

# BUGS DRUGS AND MEDICAL THUGS

A HISTORY OF SYPHILIS, THE INVENTION OF PENICILLIN, AND RESEARCH ON VULNERABLE POPULATIONS

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# University of Utah CME Statement

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- Speakers are also expected to openly disclose intent to discuss any off-label, experimental, or investigational use of drugs, devices, or equipment in their presentations.
- This speaker has nothing to disclose.

# Learning objectives

- After attending this seminar the attendee should be able to:
  1. Describe the four stages of syphilis with defining characteristics of each stage.
  2. List the compounds discovered and used historically in the treatment for syphilis in order of efficacy.
  3. Critically evaluate the ethicality of research conducted on human subjects in Tuskegee and Guatemala.
  4. Compare pros and cons of the traditional and reverse algorithms for syphilis screening.

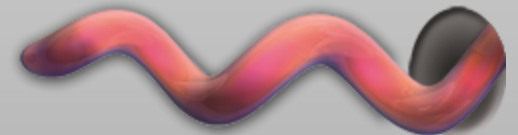
# Outline

- Case from UH
- Bugs
  - Description of syphilis
  - Symptoms and stages of disease
  - History of syphilis
- Drugs
  - Mercury
  - Salvarsan
  - Penicillin
- Medical Thugs
  - Tuskegee, Alabama
  - Guatemala
- Current diagnostic algorithms and tests for syphilis
- Conclusion

# A CASE FROM UNIVERSITY HOSPITAL

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New Orleans, LA



# Case History

- 19-year-old AA female brought to the ED
- Paramedics report her mother found her unresponsive
- Six months ago, the patient had an episode of autoimmune hemolytic anemia
  - Treated with a blood transfusion

# Physical Exam

Vitals	result	normal
Blood pressure	101/72	90/60 to 120/80 mm/Hg
heart rate	123	60 - 100 beats per minute
respirations	32	12 - 18 breaths per minute
oral temperature	34.8°C	36.5 to 37.5 Celsius
pulse oximetry	100% on room air	94% to 99% SpO2

- Rash on palms and soles

# Labs

Lab	Result	Reference
Arterial blood gas		
pH	6.92	7.35 – 7.45
CO2	9	35 – 45 mmHg
HCO3	2	22 – 26 mEq/L
Blood glucose	1500	70 – 100 mg/dL
Urine ketones	++ positive	negative



Acidosis



Respiratory alkalosis



Metabolic Acidosis



# Diagnosis?

- Diabetic Ketoacidosis

# Treatment?

- IV fluid
- Insulin

# Clinical Course

- Gave hydration and insulin therapy
- Patient regained consciousness
- Able to converse
  - Stated she was feeling “a little better”
- Repeat morning physical exam:
  - Medical student noticed a peculiar rash on patients palms and soles of her feet...



# Palmar Rash differential

- Hand, Foot and Mouth disease
- Psoriasis
- Rocky Mountain Spotted Fever
- Erythema Multiforme
- Secondary Syphilis

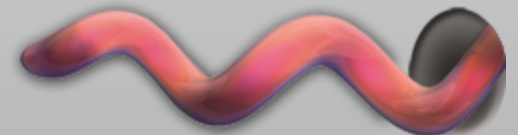
# ID workup

- HIV: negative
- VDRL: positive
- Confirmatory test, FTA-ABS: positive
- Diagnosis:
  - Syphilis

# BUGS

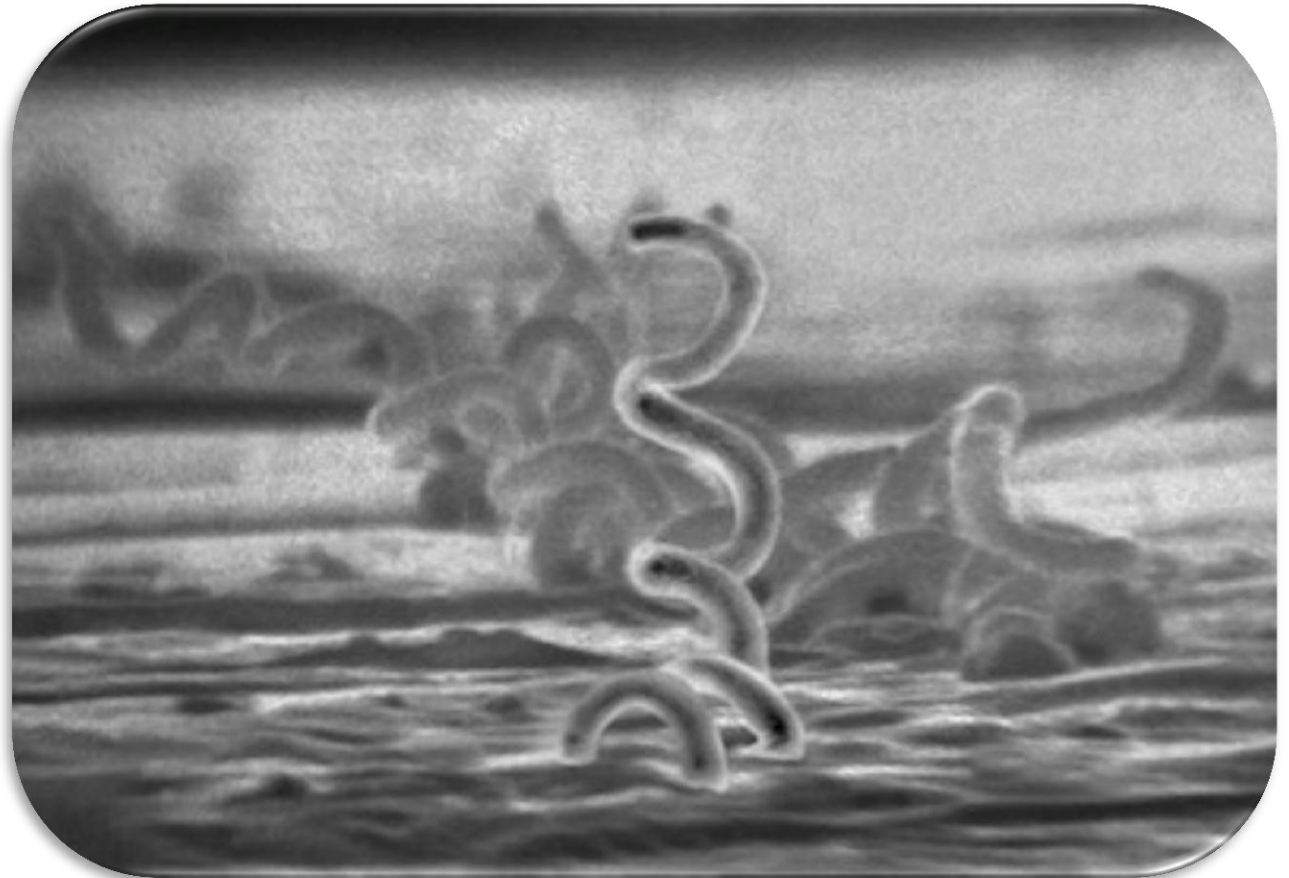
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Treponema pallidum



# Syphilis

- Caused by the bacterium *Treponema pallidum*
- Spirochete
- Motile



# Transmission

- Sexual contact
- Mucous membranes
- Placental
- Blood products
  
- 30-60% exposed will be infected



# Incidence

- 46,042 new US cases diagnosed in 2011
  - 1/3 of these primary or secondary
  - 360 cases of congenital syphilis
- CDC Est. 55,400 new infections annually
- At risk populations:
  - MSM, 72% of new cases
  - HIV
  - Babies of infected mothers

# Clinical progression

- If untreated, progresses through 4 stages:
  - ✓ Primary
  - ✓ Secondary
  - ✓ Latent
  - ✓ Tertiary
- Congenital syphilis

# Primary Syphilis

- 2-4 weeks after initial infection
- Chancre



# Secondary Syphilis

- About 2 months after the initial sore disappears...
  - Constitutional symptoms
  - Weight loss, hair loss and a skin rash

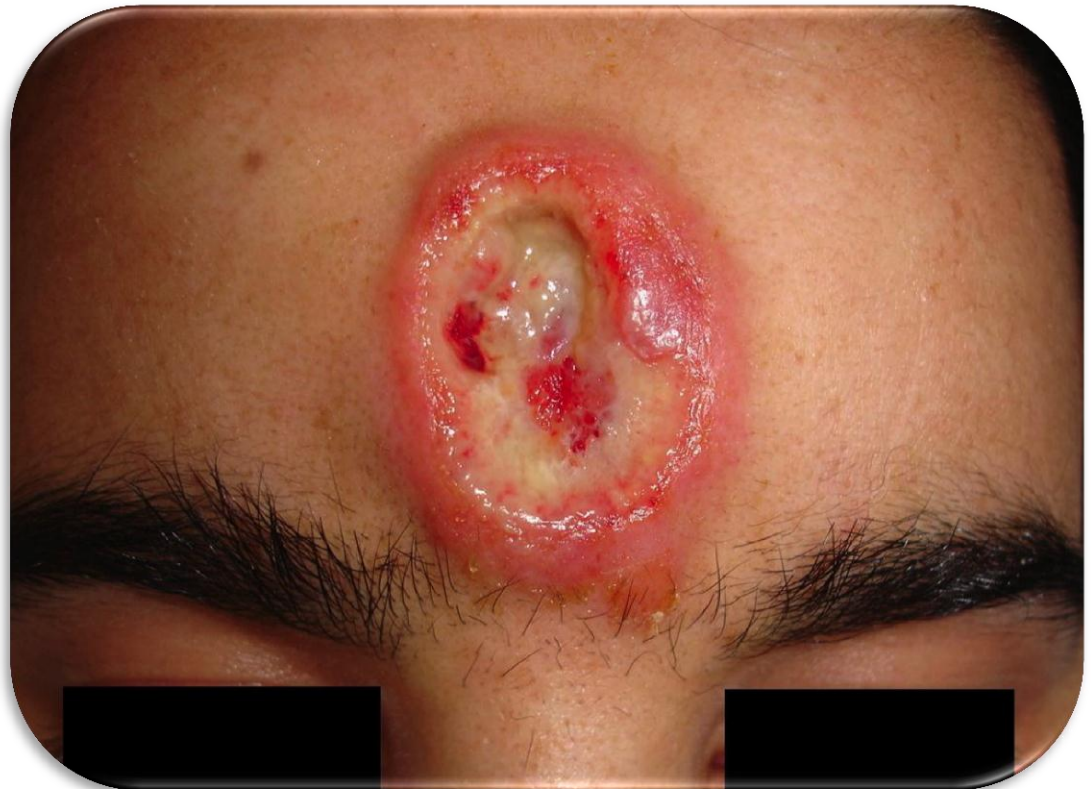


# Latent syphilis

- No obvious symptoms during this period
- Can continue indefinitely
- Fifty to seventy percent of patients do not progress

# Tertiary syphilis

- 10+ years later...
- Lesions on the skin, bone, and vital organs
  - “gummas”
- Cardiovascular
- Neurosyphilis



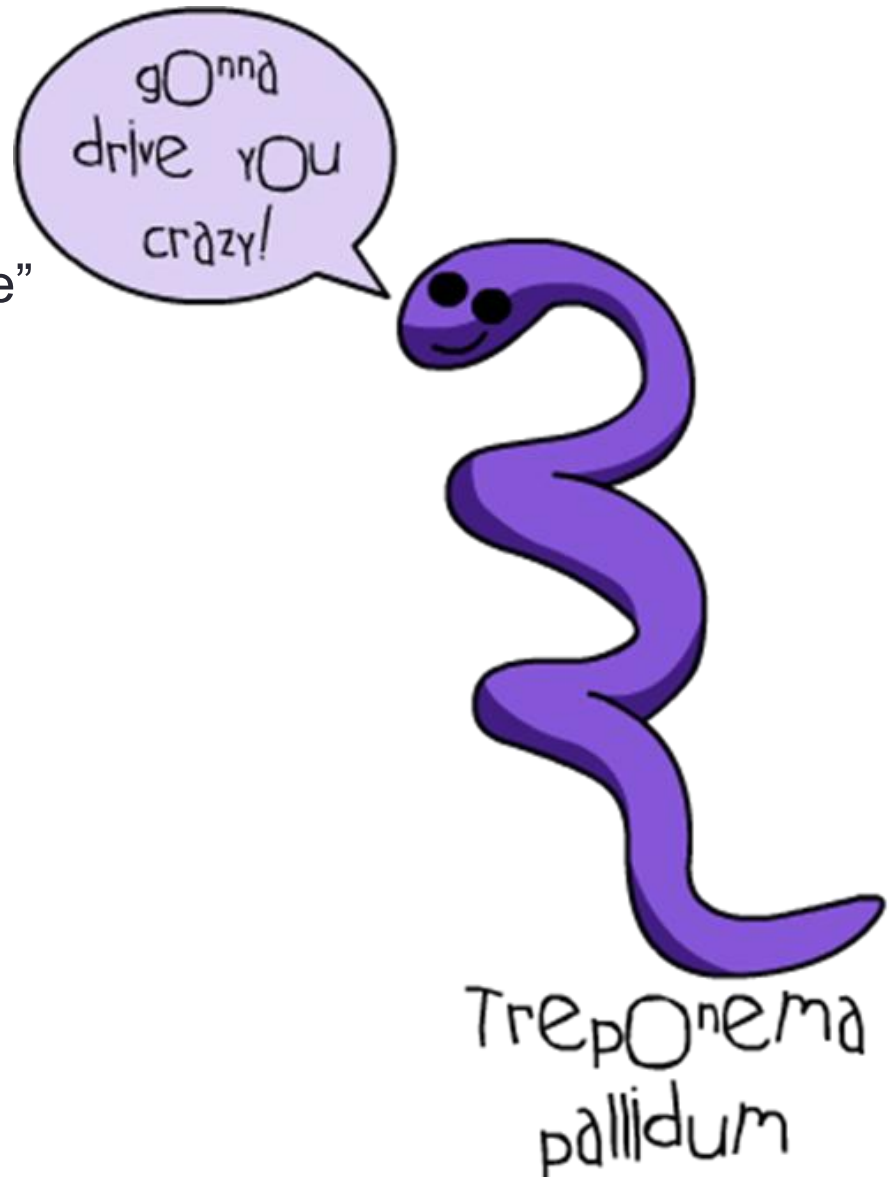


# “Cor bovinum”



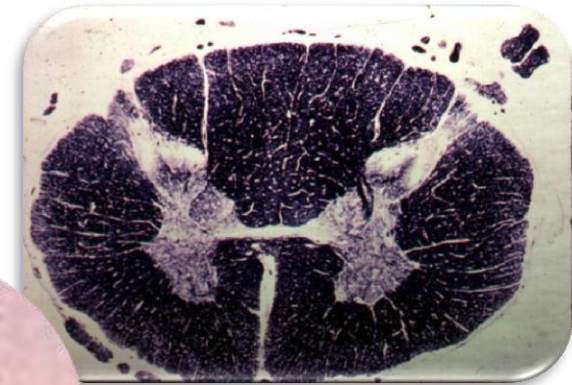
# Neurosyphilis

- Psychiatric complaints
  - “general paresis of the insane”
- Argyle Robinsons pupil
- Tabes Dorsalis





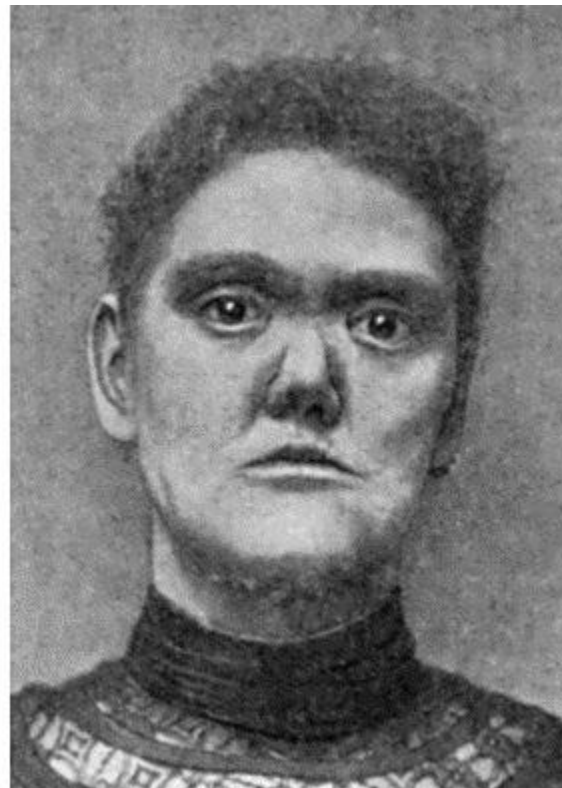
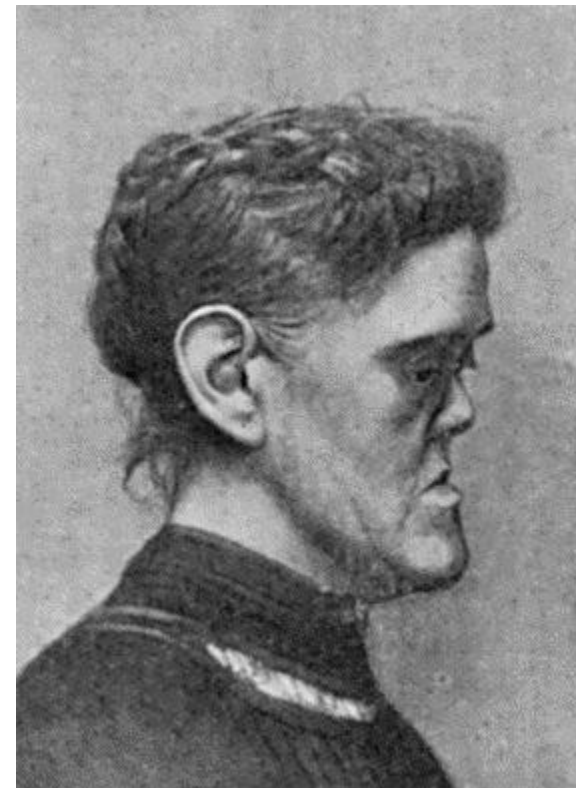
# Tabes Dorsalis



<http://luckyeahnervoussystem.tumblr.com/page/6>

# CONGENITAL SYPHILIS

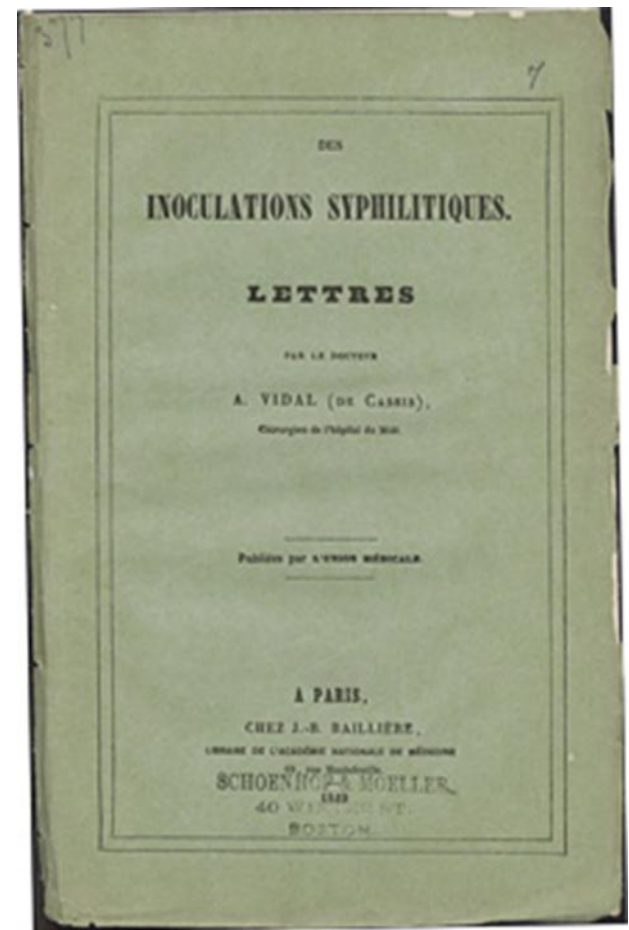
- Passed through the placenta
- Skeletal deformities



# Syphilis

- Advanced stages can mimic nearly **any** disease...
- “the great imitator”
- “The physician who knows syphilis knows medicine.”  
- Sir William Osler

Syphilis inspired literature, art, poetry...



# Syphilis limerick

There was a young man from Black Bay  
Who thought syphilis just went away  
He believed that a chancre  
Was only a canker  
That healed in a week and a day.

- But now he has “acne vulgaris” –  
(Or whatever they call it in Paris);  
On his skin it has spread  
From his feet to his head,  
And his friends want to know where his  
hair is.

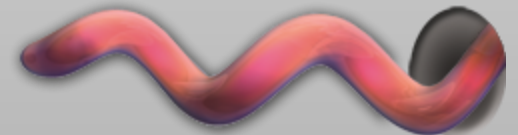
There's more to his terrible plight;  
His pupils won't close in the light  
His heart is cavorting,  
His wife is aborting,  
And he squints through his gun-barrel  
sight.

Arthralgia cuts into his slumber;  
His aorta in need of a plumber;  
But now he has tabes,  
And saber-shinned babies,  
While of gummas he has quite a number.

He's been treated in every known way,  
But his spirochetes grow day by day;  
He's developed paresis,  
Has long talks with Jesus,  
And he thinks he's the Queen of the May

# HISTORY OF SYPHILIS

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# Syphilis

- Syphilis first 'appeared' in Europe in 1496
- Caused terrible sickness
  - severe ulceration of the genitals
  - pustules on the face and body
  - foul smell
  - soft tissue eaten away to the bone





# Origins

- 2 theories:
  1. Christopher Columbus
  2. Already in Europe



- 1494 - King Charles VIII of France attacked Naples
- By end of 15th century - severe syphilis pandemic
- Physicians announced a new disease

# New disease gets a name

- "the Spanish disease," "French pox," or the "Neapolitan evil"
- "Great Pox," in distinction to "smallpox."
- 1530 Italian physician/poet Hieronymus Fracastorius published *Syphilidis, sive Morbi Gallici*
- Shepherd "Syphilis"
- Accurate descriptions





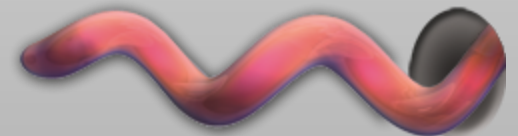
# Syphilis pandemic

- Early cases made people seriously ill
  - High death rates
- By 1500 - medical literature filled with case descriptions
- 1557 – “leper” colonies set up throughout Europe
- 1690 - syphilitic patients treated in hospitals
- Treatment of choice at this time was mercury

# DRUGS

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Syphilis - Evolution of therapy



# Mercury

- Used to treat skin infections
  - 1025 - "The Canon of Medicine" by the Persian physician Avicenna
- 1496 - Giorgio Sommariva of Verona treats syphilis
- Multiple routes of administration
- Oral, topical, ointment, fumigation



# Mercury



Fig 1 Mercury (and other minerals) thrown into charcoal in general furnaces in consequence of the laws of the Pope's prohibition

# Mercury



- Popular for three centuries
- 1800's - mercury used liberally to treat any ulcer
- Patients injured from the treatment
- Side effects:
  - tooth loss
  - skin and mouth ulcers
  - neurological damage
  - death
- “A night in the arms of Venus leads to a lifetime on Mercury.”

# Cause Discovered

- Diagnosis originally relied on visible symptoms
- 1905 German microbiologists Schaudinn and Hoffman discovered the bacteria that cause syphilis
  - Used a modified Giemsa stain
- 1906-German researchers developed the Wassermann test
  - complement fixation
- Prevalence in European cities is high
- Now disease can be caught in asymptomatic stages

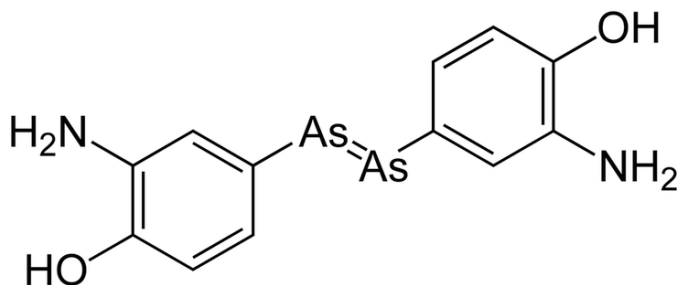
# Paul Ehrlich

- 1909 new field of chemotherapy
- Used the phrase 'silver bullet'



# Ehrlich finds cure for syphilis

- Tested 900 different compounds on mice
- Sahachiro Hata went back to #606
- Tested on mice, guinea pigs, and rabbits with syphilis
- Complete cures within three weeks
  - No dead animals!
- In 1910 the drug was released, called Salvarsan  
“Arsenic saves”





# Salvarsan

- First chemotherapeutic agent
- Revolutionized the treatment of syphilis



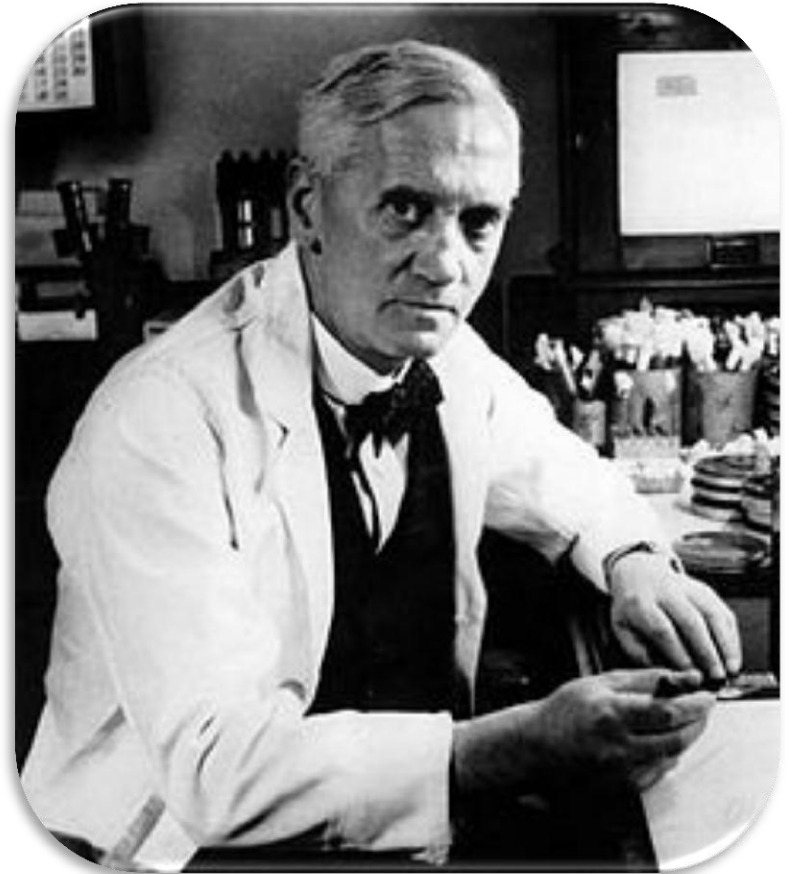
- 1915 medical textbook:

“Pregnant syphilitic women should be given four or five injections of salvarsan as soon as conception is known to have occurred, and mercury continued throughout pregnancy.”

- *"The Practitioner's Encyclopaedia of Medical Treatment"*, 1915 Edition, published by Oxford Medical Publications. Mr J. E. R. McDonough, FRCS., Surgeon to the Outpatients, The London Lock Hospitals

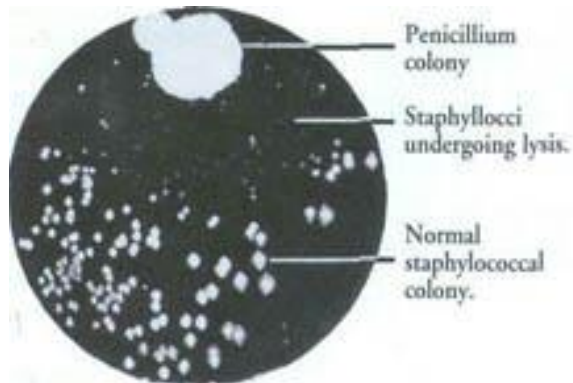
# Alexander Fleming

- First in England to administer Salvarsan intravenously
  - Such a busy practice he got the nickname "Private 606"
- World War I broke out
  - soldiers dying from:
    - Staphylococcal,
    - Streptococcal,
    - and pneumococcal infections
- Wanted a cure like Salvarsan



# Penicillin discovered

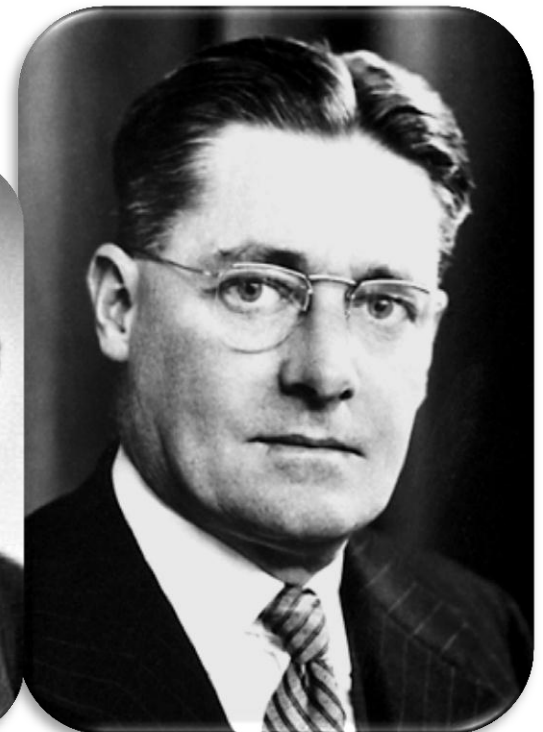
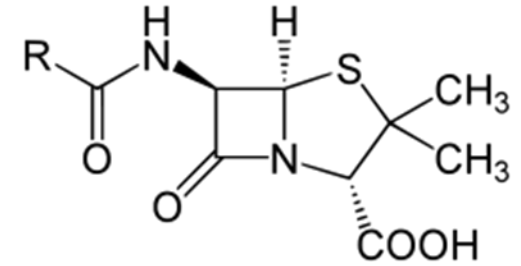
- Began experimenting
- Mold *Penicillium*



- Presented his findings in 1929
  - British Journal of Experimental Pathology

# Drug isolated

- World War II revitalized interest
- Howard Florey and Ernst Chain picked up the work
- Began experimenting with penicillium mold
- Injected live mice
- Then tried it on human subjects
- Could not make enough
- Recovered drug from urine



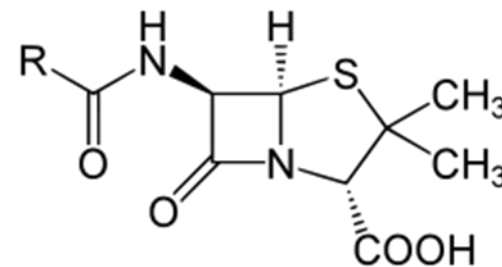
# Mass production

- Florey traveled to the U.S.
- Agricultural research center Peoria, Illinois
  - used fermentation to grow *Penicillium*, fed by CORN
- *Penicillium* loved it - 500 times yield
- United States entered World War II
  - Recruited chemical companies
- By the time the war ended
  - 650 billion units a month



# The cure

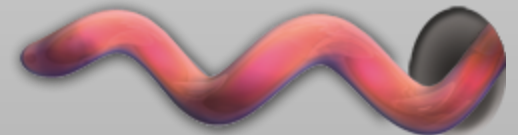
- World's most effective, life saving drug
- 1943 - Use of penicillin to treat syphilis began
- Dramatic drop in prevalence
- Still used today
- Recommended treatment for 1' and 2' syphilis:
  - Benzathine penicillin G 2.4 million units IM in a single dose



# MEDICAL THUGS

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Research on vulnerable populations



# Tuskegee

- 1932 - U.S. Public Health Service began a study
- “the Tuskegee Study of Untreated Syphilis in the Negro Male”
- 399 African-American men with syphilis
- 201 uninfected controls
- Originally 6 months...





# Tuskegee

- No informed consent
- Told men they were treated for "bad blood"
- Free medical exams, meals, and burial insurance
- Local physicians assisted – denied treatment
- Penicillin became the drug of choice for syphilis in 1947
- Intentionally denied to subjects
- 1968 - Ethics of study criticized
- 1969 - CDC reaffirmed need for study
  - Supported by AMA and NMA local chapters
- 1972 - National press coverage...study ended



# 1997 Clinton Apology



- "To the survivors, to the wives and family members, the children and the grandchildren, I say what you know: No power on Earth can give you back the lives lost, the pain suffered, the years of internal torment and anguish.
- "What was done cannot be undone. But we can end the silence. We can stop turning our heads away. We can look at you in the eye and finally say, on behalf of the American people: what the United States government did was shameful.
- "And I am sorry."



# Another study uncovered...

- John Charles Cutler
  - PHS researcher on Tuskegee study
- Led 1946 to 1948 study in Guatemala
- Sponsored by:
  - Public Health Service
  - National Institutes of Health
  - World Health Organization
  - Guatemalan government



# Guatemala

- Used prostitutes to infect:
  - prison inmates
  - insane asylum patients
  - soldiers
- Infected people with:
  - "direct inoculations made from syphilis bacteria poured into the men's penises and on forearms and faces that were slightly abraded ... or in a few cases through spinal punctures"
- Approximately 1300 people were infected, including orphaned children
- The results were never even published...



# Thomas Parran

- Cutlers' supervisor, US Surgeon General
  - “You know, we couldn't do such an experiment in this country.”
  - Did not put an end to it.



# Guatemala

- Cutler chose to do the study in Guatemala
  - Would not fly in the US
- His superior, PHS physician R.C. Arnold:
  - “I am a bit, in fact more than a bit, leery of the experiment with the insane people. They can not give consent, do not know what is going on, and if some goody organization got wind of the work, they would raise a lot of smoke.”

# Obama Administration Apology

- October 1, 2010: Hillary Clinton and HHS Secretary Kathleen Sebelius:
  - "Although these events occurred more than 64 years ago, we are outraged that such reprehensible research could have occurred under the guise of public health"
- April 2013:
  - American Sexually Transmitted Disease Association renamed "Thomas Parran Award" to "The ASTDA Distinguished Career Award."





# Reaction

- Abuse of trust by medical profession
  - Raised severe controversy
- Major changes in how patients are protected
- 1979 Belmont Report
- Requirement for Institutional Review Boards
- Informed consent for all research subjects

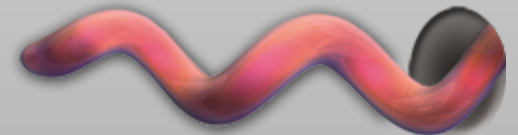




# DIAGNOSIS TODAY

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Screening algorithms and tests



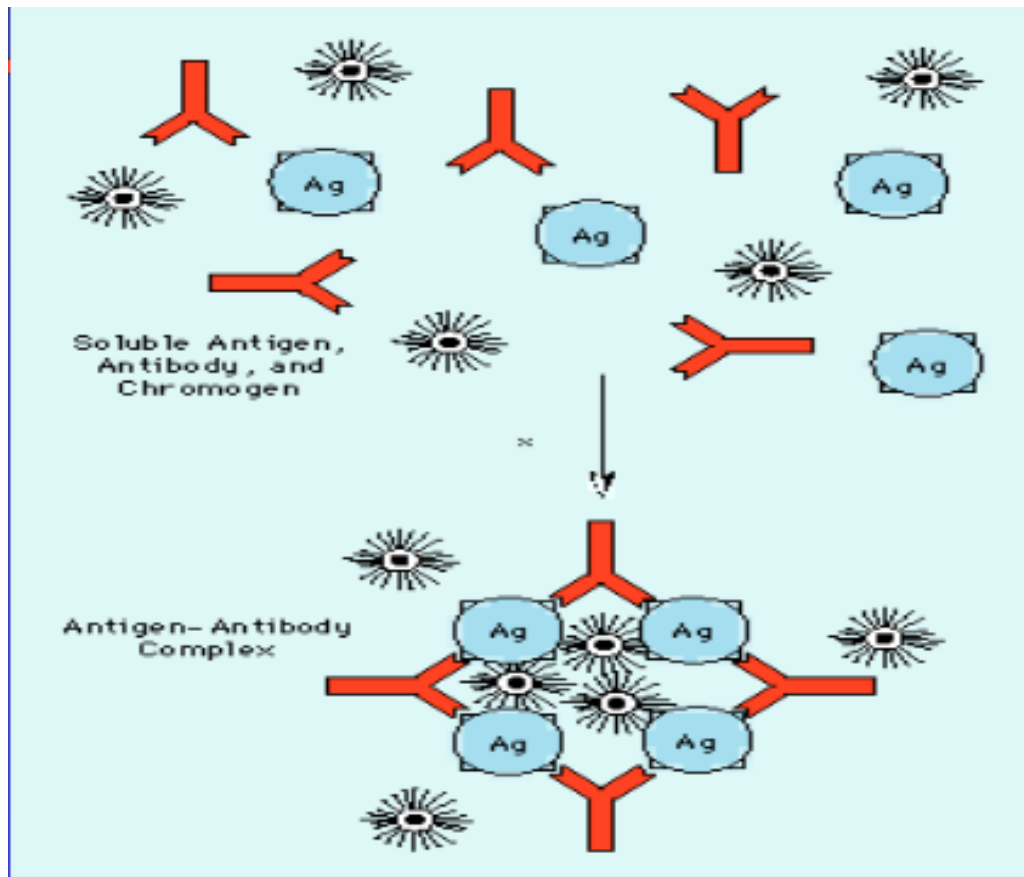
# Diagnosis of syphilis

- Cannot be cultured
- 2 types of tests
  1. Non-treponemal tests
  2. Treponemal tests
- 2 algorithms:
  1. Traditional (CDC recommended)
  2. Reverse

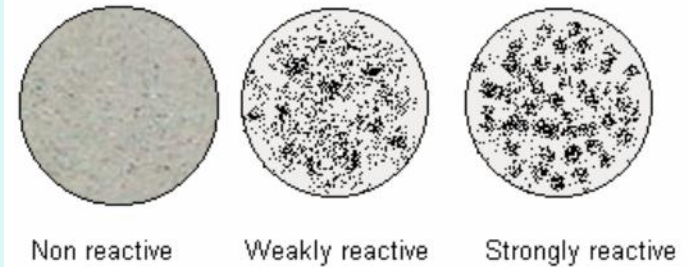
# Non-treponemal tests

- Rapid plasma reagin (RPR)
- Venereal Disease Research Laboratory (VDRL)
- Antigen is Cardiolipin
- Detects reagin
  - Antibodies against cardiolipin
- Catch **active** infection
- Monitor titers for therapy
  
- False positives with HIV, HSV, malaria, IV drug use, SLE, RA, pregnancy, leprosy, etc.
- Therefore follow up with confirmatory test.

# RPR, VDRL



Agglutination reaction



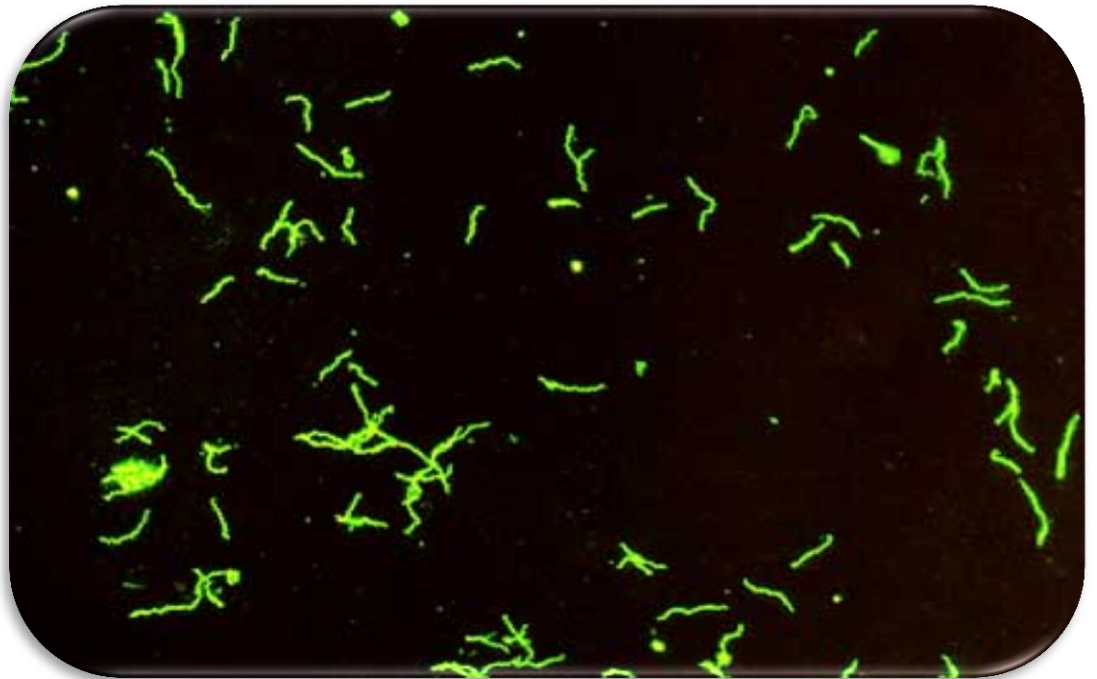
# Treponemal tests

- Fluorescent treponemal antibody absorbed (FTA-ABS)
  - Treponema pallidum particle agglutination assay (TPPA)
  - Enzyme immunoassays (EIAs)
  - Chemiluminescence immunoassays (CIAs)
- 
- Antigen is T.Pallidum
  - Detects specific antibodies
  - Positive for life



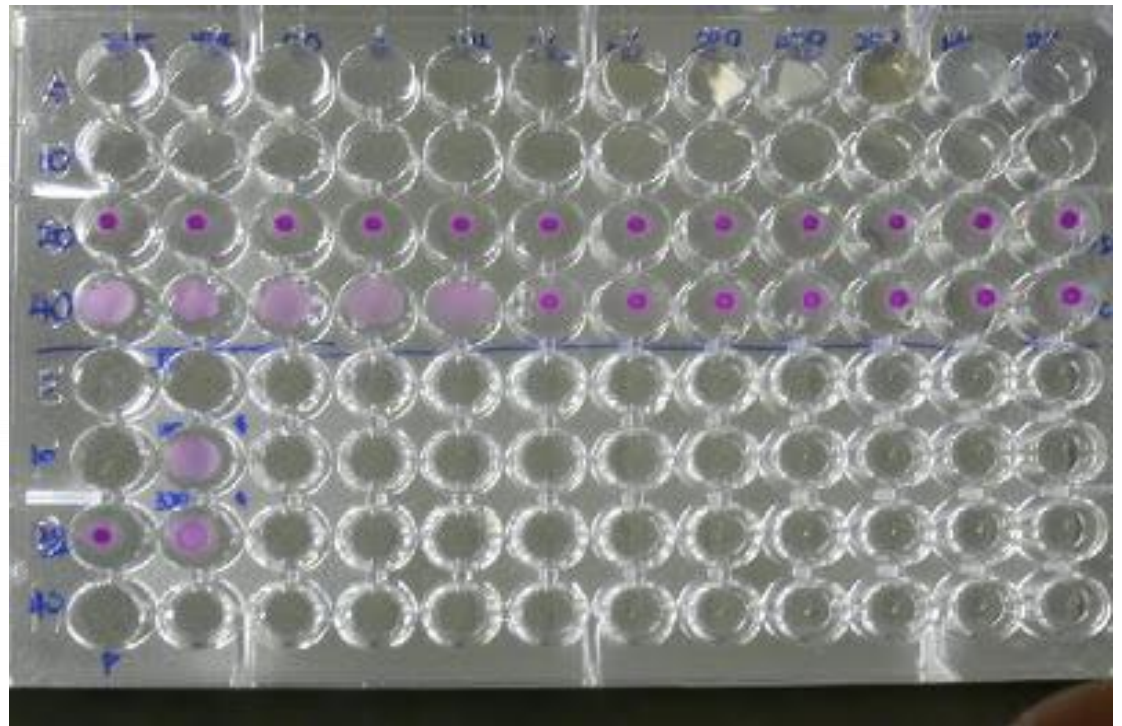
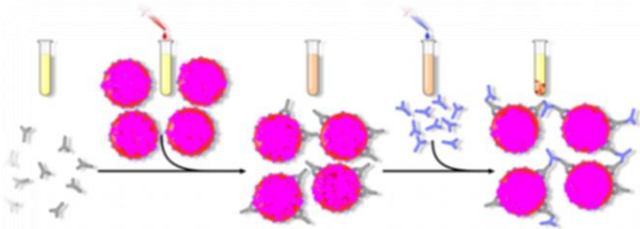
# FTA-ABS

- Fluorescent treponemal antibody absorbed
- Antigen is whole bacteria
- “absorbent” - non-pathogenic treponeme
- Fluorophore-labeled secondary antibodies
- Lower specificity
  - SLE (lupus)
  - Pregnancy
  - Leprosy
- Subjective
- Not recommended



# TPPA

- Treponema pallidum particle agglutination assay
- Gelatin particles sensitized with *T. pallidum* antigen
- Particles agglutinate with antibody, forming a mat



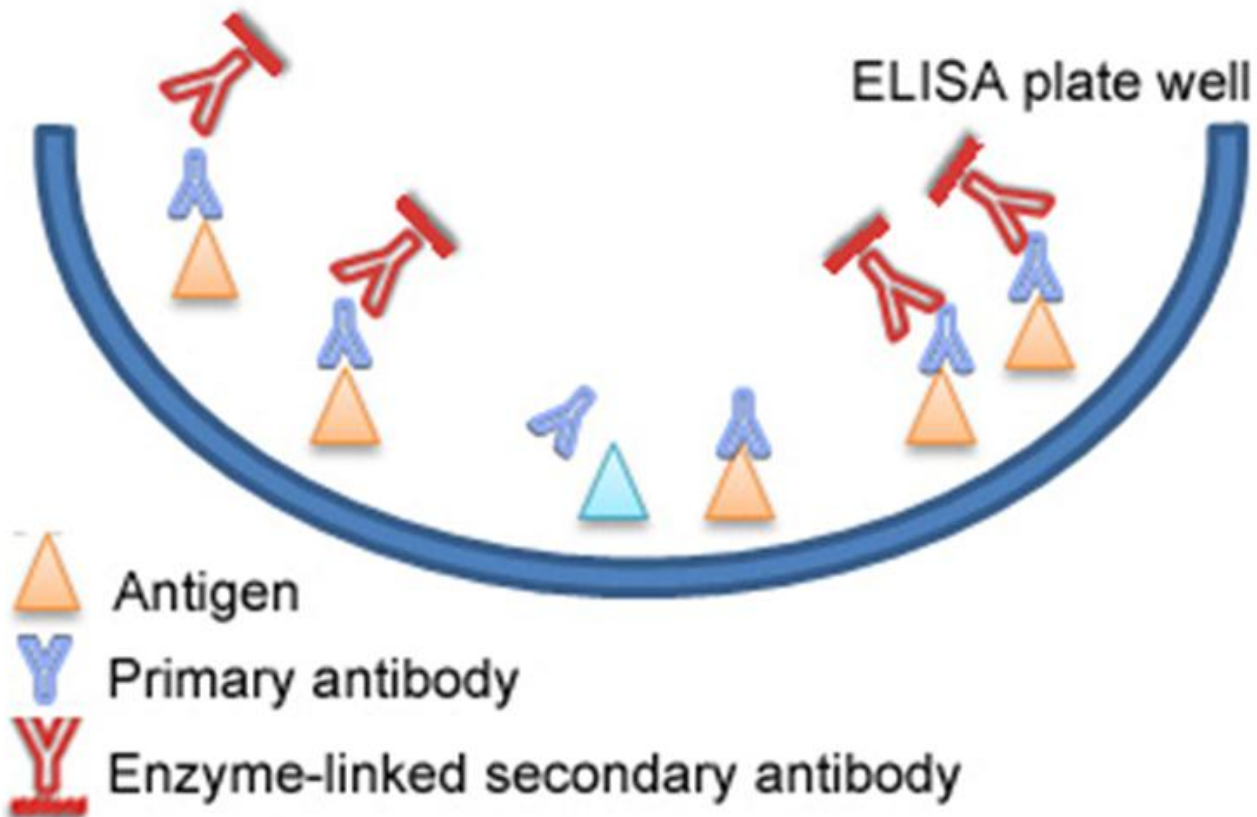
# EIA/CIA

- Enzyme immunoassays (EIAs)
- Chemiluminescence immunoassays (CIAs)
- Qualitative detection of IgG antibodies to *T. pallidum*
  
- Pros:
  - Automated
  - Low cost / high volume
  - Can catch early syphilis
  
- Cons:
  - Treated vs untreated disease
  
- Recommended screening test in EU – reverse algorithm



# EIA or ELISA

Indirect ELISA



# 2 Algorithms

## Traditional (CDC)

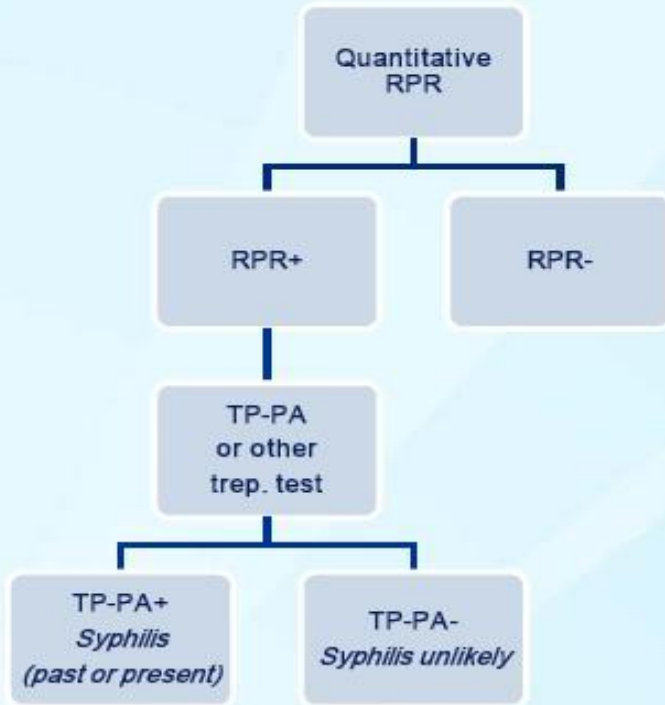
- 1<sup>st</sup> non-treponemal test
- Confirm with treponemal test
- Detects active infection
- Can miss latent or treated infection

## Reverse

- Begin with EIA/CIA
- Confirm with RPR
- Good for high throughput screening
- Catch latent/early infection
- Can't differentiate treated from untreated

# Syphilis serologic screening algorithms

## Traditional



## Reverse sequence



# Back to our case...

## Screening algorithm?

- VDRL followed by FTA-ABS
- Traditional

## Treatment?

- Penicillin G, IM

# Conclusion

- Syphilis has had a profound effect on:
  - Practice of medicine
  - Art, literature
  - Drug development
  - Laboratory medicine
  - Ethical research on human subjects



# Questions?



Earliest known medical illustration of patients suffering from syphilis  
Vienna, 1498

# Famous People with Syphilis



- Hitler
  - 1908 - Contracted syphilis from a Jewish prostitute
  - Wrote extensively in *Mein Kampf* about the “Jewish disease”
- Others
  - Shakespear
  - Pope Alexander VI
  - Ivan the Terrible
  - Henry VIII
  - Hernan Cortez
  - Al Capone





# Acknowledgements

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