NEISSER AND NEISSERIAN PRINCIPLES IN VENEREOLOGY*†

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I value very highly the honour of having been invited to give the opening address at this centenary celebration of Neisser's birth, but I am very acutely conscious of my defects as an historian and hope that members of the distinguished company here to-night will fill the gaps that are inevitable in my story, because only with your help will the Osler Club honour worthily the memory of a man who used his outstanding abilities in the service of mankind to such a degree and with such success as to entitle him to high prominence in every history of medicine; indeed in every history of social endeavour.

My brief stipulates not much biography and restricts me, by my own wish I may say, to only one of the fields in which our hero shone, but in this field I may wander a little from the strictly Neisserian path to comment on contemporary events in venereology which may not perhaps be now familiar to you, but have always seemed to me to be interesting and instructive.

For a number of the facts in my condensed biography I am indebted to Neisser's "Beitrag, zur Pathologie und Therapie der Syphilis" (Neisser, 1911a), and to the obituary which appeared in the *Lancet* (1916) Neisser's birthday was on January 22, 1855, which I calculate fell on a Monday, whatever that may have portended. He was the son of a physician, an advantage in respect of family atmosphere which, from personal experience, I have always thought very valuable to a member of our profession.

He became M.D. at the age of 22, his thesis being a monograph on diseases due to *T. echinococcus*, thus disclosing early his taste for precision in instruments of diagnosis, microscopy in particular.

He quickly became assistant to Oskar Simon, the Director of the Department of Dermatology in the University of Breslau, and in 1879, 2 years after qualification, at the age of 24, he announced in a preliminary communication (Neisser, 1879), that he had seen in gonorrhoeal pus certain cocci of distinctive

appearance which he regarded as the cause of the disease. Thus the gonococcus was presented to the world, and Neisser's priority in its discovery is universally recognized in the fact that today the proper name of the gonococcus is *Neisseria gonorrhoeae*, and micro-organisms having similar morphological characteristics are Neisseriaceae.

Five years after qualification, in spite of the fact that one does not usually become entitled to such a position until one has become much more decayed than one expects to be at the age of 27, he succeeded Oskar Simon and became Professor Extraordinary and Director of the Department of Dermatology. The events justified such an apparently courageous selection because Neisser proved to be no disciple of the learned Dr. Pangloss, who, you know, believed that everything was for the best in the best of all worlds. On the contrary, he showed himself to be a born reformer and a "live wire" in his ability to get things done; for example, by 1892 he had got the hitherto primitive Allerheiligen Hospital brought thoroughly up to date.

In 1899 and 1902, together with the foremost workers in the field of venereology, he attended the historical international conferences in Brussels at which great men now revered in the world of social endeavour, impressed by the evil effects of venereal diseases, sought to convince the world that something ought to be done about them and enunciated principles of combating these diseases which largely hold good to-day.

At the conference in 1899, Neisser made a powerful plea for greater attention to be given to gonorrhoea; a translation of his paper, published in *Medical News* (1900), was entitled "Gonorrhoea; its Dangers to Society". It ended:

"The first step in reform is for the public to know and to appreciate the dangers and the significance of venereal diseases. More effectual than all legal or police regulations will be the individual protection afforded by our present knowledge in this matter, if physicians and the laity will but realize our modern advances in this subject. I have not the slightest doubt that the present danger which

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† Read before the Osler Club to celebrate the centenary of the birth of Albert Neisser on January 22, 1855 (with some additions).

threatens the human race from gonorrhoea will be greatly lessened and the spread of the disease distinctly limited as the result of the discussion here."

In 1902, Neisser founded the German Society for combating Venereal Disease, 12 years before the corresponding body, The National Council for combating Venereal Diseases, was formed in Great Britain.

In August, 1903, stimulated by the work of Metchnikoff and Roux on experimental syphilis in monkeys and doubtless by similar researches in Vienna and St. Petersburg, Neisser began his own studies in Breslau. He soon found a number of practical disadvantages of conducting a research on monkeys in Europe. The chief were the cost of the animals and the uncertainty of their life in the European climate as against the chronicity of syphilis. So he planned an expedition to the tropics, where the monkeys he wanted to use were plentiful and in natural surroundings, and he and Dr. Baermann finally set out for Java in the middle of January, 1905, accompanied by their wives. In May, 1905, they were joined by Dr. Halberstaedter in Batavia, where the research had been set up. According to Neisser's "Beiträge" (Neisser, 1911a) he might have carried out his work in Singapore or thereabouts, but the English authorities did not favour this project. He returned to Breslau in October, 1905, but retained control of the Java work by weekly letters and a further visit in November, 1906, continuing the work there until 1907. Altogether his experimental work on syphilis in Batavia and Breslau lasted from 1903 to 1909. I am not sure how the research was financed in 1905, but think it must have been from his own pocket because in the "Beiträge" already mentioned he was careful to acknowledge outside assistance from 1906 inclusive onwards. His letter to the Reichs Chancellor asking for Government support should be read by anyone wanting to wring money out of a cold-blooded Treasury for special work in venereology; it ran to about 7,000 words and amongst the arguments for support was, besides the plea that the work would be to the nation's honour, the hope that the research would result in the discovery of a prophylactic vaccine against contraction of syphilis and also perhaps as a therapeutic anti-serum; I will revert to that later. Neisser also received assistance from a private benefactor and from two German shipping lines, the Hamburg-Amerika and the Norddeutscher Lloyd. The Government grants for his experimental work amounted to 230,000 marks.

His experimental work and that of his colleagues from 1903 to 1909 is fully described in the

"Beiträge".* I was interested to note in some of the illustrations, for example, No. 19 on p. 23 and No. 8 on p. 13, that the workers handling these syphilitic monkeys wore no gloves. It amused me very much because I never wore gloves at the Rochester Row Hospital from 1909 to 1914, and was often told what a fool I was for running such risks.

Neisser's experimental work added very greatly to existing knowledge on the behaviour of syphilis in the body and on the body's reaction to the parasite. As one result of it, he became frankly sceptical of any success resulting from efforts to immunize against syphilis or of producing a therapeutic anti-serum. His views on the prospects of obtaining a prophylactic vaccine were shared by Metchnikoff but this will o' the wisp has lately attracted some leaders in syphilology. They ought to read Neisser's and Metchnikoff and Roux's articles on experimental syphilis. History has its uses! One strong objection to vaccination against syphilis, which was voiced I think by Metchnikoff, is that a vaccine might make the body anergic to attack by the spirochaete so that, although infested and swarming with these germs, it would not respond with a surface lesion, just as mice and a certain proportion of rabbits do not respond though their bodies are swarming with the germ.

During Neisser's absence in Java, the causal organism of syphilis, which the pundits now say we must call *Treponema pallidum*, was discovered by Fritz Schaudinn. On the Schaudinn-Hoffmann combination † and its origin I hope to have time to speak a little later.

Ehrlich's dramatic reaction to the news of Schaudinn's discovery has been graphically described in Fraulein Marquardt's biography of Ehrlich (Marquardt, 1949), which ought to be read by everyone interested in medical history. His delight over it was just a little tempered by regret that the honour of it had not fallen to his great friend, Neisser. The incident testifies to the respect and friendship which the great Ehrlich felt for his friend, Albertus Magnus, as he called him, and also to the bigness of Ehrlich, who saw in the discovery of the micro-organism of syphilis a bright prospect for the forging of antisyphilitic weapons.

In Java, Neisser's team, notably Baermann, quickly confirmed Schaudinn's discovery and his experimental work led to his association with Wassermann and Bruck in the application of the Bordet-Gengou phenomenon of complement fixation‡ to the diagnosis of syphilis. For what better

* A copy brought by Dr. Worms was on show at the meeting.

† Schaudinn and Hoffmann (1905a, b, c).

‡ Bordet and Gengou (1901).

negative control in such a test could one have than a monkey which had not been inoculated with syphilis, and what better positive control than one which, having been negative had been inoculated some weeks previously and had responded to the inoculation? Also the glands, bone marrow, etc., of such an inoculated animal could be a convenient source of antigen in such a test. We know now that the antigen made of such tissues was not purely spirochaetal, as Wassermann and Bruck quite naturally imagined, but Neisser's monkeys must have seemed to Wassermann and Bruck heaven-sent material for their experiments in complement fixation for the diagnosis of syphilis.*

In 1907, the 25th anniversary of Neisser's professorship was marked, *inter alia*, by the publication of two volumes of the *Archiv für Dermatologie und Syphilis* (Wien), Nos 84 and 85 entitled *Festschrift Neisser*, to which over sixty of his pupils contributed original articles. They and the laudatory dedication written by Harttung, Jadassohn, and Schäffer (1907) testify to the affection and respect in which Albert Neisser was held by these many workers, themselves mostly notable figures in the world of dermatology and syphilology. An even greater tribute was paid in 1916 as I will mention later. In 1907 also he was made Professor-in-Ordinary.

After the discovery of "606", Neisser quickly became convinced that generally this great new remedy required the assistance of mercury, and he is thus in my mind not only the Father of the Gonococcus, as he was often called, but also one of the fathers, and a very influential one at that, of what is now often called the synergistic treatment of syphilis. I hope to speak at greater length on this subject a little later, but may say here that his views on it may conveniently be read by English-speaking students in the text of his Cavendish lecture delivered before the West London Medico-Chirurgical Society on June 27, 1911, and published in the *West London Medical Journal* (Neisser, 1911b). That lecture also discloses the high quality of Neisser's reasoning and the wisdom of his views. After it he received from the President of the West London Medico-Chirurgical Society, Dr. Phineas Abraham, the first Phineas Abraham gold medal of the Society given every 3 years for work of outstanding merit in medicine.

Neisser died on July 31, 1916. For a number of years he had suffered from diabetes and renal calculus, but in spite of these crippling handicaps he retained a lively interest in his work almost to the very end. Although he had renal colic with cystitis

he insisted on attending an exhibition in Brussels in the month he died. On his return home he set out to attend a meeting in Düsseldorf but was forced to retire to Berlin for an operation for stone in the bladder. Two days later he returned to his beloved Breslau, but sepsis and high fever developed and on July 31, as stated, he died in coma.

In the *Archiv für Dermatologie und Syphilis* (1916) 55 pages were devoted to tributes to Neisser's great qualities, and besides the 53-page account of his achievements by Jadassohn (1916), who succeeded him, was signed testimony to the affection and respect in which he had been held by over 140 of his old pupils now holding more or less important positions in different parts of the world.

Before I discuss in more detail work in venereology with which Neisser was more or less closely associated, I feel I cannot do better than quote the beginning of the obituary in the *Lancet* (1916), published, it should be remembered, at a time when rivers of hate were flowing between this country and Germany. Despite this, the *Lancet* said,

"By the death of Albert Neisser on July 30,* Germany lost one of her greatest scientists and the whole world is poorer for the loss."

According to the *British Medical Journal* (1917) he left his villa to the city of Breslau to be maintained as a museum for contemporary works of art and the rooms to be used for high-class concerts.

I should like now to speak at greater length about Neisserian principles in venereology and, whilst I do so, perhaps I may be pardoned if in passing I digress here and there to enlarge a little on discoveries in venereology which were made in Neisser's time.

In my mind Neisser's contributions to venereology which stand out most forcibly, apart from his very valuable work on experimental syphilis, are :

- (1) His insistence on the control of the treatment of gonorrhoea under guidance by microscopical examination of discharge.
- (2) His stand against the indiscriminate use of astringents in the treatment of gonorrhoea.
- (3) His very early insistence on the concurrent use of mercury, preferably in the form of insoluble suspensions with arsphenamine remedies in the treatment of syphilis.

Insistence on microscopic tests debunked a host of claims to cure gonorrhoea in double-quick time which were made by many authors who disdained or were ignorant of such a method of control and were still going strong in this and other countries until some years after I became employed in venereology. Since I undertook the delivery of

* Wassermann, Neisser, and Bruck (1906).

*The date given in the *Arch. Derm. Syph. (Wien)* was July 31.

this address, I have been interested to study the methods of treating gonorrhoea which were being practised in this and various other countries from the time of discovery of the gonococcus and afterwards right up to the war of 1914-18 and later, and I have been astonished at the claims made for them, claims which could not possibly have been supported by proper tests of cure such as were insisted upon by Neisser and are practised in all good research centres to-day.

I must not spend too much time on this subject, but may say that some of the treatments would make the modern venereologist's hair stand on end. For example, the late Sir Watson Cheyne in an article on the abortive treatment of gonorrhoea (Cheyne, 1882) mentioned a method used by Debeney in which a solution of silver nitrate, 64 grains to the ounce, was injected into the urethra. Apparently Ricord used a strength of 16 grains to the ounce, but by about 1882 a more popular line was an injection even so dilute, Watson Cheyne said, as 1 in 3,000. Cheyne at that time favoured a medicated bougie of eucalyptus oil and iodoform and at one time, following the advice of Robert Koch, incorporated in the bougie, presumably of 15 grains, one-sixteenth of a grain of mercury perchloride, which would give a strength of 1 in 240 perchloride. He does not seem to have remained favourably impressed by the results of these forms of treatment. One author claimed to cure the disease in an average of 6 days by injecting sulphurous acid in a dilution of 1 in 16. In 1883, Curtis, an American author, after criticizing existing methods of treatment, none of which, he said, seemed able to cure gonorrhoea in less than 3 weeks, recommended douching the whole urethra through a back-flow catheter with as much as 10 quarts of water as hot as the patient could stand, following this with a solution of tannic acid, 16 grains to the ounce in a suspension of iodoform, also 16 grains to the ounce. By this method he claimed cure in an average of 1 week. I once saw a patient who had been treated by a hot douche method, which seems to have been rather popular at one time; his urethra was in a horrid mess. F. P. Atkinson (1886) mentioned great improvements in the treatment of gonorrhoea and then described his own method. If the discharge was not lessened by internal treatment, the patient was to have urethral injections of zinc sulphate, 3 grains to the ounce, or of potassium permanganate, 1 in 480, or of silver nitrate 2 to 5 grains to the ounce.

The late Sir Jonathan Hutchinson (1892) seems also to have favoured astringents, recommending zinc chloride, 2 grains to the ounce.

As evidence also of the fact that quicker cures were claimed than was possible when cures were judged by microscopical examination of secretions may be quoted some periods of stay in Army hospitals mentioned by Neisser in his address to the first Brussels Conference, already mentioned. They were: Germany, 29 to 31 days; Austria, 36 to 37 days; Belgium, 27 to 34 days; France, 26 to 34 days.

Some may say that was in the 1890s or earlier and that people have since learnt better, but I can say that after I had taken over the treatment of gonorrhoea at the Rochester Row Hospital and also during the war of 1914-18 3-week cures were quoted to me *ad nauseam* by my senior officers.

As against such claims I may quote an article by Paul Neisser in the Festschrift number of the *Archiv für Dermatologie und Syphilis* (1907) already mentioned. Controlling results by microscopical tests, he compared five methods of treatment, four with different compounds of silver and one by purely medicinal and dietetic measures. The durations were 49 to 53 days by the different silver preparations and 85.5 days by purely medicinal and dietetic treatment. The author concluded that the scientific treatment of gonorrhoea without the use of a microscope was impossible, and I would say the same to-day.

I can quote one example of the truth of this dictum, against myself. In the war of 1914-18, when for my sins I commanded a large military V.D. hospital in France, I read an article in an American medical periodical in which the author claimed to cure gonorrhoea in about 10 days by giving the patient an intramuscular injection of 100 mg. mercury succinimide every other day for some days. That seemed to accord with our experience that in patients suffering from both syphilis and gonorrhoea the discharge cleared up more quickly than in those with only gonorrhoea; we had thought it was the "606" which was doing it but events proved that it was the mercury. I obtained some succinimide of mercury and tried it on the cases of simple gonorrhoea without syphilis: the effect seemed to be marvellous. The discharge seemed to clear up wonderfully and, to my shame be it said, I approved the discharge from hospital of a large number of patients in less than 14 days after admission. They had answered the usual Army tests of cure, as far I could see, and in existing circumstances it certainly was impracticable to apply microscopic tests, we simply had not the staff for it. But later when I examined a slight gleet in some of the cases I found the scanty pus cells just swarming with gonococci.

The lesson shows how right was Albert Neisser and his pupil and namesake in insisting on microscopical control of gonorrhoea. I think that venereologists who have followed such principles, and I like to think they comprise the majority of those engaged in this work under the National V.D. Scheme since 1920, must have prevented a very great amount of transmission of this disease to innocent persons.

In this microscopic control, I should think that Neisser himself and many other authors must have misdiagnosed as gonococci many very similar cocci in discharges which they examined before Gabriel Roux, in 1886, pointed out that gonococci are decolorized by the Gram method of staining.

On the question of the use of astringents in the treatment of gonorrhoea of which Neisser was a foremost opponent, he being an advocate of bactericidal methods and particularly of protargol and other organic preparations of silver, I have been interested to try to discover how long astringent methods prevailed in this country, and now I think I am entering on controversial ground. Nevertheless, some of the following facts which I have collected may possibly interest you.

In 1912, being convinced that the problem of syphilis was solved, requiring only the discovery of the optimum amount of Salvarsan and mercury to be administered, but feeling that much more work ought to be done on gonorrhoea than was then thought necessary, I asked for charge of the gonorrhoea ward at the Rochester Row Hospital and for an assistant to help me there and in the laboratory. I felt that any investigation should be made in close collaboration with the laboratory, and that the simplest way of achieving this would be to have charge of both departments.

At that time the routine method of treatment was according to the teaching of Janet (1892), by irrigation with potassium permanganate of a strength ranging from 1 in 4,000 to 1 in 2,000. I am not sure what was the prevalent treatment elsewhere but believe that, if any local treatment at all was used, it was on Janet lines, or by silver preparations, or by frank astringents such as lead acetate or zinc sulphate. I soon concluded that solutions of 1 in 4,000 potassium permanganate and stronger were definitely astringent, and I reduced the strength to 1 in 8,000 because, like Neisser, I did not believe that astringent treatment was scientific. Thereafter I discouraged the use of permanganate of greater strength than 1 in 8,000, and I believe that my views on this point prevailed throughout the Army during the 1914-18 war, and certainly in the V.D. treatment centres throughout Great Britain from 1920 onwards.

There is some evidence that in civilian circles during the 1914-18 war greater, more astringent strengths of permanganate were used because one eminent urologist poured scorn on the strengths used in the Army, saying in effect: "If you're going to use permanganate, use it, don't fiddle about with solutions weaker than 1 in 2,000". I was rather disturbed by this criticism, and discussed the question with the late Mr. Wyndham Powell, who, I believe, knew more about the inside of the male urethra than most people, and he said that such concentrations as 1 in 2,000 were all right so long as one dealt with the resulting infiltrates after the discharge had almost dried up. That, from such an authority, was sufficient to encourage me to continue with my "fiddling" low concentrations, which were non-astringent, though, as I believed, detoxicant. I am encouraged in my view that permanganate as used in the Janet manner was astringent by its taste and its classification amongst the astringents by Perutz (1934).

So, at the possible risk of having my toes trodden upon this evening, I have dared to class the treatments prevailing in civilian circles in Great Britain before the National V.D. Scheme was on its feet as more liable than later methods to be followed by stricture of the male urethra. So far as other people of British nationality are concerned, I think that most of the 200,000 British soldiers treated for gonorrhoea during the 1914-18 war escaped that risk, though the tests of cure mostly violated Neisserian principles in dispensing with microscopical examination.

It was natural that I should seek statistics which would decide whether, by the milder, non-astringent, non-irritant method prevalent throughout Great Britain from at any rate the early 1920s, stricture of the male urethra has been greatly reduced. I think anyone who has to deal with the male urethra, whether as venereologist or as urologist, will agree that stricture of the urethra has now been relatively rare for a number of years; the stricture parades of the old days are no more, and some even say that the passage of a curved sound is becoming a lost art. But those are possibly only impressions. I wanted to find something more concrete and, not having time to search through the records of many hospitals, I thought that possibly the Registrar-General's Tables showing the deaths from stricture might give some information. I think, however, that despite the old tag that one can prove anything with statistics, this is an instance where the figures do not prove the case. As, however, they are interesting, I am venturing to show what I have collected, in two Tables. Starting on the assumption that most

strictures of the urethra are due to urethritis, most commonly gonorrhoeal, or to its treatment, or to both, I aimed first to discover how long after contraction of gonorrhoea the stricture killed its man, and Table I seems to give the answer. The peak decade for contraction of gonorrhoea is from 20 to 29 years and, as the figures in this Table show, the peak decade for deaths from stricture is from 60 to 69, or 40 years later. You will notice in the Table that there was a significant fall in the deaths from stricture in the decade 1941 to 1950. Going into the matter more closely, I aimed to see just about when the deaths began quite definitely to decline and collected the figures shown in Table II. As you will see, the figures are in four main periods, from 1912 to 1920, from 1921 to 1936, from 1937 to 1943, and from 1944 to 1953.

TABLE I
DEATHS FROM URETHRAL STRICTURE IN MALES (1921-50)
BY AGE-GROUPS AND DECADES

Age Groups (yrs)	Decades		
	1921-30	1931-40	1941-50
All Ages	3,484	3,384	2,116
0-19	5	3	3
20-29	30	21	5
30-39	113	71	32
40-49	468	288	130
50-59	917	793	352
60-69	1,165	1,259	704
70-79	662	775	700
80 and over	124	174	180

In the first, with an average of 404 deaths from all urethral diseases per annum, separate figures for stricture were not obtainable, but those in the

fourth and fifth columns of the periods 1921 to 1943, which were included in those in the second and third columns, show clearly that most of the 404 in the first period must have been due to stricture.

The fourth period shows the most significant decline and this in spite of the increase in gonorrhoea which must have occurred in the civilian population in the 1914-18 war, when 200,000 British and Dominion soldiers were treated for this disease.

But before I could confidently say that the great decline during the period 1944 to 1953 was due to the better treatment of gonorrhoea from a time 30 to 40 years before 1944, I had to remember the sulphonamides and the antibiotics and possibly improvements in surgical technique which might have made the treatment of urethral stricture safer. However, the figures do show that in the past dozen years or so, deaths from stricture of the male urethra have become about a quarter of what they were in the period 1921 to 1936, and still less than in the period before 1921.

As for gonorrhoea in the female, the prevailing treatment when I first had to take an interest in this branch, in the early 1920s, seemed to me even more horrifying than those I have sketched on the male side, and I have often wondered how much of the sterility attributed to gonorrhoea in the past was due to the strictured cervixes following the terrible strengths of silver nitrate which used to be applied there.

I come now to the last portion of my essay, namely Neisser's connexion with progress in the management of syphilis, and I should like to digress

TABLE II
DEATHS FROM DISEASES OF THE MALE URETHRA, INCLUDING STRICTURE, WITH DEATH-RATES PER MILLION

Period (yrs)	All Urethral Diseases, including Stricture		Stricture only		Factors			
	Average per annum	Death- rates	Average per annum	Death- rates	Maltreatment 30-40 yrs before	Treatment of Stricture		
						Sulphonamide Guards	Antibiotic Guards	Surgical Improvements
1912-20	404	21-31	Not shown separately in Registrar-General's Tables		Yes	No	No	?
1921-36	389	18-24	355	16-23	Yes	No	No	?
1937	357	18	346	18	Yes	Yes	No	?
1938	346	17	323	16	Yes	Yes	No	?
1939	326	17	304	15	Yes	Yes	No	?
1940	301	16	277	15	?	Yes	No	?
1941	327	19	300	17	?	Yes	No	?
1942	319	19	293	17	?	Yes	No	?
1943	288	18	255	16	?	Yes	No	?
1944			226	14	?	Yes	No	?
1945			195	12	No	Yes	Yes	?
1946			188	10	No	Yes	Yes	?
1947			187	10	No	Yes	Yes	?
1948			170	8	No	Yes	Yes	?
1949			161	8	No	Yes	Yes	?
1950			131	6	No	Yes	Yes	?
1951			117	6	No	Yes	Yes	?
1952			114	5	No	Yes	Yes	?
1953			93	4	No	Yes	Yes	?

a little by talking about the discovery of *T. pallidum*. For this I am indebted largely to the story related by Metchnikoff (1908), who reported that at the International Health Congress in 1903, Bordet had told him that he and Gengou had seen in some chancre juice stained with Kühne's carbol methylene (blue) and afterwards with Nicolle's gentian violet, a large number of very fine spirilla, rolled like a corkscrew, and very faintly stained. But neither they nor Metchnikoff and Levaditi had been able to repeat this observation until after Schaudinn's discovery in 1905. Further, Metchnikoff and Levaditi had examined fresh juice to see whether they could detect any movement, but had failed to find anything which might suggest the presence there of some invisible motile micro-organism.

The stimulus to the discovery of *T. pallidum* arose really from the claim of one Siegel (1906) that a body which he had seen in syphilitic material, and which he called *Cytoryctes luis*, caused syphilis. This body is illustrated in Metchnikoff's article and was thought by most non-German authorities to be just organic debris, as indeed it later proved to be; but in Berlin, Siegel's claim was pressed so hard that Franz Eilard Schultze, Professor of Zoology, got together a commission of experts to examine the question from all angles. Fortunately, Fritz Schaudinn, a first-class protozoologist and microscopist, was chosen to examine specimens, and Erich Hoffmann, a first-class clinician, to say what was syphilitic material and what was non-syphilitic. Siegel's claim was quickly disproved and on March 3, 1905, Schaudinn and Hoffmann, by axial illumination, no high-power dark-ground condenser being then available, saw in the juice from an early syphilitic lesion the very fine pale spirillum we now know as *T. pallidum*. I suggest that anyone who wishes to realize the greatness of Schaudinn's discovery might try examining a fresh specimen of chancre juice with the usual sub-stage—not the dark-ground, of course—condenser and almost closed diaphragm. He would start with the advantage of knowing that the organism was there, but I think he could congratulate himself and the maker of his microscope if he saw the pale spirillum.

I have mentioned that Neisser after many failures gave little hope of discovering a vaccine as a prophylactic against syphilis, and also his association with Wassermann and Bruck in the application of Bordet and Gengou's phenomenon of complement fixation to the diagnosis of syphilis. It seems interesting to me that the Bordet-Gengou phenomenon was to decide a dispute between Bordet and Gengou of Brussels on the one hand and Ehrlich and the Frankfurt School on the other as to whether

complement was non-specific and able to dissolve and itself be put out of action by either cells or bacteria when these had been sensitized by their appropriate antibodies, or, as Ehrlich and his colleagues contended, there was one complement for cells and another for bacteria. The Bordet-Gengou phenomenon proved the unity of complement, and Bordet and Gengou showed that foreign proteins sensitized by their appropriate amboceptors also fixed the common complement. Wassermann and Bruck then showed that complement fixation would occur with bacterial extracts, and thus they were able to demonstrate antibody to various diseases including typhoid, cerebrospinal fever, and tuberculosis. Thus the way was paved for the demonstration of antibody to the spirochaete of syphilis and inferentially for the diagnosis of this disease by complement fixation. Thus another great discovery arose out of a polemic.

When I think of the Bordet-Ehrlich dispute on the plurality or the unity of complement and the fact that out of it arose the test commonly known as the Wassermann reaction, *almost the only practical application of complement fixation to diagnosis in clinical medicine*, I cannot help a fantastical likening of it to the fairy story of the magic carpet, Ehrlich and Bordet disputing while Wassermann and Bruck sat on the carpet, eventually flying away with it. So I am always glad that the Health Organization of the League of Nations referred to this test as the Bordet-Wassermann. Perhaps the WHO might copy their good example.

I have already mentioned Neisser's very early insistence on the importance of giving injections of an insoluble preparation of mercury concurrently with injections of Salvarsan. It is my belief that, through his great influence in this direction, he prevented a great amount of neurosyphilis of the meningovascular type. His views on the subject of using two remedies concurrently are set out shortly in his Cavendish Lecture and more fully in his "Beiträge" on the pathology and treatment of syphilis. In this larger work he referred to Ehrlich's views on the plurality of chemo-receptors of micro-organisms so that it seemed reasonable to assail the parasite with more than one poison at a time.

Ehrlich's views on this point can be read most conveniently by English-speaking students in his address to the International Medical Congress, London, 1913, which was fully reported in the *British Medical Journal* and *Lancet* (Ehrlich, 1913a, b). In it he said that uncivilized tribes, the more certainly to destroy their enemies, dressed their arrow-tips with more than one poison, and he proposed to dress his amino-benzene arrow with more than one metal.

Thus his 1+1 in therapeutic units would equal more than 2 when used concurrently. He instructed Karrer to make copper-salvarsan, which proved too toxic, but his successor, Kolle,* found that Karrer's silver and neo-silver Salvarsans were efficacious and were much used at one time.

Another preparation which appeared during the 1914-18 war was Luargol, a combination of arsphenamine, silver, and antimony. It may be interesting to note that Neisser, in his Cavendish Lecture, mentioned antimony as a possible addition to the chemo-therapeutic armamentarium. Luargol thrombosed practically every vein into which it was injected so that towards the end of a course of injections one was searching the skin surface for superficial veins, and that remedy was soon discarded. In 1924, Lehnhoff-Wyld, in Paris, having shown that the curative dose of sulpharsenol was lower when there was another metal present in the circulation, produced zinc-sulpharsenol; it proved too painful. These views and experiences supporting the general principle that the concurrent use of more than one remedy was more efficacious than the use of one at a time were later well supported on the laboratory side by Clausen, Longley, and Tatum (1942) and on the clinical side by Eagle (1944), but I would now revert to my original contention that Neisser, by his strong advocacy of this principle, has prevented a great amount of neurosyphilis of the meningovascular type. Very early in our trials of "606" at Rochester Row, he sent us a German patient for us to continue this combined treatment of his because we had shown that we too believed in it. Everybody who had much to do with the early trials of the arsphenamine group of remedies can doubtless cite cases in which "606" alone cured some cases as proved by complete tests many years later; I know of a few in which a single dose achieved that miracle. *But those people also know that many patients treated with the arsphenamine remedies alone developed signs of syphilis of the central nervous system, mostly in the form of cranial nerve palsies.* There is quite a considerable literature dealing with the subject, the Vienna school in particular contending that these sequelae of the arsenical treatment were due to a neurotropic effect of the remedy, and the Frankfort school contending, as was conclusively proved in the long run, that they were due to a recurrence of syphilis in the affected structures. We at Rochester Row were keen Frankfortian partisans and eventually we were very glad that we had early taken the advice of Neisser to give mercury concurrently with the arsenical remedy; especially so because

in our own cases treated from 1910 to 1914 we had not a single case of neurosyphilis of the kind mentioned. Further, of all the soldiers treated on these lines during the war of 1914-18, I heard of only one case of the kind mentioned in all those treated in the British Army. In the early 1920s the Medical Society for the Study of Venereal Diseases organized an inquiry, which was subsidized by the Ministry of Health, to discover whether any such cases had been seen in general clinics or in clinics for diseases of the nervous system after treatment for syphilis in the Army during the then recent war. Nicol (1925), who made the inquiry on our behalf, found only one. Further, in the cases treated at St. Thomas's Hospital from 1920 to 1928, only one had occurred, though our cases included very many that had had very little treatment; the point of importance was that in this treatment the two remedies had been given concurrently. In a report on the results of treatment of the St. Thomas's Hospital cases, published in 1929 by the Medical Research Council (Harrison, 1929), I contrasted our experience with that of the Syphilis Clinic at the Johns Hopkins Hospital in which, as reported by Moore and Kemp (1926), out of a gross material of 2,500 cases of early syphilis treated with courses of arsphenamine followed by courses of mercury, there had been no fewer than 59* neuro-recurrences manifested by syphilitic meningitis, cranial nerve palsies, and precocious vascular neurosyphilis. I believe that the reason was the withholding of mercury at the beginning of treatment whilst doses of arsphenamine *sufficiently large to stop the activity of the spirochaete in the somatic tissues* was responsible. I emphasize the importance of the size of the dose of "606", because it affects the development of anti-treponemal substances which would restrain the activity of residual nests in the coats of the cranial nerves and such-like places.

These views were later supported by the experience of one of the five American clinics which participated in the American Cooperative Clinical Studies (Moore and others, 1932). In this it was stated that at Clinic B, out of thirteen clinical relapses no fewer than five were of the neuro-recurrent type, and it was admitted that Clinic B differed from the others particularly in withholding heavy metal during the first course. If the advice of Neisser had been followed those neuro-recurrences would not have occurred.

Thus I think that Neisser has proved to be fully justified in his early insistence on the concurrent use of heavy metal with arsphenamine treatment and, as I said earlier, his stand on this point, fortified

* Kolle (1918) and Kolle and Ritz (1919).

* In my report I said 59; the correct figure was 58.

with all the power which his reputation for sound scientific wisdom endowed it, must have influenced the treatment of very many thousands of patients and must in this way have prevented an incalculable amount of harm through syphilitic neuro-recurrence.

I am conscious that, in this address, I have paid only a feeble tribute to Neisser's great service to mankind, but perhaps others better versed in medical history than I am will adequately supplement what I have said.

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