STANDARD DEVIATIONS: March Madness Begins (Last Month)

Greetings,

Okay, this may sound crazy but our march to March Madness begins back in the middle of February (Standard Deviations: Eunice Rivers Part 2, 2/8/21).

Using mercury, tree bark gum, arsenic, malaria, and mold to cure insanity may seem nuts now, but five Nobel prizes speak otherwise, no matter how wacky it seems. All these remedies were cures for **neurosyphilis**.

Remember that we discussed syphilis coming from the New World to Europe via the mercenaries of Christopher Columbus' first voyages (Columbus almost certainly died from his own syphilitic condition)? Traditional cures were naturally the first choices, but purgatives, sangrias, mineral waters, and, yes, snake syrups, and beef broths all failed.

Mercury was used in Arabic and Chinese medicines for over a thousand years. It was popular in the treatment of leprosy during the middle ages. The side effects are much more harmful than any benefit, but it has been used for a bunch of things from dental fillings to mascara to mercurochrome. Mercury poisoning is likely responsible for thousands of deaths of syphilis patients, the deafness of Beethoven, and the delirium of Van Gogh.

{Poisoning from mercury used to make felt hats caused dementia in hatters.}

Early methods involved fumigation with mercury sulfide in a heated box "stove" for days on end. Mercury salves and compounds were also used. It is not really understood why. The treatment was taken for years and was worse than the disease. Suffocation, tooth loss, excessive salivation, asthma attacks, bronchitis, pulmonary disease, headaches, seizures, paralysis, and even death were common. A common trope was "A night with Venus, a life with Mercury", and many opted to suffer the disease rather than the cure. **Much of the psychosis associated with syphilis in patients treated with mercury was caused by the drug, not the bug.**

{A fumigation stove. "For a thousand pains a single pleasure."}

That syphilis was believed to have New World origin is evidenced by treatment using plants brought back from the Americas. One New World plant, the **guaiac** tree, *Guaiacum officinale,* became widely used. A boiled decoction was given as a purgative that also caused heavy sweating (sudoration) and urination (the thinking about urine was that treatment had to originate from the same place as disease). Patients were covered in blankets with this "blood cleanser" and it's thought that the rise in body temperature affected the spirochete.

{Guaiac tree}

Physicians who saw the harm in mercury turned to guaiac wood. It was chewed as a gum or ground and liquefied, then consumed for a month. It wasn't toxic like mercury; but then again, it didn't work against syphilis, either.

But the guaiac tree has another use. Heme reacts with phenolics from this plant. When hydrogen peroxide is added to guaiac in the presence of blood, a blue color reaction occurs. This is where we get the stool guaiac test for **occult fecal blood**, a common screening tool for colorectal cancer and a bunch of other gastro-pathologies. The screening is credited with reducing colon cancer mortality by 25%.

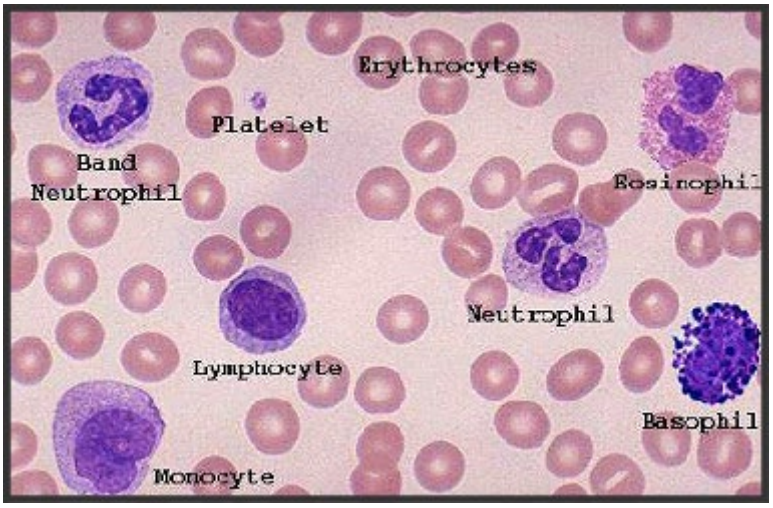
{Positive guaiac test with controls in orange.}

Guaiacum is classified as an antioxidant and used as a food additive (acidifier). Oils are used in soap fragrance. A resin derivative is made into **sarsaparilla** in old-fashioned root beer. Since 1933, the extract, **guaifenesin**, has been used as an expectorant (Mucinex). It increases volume and reduces viscosity of secretions.

Treatment for syphilis, and neurosyphilis in particular, languished until the advent of microbiology and chemotherapy at the turn of the twentieth century.

In 1907, after 605 failures, an arsenic compound was found to be effective against the trypanosome causing syphilis. **Paul Ehrlich**'s lab derived the correct formula and chemotherapy was born. His "606", Salvarsan, became the "magic bullet" for syphilis, and the most prescribed drug ever known. The original work targeted African sleeping sickness and arsenic compounds have been used in veterinary medicines for poultry and swine dysentery until 2015. Although it was effective at treating syphilis, the side effects were severe, including rash, liver disease and death.

Ehrlich is famous for another reason, staining cells. Ehrlich used both alkaline and acid dyes, and also created new "neutral" dyes. For the first time this made it possible to **differentiate white blood cells**. By studying their granulation he could distinguish nongranular lymphocytes, mono- and poly-nuclear leukocytes, eosinophil granulocytes, and mast cells. He demonstrated the existence of nucleated red blood cells. Ehrlich came across **methylene blue**, which he regarded as particularly suitable for staining bacteria.



{Seen any of these? Thank Ehrlich.}

Ehrlich started some of the first studies of **immunity**. He investigated the inherited immunity of the fetus through placental circulation, and the condition of autoimmunity. For his work in immunity, he received the Nobel in 1908.

Prior to the discoveries of microorganisms causing disease and the arsenic compounds that killed them, **Julius Wagner-Jauregg**, was using infectious disease to treat mental illness. It was understood that fever had positive effects on psychoses; typhoid outbreaks in a lunatic

asylums resulted in cured patients! Even Hippocrates had observed the effect of malaria on epileptics, and research was vibrant for malaria, typhoid, and cholera fevers as treatments. For years they infected patients with different diseases (diphtheria, Smallpox, typhus, cholera) to observe the effect on mental illness.

For decades Wagner-Jauregg infected people with tuberculin (from Koch's work) and staphylococci, watching some get better, and many die. In 1917 he tried **malaria** in patients with neurosyphilis. Most got malaria and died. It took years of experimentation to find the right dilution, the right stage of disease in the donor, and the supportive therapies that would lead to a modicum of success. Eventually, he reached a level of around 60% of patients who survived the treatment and had resolved neurosyphilis. In the early 20's the malaria treatment was introduced around the world as the "right way to treat a hopeless disease". In 1927 he was awarded a Nobel Prize.

A year later, in 1928, **Alexander Fleming** observed a fungal contamination in a culture of *Staphylococcus aureus* that appeared to kill the bacteria. He called it **penicillin** and published his work in 1929. The molecular structure was worked out in 1940 and three Nobel awards resulted. The rest is history.

{Penicillin is still the drug of choice for syphilis. Gonorrhea is proving more difficult.}

Mercury. Guaiac. Arsenic. These are crazy ways to treat mental illness. But neurosyphilis is an end-stage condition of syphilis that affected a large population and as crazy as it seems now, these were the best options, in their time.

Have a great week and be safe,

Bryan