DEMENTIA PARALYTICA: THERAPEUTIC MEASURES AND RESULTS.

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CLINICAL MATERIAL.

THE malarial treatment of general paralysis was commenced at the County Mental Hospital, Rainhill, in June 1923; and later, in March, 1927, this form of therapy was augmented by arsenical treatment with tryparsamide.

The total number of patients with general paralysis—all clinical diagnoses being confirmed by serological investigation—admitted from January, 1923 to December, 1928, was 274, and of that number 182 have died, 51 are still resident, and 41 have been discharged as 'cured.'

To claim a scientific cure of this malady there must be, in addition to a remission of the mental symptoms (which determines the discharge of the case from certification), a disappearance of the accompanying physical and serological stigmata. This paper constitutes an attempt to record the after-histories of cases discharged as 'cured' in an endeavour to determine whether or not we can claim a 'scientific cure' for the disease.

Of the 41 patients discharged as 'cured,' over a period of five years, we have been able to keep in touch with 30, 14 of whom have submitted to further investigation of their blood and cerebrospinal fluid.

A preliminary analysis of these thirty cases gives the following statistical results:

1. Four have died. Three of these patients were re-admitted to this mental hospital prior to death. The other patient died at home of an intercurrent disease, having shown no return of mental symptoms.
2. Two other patients have been admitted to other mental hospitals.
3. Twenty-four patients are still alive, enjoying normal mental health.

Of this group of patients, two have been re-admitted to Rainhill, where they have had further treatment and are now discharged as 'cured' for the second time.

In order to facilitate the arrangement of a table analysing the cases, relative to the length of time since discharge, we shall here deal with the two cases which were re-admitted, as mentioned in the previous paragraph, and then dismiss them from further consideration in this series.

CASE I. *T.E.C. Male, age 38.*

This patient was admitted to hospital in April, 1923, and presented a typical clinical picture of grandiose general paralysis, his certification reading as follows: 'Talkative, boastful, self-pleased. Very grandiose and lacking in insight. Memory poor.'

He was treated with induced malaria (twelve rigors) and was considered fit for discharge in November, 1923, having the distinction of being the first case of general paralysis to be discharged as 'cured' from the County Mental Hospital, Rainhill.

He remained in good health mentally and physically, returning to his occupation as ship's steward for three and a half years, i.e., until March, 1927, when, following a prolonged alcoholic carousal, he relapsed mentally and was re-admitted under certification.

Once again clinically he presented all the features of grandiose general paralysis, being 'restless, noisy, excited and violent with numerous delusions of a most exalted character.'

Treatment was instituted consisting of weekly injections of 3 g of tryparsamide, intravenously, for ten weeks. He improved rapidly, both mentally and physically, so much so that his relatives pressed for his discharge before a further course of malaria could be given. He was discharged for the second time in August, 1927, and has remained in good mental and physical condition since that date.

Appended are the details of the various examinations of the blood, cerebrospinal fluid and nervous system at the different times this man came under observation.

Date.	C.S.F.			Blood	
	Globulin.	Sigma.	Gold Curve.	Sigma.	
26.4.23	++	+++	5555552100	++++	At the first examination the Sachs-Georgis reaction was used.
30.3.27	++	3.9	5555543120	4.2	
3.12.28	++	6.3	5555532100	Nil.	

Examination of C.N.S.

Date.	Pupils.	Knee Jerk	Plantar.	Tremors.	Speech.
11.4.23	Unequal. R.>L. Sluggish to light.	Brisk and equal.	Bilateral flexor.	Tongue.	Normal.
18.3.27	Unequal R.>L. Sluggish to light.	Brisk and equal.	Bilateral flexor.	Tongue.	Normal.
3.12.28	Unequal. R.>L. R. Sluggish. L. Inactive.	Brisk and equal.	Bilateral flexor.	Nil.	Normal.

As an indication of the degree of mental recovery and intellectual insight in the above case the following incident may be cited. It was previously noted that the man's occupation was that of ship's steward and that his mental relapse followed an alcoholic debauch. Following his second discharge the patient effected a change in his occupation, becoming a dock-labourer, in order to avoid—as he put it—'booze and women,' a definite indication of clear insight into the cause of his relapse and also a manifestation of self-control.

CASE 2. *M. A. M. Female, age 37.*

This patient was first admitted in March 1927 and presented a clinical picture suggestive of general paralysis, the more prominent features being 'marked confusion with distinct impairment of memory and illusions with respect to the identity of those around her.' The diagnosis was confirmed by serology.

This patient was subjected to malarial therapy, having twelve pyrexial rigors, and showed such pronounced mental and physical improvement that she was discharged as 'cured' in July 1927. An interesting sidelight on her history may here be noted. Prior to her admission to hospital she had been married fifteen years without becoming pregnant.

Immediately following her discharge—after malarial treatment—she became pregnant, remaining well during the whole period of gestation. She was delivered of a child in April, 1928, and eight days later she completely relapsed mentally, necessitating readmission to hospital under certification. She was 'restless, talkative, confused and amnesic. Unable to give a satisfactory account of herself and her habits were faulty.' Immediately after her admission to hospital she had numerous epileptiform seizures associated with much mental confusion and motor restlessness.

She was given a course of ten injections of tryparsamide followed by induced malaria, which spontaneously aborted after the ninth rigor. During the course of treatment the patient had occasional seizures. Mental improvement was again quickly registered and she was discharged for the second time in November, 1928.

Appended are the details of the blood, spinal fluid, and reflex reactions.

Date.	C.S.F.			Blood
	Globulin.	Sigma.	Gold Curve.	Sigma.
30.3.27	+++	21.3	5555542100	21.3
25.4.28	+	4.9	5555431000	3
20.11.28	+	4.9	5555431000	3

Examination of C.N.S.

Date.	Pupils.	Knee Jerk.	Plantar.	Tremors.	Speech.
28.3.27	Equal, inactive to light.	Brisk.	Bilateral flexor.	Nil.	Poor.
25.4.28	Equal, inactive to light.	Brisk.	Bilateral flexor.	Tongue.	Poor.
20.11.28	Equal, inactive to light.	Brisk.	Bilateral flexor.	Nil.	Fair.

A consideration of the two cases detailed above reveals the following points.

1. Rapid and pronounced mental improvement may take place without corresponding improvement in the serological reactions.
2. The mental relapse in both cases was due to an obvious precipitating cause—alcoholic excess in the male; the stress of labour and puerperium in the female.
3. The reflex reactions showed no response to treatment.

ANALYSIS OF CASES.

Now let us consider the fate of the other patients who have been discharged as 'cured' and who are still enjoying mental health.

Below is a Table showing the various periods which have elapsed since their discharge.

Period since Discharge.	Number of Cases.		Totals.
	Female.	Male.	
6-12 months	3	5	8
1-1½ years	3	3	6
1½-2 years	0	1	1
2-2½ years	0	1	1
2½-3 years	0	1	1
3-3½ years	1	1	2
3½-4 years	0	0	0
4-4½ years	0	0	0
4½-5 years	1	2	3
	8	14	22

The above 22 cases comprise eight females and 14 males, six of whom have now been discharged from certification for over three years, during which time they have been perfectly well mentally.

An obvious commentary on the degree of mental improvement is afforded by the fact that of the fourteen male patients twelve are in regular employment; of the other two males one is a casual labourer and the other has had to give up his occupation owing to failing vision (probably a late effect of tryparsamide). In the case of the eight female patients all are performing their own domestic duties satisfactorily, while one has obtained employment as a shop assistant.

In view of the prevailing unemployment affecting practically all sections of the community the above figures are, I think, the best appraisalment of the value of treatment and furnish an indication that the degree of mental recovery is such that ex-patients can successfully compete in the labour market.

Of these twenty-two patients, all of whom have been personally examined during the past few months, twelve have submitted to an investigation of the present state of their blood and spinal fluid. The findings in the individual cases are analysed in the accompanying Tables.

As will be noted, the Sigma reaction in blood and C.S.F. is used, for the following reasons.

1. The technique is simpler than the Wassermann and the possible sources of error less.
2. The result, expressed in units per c.c., based on macroscopic flocculation, gives a quantitative as well as a qualitative index of syphilitic infection. Hence response to treatment can be more accurately gauged.

The first Table (numbers 1-5) records the serological findings and reflex reactions in five cases treated with malaria only, while the second Table

(numbers 6-12) deals with seven cases treated with tryparsamide and malaria. In view of this difference in treatment the results in the two groups will be separately analysed before final comparison is made.

GROUP A.—MALARIA TREATMENT ONLY.

Serological response to treatment.

The globulin content shows a marked diminution in all cases and has been rendered completely negative in case 1.

The Sigma factor in the C.S.F. has been profoundly affected, four of the cases being returned as negative, and case 4 showing a marked reduction from 25 to 2 units per c.c.

The gold curve in four cases has been definitely affected in the direction of a return to the normal. Cases 1 and 4 give the best readings. On the other hand, case 5 still registers a definite paretic curve.

The blood Sigma units have been reduced in all cases except case 5, in which there is an increase. It is interesting to note that no case has been returned as negative to somatic syphilis.

Reflex response to treatment.

The pupillary reflex is the only one showing any change. Case 2 is recorded as exhibiting the Argyll Robertson pupil phenomenon in 1925 and now gives normal responses. All other reflex reactions have been unaffected.

Tremors where present before treatment have completely cleared up in all cases.

Speech where impaired prior to treatment has distinctly improved.

GROUP B.—TRYPARSAMIDE AND MALARIA TREATMENT.

Serological response to treatment.

The globulin content has been materially reduced in all cases, Case 7 being returned as negative.

The Sigma factor in the C.S.F. has been rendered negative in six of the cases and materially reduced (from 6.2 to 1.2 units per c.c.) in case 10.

The gold curve has been definitely affected by treatment, in the direction of a return to normal, in five of the cases. Cases 10 and 12 still yield typical paretic curves.

The blood Sigma has been rendered completely negative in two cases, while the other five cases show material reduction therein.

Reflex response to treatment.

The pupillary response has been affected in five cases. Case 7 was recorded on admission as pre-Argyll Robertson, but following treatment the responses are now normal.

RECORDS OF FIVE CASES

Name, sex and age.	Dates of		Blood and cerebrospinal fluid.				
	admission.	discharge.	Date of examination	Globulin.	Sigma	Gold curve.	Blood Sigma.
(1) A.M. Female Age 51	11.10.1923	29.3.1924	20.10.1923	++	Sachs Georgis. +++ve	Typical Paretic.	Sachs Georgis. +++ve
			4.2.29	Nil.	Negative.	0011000000	31.95
(2) H.M. Male Age, 42	18.6.25	27.10.25	19.6.25	+++	3.9	5555544100	26.1
			20.1.29	±	Negative	2233210000	3
(3) P.J.D. Male Age, 39	27.6.25	29.5.26	30.6.25	+++	18.6	5555552100	62.7
			24.1.29	+	Negative	1121000000	13.95
(4) A.E.K. Male Age, 36	19.11.26	30.5.27	22.11.26	+++	25.35	5555554300	25.35
			27.10.28	±	2.025	0001110000	4.95
(5) E.Mc.M. Female Age, 48	8.1.26	17.1.28	13.1.26	+ ±	2.4	5555431000	Negative
			24.1.29	±	Negative	5554442000	12.6

TREATED WITH MALARIA.

<i>Mental state on admission.</i>	<i>Examination of nervous system.</i>					
	<i>Date.</i>	<i>Pupils.</i>	<i>Knee jerk.</i>	<i>Plantar.</i>	<i>Tremors.</i>	<i>Test words.</i>
Restless, noisy and confused. Says she is Queen of England and has many estates. Wet and dirty habits.	12.10.23	Small equal inactive to light.	Not elicited.	Bilateral flexor.	Nil	Good.
	4.2.29	Small equal inactive to light.	Not elicited.	Bilateral flexor.	Nil.	Normal.
Restless, talkative and confused. Delusions of an exalted character. Says he can swim the Channel and beat Jack Dempsey.	18.5.25	Equal inactive to light.	Brisk.	Bilateral flexor.	Nil.	Normal.
	20.1.29	Equal react normally.	Brisk.	Bilateral flexor.	Nil.	Normal.
Confused and exalted. Memory impaired. Cannot give a good account of himself.	27.6.25	Equal react normally.	Brisk.	Bilateral flexor.	Tongue and lips.	Normal.
	24.1.29	Equal react normally.	Brisk.	Bilateral flexor.	Tongue and lips.	Fair.
Lost and confused. He can give no rational account of himself. Habits faulty.	22.11.26	R. > L. Sluggish to light.	Brisk.	Bilateral flexor.	Tongue and lips.	Fair.
	27.10.28	R. > L. Inactive to light.	Brisk.	Bilateral flexor.	Nil.	Normal.
Restless, confused and incoherent. Occasionally noisy and excited. Wet and dirty in habits.	8.1.26	Normal.	Brisk.	Bilateral flexor.	Tongue and lips.	Very bad.
	24.1.29	Normal.	Brisk.	Bilateral flexor.	Tongue and lips.	Fair.

RECORD OF SEVEN CASES TREATED

Name, sex and age.	Dates of		Date of examination.	Findings in			
	Admission.	discharge.		Blood and cerebrospinal fluid.			
(6)				Globulin.	Sigma.	Gold curve.	Blood sigma.
T.E.C.			21.3.27	++	Negative.	5555311000	4·8
Male	18.3.27	29.10.27	12.19.27	±	2·34	4443310000	1·34
Age, 45			27.10.28	+	Negative.	0011100000	Negative.
(7)			2.8.27	+++	1·2	5555420000	1·2
R.F.							
Female	29.7.27	20.12.27	19.12.27	+	Negative.	3222100000	Negative.
Age, 42			13.10.28	Nil.	Negative.	0001000000	Negative.
(8)							
R.G.			15.8.27	++	4·3	5555553100	21·3
Male	11.8.27	24.2.28	17.1.28	±	Negative.	5554210000	21·3
Age, 35			13.10.28	±	Negative.	0011010000	0·72
(9)							
H.P.			22.6.27	+ ±	4·95	5555543100	61·2
Male	21.6.27	23.3.28	12.10.27	±	1·44	5555431000	1·5
Age, 43			27.10.28	±	Negative.	2234120000	1·7
(10)			12.10.27	++ ±	6·2	5555555210	1·4
P.M.			18.1.28	++ ±	1·3	5555554410	1·4
Male	28.9.27	23.3.28	1.3.28	++	1·3	5555310000	4·2
Age 48			24.10.28	+ ±	1·2	5545531100	0·5
(11)							
M.A.			14.9.27	++	6·9	5555554200	25·35
Female	9.9.27	28.4.28	12.3.28	+ ±	2·025	5555421000	7·5
Age 42			13.10.28	+	Negative	3444321000	4·95
(12)			6.1.28	+++	1·5	5555555500	3·9
M.F.			23.3.28	+	1·1	5555541000	0·975
Female	30.12.27	22·6.28	11.6.28	+	Negative	5555541000	1·2
Age 34			18.1.29	±	Negative.	5554210000	0·7

WITH MALARIA & TRYPARSAMIDE.

<i>Mental state on admission.</i>	<i>Examination of nervous system.</i>					
	<i>Date.</i>	<i>Pupils.</i>	<i>Knee jerk.</i>	<i>Plantar.</i>	<i>Tremors.</i>	<i>Speech.</i>
Depressed, confused and memory impaired. Takes no interest in his surroundings. Habits faulty.	18.3.27	Small, irregular, inactive to light.	Normal.	Bilateral flexor.	Tongue.	Good.
	27.10.28		Normal.	Bilateral flexor.	Nil.	Normal.
Restless, resistive and confused with impairment of memory. Habits faulty.	39.7.27	Dilated and sluggish to light.	Brisk.	Bilateral flexor.	General.	Very bad.
	13.10.28	Equal and active to light.	R. + L. ++	R. : Flexor. L. : Extensor.	Nil.	Normal.
Restless, talkative, excited and exalted. Memory poor. He was apprehended by police in an attempt to swim from L'pool to Ireland.	12.8.29	Equal and active to light.	Normal.	Bilateral flexor.	Tongue.	Fair.
	13.10.28	Equal. R. Normal L. Sluggish	Brisk.	Bilateral flexor.	Nil.	Normal.
Restless, noisy and excited, violent, resistive and grandiose.	21.6.27	Unequal L. > R. Inactive to light.	R. present L. Not elicited.	Bilateral flexor.	Lips and tongue.	Bad.
	27.10.28	Unequal L. > R. inactive to light.	Normal	Bilateral flexor.	Nil.	Normal.
Restless, excited and confused and at times noisy, violent and destructive. Habits faulty. Clinical diagnosis : Mania.	30.9.27	Equal and active to light.	Brisk.	Bilateral flexor.	Nil.	Good.
	24.10.28	Equal. R. Sluggish L. Normal.	Brisk.	Bilateral flexor.	Nil.	Good.
Restless, talkative and confused. Memory impaired. Habits faulty.	9.9.27	Unequal R. > L. Sluggish to light.	Normal	Bilateral flexor.	Nil.	Poor.
	13.10.28	Unequal R. > L. Noreaction to light.	Normal.	Bilateral flexor.	Nil.	Fair.
Restless, talkative, excited, noisy and confused. Memory impaired.	30.12.27	Unequal L. > R. R. inactive L. Sluggish	Not elicited	Bilateral flexor.	Tongue.	Normal.
	18.1.29	Unequal L. > T. inactive to light.	Not elicited	Bilateral flexor.	Nil.	Normal.

On the other hand, cases 8, 10, 11 and 12 have all shown further pupillary change of a pathological nature—an indication that the disease process continued to exercise its effects in spite of active treatment.

The knee-jerk has been affected in cases 7 and 9. The former shows exaggeration of the reflex on the left side as part of an upper motor neurone lesion which has developed. The latter manifests a return to normal.

The plantar response was only affected in one case (No. 7), becoming extensor in type, indicating together with increased deep reflexes and absent abdominal response on the same side the development of an upper motor neurone lesion.

Tremors present before treatment have cleared up in all cases.

Speech has been definitely improved in all cases affected.

It is obvious from a perusal of the two sets of findings detailed above that the results are substantially similar in both groups, the effect of treatment with malaria alone producing just as pronounced a response in the C.S.F. as the combined therapy. The only essential difference in the two groups of results is that tryparsamide seems to have effected a more substantial reduction of the somatic syphilitic factor.

In view of the above parallelism of results the question naturally arises, why use tryparsamide at all?

The answer to the query is based on clinical experience of the nursing of cases of general paralysis and in the writer's opinion can be summed up thus.

The employment of tryparsamide as a therapeutic agent succeeds in 'rescuing' patients who are in very poor physical condition and by effecting a substantial increase in body weight and distinct improvement in general physique brings them into a fit state for the employment of malaria as a 'curative' factor. Or to put this observation in another way. A fair number of patients with general paralysis are admitted in such poor bodily condition that to employ malaria as an immediate therapeutic factor is to court an early demise, due to the added physical prostration consequent upon the fever. Such cases as these materially benefit by a preliminary course of tryparsamide.

If the above observation is a true statement of fact, then we should expect to find that the death rate from general paralysis has shown a definite reduction since the advent of tryparsamide as a 'rescuing' factor.

The accompanying figures are available in confirmation of the above contention. As we have noted elsewhere, malarial therapy was commenced at this hospital in June, 1923, and tryparsamide added in March, 1927. We have therefore, chosen figures dealing with the death rate from general paralysis covering the years 1924 to 1928.

These figures show that in 1928, when the effect of the additional tryparsamide therapy was becoming operative, there occurred a pronounced drop in the percentage death rate from general paralysis. The figure 15.2 is the lowest death rate from that disease recorded at Rainhill during the past twenty years.

<i>Year.</i>		<i>Death rate from general paralysis.</i>
1924	Malaria only.	18.4 per cent. of total deaths.
1925		22.1 per cent. of total deaths.
1926		25.5 per cent. of total deaths.
1927		22.6 per cent. of total deaths.
1928	Malaria and tryparsamide.	15.2 per cent. of total deaths.

While recording these figures in favour of tryparsamide as a therapeutic agent and successful adjunct to malarial treatment, it is incumbent upon us to state that out of 90 cases of general paralysis, treated with this arsenical compound since March, 1927, the following complications have been encountered.

<i>Complication.</i>	<i>No. of cases.</i>
1. Jaundice occurring during treatment.	6
2. Arsenical dermatitis.	1
3. Peripheral neuritis.	1
4. Visual upset (a) Complete blindness	3
(b) Dimming of vision.	3

Thus while acclaiming tryparsamide as an important therapeutic factor, it is obvious from the above figures that the employment of the drug is fraught with possible danger due to the onset of serious complications, the most important of which is optic atrophy. Most of the above complications occurred during the first few months of the use of the drug, and since the adoption of greater caution in dosage, and the employment of the following methods, none have been encountered.

An attempt is made to assess the visual acuity of the patient before treatment with tryparsamide is instituted. Usually the mental condition of the patient is such as to preclude a thorough ophthalmological investigation being made, but as a general rule by asking him to read a passage from a book and noting the distance at which the print can be correctly translated, a defect of any moment, if present, can be detected. The mapping of the visual fields is in most cases impossible, as the patients are generally incapable of the requisite sustained intellectual co-operation. The fundus oculi is carefully examined.

If any visual defect is suspected, the employment of tryparsamide should be proceeded with cautiously (i.e., commence with 1 instead of 3 g and give the injections fortnightly, gradually increasing to the maximum dose). In addition the nursing staff should be taught to observe carefully the visual activities of patients under treatment and report any suspicious signs.

In a similar manner hepatic upset may be minimised by an investigation of liver function before and during treatment. The laevulose test is employed before treatment is commenced and if any dysfunction is detected proceed cautiously with the drug. During treatment the state of the liver should be gauged by the Van den Bergh serum reaction.

Further, the possible harmful effect of arsenic on liver tissue can be guarded against by the employment of the following technique :—

Patients should receive a meal, rich in carbohydrate, a few hours before the injection is to be made. The rationale is that, if the liver cells are filled with glucose, there is no room for noxious substances such as arsenic. If toxic manifestations should manifest themselves, the intravenous injection of 0.75 g of sodium thiosulphate on alternate days is useful, as a soluble arsenate is formed which augments the excretion of the drug.

CONCLUSIONS.

1. Malaria alone is as effective as the combined therapy in producing a remission of mental symptoms and changes in the serological reactions.

2. Tryparsamide is an important adjunct to malaria, acting as a general physical tonic, allaying motor restlessness, and thus making subsequent nursing through the pyrexial attack easier and less fraught with danger to the patient.

3. Tryparsamide is apt to induce serious complications, the more important being visual defect and hepatic upset. The drug should therefore be used cautiously and adequate safeguards and controls employed.

4. The word 'cure' being defined as a complete remission of mental symptoms, serological changes and accompanying physical signs, no case recorded in this series can be said to have been completely cured.

5. If we are ever to record a complete scientific cure of general paralysis, it will come from effectively following up these cases after discharge from lunacy certification, so that the ever-present syphilitic factor can be adequately treated.

I should like to express my thanks to the Medical Superintendent, Dr. E. F. Reeve, for his helpful criticism and interest, and also to Mr. H. Bean, chief laboratory assistant, who has undertaken the routine serological examinations.