

Syphilis: The Great Impostor

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"To know syphilis is to know medicine" Osler

Syphilis

- ◆ Unlike almost all other infectious diseases, it is rarely (if ever!) diagnosed by isolation and characterization of the organism
- ◆ Can affect practically any organ system
- ◆ Variable clinical presentations have resulted in syphilis being labeled "the great impostor"

History

- ◆ Nickname "lues": synonym syphilis turn 20th century
- ◆ Came from Latin *leus venereum* which means disease, sickness, or pestilence
- ◆ The merkin

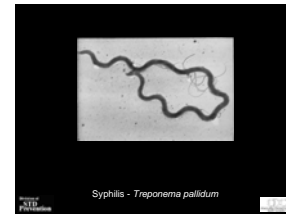
Etiology

- ◆ *Treponema pallidum* subsp. *pallidum* (Family Spirochaetaceae)
- ◆ *Treponema pallidum* subsp. *pertenue*: Yaws
- ◆ *Treponema pallidum* subsp. *endemicum*: Bejel, endemic syphilis
- ◆ *Treponema carateum*: pinta



Etiology

- ◆ Tightly coiled, helical cells 5-15 nm long and 0.09-0.18 nm wide
- ◆ Moves with a characteristic “flexuose” (undulating movement about in center)
- ◆ Movement used to distinguish from non-pathogenic treponemes on darkfield
- ◆ Cannot be cultured *in vitro*



Genome

- ◆ 1,138,006 bp (lower end for bacteria)
- ◆ Unlike most pathogenic bacteria, no transposable elements, suggesting genome is extremely conserved
- ◆ Perhaps why has remained sensitive to penicillin?

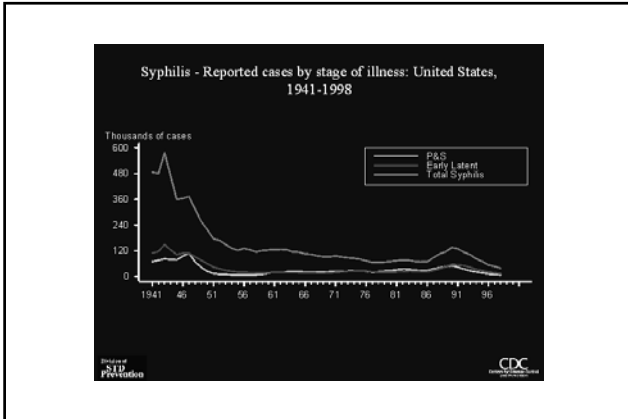
Epidemiology

- ◆ Transmission: sexual contact (overwhelming majority), kissing or other close contact with lesion, transfusion, or direct inoculation
- ◆ Most infectious early in disease: chancre, mucous patch, condyloma latum
- ◆ In most cases, immunologically intact person cannot spread by sexual contact after 4 years since acquired illness
- ◆ Blood transfusion rare: all donors RPR tested and organism cannot survive longer than 48 h using current blood bank storage techniques
- ◆ Congenital



Epidemiology

- ◆ 12 million cases worldwide
- ◆ Reported cases in USA peaked during WWII and nadir in the mid 1980's
- ◆ Sexually active population (15-30 yo)
- ◆ Incidence rose dramatically late 1980's (gay men) early 90's (heterosexual women and congenital infections: “sex for drugs”)
- ◆ For reasons that remain unclear, highest incidence persists in the southwestern USA (MD to FL to LA)



Pathogenesis

- ◆ Hours to days after penetrates intact mucosa or abraded skin travel via lymphatics to general circulation and disseminates throughout body (all organs, including CNS)
- ◆ In rabbits, 4 organisms are sufficient for productive infection
- ◆ Divides every 30 hours
- ◆ Chancre appears 10^7 organisms/mg tissue
- ◆ Incubation period directly proportional to size inoculum
- ◆ Host has immune response and resulting inflammation responsible for clinical manifestations

Pathogenesis

- ◆ Most patients control infection and do not go on to manifest late disease
- ◆ Switch from Th1 to Th2 immune response is critical event in favor of development of chronic infection
- ◆ Also proposed that paucity of proteins and lipoproteins on outer membrane contributes to evasion of effective host response
- ◆ Pathologically, most characteristic lesion is obliterative endarteritis (all stages)

The Natural History of Untreated Syphilis
Tuskegee

- ◆ USPHS prospective observational study of 431 AA men with seropositive latent syphilis of 3 or more years duration (1932-1962)
- ◆ Enrolled in 1932
- ◆ Endpoint: death of all subjects
- ◆ Penicillin became widely available in 1944
- ◆ Despite penicillin becoming standard of care to cure syphilis by 1947, participants did not receive treatment

The Natural History of Untreated Syphilis
Tuskegee

- ◆ Study ended in 1972 when exposed by the *Washington Star*
- ◆ By that year:
 - ◆ 28 men had died directly of syphilis
 - ◆ 100 men had died of related complications
 - ◆ 40 of their wives had become infected
 - ◆ 19 of their children were born with congenital syphilis

The Natural History of Untreated Syphilis
Tuskegee

- ◆ In 1997 at a White House ceremony attended by 5 of the 8 remaining survivors of the study, President Clinton formally apologized:

"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."

Clinical

- ◆ Incubating syphilis
- ◆ Primary syphilis
- ◆ Secondary syphilis
- ◆ Latent syphilis
- ◆ Tertiary syphilis
- ◆ Neurosyphilis
- ◆ Congenital



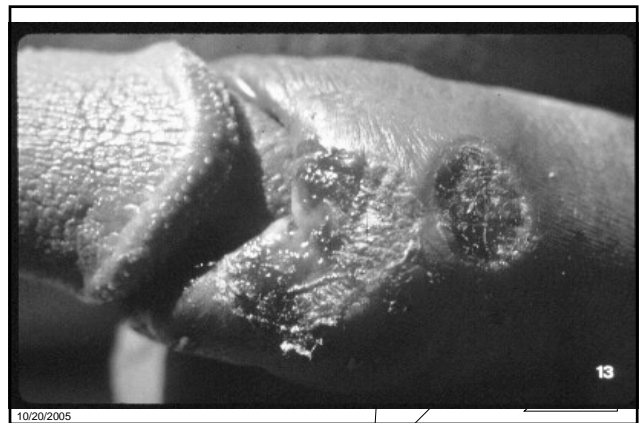
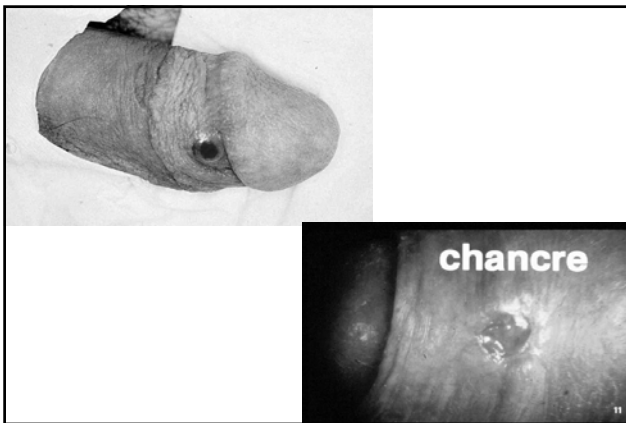
Hutchinson's Teeth

Incubating Syphilis

- ◆ Mean incubation period is 21 days (3 - 90 d) to clinical lesion (chancere)
- ◆ Treatment of other STD may eradicate syphilis at this stage
- ◆ Early spirochetemia with invasion of virtually every organ system

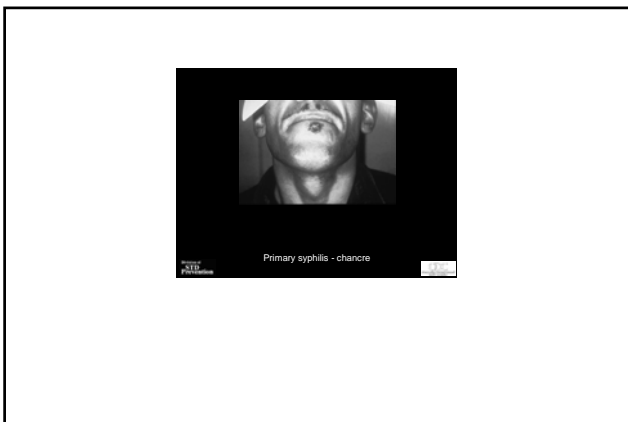
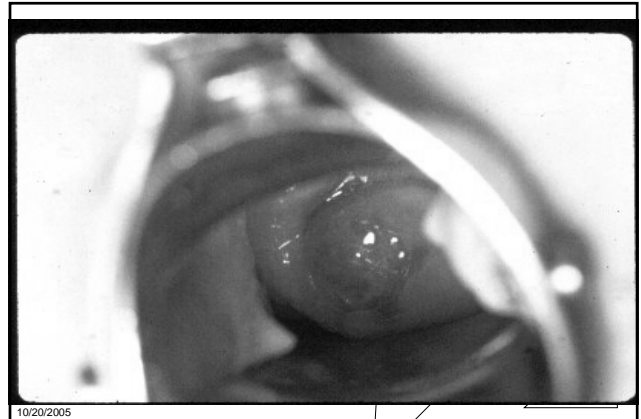
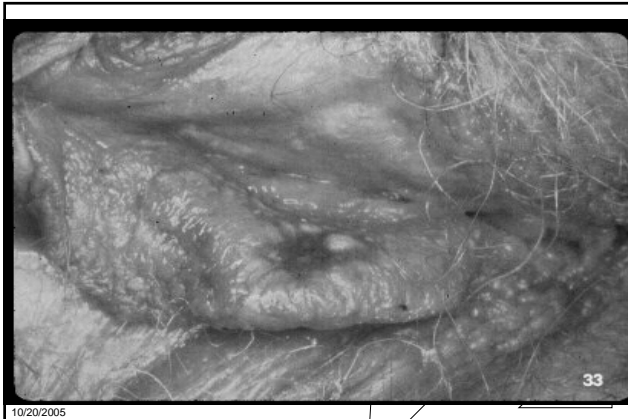
Primary Syphilis

- ◆ Chancere: site of inoculation. Initially painless papule that quickly erodes and becomes indurated
- ◆ Painless lesion (but tender on exam and can become secondarily infected)
- ◆ Highly variable: HIV-infected patients
- ◆ Regional, non-tender adenopathy
- ◆ Hx of syphilis: no lesion, or only small papule that is darkfield negative
- ◆ Heals spontaneously in 3 - 6 weeks (1 - 12 weeks)



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Secondary Syphilis

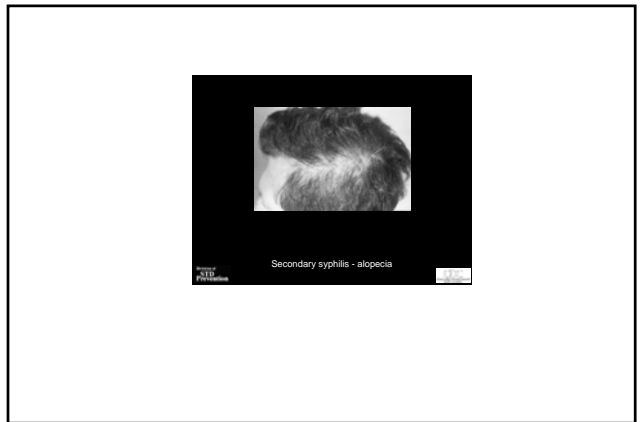
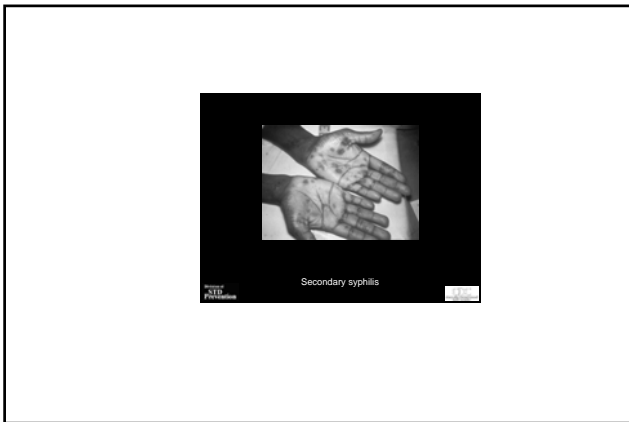
- ◆ Disseminated disease
- ◆ 2 – 8 weeks (but highly variable)
- ◆ Serology always positive (greatest chance for prozone phenomenon at this stage)

The Protean and Widespread Clinical Manifestations of Secondary Syphilis

- ◆ Rash
- ◆ Mucous patches
- ◆ Chondyloma latum (NOT a acuminata)
- ◆ Constitutional symptoms (fever, malaise, pharyngitis, weight loss, arthralgias)
- ◆ HA
- ◆ Meningismus
- ◆ Diplopia
- ◆ Tinnitus
- ◆ Vertigo
- ◆ Glomerulonephritis/nephrotic syndrome
- ◆ Hepatitis
- ◆ Arthritis

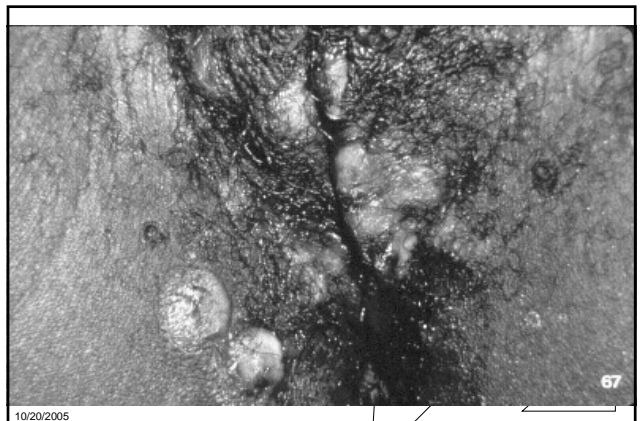
Rash

- ◆ 90% of pts
- ◆ Enderteritis with perivascular mononuclear infiltration
- ◆ Nonpruritic macular, maculopapular, papular, or pustular in any combination or variation. Scaling may occur.
- ◆ 3 – 10 mm lesions
- ◆ Any surface area (but usually start on trunk); palms and soles
- ◆ If hair follicles involved, temporary patchy alopecia, loss of eyebrows/beard
- ◆ Lasts few days to 8 weeks



Condylomata Lata

- ◆ Intertriginous areas (warm moist): perianal area, vulva, scrotum, inner aspects of the thighs, under breast, nasolabial folds, axillary and antecubital folds, webs of fingers and toes
- ◆ Coalesced papules that form painless, broad, moist, gray-white plaque
- ◆ Highly infectious
- ◆ If on mucus membranes: mucous patches





SYPHILIS

The GREAT Impostor!!!!

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Latent Syphilis

- ◆ No clinical manifestations
- ◆ Latent is not synonymous with non-progressive
- ◆ RPR and FTA positive
- ◆ Early latent: < one year from previous negative RPR
- ◆ Late latent: > one year from previous negative RPR (usually not infectious EXCEPT *in utero* or transfusion transmission routes)
- ◆ Latent of unknown duration

Late (Tertiary) Syphilis

- ◆ Slowly progressive inflammatory disease that can affect any organ system and produce symptoms years after infection
- ◆ Late neurosyphilis (e.g. meningovascular, tabes dorsalis, paresis)
- ◆ Cardiovascular syphilis
- ◆ Gummatous syphilis

Neurosyphilis

- ◆ During any stage of disease there can be CNS involvement
- ◆ Asymptomatic (acute and late)
- ◆ Acute neurosyphilis: HA, meningitis
- ◆ Late neurosyphilis
 - ◆ Correlated with pathology: usually overlap with two forms
 - ◆ Meningovascular
 - ◆ Parenchymatous

Late Neurosyphilis: Meningovascular

- ◆ Refers to endarteritis obliterans of small blood vessels of the meninges, brain, spinal cord
- ◆ Leads to small areas of infarction
- ◆ Clinical: focal ischemia and stroke, hemiparesis, aphasia, focal/generalized seizures
- ◆ 5 – 10 years

Late Neurosyphilis: Parenchymatous

- ◆ Refers to actual destruction of nerve cells, primarily in the cerebral cortex
- ◆ General paresis (15 – 20 years)
- ◆ Tabes dorsalis (25 – 30 years)



General Paresis

- ◆ Personality: emotional lability, paranoia
- ◆ Affect: carelessness in appearance
- ◆ Reflexes: hyperactivity
- ◆ Eye: Argyll Robertson pupils, gun barrel sight, any inflammatory eye condition
- ◆ Sensorium: illusions, delusions (especially megalomania), hallucinations
- ◆ Intellect: decreased recent memory, judgment, insight
- ◆ Speech: Slurred

Tabes Dorsalis

- ◆ Demyelination of posterior column, dorsal roots, dorsal root ganglia
- ◆ Ataxic, wide based gait with footslap (positive Romberg sign)
- ◆ Paresthesias
- ◆ "Shooting" or "Lightning" pains: sudden onset, rapid radiation, and sudden disappearance
- ◆ Bladder and/or fecal incontinence
- ◆ Impotence
- ◆ Loss of position and vibratory senses
- ◆ Loss of deep pain and temperature sensation
- ◆ Absent ankle and knee jerk reflexes



Asymptomatic Neurosyphilis

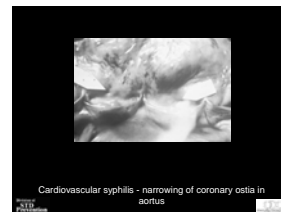
- ◆ Most common presentation of neurosyphilis
- ◆ No clinical symptoms
- ◆ One or more CSF abnormalities: pleocytosis, elevated protein, decreased glucose, positive CSF serology
- ◆ Local CNS production of antibodies to *T. pallidum*, a positive PCR, and a serum RPR \geq 1:32 are highly suggestive of neurosyphilis
- ◆ Incidence of asymptomatic acute neurosyphilis in untreated patients is as high as 40%
- ◆ Unknown how many progress to symptomatic late neurosyphilis: The need for an LP?

Late (Tertiary) Syphilis

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- ◆ Gummatous syphilis

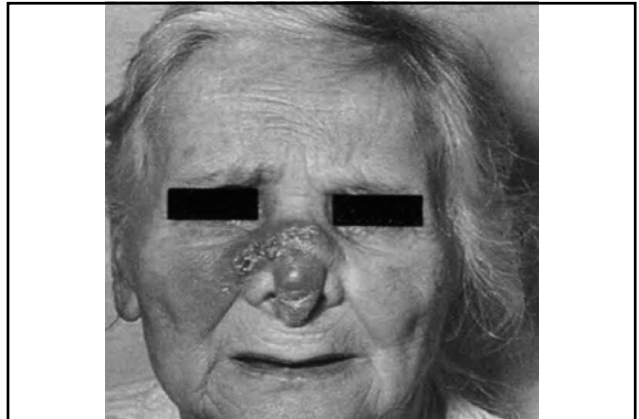
Cardiovascular Syphilis

- ◆ Endarteritis obliterans involving the vaso vasorum of the aorta
- ◆ Results in aneurysm formation
- ◆ Usually ascending aorta: aortic regurgitation
- ◆ 10% untreated cases (symptomatic)
- ◆ Clinical pearl: linear calcifications noted ascending aorta (seldom seen in arteriosclerotic disease)
- ◆ Rare since introduction of antibiotic treatment

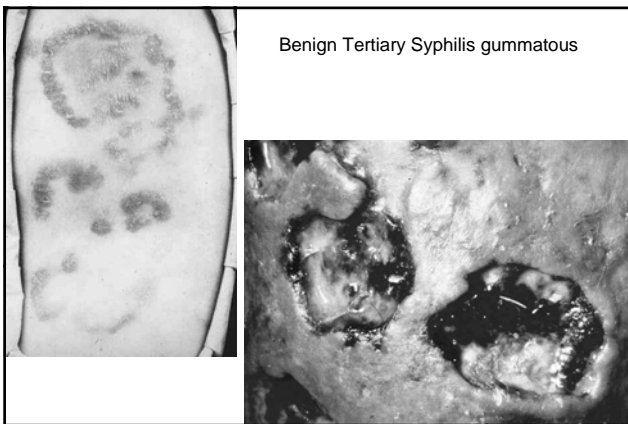


Gumma (Late Benign Syphilis)

- ◆ Gumma: non-specific, granulomatous-like lesion: tumor-like masses
- ◆ Rarely seen today
- ◆ Most common skeletal system, but can develop in any organ system: skin, liver (gummatous hepatitis, cirrhosis [hep lobatum]),
- ◆ Cause local destruction: fractures bone, nasal septum perforations
- ◆ PCN rapid and dramatic response

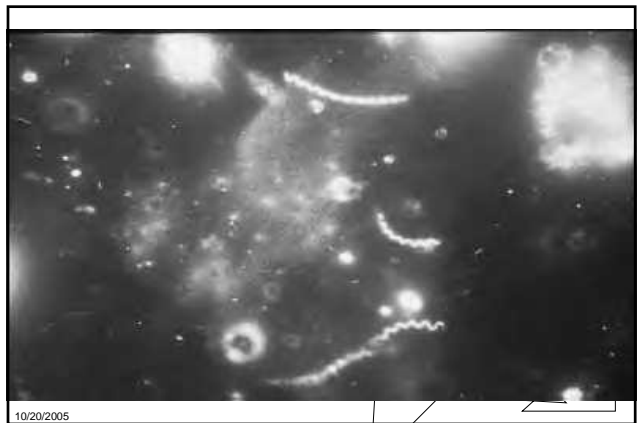


Benign Tertiary Syphilis gummatous



Diagnosis

- ◆ *T. pallidum* cannot be cultured *in vitro*
- ◆ Primary and secondary syphilis lesions: darkfield
- ◆ Biopsy with specific immunofluorescent stains
- ◆ PCR: not ready for prime time
 - ◆ Clinically, used most frequently to Dx CNS disease
 - ◆ Sensitivity/Specificity: hands of lab
 - ◆ Excellent positive predictive value
 - ◆ Does not distinguish dead from replicating spirochetes



Serologies

- ◆ Non-specific treponemal tests:
 - ◆ Rapid plasma reagin (RPR)
 - ◆ Venereal disease research laboratory (VDRL)
- ◆ Specific treponemal tests:
 - ◆ Fluorescent treponemal antibody (FTA)

Non-Specific Serologies

- ◆ Non-specific (RPR, VDRL):
 - ◆ Detect antibodies against a lipoidal antigen resulting from the interaction of *T. pallidum* with host tissues or from *T. pallidum* itself (fortuitous relationship)
 - ◆ Used to screen and follow response to therapy: should revert to "negative" with successful treatment
- ◆ Sensitivity:
 - ◆ Primary/Secondary: 70 – 100%
 - ◆ Late latent/Tertiary: 60 – 98%
- ◆ Specificity: positive result must be confirmed with specific treponemal test (Multiple causes of false positives)

Specific Serologies

- ◆ Measure antibodies against specific *T. pallidum* antigens (FTA)
- ◆ Remain positive for life
- ◆ Sensitivity:
 - ◆ Early: 50 – 85 %
 - ◆ Late: 97 – 100%

Treatment General

- ◆ PCN remains the drug of choice: PCN allergy
- ◆ Jarisch-Herxheimer Reaction
 - ◆ 1 – 2 h after initial txt
 - ◆ Abrupt onset fever, chills, myalgias, HA, tachycardia, hyperventilation, vasodilation with flushing, and mild hypotension
- ◆ Common with secondary syphilis (70 – 90%)
- ◆ Self limited 12 – 24 h (NSAIDS); neuro/cardiovascular: steroids

Primary and Secondary Syphilis

- ◆ BNZ PCN 2.4 million units IM X 1

Latent Syphilis

- ◆ Early latent syphilis (< 1 year)
 - ◆ BNZ PCN 2.4 million units IM X 1
- ◆ Late latent (> 1 year) or unknown duration
 - ◆ BNZ PCN 2.4 million units IM X 3

Tertiary (Cardiovascular and Gumma)

- ◆ r/o neurosyphilis
- ◆ BNZ PCN 2.4 million units IM X 3

Neurosyphilis

- ◆ Aqueous crystalline PCN 18-24 mu q d for 10 – 14 d

Aside From Becoming a Red Sox Fan,
The Real Danger of Life In BOSTON!

There was a young man from Back 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 gunbarrel sight.
Arthralgia cuts into his slumber;
His aorta is in need of a plumber;
But now he has tabes
And sabershineed 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 thinks he's the Queen of the May.

Anonymous, 1920's