of the reception wards had, as a rule, seven or eight occupied beds, and one nurse in charge was usually sufficient, though other nurses were available if required. It was not intended that the sanatorium treatment was the panacea for all insane persons in all their various morbid phases. But if, for example, a paranoiac was admitted with morbid excitement, he was treated with open-air rest until the excitement subsided, and then allowed to be out of bed. In deciding when the bed stage should cease, one had to consider both the mental and the bodily condition, and specially the more obvious and the finer nervous symptoms of fatigue.

Observations on the Treatment of General Paralysis and Tabes Dorsalis by Vaccines and Anti-sera. By W. FORD ROBERTSON, M.D., and DOUGLAS MCRAE, M.B., C.M., M.R.C.P.Edin.

THE investigations that have led us to employ specific vaccines and anti-sera in the treatment of general paralysis and tabes dorsalis have been the subject of several previous papers, the last of which formed the basis of a discussion at a meeting of this Association on May 16th. It is necessary, however, to state here in a few words the more immediate reasons which seemed to us some eighteen months ago to justify the undertaking of these experimental observations of therapeutic aim. Prior to their initiation we had definitely ascertained that a threading diphtheroid bacillus, isolated from the brain and the bronchus of a rapidly progressing case of general paralysis, was capable of producing a sub-acute disease in rats, in which the symptoms were distinctly comparable to those of general paralysis, that on *post-mortem* examination of the animals the brain showed the characteristic changes of general paralysis, and that there was also the characteristic invasion by the thread form of the bacillus. It was thus evident that among the various species of diphtheroid organisms that can be isolated from a general paralytic there is at least one capable of producing the disease general paralysis. We had also ascertained numerous facts which harmonised with this view. We had obtained cultures of a diphtheroid bacillus from the brain of the general paralytic in ten out of twenty-four cases; and whilst attempts to cultivate the organism from the blood and cerebro-spinal fluid of the living patient had, as in the experience of most other observers, been in most instances entirely negative, we had succeeded in obtaining pure growths from the blood in four cases and from the cerebro-spinal fluid in two. We had also

ascertained that diphtheroid bacilli, in a more or less advanced state of disintegration, are frequently recognisable in these fluids, even when a culture cannot be obtained, and that such altered bacilli are almost constantly present in the walls of the inflamed vessels of the brain in cases dying in a congestive attack. We had also evidence of the occurrence of a diphtheroid cystitis in all of several cases of tabes dorsalis examined, and of the existence of a high intra-corpuscular bacteriolytic index to certain diphtheroid bacilli on the part of such patients and of general paralytics, which we interpret as denoting that they were defending themselves against the attack of an organism of this kind.

With such and other evidence before us, and as our aim in these researches was entirely a therapeutic one, we felt justified in having recourse to specific vaccine and serum-therapeutic measures. As there was reason to believe that the bacilli with which we were concerned produced their toxic effects chiefly by means of their endo-toxines, we decided in the first instance to prepare an anti-bacterial serum, similar to that which Wasserman prepared with the Klebs-Loeffler bacillus in 1902. After we had begun to immunise sheep, we ascertained, as the result of the application of Gordon's bio-chemical tests to various strains of diphtheroids isolated from cases of general paralysis, and through further experimental observations, that at least one other species of diphtheroid bacillus is often virulent to mice and rats and is capable of causing the symptoms and lesions of general paralysis. We therefore employed both of these two types of bacilli in our therapeutic experiments.

Both have a close morphological resemblance to the Klebs-Loeffler bacillus. The first, which we have designated the *Bacillus paralyticans longus*, differs from the bacillus of acute diphtheria in producing no acid in the control broth in Gordon's bio-chemical tests, in being non-virulent to guinea-pigs, but occasionally virulent to mice and rats, and in forming threads under certain conditions of growth. The second, which we have termed the *Bacillus paralyticans brevis*, is distinguished especially by its bio-chemical reactions; it produces acid abundantly in saccharose and glucose broths, but forms no acid in lactose, salicin, starch, dextrin, glycerine and control broths; it is not virulent to guinea-pigs, but is often very virulent to mice and rats. We believe that these

are not the only species of diphtheroid bacilli that are commonly concerned in the production of the toxæmia of general paralysis and tabes dorsalis, but that, just as in the case of the pathogenic streptococci, numerous different but closely-allied species are capable of exercising a similar pathogenic action.

Method of Vaccination.

The material employed was a suspension of a weighed quantity (10—30 mgr.) of the bacilli in 2·5 c.c. of sterile saline solution heated to 60° C. for fifteen minutes.

The skin of the limb was cleansed by rubbing with a 1 *per cent.* lysol solution and injections of the emulsion were given hypodermically. Local effects varied from the merest induration at the site of puncture to erythema and œdema of the subcutaneous tissues.

The immediate general effects were the production of brief pyrexia, flushing of face, headache and drowsiness, while increase of tremors, ataxia and a return of lightning pains occurred in some cases. Mentally, there were remarkable changes in not a few of the cases.

CASE 1.—Female, a third-stage bed-ridden general paralytic, with contractures and lightning pains of an intensely distressing character. Three injections were given and the pains were increased for a time after each. Three weeks after this she began to make active efforts at dressing herself and walking about with the aid of a chair, and was able to express herself coherently, while the pains seldom recurred. Two months later she was able to scrub floors and go about the wards without support. She was never able to stand erect, however, on account of permanent flexion at the knees. This improvement was maintained for a year, when the patient was removed from the asylum.

CASE 2.—Female, a third-stage general paralytic, very helpless and intensely confused in mind. Three injections gave temperature reactions of over 100° F. each time. Increase of tremors and grosser impairment of speech followed the first inoculation. Shortly after the second the patient talked sensibly and with

clear articulation, and she was able to go about. Two months afterwards she relapsed into her former condition.

CASE 3.—Female, a stuporose general paralytic in second stage. Three inoculations were followed by rises of temperature to over 100° F. and a temporary lucidity in the patient's mental state was noticed.

CASE 4.—Female, a non-progressive general paralytic, the subject of "pains" and "neuralgias," had nausea and vomiting after the first injection and became depressed in mind with exacerbations of pains after the second and third inoculations. Three weeks later she became cheerful and employed herself in housework for the first time since admission twelve months previously. She relapsed, however, several weeks later.

CASE 5.—Female, a depressed and confused tabo-paralytic, became lucid and gave a correct account of her family history after the first inoculation. After two more inoculations she employed herself in the ward, but relapsed after three weeks to her former state.

CASE 6.—Female, was in third stage and bed-ridden for three years, became excited and impulsive a few hours after injection. She developed diarrhœa and had a marked exacerbation of leucorrhœa. No improvement was noticed.

CASE 7.—Female, a confused general paralytic in the second stage, had a return of pains and became flushed after inoculation on three occasions. Her speech, at first more defective, became for a time clearer than formerly.

CASE 8.—Female, an early third-stage general paralytic, became excited and violent after each injection and improved considerably in bodily condition later.

CASE 9 was that of a medical man who had been developing symptoms of tabes for over two years. His reactions to inoculations of the toxins of a diphtheroid bacillus of the "brevis" type, isolated from his bladder, are interesting and significant. The left arm was injected with 10 mgr. of dead bacilli, and the patient in a few hours suffered from distinct malaise and had a definite attack of lightning pains for twenty minutes. These had not troubled him for a fortnight previously. There was no

rise in leucocytes. Pains recurred on the second and third day. Leucocytes remained about 9,000. The second injection of 20 mgr. of bacilli a week later resulted in a rise of temperature to 99° F. at 3 a.m. Next day there was marked local reaction and he had considerable malaise. There was slight recurrence of "pains" and the leucocytes were 16,000. After the third injection he suffered from severe headache and had return of lightning pains for half an hour, about twelve hours from time of inoculation. Next day there was a leucocyte count of 17,000.

On the whole the patient was better and had not the same mental depression that accompanied his ailment prior to inoculations. A fourth injection caused very marked malaise, a temperature of 100·2° F., and once more a return of the pains for a short time. Subsequently he expressed himself as being better in health, much longer free from pains, which, moreover, were considerably diminished in severity.

The results of these observations would seem to show that repeated vaccinations might prove a useful mode of treatment in general paralysis and tabes. This belief is supported by the results of the independent observations of O'Brien in America,[1] who has recently reported that he has obtained considerable success by such methods in cases of general paralysis.

That we have not pursued the method further is entirely on account of the fact that our original object was to prepare a specific anti-serum, and we merely temporised with vaccines until the serum was ready for use.

In our opinion such vaccine treatment would have to be carried out under the following three conditions: (1) The bacillus ought to be one isolated from the patient; (2) there should be evidence that it is exercising a pathogenic action upon the patient; and (3) the injections should be carried out under the guidance of the leucocyte count or the opsonic index.

Preparation of the Anti-sera.

Sheep were selected as most convenient for our purpose, and in March, 1906, two healthy animals were first of all inoculated with dead cultures of bacilli of the *Bacillus paralyticans longus* type, isolated from the brain of a case of general paralysis.

Weighed quantities of the living bacilli were then injected once a week, and the temperature of the sheep was taken twice daily. The inoculations caused a local induration and tenderness at the site of puncture, a rise of temperature of from one to two degrees and a slightly torpid condition of the animal. After two months, as the injections failed to cause any of these phenomena, and as the intra-corpuscular bacteriolytic index had been raised, it was decided to use the serum. We have now twelve sheep immunised to various strains of virulent diphtheroid organisms, six to the *Bacillus paralyticans longus* type, four to the *brevis* type, and the remaining two animals to both types.

Obtaining the Serum.

The animal is lifted on to a specially contrived stool, the front of the neck shaved and sterilised with 5 per cent lysol and carbolic lotions. A large syringe needle with a bore of 2·2 mm. which has been sterilised in hot oil is grasped by means of special forceps ; the thumb of the left hand, enveloped in a carbolic swab, is pressed against the external jugular vein low down in the neck, then the needle is plunged into the distended vessel. The blood is collected in quantities of 40 c.c. in 60 c.c. glass tubes, previously plugged and sterilised in a hot-air chamber. The serum separates out in twenty-four hours to the amount of 20 c.c. in each tube, though it often takes forty-eight hours to reach this quantity. It is now ready for injection, though it may remain in contact with the clot for a month or so, till required.

Mode of Administration.

The sera have been given by hypodermic injection, by the mouth, through the nose, and, in one case, *per rectum*.

For hypodermic injection we use an all-metal serum syringe, which has been thoroughly cleansed in carbolic lotion, and then repeatedly filled and emptied with oil at a temperature of over 160° C., a method employed by Dr. Stenhouse Williams, of the Runcorn Serum-Farm, Liverpool.

The skin of the abdomen is carefully cleansed with 1 *per cent.* lysol, and the injection is given with not too small a needle (1 mm.). The skin at the site of puncture is pinched before

and after removal of the needle, and held for half-a-minute in order to seal the wound and prevent any escape. A piece of fresh wool is placed on the spot and the fluid is left to be absorbed.

Given by the mouth the serum is quite palatable if some peppermint water or cassia is added. We also administer it by means of an ordinary glass syringe through the nose, passing 10 cc. slowly along each nostril, directing the patient to retain the fluid for a little time before swallowing.

Local Effects.

Given hypodermically, the serum may produce no local effects, or merely a little induration with or without erythema, which in a few cases may spread and give rise to œdema and brawny swelling of a large area of the abdominal subcutaneous tissues. This is readily subdued (in twenty-four to forty-eight hours) by painting the skin with a solution of picric acid. Some cases are more prone to this reaction than others, and it suggests the local formation of toxins by destruction of bacilli in the tissues. It has been found also that friction of the clothing during active exercise is liable to cause a degree of inflammation if the patient is not kept in bed for the day after injection. Serum urticaria occurred in nearly every case.

When the serum was given by the mouth, local effects were manifested by the development of nausea, vomiting and diarrhœa in some cases, and the occurrence of a feeling of hunger in nearly all cases.

General Effects.

These were chiefly drowsiness, diaphoresis, and malaise, whilst polyuria and exacerbation of chronic leucorrhœa were occasionally observed.

Immediately after injection, or in about half-an-hour in oral administration, flushing often occurred ; some of the patients complained of being giddy, with a " tight feeling " in the head and a " stiffness of the face." Some experienced temporary loss of vision. In one case the patient was blind in one eye for ten minutes, nearly twenty-four hours after injection. Others asserted they felt as if they were drunk. Vomiting occurred in some

cases after hypodermic injection. Mentally, many of the patients became more confused; most of them experienced an unusual sense of well-being, and some were hilariously excited. The speech, gait and co-ordination were for a time more impaired, whilst the tremors were increased, and many of the patients complained of shooting pains and sensations of numbness and tingling, or feelings of "pins and needles."

The temperature reaction is characteristic, and so far as our experience goes it is diagnostic. It has for its features a rise to 100° F., or more, when the serum is given hypodermically, and to 99°F., or more, when given by the mouth. This rise occurs within twelve hours and is over in twenty-four, although in the case of mouth administration it may be delayed till the following day.

It has been observed that a temperature reaction may fail to occur if the patient is in a state of remission, when the serum is taken close upon the ingestion of food, or if diarrhœa occurs immediately after its administration by the mouth.

The pulse-rate is usually increased, but on account of its erratic character in cases of general paralysis and other forms of mental disease (well seen in a study of the charts of these cases kept for over a year), no useful data can be obtained.

The serum was tested originally in four cases of general paralysis in the final stage of the disease. In addition to a raising of temperature a few hours after the injection, a remarkable lucidity of mind temporarily supervened in three cases. One patient, who was in a congestive seizure and comatose, became quite conscious two hours after injection of 15 cc. of serum, and the convulsions ceased and did not recur. She remained conscious and lucid up till the time of her death, fifteen days later. Recently another patient admitted to the asylum while in a congestive attack, who rapidly developed coma, became quite lucid within an hour of the administration of the serum. The convulsions persisted, however, and she died in two days, but maintained consciousness to the end.

The therapeutic effects on the mental and motor symptoms of the patients treated can best be illustrated by a short summary of a few cases.

Cases Treated.

CASE 5.—C. S—, female, æt. 28, married. Admitted in

July, 1906, in a confused apathetic mental state, being rather fatuous and facile. There was general muscular enfeeblement with paresis and ataxia of gait, Rombergism, absence of knee-jerks, considerable dysarthria and marked labial and lingual tremors. The pupils were very irregular, unequal and sluggish to light and accommodation.

In August she developed a congestive attack lasting twelve days, during which she had ten severe epileptiform seizures which left her with flaccid paralysis of the right arm and leg for a few days. A month later she had a similar attack lasting two days, during which a leucorrhœal condition was aggravated.

Serum treatment was begun on September 24th, and had the usual effects. In January a sensation of "pins and needles," lasting for twenty minutes, was all that occurred to suggest an abortive congestive attack. In February she had so far improved as to be able to attend the weekly dance. Improvement continued up till the end of April, when it was noticed that six consecutive doses of anti-serum gave no temperature reactions. About this time she became markedly constipated and developed a congestive seizure on May 2nd, which caused a slight paresis of left side of face after twitchings had occurred over both sides of face and in left arm. There was no loss of consciousness, and, being perfectly lucid, the patient was depressed on account of this return of the seizures. On this occasion the temperature, which stood at 101° F., was raised to 103° F. after 20 c.c. of serum had been given by mouth. Three days later she was out of bed and did a hard day's work at "spring cleaning" with no ill effects.

Her present condition (July, 1907) is one of almost complete lucidity with normal articulation. The pupils react briskly, though they are still unequal and irregular. The facies is almost quite free from amimia and tremors, though the knee-jerks remain absent and the tongue still shows fibrillar twitchings.

CASE 6.—C. M—, female, æt. 48, married. Admitted in June, 1906, with obvious symptoms of general paralysis. She became a confused, amnesic, bed-ridden paralytic who lay huddled up in bed, unable to feed herself or have control of the sphincters.

Serum treatment was begun in September. The usual temperature and other phenomena were observed. Two months later she was up, able to read a book and to converse a little. In January she could knit and do light house-work, recognised her relatives and appreciated their visits. This improvement has been maintained.

CASE 7.—Mrs. S—, female, æt. 24, married. Admitted in September, 1906. Was a bed-ridden, rapidly progressive general paralytic with large bed-sores. The knees were acutely flexed, there were marked tremors, the speech was inarticulate and unintelligible, and there was complete absence of intelligent response.

Injections were begun on September 24th, and were followed by typical and well-marked reactions. Two months later the bed-sores had healed and she was able to get up for a little. Improvement has continued and she is now actively and intelligently employed in the wards. Beyond a slight degree of facility she betrays at present no mental symptoms of her disease, and the motor signs are limited to fixed pupils and abolition of knee-jerks.

CASE 10.—J. H—, female, æt. 48. Intemperate and dissolute for seven years after the death of her husband. Admitted in July, 1906, in a state of excited melancholia with symptoms suggesting peripheral neuritis. Six months later, while in a state of sub-acute mania, she exhibited marked unsteadiness of gait, and leant and lurched to the right side while walking. The articulation became very defective. The pupils were found to be unequal, very irregular in outline, and sluggish, and limited in their movements both to light and accommodation. Early in February she was put under serum treatment and gave typical reactions. The day after the first injection the patient expressed herself in a rational way for the first time since her admission eight months previously. She steadily improved and passed into a state of complete remission and has technically recovered and been discharged from the asylum. On the day she left the following motor symptoms were noted to be present: The pupils were irregular, the right particularly so; both were limited in their range of movement to accommodation, and the right was distinctly sluggish and limited in its response to light; stumbling and

occasional slurring of speech, a slight tendency to lurch to one or other side while walking, and tremors of facial and lingual muscles were also to be observed.

CASE 12.—M. A. H. B—, female, æt. 35, married. Admitted in 1900. A case of dementia with the motor symptoms of general paralysis, which had not cleared up under vigorous anti-syphilitic treatment. She had passed gradually into the third stage, had been bed-ridden, resistive, irritable and absolutely mute for over a year. She was unable to feed herself or attend to the calls of nature, and was extremely emaciated. Serum treatment was begun in February of this year and the usual reactions occurred. Within two months she was able to walk in the garden, could feed herself and had control of the bladder and bowels. She can now express herself coherently, is delighted with her improvement and proud of her ability to do light house-work. She is up and goes about all day, takes an interest in her surroundings and is sociable and amiable.

Time does not permit of a further individual survey of the cases, but we may here summarise the results obtained up to the present.

Altogether thirty-four cases of general paralysis have been subjected to the anti-sera, and all of these have yielded a positive result as regards temperature and other phenomena. Two cases of tabes have also shown similar reactions. With regard to the therapeutic results, out of twelve cases under our own immediate supervision for over a period of three months all have shown remarkable degrees of improvement. Of nine cases treated indirectly by us for a sufficiently long period to obtain therapeutic results, four have improved up to the present, and two have become well enough to leave hospital and to enjoy ordinary social life, and are considered capable of taking care of themselves. The remaining three have become progressively worse in spite of vigorous application of the sera. One of them was in a state of almost complete remission for a time, but relapsed completely while absent from medical supervision.

In the case of the medical man with tabes the employment of an anti-serum prepared with his own particular "diphtheroid" resulted in typical temperature reactions, considerable malaise

and an immediate return of lightning pains at first. He has now been under serum treatment for five months. He is satisfied that the severity of the pains is very greatly diminished, while the duration of the periods of remission is increased, and he no longer experiences unpleasant paræsthetic sensations as formerly. Similar improvement has occurred in another case of tabes of over twelve years' standing, which has been a shorter time under serum treatment. The ataxia in his gait is much less marked. He has regained his facial expression. The pains, which occasionally return about six hours after taking serum, are much less severe, and he has longer periods of freedom from them than he ever had prior to serum treatment.

Control Cases.

It may here be convenient to refer briefly to eleven cases which were subjected to the anti-sera in order to control our observations in the cases of general paralysis. Three were cases of dementia præcox, four of excited melancholia, two were suffering from alcoholic dementia, one was an epileptic, and another laboured under mania. They all had the anti-sera on at least three occasions, two cases having them as often as eleven and ten times respectively. In none of these did any specific reaction occur after mouth administration, and any rise of temperature subsequent to injection could readily be explained by other factors.

Dr. Alex. Russell, at present assistant physician at Morningside Asylum, made daily observations over a period of four months on the leucocytes of some of the cases treated by serum. He found that in the cases of general paralysis there was no material change in the numbers of leucocytes, or in the differential counts after injection of the anti-sera; whereas in control cases in most instances there was a decided rise in the number of leucocytes, while the polymorphonuclear percentage showed a tendency to rise.

Control Sera.

Cases of general paralysis were also subjected to other sera in order to test the specific character of our anti-sera.

Normal serum was obtained from each of the sheep prior to the inoculations with bacilli, and this was injected in doses of

20 c.c. into ten cases of general paralysis on more than one occasion, without the slightest reaction.

Again, nine of the patients were injected each with 10 c.c. of polyvalent anti-streptococcic serum and no reaction traceable to it followed.

The reactions resulting from the use of our anti-sera could not be confounded with "serum disease," since they do not correspond to it, and they occurred only in the general paralytics. Urticaria and occasionally accidental local inflammation at the site of injection were the only reactions common to both the general paralytics and the controls.

In conclusion we would say :

(1) That the anti-sera with which we have been working produce reactions which are diagnostic of general paralysis or tabes dorsalis ;[1] they are probably due to the liberation of endo-toxins.

(2) Cases of these diseases treated with the sera in most instances undergo improvement.

(3) A polyvalent anti-bacterial serum is likely to be more efficacious than either the mono- or bi-valent serum we have hitherto used.

(4) One of the chief obstacles in the way of obtaining a very potent serum has been the loss of virulence in the strains of the organisms used.

(5) There are grounds for believing that an anti-toxic serum would be of use, especially for the immediate treatment of congestive seizures.

(6) Lastly, in view of the presence of dissolving bacilli in the brain of the general paralytic, where in all probability they produce extremely virulent endo-toxins, another aim should be the production of a serum containing chiefly an anti-endo-toxin.

(1) *Journ. Amer. Med. Assoc.*, June 29th, 1907.

Discussion,

At the Annual Meeting held in London, July 26th, 1907.

Dr. Clouston said he could speak of the clinical facts, and confirm Dr. McRae's results. He was for a long time a sceptic in regard to the cause of general paralysis. He had run through the various views which were held during the succession of the years, believing first that it was a progressive degeneration, then that it was connected in some way with syphilis, as he believed still, and after very great searchings of heart and observations of cases he came to the conclusion that it undoubtedly was toxæmic in character, and that the toxæmia was bacterial in origin. It was a very striking fact that in every case of general paralysis where

serum was used there was an effect, whereas in the control cases there was no effect. Without being a bacteriologist he knew that was a clinical fact which would require a good deal of explanation to dispose of. He understood Dr. Ford Robertson and Dr. McRae were not in the position of imagining for a moment that they had discovered all about general paralysis, but he believed they were on the track of what might turn out to be a momentous discovery in regard to an extraordinarily difficult disease. There was something dramatic in the very notion that in studying this disease, in regard to which they had been hopeless from the time it was discovered until now, at last a ray of light had risen above the horizon. There was no doubt whatever as to the facts, and all would agree that Dr. Ford Robertson and Dr. McRae had stated their case with manifest honesty, with manifest care not to exceed the facts, and with a manifest feeling of responsibility as to what they were doing. And Dr. Robertson had been working at the subject certainly for five or six years. Clinicians must leave a great part of the subject to bacteriologists to decide. But the matter had a clinical side, and from that side he was satisfied that a definite result had been attained by the serum treatment; and there was every hope that further results would be got by the further researches of Dr. Ford Robertson and Dr. McRae. There were considerable difficulties. It would not only have been dramatic, but miraculous, if they had succeeded at once in curing general paralysis; but if they had established a diagnostic method they had gone far in the study of the disease.

Dr. MICKLE said he had not anything new to say on the subject. Reasoning on the principles of serum therapeutics which had been for some years in vogue, he devised a plan in his own mind, but owing to various causes, including illness, he did not carry out anything in that direction. So he could only say it appeared to him that serum therapeutics on general principles offered what might be expected to be a reasonable ground of amelioration and of cure of that disease when it had not gone too far. To cure an advanced case of general paralysis would be impossible, because the brain and mind effects would remain when once the case had advanced. A portion of brain once gone could not be fed, nourished, or resume its function. He was only raising the question on the general principle of serum therapeutics, which was applied successfully to other diseases.

Dr. GOODALL said he had come for the purpose of hearing the contribution, not to make any comment. He thought he understood Dr. McRae to say that the injection of the serum into some patients who were not general paralytics caused an increase in the polymorphonuclear leucocytes, and he had been wondering what was the cause of that. The conditions described appeared to be remissions, and even if they were prolonged remissions it was a considerable achievement, and something to be thankful for. From the clinical point of view a strong case seemed to have been made out, and he very heartily congratulated them on their careful, conscientious, and honest work.

Dr. DIXON said he had heard that there were thirty or forty varieties of diphtheroid bacilli, and he would like to know whether cultivations of many or several of those had been made. Also, whether any sheep had been immunised to other diphtheroid bacilli than those referred to by the authors of the paper, and, if so, with what results?

Dr. ROWS said he had had the pleasure several times of listening to demonstrations by the authors, and he had been glad to watch the gradual development of their work which had been perceptible in the series of demonstrations. It seemed to him that, in the case not only of general paralysis and tabes, but in the case of various other diseases, they had been too prone to use the word "toxic," and to rest satisfied there. He could appreciate the difficulty of the subject, but as the toxin is of bacterial origin it must be appreciated that there must be some focus in the body where the bacteria giving rise to that toxin were growing and producing that poison. Dr. Ford Robertson had localised that organism in lesions of the body and of the nervous system, and lesions had been found in sections of the spinal cord corresponding to the organ in which the micro-organism was growing. He thought there must be a close connection between the one and the other; and he was very glad that by the production of that anti-serum Dr. Robertson was obtaining a means by which the organism could be attacked in its focus.

Dr. ORR desired to add a word of congratulation to Dr. Robertson and Dr. McRae regarding the results which they had already obtained. Some months ago,

while he was in Edinburgh, the authors gave him the opportunity of observing their cases, and he could endorse everything they had mentioned to-day. There were remissions, and the condition markedly improved; tremors of face, tongue, and limbs decidedly less, and the pupillary symptoms improved also. He wished, however, to point out one thing: that although there was a marked remission in the symptoms it would be exceedingly interesting to observe how long that remission lasted; because, as everyone was aware, remissions in cases of general paralysis were very common events, and sometimes lasted a considerable time. But Dr. Robertson and Dr. McRae would be able to apply that test and compare their results with the natural remissions of general paralysis. Dr. McRae had just stated that he had already sent some cases home. His own short experience was that general paralytics who were sent home in a remission usually returned very quickly, and in a very much worse condition than before. If the authors' cases remained out a considerable time, and did not return in an acutely delirious condition, or in a markedly advanced state, they would have advanced considerable additional proof in support of the idea that the remission was the result of their injections, and that they were on the track of, at any rate, arresting the disease.

Dr. MERCIER said that as he criticised Dr. Ford Robinson's work last time—when he said he thought the verdict to be given was one of "not proven"—it was only graceful that he should take the earliest opportunity of saying that the results which had been brought forward that day rendered it necessary for him to re-consider that opinion. Dr. Orr had spoken about the remissions in general paralysis. Remissions did take place in general paralysis, but complete remissions, so far as he knew, were confined to the very earliest stages of the disease. He had never heard of or seen a complete remission occurring in so advanced a stage of the disease as in some of the cases reported that day by the authors. And he could not regard it as a mere coincidence that even partial remissions should have been in the cases in which injections had been made. That a patient who had attained to so advanced a stage in the disease that he or she had become bedridden, and the knees contracted at an acute angle, that he had large bedsores, and that he should then be so far improved as to get up and walk about, and go out into the garden, and, after being mute for a year to be able to converse, was so extremely unusual that it could scarcely be a coincidence that it occurred in a case in which injection had been given, and it seemed to indicate that a real advance had been made in the treatment of the disease. He wished to say that at once, because hitherto he might have appeared to criticise somewhat ungraciously the very admirable work which Dr. Ford Robertson had been doing, and that he had not appeared to appreciate it at the value that he really did; because when there was a chorus of praise it was natural to men to introduce a discordant note. But he thought they could not resist the evidence which had just been brought forward.

Dr. GOODALL desired to add a word to say that his experience in regard to remissions in the disease did not accord with Dr. Mercier's. He had seen cases in a very advanced stage, in which cellulitis and sloughing had occurred, get up again and be able to play at billiards, and walk about and generally exhibit a remarkable return of motor power. Those cases were, he believed, as advanced as the ones described by the authors, though in saying that he did not wish to detract from the value of their results.

The PRESIDENT said he was sure he spoke not only for himself but for all those who had attended that meeting when he expressed his gratitude to Drs. Ford Robertson and McRae for their valuable work.

Dr. MCRAE, in replying on the discussion, said he would like to deal with one or two points which had been raised. With regard to Dr. Mickle's contention as to the selection of advanced cases, it was necessary, in his opinion, to take advanced cases because they must be genuine. If cure were pronounced in an early case the obvious retort would be "the diagnosis was wrong." It was true that very advanced cases showed, *post-mortem*, such gross changes that regeneration was impossible. On the other hand, he knew it was a mistake to allow themselves to form a judgment emphatically and everlastingly that all those changes were irremovable; because often, in acute insanities, such as puerperal insanity, one found *post-mortem* a degree of chromatolysis which was astonishing; and one saw clinical cases which presumably had as much chromatolysis and yet they recovered. They had no means of knowing for a certainty that the condition

under discussion was incurable. Dr. Goodall had asked why the leucocytes went up in the control cases. If he (Dr. McRae) might put it reversely he would say the leucocytes did not go up in general paralysis because one was putting some substance into the patient's blood which supplied something to the economy of the leucocytes. On the other hand, in the case of control patients one was putting foreign material into the blood, and presumably the leucocytosis occurred to get rid of it. With regard to Dr. Dixon's wish to know whether he and his colleague had tried other diphtheroids in injecting sheep, he would say they could not go through the group of diphtheroids in the short space of time during which they had been working at them—twelve months. They had been using strains of bacilli which had specific broth reactions, and they had used only bacilli which they had shown by injection or by feeding to be toxic to rats and mice. It had been said that he and his colleague were too ready to diagnose general paralysis at Morningside; but he could say that anyone was welcome to see the cases at any time; there was more than one member of the staff to examine the cases and Dr. Clouston confirmed the diagnosis. Dr. Orr touched on what was, of course, the most important point in the whole matter. Time alone would decide if they were to be successful in pointing out the way to the cure of general paralysis. Dr. Bruce had asked him to say that in the matter of control sera he had confirmed their observations. He kindly gave anti-streptococcus serum, anti-coli serum, and anti-rheumatic serum to cases of general paralysis, and none of them reacted. He wired to him (Dr. McRae) for a couple of doses of anti-serum, which were sent, and both cases reacted. He felt that Dr. Mercier had dealt most kindly with Dr. Robertson and himself in his criticism. He trusted that the remissions which had occurred in the cases would be prolonged. He was well aware of such remissions occurring, even in so-called advanced cases of general paralysis.

Dr. FORD ROBERTSON, in reply, said he desired to add one word. They certainly wished that their results had been more successful than they were, but, compared with the results of anti-serum treatment outside diphtheria, they showed up very well. The author of a German paper the other day spoke with regret of the small measure of success attending serum treatment outside anti-diptheritic. They were only yet at the beginning of the anti-serum treatment. There were so many things which there were still grounds for trying, and which they had reason to hope would result in getting a more potent serum, that he thought they would, in future years, revolutionise the anti-serum treatment. He thanked Dr. Mercier for his appreciative remarks, and assured him he took his former criticisms as kindly. He also thanked the President for his kind words, which would be a great encouragement to Dr. McRae and himself in their future work. He drew attention to the microscopical specimens on the table. In his Morison Lectures they asserted positively that in the brain of the general paralytic, especially dying in a congestive attack, there were dead bacilli, which could not be grown, but which could be seen by means of special staining methods. Formerly they used ordinary staining methods, but now they had a special method, and found that in the *débris* in the cerebro-spinal fluid in a congestive attack there were myriads of dead bacilli. If one took a sheep's immune serum and digested in that some of the bacilli in question they became altered, and had the same appearance as those bodies which could be found in the centrifuged deposit of the cerebro-spinal fluid of the general paralytic. They were finding brains in which those bacilli occurred in enormous numbers. Two were under the microscope. For the demonstration of the dead bacilli the metallic methods were useful. They had their own silver method, which they regarded as an improvement. In the second specimen the platinum method brought them out clearly as diphtheroid bacilli. If stained by the ordinary methods one did not see them, because they were dead and no longer retained the stain.