

recommended tying bleeding arteries in primary amputation instead of applying the cauteries then in vogue; but his plan of securing the vessel was so difficult, and was attended with so much subsequent risk, that most surgeons condemned it. An English surgeon, Alexander Read, in lectures which he delivered at the Barber-Surgeons' Hall, about the year 1630, condemned Paré's practice as "a troublesome and dangerous toy, as he shall finde who shall go to make trial of it."

For more than two centuries surgeons were divided in opinion as to the value of the ligature, and even those who did employ it were afraid of injuring the arterial tunics by applying the ligature too tightly. Various contrivances were used to avoid damaging the coats of the vessel. Thick and broad threads, tapes, ribbons, cylinders of cork, wood or linen, reserved ligatures, and other expedients were employed to stop bleeding without injuring the walls of the vessel. Recurrent and secondary haemorrhages were frequent. Dr. J. F. D. Jones at the beginning of last century, by a series of ingenious experiments on dogs and horses, proved that the endeavour of surgeons to apply the ligature without injuring the arterial tunics was precisely the cause of the failure of the ligature to permanently arrest bleeding. Jones demonstrated that the true method was to employ a small, firm ligature drawn sufficiently tightly to cut through the inner and middle coats without rupturing the tougher and external coat. It is instructive, in view of the modern outcry against the experimental method, to read Jones's *Apologia*, bearing in mind that his experiments were performed before the days of anaesthetics and painless operations.

He regrets (he writes) the necessity of obtaining this important knowledge by the sacrifice of brutes. But when we remember the incessant scourge of war which has followed man through all the ages of his history, not to mention the consequences of accident and disease, it is not too much to assert that thousands might have been, and may still be, saved by the knowledge of these subjects; which can only be directly obtained by experiments on brutes; indirectly and very slowly by observations on the injured arteries of men; and even this cannot be made until he has fallen a sacrifice to the want of assistance or to the imperfect knowledge of the surgeon.

Every practical surgeon will bear testimony that, as the result of Jones's experiments, tens of thousands of lives have been saved.

I have lingered about this question because you, as future practitioners of medicine, will have to form an opinion on the justifiability of experiments upon living animals for the purposes of scientific research, and if you are satisfied that these experiments are justifiable with proper safeguards, you will be called upon to defend the practice and to justify your opinion. To do this intelligently it is necessary not only that you should be acquainted with the arguments for the defence, but that you should also make yourself master of the arguments on the other side. It is not enough to ascribe the opposition of the public to ignorance or fanaticism. There may be either or both, but objection can only be overcome and acquiescence gained by enlightening and educating the public mind. It should be remembered that the mass of a nation must be convinced of the value of a general principle which is being carried out, else what we might judge the most salutary change will be ineffectual. Ritchie, in discussing the Rights of Minorities, has remarked that on matters of public health only the scientific expert can, in the first instance, form a sound judgement. In democratic societies there is often a distrust of scientific opinion. The remedy is not despotism, but public enlightenment, and the scientific specialist is bound, therefore, by patriotism, as well as in the interests of his own science, to lend what aid he can to the popularization of science from which he is too apt to recoil. It is the sole antidote to ignorance or pseudo-science. Those whom science neglects, fanaticism and quackery will claim for their own.

Gentlemen, I have said nothing about your scheme of work or of the manner of your lives. These I confidently leave to the help and guidance of your teachers and to the moral and religious impulses which you bring with you. As touching medical ethics, I believe the Law and the Prophets are summed up in the vow prescribed by the Hippocratic oath: "In purity and in holiness I will pass my life and practise my art." You are heirs to a great inheritance. Into your care and

keeping will be entrusted the health, the happiness, and the lives of many of your fellow-creatures. So acquit yourselves that at the trial you may be found not unequal to your responsibilities.

Remarks

ON

COMPLEMENT FIXATION

AS A METHOD OF DIAGNOSIS APPLIED TO
SYPHILIS AND GENERAL PARALYSIS:
THE WASSERMANN REACTION.

BY

J. FROUDE FLASHMAN, and A. GRAHAM BUTLER,
M.D., B.Sc. M.B., B.Ch.

(From the Laboratory of the Lunacy Department, New South Wales.)

WE have investigated the method in a considerable number of cases of syphilis and general paralysis, and in presenting our results we take advantage of the opportunity briefly to review the vexed question of the nature and specificity of the reaction as applied to these diseases. Whether or not the current view that it is not "a true antigen antibody" reaction, and "not due to the interaction of antibody or syphilitic antigen in the usual sense of the word and has no relation with the *Spirochaeta pallida*" (Mott⁷⁷), be correct, the test cannot be regarded otherwise than as a highly reliable and specific one for the disease caused by that organism.

Into the technique of the method and the facts on which it is founded there is no necessity to enter in detail. The introduction of modifications⁷⁸ of the original method devised by Wassermann and his co-workers⁸ for showing the presence in syphilitic serums of substances induced or pathologically increased by the disease, and of new⁷⁸ methods for effecting the same object, is so rapid as to make it difficult to become practically acquainted with them all. It seems probable that some of these may prove more suitable for diagnosis than the original. Our experience is based chiefly on the latter, with but slight modifications; and so far we have not found sufficient reason for departing from it. A difficulty involved in the original technique described by Wassermann,⁸ by the necessity for obtaining a comparatively large quantity of serum, is satisfactorily obviated by diminishing the amounts of the reagents used. If 0.1 c.cm. of each of the properly diluted reacting substances be taken, and tubes used made from $\frac{1}{4}$ -in. glass tubing, in which the ultimate total quantity—0.55 c.cm.—can easily be thoroughly mixed by rotation between the palms, the results are as accurate as when large quantities are employed, and the gain in convenience is great. The handy 1 c.cm. pipettes graduated in one-tenths and one-hundredths can then be employed for complement, extract, and saline; for the serums and cerebro-spinal fluid, ordinary Wright's pipettes, graduated in 0.05 and 0.1 c.cm. by means of mercury, conveniently measured by Wright's small pipettes for measuring 0.005 c.cm. (0.01359 gram) of mercury, are the best.⁷¹ A convenient means of marking these graduations is a blue grease pencil, which is pressed against the glass while hot; such a mark will stand repeated sterilization.

We found it well to test the complement each time to ascertain the minimum haemolytic dose; thus:

Guinea Pig's Serum (1 in 10).	Sensitized Sheep's Corpuscle (5 per cent. Suspension of Blood).	Saline (0.9 per cent.).	Usual Result.
0.05	0.1	to 0.55 c cm.	+
0.04	0.1	"	+ ,
0.03	0.1	"	+
0.02	0.1	"	80-95 per cent.
0.01	0.1	"	30-80 per cent.
—	0.1	"	No haemolysis

The corpuscles are sensitized by the addition of rabbits' immune serum in the proportion of 1 to 500 (about five times the haemolyzing dose) to a 5 per cent. suspension of washed defibrinated blood. The corpuscles are, after incubation, rewashed, and again suspended in normal saline. Complement is obtained easily by bleeding the ear veins of one or more guinea-pigs, after washing with hot water.

With regard to antigen our experience has decidedly pointed to the watery extract of a liver rich in spirochaetes as the best. When testing cerebro-spinal fluids we thought that an alcoholic extract answered as well as a watery one. The use of two extracts in doubtful cases is sometimes of assistance. The following is a convenient and satisfactory method of conducting a test:

Number of Tube.	Normal Serum (1 in 5).	Syphilitic Serum (1 in 5).	Suspect Serum (1 in 5).	Syphilitic Liver Extract (1 in 7).	Complement (1 in 10).	Sensitized Corpuscles (5 per cent. Blood).	(Saline (0.9 per cent.).	Result + = Haemolysis.
1	c.cm. 0.1	c.cm. —	c.cm. —	c.cm. 0.1	c.cm. 0.1	c.cm. 0.1	c.cm. to 0.55	+
2	0.1	—	—	"	0.07	0.1	"	+
3	—	0.1	—	"	0.1	"	"	0
4	—	—	0.1	"	"	"	"	
5	—	—	0.1	"	0.07	"	"	
6	0.1	—	—	—	"	"	"	+
7	—	0.1	—	—	"	"	"	+
8	—	—	0.1	—	"	"	"	+
9	—	—	—	0.1	0.1	"	"	+
10	—	—	—	"	0.07	"	"	+

The complete reaction is considered to be given when 0.1 c.cm. of complement 1 in 10 (about four haemolytic doses) is "deviated." Indications of great value are, however, often obtained by reducing the complement or by increasing the extract or serum, especially the former. Readings taken at half, one, and two hours in the incubator, as well as the final one after eighteen hours in the ice chest, are sometimes of value. It need hardly be insisted upon that the greatest cleanliness and attention to details is essential for satisfactory and consistent results. The glassware should be sterilized before use and washed as soon as possible afterwards.

In the interpretation of results, apart from the general question of the specificity of the reaction, we have found some difficulty in ascertaining the exact standard adopted by the various workers. If the term "complement binding" be taken to represent accurately what occurs, then the method of estimating as accurately as possible the actual number of haemolytic doses of complement fixed, as used by McKenzie,⁸⁵ seems rational and useful. A considerable amount of European and American literature is not available in New South Wales, and we have possibly missed some papers giving more definite information on the subject. Our practice is that if there be a complete, or practically complete, absence of haemolysis and the controls be correct, we make a positive diagnosis of syphilis. In suspected cases, if haemolysis be partial or complete, the further tests above indicated are carried out, using perhaps another extract, and a judgement formed, in accordance with the results, as to the presence in modified degree of the reaction. In such cases the diagnosis is qualified. Under similar circumstances Bruck and Stern¹⁸ recommend varying the amount of antigen and of serum. In the cases tabled, only those which gave the full reaction are recorded as positive. In most of our investigations two extracts were used at the same time, one acting as a control of the other. We are much impressed with the necessity for using full controls. The serums and cerebro-spinal fluids seldom bind alone to any extent; the extract should be standardized to bind alone not more than one haemolytic dose of complement. If the duration of the test be long, as when a large number of tubes are put

up at once, the complement tends to deteriorate, and this must be allowed for.

The following are the results given by the serum and cerebro-spinal fluid of the cases of general paralysis which we investigated:

Number of Cases of General Paralysis.	Serum.			Cerebro-spinal Fluid.		
	Number tested.	Result.	Percentage of Positive Results.	Number tested.	Result.	Percentage of Positive Results.
57	56	56+ 0-	100	57	56+ 1-	98.2

In connexion with these cases we did a number of controls. The results of these are shown below:

Disease.	Number Tested.	Serum.		Cerebro-Spinal Fluid.	
		Results.	Percentage Negative Results.	Results.	Percentage Negative Results.
Dementia praecox	3	0+	100	0+	100
		3-		3-	
Epilepsy ...	2	0+	"	0+	"
		2-		2-	
Imbecility	1	0+	"	0+	"
		1-		1-	
Mania del.	2	0+	"	0+	"
		2-		2-	

Cases of syphilis or definitely suspected to be such, also used as controls:

Disease.	No. of Cases.	Serum.	
		Results.	Percentage Positive Results.
Congenital syphilis	2	2+	100
Primary syphilis	2	2+	100
Secondary syphilis with symptoms	34	33+ 1-	97
Tertiary syphilis with symptoms...	3	3+	100

In addition to the above, which represent the cases done with the definite object of adding to the sum of experience which is being accumulated with regard to the efficacy of the test in known cases of syphilis and parasyphilis, we have made a very large number of examinations of serums of cases for diagnosis. The results, while they fully confirm our experience of the high clinical value of the test, do not, on account of the doubtful nature of the clinical diagnosis in many cases, lend themselves to the purpose of comparative results.

RELIABILITY OF THE TEST FOR DIAGNOSIS.

For the practitioner who has constantly to deal with these syphilitic cases the question of the reliability of the test is one of the first importance. Can he give definite advice, the correctness of which is a matter of the most vital and far-reaching importance to his patient, based on the result of the test? In the first place, it must be definitely borne in mind that there are limitations as well as great possibilities in the test. Only harm can result from the idea that it is infallible. It is not yet an "open sesame" to every case suspected of syphilis, but it is a most valuable aid in many cases of difficulty.

Only the result of a vast number of examinations of syphilitic and non-syphilitic persons can settle the question of the absolute value of the reaction, and probably the last word in technique and method has not yet been

spoken. But sufficient work has been done to enable a fairly definite opinion to be arrived at, and extensive series of statistics by different workers are almost daily becoming available.

As regards a positive finding there can be little doubt: the experience of almost all workers seems to show that with proper technique and control a positive reaction means syphilis. Though in a few diseases, such as leprosy,^{10 28} trypanosomiasis,^{13 49 55 56 57 58 1} noma,⁵⁹ yaws,^{51 18} etc., some works report positive findings, the reaction in these diseases, though of great theoretical importance, is not likely to affect the question of diagnosis often; while, apart from an occasional case, such as that given by McKenzie,⁸⁵ where it must be considered doubtful if syphilis can be excluded, a positive reaction in non-syphilitic cases, such as scarlet fever, is usually either slight or based on doubtful technique.

With regard to the most important question of the value of a negative reaction, we have been given some indications for the formation of an opinion in the course of our own work, and we have also endeavoured to make use of the work, and to ascertain the opinion of those best qualified to judge. The outstanding fact seems to be that with improved technique the number of definitely syphilitic cases not giving a reaction becomes fewer and fewer. Undoubtedly, proved reliability of technique is essential in any one presuming to offer an independent opinion on this question.

We have touched on the indication given in cases of doubt by altering the quantities of complement, extract, etc., in the test. It is undoubtedly a remarkable tribute to the acumen of Wassermann and his colleagues that, for the test, the same substances, prepared in the same way, and used in the same quantities advised originally by them are found most generally useful to-day. It seems to us, however, that in some cases the deviation of somewhat less complement than that given in Wassermann's original paper will often furnish information of definite value. We have found also that cases giving a doubtful reaction with one extract of proved efficiency may occasionally give a positive reaction with another of no obviously greater power. The absence of the reaction in undoubted non-syphilitic, or in cerebro-spinal fluid in cases definitely not paralytic has, in our (of course, limited) experience, greatly struck us. In no normal person have we been able to obtain with any extract a reaction which could be thought syphilitic, in the conditions of the experiment given by Wassermann. The normal cases which we have used have varied to the extent of not more than 2-minim doses of complement. A curious fact was noted that the normal cases which gave the greatest deviation with syphilitic extract gave an unusually large deviation also with typhoid, with plague, and with diphtheroid "extracts."

Though of prime importance in relation to this question, it is perhaps unnecessary to consider here in detail the statistics concerning the percentage of positive reactions in different stages of the disease, and after treatment given by the recent workers on the subject.^{27 28 35 21}

A case seriously suspected of syphilis, or in whom a certain diagnosis is important, should be examined with varying amount of complement and with different extracts, well controlled with known normal and syphilitic serums. The results must, of course, be judged with due regard to the effect of any treatment the individual may have undergone, to the stage of the disease, and to the presence or absence of active morbid changes. Undoubtedly in secondary or in active tertiary untreated syphilis the value of the reaction must very nearly approach the Widal reaction for typhoid⁸⁹ done under the best conditions; while with regard to general paralysis it would almost seem that in a case whose cerebro-spinal fluid and serum have been carefully and repeatedly examined with negative results, a clinical diagnosis of general paralysis must be seriously questioned.

In addition to the matter of diagnosis, a question of the highest importance is the bearing of the reaction on the prognosis in all its aspects—for example, in the duration of treatment, in the question of marriage, and of liability to late or remote effects of the disease. On all these guidance is much needed, and will be sought from the information afforded by the reaction. It must be acknowledged that this guidance is not as yet to be obtained in any full degree, but it may confidently be expected that

when the results of investigations extending over sufficient time, and including sufficient observations directly bearing on these questions, are available, our knowledge on these most important matters will be enormously increased.

SOME THEORETICAL CONSIDERATIONS.

The discovery of the property in the cerebro-spinal fluid in general paralysis and tabes of specific complement binding, and its association with the presence therein of new substances, or increase of substances, originally present in slighter degree, has led to much investigation and conjecture as to the nature of these substances and their relation to the Wassermann reaction. In the course of our practical investigations with the Wassermann test we made some observations which bear in some degree on the subject, and these we think it well to record.

The fact that a degenerative process, associated with breaking-down of nervous elements in the central nervous system, is an essential feature in general paralysis and in tabes, suggests the possibility that in other conditions where extensive destruction of neurones is taking place the products of degeneration may, in view of the supposed chemical explanation of the phenomenon, give similar complement deviation to that given in general paralysis or tabes. To investigate this we obtained the cerebro-spinal fluid and serum of 3 cases of extensive vascular cerebral lesions leading to more or less complete hemiplegia, and investigated these for antibodies. The lesions had occurred three, twelve, and twenty-four weeks previously. No evidence whatever was obtained of specific complement deviation. The total albumen content, as shown by precipitation with salicyl sulphonic acid, was the same as that of a normal cerebro-spinal fluid obtained at the same time, and was one-tenth the amount of that in the cerebro-spinal fluid of a case of general paralysis also taken at the same time as a control. The deviation test showed that the three hemiplegic fluids, and the normal fluid did not, even in large amounts, influence the complement to the extent of one minimum haemolytic dose above the amount absorbed by the substances separately, while in the general paralytic at least twelve extra doses were neutralized.

In a case of tabo-paresis investigated at the same time the albumen content was scarcely more, as shown by centrifuging, than in the hemiplegics, though it characteristically separated in larger flakes when allowed to deposit slowly. The Wassermann reaction, however, in the tabetic was well marked. This observation is of interest in connexion with that (*vide infra*) of the absence of complement-binding property in the concentrated alcoholic precipitate of normal fluid as compared with one of similar concentration from the fluid of a case of general paralysis, and points to the responsibility of other factors than a general increase in proteins for the specific complement-binding reaction.

We have investigated the question whether a specific deviating substance could be thrown down from the cerebro-spinal fluid in general paralysis by certain chemical agents. Our choice of these was conditioned by their convenience with regard to the separation of the precipitate and supernatant fluid, and to their own intrinsic effect on the test rather than by their importance as specific precipitants, in accordance with the current views as to the nature and import of the bodies contained in the cerebro-spinal fluid.

In view of recent investigations into the nature and reactions of the globulins,⁴¹ it would appear premature to accept unreservedly the at present widely held belief^{69 47 38 32 31} that the increase in protein content is due to globulins, and that these globulins are definitely the source of the complement-deviating reaction given by these fluids.

At the outset we assured ourselves that in the cases we were working on there was a marked difference between the albuminous content of the general paralytic fluids and the normal fluids. There is no room for doubt that, apart from acute or subacute diseases, a heavy flocculent precipitate occurring in a cerebro-spinal fluid on the addition of a general albumen precipitant is very strong evidence that the fluid was derived from a case of general paralysis or tabes. It would seem that, apart from any specific reagents for precipitating globulins, or other supposed characteristic substances in the fluid,^{81 48 33 69} the simple test of complete precipitation of the albuminous contents

with any suitable reagent—for example, salicyl-sulphonic acid—will give almost equally certain diagnostic information. We estimated approximately the albuminous content of a number of cerebro-spinal fluids in the following manner. A large number of specimens were obtained at the one time. A corresponding number of small calibre tubes made from the same length of glass tubing were prepared, and into each 0.3 c.cm. of a cerebro-spinal fluid was pipetted. Three drops of salicyl-sulphonic acid were added to each tube, and the whole of the tubes were immediately centrifuged together for two minutes on the same centrifuge. At the end of this time the supernatant fluid was carefully pipetted off and discarded, and the deposits were carefully measured in a fine pipette. The results in the large number of cases examined was a definite differentiation of general paralytic from all other fluids examined. One case only of tabs was examined, that referred to above.

Three reagents were used to obtain precipitates: alcohol (80 per cent.), phenol (3 per cent. solution), and salicyl-sulphonic acid. The alcohol was added to the fluid in the proportion of 4 parts of alcohol to 1 part of fluid. The precipitate obtained—which consisted of the total precipitable contents of the fluid, as tested, after separation of the precipitate, by salicyl-sulphonic acid—was well washed and rediluted or suspended in normal saline to the original bulk of the fluid. The supernatant fluid was freed from the alcohol at a low temperature under an exhaust. Both supernatant fluid and the precipitate were then tested as original cerebro-spinal fluids. The precipitate from the normal fluid was dissolved in about six times less saline than that from the general paralytic fluid; treated in this way, the total precipitable material in the normal and the general paralytic dilutions were made approximately equal. The phenol precipitate obtained by adding 3 per cent. phenol to the cerebro-spinal fluid was treated in a similar manner. The phenol supernatant fluid contained 3 per cent., of course, phenol; the action of this was therefore examined by controls. According to Wassermann's direction, 0.5 per cent. phenol is added to the cerebro-spinal fluid to be tested before inactivation. His object in directing this we could not ascertain. In one experiment of our own, involving a large number of cerebro-spinal fluids, these were tested in duplicate with and without the phenol. The results were most definitely more satisfactory when this was added—that is, the cerebro-spinal fluid with phenol absorbed the complement more completely without the controls being affected in such a way as to influence the results of the test.

This is in accord with the action of phenol on complement when tested with and without syphilitic antigen in quantities insufficient to cause physical haemolysis. The salicyl-sulphonic acid precipitate was treated similarly, the precipitate, well washed, being suspended in 0.9 per cent. saline; the excess of the reagent in the supernatant fluid so interfered with the reaction that it could not be used.

The results of a large series of examinations can be briefly summarized as follows:

Alcohol.—The alcoholic precipitate from the cerebro-spinal fluid of cases of general paralysis had very high complement absorbing properties, but not of a specific nature, that is, the addition of syphilitic extract did not increase it. The precipitate from normal fluids fixed complement to a very slight extent indeed, even when used concentrated as described above. The supernatant fluid of normal and general paralytic cerebro-spinal fluid did not bind even in large amounts.

Phenol.—The results with the phenol precipitate were similar, but the precipitate had very much less complement fixing property than the alcoholic. There was no precipitate with normal fluids. The supernatant fluid had some slight complement fixing properties.

Salicyl-sulphonic Acid.—The precipitate exhibited no complement fixation properties when used in large amounts with or without extract.

As the complement deviating power of the cerebro-spinal fluid might have depended on two factors, one of which was precipitated and the other remained in the supernatant fluid, we examined the action of a readmixture of the washed precipitate and the supernatant fluid with regard to specific complement binding action; our results,

as far as they went, tended to show that the precipitate and supernatant fluid, when recombined, possess no specific deviating power.

It would, therefore, appear that the chemical agents used, where they did not destroy the whole binding action, destroyed its specific nature—that is to say, that as regards these precipitates, binding occurs to an equal extent with or without the presence of syphilitic virus or other antigen, which, with the unaltered fluid, brought about an enormously increased complement inhibition. Whether the explanation of this is that a specific binding substance is destroyed by the chemical agents used, or whether it is that a complex and easily disturbed relation existing between substances which occur to a larger extent in the cerebro-spinal fluid in cases of general paralysis than in others is broken down, we are unable to offer an opinion.

Recently Noguchi and Bauer have succeeded in precipitating the specific deviating bodies. Such a result cannot fail to have an important bearing on the elucidation of the theoretical aspect of the question.

It would almost appear that there may be two properties inhibitory to complement action possessed by general paralytic cerebro-spinal fluid—one a general one differentiating general paralytic from normal fluids but not specifically syphilitic, and another more definitely and specifically syphilitic and more easily destroyed.

Brain Extract as Antigen.—We tested extracts of normal and paralytic brains for antigen and for antibody. The extracts were prepared in an exactly similar manner to the liver extract. The general paralytic brain extract contained antibody, but not to a large extent. The antibody reaction with syphilitic liver extract as antigen persisted, though in greatly diminished degree, for about six weeks. The normal brain was not found to contain nor to develop any specific antibody reaction, as compared with the paralytic, on keeping.

Antigen.—No definite superiority in antigen action by the extract of paralytic over that of normal brain was found, though on some occasions we thought that there was perhaps slightly more specific complement binding with the paralytic than with the normal brain. Both extracts gave some specific binding with syphilitic serums and the cerebro-spinal fluid of cases of general paralysis, though in a very much slighter degree than the liver extract. One peculiar fact was noticed—that very much more definite and positive results were obtained when using cerebro-spinal fluid than when using serums. Serums which gave an extremely marked reaction with liver extract, gave in the same quantities hardly any result with the brain extracts, while cerebro-spinal fluid whose complement binding power with liver extract was known to be not so great as that of the serums, gave a complete reaction with the brain extract.

Antigen in Cerebro-spinal Fluid.—We examined specimens of cerebro-spinal fluid, which gave strong antibody reaction, for antigen. We did not succeed in demonstrating the presence of antigen.

In a recent paper in the BRITISH MEDICAL JOURNAL by Mott references are made to the reaction in the blood and cerebro-spinal fluid of cases of syphilis and parasyphilis. It seems that in active syphilis of the nervous system the characteristic reaction in the blood is an antigen reaction, and that it indicates the presence and activity in the body of the syphilitic virus, while in parasyphilis—for example, general paralysis—there is a different reaction. In this case the reaction in the blood is the antibody reaction, and it gives no indication of any active syphilitic process. These facts are obviously of the highest importance. We have not yet had an opportunity of becoming acquainted with the work on which these conclusions are based.

RELATION OF GENERAL PARALYSIS TO SYPHILIS.

The nature of the relationship of general paralysis to syphilis is a matter which has, since its first inception by Fournier, been productive of much investigation and many theories. The term "parasyphilitic" is but a concise restatement of the fact that there is undoubted and close relationship between the diseases included under that term and syphilis, and does not in any way explain the relationship.

The nature of the complement deviation reaction in general paralysis is especially a matter calling for much further investigation. That a disease the syphilitic

nature of which has only recently been definitely proposed and its relation thereto still generally considered secondary or remote, should give a reaction—the specific nature of which, for syphilis, investigation more and more definitely shows—in a greater proportion of cases than in any stage of the original infection, is a fact both unexpected, and undoubtedly difficult to explain on the original conceptions of the nature both of the reaction and of the disease. One or other or both of them seem to require modification. Opinions on the matter are very ill-defined and uncertain. At present it appears to be taken as undoubted that the relationship between the parasyphilitic diseases and the *Spirochaeta pallida* is an extremely remote one, and due not to the direct action of the spirochaete or its toxins on the tissues concerned, but rather to certain degenerative processes brought about by a profound alteration in the whole metabolic life of the body, the result of an infection with syphilis at some time more or less remote.

The apparent uselessness of mercury and other anti-syphilitic remedies in preventing the onset and progress of these diseases, and their steadily progressive course, their occurrence in cases of mild or even unnoticed syphilis, and where the primary disease has been vigorously and apparently effectually treated, and the ineffectiveness hitherto of the search for the spirochaete, are taken to indicate this.

But may not the theory of latent spirochaete infection, as suggested to explain late tertiary syphilitic manifestations, be applied also to general paralysis? To explain late syphilitic lesions an analogy may be drawn from other infective diseases, such as tubercle, and many protozoal diseases in man and animals. It certainly seems possible that in an apparently cured or recovered case of syphilis, an attenuated infection, or a focus, encapsuled, or otherwise rendered temporarily incapable of producing toxic results, and possibly likewise incapable of producing demonstrable "antibody" formation (meaning thereby the bodies which produce the specific complement deviation of the Wassermann reaction), may exist in the body, capable under special circumstances of being roused into activity, and of giving rise to tissue change, local or general, slight or extensive, with the accompaniment of the formation of deviating bodies. It has been proved, by the observation among others of Furecz,⁶⁶ Murero,⁶⁷ and Katzenstein,⁶⁸ that the *Spirochaeta pallida* may be found in old healed lesions even after two years, and after intense and prolonged treatment. Reuter and Schmorl,⁶⁵ and Benda,⁶⁴ found the spirochaete in the vessel walls in old syphilitic arteritis, an exceedingly common lesion, by the way, in general paralysis. Wechselmann⁶⁹ is definitely of the opinion that in "occult syphilis" the disease may be present in the internal organs. That a latent infection may exist capable after long periods of quiescence of renewed activity and the production of active pathological changes can hardly be doubted.

The disappearance, under treatment and otherwise, of the Wassermann reaction, and the latency and recrudescence of syphilis in its various forms may thereby be explained. Two cases examined by us are of interest in this connexion. In one case in which an ulcerated swelling of the tip of the tongue caused anxiety, a most definite Wassermann reaction was given, the original infection having occurred thirty-two years previously; in the other, a condition of buccal leucoplakia occurred many years after the original infection, which had been actively treated by kataphoresis, etc., and the test proved completely positive. It is to be noted that Fournier classes this condition among the parasyphilitic diseases.

In general paralysis there seems no valid reason for considering it as very improbable that the organism may not have been during years in which the disease was apparently "latent," present in or acting upon the central nervous system. The alternative conception, of an altered condition of the body fluids or blood, or of one of the internal secretions; or, as held by Mott⁴⁷ to be most probable, of a "latent toxin," produced by the action of the original infection with spirochaetes, which then presumably died out; which condition remained unaltered through years of metabolic change, to give rise ultimately to the tremendous physical cataclysm the results of which we know as general paralysis, is one of which it is difficult to form a clear conception. It seems to us more easy to account for general paralysis on the supposition, not as far

as we are aware negated by any observations, that the syphilitic infection was not, in cases of syphilis which ultimately became paretic or tabetic, ever destroyed or completely latent. Probably these cases never lost the Wassermann reaction which presumably they gave at first. The fact that apparently slight and well treated cases of syphilis have become paretic or tabetic does not negative this. A progressive deterioration, or possibly simply an increased susceptibility to adverse influences of the cells of the system most disposed (by inheritance, stress, etc.) to degeneration, would thus be the result of direct syphilitic toxæmia.

The presence of the Wassermann reaction in the cerebro-spinal fluid of general paralysis, and its absence in cases of ordinary syphilis, and even, except possibly in a very slight degree,^{27, 47} in cases of cerebral syphilis, and its constant association with the presence in the fluid of certain constituents, albuminous and otherwise, presumably the result of cerebral degeneration, is a matter of great theoretical as well as practical interest and importance. The investigations of Noguchi,⁵¹ Mott,⁴⁷ Nonne,⁶³ and many others on the albuminous, lipoidal, and other substances peculiar to or characteristically increased in the serum in syphilis and in the cerebro-spinal fluid in general paralysis and tabes, though they have much enlarged our knowledge on the subject, are still very far from giving us an exact explanation of the specific complement binding reaction in these diseases, though investigations on these lines can hardly fail greatly to enlarge our knowledge in the near future.

In connexion with the question of the specific quality of the degeneration products present in the cerebro-spinal fluid in general paralysis, our experiments (vide supra) undertaken with cases of extensive hemiplegia in various stages may be of interest. The fact that the cerebro-spinal fluid in general paralysis possesses no spirillicide properties,⁴⁴ while the serum of syphilitics does, is an observation which, if confirmed, is undoubtedly of considerable importance. The observations of Kolle and Schatilloff⁴⁰ and others, that the complement binding bodies in the blood in infections are probably antibodies *sui generis* and not possessed of bactericidal or bacteriotropic properties, may receive important confirmation from this observation.

The observations of Levaditi and Yamanouchi and others on the use of certain "chemical" substances, and of extracts of normal organs as antigen, and of Blumenthal, etc.,⁶¹ on the increased lecithin content of the blood, etc., in syphilis, has led to the belief that the reaction is only remotely connected with the *Spirochaeta pallida*.

Progressive impoverishment of the body cells in lipid substances (most marked in those of parts specially affected, for example, the brain in general paralysis) under the influence of a "latent toxin," or of a certain vicious metabolic tendency, the result of previous spirochaetal influence, is taken to account for the presence in the cerebro-spinal fluid and serum of a substance which acts as a complement binding antibody. The formation of a hypothetical soapy substance round the fat globules in the infected liver is taken to account for the superior antigen effect of an extract of that organ. Thus we are led to theories which are held by many to account for the reaction in general paralysis. According to Mott it is apparently the reaction of the body itself against the spirochaetal infection which (contrary surely to other reactions to chronic infection, unless amyloid disease be an analogy) produces changes which result later in a condition whereby the cells of specially vulnerable parts have their vitality so lowered that progressive degeneration inevitably ultimately ensues, and manifests itself, for example, in general paralysis, with the production of the various degeneration products which bring about the Wassermann reaction.

Is, then, the reaction in the cerebro-spinal fluid of general paralysis identical with that in the serum of early syphilis? If so, we must suppose an identical influence to have produced the bodies, whatever their nature may be, which give this specific complement binding reaction. In early syphilis the direct influence of the spirochaete can hardly be questioned. In general paralysis the accepted conception, as we have seen, is that of a progressive "degeneration" of the nervous elements in the cortex, the result of toxic influence acting only indirectly, and quite

independent of an actually present syphilitic toxin formation. The existence of definite tissue changes, and of the production thereby of bodies whose importance in the vital economy, and also in reactions involving complement deviation, is undoubted, cannot, of course, be denied. But, in considering the nature of this deviation reaction, its definitely specific nature in active syphilis must ever be borne in mind; whatever be the chemical composition of the substances concerned, they are definitely and specifically syphilitic in their reaction.

From these considerations we are hardly content to accept unreservedly the view that this specific reaction is only due to some body or bodies quite accidentally and fortuitously produced by the tissues as a remote result of the presence of the spirochaetes. We are persuaded that these bodies—chemical as they must be in their nature—will ultimately be shown to be due in the most direct manner to the action of the infective agent, and to be, therefore, antibodies produced by the spirochaetal antigen.

The view that lipoids and lecithin as such are the only substances playing a rôle in these reactions is also not a little doubtful.

It would seem almost incredible that in syphilis alone the characteristic and specific result of infection should be the production in the body fluids of antibodies (in the complement deviating sense) consisting of substances of almost universal occurrence normally throughout the system, and of vital importance in the ordinary bodily metabolism. It surely seems more likely that in syphilis, as much as in other infections, substances of a definitely specific nature are produced, the presence of which can be determined by the complement deviating reaction, even though their exact origin and rôle may still be uncertain. The complement binding reaction in syphilis is probably just as definitely (and no more so) a "true antigen antibody reaction" as similar reactions in other infections.

A GENERAL CONSIDERATION OF THE NATURE OF THE REACTION.

The numerous tests, chemical and biological, which have recently been devised to bring out the remarkable differences which exist between syphilitic and non-syphilitic serums and between the serums of patients at different stages and in various phases of the disease, have resulted in a corresponding activity in the formulation of theories to account for the results obtained. The masterly presentation of the whole subject by Mott⁴⁷ is full of interest, bringing to a focus, as it does, the most recent discoveries of the various workers on the subject and the theories evolved to explain them. It seems to us, after a fairly full examination of the literature, that there is a tendency in some quarters to unduly question the directness of the relationship of the *Spirochaeta pallida* to the various phases of syphilis, and especially to the phenomenon of complement binding between syphilitic serum and the "syphilitic virus." The opinions regarding the specificity or otherwise of the substances concerned in the reaction are most difficult to interpret. First the antigen then the antibody is pilloried as being solely some relatively simple chemical body with no pretence to being a "true antigen" or "true antibody." Yet the antibodies at any rate appear to be produced, in the human body at least, in no other way than by an infection with the *Spirochaeta pallida* or possibly of closely allied organisms, and it is certainly found to produce specific complement binding when combined with the syphilitic virus.

The test was undoubtedly founded on the analogy of the Bordet-Gengou reaction, in view of the specific causation of syphilis by infection with the *Spirochaeta pallida*, the only difference being in the use of extract of a highly-infected organ as antigen. Tuberculosis had just previously been investigated by Wassermann and Bruck⁷ on similar lines, and the use of extracts of highly-infected organs as antigen instead of pure culture of the causative agent is fully justified, though with limitations and precautions, as pointed out by Meyer.⁵²

Working with spirillary infections Kolle and Schatilloff⁴⁰ obtained definite complement binding in serums from patients suffering from relapsing fever, using as antigen extracts made from organs and blood rich in spirilla. In our own work one of us (A. G. B.) obtained definite results in serums from cases of plague, using as antigen a watery extract of the spleen of a guinea-pig dead from plague

(inoculation), prepared in exactly the same way as the extract of syphilitic liver. It seems generally agreed that the best antigen for syphilis can be prepared from a liver rich in spirochaetes. That there is in syphilis, in some respects at all events, a specific antigen antibody reaction definitely connected with the spirochaete and analogous to similar reactions found in other infections, it is difficult to escape. The fact that various bodies of known chemical composition and extracts of organs other than syphilitic will in some degree give the reaction cannot, we think, be taken to negative this view.

In the first place, it must be remembered that the exact nature of a "true antigen antibody" reaction has still to be defined and the chemical composition of the interacting substances ascertained. Kolle⁴⁰ says that "all complement deviating antibodies are antibodies *sui generis*," and not true protective substances, as are bacteriolysins and bacteriotropins.

Interesting observations bearing on the question in relation to syphilis are given by Wechselmann,⁵³ who gives reference also to others dealing with the question of the relation between the deviating bodies in the blood in syphilis and the protective substances. It is also ably dealt with by McKenzie⁵⁵ as well as in the paper by Mott⁴⁷ already referred to. The reaction in infection would thus seem to be placed in the same category with the complement binding which occurs with all antigen antibody reactions—for example, in the case of a serum and an anti-serum with or without precipitin reaction. It seems necessary under this supposition to consider that certain chemical substances of a highly organized nature—for example, albumens in the body of the infecting organism—produce the antibodies whose presence is evidenced by complement deviation, and that the receptors involved and their immune bodies are not in the case of bacterial infections identical with those which are concerned in immunity production. In any case, in the matter of syphilis it does not seem justifiable to characterize the reaction as not a true antigen antibody reaction, since the exact nature of the reactions which are acknowledged as such are so little understood.

With regard to antigen, the fact that the syphilitic antigen is in some degree, at least, soluble in alcohol is stated by Mott to prove that it cannot be a true antigen. But can the solubility or otherwise in alcohol be taken as the sole test of a "true antigen"? We are not ourselves aware of any sufficient evidence to show that a specific antigen antibody reaction may not be obtained with definite chemical agents in other diseases than syphilis. Possibly all complement binding reactions will eventually be explained in this way. The specific nature of the reaction in cobra venom is undoubted, yet, as Preston Keyes⁵² showed, complement may be furnished by a definite chemical substance, lecithin. But all complements are not necessarily lecithin. It is interesting to note that the same substance is a substitute for antigen in the syphilitic reaction. The composition of the body of the *Spirochaeta pallida* has yet to be determined. Mott, indeed, states that the spirochaete consists of a viscid plasma covered with a membrane consisting of lipid substance; though in spite of this he considers that "the reaction has nothing to do with the *Spirochaeta pallida*." It would almost seem that the minds of many observers have been so diverted by the discovery of the possible explanation of the Wassermann reaction by the interaction of known chemical substances that their attention has in some degree been drawn from the biological aspects of the test. All "antigen antibody" reactions are probably ultimately chemical in their nature, and sooner or later the nature of the substances which act as antigens in infection, whether contained in the substance of a micro-organism or formed by its influence and of the other reacting substances, will be more or less exactly determined. Much more light requires to be thrown on the subject before the exact nature of the Wassermann reaction and its relation to the *Spirochaeta pallida* is understood. Our knowledge of the nature of the reaction of the body to chronic infection in general is still in its infancy. But undoubtedly any conception of the nature of syphilis and explanations of its observed phenomena, to be fruitful in results, must take the fullest cognizance of its character as a chronic infection with the *Spirochaeta pallida*.

CONCLUSION.

The whole subject of syphilis has reached a stage of great interest and importance. For years the extraordinary clinical manifestations of the disease and the difficulty of obtaining a definite clue to its exact pathology engrossed the attention of observers of the highest powers of observation. Increasing attention was also given to the national importance of the disease as a factor in the production of degenerative processes resulting in serious individual inefficiency and in national physical deterioration. But until the pathology of the disease was placed on a definite and certain basis, all thought in connexion with it was more or less incoherent and action vacillating. To the genius of the lamented F. Schaudinn, in the view of practically every authority on the subject, are we indebted, by the discovery of the *Spirochaeta pallida* and of its rôle in the production of the disease, for an "open sesame" which will undoubtedly result in a coherent and definite conception of syphilis in all its aspects, biological, pathological, and clinical, and will thus clear the way for organized efforts, founded on definite knowledge of the etiology of the disease, for neutralizing its effects, and in some measure at least, minimizing its incidence. The great discovery of Wassermann—a discovery which, whatever the ultimate theoretical explanation of it may be, was undoubtedly based on the conception of syphilis as an infective disease—has opened the way for investigations into which very many workers in the field of biological research have seen sufficient inducement to enter, and new light is almost daily being thrown on the nature of the disease and of its manifestations. The method of complement deviation upon which this most important and far-reaching means for extending our knowledge of the nature of syphilis depends, is one which has proved highly fruitful in results in other fields of investigation, and engrosses a large amount of attention in both its theoretical and practical aspects. The conditions which lead to active or passive anticomplement action and the explanation of the action, the nature of complement, antibody, antigen, etc., and the meaning of their variations under different conditions are being studied with such vigour that our knowledge of them will undoubtedly soon be much more definite and certain. Our conception, indeed, of infective disease in general, and probably of many diseases not at present so regarded, will, in the not remote future, be so altered and enlarged that our present knowledge will seem rudimentary and crude. It is more and more becoming apparent that every man aspiring to practise medicine must in the future, if he wish to keep abreast of the advances, not only in the science, but in the art of medicine and surgery, have a very much fuller and more practical acquaintance than is at present considered necessary with the knowledge now available, as the result of an enormous amount of research and thought, of the mechanism and conditions of infective disease.

We desire to express our thanks to Dr. Hiller (Melbourne), Dr. McKelney, Dr. Margaret Harpur, Dr. Chapman, Dr. McMurray, Dr. Ludowici, and many others for the gift of material in connexion with the paper.

REFERENCES.

- 1 Bordet: *Annales de l'Institut Pasteur*, 1900, vol. xiv.
- 2 Bordet et Gengou: *Annales de l'Institut Pasteur*, 1901, vol. xv.
- 3 Gengou: *Annales de l'Institut Pasteur*, 1902, vol. xvi.
- 4 Malvoz: *Annales de Soc. Médico-Chir. de Liège*, 1901, vol. xl.
- 5 Moreschi: *Berl. klin. Woch.*, 1905.
- 6 Neisser and Sachs: *Berl. klin. Woch.*, 1905, p. 1388.
- 7 Wassermann and Bruck: *Medizin. Klinik*, 1905, No. 1; *Deut. med. Woch.*, 1906, No. 12.
- 8 Wassermann, Neisser, and Bruck: *Deut. med. Woch.*, 1906, No. 19.
- 9 Wassermann and Plaut: *Deut. med. Woch.*, 1906, No. 44.
- 10 Wassermann: *Deut. Zeitschrift f. Nervenheil.*, December, 1908.
- 11 Neisser, Bruck, and Schucht: *Deut. med. Woch.*, 1906, No. 48.
- 12 Levaditi et Yamanouchi: *Comptes rend. Soc. de Biol., Paris*, 1907, T. lxiii, p. 740.
- 13 Levaditi et Yamanouchi: *Bull. de la Soc. de Path. Anat.*, T. i, 1908, No. 1.
- 14 Levaditi et Marie: *Annales de l'Institut Pasteur*, 1907, vol. xxi.
- 15 Levaditi et Marie: *Comptes rend. de Biol.*, 1907, No. 42; *Semaine médicale*, 1907, No. 21.
- 16 Sachs and Altman: *Berl. klin. Woch.*, 1908, Nos. 10 and 14.
- 17 Weil: *Wiener klin. Woch.*, 1907, No. 18.
- 18 Bruck and Stern: *Deut. med. Woch.*, 1908, No. 12.
- 19 Muir and Martin: *Journ. of Hygiene*, 1906, vol. vi.
- 20 Theobald Smith: Rockefeller Reprints, 1905.
- 21 Citron: Report XIV, Internat. Cong. Hygiene and Demography, Bd. iv, p. 101.
- 22 Preston Keyes: Rockefeller Reprints.
- 23 Fornet: *Muench. med. Woch.*, 1907, No. 30.
- 24 Bauer: *Deut. med. Woch.*, 1908 and 1909.
- 25 Bauer.
- 26 Blaschko: *Deut. med. Woch.*, 1909, No. 9.

- 27 Lessar: *Deut. med. Woch.*, 1909, No. 9.
- 28 Bauer and Meier: *Wien. klin. Woch.*, 1908, p. 1765.
- 29 Fischer and Meier: *Deut. med. Woch.*, 1907, No. 52.
- 30 Porges and Meier: *Berl. klin. Woch.*, 1907; *Berl. klin. Woch.*, 1908; *Wien. klin. Woch.*, 1908.
- 31 Noguchi: *Journ. Experim. Med.*, January, 1909.
- 32 Noguchi: *Journ. Experim. Med.*, March, 1909.
- 33 Nonne: *Deutsch. Zeitsch. f. Nervenheil.*, Bd. 36, Heft 1-2, 1908.
- 34 Elias, Neubauer, Porges, and Salomon: *Wien. klin. Woch.*, 1908, No. 21.
- 35 McKenzie: *Journ. of Pathol.*, January, 1909.
- 36 Henderson Smith: *Proc. Roy. Soc.*, July, 1907.
- 37 Hiller: *Proc. Austral. Med. Con.*, 1908.
- 38 Mainwaring: Rockefeller Reprints.
- 39 Dreyer: *Journ. of Path.*, January, 1909.
- 40 Kolle and Schatilloff: *Deut. med. Woch.*, 1908, No. 27.
- 41 Mellanby, *Journ. of Physiol.*, vol. xxxvi, Nos. 4 and 5.
- 42 Ehrlich and Morgenroth: *Berl. klin. Woch.*, 1899.
- 43 Klausner: *Muench. med. Woch.*, 1908, No. 46.
- 44 Michaelis.
- 45 Tschernogubow, *Deut. med. Woch.*, 1909, No. 15.
- 46 Hugo Hecht: *Wien. klin. Woch.*, 1908, No. 50.
- 47 Mott: BRITISH MEDICAL JOURNAL, February, 1909.
- 48 Maslokowitz and Liebermann: Quoted by Tschernogubow, loc. cit.
- 49 Landsteiner, Müller, and Pötzl: *Wien. klin. Woch.*, 1907, No. 46.
- 50 Browning and McKenzie: *Lancet*, May, 1909.
- 51 Browning and McKenzie, *Journ. of Path.*, January, 1909.
- 52 McIntosh, *Lancet*, May, 1909.
- 53 Fleischmann: *Berl. klin. Woch.*, 1908, No. 10.
- 54 Selmev: Cited by McIntosh, loc. cit.
- 55 Schilling, Claus, and v. Hoesslin: *Deut. med. Woch.*, 1908.
- 56 Harloch and Yakimoff: *Wien. klin. Woch.*, 1908, No. 21 and 40.
- 57 Manteufel: *Arbeit. aus dem K. Gesundheitsamt, Berl.*, Bd. 28, 1908.
- 58 Manteufel and Woithe: *Arbeit. aus dem K. Gesundheitsamt, Berl.*, Bd. 29, 1908.
- 59 Butler: *New York Med. Journ.*, 1909.
- 60 Peritz: *Deut. Zeit. f. Nervenheil.*, 1908, Bd. 36.
- 61 Blumenthal: *Semaine médicale*, 1908, No. 12.
- 62 Kurt Meyer: *Deut. med. Woch.*, 1908, No. 20.
- 63 Wechselmann: *Deut. med. Woch.*, 1909, No. 15.
- 64 Benda: Quoted by Mott, loc. cit.
- 65 Reuter and Schmorl: Quoted by Mott, loc. cit.
- 66 Katzenstein: Quoted by Wechselmann, loc. cit.
- 67 Murero: Quoted by Wechselmann, loc. cit.
- 68 Furecz: *Med. Klin.*, 1907, No. 35.
- 69 Ross and Jones: BRITISH MEDICAL JOURNAL, May, 1909.
- 70 Fleming: *Lancet*, May, 1909.
- 71 Muir and Ritchie: *Bacteriology*, Fourth edition, p. 108.
- 72 See References 12 14 16 24 30 31 45 46 49 70.
- 73 See References 28 30 32 83 84 43 40.
- 74 Levaditi: *Comptes rendus de Biol.*, December, 1907.

NOTE ON ALCOHOL IN RELATION TO MULTIPLE NEURITIS.

By JUDSON S. BURY, M.D.LOND., F.R.C.P.,
PHYSICIAN TO THE MANCHESTER ROYAL INFIRMARY.

NEARLY nine years have elapsed since the epidemic of multiple neuritis which occurred in Manchester and the surrounding district. It will be remembered that during the latter part of the year 1900 a great increase in the number of cases of multiple neuritis was noticed, and especially in persons who were drinking beer. The idea occurred to many medical men that there must be some unusual toxic substance present in the beer, but it is to my colleague, Dr. Reynolds, that the credit is due for first thinking of arsenic, and for first detecting its presence in the beer. His discovery was soon confirmed by others, and the matter was thoroughly investigated.

Before this epidemic it was assumed that the development of neuritis in an alcoholic subject was due to the action of alcohol on the peripheral nerves. Doubts as to the correctness of this assumption were raised by the discovery of arsenic in the beer, and by the views expressed by Dr. Reynolds. The epidemic drew attention to the importance of considering not only whether neuritis in a drinker might be due to the presence in his beverage of some poison other than alcohol, but also as to whether alcohol by itself could cause neuritis.

In his account of the epidemic Dr. Reynolds stated:

I have for many years doubted whether ethylic alcohol *per se* does cause peripheral neuritis at all, and I have personally felt more and more confirmed in this opinion each succeeding year.

Again, in responding to the discussion on his paper read at the Medico-Chirurgical Society he said:

I am willing to admit that alcoholic neuritis exists, but I am not convinced thereof.

He further threw out the suggestion that all cases of so-called alcoholic neuritis might be really due not to alcohol but to arsenic. More recently he has stated that he never meant to deny the existence of alcoholic neuritis, but his belief is that it is of rare occurrence and usually slight in degree.

Such statements were opposed to the generally accepted views on the subject, and it was obvious that subsequent experience was necessary before their correctness could be