

The Infective Foci in General Paralysis and Tabes Dorsalis. By W. FORD ROBERTSON, M.D., Pathologist to the Scottish Asylums.

IN previous papers it has been contended by Dr. Douglas McRae, Dr. Dods Brown and myself, that in cases of general paralysis there are special bacterial infective foci in the nasopharyngeal and buccal mucous membranes, and that these infective foci are of importance in the pathogenesis of the disease; Dr. McRae and I have also maintained that in cases of tabes dorsalis there are similar infective foci in the genito-urinary tract. In this paper I wish to deal with some further investigations, the results of which give additional support to these views. In the fifteen minutes at my disposal it is impossible for me to describe these investigations in detail. I can only indicate their chief results and state some of the conclusions that they seem to me to warrant. All the evidence that I can lay before the meeting is shown under the ten microscopes on the tables.

In my experience it is possible, in all cases of advancing general paralysis, to demonstrate, in direct films of the nasal secretion, large numbers of small granular bacilli which frequently show metachromatic granules. In most cases such bacilli are present in very large numbers. In cultures made upon the ordinary media these micro-organisms often fail to grow. I have lately used an agar medium over which there have been poured some drops of sheep's serum containing hæmoglobin in solution. In all of sixteen cases of general paralysis recently examined with the aid of this hæmoglobin medium, I have obtained from the nasal mucosa abundant growths of a diphtheroid bacillus showing the morphological characters and bio-chemical reactions, either of the *Bacillus paralyticans longus* or of the *Bacillus paralyticans brevis*. In four out of six of these cases in which it was possible to test the virulence, the bacillus proved virulent to mice. I have endeavoured to get further information regarding this infection from histological examination of the nasal mucosa and subjacent tissues in a series of cases of general paralysis and in various controls. The following are, in brief, the conclusions that I have been able to draw from this examination. The nasal mucosa and subjacent tissues of the general paralytic are

constantly the seat of well-marked diffuse sclerotic changes and of localised acute or subacute inflammatory processes. In the cases in which these active morbid processes are going on, there is more or less dense aggregation of lymphocytes and great increase in the number of plasma-cells. Lying amongst the epithelial cells covering such areas a few diphtheroid bacilli may generally be detected. Occasionally small areas of epithelium may be observed in which these bacilli occur in dense masses; in these instances they can be seen to be pushing their way through the thickened basement membrane and invading the subjacent tissues. Small microscopic ulcers may occasionally be detected; their floor generally shows necrotic tissue, lying in which there are numerous diphtheroid bacilli. In the lymphatic channels there may frequently be seen more or less numerous bacilli of a similar kind. In this situation there are also, in some areas, very abundant and conspicuous aggregations of granules the size of micrococci, larger or smaller angular fragments, and short rods which stain of a deep blue or olive-green tint in preparations stained with Loeffler's methylene-blue. These bodies are either contained within the cytoplasm of endothelial cells or lying free in the tissue spaces. I shall refer to them again. All control cases show, in methylene-blue preparations, some plasma-cells, more or less numerous mast-cells, and generally a few aggregations of olive-green granules. None have shown invading diphtheroid bacilli.

In several cases of general paralysis diphtheroid bacilli have been found in considerable numbers lying in the lymphatics of the connective-tissue sheath of the second division of the fifth nerve as it passes through the foramen rotundum. Examination of the third division in the foramen ovale has so far given negative results, but the Gasserian ganglion and neighbouring dural tissues have in nearly all of the cases been observed to contain some of these bacilli. In several cases the dura mater lying over the cribriform plate of the ethmoid and the under aspect of the olfactory bulbs have been found to contain numerous diphtheroid bacilli. Experiments in the *post-mortem* room have shown that fluids readily pass from the nasal submucosa through the cribriform plate of the ethmoid. It is therefore evident that bacilli that have reached the lymphatics of the nasal mucous membrane can, and do, pass into the cranial lymphatic system by way of the cribriform plate of the

ethmoid and foramen rotundum. There are also other possible channels of cranial invasion from the naso-pharyngeal tissues.

In order if possible to trace the infection further I have, in a series of cases of general paralysis, examined the pia-arachnoid in horizontal sections stained with Loeffler's methylene-blue. In the majority of cases bacilli with the characteristic morphological features have been clearly demonstrated, generally in small numbers, but occasionally in abundance. In all cases of general paralysis the pia-arachnoid appears to contain, though it may be only locally, very numerous aggregations of the blue and olive-green granules and fragments already described as occurring in the nasal mucosa. These bodies, in so far as they have been observed, have probably generally been regarded as "tissue granules," the result of degenerative and disintegrative processes. In favour of this opinion there are the facts that a few granular aggregations of a similar appearance may be seen in control cases, and that in these they can often be clearly traced from the granules of mast-cells. Against it there are, however, other facts that deserve consideration. In cases of general paralysis these aggregations commonly occur, locally at least, in the nasal tissues and in the pia in very extraordinary amount; many of the rod-shaped forms have appearances identical with those presented by the alleged pathogenic bacilli grown under anaërobic conditions. It has been proved in the laboratory that these bacilli are capable of living under anaërobic conditions, and that under such conditions their growth is extremely slow. Growing out from some of the granular masses characteristic rod-forms with clubbed extremities have been detected. Moreover, it has been shown experimentally that these bacilli when injected into the tissues of the rabbit are taken up by the endothelial cells and transformed into granular aggregations very closely resembling those in question. We cannot, therefore, exclude the possibility that some of these masses represent altered diphtheroid bacilli, and even a chronic infection by these micro-organisms growing under semi-anaërobic conditions. As the question cannot be settled by the staining methods I have employed, I leave it there for the present. It remains to add that within the brain of the paralytic diphtheroid bacilli can, in my experience, be demonstrated in the majority of cases. In several instances I have found them to occur locally in large numbers.

The evidence in support of the view that tabes dorsalis is associated with a special infective focus in the genito-urinary tract is chiefly bacteriological and therapeutic. In twenty-three successive cases of tabes I have obtained from the urine or from the surface of the urethra cultures of a diphtheroid organism with the bio-chemical reactions of one or other of the two types to which importance has been attached. In several instances this bacillus has proved virulent to mice. In every case there have been other or secondary infections, represented most commonly by various Gram-fast diplococci, but also frequently by the *Bacillus coli*. In three cases of tabo-paralysis the bacilli have been traced through the pelvic lymphatics to the posterior root ganglia and the pia-arachnoid of the lumbo-sacral cord, in the connective tissues around the posterior root ganglia and in some areas of the membranes of the cord there were found very numerous, more or less dense, aggregations of blue granules and rods similar to those observed in the nasal tissues and cerebral pia-arachnoid in cases of general paralysis. The therapeutic evidence has consisted in the results obtained from the administration of autogenous vaccines and anti-serum in a fairly extensive series of cases. It shows that in early cases of tabes the symptoms readily yield to such specific treatment. In advanced cases it is much more difficult to obtain amelioration of the patient's condition, yet even in some of these pain has been relieved, walking has greatly improved, and urinary troubles have been obviated. It is impossible that such results could have been obtained if the infections against which the treatment was directed had nothing to do with the malady. It has, moreover, frequently been observed that an overdose of one of these autogenous vaccines is followed within twelve or twenty-four hours by a characteristic attack of tabetic pains.

Before concluding I desire to say a few words regarding the origin of these infective foci. In my opinion sufficient evidence has now accumulated to show that general paralysis is, as a rule, a venereal disease, not only in respect of its common ætiological relationship to previous syphilis, but also in respect to the source of the bacterial infection which experimental evidence has shown to be capable of producing many of the essential phenomena of the disease. The source of this infection is commonly a bacillary endometritis. The man gets a urethral infection usually before marriage; he accidentally

infects his nasal mucosa and invasion of the local lymphatics begins. He may, however, convey the infection to his wife; her uterus provides a suitable anaërobic culture medium. The virulence of the organism gradually rises, and in this more virulent form the bacillus is returned to the husband. Every asylum physician is aware of the fact that if he allows a man who suffers from general paralysis, and who has improved under asylum treatment, to go home, the rule is that the patient is brought back within six weeks suffering from a serious relapse. What has happened? In some instances, at least, he has become re-infected by a virulent strain of the bacillus. I have made great efforts to have some of these "carriers" investigated bacteriologically. Thanks to the kindness of two gynæcologists I have succeeded in two cases. The first case was that of a lady whose health was greatly undermined by severe endometritis. Cultures were made for me by Dr. Haultain from the interior of the uterus, and portions of the endometrium were also obtained. There developed in the cultures numerous colonies of a *Bacillus paralyticans longus*, identical with that previously obtained from the urethra and nose of the patient's husband, and sections of the endometrium showed the bacilli in the tissues. The patient consented to undergo vaccine treatment, and in preparing the vaccines I used the bacillus isolated from the husband. Each ordinary dose produced next day a definite reaction in the form of a severe and characteristic attack of endometritic pain. Subsequently this was obviated by the administration of anti-serum.

The second case was that of the wife of another general paralytic, whose nasal cavities and urethra were loaded with a virulent strain of the *Bacillus paralyticans brevis*. In this case the uterine lesion was so severe that the specialist feared at first that the patient was suffering from carcinoma. Direct films made from a scraping from the interior of the uterus showed abundant diphtheroid bacilli, with metachromatic granules. Cultures upon hæmoglobin agar yielded growths of the same organism as that previously obtained from the husband. I tested in the usual way the virulence of three separate growths. Out of six mice two died within twenty-four hours, two within five days, one within eleven days, and the last succumbed after two months.

It is clearly established, from certain features of the disease

when it occurs in early life, that syphilis specially tends to damage the nasal tissues. These highly virulent bacilli that are associated with a particular form of endometritis may find a specially suitable nidus in a nasal mucous membrane that is weakened in its defences by a syphilitic sclerosis. It is certain, at least, that these virulent diphtheroid organisms do invade the nasal mucosa of the general paralytic, and that they pass along the lymphatics to the intra-cranial cavity, whilst experimental evidence now obtained by five observers has shown that they are a sufficient cause of the characteristic histological lesions of the disease.

The relation of the urethral infection in tabes to a bacillary endometritis is not so clear. I have no direct evidence on the subject. In cases of tabes, as has been established by extensive statistics, a history of acute urethritis occurs in over 90 *per cent.* This previous acute infection is probably a far more important step in the pathogenesis of locomotor ataxia than is at present believed. It permits of various secondary urethral infections becoming established, and among others those by the neurotoxic diphtheroid bacilli. Such bacillary infection of the urethra may undoubtedly exist without tabes, but if the patient has had syphilis and has suffered from a slight syphilitic spinal meningitis he may be much more susceptible than others to the action of the toxins carried to the spinal canal by the pelvic lymphatics. He may also be less able to inhibit the multiplication of living bacilli that reach the lymph-stream. There is, however, no proof that syphilis is a constant antecedent of tabes. Many of the characteristic phenomena of the disease can certainly be produced in lower animals by the action of these neurotoxic bacilli alone.

I have to express my special indebtedness to Dr. Keay and to Dr. Muncaster, Pathologist at Bangour Asylum, for having given me facilities for obtaining nasal tissues, and my similar obligations to Dr. Muirhead, Dr. David Orr, and Dr. A. L. Taylor. I am also indebted to Dr. M. C. W. Young for valuable help in the histological work.

REFERENCES.

- Rev. of Neurol. and Psych.*, February, March, and April, 1906.
Journal of Mental Science, January, 1909.

DISCUSSION,

At the Annual Meeting held in Edinburgh in July, 1910.

The PRESIDENT thanked Dr. Ford Robertson for his paper.

Dr. ROBERT JONES asked whether the bacilli had been found in the cerebro-spinal fluid. He understood Dr. Robertson to say the bacilli were found in the brain in many cases of general paralysis. He supposed that did not apply to all cases.

Dr. IVY MACKENZIE asked whether the micro-organisms were injected subcutaneously.

Dr. PERCY SMITH said he would like to make a remark from a clinical point of view. He spoke because he had seen one of the cases referred to by Dr. Ford Robertson, a general paralytic, whose wife had endometritis, and in the secretion therefrom the *Bacillus paralyticans* was said to have been found. He had been treated with vaccines in Edinburgh, and returned to London in January last, when he was considered to be quite well; at any rate he had a remission. In February he had retention of urine, unequal pupils, which did not react to light, exaggerated knee-jerks, hesitation of speech, confusion of mind. It seemed evident it was the third stage of general paralysis. After returning home from Scotland Dr. Smith believed he had been treated by his own practitioner with vaccines which Dr. Ford Robertson supplied. Dr. Robertson appeared to have been asked about the case when the symptoms recurred, and he expressed the opinion that there must have been a reinfection of the patient, either from his wife, or from some other woman. But it was ascertained, as a positive fact, that the patient had had no intercourse of the kind. He feared that, from the clinical point of view, he must regard it as merely a remission of symptoms, and that, in spite of the vaccine treatment, the disease had followed its ordinary course. From his standpoint, the vaccine seemed not to have done any good in that case. He was very sceptical about the relationship of the *Bacillus paralyticans longus* found in the endometritis secretion to the disease.

Dr. WINIFRED MUIRHEAD remarked that Dr. Ford Robertson had said he was able to get tabetic symptoms in rabbits by inoculating those rabbits with the diphtheroid organism. She had produced similar symptoms in rabbits after inoculating them with ordinary *Bacillus coli* culture, or the streptococcus. The inoculations were done into the spinal canal, and there was a lesion of the spinal cord from the various inoculations. She had used both the *Bacillus coli* and the streptococcus, and her results from those were much more marked than with the diphtheroid organism, using two or three different strains of the latter.

Dr. ROBERTSON, in reply to Dr. Jones, said that Dr. McRae, Dr. Dods Brown, and he, had obtained cultures from the cerebro-spinal fluid of the living general paralytic in several cases, as had been recorded in their published papers; and Dr. John D. O'Brien had obtained growths in 70 per cent. of cases in a series extending to over 160. He did not agree with the statement of Dr. Percy Smith; the patient had left him in good health, with no evidence of active disease. What happened afterwards he did not fully know, but he had information that strongly supported the view that the patient did go back to the original source of infection. He would not, however, follow Dr. Percy Smith in expressing his absolute conviction upon a point that could only be one of conjecture. In reply to Dr. Mackenzie, he said that the virulence test was applied in the usual way; 1 c.c. of a twenty-four to forty-eight hours' broth culture was injected subcutaneously.