The clinical pathology of syphilis & parasyphilis : and its value for diagnosis and controlling treatment / by Hugh Wansey Bayly.

H. HOUSTON MERRITT, M. D.

THE CLINICAL PATHOLOGY

OF

SYPHILIS AND PARASYPHILIS

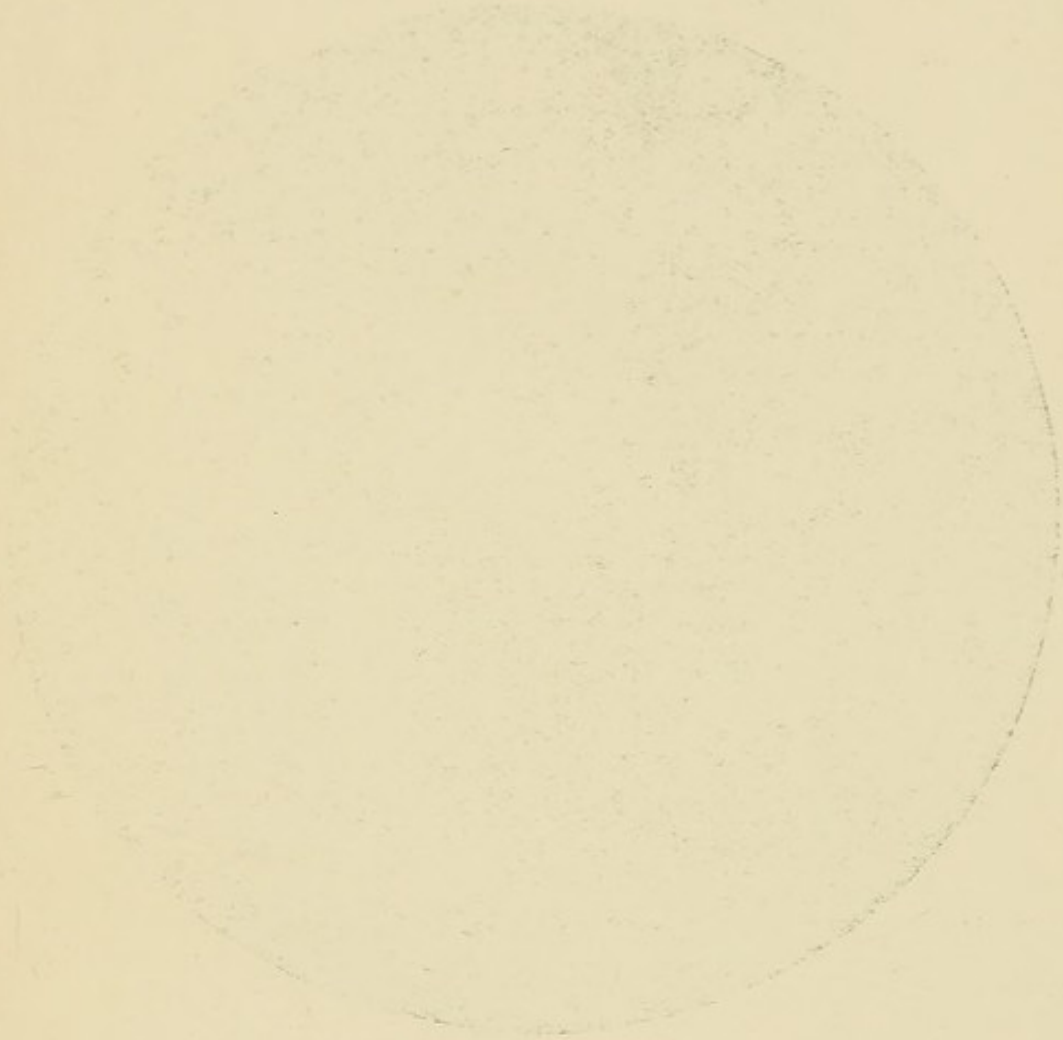

PLATE I.

FIG. 1.—SERUM FROM SCRAPING OF A CHANCRE. (P. GASTOU.)

Numerous *Spirochætæ pallidæ* are seen. Above one *Spirochæta refringens* with very open spiral is seen. Three epithelial cells and several red blood-cells (fine circles) are present.

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THE CLINICAL PATHOLOGY OF SYPHILIS & PARASYPHILIS ≠

AND ITS VALUE FOR DIAGNOSIS AND CONTROLLING TREATMENT

BY

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TO

CHARLES SLATER, M.A., M.B., F.C.S.,

Director of the Clinical Laboratories of, and Bacteriologist (since 1889) to, St. George's Hospital;
Reader in Bacteriology to the University of London,

WITH HIS PUPIL'S GRATITUDE AND HOMAGE.

AUTHOR'S PREFACE

THIS little book is intended for the use of the general practitioner and medical student, and not in any way as a book of reference for the pathologist. I have frequently been asked by students and practitioners if I could tell them of a *small* book containing the essentials of the clinical pathology of syphilis, and I hope this little book will meet that demand. I have endeavoured to collect and review the essential points in the clinical pathology of syphilis and parasyphilis and to present them in such a manner as to emphasize their practical value for diagnosis and treatment. Theory has been omitted as much as possible, as have also detailed accounts of research and experimental work. The literature on this subject is immense, and I have made no bibliography in this volume. The majority of the references, however, will be found in the books referred to below, or in articles by others and myself that have appeared within the last three years in the *Lancet*, the *Practitioner*, the *British Medical*

Journal, and the *Quarterly Journal of Medicine*. Readers wishing for greater details will find them in the works mentioned on p. 185, from which I have freely borrowed.

HUGH WANSEY BAYLY.

Bacteriological Department,
St. George's Hospital, S.W.
July, 1912.

INTRODUCTION

SYPHILIS at the present time furnishes an excellent example of the value of the scientific use of the imagination and of modern methods of research in the elucidation of the etiology of a disease, and in the discovery of means for diagnosis and treatment.

Before 1903 an enormous amount of valuable material had been collected by the clinicians, the various stages and manifestations of the disease were well known, the obscure relations existing between syphilis and certain nervous diseases had been unravelled with the greatest ingenuity, and certain lines of treatment had been discovered and adopted with success. This material did not, however, acquire its full value until Roux and Metchnikoff showed that syphilis could be transferred to the lower animals, and could thus be subjected to experimental conditions, and until Schaudinn in 1905 had discovered the cause in the *Spirochæta pallida*, and thus provided an infallible means of determining the true nature of a suspicious lesion.

From a series of bacteriological observations made

in connection with the study of immunity, and remote alike from syphilis and considerations of practical medicine, sprang that most valuable of diagnostic methods, the Wassermann reaction, whose reliability now rests on a solid basis of experience.

This disease also furnishes an example of the deliberate experimental search for a drug which, while harmless to the patient, should be capable of destroying the causal organism, a search which, as is well known, ended in the discovery of Salvarsan.

As is to be expected, these new discoveries, which give rise to hopes that we might control if not eliminate a disease so widely spread, so often recurring during many years of a patient's life, and of such social importance, are naturally of the greatest interest and importance, and have been the subjects of innumerable investigations, so that the literature of the subject is enormous. Some guide, therefore, is wanted by the practitioner which shall sift the observations which are of practical importance, and which shall show him how to apply this recent knowledge to the study of his own cases. It is the intention of this book to provide such a guide, and to consider our clinical knowledge of the disease in relation to these new diagnostic and therapeutic measures.

CHARLES SLATER.

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CHAPTER I

PARASITOLOGY

History of Parasitology.—Since the occurrence of the historical epidemic of syphilis that spread over Europe in 1495, the contagious character of the disease has been recognized, and this was verified by means of experiments by Hunter in 1778. In 1819 Swediaur put forward the suggestion that the syphilitic virus was a ferment spreading by the lymphatics and so infecting the lymphatic glands, and that the action of this ferment was capable of producing ulcerations. Donné, in 1837, made the first bacteriological researches of syphilitic ulcerations and demonstrated the presence of spirilla, which he considered were the causal organisms. Klebs, in 1878, described small bodies which he named 'helicomonades,' resembling small grains or short rods, which were easy to cultivate, and which he said produced syphilitic lesions in animals. Lustgarten, in 1884, discovered a bacillus, somewhat like the tubercle bacillus, in chancres, papules, enlarged glands, and gummata. This bacillus was more easily decolourized than the tubercle bacillus, and was about 3 to 4 μ long and 0·3 μ broad. It was stained by means of a solution of gentian violet, heated to 40°C. for two hours, and the preparation

then decolourized by a mixture of permanganate of potash and sulphuric acid, and dehydrated by alcohol, when the Lustgarten bacillus remained stained. Lustgarten's results were confirmed by Doutrelepont and Giacomi, who used 1 per cent. solution of gentian violet and decolourized for a few seconds in a dilution of acetic acid and then in 60 per cent. alcohol. In 1896 Neisser discovered a polymorphic bacillus in the blood of syphilitics. In 1897 pure cultures of the bacillus of smegma were obtained by Laser and Czaplewsky, who considered that this might be the causal organism of syphilis.

The above are only a few of the organisms claimed by their discoverers to have been the cause of syphilis, but there was never sufficient evidence of their specificity to satisfy the profession at large.

In 1905 Schaudinn discovered a thin spiral organism which could be demonstrated in Hunterian chancres in practically every case. He gave this organism the name of *Treponema pallidum*, on account of its slight refractive and staining qualities, which, combined with its extreme tenuity, rendered it difficult of demonstration by most methods of staining. This organism was so constant in its appearance and characteristics that Schaudinn was able to write:

'It is easy, after a certain amount of diligence, to differentiate the *Treponema pallidum* from other types of spirochætes in fresh preparations. The fineness and feeble refractility of this spirochæte, the constant, close, deep, and regular character of its spirals which are numerous (10 to 20), render it impossible to confuse it with other micro-organisms of the same type. Its chief characteristic, however, lies in the fact that it

retains its spiral arrangement not only during movement, but also in the state of rest, while the spirals of most of the other spirochætes disappear when they are in the condition of repose.'

This description of Schaudinn's still holds good, and makes it one of the easiest organisms to diagnose in fresh preparations. As its characteristic movements are one of its diagnostic features, it is best examined by the dark-ground illumination method (ultra-microscope), which is the only satisfactory means of examining the organism alive.

Characters of Spirochæta Pallida. — When examined by dark-ground illumination, its characteristic appearance is that of an extremely fine, silvery spiral from 5 to 25 μ in length, with very regular and closely set spirals (about seven to the diameter of a red blood-disc), the distance between the spirals being 1 μ. The number of the spirals range from 5 to 25, and the extremities of the organism are pointed. It may happen that the light is only reflected from the summit of the spirals, in which case the organism will have the appearance of a chain of equidistant luminous dots not unlike a chain of streptococci. By careful focussing, however, this chain of dots will be seen to be a spiral (see Figs. 1 and 2). The living *Spirochæta pallida* preserves a helicoidal form, but as its vitality diminishes the spiral tends to disappear.

In serum, but never in water, giant forms up to 45 μ are sometimes seen; these are probably formed by several spirochætæ becoming attached end to end. This Dr. Comandon describes as 'linear agglutination.'

If a drop of water is added they are seen to break up into several organisms.

The movements are more active and last longer in the patient's own serum than in distilled water or saline. In serum, also, the movements are more rapid and the spirals closer together than in water. The movements vary with the vitality, and are increased by warming the preparation.

In water the *Spirochæta pallida* is but feebly motile compared with most of the other spirochætæ met with. If there is no current in the fluid the spirochæte will remain in the field for a long time. Care must be taken to distinguish the movements proper to the organism from those imparted to it by a current of the fluid in which it is being examined. It preserves its spirals during rest, while all other analogous spirochætes, which present marked undulations, show them only when they are moving vigorously, and when at rest they have long, flattened-out undulations, and, indeed, are very nearly straight. This peculiar appearance of the *Spirochæta pallida* is due to the fact that in it the spiral arrangement is permanent, whilst in other varieties the deep spiral is only produced during rapid movement, and is straightened out at rest. There is only one spirillum, that of the mouth or *Spirochæta dentium* which has a small fixed spiral arrangement, but this variety can be distinguished by other characteristics from the organism of syphilis. No undulating membrane has yet been demonstrated in *Spirochæta pallida*.

The movements consist of—

1. Bending, which is the most marked.

2. Snake-like undulations.

3. Rotation round its long axis like a screw.

4. Concertina-like movements, by which the spirals are drawn out or approximated, so that organism becomes lengthened or shortened respectively.

5. Occasionally a local wave of contraction may be seen which flattens out the spirals. This movement is very rarely seen with any other spirochæte than *Spirochæta pallida.*

Schaudinn considered that on section the *Spirochæta pallida* was probably round, and that the organism was cylindrical and not flattened, as is the case with most of the other spirochætæ.

The peripheral protoplasm is continued at each end of the organism in the form of a cilium whose length equals about four to six undulations. The largest *Spirochætæ pallidæ* are distinguished by the presence of two cilia at one pole. Schaudinn considered that these double cilia indicated the commencement of longitudinal division, and wrote in December, 1905:

'I have already succeeded in three cases in observing the longitudinal division of the organism. To follow out this process I have chosen individuals which already possessed two fine cilia at one of the poles, and I have seen the longitudinal division progressing rapidly after beginning at this pole. At the moment of division the organism abandoned its marked spiral form, and appeared to be very irregularly contorted.'

The question whether the *Spirochæta pallida* is to be classed with the bacteria or protozoa has still to be settled, and its cycle of development has still to be demonstrated. Krzyztalowicz and Siedelecki think

that they have recognized female elements in the form of large spirilla, and male elements in the form of small spirilla, and state that they have seen these two elements unite.

A. Neisser hazards the opinion that there may exist an unknown stage of development, or rest stage, of the spirochæte, analogous to the spores and granular forms of many bacteria, which may be far more difficult to influence by any medicament than the spirochæte itself.

The possibility of this theory being correct is heightened by the observations of Dr. Reinke, of Wiesbaden, who in 1910 demonstrated granules in the lung of a congenital syphilitic infant in an autopsy performed after treatment with salvarsan. He considered that the granules were derived from spirochætes, and Dr. A. Balfour is of the opinion that granule-shedding in *Spirochæta pallida* occurs before any treatment of the case is begun. It is, therefore, in all probability, a feature in the life-history of the spirochæte. This same phenomenon of granule-shedding is true of other spirochætes associated with that of syphilis, and is especially well seen in the case of the *Spirochæta refringens*. Balfour thinks that the granules are of the nature of resistant spores, that they play an important part in relapse, and that they are influential factors in the occurrence of the later manifestations of syphilitic infection.

AGGLUTINATION

The *Spirochætæ pallidæ* may be preserved in normal saline solution for several hours without showing any

traces of agglutination, but if to the saline solution the filtered product of a chancre or syphilitic papule is added, agglutination is at once produced.

There is only a feeble agglutination if the serum of the same individual is used, showing that the agglutinins are present in smaller quantity in the serum than in the fluids immediately surrounding aggregations of spirochætæ.

Agglutination has been observed in the blood in very intense general infection.

Agglutination phenomena are most clearly observed in the serum during the period of the rash.

Agglutination has never been seen at a higher dilution than 1 in 1,000, and usually only occurs in a dilution of 1 in 10.

SPIROLYSIS

Spirolysins—that is to say, substances having the property of dissolving spirochætæ—have also been observed in the serum, and clumps of agglutinated spirochætes after some time become granular, of irregular form, and finally disappear, whereas control specimens, treated with normal serum or salt solution instead of specific serum, preserve their shape for several days or even weeks.

VISCOSITY

In fresh serum the spirochæte pushes past any solid object that it touches, but as it becomes less mobile it develops a tendency to stick to any such object.

MICROSCOPICAL EXAMINATIONS

1. **Dark-Ground Illumination.**—By means of a disc of black enamel painted on the under surface of the condenser (see Fig. 3), all rays of light from the

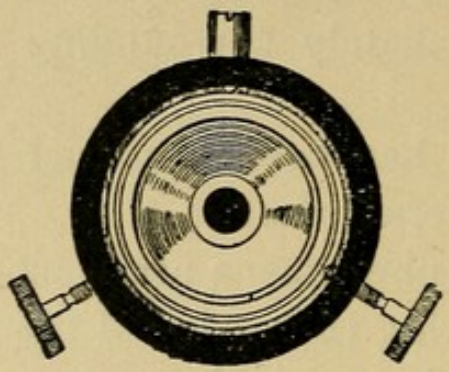


FIG. 3.—UNDER VIEW OF ULTRA-MICROSCOPE, SHOWING LENS IN CENTRE (WHITE), WITH BLACK ENAMEL DISC PAINTED ON IT. THE TWO CENTRING SCREWS AND THE SPRING ARE ALSO SHOWN.

microscope mirror, with the exception of those at the periphery of the condenser, are cut off. Those passing through the clear periphery are deflected by suitably

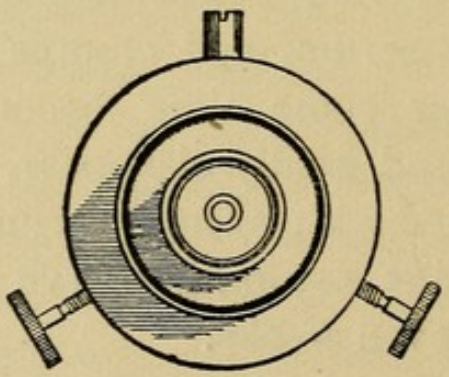


FIG. 4.—UPPER SURFACE, SHOWING CONCENTRIC CIRCLES SCRATCHED ON IT, BY MEANS OF WHICH IT CAN BE RAPIDLY AND ACCURATELY CENTRED.

cut lenses so that they converge obliquely on the object examined, which appears as a bright refractive body on a dark background. In this way very trans-

parent objects, which are invisible by direct illumination, are easily seen, and their shape and movements studied.

On the upper surface of the condenser are lightly scratched several concentric circles, by means of which, using a 1-inch or $\frac{2}{3}$-inch objective and a No. 1 or 2

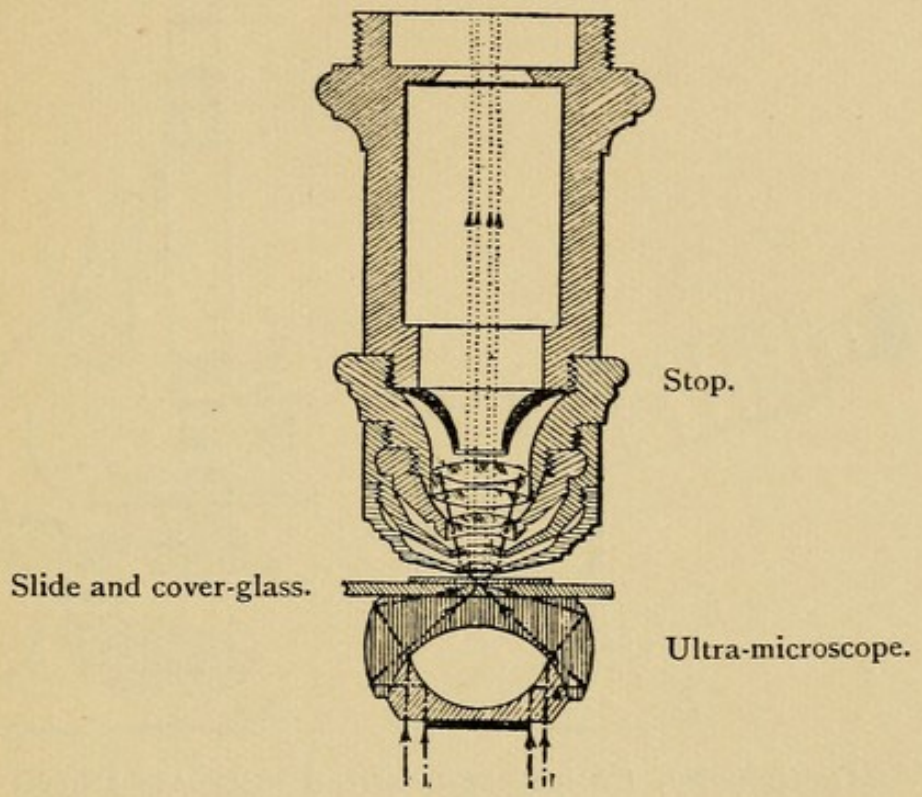


FIG. 5.—SECTION OF OBJECTIVE SHOWING 'STOP,' AND OF REFLECTING CONVERSION CONDENSER.

The black line below the condenser represents section of the black enamel disc.

eyepiece, the apparatus can be readily centred (see Fig. 4).

An ordinary $\frac{1}{12}$ oil-immersion objective admits too much light, and a special mount for the lenses, containing a stop, is required. A sectional diagram of the condenser and objective with stop is shown in Fig. 5. It will be seen that no rays from the source

PLATE II.

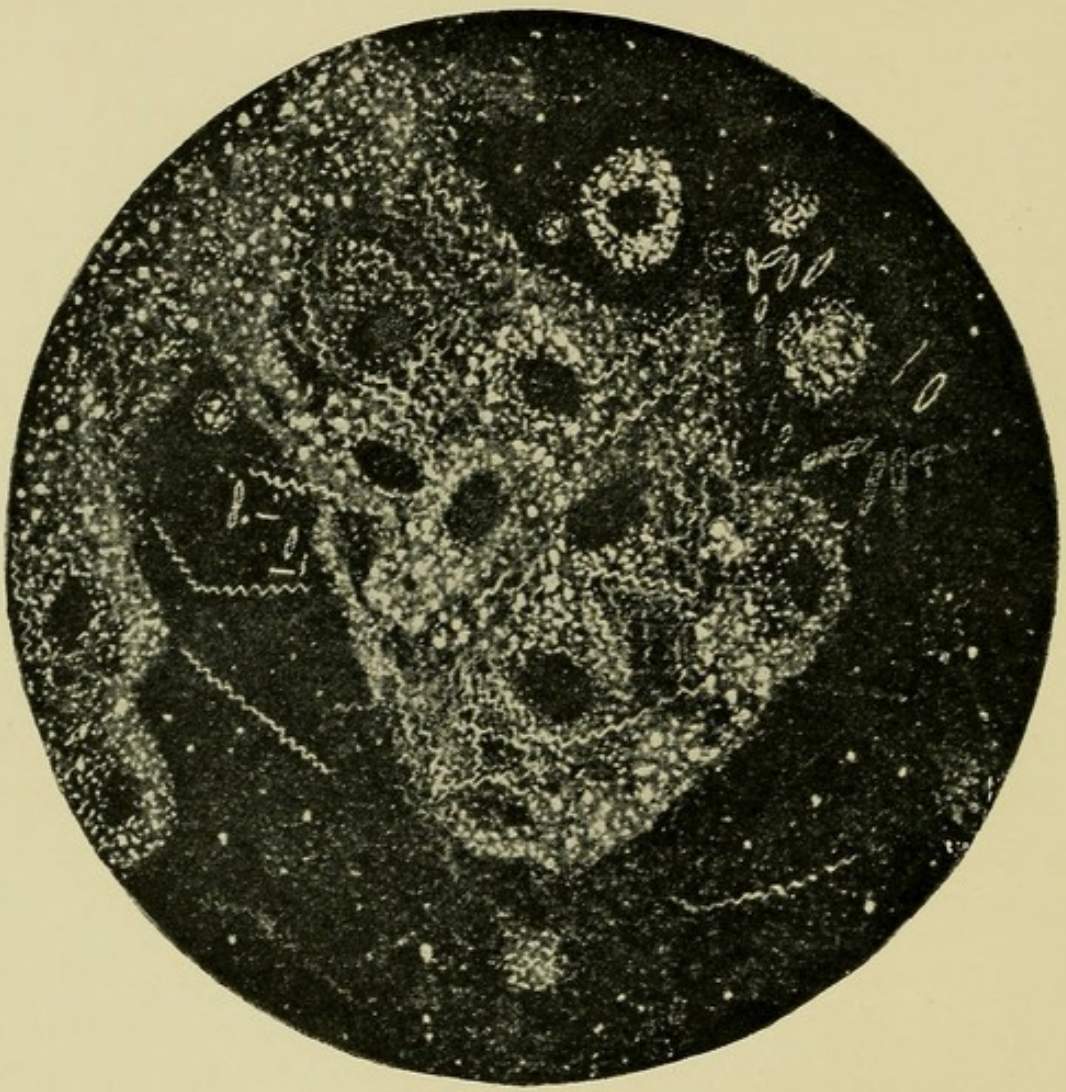


FIG. 2.—SCRAPING FROM CENTRE OF A SYPHILITIC CHANCRE. DARK-GROUND ILLUMINATION. (J. COMANDON.)

In centre is seen a mass of epithelial débris containing numerous *Spirochætæ pallidæ*. Below free *Spirochætæ pallidæ* are seen. Above and to right some bacilli are seen.

To face p. 11.

now gently scraped until blood just begins to exude. The surface is now again dried with some sterile gauze, and a little blood or serum expressed. A small drop of this is removed with a platinum needle, and mixed with a drop of distilled water on a thin glass slide. If this slide is too thick, the rays of light may come to a focus below the surface, and an unsatisfactory illumination be obtained. A large cover-glass is now pressed down firmly so that only a thin layer of the fluid remains between the slide and cover-glass. This can be conveniently done by spreading a piece of lint over the knee and holding the slide by each end, with the cover-glass downwards, and pressing it against the knee till the superfluous fluid is squeezed out and absorbed by the lint. After use the lint can be destroyed. A drop of immersion oil is now placed below the slide and also on the upper surface of the cover-glass. The slide is now placed in position on the microscope stage so that the drop of oil on the under surface touches the upper surface of the condenser. The $\frac{1}{12}$ objective is now lowered into the drop of oil on the upper surface of the cover-glass in the usual way. The condenser must now be racked up or down, and the mirror adjusted until bright illumination with a dark background is obtained.

Distilled water is the best medium in which to examine the spirochæte, as by osmosis the organism becomes swollen and so is more easily seen than if examined in normal saline or serum. The distilled water, also, by producing hæmolysis of the red cells, gives a clearer view of any organism that may be present. After about half an hour, the spirochæte

becomes more rigid and the movements sluggish, and in two to three hours' time all movement ceases in the majority of cases.

Phillips and Glynn recommend a slightly modified technique for the collection of material for examination by dark-ground illumination. The primary sore is first cleaned with absorbent wool, rubbed with the wool, and then swabbed two or three times with wool soaked in methylated spirit; in a minute or two the spirit is wiped off, and soon clear serum begins to exude, which is collected in a capillary tube. The following advantages are claimed:

(1) There is very little or no blood.

(2) The serum washes the spirochætes from the deeper parts where they are more constantly present; other spirochætes and bacteria are usually absent.

(3) Plenty of material is obtained, more than by any other way.

2. **Burri's Indian-Ink Method.**—The ink (Gunther-Wagner's) must be well centrifuged, and after the coarser particles have been deposited the supernatent fluid containing the finer particles should be pipetted off and kept in a stoppered bottle.

The material from the chancre is obtained in the same way as that for the dark-ground illumination, and a drop of the Indian-ink suspension is used instead of distilled water. The mixture is spread in a thin film and allowed to dry without heat. No fixation is required, neither is a cover-glass necessary unless a permanent specimen is desired.

When employing Burri's method, Phillips and Glynn use 1 drop of serum to twice the volume of Indian ink.

3. **Staining of Films.**—*Giemsa Stain*, which consists of azur II eosin, 3 grammes; azur II, 8 grammes; chemically pure glycerine, 250 grammes; and methyl alcohol, 250 grammes. The following are Giemsa's directions:

(1) Fix films in absolute alcohol from fifteen to twenty minutes; dry with filter-paper.

(2) Dilute the stain with distilled water, 1 drop of stain to 1 c.c. of water, the mixture being well shaken.

(3) Stain for fifteen minutes.

(4) Wash in a brisk stream of distilled water.

(5) Drain with filter-paper, dry, and mount in Canada balsam.

The *Spirochæta pallida* should appear stained rose-pink. This staining reaction, however, is not invariable, and Metchnikoff and Roux give instances where *Spirochætæ pallidæ*, obtained from the experimental chancre of an ape, were distinctly blue with Giemsa's stain.

Phillips and Glynn, when staining by Giemsa's method, spread a drop of the serum, obtained as for dark-ground illumination, as thin as possible on a slide, and, after drying and fixing in absolute alcohol, it was stained face downwards with Giemsa's stain diluted, 1 in 8, for twelve hours. They considered this long method of staining the most reliable.

Marino's Stain.—The films are first dried without being fixed in any way, then they are treated with a mixture of Marino's blue (0·1 gramme) and of methyl alcohol (20 c.c.); after three minutes some drops of a watery solution of eosin (0·005 per cent.) are added.

Two minutes after this the films are thoroughly washed and are then ready to be examined.

Loeffler's Method should be employed to show the terminal cilia. A freshly made mixture is used, consisting of 10 c.c. of a 20 per cent. solution of tannin, 5 c.c. of a cold saturated solution of sulphate of iron, and 1 c.c. of saturated alcoholic solution of fuchsin. This mixture is put on the films and heated three minutes until steam comes off. It is then washed in distilled water and stained with Ziehl's solution of carbol-fuchsin, gently heated at the same time. By this method the spirochæte is stained a dark red, while its cilia are shown in a light rose colour.

Care must be taken in all these methods to dilute the syphilitic products with some drops of distilled water.

Leishman's Method. — A film dried in the air and not fixed is treated with a mixture of distilled water and Leishman's stain in the proportion of 2 parts of water to 1 of stain. Optimum staining takes place in twenty-five minutes, when the stain must be washed off very gently with distilled water, and, when blotting in order to dry, care must be taken that only slight pressure is used, and that the film is not rubbed.

4. **Levaditi's Silver Method for Staining Sections.**—(1) Fix small pieces of tissue in 10 per cent. formalin for forty-eight hours.

(2) Wash for an hour in water.

(3) Keep in 96 per cent. alcohol for twenty-four hours.

(4) Place in a 1·5 solution of nitrate of silver in a dark bottle.

(5) Incubate at 37° C. for three days.

(6) Wash in water for twenty minutes.

(7) Place in a mixture consisting of pyrogallic acid 4 parts, formalin 5 parts, distilled water up to 100 parts. Keep the material in this mixture in a dark bottle for forty hours at room temperature.

(8) Wash in water for a few minutes, take through an increasing strength of alcohol, and embed in paraffin in the usual way.

The sections ought to be as thin as possible. In satisfactory preparations the spirochætæ appear almost black against the pale yellow background of the tissues.

Differential Diagnosis of Various Spirochætes likely to be Confused with the Spirochæta Pallida.

The Spirochæta Refringens, found in ulcerative lesions, is much larger, longer, and thicker than the *Spirochæta pallida*, the curves are much more open and shallow, and the organism moves with far greater rapidity (see Fig. 7).

The Spirochæta Buccalis, found in the mouth, is also much coarser, and is quite unlike *Spirochæta pallida* (see Fig. 8).

The Spirochæta Dentium, found in carious teeth, is very like the *Spirochæta pallida*, but it is shorter, being only 5 to 10 μ, and the depth of the spirals is

considerably less than in the *Spirochæta pallida.* Like the *Spirochæta pallida*, it retains its spirals during rest (see Fig. 9).

The Spirochæta Pertenuis of Yaws, described

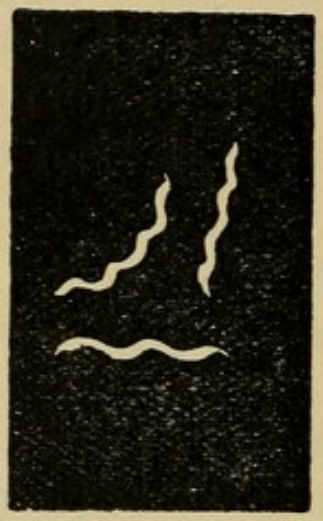


FIG. 7.—SPIROCHÆTA REFRINGENS.

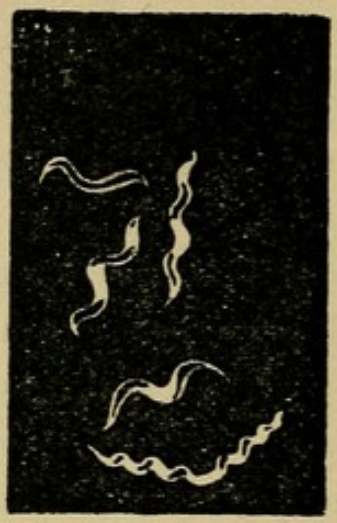


FIG. 8.—SPIROCHÆTA BUCCALIS.

FIG. 9.—SPIROCHÆTA DENTIUM.

FIG. 10.—SPIROCHÆTA PSEUDO-PALLIDA.

by Castellani, is the organism most like that of syphilis, and it is extremely difficult, if not impossible, to distinguish them morphologically.

The Spirochæta Pseudo-Pallida of ulcerated cancers, described by Loewenthal, does not appear to

justify its name, as it is not very like the true pallida, and is not likely to be mistaken for it except, perhaps, in badly stained films (Fig. 10).

The Spirochæta Balanitis of Hoffmann is a band-shaped spirochæte with 6 to 10 twists, is 0·5 to 0·75 μ broad, with an undulating membrane, and moves rapidly backwards and forwards, crossing the whole field at one dash. It moves by snake-like undulations or by screw-like rotation on its long axis (Fig. 11).

FIG. 11.

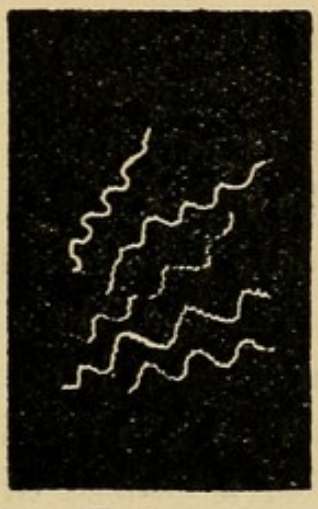


FIG. 12.

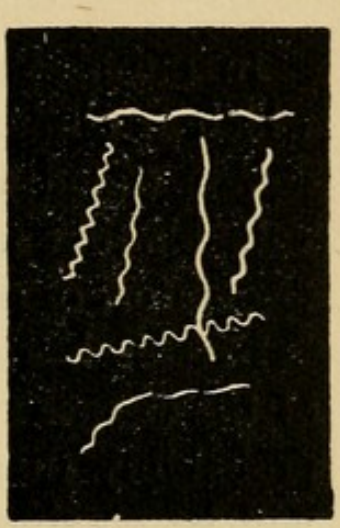


FIG. 13.

Other spirochætes occasionally seen are pictured in Figs. 12 and 13.

Diagnosis by Gland Puncture.—Phillips and Glynn have recorded that they obtained the *Spirochæta pallida* in 37 per cent. of cases of puncture of enlarged lymphatic glands corresponding to the primary lesion.

Preis states that he was successful in nearly 100 per cent. of cases in the secondary latent stage, and that he never failed to find the organism during the period between the typical hardening of the glands and the first appearance of a rash.

Phillips and Glynn, however, state that they never failed to find the spirochæte in the primary sore in any of the cases when they found the organism by gland puncture.

The fact that gland puncture has been successfully performed can be demonstrated by the presence of lymphocytes in the material obtained.

Importance of Early Diagnosis.

In the absence of treatment, a sore, the nature of which is clinically doubtful, can in a few moments be demonstrated to be clearly syphilitic, and so much valuable time may be saved, and the annoyance and discomfort of secondary manifestations prevented.

Neisser has observed that the earlier in the course of the disease that treatment is commenced, the more probability there is that a negative serum reaction will be obtained after a course of treatment. Thus, cases showing no symptoms of syphilis (early latent) that had received treatment as soon as possible after the primary lesion had appeared, give a negative serum reaction in 75 per cent. of cases, whereas in similar cases in which the treatment had not been commenced until six months after the primary lesion occurred, only 33 per cent. of cases were negative.

By early treatment the period of infectivity is shortened, which is obviously a matter of the greatest possible importance from both the public health and social points of view. An early diagnosis is therefore of paramount importance, both to the patient and to those with whom the patient is brought in contact.

Reliability of Microscopical Diagnosis.

Either general or local treatment has a marked effect on the number of *Spirochætæ pallidæ* found, and the organisms tend to disappear from the site of the primary inoculation after a few weeks, even without treatment. If a local antiseptic has been applied, the patient should be instructed to wash it away with plain warm water, and return in a few days' time for another examination.

As with most pathological findings, however, a positive result is much more conclusive than a negative one, and syphilis cannot be put out of court till three or four examinations on different days have been made, and the possibility of all antisyphilitic treatment, either general or local, excluded.

Out of a very large number of recent untreated chancres, very few have failed to show the *Spirochæta pallida* when examined by this method. The demonstration of this organism in primary syphilis is therefore, from a diagnostic point of view, of equal importance to, or even, perhaps, of greater importance than, that of Koch's bacillus in pulmonary tuberculosis or the Klebs-Loeffler bacillus in diphtheria.

The use of this method of diagnosis has shown that sores diagnosed from their clinical appearance to be non-syphilitic were really syphilitic, and *vice versa*—that sores considered syphilitic were not syphilitic. No patient, therefore, should be condemned as a syphilitic and placed on antisyphilitic treatment on the clinical appearance of the sore alone, but only after demonstration of the *Spirochæta pallida*.

CHAPTER II

PARASITOLOGY—*Continued*

CULTURE OF SPIROCHÆTA

Noguchi claims to have cultivated the *Spirochæta pallida* in serum water (sheep's, horse's or rabbit's) to which a piece of sterile rabbit tissue has been added. He considered the rabbit tissues best adapted to this purpose are the kidney and testicle. He uses test-tubes 20 cm. high and 1½ cm. wide, and fills them with 16 c.c. of serum water, 1 part serum and 3 parts distilled water. After completion of the usual precautionary sterilization at 100° C. for three days, fifteen minutes each day, a small piece of freshly removed sterile tissue is placed in each tube. The tubes are incubated at 37° C. for two days, and then examined for their sterility. To each tube a layer of sterile paraffin oil is now added in order to shield the medium from contact with the air and to prevent evaporation. Strict anaërobic conditions are very important in obtaining the first generation of *Spirochæta pallida*, and Noguchi employs a combination of hydrogen gas, vacuum, and pyrogallic acid in an anaërobic apparatus.

To obtain the first generation of *Spirochæta pallida* in virulent form, it is essential that there should be—

1. Suitable fresh sterile tissue in serum water.

2. Strict anaërobic conditions.

3. A slightly alkaline reaction furnished by the serum and tissue.

4. Temperature, 35° to 37° C.

A large number of unsuccessful attempts will be made for one successful. Noguchi states that in the serum-water tissue the spirochætæ commence to multiply after forty-eight hours, and continue to grow slowly for four or five weeks. He states that in the young cultures many short and rather heavy specimens are seen, some with only few curves, while in a culture ten or twelve days old the spirochætæ are of the usual length and have typical curves. As they grow older the spirochætæ may become very long and often form a tangled mass. Noguchi also states that of two strains of pure cultures experimented with, both produced typical lesions in the testicle of the rabbit.

HABITAT

In experimental infection the spirochætes are found at the point of inoculation. They stay in its immediate neighbourhood for a certain time while they adapt themselves to their new environment before they commence to multiply. They irritate the tissues by their toxins, and provoke a characteristic reactionary infiltration and development of the connective tissues. The body-cells oppose to the spirochætes their specific antitoxins, to which the spirochætes gradually become accustomed. They then develop along the lymphatic vessels and invade the lymphatic glands, which repre-

sent the first line of defence. They then develop in the glands and provoke a reactionary adenitis.

The spirochætes are irregularly distributed in the hard chancre and in the lymphatic glands. In the chancre they are found in the deeper layers around the vessels or in the vessel walls In the glands they are unequally disposed in groups, which explains the rarity of their presence in sections. The largest masses of spirochætes are found in the walls of the vessels and the trabeculæ of the glands. The spirochætes penetrate little by little into the blood-stream.

Agglomerations of spirochætes produce embolism of the capillaries, and as a consequence the characteristic lesions of the skin and mucous membrane.

During the secondary period the spirochætes are found in the papules, blood, and organs.

It is very difficult to find spirochætes in the blood on account of their small numbers.

In *congenital syphilis* spirochætes are often found in large numbers in the liver, spleen, and lungs. The spirochætes are usually disposed around the vessels. They are also found in the vesicles of pemphigus. Spirochætes have been found in the blood, the skin lesions, in the lymphatic glands, in the liver, in the suprarenal capsules, in the ovaries or testicles, in the lungs, in the spleen, in the pancreas, in the nerves, and in the bone cartilages. They are also found in the rachidien fluid and nasal mucus, sputum, ascitic fluid, bile, urine, meconium, and in the gastric juices.

Levaditi and Roche quote nine instances of inoculation of syphilis on men by means of syphilitic blood, including Julien's two cases.

Hoffmann was the first to demonstrate the infectivity of blood obtained from patients in the florid secondary stage of syphilis by inoculation experiments on apes. He showed that the blood was infective before the rash appeared, and remained so for as long a period as six months after the first appearance of the disease. The blood, however, cannot contain any large numbers of spirochætes, as only a small percentage of experiments give positive results. The infectivity of the spermatic fluid of a secondary syphilitic was demonstrated by Finger and Landsteiner.

Trinchese has reported his results of the examination of the *placenta* in a hundred cases in which the fœtus was syphilitic. He found the results agreed with those from examinations of the fœtal organs, and only failed in one case to find spirochætes in the placenta when their presence could be demonstrated in the fœtal organs. They are, however, much less numerous in the placenta than in the organs. He was able to demonstrate the passage of the spirochæta through the walls of the villus, and he considers that the spirochætæ circulate in the fœtal blood and penetrate through the vessel and villus, setting up a nodular thickening of the syncytium. The macroscopic appearance of the placenta in these cases did not differ from that of the normal placenta. In the fœtal organs the spirochætes were found in the largest number in the adrenal bodies; the liver and lungs were the next most infected organs, and here the organism occurred most frequently in the neighbourhood of the vessels. The ovary, testicle, and epididymus almost constantly contained organisms.

Experimental inoculations in animals have proved that blood in secondary syphilis, semen in secondary syphilis, saliva in secondary syphilis, and gummata in tertiary syphilis, all contain the syphilitic virus.

The occurrence of spirochætæ in the semen is a tardy proof of conceptional syphilis, which was long suspected, and appears to have been clinically proved by the case recorded by Buschke and Fischer, in which a mother, previously healthy, gave birth to a syphilitic child, and subsequently developed the disease.

INOCULATION

The first successful inoculation on animals was performed by Metchnikoff and Roux on a female chimpanzee two years old. The sites selected were the clitoris and eyebrow, and the material used was serum from a human primary sore. After about twenty-six days a chancre developed on the clitoris, and a papular rash occurred a month after the appearance of the chancre.

Metchnikoff and Roux have since reported the development of a secondary rash in 60 per cent. of animals whose inoculation was followed by a primary sore, and that this rash usually commences thirty-three days after the first appearance of the chancre. In the chimpanzee the rashes can be seen on the skin of the head, back, and abdomen, and are usually either papular or macular. Mucous plaques also are found on the mucous membranes.

The lower monkeys can also be successfully inoculated, and a chancre produced, but there is not such

a large percentage of successful inoculations, and secondary symptoms seldom, if ever, occur.

Bertarelli was the first experimenter to obtain satisfactory results with rabbits. He inoculated the cornea, and a well-marked keratitis was produced, which commenced four weeks after inoculation. The lesion first appeared as a greyish opacity, accompanied by some injection of the ciliary vessels. The opacity increases in size until half the cornea may be affected, and later the bloodvessels grow in from the sclerotic. The lesion tends to heal spontaneously, and in a couple of months or so recovery usually takes place.

Parodi later was successful in inoculating rabbits in the testicle. He introduced the virus into the substance of the testicle, but Truffi soon afterwards was able to show that it was sufficient to introduce the virus under the skin covering the testicle. When transmitting the infection, some observers use the serum obtained in a similar way to that required for examination by dark-ground illumination, which has already been described; others use the fluid obtained from the inside of an infected testicle, and others transplant small pieces of the lesion containing spirochætes.

One of two techniques is usually employed for the inoculation. In the first the epithelial layers of the skin are scarified with a scalpel, and the virus then rubbed in, the procedure being similar to that of ordinary vaccination with calf-lymph. Finger and Landsteiner introduced the second, or subepidermal technique. Here the epithelium is deeply scarified, and the virus rubbed and pushed into the deeper layers of the skin.

With a primary inoculation, in from five to eight weeks a small nodule occurs in the skin, which gradually increases in dimensions up to about the size of a pea, which may or may not ulcerate. Occasionally, infiltration of the skin takes the place of a definite nodule.

If the testicular substance is involved, the testicle will become enlarged, hard, and nodular.

Repeated passages apparently increase the virulence for the species, as the incubation period is shortened, even to as little as a fortnight, and a far higher percentage of successful inoculations are recorded, even up to 80 or 90 per cent.

The infection in rabbits is nearly always a local one.

Repeated rabbit passages do not apparently increase the virulence of the spirochæte for apes.

Roux, Metchnikoff, Levaditi, and Roche, of the Pasteur Institute, have elicited many interesting facts bearing on the pathology of syphilis, by means of inoculation experiments on the higher apes. They found that a small effusion of blood or serum facilitates the penetration of the virus, that a larger hæmorrhage prevents successful inoculation, and that the most constant results were obtained with superficial scarification of the epidermis. The spirochætes were found to be easily destroyed by phagocytes, and were seen inside the macrophages and polymorphonuclears in the lungs, liver, and spleen of new-born congenital syphilitics. Neisser, in fifty-one cases of subcutaneous injection, did not obtain one positive result. Thirty-three of these cases showed themselves later sensitive to inoculation by the epidermis, and certain of these

which resisted the first scarification reacted to the second. Thirteen were immune to all methods of inoculation, probably due to natural immunity, and not to the fact that the subcutaneous inoculation had 'taken.' Probably the subcutaneous inoculations excite a greater leucocytosis than inoculation of the superficial layers of the skin, with the result that the spirochætes are destroyed. Intravenous or intraperitoneal inoculation gave no positive results; inoculation into a lymphatic gland was also negative. Inoculation into testicles was followed in one case by a general immunity without local lesion, and in a second the spirochæte was found in the bone-marrow of an animal killed fifty-six days after the inoculation. The general opinion of experimenters seems to be that the spirochæta is incapable of effecting an entrance through sound skin or mucous membrane, and if their results are correct the great importance and danger of little superficial erosions and abrasions are emphasized.

J. Hutchinson, junior, expresses the firm belief in the frequent passage of the syphilitic virus through unabraded or normal skin and mucous membrane.

Positive inoculations were obtained in orang-outangs (not in other apes) with material from bone-marrow and spleen, and much less frequently with material from the testicle and lymphatic glands, thus showing a marked preference for blood-forming tissues. Negative results were obtained with inoculation with material from broken-down gummata, but with unbroken gummata that were opened and scraped, and the evacuated material ground up and inoculated, chancres developed in 60 per cent. of cases.

In man seven positive results were obtained out of eighteen cases inoculated with blood taken from cases with marked secondary syphilis.

Spermatozoa may occasionally contain the virus; inoculations with milk have so far all proved negative, and cerebro-spinal fluid has only very rarely given a positive result.

Filtering destroys the power of the virus as estimated by inoculation. The virus may be sterilized by desiccation, by keeping for three hours at a temperature of 10° C., or half an hour at 48° C., or subjecting it to the rays of the uveal lamp or the X rays. After twenty-two passages through apes the virus becomes attenuated, and the period of incubation lessened from nineteen to seven days.

Levaditi and Roche, in their book, 'La Syphilis,' mention the case of a man, aged seventy-nine, who was inoculated with a virus attenuated by passage through several apes, and who developed small papules at the point of the inoculation; but no ulceration of the papules occurred, nor any secondary symptoms.

INCUBATION PERIOD

It has been observed that the more resistant the animal is to infection, the shorter is the incubation period. Neisser considers that the duration of incubation depends, not on the virulence of the organism, nor on the resistance of the individual, but only on the quantity of virus introduced. Levaditi, on the other hand, considers that resistance and virulence both play an important part. Of six animals in which

the scarified spots were excised ten minutes, twenty minutes, two hours, four hours, ten hours, and twelve hours after, no subsequent lesion appeared. In another experiment, when the points of inoculation were excised eight and fourteen hours after scarification, chancres appeared. The duration of the period of incubation is due to the slowness of multiplication of spirochætæ transplanted into new surroundings. Already, long before the appearance of the chancre, the virus has reached the circulation. The organism spreads by the blood, and, perhaps by preference, by the lymphatics.

REINFECTION

There appears to be conclusive evidence that no individual is immune to syphilis, or that a syphilitic infection confers immunity. Numerous well-authenticated cases are now reported of reinfection with syphilis, and if an individual is immune to syphilis, we may conclude that he is still infected with it.

Cases of tabes and general paralysis have been inoculated without success.

J. Hutchinson, junior, has shown that the interval between two attacks of syphilis may be so short a time as eighteen months, and that the second attack may be either slighter or more severe than the first. Nothing positive can be laid down on this point.

J. Hutchinson, senior, has recorded one definite example of a patient having three attacks of syphilis.

Only a small number of undoubted cases have been recorded of the development of acquired syphilis in

congenital syphilitics, and J. Hutchinson, junior, doubts whether he has seen more than three or four in twenty years' very extensive experience.

Since the introduction of salvarsan several cases of reinfection within a few months are recorded, and successful reinfection has been performed on a chimpanzee with only three months' interval between the two inoculations, salvarsan having been administered after the appearance of a chancre had demonstrated that the first inoculation was successful.

The immunity to superinfection produced by the presence of syphilitic infection is not developed at once, and is not absolute.

Metchnikoff and Roux obtained positive reinoculations in monkeys ten days after the primary chancre had appeared.

Finger and Landsteiner could not obtain inocula tions after the chancre had been present for more than five days.

Neisser obtained seventeen positive results in fifty reinoculations on apes; of these, eight were made on the appearance of the primary sore, and nine later.

Positive results have been obtained when the second inoculation was made as late as fifty days after the appearance of the primary sore.

In the secondary stage of syphilis there is usually, but not invariably, complete immunity to superinfection, and this is also true of tertiary syphilis. This pseudo-immunity disappears with cure.

Frage and Landsteiner have succeeded in obtaining reinfection in the primary period and in the secondary and tertiary periods. According to their observations,

reinfection was expressed by a sclerosis in the primary period, by papules in the secondary period, and by gummas in the tertiary period.

The sequence of events in syphilis, which has been roughly divided into primary, secondary, and tertiary syphilis and parasyphilis, is capable of two explanations: (1) That the *Spirochæta pallida* undergoes a series of changes when resident in the tissues, and that in each of these successive phases the symptoms to which it can give rise are peculiar to the stage at which it has arrived; (2) that it is the tissues which change, so that the longer the spirochæte acts on them, the more the lesions which result from any increased activity of this parasite approach first the characters peculiar to the so-called secondary, and then those of the tertiary, stage.

The first explanation would be difficult to prove, and against it is the fact that infection with spirochætes derived from a secondary or tertiary lesion results in a primary sore. In favour of the second explanation is the well-known fact that in the majority of cases of syphilis, whether untreated or treated with mercury, reinoculation does not result in the production of a second chancre. As Queyrat showed, this refractory behaviour of the skin and mucous membranes to infection from without is gradually developed during the ten days which succeed the appearance of the primary sore; as the end of the period approaches, the sore resulting from reinoculation becomes more and more evanescent till, finally, no chancre follows. Finger and Landsteiner succeeded in producing skin lesions in such cases by inserting large amounts of

syphilitic virus in pockets under the epidermis; these were not chancres, however, but simulated the lesions from which the patient was suffering at the time. Thus in the secondary stage a papule followed the inoculation, while in patients suffering from gummata or ulcerating syphilides identical lesions formed at the sites of inoculation. That these were due to the newly introduced spirochætes, and not to those already infecting the patients, was shown by the fact that, if the former were previously killed, the result of the inoculation was negative.

The evidence is, therefore, strongly in favour of the theory that it is the length of time during which the spirochætes have acted on the tissues which determines the characters of the successive manifestations of syphilis.

Neisser argues that a really cured syphilis does not leave behind it a state of immunity, but thinks, on the contrary, that only in those cases in which the disease was still present was there a kind of so-called immunity—that is to say, a resistance to a fresh inoculation. He cannot accept the old dogma that during the presence of syphilis an absolute prevention against new inoculation exists, but neither can he agree with the opinion of Finger, Ehrmann, and others, who regard super-infection as quite a usual occurrence. He, Neisser, believes that we must accept the statement that, especially during the first few years of the disease, as long as the virus of syphilis still remains in the body, there exists a nearly complete resistance to a second infection.

Doubtless in the future many more cases of re-

infection will occur, since modern methods of treatment will probably succeed in rapidly effecting a cure of syphilis in many instances.

The old supposition is thoroughly false which states that a person with syphilis, or one who has had syphilis, can run the risk of acquiring further infection without fear of penalty.

IMMUNITY

The susceptibility of individuals with regard to syphilis depends on the degree of their immunity, either natural or acquired. Certain races have up till now been considered but little susceptible to its infection, as, for example, the inhabitants of Iceland, Greenland, and Central Africa. It is now recognized, however, that this immunity is only apparent, as, since intimate relations with Europeans were established, syphilis has appeared.

The question of immunity in the descendants of families of a syphilitic taint cannot be considered as proved. The only certain proof is the resistance to inoculation, and it is evidently impossible to state whether the absence of infection after coitus with an individual showing infective lesions has been due to the integrity of the mucous membrane or not.

The rarity of cases of reinfection has long been considered proof of an acquired immunity. There is, however, a possibility of reinfection. Since the Congress in London in 1896, many reliable observers have published cases of reinfection.

Numerous works on the serum therapy of syphilis

have shown that the serum is capable of producing some effect, but the problem cannot be solved until we are able to obtain a very active animal serum.

The possibility of active immunization of animals against syphilitic virus was shown for the first time by Roux and Metchnikoff, who employed a virus attenuated by several passages through macaques. They considered that the slight form of the disease produced by such an inoculation prevents an infection following an inoculation with non-attenuated virus.

Metchnikoff has satisfied himself by experiments on macaques that attenuation is obtained by passage. Only local lesions occurred in which the spirochætes were found, and general symptoms did not appear.

Metchnikoff and Neisser have tried to obtain passive immunity with the help of serum from monkeys who have recovered from infection. Satisfactory results, however, have not been achieved, and the monkeys were not guarded against subsequent infection. They have also vainly tried to obtain an immune serum from the goat, injected with material very rich in spirochætes.

In the hope of provoking an active immunity in cases of primary syphilis, and with a view to prevent the occurrence of secondary syphilis, Kraus and Volk inoculated with a carbolized emulsion of syphilitic lesions; they consider that they have abated the disease in a few instances.

For the active immunization of monkeys, emulsions have been tried made with the glands corresponding to the chancre, and also with organs of congenital syphilitics containing large numbers of spirochætes.

These emulsions were cooled in the ice-chest, and carbolic acid added in a dilution of 0·5 per cent. Repeated inoculations of the same product have not produced immunization of animals.

If, also, the degree of immunity of the organism is not very high, it will manifest itself by the presence in the blood and in the organs of specific antibodies, the formation of which corresponds usually with the elaboration of immunity. These antibodies are represented by agglutinins, bacteriolysins, precipitins, and a specific body producing the fixation of complement. The agglutinins are formed after appearance of the primary chancre.

Effect of Treatment on the Spirochæta.—Salvarsan, especially if given intravenously and in efficient dosage, causes a very rapid disappearance of the spirochætæ, which usually cannot be found after twenty-four hours, and can practically never be demonstrated after three days.

McIntosh and Fildes have recorded an experiment to show the relative merits of salvarsan and mercury. They selected two rabbits with severe testicular syphilitic lesions, and injected one intravenously with 0·1 gramme of salvarsan, and gave the other two doses of biniodide of mercury intravenously, giving in all 0·02 gramme of biniodide. No spirochætes could be found in the salvarsan-treated rabbit after seven hours, while they persisted in the mercury-treated rabbit for four days.

Metchnikoff and Roux have found that a chimpanzee, inoculated with virus and the part rubbed for ten minutes with calomel ointment three-quarters of an

hour after inoculation, developed no signs of syphilis, and showed itself sensitive to subsequent inoculations. A medical student, inoculated with the virus and rubbed with calomel ointment for five minutes one hour after inoculation, developed no signs of syphilis; but an unrubbed monkey and a monkey rubbed twenty-four hours after inoculation both developed syphilis.

CHAPTER III

SYPHILITIC ANÆMIAS

Anæmia has been recognized for a long time as often associated with syphilis, and it can be looked upon as probably the most constant of the constitutional changes of this disease, and is especially noticeable in the secondary stage.

In 1869 Virchow demonstrated a leucocytosis coincident with the enlargement of the lymphatic glands, with a relative increase in the number of lymphocytes. Zehleneff examined the blood of twenty patients daily for several weeks, and found a lymphocytosis in seventeen.

In 1872 Molassi first demonstrated the existence of a pronounced decrease in the number of red cells in three infected wet-nurses, and considered that the anæmia coincided with the general manifestations of the disease.

In 1874 Wilbowcheivitch demonstrated a reduction in the number of red corpuscles in the primary period coincident with an increase in the leucocytes. Outré noticed the appearance of large nucleated red cells (megaloblasts) during the appearance of the anæmia, and small nucleated red cells (microblasts) at the end

of this period. Gram considers that there is an increase in the number of microcytes, and that red cells of an irregular shape (poikilocytes) are always present.

Marie has recorded that the red cells show a diminished resistance to cold, so that they become laked when placed on ice more easily than normal cells.

The leucocytosis does not usually go above 15,000 to 18,000 per c.mm., but it is an early and very constant symptom and lasts for a long time, so that often it is the first and last syphilitic abnormality of the blood which is recorded. It commences independently of any local inflammatory or erosive condition of the skin or mucous membrame, and usually occurs between the healing of the chancre and appearance of the rash.

Most authors agree that anæmia reaches its climax during the secondary period, but different authorities vary as to the exact time of its onset, some stating that it precedes the rash, and others that it coincides with or follows it.

A lymphocytosis is usually first noticed, to be followed later by a diminution of hæmoglobin and in the number of the red cells. All these factors have been noticed three weeks before the appearance of the rash. After the appearance of the rash the anæmia grows worse, and tends to run a parallel course with the clinical manifestations, becoming intense with malignant syphilis, or passing off as the symptoms clear up.

In certain cases, coincident with the amelioration of the anæmia, there is an increase of nucleated reds and

blood platelets. The oscillations in the condition of the blood can therefore give an index of the resistance of the individual to infection.

In latent syphilis with no clinical manifestations, an anæmia may be the only symptom besides the Wassermann reaction, which shows that the cure is not complete and permanent. Sometimes, however, though the blood appears to have become completely normal, the anæmia returns with a reappearance of symptoms.

The rise and fall in the amount of hæmoglobin is coincident with the increase and decrease in the number of lymphocytes, and Mott considers that this may indicate that, with the pouring out of an abundance of lymphocytes from the lymph-stream into the blood-stream, there was associated a pouring out of the virus, causing the irritation and hyperplasia of the lymph-cell elements. He considers that the anæmia may be due to interference with the functions of the blood-forming tissues. In support of this is the fact, established experimentally by Neisser, that the red marrow and spleen are especially rich in the virus. Since mercury rapidly improves the anæmia, Mott thinks it probable that it does so by arresting the development of the spirochætes in the blood-forming tissues.

The anæmia seems to have a particular predilection for women and weak and over-worked young people, and seems to be usually of the nature of a chlorosis. This, however, is not invariable, and syphilis may produce alterations of the most different kinds in the blood, and the blood-picture may not be characteristic of any particular clinical form of anæmia. Though the

early stages almost invariably show the anæmia of a chlorotic type, later on the appearance may be that of pernicious anæmia.

In late syphilis the blood is usually very nearly normal, but really severe anæmia, when it occurs in syphilis, does so only in the later stages.

The cause of this occasional appearance of grave anæmia is unknown.

That the anæmia is not due to the mercury taken as treatment is shown by the fact that it exists prior to mercurial treatment, and that the blood condition improves under treatment. It is only when mercury has been given for a long time that its deleterious effect upon the blood is shown.

Dominici divides syphilitic anæmias into three classes:

1. Chlorotic type, without leucocytosis.
2. ,, ,, with leucocytosis.
3. Pernicious type.

Chlorotic Type, without Leucocytosis:

Twelve days before rash.

Red cells ...	...	...	5,350,000.
Hæmoglobin	...	...	100 per cent.
Leucocytes	...	...	5,000.

Twelve days after rash.

Red cells ...	...	...	3,950,000.
Hæmoglobin	...	...	80 per cent.
Leucocytes	...	...	8,000.

Chlorotic Type, with Leucocytosis:

Red cells ...	...	...	4,300,000.
Hæmoglobin	...	...	75 per cent.
Leucocytes	...	...	12,200.
Colour index	...	...	0·87.

Pernicious Type:

Red cells ...	...	...	1,540,000.
Hæmoglobin	...	...	40 per cent.
Colour index	...	...	1·33.

Influence of Treatment on Syphilitic Anæmia.

Justus states that when a large inunction or injection of mercury is given before the rash appears, but not before the time when the general enlargement of the lymphatic glands shows that the toxin is disseminated throughout the body, the treatment is followed by an immediate decrease in the percentage of hæmoglobin, from 10 to 20 per cent., to be followed by a rise, even above normal, in a few days. This fall followed by a rise is so constant that it can be used as a reliable test for the presence of syphilitic infection. Justus considers that this drop in the amount of hæmoglobin, which is both rapid and considerable, is a specific test for a case of florid syphilis, and may be obtained in any form of syphilis—late primary, secondary, tertiary, or hereditary—provided the disease be at that time florid, and not when or just before the symptoms begin to recede. It may again be obtained in cases of relapse and until the relapse has passed its climax. It is not present during the primary stage so long as the infection is limited to the chancre and its neighbouring glands, but only after the toxin has become widespread, as shown by the enlargement of distant glands. Justus's claim that this test is pathognomic cannot be taken as proved, though it is undoubtedly present in a large percentage of cases. Iron has no, or but a slight and transient, influence on syphilitic anæmia.

Syphilitic Anæmias of Infancy.

The form of anæmia occurring in congenital syphilitic children may be divided into three classes:

1. **Chloro-anæmia with Leucocytosis,** in which the number of red cells may be normal, and the hæmoglobin greatly reduced with a moderate leucocytosis. The following example is from a child of ten months:

Red cells ...	...	...	4,637,000.
Hæmoglobin	...	...	35 per cent.
Leucocytes	...	..	17,880.
Colour index	...	...	0·38.

2. **Pernicious Type,** where the red cells are greatly diminished in number, and, although the hæmoglobin is reduced also, it is not so to such an extent as the red cells, and therefore the colour index is raised. In this type there is but slight leucocytosis, if any. Example:

Red cells ...	...	...	1,236,000.
Hæmoglobin	...	...	30 per cent.
Leucocytes	...	...	11,700.
Colour index	...	...	1·25.

In this type there are usually very few nucleated red cells, but large numbers of megalocytes and gigantocytes.

3. **Leucæmic Type.**—Here the leucocytes may reach very large numbers and almost present the appearance of a myologenous leucæmia. The combined count of lymphocytes, myelocytes, and polymorphonuclears may number 50,000 or more. This type usually shows a large number of nucleated reds, many of these showing division of the nucleus.

Drysdale and Thursfield consider the following blood-count typical of ordinary congenital syphilis:

Red cells ...	...	...	4,224,000.
Hæmoglobin	...	...	76 per cent.
Leucocytes	...	...	13,463.
Colour index	...	...	0·9.

Mott considers that there is nothing in most cases of hereditary syphilis which is in any way remarkable or different from what may be seen in any moderate secondary anæmia in infancy. He considers that it is impossible to lay very much stress on the importance of lymphocytosis, as this is an hereditary feature of all infantile anæmias, and he considers it impossible to name any one feature in the blood-count which is distinctive of syphilis.

Following mercurial treatment there is often a fall in the number of cells coincident sometimes with hæmoglobinuria, owing to the destruction of those red cells which have been weakened by the syphilitic toxin. If the treatment is carried too far it may then be the cause of an anæmia.

It has been suggested that as cases of spasmodic hæmaturia practically always show a syphilitic history, the blood of syphilitics contains a hæmolysin. The author has examined the serum of twenty-five cases of syphilis, and has been unable to find any trace of such hæmolysin.

Primary Syphilis.—No blood change is noticed during this period, the first alteration usually appearing during the healing of the chancre a fortnight or three weeks before the onset of any secondary manifestations. Probably the first change is that of a leucocytosis with

a relative and absolute increase of lymphocytes. A slight deficiency in hæmoglobin then follows, to be followed again a little later by a decrease in the number of red cells.

Secondary Syphilis.—The red cells drop very rapidly, about 200,000 a day, and in untreated cases may fall to 2,000,000; at the same time the quantity of hæmoglobin decreases. The red cells are pale and vary in size and shape, showing a diminished resistance to cold. The leucocytes average 12,000 to 16,000, and may reach 25,000. At this stage the increase is both of polymorphonuclears and lymphocytes, and later there may be a slight eosinophilia.

Leoper thinks that the polymorphonuclear leucocytes appear with each exacerbation of the symptoms, and that the lymphocytes appear in the intervals between such exacerbations, when there may be a diminution in the number of polymorphonuclear leucocytes. Nucleated red cells appear to increase with the amelioration of the symptoms.

Mast cells may be numerous or may appear only occasionally.

Most observers agree that there is an increase in the amount of albumin in the serum in secondary syphilis. This was first observed by Aparis in 1840, who reported that the albumin of the plasma was increased proportionately with the decrease of red blood cells, the fibrin and serum being still of normal proportions. Gram later confirmed the increase in the amount of albumin.

In 1896 Valerio noticed a decrease in the alkalinity, density, and the amount of chlorides present in the

serum, and, proportional to the destruction of the red cells, there must be an increase in pigment, potassium salts, and phosphoric acid.

Tertiary Syphilis.—There is generally little blood-change at this stage, although, as stated above, very severe anæmias, when they occur, usually are found during this stage. As a rule, there is a slight increase in the number of leucocytes from 9,000 to 13,000, but sometimes the leucocytes are less than the normal (leucopeny). The increase may be either in the polymorphonuclears or lymphocytes. Some observers state that eosinophiles are present in greater numbers in this than in other stages.

During the tertiary stage with severe anæmia there is usually leucocytosis with a high lymphocytosis, myelocytes also being present. A marked leucocytosis is an aid in excluding pernicious anæmia. In an adult high lymphocytosis and an increase in eosinophiles suggest syphilis, and in a child this blood-picture might suggest rickets also. A low hæmoglobin percentage and a high percentage of small mononuclears have been considered indications that the infection is acute.

Parasyphilis.—*Tabes.*—In tabes there is but little change; perhaps there may be a slight excess of polymorphonuclears.

General Paralysis.—In G.P.I. the blood-changes are not very constant; sometimes there is an increase in the number either of polymorphs or lymphocytes; sometimes there is an increase in the eosinophiles, and sometimes the white count is normal.

CHAPTER IV

THEORIES FOR AND NATURE OF WASSERMANN REACTION.

Pfeiffer's Phenomenon. — Pfeiffer found that if certain organisms, such as the cholera spirillum, were injected into the peritoneal cavity of a guinea-pig that had been immunized against these organisms, they almost immediately lost their mobility, and gradually became granular and swollen, and subsequently disappeared. Later he found that the same phenomenon was present if a small quantity of antiserum was added to an emulsion of the organisms, and the mixture injected into the peritoneal cavity of a normal guinea-pig. Later it was shown by Metchnikoff and Bordet that the destruction of the bacteria (bacteriolysis) occurred outside the body if to the mixture of antiserum and bacteria a little fresh serum was added; and Pfeiffer found that if the antiserum was heated at from 55° to 70° C. for an hour, and added to the bacteria emulsion, no bacteriolysis would be produced, but that on the addition of some fresh serum bacteriolysis would occur.

Ehrlich gave the name of 'complement' to this substance present in fresh normal serum which had the power of enabling specific antigens and antibodies to produce their action.

Antigen-Antibody Reactions and Complement Fixation.—Before commencing the serum diagnosis it may be stated that by 'antigen' is meant a substance which, when it is introduced into a living body, stimulates the cells of that body to produce a substance which destroys or neutralizes it, and to which the name 'antibody' has been given. It is probably by this antigen-antibody action that recovery takes place in most bacterial diseases, and the antigen or virus is ultimately neutralized by its specific antibody. In the case of toxin and antitoxin this reaction can take place directly in the body or *in vitro*, and the reaction appears to be a purely chemical one. With cells or micro-organisms, or the extract or solution of cells or micro-organisms, however, the action is more complex. The antigen and antibody do, indeed, become linked together, but the presence of a *third* substance is necessary to activate or stimulate this union of antigen and antibody before the neutralizing or destructive process can be completed. Various names have been given to this third activating body by different workers, but the author will only refer to it by its most familiar name, 'complement.'

The complement in activating the mixture of antigen and antibody becomes used up, and is therefore not available for further use.

It need hardly be mentioned that 'lysis' means solution, and that therefore 'bacteriolysis' signifies solution of bacteria, or 'hæmolysis' solution of red corpuscles.

Antigen and antibody are generally specific, so that a diphtheria antigen produces only a diphtheria anti-

body, and a hæmolytic antigen—viz., red blood-cells—produces only an antibody to the same or closely allied variety of blood-cells. The specificity is so delicate that strains of organisms so closely allied as to be morphologically and culturally similar can be differentiated by a complement fixation test. In the case of bloods, however, when the species are closely allied, this method cannot be used for differential diagnosis, as an antibody obtained by injection of a rabbit with ox corpuscles will produce hæmolysis of sheep's corpuscles.

Fischer uses the analogy of a lock and key and hand, for antigen, antibody, and complement respectively. Thus, as any hand can turn any key in its own lock, the key can only turn its own lock, and the key cannot turn in the lock without the hand, so any complement can complete the action of any combined antigen and antibody, but the specific antibody only unites with its own antigen, and the combined antigen and antibody cannot complete their interaction without the aid of complement.

The antibody unites readily with the antigen even at room temperature, so that if, after standing for half an hour, the mixture of antibody and antigen be centrifuged and all the serum removed with a pipette, it will be found, on the addition of complement and incubation for a while at 37° C., that the specific action is produced, thus showing that the essential factor in the immune serum has become linked to the antigen during the period when they were in contact.

Complement, however, which is a normal and constant constituent of all fresh blood sera, is not specific

(although probably several complements exist), and can activate any antigen that has united with its own antibody. It is as yet an unisolated and little understood substance, and is really only the name given to a property, present in all fresh sera, which enables an antigen and antibody not only to unite—which, as shown above, they can readily do without complement—but, having united, to produce their specific action.

In the Wassermann reaction fresh guinea-pig's serum is generally used for complement, for the reason that guinea-pig's serum contains a large amount of complement (usually about five to ten times as much as a similar quantity of rabbit's serum).

Complement has no power of fixing by itself either to the antigen or antibody.

The optimum temperature of a complementary action is 37° C.; it is, however, capable of action slowly at room temperature; but its action entirely ceases at 0° C.

Antibodies are very stable and preserve their properties for a very long time, and are not destroyed or greatly decreased in potency by a temperature of 55° to 57° C.

Complement is not a ferment, and a definite amount of complement is necessary to produce the action of a definite amount of antigen and antibody; so that if twice the amount of antigen is used, twice the amount of complement will be required.

Everyone with much experience of the Wassermann reaction, however, has noticed that with a large excess of antibody hæmolysis of the sheep's corpuscles is

produced with a smaller quantity of complement than would be necessary with a smaller amount of antibody. And the converse is also true—an excess of complement will produce hæmolysis with a smaller quantity of antibody.

Browning and Mackenzie have aptly described this interaction when they say: 'The amount of antibody required is a minimum when an excess of complement is present, and *vice versa*.'

All complement fixation tests are quantitative, and for this reason beginners are very likely to be led into error, for a reading which at one time would be reported as doubtful, at another time would be reported as positive or negative.

Bordet-Gengou Phenomenon.—The Bordet-Gengou phenomenon, discovered in 1901, is founded on the elementary axiom that 2 into 1 won't go; two antigens, two antibodies, and one complement being used—viz., sufficient complement to activate one combined antigen-antibody. If, for example, an emulsion of cholera vibrios and inactivated anti-cholera serum—*i.e.*, serum containing cholera antibody which has been decomplementized by heating to 55° C.—is mixed with some fresh complement and incubated for one hour at 37° C., and sheep's corpuscles and a decomplementized serum containing a hæmolytic antibody are added, and the mixture incubated for another hour, no hæmolysis will take place, because the entire quantity of complement will have been used up in activating the cholera antigen which has united with the cholera antibody, so that solution of the bacteria is produced, and therefore no comple-

ment will be left over to activate the hæmolytic system and produce a solution of the corpuscles.

The converse of this experiment is also true; for if sheep's corpuscles and hæmolytic antibody and complement be mixed together and incubated, solution of the corpuscles will occur; but if this mixture is then added to a mixture of an emulsion of cholera vibrios and cholera antibody, no solution of bacteria will now occur. By this reaction antibodies have been found and demonstrated in typhoid, diphtheria, tubercle, gonorrhœa, dysentery, cerebro-spinal meningitis, and leprosy (James McIntosh).

Wassermann Reaction. — The Wassermann reaction, as originally described, was merely a modification of the Bordet-Gengou reaction, using for antigen an aqueous or alcoholic extract of the liver of a syphilitic fœtus, which experience has shown to contain enormous numbers of *Spirochæta pallida.*

The test was originally supposed to turn upon ascertaining the presence in the tested serum of any syphilitic antibody, the extract of liver being used as antigen. A hæmolytic system is used for the second part of the experiment in order to test whether the complement has been used up in the first part of the experiment or not.

The addition of the hæmolytic system is not an essential part of the test, but simply a biological indicator for the presence of complement, in the same way as the addition of litmus is a chemical indicator for the presence of an acid or alkali produced as the result of a chemical reaction.

The specific antigen and antibody, or any other

antibody present in a normal serum, can each separately absorb a small quantity of complement, but a very much greater quantity of complement is used up in activating the *combined* antigen-antibody, so that the specific antigen destroying reaction can occur. Thus, if one volume of complement is absorbed by two volumes of specific antigen, specific antibody, or normal serum, when acting on each separately, making three volumes in all, five, ten, or more volumes of complement will be absorbed by the combined specific antigen and antibody.

Absolute alcohol alone will absorb or destroy a certain quantity of complement.

When testing for the presence of any antibody in the test serum, therefore, we must add an excess of complement over the amount that could be absorbed by specific antigen, or normal serum.

If the patient's serum contains no antibody, the complement will remain free, and therefore will be able to sensitize the hæmolytic system, with the result that hæmolysis occurs.

Levaditi considers the Wassermann reaction not due to antibody, but to some other substance produced by a pathological metabolism of cells. He demonstrated that antigen was not true antigen, as extracts from normal liver produced the reaction, while Weil and Braun showed that an extract made from a congenital syphilitic liver, from which all lipoids had been extracted, could still be used as antigen. They also demonstrated that jaundiced and lipæmic sera gave negative reactions, thus showing that lipoids were not the cause of the reaction.

Bordet, with his absorption theory, suggested that the active substance in syphilitic serum brings about some change in the antigen, so that the altered antigen acquires a greater absorptive power for complement. Noguchi and others consider the reaction due to interaction between albumin of the antibody and lipoids of the antigen, probably as the result of the precipitation of some of the colloids of the serum.

Wassermann thinks that the antigen is derived directly from the *Spirochæta pallida*, but this opinion seems to be based on data inconclusive to most other workers. If the Wassermann reaction is purely a specific one, consisting of the union of antigen (derived directly or indirectly from the spirochæta) and the antibody present in the infected patient's serum, as the result of infection with the spirochæta, we should expect that the reaction would only be produced when extracts from syphilitic tissues were used. This, however, is not the case, and a mixture of syphilitic serum and an extract of non-syphilitic organs fix the complement very nearly, if not quite, as satisfactorily.

Whatever may be the nature of the reaction, we are faced with the conclusion that clinically the test is, with a few exceptions, pathognomic of syphilis, and that this test holds good if substances are used for antigen which have nothing whatever to do with syphilis. Plaut thinks that the most probable explanation is that the antigen obtained in syphilitic or normal tissue is identical, but that syphilitic organs usually contain this antigen in larger amount or in a more easily extractable form than non-syphilitic organs. He considers that it is proved that a sub-

stance is found in syphilitic serum which reacts also towards the products of normal tissues, and that the original conception of the biological specificity of the reaction is therefore no longer to be held as correct in its full sense.

Many observers consider the antigen to be in the nature of a lipoid, and Levaditi and Yamanouchi further consider that the antibody found in the cerebro-spinal fluid of general paralytics is also a lipoid, and soluble in alcohol. Pure lipoids, however, although they fix complement, show but little difference in the quantity of complement they fix when mixed with syphilitic serum or normal serum.

Sodium oleate, cholesterin, sodium glycocolate, etc., have all been proved to fix complement, but fix but little more, if any, in the presence of syphilitic sera than they do in the presence of normal sera.

Browning and Mackenzie have found that a mixture of cholesterin and lecithin not only fixes much more complement than either of the constituents of the mixture by itself, but that much more complement is fixed in the presence of syphilitic sera than in the presence of normal sera. The author has investigated their claim in over a hundred sera, having made parallel tests of the same sera, using extract of syphilitic organs, extract of normal organs, and cholesterin-lecithin mixture as antigen, and has obtained practically identical results with all three.

As regards the serum, exposure to a temperature of 55° to 57° C. for half an hour certainly seems to diminish the reaction. Prolonged exposure at these temperatures can destroy the reacting power altogether.

Bruck considers that a temperature of 60° C. increases the complement fixing-power of sera by themselves. It has also been shown that normal sera may have a complement fixing-power in the unheated state which disappears if it is heated at 55° C.

No definite conclusion has yet been arrived at as to what the Wassermann reaction really is.

Weil and Braun consider that in the course of the disease tissue-products, mixtures of albumin and lipoid probably, are absorbed and give rise to antibodies.

Citron considers that the syphilitic toxin becomes combined with lipoids, and that this combination of toxin and lipoid acts as an antigen, and leads to the production of an antibody in the sera.

Bruck and Stern think that the reaction may be brought about by the interaction between mixtures of albumin and lipoid found in the extract and mixtures of albumin and lipoid found in the serum.

Mott considers that the substance present in the serum or cerebro-spinal fluid necessary to produce the reaction may be the detachable products of nerve-tissues.

Neither lecithin nor cholesterin, if used as antigen, can produce antibody.

Plaut comes to the conclusion:

1. That the Wassermann reaction is a biological specific antigen-antibody reaction for syphilis, in which the antibodies on the one side have the peculiarity of reacting, not alone with syphilitic antigen, but also with normal tissue constituents, and that the antigen, on the other hand, is very closely related to the lipoids, and probably is an albumin lipoid compound.

2. The reacting substances of the syphilitic serum are not antibodies, but substances which owe their origin to syphilitic infection and possess a chemical affinity for lecithin.

3. In the Wassermann reaction specific and non-specific fixation processes go hand in hand.

That the complement-fixing substance (antibody) exercises no spirochæticidal action has been proved by experiments both *in vivo* and *in vitro*. In the one case an ape was injected with large quantities of serum containing a large amount of complement-fixing substance which, however, did not prevent successful inoculation with syphilitic virus, and in the second serum obtained from a chancre, and containing large numbers of spirochætes, was treated with a mixture of complement and serum containing a large amount of complement-fixing substance. This mixture was then used to inoculate an ape, with positive results.

According to Citron's theory, mentioned above, the antibody produced is one in which the mixture of toxin and lipoid is the antigen and not the spirochæte. This antibody, therefore, could not be expected to produce immunity to the *Spirochæta pallida*, which agrees with experimental findings.

Weil and Braun found that an extract of syphilitic liver from which all lipoids were removed yet remained an efficient antigen.

McIntosh and Fildes point out that Sach's observation that the Wassermann bodies are destroyed by a temperature which does not affect true antibodies, and that Satta and Donetti's demonstration that fixation of complement in the Wassermann reaction can take

place in the ice-chest as well as at 37° C., and Mutermilch and McIntosh's observations that the Wassermann body does not pass through a filter, all tend to show that the reaction is rather physico-chemical than biological.

The effect of treatment, also, is to destroy the Wassermann body, and not to produce it, the disappearance of symptoms coinciding with the diminution or loss of complement-fixing substance. This is paricularly striking after treatment with salvarsan.

The physico-chemical theory was first suggested by Levaditi and Yamanouchi, who thought that the fixation of complement was due to an interaction between substances in the serum and in the extract used as antigen, so that the resulting mixture had a greater affinity for complement.

Wolfsohn and Reicher, and later Boas and Petersen, have shown that if blood is obtained towards the end of a period of deep anæsthesia, some specimens will give a positive Wassermann reaction. These experiments certainly suggest that the reaction is produced by some form of cell destruction, and could not be the result of an antibody.

The high percentage of positive Wassermanns obtained with blood taken from the cadaver also supports this view.

From the above opposing theories, and from the rather contradictory nature of the evidence at present available, it is obvious that the precise nature of the reaction has yet to be discovered. We are, however, able to arrive at two conclusions :

1. That the reaction in the absence of a few diseases and conditions, which can easily be eliminated, is a reliable clinical test for syphilitic infection.

2. That the reaction is not strictly specific, that the substance produced is not a true antibody, and that the so-called antigen is not a true antigen.

CHAPTER V

PREPARATION AND TITRATION OF REAGENTS REQUIRED FOR WASSERMANN REACTION

The materials required in the original method for the estimation of the Wassermann reaction are five in number.

1. Syphilitic antigen, or rather pseudo-antigen, prepared either from syphilitic organs, normal organs, or lecithin and cholesterin.
2. The patient's blood-serum.
3. Complement from fresh guinea-pig's serum.
4. Washed sheep's corpuscles (hæmolytic antigen).
5. A serum hæmolytic to sheep's corpuscles (hæmolytic antibody).

1. Syphilitic Pseudo-Antigen.

(1) **Extract of Syphilitic Organs as prepared by Noguchi and Mott.**—The weighed liver of a syphilitic fœtus is ground up with a sufficient quantity of silver-sand and plaster of Paris, so that after a few hours it can be reduced to a powder; this powder is then washed with acetone, which removes bodies which have anticomplementary and hæmolytic

properties. The acetone is then filtered off, and the remaining solid material is allowed to dry at room temperature. The dry residue is then transferred to a flask and a sufficient quantity of alcohol added; this flask is kept at room temperature and occasionally shaken. After two days the alcoholic extract is filtered off, and the filtrate made up with alcoholic washings of the powdered organ so that 4 c.c. is equivalent to 1 gramme of liver. The extract keeps well for several months without much deterioration, and should be stored in the dark and in the cold.

(2) **Extract of Normal Organs.**—Human heart, ox's heart, guinea-pig's heart, all have their advocates, but personally the author prefers an extract of rabbit's heart, with which excellent results have been obtained. The heart should be fresh, should be washed in saline to remove all blood, as much connective tissue as possible should be removed, and the opened heart roughly dried between filter-paper. The heart is now weighed and afterwards cut up into small pieces with scissors. A little absolute alcohol is added, and the mixture well ground in a pestle and mortar. More alcohol is slowly added, till the final quantity of 10 c.c. of alcohol to 1 gramme of heart is reached. The mixture is kept in a stoppered bottle at room temperature for two days, and occasionally shaken; it is then centrifuged, and the supernatant fluid pipetted off and stored in the cold and in the dark.

(3) **Mixture of Lecithin and Cholesterin** (Browning, Cruikshank, and Mackenzie).—The *lecithin* is obtained by making an alcoholic extract of fresh and finely minced ox liver, one part of liver being taken to

four parts of 95 per cent. alcohol. This is kept at room temperature and occasionally stirred; after four days the supernatant fluid is pipetted off and evaporated at 60° C. till a syrupy mass remains. This is treated in succession with ethyl-acetate, water-free ether, and acetone, and the alcoholic lecithin solution so obtained is kept in a stoppered bottle in the dark. The *cholesterin* used by the authors of this method was obtained from Kahlbaum or Roulene Frères. It is added in excess to a 0·75 solution of lecithin in alcohol. As saturation occurs only slowly at room temperature, the mixture should be allowed to stand for a week before the clear fluid is drawn off and stored for use.*

A good antigen, no matter how prepared, is one producing a large deflection of complement in the presence of a syphilitic serum, and which fixes but little complement by itself or in the presence of a normal serum. Absolute alcohol alone and alcoholic extracts in the presence of normal sera have power to fix a certain amount of complement.

When standardizing the antigen various quantities of antigen are added to test-tubes containing constant quantities of syphilitic serum and complement, and the tube noted in which the smallest amount of antigen is capable of producing complete inhibition of hæmolysis, indicating complete fixation of complement.

* Particulars of the method of preparation will be found in Browning and Mackenzie's book on 'Recent Methods of Diagnosis and Treatment of Syphilis,' p. 38. The mixed alcoholic solution of lecithin and cholesterin can be obtained from Messrs. Thompson, Skinner, and Hamilton, 38, Sauchiehall Street, Glasgow.

A second row of test-tubes contain complement and antigen alone, and no serum; and a third row complement and antigen, and normal serum in place of the syphilitic serum. The antigen selected for use should fix very little complement by itself alone or in the presence of normal serum, and at least three times as much antigen should be necessary to fix a given quantity of complement with normal serum than would be required with syphilitic serum.

2. Patient's Serum.

Test Serum.—The blood is collected in a sterile tube. After being allowed to stand for a couple of hours, it is centrifuged and the clear serum drawn off with a sterile pipette, sealed in small sterile glass phials, heated in a water-bath at a temperature of 55° C. for fifteen minutes in order to destroy the complement which it contains, and stored in a cool place in the dark. It is preferable to have a considerable quantity of serum, so that a quantitative measurement of the complement-fixing substance may be undertaken, and in order that the experiments may be repeated should the controls not work out satisfactorily. For this reason the author prefers obtaining blood by venipuncture rather than by pricking the finger. When collecting numerous samples of blood by venipuncture, the use of a syringe necessitates a considerable waste of time, as the syringe cannot, after use, be plunged into boiling water for re-sterilization without great danger of cracking, neither can it safely be removed from boiling water. If the temperature is gradually raised to boiling-point, and

then lowered, at least ten minutes will be required for each case. Instead of a syringe, therefore, the author uses a hollow metal holder, $2\frac{3}{4}$ inches long, having a finger-grip half an inch from the nozzle end. The bulbous distal end is connected to about 4 inches of rubber tubing, leading to a sterile test-tube, into which the blood flows directly (see Fig. 14). The author uses needles 1 inch long, and with the calibre of a large exploring needle.

Technique.—After washing the bend of the elbow with ether and absolute alcohol, a firm bandage is applied round the upper arm, and the patient is told

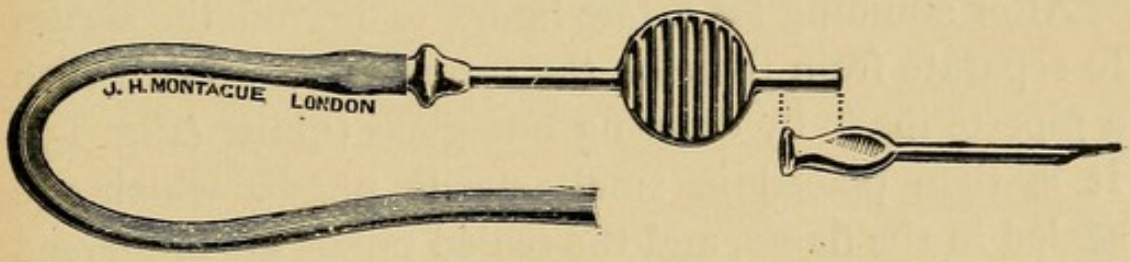


FIG. 14.—VENIPUNCTURE NEEDLE AND HOLDER (AUTHOR'S PATTERN).

'to make a fist.' Either the median basilic or median cephalic vein can then easily be seen. The needle, after being lubricated with sterile oil, is plunged boldly into the vein with a quick stab, keeping the needle and holder in the direction of the long axis of the vein, taking care not to depress the point too much in order to avoid transfixing the vein. The blood will flow directly into the tube, and it will only take a few seconds to half fill it. The glass test-tube and the needle-holder, with the rubber tubing leading into the test-tube, can be held quite easily in the right hand. Before making the puncture, the skin over the vein should be rendered tense and pulled a little down over

with the thumb of the left hand. The bandage must be loosened and the patient told to unclasp his hand before the needle is removed, otherwise a subcutaneous hæmatoma may be produced. If a small pad is held over the puncture, and the patient told to hold his arm in the air for a few minutes, there will be no bleeding, and no dressing will be required. The author always places a sterile swab soaked with methylated spirit over the puncture before removing the needle, and in this way not a single drop of blood escapes, except into the test-tube, and the patient sees no blood at all.

After standing for a few hours to permit the serum to separate from the clot, the serum is withdrawn with a pipette made by drawing out glass tubing (Fig. 15). It is then placed in small sterile phials, which are sealed in the flame, and the sealed phials are immersed in a water-bath at a temperature of 55° C. for fifteen minutes to destroy the complement contained in the serum.

After use, the holder and rubber tube should be washed through with a small glass urethral syringe to remove the blood before replacing in the sterilizer.

If, as very occasionally happens, a patient objects to venipuncture, or a vein of sufficient size cannot be found, or, as with children or infants, the test has to be undertaken with a smaller quantity of serum, then in these cases the blood is obtained by pricking the finger, or, as the author usually finds more suitable with small infants, the great toe or heel. In small, marasmic infants it will be necessary to soak the limb in hot water before pricking. The blood is collected in

large Widal tubes, which are filled by capillary attraction.

3. Complement.

This is obtained from fresh guinea-pig's serum, a guinea-pig being selected because its blood is very rich in complement, and its complement content is very nearly constant; guinea-pig's serum usually contains from five to ten times the amount of complement found in rabbit's, horse's, or human blood. The author thinks that the largest amount of serum is obtained from a guinea-pig in the following way: Some cotton-wool is placed in the bottom of a wide-necked glass jar of such a size as to easily admit the guinea-pig's head; a few drachms of

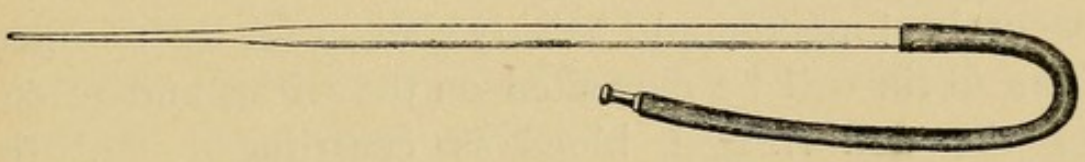


FIG. 15.—PIPETTE FOR DRAWING OFF BLOOD OR SERUM.
(One-third natural size.)

ether are poured on the cotton-wool, and the jar is then slipped over the guinea-pig's head. When anæsthesia is complete, the chest is opened and the blood removed by puncturing the heart with a pipette (Fig. 15). If the heart and lungs are now removed, a little additional blood can be collected from the thoracic cavity. After standing for a quarter of an hour, the blood should be whipped for a few minutes and then centrifuged, when the clear serum is pipetted off. The author thinks it is best to prepare the complement on the evening before, and store it in the ice-chest for use the following day.

The complement-content of fresh guinea-pig's serum does not usually vary very much, but it is wise to put up three tubes containing the amount of complement to be used in the test, and containing respectively the usual quantities of antigen alone, antigen and normal serum, and antigen and syphilitic serum. Complete hæmolysis should be produced in all but the tube containing the syphilitic serum, in which there should be no hæmolysis.

4 and 5. Hæmolytic System.

(*a*) **Sheep's Corpuscles.** — Fresh blood is collected at the slaughter-house into a sterilized wide-necked glass bottle containing several pieces of wire. The bottle is half filled with blood, when it is securely stoppered and briskly shaken for ten minutes. The fibrin will be deposited on the wires, and 10 c.c. of the defibrinated blood is centrifuged and the supernatant fluid pipetted off. Normal saline solution is added to the deposit of red cells, which are shaken up, and the mixture of salt solution and corpuscles again centrifuged. The supernatant fluid is again pipetted off and thrown away, and fresh normal saline added to bring the volume up to the original 10 c.c. In this way a suspension of sheep's corpuscles free from serum and complement is obtained.

Eight c.c. of this suspension is added to 92 c.c. of normal saline solution, producing an 8 per cent. solution of washed sheep's corpuscles, which is the strength the author employs. If stored in an ice-chest, the corpuscles will usually keep three or four days without hæmolyzing.

Some observers consider that greater accuracy is demanded, and count the corpuscular suspension with the Throma-Zeiz, in this way insuring that the corpuscular suspension is always constant as regards numbers. It appears to the author, however, that different corpuscular suspensions vary in their susceptibility to hæmolysis, and that therefore we cannot insure that any two corpuscular suspensions are constant factors.

The quantity of immune body required is in direct proportion to the number of red cells, a 20 per cent. suspension requiring just twice as much hæmolytic serum to produce complete hæmolysis as does a 10 per cent. suspension.

Some authorities consider that the corpuscles keep longer if a little formalin has been added to the normal saline solution (in proportion of 0·1 per cent.). Personally, the author prefers to use fresh blood, as he thinks that the formalin tends to harden the corpuscles and retard or prevent hæmolysis.

(*b*) **Hæmolytic Serum.**—This can be obtained by treating a rabbit with washed sheep's corpuscles. The rabbit may be injected either intravenously in the marginal auricular vein or intraperitoneally. In the latter case, which is easier, but perhaps not quite so satisfactory, the rabbit should be held with its head downwards, the abdominal walls being grasped with the fingers and thumb of the left hand so as to make a fold containing no intestines, and this is *transfixed* with a needle attached to the syringe containing the sheep's corpuscles. When the left hand is taken away, the fold disappears and the needle is withdrawn,

so that the point re-enters the abdominal cavity; the contents of the syringe are now injected into the peritoneal cavity, and the needle removed. Usually about three injections are required to obtain a potent serum, the injections being given at intervals of four to six days.

Recently, Burroughs and Wellcome have placed a hæmolytic serum, obtained from the horse, on the market, and the author has found it quite satisfactory in use. The horse serum, however, contains hæmo-agglutinins as well as hæmolysins, but the agglutinins do not act in dilution above 1 in 400. It is important, therefore, that the serum should have a high hæmolytic titre, such as 1 in 800 or 1 in 1,000, as, if agglutination occurs, the red cells clump and fall to the bottom of the test-tube before the hæmolysin has had time to act on them and dissolve them.

Hæmolytic serum, whether obtained from the rabbit or the horse, keeps its hæmolytic power for a long time, and the hæmolytic titre falls very gradually as a rule.

The hæmolytic serum should be used in excess, about twice the hæmolytic dose being recommended by Wassermann. Varying dilutions of hæmolytic serum are added to tubes containing constant quantities of complement and suspension of sheep's corpuscles, and the tube noted in which complete hæmolysis is just produced in five minutes in a water-bath at a temperature of 37° C.

If a smaller dilution than 1 in 400 is necessary, the serum cannot be considered satisfactory, as agglutination of the corpuscles may be produced, which may interfere with the action of the hæmolysin.

A rapid dilution can be effected in the following way: Into two test-tubes measure 9 c.c. of saline solution; to the first add 1 c.c. of the hæmolytic serum to be tested, shake and add 1 c.c. of this to the second; this will give a solution of 1 in 100. Now put 5 c.c. of saline into five test-tubes and to the first tube add 5 c.c. of the mixture from the test-tube containing the dilution of 1 in 100, shake and take 5 c.c. of this and add it to the next tube, and so on. In this way dilutions of 1 in 200, 400, 800, 1,600, and 3,200 will be rapidly effected. If complete hæmolysis is produced in 1 c.c. of an 8 per cent. suspension of sheep's corpuscles containing 0·05 c.c. of fresh guinea-pig's serum with 1 c.c. of hæmolytic serum in a dilution of 1 in 800 to 1,600, the hæmolytic serum may be considered a good one.

CHAPTER VI

WASSERMANN REACTION

ORIGINAL TECHNIQUE

Quantitative Measurement by Variation in Amount of Complement.

The first technique described is a modification of Neisser's and Wassermann's that the author uses, and in which all the essentials of Wassermann's original technique are preserved.

Two test-tubes are required for each serum examined, whether sera to be tested or controls. The latter consist of a known syphilitic serum, a known normal serum, and a tube without any serum at all.

The tubes are arranged in two rows, those in the back row containing three times as much complement as the front row, so as to obtain a roughly quantitative estimation of the complement fixing-power of the serum. The quantities of the various ingredients, which the author has found to be most convenient, are—For the front row, 1 c.c. of normal salt solution, 0·1 c.c. of antigen, and 0·05 c.c. of fresh guinea-pig's serum per each tube. Considerable time is saved and greater accuracy obtained if these three constant factors (salt solution, antigen, and complement serum)

are first mixed in bulk (instead of separately in each test-tube) and afterwards 1 c.c. of the mixture measured into the test-tubes, to which 0·15 c.c. of the serum to be tested is added. Let us suppose that there are seven sera to be examined, making a total of ten with the three controls. Ten c.c. of saline solution are then taken, 1 c.c. of antigen, 0·5 c.c. of fresh guinea-pig's serum. These are well mixed together, and 1 c.c. of the mixture put into each of the test-tubes in the front row. For the back row similar quantities of saline and antigen are used, but three times the amount of complement—namely, 0·15 c.c. per each tube, or 1·5 c.c. for the ten. By this mixing of the saline, extract, and complement in bulk, only two pipette measurements are required instead of four, which would be necessary if the saline, antigen, complement, and test-serum were added separately to each tube.

If the antigen alcoholic extract is mixed with the full quantity of normal saline, only a slight opalescence is produced. If, however, the antigen extract is first mixed with its own quantity of saline, a marked turbidity results, and if this is then added to the rest of the saline, the turbidity remains. Browning and Mackenzie and the author, working independently, arrived at the conclusion that the best results were obtained when the turbid emulsion was used, and this is still the author's opinion. MacIntosh and Fildes, on the other hand, consider that if a turbid emulsion is used, there is a liability to complement fixation even with normal sera, and they recommend, therefore, that the antigen extract should be rapidly mixed with the

full quantity of serum, so that there may be as little turbidity as possible.

The neck of the ampule containing the decomplementized test-serum is now broken off and the required quantity (0·15 c.c.) removed with a teat-pipette (Fig. 16) and added to the front row and corresponding back-row tubes.

After adding the 0·15 c.c. of the various sera to be tested to their respective tubes, using the same quantity for both front and back rows, the tubes are inverted, keeping the thumb over the open end, so as to diffuse the serum equally in the test-tubes. The test-tube rack is now placed in a water-bath at 37° C.

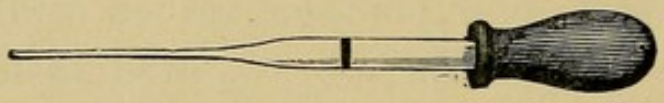


FIG. 16.—TEAT-PIPETTE, MARKED TO MEASURE 0·15 C.C.

for half an hour (Fig. 17). Having previously ascertained the strength of the hæmolytic serum, a dilution of such serum is now prepared of such a strength that each tube will contain *twice* the dose necessary to produce complete hæmolysis in 1 c.c. of an 8 per cent. suspension of washed sheep's corpuscles. Let us suppose that the hæmolytic serum previously tested produced complete hæmolysis of an 8 per cent. suspension of sheep's corpuscles in a dilution of 1 in 1,600. We must obtain a dilution of 1 in 800 in the final test. For our twenty tubes (ten in each row) we required 20 c.c. of the sensitized corpuscles; we therefore take 10 c.c. of a dilution of 1 in 200 of hæmolytic serum and add to it 10 c.c. of an 8 per cent. suspension of sheep's corpuscles, when we shall have

a dilution of 1 in 400, making 20 c.c. in all; this mixture of hæmolytic antigen and antibody is called the 'hæmolytic system.' One c.c. of this mixture is then added to each of the tubes which have been incubated for half an hour, so that the final dilution of 1 in 800 is arrived at. The tubes are now inverted

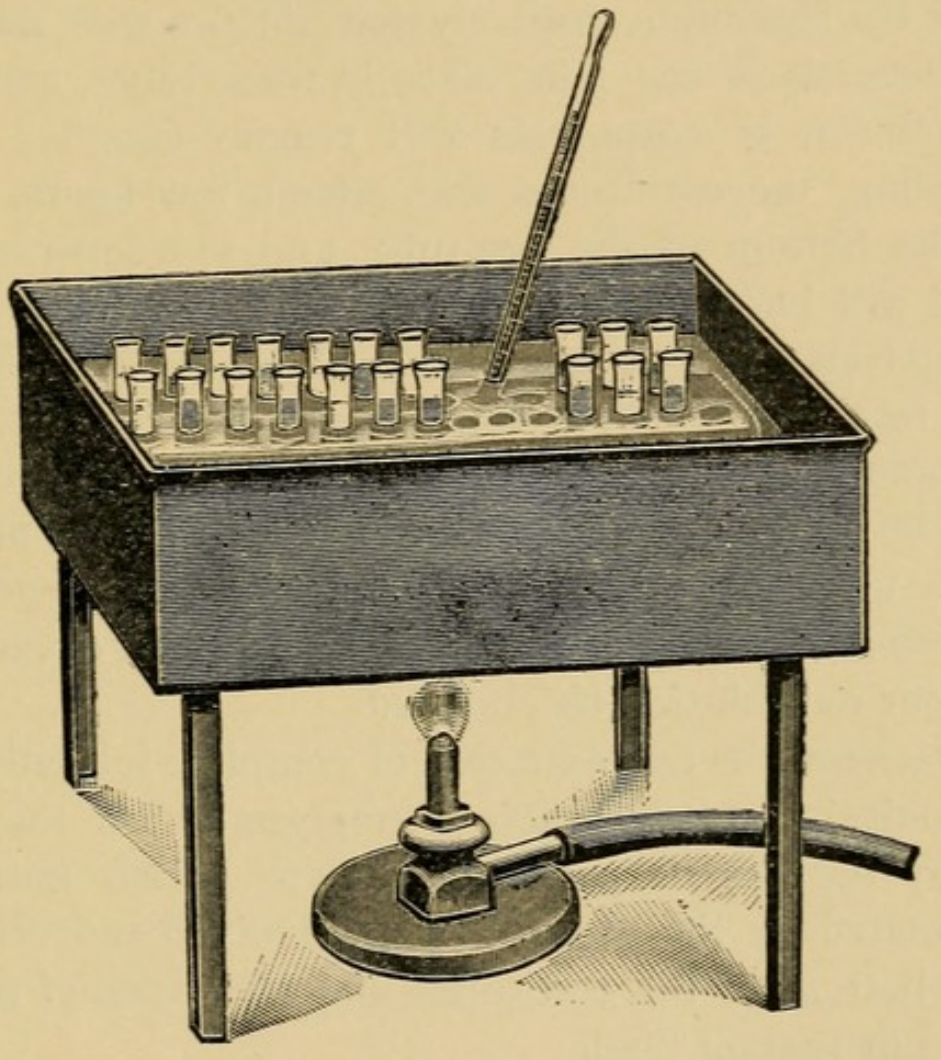


FIG. 17.—WATER-BATH.

again and replaced in the water-bath until such time as complete solution of the corpuscles is produced in the two control-tubes containing normal serum and no serum. When complete solution occurs in these two control-tubes, the test-tube rack can be removed from the water-bath and the tubes examined.

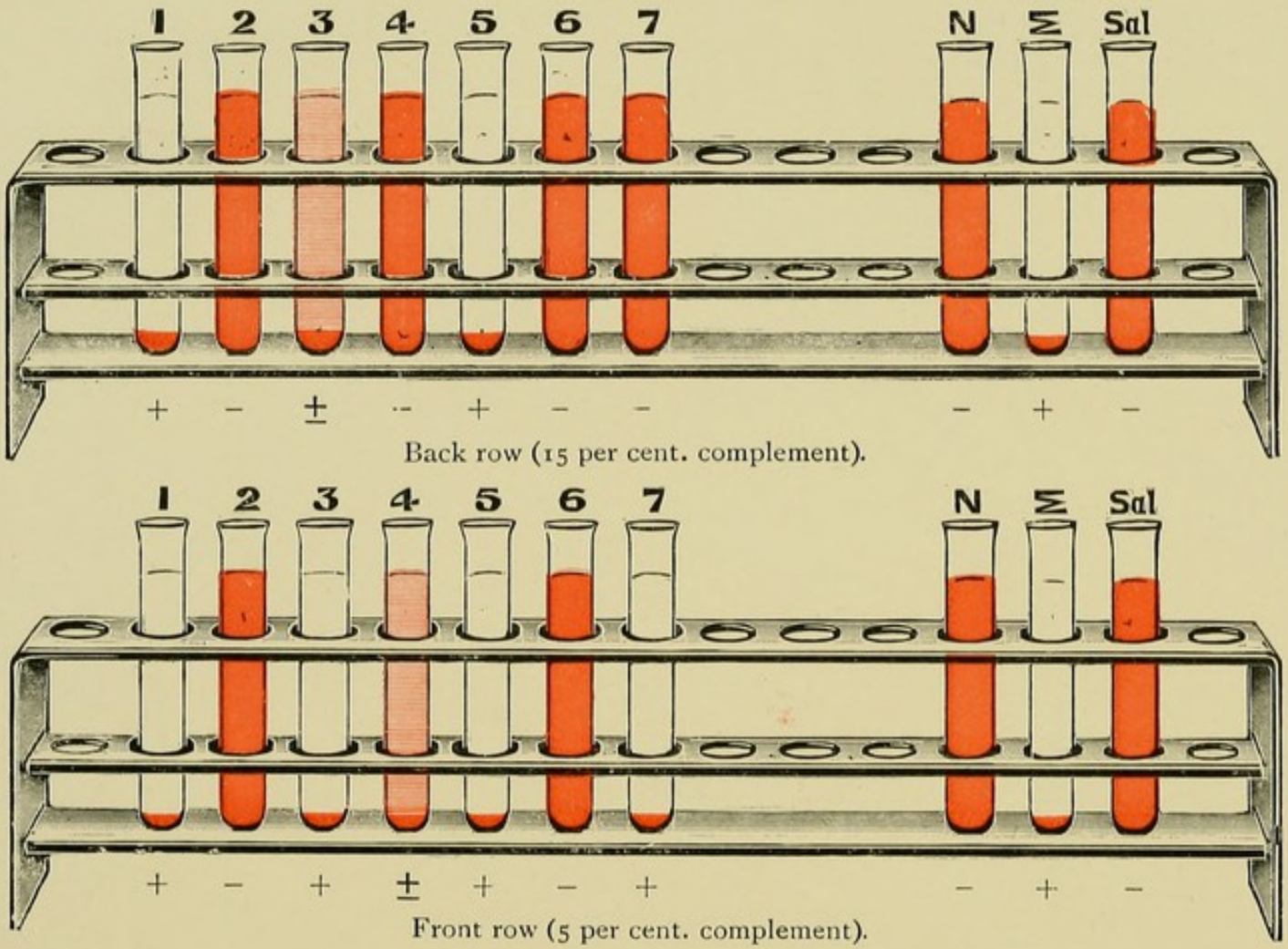
If the test-tube contains serum from a case of syphilitic infection, a substance having the power of uniting with the antigen will be present, and the complement will have been used up by these two combined substances. There will therefore be no complement left over for the second incubation period after the hæmolytic antibody and antigen were added. No hæmolysis can take place in these tubes, and the suspension of corpuscles will remain opaque. On standing, the corpuscles will, after a few hours, sink to the bottom of the test-tube, and the supernatant fluid will be clear and colourless if the inhibition of hæmolysis has been complete. If, on the other hand, the test-serum is free from syphilitic infection, the substance having the power to unite with the antigen will be absent; the complement will, therefore, not be used up, and will be free to activate the hæmolytic system, and solution of the corpuscles will occur and a clear red solution be obtained.

Between the two extremes of complete inhibition of hæmolysis and complete hæmolysis there may be many degrees of partial hæmolysis which must be estimated by the amount of undissolved red cells at the bottom of the test-tubes and the depth of tint of the supernatant fluid.

The hæmolytic system should be prepared and incubated at 37° C. for a short while before being used, so that the corpuscles may be fully sensitized and only require the addition of complement to produce rapid hæmolysis.

It will be found that a strongly positive serum will contain sufficient complement-fixing substance to fix

PLATE III.



1 = + + Strongly positive.
2 = − − Negative.
3 = + ± Positive.
4 = ± − Doubtful.
5 = + + Strongly positive.
6 = − − Negative.
7 = + − Positive.
N = Normal serum, negative.
Σ = Syphilitic serum, positive.
Sal = Saline solution, negative.

FIG. 18.—FINAL STAGE OF WASSERMANN REACTION.
Test-sera on the left, controls on the right.

To face p. 75.

the triple dose of complement in the back row, but that in some cases only sufficient will be present to fix the smaller dose of complement in the front row, and complete hæmolysis may be produced in the back row (Fig. 18).

Frequently, as a patient comes under the influence of treatment, the blood will pass through the stages of—

(1) Complete inhibition of hæmolysis in front and back tubes;

(2) Complete inhibition of hæmolysis in front tubes, partial hæmolysis in the back tubes;

(3) Complete inhibition in the front tubes, complete hæmolysis in the back tubes;

(4) Partial hæmolysis in the front tubes;

until finally a completely negative reaction is reached —namely:

(5) Complete hæmolysis in front as well as back tubes.

The author uses the symbol + to denote complete inhibition of hæmolysis, ± to denote partial hæmolysis, and − to denote complete hæmolysis.

If the left-hand symbol of each pair denotes the degree of reaction in the front tube, and the right-hand symbol that in the corresponding back-row tube, the five degrees of reaction mentioned above will be recorded respectively—

$$+ +,\ + \pm,\ + -,\ \pm -,\ - -.$$

It is obvious that a quantitative measurement for the complement-fixation substance in the serum can

be made either by using varying quantities of complement, keeping the other factors constant, as above described; or by varying the quantity of antigen, keeping the complement and test-serum constant; or by altering the quantity of test-serum, keeping the antigen and complement constant. The author finds that the greatest range is obtained when the quantity of the serum is altered; but, if to be of value, at least five dilutions must be made, and this takes a considerable time, and therefore the author only employs this method in doubtful cases. If a serum is strongly positive, it will appear so by both methods, and will by the first one fix a large amount of complement, or by the second will fix complement when the serum is present only in very small quantities.

Quantitative Measurement by Variation in Amount of Test-Serum.

In the second method the ingredients are used in the same proportion as in the front row of the first method—namely, 1 c.c. saline, 0·05 c.c. complement, and 0·1 c.c. antigen. Five tubes are required for each serum to be tested, each containing the above quantity of saline, complement, and antigen, and dilutions of the serum are prepared in the following way: $\frac{1}{2}$ c.c. saline is put into four small test-tubes, $\frac{1}{2}$ c.c. serum added to the first; this is shaken, and $\frac{1}{2}$ c.c. put into the next tube, and so on. In this way dilution of 1 in 2, 1 in 4, 1 in 8, and 1 in 16 are obtained. 0·2 c.c. of the pure serum and 0·2 c.c. of each dilution are added to the tubes of saline, complement, and antigen. These

tubes will thus contain 0·2, 0·1, 0·05, 0·025, 0·0125 of test-serum respectively. It will be found that the smallest amount in this series is capable of producing complete inhibition of hæmolysis with a very strong serum. This potency of the serum, however, is rare, and a serum is definitely syphilitic when it fixes complement completely in the 0·2 or 0·1 c.c. tubes. Sometimes a case will be found gradually to come down in complement-fixing power, from at first being able to fix complement in all the tubes up to the last tube, until the first tube alone is fixed, then only partially fixed, and at last all the tubes show complete hæmolysis. The author considers this method of making a quantitative examination the most satisfactory; but as the results obtained by the two methods always agree, the longer process is unnecessary in the majority of cases, and need only be used for the more accurate estimation of improvement under treatment.

Quantitative Measurement when only a Small Amount of Blood is Available.

Occasionally, as in infants or fat persons, venipuncture is impossible, and the pathologist has to content himself with a small quantity of blood obtained from the finger or toe in a Widal tube. In these cases we have to modify the technique as regards the quantity of serum used, though not as regards the relative proportion of the ingredients.

A piece of glass tubing having been heated in a blowpipe and drawn out so as to form a pipette, the capillary portion of which is about 6 inches long, a

mark is made with a pencil about 1 inch from the end of the capillary portion to mark one volume. A rubber teat having been adjusted to the broad end of the pipette, the mixture of saline, antigen, and complement is sucked up to the chalk mark; the point of the pipette is then taken out of the fluid and a little air drawn in, and then another volume is drawn in up to the mark, and so on until seven volumes have been sucked up. These are then squeezed out into a clean watch-glass and again sucked up, this time without leaving any intervening air-bubbles, and a chalk mark made on the capillary at the point to which the mixture reaches (Fig. 19). A small air-bubble is now

FIG. 19.—TEAT-PIPETTE, MARKING ONE AND SEVEN VOLUMES.

admitted into the capillary, and then one volume of the serum to be tested is sucked up. The contents of the pipette are then ejected into a front-row test-tube of small bore, made by drawing out glass tubing. The pipette is then washed by sucking up and ejecting normal saline one or twice, and the same process repeated—on this occasion, however, sucking up the mixture with the triple quantity of complement to the 7-volume mark, and then ejecting it into a test-tube in the back row. The same technique is followed with each serum to be tested, and with the controls. We have, as before, two rows, the front row containing a third of the amount of complement contained in the back row, the only difference being the absolute

quantities used, relative amounts being practically the same.

After incubating for half an hour, eight volumes of hæmolytic system are added, and the tubes replaced in the incubator until complete hæmolysis occurs in the control-tubes containing normal serum and no serum.

Reasons for Superiority of Original Technique.

It will be seen that the same principle underlies all the above techniques — namely, that all the factors are constant, except the test-serum. Any difference in hæmolysis must therefore be due to this, the only variant factor, and the results obtained will be strictly comparable one with another, though not strictly comparable to another series of tests. Thus, if in any given experiment the guinea-pig's serum is rather deficient in complement, or contains complement that is easily deviable, perhaps not quite complete hæmolysis will be produced in the tubes containing normal sera. The test-tubes showing a similar amount of hæmolysis we may then report as normal, although complete hæmolysis is not produced. Or, again, if we use an excessively potent complement, there may be a trace of hæmolysis even in the tube containing syphilitic serum; all the test-tubes showing a similar trace of hæmolysis, we may then report as positive. It cannot be too strongly insisted upon that this test is a quantitative one, and not an absolute one, and that therefore a result which in one test we should report as doubtful may in another test be reported as either positive or negative, according to the results obtained from the control-tubes.

Strictly comparable results cannot be claimed for any of the so-called 'simplified methods' given in the next chapter.

The author has always urged the importance of maintaining the principle of Wassermann's and Neisser's original technique, and nearly all pathologists with an extensive experience of the Wassermann reaction (Wassermann, Neisser, Plaut, Noguchi, Harrison, MacIntosh, Browning, Mackenzie) now advise that only a technique embodying these principles is to be recommended for purposes of diagnosis. Practically every worker of experience has his own modifications. These, however, are immaterial so long as the original principles are adhered to—namely, the only variant factor shall be the test-serum, and that the results in any one series of tests shall be strictly comparable.

The technique employed by the workers at the Lister Institute, and by Mott and Candler in the Pathological Laboratory at Claybury Asylum, is the original one. General experience has shown that this method is by far the most reliable, and admits of more accurate standardization than do any of the labour-saving modifications which have been suggested as substitutes for the original method.

CHAPTER VII

WASSERMANN REACTION—*Continued*

SIMPLIFIED TECHNIQUES

1. **Stern's Method.**—Margaret Stern makes use of normal complement existing in the serum tested instead of using guinea-pig's complement. This considerably simplifies the reaction in that guinea-pigs are not required, and the test-serum is not decomplementized in the water-bath. The quantity of complement contained in human sera is very variable. Complement is also gradually destroyed by keeping. As each serum tested varies, therefore in the quantity of complement, and, unless all are drawn on the same day, the depreciation of complement produced by time is also variable, the results obtained by this method are not quite comparable. In order to minimize the variability in complement, Stern advises using a large excess of hæmolytic serum, and only a weak suspension of corpuscles (2·5 per cent.). Although satisfactory results are obtained by this method in the very large majority of cases, still there is undoubted evidence from records published by independent observers in many countries that with this technique positive results are sometimes recorded in diseases other than

syphilis, and there is practically always a higher percentage of positive results. Stern herself admits that her method is not reliable in wasting diseases, where there may be a deficiency of complement. There is little doubt but that Stern's method is more delicate than Wassermann's original technique, and Harrison makes use of this method when estimating the result of treatment on the reaction, although he is strongly of the opinion that Stern's modification is unsuitable for diagnostic purposes. Neisser considers this technique useful as a control of the original technique.

2. **Hecht's Method.**—This observer uses the test-serum not only for complement, as in Stern's method, but also for hæmolytic antibody, for he has shown that an antibody to sheep's corpuscles is present in the great majority of human sera. The author compared the results obtained with Hecht's technique and the original technique with one hundred sera, and found that 10 per cent. of human sera contained no, or very little, hæmolytic antibody to sheep's corpuscles, and that therefore 10 per cent. of human sera cannot be examined with this technique, and of the remaining 90 per cent. the author found a higher proportion of positives than with the original technique. Hecht emphasizes the importance of using only fresh serum. Flemming has adapted a capillary tube method of measurement to this technique, and his modification has been considerably used in this country: he states that the freshness of the serum is not of importance, and that satisfactory results are obtained even if the serum is a week old. Little can be said for this

technique on theoretical grounds, as both complement and hæmolytic antibody are variants, and variations in hæmolysis may be due not only to varying quantities in the complement-fixing substance present in syphilitic sera, but to deficiency in either complement, hæmolytic antibody, or both.

3. **Noguchi's Method.**—Noguchi, according to his latest method, endeavours to simplify the reaction by substituting human corpuscles for the sheep's corpuscles, using the patient's own corpuscles, acetone insoluble antigen, and fresh guinea-pig's complement. The corpuscles, after washing, are used in a strength of 1 per cent. suspension. The controls consist of syphilitic serum, normal serum, and a tube without antigen. The decomplementized patient's serum, the patient's washed corpuscles, the fresh guinea-pig's serum for complement, and the antigen are incubated together in a water-bath for half an hour. The serum hæmolytic to human corpuscles is now added, and the tubes are reincubated.

SOURCES OF ERROR

The dose of complement in different samples of different guinea-pig's serum, though more constant than in human serum, still may vary, and Browning and Mackenzie have shown that different samples of guinea-pig's complement may vary considerably also in deviability, and this deviability is particularly influenced by age ; they found that the complement of freshly drawn serum was hypersensitive in deviability, and considered it best that complement should be kept from eighteen to twenty-four

hours in the ice-chest, or at room temperature, before use. They consider that complement is hypersensitive if five times the quantity of complement is required to produce hæmolysis with antigen, corpuscles, and hæmolytic serum, than with corpuscles and hæmolytic serum alone.

From the above remarks it will be seen that there are numerous pitfalls open to those inexperienced in the technique when using any of the so-called 'simplified techniques.'

When using either Stern's or Hecht's technique, or Flemming's modification of Hecht's technique, it is obviously impossible to make a quantitative examination, as we are unable to increase the amount of complement-fixing substance which is being tested for in the patient's own serum, without, at the same time, increasing the complement, and with Hecht's the hæmolytic antibody also. With cerebro-spinal fluid these techniques cannot be used.

Reliable quantitative estimation can alone be made by using the original method, in which the patient's own serum or cerebro-spinal fluid is simply used for supplying the complement-fixing substance. The quantitative measurement may be arrived at by giving increasing or diminishing doses of either of three factors —namely, either complement, antigen, or test-serum. It will be seen that false results may be obtained :

1. By the use of fresh guinea-pig's serum containing abnormally little or abnormally much complement ; by using too much complement or complement which is too easily deviable or not sufficiently deviable.

2. By using antigen which is too potent or not sufficiently potent ; one which fixes too much comple-

ment by itself, or with normal serum; or one in which the units of complement fixed in conjunction with syphilitic serum are not sufficiently in excess of those fixed in conjunction with normal serum.

3. Some corpuscles, also, are more easily hæmolyzed than others; or, again, if too thick a suspension of corpuscles be employed, there may not be complete hæmolysis, even with normal sera, while, if the suspension is too weak, each corpuscle will be provided with an excess of hæmolytic serum, and hæmolysis will be produced with a minimum amount of complement that would fail to produce hæmolysis in a thicker suspension.

4. The hæmolytic serum, if too potent, will for the same reason produce hæmolysis, and if too weak the serum will have to be used in such large quantities that agglutination of the corpuscles may be produced, and the clumps fall to the bottom of the test-tube before they are dissolved.

5. The patient's serum, if not decomplementized, may, according to Neisser, Noguchi, and others, fix complement, even if non-syphilitic, or if decomplementized at too high a temperature, or for too long, the complement-fixing substance may be greatly reduced in quantity, or even destroyed.

For this reason none of the outfits supplied by instrument makers can be regarded as satisfactory. The accumulated evidence of responsible workers points unmistakably to the superiority of the original technique in which the only variant factor is the tested serum, and any variation in hæmolysis in the final tubes must therefore be due to this the only variant factor.

CHAPTER VIII

WASSERMANN REACTION—*Continued*

SPECIFICITY OF REACTION

The first question to be settled is whether the reaction is sufficiently specific to render the test a reliable one for the diagnosis of syphilitic infection. Wassermann states that out of 10,000 sera examined, he has not once diagnosed syphilis wrongly, and Hoehne only obtained two positive results out of 1,100 sera taken from healthy persons, or patients suffering from diseases other than syphilis, and in neither of these two could syphilis be excluded. McDonagh, Muller, and Morawitz, in reporting 5,000 cases examined by them in Finger's clinic, state that they did not obtain a single positive result in any case where syphilis could be definitely excluded; and Blaschko of Berlin, as the result of the examination of 900 cases, found the result in accordance with the clinical diagnosis in all but 30 cases.

Blumenthal found in 3,000 cases a positive reaction in 95 per cent. of secondary and tertiary cases. There was no relation to the duration and the gravity of the disease. Congenital syphilis behaved in just the same way as acquired syphilis. Of 400 control cases

5 only gave a positive reaction. In latent syphilis the reaction was positive in 68 per cent. of cases in the first year of the disease, and in 42 per cent. of cases afterwards.

Fritz Hoehne found that of 317 known non-syphilitic cases only 3 were positive, and in 2 of these syphilis could not be absolutely excluded, and 1 was a case of scarlet fever.

Koefting, R., of Christiania, obtained 100 per cent. of positive results out of 317 secondary cases examined; and of 426 non-syphilitic cases all were negative.

Markus, K., of Stockholm, records 374 positive reactions in 445 cases of syphilis examined, and 9 out of 338 cases diagnosed as non-syphilitic, but out of these 9, in 7 syphilis could not be excluded, and the remaining 2 consisted of typhoid and tubercular meningitis.

Out of 50 sera examined by Beckers, and taken from patients with tuberculosis, typhoid, scarlet fever, arterio-sclerosis, and heart failure, only 2 gave a positive reaction, in neither of which syphilis could be excluded.

Jenonck and Meirowski examined 110 certainly non-syphilitic cases, and only found 1 positive result, which was that of a child dying with tuberculous meningitis, and they and other observers have recorded that a positive result is often obtained with dying persons or cadavers.

Statistics taken from very many thousands of observations made by skilled workers in England, France, Germany, Austria, Sweden, America, and Australia, show that of all cases of syphilis examined, from

80 to 90 per cent. give a positive reaction. The percentage differs but slightly with different observers. The author has determined the reaction in over 500 untreated, or but slightly treated, cases, and obtained a positive reaction in 85 per cent., and out of over 3,000 sera personally examined by him has not recorded a single positive reaction in any case in which syphilis could be excluded, with the exception of a few post-critical pneumonias.

Different results are obtained with syphilitic lesions of different tissues; thus a very high percentage of positive results is obtained with aneurism of the aorta, and only a low percentage with cerebral syphilis.

REACTIONS IN CONDITIONS OTHER THAN SYPHILITIC

Of the diseases certainly not syphilitic in which a positive reaction is obtained—

Yaws heads the list, and in this disease as high a proportion of positives is obtained as with syphilis itself. Baermann obtained 90 per cent. of positives in untreated cases.

Leprosy also produces a high percentage of positive results, Baermann reporting 40 per cent. and Noguchi 80 per cent. Meier also reported that the majority of cases gives a strongly positive result. It appears, however, only to be the tuberculous form of the disease that produces a positive reaction.

Trypanosomiasis has been reported frequently to give a positive reaction, but the author has been unable to obtain any statistics for the reaction in this disease.

In *malaria* Baermann obtained 20 per cent. positive

in untreated cases with fever, and 4 per cent. positive in treated cases without fever.

Scarlet fever was at first believed to produce a positive reaction, and Much reported 59 positives out of 130 cases examined. Later observers have, however, failed to confirm his figures, and have only obtained positive results very rarely. In any case the positive reaction is said to be very transient, and Blaschko has observed that when the positive result does occur, it is not till about fourteen days after the rash that it appears, and that it disappears within three months (see Table I.).

Pneumonia.—Weil and Braun and the author have reported 36 cases of pneumonia in which a positive reaction was obtained in 11. The author found that the positive reaction did not appear till after the crisis, and only lasted a few days.

Weil and Braun have also reported 3 positive results out of 20 sera taken from *typhoid* patients (see Table I.).

Heart Disease.—No case of heart disease in which syphilis can be excluded has been reported as giving a positive reaction.

Relapsing fever has been reported as giving a positive reaction.

Cancer or *tuberculosis* practically never gives a positive reaction in cases in which syphilis can be excluded. The reports of some experienced observers as regards the reaction in various diseases will be found in Table I.

Reinhart has not obtained a single positive result in malignant disease, phthisis, typhoid, pneumonia, nephritis, leukæmia, pernicious anæmia, diabetes,

measles, or diphtheria, but he has recorded positive reactions in scarlet fever and malaria.

Of 39 cases of various *non-syphilitic skin diseases* examined by Bassett-Smith, all gave a negative reaction. Of 58 examined by Noguchi, all but 1 were negative, this solitary case giving a doubtful reaction. Of 15 cases examined by the author, 10 gave a negative reaction, and 5 cases—all leucoderma cervices and probably syphilitic—gave a positive reaction.

Positive reactions have also been recorded with blood taken during deep *anæsthesia*, or in *narcosis* produced by various drugs; also in *moribund* patients and in the *cadaver*.

Of 80 cases of *gonorrhœa* examined by Bassett-Smith and the author, only 1 was positive, and here syphilis could not be excluded.

Acute rheumatism, measles, and acute nephritis have all given negative results.

Of 76 cases of *aortic aneurism* examined by Donath, Gastau, Koefting, and the author, all but 4 have given a positive reaction. Koefting also obtained 15 positive reactions out of 17 cases of aortic incompetence, but out of 21 cases of morbis cordis examined by Bassett-Smith and the author, only 1 gave a positive reaction, and here there was a history of syphilis.

Wassermann says:

'It should cause no surprise that the serum of patients suffering from other protozoal diseases gives a like reaction, considering the close relationship between spirochætæ, trypanosomes, and other protozoa. It follows that one should employ the reaction with people who have been in the tropics and contracted malaria there, only when one is convinced by

their history that they have had no malarial attack during the last quarter of a year. I also advise you that whenever you wish to employ the serum reaction first to determine by the patient's history that he has gone through no acute febrile infectious disease up to at least a month previously. If one holds to the necessary preliminary precautions regarding the technique and the anamnesis, then, in cases of a positive reaction, it can be said with certainty that the investigated case is syphilitic. On the other hand, if the reaction be negative, syphilis cannot be excluded absolutely, but only with a probability of about 90 per cent.'

TABLE I.—REACTION IN VARIOUS DISEASES.

	Typhoid.		Scarlet Fever.		Tuber-culosis.		Carcinoma.		Pneumonia.	
	Cases.	No. Positive.	Cases.	No. Positive.	Cases.	No. Positive.	Cases.	No. Positive.	Cases.	No. Positive.
Bassett-Smith	3	0	7	1	9	0	—	—	—	—
Bayly ..	6	0	20	1	22	0	34	0	24	7
Boas	—	—	61	1	—	—	—	—	—	—
Browning and Mackenzie	14	0	37	0	11	1	5	0	4	0
Hecht ..	—	—	105	1	—	—	—	—	—	—
Hoehne ..	—	—	37	0	—	—	—	—	—	—
Jochmann ..	—	—	33	0	—	—	—	—	—	—
Meier ..	—	—	52	0	—	—	—	—	—	—
Much ..	—	—	130	59	—	—	—	—	—	—
Noguchi ..	—	—	63	3	52	0	51	3	—	—
Weil and Braun ..	20	3	—	—	—	—	—	—	12	4

REACTION AT VARIOUS STAGES OF INFECTION

The percentage of positive reactions obtained varies considerably with the period of the disease, and whether

the infection is acute or latent. Thus, primary cases in which the lesion has been present for less than a fortnight almost invariably give a negative reaction, while 75 per cent. of positive reactions are obtained if the primary sore has been present for over a month. Secondary syphilis with symptoms gives a positive result in over 90 per cent. of cases, and tertiary syphilis in about 75 per cent. In cases of latent syphilis—viz., syphilis without symptoms—the early cases give a positive reaction in 75 per cent., and the late cases in 76 per cent., in the untreated cases.

Primary Syphilis (see Table II.).—Levaditi and Yamanouchi found a positive reaction in primary cases in from ten to thirty days after the appearance of the sore.

Bruck and Boas collected records of 1,081 cases of primary syphilis, and of these 709, or 65 per cent., gave positive reactions.

Fischer found a positive result the rule after five or six weeks.

Blumenthal found a positive reaction in the primary period in 63 per cent. of cases. It only appeared in the fifth or sixth week, and became more and more strong as time progressed. In other periods the reaction was positive.

Secondary Syphilis (see Table II.).—Bruck and Boas obtained 90 per cent. of positive results in 2,754 cases. Probably, however, many of these had received some treatment.

Recent observations seem to show that in florid secondary syphilis practically every case gives a positive reaction.

Tertiary Syphilis (see Table II.). — In 63 untreated cases recorded by Boas, every case gave a positive reaction, and in 60 cases examined by MacIntosh and Fildes, only 1 negative result was obtained.

Very many cases of aneurism of the aorta give a positive reaction, and in the majority a history of syphilis can also be obtained. Bassett-Smith has informed the author that in his report on late secondary and tertiary syphilis giving positive reactions, he included many cases of aneurism, chronic endocarditis, and cases with cerebral symptoms in which a distinct history of syphilis had been obtained.

Congenital Syphilis (see Table II.).—Practically all infants or children showing symptoms of hereditary syphilis give a positive reaction, but not all babies born of syphilic mothers; while of living children born of syphilitic mothers nearly 50 per cent. give a negative reaction.

Of 44 cases examined by Boas, 20 gave a positive reaction and 24 a negative; of the 20 that gave a positive reaction, 16 either showed symptoms at birth or within three months after birth, and the remaining 4 showed no symptoms in three months, and the reaction rapidly became negative. Of the 24 cases showing a negative reaction, 17 remained negative and showed no symptoms, 5 developed both symptoms and a positive reaction, and 2 died with a negative reaction and yet proved to be syphilitic.

Knopfelmacher obtained 90 per cent. of positive reactions in mothers tested within a few months after the birth of a syphilitic child, and he has shown that

children with hereditary syphilis almost invariably give a positive Wassermann reaction at the time of the rash and often for long after its disappearance. Older children with hereditary syphilis show a positive reaction even more frequently than adults with acquired syphilis in a late stage, and the reaction often remains positive in children suffering from the disease in spite of energetic treatment. That antisyphilitic treatment of the mother during pregnancy can result in the birth of a healthy child is confirmed by the negative reaction. These children are free from syphilis, and they may be quite healthy or show various defects. In two instances a woman, who had previously had several syphilitic children, has borne a child which has remained healthy in the first years of life, and yet given a positive Wassermann reaction. Such children are to be regarded as latent syphilitics. On this basis Profeta's law (immunity of the healthy children of syphilitic mothers) finds its explanation on the ground of latent syphilis in the child.

Out of 1,822 sera Fritz Hoehne obtained positive reactions in :

38 per cent. in primary syphilis.
79 ,, ,, untreated secondary syphilis.
48 ,, ,, treated secondary syphilis.
63 ,, ,, tertiary syphilis.
100 ,, ,, syphilitic aortitis.
17 ,, ,, cerebro-spinal syphilis.
31 ,, ,, latent syphilis.
88 ,, ,, congenital syphilis.
60 ,, ,, tabes.

Of 427 doubtful cases, 101 were positive.

Table II.—Reaction at Different Stages of Infection in Cases showing Clinical Symptoms.

	England.				America.		Germany.		Sweden.			
	Bassett-Smith.		Bayly.		Noguchi and Kaplan.		Hoehne.		Markus.		Boas.	
	Cases.	Per Cent. Positive.	Cases.	Per Cent. Positive.	Cases.	Per Cent. Positive.	Cases.	Per Cent. Positive.	Cases.	Per Cent. Positive.	Cases.	Per Cent. Positive.
Congenital ..	—	—	20	95	37	95	?	88	29	90	72	100
Primary	183	76	38	75	208	90	?	38	120	75	76	73
Secondary ..	407	94	308	90	478	90	?	79	250	91	2,754	90
Tertiary	51	94	52	76	368	80	?	63	46	100	63	100

CHAPTER IX

CEREBRO-SPINAL FLUID

The normal cerebro-spinal fluid is limpid and colourless, and has a specific gravity of 1005; it contains no cellular element, except, perhaps, a few large endothelial cells and a very occasional lymphocyte, and its reaction is slightly alkaline. True albumin is absent. Only faint traces of proteid are present, which, however, are sufficient to produce a slight cloudiness on heating. The proteid present consists of globulin. No ferments can be demonstrated. Of salts, the principal is sodium chloride, but it also contains traces of carbonates and phosphates. Traces of dextrose and urea are also usually found.

From 120 to 150 c.c. of cerebro-spinal fluid are usually secreted daily, the secretion being produced at the choroid fringes, and being a definite secretion and in no sense an exudation. The amount secreted varies in pathological conditions, and may be enormously increased in general paralysis.

Hoffman states that he has been able to demonstrate the presence of the *Spirochæta pallida* in the cerebro-spinal fluid of infected persons by means of successful inoculation, but the organism itself has up till now not been seen in this fluid.

LUMBAR PUNCTURE

Cerebro-spinal fluid is best obtained by thecal puncture at the interlaminal spaces, either between the third and fourth or fourth and fifth lumbar vertebræ. The upper border of the fourth lumbar spine is on a level with a horizontal line joining the summit of the iliac crests, and the puncture should be made below this line, ½ inch below and to the right of the fourth lumbar spine, directing the needle forwards and inwards.

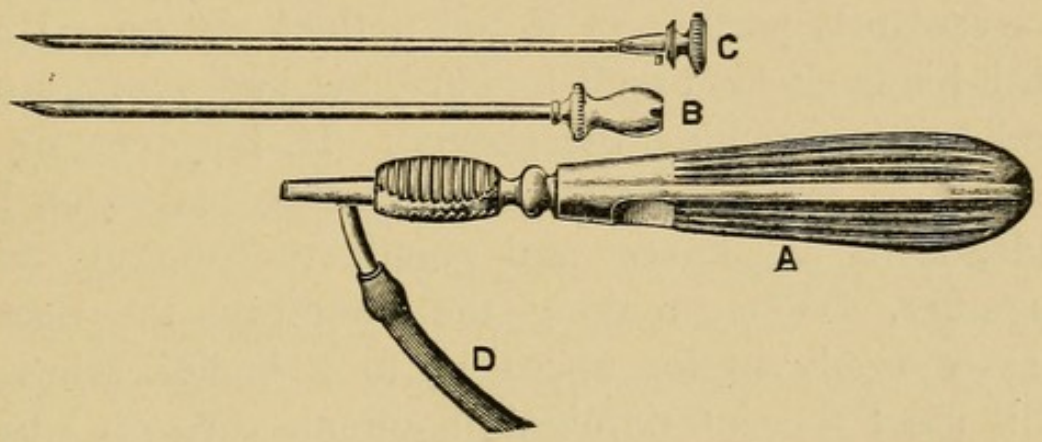


FIG. 20.—LUMBAR PUNCTURE NEEDLE AND HOLDER (AUTHOR'S PATTERN).

A, holder; B, needle; C, stilette; D, rubber-tubing.

Before puncture, the skin should be cleaned with ether and alcohol, and sterilized with a saturated solution of iodine in chloroform. The needle is often attached to the nozzle of a syringe. Most authorities agree that suction should not be employed, and therefore the syringe usually serves only as a handle.

The author uses the apparatus illustrated in Fig. 20, which consists of a stout steel needle, about 3 inches long and of fairly large calibre, and a hollow needle-holder to which a piece of rubber-tubing can be

attached so that the cerebro-spinal fluid is conducted directly into the sterile test-tube without fear of contamination. If, after the puncture has been made, the fluid does not flow into the test-tube, the holder is removed and a stilette passed down the needle. Before adjusting the needle to the holder, the needle should be dipped into a test-tube containing autoclaved olive oil. When making the lumbar puncture, the spine should be flexed so as to open out the interlaminal spaces as much as possible. If the patient is able to sit up, lumbar puncture is most easily and conveniently performed if the patient sits on a stool with his back bent well forward, his knees separated, and hands touching the ground. If, however, he is unable to leave the bed, he should be placed on his side, with his knees and shoulders brought close together. When making the puncture, the needle passes easily in for about $1\frac{1}{2}$ to 2 inches, when it will meet the interlaminal ligament, through which it must be firmly pushed into the cerebro-spinal canal, when the fluid escapes into the tube. Occasionally the needle becomes blocked in its passage through the tissues, and no cerebro-spinal fluid escapes, although the point is in the cerebro-spinal fluid. The tube should be removed before the needle is withdrawn, as during the withdrawal some blood may escape into the needle and contaminate the fluid. It is obvious that no correct leucocyte count can be made if there is any blood present. It is therefore wisest to allow a few c.c. of cerebro-spinal fluid to escape into the first test-tube, and then, removing this tube, to replace it by a second. Any trace of blood

will be washed away by the passage of the first sample, and the second sample will be uncontaminated. The second tube is now removed, and kept for cytological examination. The first tube is used again during the withdrawal of the needle.

CYTOLOGICAL EXAMINATION

Lymphocytosis of the cerebro-spinal fluid occurs in tabes and general paralysis, which, according to Mott, is not diminished with antisyphilitic treatment. Plaut, however, has recorded a distinct sinking in the cellular contents (424 to 120 cells per c.mm.) in a case of cerebral syphilis, without any change in the Wassermann reaction.

Lymphocytosis also occurs to a marked degree in sleeping-sickness, and has been found in Landry's paralysis and in the subacute combined degeneration of pernicious anæmia, and, according to Sicard, in herpes zoster. Lymphocytosis, however, cannot be regarded as absolutely diagnostic of meningitis; but Mott considers it strong presumptive evidence, and, when combined with other facts, he considers the existence of a lymphocytosis of the cerebro-spinal fluid as a valuable sign of syphilitic or parasyphilitic affections of the central nervous system or meninges.

Normal cerebro-spinal fluid contains no polymorphonuclears, and very few, if any, lymphocytes. The lymphocytosis of tabes and general paralysis is, according to Purves Stewart, more marked than in any other form of organic disease. In acute inflammatory

processes there is a polymorphonuclear leucocytosis, and in chronic inflammatory processes a lymphocytosis. In acute tubercular meningitis both polymorphonuclears and lymphocytes may be present in large numbers, the majority of cells present being lymphocytes, though as many as 30 per cent. of polymorphonuclears are sometimes present.

Plaut considers that a cytological examination is normal if less than six leucocytes are found per c.mm. If ten or more cells are present, the fluid must be considered pathological. Countings from six to ten he considers doubtful. Out of fifty-six cerebro-spinal fluids obtained from cases that were definitely non-syphilitic, in forty-eight cases the cell-findings were entirely negative, and there were under six cells in each c.mm. In four cases normal findings were increased, but not above the number which was to be regarded as pathological (ten cells to 1 c.mm.). In the remaining four cases, however, there was found a pathological cell increase, while both the spinal fluid and blood-serum gave completely negative Wassermann reactions.

Out of ten cases of syphilis with secondary symptoms that were examined, three showed a positive cytological count; while of nine cases of latent tertiary syphilis showing a positive Wassermann reaction in the blood, two showed a positive cytological count of the cerebro-spinal fluid.

Ravaut found a marked lymphocytosis of the cerebro-spinal fluid during the secondary stage of syphilitic infection which ran *pari passu* with the cutaneous eruption. In a case of extensive papular

syphilis he found the cerebro-spinal fluid quite turbid with lymphocytes. The lymphocytosis was not seen in tertiary syphilis unless the eye or central nervous system were affected.

Plaut comes to the conclusion that the phenomenon of lymphocytosis does not go parallel with the Wassermann reaction of the spinal fluid, and that the mechanism which produces the lymphocytosis is not identical with that which causes the appearance of a complement-fixing substance in the cerebro-spinal fluid. He also considers that the appearance of the Wassermann reaction in the blood need not be accompanied by an increase of the lymphocytes in the spinal fluid, and that there may be a cellular increase in the cerebro-spinal fluid in the latent tertiary stages without any syphilitic manifestations in the central nervous system.

There appears to be no parallellism between the results obtained by a cytological examination of the cerebro-spinal fluid and the Wassermann reaction. There may be a distinct lymphocytosis without any power whatever of complement-fixing.

The cell-count should be made shortly after the withdrawal of the fluid, and the author thinks Fuch's and Rosenthal's counting chamber the most convenient for the absolute leucocyte count. This chamber has a depth of 0·2 mm., and since its ruled floor occupies an area of 16 mm. square, the entire column which comes under the operation of counting measures 3·2 mm. The fluid is mixed in a mixing pipette whose bulb has a capacity which is ten times greater than that of the capillary portion. The

diluent is a staining solution of the following composition:

Methyl violet	...	0·10 parts.
Distilled water	...	50 ,,
Glacial acetic acid	...	2 ,,

With this medium the cerebro-spinal fluid is mixed in the proportion of 1 of stain to 9 of cerebro-spinal fluid. To prepare the diluted mixture, obtain a sample of the cerebro-spinal fluid immediately after puncture, and, after repeatedly shaking it up lightly, transfer a small quantity to a dish, aspirate some of the stain with the pipette up to the gauge-mark 1, and then draw up a sufficient quantity of the cerebro-spinal fluid until the bulb is filled up to the gauge-mark 11. Close the point of the pipette with the tip of the finger, and shake the fluid in the bulb well for some time. Having insured a good mixture, expel the fluid contained in the capillary stem, and then transfer a drop of the mixture to the counting chamber. The floor of the chamber should be counted right through, since the cerebro-spinal fluid contains a relatively small number of cells. The average number of cells contained in a cubic millimetre of the cerebro-spinal fluid is accordingly:

$$x = \frac{10 \times z}{3{\cdot}2 \times 9} = \frac{10z}{28{\cdot}8}, \text{ or very nearly } \frac{z}{3},$$

where z is the total number of cells counted over the entire floor of the chamber.

Should the total number of cells covering the floor of the chamber happen to be excessively small, the latter should be charged once more and a fresh count made.

A differential leucocyte count should also be made, and for this purpose the cerebro-spinal fluid is centrifugalized in a conical glass tube, and a film made of the deposit at the tapered end of the tube. This film should be stained with Jenner's stain.

Of 21 normal cases of cerebral syphilis examined by Plaut, only 1 was cytologically negative; 3 were on the border-line (5 to 9 cells per 1 c.mm.), and 17 showed a distinct cellular increase, the highest count showing 424 cells.

Leucocytosis is absent in functional neurosis.

Ravaut has shown that in acute and chronic meningitis the cellular element and spinal fluid are proportional to the degree and intensity of the inflammation. He considers the presence of lymphocytosis as an indication for energetic antisyphilitic treatment. He considers the degree of lymphocytosis greater in early than late cases; and in old syphilitics, other than parasyphilitics with no manifestations, the cerebro-spinal fluid is normal.

Babinski and Naglotti have said that lymphocytosis may precede the appearance of the Argyll-Robinson pupil in tabes.

Funhe considers that lymphocytosis is not characteristic of syphilitic nervous diseases, and that it is only present if the meninges are involved.

From the above it will be seen that most authorities agree that a negative cytological examination—namely, the presence of less than six cells per c.mm.—will exclude general paralysis, syphilitic meningitis, and tabes. In syphilitic or parasyphilitic affections particularly no polymorphonuclear cells are seen; whereas

in chronic tubercular meningitis, although in later stages there may be as many as 10,000 lymphocytes per c.mm., there are usually also a considerable number of polymorphonuclear cells, which will probably form 25 per cent. of the total leucocyte count.

With acute meningeal diseases, such as acute syphilitic meningitis, acute cerebro-spinal meningitis (or acute tuberculous meningitis), the cellular increase is chiefly polymorphonuclear.

WASSERMANN REACTION

Of 9 cases of active secondary syphilis examined by Plaut, the cerebro-spinal fluid was negative in all, as it also was in 4 cases examined in the secondary latent stage.

Of 11 cerebro-spinal fluids taken from patients in the latent tertiary stage, all were negative.

Of 154 cases of general paralysis, 146 were positive, 6 negative, and 2 doubtful; while of 20 cases of cerebral syphilis, 17 were negative, and only 3 positive.

General paralysis is the only syphilitic or parasyphilic affection in which a negative result is of any very great value; but here it is of very great value indeed, and a negative Wassermann reaction in the blood or cerebro-spinal fluid will practically exclude this condition.

A positive Wassermann reaction of the cerebro-spinal fluid indicates that the patient either has general paralysis, tabes, or cerebral syphilis.

Plaut has obtained a positive Wassermann reaction in the blood-serum in every case in which a positive

reaction was recorded in the cerebro-spinal fluid ; but other observers, including the author, have very occasionally met a cerebro-spinal fluid that was positive in which the blood-serum was negative.

In cases in which the question for diagnosis is the presence or absence of general paralysis, Plaut recommends that the blood should be first examined. If there is a positive result, lumbar puncture is then performed; but if the blood reaction is negative, lumbar puncture is considered contra-indicated, as the case can be considered almost certainly not one of general paralysis ; whereas a positive reaction in the serum alone indicates absolutely nothing concerning general paralysis, and only shows that the patient has syphilis.

A positive Wassermann reaction in the cerebro-spinal fluid does not appear to be influenced by antisyphilitic treatment. This may possibly be due to the drugs used failing to reach the cerebro-spinal fluid.

It has been found in certain cases of trypanosomiasis that some arsenical preparations are able to remove the trypanosomes from the blood, but not from the cerebro-spinal fluid ; and it has also been recorded that potassium iodide, though present in the blood, cannot be found in the cerebro-spinal fluid.

This isolation of the cerebro-spinal fluid may also account for the difficulty in influencing parasyphilitic affections by means of drugs administered either intravenously, intramuscularly, or by the mouth, and possibly there may be a future for treatment directly applied to the cerebro-spinal fluid. Success has already

been reported by MacIntosh, Martin, Flexner, and Knolle in the treatment of cerebro-spinal fever by means of intraspinal injections of serum containing antibody.

Schmorl is of the opinion, also, that the cerebro-spinal fluid is cut off from the intraventricular fluid, and finds that in cases of marked jaundice the intraventricular fluid contains no trace of bile pigment, although the pigment may be present in the cerebro-spinal fluid. He also reports that in one case of diabetes, though a reducing substance was found in considerable quantity in the spinal fluid, yet none was found in the intraventricular fluid. The cerebro-spinal fluid was examined for the Wassermann reaction in seven cases of general paralysis; in all cases the Wassermann reaction of the blood and cerebro-spinal fluid was positive, whereas in only one was the reaction of the intraventricular fluid positive. Schmorl therefore considers that the intraventricular cavities are closed off from the subarachnoid space.

In the cases in which the intraventricular fluid contained bile pigment or gave a positive Wassermann reaction, Schmorl found that the epithelium of the choroid plexus was degenerate; whereas in those cases in which the fluid was free from pigment, or the Wassermann reaction negative, the epithelium of the choroid plexus was intact.

Browning and Mackenzie made a similar examination in four cases of general paralysis. The cerebro-spinal fluid was positive in every case, whereas in only two did the intraventricular fluid give a positive reaction. They also found that both the cases which

gave a positive reaction showed a degenerative condition of the choroid plexus, whereas in the negative cases these degenerative changes were not observed.

Mott has also found that, though reactions which at first are negative may later become positive, no patient suffering from general paralysis, whose cerebro-spinal fluid has once given a positive reaction, has ever given a negative reaction at any subsequent examination. He considers that antibodies accumulate in the cerebro-spinal fluid in proportion as the process of decay of the neurones proceeds, and he thinks that there is a parallelism between the amount of decay of the brain and the degree of the positive character of the reaction.

Marie and Levaditi have also found that there is a parallelism between the rapidity of the progress of general paralysis and the degree and intensity of the Wassermann reaction.

Mott considers that the Wassermann reaction gives a valuable means of diagnosis, which is especially useful when applied to the cerebro-spinal fluid to determine the presence or absence of general paralysis. He considers that the amount of complement-fixing substance is in proportion to the activity and length of duration of the diseases, and that these substances are lipoids and globulins, which are of tissue origin, and arise from tissue destruction caused by the present or past action of the syphilitic virus.

Nonne has pointed out that, when making the Wassermann test with cerebro-spinal fluid, considerably more of the test-fluid should be used in the case of cerebro-spinal fluid compared with serum. He

states that 1 c.c. can be employed in the original technique without fear of the positive reaction in non-syphilitic cases.

Candler is also of the opinion that a positive reaction may be missed unless considerable quantities of the cerebro-spinal fluid are used, and instances a case in which complete complement-fixation occurred when 0·8 c.c. of fluid was used, although there was complete hæmolysis with 0·5 c.c.

As the cerebro-spinal fluid contains no complement, it is unnecessary to heat it.

CHEMICAL EXAMINATION

The increase in proteid-content can usually be demonstrated in general paralysis and tabes, especially in the former.

Globulin Reacton: Nonne and Afelt.—The fluid is mixed with an equal quantity of saturated ammonium sulphate. If turbidity appears in three minutes, the reaction is positive.

Marie also considers that there is a marked parallelism between the Wassermann reaction of the cerebro-spinal fluid and the albumin reaction, for which he uses equal quantities of centrifugalized cerebro-spinal fluid and saturated ammonium sulphate solution. He regards the reaction as positive when boiling produces a turbidity.

Noguchi's Method.—One or two parts of spinal fluid are mixed with five parts of a 10 per cent. dilution of butyric acid in physiological salt solution, and the mixture is boiled for a few seconds. One part of

normal NaOH solution is added quickly to the heated mixture, and the whole is again boiled for a few seconds. The actual quantities recommended are:

Cerebro-spinal fluid ...	...	0·1 c.c. or 0·2 c.c.
Butyric acid solution ...	...	0·5 c.c.
Normal sodium hydrate solution		0·1 c.c.

The rapidity with which the precipitation falls is proportional to the amount of proteid present, and Noguchi considers that a positive result has been obtained when the precipitate settles within two hours.

On adding fresh Fehling's solution and boiling, a reducing body (? dextrose) is found in normal cerebro-spinal fluids, which is reduced in amount or may be absent if meningitis is present.

CHAPTER X

URINE

A CONSIDERABLE percentage of syphilitics show evidence of nephritis in their urine. It is, however, difficult to say to what degree this nephritis is primarily syphilitic or only the ordinary forms occurring in syphilitic subjects.

Speiss has reported that of 220 syphilitic patients examined post-mortem, the kidneys were affected in 131, grouped under the following heads:

Amyloid degeneration	42
Parenchymatous nephritis	21
Sclerosis	18
Interstitial nephritis	16
Atrophy	11
Sclero-gummatous nephritis	7
Various inflammations only partly attributable to syphilis	16

Petersen considers that the kidneys are affected in 3 per cent. of cases in secondary syphilis.

The onset of secondary symptoms is frequently accompanied by albuminuria which, however, may be slight and transient, and of the same nature as the albuminuria accompanying any other acute infection which cannot be considered a definite nephritis.

Acute nephritis arises during the secondary stage

and generally within the first year, or at least two years from infection.

Many cases of syphilitic nephritis present an extraordinarily intense albuminaria with few other signs. The urine becomes solid on boiling, and the conditions may be present for weeks without any other marked signs of illness. Notwithstanding the large quantity of albumin there may be very little sediment and few casts, leucocytes, or red blood-cells.

In **subacute syphilitic nephritis** the urine is diminished in quantity, when at the height of the disease it varies from 200 to 250 c.c., and as the case improves it increases, and, if the patient be encouraged to drink, may reach 5 to 6 litres. Its specific gravity is normal or slightly increased, in some cases up to 1040. The albumin is present in quantities of about 0·4 to 0·8 per cent. The specific gravity varies inversely with the quantity. The reaction is faintly acid, but in some cases alkaline, even when fresh, and in all cases quickly becomes alkaline. It is usually cloudy from the large amount of sediment, and foaming easily on shaking, because of the amount of albumin which is present. It seldom reaches 1 per cent., though for months it may vary from 0·4 to 0·8. The urine is somewhat diminished. Red blood-cells are practically always found, and coarsely granular, fatty, and waxy casts.

Several writers state that they have found the *Spirochæta pallida* in the urine of patients suffering with florid secondary syphilis, but the majority of observers have failed to detect the organism in urine.

In **chronic intestitial nephritis** the urine is usually

increased in quantity. The specific gravity is usually lower than normal—1005 to 1010; this is especially noticeable in the morning. There is usually only a trace of albumin, which is seldom present in greater quantities than 0·05 per cent. A few hyaline casts, red blood-cells, and epithelial cells are usually found.

Lardaceous (amyloid) disease of the kidney may be superimposed on any form of nephritis.

Traube's classical description of urine in lardaceous disease of the kidney is that 'it is increased in amount, pale, clear, faintly acid, of low specific gravity (1002-1005) and that it contains abundant albumin and very few casts.' Albumin, however, may not be found at all, or only in traces, and casts may be numerous when they are usually fatty or hyaline. Epithelial cells and red blood-discs are rarely seen.

CHAPTER XI

CLINICAL VALUE OF THE WASSERMANN REACTION

LATENT SYPHILIS

In the old days the only method of diagnosing the presence of syphilitic infection was by clinical symptoms, and it was extremely difficult to give an opinion as to when the patient was cured or for how long treatment should be continued, as frequently, after the patient had been six months under treatment, all symptoms would disappear. At first, a year's treatment was considered sufficient. This period was gradually lengthened to two and three years, and recently five years' treatment has been considered necessary by some authorities, with occasional courses prolonged indefinitely afterwards.

It is generally accepted now that a positive Wassermann reaction is sufficient evidence of active infection to justify a continuation of treatment, even when no other symptoms are present.

In syphilis which has been treated there is always a tendency for the symptoms to disappear spontaneously, only to recrudesce later. Browning and Mackenzie describe this latent period as 'a state of

equilibrium between the host and the parasite,' and Ehrlich has given it the name of 'non-sterilizing immunity.' During this latent period about 50 per cent. of cases still give a positive Wassermann reaction, which enables the infection to be diagnosed so that the patient may be placed on appropriate treatment, and the recrudescence of the infection and the consequent formation of lesions prevented.

In some cases in which the blood is examined during the latent period, the Wassermann reaction is found to be negative, but if antisyphilitic treatment is given the reaction becomes positive. Similarly, occasionally the symptoms are aggravated for a short time when the patient is put under treatment. This lighting up of the disease, as evidenced by the appearance of a positive Wassermann in a blood which before was negative, or by an increase in the manifestations of the disease, has been given the name of the 'Jarisch-Herxheimer reaction.' It is supposed to be caused by the setting free of the endotoxins contained in the bodies of the spirochætes which have been destroyed as the result of the treatment. Another theory advanced is that the reaction is produced by the stimulation of the spirochætes by a dose of a drug which has been insufficient to kill them. The author is of the opinion that the former rather than the latter theory is the correct one.

A positive Wassermann reaction must be regarded as resulting from some alteration or destruction of tissue, caused by a toxin produced by the spirochætes. It therefore takes a little time for a positive reaction to develop, and the reaction is not due simply to the

presence of the spirochætes themselves. Bruck has shown that the serum of monkeys becomes positive about the same time as the organs become infective, as shown by inoculation experiments, and Levaditi and Yamanouchi consider that the time when the skin becomes immune to further inoculations and the time when the Wassermann reaction becomes positive, synchronize.

FOR DIFFERENTIAL DIAGNOSIS

That the Wassermann reaction is of the greatest possible value for diagnosis has been proved beyond question, and the physician, surgeon, gynæcologist, ophthalmic surgeon, laryngologist, aurist, dermatologist, and the neurologist, are all equally aided in diagnosis by this reaction.

Medicine.—The syphilitic fever, which sometimes accompanies either the primary, secondary, or tertiary lesions, may be accompanied by anæmia, loss of weight, pain or swelling of joints, and may be mistaken for rheumatic fever, phthisis, malaria, or enteric fever.

Pulmonary syphilis, though extremely rare, when present may be exceedingly difficult to diagnose from phthisis, and, in the absence of the tubercle bacilli from the sputum, the Wassermann reaction is the most important guide to a correct diagnosis.

In syphilis of the heart, producing symptoms of heart failure or anginal attacks, the syphilitic origin of the disease is often missed, and Osler considers that the presence of heart failure in a young or middle-aged person in whom there is no history of rheumatic

fever should always arouse a suspicion of syphilis. It has long been suspected that the majority of cases of aortic aneurism and aortitis were syphilitic in origin. This has been proved to be the case by the Wassermann reaction, practically every case of aortic aneurism giving a positive result. In the absence of antisyphilitic treatment, therefore, a negative Wassermann almost excludes aortic aneurism.

A certain proportion of cases of gastric ulcer are considered by some observers to be syphilitic in origin.

The liver is frequently attacked in syphilis. Osler and Gibson consider that in about 5 per cent. of cases of tertiary syphilis, exclusive of amyloid diseases, symptoms are referable to diseases of the liver.

As we have seen in the last chapter, syphilis may frequently be the cause of renal diseases.

Surgery.—The value of the Wassermann reaction for the differential diagnosis of malignant disease or tubercular disease from syphilis is obvious.

There is hardly any tumour of the bone or skin, or any form of chronic ulceration, in which operative procedure should be undertaken, without first testing the Wassermann reaction, and, if positive, giving the patient some antisyphilitic remedy with a view to finding out whether the lesion in question is syphilitic or not.

Syphilitic adenitis, especially that occurring in the tertiary stage, has been erroneously diagnosed as Hodgkin's disease.

Obstetrics and Gynæcology.—Dr. Franz Weber has shown that some cases of endometritis and of persistent menorrhagia may depend on a latent syphilitic

affection, the recognition of which by the Wassermann reaction may indicate the line of successful treatment.

Weber determined the Wassermann reaction in 67 cases of pregnancy which terminated before the twenty-eighth week, and found that of 35 ending within the first sixteen weeks, not one gave a positive result. On the other hand, of the 32 later cases, 12 without any ascertained history or clinical evidence of syphilis gave a positive reaction, and in the examination of 9 dead fœtuses from these 12 cases spirochætes were found in the organs of 6. Among 33 cases of recurrent abortion, 6 only gave a positive reaction. The examination of the macerated fœtus show that in 84 per cent. the organs contain spirochætes, which were found in the largest number in the adrenal capsules.

Ophthalmology.—Chancre, gummata, and tertiary syphilitic ulcers occasionally occur on the eyelids, and keratitis, iritis, retinitis, choroido-retinitis, and optic neuritis may all be syphilitic in origin.

Nervous Diseases.—The value of the Wassermann reaction in nervous diseases is discussed in the next chapter.

Although, in the absence of a few diseases, a positive reaction can be taken as pathognomic of syphilis, it must always be remembered that a negative reaction does not necessarily put syphilis out of court, especially in cases in which obvious lesions are absent. In the secondary and tertiary stages from 10 to 20 per cent. of cases fail to give a positive reaction, and in latent cases and cases in which there are no symptoms 50 per cent. of cases are negative. A *succession* of negative reactions must be obtained before syphilis

can be excluded, and even then the exclusion would not be absolute, but only probable.

FOR CONTROLLING TREATMENT

Neisser is firmly convinced that a positive reaction is a sure symptom of disease and an indication of the continued presence of spirochætes in the infected body, and that consequently in all cases which give a certain positive reaction a recurrence is possible, and that all such cases should be put under treatment.

The Wassermann reaction, therefore, furnishes grounds for the treatment of those patients whom we previously did not treat because the affection was not recognized, and of those whom we had ceased to treat because we believed them to be cured.

Neisser considers that the serum diagnosis is indispensable before giving an opinion on any syphilitic cases which presents no manifest symptoms of syphilis, and he considers that the Wassermann reaction alone can help us to decide the difficult question as to how long treatment must be continued.

In the Cavendish Lecture in 1911, Neisser said:

'I cannot understand how in the present day medical men fail to make use of this excellent aid to the diagnosis of syphilis. One must urgently demand that every individual, of whom even the slightest suspicion is entertained that any disease may be produced by a known or unknown syphilitic infection, must have his serum examined so as to disclose these hidden or latent cases, and in this way to cure them and to protect them against the much-dreaded parasyphilitic complication.'

A single negative reaction obtained with the serum of a patient undergoing treatment by mercury or salvarsan means little but that the patient is reacting to such treatment. A series of negative results taken at intervals of three to six months after all treatment has been given up is necessary before the patient can be regarded as cured, and even then, until twenty years have passed, we cannot be absolutely certain that the disease is completely and permanently obliterated and that no late manifestations will ever occur. It is most important to remember that about 10 per cent. of untreated cases of syphilis fail to give a positive reaction at the first examination, and that therefore a negative reaction only gives a 90 per cent. probability of freedom from infection.

If in recently acquired syphilis after several months' treatment the reaction continues to be strongly positive, and large doses of complement are still fixed, this is an indication that the treatment is inefficient, and that more rigorous methods should be adopted. If, however, after each course of treatment a smaller amount of complement is fixed, or the intervals before a positive reaction returns become longer and longer, we may conclude that the treatment is satisfactory, and that there is no necessity to increase the dose.

MARRIAGE AND OFFSPRING

Bayet considers that as regards the question of marriage and offspring, the serum diagnosis, contagiousness, and the transmission of infection to offspring must be regarded as three distinct matters.

He thinks that clinical experience must be considered of equal value with the Wassermann reaction, and the question of date of infection, length and nature of treatment, and time since the last appearance of any symptoms, must be thoroughly gone into when the practitioner is asked his advice as to the permissibility of marriage. He does not consider a positive Wassermann reaction an *absolute* contra indication to marriage, providing that *all* other considerations are satisfactory. If, however, marriage of a man giving a positive reaction is permitted and pregnancy occurs, he advises that the mother should undergo antisyphilitic treatment even if she presents no symptoms and gives a negative Wassermann reaction.

The reaction is of great value in obstetric practice as a means of diagnosing latent syphilis in the mother, for (if positive) then energetic antisyphilitic treatment holds out great hopes of the birth of a full-time and healthy child. Bat and Daunay consider that in a pregnant woman one solitary negative reaction does not authorize the conclusion that the woman is free from infection, but that one positive reaction is diagnostic of certain maternal and probable fœtal infection, and indicates active treatment. They find, when infection has occurred some time after conception, that there is a higher percentage of positive results with the mother than with the infant. Treatment of the mother during pregnancy produces a negative reaction in the infant, but one negative reaction does not authorize the conclusion that the infant is healthy and can be suckled by a healthy wet-nurse. Colles's and Profeta's laws have been proved in part by this

reaction. The immunity, however, of the mother in Colles's law and the child in Profeta's law is only apparent; they cannot contract the disease because they already have it in a latent form.

Thomsen and Boas examined the reaction of 44 newly born infants, which either themselves showed syphilitic lesions or were born of syphilitic mothers, and obtained 20 positive and 24 negative reactions. Sixteen positive cases either showed clinical evidence of syphilis within three months or died in the interval, the post-mortem examination showing characteristic changes in the organs. In the remaining 4 positive cases the reaction disappeared completely, and did not return in three to nine months, nor did these cases develop any evidence of syphilitic infection. Of the 24 negative cases, 17 remained negative, and the infants, during a period of observation extending over several months, showed no signs of disease. Of the mothers of these 17 infants, 10 gave a negative reaction and 7 a positive reaction.

Of 35 mothers whose children showed signs of syphilis, 26 gave a positive and 9 a negative reaction.

Browning and Mackenzie conclude that the large majority of cases with a positive reaction of the blood at birth subsequently develop symptoms of disease, and that the large majority of those with a negative reaction at birth remain healthy. They also consider that the examination of the blood from the mothers showed that—

1. The mother may be positive and the child negative.

2. The mother may be negative and the child positive.

3. The mother and child may both be positive.

4. The mother and the child may both be negative.

As regards older children, Thomsen and Boas found that 37 children up to two years of age with signs of congenital syphilis all gave positive reactions. They further found that of 27 older children and adults with manifestations of congenital syphilis, each gave a positive reaction. The specific affections in these latter cases included interstitial keratitis, osteitis, choroiditis, and juvenile general paralysis.

Accordingly, a negative reaction in a case presenting active lesions is strongly against the latter being due to congenital syphilis.

The presence of the positive reaction can only be held to denote syphilis. A passive absorption of the reaction bodies from the child *in utero* is excluded by the fact that the reaction is not transient, but permanent.

Probably a man need have but little fear for the safety of his children so long as his wife has a negative reaction.

CHAPTER XII

SERUM AND CEREBRO-SPINAL FLUID IN NERVOUS DISEASES

GENERAL PARALYSIS

The well-known dogma, 'General paralysis is the product of syphilization and civilization,' was advanced by Krafft-Ebing, and was based on inoculation experiments, in which he found that general paralytics invariably gave a negative result when inoculated with syphilitic virus.

Many authorities consider general paralysis and tabes to be a fourth stage in syphilitic infection, but Mott considers that there is a primary neuronic decay which cannot be accounted for solely by the changes in the supporting, enclosing, and nutrient tissues. He considers that the pathology of parasyphilitic affections is that in certain acquired or congenital syphilitic individuals the durability of the neurones is greatly curtailed, so that they decay and die prematurely, thereby giving rise to a series of symptoms which may be associated either with the irritation of definite nerve structures—*e.g.*, lightning pains, visceral crises, mania, and epileptiform convulsions; or with neural destructions—*e.g.*, ataxy, paræsthesia, anæs-

thesia, paresis, and dementia. The irritative phenomena may be the sign of increased neural irritability due to degeneration of neurones prior to their death and loss of function. He does not, however, affirm that the lymphatic and vascular changes play an unimportant part in the process of decay and death of the neurones.

He considers that if the *Spirochæta pallida* is the cause of these neuronic degenerations occurring after a lapse of an average of ten years, this is only to be explained by the existence of an intracellular granular resting form becoming active and causing inflammatory changes in the membranes and vessels and connective tissues, with secondary irritation and destruction of the neural elements. This theory he considers purely hypothetical, and one that cannot be accepted without further proof.

He points out that, whereas in active syphilis giving a positive Wassermann reaction treatment will cause the reaction to become negative, in general paralysis treatment has no effect on the Wassermann reaction.

Neisser considers that the late manifestations of syphilis in the form of general paralysis or tabes may be the result of a modification of the action of the specific organism by the widespread use of mercury, and others have put forward the suggestion that there may be a specific spirochæte for these diseases.

Whereas some strains of spirochætes seem to affect bone and viscera, others appear to chiefly attack the central nervous system. Both Brosius and Erb quote cases in which several individuals were infected from one source, and in which the majority of those infected

developed later either general paralysis or tabes; and cases of general paralysis or tabes occurring in both husband and wife appear to be more common than can be accounted for by coincidence.

Browning and Mackenzie, in reviewing the work of Mott and Spielmeyer, emphasize the resemblance between lesions of the central nervous system produced by dourine, by experimental trypanosome infection in dogs, and by sleeping-sickness, and the lesions produced in parasyphilitic conditions. The lesions of the central nervous system in dourine, in the dogs experimented on, and in sleeping-sickness, were all produced by a trypanosome, and these lesions were very like those found in parasyphilis. They therefore conclude that it seems highly probable not only that parasyphilis is caused by the *Spirochæta pallida*, but also that the *Spirochæta pallida* is a protozoon.

In countries where syphilis has recently been introduced, and the disease often takes a malignant form, general paralysis is almost unknown; and it has been suggested that general paralysis and tabes may be the result of a partial immunity arising in populations which for several generations have been infected.

Blood in General Paralysis. — Plaut, Mott, Chandler, and many other workers agree that a positive Wassermann reaction is given by the blood of practically all general paralytics.

Of 156 cases examined by Plaut, all were positive; and of 64 cases examined by Mott, Chandler, and Henderson-Smith, 92 per cent. were positive. Boas

obtained positive results in every case in 139 cases examined.

Plaut points out that other syphilitic affections, even in the florid stage, exhibit no such complete regularity in reaction, and he considers that general paralysis occupies in respect to the Wassermann reaction a unique position among all the varied clinical forms of syphilis. He considers that we may have to count on the possibility that perhaps the syphilitics who lack the reaction in the florid stage have no tendency to develop paresis later, and that therefore the production of the reacting substance represents a primary condition in the development of a metasyphilitic disease. He considers that the existence of general paralysis can practically be excluded if the serum of the patient gives a negative Wassermann, and that general paralysis is the only one of all the syphilitic affections in which a negative result is of definite clinical value. He points out that for differential diagnosis the negative result is of more importance than the positive; for, while a negative finding excludes the diagnosis of general paralysis, a positive reaction proves absolutely nothing concerning general paralysis, but simply shows that the patient has had syphilis. He therefore advises in every case in which general paralysis is suspected that the blood should be first examined, and, if the result is negative, that lumbar puncture should not be proceeded with. If, however, a positive result is obtained in the blood, lumbar puncture should then be performed for the purpose of biological and cytological examination of the cerebro-spinal fluid.

Cerebro-Spinal Fluid in General Paralysis.—Plaut considers that, with few exceptions, there is a positive Wassermann reaction and an increase in the lymphocyte count.

Of 154 cases examined, all of which gave a positive Wassermann with the blood, 146 cases gave a positive reaction of the cerebro-spinal fluid, 2 a doubtful reaction, and 6 a negative reaction; 146 gave a lymphocytosis, and 8 showed no cell increase.

GENERAL PARALYLIS, 154 CASES (PLAUT).

Number of Cases.	Blood (Wassermann Reaction).	Cerebro-Spinal Fluid (Wassermann Reaction).	Cytology.
138	+	+	+
6	+	−	+
2	+	+	+
8	+	+	−
	100 per cent.	95 per cent.	95 per cent.

The lymphocytosis in general paralysis, according to most observers, is not influenced by antisyphilitic treatment.

Chandler reports that in 80 cases diagnosed as general paralysis, in which the cerebro-spinal fluid was withdrawn during life by lumbar puncture and examined by the Wassermann test, the clinical diagnosis has been controlled by post-mortem examination; 67 cases gave a positive reaction, and the post-mortem examination showed the characteristic changes of general paralysis. Of the 13 cases

that failed to give a positive Wassermann, 2 were found at the post-mortem examination to be cases of general paralysis: the remaining 11 were shown by the post-mortem examination not to be cases of general paralysis, although in six of them this condition was diagnosed by the clinical symptoms.

In another series of six cases which gave a negative reaction with the cerebro-spinal fluid, although general paralysis had been diagnosed, in every case the subsequent progress of the cases showed that the diagnosis had been erroneous. Five of these were discharged cured, the remaining case being finally diagnosed as dementia præcox.

Chandler concludes that a positive reaction cannot be obtained in the cerebro-spinal fluid except in general paralysis and tabes and in a few rare cases of syphilis of the central nervous system. He considers that in all cases an excess of lymphocytes indicates an organic disease, but not necessarily either syphilis or parasyphilis. He thinks that a positive reaction of the cerebro-spinal fluid in conjunction with a lymphocytosis points much more strongly to parasyphilis, especially general paralysis, than to cerebral syphilis or spinal syphilis.

He considers that if there is a positive reaction with the serum associated with nervous or mental phenomena, lumbar puncture should be performed; and if the cerebro-spinal fluid gives a positive reaction, the indication is strongly in favour of general paralysis.

TABES DORSALIS

The Wassermann reaction is not nearly of as much value in the diagnosis of tabes as in general paralysis, since a positive reaction is only obtained in the blood in about 60 per cent. of cases, and in the cerebro-spinal fluid in only about 50 per cent. Cases sometimes occur in which a positive reaction is present in the cerebro-spinal fluid and not in the blood.

A pathological increase in the lymphocytes is also found in only about 60 per cent. of cases.

It therefore follows that, though a positive Wassermann reaction in the blood and cerebro-spinal fluid accompanied by a cellular increase may be of considerable diagnostic value, yet a negative reaction cannot put tabes out of court.

Of 43 cases examined by Boas, 28 were positive and 15 negative. If these cases were given under the headings of 'treated' and 'untreated' cases, it would be found that of the 17 cases that did not receive treatment all were positive, whereas of the 26 cases which had received treatment 11 were positive and 15 negative.

Of 36 cases examined by Browning and Mackenzie, 72 per cent. gave a positive reaction with the serum.

Of 50 cases examined by the author, 30 (60 per cent.) were positive.

CEREBRAL SYPHILIS

In this condition a positive reaction is usually given with the serum, but not with the cerebro-spinal fluid.

Of 18 cases examined by Plaut, 14 were positive

with the serum and negative with the cerebro-spinal fluid, 3 were positive with both serum and cerebro-spinal fluid, and 1 was negative with both.

Nonne, however, obtained a positive reaction in the cerebro-spinal fluid in 4 out of 16 cases examined.

Mott considers that 25 per cent. give a positive reaction with the cerebro-spinal fluid, and that most of the cases show a well-marked lymphocytosis.

MENTAL DEFICIENCY

Still found six idiots amongst 142 consecutive cases of congenital syphilis (4·2 per cent.). He considers that the proportion of cases of idiocy due to syphilis would be considerably higher if mental degeneration, as an acquired condition beginning after some years of apparently normal mental power, were included.

Tredgold found definite clinical evidence of syphilis in 2·5 per cent. of cases out of 150 inmates of idiot asylums. Doubtless the Wassermann reaction would have greatly raised the percentage of cases demonstrable as syphilitic in this series.

Of 36 cases examined by Plaut, 23 gave a positive Wassermann; in only 10 cases was the cerebro-spinal fluid examined, and these included 4 cases of general paralysis, which were all positive, and 2 cases of acute cerebral syphilis, which were both positive; 2 cases of secondary syphilis, and 2 cases of meningococcus meningitis with manifest hereditary syphilis, were both negative.

In a very interesting series of 330 cases of congenital mental deficiency examined by Dean, 55 gave a posi-

tive Wassermann reaction—namely, 15·5 per cent. Among the 55 positive cases there were 13 which showed other evidence of syphilitic infection.

DIFFERENTIAL DIAGNOSIS

Individuals who have contracted syphilis occasionally develop hysteria, hypochondriasis, or syphilophobia, and in such cases, as Mott points out, a negative Wassermann reaction may be able to allay their ungrounded fears and their desire for salvarsan treatment.

Neurotics suffering with arterio-sclerosis may become melancholic and irritable, and develop symptoms suggesting general paralysis. Examination of the cerebro-spinal fluid will at once settle the diagnosis.

Mott considers that parasyphilitic affections may be definitely differentiated from neurasthenic conditions by an examination of the cerebro-spinal fluid, and that a lymphocytosis points definitely to a chronic inflammatory condition of the central nervous system, of which, however, syphilis may not be the only cause.

Chronic alcoholism and syphilis are so often associated that cases frequently occur in which there is considerable difficulty of diagnosis from general paralysis. A negative Wassermann in these cases will exclude general paralysis; but if the reaction is positive, and the symptoms suggest the possibility of general paralysis or syphilitic disease of the central nervous system, recourse should be had to lumbar puncture.

One must not lose sight of the diagnostic value of

the influence of treatment on lymphocytosis of the cerebro-spinal fluid. It is difficult to diagnose between syphilitic cerebro-spinal meningitis, tabes, and general paralysis. In all three conditions there may be a high lymphocytosis, and a positive Wassermann may be present, though rarely in the syphilitic cerebro-spinal meningitis, as well as in parasyphilitic conditions. If, however, after a short course of mercurial inunctions or intramuscular injections, a rapid fall in the number of leucocytes in the cerebro-spinal fluid is recorded, parasyphilis can be excluded.

In toxic peripheral neuritis with ataxia the symptoms may be confused with those of tabes. Examination of the cerebro-spinal fluid, however, will settle the diagnosis. The reaction will be negative, and there will be no lymphocytosis.

Mott is of the opinion that a person suffering with an affection of the nervous system, whose blood gives a positive serum reaction, is much more likely to be suffering from a syphilitic affection than one who has had syphilis, but whose blood does not yield the reaction. An examination of the cerebro-spinal fluid in such a case will afford most valuable evidence, and he considers that *such evidence is of vital importance.*

In the case of acute syphilitic disease, antisyphilitic treatment will cause a disappearance of the Wassermann reaction and of the lymphocytosis in the cerebro-spinal fluid. There will be either cure or improvement in the symptoms.

In the case of general paralysis or tabes, especially general paralysis, however, both the serum and cerebro-spinal fluid will give a positive Wassermann,

which will be uninfluenced by treatment, and in the majority of cases the lymphocytosis of the cerebro-spinal fluid will not be improved by the treatment.

Hysteria, hystero-epilepsy, neurasthenia, chronic alcoholism, dementia præcox, disseminated sclerosis, tubercular meningitis, and cerebral abscess, will all give negative Wassermann reactions of the blood except in those cases in which a syphilitic affection may be coincident, but none will give a positive Wassermann of the cerebro-spinal fluid.

Paraplegia, hemiplegia, cerebral tumour, meningitis, or idiocy, may be syphilitic in origin. An examination of the blood and cerebro-spinal fluid will be of great importance for arriving at appropriate treatment.

The following tables give the relation between the diagnosis of tabes and general paralysis and the Wassermann reaction of the blood and cerebro-spinal fluid as recorded by various observers :

TABLE III.

	Diagnosed as Tabes.				Diagnosed as General Paralysis.			
	Serum.		Cerebro-Spinal Fluid.		Serum.		Cerebro-Spinal Fluid.	
	Number of Cases.	Per Cent. Positive.	Number of Cases.	Per Cent. Positive.	Number of Cases.	Per Cent. Positive.	Number of Cases.	Per Cent. Positive.
Noguchi	205	60	11	54	61	65	60	73
Marie and Levaditi	—	—	9	66	—	—	—	—
Wassermann ..	—	—	15	53	—	—	35	94
Mott, Chandler, and Henderson-Smith	—	—	—	—	—	—	64	92
Bayly..	50	60	20	45	20	85	8	87
Plaut	—	—	—	—	150	100	150	96

Table IV.

The Wassermann Reaction of the Blood in Nervous Diseases other than General Paralysis and Tabes (Author's Series).

Diagnosis.	Number of Cases.	Per Cent. Positive.
Cerebral tumour	31	24
Paraplegia	25	24
Hemiplegia	16	25
Pachymeningitis	16	25
Disseminated sclerosis ..	13	15
Epilepsy	10	0
Optic atrophy	4	75
Mental Deficiency	4	50

CHAPTER XIII

TREATMENT

SALVARSAN

DIOXY-DIAMIDO-ARSENO-BENZOL ("606"), discovered by Ehrlich and Hata in 1909, not by chance, but as the direct outcome of long and patient research, is now universally recognized as one of the most potent anti-syphilitic remedies. Like all new remedies, it has its strong advocates and equally strong detractors. It has now passed through the fire of most searching criticism, and has emerged from the experimental stage to permanently take its place amongst the most valuable antisyphilitic remedies. Its remarkable efficacy in clearing up syphilitic manifestations has been established, and, though at present it is impossible to state that any given number of injections with salvarsan will definitely cure every case of syphilis, still we know that in the vast majority of cases it has great therapeutic value. It would be as foolish to say that salvarsan is useless because it does not permanently cure with two or three injections as to say that mercury is useless because two years of pill treatment, or two courses of inunctions or intramuscular injections, do not produce permanent cure in the majority of cases.

In every case of microbic invasion we have to consider a variety of factors—variations in strain of the invading organism, the soil, and the reaction of the individual to the infection. Syphilis is no exception to this general rule, and it is not to be wondered at that no two cases behave in a precisely similar manner either towards the infecting agent or towards the remedy prescribed to combat it. In no given case can the progress of the syphilitic infection be foreseen, and no one who undertakes the treatment of a primary lesion can predict the course that will be taken by the disease.

Method of Administration.

Apparatus.—The apparatus used by the author consists of a container surrounded by a hot-water jacket; a rubber tube about 4 feet long, which connects the container and the needle-holder; and a stout needle $1\frac{1}{4}$ inches long and of the calibre of a fine exploring needle. About 3 inches from the needle-holder a piece of glass tubing is let in to act as a window. The container, tube, and needle-holder are connected up and sterilized before use. The rate of flow is regulated by altering the height of the container, and a clip is applied to the rubber tube about a foot from the needle-holder (Fig. 21).

Technique.—The patient should be in bed, with the arm selected for the infusion supported on a pillow. Having sterilized in the autoclave a glass measure graduated to 300 c.c. and also a glass stirring rod, 100 c.c. of sterilized normal saline is poured into the measure. The end of the phial containing the

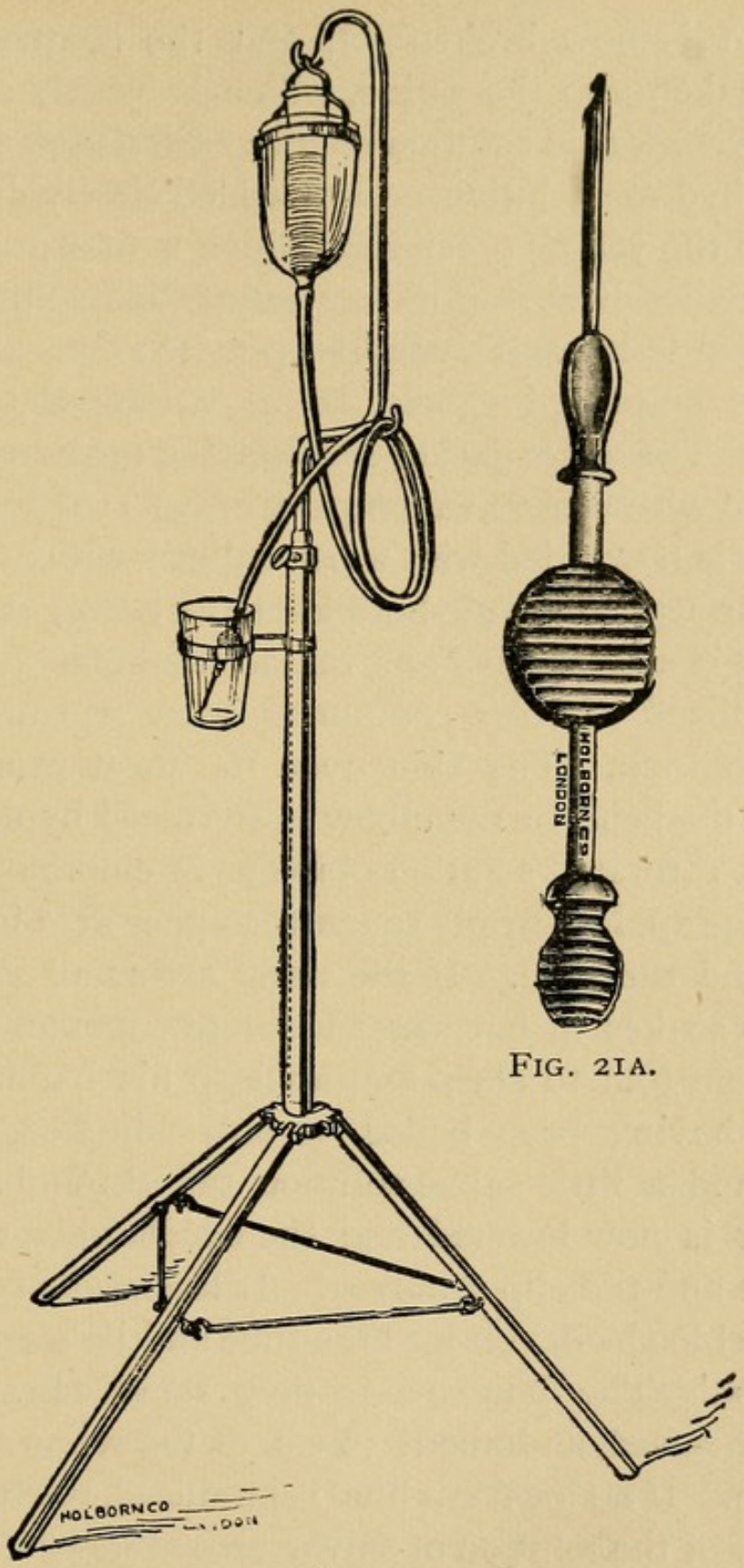


FIG. 21A.

FIG. 21.

APPARATUS FOR INTRAVENOUS INJECTION OF SALVARSAN (AUTHOR'S PATTERN).

salvarsan is now broken off, and the contents are *slowly* shaken into the saline, which is briskly stirred. A clear yellow acid solution results. Sterilized normal sodium hydrate solution is now added slowly drop by drop, till the yellow precipitate which is first produced is just redissolved. More normal saline solution is now added to bring the volume up to 300 c.c. All the solutions employed should be at a temperature of 110° F. The water-jacket surrounding the irrigator is also filled with water at a temperature of 110° F. The irrigator is now filled with warm saline solution, which is run through till all air-bubbles have been got rid of. The clip is now applied and the needle-holder put into the sterilized tumbler containing some warm sterile saline solution. The skin over the most prominent vein at the bend of the elbow is sterilized by dabbing it with a saturated solution of iodine in chloroform and a bandage applied firmly round the upper arm in order to distend the vein. If the veins are small the arm must be soaked in hot water for a few moments, and the patient told to clasp and unclasp his hand. The needle, having been boiled, is now adjusted to the holder and a little saline solution run through. The irrigator is now lowered and the needle plunged into the vein and the clip removed. If the needle is in the vein the blood will run into the tube and be seen at the 'window.' The bandage is now removed and the irrigator raised, and about 50 c.c. of the saline allowed to run in. If no local swelling is produced, the required quantity of the solution of salvarsan can now be poured in. If, however, any local swelling is produced by the saline, the needle must be removed and the procedure

recommenced in another vein. The solution should only be allowed to run in *slowly* so as to be well diluted by the blood-stream, and it should take about ten minutes to run in all the solution. 0·6 gramme of salvarsan having been diluted up to 300 c.c., 50 c.c. of the diluted fluid contains 0·1 gramme of salvarsan. 0·6 gramme is the author's usual dose for a healthy male adult and 0·5 gramme for a woman. About 100 c.c. of normal saline solution should be poured into the irrigator when the salvarsan solution has almost run out, so that the needle may be washed free of salvarsan before being withdrawn; otherwise some salvarsan may escape along the needle track and produce some local inflammation and possibly phlebitis and thrombosis.

Preparation of the Patient.—The preparation of the patient is of great importance, as, if the infusion is given with a full stomach and high blood-pressure, an alarming condition of feeble rapid pulse and collapse may supervene, which, however, usually passes off when vomiting occurs. Rigors are not uncommon in florid syphilis, and may occur from one to three hours after the infusion. The patient sometimes complains of throbbing in the head and a metallic taste in the mouth and a sense of fulness in the throat. The author prepares the patient by giving a pill the night before and a brisk saline purge on the morning of the infusion. Only a light breakfast is allowed, with but little fluid and no food or drink for four hours before the infusion. Since the author has adopted these precautions he has recorded no alarming symptoms.

Dosage.

The question of dosage and mode of administration appear to be of vital importance, and the experiments of Hata carried out upon animals lend great support to this view. In mice inoculated with organisms of relapsing fever, a single injection of $\frac{1}{800}$ gramme (per 20 grammes of weight) of salvarsan gave 100 per cent. of cures, while the administration of half this dose was followed by 82 per cent. of failures. Similarly, suggestive results were obtained in 'syphilized' rabbits with scrotal chancres, 0·0075 per kilo-weight effecting complete cure, while 0·004 gramme proved ineffective.

The usual dose for adults given by the intravenous route is 0·5 gramme for a woman, and 0·6 gramme for a man.

In the absence of temperature and nephritis, the author repeats the dose after forty-eight hours.

Therapeutic Results.

1. **Primary Syphilis.**—In the majority of primary cases the effect of salvarsan, whether administered by the intramuscular or the intravenous route, is prompt, and some degree of softening of the hard chancre is frequently observed within twenty-four hours. According to Wechselmann, eroded chancres become clean after from twelve to twenty-four hours, and, further, the *Spirochæta pallida* is no longer found in scrapings taken after one or two days. The rapidity with which absorption takes place depends upon several factors—

the degree of induration present, the actual size of the lesion, and the dose of the drug exhibited.

Gibbard, Harrison, and Cane, in order to compare the effect of salvarsan with that of mercury in preventing the onset of secondary symptoms when treatment was commenced in the primary stage, treated 38 cases of primary sore with salvarsan, and another series of a similar 38 cases with mercurial injections. In all cases the *Spirochæta pallida* had been demonstrated. All the cases were under observation for at least four months. Of the 38 salvarsan-treated cases, only 2 (5·2 per cent.) developed secondary symptoms, while of the 38 mercury-treated cases, 36 (94·8 per cent.) developed secondary symptoms.

These extremely valuable parallel investigations in strictly comparable cases emphasize clearly and beyond all doubt the very great importance of the early administration of salvarsan.

2. **Secondary Syphilis.**—As regards the effect of salvarsan on the manifestations of secondary syphilis, it is almost impossible to write a *critical* report, as the innumerable contributors to the literature are almost unanimously in favour of the drug. Ernest Lane and C. F. Marshall of this country, working independently, and Engmann, Mark, and Marchildon, working together, consider that equally good effects can be obtained with mercurial treatment. These observers, however, had, when they first advanced these opinions, personal experience of only quite a small number of salvarsan-treated cases, and probably with efficient doses given by the intravenous route their future reports will not be so pessimistic. Ernest Lane,

indeed, has already modified the opinions he first expressed, which were that intolerance to mercury would be the only justification for looking elsewhere for a remedy.

As is to be expected, secondary manifestations differ very considerably in their reaction to salvarsan, and sclerosed lesions take much longer to resolve than soft conditions, such as mucous plaques, condylomata, and superficial ulceration of the mucous membrane, which usually disappears in twenty-four to forty-eight hours, Wechselmann stating in respect to mucous plaques of the mouth, 'even if the patient smokes continuously.'

The pains arising from secondary syphilitic infection of periosteum or joints are frequently relieved in an extraordinarily short time, and, indeed, pain of any kind arising during the course of syphilis, either early or late, is usually most favourably influenced by salvarsan.

It is particularly in malignant syphilis, reacting little or not at all to mercurial treatment, that the value of salvarsan is most strikingly seen. Numerous cases are recorded of patients apparently doomed to death, owing to the entire failure of mercury to check the morbid processes, who have been saved by the administration of salvarsan.

Gibbard and Harrison found that of thirty-two cases which were either uninfluenced by or intolerant to mercury, all but one were to all appearance completely cured by salvarsan. Intolerance to mercury on the part of the patient and immunity to mercury on the part of the spirochæte being rare, the cases

recorded by these officers, which were collected from all the military stations of Great Britain and Ireland, are of extreme interest and value.

3. **Tertiary Syphilis.**—In no stage of syphilis is improvement by salvarsan more marked than in the tertiary, and there can be few clinicians with any considerable experience of Ehrlich's specific who have not met cases of severe and intractable ulcerations, or bone lesions, in which the new treatment acted 'like a charm.' Within a few hours the symptoms begin to subside, and within one to three weeks not only have the lesions healed, but the patient's general condition has also remarkably improved. Cases of chronic superficial glossitis have been most successfully treated by salvarsan.

The author's own experience but confirms the results reported by previous contributors to the literature, and only adds to the indisputable evidence as to the value of salvarsan in removing the symptoms of tertiary syphilis.

4. **Congenital Syphilis.**—The opinion as to the value of the drug in interstitial keratitis is still divided, and it is only to be expected that the least effect would be produced in non-vascular tissue, such as the cornea. Infants under six months should not, by preference, be treated directly, on account of the enormous number of spirochætes present and the large quantity of endotoxin set free by an efficient dose of salvarsan, but indirectly through the milk of the mother who has been treated. If the mother cannot feed her baby, so that treatment via the milk is impossible, intramuscular injection of not more than 0·02 gramme may be given

to newly born infants in urgent cases, or if the child is several months old, McDonagh does not think 0·004 to 0·005 gramme per pound weight of child to be too large a dose.

Pregnant women, if healthy, may with safety be treated, and Wechselmann has reported a case injected five weeks before delivery, in which an apparently healthy baby with a negative Wassermann reaction was born.

5. **Parasyphilis.**—(1) *Tabes.*—The evidence that has accumulated as to the value of salvarsan in early cases of tabes is considerable. Not every case, however, benefits from the treatment, and, indeed, occasionally an exacerbation of symptoms has been noticed. The rule, however, seems to be that there is diminution in the pain, ataxia, and frequency of crises with improvement in general health, and of the bladder and rectal symptoms.

Wechselmann and McDonagh have each reported a case in which return of sexual power has followed treatment, and have noticed in a few cases a return of mobility in rigid pupils and of the patella reflex. Wechselmann writes: 'In view of extensive subjective improvements I no longer hesitate to administer injections, even in cases where the Wassermann reaction is negative. Undoubtedly an important part in this happy result should be attributed to the stimulating and tonic effect of the remedy. We cannot for some years conclude that the remedy permanently stops the progress of the disease.'

Out of a large number of cases treated by James Collier, he has recorded no permanent ill-effect referable

to the medication, and no aggravation of the tabetic symptoms after injection. In the majority of cases marked improvement in general health, nutrition, colour, and feeling of well-being occurred within a couple of weeks of the injection.

The ataxy improved conspicuously in several cases, and occasionally sphincter trouble seemed benefited; on the other hand, he did not see any of the characteristic physical signs of the disease disappear entirely. In those cases where pains were present and troublesome, very striking relief followed the salvarsan injection. Four patients, who suffered from severe gastric crises, improved remarkably.

The results obtained suggest that salvarsan may be of considerable value in the treatment of tabes, especially in early cases occurring soon after infection.

Marcus concludes that 'we are certain now that salvarsan is very useful in syphilitic nervous diseases, and that it acts more rapidly and is more convenient than mercury or potassium iodide.' He thinks it justifiable to give salvarsan even in advanced cases of tabes, as it may ameliorate the pains and lengthen life, although there may be no hope of cure.

(2) *General Paralysis.* — A few cases of apparent recovery following injection with salvarsan have been reported. Treupel has frequently noticed a transient improvement. Most writers, however, report complete absence of improvement, and the cases that are benefited must be few. Still, in the light of occasional successes, early cases should be given the chance of cure or improvement, even if this be an extremely small one.

Dangers.

Toxicity.—Professor Ehrlich, after investigating reports of 10,000 cases, stated that only a single fatal case had been recorded in which the patient's life had not been directly in danger from the disease itself. In this connection it is only fair to state that a considerable number of the fatalities reported on the Continent have been described as cases of death 'following the administration of salvarsan,' which would have been more justly recorded as cases of death 'occurring in spite of the administration of salvarsan.' Gibbard and Harrison have not met one case in over 1,000 injections that has given rise to anxiety.

In the very large number of cases treated at the London Lock Hospitals two deaths have followed treatment. In one, no error of technique or any cause other than the toxicity of the fluid injected could be found. The post-mortem examination showed the changes characteristic of toxæmia. The symptoms did not develop until three days after the second dose. Degenerative changes were found in the liver, and possibly these changes were induced by the salvarsan, and were the cause of the toxic symptoms. The second death was from pulmonary embolism, resulting from the shifting of a clot from a vein inflamed above the point of injection. The embolism occurred three days after injection.

The author, in a considerable personal experience, has met no case giving rise to apprehension, with the exception of two cases of phlebitis, one of slight transient albuminuria, and one of syncope. This last

case occurred in a patient that had not been properly prepared by starving and purging.

The author is of the opinion that salvarsan given in the present dosage is practically non-toxic, and that most, if not all, of the few fatal cases recorded are due to some accident, such as decomposition of the drug owing to a flaw in the glass ampule, so that the vacuum is destroyed, or to error in technique.

Blindness.—Cases of blindness have been recorded in lay journals on the Continent; but Ehrlich categorically states that no case has been reported to him, and that, despite penetrating research, it has not been possible for him to run one of these rumoured cases to earth. In medical literature the danger has been constantly hinted at, but the author has been unable to find any authenticated case of actual loss of sight following treatment by salvarsan.

On the other hand, many observers have published cases of optic neuritis which have been definitely improved by the exhibition of salvarsan.

Phlebitis sometimes occurs in the vein receiving the injection. If this sequel arises, the arm must be kept at rest and the limb fomented with lead and opium lotion. The author knows of one case in which death occurred from pulmonary embolism caused by the shifting of a clot from a vein in which phlebitis had occurred as a result of the injection.

Nephritis.—Transient *albuminuria* has been observed in several cases, and a very few cases of severe and *acute nephritis* have been recorded in the literature. A few cases of suppression and retention of urine have also been reported.

After-Effects.

Pain in intravenous injections should, with correct technique, be limited to the momentary discomfort caused by entrance of the needle. Occasionally *painful local infiltration* has been noted, but should be regarded purely as occasioned by faulty technique, by which some of the salvarsan solution escapes into the tissues around the vein and there sets up an aseptic inflammation.

Salvarsan Fever and Saline Fever.—As has been pointed out, the intravenous injections of salvarsan are sometimes followed by a rise in temperature, sometimes reaching 102° F., and occasionally as high as 105° F. This rise in temperature may be accompanied by rigors, vomiting, headache, and pains in the back. The onset of the symptoms usually occurs from half an hour to two hours after the injection. The symptoms usually subside in a few hours.

Wechselmann has suggested that these symptoms might be caused by contamination of the saline solution, and not be due to the salvarsan, and Gibbard and Harrison, MacIntosh and Fildes, and Holt and Penfold, working independently, have all come to the conclusion that in many cases it is the saline solution and not the salvarsan that is the cause of "salvarsan fever.'

Gross contamination with living organisms is not the only cause, for the fever may be produced if the saline solution is autoclaved just before use, so that all the organisms are killed.

The question has not been definitely settled as to

whether the toxic symptoms are produced by the dead bodies of the bacteria acting as a poisonous foreign albumin, or by thermo-stable exotoxins produced in the saline as the result of bacterial action. The results of numerous experiments, however, make it clear that, if the salt solution is only prepared immediately before use, is made with freshly distilled water, and is autoclaved directly it is mixed, these toxic symptoms will only occur in cases of florid syphilis.

MacIntosh and Fildes point out that the rigors and toxic symptoms, which occur in secondary syphilis, must be different in origin from those occurring in other forms of syphilis, because they continue in spite of the use of microbe-free saline solution. These authors also state that the toxic symptoms which occur in secondary syphilis, and are uninfluenced by the careful preparation of the saline, occur later than the saline rigors, the temperature seldom starting to rise for three or four hours.

Schreiber suggests that fever in secondary syphilis is the result of the liberation of large quantities of endotoxins from the destroyed spirochætæ, and this view the author shares.

In order to eliminate the risk of saline fever—

1. Freshly distilled water should be used.
2. Pure sodium chloride.
3. The salt should be added to the distilled water and filtered, and the filtered solution should be autoclaved immediately before use.

The author, with an experience extending over nearly two years, has not met with rigors in more than

5 per cent. of cases, vomiting has been very occasional, and the temperature has rarely been raised above 100° F. except in a few cases of florid syphilis.

Vomiting, when it occurs, usually takes place from half an hour to three hours after the injection.

Rigors are rare, but occasionally occur from half an hour to four hours after injection.

Headache and pains in the back are met with in a considerable percentage of cases.

Diarrhœa and constipation are occasional effects of treatment, the former occurring soon after the injection, and the latter after an interval of a few days. Neither condition is, as a rule, of serious import.

Both **jaundice and rectal tenesmus** occur as very rare sequels.

A temporary exacerbation of an existing skin eruption (the Jarisch-Herxheimer reaction) is not infrequently seen. Two hours or so after the injection cutaneous lesions become deeper in colour and more diffuse. This effect reaches its highest point in about twelve hours and then gradually disappears in the course of the next few days.

A sense of **cardiac oppression**, sometimes going on to syncope, and throbbing in the head have been described as occurring at the time of intravenous injection, but the author has not observed these symptoms in properly prepared cases. Purgation and abstinence from food before treatment should be enforced in each case, and this preparation of the patient, combined with slow injection of the drug, can be relied upon to obviate the occurrence of these symptoms.

The effect on the general health is strikingly beneficial in the vast majority of cases. There is at first a slight depression, with loss of appetite, lasting twelve to forty-eight hours, after which rapid improvement is usually seen. In most cases there is a very definite gain of weight, varying from a few pounds up to twenty or more in a month.

The composition of the blood is modified by salvarsan, but the changes observed are not constant. Normally there is a definite increase in the number of red corpuscles, and also in the amount of hæmoglobin. Levy-Bing and Duroeux, however, quote a case in which a fall of red cells, amounting to 1,400,000 is recorded. Leucocytosis is the rule. It may be as high as 30,000, but a more usual count is 17,000. The increase occurs chiefly in neutrophil cells, but eosinophilia has occasionally been observed. Sabrazès has worked out in minute detail the various changes occurring in the blood after treatment. Clinically, very striking improvement is seen in cases of syphilitic anæmia, the pallor and sallowness disappearing in the course of a week or two.

Relapses.

Several cases of chancre successfully treated, in so far as complete resolution had resulted in a week or so, have subsequently developed typical secondaries. Most of these have cleared up in a few days after a second injection. Many relapses have also occurred in cases treated in the secondary and tertiary stages of the disease, and in these also reinjection has, in the

majority of instances, caused disappearance of the fresh lesions.

Various causes have been put forward to explain the incidence of relapse which may be summarized as follows:

1. That the dose of salvarsan has been insufficient to kill the spirochætæ.

In this connection it is interesting to recall the experiments of Hata upon animals, which showed that half a curative dose was ineffective. Moreover, Duhot attributes his success to the large doses (maximum 1·1 gramme) which he has invariably employed.

2. That some of the spirochætæ lie embedded in thrombi or protected by dense inflammatory tissue, and only escape after the complete excretion of the drug.

Reinduration of a chancre might be explained on this hypothesis, and excision of the chancre at the time of the injection, as advocated by many authors, would thus appear to rest on a rational basis. The simultaneous administration of fibrolysin or reinjection with salvarsan at an early date has also been recommended with the same object in view; in the latter case on the supposition that the first dose, although unable to reach the 'protected' spirochætæ, yet promotes sufficiently extensive tissue reaction to enable the second to achieve this purpose.

3. That in certain cases some or all the spirochætæ are resistant to salvarsan.

We know that in a few rare instances spirochætæ are resistant to mercury, and it is conceivable that an arsenic-fast strain is occasionally met with, although Ehrlich strongly opposes this view.

4. That some spirochætæ, which are not originally arsenic-fast, become so after the administration of a dose insufficient to kill them.

This hypothesis would explain those cases which have relapsed owing to an insufficient dosage after an apparently successful treatment, and have then failed to react to a second injection.

Contra-Indications.

The contra-indications for treatment with salvarsan are few. The remedy is very well tolerated by tuberculous persons in all stages. Optic atrophy and diabetes were till recently considered contra-indications, but most authorities consider that salvarsan is harmless in these conditions.

Herxheimer considers lesions of the heart, fœtid bronchitis, and non-syphilitic disturbances of the optic nerves to be contra-indications. Great caution is required with subjects exhibiting hæmorrhagic tendency. Arsenic exerts a toxic effect upon the walls of arterioles and capillaries, and the drug should not be given in advanced disease of the heart or arteries, but small thoracic aneurisms have been treated by Wechselmann without any injurious effect. McDonagh considers bulbar paralysis a contra-indication. He also recommends that care should be exercised in cases complicated by jaundice.

It is generally conceded that cases of nephritis which are not of syphilitic origin should not be subjected to the treatment, unless albuminuria is of slight degree.

Treatment in cases of intracranial gumma must be regarded as fraught with danger, and advanced degeneration of the central nervous system or cerebral hæmorrhage are considered a contra-indication by the majority of observers.

Conclusions.

Ehrlich's idea of *therapia sterilisans magna*—that is to say, complete and lasting cure of the disease by a single dose of the drug—has undoubtedly been realized in relapsing fever. In the case of syphilis the question must be held to be 'not proven' at the present date. Many years must necessarily elapse before one can arrive at a definite decision when dealing with a disease which may lie dormant for as long a period as twenty years, and then recrudesce spontaneously.

Salvarsan has a striking and rapid effect on the clinical manifestations of syphilis; this is particularly the case in malignant syphilis when ulcerative lesions of skin and mucous membranes are present.

Pain disappears as if by magic.

Salvarsan, when it does produce an alteration of the serum reaction, does so more rapidly than mercury. On the other hand, in the present state of our knowledge, it would appear that the percentage of negative results after one or two injections is lower than that observed after a year's course of efficient mercurial treatment.

Spirochætæ disappear in two or three days from all superficial lesions, and the period of infectivity is thus reduced to a minimum—a fact of great sociological importance, especially in military stations.

The danger of death, of blindness, or other grave lesion, is so slight in carefully selected cases that there is no justification for withholding salvarsan.

The best results are obtained with administration by the intravenous route, but this should only be undertaken by workers who are skilled in the technique.

Neo-Salvarsan, which is the name that has been given to a neutral preparation of the drug, is a recent modification. It is more easily soluble than salvarsan, and does not require neutralizing with sodium hydrate. It is said to be less toxic than salvarsan, but as the toxicity of salvarsan is minimal, the advantages of the new salt consist chiefly in simplicity in preparation. 0·6 gramme can be mixed with 250 c.c. of sterile distilled water, and injected without any further preparation. This simplicity of preparation, however, is of some importance, as it obviates the possibility of adding an excess of alkali, which excess might alone produce toxic symptoms. The question as to the relative therapeutic value of salvarsan and neo-salvarsan has yet to be proved.

MERCURY

As will be seen in the next chapter, the administration of mercury by the mouth does not appear to be nearly as effective as when given intramuscularly in the form of insoluble preparations. The administration of mercury by suppositories appears to have little to recommend it, but mercurial inunctions are very potent. There is, however, but little to choose between

mercurial inunctions and intramuscular injections, any slight superiority in potency in the former being discounted by the obvious social inconvenience of this method of treatment in the majority of cases. The only form of mercurial treatment detailed here, therefore, will be intramuscular injections.

Site of Injection.—The most convenient sites for the injections are—

1. An area at the junction of the middle and posterior third of a line from the anterior superior iliac spine to the great trochanter.
2. The upper and external quadrant of the gluteal region.

The site of puncture should be cleaned with ether and alcohol, and sterilized with a saturated solution of iodine in chloroform.

Calomel cream is probably one of the most efficacious preparations, and may be used of such a strength that 5 minims of the cream contain 0·75 grains of calomel, 10 minims being given as a dose for an adult.

Mercurial cream can be used of such a strength that 5 minims contain 1 grain of metallic mercury, 10 minims being given as a dose.

A course of mercurial injections usually consists of twelve doses, the first four of which may be calomel cream, and the last eight mercurial cream.

A detailed account of mercurial treatment of syphilis lies outside the scope of this work, and will be found in any textbook dealing with syphilis.

As regards parasyphilis, Dr. Risien Russell is fully convinced of the efficacy of mercury administered by inunction or injection in tabes, and considers that no

patient in the early stages of this disease should be allowed to go untreated. He has obtained no improvement in general paralysis.

This appears to be the opinion of the majority of neurologists.

A convenient syringe and needle for intramuscular injection are shown in Fig. 22.

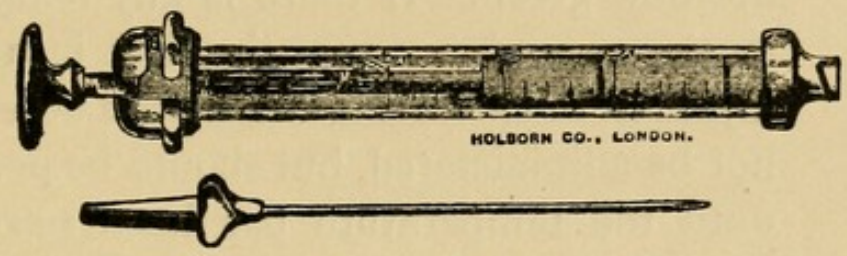


FIG. 22.—SYRINGE AND NEEDLE FOR ADMINISTRATION OF INTRAMUSCULAR INJECTIONS OF MERCURIAL CREAM.

COMBINED SALVARSAN AND MERCURIAL TREATMENT

Neisser has given it as his opinion that in order to obtain a curative result it must be better to attack the enemy from two sides rather than from one side alone. He states that it is beyond all doubt that a surer, more brilliant, and more lasting curative effect will follow if we combine the two remedies—salvarsan and mercury.

The author suggests that the combined treatment should be given as a matter of routine in all cases, and in the following way :

1. The intravenous injection of 0·6 gramme of salvarsan to be repeated in forty-eight hours by a second dose, providing that the tempera-

ture has been normal for twenty-four hours, and that no nephritis has developed.

2. This is followed by twelve mercurial intramuscular injections, the first four consisting of calomel cream, and the last eight mercurial cream.
3. Two more intravenous injections of salvarsan are now given. If there is any temperature on the second day after the first intravenous injection of salvarsan, the second dose should not be administered, but should be postponed until the temperature has been normal for twenty-four hours.
4. The Wassermann reaction should be examined two months after the last dose of salvarsan, and, if positive, a second course of mercurial injections should be given. If the reaction is negative, immediate further treatment is not indicated.
5. The Wassermann reaction should be examined every three months for two years, and occasionally afterwards, and a further course of treatment undertaken should the reaction return to positive.

CHAPTER XIV

EFFECT OF TREATMENT ON THE WASSERMANN REACTION

MERCURY

The effect of **mercurial treatment** is usually clearly seen, and depends on the time in the history of the infection that treatment began, and the length and nature of the treatment. Neisser has observed that the earlier in the course of the disease that treatment is commenced, the more probability there is that a negative result will be obtained after a course of treatment. Where treatment began as soon as possible after the primary lesion had appeared, 75 per cent. of negative reactions were subsequently obtained, whereas, if treatment has been delayed for six months, only 33 per cent. of negatives were obtained after treatment.

Of late latent cases—that is, cases several years after infection in which there are no symptoms—he found that the early treated cases gave negative results in 80 per cent. of cases, and the late treated cases in only 58 per cent. Pürckhauer reports the result of treatment on 165 cases at different stages of the infection, all of which were positive before treatment. Of 116 primary and secondary cases, 75 per cent. became

negative; of 15 late latent cases, 4 became negative; and of 18 tertiary cases only 2 became negative. Of 4 cerebral cases only 1 became negative after treatment. The longer infection has persisted, the more stable the positive reaction seems to become, and the greater difficulty there is in inducing a negative reaction after treatment. In some late tertiary and parasyphilitic conditions a negative reaction is never produced even by the most rigorous mercurial treatment.

Occasionally a case is diagnosed as syphilis and gives a negative reaction, and yet after being on mercury for a while positive reaction is obtained. This probably is due to the fact that the mercury destroys numbers of spirochætæ, whose endotoxins are then liberated, and stimulate the production of the complement-fixing substance. If 5 per cent. of complement is fixed, the case must be reported as positive, and 15 per cent. of complement is only used in order to obtain a rough idea of progress under treatment. Active syphilis will generally deviate 10 to 15 per cent. of complement, but as the infection becomes less the amount of complement deviated also becomes less. In this way it is possible to make a rough quantitative measurement of the amount of complement fixed and of the progress made under treatment, even though the case must still be returned as 'positive.'

Using this method, the author has compared the therapeutic value of some of the different methods of administering mercury.

The tables in this chapter show the results that were obtained with the various treatments as far as

the Wassermann reaction is concerned. Complete inhibition of hæmolysis is indicated by the sign + ; partial inhibition, by the sign ± ; and complete hæmolysis by the sign −. Complete inhibition of hæmolysis with both amounts of complement the author calls 'strongly positive,' while 'positive' denotes that, though there is complete inhibition with the smaller amount of complement, there is hæmolysis with the larger amount. If the hæmolysis with the smaller amount of complement is partial only, the result is recorded as 'doubtful.' All the cases recorded were 'strongly positive' before the treatment was commenced, and therefore 'positive,' 'doubtful,' and 'negative,' all show influence of treatment in a roughly quantitative manner. Very frequently cases are met with that begin at 'strongly positive,' pass through the 'positive' and 'doubtful' stages, and end at 'negative.'

TABLE V. (HARRISON).—EFFECT OF TREATMENT WITH INTRAMUSCULAR INJECTION.

	Number of Cases.	+ with 0·2 Complement.	Additional + with 0·1 Complement.	Per Cent. Showing some Effect of Treatment.	Total +	Per Cent. +
After 1 course (of 3 months)	55	17	29	69·0	46	83·6
After 2 courses	49	24	14	51·0	38	77·5
,, 3 ,,	42	8	19	80·9	27	64·5
,, 4 ,,	30	3	14	90·0	17	56·5
,, 5 ,,	34	4	13	88·2	17	50·0
,, 6 ,,	26	3	6	88·4	9	34·6

Pills and suppositories seem to be of the slowest and least efficient forms of treatment, and inunctions and intramuscular injections of insoluble compounds the quickest and most efficient. Harrison has shown clearly the *influence* of only short treatment, for, although the percentage of 'positives' remains high, some effect of treatment is recorded in 69 per cent. of cases after only one course (see Table V.).

With **pills**, on the other hand, 95 per cent. of cases treated for six months or under are positive, and only 5 per cent. show any effect of treatment (see Table VI.).

TABLE VI.—PILLS (122 TESTS).

Wassermann Reaction with less than Six Months' Treatment in 45 Cases.

Complement, per cent.	5 15	5 15	5 15	5 15
Wassermann reaction ..	+ +	+ −	± −	− −
	Strongly positive.	Positive.	Doubtful.	Negative.
Number of cases ..	41	2	1	1
Percentage of cases ..	91	4	2·5	2·5

Wassermann Reaction with Six to Twelve Months' Treatment in 33 Cases.

Complement, per cent.	5 15	5 15	5 15	5 15
Wassermann reaction ..	+ +	+ −	± −	− −
Number of cases ..	20	3	3	7
Percentage of cases ..	61	9	9	21

Wassermann Reaction with Treatment for Eighteen Months or Over in 44 Cases.

Complement, per cent.	5	15	5	15	5	15	5	15
Wassermann reaction ..	+	+	+	−	±	−	−	−
Number of cases ..	8		5		10		21	
Percentage of cases ..	18		11		22		48	

When the **inunction** method was employed, after three months' treatment, only 16·6 per cent. remained positive. Daily inunction is obviously an inconvenient method of treatment, and all skins do not tolerate this method, but otherwise inunction would seem by this too short series to be the most satisfactory form of administration of mercury. The author has had but little opportunity of investigating the effect on the reaction of treatment by inunction or suppositories, but the short series examined have been recorded in Tables VII. and VIII.

TABLE VII.—SUPPOSITORIES (33 CASES).

Treatment for Six Months and Under.

Complement, per cent.	5	15	5	15	5	15	5	15
Wassermann reaction ..	+	+	+	−	±	−	−	−
Number of cases ..	20		6		4		3	
Percentage of cases ..	61		18		12		9	

Table VIII.—Inunction (26 Cases).

Treatment of Two to Three Months.

Complement, per cent.	5 15	5 15	5 15	5 15
Wassermann reaction ..	+ +	+ −	± −	− −
Number of cases ..	3	10	3	10
Percentage of cases ..	11½	38½	11½	38½

Table IX.—Calomel Intramuscular Injections (109 Tests).

Wassermann Reaction after One Course of Twelve Injections in 54 Cases.

Complement, per cent.	5 15	5 15	5 15	5 15
Wassermann reaction ..	+ +	+ −	± −	− −
Number of cases ..	27	13	5	9
Percentage of cases ..	50	24	9	16

Wassermann Reaction after Two Courses in 35 Cases.

Complement, per cent.	5 15	5 15	5 15	5 15
Wassermann reaction ..	+ +	+ −	± −	− −
Number of cases ..	11	7	4	13
Percentage of cases ..	31	20	11	37

Wassermann Reaction after Three Courses in 20 Cases.

Complement, per cent.	5 15	5 15	5 15	5 15
Wassermann reaction ..	+ +	+ −	± −	− −
Number of cases ..	2	2	0	16
Percentage of cases ..	10	10	0	80

Intramuscular injection, however, appears almost, if not quite, as potent as inunction, and to be undeniably superior to pill treatment. That it is not the presence of the mercury itself in the blood that produces a negative reaction, was shown by Bauer, who demonstrated that a strong positive can be obtained when the mercury excretion in the urine is most marked, and that a negative reaction may be present when the mercury excreted in the urine is weak or absent. He showed that a previous negative reaction may become positive in spite of a large quantity of mercury in the blood, and that a reaction which has become negative under treatment can become positive in spite of mercury persisting in the urine.

Nearly all authorities, both Continental and American, agree that in the future treatment, whether by mercury or salvarsan, must be regulated by the Wassermann reaction. A solitary negative reaction obtained with the serum of a patient undergoing mercurial or salvarsan treatment means little but that the patient is reacting to the treatment. A *series* of negative results taken at intervals of three to six months after all treatment has been given up is necessary before the patient can be regarded as cured, and even then until another twenty years have passed we cannot be absolutely certain that the disease is completely and permanently obliterated, and that no late manifestations will ever occur. It is important to remember that about 10 per cent. of untreated cases of syphilis fail to give a positive reaction at the first examination, and that therefore a negative reaction only gives a 90 per cent. *probability* of freedom from infection. If, *in*

recently acquired syphilis, after several months' treatment, the reaction still remains strongly positive, and large doses of complement are still fixed, it is an indication that the treatment is inefficient, and that more rigorous methods should be adopted. If, however, after each course of treatment a smaller amount of complement is fixed, or the intervals before a positive reaction returns become longer and longer, we may conclude that the treatment is satisfactory, and that there is no necessity to increase the dose.

The author's further experience confirms his original conclusions, that inunction and intramuscular injection are by far the most rapid methods of producing a negative Wassermann reaction by mercurial treatment.

SALVARSAN

Salvarsan usually produces a negative reaction more quickly than mercury, but apparently the percentage of negative results after one or two intravenous injections of the doses employed (0·4 gramme) is lower than that observed after a year's course of efficient mercurial treatment. The following results were obtained in fifty cases where the reaction could be followed for several months:

Changed from positive to negative	31
Reduced quantity of complement fixed	7
Reaction unchanged	6
Relapsed from negative to positive	6

Of the total 50 cases treated with salvarsan and examined four weeks and over after treatment, 30 (60 per cent.) became negative, while, when examined under four weeks, only 9 (18 per cent.) were negative.

The results obtained which give 42 per cent. negative after intramuscular injections, 52 per cent. after one intravenous injection, and 74 per cent. after two intravenous injections, seem to indicate that the intravenous route is the best, and that at least two injections should be given (see Table X.).

The dose given in the great majority of intravenous cases was 0·4 gramme, and now that we know that usually larger doses can safely be employed, we may hope to obtain a higher percentage of negative results and a lower percentage of relapses.

TABLE X.—INJECTIONS OF SALVARSAN (200 TESTS).

Wassermann Reaction Four Weeks after One Intravenous Injection in 21 *Cases.*

Complement, per cent.	5 15	5 15	5 15	5 15
Wassermann reaction ..	+ +	+ −	± −	− −
Number of cases ..	3	5	2	11
Percentage of cases ..	14	24	10	52

Wassermann Reaction Four to Eight Weeks after Two Intravenous Injections in 50 *Cases.*

Complement, per cent.	5 15	5 15	5 15	5 15
Wassermann reaction ..	+ +	+ −	± −	− −
Number of cases ..	6	3	4	37
Percentage of cases ..	12	6	8	74

Wassermann Reaction Four to Eight Weeks after Intramuscular Injection of Salvarsan in 12 *Cases.*

Complement, per cent.	5 15	5 15	5 15	5 15
Wassermann reaction ..	+ +	+ −	± −	− −
Number of cases ..	5	1	1	5*
Percentage of cases ..	42	8	8	42

RELAPSES.—*Wassermann Reaction Six to Twelve Months after Two or more Intravenous Injections of Salvarsan in* 37 *Cases that had become Negative as the Result of such Treatment.*

Complement, per cent.	5 15	5 15	5 15	5 15
Wassermann reaction ..	+ +	+ −	± −	− −
Number of cases ..	2·0	3	2·0	30
Percentage of cases ..	5·5	8	5·5	81

It will be seen from Table X. that over 70 per cent. of cases treated with salvarsan became negative in from four to eight weeks after the second intravenous injection, and that 80 per cent. of these negatives remained negative six to twelve months afterwards. Over 50 per cent., therefore, of cases that before treatment were strongly positive became negative, and still remained so when examined six to twelve months after treatment. Of course, a negative reaction persisting for six to twelve months does not necessarily mean permanent cure, but it is at least extremely encouraging that there is no pathological evidence of relapse in over half the cases. In some cases salvarsan, even in repeated doses (sometimes as many

* Two of these relapsed to positive or doubtful.

as six have been given), has no effect whatever on the reaction. The author is inclined to think that cases that are going to relapse will show evidence of such relapse by the Wassermann reaction in under six months in the great majority of instances. On comparing Tables VI., IX., and X., it will be seen that only 48 per cent. of cases treated with pills become negative after eighteen months' treatment, whereas 80 per cent. become negative after three courses (one year's treatment) of intramuscular injections. How many of these, however, would remain negative six months later if all treatment were discontinued it is impossible to say, as the author had not opportunities for such investigation. At the London Lock Hospitals considerable difficulty is experienced in getting patients to return for blood-examination after they have severed their connection with the hospital.

Table XI. shows the periods at which reactions became negative in seven cases in which several examinations have been made over the period of twelve months.

TABLE XI.

	Before Treatment.	Month.											
		1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.
M. B.	+ +		− −	− −						− −			
S. C.	+ +					− −	± −				− −		− −
C. D.	+ +		− −					− −					− −
E. H.	+ +			− −		− −		− −				− −	− −
M. L.	+ +	± −	+ +	± −							− −		− −
H. S.	+ +	+ −	+ ±	± −	± −			± −			− −		− −
A. S.	+ +	− −	− −	± −		± −			− −	± −			− −

Table XII. gives the results obtained in the seven cases in which the quantity of complement-fixing substance was reduced by salvarsan treatment although a negative reaction was not obtained.

TABLE XII.—INCOMPLETE RESULTS.

	Before Treatment.	Month.											
		1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.
F. H.	+ −		± −	− −			± −						
M. S.	+ +	+ +	+ +				± −						
J. B.	+ +								+ −				
R. C.	+ −	+ −									± −		
W. E.	+ −			± −									
E. H.	+ ±		+ ±			− −							
A. H.	+ +	+ +	± −		+ +		+ −						

All the six relapses occurred during the first six months following treatment, such cases that were negative six months after treatment still being negative after twelve months (see Table XIII.).

TABLE XIII.—RELAPSES.

		Month.											
		1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.
E. D.	+ +	− −	− −		+ +	+ +							
N. H.	+ +	− −	− −	+ −									
B. L.	+ +	− −	+ −	+ −									
E. R.	+ +	− −	+ ±	± −									
L. W.	+ +	− −	− −	+ −									
L. W.	+ +	± −	− −	− −			+ +						

If rapidity of change of reaction be taken as a test of efficiency of treatment, the author would place salvarsan first, inunction or intramuscular injection of insoluble mercury compounds second, and mercurial pills and suppositories a bad third. The author considers the results obtained suggest the advisability of combined salvarsan and mercurial treatment.

CHAPTER XV

ANAPHYLAXIS AND SYPHILIS

By anaphylaxis is meant a condition of increased sensitiveness to any antigen as the result of inoculation with such antigen.

It is therefore the opposite of immunity, which is a state of decreased sensitiveness to the antigen.

Anaphylactic phenomena, like immunity phenomena, are the result of an antigen-antibody reaction, and are strictly specific in nature. Thus a state of anaphylaxis to any given antigen can only be produced by a second inoculation with *the same kind of antigen*, and after sufficient time has elapsed to permit of the development of the corresponding antibody.

Although the phenomenon is the result of a specific antigen-antibody reaction, the symptoms of acute anaphylaxis are similar whatever the antigen used may be, whether serum, organism, toxin, or other foreign proteid.

Two varieties of hypersensitiveness to serum deserve special mention, as they are typical of anaphylactic phenomena, however produced:

1. **Arthus' Phenomenon.**—Arthus' phenomenon appears when a guinea-pig receives several subcutaneous injections, at intervals of a few days, of normal horse serum, a substance which in itself is

scarcely more toxic than normal solution. After a few such inoculations the animal becomes hypersensitive, or anaphylactized, and after another injection an œdematous mass, an aseptic abscess, or an area of necrosis, appears at the site of a new inoculation, which need not be in a region in which a previous injection has been made; the alteration is a general, and not a local one. After several of these injections the animal becomes cachectic, and dies after several weeks.

2. **Theobald Smith's Phenomenon.**—Theobald Smith's phenomenon occurs when an animal has been sensitized by a very small injection of horse serum, and kept for a fortnight or more. If, then, a second injection of a larger amount of the same serum be made, the animal develops a series of remarkable symptoms, the most noteworthy being respiratory failure, paralysis, and clonic spasms. Symptoms usually appear within ten minutes, and death occurs within an hour. Death does not always follow. The less sensitive the animal the later the development of symptoms, and the greater the chance of survival. The process evidently affects the nervous system in a very special way.

Various phenomena that sometimes occur during the course of syphilitic infection may perhaps be the result of a state of anaphylaxis to the toxin produced by the *Spirochæta pallida*. Thus—

The Jarisch Herxheimer Reaction (the temporary lighting-up of symptoms very occasionally produced by an injection of salvarsan or by a large mercurial inunction);

Salvarsan Fever, accompanied by rigors, vomiting, headache, diarrhœa, etc., that occasionally occurs in florid syphilis;

And **Justus' Test,** in which a fall in the hæmoglobin content of the blood follows a large inunction or injection of mercury;

may all possibly be caused by a state of anaphylaxis produced by the setting free of a large quantity of specific endotoxin as the result of destruction of the spirochætæ.

Of the very few deaths following the administration of salvarsan that cannot be explained by errors in technique, several have been preceded by symptoms suggestively similar, in the author's opinion, to those occurring in acute anaphylaxis of the Theobald Smith type.

Studies in anaphylaxis by numerous observers have shown that the hypersensitiveness to the foreign protein (antigen) takes some time to develop, and does not develop at all if the inoculation process is continuous; in other words, there must be a cessation of inoculations for a certain period of time, generally about ten to fourteen days, before the anaphylactic phenomenon develops, and the continuance of the inoculations at regular short intervals does not produce anaphylaxis.

NOGUCHI'S LUETIN REACTION

Noguchi points out that an anaphylactic condition is more likely to develop in those patients who are infected with certain organisms which remain in their

bodies for a long period, during which their activity undergoes fluctuations either spontaneously or as the result of treatment. He considers that the clinical course of syphilis indicates that the infective agent (the *Spirochæta pallida*) fulfils all the requirements that lead to the development of an anaphylactic condition in syphilitic patients. He therefore concludes that an anaphylaxis test should theoretically be as possible in syphilis as in tubercle with Koch's tuberculin test, or with Von Pirquet's cutaneous test, or in glanders with the Malein test. He uses extracts of pure cultures of the *Spirochæta pallida* as antigen, and to this extract has given the name of 'Luetin.'

The experiments on rabbits proving successful, he proceeded to test the reaction in man, using the intradermic method of inoculation.

Mantoux and Roux in their original description of the technique of intradermic inoculation, say: 'After having made a fold of skin, the needle is pushed in almost parallel to the surface. Care must be taken that the bevelled side of the needle-point is turned upwards. In subjects with a very thin skin one must boldly push the needle in till it enters the hypodermic region, and then elevate the point and enter the dermis from its under-surface. A fine needle and small syringe are required, which must, of course, be sterilized before use. Only one drop of fluid is injected.'

Of 250 control non-syphilitic cases examined, all gave negative reactions; while of 315 cases of syphilis at different stages, 213 gave a positive reaction.

Noguchi points out that theoretically one would not expect an anaphylactic reaction to appear as long as

the activity of the *Spirochæta pallida* is maintained at its maximum, as would be the case during the early period of infection. This theory was borne out by the results obtained, practically all cases of primary syphilis and secondary syphilis with symptoms giving negative results, as also did congenital syphilitics under one year of age. The majority of cases, however, to which the test was applied after treatment, with a consequent absence of symptoms and diminution in the activity of the spirochæte, gave a positive reaction (see Table XIV.).

Negative Reaction.

In the majority of normal persons after twenty-four hours, a small erythematous area appears round the point of injection; there is no pain or itching, and the reaction passes off within forty-eight hours and leaves no induration. Occasionally a small papule may be formed after twenty-four to forty-eight hours, which, however, begins to subside within seventy-two hours, leaving no induration.

Positive Reaction.

This Noguchi divides under three headings:

1. **Papular Form.**—A large, raised, reddish, indurated papule, usually from 5 to 10 millimetres in diameter, makes its appearance in twenty-four to forty-eight hours. The papule may be surrounded by a zone of redness. The dimension and degree of induration slightly increase during the following three or four days, after which the inflammatory processes

TABLE XIV.—LUETIN REACTION IN VARIOUS SYPHILITIC CONDITIONS AND IN CONTROLS (NOGUCHI).

	Primary Syphilis.		Secondary Syphilis.				Tertiary Syphilis.				Congenital Syphilis.				Cerebro-Spinal Syphilis.		Latent Syphilis.		Controls.			
	Symptoms Present.		Symptoms Present.		Symptoms Absent.		Symptoms Present.		Symptoms Absent.		Under One Year.		Late Cases.		Symptoms Present.				Normal Individuals.		Non-Syphilitic Cases.	
Luetin reaction ..	+	−	+	−	+	−	+	−	+	−	+	−	+	−	+	−	+	−	+	−	+	−
No antisyphilitic treatment ..	...	13	..	..	..	..	..	..	..	..	..	..	..	..	..	..	24	6	..	50	..	200
Slight mercurial treatment ..	1	12	2	25	..	..	12	..	..	..	5	18	..	..	..	..	..	..	..	..	..	..
Regular mercurial treatment ..	..	..	..	..	14	3	31	..	29	1	1	3	15	1	5	5	..	..	..	..	..	..
Salvarsan and mercurial treatment	..	..	1	..	42	12	..	..	22	3	..	..	9	..	..	..	..	..	..	..	..	..
	1	25	3	25	56	15	43	0	51	4	6	21	24	1	5	5	24	6	0	50	0	200
	26		99				98				52				10		30		250			
	215																					

begin to recede. Induration disappears within a week in the majority of cases.

2. **Pustular Form.**—In this form at about the fourth day after injection the papule begins to soften at the centre, and within twenty-four hours becomes first vesicular, then pustular. The pustule soon discharges, and a scab is formed, which falls off after a few days. This form of the reaction occurred in nearly every case of tertiary or late hereditary syphilis.

3. **Torpid Form.**—In this, the least common form, the reaction pursues a course practically similar to a negative reaction, but after ten days, or even longer, the reaction lights up again and progresses to the formation of a small pustule.

Noguchi states that neither in syphilitics nor in parasyphilitics did a marked constitutional change follow the intradermic inoculation of luetin. In most positive cases a slight rise in temperature takes place, lasting for one day.

The author up to the present has had no opportunity of investigating this test, but if extended trials by independent observers confirm the results obtained by Noguchi, it would appear that this test will be of considerable diagnostic value.

As, however, this test is not available for early congenital syphilis, primary syphilis, or early secondary syphilis, it does not appear probable that it will be of very great practical use, except as a confirmatory test in those cases of doubtful latent or tertiary syphilis which fail to give a positive Wassermann reaction.

CHAPTER XVI

LIFE INSURANCE AND THE WASSERMANN REACTION

Syphilis by itself is accountable for a comparatively small number of deaths, with the exception of deaths of children under five years owing to congenital syphilis.

If, however, the sum of all the deaths produced by diseases either directly or indirectly resulting from previous syphilitic infection be collected together, a considerable number of deaths will be found attributable to the *Spirochæta pallida.*

If to this already considerable death-rate we add deaths from intercurrent diseases having nothing to do with syphilis, but in which one may reasonably conclude that the resisting power of the individual was lowered by syphilitic infection so that a higher death-rate resulted than would have been the case if these diseases had attacked patients free from syphilis, then the death-rate due to diseases in which syphilis is one of the predisposing causes will probably be greatly increased.

REGISTRAR-GENERAL'S REPORT

1. **Deaths from Syphilis alone.**—The Registrar-General's report for 1909 gives the death-rate under

the head 'Syphilis' as 0·047 per thousand persons. This includes 968 deaths amongst males and 717 amongst females. Far the greatest number of deaths occurred in children under five years of age, and consisted of 677 males and 540 females. Of deaths between the ages of twenty-five and fifty-five, only 206 occurred amongst males and 117 amongst females.

Syphilis, therefore, as the direct cause of death amongst adults during the period when the majority of people seek insurance, is small.

2. **Deaths from Diseases Syphilitic in Origin.**—The deaths from the three diseases—general paralysis, tabes, aneurism of the aorta—however, which are undoubtedly syphilitic in origin, give very different results.

General paralysis was given as the cause of death of 1,817 males and 546 females, and of this number 1,386 deaths occurred amongst males and 338 amongst females between the ages of twenty-five and fifty-five years. The total death-rate per 1,000 from general paralysis was 0·066.

The death-rate from tabes was about one-third that from general paralysis, and about half the number of deaths out of the total, both of males and females, occurred between twenty-five and fifty-five years of age.

The death-rate from aneurism is 0·033; 946 occurred amongst males and 221 amongst females, and of this number 558 and 82 respectively occurred between the ages of twenty-five and fifty-five.

The total death-rate from general paralysis, tabes, and aneurism combined, therefore, is 0·116 per 1,000,

and the great majority of these occurred between the ages of twenty-five and fifty-five years.

It has been shown in the previous chapters that practically all causes of general paralysis and aneurism and 60 per cent. of tabes give a positive Wassermann reaction, and in all probability have given a positive Wassermann reaction for many years before the onset of symptoms. It therefore appears highly desirable, from the point of view of the insurance companies, that the possibility of the occurrence of these diseases should be excluded if the life is to be returned as a first-class one.

The death-rate per 1,000 from all causes was 14·5, while the combined death-rate from syphilis, general paralysis, tabes, and aneurism was 0·163 per 1,000. One death in every eighty-eight, therefore, was due to syphilis, parasyphilis, or aneurism.

TABLE XV.

Cause of Death.	Deaths per 1,000 Persons.		Males.	Females.
Syphilis	0·047	All ages	968	717
		Under 5	677	540
		25 to 55	206	117
General paralysis ..	0·066	All ages	1,817	546
		Under 5	1	0
		25 to 55	1,386	338
Tabes	0·017	All ages	496	123
		Under 5	0	0
		25 to 55	250	59
Aneurism	0·033	All ages	946	221
		Under 5	1	1
		25 to 55	558	82

Table XVI.

Cause of Death.	Deaths per 1,000 Persons.		Males.	Females.
Cerebral hæmorrhage and cerebral embolism	0·502	All ages	7,999	9,939
		Under 5	17	20
		25 to 55	1,289	1,618
Chronic Bright's disease	0·294	All ages	5,627	4,877
		Under 5	35	34
		25 to 55	1,899	1,707
Apoplexy and hemiplegia	0·226	All ages	3,609	4,485
		Under 5	9	7
		25 to 55	540	688
Meningitis	0·149	All ages	2,902	2,442
		Under 5	1,862	1,471
		25 to 55	325	287
Brain tumour ..	0·022	All ages	392	377
		Under 5	22	12
		25 to 55	192	204
Softening of the brain	0·060	All ages	1,105	1,023
		Under 5	2	0
		25 to 55	110	129
Paraplegia and diseases of the cord ..	0·059	All ages	1,15[illegible]	948
		Under 5	47	48
		25 to 55	400	311
			Per Cent.	Per Cent.
All causes	14·5	All ages	15·4	13·7
		Under 5	40·3	33·2
		25 to 55	31·1	24·8

Total deaths, all persons, 25 to 55, 111,122.
,, ,, Table XV., ,, 2,996 (=1 in 37) deaths.
,, ,, Table XVI., ,, 9,699 (=1 in 11) ,,

3. **Deaths from Diseases partly Attributable to Syphilis.**—The deaths partly attributable to syphilis will include those from:

1. Cerebral hæmorrhage and cerebral embolism.
2. Apoplexy and hemiplegia.
3. Chronic Bright's disease.

4. Meningitis.
5. Brain tumour.
6. Softening of the brain.
7. Paraplegia and diseases of the cord.

Table XVI. shows the death-rate per 1,000 persons from these diseases, also occurring amongst males and females during the period of twenty-five to fifty-five years.

4. **Deaths in which Syphilis may be a Contributory Cause.**—It is difficult to estimate the deaths occurring in this class—namely, amongst those debilitated by syphilis, in which death might not have occurred otherwise. It is, however, a matter of common knowledge that tuberculosis is especially apt to develop amongst persons who have recently acquired syphilis, and that tuberculosis occurring in such subjects is particularly to be dreaded.

INCREASED MORTALITY RATE AMONGST SYPHILITICS

Brockbank has collected the following statistics of the experience of assurance companies of the mortality of syphilitics, which are of great interest, and appear to point conclusively to the importance of a routine examination of the blood of all proposers for assurance. Practically every series of investigations shows a considerably increased mortality amongst syphilitics.

Runeberg's statistics show that out of 84 cases of acknowledged syphilitic infection, the average age of death was 43·4 years, and out of 734 cases that

had probably had syphilis, 15 per cent. of the deaths were probably directly due to syphilis.

Tiselius recorded 650 deaths due to syphilis out of 5,175 persons (17·35 per cent.), and he recommended an increased premium of from 20 to 50 per cent. for each proposal with a history of syphilis.

Salomonson, out of 121 persons who acknowledged syphilis, recorded 17 deaths at an average of 46 years, whereas the mortality expectation was only 9·14.

Blaschko and Jacobsohn examined the causes of 5,724 deaths, and came to the conclusion that 25·5 per cent. were certainly caused by syphilis, and 40 per cent. probably.

Kleinschmidt states that the average age of death of eighty-eight policy-holders who gave a history of syphilis was 47·5 years.

Out of the collected experience of several American insurance companies, the mortality amongst those who had a history of syphilis was 33·3 per cent. above the expectation.

As it is acknowledged to be extremely difficult to get truthful histories in regard to syphilitic infections from candidates wishing to be insured, and as nearly all authorities agree that syphilitics should be accepted with caution, and even the most satisfactory cases with an increased premium, the routine examination of the Wassermann reaction appears advisable in the interest of the assurance companies.

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