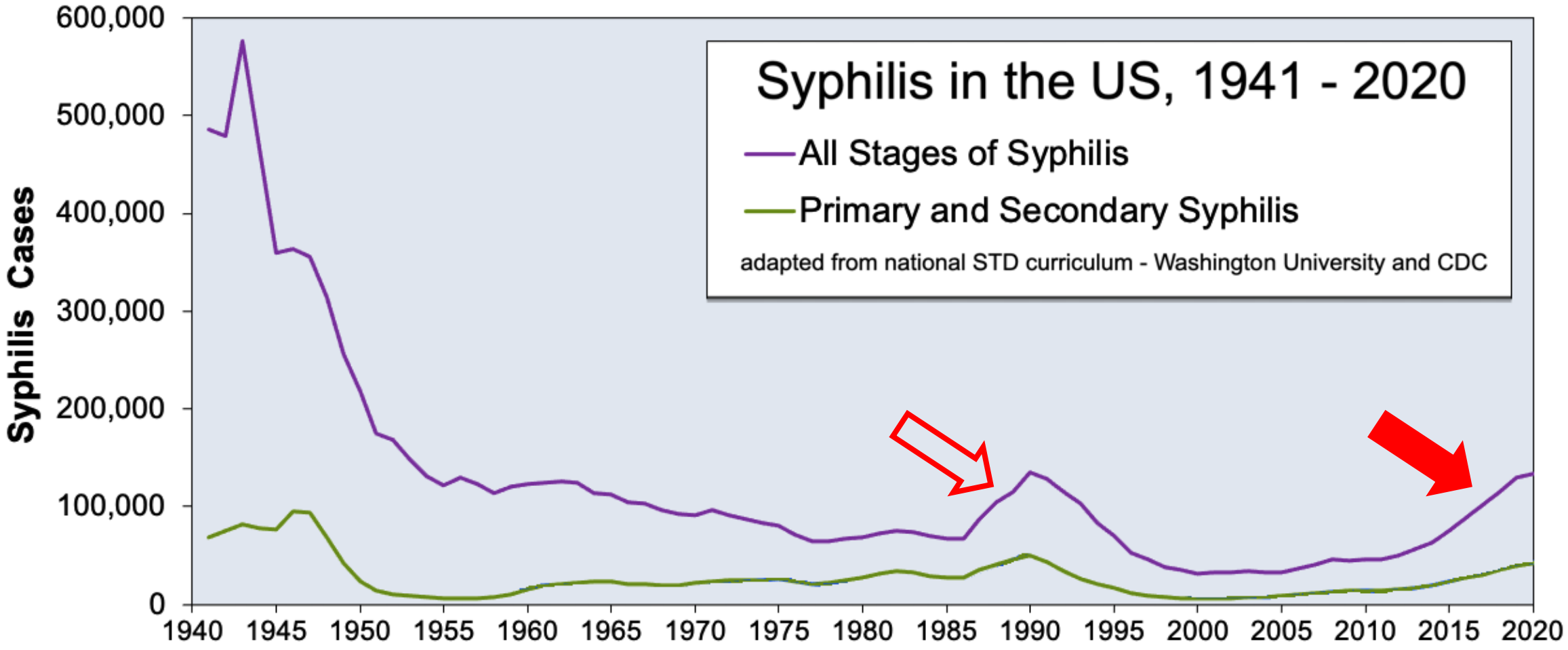
Some basics of syphilis

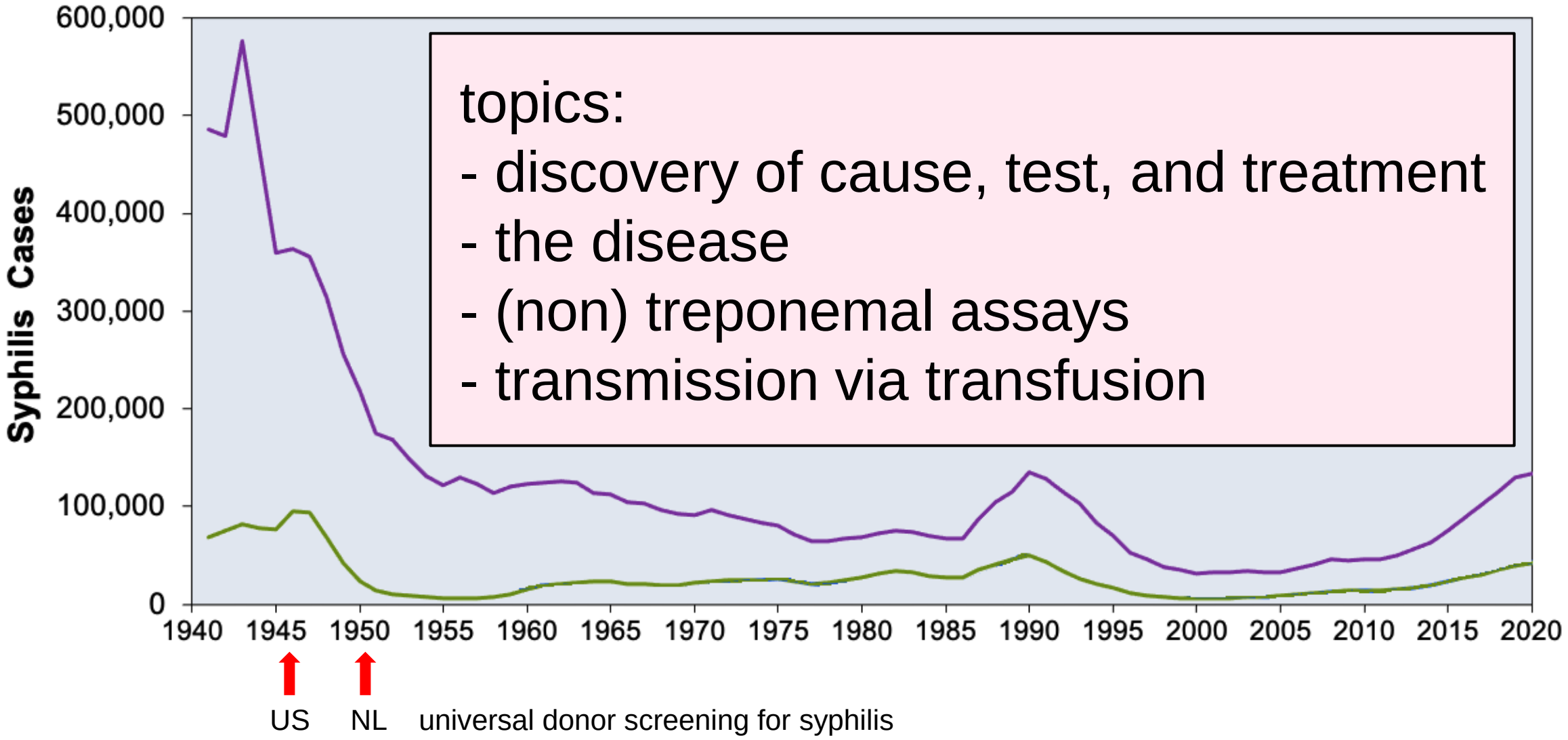
31st IPFA/PEI Workshop on Blood-borne Pathogens
Heidelberg 2025

prof.dr. Hans L. Zaaijer
h.zaaijer@sanquin.nl

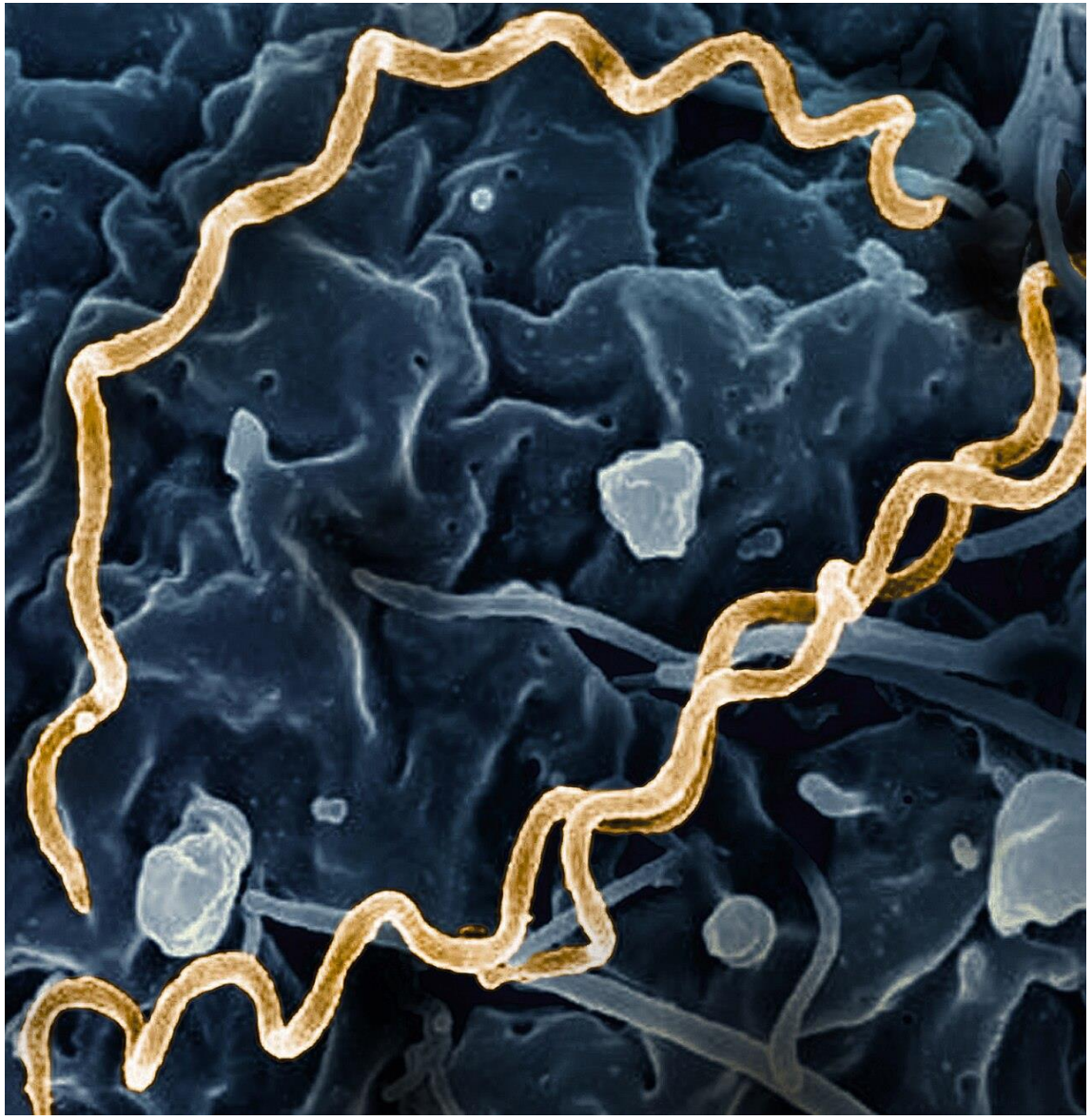
syphilis returns (again)



syphilis returns (again)



syphilis - an STD caused by *Treponema pallidum*





in a poem by Girolamo Fracastoro
the shepard Syphilus was punished for his sins
with a nasty disease: Syphilis
(1530)

Infected celebrities

syphilis



Lenin



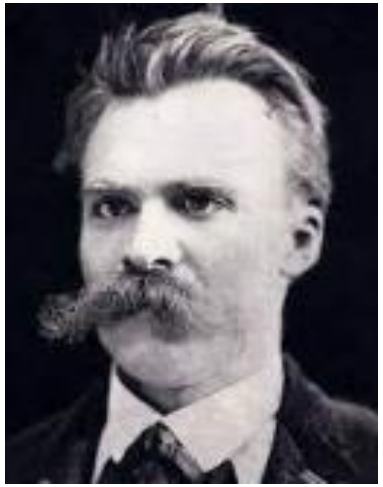
Schumann



Hughes



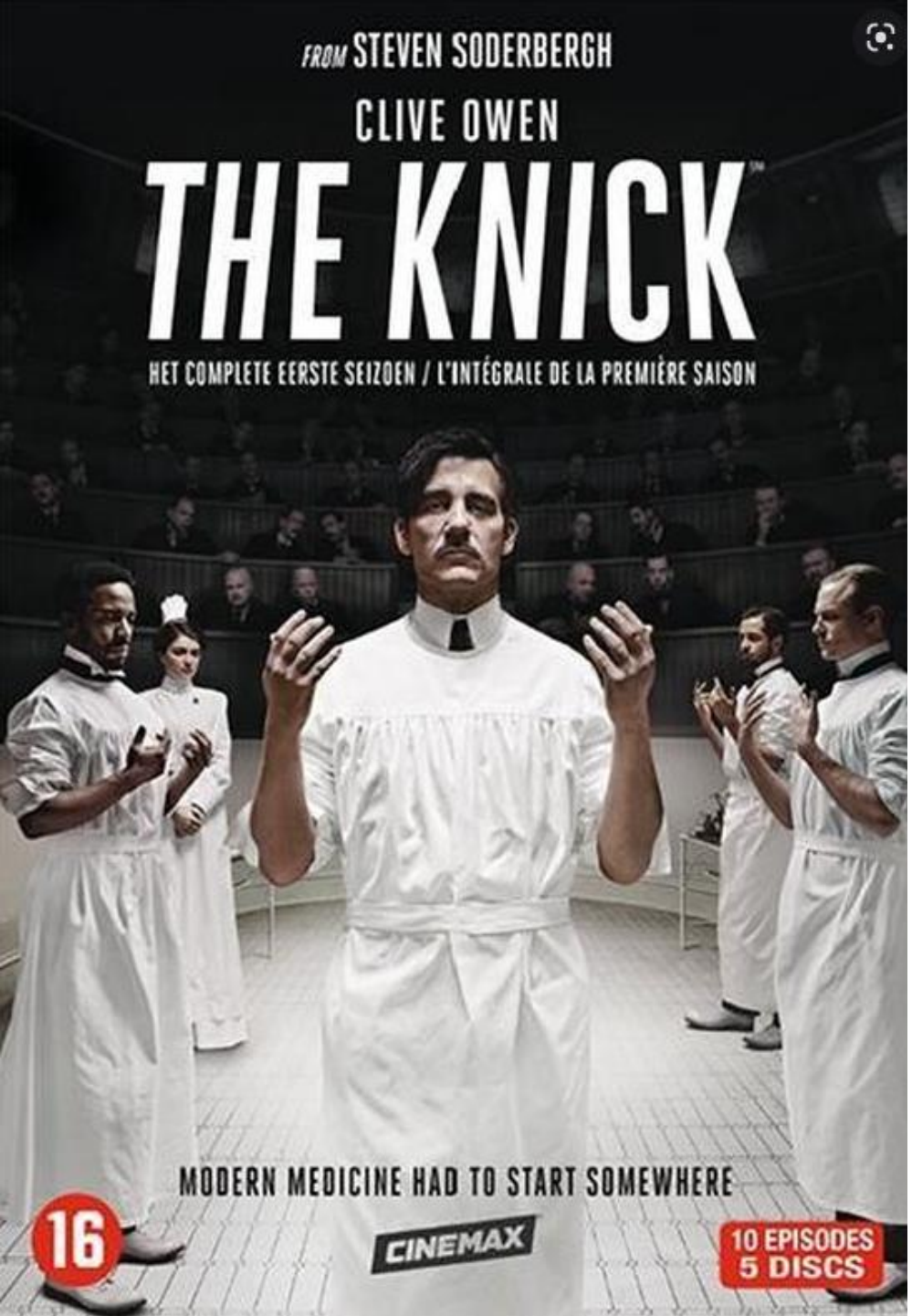
Al Capone



Nietzsche



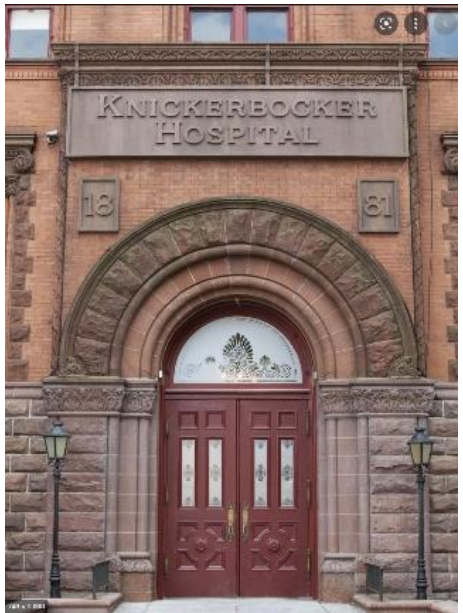
Blixen



start of:
- blood transfusion
- electric hemostasis
- use of rubber gloves

syphilis:
- experimental therapy
- reconstructive surgery

inspired by the life of William Halsted, who performed one of the first blood transfusions in the US.









Argyll Robertson pupils
do not constrict
in bright light





swing flap surgery

course of untreated syphilis

infection

↓ *after 3 weeks (10-90 days):*

primary syphilis

↓ *0 - some weeks later:*

secundary syphilis

↓

early latent (< 2yrs, infectious) and late latent syphilis

↓ *in 5-30 %, 3 - 30 years later:*

tertiary syphilis

+/- on top of 1°/2°/3°-syphilis:

- neurosyphilis (ao: madness; paralysis, dementia)
- syphilis of eyes/ears
- local tissue destruction (eg. nose)

course of untreated syphilis

infection

↓ *after 3 weeks (10-90 days):*

primary syphilis — painless ulcer(s), firm edge. Heals spontaneously in 3-6 wks.

↓ *0 - some weeks later:*

secundary syphilis — non-itchy rash on trunk, palms, soles; **+/-** lnn, fever, headache, condylomata. Disappears spontaneously.

↓

early latent (< 2yrs, infectious) and late latent syphilis = less infectious

↓ *in 5-30 %, 3 - 30 years later:*

tertiary syphilis — gummatous syph. / late neuro-syph. / cardiovascular syph.

+/- on top of 1°/2°/3°-syphilis:

- neurosyphilis (ao: madness; paralysis, dementia)
- syphilis of eyes/ears
- local tissue destruction (eg. nose)

syphilis

syphilis is the great imitator

primary syphilis:






secundary syphilis:





congenital syphilis

T. pallidum passes placenta:
congenital syphilis
> screening of pregnant women

Gerard de Lairesse (1640-1711) ➔
as painted by his friend Rembrandt in 1667:
saddle nose caused by congenital syphilis,



syphilis: in 1690 Gerard became blind,



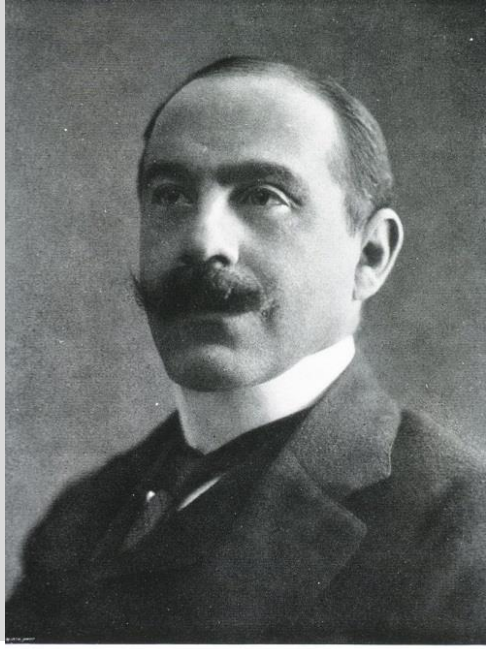


just when he was invited to paint the ceilings in Amsterdam's city hall

1900 mental instutions filled with neurosyphilis patients, unrecognized! "General paresis of the insane"

1905 Schaudinn & Hoffmann: *T.pallidum* causes syphilis.

1906 August von Wassermann:



* 1866 Professeur August Von WASSERMANN

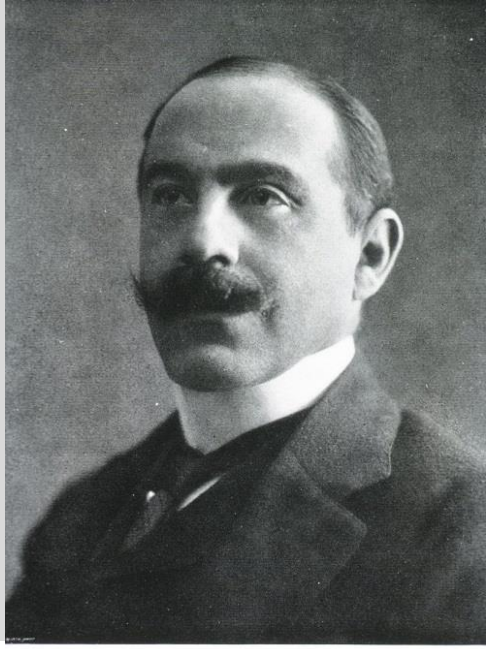
alcohol extracted antigens from livers from stillborn syphilitic babies,
for a complement fixation assay.

principle:
- patient antibodies bind to the syphilis antigens,
- the Ab-Ag complexes bind (fixate) complement,
- which no longer is available for lysis of RBCs by Abs.

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- the Ab-Ag complexes bind (fi
- which no longer is available f



However: extract from bovine heart
or beef works as well !

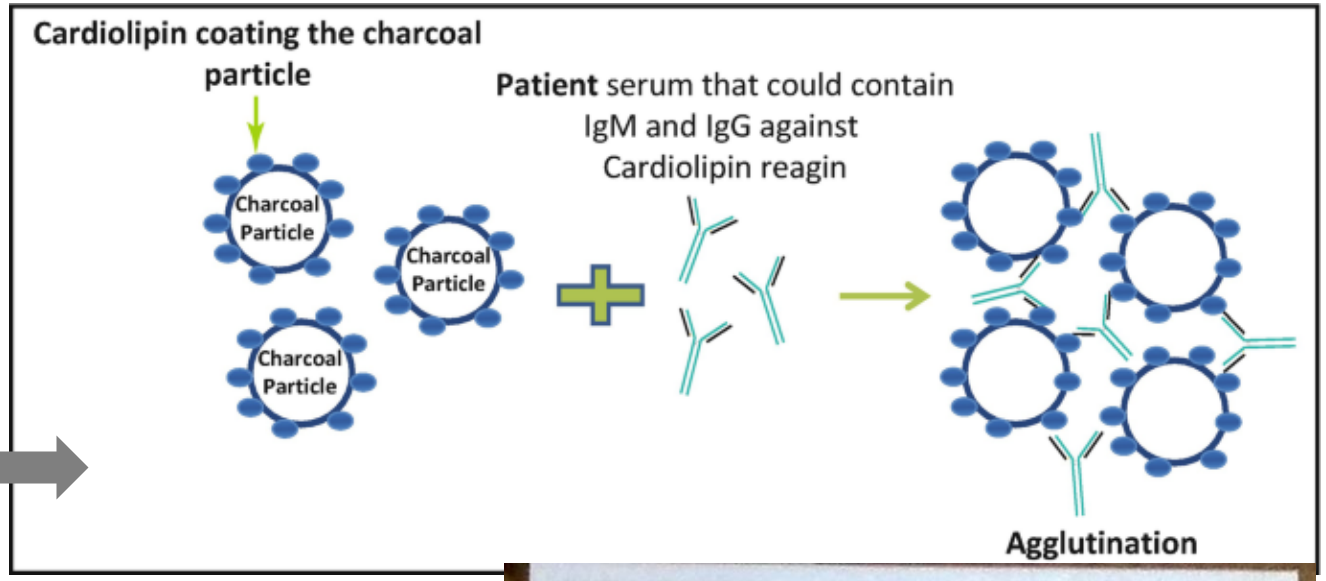
Hence the "non-treponemal" syphilis assays:

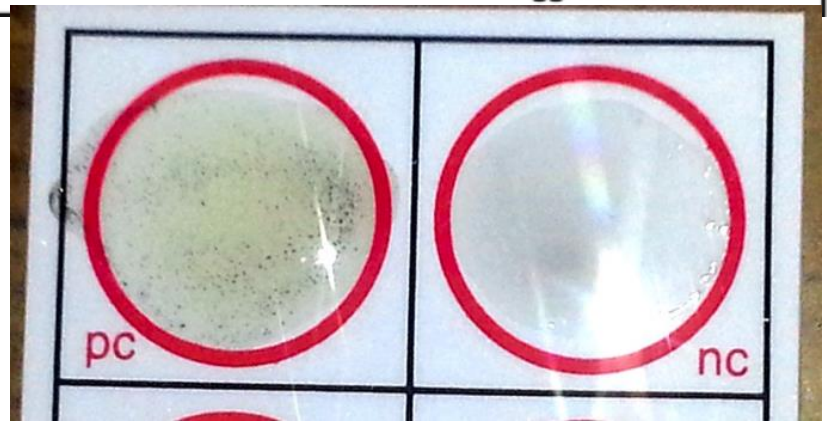
Syphilis patients have antibodies to cardiolipin (a phospholipid).

1. Wassermann test

2. Rapid Plasma Reagine test

3. Venereal Disease Reference Lab. test





false positives due to: auto-immune diseases, malaria, pregnancy

false negatives due to: prozone effect; sample too early, late-latent stage of syphilis, treatment, etc.

is "non-treponemal" correct ?

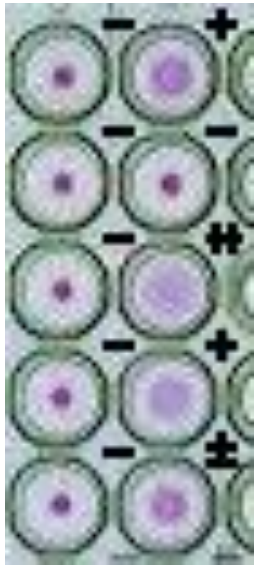
In 1979 Matthews and colleagues reported that the outer membrane of *T.pallidum* contains the phospholipids as used in the "non-treponemal tests". However: these are host-derived, no bacterial genes involved.

The "non-treponemal" antibodies in syphilis patients are directed
against phospholipids: from damaged tissue?
from *T.pallidum* bacteria?

HM Matthews ea. Unique lipid composition of *Treponema pallidum* (Nichols virulent strain). Infect. Immun. 1979;24:713–9

True treponemal syphilis assays:

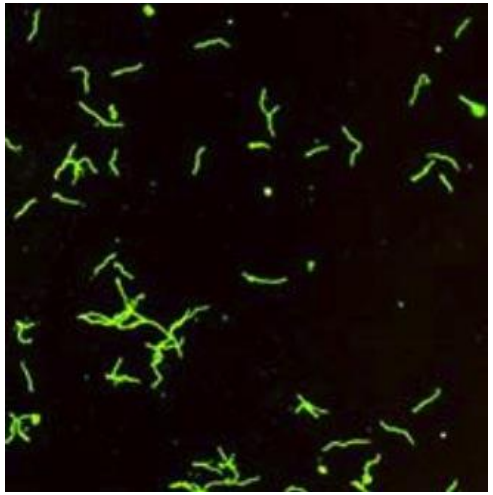
1. dark field microscopy on fresh material from chancre



2. T.pallidum inhibition assay = slowing down of living (cultered) Treponema by Abs

3. T.pallidum haem- or particle-agglutination (TPHA, TPPA)

4. fluorescent treponemal antibody absorption test (FTA-ABS)
   = IFA, after removal by absorption of cross-reacting antibodies to commensal spirochetes



5. Modern EIAs:
   1971 - ELISA enzyme linked immuno sorbent assay
   ≥1990 - MEIA, CMIA, etc

False test results:

false positive due to non-venereal Treponema infections:

yaws *T. pallidum* subspecies *pertenue*
pinta *T. pallidum* subsspecies *carateum*
bejel *T. pallidum* subspecies *endemicum* = "endemic syphilis"

(syphilis is caused by *T.pallidum* subspecies *pallidum*)

false negative due to: sample too early
effect of treatment
waning during late latent syphilis

Non-treponemal assays are ~ less sensitive than true treponemal assays.

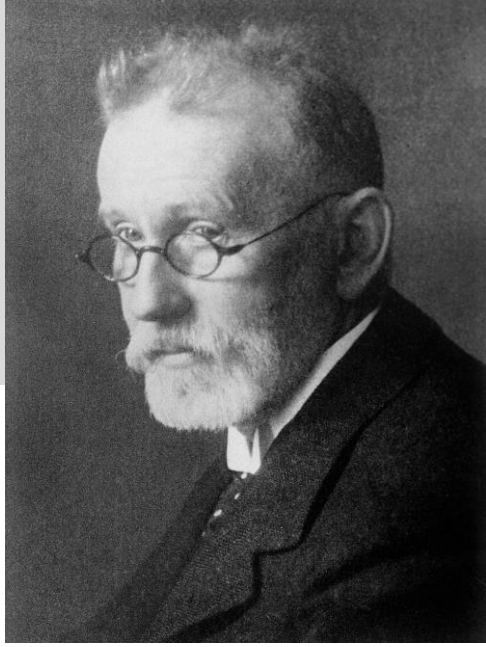
Borrelia and *Treponema* share some epitopes → mutual cross-reactions in serology.

Magnarelli J.Inf.Dis. 1987 May be resolved by Borrelia and Syphilis immunoblots.

Reactive Lyme screening, with negative Lyme-confirmation, caused by Syphilis.

R.Naesens ea. Acta Clin Belg. 2011;66(1):58-9. False positive Lyme serology due to syphilis: report of 6 cases and review of the literature.

1905 T.pallidum causes syphilis
1906 Wassermann test
1909 Paul Ehrlich & : arsphenamine = Salvarsan
Sahachiro Hata



salvare = to save
arsenik = arsenic
sanus = healthy

- Systematical testing of compounds for spirochete-killing properties. Compound 606 cured a syphilitic rabbit, without killing it.
- Difficult to handle, unstable in air. Special i.v. preparation kit:



- 1912: NeoSalvarsan = easier to prepare
- 1910 -1940: most widely prescribed drug
- 1923: 2.000.000 doses produced in USA
- 1935: 700.000 patients treated/year in USA
- 1945: penicillin available for public use



Transfusion transmitted syphilis

Fordyce, Am.J. of Med. Sciences, 1915:
first report of transfusion transmitted syphilis

a personal communication by Dr. Dade, in which he related the infection of a young girl by blood transfusion. Her brother, whose blood was used for the treatment of her anemia, was at the time of the operation in the second incubation period of the disease. She in due course of time developed a secondary rash.

McCluskie, Br.Med.J., 1939:
review of transfusion transmitted cases

almost all the infections occurred when the donors were in the primary or secondary stage of the disease.

undoubted infection has been recorded with blood from donors who were in the pre-chancre stage

The view that syphilis is transmissible by blood transfusion has long been accepted, chiefly on the basis of animal experiments. A review of the literature also indicates that well-authenticated examples of transmission in man have been fairly frequently recorded, there being some seventy cases since the first description by Fordyce in 1915.

?

"...by 1941:
138 cases of transfusion transmitted syphilis..."

C.Gardella, J.Inf.Dis., 2002:

Only 3 cases of transfusion-transmitted syphilis have been reported in the English literature during the past 35 years. All reported cases were linked to transfusion of fresh blood products

Transfusion transmitted syphilis

Needle stick accidents and transfusion accidents demonstrate:
blood from syphilitic person is infectious:

- before appearance of ulcer
- during primary syphilis
- during secundary syphilis
- in early latent syphilis

Prolonged cool storage inactivates *T.pallidum*,
but hard supportive experiments are lacking:

D'Aes, Vox Sanguinis, 2024,
review of effect of cold storage:

> The evidence is very uncertain, and conclusions are hindered by a lack of sufficiently powered studies and studies in humans.

NB: Freezing does not inactivate *T.pallidum*.

Donor screening algorithms for syphilis:

Traditional algorithm:

1. screen using non-treponemal assay, if reactive:
2. confirm using a treponemal assay

Reverse algorithm:

1. screen using (automated) treponemal assay, if reactive:
2. additional quantitative non-treponemal assay, if neg.:
3. additional other treponemal assay

How do you screen your donors for syphilis?

using a non-treponemal assay	using a treponemal assay		donors not screened for syphilis
RPR, VDRL, etc.	(micro-) TPPA, TPHA	ELISA, MEIA, CMIA, etc.	-

Conclusion

- Compared to the 19th and the first half of the 20th century:
  syphilis = defeated.
  But it is on the rise... (next speakers)

- More new infections among donors? ➡
  Increased risk of transmitted window-fase syphilis
  or untested syphilis,
  via uncooled or shortly cooled blood components.

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Thank you