

important matter) and the length of time during which the blood remained in the tube—it would be very difficult to obtain anything like uniform results. He did not think that observations concerning the coagulation-times were of any great value, especially now that it seemed fairly well-established that those drugs which were thought to have an influence on the coagulation-time, although they produced the clinical effects with which they were credited, acted in some other way than by affecting the coagulation-time.

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*On the Wassermann Reaction, and especially its Significance in Relation to General Paralysis.*<sup>(1)</sup> By CARL HAMILTON BROWNING, M.D., Lecturer on Bacteriology in the University of Glasgow, and IVY MCKENZIE, M.B., Carnegie Research Fellow. (From the Pathological Laboratory of Glasgow University and Western Infirmary, Glasgow.<sup>[2]</sup>)

THE discovery by Schaudinn of the *Spirochæta pallida* was the starting-point of an extensive series of investigations which have thrown much light on the nature of syphilitic infection and its consequences. Reliable authorities are agreed as to the ætiological relationship between this organism and syphilitic disease, and its presence can with ease be demonstrated in chancres, syphilides, and the tissues of cases of congenital syphilis. In tertiary lesions its presence has been noted in gummata and in aortitis, though only in a very few cases. In the so-called para-syphilitic diseases it has not yet been seen. If it be the case that the presence of the organism be indispensable to the production of tertiary and para-syphilitic lesions, the difficulty of demonstrating it may be due to one or both of the following causes: (1) The organisms may be present in another form representing a different stage in their life cycle; or (2) they may be so few in number as to render demonstration extremely difficult, as is the case with the tubercle bacillus in the lesions of chronic fibroid phthisis. The difficulty consequent on a paucity in numbers may be enhanced by difficulty in staining. Two methods of staining the spirochæte are in use—Giemsa's stain for film preparations, and a silver impregnation method for the examination of tissues. It is a remarkable fact that tissue which shows enormous numbers of silver impregnated organisms may show very few or none at all in the films stained by Giemsa's method, while on the other hand

we have noted an extreme variability in the extent to which impregnation by silver may be obtained ; for example, if the tissues of a syphilitic infant be fixed soon after death and while still in a very fresh state, impregnation may be very slight in some parts and distinct in others ; thus, in the case of a syphilitic pneumonia, the organisms in the fresh proliferating pneumonic tissue are not seen, or are represented by delicate spirals which are recognised with difficulty, while in the desquamating and degenerating epithelium of the bronchi they may be much more distinct. It is, on the other hand, a striking fact that the spirochætes in a syphilitic fœtus which has been dead for some time are usually impregnated easily with silver, and this is in accord with other observations in the use of the silver impregnation method in demonstrating structures.

The conclusions based on the demonstration of the spirochæte in the lesions of syphilis have been amply substantiated by experimental work. The organisms have been demonstrated in the lesions of experimental syphilis in monkeys ; they have been inoculated into the cornea of the rabbit and transmitted through a series of these animals, after which the introduction of infected cornea beneath the eyelid in apes led to syphilitic infection in which spirochætes were present. Hoffmann has succeeded in inoculating an ape with the cerebro-spinal fluid of a man suffering from a papular syphilide.

Not less important than these discoveries is the fact that chemical changes peculiar to syphilis may be demonstrated in the blood-serum of those suffering from syphilitic or so-called para-syphilitic disease. The evidence of such chemical change consists in this, that syphilitic serum in the presence of an alcoholic or watery extract of liver, or other tissue rich in lipoid substances, is capable of inhibiting the action of hæmolytic complement. This is shown by placing a mixture of the patient's serum and organ extract in contact with the complement (fresh guinea-pig's serum) for one and a half hours at  $37^{\circ}$  C., and subsequently adding red blood-corpuscles adequately sensitised beforehand by the addition of the homologous immune serum. Absence of lysis in the added corpuscles after further incubation for an hour at  $37^{\circ}$  C., constitutes a positive reaction and indicates that the serum proceeded from a case of syphilis. It may be added that while lipoid compounds are probably the active agents in the organ extract, on the other

hand nothing is known as to the nature of the substances in the serum (or cerebro-spinal fluid) which give rise to the reaction. Fresh normal human serum in the presence of organ extract may possess the property of deviating complement to a slight extent, but this is abolished by heating for half an hour at 55° C., while in the great majority of syphilitic sera (80 to 90 *per cent.*) the property is still present after such treatment. The reaction was at first considered by Wassermann and his collaborators to depend upon the receptors of the spirochætes in syphilitic liver acting in conjunction with specific anti-bodies in the syphilitic serum. It has, however, been established that the effect is not due to the presence of the specific syphilitic antigen, but that a great variety of lipoid compounds may serve to produce similar results along with a syphilitic serum. Thus the reaction is not a specific one in the usual biological sense of the term.

It has been pointed out that in the very early stages of syphilitic infection the complement-deviation test may be negative. The earliest cases which we have examined were three in the second month of the chancre, and all were positive. Levaditi, Laroche, and Yamanouchi state that the reaction becomes notable from the fifteenth to the thirtieth day after the appearance of the primary sore. Practically every case in the second stage with constitutional signs gives a positive result. In the latent period, that is, in cases where there is a history of syphilis but no symptoms, there is a negative reaction in 50 *per cent.* of the cases. In the later stages of the disease, in gummata, and in the para-syphilitic affections, the serum reaction can again be obtained in practically every case at some stage of the condition; in thirty-two cases with gummata we have found a positive reaction in thirty-one, and in thirty-four cases of general paralysis only two have been found negative. These negative cases of general paralysis were examined early in the course of the disease, while all the others were examined at a later stage, and this accords with the general finding that in advanced cases the amount of deviation is very considerable. The important point, then, is that the reaction does not become apparent until some time after the appearance of the primary sore; in the secondary or acute stage it is usually present; in the latent period it is often absent; while in the tertiary and

advanced para-syphilitic conditions it is usually present. It is only in cases of locomotor ataxy and general paralysis that the cerebro-spinal fluid has been found to give the reaction. The substance or substances in the serum which give rise to the reaction are peculiar to syphilis. This is true, at least, as far as the diseases common to this country are concerned. In the blood-serum, however, of cases of trypanosomiasis and frambœsia such changes may occur; the constancy and the degree of the reaction in these latter conditions is, however, unknown, but that it does occur is certain.

With regard to the significance of the deviation-reaction, it must be admitted that it is as yet impossible to say whether or not the fact that a serum yields a positive result is a proof of the presence and pathogenic activity of living organisms in the host. The frequent absence of the reaction in the latent period, its absence in some cases of early general paralysis, and its notable presence in the later stages might be explained on the hypothesis that some intercurrent condition may call from abeyance into renewed activity metabolic processes which were originally set up as the result of the syphilitic infection.

With reference to trypanosome infection it is now accepted as a fact that sleeping sickness, or negro-lethargy, and trypanosome fever are different phases of the same disease. The infection with trypanosomes is conveyed by a biting fly (*Glossina palpalis*), which carries the parasite from one host to another. The various stages of the disease cannot be sharply demarcated; the first stage or latent period, which includes the time that elapses between the bite from the fly and the first appearance of symptoms, is very variable, and may be anything up to seven or eight years; in this prodromal stage the presence of organisms can usually be demonstrated by examination of the blood or the juice of the lymph-glands; the occurrence of some change which disturbs the relation of mutual accommodation between the parasite and its host would apparently give rise to the second stage known as trypanosome fever. The onset of this second stage is marked by severe headache and attacks of fever resembling malaria; transient œdema of the face or limbs may be accompanied by a rash of erythematous, urticarial or erysipelatous character; the spleen is usually swollen; in this stage the organisms are easily recovered from the blood or lymph-glands. Following this

phase there may be apparent recovery, or after months or years of well-being the third stage, known as sleeping sickness, may supervene. The symptoms here are slight at first and the progress of the condition is slow. Disinclination to work, exhaustion on slight exertion, and slight transient œdema of the face may be the first signs. The nervous changes, however, gradually assert themselves in a more definite manner; a previously industrious and reliable worker may become careless and unreliable, and a cheerful and happy disposition may give way to a morose and melancholy turn of mind; acute maniacal attacks are not infrequent; there is marked tremor of the tongue, the speech may be stuttering or *staccato* and there is difficulty in pronunciation. According to Mense the clinical picture of the disease presents features which are fairly constant, more so in young people than in adults, and in negroes than in Europeans. He points out that in this stage, also, after symptoms have become pronounced, a period of apparent well-being, it may be for months, may ensue; on the other hand the natural course of the disease may be interrupted by epileptiform attacks, convulsive seizures of laughing and weeping, and periods of great talkativeness. Hallucinations of various kinds may be present, and attempts at murder or suicide have also been noted. In the great majority of cases, if not in all, the disease progresses to a fatal issue; the appetite, which was at first good, gradually diminishes, and the patient, falling into long periods of sleep, loses flesh, develops decubitus, muscular contractures and abscesses, and dies perhaps as the result of the secondary infections to which his weakness and decubitus have exposed him. The great similarity to general paralysis is thus evident.

Coming now to the anatomical side of the question, not only is there a polyadenitis in early trypanosomiasis as in early syphilis, associated with the presence in the lymphatic tissue of trypanosomes on the one hand and spirochætes on the other, but the lesions in the brain are similar in both cases in the stages of sleeping sickness and general paralysis. Further, it is to be noted that there is a great similarity in the character of the lesions in all stages of syphilitic infection—in primary, secondary, and tertiary, and also in para-syphilitic lesions there is an infiltration of plasma-cells and lymphocytes with marked perivascular arrangement. This perivascular

exudate of lymphocytes and plasma-cells, which was thought to be pathognomonic of general paralysis, is now acknowledged to be a constant feature of late trypanosome infection. It is an interesting fact that in the *mal-du-coit* of horses an ataxic paraplegia occurs with posterior root-degeneration and sclerosis of the posterior columns of the cord, and Spielmeyer, by experimental trypanosome-infection of dogs, has produced optic atrophy and a lesion of the posterior columns of the cord simulating the ataxic lesion.

Reviewed shortly, the points of resemblance between trypanosome and syphilitic disease are as follows :

(1) In trypanosomiasis the infecting agent is a protozoon, and this is probably also the case in syphilis ; both diseases may be transmitted to animals.

(2) In experimental trypanosomiasis it is possible to demonstrate a change in the blood-serum resembling that found in syphilis and so-called para-syphilitic disease (the Wassermann reaction).

(3) There is a considerable similarity as regards early lymph-gland involvement, early febrile and constitutional disturbance with exanthemata, periods of latency, and late involvement of the central nervous system.

(4) The cellular character of the lesions are similar in both cases ; lymphocytes and plasma-cells play a prominent part in the reaction, and the perivascular infiltration in general paralysis closely resembles that seen in sleeping sickness.

The failure to demonstrate the organism of syphilis in general paralysis constitutes the missing link in the chain of comparison, though the similarity of the anatomical changes in sleeping sickness and general paralysis, and the association of the former with the presence of trypanosomes in the cerebro-spinal fluid strongly suggests the possibility that the syphilitic virus is an active agent in the production of para-syphilitic disease.

Mott has recently brought the older theories concerning general paralysis into line with modern investigation. He has shown that the clinical observation of "no syphilis no tabes" has been strongly supported by the bio-chemical reaction, and he attempts to show how the substances which are supposed to interact in this test are related to the substances concerned in the breaking down of the nervous system. He takes his stand

on the hypothesis that general paralysis means a premature decay of certain neurons brought about by damage received in the early syphilitic attack, since it has been supposed that "the nerve elements, being perpetual, and having acquired a habit of increased metabolic activity, will continue it during life, and will contribute to the excess of lipoids in the blood"; and he advances the theory that it is in virtue of the entrance of the products of the degeneration of nervous tissue into the blood and cerebro-spinal fluid that they yield the reaction. It must, however, be borne in mind that while increased dissimilative metabolism occurs in many diseases, it is only in syphilis, trypanosomiasis and framboesia that a positive Wassermann reaction has up till now been demonstrated; and this is true whether the reaction depends on the quantitative or the qualitative character of the substance or substances involved.

Now if it is to be suggested that the *contagium vivum* of syphilis is still active in general paralysis, we must inquire what interpretation is to be put on certain outstanding features of the disease in the light of such a hypothesis. Let us consider the following points:

(1) The immunity of general paralytics to syphilitic reinfection; (2) the latent period between syphilitic and so-called para-syphilitic disease; (3) the distribution of the lesions in para-syphilitic disease; and (4) the resistance to anti-syphilitic treatment.

(1) Mott, as the result of a very large experience, observes that he has never seen or had his attention called to a case of general paralysis showing a primary sore or a secondary rash, notwithstanding the fact that such subjects are likely to be more than ordinarily exposed to infection. It is quite a natural assumption from such observations that the general paralytic is immune to syphilis, and such a conclusion is supported by the results of Krafft-Ebing's experiments, in which he failed to inoculate with the virus of a typical hard chancre nine cases of general paralysis which gave no history and showed no signs of syphilis. On the other hand, such observations are equally explicable on the assumption that the patient still harbours the organism of the disease; as Neisser has shown experimentally, if the spirochæte be still present, reinoculation is impossible; and the contention that in the absence of the spirochæte reinoculation could be effected is supported by the findings of

Neisser, Browning, and others, who, working on the experimental side of syphilis and trypanosomiasis, point out that immunity to these infections is short-lived.

(2) The occurrence of the latent period has been explained on the assumption of an acquired immunity; but here the meaning of the term must be made clear. Immunity may be taken to mean either absence of symptoms (*immunitas non sterilisans* of Ehrlich), or insusceptibility to reinfection after the causal agent has been destroyed. The early and judicious administration of drugs may cause a rapid and complete disappearance of the symptoms in syphilis without killing the organisms, as may be seen by the reappearance of the disease after months or years; and in the case of a mother who gives birth to a number of syphilitic children without herself showing any symptoms, it would be a grave assumption to suppose that she does not harbour the virus. The probability that the virus may remain latent for long periods is strengthened by knowledge of the fact that tubercle may lie dormant for years without manifesting any evidence of its presence, its activity being called into play by some supervening circumstance which disturbs the balance of accommodation between organism and host. Thus an attack of measles, trauma, or an attack of influenza are not the causes of tubercular infection; they are the conditions which give rise to disturbed relations between the patient and the organism which may have already been present for some time. We have made similar observations in the case of cerebro-spinal fever, where a blow on the head would seem to have been the determining factor in the production of the acute manifestations of the disease. In a recent address Sir Hector Cameron has called attention to the occurrence of such latent periods extending from twenty to thirty years in cases of cancer; he also emphasises the recrudescence of pyogenic disease in the abdomen after periods of well-being. It is a well-recognised fact that after typhoid fever the bacilli may persist in the body for years without giving rise to trouble, but that conditions may supervene at any time leading to an osteomyelitis or cholecystitis in which the typhoid bacillus is the only organism concerned. In the case of the latent period in syphilis occurring between the syphilitic and para-syphilitic symptoms, it is not too much to suppose that the *contagium vivum* is still present in a state of accommodation



with its host, but capable of giving rise to further disturbances on the occurrence of changes depending on external or internal agencies. With reference to the occurrence of inherited general paralysis, it is doubtful whether, accurately speaking, such a condition is possible. It is more reasonable to suppose that the so-called inherited general paralysis is the result of a syphilis acquired *in utero*. In many of the reported cases it is stated that there was evidence of congenital syphilis; and in those cases in which there was no evidence it is possible that the organism was present in a state of accommodation to its host so far as the ordinary manifestations of syphilis were concerned. In any case it is unlikely that the neuron-degeneration acquired in one generation as a result of syphilitic infection could be transmitted to the offspring in the absence of the pathogenic agent.

(3) Another point adduced in favour of para-syphilitic as opposed to the syphilitic origin of general paralysis has reference to the definite distribution of the lesion. It is maintained that a definite distribution of the lesion is inconsistent with a generalisation of the virus. As against this it might be said that there are many conditions in which a selective action of certain tissues for specific poisons is universally recognised. Why is it that drop-wrist occurs in lead poisoning? Why is it that tetanus toxin has a selective action as a stimulant, especially of the motor cells of the spinal cord? Why does diphtheria toxin produce vagus paralysis? To say that these elements have a specific affinity for a particular toxin is only to state the obvious. The cause of such affinity has not been explained, but it is an incontrovertible fact that generalisation of virus is not incompatible with localisation of lesion.

(4) It has been argued that the failure of response to anti-syphilitic treatment is evidence in favour of the view that general paralysis is not a true syphilitic disease. There is, it is said, an increased irritability and functional activity of the neurons whereby lipoid complexes are thrown off in increasing numbers. "The uselessness of anti-syphilitic remedies would thus be accounted for," and it is Mott's experience that they are positively injurious in true tabes and general paralysis, "because they lower the vital energy of a system which has over-immunised itself against the syphilitic virus." We have

already referred to the reasons whereby the general paralytic cannot be reinfected with the syphilitic virus, and the possibility must be borne in mind that the virus may have become serum-resistant or drug-resistant—a condition which is well known in experimental trypanosomiasis. There is also good reason for believing that such resistance may be more readily developed in one individual than in another (Browning). Again, it may be that the anti-syphilitic treatment is not effective in general paralysis on account of the site of the lesion. In investigating the pathology and treatment of cerebro-spinal fever, McKenzie and Martin pointed out that the immune substances elaborated in defence and present in the blood-serum could not be detected in the cerebro-spinal fluid. On the strength of this observation they recommended and tried with apparent success in a considerable number of instances the local introduction of an immune serum. In two severe cases the patients were successfully treated by the intra-spinal injection of their own serum. The general principle relative to cerebro-spinal fever has been substantiated by Flexner, Kolle, and others, and now the intra-spinal treatment of this disease is universally recognised as the most efficacious. It is not only in the case of bacterial anti-bodies that this condition with regard to the impermeability of the spinal membranes holds good; it has been found, for example, that in sleeping sickness potassium iodide does not pass into the cerebro-spinal fluid from the blood-stream. It is quite possible that in the case of general paralysis it is not the nature but the site of the lesion which is responsible for the failure of the anti-syphilitic treatment.

It has been the object of this review to indicate that the independence of syphilitic and para-syphilitic infections has not yet been established, and to suggest that on the one hand further search for the *contagium vivum* of syphilis in the body during the stage of general paralysis is necessary, and that on the other a line of treatment might be adopted on the supposition that the disease is the manifestation of an active and progressive process. On the advice of Dr. Andrew Balfour, of Khartoum, an attempt is to be made to treat sleeping sickness by the intra-spinal injection of the patient's own blood-serum after the organisms have been driven from the blood by the remedial agencies which are now employed. In consideration of

the hopeless character of general paralysis a trial of this same method might be recommended, and here also the principle of combined therapy should be borne in mind.

(<sup>1</sup>) A paper read at the Scottish Divisional Meeting in Glasgow, March 19th, 1909.  
—(<sup>2</sup>) We have pleasure in recording our indebtedness to the Carnegie Trustees for a grant in aid of the expenses connected with the experiments on which the observations in this communication are founded. We have also to thank Dr. Carswell and Dr. Marr for permission to examine cases in Duke Street Hospital and Woodilee Mental Hospital.

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*A Bacteriological Investigation into General Paralysis of the Insane, and a Table of Blood-counts.* By  
DAVID THOMSON, M.B., Formerly Assistant Medical Officer at Horton Asylum, Epsom.

THIS research was carried on in the laboratory at Horton Asylum, and was directed to that vexed question as to whether the *Bacillus paralyticans* (which Dr. Ford Robertson has described) was the cause of general paralysis of the insane or not.

I was led into this research by the following incident: One morning, whilst making a *post-mortem* on a case of general paralysis which had died from an acute attack of erysipelas, I noticed that the spleen showed on section numerous little hæmorrhagic-like areas scattered throughout its substance. An agar tube was inoculated from the pulp, and next day there appeared a diffuse greyish-white growth which proved to be a bacillus, showing a chromatin point at each end. There were long and short forms present which produced strong acid formation and gas in glucose broth and was Gram-negative. A few streptococci were also present. A stained paraffin section of the same spleen showed short, thick, curved chains of these bacilli. A section of the kidney showed the same organisms, but they tended to remain separate rather than form short chains.

Thinking that this might possibly be the bacillus mentioned by Ford Robertson, I began to search for them in the spleen, liver, kidneys, lungs and brain of every case of general paralysis which died in the asylum.

Smear preparations were made, sections cut and stained, and