that these cases did not include any with disease of the optic tract, the presence of which is generally regarded as a contra-indication to this mode of therapy.

I am particularly indebted to Prof. G. M. Robertson for his help and for permission to publish these notes.

I also desire to acknowledge most gratefully the assistance of Col. W. Glen Liston and Dr. W. O. Kermack, of the Royal College of Physicians Laboratory, Edinburgh, for carrying out the serological tests.

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*The Treatment of General Paralysis by Tryparsamide.**

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In spite of the inability of organic arsenical compounds to stem the course of general paralysis, nevertheless, as each new member of this group appears it is given a trial in the hope that it may do good. This has been done in many cases in the absence of evidence supporting the use of the drug, and where the only justification for its use appears to have been its relation to salvarsan. The results have always proved discouraging, and indeed in many cases the dissolution process has actually been hastened.

Therefore when we came to consider tryparsamide, we felt that it was necessary to obtain somewhat stronger evidence before we were justified in using it even upon a small scale.

The history of the drug showed that each step from its synthesis to its application had proceeded as a logical development based at first on pure experimental evidence and later on clinical experience.

Strictly speaking tryparsamide is not a new drug. Adopting Ehrlich's procedure in his preparation of salvarsan, it was first synthesized by Jacobs and Heidelberger at the Rockefeller Institute in 1915. It is the sodium salt of n-phenylglycineamide-p-arsonic acid, a pentavalent arsenical compound containing 25·4% of arsenic. Its action on various organisms was studied by Brown and Pearce,

* A paper read at a meeting of the Scottish Division held at Gartloch Mental Hospital, November 16, 1926.

who state that in their series of 243 arsenicals there was no other substance that combined so many favourable therapeutic qualities. It remained for five years at the experimental stage, and was exhaustively studied in relation to animal infections due to *Trypanosoma Brucei*, *Gambiense* and *equinum*, and to infections due to *Spirochæta Obermeieri* and *Spirochæta pallida*.

It was first used clinically by Louise Pearce in 1920 in cases of African sleeping-sickness with outstanding results, which have since been confirmed. Smillie used it with success in the *mal de caderas* of horses, and Tyzzer reported favourably on its use in Blackhead in turkeys.

As a result of these extensive investigations certain facts emerged which aroused interest in its use in syphilis, particularly syphilis involving the central nervous system. Below we summarize these important facts. (For references see appended bibliography.)

(1) The drug possesses a marked affinity for the tissues of the central nervous system.

(2) There is no known substance with an equal degree of spirochæticidal action that possesses the same high power of penetrability. Expressed in other words, there is no other substance capable of developing a comparable measure of parasiticidal action in those parts of the body where it is most needed.

(3) The drug has a remarkable stimulating effect upon animal economy. With the exception of cattle, animals not only bear large doses, but appear to thrive on it. It is capable of reinforcing the natural processes of resistance and promoting recuperation.

(4) This stimulus to the defensive mechanism is shown by its action in rabbits infected with *Spirochæta pallida*. Here, small doses augment and hasten spontaneous recovery and induce resolution and healing of syphilitic lesions even in the presence of actively motile spirochætes.

(5) In rats and mice infected with *Spirochæta Obermeieri* the course of the infection could be influenced and spontaneous recovery hastened, although again it was noted that sterilization of the blood-stream was impossible.

(6) The drug yielded wonderful results in rabbits with trypanosomiasis, in which disease there is a distribution of organisms and of lesions in the central nervous system comparable to those of cerebral syphilis in man.

(7) Its value did not depend upon parasiticidal action *per se*, and it was not advocated in the early stages of syphilis, but its value depended on its power of developing spirochæticidal action in hitherto inaccessible foci, and of stimulating the processes of natural resistance.

It is interesting to note at this stage that, according to some observers, the reinforcing of the body's defence mechanism is the rationale for the present malarial treatment of general paralysis.

The first publication on the use of tryparsamide in neuro-syphilis did not appear until May 26, 1923, when Lorenz, Loewenhart and coworkers reported very favourably on a series of 180 neuro-syphilitics that had been under treatment for two years. They stated that it was more effective than any other form of treatment and that clinical and serological improvement was striking. Further reports appeared to confirm these results.

At this critical stage, and when the drug was about to be released

for distribution, the widespread interest in the malarial treatment of paresis tended to direct attention from the arsenical compounds, with the result that further literature was slow in forthcoming, and it would appear that extensive and prolonged investigation has still to be carried out.

We have made a careful analysis of all available literature on the subject, and find that up to April, 1926, about 2,000 cases of neuro-syphilis had been treated by tryparsamide and reported. Most of this work was carried out in America. The great balance of opinion favoured tryparsamide, and there was clinical improvement in about 30% of cases and serological improvement in about 75% of all cases.

Owing to the difficulty in obtaining the drug investigations have been somewhat restricted in this country, and proper interest was not aroused until recently, but work is now being carried out in various hospitals and reports are eagerly awaited. So far British workers have not reported as favourably as American workers, but on the other hand the latter have had more experience.

In October, 1925, we commenced investigations at Gartloch Mental Hospital, and below we give a short account of our experience with tryparsamide therapy.

Seventeen cases of general paralysis were placed under treatment. We regarded as general paralytics these cases which, in addition to the usual physical and mental signs, gave the following readings on examination of the cerebro-spinal fluid.

(1) Positive Wassermann with 0·1 c.c. fluid.
(2) Paretic colloidal gold curve.
(3) Positive Ross-Jones and Pandy tests.
(4) Marked lymphocytosis.

We also regarded a strongly positive serum Wassermann as additional evidence, as it is rarely that the blood in paresis gives a negative reaction. Although contra-indicated by some authorities, we included in the seventeen cases patients in all stages of the disease, among whom were three bed cases showing marked mental and physical deterioration.

We commenced with six 1-grm. doses of tryparsamide, given at weekly intervals; fifteen cases were treated by the intravenous route and two intra-muscularly. During this period one patient was transferred to another hospital and one patient died. The latter had been regarded as a slowly dementing paretic of the facile type. He had been here for three years, his physical condition was good, and he showed slight mental deterioration with no other psychotic symptoms. A week after his sixth injection he complained of feeling unwell. He developed a marked rise in temperature followed by severe congestive seizures, and he died in

a few days. *Post-mortem* showed typical brain changes with marked congestion, but there was no excess of cerebro-spinal fluid and no spirochætes could be found by dark ground microscopy. The liver, kidneys and spleen were somewhat congested, but otherwise normal.

This unfortunate "neuro-relapse," which has already been observed by other workers, was the only outstanding feature of this preliminary trial. There were no eye complications, nausea, vertigo, or other manifestations of toxic disturbance even among the bed cases. We felt justified in increasing the dose. Each patient now received eight 2-grm. injections at weekly intervals, half to one hour after the mid-day meal. No other drug was administered in conjunction with the tryparsamide, as we did not wish to obscure any results that might be forthcoming. For the same reason no alteration was made in the diet or environment of the patients during the treatment.

Two deaths occurred before the course was completed, and in both instances the patients were of the slowly dementing, apathetic type with no other psychotic symptoms; one was more advanced than the other and confined to bed. Death was similar to that mentioned above, and followed a period of severe congestive seizures accompanied by pyrexia. A *post-mortem* was refused in one case, and in the other the *post-mortem* findings were typical. These appeared to be cases of what American workers call "neuro-relapse." On the other hand, the form of paresis present in these cases nearly always proves to be most progressive, most resistive, and the least likely to remit, whereas it is the expansive active, psychotic type which provides the greater number of stationary and protracted forms and appears to be less resistive. Our subsequent results bear this out to a certain extent.

The number of cases under observation was now limited to thirteen. After conclusion of the treatment we allowed two months to pass and then carried out further clinical and laboratory investigations.

Clinical Findings.

(1) Improvement first showed itself during the months of January and February, and in all cases this improvement has held up to the time of writing.

(2) Only two cases failed to benefit (Nos. 12 and 13 in the accompanying list).

(3) Speech, tremor and gait all improved, more especially the latter, and this was one of the first changes to be manifested.

(4) Argyll-Roberston pupils, when present, were unaffected.

(5) Five cases (Nos. 1, 2, 3, 4 and 5) have shown marked remission of mental and physical symptoms and are exceptionally well. They are very steady and useful workers. Nos. 1, 2 and 3 have been granted parole, and Nos. 4 and 5 are being discharged to care of friends.

(6) Three cases (Nos. 6, 7 and 8), previously unemployable and inclined to be dull, listless and foolish, are now willing workers with some degree of initiative.

(7) Two bed cases (Nos. 9 and 10) recovered sufficiently to be up and capable of doing light ward work.

(8) One case, No. 11, a paretic of four years' standing, has remained stationary mentally, but is improving physically.

(9) Case 12 showed no change whatever.

(10) In Case 13, a tabo-paretic with an alcoholic history, the physical condition gradually became worse. He developed bladder complications and broncho-pneumonia and died two months after the course was finished. Throughout he was wonderfully clear mentally. An interesting feature of this case was the development of an optic atrophy. *Post-mortem* showed nothing of particular interest.

(11) Changes were most marked in the expansive type of paretic (Nos. 1, 2, 3, 5, 9), and in the depressed, agitated type.

(12) The slowly dementing, facile and apathetic form showed least change.

(13) Although mental deterioration is still present in a varying degree in all cases there is a marked absence of the psychotic symptoms.

(14) Of the early paretics treated (Nos. 3, 6 and 7), No. 3 improved most. All our other cases were of long standing.

(15) Since the commencement of treatment in October, 1925, there has been a total absence of congestive seizures in the 13 cases cases listed below.

(16) All the patients gained weight with the exception of Nos. 12 and 13. Increase varied from 7 lb. to 28 lb.

Toxic Disturbances.

The cases of so-called neuro-relapse which proved fatal might be regarded as toxic, but on the other hand this occurrence is quite compatible with the progressive nature of the disease. Recent reports, however, incline us to the former view.

Although amblyopia is a very common development in cases treated with tryparsamide and is the one serious complication to

be avoided, the optic atrophy which occurred in Case 13, we regarded as a tabetic development.

Laboratory Findings.

The following table shows the results of tests carried out with blood-serum and cerebro-spinal fluid of thirteen cases of general paralysis, before and after treatment by tryparsamide.

Patient.	Wassermann.		Colloidal gold.	Pandy.	Ross-Jones.	Cell count.
	Blood.	C.S.F.				
1. Before	++++	++++	555554300	+	+	28
After	++−−	++−−	540000	+	+	18
2. Before	++++	++++	555543	+	+	150
After	+−−−	+++∓	00000	±	±	21
3. Before	++++	++++	555542	+	+	55
After	+++−	++−−	5333	+	+	42
4.* Before	++++	..	..	..	..	..
After	++++	+++−	0000	−−	−−	12
5. Before	++++	++++	555540	+	+	18
After	+−−−	+∓−−	0000	++	++	12
6. Before	++++	++++	555540	−	−	55
After	++++	++++	553333	+	+	48
7. Before	++++	++++	5555530	+	+	28
After	++++	++++	55554	+	+	19
8. Before	++++	++++	55554	+	+	82
After	+++−	++++	555543	+	+	81
9. Before	++++	++++	555554	+	+	28
After	++++	+++−	33322	±	±	37
10. Before	++++	++++	5555543	+	+	29
After	++±−	++++	554433	+	+	18
11. Before	++++	++++	5555543	+	+	55
After	++++	+++−	555543	+	+	25
12. Before	++++	++++	555543	+	+	12
After	++++	N———	00000	−	−	18
13. Before	+++−	++++	555554	+	+	14
After	N———	++−−	43	+	+	12
Positive control (repeated)	++++	++++	5555543	+	+	58
Negative control (repeated)	N———	N———	0000	−	−	3

* Too resistive to submit to lumbar puncture.

In cases of general paralysis undergoing no specific treatment the laboratory findings may show extreme variations, and in rare instances during remissions the pathological findings in the serum and the cerebro-spinal fluid are negligible. For these reasons the results of treatment are difficult to gauge. As a rule, however,

the Wassermann and the colloidal gold reactions remain constant and are extremely resistant to arsenical treatment.

In view of this it is interesting to note that in over 50% of the above cases alterations took place in the colloidal gold curve and in the Wassermann reaction. The paretic curve shows a tendency to disappear, with complete absence in four instances, while the Wassermann reaction in both cerebro-spinal fluid and blood-serum shows a tendency to become weaker. These changes were most marked in those expansive and active paretics who had undergone marked mental and physical improvement. In Cases 1, 2, 3, 4, 5 and 9 the laboratory and clinical findings closely coincide.

Conclusion.

In dealing with the treatment of general paralytics, there are certain factors always to be borne in mind which obscure results and lead to misinterpretation. These are: (1) The possible tonic effect of arsenic, resulting in temporary inprovement. (2) The beneficial effect of arsenic in certain meningeal complications which frequently accompany paresis. (3) The possibility of paretic serum and cerebro-spinal fluid undergoing in themselves marked variation. (4) The tendency to remissions.

Taking these facts into consideration, and in view of the limited number of cases which we had under observation, it is extremely difficult to come to any definite conclusion. As, however, only one course of treatment has been tried, and as the improvement which took place in the majority of cases has now held for over six months, we consider these clinical results together with the coincidental laboratory findings of sufficient import to justify further investigations along similar lines.

The most significant features in our series of cases were:

(*a*) Disappearance of the psychoses.*

(*b*) Increase in weight.

(*c*) Absence of seizures.

(*d*) The conversion of listless, dull patients into useful units.

When it is remembered that the successful treatment of ordinary syphilis by arsenic can only be brought about after a three years' course, it would appear in view of the above results that prolonged administration of tryparsamide in general paralysis is at least worthy of a trial, particularly in the expansive, psychotic forms.

* Exception may be taken to this use of the word "psychoses." In using it, however, we have in mind the method of classification of general paralysis adopted by Ebaugh and Dickson: (A) the organic group, (B) organic reactions with functional colouring, (C) transitory psychoses without signs of deterioration.

We are unable to compare tryparsamide therapy with the Wagner-Jauregg treatment as we have had no experience of the latter, but Kirby and Bunker have stated that malaria is the more satisfactory treatment, although serological results are, at times, better with tryparsamide. O'Leary and Baker, at the Mayo Clinic, have treated over 207 cases with tryparsamide and are of the same opinion, but state that it is available for those not suited to the risk of the malaria treatment. Silverston, of Preston, has combined the two, but his results are so far not conclusive.

In view of the general consensus of opinion, it would appear that a preliminary course of tryparsamide followed by malarial injection is at present the most rational method of treatment, particularly in the debilitated type of early paretic.

Technique.

(*a*) Serum Wassermann.

Four-tube method using decreasing amounts of serum down to 0·012 c.c. Stong positive controls (++++) and weak positive (++) were used throughout, also negative controls.

(*b*) Cerebro-spinal fluid Wassermann.

Four-tube method as above, using decreasing amounts of fluid to 0·1 c.c. Fluid was tested as soon after withdrawal as possible.

(*c*) Colloidal gold reaction.

After three years' experience we fully realize that the reliability of this test depends to a great extent upon the colloidal solution. Using triple distilled water we were successful in obtaining solutions of exceptional clarity, of known pH, standardized by the method advocated by Cruikshank and others, and which gave a constant reading in a known case of paresis, but showed no precipitation greater than in a known negative control.

The actual test was a modification of the Lange method advocated by E. R. Stitt. All fluids were tested twice.

Permission to carry out these investigations was readily granted by Dr. A. M. Dryden, the Medical Superintendent of Gartloch Mental Hospital. In the laboratory we were ably assisted by Mr. L. Winkworth, whose experience, especially in connection with colloidal gold technique, proved invaluable. The supplies of tryparsamide used were manufactured by Messrs. May & Baker, Ltd., by arrangement with the Rockefeller Institute.

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*Introverted and Extroverted Tendencies of Schizoid and Syntonic States as Manifested by Vocation.**

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INTRODUCTION.

IT is to Jung, of Zurich, that we are indebted for the attempted division of attitudes of mind into the introverted and the extroverted types. In his *Analytical Psychology* (1) he gives us a chapter on types, and in 1924 appeared his large work on *Psychological Types* (2). According to Jung (1), the introverted type of individual is

* A paper presented at a meeting of the South-Western Division, held at Hereford on October 28, 1926.