I

NEUROSYPHILIS: ITS TREATMENT AND PROPHYLAXIS

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It is now twelve years since the malaria centre at Horton was first established for the treatment of cases suffering from general paralysis of the insane. Before the new Mental Treatment Act came into operation treatment was limited to certified cases, but since 1930 it has been possible to admit voluntary patients: prevention and treatment of mental illness are the aims of present-day psychiatry and have replaced the old idea of detention and, to some extent, the necessity for certification.

Some 800 cases of G.P.I. have been treated by malaria, and nearly 200 have been admitted in whom the disease was too far advanced to allow of any treatment, other than adopting palliative measures until an early death supervened. Unfortunately, much of our information regarding the history of the patient, his relatives and his family, is inadequate, but during the past year it has been possible to conduct more extensive inquiries into family histories, a great deal of very painstaking and valuable work having been done for us by our social worker, Miss Le Mesurier, without whose help this investigation could never have been carried out. We would like also to record our thanks to Colonel Harrison for his advice and criticism. It will not be possible to analyse all our material for some time to come, but the figures given to you to-night relate to 458 cases, 320 men and 138 women.

To workers in venereal diseases the interest lies primarily in curing syphilis in the initial stage. Yet, in spite of apparently adequate treatment, late nervous manifestations supervene in some cases; and there is also the problem of the defaulter, and of the syphilitic who acquires an infection of which he or she is unaware and who therefore does not seek treatment. A further problem is the question of the subsequent marriage of the

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syphilitic, and of the risk of infection in the marital partner and offspring. The criterion of cure in the early stage is your concern. Are you satisfied that it will prevent late neurosyphilis? The long latent period of neurosyphilis calls for a better liaison between the V.D. worker on the one hand and the neurologist and psychiatrist on the other. Having this in mind, we would illustrate our meaning by bringing to your notice three aspects of the problem of neurosyphilis: (1) the employment of ordinary antisymphilitic treatment, (2) the incidence of syphilitic infection in partners and their families, and (3) the prognosis and treatment of the asymptomatic case with positive serological findings in the blood and C.S.F.

ANTISYPHILITIC TREATMENT BEFORE MALARIA

In all our cases, unless otherwise stated, the patient has definitely developed G.P.I., some cases being admitted in the early, others in the fully developed or advanced stages. The diagnosis has been confirmed by the examination of the cerebro-spinal fluid. We have divided our patients into three groups: (1) those who received treatment for primary or secondary syphilis only, (2) those who were treated in the primary stage and in addition at some later period, and (3) those who only received antispecific treatment for late or latent syphilis. The distribution of the cases is shown in Table I. It is well

TABLE I
PATIENTS TREATED FOR SYPHILIS

	Total number of cases			
	50 Women, including 1 meningo-vascular		84 Men	
		Per cent.		Per cent.
For congenital syphilis.	4	...	8	—
For 1 ^y or 2 ^y syphilis	8	...	16	37 ... 44
For 1 ^y or 2 ^y and late or latent syphilis .	4	...	8	21 ... 25
For late or latent syphilis	34	...	68	26 ... 31

known that with parenchymatous involvement of the C.N.S., a history of primary syphilis or of any secondary manifestations is often not forthcoming. A history of primary infection is more common in men than in women,

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but a relatively higher proportion of women seek advice in the late neurosyphilitic stage.

The data available can be usefully considered under the following headings: (1) the incubation period of G.P.I., (2) the reasons for which patients seek treatment in the late stage of syphilis, (3) the duration and nature of the treatment prior to malaria, (4) serological examinations, (5) the fate of these cases following malaria therapy and (6) the effect of malaria on the serological reactions.

THE INCUBATION PERIOD OF G.P.I.

The date of the original infection is known in fourteen women and sixty-eight men. It is not possible to draw any definite conclusions regarding the length of time that elapses between the primary attack and the subsequent onset of G.P.I. Even if one merely divides them into two groups, (1) those cases who received treatment in the pre-arsenical period, and (2) those who have been treated by compounds of arsenic, one must remember that the incubation period of the pre-arsenical era is necessarily long; no doubt shorter incubation periods were met with, but such cases have long since died before the advent of malaria therapy. Consequently those pre-arsenical cases now under review must have acquired the infection at the latest before 1910, and we find that for 20 men the average incubation is 33 years, ranging from 50 years to 26. There are only four recorded instances among the women, and they vary from 25 to 31 years, an average of 28 years. In the remaining cases arsenical therapy was employed, in some supplemented by mercury and iodides; here again the average incubation period for the women shows a tendency to be shorter, 14 years for the women and 17 for the men, the shortest periods being 7 and 9 years respectively, and the longest 20 and 22. Several years have yet to pass before one can draw any conclusion as to the influence of modern treatment on the subsequent development of G.P.I. Will long incubation periods of 30 years and over still occur? Our figures are too small to allow of any precise statement regarding the effect exercised by adequate or inadequate treatment for the primary attack. Among 48 men it would appear that there is no appreciable difference, but in 10 women, 5 receiving three and two

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years systematic treatment, and 5 defaulting before the expiry of seven weeks (most of them after two weeks) there is a striking difference, the incubation for the intensive treatment being on an average 10 years, while in the second group the period is lengthened out to 18 years.

THE REASONS FOR WHICH PATIENTS SUFFERING FROM LATE OR LATENT SYPHILIS HAVE BEEN GIVEN TREATMENT

These are shown in Table II., and include the onset of tabes (sometimes with ocular disorders), somatic lesions,

TABLE II
REASONS FOR ANTISYPHILITIC TREATMENT

	Men	Women
Tabes	19 (4 with optic atrophy)	10 (3 with optic atrophy)
Somatic lesions	4	3
Paralysis or other meningo-vascular signs	4	3
Latent syphilis	7	6
Mental symptoms	11	14
Total	45	36

motor paralysis, fits, early mental symptoms and lastly latent syphilis discovered in the course of a routine examination.

In the tabetic group commencing optic atrophy is often the first reason for seeking advice. Inco-ordination and other tabetic signs also demand notice. Somatic lesions are of interest if only for the reason that they do coexist with neurosyphilis; amongst the men a perforated palate, an aortic aneurysm, V.D.H. and syphilitic ulcers on the leg are recorded; in the women syphilitic laryngitis, ulceration of the palate and leucoplakia of the tongue. Hemiplegia, diplopia, and fits are exhibited in the meningovascular type of lesion, and there is no reason to doubt that G.P.I. does become superimposed in some of these cases at a later date.

Those cases who are regarded as suffering from latent syphilis are generally discovered in the course of routine examination or because some other member of the family

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has been found to be suffering from syphilitic manifestations. One man (as shown in Table III.) presented himself at intervals of six years with acute gonorrhœa ;

TABLE III¹
TREATMENT FOR PRIMARY AND LATENT SYPHILIS
A.E.C., born 1897

1917	1 st syphilis.	4 courses, about 24 injections. Last W.R. —ve	
1924	Acute gonorrhœa	N.S. 3.4 gm.	
	W.R. ++	Bi 1.6 gm.	
1934	Gonorrhœa	N. Stab. 1.65 gm.	
		Bi 9.96 gm.	
7.5.36	Admitted Horton, depressed.	B.T. Malaria	Died 24.6.36
	Serum +30+ ++++		P.M. Iron reaction ++
	C.S.F. +30+ ++ ++		Typical histological ap- pearances of G.P.I. fairly well marked.
	55555432 ¹		

on each occasion he received antisyphilitic treatment in addition to the usual irrigation because he had a strongly positive Wassermann reaction of the blood. The mental symptoms presented were nearly always the precursors of the development of G.P.I. itself, in other words the patient was entering the preparetic stage of the disease. In these latter cases the time period before G.P.I. is fully established is short, for the men an average of eight months, but in the case of the women the period is longer, possibly because the simple dementing form of G.P.I. with its insidious onset is more common. Many tabetics, too, are not discovered until the preparetic stage is reached ; of the 19 males, 7 were definitely beginning to exhibit mental symptoms. Other tabetics and the patients in the remaining groups were all diagnosed several years before the onset of G.P.I. The complete absence of any nervous lesion at the time when they received antisppecific treatment has been recorded in a few cases.

The length of time before these various groups were admitted to hospital with G.P.I. is shown in Table IV.

¹ Where serological results are tabulated, the first column for serum is the Wassermann reaction, the second the Meinicke Klarifikation Reaktion. In the C.S.F. results the first column is the Wassermann, the second the cell content, the third the protein content, sometimes recorded as milligrammes per cent., and the fourth the colloidal gold reaction. In all cases reported from Horton the tests have been carried out at the Central Pathological Laboratory, Maudsley Hospital.
For technique see "Memorandum on the Wassermann Reaction in Mental Hospital Practice," by S. A. Mann and F. Partner, L.C.C. Publications.

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TABLE IV
TIME INTERVAL BETWEEN ANTISYPHILITIC TREATMENT
AND CERTIFICATION

Clinical Group	Men				Women			
	No. of cases	Average interval	Shortest interval	Longest interval	No. of cases	Average interval	Shortest interval	Longest interval
Latent syphilis . . .	7	7 yrs.	2 yrs.	14 yrs.	8	6 yrs.	4 yrs.	9 yrs.
Somatic lesions . . .	4	7 "	2 "	20 "	2	5 "	2 "	8 "
Tabes	15	8 "	2 "	14 "	6	3.5 "	2 "	10 "
Tabetic optic atrophy .	4	6 "	5 "	7 "	3	3.5 "	6 mos.	7 "
Meningo-vascular lesions	4	7 "	4 "	9 "	3	3 "	1 yr.	4 "
Mental	11	8 mos.	1 mo.	1 yr. 8 mos.	13	1 yr.	9 mos. 1 mo.	3 "

THE NATURE AND DURATION OF TREATMENT

In the majority of cases it has not been possible to obtain details of treatment for primary and secondary syphilis ; in many patients either the infection passed unnoticed or they prevaricate. Some, although aware of

TABLE V
G.P.I. FOLLOWING INTENSIVE TREATMENT FOR
SECONDARY SYPHILIS
H. H., born 1884

Symptoms and Serology	Treatment
3.9.20 2 ^y syphilis, sore 3/12, rash, sore throat 2/12 Throat patches, Sp ^s . ++ W.R. ++	Sept.-Nov. 1920 N.A.B. 6.3 gm., Hg 9 gm. Jan.-May 1921 " 6.3 " " 9 "
May, 1921 W.R. negative	Aug.-Nov. 1921 " 6.3 " " 8 "
Nov. 1921 W.R. negative	Feb.-Mar. 1922 " 3.4 " " 4 "
20.9.22 W.R. ++	Oct.-Dec. 1922 " 4.8 " " 7 "
4.5.23 } W.R. negative	Defaulted.
13.7.23 } W.R. ++	Nov. 1923-Mar. 1924, Novarsan, 4.5 gm., Hg 1 gm., Bisoxyl 10 c.c.
22.10.23 W.R. ++	Defaulted.
30.5.24 W.R. negative	5.12.34 Pil. Hg. Flav. Iod. (28). Ceased attendance.
Nov. 1934 Certified. Grandiose and hallucinated. Serum +30+ +++++ C.S.F. +30+ ++ ++ 555554321 G.P.I. now arrested. Physical condition fair, mental condi- tion poor.	

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infection, received no treatment, some defaulted soon after treatment was initiated, while others received courses up to two or three years (*e.g.*, see Table V.), and in one or two instances “ until the patient was cured and the blood Wassermann negative.”

Our main interest lies in the nature of the treatment applied to those cases who came under the notice of a physician in the late and latent stages of neurosyphilis. Particulars of treatment in the late stages of syphilis have been obtained in most of our recorded cases (36 women and 45 men). Here, too, by reason of defaulting, treatment is totally inadequate in several cases, but, on

TABLE VI
TABO-PARETIC TREATED FOR NINE YEARS UNTIL
CERTIFIED
C. C., born 1881

Symptoms and Serology	Treatment
1905 1 st syphilis.	
Feb. 1926 Muscular pains W.R. +3	Feb.-Mar. 1926 KI, gr. x, t.d.s.
Apr. 1926 Tabes	Apr.-Sept. 1926 Iodo-Bi of Quinine. 20 injections.
Oct. 1926 W.R. negative	Sept. 1926-Feb. 1928 Hg Biniodide
Jan. 1927 W.R. negative	Bismogenol. 8 injections.
Sept. 1929 C.S.F. W.R. ++	Feb. 1928-May 1935 Hg Biniodide, Mist. Pot. Brom., at fairly regular intervals.
July 1934 C.S.F. W.R. ++	
May 1935 Certified	July 1935 Quartan Malaria.
Serum +30+ ++++	
C.S.F. +30+ + ++	
5554321000	
Apr. 1937 Demented.	

the other hand, some patients submit to years of repeated courses of arsenical injections, alternating with mercury and iodides by the mouth. In the tabetic group of men we have instances of patients continuing treatment over four, six, eight and even nine years. The same story is found with some of the latent group, indeed in some cases (*e.g.*, as shown in Table VI.) treatment is continued over several years until G.P.I. supervenes, with the consequent removal of the patient from the clinic to which he has been so faithful.

Mercury and iodides alone were given to four women and five men, and in the remainder mercury and iodides

were frequently included, though the main basis of treatment was a course, or repeated courses, of N.A.B. and other trivalent preparations. One man, probably a congenital G.P.I., received a course of salvarsanised serum. Only in two men and two women was pentavalent arsenic given in the shape of tryparsamide, and all four were tabetics in the preparetic stage. The treatment to other preparetic cases consisted solely of various combinations of N.A.B., stabilarsan, acetylarsan, bismuth preparations, mercury and iodide and mercury inunctions.

SEROLOGICAL EXAMINATIONS

Serum Wassermanns were done in many cases, and in one or two instances were repeated after treatment until a negative serum was obtained. Of far greater importance is an examination of the cerebro-spinal fluid. It is true there are cases who refuse to submit to this examination ; *yet the importance of doing a lumbar puncture in a late or latent case with a seropositive Wassermann reaction cannot be overestimated.* It is a matter for regret that so few spinal fluids are examined ; in the group of patients now under discussion, the fluids of 6 women and 18 men were tested ; 5 of the women had already reached the preparetic stage, and the sixth was a tabetic. Of the men examined 8 were tabetics, 6 were incipient G.P.I.'s, 2 had fits and 2 hemiplegia. There is no record of a case being investigated with a negative result ; every case had evidence of involvement of the nervous system, and we have no record of a lumbar puncture ever having been done in a case which showed *no* mental or neurological signs and symptoms. A seronegative Wassermann reaction, where the Wassermann reaction has previously been positive, is no guarantee against invasion of the nervous system by the spirochaetes, unless a lumbar puncture is performed and the Wassermann reaction of the C.S.F. is found to be entirely negative. Nowadays it is not uncommon to find a serum negative and the C.S.F. positive (see Tables VII. and VIII.), which, if the serum alone is tested, leads the physician to an erroneous conclusion and affords the patient a false security. At the risk of making invidious comparisons, we have a record of a female patient who was attending the V.D. clinic at St. Thomas's in 1927. The blood W.R. was

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strongly positive. After treatment this had become negative in 1929 and she was strongly advised to submit to a lumbar puncture, but refused. This woman is the only instance in our records of a non-paretic or non-

TABLE VII
PATIENTS WITH NEGATIVE SERA AND POSITIVE C.S.F.'s
Men

	Previous treatment where known	Serum	C.S.F.		
1. L. S.	1930 N.A.B. 7-15 gm. Bi Sal 15 c.c.	- -	++		5555554320
2. J. S.	1932 B.T. malaria 1932 N.A.B. Hg inunc- tions. B.T. malaria	- -	+15+ ++ ++		5555542100
3. F. T. C.	1933 Artificial pyrexia. Hg and KI	- -	+3 + →		4432221000
4. L. O.		- -	+3 + - +		5443211000
5. R. M.		- -	+2 + + +		5544321000
6. T. B. J.		- + + +	+30+ + + +		5555554210
7. T. E. B.		- + + +	+3 + + + +		555555321
8. J. E. R.		- + + + +	+2 + + +		5555432100
9. A. J.		- + + + +	+3 + + +		5543211000
10. A. H.	2 years treatment	- + + + +	+3 - + +		5544332100
11. W. S.	1934 B.T. malaria	- + + + +	+6 - + +		0012321000
12. E. H.	4.11.33. B.T. malaria	- + + + +	+6 + + +		5544332100
13. V. K.	1933 Hg and KI 7'35 B.T. malaria	{ - + + +	+ + - -		-
14. A. G. B.		-	+3 - -		1122210000
15. T. H.		-	+3 + + +		5555443210

TABLE VIII
PATIENTS WITH NEGATIVE SERUM AND POSITIVE C.S.F.
Women

	Previous treatment where known	Serum	C.S.F.		
1. L. D.	1934 B.T. malaria	- -	+15 ++ ++		2345432100
2. K. B.		- -	+15 ++ +		3455432100
3. L. F. W.		- -	+3 + - -		3322110000
4. A. S.	Treated for 1 ^y syphilis	- + + + +	+15 + + +		5555554321
5. L. N.	1928 Treated	- + + + +	+6 + + +		5555543210
6. B. R.		- + + +	+6 + + +		555555421
7. E. D.		- + + +	+8+ + + +		5555543210
8. A. D.		-	+20+ + + +		5555432110
9. E. L. B.		-	+20+ + + +		444322100
10. J. A. W.		-	+40+ + + +		555555432
11. R. E. A.		-	+30+ + + +		5555543000
12. S. G.		-	+6+ + + +		5555554321
13. E. J. H.	Treated for eyes	-	+6+ + + +		5544321000
14. E. O.	30 injections N.A.B.	-	+30+ + + +		5555554320

tabetic who was urged to have the C.S.F. examined. In 1935, six years later, she was admitted to Horton, with the following findings: Serum W.R. +30+, M.K.R. + + + +, C.S.F. W.R. +30+, Cells ++, protein ++, Lange 5555554321.

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THE FATE OF THE CASES FOLLOWING MALARIA THERAPY

Of 50 women 10 are dead and 22 discharged, of whom 4 have been readmitted; of 84 men 26 are dead and 25 have been discharged, 2 being readmitted. Time does not permit of analysis of these figures, but we have pointed out elsewhere* that results of malaria therapy, though undoubtedly superior to other forms of therapy, are disappointing. Nevertheless, we believe that malaria is an effective therapeutic agent in about 85 per cent. of our cases, and we consider that the relatively small number of clinical recoveries which we obtain is due to the fact that irreparable damage is done to the brain by the spirochætes before the malaria therapy is given. Is this a matter for surprise when patients receive varying and apparently useless kinds of treatment over still more varying periods of time, until finally they become psychotic? Malaria, in order to achieve successful results, must be applied at the onset of the disease, and it strikes one as being somewhat Gilbertian that this most hopeful method of therapy should in the majority of cases be withheld from the patient until he has acquired the stigma of insanity, so that his one chance of salvation is to fall into the dread hands of the psychiatrist and not into those of our non-alienist brethren.

THE EFFECT OF MALARIA ON THE FLUIDS

In the past year we have examined the fluids of all our treated cases in hospital and have been impressed with the significance of the results. Table IX. illustrates the examination of those cases referred to in this paper.

A word of explanation is needed regarding these figures. The proportion of completely negative and partially reduced fluids is considerably higher in the women than the men. This can be explained by the fact that the women examined were older hospital cases than the men; malaria therapy for women was commenced at Horton in 1925, but it was not until 1932 that facilities for treating men were provided. The result is that in the majority of the men tested not more than one year has elapsed since the induction of malaria; the twenty-two reduced fluids

* "After Results of Malaria Therapy," W. D. Nicol and E. L. Hutton, *Proc. Roy. Soc. Med.*, March, 1937, Vol. XXX.

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will probably give completely negative results at the end of another year or so, and of the fifteen still strongly positive many will have become reduced. The interesting feature is that malaria alone will produce these negative results. In the majority of the women malaria and no subsequent antisyphilitic treatment has been employed ; with the men for some time tryparsamide was combined with malaria therapy, but for the past year, in the light of our findings in the case of the women, we have discontinued all supplementary forms of treatment. It has long been our experience that if a patient does not react favourably to pyrexia induced by an adequate course of malaria further treatment will produce little or no mental improvement. On the other hand, those patients

TABLE IX
SEROLOGICAL FINDINGS IN THE C.S.F. FOLLOWING
MALARIA

	Women	Men
Number examined	20	41
Completely negative fluid	6	4
Reduced fluid	10	22
Strongly positive fluid	4	15

who have relapsed mentally after discharge and have been readmitted with symptoms resembling those of an untreated general paralytic, are found without exception to have a strongly positive fluid. Assuming that a negative fluid is the reflection of the therapeutic action of the malaria, it would appear that there is a very strong case for giving a second course of malaria to those patients who are discharged and keeping mentally well, but in whom the fluid remains persistently positive. In the fifteen male cases where the fluid remains strongly positive a further examination will be carried out at the end of six months. If some of these patients are improving mentally and the fluid is still positive then a further course of malaria will be given. Such a state of affairs can only be discovered by performing lumbar punctures at regular intervals. This we are now doing with our discharged cases, and it is only possible to get the co-operation of the patient by education and explaining to him the need for following up his treatment.

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a request for information: "Out-patient records are not kept after a limited number of years," in some hospitals the period being as short as two years. This surely reveals a sad lack of foresight; much has been written recently about the importance of "follow-up" clinics, and a timely reminder should be given to those in authority who permit the wanton destruction of records from which much valuable data could be extracted.

The presumptive evidence of negative or positive findings should be included under the heading of inadequate information, because, even though histories may be fairly full, no blood tests have been done. In other words, these cases have never been recognised clinically as syphilitic. Evidence of clinical syphilis in families and negative and asymptomatic positive serological findings explain themselves.

What is the incidence of syphilis in these families? If the single men and those in whom information is inadequate are deducted, we are left with 170 cases. Of these 170 cases there is negative serological evidence in the members of their families in 89, and in 18 it is presumed that their wives and children have escaped infection, *i.e.*, in 107 the family findings are negative and in 63 positive.

TABLE XI

87 MEN WHOSE FAMILIES SHOW NEGATIVE SEROLOGICAL FINDINGS

						Average age on marriage
15	1 st syphilis acquired before marriage					
	Average interval 9.5 years	.	.	.	.	
	Shortest " 3 "	.	.	.	.	
	Longest " 36 "	.	.	.	.	
2	1 st syphilis acquired after marriage					
	(1) intensively treated always used condom	.	.	.	.	
	(2) no further intercourse	.	.	.	.	
1	1 st syphilis probably acquired after death of wife and birth of child	.	.	.	.	
2	Very doubtful history of syphilis acquired after marriage	.	.	.	.	
67	No history of 1 st syphilis.					

Average age
on marriage

32
29

We would first consider the negative cases. What explanation is there to account for 63 per cent. of families being free from infection? On further analysis of the 87 cases whose families show negative serological reactions (see Table XI.) a history of primary syphilis is recorded in 20 cases, and in 17 of these the date of infection is known. The average interval between infection and

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marriage for 15 of these cases is 9.5 years, the shortest interval 3 years and the longest 36. The date of marriage is known in 17 of these cases, and the average age on marriage is 32; for the whole series the average is 29. In 2 cases infection is definitely known to have occurred after marriage. One received intensive treatment for secondary syphilis and always used a condom, in the second case intercourse is said to have been dis-

TABLE XII

90 FAMILIES WITH NEGATIVE SEROLOGICAL FINDINGS
87 Men. 3 Men were Married Twice

22 Wives nulliparous.

39 No abortions, miscarriages, stillbirths, serious illnesses or deaths.

29 Give a history of the above.

TABLE XIII

FAMILY HISTORIES SUGGESTIVE OF SYPHILIS

	Date of marriage	Age on marriage	Wife	Children							
				1	2	3	4	5	6	7	8
R. D.	1915	29	Widow with 4 healthy children W.R. -ve	1915 ♀ W.R. -ve	Miscarriage	1921 ♂ died 10/12 meningitis	1923 ♀ W.R. -ve				
G. L.	1906	27	W.R. -ve	1908 ♂	1910 ♂	1912 ♂	1914 Twins died 2/12 mening. died 1 yr. bronch.	Miscarriage	Miscarriage	1916 ♂ W.R. -ve	1920 ♀ W.R. -ve
C. C.	1910	28	W.R. -ve	1910 ♂	1911 ♂	1915 ♀	1924 ♀ 1931 fits W.R. -ve. Physical signs suggest cong. syphilis.				

continued after the infection, shortly after the birth of the only daughter. A third case probably acquired syphilis after the death of his wife and two children from influenza; the sole surviving child of this marriage is healthy and has a negative serum. In two other cases there is a very doubtful history of syphilis having been acquired after marriage. With these five exceptions it is significant that the infection is always at least three years pre-marriage.

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In 11 of the families with negative serological findings we have only the wife's statement to the effect that the tests have been done and were negative. In the remaining 79 families we have either done the tests ourselves or have had the wife's statement confirmed. 22 of these wives were nulliparous, and in 39 of these families there is no record of miscarriages, stillbirths or serious illness of any kind. In the remaining 29 families abortions, miscarriages, illnesses or deaths among the children have occurred (see Table XII.) ; and in one or two of these families (see Table XIII.) we feel that this may have been due to syphilis, even though the wife and the surviving children have negative serological findings. This is of interest, as it is possible that there may have been a mild infection, followed by spontaneous recovery. That this does happen was shown by Bruusgard* in his paper on the fate of syphilitics left without specific treatment.

TABLE XIV

18 FAMILIES. PRESUMPTIVE EVIDENCE OF NEGATIVE FINDINGS

- 8 Date of primary syphilis known.
Marriage occurred three or more years after infection.
- 10 Marriage occurred after 1920.
Average of these husbands on marriage is thirty-four.
The obstetrical histories show no evidence of syphilis, *i.e.*, no abortions, miscarriages, serious illnesses, or deaths.

In 18 families, not tested, there is presumptive evidence that they are free from infection (see Table XIV.) ; in 8 the date of infection in the husband is known to have occurred several years before marriage, an average of 6 years, the shortest being 4 years, and in the remaining 10 families marriage has taken place since 1920 and the incubation period of G.P.I. renders it unlikely that infection of the wife has occurred after the birth of her children. Moreover, the obstetrical history in these two groups is not suggestive of infection.

When we come to examine the 63 families with clinical evidence of syphilis, or asymptomatic syphilis confirmed by positive serological findings, there are some striking differences (see Table XV.). We are fully aware that it cannot be proved in every case that the wife acquired the disease from her husband ; indeed, in a few cases it is highly probable that the infection came from some

* *Archiv. für Dermat. u. Syph.*, 1929, 157, II., p. 309.

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other source. Nevertheless, the average age for marriage in these cases is very much lower than in the negative families. In the three groups, with presumptive evidence of positive findings, in the serologically positive and in

TABLE XV
63 FAMILIES WITH CLINICAL, SEROLOGICAL OR PRESUMPTIVE EVIDENCE OF SYPHILIS

<i>Men</i>					Average age on marriage
3	Primary syphilis acquired two years before marriage	.	.	}	24
9	Primary syphilis acquired after marriage	.	.	}	
51	No history of primary syphilis	.	.	}	

those families with clinical evidence of syphilis, the average age of the husband on marriage is twenty-four. There are 3 recorded cases in which syphilis was acquired two years before marriage; compare this with the series of negative families in which the shortest known interval between primary syphilis and marriage is three years. In 9 cases there is a definite history of syphilis after marriage.

In the group of 29 families with asymptomatic syphilis, a strongly positive W.R. has been found in 25 wives, and in the remaining 4 the M.K.R. is positive (see Table XVI.).

TABLE XVI
FAMILIES WITH EVIDENCE OF SYPHILIS

<i>Men</i>				
29 with asymptomatic syphilis				
25	wives.	Serum W.R. strongly positive.		
4	"	"	"	negative, M.K.R. positive.
21 with clinical evidence of syphilis				
5	wives	1 ^y or 2 ^y syphilis.	1 now asymptomatic neurosyphilis.	
5	"	Neurosyphilis.	3 G.P.I., 1 tabes.	1 "nerves" with serum W.R. negative, C.S.F. W.R. positive.
2	"	3 ^y syphilis.	Syphilitic throat.	3 ^y glossitis.
6	"	Serum W.R. positive.	3 lumbar punctures.	2 C.S.F. negative.
2	"	Serum W.R. negative.	1 C.S.F. $\pm$, cells 1.	
1	wife	Not tested.		

In the 21 families with clinical evidence of syphilis, with only two exceptions, the wife shows clinical or serological evidence of syphilis; one is the mother of a child who at the age of eight developed inner ear deafness and interstitial keratitis, while the other has two sons, both of whom have been admitted to mental hospitals with a

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diagnosis of congenital cerebral syphilis at the ages of fourteen and twenty-five respectively. In one other family there is no obstetrical evidence of syphilis, *i.e.*, no history of abortions, miscarriages or early deaths, but the wife has a positive Wassermann reaction and the elder of the two children suffers from interstitial keratitis; it is thought that the husband acquired syphilis two years before marriage. Five wives have received treatment for primary and secondary syphilis; one of these now has asymptomatic neurosyphilis, but the C.S.F.'s of the other four have not been investigated. Late manifestations of syphilis are exhibited in two cases. One woman was treated for a syphilitic throat and a second one attended hospital for a tertiary glossitis. Seven wives show evidence of neurosyphilis, 4 developed G.P.I., 1 tabes and 2 are asymptomatic.

TABLE XVII

50 FAMILIES SHOWING CLINICAL OR SEROLOGICAL EVIDENCE OF SYPHILIS

Men

- 10 Wives nulliparous.
- 8 All pregnancies resulted in living healthy children. Wives probably acquired syphilis after their last pregnancy.
- 32 Families' histories contain records of abortions, miscarriages, stillbirths, meningitis, fits, nerve-deafness, mental deficiency and interstitial keratitis.

The obstetrical histories of these families can conveniently be taken *en bloc* (see Table XVII.). In about 8 cases syphilis was probably acquired after the wife's last pregnancy, so that healthy children occur in those families; 10 wives were nulliparous. In the other 32 families the clinical pictures encountered in the children present a trail of havoc; miscarriages, stillbirths, meningitis, fits, nerve deafness, mental deficiency and interstitial keratitis. It is a significant fact that in some families where pregnancies are numerous, the syphilitic infection works itself out, until finally some healthy children are born. These figures offer a striking contrast to the 39 entirely healthy families whom we mentioned in the group of serologically negative cases, and suggest that the incidence of abortions, miscarriages and infantile deaths is much higher in the syphilitic than in the non-syphilitic mother.

The incidence of neurosyphilis in those children is high,

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there is only one recorded instance of somatic syphilis, namely syphilitic periostitis. Table XVIII. represents the fate of pregnancies in these syphilitic families, (where

TABLE XVIII
ANALYSIS OF PREGNANCIES IN SYPHILITIC FAMILIES

Men

Children born before the mother acquired syphilis are excluded

Group	Living	Miscarriages	Stillbirths	Died under 2 yrs.	Died over 2 yrs.
1. Families with presumptive evidence of syphilis	18 4 mentally backward	10	4	8 2 with fits	2
2. Families with clinical syphilis	28 2 nerve deafness, 2 interstitial keratitis	8	4	11 3 from meningitis	2
2. Families with asymptomatic syphilis	60	19	7	16 2 from meningitis 2 from whooping cough 1 with fits	1 from meningitis
Total . . .	106	37	15	35	5

possible healthy children, known to be born before infection, are excluded).

Out of 198 pregnancies, syphilis is possibly responsible for the death of the foetus or child in 92 cases, and in the remaining 106 (of whom some are healthy), congenital

TABLE XIX
SYPHILITIC FAMILIES OF 33 FEMALE G.P.I.'s
5 women had been married twice, giving a total of 38 men

Husbands	Children
G.P.I. 9	Congenital G.P.I. 3
Tabo-paresis 2	Congenital tabetics 2
Tabes 6	Congenital syphilis 5
Syphilitic myelitis 1	
Syphilitic polyneuritis 1	
Somatic syphilis 2	
History of primary syphilis only 2	
Serum W.R. positive 3	
Serum W.R. negative 3	
Unknown 9	
Total 38	

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syphilis, mental deficiency and interstitial keratitis reveal evidence of infection through the mother.

The same story is reflected in the families of our female G.P.I.'s. In 38 families with clinical evidence of syphilis, (see Table XIX.), 3 congenital G.P.I.'s and 2 congenital tabetics with optic atrophy have been discovered, and congenital syphilis is known to be present in five other children, of whom three are being treated. Presumptive evidence of syphilis with its train of miscarriages and stillbirths has been found in 14 families, while asymptomatic syphilis has been confirmed serologically in a further 8 families. In this last group there are only two surviving children, both with positive serum.

In the 38 families with clinical evidence of syphilis, the fate of the husbands or cohabitants is summarised in the foregoing table. Of 26 partners with clinical syphilis, the high proportion of 19 exhibits neurosyphilis, 17 of these suffering from the parenchymatous form of the disease. The incidence of presumably conjugal G.P.I., tabes and taboparesis is particularly high. It would appear that in conjugal syphilis G.P.I. comes on in the male earlier than the female, as shown in Table XX.

TABLE XX
PARENCHYMATOUS NEUROSYPHILIS IN CONJUGAL PARTNERS

No. of cases	Clinical type	Average time interval before onset of partner's illness.	Clinical type
11 men 6 "	G.P.I. Tabes	5 years 12 "	Wives G.P.I.
3 women 1 woman 1 "	G.P.I. Tabes Epileptic insanity with neurosyphilis	4.5 years 11 " 23 "	Husbands G.P.I.

In the case of tabes occurring in the male partner, the average period of the tabetic incidence is twelve years before the female partner develops G.P.I. Only in 4 cases have we records of G.P.I. developing in the male partner first.

With regard to the 27 women in whose families we have obtained negative serological results (see Table XXI.), 3 women had 3 conjugal partners and 3 had 2, giving a

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total of 36 men. Of these men 22 are known to be negative, but 5 of these are the patients' second or third husbands; this therefore reduces us to 17 women in whose husbands the W.R. is negative; but even of these 17 husbands it is possible that 2 of them had previously had syphilis, one had a spastic paralysis, probably due to syphilitic myelitis, and the other died from cerebral hæmorrhage at the age of fifty-five; 14 have never had blood tests done, but one of these died of aortic regurgitation.

Fourteen of these unions were nulliparous, and in 8 there is no obstetrical evidence of syphilis, but in these

TABLE XXI
FAMILIES WITH NEGATIVE SEROLOGICAL FINDINGS
Women. 27 Patients

Husbands	Children
<p>22 Serum W.R. negative. 5 are patients' 2nd or 3rd husbands. 1 with spastic paralysis, probably due to syphilis. 1 died cerebral hæmorrhage, æt. 55.</p> <p>14 W.R. not tested. 1 died aortic regurgitation.</p>	<p>14 unions. No pregnancies. 8 unions. Obstetrical histories show no evidence of syphilis. 7 The pregnancies occurred 13 years or more before the mother developed G.P.I., <i>i.e.</i>, possibly before the mother acquired syphilis. 1 The pregnancy occurred only 2 years before, <i>i.e.</i>, probably years after the patient's primary syphilis.</p> <p>14 unions. 20 surviving children. 24 abortions, miscarriages, stillbirths and early deaths.</p>

cases, with only one exception, the pregnancies occurred thirteen years or more before the mother showed symptoms of G.P.I., *i.e.*, possibly before the mother acquired the infection. In the one case the pregnancy occurred only two years before admission to hospital, *i.e.*, probably years after the mother's primary infection. In the remaining 14 cases, in spite of negative serological findings in the husband or in some of the children, our data lend support to the view that, even in these families, syphilis has exacted quite a heavy toll. Out of 27 women and 36 marital unions it seems likely that only 20 surviving children have been born after the mother acquired the infection, while the number of abortions, miscarriages

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and early deaths is at least 24. This agrees very closely with the statistics which we have previously given to you relating to the offspring of syphilitic mothers.

In 27 relatives in whom we have found a positive W.R. in the serum, the C.S.F. has also been tested. The results may be summarised, as in Table XXII.

TABLE XXII
RESULTS OF LUMBAR PUNCTURES IN RELATIVES

	Serum	C.S.F.			Serum	C.S.F.					
15 wives	1.	+30+	+++++	+30+	+	+	4444321000	8.	+30+	+++++	negative
	2.	+30+	+++++	+	+	+	5555432100	9.	+	++++	"
	3.	+30+	+++++	+30+	+	+	5555543210	10.	+	+	"
	4.	+30+	+++++	+30+	+	+	5554432110	11.	+	+++++	"
	5.	+30+	+++++	+6+	+	+	5555543210	12.	+7.5	++++	"
	6.	—	++	+2	—	+—	3322100000	13.	+7.5	++++	"
	7.	+		+—	I			14.	—	++++	"
								15.	+30+	+++++	"
2 husbands	1.	+30+	+++++	+2	+	35	2334321000	2.	+		"
7 children	1.	+30+	+++++	+		90	5543321000	5.	+30+	+++++	"
	2.	+30+	+++++	+++++	2I		55554322100	6.	+30+	+++++	"
	3.	+30+	+++++	+++++	18		2233330000	7.	+30+	+	"
	4.	+30+	+++++	+±	I		1111000000				
3 parents of congenital G.P.I.'s								1.	+30+	+++++	"
								2.	—	++++	"
								3.	—	—	"

The incidence of asymptomatic neurosyphilis in these cases is thus 33 per cent., and of the 12 positives, with 4 possible exceptions, every case must be regarded as a potential G.P.I. In the case of the three children the condition was only discovered as the result of our present routine familial examination ; but on subsequent clinical examination it has been found that one has shown some minor mental symptoms and is probably an early con-

TABLE XXIII
FAMILY HISTORY OF A FEMALE G.P.I.
F. A. H.

Husband.	Married 1906. October 1936 W.R. negative, M.K.R. negative.
W. H.	Liaison with patient for many years during the war. 1st syphilis 1913. 1920 G.P.I.; C.S.F. +40+. 1922 died.
1907 ♀	Healthy.
1908 ♂	Healthy.
1910 ♂	Healthy, but 1936 W.R. ++, Kahn +. Hutchinson's teeth. C.S.F. negative.
1916 ♀	Died, convulsions. 1 or 2 miscarriages.
1923 ♀	Healthy, but recently slight mental changes. 1936 serum +30+ +++++ C.S.F. +++++ 21 cells 5555543310
1926 ♂	Healthy. 1936 serum +30+ +++++ C.S.F. +++++ 18 cells 2233330000

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genital G.P.I.—she is now receiving treatment at St. Thomas's (her family history is given in Table XXIII.)—while the second child has now been diagnosed as a case of congenital tabes with commencing optic atrophy. He had previously been diagnosed as suffering from myopia and had been wearing glasses for the past three years. He, too, is receiving treatment at St. Peter's Clinic and the London Hospital. The one husband with a negative fluid is worth mentioning; he infected his wife in 1912, when both received a short course of treatment. The wife developed G.P.I. in 1932; the husband had a severe attack of malaria when on active service during the last war. Did this attack of malaria act as a prophylactic against the subsequent development of G.P.I.?

The number of cases in whom the serum only has been tested can be studied in Table XXIV.

TABLE XXIV
RELATIVES WITH POSITIVE W.R. OF SERUM, BUT C.S.F.
NOT TESTED

	No. of cases W.R. positive	No. of cases W.R. originally positive; negative after treatment
Wives of G.P.I.'s	19	7
Husbands	8	—
Children	12	8
Parents of congenital G.P.I.'s	6	1
Total	45	16

If the ratio of positive to negative in the series just given, namely 1 in 3, is a general average, one may assume that of these 45 cases with positive sera 15 might have positive fluids.

This raises another important point: in how many of our patients under review could the existence of neuro-syphilis have been discovered earlier? On searching our records, the number is surprisingly high. In 55 cases (see Table XXV.), the previous diagnosis of syphilis in a member of the patient's family supplied the clue which, had it been followed up, would surely have led to the detection of the patient's potential danger and to the adoption of appropriate therapeutic measures to avert the subsequent fall of this Damoclean sword. If to these

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An excellent monograph* dealing with the course of changes in the spinal fluid of syphilitics by Lomholt is worth the attention of venereologists, neurologists and psychiatrists alike. He considers that the optimum time to conduct this examination is when "the septicæmic period has passed," *i.e.*, after any clinical relapse. He warns the clinician against accepting a negative C.S.F., which may remain normal as long as anti-syphilitic treatment is going on, but which may become abnormal as soon as the treatment is discontinued. In the case undergoing energetic anti-syphilitic treatment a year should elapse before the fluid is tested. If these tests are to be carried out in every case, the doctor must be in a position to draw some prognostic conclusion. We cannot do better than quote Dr. Lomholt himself: "If it be not practicable on the basis of this examination to say something decisive, one way or the other, with regard to the future of the individual patient, there is hardly any doubt that we will have to give up all hope of having this examination carried out to the desired extent. Neither patients nor physicians can be expected to take any interest in a prognostic examination like the spinal puncture, unless the result is of actual value to the patient."

Nevertheless, we feel very strongly that the present unsatisfactory recovery rate in G.P.I. cannot be appreciably improved until it is recognised in this country that examination of the C.S.F. is as essential as examination of the serum. True, a lumbar puncture is more difficult than a venepuncture, and it may have more distressing after effects for the patient, so that one does not advise its use unnecessarily. By means of the fine Vienna needle, however, most of the disadvantages can be eliminated. If it is skilfully performed the patient experiences little pain, headache and vomiting rarely follow, and detention in hospital for longer than fifteen to twenty minutes is unnecessary. These needles were devised by Dattner in Vienna and have since been introduced into this country.

If lumbar punctures are adopted as a routine measure, the next problem will be to decide what form of therapy should be given to those patients who are found to have

* "Course of Changes in the Spinal Fluid of Syphilitics: a Clinical and Catamnestic Study." Esbern Lomholt: Levin and Munksgaard, Copenhagen, 1936.

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a positive C.S.F. Various alternatives offer themselves: injections of pentavalent arsenic, such as tryparsamide or stovarsol, or some form of pyreto-therapy, malaria, diathermy, sulfosin, ratbite fever, relapsing fever, etc.

Our experience is limited to malaria and tryparsamide, and of these we prefer the former. In about 80 per cent. of our cases one course of malaria is sufficient to produce a negative C.S.F. and, in those cases who remain positive, a second course will in most, if not in all, achieve the desired result.

Undoubtedly malaria therapy is not without its risks and dangers, but most of these can be avoided if the treatment is carried out in a special centre under expert supervision. Under these conditions the mortality rate has proved to be very low and the occurrence of complications or sequelæ extremely rare. Unfortunately it entails admission to hospital, but the duration of the stay is probably not longer than four weeks, and in certain cases the treatment could probably be completed in two to three weeks.

In favour of pentavalent arsenic is the fact that its administration is so much easier, entailing merely a weekly attendance for the injection. One gathers from the literature that large amounts of tryparsamide and stovarsol are necessary to make the C.S.F. negative, as many as 70 or more injections being required. In the careless or ignorant patient this may prove a serious disadvantage, for, in the absence of symptoms, he may weary and, by defaulting, may rob any treatment he has had of all value and finally succumb like the untreated patient. Further, ocular and other complications have been reported following the use of these drugs. We hold the view that both these methods, *i.e.*, malaria and pentavalent arsenic, if not all the methods enumerated before, should be tried in the treatment of asymptomatic neurosyphilis, for only in this way can the most satisfactory method be ascertained.

From statistical evidence in this country, the incidence of syphilis is falling, and consequently the incidence of G.P.I. should drop. It may even be argued that the numbers of neurosyphilitics seen by the general practitioner are very few and perhaps some of us may live to see cases of neurosyphilis and G.P.I. reported in medical literature as pathological curiosities: this is already

foreshadowed in Denmark by Lomholt, who remarks : " The youngest generation of physicians in this country knows fresh syphilis only as a rather rare disease. Hence, the eradication of this disease is not by far so great a problem now as it was fifteen to twenty years ago. Most people here look upon syphilis as being almost eradicated. Consequently the interest in problems concerning syphilis is decreasing distinctly." It would seem that we are hardly in a position to say this of ourselves. G.P.I. in this country still claims much accommodation in mental hospitals, even though many cases are nowadays treated in the general hospital : it is our duty to the public to diagnose these cases, if possible, in the latent stage, before the development of G.P.I. and apply prophylactic methods, and we would stress at the risk of repetition that an early diagnosis can only be arrived at by careful investigation and confirmed by a lumbar puncture.