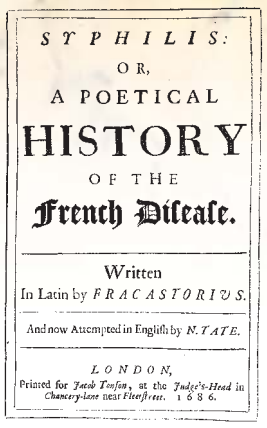
The Great Pox

A History of Syphilis and its Laboratory Diagnosis


SYPHILIS:
OR,
A POETICAL
HISTORY
OF THE
French Diseale.
Written
In Latin by FRACASTORIUS.
And now Attempted in English by N. TATE.
LONDON,
Printed for Jacob Tonson, at the Judge's-Head in Chancery-lane near Fleet-street. 1686.

New World – New disease

In 1492 Christopher Columbus sailed west and found an undiscovered New-World. On his return he and his companions brought back many strange tales and treasures and, it is widely believed, syphilis – the GREAT POX.

Over the next few decades this infection spread like wildfire throughout the known world and was, for four and a half centuries, the HIV/AIDS of its day. It was feared, took no account of the race, creed or social standing of its victims and destroyed the lives, well being and reputations of millions of people. Only the use of penicillin for the treatment of this infection from the mid 1940's allowed medical science the opportunity to treat, cure and bring this scourge under control.

This presentation aims to give an insight into the history of the disease, the role of Medical Laboratory Science and Scientists in elucidation of the cause and its laboratory diagnosis.

The Fleet of Columbus

Not all Historians agree that syphilis was a new disease many believe that it was already present in Old World. The arguments are complex and only summarised below

- The first documented outbreak of syphilis, or "the great pox," followed the siege of Naples by the French in 1494, giving rise to the legend that Columbus' men had brought the disease back from the New World.
- It is said that there is no evidence of treponematoses on mainland Europe prior to 1492.
- However the bones of a medieval woman found in a churchyard in Rivenhall, near Chelmsford Essex, who died between 1296 and 1445, show signs of what is believed to be syphilis, already present in England before Columbus discovered the New World.
- But skeletons have also been found in the United States, which are believed to show that the disease was present before 1492.
- There is disagreement whether it is possible to reliably differentiate Yaws and Syphilis in ancient skeletons. Unfortunately as yet there is no DNA evidence to prove or disprove which of these trepanematoses is involved.
- There are allusions to "Venereal Leprosy" and "Congenital Leprosy" before 1492 suggesting that some medieval "lepers" might have been syphilitics.
- But Milanese physicians had been attributing death to Leprosy since at least 1452 and did not attribute any to the 'French Disease', [Syphilis] until 1503.
- Some hold the view that this 'outbreak' was the result of large scale population movements across Europe during times of war leading to new strains being moved around. There were large armies amassing in several areas and large-scale troop movements. Wherever there are armies there are likely to be illicit sexual activities that spread sexually transmitted diseases; these, coupled with troop movements, hastened the spread of syphilis. Descriptions recorded by first-hand observers at the time tell of patients with many pustules, rather than the single pustule usually seen today, and with the symptoms of rash and painful swellings that are now associated with secondary syphilis occurring much more rapidly than they do today. After about 50 years, this particularly virulent form of syphilis seems to have subsided and was replaced by the more slowly progressing form that we see today.
- What everyone does agree on is that the form of syphilis which spread at the time was much more dangerous and deadly than it had been in the past or was to become in the future. Spread by sexual contact, it was highly contagious and caused pustules, pain, and itching of the skin, often spreading all over the body. These symptoms were followed by intense pains and a deterioration of the bones. This stage of the disease often ended in death. A possible explanation for these symptoms is not that they were caused by a new disease, but by a more virulent or deadly form of a long-occurring organism. This is not an uncommon phenomenon among bacterial infections; with a modern-day example being that of toxic shock strains *Staphylococcus aureus*, arising in the 1980s.
- Another view is that it did arise in the New World but, it was brought back by the Vikings, and it was through them that it spread and became established in Europe.

Christopher Columbus

What's in a Name?

It has been called "*The Scourge of the Renaissance*".

It was a disease greatly feared by the Tudors who called it ***The Great Pox*** to differentiated it from the ***Small Pox***.

In 1530 an Italian pathologist, **Hieronymus Fracastorius /Girolamo Fracastoro** (1478?-1553), wrote a poem entitled ***Syphilis Sive Morbus Gallicus (On Syphilis, or the French Disease)*** which described the plight of a mythical shepherd lad named Syphilis afflicted with the disease as a punishment for cursing the gods. The poem recognized the venereal nature of the infection and was a compendium of knowledge of the time regarding the disease.

Paracelsus (1493?-1541) called the new venereal disease **"French Gonorrhoea"** and suggested that it arose through sexual intercourse between a leprous Frenchman and a prostitute with gonorrhoea

Lues Venereum. Lues from the Latin for plague, Venereum – associated with sex

It has been called the "great mimic" because its symptoms are similar to those of many other diseases. In fact, before the introduction of specific bacteriological and immunological tests, many physicians believed that **"whoever knows all of syphilis knows all of medicine".**

The disease had many names, most were xenophobic:

The Germans and English called it:
"The French pox"

The Russians called it:
"The Polish sickness"

The Poles called it:
"The German sickness"

The French called it:
"The Neapolitan sickness"

The Flemish, Dutch, Portuguese, and North Africans called it:
"The Spanish or Castilian sickness"

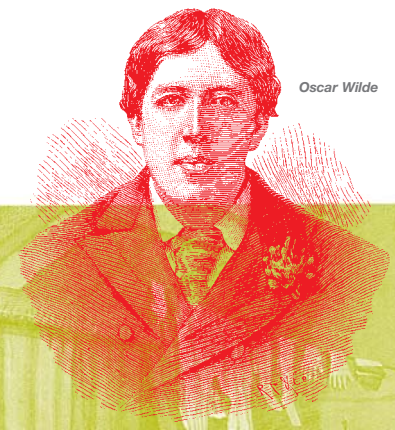
The Japanese:
"The Canton rash" or "The Chinese ulcer"

Persian Physician Baha'al-Dawal called it:
"The Armenian Sore" or "The Frankish Pox"

Syphilis and Blood Transfusion

King Henry VIII

Oscar Wilde



The Harlot's Progress - Hogarth

Franz Schubert

The early practice of blood transfusion usually involved connecting the donor directly to the patient creating a serious problem through the potential transmission of syphilis from donor to recipient.

The introduction of effective anticoagulation and storage of blood during the 1914-18 War, resulted in the transmission of syphilis by transfusion being virtually eliminated.

In two reports, published in 1941, Bloch[1] and Turner & Diseker[2] showed that Treponema pallidum (the causative organism of syphilis) did not survive in blood stored at 50ºC.

It is of interest that despite this knowledge, routine testing of donor blood for syphilis is still carried out in the United Kingdom. The continuation of this practice is based on the increasing use of blood components (rather than red cells) especially platelets, which are stored at 22ºC prior to transfusion.

The initial techniques for screening blood for syphilis were the Kahn Test and later, the Price-Precipitation Test (PPR) which were not wholly satisfactory as false negative results occurred due to the prozone phenomenon. The Berger – Kahn slide test was also used, which although not affected by prozone effect, unfortunately gave rise to frequent false positive results.

A review of techniques was undertaken by King[3] and Wilkinson[4] in 1960 and 1969 which resulted in recommendations to Blood Transfusion Centre Directors to employ the Treponema pallidum Immobilisation test (TpI) and the Wasserman Reaction using refined cardiolipin antigen for improved specificity and accuracy.

A simple slide test devised at the Venereal Disease Reference Laboratory (VDRL) became widely used for screening blood donations. This test remained popular until fully automated screening of blood was introduced. The manual VDRL test did not transfer to automation and the Treponema pallidum Haemagglutination test (TpHA) became the method of choice, following the publication of a paper by Barbara[5] et al in 1982. Subsequently, Enzyme Linked Immuno-absorbent Assay (ELISA) automated methods which give increased specificity and sensitivity, remain in use for blood screening to the present.

Impact on Society

Syphilis in the Army and Royal Navy

1493 seems to be the pivotal date for the first incidence of syphilis, when Columbus and his sailors returned to Europe from the Americas, although this is a contentious point, even to this day. The disease grew to epidemic proportions among knights and foot soldiers alike, reaching Italy and Spain by 1494 and arriving in England by 1497. It had catapulted the disease from beyond the ocean into an epidemic that would last more than 500 years.

In 1903 the Advisory Board for Army Medical Services requested an inquiry into "The Treatment of Venereal Diseases in the Army and to Inquire into the Treatment of the Itch (Scabies)". The final report was published in February 1906 under the title "The Treatment of Venereal Disease and Scabies in the Army". The plan of investigation was (a), To ascertain the exact references and records at headquarters dealing with the subject, and b), To classify this information. This involved methods of prevention and measures adopted for prophylaxis.

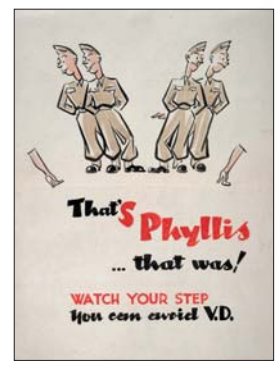
Treatment by mercury was quoted as being the only known drug that had a distinct effect in curing the disease. The evidence gained by experience was, at that time, unanimously in favour of mercury. It included intra-muscular injection, injection of soluble salts, intravenous injection of mercurial salts, by mouth and mercurial baths. Other methods recorded administration by inunction, application of plastars, use of iodides, heat and open air. Other drugs and methods of treatment were secondary. In every case of non-mercurial treatment results appeared to be unsatisfactory.

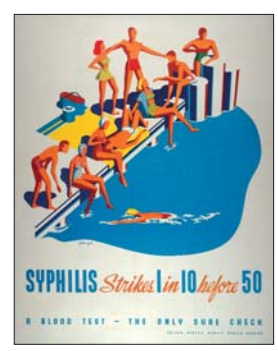
Army records appear to first record the incidence of syphilis in their men in 1881. Records from 1888 show that 30% of a strength of 101,695 to be infected with venereal diseases (including syphilis, soft chancre and gonorrhoea). Of these, 41 were constantly sick and 6% invalids. The number of candidates for recruitment that were refused on account of syphilis, per 10,000 offering for enlistment, ranged from 160 in 1870 down to 16 by 1910.

Testing was by the original method of Wassermann, Neisser and Bruck (1906) for the WR, with modifications considered for patients under treatment "to recognise the last traces of Wassermann substance".

The final report concluded with a design for a treatment block and a schedule for existing hospitals. "The measures to be adopted in each case must be carefully considered and adapted to existing conditions, with due regard to efficiency and economy". (Nothing new here!)

A Royal Commission on Venereal Disease was established in 1916 to consider syphilis, gonorrhoea and soft chancre. The report contained a memorandum on the results of treatment of venereal disease with Salvarsan and Neo-Salvarsan in the Royal Navy. 4.203 cases were treated and 9,912 injections were given. The course of treatment for primary, secondary and tertiary syphilis was monitored by the WR. Two deaths occurred due to neo-salvarsan and one following a second injection of salvarsan, which was complicated also with diphtheria.





In a report by Lieut. Colonel Gibbard RAMC he listed the chief causes of a decrease of syphilis in the Army as:

1. Improved methods of treatment
2. Lectures and individual talks
3. Increased temperance
4. Increased attractions in barracks
5. In India the provision of the Cantonment Act

Here the reduction of venereal disease tell from 298 in 1900 to 117 in 1906 based on the admission ratio per 1000 strength.

In further reference to temperance, "Many patients contract the disease whilst under the influence of drink who would not otherwise have done so, as they then fell an easy prey to the first bad woman they meet". In 1901 the daily consumption of beer per head of drinking men (British troops in India) was two quarts. By 1906 this had reduced to 2 ? pints. Similarly admissions for alcoholism had fallen.

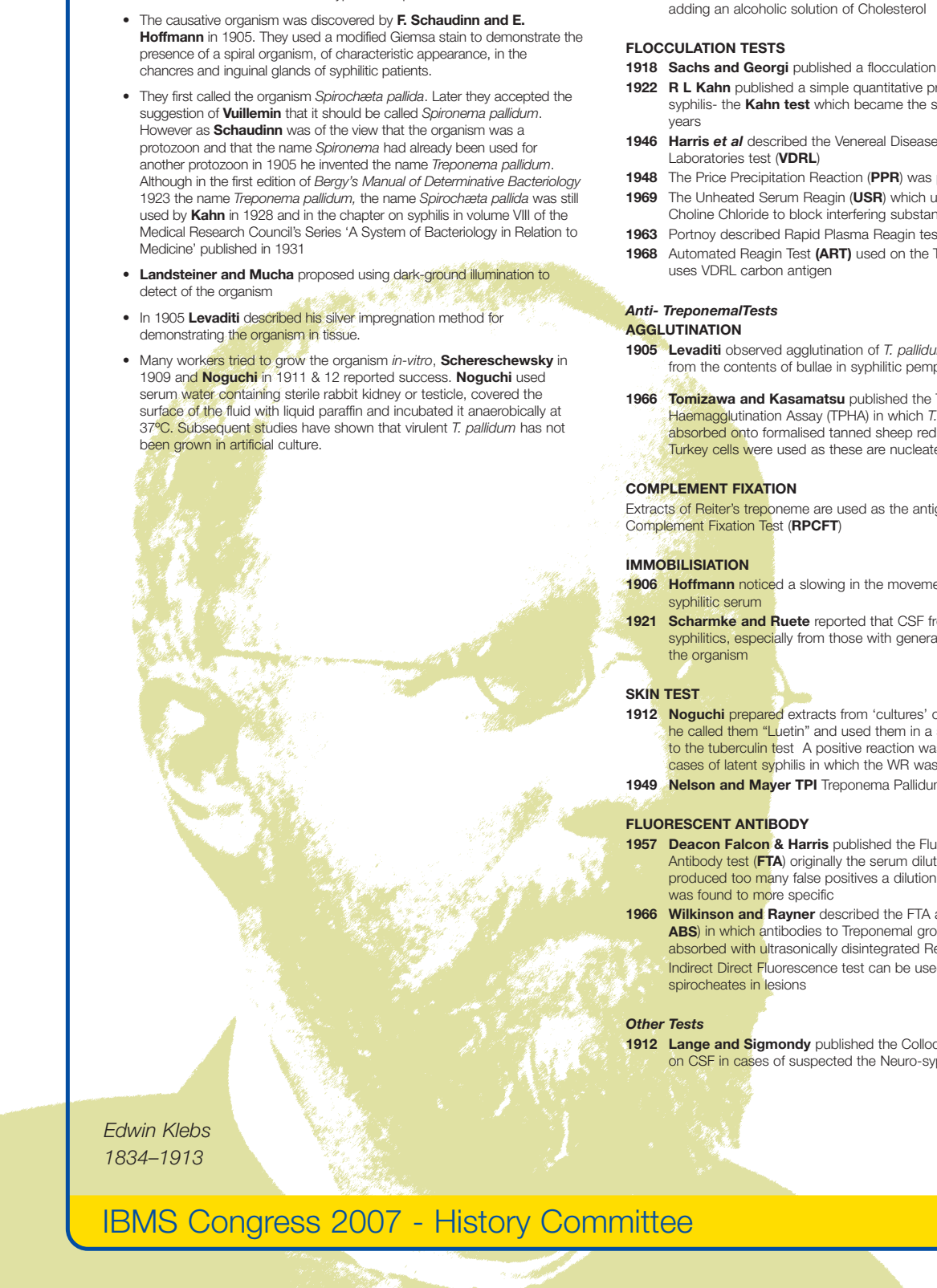
The report concludes that if efficient treatment is carried out in the primary stage, syphilis can be abated in the vast majority of cases.

Discovery & understanding

Fritz Schaudinn
1871–1906

Discovery of the Cause

- **Edwin Klebs** in 1879 was apparently the first to see spirochaetal bodies in syphilitic material and to transmit the disease to monkeys
- **Haensell** in 1881 was the first to convey the disease to lower animals; by inoculation of the eye he produced local lesions in the rabbits
- **S. Lustgarten** 1884 & 1885 used staining methods to demonstrate **'Syphilis bacilli'** in syphilitic sores of the genitals and other sites. But it was shown that similar if not identical bacilli were present in normal secretions
- The studies by **Metchikoff and Roux** published between 1903 & 1905 showed that syphilis was transmissible to apes.
- These findings were confirmed by **Lassar** (1903), **A. Neisser** (1904) and **Finger and Landsteiner** (1906)
- **E. Bertarelli** in 1906 & 7 demonstrated the production of syphilis in the eye, and **Parodi** in 1907, the testicle of rabbits.
- Filtration experiments by **Klingmüller and Baermann** in 1904 demonstrated that the cause of syphilis was particulate.
- The causative organism was discovered by **F. Schaudinn and E. Hoffmann** in 1905. They used a modified Giemsa stain to demonstrate the presence of a spiral organism, of characteristic appearance, in the chancres and inguinal glands of syphilitic patients.
- They first called the organism *Spirochæta pallida*. Later they accepted the suggestion of **Vuillemin** that it should be called *Spironema pallidum*. However as **Schaudinn** was of the view that the organism was a protozoon and that the name *Spironema* had already been used for another protozoon in 1905 he invented the name *Treponema pallidum*. Although in the first edition of *Bergy's Manual of Determinative Bacteriology* 1923 the name *Treponema pallidum,* the name *Spirochæta pallida* was still used by **Kahn** in 1928 and in the chapter on syphilis in volume VIII of the Medical Research Council's Series 'A System of Bacteriology in Relation to Medicine' published in 1931
- **Landsteiner and Mucha** proposed using dark-ground illumination to detect of the organism
- In 1905 **Levaditi** described his silver impregnation method for demonstrating the organism in tissue.
- Many workers tried to grow the organism *in-vitro*, **Schereschewsky** in 1909 and **Noguchi** in 1911 & 12 reported success. **Noguchi** used serum water containing sterile rabbit kidney or testicle, covered the surface of the fluid with liquid paraffin and incubated it anaerobically at 37ºC. Subsequent studies have shown that virulent *T. pallidum* has not been grown in artificial culture.



Edwin Klebs
1834–1913

Laboratory Diagnostic Methods

Reagin Tests

COMPLEMENT FIXATION TESTS

1901 **Bordet and Gengou** describe the complement fixation reaction

1906 **Wassermann, Neisser and Bruck** described a complement fixation reaction using aqueous extract of foetal syphilitic liver as antigen – *Wassermann test. Wassermann Reaction* (**WR**)*, Bordet-Wassermann Test*

1907 **Marie and Levaditi** used aqueous extracts of normal liver and other organs as antigen. They found that an alcoholic extract was better

1908 **Porges and Meier** showed that that the reacting substance was the lethicin fraction of lipoids, soluble in alcohol but not acetone

1924 **Browning & Mackenzie** improved the sensitivity of the test by adding an alcoholic solution of Cholesterol

FLOCCULATION TESTS

1918 **Sachs and Georgi** published a flocculation test

1922 **R L Kahn** published a simple quantitative precipitation reaction for syphilis- the **Kahn test** which became the standard test for many years

1946 **Harris *et al*** described the Venereal Diseases Research Laboratories test (**VDRL**)

1948 The Price Precipitation Reaction (**PPR**) was published

1969 The Unheated Serum Reagin (**USR**) which uses VDRL antigen plus Choline Chloride to block interfering substances in plasma

1963 Portnoy described Rapid Plasma Reagin test (**RPR**)

1968 Automated Reagin Test **(ART)** used on the Technicon Auto-Analyser uses VDRL carbon antigen

Anti- TreponemalTests

AGGLUTINATION

1905 **Levaditi** observed agglutination of *T. pallidum* in specimens made from the contents of bullae in syphilitic pemphigus

1966 **Tomizawa and Kasamatsu** published the Treponema pallidum Haemagglutination Assay (TPHA) in which *T. pallidum* antigens are absorbed onto formalised tanned sheep red cells, later Chicken or Turkey cells were used as these are nucleated and settle faster.

COMPLEMENT FIXATION

Extracts of Reiter's treponeme are used as the antigen in the Reiter Protein Complement Fixation Test (**RPCFT**)

IMMOBILISIATION

1906 **Hoffmann** noticed a slowing in the movements of *T pallidum* in syphilitic serum

1921 **Scharmke and Ruete** reported that CSF from secondary syphilitics, especially from those with general paresis, immobilised the organism

SKIN TEST

1912 **Noguchi** prepared extracts from 'cultures' of *Treponema pallidum* he called them "Luetin" and used them in a skin test in a similar way to the tuberculin test A positive reaction was often obtained in cases of latent syphilis in which the WR was negative

1949 **Nelson and Mayer TPI** Treponema Pallidum Immobilisation Test

FLUORESCENT ANTIBODY

1957 **Deacon Falcon & Harris** published the Fluorescent Treponemal Antibody test (**FTA**) originally the serum diluted 1 in 5 but this produced too many false positives a dilution of 1 in 200 (**FTA 200**) was found to more specific

1966 **Wilkinson and Rayner** described the FTA absorbed test (**FTA-ABS**) in which antibodies to Treponemal group antigens were absorbed with ultrasonically disintegrated Reiter treponemes

Indirect Direct Fluorescence test can be used for the detection of spirocheates in lesions

Other Tests

1912 **Lange and Sigmondy** published the Collodial Gold Sol Test for use on CSF in cases of suspected the Neuro-syphilis

'WR DAY'

From the 1930s until the end of the 1960s in most routine Bacteriology Laboratories there was one day a week known as 'WR Day'. This was the day on which the WRs – the Wasserman Reaction a complement fixation test for syphilis and Khans a flocculation test for syphilis - were done; and until it was known that they had worked it was often a tense day. This was particularly so when a Junior Technician was allowed to do the tests on their own for the first time. This was a significant 'rite of passage' in a bacteriology technician's life. If all went well it would mean that they were ready to sit their Final and if successful become a qualified Technician – with a pay rise!

For the WR

Materials & Equipment

- 56ºC Water bath, 37ºC water bath
- Racks for 3 x ? inch glass tubes
- 37ºC incubator
- Donald's Dropper – a separating funnel fitted with a short glass tube 76mm outer diameter (at 30 drops per minute this delivers 0.11ml, i.e. One volume)
- Pasteur pipette with an end diameter equal to 56 hole of a Starrett-Morse gauge (Delivers 0.022ml of serum, i.e. 1/5 volume)
- 100 ml glass measuring cylinders, graduate 10ml pipettes

Reagents

- 0.9% Sodium Chloride (zinc free)
- Complement (C') – Guinea-pig serum preserved by Richardson's method
- Wasserman antigen
- Control sera
- 2.5% suspension of Formolised Sheep cells sensitised with 5 MHD* amboceptor
- 3 x ? inch glass tubes or WHO Perspex trays

*Minimum Haemolytic Dose

Method

9.00am Inactivate test and control sera in 56ºC water bath to for 30 min.
Wash sheep cells (RBCs) x 3, check PCV and make a 5% suspension
Run out diluent saline for tests and for Complement titration (C'T) with Donald's Dropper
Dilute antigen leave to ripen for 20 min

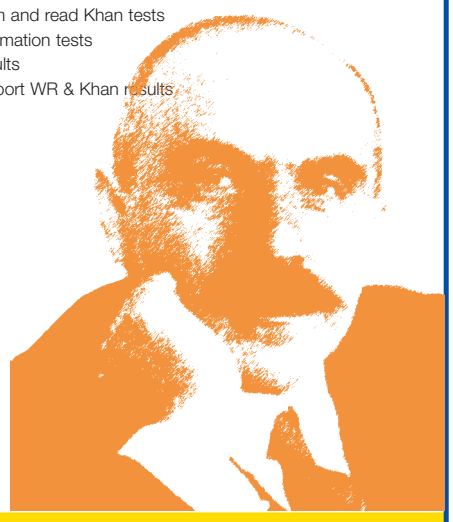
9.30am Remove sera for 56ºC and add control sera to C'T
Add antigen to C'T
Prepare 10 fold dilutions of complement from 1:10 – 1:70 and add to C'T
Incubate C'T at 37^{O}C for on hour
Add 1/5th volume test and control sera to diluent saline
Prepare sensitised RBCs

10.00am Go to coffee

10.30am Remove C'T from incubation add 1volume sensitised RBCs, then reincubate at 37^{O}C for 15 mins, shake and incubate for a further 15min
Add one volume of antigen to test wells and one volume diluent to control wells

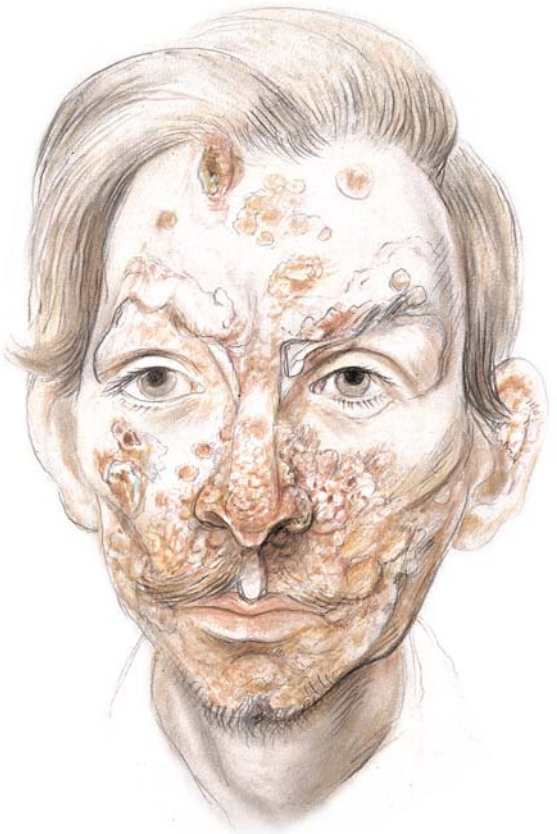
11.00am Read C'T titration, calculate 1MHD C'
Pepare1.25 MHD and 1 MHDC' dilutions
Add 1 volume 1.25 MHD C' to test wells
Add 1 volume 1MHD C' to control wells
Incubate and add RBCs as in C'T
Set up, perform and read Khan tests
Do Khan confirmation tests
Read WR Results
Record and report WR & Khan results
Tidy up

13.00pm Go to Lunch



August von Wassermann
1866–1925

Symptoms of Syphilis



Sexually transmitted

Primary Disease

- A local infection involving mucocutaneous sites and their draining lymph nodes
- Incubation 10days to 10 weeks
- Painless ulcer with a border and base of induration
- Eventually clears up

Secondary Disease

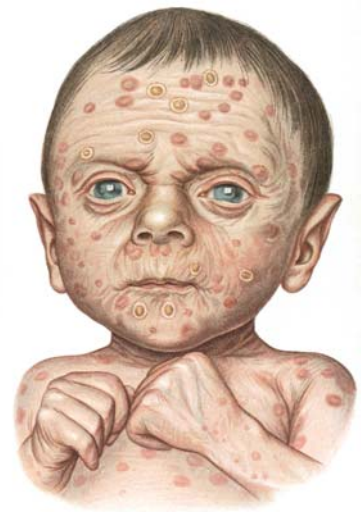
- Six to eight weeks after primary lesion
- Spirochaeteamia with fever, rash and generalised lymphadenopathy.
- Rash is generalised maculopapular involving the palms and soles
- 'Snail track' ulcers in the mouth
- May also be meningitis, arthritis, arthralgia and iritis or retinitis

Latent Disease

- Asymptomatic phase which may persist for years
- Slow tissue damage occurs, some show signs of CNS involment

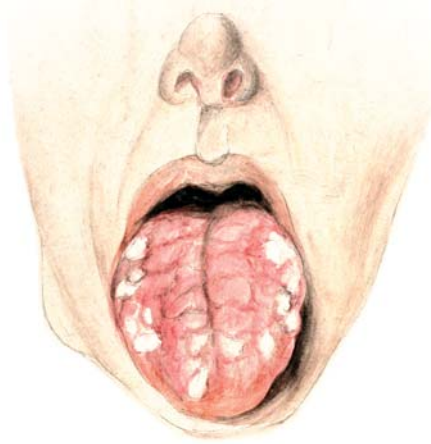
Tertiary Disease

- May occur after one year or may take 10 years to develop
- It affect many systems of the body
- Patients develop gumma, which is an indolent ganulomatous lesion which may undergo central mucoid degeneration
- Skeletal damage may give rise to Charcot joints
- paresis of the insane may occur giving rise to syphilitic psychosis
- Tabes dorsalis lesions in the spinal cord resulting in a typical shuffling gait
- Cardiovascular disease can include aortitis, aneurism aortic regurgitation



Pregnancy

- In pregnancy syphilis infection can result in miscarriage, premature birth, still birth or infant death



Congenital

Infants born with syphilis can suffer from

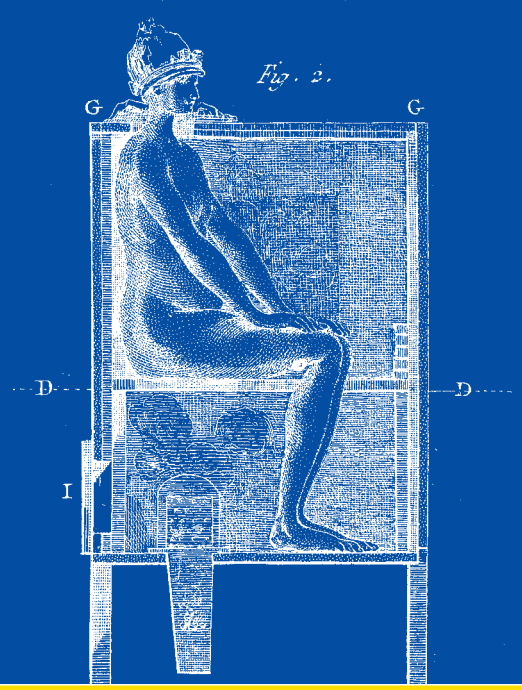
- Deafness
- Hutchinson' teeth and facial disfigurement
- Interstitial Keritits
- Hepato-splenomegaly
- Rashes
- Sabre shins
- Saddle nose
- Etc etc

Symptoms & Treatment

Wasserman

Erlich & Hata

Fleming



Historical Treatment of Syphilis

The earliest documented treatment of the pox (syphilis) involved the use of mercury from the early part of the XVI century onwards. There are accounts of ointments and balms, almost certainly of a mercurial base, being used by Arab physicians, to treat 'yaws' at the time of the Crusades in the XII century. Treatment of leprosy with mercury preparations was known at this time and possibly syphilis also?

There are numerous descriptions of topical and oral preparations being administered, some of the effects of the treatment being as hideous as the disease itself.

The other treatment described alongside mercury in the XVI century is gaiac.

Gaiac is powdered wood from the guaiacum, a tropical tree found in the Caribbean and Central American region. The powdered wood is made into a potion by boiling it down to a decoction, which is administered in large doses after the patient has previously been given purgatives and dieted to a meagre ration over several weeks.

This treatment took place in a heated room with the patient wrapped in blankets to induce sweating until 'the sickness had been rooted out'

There was strong opinion for and against both treatments and many scholars reported that both treatments were often administered together, rather than a single remedy.

However, mercury treatments held sway for around 300 years, even showing a revival in the1860's when mercury preparations began to be injected despite the knowledge of the side effects of these treatments.

In Victorian times the advent of commercial potions to treat almost anything was rife and many preparations were offered to treat syphilis including potassium iodide, which was described in the Lancet in 1835.

The first great breakthrough in the treatment of syphilis involved the use of arsenic compounds in the twentieth century, although arsenic had first been cited as a cure as early as 1498.

In 1909, Paul Ehrlich and Sahachiro Hata created 'Compound 606' an arsphenamine, which was the constituent of the drug they called Salvarsan. This was shown to destroy Treponema pallidum, the causitive organism of syphilis infections.

The use of bismuth, as an effective treatment was described by Sazarac and Lavaditi in 1921, who used tolerable doses to treat their patients, although Balzer had first described its use in 1899.

Undoubtedly, the turning point in the treatment of syphilis was the use of the antibiotic, penicillin, first described by Alexander Fleming in 1928. Following the work of Chain and Florey to purify the substance for safe human use, commercial production was possible.

Mahoney, Arnold and Harris, successfully treated four cases of syphilis in 1943 in U.S.A, with the newly produced drug. This treatment found rapid acceptance especially by military doctors throughout the forces in the Second World War.

The effectiveness of penicillin was demonstrated against all stages of the infection and in a timescale of a few weeks, compared with the years of treatment with previous remedies.

IBMS Congress 2007 - History Committee