required for such work is comparatively simple, and diagnostic sera, etc., are provided free by the Standard Laboratory at Oxford. The expense and trouble is soon repaid in the decreased incidence of the disease.

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General Paralysis: its Unsolved Problems.[1] By R. M. STEWART, M.D., M.R.C.P.Edin., D.P.M., Medical Superintendent, Leavesden Mental Hospital, Herts.

THERE is probably no disease in regard to which our views have undergone so radical a change during the past few years as general paralysis of the insane, and none in which the discovery of the causative agent has been followed by so rapid a revolution in standpoint. Although almost from the time of its definition, more than a century ago, the essentially organic nature of the disease and its close relationship to syphilis have been universally recognized, it has required many years of patient study to free it from the hypotheses which have been invoked to explain its obscurities, and, as always happens in scientific progress, in the process of unravelling the knotty problems of this disease, we discover that there are new obstacles and difficulties to be overcome. Is the *Spirochæte pallida* alone responsible for the genesis of general paralysis? When does it gain access to the nervous system, and how? Is there a special strain of spirochæte, or must the individual resistance of the infected person be considered the deciding factor in the development of the disease? What is the meaning of the long latent interval before the onset of symptoms? What determines the peculiar distribution of the lesions in general

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paralysis, and is there some particular place in the brain from which the spirochæte starts its wandering? What is the significance of the absence of spirochætes in other organs of the body, and why does the cerebro-spinal fluid contain no organisms at a time when the brain contains millions? Why do tabes, general paralysis and optic atrophy, supposedly of similar origin, not occur in conjunction more frequently? Why is it that arsenical compounds fail to effect a cure?

These are a few of the problems which confront us, and since it will be impossible within the limits of a short paper to enter fully into the answers which have been given, I shall restrict myself to two of the questions which have lately aroused considerable discussion—the time of invasion of the nervous system in general paralysis, and the question of the existence of special neurotropic strains of the *Spirochæte pallida*.

The Time of Invasion of the Central Nervous System.

It is well known that the period of time intervening between the date of infection and the onset of neurosyphilis varies for the different types of disease: in cerebro-spinal syphilis it is seldom more than three years, in general paralysis it is seldom less than six to ten years, and in tabes the time interval is usually considerably longer. Time, therefore, is one of the essential factors in the development of neuro-syphilis, and by reason of its practical importance completely overshadows all other questions; for, until it becomes possible to be reasonably sure of the time-limits within which the spirochæte gains access to the nervous system, the prevention of neuro-syphilis will remain an almost hopeless task.

The precise significance of the latent period has long been a subject of conjecture, and no entirely satisfactory solution has been put forward.

According to one view the delayed onset of nervous lesions in syphilitic subjects is brought about by the passage of toxins along perineural lymphatics from some peripheral focus. Long before Noguchi's discovery of the *Spirochæte pallida* in the brain cortex, Orr and Rows (1) suggested that the lesions of general paralysis were due to the presence of toxins in the cerebro-spinal lymph, and from an experimental study of lymphogenous infection of the nervous system they concluded that infection of the lymph-stream of nerves played an all-important part in the origin of this disease. In the case of syphilis, however, it seems more than doubtful whether a toxin, no matter how potent, could bring about such a profound lesion; and, since we now know that in general paralysis we are dealing with live organisms and not their toxins, the theory of Orr and Rows

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must be modified to this extent—that for toxin we must substitute virus.

As early as the period of the primary sore the spirochæte has been found lying in perineural lymphatics, and it must be admitted that, in the secondary stage when the skin is the seat of innumerable colonies, there is abundant opportunity for the virus to gain access to the peripheral nerve-trunks, and then to ascend by an easy and direct path to the nervous system. Owing, however, to the very marked motility of the spirochæte, it is questionable whether its discovery in the nerves of the skin was anything more than a coincidence; and it is significant that the most painstaking search for the spirochæte in the peripheral nerves in general paralysis has always yielded negative results.

Then, again, it may be objected that there is no source for this virus save during the period of secondary manifestations when the skin is infected, and it seems hardly possible that a chronic lymphogenous infection of the nerves can exist during the whole interval of time between the secondary period and the onset of general paralysis without producing obvious symptoms.

Lastly, if the spirochæte reaches the brain by the lymphogenous route, it might be anticipated that the position of the primary lesion and the severity of the skin eruption would influence the period of onset of the disease. Inquiry shows that this relationship does not exist; cephalic or digital chancres are not more prone to be followed by general paralysis than are genital chancres, and strangely enough a florid eruption seems actually to protect the individual against the disease.

As far as I am aware, Weygandt and Jakob (2) are the only investigators who have used the specific organism itself in attempting to solve this problem, but unfortunately their results are not altogether conclusive. By injecting syphilitic material into rabbits they were able to produce changes in the nervous system in about 50 *per cent.* of the animals, but the inflammatory lesions were the same whether they were from a localized testicular or a generalized blood infection.

If we reject the view that infection of the nervous system takes place by the lymphogenous route at a late stage of syphilis we must fall back on the other possibility, namely, that the spirochætes circulating in the blood-stream gain access to the brain or its membranes during the period of general dissemination, and lie dormant in these situations awaiting a favourable opportunity for their multiplication. This conception of an early infection of the nervous system in general paralysis is, of course, by no means new, but in recent years it has received additional support from studies of the biochemical and other changes in the cerebro-spinal fluid, which are

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of such importance that I must ask permission to review the evidence in considerable detail.

Before doing so, however, I would like to refer to certain facts in regard to syphilis which have a direct bearing on this subject.

First of all it is instructive to note how the tissues behave in response to the entrance of the organism. When spirochætes are inoculated on a mucous or cutaneous surface they excite a rapid multiplication of tissue-cells, and a migration of lymphocytes to the affected area, with the result that after a period of three or four weeks the Hunterian sore makes its appearance. This local formation of granulation-tissue is probably a defensive reaction on the part of the host, designed to check the growth of the organisms, and is the first indication of an altered state of immunity in the body. At this period, too, the blood seems to possess powerful spirillicidal properties, for experiment has shown that when infected material is injected into the tissues or blood-stream the spirochæte is rapidly destroyed. Soon, however, the blood loses its spirillicidal power, and the organisms are free to pass through the lymphatic vessels and thoracic duct into the general circulation. The disease has now become generalized, spirochætes invade every tissue of the body, and the patient suffers from a spirochætal septicæmia.

There seems no reason to suppose that at this stage the nervous system is spared, and, as I shall presently show, recent work in this and other countries makes it abundantly clear that the nervous tissues are infected in a very large percentage of cases.

Towards the end of the stage of secondary manifestations another and equally important event takes place, namely the spontaneous disappearance of the objective and subjective symptoms; the skin eruption gradually fades, headache and pyrexia cease, and the patient recovers his former good health. The logical explanation of this phenomenon would appear to be that the body manufactures anti-bodies, or immunizing substances, which have a deterrent or lethal effect on the organism. Up to the present no satisfactory proof of the presence of such substances exists, but in any case we must admit that the pathogenic action of the spirochæte is diminished to such an extent that it is permitted to remain latent in the system for many years. Just what latency means in this instance has not been demonstrated, but it is highly probable that there is established a more or less enduring equilibrium between the attacking forces of the spirochæte and the defensive forces of the body. Clinically, this type of latency is well illustrated in the so-called Colles's law, which postulates that a woman bearing syphilitic children (and herself presenting a positive Wassermann reaction), may show no signs of syphilis. Now this balance between the spirochætes and the cells

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of the host may be upset when any change occurs which lowers vitality or adversely affects the general well-being of the individual, and, as we know, only too frequently signs of active syphilis reappear in the late stages of the disease. In regard to the factors which determine sites of exacerbation in tertiary syphilis there is considerable uncertainty. It is possible that there exist in the body certain localities, more or less sheltered from the blood, which offer a safe resting-place for the virus, and that from these foci spirochætes are attracted to areas of the body whose resistance have been lowered. It is more probable, however, that the sites of tertiary manifestations are governed by an accidental localization of the organism during the early stage of the disease, and if this be so, the predilection of the spirochæte for certain localities can only be explained on the assumption that such areas are more exposed to stresses than other parts of the body. A striking demonstration of the prevalence of latent syphilis is to be found in the pathological studies of Warthin.(3) He examined organs from patients who died at a time when all clinical manifestations of syphilis had disappeared, and was able to demonstrate colonies of spirochætes in various parts of the body. The lesions consisted of a low-grade chronic inflammation with lymphocytic infiltration, and were most often found in the heart. Although active foci of spirochætes could not be discovered in the nervous system, the meninges in all cases showed some signs of thickening, and when investigated microscopically the changes bore a marked resemblance to those seen in general paralysis, the difference being principally one of degree. Minute lesions such as occur in other syphilitic organs were found in the brain substance itself. From the pathological standpoint a cured case of syphilis was never seen, and Warthin concludes that every syphilitic remains a spirochæte carrier for many years, if not for life. Urechia's (4) investigations yielded results of a similar character. His patient succumbed to an aortitis with involvement of the coronary arteries of the heart. Microscopic examination showed meningitic plaques, syphilitic endarteritis, and discrete perivascular infiltration in a few areas. In the cerebrum a small area of gliosis was discovered resembling those which recent studies have shown to be common in the general paralytic's brain. These investigations are very instructive, since they have some bearing on recent experimental work on latency. Engman and Eberson (5), studying the prevalence of latent syphilis by the application of the Wassermann reaction, found that 15 *per cent.* of their patients were definitely latent, and that in some the spirochæte had retained its virulence for many years and was capable of producing typical syphilitic lesions in the testicles of rabbits.

Now if living spirochætes may be found in the lymph-glands of

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persons with no objective signs, and clinically free from the disease, is it not possible that they may also hide in the remote fastnesses of the nervous system? The occasional presence of neurological signs, such as the Argyll-Robertson pupil or optic atrophy for many years before the onset of general paralysis or tabes, suggests that this possibility must be seriously entertained. Consider also the general paralytic whose disease is in a remission. In his case the spirochæte has at one time been present in the brain in sufficient numbers to cause serious mental disturbance, but its action having become repressed or diminished, the symptoms for the time being cease to progress, and the patient may be capable of resuming his usual occupation. Sooner or later the spirochætes gain the upper hand, and signs of active disease reappear. I have seen a spontaneous remission which lasted five years, and even longer periods have been recorded, so that there are very good grounds for stating that the organism of syphilis may dwell in the nervous system, or, indeed, in any organ of the body for quite long periods.

But further and I think more convincing proof of this contention is to be found in a study of the spinal fluid abnormalities in syphilis, which have been shown by a large number of workers to be frequent in all stages of the disease.

In a series of 624 cases of early unselected syphilis, Fildes (6) and his co-workers found evidence of a meningeal reaction in 29 *per cent.* Of 49 cases of primary syphilis investigated by Van der Valk (7), the cerebro-spinal fluid showed changes in 8, and in a series of 118 fluids from cases of secondary syphilis, 42 were abnormal. Nicolau (8), in a study of 51 cases of primary syphilis, found abnormal fluids in 18. Keidel and Moore (9) state that from 30 to 50 *per cent.* of spinal fluids are pathological in early syphilis, while both Dreyfus (10) and Plaut (11) assert that the incidence is nearer 80 *per cent.*

It will be observed that the figures given by different authors range from 84 *per cent.* to 3 *per cent.*, and this lack of agreement in their findings is doubtless due to the absence of any accepted standard of abnormality. One author may regard an increased globulin content with a cell-count not higher than 10 as sufficient proof of syphilitic involvement, whereas another may only be satisfied with a marked pleocytosis and a positive Wassermann reaction.

Probably it is safe to say that 40 *per cent.* of all syphilitics show early spinal fluid changes, and that this percentage is even higher during the stage of secondary manifestations. This statement does not necessarily imply that in the other 60 *per cent.* the nervous system remains free, for if the number of organisms reaching the meninges is small, or if the cells of the host fail to react, it will naturally follow that there will be no signs of nervous infection, and the cerebro-

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spinal fluid will be normal. As every clinician is fully aware, much the same thing may happen in the systemic portion of the body; during the stage of generalization the patient may develop no signs or symptoms, and in a few cases the Wassermann reaction may even be negative.

Many are convinced that the fate of every syphilitic is determined during the first few months of infection; if the spinal fluid remains normal it will not be invaded later on, while on the other hand, if early changes make their appearance the physician may confidently expect the development of neuro-syphilis at a later date. It must be observed, however, that this conception of the origin of neuro-syphilis is rejected by many competent observers, who cite instances where patients under observation for long periods have had normal fluids during the years immediately preceding the onset of general paralysis. In reply to this criticism it may be pointed out that even when the signs of general paralysis are well established, the cerebro-spinal fluid does not always show characteristic changes. Variations and fluctuations may be encountered, and on more than one occasion I have seen the spinal fluid of an untreated general paralytic slowly return almost to normal. Moreover, as Head has shown, the cerebro-spinal fluid may be normal in the presence of active brain syphilis provided the disease is limited to the intra-cranial contents.

It may, indeed, be almost normal, for Valente (12) found living spirochætes in small fragments of brain removed during life from three paralytics whose fluids gave a negative Wassermann reaction.

The question of early involvement of the nervous system has been very fully discussed by Moore.(13) In the first place he notes that the percentage of patients found to have early spinal fluid abnormalities approximates the incidence of late clinical neuro-syphilis. Secondly, he points out that if infection of the nervous system occurs within the first few months of the disease, one would expect a gradually increasing incidence of abnormal fluids, reaching a maximum during the first or second years, and thereafter remaining at approximately the same level. If, on the contrary, invasion of the nervous system takes place at any time the curve of incidence should be a constantly increasing one. In a chart compiled from 480 cases, arranged to show the duration of infection in months at the time of puncture, Moore finds that there is a rapid rise in the incidence of abnormal spinal fluids which reaches its maximum at the end of about twelve months, and thereafter remains at about the same level; such a finding of course is in favour of early infection.

According to Moore, neuro-syphilis appearing within a year or less of the date of infection may be classified into five clinical groups:

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(1) acute syphilitic meningitis, (2) precocious vascular neuro-syphilis, (3) neuro-recurrence in early cases in which treatment has been allowed to lapse, (4) neuro-syphilis manifested by very slight physical signs, and (5) asymptomatic neuro-syphilis in which invasion of the central nervous system is detected only by examination of the cerebro-spinal fluid.

Groups 4 and 5 together constituted 76·6 *per cent.* of all forms of early neuro-syphilis investigated by Moore, and the changes found in the spinal fluids could be classified into three categories: fluids showing slight pleocytosis and slight increase of globulin; fluids showing a higher cell-count, more globulin, and a negative or weakly positive Wassermann reaction; and lastly, spinal fluids in which the changes were of a much more advanced type, the cell-count being very high, the Wassermann reaction strongly positive, and the gold curve of a paretic type. The effects of treatment on these three degrees of abnormality were very striking, for while the abnormalities in Groups 1 and 2 cleared up in practically all cases, those in Group 3 showed practically no improvement, even after 20 or 30 intravenous and intraspinal injections of salvarsan. Moore was able to keep under observation 8 patients belonging to this group, and after an interval of five years two developed general paralysis, a third neuro-syphilis, while the remainder continued to show no symptoms. Such considerations go far to justify the conclusion that the fate of every syphilitic is determined during the first few months of infection.

The Question of the Resistance of Special Strains of the Spirochæte pallida.

It now becomes necessary to consider another aspect of this problem which is still the subject of much controversy. If the spinal fluid and the nervous system are infected in from 30 to 40 *per cent.* of all cases of syphilis, why does general paralysis only develop in approximately 5 *per cent.* of infected persons? In reply to this question two explanations may be offered.

First, the organisms which attack the nervous system may do so because they possess a special neurotropic action, or secondly the disease may make its appearance because the patient possesses a neuropathic disposition—that is to say, a reactive mechanism which is less efficient to cope with the spirochæte than that possessed by the 95 who escape general paralysis.

Let us consider these two hypotheses separately.

(1) *Neurotropic strains.*—The possibility of there being variations in the biological properties of the *Spirochæte pallida* was first suggested by Noguchi (14), and later made the subject of experimental investigation by Nichols (15), Reasoner (16), Levaditi and Marie. (17) But

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before outlining the evidence favouring the existence of special strains of spirochætes, it will be convenient to refer to the clinical records bearing on this point.

At various times groups of cases of parenchymatous syphilis have been reported having apparently a common source of infection, and probably the earliest and best-known example is that of Brosius (18): seven glass blowers infected by one of their comrades developed chancres of the lips, and of the five who came under observation ten years later, two were suffering from general paralysis and two from tabes.

Erb cites another instance where five men, infected from a common source, all subsequently developed tabes or general paralysis, while Nonne (19) speaks of three friends who, infected by the same mistress, became victims of these diseases.

Another striking illustration of multiple infection from a common source is recorded by Morel-Lavallée (20): A woman, Martha X—, infected her lover, who died of syphilitic meningitis. A year later X— became the mistress of a student, B, whom she likewise infected. Later she deserted B, and lived with C. B married and had two healthy children, but died of general paralysis. Fifteen years after his infection C died of general paralysis after an interval of nine years. Finally Martha X— left C, and passed on her disease to two more men; one of these succumbed to general paralysis, the other to a syphilitic psychosis. The importance of these and other cases has been questioned on the grounds that they might be explained by coincidence, and that instances of familial and conjugal general paralysis should be much more common if a neurotropic strain exists. It is notorious, however, that accurate and truthful histories are very seldom obtained, and I do not consider that the paucity of statistical evidence constitutes a serious objection. Only a few months ago I had an experience which shows how easily examples of this kind may be overlooked.

A young woman in the Leavesden Mental Hospital, who was in the last stage of general paralysis, had a history of blindness and ataxia dating from the age of 11. The father stated that the patient lost her mother in 1919, the cause being "neurasthenia, following air raids." However, from Claybury Mental Hospital I learnt that the mother died of general paralysis and that *post-mortem* examination had confirmed the diagnosis. A slight defect in the father's articulation led me to examine him rather closely, when I discovered irregular unequal pupils, facial tremor, and other signs of incipient general paralysis. Here, then, was another striking example of conjugal paralysis which might easily have been missed. Some interesting statistics relating to the incidence of conjugal

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neuro-syphilis have been given by Fischer (21), who computed the frequency with which the husbands of syphilitic wives developed general paralysis, and comparing these with the total paretic mortality in syphilis, found a percentage of 10·5 in conjugal paralysis, which, compared with 3·7 *per cent.* for syphilitic men in general, is certainly in favour of a neuropathic strain.

Passing now to the epidemiological evidence, there is first of all the well-established fact that the natives of certain tropical or subtropical countries, although sodden with syphilis, rarely develop general paralysis or tabes, and it has been suggested that the rarity of parenchymatous syphilis in these localities can be best explained by the well-established facts of racial immunity. That some other factor must be taken into account is, I think, shown by Christidi's (22) report on syphilis in Persia. In this country syphilis is appallingly common, but fortunately of so benign a character that a few injections of mercury serve to banish its manifestations, and even in untreated cases the Wassermann reaction usually becomes negative by the end of the first year of infection. Among 3,000 cases of syphilis Christidi never found a case of general paralysis, and this in spite of the fact that the Persians are intellectual workers, and use both alcohol and opium. Further, the same benign characters which distinguish syphilis in the natives of Persia are also found when European residents are infected, there being a singular freedom from complications of all kinds, but—and this is the important point—when Europeans resident in Persia contract the disease from outside sources the disease manifests itself in severe form. Thus, out of twenty-two Europeans infected by non-Persian women, two developed general paralysis.

We are thus impelled to the conclusion that neither the influence of climatic conditions nor race immunity can be used to explain these differences, and, as Levaditi and Marie point out, since animals recovering from the African type of relapsing fever are still susceptible to the European variety, it is not illogical to conclude that other spiral organisms, such as the *Treponema pallidum*, may also show analogous variations.

Much has been written concerning the absence of general paralysis in the coloured races, and here again the evidence is suggestive. Lennox (23) points out that in China, although syphilis is three times more common than in America, neuro-syphilis is extremely rare, the incidence being only one-seventh or one-eighth of that in the States, and, moreover, the few patients who do occasionally come into hospital with this disease are found to be usually steamship employees, who derive their infection from European sources.

Coming now to the attempts made to solve the problems of general

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paralysis from the experimental standpoint, there is first the observation of Noguchi (24) that certain strains of spirochæte appear notably thinner than others, and that this variation in morphology has some relationship to their motility, infectiousness and cultural characters. The incubation period with the thicker forms is long, and the lesions nodular, hard and sharply defined. With the thinner and more active types large diffuse lesions are produced.

A year after Noguchi published his paper Nichols (25) succeeded in inoculating the testicles of a rabbit with cerebro-spinal fluid from a case of secondary syphilis. The strain isolated in this manner resembled the thick type described by Noguchi, and was thought by Nichols to be a neurotropic variety, but continuing experiments with the same strain, Zinnser (26) found it possible to imitate practically all the ordinary lesions in rabbits obtained by inoculating strains from other sources.

Similar experiments by Steiner (27), Weygandt and Jakob (28) likewise give little support to the claims of Nichols, for they were able to show that a single strain does not invariably produce lesions of a similar character. In 1919 the controversy was again revived by Levaditi and A. Marie (29), who claimed that their experiments gave the final answer to this question. They succeeded in obtaining lesions in the rabbit with blood from a general paralytic, and were able to transfer the strain to other rabbits. Having isolated in this way a virus which they considered to be neurotropic, they next proceeded to compare it with a strain of spirochæte obtained from a chancre—the dermotropic virus—and found that the two show wide differences in their incubation period, in the character of the lesion, and in the progress and virulence of the disease. With the dermotropic strain the incubation period is about fourteen days; the primary lesion is deeply infiltrated and ulcerated, and persists for about three months. It maintains its virulence for apes even after a large series of passages through the rabbit, and continues to be pathogenic for man, although not for the general paralytic. The neurotropic strain has a much longer incubation period, the primary lesion is superficial, and is extremely slow in disappearing, and the virus has no pathogenicity for man or ape. Lastly, the two viruses fail to induce a crossed immunity against each other, for rabbits recovering from the local lesions provoked by either virus are refractory to superinoculation with the homologous organism, but are incapable of resisting the heterologous virus. Hence it is concluded that there is a biological difference between the two strains, and that the human subject suffers from a true specific *syphilis nervosa*. As to whether individuals destined to develop general paralysis are contaminated by a special spirochæte, or whether a special type is created in the

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nervous system as the result of a progressive adaptability, is a question Levaditi and Marie find difficult to answer.

While some of the observations cited appear to indicate an original contamination, the authors believe that the two hypotheses are not only perfectly compatible, but rather confirm the theory of a neurotropic virus. Among the numerous strains of spirochæte, morphologically similar, but differing in virulence, which transmit syphilis in civilised countries, there are some which are distinguished by a special tendency to localise in the nervous system. This does not imply that they are incapable of localising in the skin or certain viscera, as otherwise how could they be transmitted from one individual to another by the cutaneous route? But they do seem from the start to have a weak reaction on the skin, as is evidenced by the transitory and mild characters of the symptoms in the patient destined to become a general paralytic.

Although extremely suggestive, these experiments contain more than one possible source of fallacy. First, the differences observed in the two strains are those which can be found between any recently isolated strain of spirochæte, and one which has been kept going by regular passages through an animal for years. Secondly, the neurotropic virus of Levaditi and Marie shows a striking similarity to the *Treponema cuniculi*, the organism of spontaneous venereal spirochætosis in rabbits, for both possess the same degree of virulence, and both cause lesions hardly distinguishable from each other. Consequently the lesions ascribed by Levaditi and Marie to their neurotropic virus may, in reality, have been those of *Spirochæte cuniculi*. In their first paper this possibility was overlooked, but they have since returned to the question, and now claim to have established a complete lack of relationship between the two organisms.

It must be understood that these authorities recognise only two diseases—general paralysis and tabes—as conditioned by the activity of the neurotropic virus, all other forms of neuro-syphilis in their view being caused by the dermatropic virus, and the infrequency of syphilitic meningitis, cranial nerve palsies and so on in general paralysis lends some support to their contention. Presumably in those rare cases in which meningo-vascular and parenchymatous lesions co-exist, the neurotropic strain must be present in symbiosis with the parasite of ordinary syphilis, and moreover, without some such hypothesis it would be impossible to explain the occurrence of different types of syphilis in a family of congenital syphilitics, one member of whom, free from nervous involvement, may have the Hutchinsonian facies, while another, free from all stigmata, may be suffering from general paralysis.

So far I have dealt with the evidence supplied by the proponents

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of neurotropism. It remains now to consider the alternative hypothesis of tissue predisposition.

(2) *Tissue predisposition.*—From this aspect it is considered that general paralysis owes its origin to the action of a spirochæte on cells which have become sensitised by certain methods of treatment, or which possess some inherited peculiarity. Fournier (30) appears to have been the first to note that the initial infection is often peculiarly benign in the future general paralytic, and arguing that such cases would be likely to receive inadequate treatment, he advanced the view that insufficient treatment might play some important part in determining the onset of this disease.

Without committing oneself to any definite hypothesis, it may be supposed that the injection of salvarsan during the period of secondary manifestations kills all the organisms in the skin and systemic portion of the body, and so, by checking the formation of antibodies, cuts off an important supply to the nervous system at a time when it is most needed. From the experimental standpoint there is something to be said for this view, for, as Brown and Pearce (31) have shown, under experimental conditions, subcurative doses of salvarsan render syphilitic animals more susceptible to infection.

With regard to familial predisposition, no experimental data are available, and I shall content myself by remarking that the neuropathic virus cannot possibly be invoked to explain the few recorded instances of families whose several members, after acquiring syphilis from widely different sources, have all developed neuro-syphilis. One of the most striking instances is that furnished by Burrow (32), who had under his care four certain cases of tabes and one probable one among six members of a family who had all acquired syphilis from different sources and at different dates. Three other examples have recently been reported by Kiedel and Moore (33), and careful investigation will probably show that such occurrences are not more rare than the instances of conjugal neuro-syphilis so often quoted by the advocates of spirochæte strains.

Lastly there are a number of pathologists, especially, perhaps, those of the American school, who believe that the key to the understanding of general paralysis is to be found in the reactive mechanism of the host. It has been shown by Brown and Pearce that when the rabbit is experimentally inoculated with syphilis certain groups of tissues tend to become involved in a given order, and that it is possible to produce infection or to confer protection on a given group of tissues according to the nature of the means employed. Thus, by early castration, it is possible to convert syphilis which is usually localised into a generalised disease, or conversely, by permitting the testicular reaction to progress to a given point, to maintain the disease in its

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localised form. Further, it is found that when a high degree of protection is produced in other tissues of the body, it is sometimes inadequate for the eyes, and lesions of the cornea and iris appear as the only clinical manifestations. A further point of interest noted was that the eye lesions are not only terminal, but relatively slight, and more prone to repeated relapse than any other class of lesions. Such circumstances suggest that all tissues are not equally protected by the general reaction which occurs during the early stages of a syphilitic infection, and that certain tissues which fail to receive this protection may be capable of self-protection only to a relatively slight degree. In other words, the selective action of the *Spirochæte pallida* is governed by the manner in which the tissues of the host react to the invader. Now this seems to be undoubtedly the case in the experimental animal, and if similar conditions obtain in man, such diseases as general paralysis and tabes may be explained on this basis. It may be supposed, as Hauptmann (34) and also Sézary (35) have suggested, that the peculiar degenerative character of the lesions in the general paralytic's brain and the striking failure of the cerebral tissue to defend itself against the spirochæte are attributable to an immunity weakness of the nervous tissues, and on the other hand, that when the response is adequate, gummata and other formative lesions are developed which save the patient from the graver forms of neuro-syphilis. It must not be supposed, however, that the presence or absence of syphilitic antibodies has been definitely proved, and until this and other hypotheses are placed on the safe basis of experimental study, the pathology of general paralysis is likely to remain an unsolved problem.

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Basal Metabolism in Mental Disorders, especially Dementia Præcox, and the Influence of the Diathermic Current on the Same.[1]

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METABOLISM means the chemical changes of materials under the influence of living cells, and basal metabolism as the rate of energy exchange during rest when only the essential vital processes of the body are at work.

The consideration of the basal metabolism in cases of mental disorder is of interest for two special reasons. It is an established

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