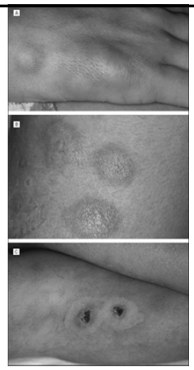
- Taken off market for causing birth defects
- In recent years made available again for other uses
- Mechanisms of action include anti-angiogenic and anti-inflammatory properties (Birth defects not likely due to only one mechanism)



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

Magazine

Brazil's new generation of Thalidomide babies

By Angus Crawford
BBC Newsnight

24 July 2013

Example B

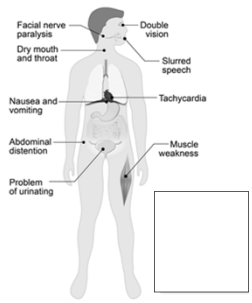
Bacterium that produces this toxin

- 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

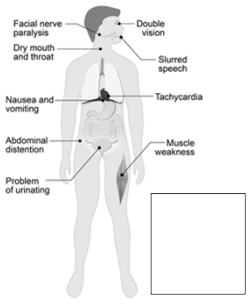
Neurotoxin (attacks nerves)

- 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

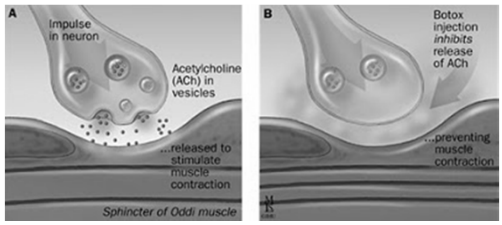


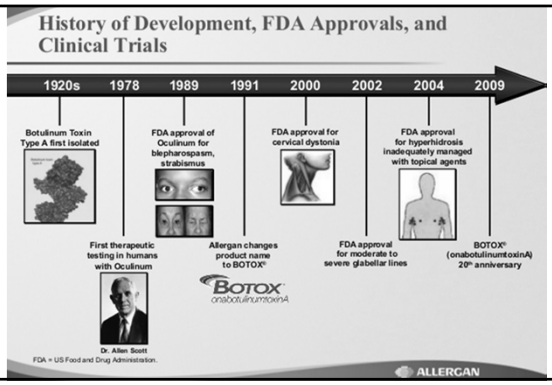
Do you know what this 'good poison' is?

Botox

Botulinum toxin

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





Botox other uses – FDA approvals

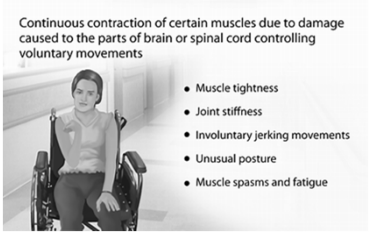
2010 – chronic migraines
upper limb spasticity

2013 - overactive bladder

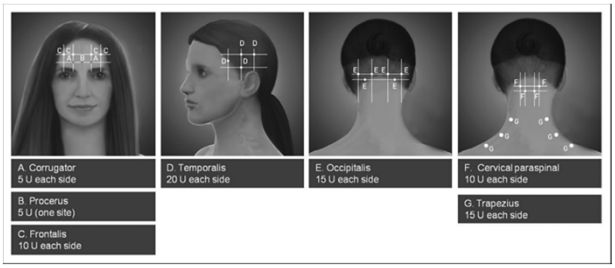
2016 - lower limb spasticity

In all cases, mechanism is essentially the same

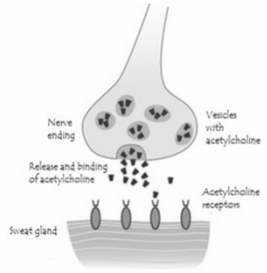
Spasticity

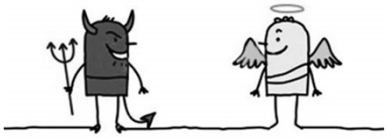


Chronic migraines



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!)

BOOKS

The [ ] 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 Fergusson

Do you know what this 'good poison' is?

BOOKS

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

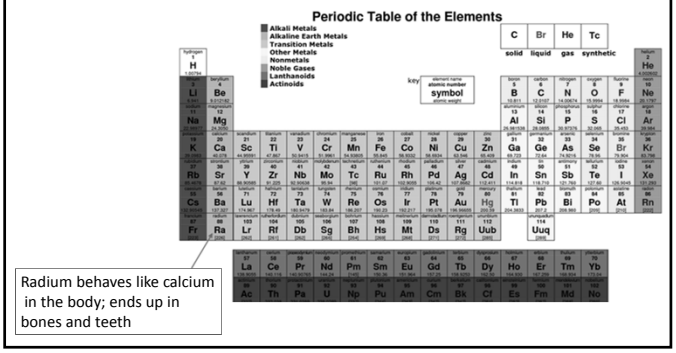
Maggie Fergusson

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



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

Marie Curie

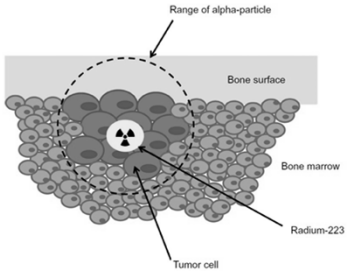
- Died, 1934, of aplastic anemia, believed to be caused by prolonged exposure to radiation.
- Known to carry test tubes of radium around in the pocket of her lab coat

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

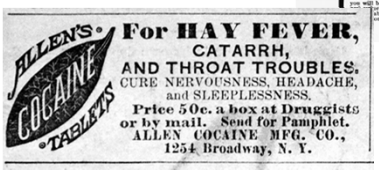
- Dr. Harvey W. Wiley is made chief chemist at the Bureau of Chemistry's food adulteration studies
- He took his position very seriously

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

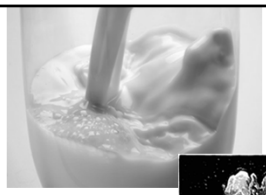
- In the late 1800s cocaine was found in Coca Cola among other things.



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

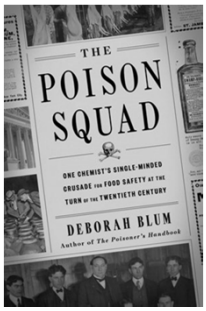
Milk



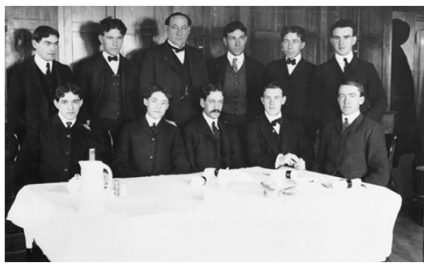
- Watered down (not always with clean water)
- Additives for color, consistency – chalk or plaster powder
- Preservative - formaldehyde

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:

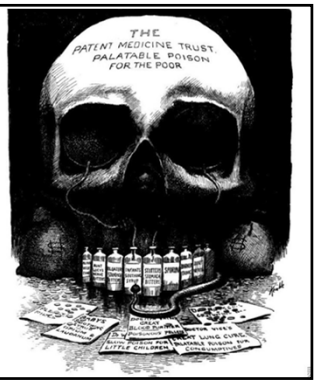
On prussic acid we break our fast
We lunch on morphine stew
We dine with a matchhead consummé
Drink carbolic acid brew

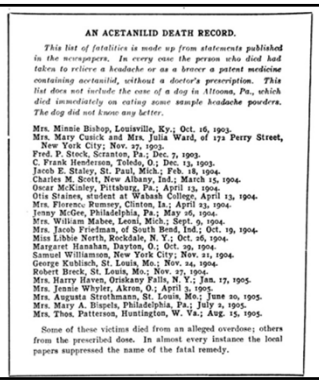
In the end

- 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.

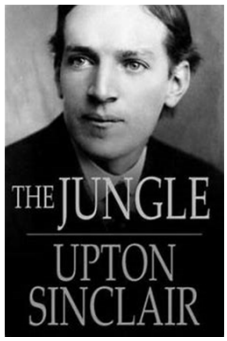
This list of fatalities is made up from statements published in the newspapers. In every case the person who died had taken to relieve a headache or as a bracer a patent medicine containing acetanilid, without a doctor's prescription. This list does not include the case of a dog in Altoona, Pa., which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

Mrs. Minnie Bishop, Louisville, Ky.; Oct. 16, 1903.
Mrs. Mary Cusick and Mrs. Julia Ward, of 172 Perry Street, New York City; Nov. 27, 1903.
Fred. P. Stock, Scranton, Pa.; Dec. 7, 1903.
C. Frank Henderson, Toledo, O.; Dec. 13, 1903.
Jacob E. Staley, St. Paul, Mich.; Feb. 18, 1904.
Charles M. Scott, New Albany, Ind.; March 15, 1904.
Oscar McKinley, Pittsburg, Pa.; April 13, 1904.
Otis Staines, student at Wabash College, April 13, 1904.
Mrs. Florence Rumsey, Clinton, Ia.; April 23, 1904.
Jenny McGee, Philadelphia, Pa.; May 16, 1904.
Mrs. William Mabee, Leoni, Mich.; Sept. 9, 1904.
Mrs. Jacob Friedman, of South Bend, Ind.; Oct. 19, 1904.
Miss Libbie North, Rockdale, N. Y.; Oct. 26, 1904.
Margaret Hanahan, Dayton, O.; Oct. 29, 1904.
Samuel Williamson, New York City; Nov. 21, 1904.
George Kubisch, St. Louis, Mo.; Nov. 24, 1904.
Robert Breck, St. Louis, Mo.; Nov. 27, 1904.
Mrs. Harry Haven, Oriskany Falls, N. Y.; Jan. 17, 1905.
Mrs. Jennie Whyler, Akron, O.; April 3, 1905.
Mrs. Augusta Strothmann, St. Louis, Mo.; June 20, 1905.
Mrs. Mary A. Bispels, Philadelphia, Pa.; July 2, 1905.
Mrs. Thos. 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 serives 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- aldulteration

- 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

IN THE LAB

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

By SHARON BEGLEY @sbegley / JUNE 11, 2018

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 …