



Fascinating Features and Mysterious Manifestations of Disease

OLLI @ University of Illinois
Fall 2022 Semester

Plan for the Course

- Session 1: Diseases with a color
 - Session 2: Diseases with an odor or a taste
 - Session 3: Textures or Sounds of Disease
 - Session 4: Diseases with unusual appearance
 - Session 5: Flying, crawling & burrowing critters
 - Session 6: Forgotten or ignored epidemics
 - **Session 7:** }
 - **Session 8:** }
- Medical detectives solve mysterious cases

Plan for the Session

- The Physician as detective
 - Start the investigation (Clinical)
 - Follow the clues (laboratory and imaging tests)
 - The final word (Pathologist)
- The diagnostic process
 - Inductive reasoning
 - Deductive reasoning
- Pitfalls and Failures
- Cases

Plan for the Combined Session

Cases for The Physician as Detective:

- Eleven Blue Men in New York City
- It's Good Until It's Bad
- The Line Dancer's Red Lines
- Old - Fashioned Skin
- The "Disney Rash"
- Salad With Lettuce...and Tomatoes



Sessions 7 & 8

The Physician as Detective

Detectives and Physicians

Detective

- Take on the case
- Interrogate victim/witness
- Get physical evidence
- Other witnesses
- Ancillary tests
- Organize information
- Formulate hypothesis
- Look for culprit(s)
- Re-evaluate.
- Look for new information

Physician

- Accept the patient
- Obtain patient History
- Do Physical exam
- Family corroboration
- Ancillary tests
- Classify/analyze information
- Initial working diagnosis
- Begin treatment (s)
- Re-evaluate
- Look for new information

Ramírez 2022

The Diagnostic Process

- The three “L’s”:
 - The most **L**ikely possibility
 - The most **L**ethal possibility
 - What’s **L**eft
- In medicine, it is essential to rule out the diseases that kill, and then move on to those that may only make you wish you were dead.
- Famous “” Rules of Medicine:
 - Occam’s Razor
 - Hickam’s Dictum
 - Woodward’s Rule
 - Crabtree's bludgeon

Mnemonic for Systemic Review

- V – Vascular
- I – Infectious
- N – Neoplastic
- D – Degenerative
- I – Iatrogenic/intoxication
- C – Congenital
- A – Autoimmune
- T – Traumatic
- E – Endocrine/metabolic

Reasoning

- If you can strengthen your argument or hypothesis by adding another piece of information, you are using inductive reasoning.
- If you cannot improve your argument by adding more evidence, you are employing deductive reasoning.

Inductive vs Deductive

Inductive Reasoning

- Specific Observation (s)
- Pattern recognition
- General conclusion

Deductive Reasoning

- Existing theory
- Formulate hypothesis
- Collect data
- Analyze data
- Reject/accept hypothesis

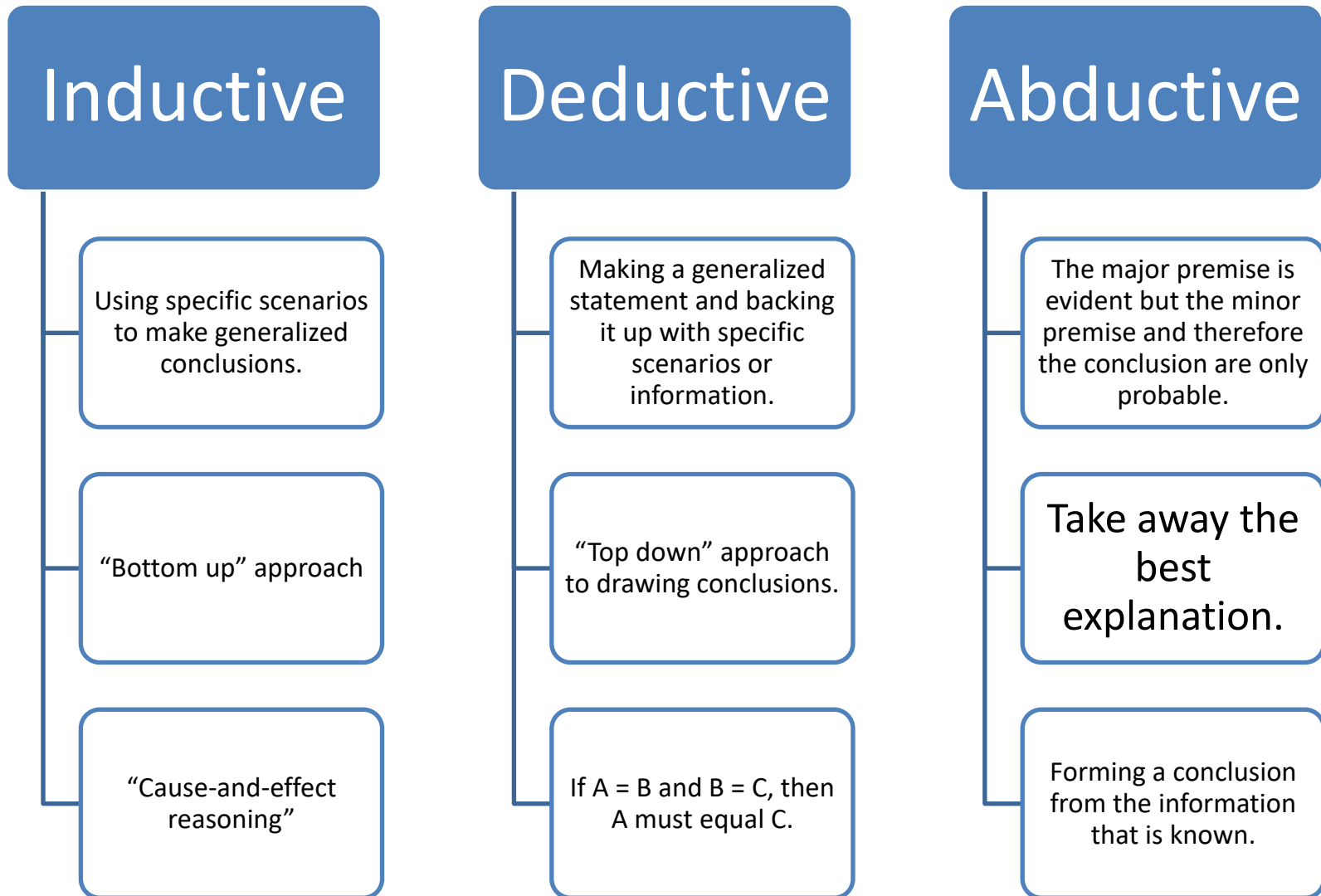
Inductive Reasoning

- Inductive reasoning is the act of using specific scenarios and making generalized conclusions from them.
- Also referred to as “cause-and-effect reasoning,” inductive reasoning can be thought of as a “bottom up” approach.
- For example, you might observe that your older sister is tidy, your friend’s older sister is tidy and your mom’s older sister is tidy.
- Inductive reasoning would say that therefore, all older sisters are tidy.

Deductive Reasoning

- Deductive reasoning is the act of making a generalized statement and backing it up with specific scenarios or information, or a “top down” approach to drawing conclusions.
- Consider the statement “all apples are fruits.”
- If you introduce a specific piece of information like “all fruits grow on trees”, you can then deduce that all apples grow on trees.
- Another classic example of deductive reasoning is:
If $A = B$ and $B = C$, then A must equal C .

Logical Reasonings



Occam's Razor

Ockham's Razor



William of Ockham

- *Pluralitas non est ponenda sine necessitate* (“Plurality should not be posited without necessity”).
- Of two competing theories, the simpler explanation of an entity is to be preferred.
- Also: “Entities are not to be multiplied beyond necessity”, or “Simpler solutions are more likely to be correct than complex ones.”

Hickam's Dictum

John Hickam (1914-1970)

- Stated as “Patients can have as many diseases as they damn well please”.
- Chair of the Department of Medicine at Indiana University.
- Hickam's dictum is a counterargument to the use of Occam's razor in the medical profession.
- While Occam's razor suggests that the simplest explanation is the most likely, implying that diagnosticians should assume a single cause for multiple symptoms, Hickam's suggest the possibility of several diagnoses.

Woodward's Rule

- Rule of Simplicity.
- The "Zebra": a physician should reject an exotic medical diagnosis when a more commonplace explanation is more likely.
- When you hear hoofbeats, think of horses first, not zebras.

Procrustes and Crabtree's Bludgeon

- Procrustes was a robber who killed his victims by making them lie on an iron bed.
- He forced them to fit the bed by cutting off the parts that exceeded the bed's length or stretching those people who were too short.
- It is the tendency to make data fit our favorite diagnostic explanation.

Ramirez's Non-Laws

- Always do a Complete History and Physical exam.
- Every solution to a problem creates a new problem, usually harder to solve than the 1st.
- When looking at a Chest X-Ray, first look at the cage, and then look at the birdie.
- Trust the patient but verify everything they say.
- A laundry list is always incomplete.
- Don't trip on your own shoelaces.

Famous Fictional Physicians

- Marcus Welby, MD
- Dr. Gillespie
- Dr. Kildare
- Dr. Zorba
- Ben Casey
- Quincy, ME
- Shaun Murphy
- Hawkeye Pierce
- Trapper John McIntyre
- Michaela Quinn
- Doogie Howser
- Jordan Cavanaugh
- Maura Isles
- J.D. Dorian

Fictional Hospitals

- Scrubs (Sacred Heart, Sacramento)
- Saint Elsewhere (St. Eligius Hospital, Boston)
- Chicago MED (Gaffney Chicago Medical Center)
- New Amsterdam (New York City hospitals)
- E.R. (LA County ER)
- Royal Pains (Hamptons Heritage Hospital)
- CSI (Las Vegas Crime Lab)
- M.A.S.H 4077
- Gray's Anatomy (Gray-Sloan Memorial, Seattle)
- The Good Doctor (San José St. Bonaventure Hospital).

CT vs MRI

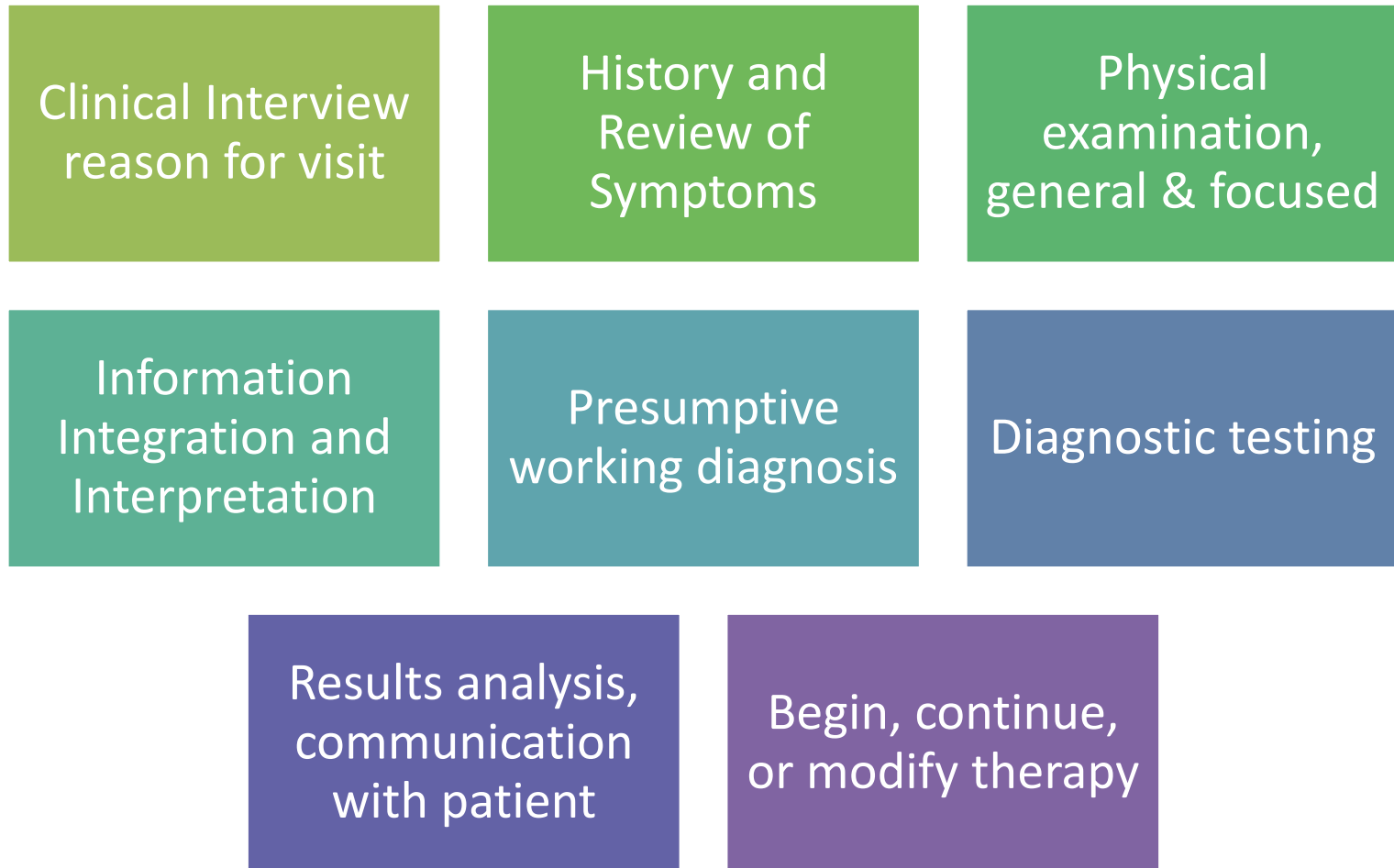
Computed Tomography

- Better for injuries from trauma, staging cancer, and conditions in blood vessels.
- Powered by radiation, avoid in children, expectant mothers, and certain organs.
- Image bones and blood vessels better than MRI's.
- Far quicker than MRI's, good for emergencies.

Magnetic Resonance Imaging

- Create very detailed 3D images of soft tissues, tendons, ligaments, spinal cord and brain.
- Powered by magnets, avoid in patients with metal implants or pacemakers.
- Image soft tissues much clearer than CT's.
- Longer acquisition and processing times.

The Diagnostic Process



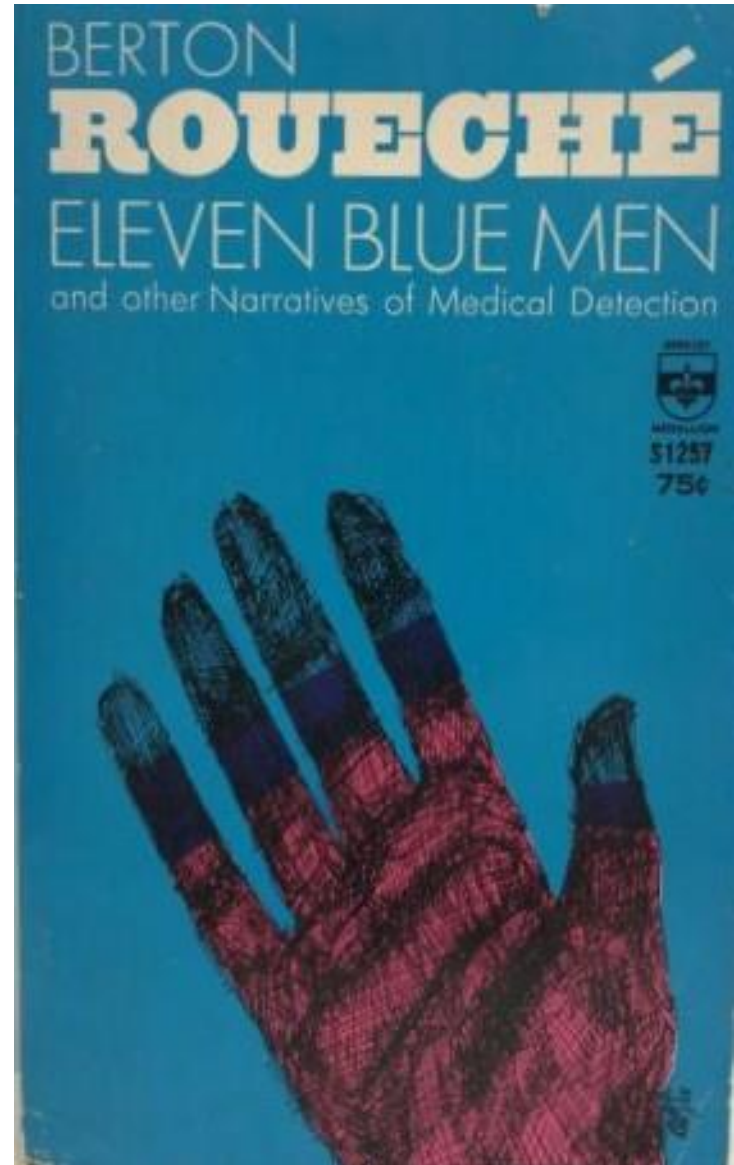
Questions? 1



Challenging Clinical Cases

Case No. 1

ELEVEN BLUE MEN



11 Blue Men in New York ⁽¹⁾

Monday at 8AM, a ragged 82-year old man collapses on the sidewalk near Hudson Terminal.

He is doubled up with abdominal cramps, and in agony with retching.

A policeman comes to his aid thinking it's a street drunk.

Man's nose, lips, ears, and fingers are sky-blue.

11 Blue Men in New York (3)

Case Progression

Case # 1 in hospital emergency room at 8:30.

He is unconscious on admission

The blueness has spread over most of his body.

ER doctor thinks the old man's morbid color is cyanosis, a condition that results from an insufficient supply of oxygen in the blood.

The patient is diarrheic and in a severe state of shock.

11 Blue Men in New York (2)

Possible diagnoses

A) Respiratory Disease?

B) Cardiac Disease?

C) Infectious Disease?

D) Street drug overdose?

E) Food Poisoning (Intoxication)?

11 Blue Men in New York (4)

Treatments

- A) Respiratory: ➡ Oxygen therapy
- B) Cardiac: ➡ Heart stimulants, IV fluids
- C) Infection: ➡ Cultures, prophylactic antibiotics
- D) Food poisoning/Intoxication: ➡ Gastric lavage
- E) Street drugs: ➡ Bed rest, observation

11 Blue Men in New York (5)

- 1st Diagnosis: Carbon Monoxide poisoning
- Cause: leaking gas pipe? automobile exhaust?
- Isolated gas poisoning extremely rare in NYC
- Planning for more victims

11 Blue Men in New York (6)

10:25 AM, 2nd case brought to ER

11:05 AM, ambulances brings 3rd, 4th, 5th cases

11:20 AM, 6th and 7th cases brought to ER

11:35 AM, 8th and 9th cases brought to ER

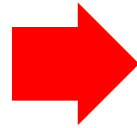
12:00 Noon, 10th case arrives in ER

6:45 PM, 11th victim brought to ER

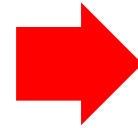
11 Blue Men in New York (7)

Common Findings

All 11 were elderly and dilapidated



All had been in misery for at least an hour



All were rigid, cyanotic, and in a state of shock

The entire body of a bony, 73 yo consumptive, was blue.**

**(He died Tuesday 8PM)

11 Blue Men in New York (8)

Common historical factors

- All had eaten breakfast at the Eclipse cafeteria
- All ate between 7AM and 10AM
- Only 3 ate at the same given time
- Onset was extraordinarily sudden: 30 minutes
- All but 1 had coffee, rolls & oatmeal
- That 1 ate only oatmeal!

11 Blue Men in New York ⁽⁹⁾

So, was it the
oatmeal?

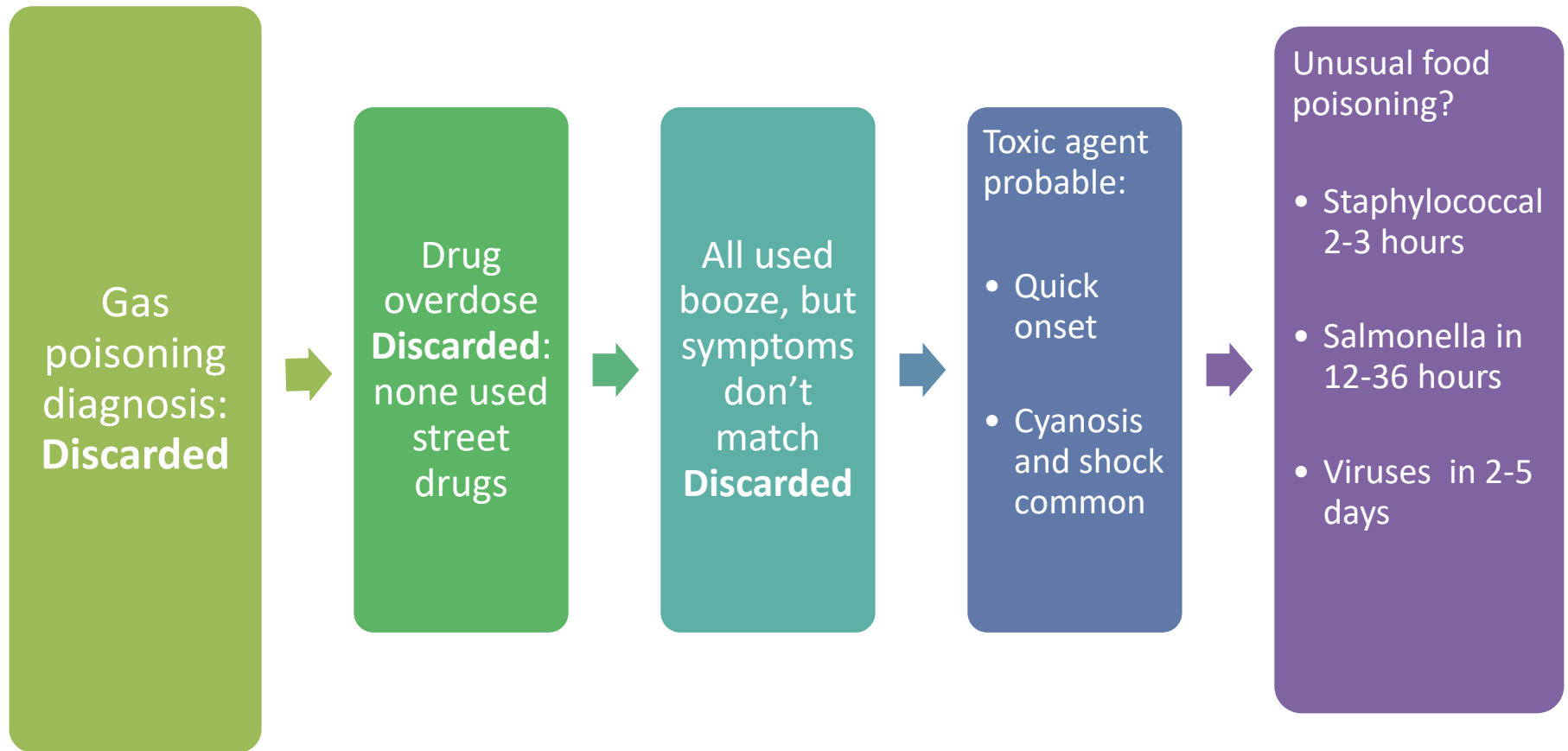
Cook prepared 6
gallons of
oatmeal daily

Enough to feed
125 people

But 114 did not
get sick!

11 Blue Men in New York (10)

New Diagnostic theories



11 Blue Men in New York (12)

Building the case

Cook prepared oatmeal with 5 lbs. cereal, 4 gallons city water, and a *handful* of salt.

Salt can was refilled from a large can on top shelf.

This can was next to a can of saltpeter (sodium Nitrate), which looks and feels like salt.

Cook thinks that he might erroneously have refilled salt can from the Nitrate can.

But sodium Nitrate is not toxic!

11 Blue Men in New York ⁽¹¹⁾

Labs


- Samples drawn on cases showed **brown** blood
- Pulse oximetry not >85% despite giving O₂
- Blood from all the cases was (+) for Nitrite
- Blood samples were (+) for ***methemoglobin***

11 Blue Men in New York (13)

Building the case

- NYC Health Department re-enacted the oatmeal preparation using the cook's *handful* of "salt" from the salt/saltpeter can.
- Both the small salt can and the saltpeter can tested positive for sodium Nitrite.
- Sodium Nitrite causes *methemoglobinemia* and also all the men's symptoms.

Mechanism

- Nitrites: hemoglobin  methemoglobin (*metHb*)
- *metHb* is unable to bind and transport oxygen
- Nitrites oxidize iron from ferrous to ferric
- Healthy people may not have many symptoms with *metHb* levels as high as 15%
- Patients with comorbidities may have symptoms if they have *metHb* as low as 5.8%.

11 Blue Men in New York (14)

Building the case

- Eureka!
- AHA!
- Mystery solved!
- **But wait...**

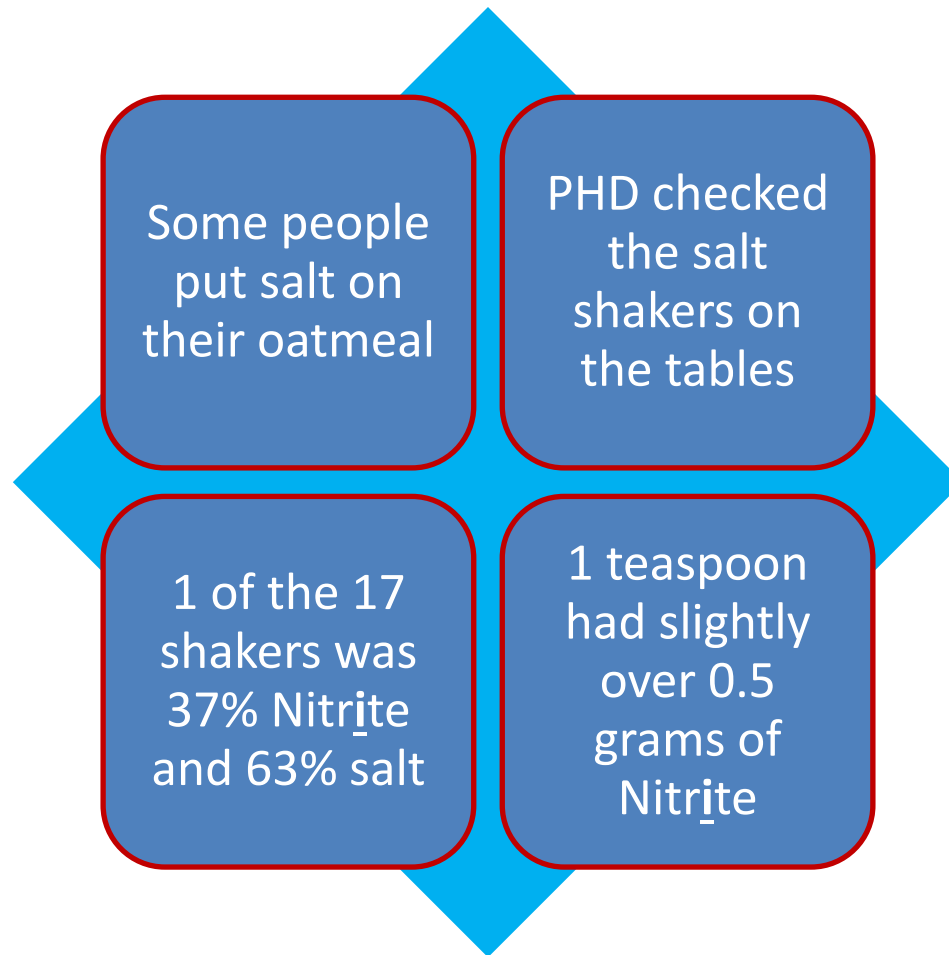
11 Blue Men in New York ⁽¹⁵⁾

Building the case

- The cook's handful of salt (100 grams) must have contained more than the allowed 1 part per 5,000 of Nitrite to produce toxicity.
- A typical diner's oatmeal portion contained 2.5 grams of Nitrite.
- Toxicity begins above 3 grams.
- Where did 11 people get the additional 0.5 gram?

11 Blue Men in New York (16)

Final findings



11 Blue Men in New York (17)

Conclusion

- But, why would anybody use that much salt?
- The men were usually seated at the table with the large salt shaker, by owner's request.
- They were older and had comorbidities.
- The men were heavy drinkers, **low in salt**, so they used lots of salt in their oatmeal!

11 Blue Men in New York ⁽¹⁸⁾

History of Nitrite Intoxication

Most cases have been of accidental ingestion, in families or small groups.

Butchers are at risk if confusing salt with sodium nitrite.

Rarely, larger groups have been intoxicated because of intentional addition to foods.

Nowadays, frequent suicide attempts with Sodium Nitrite “kits” from Internet

Sodium Nitrite Suicide Kits Online



Sodium Nitrite

(Suicides)

- eBay has globally prohibited the sale of sodium nitrite since 2019.
- Sodium nitrite/salt sold as a food additive in the US is dyed bright pink (“pink salt”)* to avoid mistaking it for plain salt or sugar.
- In other countries, nitrated curing salt is not dyed but is strictly regulated.

Sodium Nitrite



- Antibacterial and preservative, which fixes the pink color of cured meats, fish and cheeses.
- NaNO_2 is also used as antifreeze admixture to prevent corrosion of pipes and tanks.
- It is an antidote for cyanide poisoning.
- Our body converts about 12% of ingested Nitrates into Nitrites.

Sodium Nitrite



- Salt was used for the preservation of meat but the final product was usually brownish - gray in color.
- Potassium nitrate (KNO_3) and sodium nitrite (NaNO_2) (mixed with salt) are used in curing meat, because they bond to the myoglobin, act as a substitute for oxygen and turn myoglobin red.
- We like this red/pink color in cured meats such as ham, bacon, hot dogs, and bologna.
- Nitrite is ineffective against botulism and has proven carcinogenic effects when added to meat.

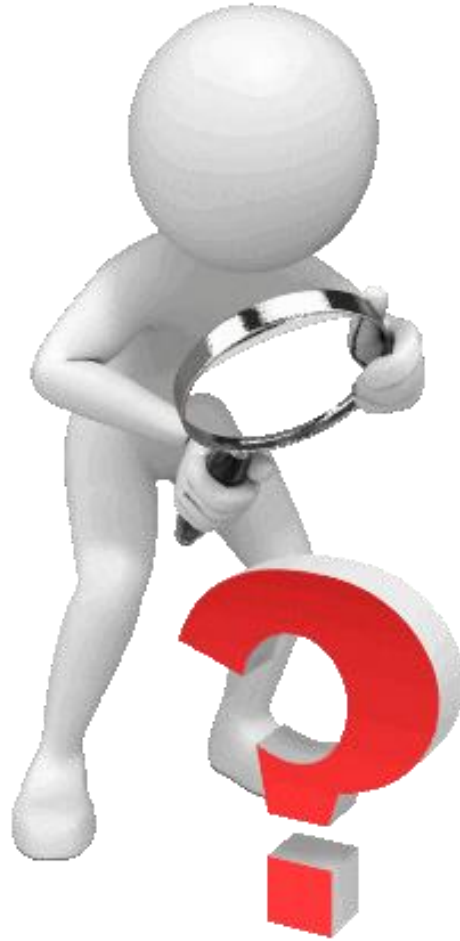
Sodium Nitrite

- In meat-processing, sodium nitrite is never used in a pure state but is always mixed with common salt, a mixture known as nitrited salt, curing salt or nitrited curing salt.
- In Europe, nitrited curing salt contains between 99.1% and 99.5% common salt and between 0.5% and 0.9% nitrite.
- In the US, nitrited curing salt is dosed at 6% and must be remixed with salt before use.

Take-home points

- Severe *methemoglobinemia*, a potential fatal condition if left untreated, may be managed effectively with administration of IV 1% *methylene blue*.
- In a cyanosed patient not responding to oxygen, awareness of this condition and timely administration of methylene blue may be life saving.
- Watch your “salt” intake and consumption of cured meats!

Questions? 2

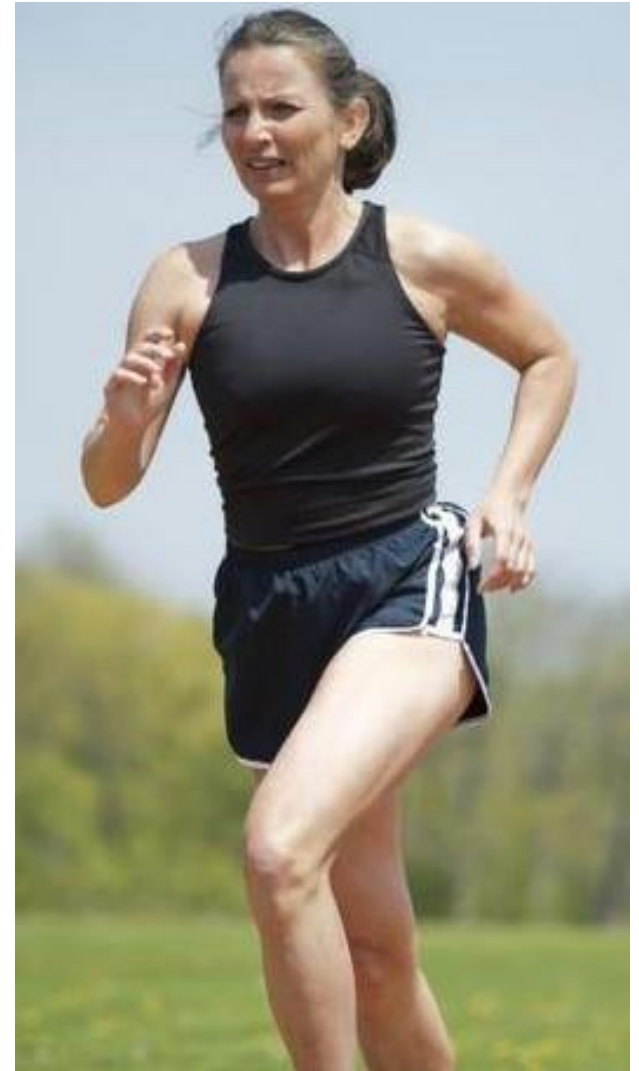


Case No. 2

IT'S GOOD UNTIL IT'S BAD

It's Good Until It's Bad

- Mary Smith, 44 yo, teacher single, lives in Midwest.
- Fit, no smoking or drugs, rare alcohol.
- Healthy, nutritious diet, jogs 5 miles/day.
- No history of significant illness.



It's Good Until It's Bad

- Went on vacation to Hawaii in January, where she noted swelling in feet and mid-abdomen.
- Gain of several lbs. of weight.
- Initially no other symptoms after coming home.
- Dismissed swellings as not dangerous

It's Good Until It's Bad

Mary's self-explanations:



- A. Water retention from vacation?
- B. Beginning of menopause?
- C. Imbalance of energy fields with maladjustment of chakras?
- D. Lack of prebiotics in diet.
- E. Long flights with jet lag?
- F. Kidney problem/salt overload

It's Good Until It's Bad

- By March, weight gain was 20 lbs.
- Mary went to her doctor and her doctor said:

“Mary, you’ve got ascites!”

“Ascites, what’s that?”

Ascites

- Ascites is the buildup of excess fluid in the abdominal cavity; by volume it can be:
 - Grade **1** Mild: only visible on ultrasound or CT
 - Grade **2** Moderate: detectable, with flank bulging, shifting dullness
 - Grade **3** Large: directly visible, (+) fluid wave thrill test
- Two types:
 - Uncomplicated: most common, responds well to treatment.
 - Refractory: less common, often associated with kidney failure, very difficult to treat, and leads to high mortality.

Ascites

- Transudates result of increased pressure in the portal vein (>8 mmHg, usually ~20 mmHg.), while exudates are actively secreted fluids due to inflammation or malignancy.
- Fluid within the abdomen leads to additional fluid retention by the kidneys because of stimulation of blood pressure hormones, notably aldosterone.
- The sympathetic nervous system is also activated, and renin production is increased due to decreased perfusion of the kidney.
- Serious decrease of renal blood flow leads to hepatorenal syndrome (~50% mortality).

Exudates and Transudates

Value measured	Exudates	Transudates
Protein	High	Low <30 g/L
Lactate dehydrogenase LDH	High	Low
pH	Low <7.30 (acidic)	High >7.35 (alkaline)
Glucose	Low	Normal
White Blood Cells	High, abundant	Low <1 cell/1000 mm ³
S.A.A.G.	Low	High
Appearance	Cloudy	Clear

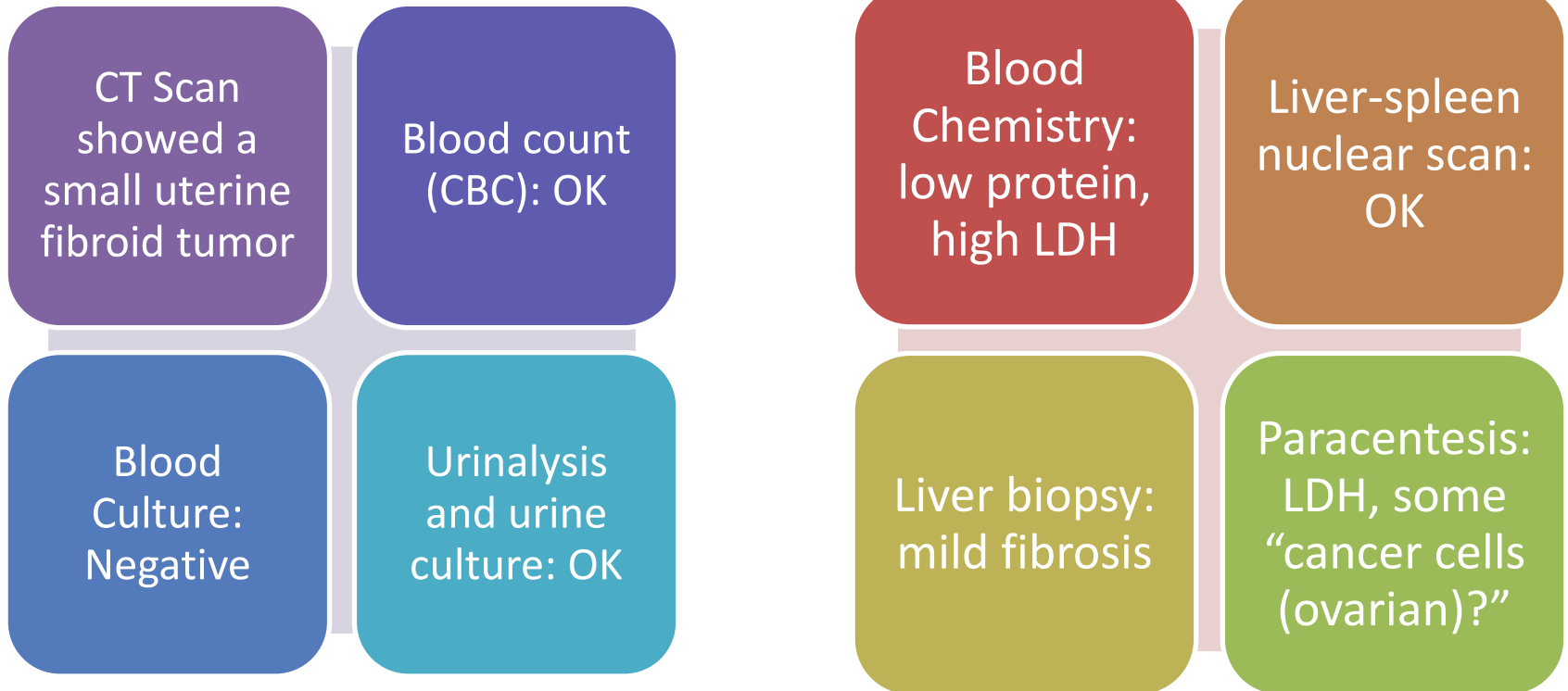
SAAG is gradient between ascites and serum albumin concentration.

$$\text{SAAG} = [\text{serum albumin}] - [\text{ascitic fluid albumin}].$$

A SAAG of > 1.1g/dl implies a transudate from portal hypertension.

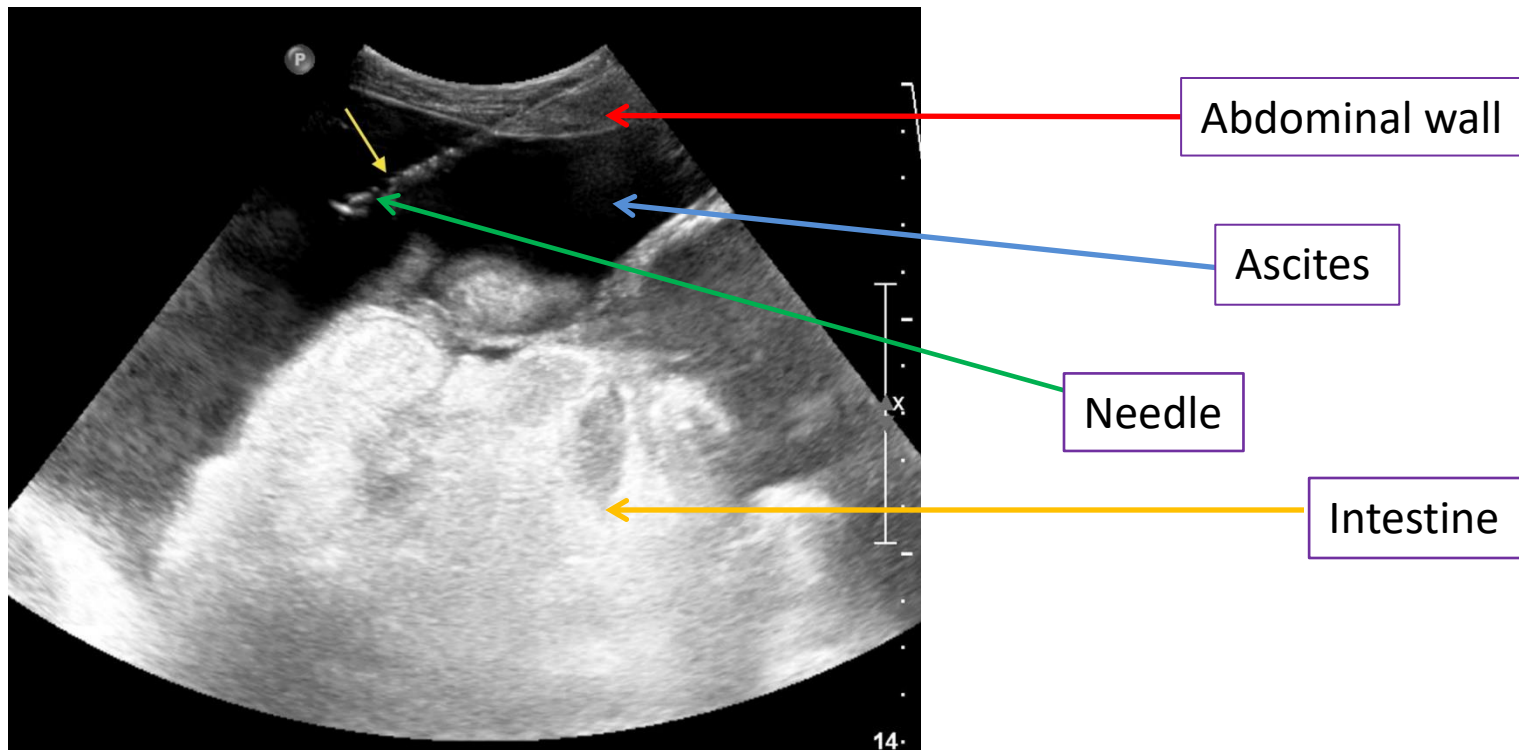
Mary Admitted to Hospital

Many tests:



It's Good Until It's Bad

- The Dr. did an abdominal ultrasound to determine extent of problem.



It's Good Until It's Bad

Abdomen CT scan

Grainy Red: Liver
Sky Blue: Stomach
Bright Red: Spleen
Green: Ascites fluid



Ascites

(Possible Causes)

- Liver disease, Cirrhosis (scarring)
- Infections, viral or others
- Heart failure
- Metastatic cells from ovarian cancer
- Portal hypertension from hepatic venous occlusion

What's Happening, and Why?

- Mary wasn't happy:
 - No results were explanatory
 - The shadow of ovarian cancer was now present
 - Laparoscopy: still some cancer cells in fluid
- Ascites had decreased but increased again:
 - Pressure from fluid caused shortness of breath
 - Could not run or bike anymore
 - Abdominal pain
 - Barely eating

What's Happening, and Why?

- Drs. were concerned that Mary secretly took many non-prescription vitamins, enzymes and herbal teas.
- Tested for: copper, Vitamin A, Iron, Mercury, Zinc, porphyria, hemoglobinuria: All OK
- An exploratory laparotomy was OK, and the fluid showed NO cancer cells.

Fluid in Chest

(Hydrothorax)



- “Cancer cells” re-examination showed that cells of the abdomen wall had become distorted by inflammation and mimicked cancer cells.
- Fluid was now around her lungs, so thoracentesis was done: Cells OK, no TB or infection.
- June came, and Mary was still without a diagnosis; Drs. had almost used up their bag of tricks.

Enough for a Choir

Drs. who had seen Mary:

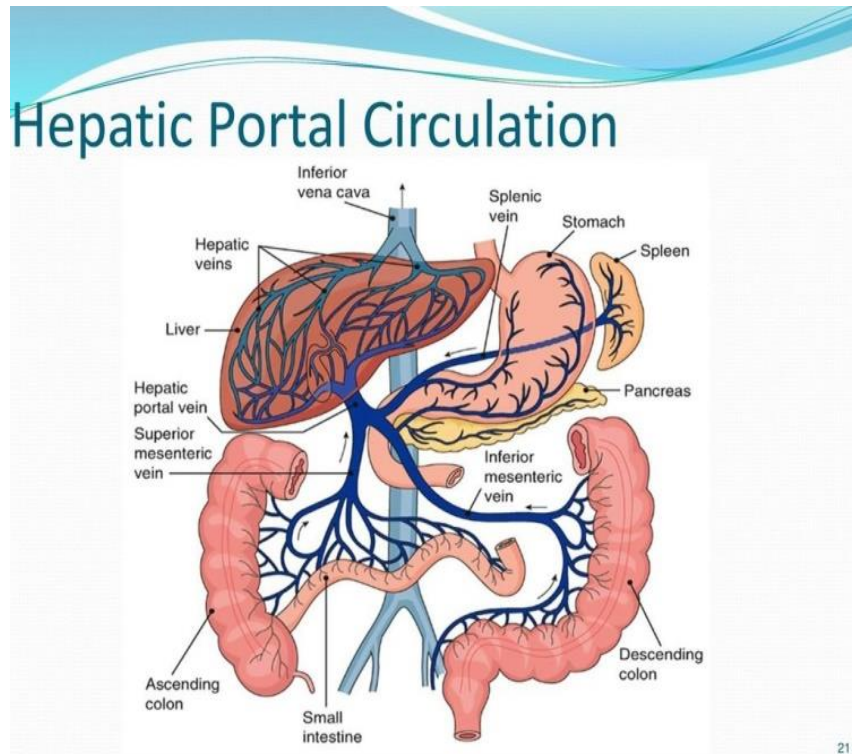
- Family Practice
- Internist
- Interventional Radiologist
- Infectious Disease
- Surgeon
- OB/GYN
- Gynecologic Oncologist

So What now?

- By August, Mary was emaciated, with a very distended abdomen, marked weight loss, muscle wasting and sunken eyes.
- A liver specialist saw Mary and repeated the liver biopsy with a deeper tissue sample.
- The findings were supportive of Budd-Chiari syndrome, but not conclusive.



Budd-Chiari Syndrome



- Obstruction of outflow from liver by blockage of the hepatic vein.
- Most cases caused by a blood clot in the hepatic vein.
- Sometimes, an inflammatory process in the small liver veins causes clotting.
- This leads to portal hypertension and ascites.

Strike Three!

- Liver specialist ordered a hepatic venogram.
- The test measures pressures in the hepatic vein and tries to locate a clot.
- Pressures were increased, as expected.
- But NO Large clot!!!

Batter Up!

- A highly respected surgeon was consulted.
- He performed a porto-caval shunt operation.
- The ascites stopped, decreased and Mary was discharged after 5 days. **GOOD!**
- In December, she had a brief episode of hepatic encephalopathy, which cleared up with treatment.

Hepatic Encephalopathy

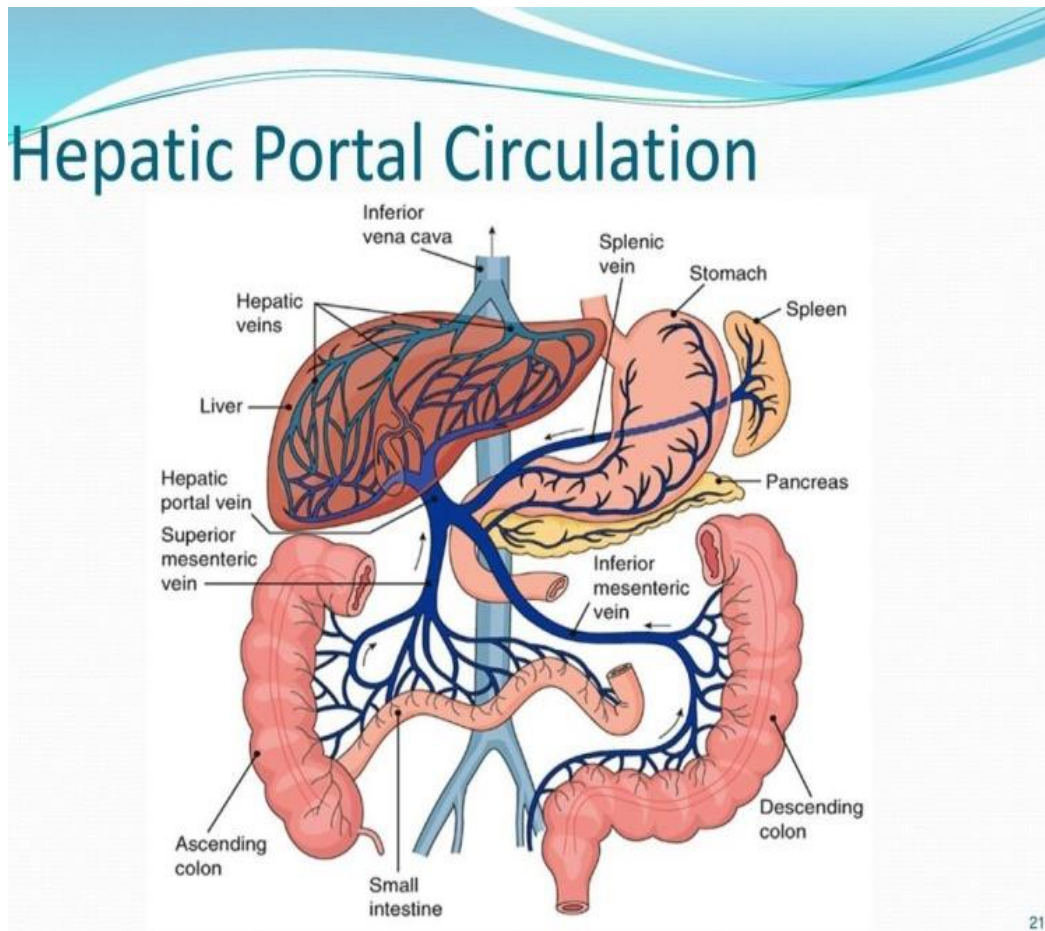
Sudden or gradual onset of:

- Movement problems
- Confusion
- Forgetfulness
- Changes in mood
- Changes in personality
- Irritability
- Inversion of sleep cycles

Hepatic Encephalopathy (HE)

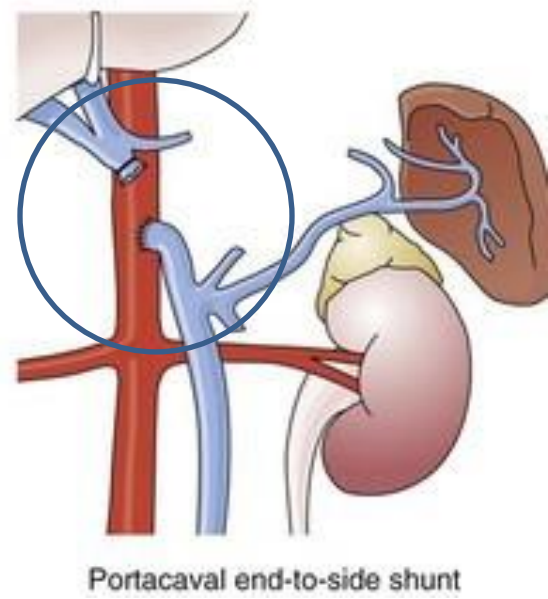
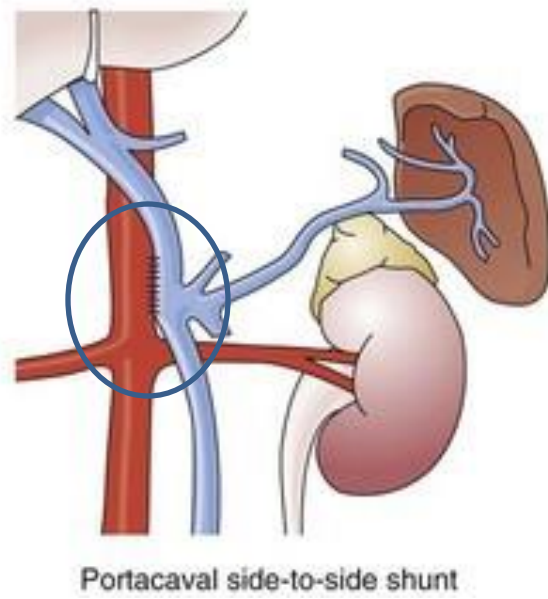
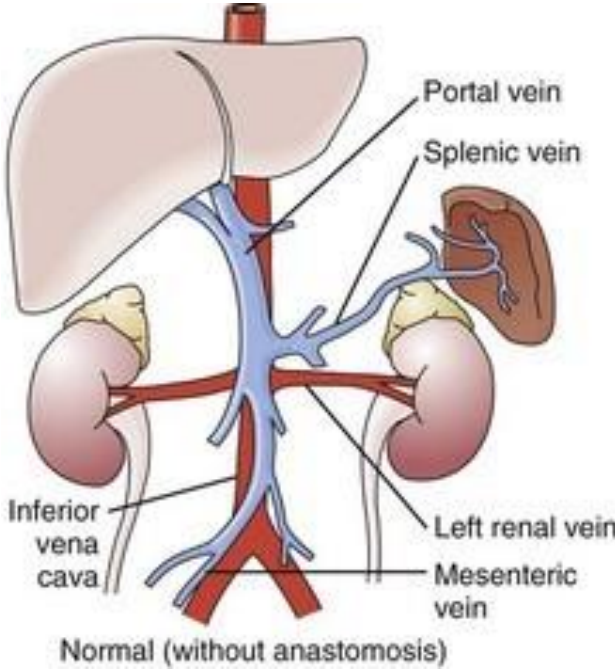
- Body overloaded by ammonia from Nitrogen in increased protein handling.
- Portocaval shunt was the procedure of choice a few years ago.
- Nowadays, a Transjugular Intrahepatic Porto – Systemic (TIPS) shunt is preferred, but the incidence of HE is about 35%.

Hepatic Portal Venous System



- A portal venous system occurs when a capillary bed pools into another capillary bed through veins, without first going through the heart.
- The hepatic portal system delivers about $\frac{3}{4}$ of the blood going to the liver.

Portosystemic Shunts



Light at the End of the Tunnel

- At the start of year 2, none of her doctors had any idea about the cause of Mary's problems.
- One day, reviewing the case for an M&M conference, the surgeon, the hepatologist and a Medical student discussed possible causes for Mary's illness.
- They recalled an article from the 1950's about several Jamaicans with atypical liver disease and ascites, who regularly drank "bush" teas.

Was it Something They Ate?

- In early 1970's, in Afghanistan, 1600 cases of enlarged livers and ascites with 100's dying were reported; the autopsy showed liver damage as described by Budd-Chiari.
- In 1974, in India, 67 were affected, enlarged liver with ascites, 28 died (mortality rate of 42%).
- In 1994, in Iraq, 14 Bedouins admitted to the hospital with ascites and enlarged livers, 2 died.

Common Factors



Comfrey

- Eating bread made with flour contaminated by a *Heliotropium*, *Senecio* or *Crotalaria* plant.
- Drinking herbal “bush” teas that contained similar plants.
- Lack of knowledge, information and caution.
- Belief that “natural is good”.

In Search of Lost Time

(À la recherche du temps perdu)

- Mary was told to bring to the hospital all the different herbal, natural, and homeopathic remedies that she used.
- The Med student, of course, was charged with the scut work.
- He went to all the area health food stores, bought the products on the list, and then went to study them in the Harvard MedSchool botanical library.

Means, Motive and Opportunity

- Two suspects emerged from the search:
 - **Comfrey-pepsin capsules:** Analysis revealed extremely high amounts of toxic *pyrrolizidine alkaloids* (PA's).
 - **MU-16**, an herbal tea supposed to contain ginseng, but instead contained very large amounts of PA's.
- Mary had been drinking about 32 oz/day of the **MU-16** tea (liked the good flavor) and taking 6 capsules per day of the capsules (for digestion).

Comfrey

pyrrolizidine alkaloids (PA's)

- In the past, people ate comfrey leaves as a vegetable, drank dried roots and leaves as a tea, and traditional healers used oral preparations of comfrey to treat ulcers, colitis, and diarrhea.
- Today, eating or taking any form of comfrey by mouth **isn't recommended** and it's considered **unsafe**, due to the *pyrrolizidine alkaloids* (PA's) in it.
- There are >600 different PA's identified in over 6K plants, most are harmless.

Comfrey

Other Names

- 
- Ass Ear,
 - Black Root,
 - Blackwort,
 - Bruisewort,
 - *Consolidae Radix*,
 - Consound,
 - Consoude,
 - Consuelda,
 - Gum Plant,
 - Healing Herb,
 - *Herbe aux Charpentiers*,
 - *Herbe à la Coupure*,
 - Knitback
 - Knitbone,
 - *Langue-de-Vache*,
 - Oreille d'Âne,
 - Salsify,
 - Slippery Root,
 - *Symphytum officinale*,
 - Wallwort.

**Mary had been
poisoning herself for
about 6 months before
her first doctor visit!!!**

Comfrey

pyrrolizidine alkaloids (PA's)



Comfrey



Foxglove

- *Can be confused with foxglove (*Digitalis purpurea*).*
- PA's are found in the borage, aster, orchid and pea families and are a plant's defense against being eaten by herbivores.
- These dangerous chemicals can cause cancer, severe liver damage, and even death, in both animals and humans.
- The Food and Drug Administration (FDA) in 2001, and several European countries have banned oral comfrey products.

Comfrey

pyrrolizidine alkaloids (PA's)

- The main concern regarding humans and comfrey is *Veno-occlusive disease* or VOD, also known as *Sinusoidal Obstruction Syndrome* , or SOS.
- The very small veins of the liver get obstructed, prevent normal liver function and cause a backup of blood, that leads to liver engorgement, increased portal vein pressure, ascites, enlarged spleen, and cirrhosis.
- **25%** of the people diagnosed with hepatic VOD die.

Yerba Mate and VOD

(Veno-occlusive disease)

- Paraguayans have a tradition of mixing *yerba mate* with crushed leaves, stems, and flowers of the plant known as *flor de Agosto* poty, a type of ragwort or groundsel.
- These plants of the genus *Senecio*, particularly *Senecio grisebachii*, contain pyrrolizidine alkaloids (PA's).
- Yerba mate by itself is not harmful, but modifying *mate* like this is potentially toxic, because the alkaloids can cause *veno-occlusive disease (VOD)*.



So, How is Mary Now?

- Mary has stopped using natural medications.
- She now rarely drinks a cup of chamomile tea.
- She is in good health, gradually starting to jog and cycle again.
- **NO** more ascites!

Warning!

- Many natural/herbal websites state that comfrey has been given a bad name, argue that there are no proven human cases of hepatic VOD and that it is safe to use the herb.
- Topical use is believed to help heal sprains, burns, closed fractures, and other injuries, but even for topical uses, the UK warns about the duration, frequency and extent of exposure.
- While there certainly could be merit in ancient tea-based remedies, without studies to back them up, you might as well fall back on a traditional **New York prescription for your problems:**
Long Island Iced Tea!!!
- Because you definitely won't be feeling much pain after a couple of those.

Take-Home Lessons

Check labels for place of origin, certifying authority and a verified list of ingredients for any medication you put on or into your body.

Just because it's natural or herbal, it doesn't mean it's safe or good.

There are many good things about plants, but there are also many bad things about plants.

Do not fully trust Dr. Internet, Dr. WW Web, or Dr. Facebook.

Questions? 3



Case No. 3

THE LINE DANCER'S LINES

The Line Dancer's Lines



- “Ellen, what’s wrong with your legs?” her co-worker asked.
- She looked at her legs, which showed a red streaky rash from the hip to the ankle.
- It did not itch or hurt so she hadn’t worried about it.

The Line Dancer's Lines

- Ellen was part of a line dancing group that was rehearsing in an old barn in Martha's Vineyard.
- Between practices, they enjoyed the beach.
- Ellen wouldn't have thought about it, except that everyone kept asking her about the streaks.
- Every dancer had their own theory about the red rash.

The Line Dancer's Lines

- Ellen liked to keep hydrated, so she drank water from her designer jug.
- She liked to flavor the water with some lime, which she squeezed into her jug.
- Before going to the beach, she took a couple of extra limes to refill the jug as needed.

Friends' Diagnoses

- Poison Ivy
- Jellyfish sting
- Fungal Infection
- *Lyme Disease (Erythema migrans)*
- Sunburn
- Sporotrichosis (rose gardener's disease)



The Line Dancer's Lines



- The rash had gotten elevated, bumpy and slightly scaly, with a couple of blisters, and now affected her arms also.
- Ellen went to the ER: a PA and a NP did not know what the rash was, but ordered a steroid cream*
- A co-dancer sent a picture of Ellen to his mom, an Infectious Disease specialist.

The Line Dancer's Lines

- She and several colleagues, even if not certain that this was atypical Lyme disease, ordered doxycycline.
- Martha's Vineyard is practically epidemic for Lyme disease.
- Ellen had carefully checked herself every day for ticks, with negative results.

The Line Dancer's Lines

- Ellen started the medication as soon as she returned to NYC.
- She sent a picture of the rash to her Primary Care Doctor, who recommended a formal Infectious Disease consult.
- The ID Doctor took one look at Ellen's rash and asked her a couple of questions.

The Line Dancer's Lines

- “Ellen were you drinking Coronas on the beach?”
- Ellen emphatically denied drinking **any** kind of beer on the beach.
- “Have you been squeezing lime into any drink while on the beach?”
- Ellen agreed that she squeezed lime into her drinking water, of which she drank a lot of due to the rigorous rehearsals.

The Line Dancer's Lines

- Then, he immediately made the diagnosis.
- “Ellen, you’ve got:”

Phytophotodermatitis!

“You don’t have Lyme disease,
you’ve got **Lime** disease”!

Phytophotodermatitis (PPD)

- People with a mild case of PPD may never even notice it, as the condition tends to clear up on its own.
- 24-48 hours after exposure to sunlight, the skin with the juice becomes red, inflamed, and in worse cases, severely blistered.
- Ulceration may occur, the area will scale and heal after several weeks leaving post-inflammatory pigmentation, which may last for several years.
- Degree of photosensitivity depends on the amount and concentration of juice.

Phytophotodermatitis (PPD)

- People who squeezed a lot of limes or had a drink spilled on them and then had a lot of sun exposure may have significant blistering, like a 2nd or 3rd degree thermal burn.
- They can have open sores and wounds requiring medical care.
- Doctors can typically diagnose *PPD* with a physical examination and asking questions about a patient's recent activity.
- The condition is often misdiagnosed as a fungal skin infection, sunburn, poison ivy rash, a chemical burn, or even child abuse.

Phytophotodermatitis (PPD)



- Berloque dermatitis" (French "*berloque*", trinket or charm) describes the pendant-like streaks of pigmentation on patients' neck, face, and arms.
- In 1916, Freund had observed that these effects of hyper pigmentation happened with sun exposure **after** the use of *Eau de Cologne*, a perfume with *bergamot* oil.
- Bergamot oil contains a significant amount of *bergapten*, a linear furanocoumarin that gets its name from the bergamot orange.
- *Phytophotodermatitis*, the term coined in 1942 by Klaber, emphasizes that both plants and light are required to cause a reaction.



Phytophotodermatitis (PPD)

- Symptoms include erythema, edema, blisters (vesicles and/or bullae), and delayed hyperpigmentation.
- Hyperpigmentation of skin is caused by the production of melanin triggered by the *furanocoumarins*.
- Heat and moisture tend to exacerbate the reaction.
- A person exposed to adequate amounts of both a photosensitizer and UV light will get the reaction.



Phytophotodermatitis (PPD)

- The substances found in phototoxic plants belong to a class of compounds called the *furanocoumarins*, which are activated by long-wavelength ultraviolet (UVA) light.
- The most toxic of these organic compounds are called the linear *furanocoumarins* since they exhibit a linear chemical structure.
- *The linear furanocoumarins bergapten and anthoxin (methoxsalen)*, derived from *psoralen* are invariably found in plants associated with PPD.

Psoralen

- This photocarcinogenic occurs naturally in the common fig, celery, parsley, West Indian satinwood, and in **all** citrus fruits.
- Some patients have had severe skin loss after sunning with psoralen-containing tanning activators (banned in 1996).
- Widely used in PUVA (psoralen + UVA) treatment for psoriasis, eczema, vitiligo, and cutaneous T-cell lymphoma.



Used as a tanning activator in sunscreens because it increases skin's sensitivity to light.

Groups at Risk

- Vegetable pickers
- Hikers and walkers who brush past plants
- Bartenders with lime juice and sun exposure
- Gardeners
- Users of brush cutters or string trimmers
- Tourists on beach drinking cocktails or beer with lime

Some plants that may cause PPD

- Burning bush of Moses
- Carrots
- Celery
- Citrus fruits (limes)
- Figs (sap)

- Giant hogweed
- Queen Anne's Lace
- Wild dill
- Wild parsley
- Wild parsnips

Phytophotodermatitis (PPD)

- Many plants contain *furanocoumarins*, which cause the acute phototoxic reactions when exposed to ultraviolet A radiation (UVA), inflaming and damaging cell membranes.
- Local accidental smearing of plant sap/juice onto the skin followed by sunlight exposure is the most common type of reaction, this is a direct toxic effect and does not involve the immune system.
- Ingestion of plants rich in *furanocoumarins* cause a more generalized photosensitivity.

Children with PPD

Children may contaminate their lips, or suck on orange or lime wedge, causing burns



The hands may also be affected

The Line Dancer's Lines

- So, how's Ellen now?
- 2 months after the Martha's Vineyard incident the red line was still on her leg, it was now smooth and the color was visible but faded.
- At least now, when asked about the line on her leg, she has a story to tell!

Case No. 4

OLD-FASHIONED SKIN

Old-Fashioned Skin

- Jim, a 68 year-old African American man comes in with a “swimming in his head”.
- He appears weak, severely dehydrated, and with a dangerously **low** blood pressure.
- He can not stand without feeling faint and dizzy.
- He is conscious, alert, but doesn’t talk much.

Old-Fashioned Skin



- Jim had been afflicted with severe diarrhea for several months, 6 to 10 times a day.
- No pain no fever, no chills, except the endless trips to the bathroom.
- For many weeks, possibly months, he also had a rash in hands, back, chest and feet (palms and soles).
- The rash went from the knuckles to the fingers, appeared like dark stripes of dark, thick, rough skin.

Old-Fashioned Skin

- Jim is currently severely dehydrated.
- His kidneys could shut down because of decreased blood flow.
- He is at risk of neurological complications.
- After hydration and stabilization of his vital signs, the doctors concentrated on his diarrhea.

Old - Fashioned Skin

- Jim was *hypertensive* (!), diabetic, and had atherosclerotic disease.
- He was on treatment with oral hypoglycemic agents, diuretics and hydralazine for high BP.
- His medications had changed 10 months ago but he didn't notice any symptoms until much later.

Old - Fashioned Skin

Jim's doctor analyzed possible causes of diarrhea:

- Infection: virus or bacteria
- Cancer
- Ischemia (blood flow impairment) of the bowel
- Lactose intolerance
- Drugs
- Zinc or B-vitamin deficiencies.
- Celiac disease (diarrhea and rash)

Old - Fashioned Skin

- Stool samples looking for blood and hormones like FGF-19 (**F**ibroblast **G**rowth **F**actor): Normal
- Stool cultures for bacteria and virus: no pathogens found.
- Ultrasound of blood vessels of the gut: No impairment of circulation.

Old - Fashioned Skin



- Jim's levels of iron and zinc were normal.
- He had an extremely low levels of Vitamin B₆!



- But this is extremely rare in the US.
- It can cause pain in hands and feet but not diarrhea and rash.

Old - Fashioned Skin

- So what now?
- Jim's blood levels of Niacin (Vitamin B₃) were also very low.
- This can lead to pellagra, with it's diagnostic mnemonic of the Four D's:
Diarrhea, **D**ermatitis, **D**ementia and **D**eath.



Old - Fashioned Skin

- The explanation was not fully satisfying: both deficiencies are rare in modern day US.
- Jim's doctors researched all his medications.
- They found that hydralazine (Apresoline), an old blood pressure medication seldom used now may cause elimination of Vitamin B₆.

But Why Hydralazine?

- A 2004 article suggested that hydralazine was very effective for hypertension in African-Americans.
- When the medication had its second life, its effects on vitamins fell through the cracks.
- What was originally known by older doctors was now unknown to younger physicians.

Old - Fashioned Skin

- OK, so that explains the low levels of B_6 , but what about the low B_3 causing *Pellagra*?
- It happens that our body can make B_3 but it needs a sufficient supply of B_6 to do so.
- So Jim was losing B_6 , so he couldn't make enough B_3 , and therefore developed *Pellagra*.

Niacin

(Nicotinic acid, Vitamin B₃)

- In 1873 the Austrian chemist Hugo Weidel managed to synthesize B₃ by oxidizing nicotine with nitric acid.
- This has been the only reason this substance was then called “Nicotinic” acid, even though it was not biochemically or toxicologically related to the tobacco alkaloid.

Niacin

(*Nicotinic acid* Vitamin B3)

- In 1942, when flour enrichment with nicotinic acid began, a headline in the popular press said "Tobacco in Your Bread."
- The AMA approved new names *niacin* and *niacin amide* for use primarily by non-scientists.
- Choosing a name to dissociate nicotinic acid from nicotine, avoided the perception that vitamins or niacin-rich food contain nicotine, or that cigarettes contain vitamins.
- The resulting name *niacin* was derived from nicotinic acid + vitaminin.

Back to Jim, now

Hydralazine caused the B₆ deficiency, which led to niacin deficiency and Pellagra.

Pellagra caused the serious diarrhea, and thus the hypotension.

In the hospital, he did not receive hydralazine because his blood pressure was low.

Without hydralazine, he was able to absorb B₆ and make niacin.

On discharge, his diarrhea had markedly improved.

He was started on B6 supplements and the skin rash disappeared in 2 weeks.

A Lesson to Learn

- When using any medication, physicians need to understand the potential side effects.
- This is very true of older or seldom - used meds, because we may have forgotten their specific side effects.
- Old diseases, like *Pellagra*, can come back to haunt us.

Questions? 4





Case No. 5

THE “DISNEY” RASH

The Disney Rash

- John Smith, his wife, son and daughter went to Disney World in Florida for a 10-day trip.
- Their neighbors, the Joneses, husband, wife and 2 children, traveled with them.
- Both families stayed in the same resort.

The Disney Rash

- The Smiths are physical fitness nuts and like to walk everywhere and see more of the parks, they are driven and don't have time for sunscreen or shade breaks.
- The Joneses are more laid-back ,take it easy, move slowly and savor it all at their pace, they wear SPF-30 lotion and try to avoid excessive sun time.

The Disney Rash

- The Smith family came back to the resort on the second afternoon, and noticed redness of their legs.
- The extremities felt warm, but were painless and didn't itch.
- Mr. Smith, ever the conflictive, forceful man, went to the manager of the Disney Resort and complained loudly.

The Disney Rash

- “Look here, my family has got some sort of rash in the legs from the parks or the resort.”
- “Lord knows what kind of serious infection this is!”
- “For all we know it could be bedbugs, or an allergic reaction to your cheap laundry soap!”
- “I demand medical evaluation and treatment and want to be comped for my room until the rash is resolved!!!”

The Disney Rash

- The Joneses came back the same afternoon.
- They were fine, did not have any rash.
- Mr. Jones tried to calm down Mr. Smith.
- He gave him a rational, clear explanation.

The Disney Rash

- Mr. Jones explained to Mr. Smith that it wasn't the resort's fault.
- He told him it was Mr. Smith's actions that had caused the "rash".
- He pointed out that multiple websites and Disney user blogs warn visitors and explain how park-goers get the condition.

The Disney Rash



Exercise Induced Vasculitis (EIV)

- The medical name for “Disney rash” (golfer’s rash, hiker’s rash, golfer’s vasculitis) is Exercise-Induced Vasculitis (EIV).
- This condition results from a combination of:
 - hot weather
 - sunlight exposure
 - sudden, prolonged periods of walking
 - prolonged exercising outdoors
- That’s why people who spend long days strolling at theme parks may be more prone to it.

Exercise Induced Vasculitis

EIV

- Although EIV is often called “Disney rash”, the condition isn’t a true rash and is not limited to Disney parks.
- Small blood vessels in the legs are inflamed, with discolorations and swellings on one or both ankles, legs, thighs, calves, and shins.
- EIV can include large red patches, purple or red dots, and raised welts; it may itch, tingle, burn, or sting, and may also cause no symptoms.

Exercise Induced Vasculitis (EIV)

- Dermatologists think that EIV occurs when the temperature regulation mechanisms within the calf muscles break down.
- Palpable purpura can also occur with red, purple, or brown spots that a person can feel when touching the affected area.
- Purpura results from bleeding into the skin caused by inflammation of the blood vessels (vasculitis).
- EIV is most common in females >50 years old, but it can affect children and adults of any age.

Exercise Induced Vasculitis

(EIV)

- EIV is typically confined to exposed skin and doesn't occur under socks or stockings.
- It's not dangerous or contagious, and usually resolves on its own.
- Typically clears up around 10 days after returning home, once you're away from the conditions that brought it on.

The Disney Rash

- Mr. Jones and the resort manager were finally able to convince Mr. Smith to stop being so “rash” in his actions.
- He and his family learned a preventive lesson.
- They finished their vacation uneventfully, and were red in the legs as well as in the face.

Case No. 6, Part 1 : The green leaves

WITH LETTUCE...and TOMATOES

With Lettuce...and Tomatoes

- Alexa is 27 years old, athletic, jogs daily, and is a resident in Family Practice medicine.
- She came to the ER, brought by her fiancé, because of racing heart rate and incoherent babbling.
- She had been fine until after dinner, when she felt queasy and lightheaded

With Lettuce...and Tomatoes

- The light hurt her eyes, so the ER nurses had dimmed the exam room lights.
- Her heart rate was 150, blood pressure was elevated, and she appeared anxious.
- She was speaking random senseless words, meaningless and incoherent thoughts in a very accelerated fashion.

With Lettuce...and Tomatoes

- She had had a few fainting spells last year, but an extensive cardiac work-up was normal.
- She was on the antidepressant Paxil and occasionally also took Elavil for sleep.
- She doesn't smoke, rarely drinks and does not use illicit drugs.

With Lettuce...and Tomatoes

- The exam in the dimmed room showed quite warm skin , but not sweaty, with no fever.
- Her mouth was dry, and the rest of the exam was normal.
- She was very agitated and restless, seemed to hallucinate, picked up patient charts and put on gloves, as if she were at work.

With Lettuce...and Tomatoes

- The ER doctor, who was a friend of Alexa's had several diagnostic considerations:
 - Hyperactive thyroid
 - Overdose of Ellavil
 - Mini-strokes
 - Drug Toxicity
- Her cardiologist and a neurologist were consulted.
- An MRI of the brain and CT of chest were OK.

With Lettuce...and Tomatoes

- The fiancé informed that after dinner, he had also felt a little funny, nauseated and jittery.
- His heart rate had been racing, but he felt fine now.
- Dinner was a salad with lettuce and greens from their garden.
- Could that have anything to do with Alexa's condition, he wondered?



Green and purple Lettuce



Datura (jimsonweed)

With Lettuce...and Tomatoes

- The ER doctor recalled a patient who had been delirious, but without high heart rate or BP, and had been sweating profusely.
- He had pesticide poisoning, and almost died.
- Alexa's doctor ordered labs, toxicology screens, thyroid tests, and cultures for infection.
- All results came back normal.

With Lettuce...and Tomatoes

- Through the night and over the next 3 days, she improved and had normal speech.
- Her delirium had resolved, and her eyes were not sensitive to light any more.
- Her blood pressure and heart rate normalized.
- She was discharged with a big ? diagnosis.

With Lettuce...and Tomatoes

- Alexa went home, still worried about her brief episode of madness.



- She went to her garden to do some weeding and noticed a plant with pretty white flowers among her green and purple lettuce.
- She picked some, put them in a baggie and went to the local nursery for identification.

With Lettuce...and Tomatoes

- When Alexa showed her the baggie, the owner of the nursery yelled:
 “Don’t touch those. They’re very toxic!!!
 That’s Jimsonweed”.
- Alexa went home, read up on the plant, and carefully eliminated it from her garden.
- She thinks that the effects on her fiancé were not as intense because of the Paxil she was taking.
- But it was a good lesson for all!

Jimsonweed

- *Datura stramonium* is a member of the toxic nightshade (*Solanacea*) family (tomatoes, eggplant, potatoes, bell & chili peppers).
- Called Jamestown weed, after intoxication was first recorded in Jamestown, VA, in 1676.
- Also known as trumpet, stink- weed, green dragon, and locoweed.

Jimsonweed

- Long used to treat asthma, diarrhea, cramps, and nicturia because of its anticholinergic effects.
- Its hallucinogenic effects were mentioned in Homer's tale, *The Odyssey*.
- All parts of the plant are poisonous, but the leaves and seeds contain the highest amounts of atropine, hyoscyamine, and scopolamine.



Datura stramonium

Jimsonweed

- 100 seeds contain approximately 6 mg of atropine.
- A dose of atropine exceeding 10 mg is regarded as potentially lethal.
- Today, jimsonweed poisoning is found primarily among adolescents who seek the hallucinogenic effects of the plant.

Jimsonweed

- Symptoms of toxicity usually occur within 30 to 60 minutes after ingestion and include:
 - Hallucinations
 - Dry mucous membranes,
 - Thirst
 - Dilated pupils
 - Blurred vision
 - Difficulty speaking and swallowing
 - Tachycardia
 - Urinary retention and ileus.
- Rare, late symptoms may include hyperthermia, respiratory arrest, and episodes of seizures.

Jimsonweed

- The 3 toxins: atropine, scopolamine and hyoscyamine are potent anticholinergics.
- The mnemonic for the symptoms is:
 - Mad as a hatter
 - Blind as a bat
 - Dry as a bone
 - Red as a beet
 - Hot as a hare

A Lesson to Learn

- The ER doctor, Alexa's friend, missed some of the characteristic signs because out of consideration for her, he neglected to examine the skin tone and the dilated pupils.
- Many times, nowadays, doctors rely more on the technical, machine-driven tests, than on the simple physical exam.

Case No. 6 Part 2 : The red fruits

WITH LETTUCE...and TOMATOES

With Lettuce...and Tomatoes

- Around noon, on a Saturday, 5 people, 2 men, 2 women, and a child sat down to lunch in their house on a tobacco farm in Tennessee.
- They were Homer Mason and his wife Louise, Grace and Leroy Smart, and Buddy, the Smart's son.
- Mason and the 2 women had spent the morning stripping and bundling tobacco leaves.

With Lettuce...and Tomatoes

- Leroy Smart prepared the meal: split-pea soup, spaghetti with meat sauce, sliced tomatoes, sweet milk and corn bread.
- Homer Mason was the first to finish and left the table to go to the barn and continue working.
- As he walked through the yard, he staggered, lurched against a tree and noticed that he could not see the house clearly.

With Lettuce...and Tomatoes

- When Mason got to the house, Mrs. Smart said she was dizzy and going blind.
- Leroy Smart and Buddy were all right, but Louise started getting sick.
- They initially thought of poisoning because the 3 were the ones working in the barn that morning.

With Lettuce...and Tomatoes

- Homer, whose mouth was dry and cracked said that it could be nicotine poisoning.
- He was starting to hallucinate and told Leroy to take them to the doctor.
- When they got to the Doctor's office, the 2 women were twitching, jerking and moaning, and Homer was talking gibberish, making grabs at the air and waving his arms.

With Lettuce...and Tomatoes

- Mr. Smart talked to the doctor and explained the sequence of events.
- The symptoms were:
 - Vertigo
 - Blurred vision
 - Dry mouth
 - Generalized weakness
 - Nausea
 - Hallucinations

With Lettuce...and Tomatoes

- The Doctor ruled out nicotine poisoning because that couldn't happen from superficial contact.
- He definitely agreed on poisoning probably from food.
- All the patients had insatiable thirst and showed widely dilated and glassy pupils.

With Lettuce...and Tomatoes

- He gave them an injection to relieve the nausea, but the women were also starting to hallucinate and thrashing about.
- The doctor considered *botulism*, because there had been a recent outbreak in Tennessee, with 7 cases and 2 deaths.
- All the symptoms didn't fit, but he was still concerned enough to hospitalize the patients.

With Lettuce...and Tomatoes

- In the waiting room of the ER, Buddy began to complain of vision symptoms, and Mr. Smart was starting to feel abdominal pain and nausea.
- The Doctor was talking to the University of Tennessee Knoxville and requesting botulism antitoxin.
- But then, Mr. Smart in passing, said something about eating Jimsonweed.

With Lettuce...and Tomatoes

- The doctor and the consultant internist, neurologist and pathologist, immediately started researching jimsonweed poisoning.
- They also asked Smart for further details.
- He explained that the tomatoes they had eaten were graft tomatoes from a plant that Mason had grafted onto a jimsonweed plant.

With Lettuce...and Tomatoes

- Mason wanted a chill-resistant tomato and since jimsonweed is frost-resistant, he grafted his tomato onto it.
- Mason had eaten several slices from the center of the tomato, while the others had eaten less, and Buddy had eaten only a small piece.
- All the patients received some doses of oral pilocarpine with some relief.

With Lettuce...and Tomatoes

- Over the next few days, all of them got better and went home.
- Hopefully they would not eat any more jimsonweed tomatoes!
- Adults are victims of jimsonweed poisoning:
 - Because of homespun credulity
 - Because of credulous sophistication
 - Because of simple ignorance

Questions? 5



Thank You

Thank you for taking my course on **Fascinating Features and Mysterious Manifestations of Disease** during the Fall 2022 semester at OLLI.

I hope you enjoyed learning something about the topics and that you have finished this course having new perspectives on Medicine.

If approved, I will be offering a Spring 2023 course on **Battlefield Medicine, How War has changed Medicine, and how Medicine has affected War.**