

2550.—⁽⁵⁾ In this connection the assistance of Dr. Sinclair, Medical Officer, H.M. Prison, Barlinnie, and Dr. McWalter, Medical Officer to H.M. Convict Prison, Peterhead, is recognised with thanks.—⁽⁶⁾ "Anthropometry of Scottish Insane," *Biometrika*, vol. v, part 3, February, 1907.—⁽⁷⁾ Aided by the Carnegie Research Fund.—⁽⁸⁾ The shires of Kirkcudbright and Wigton.—⁽⁹⁾ Within living memory in Glasgow these weary wayfarers in the night shelters, there being no shake-downs, laid their chests across a taut rope which the keeper in the morning cut in order to wake them all up, as the gong does the guests at a hotel.

Further Bacteriological and Experimental Investigations into the Pathology of General Paralysis and Tabes Dorsalis. By W. FORD ROBERTSON, M.D., and DOUGLAS MCRÆ, M.B., C.M., M.R.C.P.Edin.

In previous papers (1) we have recorded observations on the ground of which we have contended that a diphtheroid bacillus, having cultural and morphological characters resembling those of the Klebs-Löffler bacillus, plays the chief part in the production of the toxæmia of general paralysis. We have at the same time insisted upon the importance of weakening of the local and general defences against bacteria, and have attributed the chief part in the production of this impairment to syphilis, chronic alcoholic intoxication and the excessive use of nitrogenous foods. A little more than a year ago we thus summarised the case in support of the diphtheroid hypothesis:

The evidence that a diphtheroid bacillus—either an attenuated form of the Klebs-Löffler bacillus or more probably an altogether distinct micro-organism—is the specific etiological factor in general paralysis and tabes dorsalis is briefly as follows: A bacillus of this nature is, according to the results of our investigations, present in large numbers, either in the alimentary or respiratory tract, or in both, and in the genito-urinary tract, in all cases of advancing general paralysis. This bacillus has a thread form, which has been found invading the walls of the respiratory or alimentary tract in five cases of general paralysis. It can be shown that this bacillus invades the pulmonary tissues in cases of general paralysis, and that it is commonly the only micro-organism present in large numbers in the catarrhal pneumonic foci that occur in most of such cases dying in congestive attacks. A growth of a diphtheroid bacillus has now been obtained in cultures made from the brain

post-mortem in ten cases of general paralysis out of twenty-four in which cultures were made from this organ. Diphtheroid bacilli exhibiting metachromatic granules in Neisser preparations have been detected in the fresh blood in one case and in sections of the brain in two cases. It has been ascertained by experimental methods that these diphtheroid bacilli in contact with the living blood are rapidly taken up by the polymorphonuclear leucocytes, and that they may be completely digested in the course of two or three hours. Bodies exactly corresponding in appearance to these dissolving bacilli can be detected in the blood and cerebro-spinal fluid of the living general paralytic, especially during a congestive attack. Whilst the fact that most of the bacilli present are in process of disintegration satisfactorily explains the long succession of negative results of endeavours to obtain cultures from the blood and cerebro-spinal fluid, we have, by the use of special methods, succeeded in obtaining pure growths of a diphtheroid bacillus from the fresh blood in four cases of general paralysis, and from the cerebro-spinal fluid withdrawn by lumbar puncture in two cases. In sections of the brain prepared by special methods disintegrating diphtheroid bacilli can be recognised in the walls of the vessels and in the pia-arachnoid in many cases of general paralysis. The centrifuge deposit from the urine of the general paralytic, especially during a congestive seizure, commonly contains abundant diphtheroid bacilli that have been more or less affected by lysogenic action. In seven consecutive cases of general paralysis combined with tabes we have found the centrifuge deposit from the urine to contain, not only these altered diphtheroid bacilli, but also living ones, showing distinct metachromatic granules. In such cases a culture of the bacillus can be obtained from the urine. Experimental infection of three rats and a goat with diphtheroid bacilli, isolated from a case of general paralysis, has resulted in the production of symptoms and tissue changes resembling those of general paralysis. Lastly, there is evidence that the active polymorphonuclear leucocytes of the general paralytic have, as a rule, a greater power of dissolving these diphtheroid bacilli than that possessed by the normal leucocyte. It would therefore appear that the general paralytic has acquired against these diphtheroid bacilli a certain degree of specific immunity, by means of which he is enabled to maintain the struggle

against these bacilli, notwithstanding an otherwise defective local and general power of resistance.

These views have been opposed in this country by Eyre and Flashmann (2), Mott (3), Ferrier (4), Bulloch (4), Hamilton Marr, and several of the medical journals. On the other hand, there have not been wanting those who have recognised that the various points of evidence we have brought forward are entitled to consideration, and some have accepted the conclusions that we have drawn from them. As regards general paralysis, many of our observations have been confirmed by those of O'Brien (5) and Langdon (6) in America. O'Brien's work has been extensive, and in respect of his experimental observations he has gone ahead of us. He has isolated an organism resembling the Klebs-Löffler bacillus from 95 *per cent.* of cases of general paralysis. He has found that lower animals inoculated with the bacillus have passed through attacks similar to congestive seizures, hemiplegia, and objectively typical paresis. *Post-mortem* examination revealed conditions similar to those seen in an early case of general paralysis. He produced a bactericidal serum in the goat, and found that it had a protective action upon dogs infected with the bacillus. More recently he has treated cases with vaccines consisting of the killed cultures, using the opsonic index as a guide, and has had a considerable measure of success.

The further observations that we have now to record concern chiefly the broth reactions and virulence of a series of diphtheroid bacilli obtained from various sources, the experimental production of general paralysis in rats, the experimental and clinical study of intracorpuseular bacteriolytic indices in relation to certain species of these diphtheroid bacilli, and also some special phenomena that bear upon the views maintained.

In 1903, when we first advanced the diphtheroid hypothesis of the etiology of general paralysis, we provisionally regarded the organism as an attenuated form of the Klebs-Löffler bacillus, in accordance with the authoritative teaching of the time, that an organism differing from the diphtheria bacillus solely in its want of virulence must be regarded merely as a diphtheria bacillus in an attenuated condition, and should be spoken of as such. In taking up this position we left it an open question whether the bacillus might not be a special one, differing from the bacillus of acute diphtheria in certain respects afterwards

to be determined. A year ago, though we could not absolutely distinguish the cultural and morphological characters of the organism from those of every other species of the diphtheroid bacillus, we felt justified, in view of additional evidence we had collected, in maintaining that the organism is a special one, and we proposed to refer to it as the *Bacillus paralyticans*. It was suggested to us by Dr. M. H. Gordon that we might be helped in the differentiation of this organism from other diphtheroid bacilli by applying litmus broth tests to all of the organisms of this nature that we isolated from time to time in the course of our investigations. We would take this opportunity of acknowledging our great indebtedness to Dr. Gordon for suggesting the application of these tests, and also for other valuable advice regarding our special bacteriological investigations. We have applied Dr. Gordon's method and have used as test-substances glucose, saccharose, lactose, salicin, starch and dextrin. The following table shows the reactions previously ascertained to be given by various of the already known members of the diphtheroid group to the first five of these substances. The results are those obtained by Dr. Gordon, supplemented by some ascertained by Benham (7). The reaction of each organism to Neisser's method is added.

Bacillus.	Glucose.	Saccharose.	Starch.	Salicin.	Lactose.	Reaction to Neisser's method.
Klebs-Löffler . . .	+	—	—	—	—	Positive.
Hoffmann's b . . .	—	—	—	—	...	Negative.
Xerosis b . . .	—	—	—	—	...	Negative.
Diphtheroid x . . .	+	+	—	+
Diphtheroid y . . .	+	+	+	—
<i>Bacterium muris</i> (Klein)	+	+	...	+	...	Positive.
<i>B. corynebacterium</i> <i>segmentosus</i>	+ or —	+ or —	+ or —	Negative.

The sign + indicates that a distinct acid reaction is produced by the organism after incubation at 37° C. for three days.

The results obtained by Knapp (8) and Graham-Smith (9) with the media of Hiss, differ as regards the above test-substances only in certain points that are hardly material for our present purpose. It is, however, to be noted that both

state that an acid reaction is produced in dextrin broth within seven days by the Klebs-Löffler bacillus.

It has not been possible for us to make any very extensive investigation into the broth reactions of the diphtheroid bacilli that can be isolated from general paralytics and tabetics. We have simply tested with what appeared to be the most important substances the various diphtheroid bacilli that we have happened to obtain in pure culture in the course of our recent work. The following table shows our results up to the present date. All of the strains gave a positive reaction with Neisser's method, but in the case of Nos. 9, 10, and 12 the metachromatic granules were minute, and occurred in only a comparatively small number of the bacilli.

Table showing the Litmus Broth Reactions of Diphtheroid Bacilli isolated from Cases of General Paralysis and Tabes Dorsalis.

No.	Patient.	Disease.	Source of bacillus.	Glucose.	Saccharose.	Starch.	Salicin.	Lactose.	Dextrin.
1	L.	G. P.	Cerebro-spinal fluid	+	-	-	-	-	-
2	M.	G. P. and tabes.	Urine	+	+	-	-	-	-
3	M.	"	"	+	+	-	-	-	...
4	M.	"	"	+	+	-	-	-	...
5	N.	G. P.	Bronchial gland	+	+	-	-	-	...
6	M.	G. P. and tabes.	Urine	+	-	-	-	-	...
7	M.	"	"	+	-	-	-	-	...
8	M.	"	"	+	-	-	-	-	...
9	M.	"	"	-	-	-	-	-	...
10	M.	"	"	-	-	-	-	-	...
11	M.	"	"	+	+	-	-	-	...
12	W.	G. P.	Conjunctiva	-	-	-	-	-	...
13	M.	"	Peritoneum	+	+	-	-	+	...
14	M.	"	"	+	+	-	-	+	...
15	C.	Tabes	Urine	+	+	-	-	-	...
16	G.	"	"	+	+	-	-	-	...
17	N.	G. P. and tabes	"	-	-	-	-	-	...
18	G.	G. P.	Cerebro-spinal fluid	+	+	-	-	-	-
19	B.	"	Urine	+	-	-	-	-	-
20	Klebs (from	- Löffler bacillus a case of diphtheria)	Urine	+	-	-	-	-	-

In this series, among the strains of bacilli having very prominent metachromatic granules, it seems to be possible to recognise two special types, one having the broth reactions of the Klebs-Löffler bacillus, causing an acid reaction in glucose broth only, and the other differing from this in producing acid

also in saccharose broth. Two strains, in other respects similar to the latter, were found to produce acid also in lactose broth. It seemed to us at one time that the negative reaction of the first type to dextrin might serve to distinguish it from the Klebs-Löffler bacillus, but we have been unable with the dextrin broths we have used to obtain an acid reaction with the Klebs-Löffler bacillus even after seven days. The reactions given by the bacillus of the second type do not seem to correspond exactly to those of any diphtheroid bacillus hitherto described. The clear differentiation of these two types has been the main result of the application of these tests.

The virulence of six of these strains (Nos. 1, 4, 13, 16, 18 and 19) has been tested upon guinea-pigs. Hypodermic injections of 100 mgrm. of agar cultures have produced no apparent effects. With bacillus No. 1, the results of hypodermic injection into mice of doses of from 20 to 60 mgrm. have been inconstant. Some of the mice, after showing a few morbid symptoms, remained well. One which received an injection of 40 mgrm., and after twenty-three days another injection of 30 mgrm., died three days later. Another mouse injected subcutaneously with 40 mgrm. of the killed culture (heated to 128° C. for half an hour) died six weeks afterwards. Another mouse injected with 2.5 cc. of immune sheep's serum taken from a tube containing 5 cc. of this serum which had been incubated at 37° C. along with 40 mgrm. of the bacilli for forty-eight hours, became acutely ill ten minutes after the injection and died within forty-eight hours. Bacillus No. 4, which, as will presently be described, has caused acute and chronic disease in rats when given in the food, has not proved very virulent to mice when injected subcutaneously. Four successive injections, at intervals of from nine to fourteen days, resulted in the death of one mouse about four weeks after the last injection. Single injections of the usual dose of cultures of bacilli Nos. 8 and 13 had no distinct effect upon mice. Single injections of 40 mm. of cultures of bacillus No. 18 proved fatal to each of two mice on the fifteenth day.

The Experimental Production of General Paralysis in Rats.

In previous papers we have described the results of experiments, carried out by Dr. Shennan and one of us, in which rats

were fed for several weeks with cultures of a threading diphtheroid bacillus isolated from the bronchus of a general paralytic. It is certain that the organism belonged to the first of the two types that we have reason to believe to be of importance in general paralysis. We have recently made a more complete examination of the tissues of the animals that were the subjects of this experiment, and find that the lesions presented by them resemble those that occur in certain cases of general paralysis even more closely than we have hitherto claimed. All of four animals in which the experiment was fully carried out died after manifesting paretic symptoms, and their cerebral tissues show periarteritis, neuroglia proliferation and severe nerve-cell lesions. Three out of the four show extensive invasion by the thread form of the bacillus identical with that which occurred in the patient from whom the bacillus was isolated, and with that which has been found in several cases of general paralysis and in the bladder-wall in one case of tabes.

Last autumn we commenced another series of similar experiments with rats. Sixty animals in all have been fed with cultures of various strains of diphtheroid bacilli derived from cases of general paralysis or of tabes dorsalis. These cultures were simply added from time to time to food similar to that upon which control animals were fed. The strains selected were Nos. 1, 4, 8, 13, and 16 in the foregoing list. Very small doses were given during the first three or four weeks, the object being to immunise the animals if possible, and to ascertain the nature of any morbid changes that might occur as the defences of the animals gradually broke down before the persistent attack of the bacilli. This plan was adopted because in the previous series of experiments the rats succumbed far too quickly to permit of advanced chronic changes being established. A certain number of the animals have already died, but the experiments are not yet completed, and we shall therefore here deal only very briefly with some of the results so far obtained.

The first experiment has consisted in the feeding of twelve animals with cultures of a diphtheroid bacillus isolated from the cerebro-spinal fluid of a case of general paralysis *post mortem*. It was originally a threading bacillus, and it was the only organism that developed in the media. It produces acid in glucose broth only. It is undoubtedly a bacillus identical

with the one used in the previous set of experiments upon rats. As yet only three of the animals have died. They did not exhibit very evident parietic symptoms. All of them were found to have advanced tuberculosis affecting the lungs. The cerebral changes are of too slight a nature to be regarded as of any importance. Some of the remaining rats are now showing signs of paresis. It is evident that this organism is one of much less virulence to rats than the bacillus used in the experiments carried out in 1903.

In the second experiment twelve rats have been fed with a bacillus isolated from the urine of a case of tabo-paralysis. The organism has prominent metachromatic granules, but has never shown any tendency to form threads. It produces acid rapidly and abundantly in glucose broth, somewhat less rapidly in saccharose broth. This bacillus has proved much more virulent than the preceding one. After about seven weeks one of the animals was seen to be acutely ill. It was slow in its gait, feeble, and extremely irritable. Next day it was paralysed in all its limbs. It lay for several hours quite motionless, excepting for the respiratory movements, which gradually became reduced in number, until they occurred only four times per minute. The animal died within thirty hours of the first appearance of acute symptoms. Tubes inoculated from the heart's blood and spinal cord remained sterile. The chief morbid change revealed by microscopical examination is acute degeneration of most of the nerve cells of the spinal cord. The nerve cells of the brain present similar changes, but they are much less severe. A few days after the death of this animal two other rats began to show similar but less marked symptoms. After four or five days the acute symptoms passed off, but the animals remained lethargic and feeble. Two months later both of them were noted to be more feeble, very slow and uncertain in their gait, and much emaciated; they were dull, drowsy, and stupid. All of these symptoms gradually increased, and the two animals died within about a fortnight of each other, twenty-two and twenty-four weeks from the commencement of the experiment. The remaining nine rats have never had any acute illness, but all of them have gradually become thin, enfeebled, lethargic, impaired in their power of co-ordination, and stupid-looking. Five of them are now dead. The four that remain are extremely feeble, irresponsive and demented-

looking. All of the rats of this series that have succumbed to a chronic illness showed similar changes affecting the nervous system, differing only in degree in the individual cases. There are extremely well-marked chronic degenerative changes in the nerve cells of the spinal cord, less advanced changes of a similar character in the nerve cells of the cerebral cortex. In several of the cases the cerebral arterioles show distinct periarteritis, and the neuroglia also shows some proliferative changes. Cultures were made from the blood and various internal organs of most of these rats, but no growth of the bacillus with which the animals had been continually fed could be obtained.

In the rats the subjects of the three other experiments the morbid phenomena have been much less distinct, but parietic symptoms are now developing in some of the animals in two of the cages.

On the ground of these and other observations that we shall allude to presently, we maintain that there are at least two different species of diphtheroid bacilli that are capable of producing general paralysis and tabes dorsalis. The one is an organism which, morphologically and in its broth reactions, in so far as we have yet been able to ascertain them, resembles the Klebs-Löffler bacillus, but is distinguished from it in frequently being virulent to mice and rats, and in having a thread form, which is assumed when it invades the partially immunised animal, and under analogous conditions *in vitro*. It is the organism for which we have already suggested the name *Bacillus paralyticans*. The other species of diphtheroid bacillus is one which has a very similar relationship to the *Xerosis bacillus*, which by some observers has been found to produce a small amount of acid in glucose and saccharose broths. It differs from it, however, in showing prominent metachromatic granules, in producing acid quickly and abundantly in glucose and saccharose broths, and in frequently being virulent to mice and rats. This organism has little or no tendency to form threads. It is thinner and shorter than the other. We therefore propose to refer to the first organism as the *B. paralyticans longus*, and to the second as the *B. paralyticans brevis*. Just as it is known that individual strains of the Klebs-Löffler bacillus vary considerably in their microscopical and cultural characters and in their virulence, so also individual strains of these two species that have proved capable of causing paresis in rats present differences that

cannot be regarded as essential. Chief among these differences is that of virulence. Corresponding to infection by one or other of these two types of diphtheroid bacilli, there are, we maintain, two different types of general paralysis, closely resembling each other and yet essentially distinct. Cases of infection by both organisms are probably common. We believe that in all cases of advancing general paralysis and tabes dorsalis one or other of these bacilli, or some other organism endowed with similar pathogenic powers, is gaining access to the lymph-stream and to the blood. It seems to us very probable that we have not yet differentiated all of the species of diphtheroid bacilli that may occur in such cases and exercise a pathogenic action of a similar nature.

Intra-corporal Bacteriolytic Indices of Immunised Sheep and of Persons suffering from General Paralysis and Tabes Dorsalis.

In a previous paper we have described a method of estimating the bacteriolytic power of the polymorphonuclear leucocytes in relation to the *Bacillus paralyticans*, and have contended that, as a rule, the index expressive of this power is abnormally high in general paralytics. In the course of the immunisation of four sheep with bacillus No. 1 in the foregoing list, we have endeavoured to ascertain the effect of the process upon this index. The following table shows the results:

Sheep.	Before immunisation.	Time after commencement of process of immunisation.		
		Six weeks.	Six months.	Thirteen months.
No. 1	4.3	41	—	73
„ 2	0	48	—	78
„ 3	2.5	—	—	59.5
„ 4	6	—	85	—

These results seem to us to justify the conclusions we have already formed in regard to these indices in cases of general paralysis, although in the human subject the matter is complicated by the circumstance that more than one species of diphtheroid bacillus is capable of causing the disease. The following table shows the observations that we have made upon the human subject during the past year:

No.	Nature of case.	Bacillus used.	Index.
173	Control, healthy	<i>Bacillus paralyticans longus</i>	13
187	Dementia præcox	" " "	17.5
188	Control, healthy	" " "	8
189	" "	" " "	16
190	" "	" " "	28
196	" "	" " "	12.5
170	General paralysis	" " "	76
171	" "	" " "	75
172	" "	" " "	74
174	" "	" " "	92
175	" "	" " "	78.5
177	" "	" " "	83.5
186	" "	" " "	67
191	" "	" " "	61
192	" "	" " "	81
197	Tabes dorsalis	{ " " " <i>brevis</i>	7.5
		{ " " " <i>longus</i>	61
198	General paralysis	{ " " " <i>brevis</i>	44
		{ " " " <i>brevis</i>	42.5
199	" "	{ " " " <i>longus</i>	66
		{ " " " <i>brevis</i>	37
200	" "	{ " " " <i>longus</i>	17
		{ " " " <i>brevis</i>	71

Evidence of the Rapid Destruction of the Bacilli in the Blood.

Although we have succeeded in obtaining cultures of diphtheroid bacilli from the blood and from the cerebro-spinal fluid of general paralytics during life, there can be no doubt that in the vast majority of cases it is impossible by any method yet known to obtain such cultures. We have maintained that this difficulty is due, not necessarily to the absence of the bacilli from these fluids, but to the fact that the organisms are quickly taken up by phagocytic cells, and devitalised and dissolved. We have made some observations upon sheep in process of immunisation to the *Bacillus paralyticans longus*, the results of which are consistent with this explanation, as well as with the failures to obtain growths from the blood of general paralytics.

Two sheep, which had previously received seven injections of bacilli in the course of about five weeks, were each injected subcutaneously with 40 mgrm. of living bacilli, and two hours afterwards several large platinum loopfuls of blood were smeared upon agar surfaces. The tubes were allowed to remain in the cold for two hours, and were then incubated. No

diphtheroid bacilli appeared. In blood films made at the same time as the inoculations of the tubes, diphtheroid bacilli could be seen in considerable numbers, especially in the lymphocytes.

After the immunisation of these two sheep had been continued for over six months, inoculations were again made from the blood four hours after the subcutaneous injection of 80 mgrm. of bacilli into each. Two agar tubes and one broth tube were used. All of the tubes from the first sheep remained sterile. In the case of the second sheep a few colonies of the bacilli appeared in one of the agar tubes, and there was also a growth of the organism in the glucose broth.

Observations in a Case of Tabes.

We also wish to mention some special observations we have made in a case of early tabes dorsalis, as they support in a remarkable way some of the views that we have advanced. The patient's urine was found to be loaded with two microorganisms, a diphtheroid bacillus of the type described as the *Bacillus paralyticans brevis* and a diplococcus resembling the gonococcus, but Gram-fast. For a time we treated the patient by the vaccine method, injecting definite doses of killed cultures of the bacillus isolated from his urine. On several occasions these injections were succeeded, after a few hours, by a recurrence of the patient's lightning pains. It was quite clear that these attacks were consequent upon the injections. Very considerable improvement took place in the patient's condition when this treatment had been continued for some weeks. His attacks of pain became much less frequent and less intense. Having, with the same bacillus, immunised a sheep in such a way as to produce a bactericidal serum, we treated the patient for several weeks with this serum, given first hypodermically and subsequently by the mouth. This treatment has resulted in further improvement, but it has been found that if four or five days are allowed to elapse without a dose of the serum there is still some return of the pains. It is also of interest to note that in this case the urine is now sterile. The patient has been taking helmitol for about six months. In another case of tabes with the same two organisms in the bladder, the continuous administration of helmitol has been followed by the disappearance of the diplococcus, but the bacillus is as abundant as ever. It,

therefore, seems probable that the eradication of the bacillus from the bladder in the first case was due to the action of the serum.

The Infective Foci in General Paralysis and Tabes Dorsalis.

In previous papers we have maintained that in all advancing cases of general paralysis and tabes dorsalis there is some more or less extensive infective focus in which the pathogenic bacilli are invading the tissues. We have obtained histological evidence of the presence of such foci in the alimentary tract and bronchi of general paralytics, and in the bladder of tabetics. In the course of the past year we have made some observations upon the living subject which seem to us to confirm the doctrine of the infective focus and also to throw some fresh light upon the subject.

In association with the presence of abundant diphtheroid bacilli in the female genital tract, we have, in two cases, found scrapings from inflamed cervix to show numerous diphtheroid bacilli in the interstices of the tissues, proving that the bacilli were invading. Similarly, in two cases of chronic conjunctivitis in general paralytics, scrapings from the conjunctiva showed diphtheroid bacilli with prominent metachromatic granules invading the tissues. In another case of advancing general paralysis, a scraping from the nasal mucosa, taken from about the middle of the septum, showed abundant similar diphtheroid bacilli lying between the epithelial cells and among the connective tissues. Further, we find that general paralytics usually have more or less swollen and spongy gums, which readily bleed. This morbid condition occurs especially in proximity to the teeth. Between the tooth and such a swollen gum there is almost constantly a distinct pocket in which material collects, and this material, according to our observations, is loaded with diphtheroid bacilli showing prominent metachromatic granules. In fifteen cases of general paralysis presenting this swollen and spongy condition of the gums, we have made a microscopical examination of the spongy tissue after scraping some of it away with a sharp spoon. In thirteen of the cases diphtheroid bacilli have been recognised in the tissue-spaces.

We have previously advanced evidence in support of the

view that in *tabes dorsalis* the special infective focus is in most cases in the bladder-walls, and we have pointed out how this opinion harmonises with the results of the experimental work of Orr and Rows. The more recent observations that we have made in cases of *tabes* have served to confirm our view, which we maintain to be correct notwithstanding the criticisms that have been passed upon it. We would, however, extend the possible area of the infective focus to the whole of the genito-urinary tract and the lower portion of the alimentary canal. We now feel justified in drawing a similar inference with regard to general paralysis, and in stating that the infective focus in this disease is chiefly located in the buccal and naso-pharyngeal mucosæ. We assert that the clinical phenomena of *amimia*, affecting mainly the lower part of the face, *dysarthria* and facial tremors are essentially dependent upon this local invasion and consequent formation of toxins, which are in large part carried to the cranial cavity by way of the cranial nerves. This view is also in harmony with the more recent experimental observations of Orr and Rows (10), who have found that, just as tabetic lesions can be produced by toxins passing up the sheaths of the spinal nerves, so also certain of the central lesions that occur in general paralysis can be produced by toxins that are experimentally made to pass up the sheaths of the cranial nerves. On the ground of their observations they definitely apply the lymphogenous theory of infection to general paralysis as to *tabes*.

There are one or two points that we should like to emphasise in concluding this paper. The diphtheroid group is a very much more extensive one than has generally been supposed, and the bacillus of acute diphtheria is by no means the only member of the group that is pathogenic to man. Within the last two or three years the multiplicity of species in the diphtheroid group has come to be recognised by various workers, more especially by Gordon in this country, who has directed attention to the fact that many of these organisms that have commonly been regarded as non-virulent diphtheria bacilli give an acid reaction with saccharose broth, and by Hamilton and Horton (11) in America, who have isolated very numerous species. We would endorse the opinion of Benham that the further study of this group will probably lead to great advances in our knowledge of the pathology of some obscure

diseases. In this large group of organisms there are at least two species which are capable of causing paresis in rats, and which can be isolated especially from cases of general paralysis and tabes dorsalis. In patients suffering from these diseases, as well as in other persons, the mere presence of these organisms upon a mucous surface is of little significance. It is necessary to find evidence of invasion of the tissues by the bacilli. The occurrence of such invasion can be demonstrated in cases of general paralysis. There are good grounds for believing that a bacillus so invading tends gradually to become raised in virulence, especially towards the individual attacked. The rational therapeutic aim in cases of general paralysis and of tabes dorsalis ought to be to eradicate the infective focus. Our own researches during the past year have been mainly directed to this end, and we have used as our chief therapeutic agents bactericidal sera corresponding to the two varieties of diphtheroid bacilli we have found to be capable of producing paresis in rats. The work has been beset with very many difficulties, chief among which, we are now realizing, have been those occasioned by loss of virulence on the part of the organisms we have been using. Notwithstanding this, the results of serum treatment have in many instances been very encouraging. We hope to deal with this portion of our investigation at the Annual Meeting of this Association in July.

REFERENCES.

- (1) *Rev. of Neurol. and Psychiat.*, April, 1903; May, 1903; July, 1903; *Brit. Med. Journ.*, October 24th, 1903; *Rev. of Neurol. and Psychiat.*, May 1905; February, March, April, 1906.
- (2) Eyre and Flashman, *Brit. Med. Journ.*, October 28th, 1905; *Arch. of Neurol.*, vol. iii, 1907.
- (3) Mott, *Brit. Med. Journ.*, October 28th, 1905.
- (4) Ferrier (and Bulloch), *The Lumleian Lectures*, 1906.
- (5) O'Brien, see *Brit. Med. Journ.*, September 29th, 1906.
- (6) Langdon, *American Journal of Insanity*, October, 1906.
- (7) Benham, *Brit. Med. Journ.*, May 25th, 1906.
- (8) Knapp, *Journal of Medical Research*, vol. xii, 1904.
- (9) Graham-Smith, *Journal of Hygiene*, July, 1906.
- (10) Orr and Rows, *Brit. Med. Journ.*, April 27th, 1907.
- (11) Hamilton and Horton, *Journal of Infectious Diseases*, March, 1906.

DISCUSSION

At the Quarterly Meeting in London, May 16th, 1907.

The PRESIDENT (Dr. ROBERT JONES) said this was a very important paper, and that if Dr. Ford Robertson was able by his researches to modify in any way that most awful scourge, general paralysis, he deserved to be looked upon as a benefactor to mankind. The question seemed to be essentially one for the bacteriologist. He had hoped that Dr. Mott would have been present at the meeting, but he wrote saying he greatly regretted that he was unavoidably prevented. He (the President), in the name of the Association, invited the visitors to take part in the discussion. He himself helped Dr. Flashman, who was working at the Claybury Pathological Laboratory, to get cultures from the throats of subjects of various forms of insanity, and those were taken to Dr. Eyre for further investigation. Perhaps Dr. Eyre would describe the results of his investigations.

Dr. EYRE thanked the President for his kind invitation to him to hear the extremely interesting paper of Dr. Ford Robertson. In the first place, he wished it to be clearly understood that wherever his opinions differed from those of Dr. Ford Robertson—*i.e.*, where he did not see eye to eye with that gentleman—it was purely a difference of opinion, for in this matter his aim was the same as that of the author's, namely, to get at the ultimate truth, and that there was nothing beyond that in his remarks. He had hoped to have had rather more time to look over some of the records of the Bacteriological Department of Guy's Hospital, where he had the honour of carrying on the work, to find the number of clinical specimens in which one could detect micro-organisms which were morphologically comparable to those which Dr. Ford Robertson had introduced as being closely associated with the production of general paralysis of the insane. But he had only had time that day to run over the records of two or three months. But even in that time he had been able to pick out a lot of cases where organisms which, for purposes of statistics, he regarded as diphtheroids, had been isolated, and where he had considered they had not had any causal association with the condition under investigation, and he had merely made a few observations, so as to see that they were not the true diphtheria bacillus—the Klebs-Löffler—and had then discarded them, and gone on to the other organisms which were present in the material under examination. He found, for instance, that there was a case of tuberculous meningitis, where cerebro-spinal fluid was drawn off during life, and the only organism which could be obtained in the cultures from that material was an organism which, morphologically, was almost identical with the Klebs-Löffler, but it was non-virulent, and had certain other cultural peculiarities, which led him to call it, provisionally, the Xerosis bacillus. Some fluid from the pleura showed the same thing. Then there were two cultivations of the blood taken during life from cases of (?) infective endocarditis, and here, again, an organism was cultivated which was diphtheroid, but not true diphtheria. In tuberculous cystitis, again, there was found the Xerosis bacillus in company with the tubercle bacillus. In material from antral disease he had found the *Staphylococcus albus* and the bacillus Xerosis. He had not bothered about the film preparations of pus, etc., from chronic gleet, cases of gonorrhoea, and vaginal discharges, and so on, because, as was known to those who were accustomed to do much work on material supplied by general hospitals, the Xerosis bacillus, or at any rate a diphtheroid bacillus, was the commonest organism found in that material. What he had said was based upon 500 or 600 ordinary bacteriological examinations, carried out during a period of about three months. That would go to show that diphtheroid organisms were quite common contaminations of clinical material; that a diphtheroid organism was not the diphtheria bacillus, and very frequently it was undoubtedly one or other of the types of Xerosis bacillus. His own impression was that many of the organisms which Dr. Ford Robertson had been working with were types of the Xerosis bacillus. With regard to the cultural characters, Dr. Robertson had given some of the results of his cultivations in sugar media and carbohydrate media generally. Those reactions for the diphtheria group were worked out first by Knapp, in America, and he showed that with the organisms he was testing he could make out a fairly constant and definite difference between the three main types—*vis.*,

Klebs-Löffler bacillus, Hoffman's bacillus, and the Xerosis bacillus. One of the peculiarities of His's medium was not only that it showed the production of acid, but also that the medium became semi-gelatinous, almost clotted, because it was prepared with serum-water. Again, Gordon had been able to distinguish those three or four types by sugar reactions. It seemed to the speaker that when one commenced to include very large numbers of types, and strains of each of those types in one's sugar tests, one found that the reactions were not absolutely constant, but one found the Klebs-Löffler bacillus fermenting, not only glucose, but many of the other sugars. Fermentation in dextrin or starch was fairly characteristic of the diphtheria bacillus; and if one took a large number of strains it would be found that the Xerosis bacillus did not usually ferment glucose, though many of the strains would ferment glucose; and so on with all those organisms. In fact, the same thing happened with the diphtheria group of bacilli when tested with sugar reactions as happened with streptococci. Streptococci and staphylococci were said to be capable of differentiation according to their sugar reactions, but when they had been tested at varying intervals, after isolation, it was found that their sugar reactions were not absolutely constant, but one group would run imperceptibly into another. Another point upon which Dr. Ford Robertson laid considerable stress was the reaction to Neisser's stain. Neisser's staining method was not a constant attribute restricted to the bacillus of diphtheria, to start with. Taking large numbers of diphtheria bacilli examined when first isolated from the body, it would be found that 70 per cent. or 80 per cent. gave a very definite and characteristic "Neisser" stain, but the remaining 20 per cent. or 30 per cent. did not give that reaction. The Hoffman bacillus differed very markedly, in morphological character, from the Klebs-Löffler bacillus, so that it scarcely entered into consideration. But, as a matter of fact, about 40 per cent. of the strains of Hoffman's bacillus, when first isolated from the human body, would give a very typical Neisser reaction, in which metachromatic granules would be apparent. But they often varied rather from those presented by the diphtheria bacillus in their arrangement and size. Of the various types of Xerosis bacillus, 70 per cent. gave a permanent Neisser reaction, with metachromatic granules which were indistinguishable from those presented by the bacillus of diphtheria. Therefore it seemed to him that the "Neisser" differentiation of those diphtheroid organisms which were responsible for the production of general paralysis of the insane was hardly sufficient to justify the statement that those were not Xerosis bacilli on the one hand, or were not, occasionally, diphtheria bacilli on the other. Then, again, there seemed to be something lacking about the experimental work. For instance, the animals fed on those micro-organisms for such a long period did not show any marked symptoms for a long time, and then, when they had been kept in captivity twenty or forty weeks, and when death occurred, the fact that the organisms were found in them did not necessarily support the suggestion that death was due to the organisms. A good deal might happen to animals kept in confinement so long.

Dr. FORD ROBERTSON: But the controls were not affected, though they were in the same room.

Dr. EYRE said he failed to catch what Dr. Ford Robertson's objection was, but probably the meeting would be told more by that gentleman. The only other point he wished to mention was, that the estimation of the bacteriolytic index of the sheep before and after immunisation depending on alterations in the bacilli was surely open to a very big difference of interpretation, just in the same way as the identification of altered bacilli in the leucocytes of the patient was also open to a grave fallacy. He would be very glad to hear the exact method of estimating those alterations, and of the steps taken to render it absolutely certain that what were suggested to be "altered bacilli" in the leucocytes of the patient were really the remains of diphtheroid bacilli.

Dr. DAVID FERRIER said he had listened with great interest, as he was sure everyone in the room had done, to this most important communication of Dr. Ford Robertson. He feared that on most of the subjects brought forward in the paper he (Dr. Ferrier) was not competent to express an opinion, because he was not a bacteriologist. But as he had ventured to comment on Dr. Ford Robertson's views in a spirit of scepticism, he would like, on the present occasion, to define his attitude exactly in regard to them. He had expressed the view, in harmony with Dr. Mott and others, that tabes and general paralysis of the insane were the

same disease, and that in all cases not only was the prime origin, syphilitic infection, hereditary or acquired, but the degeneration itself was not syphilitic, in so far as it did not yield appreciably to anti-syphilitic remedies. He believed the evidence was in favour of there being a toxin circulating in the blood, which toxin must be generated continuously in order to cause the progressive deterioration and degeneration in the spinal cord and cerebral cortex. The question was, What was that toxin? where was it produced? And the further question which now arose in relation to Dr. Ford Robertson's paper was, Had he discovered that toxin and its origin? That was a question which was essentially bacteriological, and he could not pretend to express an opinion upon it. The objections which he had urged against the author's views, at least as they were propounded in the Morisonian Lectures, were founded upon the investigations of other bacteriologists. And one of the chief was that the *Bacillus paralyticans* of Dr. Ford Robertson was not sufficiently distinctive from other bacillary and diphtheroid organisms, which were found, both in health and disease, in almost every tissue. And Dr. Eyre, in his remarks that day, had indicated the same thing, that those micro-organisms were always with us. He did not find, in his previous investigations, that the diphtheroid organisms described by Dr. Ford Robertson were more common in general paralytics than among other forms of insanity, or even than among ordinary people. Certainly he, Dr. Ferrier, had never found the slightest trace of any organism in the cerebro-spinal fluid of patients suffering from tabes or general paralysis. In conclusion he wished to add that he would be greatly pleased if Dr. Ford Robertson's views should be proved to be correct, and thus place him in the happy position of having made one of the most important discoveries in medicine.

Dr. GEORGE DEAN desired to thank the Society for the honour conveyed by the invitation to be present. He thought the position with regard to the question under discussion was one of caution, both in regard to criticism and in reference to the acceptance of Dr. Ford Robertson's views. In the first place, one must realise the extraordinarily wide distribution of diphtheroid bacilli in Nature, and therefore the frequency with which they occurred—he might say the enormous frequency. For example, they were frequently met, as Dr. Eyre had already indicated, in accidental association with a pathogenic organism definitely known to cause the particular morbid condition in which the associated organisms were found. In addition, diphtheroids had been found in many normal conditions. For example, they were frequently found in connection with smegma, in both female and male, in the normal condition. They were frequently found in milk; and in the udders of a number of normal cows which he examined he found diphtheroids present. That might have some relation to the frequency with which Dr. Robertson found those diphtheroids in the stomach. At any rate, diphtheroids in milk was a common find. The same organisms were also found frequently in urine examined under ordinary conditions without any relation to the particular question under discussion. Therefore, as they were found in smegma and other sebaceous secretions, in urine, in milk, and as associated organisms in other pathological conditions, great caution ought to be observed in accepting any diphtheroid as having a causal relation with general paralysis unless it had very well-marked characteristics, including pathogenic action on experimental animals. In regard to the sugar fermentations which had been mentioned, it must be remembered that only a very small number of the diphtheroids which had been isolated had been submitted to those tests. So that until a much wider application of those tests had been entered into he thought no great weight should be placed on them. In regard to the results obtained by Dr. Robertson in the sheep, no matter whether the bacillus had any relation to tabes or not, the serum of the sheep would probably yield the results which the author had described. Taking almost any bacillus, one would expect to find an increase in the action of the serum after injection. So that in regard to the main issue as to whether the bacillus in question was the cause of the disease, that observation could not weigh very heavily. In reading Dr. Robertson's former paper, a point which struck him (Dr. Dean) very strongly was the absence of mention in detail of controls in setting forth the cultural results obtained from other forms of disease. He had read Dr. Robertson's papers with great interest, and he thought they deserved great consideration on the ground that they gave evidence of much perseverance

and close study of the whole question; and, as several speakers had already said, it would be an epoch-making discovery if it turned out to be true. He thought it possible that Dr. Ford Robertson had made the controls, but there was an absence of statement in regard to them. Recently he and others had been examining brains and cerebro-spinal fluid. Dr. Arkwright, working in the Lister Institute, had examined the brains and the cerebro-spinal fluid of cases whose death was suspected to be due to cerebro-spinal meningitis. Out of seven cases in which the brain and meninges were examined *post mortem* he twice found diphtheroids, and out of twenty-three cases in which he examined cerebro-spinal fluid he found diphtheroids on two occasions, and sometimes they were associated with other organisms, such as the meningococcus. That had been done in only the few months during which the matter had been worked at in the Lister Institute. So he thought if a large number of controls had been taken diphtheroids would have been found in many of them, and that naturally complicated the question very greatly.

Dr. C. E. BEEVOR said it seemed to him that if the bacillus was the cause of the disease it ought always to be found in cases of general paralysis of the insane, and also in all cases of tabes. Yet they had heard from Dr. Ferrier that in the observations he had made it was not found. And if Dr. Robertson's view was correct the bacillus ought not to be found in healthy people, or in cases of other diseases. Yet it was found in such circumstances. Moreover, if injected into animals it ought to produce the disease in them. But, as far as he could gather, the symptoms which had been caused by such injections were not those of general paralysis of the insane; neither, he believed, were the pathological changes resulting the same as those in that disease. He did not notice in the paper any reference to observations on the pupil. Fixation of the pupil was a symptom which was common to both general paralysis and locomotor ataxy; indeed it was the most important symptom there was in the earlier stages of general paralysis. On the other hand, he did not gather that there were changes in the posterior columns of the cord. The anterior horns appeared to have been affected in some of the animals injected, but that was not an evidence of either locomotor ataxy or general paralysis of the insane. Of course, everyone would be very delighted if what Dr. Robertson had set forth should prove to be one of the means of combating such a terrible scourge, but at present he did not think they could say they were on the high road towards that desirable end.

Dr. CANDLER asked that he might be allowed to make one or two remarks in connection with Dr. Ford Robertson's interesting paper, because he thought some mention of the work which had been going on at Claybury, in pursuance of Dr. Eyre and Flashman's work, might be of interest. Through the kindness of Dr. Jones, the President, he had been enabled to undertake an investigation with regard to the incidence of diphtheroid organisms in general paralysis, and in other forms of insanity, from cases in the wards of Claybury Asylum. The number of cases which he had examined in that way up to the present was not sufficient to be judged statistically. First of all, he took *post-mortem* material, and examined the blood, cerebro-spinal fluid, the intestinal tract, and the urinary tract of these cases. The number of *post-mortem* cases he had examined was 79, and of those 20 were general paralytics. In 3 of those 20, or 15 *per cent.*, he was able to obtain diphtheroid organisms. In one case he isolated it in pure culture from the blood; it was isolated from the respiratory tract, where it was present in association with other organisms, and he could see it in the cerebro-spinal fluid, but he failed to isolate it on culture. Another case was from the stomach of a general paralytic, in which there were some erosions and catarrh. A third case came from the respiratory tract. Of the 59 cases occurring in insanities of other kinds than general paralysis he was able to isolate the diphtheroid organism in 4; in 3 the organism came from the respiratory tract, and in the fourth from the urethra. He then turned his attention to the examination of the urine of patients in the wards of the asylum, and he was assisted in drawing off the urine by Dr. Barham. It was done by inserting a sterile catheter, so as to, as far as possible, obtain the urine in a proper condition for examination. The centrifugal deposit was first subjected to microscopical examination, and then the material was grown. Out of 26 cases of general paralysis he obtained a diphtheroid bacillus in 2, an average of about 8 *per cent.* With regard to the urethras, he

scraped the mucous membrane of the urethral canal by means of a platinum loop, after sterilising the tip of the meatus. In general paralysis he examined about 30 cases in that way, and found a diphtheroid organism in 5, or about 16 *per cent.* In the urine of cases not associated with general paralysis he obtained the organism only once out of 28 cases, and in the urethras of such cases 6 times in 44 cases, or 13·6 *per cent.* The points he wished to bring before the meeting were: that he had not been able to isolate the diphtheroid organism in any large proportion of the cases which he had examined for it, and that, therefore, the researches he had made were more in conformity with Dr. Eyre and Flashman's work, which was undertaken one or two years previously. In regard to the urinary tract he found there was an organism resembling what he believed to be of the Xerosis type, and that it was fairly prevalent. Recently, he believed, some reports had been published in foreign journals on the subject of the investigation of urethras in patients who were not the subjects of insanity, and that the percentage in which an organism of a diphtheroid type was found was commented upon as being fairly high. With regard to the circulating blood, he, like Dr. Robertson, had failed to obtain a diphtheroid organism, or at least in only one case did he find an organism which he suspected to be diphtheroid. But, though due care was taken to ensure sterilisation, both of arm and instruments, before venous puncture was carried out, he had obtained in one or two instances what he believed to be organisms of the pathogenic group. And although he could not make confirmatory statements on the subject, he suggested that it might be possible, during the final stages of general paralysis, for organisms of different varieties to obtain entrance into the blood-stream, and help in bringing about the end of the case. He desired to ask Dr. Ford Robertson one question about his investigations, namely, whether, during his examinations of blood from living patients, he had ever obtained other organisms as well as diphtheroid ones; or had he obtained nothing but diphtheroids in pure culture? He understood that Dr. Ford Robertson also examined the buccal mucous membrane by making scrapings of it and examining the stained specimens. Had he obtained pure cultures of the diphtheroid organism from that region? He asked those questions because the microscopic evidence in regard to particular organisms was often very deceptive, and could only be confirmed by isolation of them in pure culture.

Dr. GEORGE ROBERTSON said that it might be remarked about most of the speakers on the subject that day that their evidence had been more or less of a negative kind, and it had been, if anything, rather against the theory which had been put forward by Dr. Ford Robertson than otherwise. Three or four years ago Dr. Ford Robertson put forward a theory that general paralysis was almost constantly associated with the presence of a diphtheroid organism, and recently he had called it the *Bacillus paralyticans*, expressing his belief that it was the cause of general paralysis of the insane. He (Dr. George Robertson) was very pleased to be able to say he could confirm, right up to the hilt, Dr. Ford Robertson's original theory that general paralysis was associated with a diphtheroid organism. He and others had been, during the last six months, making an important series of observations in the laboratory of Stirling District Asylum, which confirmed Dr. Ford Robertson's original thesis. But when he said that, he did not wish anyone to go off with the idea that he believed that organism to be the cause of general paralysis of the insane. In the observations at his asylum, out of thirteen cases of general paralysis examined the organism had been found in eight. Their observations had been, in some respects, carried out under more severe conditions than those of Dr. Ford Robertson appeared to have been. Dr. Ford Robertson had himself very generously stated that the Stirling Asylum observations were in some respects ahead of his own. In the first place, Dr. Ford Robertson had made a collection of diphtheroids from various regions of the body—from the nose, pharynx, throat, bronchi, stomach, intestines, from pneumonic patches, from the bladder, the urine, and in one case they were discovered in a carious tooth. He did not know that the fact of diphtheroid organisms being obtained from all those places was any evidence in support of the idea that they had anything to do with general paralysis, because a diphtheroid organism, as other speakers had pointed out, was fairly common in the throats of people who were in perfect health at the time. They, at Stirling, had restricted their observations almost entirely to the blood and the cerebro-spinal fluid. The mere presence of an organism in the

blood meant a very serious condition, as its presence was bound to have some effects. Dr. Ferrier and Dr. Beevor had said, if the organism was the cause of the disease, it should be found in the blood or cerebro-spinal fluid, but they had not found it. Dr. Ford Robertson had obtained it in the blood in four cases, and in the cerebro-spinal fluid in two cases, according to the reports. The other respect in which he believed the Stirling work had been done under more severe conditions than Dr. Ford Robertson's was, that the organisms they obtained had been subjected to very exhaustive cultural tests and study. Instead of having a list of three or four, or even six, cultural media in which the behaviour of the organism had been studied, it had at Stirling been studied in more than a score of different media. And, under those conditions, the same organism had been obtained in seven out of thirteen cases. He was excluding one case in which the blood was taken, because in that case all the flasks were contaminated, and therefore it was impossible to say for certain whether the organism was there or not. In his paper Dr. Ford Robertson said that, owing to various reasons, it was almost impossible, by any means yet known, to obtain cultures from the blood. But at Stirling, out of the thirteen cases of general paralysis, cultures had been obtained from the blood in seven, and from the cerebro-spinal fluid in four. There was one case in which the result was negative, and that was in a patient who had a remission of the symptoms of general paralysis. The physical symptoms did not pass off, but the patient became quiet and sensible, and was able to earn his living outside the asylum, from which he was accordingly discharged. Only one examination of his blood was made, and it was found to be sterile. He would rapidly run over the nine cases he had mentioned, and state what reactions he obtained. The blood was first examined by means of smears, and in four cases the organisms were visible in such smears when stained by the Jenner stain. He had brought for exhibition photographs of organisms obtained in those cases. In the first photograph there were two groups of organisms, one containing seven and the other four bacilli. In seven of the cases a culture was made of the organism from the blood, which culture they sub-cultured and preserved, and recovered completely. They still had the different stains in their possession. In four cases the organism was obtained from the cerebro-spinal fluid, and some of them were duplicate cases. At *post-mortem* examination the organism was obtained from the heart-blood in one case, and in three cases from the cerebro-spinal fluid. In one case they saw the organism in the blood from the smears, from the cerebro-spinal fluid and blood during life, from the heart-blood after death, and from the cerebro-spinal fluid after death, and made cultures from it under every one of those circumstances. He had been interested in what Dr. Ford Robertson said about the types of organisms, because in one particular case they were more thread-like than in the others. They had gone through all the culture media in regard to these organisms, and all the organisms they found responded in exactly the same manner to the whole list of culture media—over a score of them—with the exception of the reactions in litmus milk. The majority of the organisms gave an acid reaction to milk, but some gave an alkaline reaction to it. He believed ordinary diphtheria bacilli sometimes gave different reactions to milk litmus, so that that reaction was not regarded as very important in that group. In one of the cases the organism was obtained during life from the blood and from the cerebro-spinal fluid, and it gave an alkaline reaction to the milk litmus. After death the organisms were obtained from the cerebro-spinal fluid, and it then gave an acid reaction to milk. Therefore no stress could be laid on that reaction, and it was the only reaction in which the organisms had not been alike. Thus they had established a condition which would satisfy the most strict bacteriologist that they had got hold of an organism which had been identical through all the cases. Doubtless his hearers would like to know the way in which the organism was obtained. On the staff of the asylum he had a lady who was a trained bacteriologist; she had worked for two and a half years with Dr. Parkes in the Transvaal in the Public Health Laboratory there. Dr. Parkes and his work were known to many present, and the association of the lady with him was a guarantee of thorough training. All the operations had been performed under the very strictest surgical precautions. Some of the members on various occasions had laughed at him when advocating the employment of trained hospital nurses for men, but at Stirling they had been found to be of very great

benefit, because those nurses had been instructed to prepare the patients exactly as for a surgical operation, and the assistant medical officer had to perform the operation as if it were a surgical one, with gloves on his hands and everything sterilised. A special syringe had been used for the purpose. It was a glass syringe, with a needle at the point of it (exhibited). It was put into a glass tube, cotton wool put into each end, and the whole thing sterilised by being put into a hot-air chamber at a temperature of 175° C. On the patient's arm, after sterilisation, a tourniquet was put on, causing the basilic vein to stand out, the cotton wool was taken off one end of the tube, one end of a rubber tube was slipped over the end of the syringe and the other end was put into the mouth, the syringe was plunged into the vein and the blood sucked into the tube. That was an absolutely sterile procedure. The blood was poured into flasks of broth and they were incubated. It was a very troublesome process to get the organisms to grow, but they had succeeded in all those cases. He hoped he had done Dr. Ford Robertson full justice when he said they had at Stirling confirmed his original statement that general paralysis was associated almost invariably with a diphtheroid organism. But he wished to make a further remark before closing in order to do justice to Dr. Muirhead, their bacteriologist. When they started those observations they wrote to Dr. Ford Robertson to obtain from him a culture of the *Bacillus paralyticans*. Dr. Ford Robertson sent a culture which he said was, in his opinion, the *B. paralyticans*. A very careful study of the organism was made at Stirling, with all its cultural reactions, and the organism which Dr. Robertson sent them was totally different from that which they had themselves discovered, *i.e.*, in many respects. In the first place, Dr. Ford Robertson's organism was a very luxuriant grower in all fluid media. And there was also a pellicle produced on many fluid media in which it grew. But the organism they obtained in their cases of general paralysis he had mentioned was not one of luxuriant growth. It grew differently on gelatine, it grew differently on saccharose broth. The Stirling organism produced an acid reaction. Though he said all that, he did not wish his hearers to suppose that the organism which Dr. Ford Robertson discovered might not also be associated with general paralysis; it was possible it might be. At Stirling they had not yet obtained in any case Dr. Ford Robertson's organism, but possibly they might come across it later. It was possible that they might yet find that a large group of diphtheroids produced toxins which reacted on the nervous system and which, if it could not yet be proved caused general paralysis, probably played an important part in the symptomatology of the disease.

Dr. ORR said that he felt reluctant to take part in the discussion, as the whole question seemed to centre round the bacteriological point of view; and unless one was an absolute expert in bacteriology one could not take up either a positive or a negative position. Still, he would like to offer a few remarks on the extreme possibility that tabes and general paralysis of the insane were both the result either of a toxin or of a bacillary infection of the central nervous system. As to how that came about there were not very definite data available, or as to the focus at which those bacilli were situated. But there were absolute data as to there being an anatomical path leading up the peripheral nerves, both spinal and cranial, towards the central nervous system. It was well known that toxins readily ascended in the perineural sheaths, and recently Dr. Rows and he had had the opportunity of examining one case in which a rod-shaped bacillus, often assuming a thread-like form, such as Dr. Ford Robertson pointed out, but as to whose identity he (Dr. Orr) was not yet certain, had been traced all along the perineural lymph sheaths into the cord, by the anterior and posterior roots, into the central canal, and along the numerous septa leading into the white matter. Thus there was definite evidence of the fact. And Dr. Rows and he were of opinion that the infection in general paralysis did not come about through the blood-stream, but certainly along the lymph paths. Three gentlemen at that discussion had mentioned the occurrence of diphtheroid organisms in the blood-stream. His own view was that it was not necessary for the blood-stream to be infected in order to cause tabes or general paralysis; either could come about by infection of the lymph paths. He thought it probable that any invasion of the blood-stream by the organism came late in the disease, or might be due to some accident.

Dr. WASHINGTON WILLIAMS said it appeared to him that before one could

accept as authoritative the controversion of the statements of Dr. Ford Robertson, it must be known that the organisms mentioned by those who criticised his observations were the same as the author spoke of, namely, those which consistently gave certain reactions and did not give others. That had not yet been stated, and until it had been, he, as a neurologist, would accept with great diffidence the criticisms directed against Dr. Ford Robertson's work.

Dr. CHARLES MERCIER said he had the same qualifications, when intervening in the debate, which certain of the other speakers had, in that he was no bacteriologist. But if medical men applied to the question the ordinary canons of evidence and of causation, he thought that they would be obliged, at present, to return a verdict of "not proven." If they were to accept the doctrine that there was a certain bacterium which was the cause of general paralysis, then certain conditions must be satisfied. The organism must be identifiable. At present it was not identifiable with certainty. In the second place, it must be found in every case of general paralysis; but he gathered that it was not yet found in every case of that disease. In the third place, it must not be found in any case which was not one of general paralysis, and he gathered that it was found in cases which were not general paralysis. Those were the ordinary canons of evidence and causation, and those canons, he thought, must be satisfied before one could admit the existence of a definite *Bacillus paralyticans*. It must be remembered that general paralysis was one of the most distinct of all diseases, and so also was tabes. It was very rarely that a difficulty arose in connection with a case of general paralysis or tabes, except in the very early stages. And one would expect it to have a cause which was equally distinct. One would expect the cause to be such that it was recognisable in every case. It had also to be remembered that general paralysis was a disease which led to a very slow death—the patient died slowly, and as he was dying his tissues were all in a state of what might be metaphysically called very low vitality for weeks, months, and even years. And tissues in that state were, he supposed, a most favourable nidus for all kinds of different micro-organisms, and it would be very strange if, when a patient was in the later stages of general paralysis, many micro-organisms of many kinds were not found in the various tissues and fluids. That was how the matter struck him, as an outsider, judging it by the ordinary canons of evidence, without any special knowledge of the subject.

Dr. McRAE said he thought it would be better if Dr. Ford Robertson would reply on the discussion, and he (Dr. McRae) would make a few general remarks. With regard to the point which had been made as to the presence of the bacillus, the authors had said from the beginning that the mere presence of the organism was no proof that the bacillus was or was not the cause of the disease. Several of the bacteriological experts who criticised the paper laid great stress upon finding the bacillus everywhere. As a matter of fact, it was well known that the skin and genitalia were commonly infested with diphtheroid bacilli. If one could show by various methods a specific reaction in animals and human beings to that bacillus, or, as they had done, to anti-sera produced in animals by that organism—and he had been working for ten months with sera, and had clinical records which were being held over until the July meeting—surely they were getting very near to establishing at least a very strong suspicion that they were dealing with the cause of a certain specific disease. For fifty years the profession had been subjected to the tyranny of the belief that in general paralysis all the bacterial infections were secondary to the degenerative process. But he wished to point out that the authors were not dealing with terminal infections, but with cases which were going about and able to work, and blood-films taken from such patients showed those micro-organisms. With regard to this so-called secondary invasion of organisms, or, as it had been called, terminal invasion, why should a specific disease like general paralysis allow itself to be subjected to a particular terminal form of invasion? Any form would be sufficient to cause the death of the patient if he was already suffering from a degenerating disease. It was customary to believe that general paralysis was a primary degeneration of the brain, but how did a degenerating disease have remissions? How was it that a man went into the asylum with the disease, in some instances practically moribund, but subsequently improved so that he could wheel barrows about? The toxic theory seemed the most reasonable; it enabled one to understand how the patient might form immune

bodies which enabled him to get better for a time. With regard to the bacteriological point, the authors were cognisant of the fact that there were many varieties, and Hamilton and Horton, of America, had found thirty-three varieties of the bacillus, eighteen of which had been proved to be virulent. The two species of bacillus dealt with had specific broth reactions, and when these tests were tried again after many months they gave the same reactions. These reactions were distinct from those hitherto described in the case of any other diphtheroid bacillus.

Dr. G. H. SAVAGE, in response to the President, said he came entirely to learn. He had seen a great number of specimens by Dr. Ford Robertson when he was in Edinburgh, and he left him with a very open mind. He (Dr. Savage) felt very strongly that general paralysis had a toxic origin, and that the particular toxin would be found sooner or later. Such good work as Dr. Ford Robertson was doing was to be encouraged in every way, and it was recognised by the Society and by other medical societies in London. He felt very grateful to Dr. Ford Robertson. He was a botanist himself, and the more knowledge he acquired of the lower organisms the more impressed was he by the enormous differentiations between the varieties. He thanked Dr. Ford Robertson, in the name of the older men, who were too old to work along the lines which he was following out. They were grateful for what they had heard, and would be glad of more.

Dr. URQUHART said that, as one of the supporters of the Scottish Asylums Laboratory, he felt very much indebted to Dr. Savage for the way he had spoken of the work done at that laboratory. He (Dr. Urquhart) did not wish to intervene between the meeting and Dr. Ford Robertson, because he fully expected that gentleman to say something about the possibility of mixed toxins, and especially about the numerous control experiments which had been made during the past six years.

The PRESIDENT (Dr. ROBERT JONES) said he would be glad to associate himself from the chair with the remarks from both Dr. Savage and Dr. Urquhart. Dr. Ford Robertson had come down to have his opinions challenged, and they had been challenged from a special expert point of view. He confessed to having a marked sympathetic appreciation of Dr. Robertson's work, and was ready to try the treatment suggested by the investigations on some cases of general paralysis, and he did hope to do so. He believed that Dr. Mott was arranging with the Lister Institute to have some special serum prepared of that organism, or mixed organisms, and he (Dr. Jones) hoped to be able to try that at Claybury. Dr. McRae referred to one point which he (the President) regarded as very important, namely, remissions in general paralysis; and one was apt to draw conclusions as to the result of treatment from the fact that spontaneous and ordinary remissions did occur in some cases of general paralysis. He had two cases in his memory. On one, at Claybury, succinate of mercury was tried, and that patient went out very much improved. Another had a thorium hydroxide cap, which he wore for a time and got very much better, yet he was, so far as his (Dr. Jones') diagnosis went, a typical case of general paralysis. He heard of him for nearly two years afterwards, and he was quite well. One was apt to draw conclusions from such cases that *post hoc* was *propter hoc*. The general opinion seemed to be, as summarised by Dr. Mercier, that the association of the special bacillus as the proximate cause of general paralysis was not proven; but Dr. Ford Robertson's paper and his work had had the effect of causing interest and work in others, and thus was a marked mental stimulus in the profession.

Dr. FORD ROBERTSON, in replying on the discussion, said there were several points which he would like to meet. It seemed to him that all the examples that Dr. Eyre had given of diphtheroid bacilli being found in meningitis, infective endocarditis, etc., were strong presumptive evidence in favour of Dr. Benham's view that the further study of the diphtheroid group would probably lead to important advances in our knowledge of some obscure diseases; but he did not see any other bearing which those observations had upon this particular research. Dr. Eyre seemed to think that many of the types described in the paper were simply the Xerosis bacillus; he regarded as this bacillus many organisms which could be shown to produce a strong acid reaction in glucose and saccharose broths. He (Dr. Robertson) would point out that in making such a contention Dr. Eyre was differing from other bacteriologists. Dr. Eyre and Dr. Flashman in their paper tried to classify the diphtheroid bacilli found into three species, but the investiga-

tions of others were proving that there were really very numerous separate species. Dr. Eyre said Dr. Gordon had followed Dr. Knapp in using the litmus broth tests, but he (Dr. Robertson) believed that Dr. Gordon preceded Dr. Knapp by a considerable time. Dr. Eyre said the reactions were not constant. That might be his experience, but as far as he (Dr. Robertson) could see from Dr. Eyre's paper, he had not studied those broth reactions to a very great extent. He knew that in the experience of others those broth reactions were remarkable in their constancy. Dr. McRae and the speaker had tested various strains again and again, at intervals of many months, and it was remarkable how the results had come out exactly the same. Whatever changes in virulence these organisms might undergo with the lapse of time, they underwent none in their broth reactions. It was simply a matter of Dr. Eyre's criteria of differentiating diphtheroid bacilli being different from those of other people. Dr. McRae and he did not attach very much importance to the presence or absence of metachromatic granules; that was largely a matter of the media on which the organisms were grown. Dr. Eyre had said that their method of estimating the intra-corporal bacteriolytic index was open to grave fallacy. He (Dr. Robertson) supposed there was a margin of error in all such methods, as there certainly was, for example, in that of estimating the opsonic index. But Dr. Eyre had not worked with their method, and was therefore not in a position to say that it was fallacious. He also said he would like to read the account of the method, but it had been published in detail. It would conduce more to good feeling in these discussions if Dr. Eyre read their papers before criticising them. He desired to make a protest against the action of Dr. Eyre and Dr. Flashman in re-publishing quite recently a paper which first appeared in the *British Medical Journal* in November, 1905. He protested at the time in a letter to the Editor of the *British Medical Journal* that it was a gross misrepresentation of the views of himself and his colleagues, and notwithstanding that protest, the paper had been re-published in the *Archives of Neurology* of 1907. Such a procedure led to the dissemination of grossly erroneous views of their work. As he said in his letter, the grounds upon which the contentions of his colleagues and himself rested were ignored, and the only reference made to the evidence adduced was an erroneous one. Dr. Ferrier had expressed his adherence to the view that syphilis was the cause of general paralysis and tabes. He (Dr. Robertson) would be glad to endorse that view if Dr. Ferrier could produce any experimental evidence in support of the thesis. So far nobody had produced any. He had listened to Dr. George Dean's remarks with very great interest. Dr. Beevor asked about the fixation of the pupil in the experiments on rats. It was very difficult to examine the pupils of rats. If they had brought the rats with them and shown them to the meeting, he did not think anyone would have any doubt about their being general paralytic rats; the condition of the animals simulated that of general paralytics about as closely as was possible. The histological changes were such that both Dr. McRae and he were convinced that the lesions were those of early general paralysis. The rats died too soon for the complete picture of the disease to be developed. Accompanying periarteritis there were in some of the animals plasma-cells, just as in the general paralytic. Dr. Candler's observations were of very great interest; they were careful and painstaking observations, and he looked forward with interest to their publication. With regard to finding the bacilli in other patients besides those suffering from general paralysis, it must be remembered not only that diphtheroid organisms were very common on mucous surfaces, but that those other patients were contacts. He had read the paper by Stanziale, who found diphtheroid bacilli in the urinary tract in control cases and in patients in his skin clinique at Naples; but that observation did not disprove any of their contentions. They had themselves pointed out that diphtheroid bacilli could be isolated from this tract in some control cases. Such organisms might be devoid of virulence, and even if virulent they were not necessarily invading the patient. They did not attach importance to the mere presence of the organism. The remarks of Dr. Orr were very gratifying, because he and Dr. Rows had been in this country the pioneers in the experimental investigation of these lymphogenous bacterial invasions, and the work of Dr. McRae and himself was tending more and more to prove that in general paralysis there was such lymphogenous invasion. There was no man whom he (Dr. Robertson) had greater respect for than Dr. Mercier, and he was sorry to come into conflict with him.

Dr. Mercier said the organism must be identifiable, and their reply was, that it was so. They had obtained two varieties, which had special broth reactions and which produced paresis in rats, and until someone showed there were fallacies in them these observations must stand. He thought Dr. Mercier was in error in saying that the bacillus must be found in every case. Sometimes the organism was difficult to find; but if it were missed in one place it might be present in another. It was too much to ask that it must be found in every case. Dr. Mercier also said the organism must not be found in any case which was not one of general paralysis, but on that ground one would have to deny the specificity of the true diphtheria bacillus, because it was found in many healthy people. Importance was not attached to mere presence, but to invasion. He was much gratified by the remarks of Dr. Savage and Dr. Urquhart, and thanked the President for his sympathetic appreciation of their work. Many points in regard to their work were not included in the paper, but he thought that if some of those who had spoken had seen their charts showing the specific reactions with anti-sera, they would have hesitated to make some of their criticisms. He was very glad the discussion had taken place; it had been very gratifying to both Dr. McRae and himself.

Clinical Notes and Cases.

Study of a Case of Melancholic Folie Raisonnable. By
Dr. M. J. NOLAN, Resident Medical Superintendent,
Down District Asylum, Downpatrick.

THE following case is of such a rare character, yet it is so perfectly true to type, and it presents such striking points of psychological interest, that its consideration is deemed noteworthy.

Briefly, the facts of the case are these: M. McI—, æt. 50, spinster, farmer, in easy circumstances, consulted me on several occasions as a private patient, and was eventually admitted to the Down District Asylum as a "paying patient" on August 17th, 1906. She is the ninth child of a family of eleven, two only surviving; her mother and eight brothers and sisters died of consumption; one brother exhibited unusual ability; became "too learned" and died of "exalted mania" (G. P.?).

When patient was eighteen years of age her father died very suddenly of heart disease. She had left him in the morning apparently in good health, and on returning home some hours later she found him "laid out for the wake" in his grave-clothes. The shock of this sad event "upset my nerves; I was never the same." She ceased to menstruate, and suffered from leucorrhœa, and later from retroflexion of the uterus. "Queer sensa-