

SOME CHEMOTHERAPEUTIC STUDIES.

PART I.

Preface.

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Synopsis.

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Thesis . Some Chemotherapeutic Studies

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P R E F A C E .

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This thesis is primarily the account of two lengthy experiments.

The first experiment is a long range one, in an attempt to set up criteria by which standard courses of treatment employed in early syphilis, might be assessed. It was also hoped that, thereby, arguments might be derived for the improvement of existing methods of therapy. It was felt that a considerable time was necessary for such criteria to be evolved. Accordingly, a standard method of treatment has been adopted, and the results obtained over a period of twelve years have been examined. This standard treatment was difficult to maintain in face of criticism, both from within, and from without, the department. It is hoped that the success of the change of methods of treatment advocated may be its justification. No such homogeneous long-range experiment has been met with in the literature.

It is widely known that the problems raised by the presence of late or chronic syphilis are of a totally different nature from those present in the early stages of disease. Accordingly, an analysis of the results achieved by the varied methods used in the treatment of latent syphilis

and late muco-cutaneous syphilis has been incorporated. These sections, by themselves, may afford aid in the guidance of the treatment of such conditions. They will also serve to show up, in contrast, the very different questions raised by early syphilis, and it is hoped they will add force to the conclusions reached regarding the treatment of the early stages. In the course of years much experimental work has been done within these imposed limits. Such work has dealt with the problems raised by late syphilis, by intolerance, with the examination of new drugs designed to treat syphilis, and with many clinical side tracks which proved attractive. They are dealt with in the text, but a special section on methods to be employed in the investigation of new drugs designed for the treatment of syphilis is incorporated. No such detailed instruction is found in the literature.

The second experiment is concerned with the use of iodine in the treatment of syphilis. The lack of modern detailed clinical experiments led to the commencement of observations in 1923, and these have been continued for over nine years. The number of cases dealt with exceeds 1,750; the number of experiments exceeds 3,500. Complete protocols would make this thesis, already very lengthy, of an intolerable size. The method of summary has therefore had to be employed, and the mass of observations is compressed into

the limits of a single section.

It is proper to mention here the methods employed in preparing the large masses of information for analysis. A record card was designed to incorporate the main data desired, and a card was completed for each individual case. From these cards the chief tables were constructed. On the back of the card any special experiments, observations, or clinical data were recorded. A specimen card is attached. The details concerning the iodine experiments were kept on a special series of blank cards.

The task has been a very lengthy and highly laborious one, and the writer wishes most gratefully to acknowledge that, but for the exhortations of numerous friends, it might never have been completed.

The assistance of Dr. A.S.M.McGregor, Medical Officer of Health for Glasgow, and of Dr. R. J. Peters and his staff has been of great value. Dr. Peters' statistical advice has been especially helpful. With regard to the daily problems raised by the cases, thanks are due to Professor C. H. Browning and Professor E. M. Dunlop for their unwearied assistance. The fact that all the Wassermann tests have been performed by them, renders this thesis completely homogeneous. Finally, thanks are due to Dr. McGregor Robertson and the numerous

members of the staff of the department for their continued co-operation. This has ensured the continuity of the methods desired in the clinic.

There is now submitted for the guidance of the reader:-

- (1) A specimen record card.
- (2) A list of contents of the sections.
- (3) A synopsis in which the main points of the various sections are briefly tabulated. This synopsis is, naturally, intended as a guide rather than a complete substitute.

TYPE OF RECORD CARD.

Disease										Sex		Age		No.		6910	
Years since Primary		Previous Treatment			Lesion			Other Lesions									
		Medicinal	Injections		Site	Type											
D.C.		W.R.	Before Treatment	As.	Hg.	Total Treatment	Bi.	I	O.	I.V.	Intolerance	Months treatment and observation					
		B.	C.S.F.	Grammes	P.	U.											
Arsenical		Other Drugs	Hg.	Bi.	I.	Weeks Duration	Result	Intolerance	Relapse	Intolerance							
No.		Grammes	Drug	P.	U.	C.C.	Clin.	B.	C.S.F.								

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SOME CHEMOTHERAPEUTIC STUDIES.

Synopsis of Sections.

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There are eleven sections in this thesis. Each is a carefully compiled record of certain data with deductions therefrom. The sections are logically planned and individually coherent. Each is intended to present the principal conclusions arising out of the investigation started in virtue of the title of the section. Although these sections can thus be read and understood, yet there are so many side tracks and, as a result, so many experiments that any reader must find it a difficult matter to grasp, at one and the same time, both the general argument of the whole thesis and the particular arguments involved in the numerous lesser questions which have continually been raised. Further, bulky though the thesis is, it covers more than twelve years of activity in clinic work, and therefore the subject matters condensed and compressed into it are unlikely to be in the immediate forefront of the reader's mind. To the writer, who has spent years in reflection upon them, they must inevitably appear much simpler and more straight forward than they can to anyone encountering this mass of experiments, cases,

figures, analyses and conclusions for the first time. The purpose, therefore, of this synopsis is an attempt to present the main objectives, facts, and conclusions in a more readable fashion. The references to the appropriate section will serve to provide a guide to the detailed evidence.

It has been said in the preface that the first of the two main experiments was directed towards the acquisition of data, from which improvements in the treatment of syphilis might be suggested. This is no easy matter, but, pending the arrival of therapeutic agencies with a new method of attack upon the spirochaete, it is of the highest importance. In this year, 1934, the arsenobenzols have been in use for some twenty-two years, mercury for generations, even bismuth for twelve years, yet there is no uniformity anywhere in the world as to the most advantageous methods of their employment. This is seen by the variable ^{and} methods employed in Great Britain at the present day, and by the differences brought out in the American report, V.D.I. 1932. It was equally so in 1919 when the work of this thesis started. Then, as now, this country tended to use "914", America tended to use "606", but individual clinics showed profound variations in the method of handling the preparation. Further, the evidence submitted by the literature as to the values

of these methods was highly unsatisfactory. It usually either consisted of the observation of a fairly large number of cases over a short period of time, rarely more than two years in duration, or it consisted of the eclectic choice of special cases which could not afford an answer to broad simple questions concerning the best methods of treatment of masses of patients. Therefore, it was considered in 1919, after choosing a model course for routine treatment, that this course should be adhered to for a considerable period of time, and that all further experiments would be performed upon it as a basis. This programme was followed out for twelve years. No observations of such long duration have been recorded in the literature. The cases analysed by the American group of investigators were treated in various ways and had no common principle running through them. In our series the total number of cases investigated was over 3,800, but the necessity for some further controlled observation to make these cases of any value, necessitated certain standards of selection. It was felt that no case which did not have a second Wassermann reaction of the blood serum performed after a period of treatment or observation, could be included. By this and other criteria, the total available cases were reduced to 1,766. Of these, 570 were

cases of syphilis treated within two years of its first appearance, and 1,196 cases in which the infection had been present for more than two years.

It became at once apparent that different methods of treatment were required for these two main groups. A model course could conveniently be applied to the majority of cases of early syphilis, for these patients were, in the main, healthy young adults. Accordingly the first six sections of the thesis deal with various aspects of treatment in such a group of patients. It was also seen that such routine methods were not applicable to late syphilis, partly because of the varied nature of the late manifestations of disease, (a case of subcutaneous gumma is not comparable with a case of aortic regurgitation), and partly because the patients tended to be more elderly in age grouping, and thus exhibited numerous other disease factors. It was also soon realised that certain types of disease could not be adequately dealt with on a purely out-patient basis, and reasons are given to show that cardiac and neuro- p.336-7 syphilis can only adequately be treated in association with an in-patient department. Accordingly latent

syphilis and tertiary muco-cutaneous syphilis were selected for more careful examination, and sections seven and eight deal with their problems. The ninth section, dealing with the methods of use of iodine in syphilis, has entailed a very large amount of experimental work. It was started in view of the lack of detailed clinical observations and, as stated in the preface, has involved some 3,500 experiments on some 1,750 cases. It represents the second main experiment dealt with in the thesis. It has been concentrated into a single section which, in view of its condensation, demands that it be read in detail. It represents an attempt to determine definitely the role played by iodine in respect of the spirochaete, and the primary, secondary, latent, tertiary muco-cutaneous, cardiac and neural manifestations of syphilis, as well as its effect upon the Wassermann reaction of the blood serum, and the cerebro-spinal fluid. The tenth section deals with the most advantageous methods of investigating new antisyphilitic preparations. Thirteen drugs have been reported on: no paper has been found giving details as to how such investigations should be made. It is a natural introduction to the final section, the eleventh, which

suggests a change in the methods of treating early syphilis. Although in this section no new drugs are employed, yet it must repeatedly occur that new preparations demand a trial under this proposed scheme, and thus the tenth section naturally precedes this one. Now this final section deals with the methods required for the treatment of early syphilis. It will be shown in sections seven and eight that definite conclusions are reached as to the most advantageous methods of treating latent syphilis and tertiary muco-cutaneous syphilis.

Section 1.

This deals with the general results of the treatment of early syphilis. There were 570 cases considered suitable for analysis. The model course consisted of the combined use of "914" by intravenous injection and a heavy metal by intramuscular injection; an essential feature of the scheme was a uniform time spacing of the doses.

p. 2
p. 5-7
p. 8-10
p. 11-12

Ten injections of "914" and twelve of metal were given in fifteen weeks. A week's rest from "914" was given after the third and fifth injections, and three weeks' rest from both "914" and metal were given after

the seventh injection of "914". Otherwise the injections were given at weekly intervals. Neokhar-sivan, novarsenobillon and neosalvarsan were the preparations of "914" chiefly used. Calomel cream was employed as the heavy metal until 1924, and thereafter bismuth metal in the form of Bicroel or Bismo-stab was substituted for mercury. The quantities of "914" given in a single course varied from 5.55 grams to 6.75 grams; the quantity of mercury was 12 grains, and of bismuth 2.4 grams. "Adequate total treatment" is now defined. Prior to 1921 it consisted of one such course of treatment, and thereafter Hutchinson's p.11 pills for at least six months with a total of at least eighteen months observation; after 1921 two complete courses of injections, pills and subsequent observation up to at least eighteen months were required, provided that the case had been clinically and serologically negative for at least six months. All cases not com- p.17 plying with these standards are said to have had "inadequate treatment".

Unfortunately default is a frequent occurrence. Thus, out of the 570 cases, 118 defaulted within six p.13 months, and only 177 attended for two years or more.

A similar result is found on analysing the cases attending all the Glasgow clinics where, in 1930, 48% of males and 47% of females did not complete one course of treatment. Thus attention is at once focussed upon the great importance of the first course of treatment, which is often the only course. Therefore the results of the first course call for particular analysis - both as to early, and as to late results. p.14

The first factor considered is the quantity of "914" given in the first course of treatment in the series of 570 cases. The quantities will be divided into five groups :-

- (1) Less than 3.5 grams: an expression of idiosyncrasy, intolerance, default or experimental treatment. pp.15&30
- (2) 3.5 to 5 grams: the causes being the same as in (1) but to a lesser extent. pp.16&30
- (3) 5 to 6 grams: a normal group; bismuth was the usual associated metal. pp.16&31
- (4) 6 to 7 grams: a normal group; mercury was the usual associated metal. p. 31
- (5) More than 7 grams: mercury was the associated metal. p. 31

Under these five headings the various data have been tabulated. p.16-25

9

End results in relation to duration of disease at commencement of treatment : the information thus obtained shows that primary syphilis, where the blood Wassermann is negative and the dark ground examination positive, gives the best results at the end of the first course, cases of primary syphilis with positive blood Wassermann the second best, and cases of secondary syphilis the worst results. This is quite straightforward. p.26

The total end results of cases receiving adequate total treatment are as follows, 10.6% were not negative serologically when last seen, and of cases receiving inadequate total treatment, 22.8% were not serologically negative. The percentage of final unfavourable results rises steadily with the age of the syphilitic infection. The American figure of 26.6% is given as their final unsatisfactory result in all cases of early syphilis: it compares with our percentage of 16.6% in all the 570 cases. p.28 p.29

The end results are then considered in terms of the amount of "914" in the first course of injections. It is clear that less than 5 grams of "914" is inadequate to secure immediately favourable results, but that total adequate treatment can compensate to a p.31-2

large extent for this early failure. A study of those cases which were not negative at the end of their first course shows, however, that larger amounts of treatment are required to produce a permanently negative result in such cases.

In order to determine the relative efficiency of mercury and bismuth, those cases which received normal amounts of "914" in their first course are examined. It is found that bismuth gives slightly the more favourable results as determined either (1) after the first course, or (2) after total treatment whether adequate or inadequate, or (3) after two years' observation. Further, bismuth does not yield an increase in clinical relapses or in incidence of intolerance as compared with mercury.

Effect of amount of later treatment in assessing the value of an adequate first course. In those groups receiving in their first course normal amounts of "914", i.e. 5-6 grams or 6-7 grams, the final end results show very little improvement in respect of whether total treatment was adequate or inadequate. If inadequate, there were 11.1% failures; if adequate, 10.5%. This is a striking tribute to the value of an adequate first course and is of value in estimating the prognosis in

the numerous defaulters.

p.36

The American figures in the most successful group show 13.1% failures and our similar group shows 10.5% failures. Therefore it is apparent that there is no obvious reason for employing "606" in place of "914". It is to be noted, however, that this American group has a slightly higher standard of cure - the cases were all observed for one year after being negative, and nearly all had the cerebro-spinal fluid examined. In our series only three quarters of the cases had a lumbar puncture performed and they were observed for only six months after a negative Wassermann had been obtained.

p.37

p.44

p.44

The effect of the time over which the first course extends is next considered in the light of the informative Wassermann reaction taken at the sixteenth week after the commencement of treatment. Three time groups for the course are given, using this sixteenth week as a cardinal point. These are :- less than 14 weeks, 14 to 18 weeks, more than 18 weeks.

p.37-8

If total adequate treatment be given the duration of the first course matters but little. If the total treatment be inadequate the cases receiving treatment in less than fourteen weeks show the worst results.

p.40

This is, however, usually also an expression of inadequate amounts of "914". If the first course takes more than eighteen weeks, the results are inferior to the normal time group. Here the quantities of "914" are comparable and it suggests that extended rest periods are injudicious.

The cases under observation for more than two years are separately examined. p.41-3

If adequate total treatment be given, males show rather better results than females, secondary syphilis shows a worse outcome than earlier stages, the amount of "914" in the first course is of little importance, and ultimately there is little to choose between mercury and bismuth.

On the other hand, if the total amount of treatment be rendered inadequate through default, it is most important that not less than 5 grams of "914" be given in the first course. p.45

The General Conclusions of this section :-

(1) If ten injections of "914", amounting to 5.85 grams, and twelve injections of a heavy metal be given to cases of early syphilis in a period of sixteen weeks; if this course be repeated, so that each

case receives one course after being Wassermann negative; and if the case then be treated with mercury pills and observed for a period up to two years, the percentage of unfavourable results is 10.5%. This unfavourable percentage increases (a) if the quantity of "914" in the first course falls below 5 grams, (b) if the time period of the first course is increased beyond eighteen weeks.

Should a case not receive supplementary treatment, but if it receives in one course more than 5 grams of "914" and the equivalent amount of heavy metal, the percentage of unfavourable results is 11.6%. If less than 5 grams of "914" be given, and if the time period of its administration be greatly altered, the percentage of unfavourable results is much increased.

(2) Bismuth appears to give slightly better results than mercury.

(3) Results are most favourable in sero-negative syphilis; less so in sero-positive primary syphilis, and least so in secondary syphilis.

Since the only criteria employed in assessing these results can be clinical or serological, an examination must be made of these factors. Sections

two, three and four deal with the serological side, and section five with the clinical aspect.

Section II.

This deals with the Wassermann reaction of the blood serum in early syphilis, and its response to treatment. It is important because any clinical examination can only be superficially successful and can only be of value for a short and indefinite time. The significance of the various grades of Wassermann reaction is thus of the highest importance in the routine examination of patients. It is fortunate that our Wassermann tests are, like the clinical work, homogeneous. They have all been performed in Professor C. H. Browning's laboratory, by his method. According to his criteria, a "positive" result is of diagnostic importance; a "weak positive" or a "suspicious" result is of therapeutic value where syphilis has been known to be present.

The results of Wassermann tests prior to treatment are quite in accord with clinical facts. All primary syphilis, except in presence of the Sp. Pall., has yielded, in a preliminary test, a higher grade than suspicious; all secondary syphilis has shown

a fully positive reaction before treatment. There are presented in detail all cases in the series of 570, in which Wassermann variation took place; and all cases in which a positive Wassermann reaction was maintained after antisyphilitic treatment. The total amounts to 28.8% , but if those cases which defaulted within six months be excluded, the total is 24.5%. There is a steady rise in the incidence of Wassermann relapse with the age of the syphilitic infection prior to treatment. There is no appreciable difference between the sexes.

p.52-6

p.57

Certain data concerning Wassermann relapse are given. There is a percentage incidence of 24.5%. Five per cent remained Wassermann fast for more than six months; an additional 5.1% took more than six months to obtain a completely negative reaction. After a negative result had been obtained, 17.4% of cases showed relapse, and if the grade negative to suspicious be excluded, 12.2% of relapse occurred.

The Wassermann fast cases:- These constitute 5% of all cases. It is clearly shown that Wassermann fastness is chiefly an expression, in this clinic, of an inadequate first course of treatment (less than 5 grams "914"), whether caused by default or by

p.57-60

p.61-5

intolerance. Only 6 cases out of twenty-seven received an adequate initial course, and of these, only 1 maintained this positive reaction for more than twelve months. Indeed no cases remained permanently fast in face of adequate initial and total adequate treatment, while only 2 cases remained fast (for 52 and 17 months respectively) in face of a total adequate treatment. Now a Wassermann fast condition of the blood is highly significant in early syphilis, for it indicates a state in which clinical relapse occurs. It seems clear that such a continued positive reaction indicates a manifestation of the syphilitic virus. In seven cases Wassermann relapse occurred, and persisted for more than one year after a negative test had been obtained. These cases gave a high percentage of final non-negative blood Wassermann reactions. A Wassermann relapse with fastness suggests a worse prognosis than does the maintenance of the initial positive reaction.

p.66

p.67

p.68

The significance of a "suspicious" reaction is now investigated. It is considered important to examine this grade in the light of clinical results. If it occurs as a relapse during the first course, it is of no moment. It may be a prelude to clinical relapse and must thus be regarded as an unsatisfactory result

at the end of a course. It may be a prelude to a Wassermann fast state lasting for twelve months or longer and is thus again an unsatisfactory reaction. It may be maintained unchanged for more than twelve months, and is, in such event, usually the expression of inadequate initial treatment. It has been seen in twenty-two cases as the sole relapse, and here, if adequate total treatment be given, a negative end result is usually attained. This merely shows that it is not of such strong positivity, and naturally, in absence of weak positive or positive relapses, a final negative is more easily obtained. The outcome of all cases in which this grade of relapse occurred in the absence of further treatment, shows it to be a forerunner of the weak or positive grades of reaction, and this occurs equally with all types of treatment.

To sum up, a suspicious reaction in treated early syphilis is of unfavourable omen, and calls for further antisyphilitic treatment.

Sudden reversal from negative to positive occurred twenty-nine times. An expression primarily of an inadequate first course of "914", secondarily of the use of mercury rather than of bismuth, and lastly of default

on the patient's part, it is of unfavourable omen as shown by the high incidence of clinical relapse, but fortunately, if adequate total treatment be given, a successful end result is not unduly prejudiced. p.76

Serological relapse after eighteen months of negative tests occurred ten times. Wassermann tests are usually made three times in each year. Eight of these cases were originally well treated. It is simply an expression of the failure of the present course of treatment. It must lead to life long supervision of any one patient. p.77 p.78

Weak positive relapses :- These were 42 in number and they show a worse prognostic significance than does the suspicious relapse. There is a very high incidence of clinical relapse, and of unfavourable end results. Where, as in 16 cases, no further relapse to positive was noted, the end serological results are worse than in those cases where only a suspicious grade of relapse occurs. p.79 p.81

If more than three relapses occur in any single case, such a case may be termed one showing a variable Wassermann. There were only four such cases. They indicate a high grade of syphilitic activity, marked by clinical relapse and unfavourable end results. p.82

The ultimate fate of those cases in which any Wassermann relapse occurred shows definitely that whether adequate or inadequate initial treatment, adequate or inadequate total treatment be given, in all stages of disease, in both sexes, there is a definite increase in the percentage of finally unfavourable results. The one exception is those cases receiving total adequate treatment, in which the sole serological relapse was of the grade suspicious. p.82 p.83 p.84

The chief conclusion reached is, that an inadequate initial course of treatment is the most important factor in producing Wassermann relapse. It is thought that Wassermann relapse is the most important single criterion in evaluating new drugs or new combinations of old drugs designed to treat syphilis. p.84

Section III.

This deals with the serial examination of the Wassermann reaction of the blood at fortnightly intervals during the first course of treatment in 169 cases of early syphilis. There were 12 males with original seronegative tests and positive dark fields. All did well. One showed a positive reaction from the third to the fifth week. Perhaps in the early weeks of treatment more "914" might be given. One hundred and fifty-seven sero- p.95-7 p.98 p.90

positive cases were examined. About one third of all p.101
such cases showed their first negative result between
the fifth and the eighth weeks, and one third between
the ninth and the twelfth weeks. The earlier negative
results tend to occur in primary syphilis. Only p.102
three cases, all females with secondary syphilis, were p.103
still positive after twenty weeks. This time express-
ion of the first negative Wassermann result, is also p.104
shown to be an expression of the amount of "914" received,
and this may be summed up in the statement that two thirds
of the cases showed a negative result after redeiving p.105
between 3 and 4 grams of "914" and 1.6 or 1.8 grams of p.106
bismuth metal. Yet, as 12.5% of all cases required
the full course of "914", (5.55 to 6.3 grams), before p.108
becoming negative, it is most unwise to consider any
reduction in the amount of "914". It should never be
less than 5 grams in the first course. It is suggest- p.109
ed that in view of default, and in view of the value of p.110
an early negative result, concentration of treatment
might take place in the earlier weeks.

Some associated factors are now considered.

Thus the duration of the disease and the time at p.111
which the first negative is obtained are investigated.
In respect of primary syphilis the earlier the patient
comes, the quicker will a negative reaction be obtained.p.112

This is of great practical importance. In respect of p.113
 secondary syphilis, the evidence is not so clear, but p.114
 it suggests the same conclusion.

The question of sex does not influence the time at which
 the first negative result is noted. p.115

With respect to the type of lesion, it is thought that p.116

in primary syphilis, after allowing for the duration of p.117

the lesion prior to treatment, there is a slightly more
 favourable early outcome when there is only little sec- p.118

ondary infection. In secondary syphilis no difference p.119

in the time at which the first negative result is ob-
 tained is seen as between slight, medium or florid con-
 ditions of comparable age.

In this group of serial Wassermanns, the end Wasser- p.120
 mann results are much more satisfactory than in the whole
 series of 570 cases. Therefore no deduction can be made
 from the observation of the serial Wassermann reaction as p.121
 to the final serological result in the main group of 570
 cases.

The rapidity with which a positive serological result p.122
alters to a completely negative one. Twice this occurred

in one week. Usually it is a gradual process taking
 from 4 to 6 weeks. There is no difference between the p.123

sexes, or between the primary or secondary stages of
 disease. Further the rate of change is much the same

no matter at what stage in the course of treatment it is

initiated. Such data would be interesting in the late stages of syphilitic disease, but we have none to offer. p.124

All relapses in the Wassermann reaction which occurred p.125
 in this special series are now examined. Out of 1,086 p.128
 tests in 157 cases, there were 31 changes in an unfavourable direction. Only 14 were other than negative to suspicious, and out of these 14, only 4 occurred after the first eight weeks. Minor changes in the first eight weeks are not considered of much importance. One case of female secondary syphilis showed two of these relapses and defaulted after six months with a positive reaction. Minor changes in this series are uncommon and do not prejudice a final negative result.

On three occasions sudden reversal from negative to p.129
 full positive was seen. No special difficulty occurred in securing a favourable end result. p.130

Nine cases defaulted with non-negative blood Wassermann reactions after receiving at least 4 grams of "914". They all returned at intervals of eight to forty months, and all, in absence of treatment, showed a negative Wassermann reaction except one case in which the reaction was suspicious. This is of great importance, as it indicates that therapeutic benefit continues after the termination of a course of treatment.

The maintenance of a persistently positive Wassermann with a negative clinical state in face of much treatment occurred in three cases - in one case for 52 months. p.131

It is suggested that serial examination of the Wassermann reaction of the blood is a useful method of evaluating new remedies. p.132

Section IV.

The examination of the cerebro-spinal fluid in early syphilis. p.147

Out of 570 cases, 145 were subjected to lumbar puncture. This is difficult in a purely out-patient clinic, where men insist on going back to work, or have to travel long distances home after examination. The mere suggestion of lumbar puncture sometimes leads to default. Intentionally there has been a haphazard choice of the time at which lumbar puncture was performed, in order to secure a representative sample. The result has been a fairly even spacing of examinations in twenty week periods from the date of first attendance. p.148 p.149 p.150 p.151

There were 123 cases in which the Wassermann reaction was negative on first examination. In 9 of these, a second examination was made. Twice the re- p.155

action was suspicious, but in these cases clinical signs p.155
of nervous disease were never found during twenty-five
and ninety-one months of further observation. In no
case in these 123 was any clinical relapse noted of any
type.

Only 22 cases showed a Wassermann reaction other p.151
than negative on first examination. 12 were suspicious, p.152
6 were weak positive, 4 were positive. Suspicious re-
actions, occurred during the earlier weeks, positive re- p.154
actions during the later weeks of attendance.

In order to assess the significance of these 22 re-
actions which were not all negative on first examination, p.156
all relevant data have been carefully analysed. to

There were 12 in which the grade first found was p.160
suspicious; 5 showed this same grade on subsequent ex-
amination. All were well treated; none had other than
a negative blood Wassermann and none developed any further
signs of disease during four years of observation. It
may be taken as established that a suspicious Wassermann
reaction of the blood serum indicates a need for further
treatment. But this is not determined in the case of
cerebro-spinal fluid, and as no further signs of disease,
clinical or serological, appeared in these patients, it
would be well to keep such cases under observation with-
out treatment, to determine the significance of the

suspicious Wassermann reaction in the cerebro-spinal fluid.

Six cases gave a weak positive Wassermann reaction p.162 in the cerebro-spinal fluid on first examination. They had been well treated and in each case the weak positive reaction was transient. All ultimately appeared to be cured and no clinical signs of disease appeared.

Four cases showed a positive Wassermann reaction in the cerebro-spinal fluid on first examination. One case, after observation and treatment for one hundred and thirty-two months, showed, as a result of her last lumbar puncture, a cell count of fifteen, and a doubtful negative p.164 Wassermann reaction in the C.S.F. She is still to be regarded as a candidate for neuro-syphilis, and thus exhibits the importance of the grade positive as an initial finding. The other three cases ultimately appeared to be cured clinically and serologically.

No correlation between the results of the Wassermann tests in the blood serum and in the cerebro-spinal fluid p.165-7 can be detected after the first six months. The subsequent variations are not inter-related. This is important and shows clearly that lumbar puncture is essential before concluding that a case is cured.

Cell counts, protein estimation, colloidal gold p.168

reactions have not been performed sufficiently frequently to enable firm deductions to be made. It is, however, thought that a rise in the number of cells above 10, is of great value, and may be independent of the Wassermann reaction. It is suggested that an increased cell count during the first two years of disease is only of transitory importance. p.168

By analysis it is seen that abnormal Wassermann reactions in the cerebro-spinal fluid are associated with a Wassermann fast condition of the blood serum lasting for six months or more. This statement may be compared with that of the American investigators, V.D.I. 1932, which it parallels. On the other hand, in this series no persistently Wassermann fast reactions were found in the cerebro-spinal fluid, nor did any of our 570 cases develop clinical signs of neurosyphilis. p.168 to p.172 p.173

It is to be noted that adequate initial treatment together with an adequate total treatment does not necessarily protect against unfavourable changes in the cerebro-spinal fluid. The incidence of unfavourable reactions in such cases is not, however, high enough to call for any special modification of treatment methods, and further, all but one of the unfavourable reactions in the C.S.F. have yielded to further p.175

treatment.

The main findings arrived at from the work of this section suggest that all patients require a lumbar puncture with an examination of the Wassermann reaction and the cell count. In view of the transitory nature of early changes, it is not necessary to make this examination until after total treatment is completed. The end of the second year of treatment and observation is suggested as the most suitable time, but a further examination at the end of five years is desirable. This should prove, if negative, an indication that the development of neuro-syphilis is most unlikely.

Section V.

Clinical Relapse.

There were 25 cases, an incidence of 4.38%, in the 570 cases of early syphilis. There was only 2.8% of relapse in those cases receiving at least 5 grams of "914" in their first course, but 7.6% in such cases as did not receive an adequate first course of treatment.

In search of factors likely to be associated with, or causal of, relapse in these 25 cases, it was found that in six cases the first course was unusual or experimental in type, that two cases received only small

quantities of "914" as a result of intolerance or irregular attendance and that six cases, though normally treated during their attendance, defaulted at early dates. p.198

There are thus only 11 relapsed cases, out of the 25, which received an adequate initial course of treatment. p.199

An examination of all cases receiving inadequate total treatment, and yet observed for more than two years, and of those cases receiving inadequate initial treatment and then defaulting for six months, shows clearly that the commonest factor in clinical relapse is inadequate initial treatment. p.200

Clinical relapse has, in this series, occurred more frequently when mercury was the associated heavy metal, in comparison with bismuth. p.201

Further, the end results show that those cases of relapse treated with bismuth gave more satisfactory end results than did the mercury treated cases. p.206 to p.207

Early relapses at the site of the original lesion show a high percentage of satisfactory end results, if treatment be adequate. Cases showing relapse lesions, which are tertiary in type, yield a high percentage of unfavourable end serological results. p.208

Clinical relapse is associated with serological relapse. Clinical relapse is particularly a feature of p.209

a prolonged Wassermann fast state of the blood. Indeed p.210
any case which is Wassermann fast for twelve months
should be made the subject of special clinical study and
intensive treatment.

The grade of severity of the lesions in secondary p.211
syphilis bears no relation to the tendency to relapse.
No cases of malignant syphilis were seen. The later a
relapse occurs, the worse the ultimate serological out-
come tends to be, but increased total treatment can p.212
largely overcome this tendency.

It is now desirable to consider the ultimate fate
of all relapsed cases. Although with clinical relapse p.213
there is also a higher incidence of relapsed serological
reactions, yet the ultimate outlook of the cases is not
unfavourable. Each relapse should be regarded as a new p.214
case of syphilis of equivalent age, reckoned from the
date of the primary sore, and in no such case, when a com-
plete course of treatment was given after the Wassermann
reaction of the blood serum had been negative for six months,
did any further clinical or serological relapse occur. Yet,
even in this statement, there is also to be seen the quali-
fying effect of adequate initial treatment. Cases which p.215
showed relapse after an adequate first course did better
ultimately, and required less total treatment before
achieving a good result, than did those other cases

which relapsed after inadequate initial treatment.

p.216

It is here emphasised that general results, serological examination of blood and C.S.F., and clinical relapses all point to the vital importance of the first course of treatment. Mistakes made in it are dearly paid for in respect of the increase in the amount of total treatment needed. The data from this series of clinical relapses deserve to be summed up again.

(1) There is a slight difference between the antisyphilitic action of bismuth and mercury when combined with "914". Bismuth may be used as such difference seems in its favour. p.217

(2) The severity of the original primary or secondary lesions does not appear to affect the tendency to clinical relapse.

(3) The later the first relapse occurs, the more difficult is it to secure a final negative clinical and serological result.

(4) Cases showing the tertiary type of cutaneous relapse are more difficult to treat satisfactorily than the secondary type.

(5) A Wassermann fast condition of the blood indicates a state in which relapse tends to occur. This is

significant when fastness persists for more than a year.

(6) Relapsed cases treated with adequate antisyphilitic measures are as likely to yield final favourable results as are cases of blood W.R. fastness, without clinical signs, of more than one year's duration, when comparably treated.

(7) Adequate initial treatment is the factor of greatest importance in the prevention of clinical relapse.

If our figures be compared with those of the American p.218 investigators, it is seen that our incidence of 4.38% re- to lapses compares with theirs of 6.05%. Their treatment p.221 regimes usually employ "606", ours "914". They employ alternating treatment with "606" and metal, we use combined "914" and metal. There is nothing to suggest that our methods of treatment are unsound in principle. The Americans greatly stress the necessity for continuous treatment, i.e. alternation of "606" and metal without rest periods. They point out that the dangerous period lies between the fifth and the ninth injection of arsphenamine. The point concerning continuous treatment must be remembered by us in making up a fresh scheme of therapy.

Finally, it cannot be too often or too strongly

repeated that, as a result of this analysis, the commonest factor in relapse, both clinical and serological, is found to be inadequate initial treatment, and it becomes more and more suggestive that, keeping the production of intolerance in mind, there should be a concentration of treatment in the earlier weeks. p.220

Section VI.

Intolerance to "914", mercury, and bismuth.

The important question of intolerance is dealt with and, although the close analysis of all unfavourable events occurring in the treatment of early syphilis is especially considered, the problems raised in the treatment of late syphilis will also be broadly dealt with. p.221

In early syphilis the incidence of intolerance was 27.8% or, if local reactions to injection and stomatitis be excluded, 16.9%. In tertiary muco-cutaneous syphilis, there was an incidence of 44% of all types of intolerance to treatment. p.222

It may firstly be stated that a higher percentage of unfavourable reactions occurred when neokharsivan was used as compared with novarsenobillon. This statement seems to be significant after taking into account all associated factors. It is also considered that the intolerance shown to bismuth, though almost as frequent p.226 p.227-8

as that shown to mercury, is less severe, less difficult to treat, and less liable to cause prolonged interruption of treatment.

An experiment conducted on 791 cases of syphilis showed that neither the oral use of glucose, nor the administration of sodium thiosulphate, nor their combined use during, or just before, the injection of a "914" substitute, diminished either the general incidence of intolerance or its severity. p.229 to p.231

The whole question of the mechanism and prevention of intolerance is so important that it must be discussed in detail in the light not only of the analysed figures of this series, but also in view of the clinical experience of the writer. p.232

The following headings have been selected for discussion and the conclusions reached are briefly shown in this synopsis. The relevant pages in this section require, however, to be read in detail. p.233

(1) The general health and reaction of the patient.

Pay attention to focal sepsis. Eliminate it after causing resolution of any large tertiary lesion. p.234

Cutaneous irritability or skin allergy is of the greatest importance. It is common in cases which show asthma, hay fever, food idiosyncrasy, urticaria, eczema,

scaly dermatitis, hyperchlorhydria, constipation with p.235
 spastic colon or mucous colitis, low blood pressure.
 It shows itself as an increased tendency to arsenical
 intolerance. It cannot be detected in advance by a
 "patch test" by use of watery solution of "914" in com- p.237
 presses on the arms. Probably a mercurial purge and
 saline every fifth day, and the administration of kaolin
 and the heavy carbonate of magnesia are the best methods
 of treating susceptible patients.

If chronic bronchitis is present, care in the use
 of "914" is indicated: if pulmonary tuberculosis exists, p.238
 iodides are contra-indicated.

Therapeutic shock may occur in a dangerous form if
 full treatment be given immediately to cases of cardio- p.238-9
 vascular or central nervous syphilis. Well known in the
 case of the arsenobenzols, it is not so generally recog-
 nised in the case of the iodides. It has been found
 thus to occur in cases of tabes and G.P.I. and is over- p.239
 looked because the ensuing mental deterioration is insid-
 ious. The only method of commencing treatment in neuro-p.240
 syphilis is to use bismuth or mercury by the intramuscular
 route for a few weeks. Special care is required in
 choosing cases of cardio-vascular disease suitable for p.241
 "914" treatment and the initial doses should always be
 small ones.

Pre-existing renal disease has always demanded great therapeutic caution. Antecedent catarrhal jaundice on the other hand, has not caused undue susceptibility, and all such cases tolerated ordinary clinic treatment. The general habits and mode of life of patients are of remarkably little importance.

(2) The preparation of the patient and the technique of injection are in accordance with standard practice. It is, however, remarkable how quickly a series of new clinical clerks can produce unfavourable local reactions. It is also noteworthy how frequently patients disregard instructions not to eat for two hours before or after an arsenical injection, and how seldom toxic effects follow breaking this rule.

(3) Arsenical reactions. Nitritoid crisis, a condition resembling clinically an overdose of amyl nitrite, is often seen in the treatment of tertiary syphilis immediately following the administration of "914". It leads to default. Twelve methods of prophylaxis were experimented with, and the very slow administration of the drug, the antecedent subcutaneous injection of $\frac{1}{2}$ c.c. of 1/1,000 adrenalin hydrochloride, and heavy purgation on the day preceding the injection were found to be the

most satisfactory means of coping with this complication.

Malaise and gastro-intestinal reactions are the commonest forms of intolerance. Due usually to dietetic indiscretions and occupational strains, these may be relieved by suitable instructions. Diet must be adequate, and loss of weight is usually associated with loss of appetite and a mild anaemia, curable by Bland's pills. p.246

Jaundice showed a case percentage incidence in early syphilis of 4.0% - or one jaundice to every 321 injections. It occurs in or after the first course of treatment. As prodromal symptoms, fatigue and a distaste for fat or fried food are singled out as important. It is difficult to get early information from the blood serum. The Van den Bergh reaction and Fouchet's test for blood bile pigments have not been helpful. The extended use of Ehrlich's aldehyde reaction for urobilin in the urine might be tried. Jaundice in the first few weeks, as a manifestation of syphilis, has not been recognised. Jaundice, eight to twelve weeks after a course of treatment, is thought to be due entirely to "914" in this series, and never to syphilis or epidemic catarrhal jaundice. p.247 p.250 p.251

Skin intolerance to "914" is considered. The increased toxicity of N.K. compared with N.A.B. has already been noted. p.252

With regard to aetiology, it is suggested that patients p.252 with greasy seborrhoeic skins or with focal sepsis, i.e. to those likely to react to potassium iodide, are likely p.254 to do badly with "914". A search for a specific factor in the skin has failed. The intra-dermal injection of agar, painting the skin with various aniline dyes, the p.255 application of moist compresses of watery solutions of "914", yielded no information as to the type of case likely to do badly. A careful analysis of the diet, action of the bowels, alcoholic habits, urine, blood pressure, and state of the arteries in 40 cases, suggested that intestinal stasis might be a factor leading to increased intolerance.

The prophylaxis of arsenic intolerance is difficult. It is very important. Research is needed. Experiments p.256 were made with glucose, sodium thiosulphate, glucose and sodium thiosulphate, atropine, fractional dosage, adrenalin, aromatic spirit of ammonia, acid sodium phosphate, alkaline sodium phosphate, sodium bicarbonate and sodium iodide. The use of these preparations failed to produce any reduction, either in the incidence of skin intolerance, or in its further prevention in cases which had already been intolerant.

The correlation of the appearance of arsenical intolerance with the end results of treatment in early syphilis, is most interesting. Intolerant cases do well. This p.257 will later be explained.

Intolerance to "914" is seldom seen before at least 3 grams have been given.

(3) Metal reactions. Bismuth intolerance was slightly p.258 less common than mercurial. Preliminary cleansing of the mouth is the best prophylactic. The routine administration at night of 60 grains of precipitated sulphur did p.259 not diminish the incidence of intolerance. Bismuth intolerance is less severe and disappears more quickly than does mercury intolerance. Idiosyncrasy is undoubtedly seen. Acute bismuth intolerance has not been met with. Acute mercurial intolerance, shown by gastro-enteritis and renal disturbance, is associated with the intravenous use of mercury. This mode of administration is not required in the treatment of syphilis. Metal intolerance is very common in tertiary syphilitics, probably because p.261 of their age, their poorer powers of elimination and their unhealthy mouths.

(5) The association of intolerance with the final serological results is investigated. This is most interesting. It may be briefly summed up by stating that p.261

those cases which showed intolerance showed a higher per- p.262
centage of final negative results than did the cases in
which no intolerance occurred. It is even more striking
on considering those cases in which, after intolerance p.265
appeared, no further arsenobenzol was given. There were
101 cases in this group, the final percentage of unfavour-
able results being only 7%. This is the lowest recorded un-
favourable group in this series. Further, too, in this
group Wassermann relapse was only 15% as compared with
24.5% in the whole series. This points to the truth of
Ehrlich's view that the maximum therapeutic effect is pro-
duced by a dosage which lies near the limit of toxicity.

The lessons learned may be briefly summed up: apart
from general care in examining, selecting and preparing
suitable cases for treatment, specific methods of prevent-
ing intolerance are lacking. Research on this matter is
probably one of the most urgent needs concerning the man-
agement of syphilis. Intolerance lessens the total amount
of treatment received, and the total attendance of the p.266
patient. Intolerance does not, however, necessarily
lead to unfavourable end results. On the contrary, in-
dividual intolerance in some cases seems to coincide with
maximum therapeutic efficiency. Therefore increase in
the average power of tolerance in a group of patients

should lead to an increase in the amount of "914" and metal to be given with correspondingly increased benefit.

These sections conclude the review of early syphilis treatment results, and before proceeding further it may be as well to remind the reader of the main conclusions reached:-

If a combined course of "914" and bismuth metal be given in 15 weeks: if the amount of "914" be in the neighbourhood of 5.55 grams and the amount of bismuth metal 2.4 grams: if this course be repeated until the case receives one course after being Wassermann negative, and if the patient then take mercury by mouth until two years have elapsed from the date of commencement of treatment, he has almost a 90% chance of then being clinically and serologically negative. Should the initial course of "914" be less than 5 grams, or should the time of the first course be prolonged, his chances of cure are much diminished.

Early clinical or serological relapse can be compensated for, in the main, by increased total quantities of treatment. Later clinical or serological relapse is not so easily rendered permanently negative both clinically and serologically.

Default is one of the main factors in producing unfavourable results.

Intolerance, however, is often associated with good end results, particularly intolerance to "914".

Every analysis shows the extreme importance of the first course of treatment, and it is suggested that some increased concentration of treatment in the earlier weeks might be beneficial.

The consideration of the later stages of syphilitic infection is now undertaken, partly for review on their own account, and partly to ascertain what bearing they may have upon the treatment of the early stages.

Section VII.

Latent Syphilis.

Cases are defined as those, which on their first p.276 arrival at the clinic, showed a positive Wassermann reaction of the blood serum without any clinical signs of dis- p.277 ease, and in whom the original infection, if ascertained, occurred more than two years earlier. Every care was taken to exclude hereditary syphilis. Particular attention was given to signs indicative of glossitis, adenitis, p.278 cardio-vascular or neuro-syphilis. 239 cases were con- p.279 sidered to be examples of true latent syphilis as above defined.

Should such cases receive treatment at all ? p.281

Several points require consideration in answering this p.282
question. Is an untreated case of latent syphilis more
liable to develop clinical signs of syphilis than a
treated one ? There is strong a priori evidence in p.283
favour of the affirmative, since many cases of late syph-
ilis show long periods of latency. In Bruusgaard's
series of cases of early syphilis, amounting to 2,181, p.284
no treatment was given during the early years. Some
twenty years later, 473 cases were traced. 37% had an
active lesion, while only 27% were apparently cured. In
the present series it is to be shown that treatment of p.285
latent syphilis results in 50% cure.

Apparently, then, it is of advantage if the latent
syphilitic receives treatment.

Is such a case contagious ?

With respect to their marital partners, no unequiv-
ocal case of infection is noted, but the criteria are
difficult to obtain. On the other hand, it is reported
that spirochaetes have been found in the spermatic fluid p.287
of latent syphilitic males and transmission of disease to
the eye of the rabbit has been performed. In this ser-
ies the correlation of the examination of the consorts p.288
with the dates of infection, or the absence of known
primary disease, suggests most strongly that in several

instances infection has occurred during latent periods. But the strongest argument for treating latent syphilis, p.299 is found when the possibility of hereditary transmission is considered. In this series, out of ninety-nine children of latent syphilitics, born more than two years after p.290 the onset of the primary disease in the mother, sixty were syphilitic. After adequate treatment of latent syphilitic women attending this clinic, eighteen children have been born. None were syphilitic. p.291

Thus latent syphilitics should be treated - for the sake of the individual, the consort, and any prospective family.

On commencing this work no rules for the treatment of latent syphilis existed. Apart from treatment being essentially a personal matter for each case: apart from a feeling that when the blood Wassermann became negative, treatment might thereafter be continued only for a few months, p.292 there was nothing to guide clinic practice. The usual standard course of combined "914" and metal was employ- p.293 ed, and such courses were repeated at intervals of from four to six months. In elderly, or feeble persons metal was frequently used without any concomitant "914", In- p.294 tensive treatment, advised by Naegeli, has not been

carried out here, and, in proof of the absence of necessity for it, only in one case has neuro-syphilis later appeared. p.294

In presenting the results of treatment the terms adequate and inadequate are used. Adequate implies the equivalent of at least two courses of injections and a year of observation thereafter. Inadequate implies less. A result is satisfactory if the final clinical and serological result is negative: if it is not, it is termed unsatisfactory. p.295

One hundred and forty-two cases received adequate treatment: 48.2% showed a satisfactory result; 51.8% showed an unsatisfactory result: 98 cases received inadequate treatment: 20.4% showed a satisfactory result; 79.8% showed an unsatisfactory result. Now although 142 cases received adequate treatment, only 105 of these were observed for more than two years. In this group the percentage of satisfactory end results is 63%. It is strongly felt that with the lapse of time the percentage of satisfactory results would tend to rise even in absence of further treatment. In the American series the average percentage of comparable satisfactory results is 51.7% - the best group shows 60.2%. p.296 p.297

The 105 cases observed for more than two years
are considered in detail. p.298
to

It is seen that a satisfactory result has been p.232
attained with the most varied amounts of treatment.
Some such cases got no injections of "914"; some re-
quired more than forty; some received less than twenty
injections of metal; some received two hundred. This
variation is explained by the cessation of treatment
shortly after a negative Wassermann is obtained. Thus
in the small treatment groups there is little Wassermann
variation; it is frequent in the large treatment groups.
If we then group the cases in accordance with the amount
of treatment received, it is found that if three courses p.303
of ten injections of "914", equivalent to 16 or 17 grams,
be given, 57% of cases will be apparently cured after p.304
two years. These figures are very like those in the
American series, and an analysis of their methods of
treatment shows that such results can be obtained in the p.305
most varied ways. Their best groups show a preponder-
ance of metal rather than intensive arsphenamine therapy.
Regrouping our 105 cases to illustrate this point does p.306
not indicate that more than 30 injections of bismuth p.307
will produce an equivalent increase in satisfactory end
results. Some special features call for examination in

order to appreciate the significance of our results. Firstly, out of the 105 cases, 23.9% had a positive Wassermann reaction of the blood and 13.3% a weak positive when last seen. Regrouping these cases in terms p.308 of the amount of treatment received, it is shown that end positive serological results occur in higher incidence if little treatment is given. When, however, the 23.9%, (25 cases), of positive end results are examined, p.309 it is found that no fewer than 20, or 19%, of the total 105 cases, were Wassermann fast. These Wassermann fast cases tended to receive the largest amounts of treatment, and it becomes apparent that some 10% to 15% of latent syphilis seems serologically unaffected no matter how much treatment be given. But all those cases were clinically well - from periods of two to eleven years. Therefore Wassermann fastness in latent syphilis is not apparently by itself a criterion for pursuing treatment in a relentless manner. On the other hand, since only five of the twenty-five cases which finally showed a positive Wassermann showed any variation, and since twenty-two out of fifty-three successful end results showed variation, any temporary reversal of a positive serolog- p.310 ical result is of good omen, and should lead to further treatment.

The duration of the syphilitic infection is considered. Out of the 239 cases, 27.6% gave no antecedent history of disease. None of these cases developed neuro-syphilis. As the percentage of females without antecedent history of disease was 48.3%, the question of latent infection in pregnancy is of great importance, and suggests the need for an extensive routine use of the Wassermann test. In considering the final outcome of treatment, it is found that such latent cases yield as high a percentage of satisfactory results as do those cases which have a known history of disease.

Where the date of the original infection is known, analysis shows that latency of under four years gives a more favourable end result, and if the infection be of from four to ten years standing, there is a slightly increased chance of cure as compared with those of more than ten years. When the age of the patient on first coming to the clinic is examined, a curious point emerged, namely, that females, if they are aware of their infection, come at an earlier date than males; if unaware of their condition, they come at later age groups than do male cases. Age, roughly between 20 and 65 years, has nothing to do with the outcome of treatment, apart from expressing the duration of disease. It is noted,

however, that 65 out of the total 93 females and 91 of the total 146 males were under forty years of age. The need for treatment in view of potential pregnancy becomes apparent.

The question of antecedent treatment is now investigated. 76% females and 55.4% males had none. Most varied amounts of treatment had been given to the remainder. All that can be said, but it is important, is that earlier treatment did not prejudice a finally satisfactory result.

Clinical relapse in latent syphilis is difficult to assess. Many conditions, for example anaemia or arterial disease, may be either syphilitic or non-syphilitic. Accordingly a complete list of all doubtful conditions has been appended.

The total incidence of relapses is placed at 19, or 8.9%. Fourteen of these relapses occurred within two years of their first attendance at the clinic. These figures are roughly comparable with those in the American series. Clinical relapse is of bad omen, for, though curable in itself, it yields a greater percentage of final unsatisfactory results, even if adequate treatment be given. Five cases which relapsed after two years'

attendance are examined in detail. They are, on the whole, well treated cases. Their incidence, 5% in cases attending for two years or more, is not high enough to justify indefinite prolongation of treatment for all. None were Wassermann fast.

Cerebro-spinal fluid examination has not been routinely carried out. Only 52 cases were examined at the outset. These showed in 43 cases a negative, in 9 cases a suspicious Wassermann reaction. All cases giving a weak positive or positive Wassermann reaction have been excluded from this series. The nine cases which originally gave a suspicious result, all later gave a negative reaction, and none developed clinical neuro-syphilis. One case, originally showing a negative Wassermann reaction in the C.S.F., developed G.P.I. three years later. This is in contradiction to the American dictum that "a negative spinal fluid. . . is a practical guaranty against the subsequent development of neuro-syphilis."

Out of the 25 blood Wassermann fast cases of latent syphilis, twenty were observed for more than two years, and they form an important group demanding further attention. Seventeen received adequate treatment and none of these showed clinical relapse. This is curious in view of the over all 8.9% incidence of relapse. This

absence of clinical relapse may be a coincidence or it may have significance. Bruusgaard showed 14% of latent Wassermann positive - presumably Wassermann fast - in untreated syphilis, at a similar stage. This series suggests firstly, that there is no need to prolong routine treatment and frequent observation beyond the two year period, but also it invites a careful examination of all such cases in an attempt to ascertain if any facts, other than the activity of the syphilitic virus, may not play a part in the maintenance of this continually positive result. This series does not corroborate the American contention that Wassermann fastness is associated with intensive arsenical therapy and diminished by intensive metal therapy. p.334

The conclusion suggested by this brief review of latent syphilis is that treatment is advisable in the interest of the patient, the consort, and potential children.

Treatment of latent syphilis might reasonably consist of some 30 injections of "914" divided into three courses of 10 injections in each, and of some 30 injections of bismuth metal. After such treatment, there is a 50% chance of securing a negative blood Wassermann. Yet, as, after two years, 5% clinical relapse has been recorded, the cases must be carefully watched. If the

patient be under forty years of age, and fail to secure a negative blood test at the end of two years, treatment should be continued, provided that the Wassermann reaction of the blood serum has not remained positive throughout the antecedent two years.

This picture contrasts with the greatly increased chances of obtaining a cure in early syphilis, and it merely emphasises the need for continued concentration on problems raised in the treatment of early syphilis.

Section VIII.

Tertiary muco-cutaneous syphilis.

This group offers some resemblances and some contrasts to latent syphilis. It can only afford further confirmation of the importance of adequately dealing with the early lesions. This type of late syphilis is really the only one capable of being systematically valued at an out-patient clinic in respect of therapeutic results. Both cardio-vascular and neuro-syphilis require the association of in-patient treatment, for it is impossible for many cases with these lesions to attend as out-patients.

473 cases of gumma, whether in the form of a subcutaneous nodule, a rash, or an ulcer will be reviewed. The cases are, on the whole elderly, and, on the whole, show

effects of other diseases and degenerations. Accordingly treatment can seldom be routine, and seldom be intensive. These cases, however, have been selected on account of their showing an absence of any syphilitic disease of the vascular or nervous system. It is thus interesting to note that only in two of this series did later vascular syphilis appear; in only one did a negative C.S.F. later become positive. p.340

"Standard" courses of treatment are not so much employed here. Frequently iodide is given first, then metal combined with "914". Intensive treatment has been tried. It does not seem justified by the results, and it is noteworthy that small amounts of treatment, insufficient to reverse the blood Wassermann, have produced clinical wellbeing for periods of two to five years. p.341

Finally, the end results of treatment, taking into account the serological tests themselves, do not justify heroic measures. What is desired is information as to the average amount of treatment likely to produce restoration of health, so that either progressive lesions or relapses are unlikely to occur. p.342

Of the 473 cases, 180 attended for more than two years. The majority of the lesions were various types of ulceration. The results have been examined in p.344

respect of the actual amounts of treatment received by each case. Thus with respect to "914", any number of injections from "none" to "more than forty" may be encountered, and similarly in respect of metal. The end results are shown as negative, suspicious, or positive (including weak positive), depending on the final blood Wassermann. In all cases treatment had produced resolution of the syphilitic lesion.

p.345

p.346

The general result was as follows :-

293 cases treated and observed for less than 2 years,

13.5% negative.

180 cases treated and observed for more than 2 years,

37.2% negative.

In connection with these two groups of cases, it is desired to stress the effect of time as a factor. Thus if any two equivalent groups of treatment be taken, the percentage of final negative results increases with the lapse of time. The records show numerous cases of Wassermann reversal from + to -, four to eight months after the cessation of treatment.

p.347

The cases are grouped according to whether they have had "less" or "more" than twenty injections of "914" and "less" or "more than" twenty injections of metal, thus giving four groups. This shows that the best results occur

p.348

in those cases receiving little arsenic and little metal. But the fact that that group also shows the smallest amount of Wassermann variation merely indicates that cases which are easily "cured" receive no further treatment in the absence of Wassermann relapses. The general conclusions are interesting so far as the cases observed p.349 for two years are concerned. Out of these 180 cases, 10% were negative after receiving less than twenty injections of "914" and twenty injections of metal. Further treatment secured a favourable result in almost one p.350 third of the residue. It becomes important then to ascertain at what stage the rise in serological improvement stops, or, in other words, what is the optimum amount of treatment for the average person. The cases are thus regrouped firstly according to the actual number of injections of "914" given, and it is seen that the p.351 percentage of serological failures tends to rise after twenty injections of "914". The cases get increasingly difficult to cure. If the number of injections of metal be considered, it is seen that, if "much" metal be given, p.352 the associated number of injections of "914" varies from 5 to 30 in the more successful end groups. Those cases which received less than twenty injections of metal and p.353 were serologically negative when last seen, have special

factors explaining the results. Accordingly it seems reasonable to state that the average case, which is p.354 going to give a final negative Wassermann result, will give this result after receiving twenty injections of "914", and at least thirty injections of metal, usually bismuth metal.

Failures which may influence this simple statement require consideration.

Firstly clinical relapse is dealt with. There were 10 cases of skin relapse, 2.1%. Only two of those re- p.355 ceived more than 5.85 grams of "914", only one received more than twenty injections of metal. Skin relapse in this series is practically unknown if adequate initial treatment be given. All cases of relapse showed final positive Wassermann reactions.

Wassermann fast cases:- There were sixty, $33\frac{1}{3}\%$, p.356 of the 180 cases observed for more than two years. Thus one third of our cases appear cured, one third show Wassermann variation with a final positive, one third p.357 are Wassermann fast. Considering the percentages of successful results at all stages of treatment, it seems that thirty injections of "914" and more than thirty of metal should bring out clearly whether a case is or is not Wassermann fast, and although further treatment

reverses a number of cases, yet the absence of clinical p.358
relapse and the high incidence of intolerance (44%)
makes such treatment of a very doubtful value. Intoler-
ance is so frequent as to demand consideration in planning
schemes of therapy or dealing with any given case.

Sex is a factor of some importance. In the 180 p.359
cases observed for at least two years, 46.3% of females p.360
showed negative end results as against 27% of males.
It is also thought that the clinical lesions are less p.361
extensive and severe in the female. An analysis of
the age groups in the female does not suggest that the
period of the climacteric is more prone to be marked by
clinical syphilis than other age periods. The type of
lesion has no effect upon the ultimate outcome of treat-
ment. Rashes, ulcers and subcutaneous gummata do equally
well.

A discussion of these various data leads to the p.362
suggestion that, where the risks of the production of
marital infection or of hereditary syphilis are not in to
question, the individual will achieve adequate protect-
ion, and will not be unduly submitted to toxic effects,
if he receives:- two courses of ten injections of p.365
"914" (• 11.7 grams) and thirty injections of bismuth
metal (• 7 - 8 grams), along with considerable quant-
ities of potassium iodide by mouth. Such treatment

might be given in one year.

A case so treated has a thirty per cent chance of being Wassermann negative at the end of two years, a thirty per cent chance of being Wassermann fast. His relapse incidence is less than 1%. If the cerebro-spinal fluid was negative at the outset, it is most improbable that neuro-syphilis will develop. The further treatment of such a case is not likely to modify in a favourable direction his chances of developing cardiovascular disease. Finally, treatment considerably in excess of this amount will still leave 20% of Wassermann fast cases. No additional benefit appears to accrue. If prolonged and intensive treatment be carried out over a series of years (not under five), it is considered that the chance of achieving a permanently negative blood Wassermann is still less than 50%. Should a patient who is otherwise healthy, under the age of forty, and in circumstances of work and economic surroundings which permit of reasonable care of his person, desire this intensive treatment, it is legitimate to carry it out, but only after a full explanation of the attendant risks.

Again there falls to be noted the significant differences between early and late syphilis.

The crude results are stated once more :-

Early syphilis	-	90% "cures"	} On a clinical and serological standard.
Latent syphilis	-	50% "cures"	
Tertiary mucocutaneous syphilis	-	37% "cures"	

All stress must be laid on the management of early syphilis.

Section IX.

The use of Iodides in the treatment of syphilis.

This section represents an enormous amount of work. There is a lack of detailed clinical observation on this subject, and such studies as the literature affords, are concerned only with limited aspects of the use of iodide. An endeavour has been made to render this series of experiments so complete, that a definite answer may be found in respect of any question regarding the most advantageous methods of employing the iodides in all stages of the syphilitic infection. It is also hoped that the limitations of iodide therapy can be authoritatively stated. While a full understanding of the points at issue can only be obtained from the section itself, the following is a synopsis of the main conclusions.

The first reference to the use of iodide has been p.379 traced to Coster in 1823, but the first practical regime was established by Wallace in the Lancet in 1836.

There he recommends 15 to 30 grains of potassium iodide p.380
thrice daily in cases of late ulceration. No better
work has been noted and no extension of this regime p.381
found in the literature. McLean stated that organic
compounds of iodine were inferior in antisyphilitic
effect to the simple potassium salt. p.382

The mode of action of iodine is still unproven.
Many hypotheses have been suggested and objected to, and
probably the hypothesis of Jobling and Petersen has p.383
the fewest valid criticisms. These workers assert that
iodide combines with certain unsaturated fatty acids, p.384
and that this diminishes the antitryptic effect of the
blood serum. Accordingly, after the administration of
iodide, autolysis of gummatous tissue with absorption p.385
can take place.

The fate of the iodides after administration has
been much studied, and it would appear that either the p.386
potassium or the sodium salt may be employed for oral
use, in an interchangeable manner, so far as clinical
results are concerned. Osborne studied in great de- p.387
tail the fate of iodide after oral, intravenous, and to
rectal administration, and his conclusions are, at p.390
least, compatible with our clinical experiments. Few
pharmacologists can resist iodides, and the literature

is colossal. Thus there is quoted a series of experiments actually dealing with the fumes of iodine as an antisyphilitic remedy.

The use of iodine by the intravenous route is quite modern. The first paper was written in 1917 by Engener, and there are many others. Undoubtedly this method of administration is an effective way of employing sodium iodide. Many observers attempted to investigate the passage of iodine into the cerebro-spinal fluid, with contradictory results, but the publication by Kendall, in 1912 and 1914, of a delicate method of analysis led the writer and Professor David Campbell to investigate the matter. Undoubtedly iodine does penetrate into the cerebro-spinal fluid, and its concentration can be enhanced by the use of the intravenous route of administration. A very significant point, from the aspect of treatment, is that after intravenous injection of sodium iodide, a maximum concentration in the C.S.F. is not attained until some six or eight hours later.

The results of the present clinical investigation now follow. The best method of giving potassium iodide by mouth is to dissolve the salt in plenty of water, and administer it immediately before food. Milk may be substituted for water if the taste is complained

of. For intravenous use a 10% aqueous solution of sodium iodide is safe and painless, the dosage is easily calculated, and it is easily administered by a syringe and needle. p.405

For rectal administration solutions of sodium or potassium iodide should be in water, and of not more than 10% strength. The single oral dosage of potassium iodide may vary from one forty-eighth of a grain to two hundred and forty grains: the single intravenous dose of sodium iodide may safely reach twenty-two grams. p.406 p.407

For repeated administration tolerance is high and 90 grains of potassium iodide may be given four times a day by mouth, combined with 10 grams of the sodium salt daily, by the intravenous route, for a fortnight, without toxic effect.

Iodism, of common occurrence, can be stopped by the intravenous injection of four grams of sodium iodide. p.409

The effects of iodide upon the spirochaete content and the resolution of the primary and secondary lesions, may be summed up by stating that, apart from the hyper-tonicity of solutions, iodide has no local antisyphilitic action, and short range (one week) experiments with oral, intravenous and rectal administration produce no resolution p.412 p.413-6

of lesions. The persistence of pigmentation in secondary syphilis is inhibited.

In many cases of skin lesions in late syphilis, oral potassium iodide was tried in dosage of from one forty-
eighth of a grain thrice daily to ninety grains four
hourly; sodium iodide was given intravenously at daily
or weekly intervals in quantities up to twenty-two grams.
Sodium iodide was also given by the rectal route. These
methods were tried singly and in combination.

If a single dose is given by the oral route it was concluded that potassium iodide exerts an action which is roughly in proportion to the dosage. It does not initiate a continuous process of progressive resolution. The amount of resolution increases while the single dose is being increased from one to thirty grains, and little further benefit accrues from larger dosage. So, too, with repeated dosage of potassium iodide. The rate of resolution of gummatous lesions increases while the dose is being increased from one to fifteen grains, thrice daily. There is only very slight increase in the rate of resolution with any larger dosage. An exception is seen in the case of visceral syphilis, where large doses, 60 grains four times a day, may yield the maximum benefit. In

cutaneous gummata no increase in the rate of absorption followed upon increasing the frequency of a fifteen grain dose of potassium iodide beyond thrice daily. It p.421 was tried at two hourly intervals. This accords with Osborne's observation that it takes some four hours to to secure the maximum blood concentration of iodine, after the oral administration of the simple salt. It is not, p.425 however, necessary to raise the blood concentration more than three times in the 24 hours in order to secure the maximum therapeutic effect.

There is one exception to these statements. In any case, on any dosage, the interpolation of a single large intravenous dose of sodium iodide temporarily accelerates resolution. Its repetition daily produces no increased benefit.

The conclusion is inevitable that no further change in the dosage suggested by Wallace in 1836 need be con- p.424 sidered.

Single daily injections of sodium iodide by the intravenous route were no better than the oral administ- p.426 ration of the potassium salt thrice daily. Four or six grams were found to be the most effective dose for p.427 intravenous work. Four grams of sodium iodide given once daily by the intravenous route is nearly equivalent

to fifteen grains of potassium iodide given thrice daily by the oral route. p.428

Rectal administration is unnecessary, but therapeutic results can be obtained. p.429

A summary of the suggested use of iodide in the treatment of tertiary muco-cutaneous lesions is:- p.430

- (1) Give 15 grains of potassium iodide, well diluted in water, thrice daily before food.
- (2) If intolerance is met with, give an intravenous injection of four grams of sodium iodide in 10% aqueous solution, and continue the use of the oral potassium iodide.
- (3) If resolution appears unduly delayed give, at weekly intervals, an injection of 6 or 8 grams (10% aqueous solution) sodium iodide, and continue to employ the potassium salt by mouth, in 15 grain doses, thrice daily.

The concomitant use of "914" and metal does not entail modification of these conclusions.

In the treatment of latent syphilis, the prolonged administration of iodide, by either the oral or the intravenous route, does not produce a negative blood Wassermann, nor does its exhibition appreciably enhance the effect produced by "914" and metal upon the Wassermann reaction of the blood serum. p.431

In the treatment of early syphilis the continuous administration of potassium iodide throughout courses p.433

of "914" and metal is not shown to be of value in the p.434
 production of a negative Wassermann reaction (1) at
 the end of the first course of treatment; (2) at the to
 end of two years; (3) at the end of five years. On
 the other hand, it does not prejudice the chance of se-
 curing a negative result at any of these periods. p.437

In tertiary skin syphilis and hereditary syphilis,
 neither the extended oral use of potassium iodide nor p.438
 the extended intravenous use of sodium iodide produces
 significant improvement in serological reaction. There p.439
 seems to be a slight increase in the number of negative p.440
 results temporarily produced when these methods of
 treatment, if used alone, are compared with rest periods,
 or, if given in combination with "914" and metal, are
 compared with the use of these drugs without iodide.
 The final serological outcome is, however, not affected.

In neuro-syphilis clinical benefit often follows
 the use of intravenous sodium iodide. It may thus ad- p.441
 vantageously be used at some stage or other in all cases,
 but should not be employed in the first weeks, in case
 the Jarisch Herxheimer reaction appears.

Hypertonic solutions of sodium iodide were used in
 an attempt to facilitate the entrance of arsenic into p.441
 the cerebro-spinal fluid. The rationale of this pro-
 cedure is:- C.S.F. pressure falls after the administration

of hypertonic solutions, and restoration of pressure starts six hours later. Therefore if NaI be given in hypertonic solution, there will be initiated, at the sixth hour, a maximum penetration of iodine into the C.S.F., and "914", given intravenously six hours after the administration of NaI, should penetrate more easily on the tide of rising C.S.F. pressure. Six cases were so treated. It is noteworthy that in each of these cases of old standing disease, serological improvement in blood, C.S.F., or both, was produced in 10 weeks. It was, in view of the amount of treatment given, naturally only of a temporary nature.

p.441

to

p.447

This section, then, is concerned chiefly with the rules laid down for the employment of iodide in late syphilis. It is noteworthy that its continued employment has not been found to benefit cases of early syphilis.

Section X.

The methods to be employed in the investigation of new substances designed for the treatment of syphilis.

p.448

This is inserted because no similar work has been discovered in the literature.

Preparations should come via the Therapeutic Trials Subcommittee of the Medical Research Council. Full

p.449

liberty of action is essential. The chemical composition of the preparation and its stability should be known, and all the data concerning animal experiments. The following points should be investigated in the order shown:-

(1) Toxicity - early and late, with which is associated elimination and storage of the drug.

(2) Clinical effect on late skin syphilis or sub-cutaneous gummata .

(3) Serological effect on late Wassermann positive syphilis.

(4) Clinical and bacteriological effect upon early syphilis.

(5) Serological effect upon early syphilis.

(6) Relapse, clinical and serological, will at this stage fall to be considered.

If a preparation survives the initial tests for toxicity and for action upon syphilitic lesions, great caution is required before subjecting cases of early syphilis to its action, without immediate subsequent use of known anti-syphilitic remedies. Assuming the drug to show action upon the clinical and serological lesions in a reasonably short time, the most important single criterion is Wassermann relapse, whether early or late.

Section XI.

The reader is asked to consider, in the eleventh section, a series of arguments developed with the intention of providing a fresh regime of treatment for early syphilis. Many of these arguments are contained in the preceding sections - some are freshly stated - and information has been obtained concerning the present and past methods of treatment in a number of British clinics. The section must be read in detail, and this synopsis can only indicate the main conclusions. It may, however, facilitate the approach to this section. p.465

It will be recalled that 570 cases of early syphilis were treated in a uniform manner; that such treatment consisted of the combined use of "914" and metal; that a course contained 10 injections of "914" and 12 of metal in 15 weeks, with uniform time spacing and rest intervals. Observation of such cases has been maintained throughout a twelve year period. p.469 p.470

As criteria for any course of treatment, freedom from clinical and serological relapse is, of course, indicated, but clinical relapse is relatively so infrequent that Wassermann relapse must be the main single criterion. In addition, the prevention of intolerance and of default demand consideration. Adequate time for observation, p.471

and an adequate number of cases are also required. At least one hundred cases should be observed for at least two years before coming to a favourable opinion on any method of treatment. Unfavourable judgment can usually be given at an earlier date. p.473

The details concerning the analysis of this series of 570 cases concern observed facts. They must simply be stated categorically in order to establish the desired argument.

Adequate first course = 5 grams or more "914".

Adequate total treatment after 1921 = one course treatment, and six months observation on Hg pills after being serologically negative.

1. 570 cases : 83.4% negative - a figure with no assessable value.

2. 570 cases : 178 observed for more than two years p.474
88.8% negative.

Subdivided into groups according to whether first course was adequate, or inadequate, and total treatment adequate, or inadequate, they show (1) the importance of the first course; (2) total adequate treatment maintains first course but can also compensate for its deficiencies. p.476

Adequate first course - 10.6% failures.

Adequate total treatment - 11.1% failures.

3. (1) All serological results immediately after first course.

Course adequate - 25.1% not negative (11.1%+) p.476

Course inadequate - 40.0% not negative (29.7%+)

(2) final results in all cases receiving inadequate total treatment.

Adequate first course - 11.4% failures.

Inadequate first course - 40.0% failures.

4. With respect to need for adequate total treatment.

17 cases showed serological relapse at least 12 months after adequate first course and inadequate total treatment. p.477

5. Time as a factor.

(1)	<u>No. of cases</u>	<u>Not negative at end of 1st course.</u>	<u>Percentage of those receiving no further treatment and finally not negative.</u>
Adequate first course	376	25.1%	12.4% (i.e. 87.6% negative)
Inadequate first course	194	40.0%	40.0% (i.e. 60.0% negative)

(2) Normal time of course = 16 weeks.

If adequate first course given in 10-14 weeks, result satisfactory. p.479

If time of course increased, e.g. 18 weeks, result unsatisfactory.

(3) On adequate first course :-

One third of cases alter from + to - between 5th and 8th weeks. p.480

One third of cases alter from + to - between 9th and 12th weeks.

6. As. + Hg. - 13.8% finally positive.

As. + Bi. - 8.6% finally positive.

Intolerance to Hg= 4.74%

Bi= 3.33%

Hg by oral route is of little value.

7. Default at any stage increases unsatisfactory percentages. p.481

8. Arsenic intolerance. The maximum therapeutic dose lies near the toxic dose. p.482

9. The continuous employment of iodide throughout the course is of no value.

Further information was sought and obtained from nine British clinics in respect of :- p.483

Treatment in 1921; treatment in 1931; any reasons for change.

On analysis :- Five clinics use "914" and metal concurrently, somewhat in the manner of this clinic. One clinic starts with short intensive bi-weekly treatment. One clinic employs solely bi-weekly injections of "914" and p.487

metal. One clinic gives consecutive treatment of "914" and metal. One clinic gives short intensive treatment with long rest periods. All but one use bismuth.

Our clinic gives a relatively fairly large first course of "914": the total "914" given is medium in amount. The total amount of bismuth is low. Hg pills are used. p.489

From the reports of these nine clinics it may be said (1) that bi-weekly injections are not too toxic; (2) that more continuous treatment is advisable. p.490

The American conclusions, V.D.I. 1932, stress (a) the importance of continuous treatment, with no rest periods; (b) the importance of more than twenty injections of arsphenamine and metal. p.491

The Americans use "606" and metal consecutively. Their results are not much better, if any, and "606" has here been found too toxic for use in our out-patient clinic. p.493 p.494

In the light of our own experience, and the additional data derived from considering the experience of these other clinics, our desiderata for a new course are :- p.494

- (1) First course to be "914" and metal in combination.
- (2) Metal to be bismuth.

- (3) Not less than 5 grams of "914" in a course.
- (4) Concentration of treatment should take place in earlier weeks.
- (5) This may be bi-weekly injections of "914" and bismuth.
- (6) Total treatment should be more than two courses.
- (7) Continuous treatment should be given.
- (8) Mercury by the oral route cannot be considered adequate continuous treatment.

The details are now discussed, from page 494 onwards.

They must be read. In making up a first course, bi-weekly p.495 injections of "914" should be given to secure primary saturation with due regard to toxicity, and thereafter weekly p.496 injections until 5.55 grams "914" be given. The course p.497 suggested is :- p.500

	<u>"914"</u>	<u>Bismuth metal</u>
1st day . . .	0.45 gram . . .	0.2 gram
4th "	0.60 "	0.2 "
8th "	0.45 "	0.2 "
12th "	0.60 "	0.2 "
15th "	0.45 "	0.2 "
19th "	0.60 " = 3.15gms.	0.2 "
26th "	0.60 "	0.2 "
33rd "	0.60 "	0.4 "
40th "	0.60 "	0.4 "
47th "	0.60 "	0.4 "

Total = 5.55 grams 2.6 grams in 47 days.

Thus 3.15 grams of "914" are given for primary penetration. No rest period longer than a week is employed. Bismuth is universally used. The amount administered

p.498
p.499
p.500

may well be 0.4 gram per week. This gives 2.6 grams p.501
 in 47 days, as compared with 2.4 grams in 105 days in
 the old course. Bismuth metal seems the preparation
 most suitable for use.

More than one course of injections is necessary. p.502
 In an attempt to maintain continuous treatment, mercury
 by mouth is thought insufficient, but, in view of its p.503
 known anti-syphilitic action, mercury should be given p.504
 by the intramuscular route.

After this first course, a period of four months
 will permit of time to allow jaundice or evidence of skin
 intolerance to appear. After one month's rest during p.505
 which the bismuth will maintain antisiphilitic action, eight
 weekly injections of one grain of calomel cream may be given.
 Potassium iodide may also be employed in view of its known
 action upon gummatous tissue. Then a rest of one and a
 half months should be followed by a further series of in- p.506
 jections of "914" and metal. These should be given as
 in the first course. No new factors have appeared.

A third course is really desirable in all cases of p.507
 early syphilis, and it may be of the same nature as the
 first two. The rest interval should be extended to six p.508
 months, and in this time ten injections of calomel cream
 will maintain the principle of continuous treatment.

If this method is employed, the total amounts of "914", bismuth, and mercury are not excessive when judged by the standards of other clinics. The total time thus occupied is fourteen and a half months. There is much greater concentration than at present. It is thought, if this be not too toxic, that it should be an improvement on the present regime. Cases should then be examined, and the Wassermann reactions ascertained at regular intervals, for an indefinite period. The cerebro-spinal fluid must be examined at the end of the second year.

Scheme of Treatment and Observation for Early Syphilis in

which the W.R. of the Blood becomes

Negative by the fourth Month.

	<u>"914"</u>	<u>Bismuth metal</u>
1st day.	0.45 gram.	0.2 gram
4th "	0.60 "	0.2 "
8th "	0.45 "	0.2 "
12th "	0.60 "	0.2 "
15th "	0.45 "	0.2 "
19th "	0.60 "	0.2 "
26th "	0.60 "	0.2 "
33rd "	0.60 "	0.4 "
40th "	0.60 "	0.4 "
47th "	0.60 "	0.4 "
1½ months	5.55 grams	2.6 grams <u>W.R.</u>
1 month off treatment.		
2 months	8 x 1 grain calomel cream.	8 x Kl gr.xv. t.i.d. <u>W.R.</u>
1 month off treatment.		
1½ months.	Repeat combined course.	<u>W.R.</u>
1½ months off treatment.		
2½ months	10 x 1 grain calomel cream.	10 x Kl gr.xv t.i.d. <u>W.R.</u>
2 months off treatment.		
1½ months	Repeat combined course.	<u>W.R.</u>
14½ or 15 months = 16.65 grams "914"; 7.8 grams bismuth metal; 18.0 grains calomel cream.		
Thereafter observation, repeated blood Wassermanns and injections of Bi, or Hg, until the end of the second year, when C.S.F. is examined.		

Some Chemotherapeutic Studies

Part 11

Sections 1 to VI

S E C T I O N I.

PRIMARY AND SECONDARY SYPHILIS.

Pages 1-47.

PRIMARY AND SECONDARY SYPHILIS.

The material to be considered is arranged under the following headings :-

1. Primary sero-negative syphilis. These are cases with a positive dark ground field, and a negative Wassermann reaction in the blood serum. To be termed :- DG+ W.R.- .
2. Primary sero-positive syphilis. These are cases with a positive or weak-positive Wassermann reaction of the blood serum, and the clinical appearances of primary syphilis, with or without a positive dark ground field prior to the onset of any secondary signs. To be termed :- Primary W.R.+ .
3. Secondary syphilis. This includes all cases in which the syphilitic infection is not of more than two years' duration. The majority showed definite lesions, a few were in a latent stage. All had a positive Wassermann reaction of the blood serum. No cases attended the clinic for the first time in which typical tertiary lesions appeared within two years from the date of primary infection. To be termed :- Secondary .

These three groups will be considered under the two sexes, male and female, and where these are referred to, the

headings will be :- M.1 DG+ W.R.-
 F.1 DG+ W.R.-
 M.1 W.R.+
 F.1 W.R.+
 M.2
 F.2

The summation of these groups will be termed :- Early syphilis.

All cases of early syphilis were either untreated before their attendance at the Western Infirmary, or had received, immediately prior to their attendance, treatment of which full details were known to the writer personally.

This material is shown in Table 1.

Table 1.

	Male	Female	Total
DG+ W.R.-	48	2	50
Primary W.R.+	126	36	162
Secondary	172	186	358
Totals	346	226	570

In this table is included the records of all cases which attended the Western Infirmary for the first time between January 1919, and the end of April 1932, provided that they received treatment and attended for a period long enough to permit of subsequent examination of the W.R.

of the blood. No case of clinical relapse was observed which is not included.

This material will be the sole subject of investigation. A considerable number of cases, prior to attending the Western Infirmary, had received, for verified syphilis, treatment the exact nature of which could not be definitely ascertained. Such cases fall under the following groups :-

1. Primary syphilis: These are cases with a verified primary infection of less than two years duration, which were treated elsewhere, in whom no history of secondary syphilis was obtained. They showed a positive, weak-positive or suspicious Wassermann reaction of the blood serum and no clinical lesion. To be termed : Treated Primary, W.R.+ .
2. Secondary syphilis: These are cases of less than two years standing, giving a clinical history of secondary syphilis treated elsewhere, and showing a positive, weak-positive or suspicious Wassermann reaction of the blood serum without any lesion. To be termed : Treated Secondary, W.R.+ .
3. Early syphilis, cured: This includes all cases of primary or secondary syphilis, which received treatment elsewhere at that stage of their infection, and were apparently cured when seen at this clinic. Proof of the nature of the condition for which they received anti-syphilitic treatment is naturally wanting in many instances, but no case has been

included without careful consideration. The majority of these cases had been infected more than two years before coming to this clinic. To be termed : Treated early syphilis, cured.

A small residual group consists of cases of primary syphilis in which the diagnosis was not verified. This comprises five cases whose treatment was started at this clinic, but in whom the diagnosis, on revision, was considered to be insufficiently established. To be termed :- Primary - not verified.

This material is shown in Table 2.

Table 2.

	Male	Female
Treated Primary, W.R.+	20	2
Treated Secondary, W.R.+	35	0
Treated Early Syphilis, Cured	125	8
Primary, not verified	5	0

It is felt that although the cases in Table 2 have been observed, treated and recorded in this clinic, there are too many unknown factors to permit of a critical analysis, and, in contradistinction to the group investigation carried out in America by five large clinics into early syphilis and its treatment, such cases are excluded from this series.

A uniform principle of treatment has been adopted throughout . This has been the combined use of a "914" preparation by the intravenous route and a heavy metal by intramuscular injection, employing a constant time factor and spacing of doses. The scheme is illustrated by Table 3.

Table 3.

Scheme of course adopted.

1st day-----	"914"-----	Hg. or Bi.
8th day-----	"914"-----	Hg. or Bi.
15th day-----	"914"-----	Hg. or Bi.
22nd day-----		Hg. or Bi.
29th day-----	"914"-----	Hg. or Bi.
36th day-----	"914"-----	Hg. or Bi.
43rd day-----		Hg. or Bi.
50th day-----	"914"-----	Hg. or Bi.
57th day-----	"914"-----	Hg. or Bi.
64th day-----		Kl. orally. W.R. of blood.
71st day-----		Kl. orally.
78th day-----		Kl. orally.
85th day-----	"914"-----	Hg. or Bi.
92nd day-----	"914"-----	Hg. or Bi.
99th day-----	"914"-----	Hg. or Bi.
106th day-----		W.R. of blood.

This basic course thus consists of 10 x "914" and 12 x Hg. or Bi. given in fifteen weeks.

The following reasons led to the adoption of this scheme in 1919. Experience in the army in 1918-19 led to the conclusion that the routine use of "606" was unsuitable for an out-patient clinic in which the majority of the patients were working men and women. This is corroborated by the results of a series of cases investigated at this clinic in 1924 in which "606" was employed.

In 1919 medical opinion in Great Britain approved of the simultaneous use of a heavy metal by intramuscular injection and a "914" substitute by intravenous injection, suggesting that the slow continuous action of the metal proved a useful adjunct to the immediate and more evanescent effect of the "914" substitute. The opposite view, held mainly in the U. S. A., asserted that better results might be obtained from the repetition of a series of courses of arsphenamine followed by a series of mercurial injections. The main argument in its favour was that thus the patient was kept under continuous powerful anti-syphilitic treatment for a much longer time, as the British scheme necessitated earlier and longer rest periods. A standard British practice was adopted.

The spacing of the doses of "914" was suggested on the grounds that an interval from time to time allowed the patient

an opportunity of excreting more of the drug, thus diminishing liability to accumulation with toxic results, and also obviated the theoretical objection that the continued use of "914" might engender an arsenic fast strain of spirochaete.

The use of potassium iodide during the long interval between the sixty-fourth and seventy-eighth days was advocated chiefly as an eliminant, no doubt with an undercurrent of belief in its action upon all gummatous tissue whether old or new.

A scheme which only demanded of the patient one attendance per week suited the clinic hours, and also made less demand on the patient with, one hoped, a better chance of this demand being obeyed.

As the years passed, numerous alternative groupings of injections have been temporarily advocated, but it is a comment on the value of this scheme that in 1932 comparable schemes were in use in the Royal Infirmary, Edinburgh; Dundee Infirmary, and St. Thomas's Hospital, London.

It should be remembered that the treatment of any individual case of early syphilis is a matter to be considered as personal to the one individual, and no attempt was ever made to adapt everyone to the unyielding requirements of a rigid course. Yet early syphilis is essentially a disease of the healthy young adult, and, in such otherwise healthy patients,

the clinical phenomena of the first two years run a very comparable course, so that it is not unreasonable to prepare a model scheme for general purposes.

Variations have taken place in this course in respect of the drugs employed. Thus the arrival of bismuth as an anti-syphilitic remedy led to its adoption in this clinic, and it has been employed in the metallic form in place of mercury for intramuscular injection since 1924. The preparations used have been mainly Bicroel and Bismostab. Some Iodo bismuthate of quinine has been used in the treatment of early syphilis and various compounds have been tried experimentally. Prior to 1924 the heavy metal used was exclusively Calomel Cream.

There has also been a change in the mode of administration of potassium iodide, and from 1924 onwards the majority of the cases received a dosage of fifteen grains thrice daily before food throughout the whole of their course. The reasons for this are discussed in the section on Iodides.

Three "914" preparations have been extensively used. These were neokharsivan, novarsenobillon and neosalvarsan. Many others had a limited trial.

One other variation requires attention. That is the quantity of "914" given in a single injection, and in a single course. This has shown variations with the years, the tendency being, on the whole, to reduce both the maximum

single dose and the total quantity in grams given in a single course. One feels that this reduction was founded rather on fear caused by manifestations of arsenical intolerance than on a reasoned therapeutical basis.

The variations employed in drugs and their dosages may be most easily appreciated in tabular form.

Table 4.Variations in dosage of model course.

	"914"			Metal.		Potassium Iodide.	
	Dosage and year introduced.			C.C.	Bi.	gr. xv. t.i.d.	
	1919	1923	1929	1919	1924	1919	1924
1st week	.45gm.	.3gm.	.45gm.	1gr.	0.2gm.		Kl.
2nd week	.45	.45	.6	1	0.2		Kl.
3rd week	.75	.6	.6	1	0.2		Kl.
4th week				1	0.2		Kl.
5th week	.75 or .6	.6	.6	1	0.2		Kl.
6th week	.75 or .6	.6	.6	1	0.2		Kl.
7th week				1	0.2		Kl.
8th week	.75	.6	.6	1	0.2		Kl.
9th week	.75	.6	.6	1	0.2		Kl.
10th week						Kl.	Kl.
11th week						Kl.	Kl.
12th week						Kl.	Kl.
13th week	.75	.6	.6	1	0.2		Kl.
14th week	.75	.6	.6	1	0.2		Kl.
15th week	.75	.6	.6	1	0.2		Kl.
Total weight in grams	6.75	5.55	5.85	12grs.	2.4		

The dose of calomel cream was 1 grain of mercury; the dose of bismuth metal was 0.2 gram. Occasionally in the earlier years 0.9 gram of "914" was given in a single dose.

After a "Course" such as has been outlined was given, the patient received Hutchinson's Pills, one thrice daily for a number of months. In 1919 a single "Course" of injections was considered adequate provided that serological and clinical pictures were negative, and it was considered sufficient thereafter to give Hutchinson's pills for an indefinitely long time, perhaps one year, perhaps two years, repeating clinical examination and serological tests at intervals. It was soon felt that this gave insufficient protection to the patient and a further five injections of "914" substitute combined with intramuscular metal were given in primary syphilis, and a complete second course in secondary syphilis. In the American Journal of Syphilis, January 1924, a symposium of the views of many syphilologists showed an increase in the number of injections, particularly in the secondary stages. By the end of 1924, the routine in this clinic was to give all cases of early syphilis two courses of injections as outlined, provided the Wassermann reaction of the blood was negative after the first course, and if such was not the case, to continue treatment until the case had received one complete course of injections at a suitable period after the blood Wassermann had become negative. Such cases as either remained Wassermann fast, or showed Wassermann relapse, became the object of special treatment. By 1924 it was determined that the oral use of mercury should be continued after the

last course of injections until a period of at least two years had elapsed from the date of the onset of treatment. All cases were controlled by periodic clinical and serological examinations.

It is not yet practicable to speak of the cure of early syphilis - employing the word in a strictly scientific sense. Sufficient time has not elapsed since the introduction of the newer arsenical preparations, nor have sufficient post-mortem observations been conducted upon well treated cases of early syphilis, apparently cured, which have died from some other cause. Clinically, it is felt that cure does occur, and that it occurs frequently in early syphilis. The occurrence of second attacks of primary syphilis and the birth of a series of healthy children seem to attest this. Yet the clinician hesitates to discharge a case as "cured". Apart from a few early attempts in 1920 and 1921, no syphilitic patient has been discharged from the clinic and it is suggested that a clinical examination once a year is advisable along with a Wassermann test of the blood serum. Some such views are widely held and this has rightly led to the taking of a very long view in the management of any given case. Thus the literature abounds with various long dated instructions, such as the

examination of the cerebro-spinal fluid at the end of the fifteenth year, as advocated in the Finger clinic of Vienna.

An examination of the case records reveals conditions which are quite at variance with this long observation period. The patients simply default. This may be seen by the groupings of the cases of early syphilis according to the time observed.

Table 5.

Duration of observation of 570 cases of early syphilis.

Time observed in months.	less than 6	7 to 12	11 to 18	19 to 24	Over 24
No. of cases	118	117	88	70	177

This is bad enough amongst recorded cases, but the results are even more striking where those cases which default before the completion of a course of treatment are considered and are therefore not included in this series.

The figures of defaulters from the total new cases of early syphilis attending the clinics under the direct control of the Corporation of Glasgow are given:

<u>Males.</u>	Total cases disposed of	Year	Defaulters be- fore one course.
	381	1932	81 - 21.6%
	385	1931	105 - 26.2%
	366	1930	176 - 48%

Females.

Total cases disposed of	Year	Defaulters before one course.
70	1932	18 = 25.6%
43	1931	11 = 25.5%
17	1930	8 = 47%

In view of the fact that each year sees a decrease in the new cases of early syphilis and that the number of defaulters, before one course has been given, is relative to a year's period and not to the cases actually taken on the register during the year, a more accurate figure is given for comparison by taking the total cases disposed of during the year in question.

The causes of this colossal defaulting are not here considered. The fact is sufficient. The figures published in Venereal Disease Information, May, June and July 1932 by the American investigators are no better.

Thus, whatever view may be held about an individual case, it is simply silly to elaborate lengthy schemes of treatment and observation under the belief that a large percentage of the cases attending a clinic will benefit therefrom. Since then only a proportion of cases at present receive a single course of treatment, and of these only a minority attend for two years, it is therefore desirable to focus attention upon the first course. This cannot be too

strongly emphasised. No reference to this aspect of the problem of treating syphilis has been met with in a wide experience of the literature. It must, however, be one of the main factors in assessing the value of any line of treatment to be adopted in the future.

The cases of early syphilis will thus be examined in terms of an analysis of the first course of treatment, and this will be carried forward into the results of those cases which attended for longer periods.

In this first course the first variable to be considered will be the total quantity of "914" received in the first course.

Tables to show the effect of this variation will be given and a preliminary explanation is offered.

From Table 4 it will be seen that the quantity normally varied from 5.55 grams to 6.75 grams, and some cases receiving injections of 0.9 grams in a single dose will thus show a total of more than 7 grams in their first course. Irregular attendance, ill-health, arsenical intolerance and personal idiosyncrasy have lowered the quantity of "914" in a number of cases.

The cases are thus presented in five groups according to the amount of arsenic received in the first course.

These groups are shown as follows :-

Less than 3.5 grams: termed -3.5 grams.

From 3.5 grams to 4.95 grams: termed -5 grams.

From 5.0 grams to 5.95 grams: termed -6 grams.

From 6.0 grams to 6.95 grams: termed -7 grams.

7.0 grams and over: termed +7 grams.

Along with the quantity of arsenic given, the accompanying heavy metal is shown. Where "914" was employed alone, this is indicated; where a preliminary course of treatment by heavy metal alone was given, the case is shown in the table to which the first course of "914" given applies. The first vertical column indicates the total number of cases thus dealt with. The next three columns show all cases in which the W.R. of the blood was not negative at the end of the first course, and the grade of the reaction. The next three columns indicate the number of cases which received further treatment by injection, showing the numbers receiving "914" or "As.", mercury or "Hg." and bismuth or "Bi." The remaining columns indicate the end results of the cases with the total time periods during which they were observed. These time periods are set out at six-monthly intervals up to two years. All cases which attended for more than two years are indicated under the heading "+24". The cases are subdivided into those which received "Adequate treatment",

which includes those receiving the amount of "914" and metal considered sufficient during the year in which they first attended, provided that they had remained for treatment by Hutchinson's pills and under clinical and serological observation for at least six months after their last injection. Cases which did not fulfil these requirements are grouped under the heading "Inadequate treatment". Finally, the cases are "-" or "+". Cases labelled "-" showed a negative W.R. of the blood when last examined, a negative W.R. of the cerebro-spinal fluid if done, and a negative clinical picture. All cases not coming under this heading are grouped under "+". If the last Wassermann reaction of the blood serum was returned as "suspicious" this was considered sufficient to group the case in the "+" column.

Cases are shown by the stage of the disease, by the sex of the patient, in summary of the quantities of arsenic received during the first course and as total summaries contrasting mercury and bismuth. In the summaries the small irregular groups which received either "As." or "Hg." or "Bi." alone as their initial treatment are grouped under the heading "others".

The following Tables are thus presented :

Table 7. M.1 DG+ W.R.-

Table 8. F.1 DG+ W.R.-

Table 9. M.1 W.R.+

Table 10. F.1 W.R.+

Table 11. M.2

Table 12. F.2

Table 13. Early Syphflis - a summation of
Tables 7 - 12.

Early Syphilis.

Table 13.

Duration of observation in months.
Adequate treatment Inadequate treatment

As. & ps.	No. of Cases	WR at end of course		Duration of observation in months.																
		+	W	-18	-24	+24	-6	-12	-18	-24	+24	-6	-12	-18	-24	+24				
-3.5	As + Hg As + Bi Others	20 33 15	10 9 8	1 2 1	2 2 5	2 6 1	3 6 3	3 6 1	1 2 1	1 1 3	1 1 1	2 7 2	3 1 3	1 6 2	3 5 2	2 1 2	1 1 2	2 5 2		
-5	As + Hg As + Bi Others	66 35 6	14 7 1	6 2 1	6 2 1	6 7 2	6 7 2	11 7 1	9 5 2	4 5 1	4 5 1	2 6 1	2 3 1	2 1 1	2 5 1	2 5 1	4 1 1	1 1 1	1 1 2	
-6	As + Hg As + Bi Others	39 151 7	6 8 4	3 8 4	5 16 1	5 10 1	11 46 4	2 46 4	5 46 4	6 46 4	5 46 4	4 15 1	4 15 1	3 15 1	5 31 2	5 31 2	2 4 2	2 4 2	1 3 3	
-7	As + Hg As + Bi Others	133 33 2	16 5 1	5 2 1	13 2 1	16 5 1	27 13 1	4 3 1	5 3 1	27 13 1	5 3 1	25 4 0	29 3 1	6 1 2	6 1 2	6 1 2	1 2 1	1 2 1	3 2 1	
+7	As + Hg As + Bi Others	27 3 570	4 1 93	1 1 26	1 1 48	1 3 143	3 10 6	5 2 143	1 2 18	3 10 143	5 2 18	5 5 28	2 2 90	2 1 27	2 1 23	2 1 11	2 1 13	2 1 13	1 1 12	1 1 4

298

570

272

With reference to the preceding seven tables, certain general statements may be made concerning the ultimate observations recorded in the various stages of early syphilis.

Primary syphilis, dark ground positive, Wassermann negative :- Out of fifty cases treated, none showed a positive or weak positive Wassermann reaction of the blood serum at the end of the first course of treatment. Two were "suspicious". This immediate favourable result took place irrespective of the quantity of "914" administered and the quantity of the metal where such was given. No case on default or at the last recorded time, if still attending, presented either clinical signs of disease or a positive Wassermann reaction either in the blood serum or in the cerebro-spinal fluid, although two showed a suspicious reaction.

Primary syphilis, Wassermann positive:- Out of one hundred and sixty two cases treated, thirty-three showed a positive or weak positive Wassermann reaction of the blood serum at the end of the first course of treatment. At the time of default or last recorded period of observation, seventy-eight cases had received "adequate treatment"; of these, seven were not Wassermann negative, while out of eighty-four cases which had received "inadequate treatment," twenty-one were not serologically negative at the time of default or last observation.

Secondary syphilis :- Out of three hundred and fifty-eight cases, eighty-six showed a positive or weak positive Wassermann reaction of the blood serum at the end of the first course of treatment. At the time of default or last recorded period of observation, one hundred and seventy-two cases had received "adequate treatment"; of these, twenty-two were not Wassermann negative, while out of one hundred and eighty-six cases which had received "inadequate treatment", forty-seven were not serologically negative at the time of default or last observation. It should be noted that in the groups of primary syphilis Wassermann positive and secondary syphilis, a suspicious Wassermann reaction is recorded amongst those "not Wassermann negative".

These elementary figures show (1) that satisfactory final results are more difficult to attain the longer a case of early syphilis waits before commencing treatment, and (2) that the presence of so many unsatisfactory results indicates a very real problem to cope with. These crude figures of the results in the treatment of early syphilis are summed up by exhibiting the final line from Table 13, giving the complete totals.

Total treatment

Total cases	W.R.at end of first course			Adequate								Inadequate							
	+	w	s	-18		-24		+24		-6		-12		-18		-24		+24	
				-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+
570	93	26	48	49	5	51	6	143	18	90	28	90	27	23	11	13	-	12	4

Thus out of a total of five hundred and seventy cases, ninety-seven were not serologically negative when last seen - i.e. 16.6%.

Out of those cases receiving adequate treatment:-

243 were serologically negative;

29 or 10.6% were not serologically negative.

Out of these cases receiving inadequate treatment:-

230 were serologically negative;

68 or 22.8% were not serologically negative.

These unfavourable results are now given by sex and stage of disease, indicating such cases as showed a positive or a weak positive W.R. of the blood serum at the end of the first course, such cases as showed a suspicious W.R. of the blood serum at the end of the first course, and such cases as were clinically or serologically not negative at the end of their period of observation; subdividing them into groups which have received adequate treatment or inadequate treatment. The results are expressed as percentages in Table 14.

Table 14.Percentages of unfavourable end results.

Sex and stage of disease	Total cases	First course W.R.		<u>Treatment.</u>	
		+ or w	s	Adequate	Inadequate
M.1 DG+ W.R.-	48	0	4%	0	2%
F.1 DG+ W.R.-	2	0	0	0	0
M.1 W.R.+	136	24.4%	5.5%	8%	21.4%
F.1 W.R.+	36	16.6%	0	13.6%	42.8%
M.2	172	20.9%	10.4%	7.3%	23.3%
F.2	186	21.4%	11.2%	15.5%	27.5%
Total	570			10.6%	22.8%

16.6%

These figures and percentages call for further analysis in an attempt to determine the various factors leading to this percentage of unfavourable results. It is recalled that this investigation presents a long term view of the total experience of one clinic in which a standard method of treatment has been employed. Comparable figures are found in Venereal Disease Information*, July 1932, in the article "Co-operative Clinical Studies in the treatment of Syphilis", which represents the pooled results over a term

* These American studies will be frequently referred to, and for the sake of brevity shall hereafter in the text be indicated by the initials of the Journal, V.D.I., then by the month and year of issue, and the number of the page or table referred to.

of years of five of the largest clinics in the U.S.A. On page 276, in Table 12, the writers state that out of 2889 cases of early syphilis, 768 or 26.6% finally come under the heading of "relapse and resistant serology". This figure, 2889, includes all cases in their series and their percentage of 26.6% is to be compared with that of 16.6% in this series. It indicates that the problem is not ours alone.

For the present it is only stated that this series of cases represents the results of employing "914" in conjunction with a heavy metal and that the American series represents results in the main achieved by the use of Arsphenamine followed by a course of mercury or bismuth injections.

The results are now examined in terms of the quantity of "914" (expressed in grams) administered during the first course. The other data are unchanged.

With reference to these five groups, it is noted :-

(1) Less than 3.5 grams. Such a figure, deviating widely from the standard course, indicates some idiosyncrasy or intolerance on the part of the patient, irregular attendance, early default or an experimental course of treatment.

(2) 3.5 to 5 grams. Factors leading to this group are as above though to a lesser degree.

(3) 5 to 6 grams. This will include the common standard groups of 5.55 grams and 5.85 grams and the majority of such cases received bismuth as the metal of intramuscular administration.

(4) 6 to 7 grams. This group comprises the standard course of 6.75 grams and the majority of the cases received mercury as the metal of intramuscular administration.

(5) more than 7 grams. This small group occurred almost wholly between the years 1919 and 1921, and received mercury along with the "914" substitute.

A table, showing the results after the first course of treatment, and the final results, is given.

Table 15.

Summary of case results in terms of "914" in first course and duration of observation. Time shown in months.

As. in grams	Total cases	Adequate - Treatment - Inadequate																	
		WR af- ter 1st course			(months)														
		+	w	s	-18	-24	+24	-6	-12	-18	-24	+24	-6	-12	-18	-24	+24		
-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+		
-3.5	68	27	1	2	2	4	14	1	10	6	3	6	7	5	7	1	2		
-5	107	22	8	9	5	1	8	11	6	2	28	13	15	10	2	2	1	1	2
-6	197	18	11	21	34	2	16	1	61	6	20	3	37	2	6	2	3	4	
-7	168	22	5	15	7	1	20	4	40	9	29	4	32	7	8	1	1	5	
+7	30	4	1	1	1	1	3	12		5	3	2		1	1	1			

Table 16.

These figures are condensed statements of final results.

As. in grams in 1st course	Total cases	W.R. after 1st course			Total treatment			
		+	w	s	Adequate Final W.R.		Inadequate Final W.R.	
					-	+	-	+
-3.5	68	27	1	2	20	1	28	19
-5	107	22	8	9	29	4	47	27
-6	197	18	11	21	111	9	70	7
-7	168	22	5	15	67	14	75	12
+7	30	4	1	1	16	1	10	3

Taking the "total treatment: inadequate" first, the bad effects of default, before a standard course of treatment has been completed, are seen, for the figures under this heading for the arsenic groups "-3.5" and "5" are extremely unfavourable. This is quite understandable, and it can be simply stated that it is unwise to stop such a course as has been outlined until at least 5 grams of "914" substitute have been given. But in respect of the final result in such groups, if treatment, after the return of the defaulters, be made up to an adequate standard, the bad effects of the insufficient initial dosage definitely appear to be counteracted.

Taking note of the figures under the heading "total treatment : adequate", there are much better results in

each group, except in the "-7 grams" group where no fewer than fourteen cases out of eighty-one were not serologically negative at the last observation. This group is a normal one; most of the cases received mercury and were treated prior to 1924. It may here be said that, of the final fourteen unfavourable results, in eight the sole abnormality was a suspicious reaction in the blood serum to the Wassermann test.

Now the As. groups "-6 grams" and "-7 grams" with the largest numbers of cases, represent normal courses of treatment - they indicate such patients as attended regularly and showed no marked intolerance.

They will then be examined in respect of the heavy metal received along with the "914" substitute, taking out the few cases whose initial treatment showed any deviation from the normal routine i.e. experimental courses with new drugs.

Table 17.

Cases in As. groups -6 and -7 grams, showing results in terms of Hg. or Bi.

	Total cases	W.R. after 1st course			Total treatment			
		+	W	S	Adequate Final W.R.		Inadequate Final W.R.	
					-	+	-	+
As. + Hg.	172	22	8	18	72	12	76	12
As. + Bi.	184	13		18	101	9	68	6
Total	356	35	8	36	173	21(10.5%)	144	18(11.1%)

This table includes 356 out of the series of 570 cases. It shows a definite superiority in results when bismuth is the metal of choice, 91.4% as against 86.2%. It will be recalled, too, that the average amount of "914" received by the average case receiving bismuth is a little less than in the case of the average mercury patient (5.85 as against 6.75 grams) and this holds whether the total treatment has been adequate or inadequate.

V.D.I. July, 1922, page.274, states that "there is a distinct advantage for bismuth over mercury" in treatment lasting "4 - 12 months", but that "serologic outcome for the two drugs" in the long run "is approximately the same". In respect of our cases followed for more than two years, it is found that fifty-eight cases receiving Hg. were negative and that nine were not negative, while fifty-four cases receiving Bi. were finally negative and seven cases were not negative. In the section dealing with clinical relapse in this series, it is shown that bismuth therapy does not lead to an increase in the percentage of clinical relapse. It will also be shown later that bismuth is less liable to create severe intolerance, leading to prolonged cessation of treatment, than is mercury.

The only disadvantage to note is the theoretical one put forward in V.D.I., July 1933, page 274, where it is

stated that "the quicker reversals under bismuth in the first year have encouraged relapse through inadequately continued treatment". It is found, however, that a slightly larger percentage of the cases in this series treated with bismuth, as compared with mercury, have attended for more than two years. These cases occurred during the years subsequent to 1924 and are considered to be an expression of improvement in the clinic's technique of handling the patients.

The evidence adduced indicates that it would be wise to continue to employ bismuth as the routine metal in the early treatment of cases of early syphilis.

The percentage of final not negative serological results in Table 17 i.e. the groups receiving a normal first course, is 10.5% in those cases receiving "adequate treatment", and 11.1% in those cases which received "inadequate treatment". This is a striking tribute to the importance of the first course of treatment given to a case of early syphilis. All these cases received a normal first course. Stress has already been laid on the importance of the first course in view of the numbers that default. It now appears as a very practical safeguard against subsequent syphilitic lesions. Thus none of the cases under the heading "inadequate treatment" have had two courses of "914" substitute

and it is a little startling to find that further therapy has only been able to reduce the percentage of unsatisfactory end serological results from 11.1% to 10.5%. There were only eleven cases of clinical relapse in those cases (356) which received an adequate initial course of treatment, a percentage of 3.0%, while the total percentage of clinical relapse in early syphilis was 4.9%. Such cases as default and relapse to go elsewhere for treatment or to remain untreated are not, of course, known, but the average treated case of syphilis is well aware of the signs of disease and to judge by the number of defaulters who come back in a state of apprehension to be found clinically and serologically negative, the number of lost relapses amongst those who attend faithfully for one complete course is not likely to be high.

As these percentages represent the results of cases which have gone through the ordinary routine of the clinic, it is advantageous to compare them with similar American figures, thus to afford a commentary on the adequacy or otherwise of these methods of treatment.

In V.D.I. July 1932, page 276, Table 12 under the heading of "continuous" treatment, the percentage of final "relapse and resistant serology" is 13.1%. On page 273, "continuous" treatment is stated from various angles to be

definitely the best method of treatment. In V.D.I. June 1932, page 209, continuous treatment is defined as "uninterrupted treatment with an arsphenamine or a heavy metal, or both, whether administered in alternation or simultaneously throughout treatment, including so-called 'overlapping' treatment". The arsenic used is predominantly "606".

It seems just therefore to compare their percentage of relapses and final resistant serology, 13.1% , in their most favourable group of treatment with the figure of 10.5% of final unfavourable serological results in those cases in this series which had a normal first course and a total adequate amount of treatment. If the bismuth treated cases alone be taken out of this group, the percentage of 8.7% unsatisfactory end results is found.

Certainly when seen from this aspect this series of cases compares quite favourably, and, so far, there would not appear any reason for abandoning treatment with "914" and bismuth in favour of the sequential employment of "606" and a heavy metal.

The next point of investigation concerns the time taken to administer the first course of treatment. The course lasts fifteen weeks and the informative Wassermann reaction is taken at the commencement of the sixteenth week. Cases may vary this normal time of sixteen weeks by shortening

the period of their so called first course. This is usually done by lengthy defaulting and such cases naturally tend to receive smaller quantities of "914" in their first course. They may also show intolerance. Cases may also extend the period of the first course, usually by short periods of default or by minor grades of intolerance.

In the section dealing with the serial examination of the Wassermann reaction in early syphilis, it will be shown that two thirds of the cases showed a negative Wassermann between the eighth and the twelfth weeks of treatment and received about 4 grams of "914" prior to this negative result. This is considered to be sufficient evidence as to the early effect of time and regular treatment. It need only be added that any great deviation from the normal time and dose group- of the plan of treatment led to an increase in the unfavour- able serological results at the end of the abnormal first course.

It is important, however, to trace the late effects of variations of time in the first course. A deviation of two weeks in each direction is allowed to permit a case to be included in the normal time period. The cases are now accordingly tabulated in three time groups for the first course. (1) Less than 14 weeks. (2) 14 to 18 weeks. (3) more than 18 weeks. The end results of treatment are summated and shown in two tables, one for those cases which eventually received adequate treatment and one for those

cases which received inadequate treatment. The results are given in terms of the amount of the arsenic received in the first course, and the final result is shown as negative (negative, clinically and serologically) or not negative (clinically or serologically).

Table 18.

End results x duration of first course.

Adequate treatment.

Time of first course	End Result	
	-	+
Less than 14 weeks	64	7
14 to 18 weeks	148	16
More than 18 weeks	31	6

It is interesting to note that, provided total adequate treatment be eventually given, no great difference is seen in the end results even although great variation takes place in the time of giving the first course. It should be pointed out, however, that this table is not quite the expression of a simple time factor and from Table 19 it may be seen that those cases receiving small quantities of "914" tend to appear in greater proportion in the group "less than 14 weeks".

Table 19.

End results x duration of first course.

Inadequate treatment.

Time of first course	End result	
	-	+
Less than 14 weeks	76	33
14 to 18 weeks	124	17
More than 18 weeks	36	12

When these figures are considered with the large numbers of non-negative results in the "914" groups -3.5 grams and 3.5 to 5 grams, the importance of the first course is seen if total treatment is to be inadequate. Again it may be said that if the type of combined and interrupted treatment given in Table 2 be followed, it is unwise to stop before a complete course is administered, or, in other words, default and intolerance must be prevented.

Those cases which remained under observation for more than two years and received adequate total treatment are examined.

The results are shown firstly by sex and stage of disease.

Table 20.

Sex and stage of disease	End result	
	-	not <u>negative</u>
M.1 DG+ W.R.-	11	0
F.1 DG+ W.R.-	1	0
M.1 W.R.+	30	2
F.1 W.R.+	12	2
M.2	44	3
F.2	46	11
Total	144	18

and fourthly in respect of whether bismuth or mercury was employed with the "914", giving the end results which are summed up :-

	End result	
	-	+
Hg.	58	9
Bi.	54	7
Others	11	2

The total number of these cases is not large and therefore it is unfair to draw very definite conclusions from them. However, certain deductions may be made from these tables.

There is a slightly more favourable outcome for males as compared with females: 84.5% as compared with 63.0%.

There is a definitely worse outcome in the case of secondary syphilis as compared with earlier stages of syphilitic infection, especially in the female cases.

The amount of "914" in the first course is of little importance if adequate total treatment be eventually given.

There is little to choose in the long run between mercury and bismuth as the metal to be used in conjunction with "914" - a very slight bias in favour of bismuth may be indicated.

In V.D.I. 1932, page 221, the importance of prolonging the treatment is stressed - continuous treatment is referred to. This is implied in our cases only to the extent of

one course subsequent to negative serological results, in the absence of clinical and serological relapse. The unfavourable end results, in the "more than two years" group of this series, received much treatment but only a few of the favourable end results required more than three courses of treatment. As there are obvious disadvantages in continuing prolonged treatment, it is of interest to note that the percentage of favourable results in those cases in this series treated and observed for more than two years, is 89.4% in a total of one hundred and sixty-two cases. In W.D.I. 1932, page 280, Table 20 indicates a favourable percentage of 49.7% in one hundred and sixty-seven cases treated for more than one year by the continuous method. It is difficult to compare these two percentages. The American standard of cure is stricter in that it demands one year's negative observation instead of six months, and that practically all their cases had the C.S.F. examined, while only about three quarters of this series were so done. The cases of this series have been observed and therefore treated for a longer time. There is, however, nothing to suggest that the basic principle of the methods of treatment employed in this clinic are unsound.

The cases observed for more than two years and receiving inadequate treatment are few.

From Table 16 are reproduced these results referring to the cases which received inadequate treatment.

As.in grams	Number of cases with final W.R.	
	-	+
-3.5	28	19
-5	47	27
-6	70	7
-7	75	12
+7	10	3

This shows clearly (1) the risks of an inadequate first course of treatment as shown in arsenic groups -3.5grams and -5 grams, and (2) the value of completing a standard course as exhibited in arsenic groups -6 grams and -7 grams. The group -6 grams received bismuth as the heavy metal: the group -7 grams received mercury, and again a slight bias in favour of bismuth is noted.

As far as regards cases receiving inadequate treatment, an inspection of Table 19 shows that the duration of the first course cannot be considered apart from the quantity of "914" in grams, for all time groups show a better result provided the standard amount of "914" be given.

The results discussed in the preceding pages may be summed up briefly:

If ten injections of "914" and twelve injections of a heavy metal be given to cases of early syphilis in a period of sixteen weeks, if this course be repeated, and if the case then be treated with mercury pills and observed for a period up to two years, the percentage of unfavourable results is 10.5%. This unfavourable percentage increases (a) if the quantity of "914" in the first course falls below 5 grams, (b) if the time period of the first course is increased beyond eighteen weeks.

Should a case not receive supplementary treatment, but if it receives in one course more than 5 grams of "914" and a corresponding amount of heavy metal, the percentage of unfavourable results at all periods of observation is 11.6%. If less than 5 grams of "914" be given, and if the time period of its administration be greatly altered, the percentage of unfavourable results is greatly increased.

Bismuth appears to give slightly better results than mercury.

Results are most favourable in sero-negative syphilis; less so in primary syphilis and least so in secondary syphilis.

There are many important factors to be considered which may modify these simple conclusions, and which raise problems in themselves. Such factors will now be considered in separate sections, with the problems raised, and finally these

results will be reviewed in the light of their conclusions. All the sections will then be utilised to afford a basis for the suggestion of the future methods to be employed in the treatment of early syphilis.

SECTION II.

THE WASSERMANN REACTION IN EARLY SYPHILIS.

Pages 48-94.

THE WASSERMANN REACTION IN EARLY SYPHILIS.

Modern antisyphilitic treatment rapidly causes the disappearance of the superficial manifestations which are found in the first two years of the natural history of infection with the syphilitic virus. The fate of individuals so treated is still in considerable doubt. Many undoubtedly are cured, as may be evidenced by a life long freedom from late or relapsed syphilitic lesions; by the negative result of post-mortem examination; and possibly by the indirect evidence of a second attack of acute primary syphilis. Clinical examination is remarkably limited in its scope. Not only does it deal directly only with the skin and mucous membranes, or indirectly, by inference, with the state of the organs and main systems of the body, but its negative value is limited strictly to the time of examination and it is dangerous to prophesy far ahead in the case of any single individual. The value of clinical examination is much enhanced by its repetition, but even in the short life of this clinic, a case has been found in which, after repeated negative examinations, carried out over a period of nine years, syphilitic lesions eventually appeared in the skin and subcutaneous tissues; and of course the ranks of the tertiary cases contain many individuals who have had adequate initial

treatment and long latent periods. It is therefore of the utmost value, in the control of syphilis, to determine the significance of the Wassermann reaction, which can readily be performed as a routine test in the prolonged observation of numbers of cases.

An investigation will therefore be made of the variations in the results of the Wassermann tests of the blood serum in this series of five hundred and seventy cases of early syphilis.

All Wassermann tests have been performed by Professor C. H. Browning and Professor E. M. Dunlop, and have been done in accordance with the technique described in Recent Methods in the Diagnosis and Treatment of Syphilis, Browning and Mackenzie, 2nd edition, 1924. Invaluable advice and unwearying assistance have been received from Professor Browning and Professor Dunlop, both in the correlation of a particular result with the needs of a particular patient, and with the detailed examination of interesting sera. It is, however, only fair to point out that the conclusions drawn from this investigation are peculiar to the writer and do not necessarily represent the opinions of Professor Browning and Professor Dunlop.

Professor Browning's criteria are very fully explained, and the evidence which led to these criteria being adopted, is very fully given in his book. It may at once be said that in no case in this series has the initial Wassermann reaction

been at variance with the clinical diagnosis. With regard to primary syphilis, in every case in this series in which the initial Wassermann reaction of the blood was other than weak or fully positive, the Sp. Pall. has been found. All initial Wassermann blood reactions in secondary syphilis have been fully positive. It should here be noted that five cases (not included in this series) have been termed primary syphilis, and have received full antisyphilitic treatment, in which the initial Wassermann reaction was negative, and from which Sp. Pall. were not recovered. Treatment was instituted in these cases contrary to the writer's most considered opinion that a clinical examination alone is not enough to substantiate a diagnosis of primary syphilis, and that the presence of either the Sp. Pall. or some grade of positive Wassermann reaction is essential to the making of a correct diagnosis. This opinion is confirmed by the unequivocal case quoted by Stokes in his text book Modern Syphilology, p. 392, where a lesion, of which a photograph is given, was clinically indistinguishable from a Hunterian chancre, but where dark ground and histological examinations, serological tests and prolonged observation failed, in the absence of antisyphilitic treatment, to reveal any syphilitic manifestations.

Here then it may be said that primary syphilis in absence of the Sp. Pall. should never be diagnosed without the presence

of a positive grade of reaction to the Wassermann test of the blood serum. It will be sufficient, at this point, to add that in this series no case not showing Sp. Pall. has been treated in which the grade of reaction was termed "suspicious", and that all cases in which the initial reaction was of this grade have in one or two weeks exhibited either a "weak-positive" or a "positive" reaction on subsequent examination. This means that the reaction suspicious, in presence of a suspected syphilitic lesion, has never been followed up by a negative reading and it adds to the importance of this grade of reaction.

In respect of secondary syphilis, there is complete agreement between the clinical and the serological diagnosis, and it should be definitely recorded that in every case of secondary syphilis the Wassermann reaction was "positive". No "weak positive" reactions have been met with initially in the three hundred and fifty-eight cases, male and female, of secondary syphilis treated at this clinic. An objection may be raised here that the diagnosis of secondary syphilis in the clinic is made entirely a matter of serology. It is willingly admitted that during the earlier years a "positive" serological finding was of the greatest help in fixing the diagnosis in doubtful cases, but increasing clinical experience has led to a more accurate forecasting of the serological result. Cases have been kept under observation for a considerable time because of an initial negative Wassermann and a skin lesion, (the grade "weak positive" has never been seen), and in all

such cases a diagnosis other than syphilis was eventually made and checked by the physicians in the department of "diseases of the skin". Such diagnoses were tuberculosis, pityriasis rosea, psoriasis, eczema, seborrhoeic dermatitis and palmar secondary infection.

So far then as the initial Wassermann reactions are concerned, there is no deviation in the clinical findings in this series from the Wassermann results determined by the criteria laid down by Professor Browning as requisite to give a "positive" reaction - p.90 :-

"(a) A serum which shows practically or quite complete lysis with the same amount of complement as causes complete lysis of the negative control serum is negative.

(b) A serum which requires from one and a half times to twice as much complement as does the negative control to produce a given degree of lysis is suspicious - recorded as "?" or "+".

(c) A serum which fixes more complement than is specified under (b), but which shows complete lysis with the highest amount of complement is a weak positive.

(d) A serum which shows no lysis in any tube is a strong positive. "

It is pointed out in the Wassermann results now to be discussed, that the four grades quoted above are to be referred

to as negative, suspicious, weak positive and positive - the word "strong" will be omitted from all strong positive results.

The significance of each of these grades of reaction must be discussed in respect of the problems to be raised, and the general significance attached to them by Professor Browning is given from pp. 199-200 :-

"It is understood that there are two criteria of positive: firstly, the absolute positive which is required for diagnosis in an unknown case, and to which one would swear in a court of law, and secondly, the weak positive or suspicious reaction which is as good as positive in a case of known treated syphilis or in one which had reacted positive prior to treatment; the latter reaction might be termed the therapeutic positive in contra-distinction to the former, the diagnostic positive."

The value of this paragraph as an aid in prognosis must be considered.

The total numbers of cases are shown by sex and stage of disease. The symbols are self-explanatory.

Table 1.

Total cases by sex and stage of disease.

	<u>Males</u>	<u>Females</u>
M.1 DG+ W.R.-	48	
F.1 DG+ W.R.-		2
M.1 W.R.+	126	
F.1 W.R.+		36
M.2	172	
F.2		186
Totals	346	224

Preliminary tables have been constructed in which details are submitted concerning every case in which (1) the initial Wassermann reaction of the serum failed to become negative within six months; (2) after the blood Wassermann became negative at any time subsequent variation took place; (3) default occurred within six months but these cases showed on further examination a W.R. which was not negative; (4) while there was no blood Wassermann relapse, there was C.S.F. Wassermann relapse.

This may be summed up by stating that every case of early syphilis is presented in which any unfavourable event occurred in the Wassermann reaction subsequent to the initial observation. There will, however, be omitted any cases of primary syphilis in which an original weak positive Wassermann reaction became positive, provided that the case does not otherwise come into the previous categories. These are shown at the end of this section.

The total changes which occurred are summarised grouping (1), (2) and (3) together to show all unfavourable Wassermann events, but showing (4) separately, i.e. those cases with abnormal C.S.F. reading but no abnormal blood Wassermann results.

Table 2.

Sex and stage of disease.	(1)	(2)		(3)
	Total cases in each group	Total unfavourable blood Wassermann cases.	Total unfavourable C.S.F. cases where blood W.R. favourable.	
M.1 DG+ W.R.-	48	6	=12%	1
F.1 DG+ W.R.-	2	0	= 0%	0
M.1 W.R.+	126	32	=25.3%	0
F.1 W.R.+	36	12	=33.3%	2
M.2	172	52	=30.2%	2
F.2	186	61	=30.4%	5
Totals	346	224		3
	570	163	=28.8%	10 = 1.7%

It is obvious in this table that column (3) is not included in column (2).

If those cases be withdrawn which defaulted with less than six months attendance, the corrected table of total unfavourable blood W.R. cases is :-

Sex and stage of disease	Total unfavourable blood W.R. cases after defaulters up to 6 months have been withdrawn	
M.1 DG+ W.R.-	5	= 10.4%
F.1 DG+ W.R.-	0	= 0%
M.1 W.R.+	26	= 20.6%
F.1 W.R.+	10	= 26.1%
M.2	43	= 25%
F.2	56	= 29%
Totals	Males 74	= 21.4%
	Females 66	= 26.3%
	140	= 24.5%

These corrected figures may more reasonably be said to represent Wassermann relapse.

There is a steady rise in the percentage incidence of relapse as the age of the syphilitic process increases prior to the onset of treatment. The differences between the percentages in the various grades of male and female cases cannot be termed significant when calculated statistically, for the samples are too small to permit of any statistical computation.

The broad fact however remains that five hundred and seventy cases of treated early syphilis were encountered in the general work of a venereal clinic, treated by various drugs administered according to a common plan and observed for varying periods extending to one hundred and fifty-two months. Almost one quarter of these cases, 24.5%, exhibited some form of Wassermann relapse of the blood serum or remained Wassermann fast for six months or longer, and ten cases, or 1.7%, which did not show any blood Wassermann relapse, showed in the cerebro-spinal fluid Wassermann reactions which were not negative. The cerebro-spinal fluid Wassermann reactions will be fully dealt with in the section on the cerebro-spinal fluid in early syphilis. They must, however, be included in the totals of blood Wassermann negatives.

The next point investigated is the nature of these unfavourable Wassermann reactions. The subjoined table therefore shows by sex and stage of disease the total unfavourable Wassermann results, the total cases in which relapses occurred from any of the lower grades of reading, the total cases in which the sole relapse was from negative to suspicious, the total cases in which, though no relapse took place, the production of a negative blood Wassermann took longer than six months, and the total cases in which the Wassermann was positive at all examinations, indicating such cases as were observed

for from six to twelve months and such cases as were Wassermann fast for twelve months or longer. Further, each of these groups is subdivided according to whether the first course of treatment given could be called adequate treatment or inadequate treatment. The definition of adequate and inadequate treatment is given in the section on the treatment of early syphilis.

Table 3.

Sex and stage of disease.	Total unfavourable W.R. results	Total Relapses		Total #s relapses		Total delayed versals.		Total W.R. fast 6-12/12 Treatment Ad. Inad.		Total W.R. fast 12/12 Treatment Ad. Inad.	
		Ad.	Inad.	Ad.	Inad.	Ad.	Inad.	Ad.	Inad.	Ad.	Inad.
M.1 DG+ W.R-	5	5	0	1	0	0	0	0	0	0	0
F.1 DG+ W.R-	0	0	0	0	0	0	0	0	0	0	0
M.1 W.R+	26	8	3	3	0	6	3	0	1	4	3
F.1 W.R+	10	4	2	0	1	2	0	0	1	0	1
M.2	43	24	6	9	0	7	2	3	1	0	1
F.2	56	24	13	6	2	5	4	2	4	3	3
Totals Male	74	37	9	13	0	13	5	3	2	4	4
Totals Female	66	28	15	6	3	7	4	2	5	3	4
	140	89	22	29	12	15					

Certain basic observations are derived from this table.

(1) One hundred and forty cases showed unfavourable Wassermann events out of a total of five hundred and forty-seven cases.

(2) Twenty-seven cases, or 5%, remained Wassermann fast for periods exceeding six months from their initial blood examination.

(3) Twenty-nine cases, or 5.1%, took more than six months to obtain the first negative Wassermann of the blood. In these cases, which are not included in the preceding paragraph, weak positive or suspicious results were noted.

(4) Eighty-nine cases, or 17.4%, showed Wassermann relapse in the blood serum from a lower to a higher grade. If the grade of relapse from negative to suspicious be excluded, there were sixty-seven cases, or 12.2%.

The Wassermann fast cases are now examined in detail.

Wassermann fast sera.

Those cases which showed a Wassermann fast condition of the blood serum for more than six months are investigated.

The total numbers are shown by sex, stage of disease and duration of W.R. fastness.

Table 4.

Sex and stage of disease	Time in months of W.R. fastness				Total
	6 to 12	12 to 18	18 to 24	More than 24	
M.1 W.R.+	1	4	0	3	8
F.1 W.R.+	1	0	0	1	2
M.2	4	1	0	0	5
F.2	6	4	1	1	12
Totals	12	9	1	5	27

There is thus a total of twenty-seven cases out of five hundred and forty-three in which the Wassermann reaction of the blood serum was constantly positive for more than six months.

The cases are investigated in detail giving the sex and stage of disease, duration of W.R. fast condition and certain clinical details.

M.1 W.R.+ :- 6 to 12 months.

Case No. 1180. Jarisch Heixheimer reaction. Less than five grams "914" in first course. Clinical relapse. Irregular attendance.

12 to 18 months.

- Case No. 1255. 3 grams "914". Then absent for forty-eight weeks.
- Case No. 1918. 1.35 grams N.K. Then absent for twenty-two weeks.
- Case No. 3934. Intolerant to "914".
- Case No. 184. Well treated in first course: received more than seven grams "914".

More than 24 months.

- Case No. 1883. 4.95 grams N.K. 1.15 grams Flumerin: then absent for 325 weeks.
- Case No. 3977. Dermatitis after one course of treatment.
- Case No. 659. Well treated.

There were eight cases of Wassermann positive primary syphilis in the male which were Wassermann fast for more than six months. Four of these defaulted after an inadequate first course of treatment. One was irregular in treatment and so received an inadequate first course to show clinical relapse. Two were intolerant of "914". One was well treated and was Wassermann fast without clinical relapse for more than two years.

F.1 W.R.+ :- 6 to 12 months.

- Case No. 3866. One course of treatment. Jaundice. Death. No post-mortem examination.

More than 24 months.

- Case No. 241. She received 3.75 grams "914", then defaulted for 223 weeks. On return showed clinical relapse.

These two cases provide their own summary.

M.2 :- 6 to 12 months.

Case No. 458. Less than 3.5 grams "914": defaulted.

Case No.1558. Well treated.

Case No.3168. Well treated.

Case No. 258. Well treated.

12 to 18 months.

Case No. 29. After normal first course defaulted for 34 weeks.

There are five cases of secondary syphilis in the male which show a Wassermann fast state of the blood for more than six months. Of these, two were defaulters, though one received an adequate initial course. Three were well treated.

F.2 :- 6 to 12 months.

Case No. 239. 4.45 grams "914". Defaulted for 33 weeks.

Case No. 862. 4.50 grams "914". Defaulted for 17 weeks.

Case No.1260. 4.20 grams "914". Defaulted for 34 weeks.

Case No. 980. 0.75 grams "914". Defaulted for 35 weeks.
Clinical relapse.

Case No. 21. Well treated.

Case No.2349. Well treated.

12 to 18 months.

- Case No. 486. 1.5 grams N.K. Absent 41 weeks. Clinical relapse.
- Case No. 1267. 0.75 grams N.K. Absent 43 weeks.
- Case No. 1922. 1.50 grams N.A.B. Absent 59 weeks.
- Case No. 3845. 2.25 grams N.K. Absent 36 weeks. Clinical relapse.

18 to 24 months.

- Case No. 3634. 3.30 grams N.K. Absent 34 weeks. Clinical relapse.

More than 24 months.

- Case No. 2895. 6.60 grams N.K. Absent 40 weeks. Clinical relapse.

There were thus twelve cases of secondary syphilis in the female which showed a Wassermann fast condition of the blood for more than six months. Of these, ten were defaulters after an inadequate initial treatment, and two were well treated. There were five cases of clinical relapse.

The summary is rather striking.

The total twenty-seven cases are now shown in respect of sex, stage of disease and adequacy of initial course of treatment.

Sex and stage
of disease

First course of treatment.

	Inadequate.	Adequate.
M.1 W.R.+	7	1
F.1 W.R.+	2	0
M.2	2	3
F.2	10	2
Total	21	6

This table shows clearly that Wassermann fastness is chiefly an expression, so far as the combined course of "914" and metal used by this clinic is concerned, of an inadequate course of treatment whether due to default or to intolerance.

It is interesting to consider the six cases which were well treated in the first instance. There were no cases of clinical relapse. Only one maintained the W.R. fast condition for more than twelve months. Three cases defaulted, two within six and twelve months, and one between twelve and eighteen months. Three cases received total adequate treatment. Two were finally negative at the end of twenty-eight and fifty-five months, and one was suspicious in reaction after having been negative. Thus in this series there have been no cases which were permanently Wassermann fast after receiving adequate initial and adequate total treatment.

Amongst the twenty-one cases which had insufficient

initial treatment, there were seven cases of clinical relapse and three cases of arsenical intolerance. Ten cases eventually received total adequate treatment; of these, five were finally negative, five were finally positive. Only two of these were Wassermann fast throughout, and both were cases of male primary syphilis.

This shows that out of this series there were only two cases in all, which remained permanently Wassermann fast in face of a total adequate treatment. One was observed for thirty-two months and one for seventeen months. In two other cases, eventually negative, both cases of secondary syphilis, it was thirty-six and forty months before the first negative result was obtained.

The relationship of clinical relapse with a Wassermann fast state of the blood persisting for twelve months is examined.

Table 5.

Sex and stage of disease.	Total clinical relapses.	W.R. fast 12 months.
M.1 W.R.+	3	0
F.1 W.R.+	3.	1
M.2	4	1
F.2	10	2
Totals	20	4

A Wassermann fast condition of the blood serum is an indication of a state in which clinical relapse tends to occur. This is seen more definitely in such W.R. fast cases as default without completing a satisfactory first course. Here seven cases of relapse took place in twenty-one cases receiving inadequate initial treatment. In view of this frequency of clinical relapse, i.e. of the manifestation of syphilitic lesions, there seems no reason to call in question the significance of a continued positive Wassermann reaction in treated early syphilis as other than a manifestation of the syphilitic virus.

The therapeutic indication is equally clear. Adequate initial and suitable after treatment in absence of default should prevent Wassermann fastness from reaching any formidable proportion.

Wassermann fastness of the blood serum for a year or longer was seen as a relapse subsequent to a negative serological result in seven cases. There were three cases of clinical relapse, and of seven cases adequately treated, five were finally not negative. Although these cases are few in number they appear of considerable significance. There is a difference in prognosis between W.R. fastness seen as an initial phenomenon, and seen as a relapse after a negative serological result has been attained. Wassermann fastness as a serological relapse phenomenon yields an unsat-

isfactory end serological result in spite of adequate total treatment. It is also associated with a very high incidence of clinical relapse. This deduction seems valid in spite of the small number of cases, for it represents the actual total experience of twelve years observation of a clinic. The only suggestion to be made is that Wassermann fastness should be avoided as far as possible by thorough initial treatment, for in these few cases noted here much treatment of all types was subsequently given.

The "suspicious" Wassermann reaction of the blood serum.

This is considered of importance, for the therapeutic value of such an end reaction as "suspicious" should be determined not only by serological criteria but also, if possible, by clinical results.

(1) A suspicious reaction obtained during or shortly after a normal course of treatment, and followed shortly by a negative serological result, is of no importance as a guide to prognosis. (Vide section on the Serial Examination of the Wassermann Reaction).

(2) As a prelude to clinical relapse.

There were twenty-one cases of clinical relapse. In one male and one female case of primary syphilis, in one male

and two female cases of secondary syphilis, a suspicious result was noted prior to the relapse at which time the Wassermann was positive. In two of the secondary cases, however, a negative test was never achieved. This is an indication that a suspicious reaction of the blood serum may eventually lead to clinical manifestations of syphilis.

(3) Subsequent to clinical relapse.

This grade of reaction was seen as an end result in seven cases out of twenty-one cases of relapse. In the section on clinical relapse, it is shown that total treatment, to secure a satisfactory end result, must be prolonged beyond ordinary standards. It seems reasonable, in view of the conclusions in the other paragraphs dealing with the suspicious reaction, to conclude that such an end test, subsequent to clinical relapse, must be regarded as unsatisfactory.

(4) As a prelude to a Wassermann positive state of the blood which then lasted for twelve months or longer.

This occurred three times.

M.1 DG+ W.R.- Case No. 1165. Well treated initially.

F.2 Case No. 802. Inadequate initial treatment.

Case No. 3396. Four Wassermann relapses in first thirty-two months. The Wassermann reaction became positive at the fortieth month, to remain so till the fifty-sixth month of attendance. She became negative after the closure of the records.

Here, too, the suspicious reaction appears of significance. If the contention be accepted that in treated early syphilis Wassermann fastness as a feature of serological relapse is indicative of the presence of the syphilitic virus, then a prodromal suspicious reaction, which occurs in three cases out of seven, cannot be disregarded.

(5) Readings of suspicious reaction continued for twelve months or more.

Five cases occurred.

M.1	W.R.+	Case No. 3934.	Intolerant to "914".
M.2		Case No. 1506.	Antecedent clinical relapse.
		Case No. 113.	Well treated. "S" after sixteen months.
		Case No. 561.	Well treated. "-" after twenty-one months.
		Case No. 1113.	Well treated. "S" after twenty-five months. This case showed an initial +, then "W" for twelve months, then "S" for twelve months.

Here the suspicious reading appears to indicate:

- (a) the effects of poor initial treatment.
- (b) a delayed state of reversal to negative.

(6) Cases where the sole serological relapse was from negative to suspicious.

There were twenty-two such cases. Excluding changes

in the first six months subsequent to the initial course, there were nineteen. The end results are shown giving the sex, stage of disease, whether treatment was adequate or inadequate, and the final serological result.

Table 6.

Sex and stage of disease.	Total cases	<u>Treatment</u>			
		Adequate		Inadequate	
		-	+	-	+
M.1 DG+ W.R.-	1	1	0	0	0
F.1 DG+ W.R.-	0	0	0	0	0
M.1 W.R.+	2	1	0	0	1
F.1 W.R.+	1	0	0	0	1
M.2	6	5	1	0	0
F.2	8	7	0	0	1
Totals	18	14	1	0	3

Here, provided total adequate treatment be given, a favourable end result is to be expected. This, in view of the evidence of other paragraphs, does not negative the value of the suspicious reaction but merely indicates that it is not of the same grade of positiveness as weak or positive, and therefore, naturally, in such cases as did not exhibit relapse to weak or positive, a favourable outcome to treatment is to be expected.

(7) The outcome of treatment in all cases in which a suspicious Wassermann reaction was found after the first six months.

Table 7.

Sex and stage of disease	Total cases	Total "S" reactions	Treatment			
			Adequate		Inadequate	
			W.R.		W.R.	
			-	+	-	+
M.1 DG+ W.R.-		2	2	0	0	0
F.1 DG+ W.R.-		0	0	0	0	0
M.1 WR+		8	2	0	3	3
F.1 WR+		2	1	0	0	1
M.2		15	9	5	0	1
F.2		27	13	9	1	4
Totals		54	27	14	4	9
			41		13	

Here, out of forty-one cases receiving adequate treatment, thirteen were finally not negative - if the cases in Table 6, paragraph (6), be subtracted, i.e. those which showed only relapse from negative to suspicious, the end figures are still worse. They become twenty-six in all, of which thirteen showed final unfavourable serological results in spite of good treatment. Here, then, the suspicious grade of reaction as a fore-runner of weak or positive grades of reaction, is most significant.

It may finally be concluded that, as the result of the investigation of this series of cases of early syphilis, a suspicious reading of the Wassermann reaction after any amount of treatment, adequate or inadequate, can only be regarded as a "therapeutic positive". The clear indication is for further treatment.

Sudden reversal from negative to positive.

All cases in which this event took place are recorded showing sex, stage of the disease, the case number, clinical notes, the nature of the heavy metal used (if any) with "914", the final serological result of the blood serum and the total time observed in months.

			<u>Metal</u>	<u>Final W.R.</u>	<u>Time</u>
<u>M.1 DG+ W.R.-</u>	<u>812</u>	Irregular time of first course.	Hg.	-	11
	<u>1135</u>	Clinical relapse at forty-fifth week. ? second infection.	Hg.	-	37
	<u>1251</u>	From 1 - 12/12.	Hg.	+	18
<u>F.1 DG+ W.R.-</u>	0				
<u>M.1 W.R.+</u>	<u>954</u>	Forty-two weeks absent.	Hg.	+	16
	<u>1180</u>	Twice relapsed. Clinical relapse. Also showed J.H. reaction.	Hg.	-	20
	<u>4322</u>	Dermatitis. Inadequate initial treatment.	<u>Bi.</u>	-	31
	<u>48</u>	Well treated initially.	Hg.	-	37

			<u>Metal</u>	<u>Final</u> <u>W.R.</u>	<u>Time</u>
<u>F.1</u>	<u>W.R.+</u>	<u>3041</u>			
		At eightieth week. Also clinical relapse. Well treated initially.	0	-	41
<u>M.2</u>		<u>1506</u>	Hg.	S	33
		<u>1295</u>	Hg.	-	15
		Relapse in 6/12.			
		<u>1169</u>	Hg.	-	22
		Clinical relapse at thirty-eighth week.			
		<u>2014</u>	Hg.	+	13
		Absent for twenty-nine weeks after first course.			
		<u>1792</u>	Hg.	+	19
		Irregular first course with Flumerin only.			
		<u>334</u>	Hg.	-	39
		In second six months.			
		<u>309</u>	Hg.	-	44
		Absent for thirty-two weeks after first course.			
		<u>181</u>	Hg.	+	14
		Absent for thirty-eight weeks after first course.			
		<u>752</u>	Hg.	-	21
		Well treated. Relapsed in third 6/12 period.			
		<u>768</u>	Hg.	-	53
		Relapsed at forty-eighth week. Clinical relapse.			
<u>F.2.</u>		<u>3923</u>	Bi.	-	7
		Only 1.65 grams "914" in first course.			
		<u>3930</u>	Bi.	-	29
		Only 2.85 grams "914" in first course.			
		<u>3697</u>	Bi.	S	30
		Only 3.45 grams "914" in first course. Clinical relapse.			

F.2 (contd.).

		<u>Metal</u>	<u>Final</u> <u>W.R.</u>	<u>Time</u>
<u>8</u>	Relapsed at seventieth week. Clinical relapse.	Hg.	-	39
<u>1705</u>	Well treated.	Hg.	-	22
<u>3516</u>	Relapsed after two years. Well treated.	Bi.	-	48
<u>4208</u>	Well treated initially.	Bi.	+	12
<u>362</u>	Relapsed twice.	Hg.	-	30
<u>1061</u>	Relapsed after one year. C.S.F. +.	Hg.	-	132
<u>1284</u>	Well treated.	Hg.	-	20
<u>3396</u>	Relapsed about fifteenth month. Various minor relapses. Eventually W.R. fast at fortieth month.	Bi.	+	56

The following comments may be made. Sudden reversal from negative to positive is most commonly an expression of an inadequate first course. Seven cases received bismuth but twenty-one were treated with mercury. The next most common factor is a lengthy period of default occurring immediately prior to the end of, or just subsequent to, the completion of a normal first course. This default removes the patient from subsequent second courses of treatment, or from clinical observation. This grade of relapse is to be regarded as evidence of activity on the part of the syphilitic virus, for out of a total of twenty-nine complete reversals there were eight cases

of clinical relapse. In the event of total adequate treatment subsequently being administered, this sudden reversal is not of permanent significance. There was only one case with a final positive blood Wassermann, and two cases in which the Wassermann reaction was suspicious, in those cases observed for more than two years.

It is shown in the section on the serial examination of the Wassermann reaction, that it takes as a rule from four to six weeks for a positive reading to become negative, and that intermediate readings of weak positive and suspicious are usually noted. No such corresponding information is available to determine the rate of change in a positive direction. Several cases have been seen in which a suspicious reading was noted and the blood test has been repeated in the following week without, however, any alteration in the reading.

Serological Relapses after lengthy periods of time.

Here are shown all those cases which became negative, remained so, but relapsed after eighteen months observation or longer.

<u>Sex and Stage of disease.</u>	<u>Relapse from 18 to 24 months.</u>	<u>Relapse after more than 24 months.</u>
M.1 DG+ W.R.-	0	<u>Case No. 1325.</u> - to S. Nowadays regarded as inadequately treated.
F.1 DG+ W.R.-	0	0
M.1 W.R.+	0	<u>Case No. 1240.</u> - to S. Very adequately treated.
F.1 W.R.+	<u>Case No. 440.</u> - to W. Nowadays regarded as inadequately treated.	0
M.2	<u>Case No. 1736.</u> - to W. Inadequately treated. Defaulted for 57 weeks.	<u>Case No. 901.</u> - to S. Inadequately treated. Defaulted for 148 weeks.
	<u>Case No. 302.</u> - to S. Thoroughly treated.	
F.2	<u>Case No. 1731.</u> - to S. Inadequate treatment. Continuous observation.	<u>Case No. 3516.</u> - to +. Well treated. <u>Case No. 904.</u> - to S. Well treated then long default. <u>Case No. 146.</u> - to +. Well treated.

In this series although inadequate treatment at the onset plays its part, yet eight out of ten cases were well treated judging by the standard of the year of their attendance. None received more than two courses of "914" and heavy metal, for all responded well to their initial treatment. The two cases in which full relapse occurred were continuously under observation.

It is apparent therefore that (1) either a proportion of early syphilis is not curable with modern drugs or (2) that the present course of treatment should be modified.

The weak positive serological relapses are now considered and the subjoined table shows, by sex and stage of disease, the total cases in which this reaction occurred, the total number of end serological results according to whether treatment was adequate or inadequate, and the total numbers of clinical relapses which took place.

Table 8.

Weak Positives

Sex and stage of disease.	Total cases showing weak positive.	<u>Final Results Treatment</u>				Clinical Relapse.
		<u>adequate</u>		<u>inadequate</u>		
		+	-	+	-	
M.1 DG+ W.R.-	0	0	0	0	0	0
F.1 DG+ W.R.-	0	0	0	0	0	0
M.1 W.R.+	3	0	1	1	1	0
F.1 W.R.+	4	0	3	0	1	1
M.2	16	4	7	2	3	1
F.2	19	8	9	2	0	0
Totals	42	12	20	5	5	2

There were thus forty-two out of five hundred and seventy cases of early syphilis, in which a weak positive Wassermann

reaction was obtained in the blood serum, other than as a stage towards the production of a negative result, as a result of the initial treatment. Out of these cases receiving adequate treatment, twelve showed a final unsatisfactory serological result (a high incidence), and twenty showed a final satisfactory serological result, while, where total treatment was inadequate, five cases showed an unfavourable, and five a favourable end serological test. Amongst forty-two cases there were four cases of clinical relapse - a percentage of 9.6, which represents a high incidence.

It is obvious, therefore, that the occurrence of weak positive readings as noted, is of unfavourable prognostic importance. In fourteen cases, or 33%, of the forty-two, the serological reading immediately subsequent to the weak positive was positive. Here, too, this incidence indicates the prognostic importance of the weak positive reaction.

The end results of those cases which did not show at any period of observation a relapse to a grade higher than weak positive are examined.

Total Treatment.

Sex and stage of disease.	Adequate		Inadequate	
	+	-	+	-
M.1 DG+ W.R.-	0	0	0	0
F.1 DG+ W.R.-	0	0	0	0
M.1 W.R.+	0	1	1	1
F.1 W.R.+	0	2	1	0
M.2	2	5	1	1
F.2	3	3	2	0
Totals	5	11	5	2

Here five out of sixteen cases receiving total adequate treatment showed a final blood Wassermann which was either weak positive or suspicious. This is much worse than the end results where the only grade of serological relapse was suspicious, and indicates that weak positive is of the importance of positive in final end results.

Those cases in which at least three Wassermann relapses occurred are next examined, and may be termed cases in which repeated variability of the Wassermann reaction took place.

M.1 DG+ W.R.- :-	0
F.1 DG+ W.R.- :-	0
M.1 W.R.+ :-	0
F.1 W.R.+ :-	0

- M.2 :- Case No. 768. Adequate first course. Clinical relapse. Persistent albuminuria for two years. Total treatment inadequate, especially in respect of "914". C.S.F. negative. Total time of observation fifty-three months.
Successive W.R. readings, - + + S W S W - -
- - -.
- Case No. 1506. Inadequate first course. Clinical relapse. Total treatment adequate. Total time of observation thirty-three months.
Successive W.R. readings, - + - + - S S .
- F.2 :- Case No. 2875. Inadequate first course. Total treatment adequate. Clinical relapse occurred. Total time observed seventy-two months.
Successive W.R. readings, + + + + + W + S
+ S +.
- Case No. 3396. Adequately treated. No clinical relapse. C.S.F. negative. Time observed fifty-six months.
Successive W.R. readings, + W - + W + - + W
+ S + + + (Since records closed has become -).

Three of these four cases showed clinical relapse, but in two instances the first course was inadequate. They appear to indicate an extremely active form of syphilitic infection, and in view of the high proportion of clinical relapse lend definite value to the significance of the Wassermann reaction. Only in one of them, Case No. 768, was a satisfactory end result maintained for more than eighteen months, and it is doubtful if any are either cured or curable. It is noted that no infection of the central nervous system was detected.

The ultimate fate of those cases in which Wassermann relapse occurred. The total cases are shown in accordance with whether the total treatment was adequate or inadequate, irrespective of default or of initial inadequate treatment. The sex, stage of disease, time observed and final Wassermann reaction is given, and final C.S.F. abnormalities if final blood W.R. is negative.

A. Inadequate total treatment.

Time observed.

Sex and stage of disease.	<u>Less than 12/12</u>					<u>Less than 24/12</u>					<u>More than 24/12</u>					Total
	+ w s	- not neg.	CSF	+ w s	- not neg.	CSF	+ w s	- not neg.	CSF	+ w s	- not neg.	CSF				
M.1 DG+ W.R.-	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	3
F.1 DG+ W.R.-	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M.1 W.R.+	6	0	1	2	0	2	0	1	2	0	2	0	0	2	0	18
F.1 W.R.+	3	0	0	2	0	0	0	0	0	1	1	0	0	1	0	8
M.2	10	2	2	0	1	2	0	1	3	0	0	0	0	1	0	22
F.2	8	1	4	2	0	4	0	1	3	0	0	0	1	2	1	27
Totals	27	3	8	7	1	8	0	3	8	1	3	0	1	6	2	78

B.

Adequate total treatment.Time observed.

Sex and stage of disease	<u>Less than 24/12</u>					<u>More than 24/12</u>					<u>Totals</u>
	CSF					CSF					
	+	w	s	- not neg.		+	w	s	- not neg.		
M.1 DG+ W.R.-	1	0	0	0	0	0	0	0	3	0	4
F.1 DG+ W.R.-	0	0	0	0	0	0	0	0	0	0	0
M.1 W.R.+	3	0	0	8	0	1	0	0	2	0	14
F.1 W.R.+	0	0	0	0	1	0	1	0	4	0	6
M.2	1	0	1	9	0	1	0	3	16	1	32
F.2	2	0	2	4	2	4	1	3	18	3	39
Totals	7	0	3	21	3	6	2	6	43	4	95

These are summarised as follows :-

Total unfavourable results, 88 - 50%.

Total favourable results, 85 - 50%.

Or, if these cases receiving total adequate treatment be taken separately,

Total unfavourable results, 31 - 33%.

Total favourable results, 64 - 66%.

Or, if these cases observed for more than two years and adequately treated be examined, the totals are,

Total unfavourable final results, 18 - 30%.

Total favourable final results, 43 - 70%.

Now 174 cases have been treated, observed and recorded for more than two years.

The total unfavourable final results are 18 - 10.3%

The total favourable results are 156 - 89.7%.

This shows very definitely the final fact that the incidence of Wassermann relapse has an unfavourable effect on the end serological results of treatment.

The conclusions reached in the preceding pages, that the incidence of Wassermann relapse is chiefly the expression of an inadequate initial course of treatment, will receive due consideration in the section dealing with the proposed course for the treatment of early syphilis.

On the evidence presented, it seems not unreasonable to suggest that Wassermann relapse should be the chief criterion in the evaluation of new drugs or new methods of employing old drugs for antisyphilitic treatment. This necessitates prolonged observation, and is rather at variance with the numerous papers published, extolling the immediate virtues of new preparations in respect of the rapidity with which Sp. Pall. disappears, lesions resolve and a positive blood Wassermann shows an initial reversal to a negative reading.

No attempt has been made to compare these results with the recorded figures of the American series. In the first

place detailed information is lacking, but in the second place at least five different methods of testing the sera were employed, and such diverse criteria are involved that comparison is impossible. No comparable series of detailed observations has been discovered in the literature, and it is hoped that this series may be of use as a yard-stick to measure the relative failure or success of other schemes of therapy.

There are submitted, as an appendix to this section, tables giving details of all cases in which Wassermann variation or delay in obtaining the first negative result took place.

An explanation of the headings of the tables is given:

<u>No.</u>	-	Case Number.
<u>Age</u>	-	Age on first attendance at the clinic.
<u>Type</u>	-	In primary syphilis a "1" indicates considerable secondary infection; "C" indicates clean or little secondary infection. In secondary syphilis "S" indicates slight, "M" medium, "F" florid, "L" latent having regard to degree of the lesions and their age.
<u>1st course</u>	-	indicates the nature of the first course of treatment received.
<u>As.</u>	-	"914" substitute.
<u>AB.</u>	-	Arsenobillon.
<u>NS.</u>	-	Neosalvarsan.
<u>M.</u>	-	Metal.
<u>B.</u>	-	Metallic bismuth.
<u>I.Q.B.</u>	-	Iodobismuthate of quinine.
<u>C.</u>	-	Calomel cream.
<u>F.</u>	-	Flumerin.
<u>M.</u>	-	Merkon.
<u>Ki.</u>	-	Potassium iodide by mouth. + indicates cases which received this drug throughout the first course.
<u>Intol.</u>	-	Intolerance and a + sign indicates such cases as exhibited any intolerance during the first course.
<u>Time</u>	-	indicates in figures the weeks occupied by the first course.

- No. of courses. - indicates the total number of courses of injections of As = "914", M = metal, or Pills = Hutchinson's pills administered.
- W.R. relapse - indicates by the appropriate symbol all variations in the Wassermann reaction of the blood serum. These are shown in six-monthly periods indicated by the figures 6-24 which include all results occurring in the successive periods. Changes after two years are either summarised in the column "+24", if no further change took place, or occasionally extended into the next column.
- Clinical relapse - Here are recorded the nature of any clinical relapses and in the next column "Time" the week at which the relapse took place.
- Treatment - Here is given in some cases, a summary of the total treatment received by the case. As. in grams, B. in grams, C. in grams. Pills in weeks. Nat. in grams given intravenously. Ki. in weeks table.
- Final W.R. - This shows the grade of a final Wassermann reaction of the blood serum and of the C.S.F. if done.
- Time observed - This indicates in months the total time of attendance at the clinic.

The cases are summarised by sex and stage of disease and across the appropriate groups in the column marked "clinical relapse" is drawn a diagonal line in pencil along which is shown the total amount of "914" received during the first course. The quantities are shown in five groups:

- 3.5 - These cases receiving less than 3.5 grams "914" in the first course.
- 5 - These cases receiving less than 5 and more than 3.5 grams.
- 6 - These cases receiving less than 6 and more than 5 grams.
- 7 - These cases receiving less than 7 and more than 6 grams.
- +7 - These cases receiving more than 7 grams.

No.	Age	Type	Ml W.R.+			Intol. Time in weeks of 1st. course	No. of Courses		No. and type of relapses.					Week of Relapse	Clinical relapses	Final W.R.	Blood C.S.F. Time observed in months.			
			As.	M.	Kl.		As.	M.	Pills	-6	-12	-18	-24					+24		
1255	28	1	NAB	C		10	2	2								3.0 NAB. 6c.c.Cal. cream - left for 48 wks.	+	16		
1918	49	1	NK	F		4	2	2								1.35 NK. .75 F. - left for 22 weeks.	+	7		
1839	25	C	NK	C		6	2	2								3.15 NK. 6c.c. Cal.cream - left for 61 wks.	-	20		
3122	24		S	B		16	1	1								2.7 St. 3.1 Bi.	+	3		
3934	46	1	NK	B		4	2	4								Intolerant-sickness & oedema of hands-difficult to treat.	-	23		
2976	18	1	NK	C		14	1	1								4.8 NK. Last W.R. at 21st week.	+	6		
1065	31	1	NAB	C		13	1	1								4.5NAB.9c.c.Cal.cream.Last W.R. at 11th week.	+	3		
406	22	C	NAB	C		11	2	2								4.5NAB.9c.c.Cal.cream.Last W.R. at 11th week.	+	4		
771	41	1	NAB	C		14	1	1								4.2NAB.8c.c.Cal.cream.Last W.R. at 14th week.	+	4		
954	24		NK	C		20	2	2								Left for 42 weeks.	+	16		
1883	32	C	NK	F		15	1	1	1							4.95NK. 1.15F. Left for 325 weeks.	+	86		
2146	25	C	NK	F		16	2	2	2							Iritis. penile syphilide.	15	4.95NK. 2.6 F.W.R. + at 24th week, - at 37th week.	-	19
4256	49	1	NS	B		17	1	3	1	W+	S					4.95 NS. 2.8 B.	S	15		
1180	28		NAB	C		9	4	4	2							2nd rash after 1st. course	64	J.H. reaction.	-	20
3531	38		NK	B		17	1	1	1	S						5.7 NK. 2.2 Bi.	S	5		
4216	59	C	NS NK	B		14	2	2	3							5.7 NK. & NS. 2.4 Bi. 12 Kl.	-	16		
4322	56		NK	B		32	2	4	0							Dermatitis. Transferred in.	-	31		
2021	30	1	NK	F		16	2	2								5.4 NK. 2.15F. Left for 25 weeks.	-	15		
2758	34		NK	B		17	4	4	6	W-	W	S				5.5 NK. 2.4 B. 13 Kl.	-	65		
1917	21	1		IBQ		13	2	2	6							IBQ only - relapsed at 13thwk. - at 7th wk.	-	50		
791	25	1	NAB			13	1	1	1							0.3 NAB. Left for 13 weeks.	-	7		
817	20	1	NAB	C		15	1	1	2	W						6.75NAB. 11c.c.Cal.cream - after 24 weeks	-	10		
191	34		NAB	C		16	2	2	1							6.75NAB. 8c.c.Cal.cream.	-	8		
1331	23	C	NAB	C		10	3	3	1	S						6.3NAB.12ccCal.cream.5.55NAB.11c.c.Cal.cream	+	18		
3977	23	1	NK	B		17	1	1	2							Marked dermatitis.	+	28		
659	30	C	NAB	C		17	3	3	3							Total 17.55 "914" 32cc Cal.cream. 1yr pills. 3wks. Kl.	+	32		
830	26	1	NK NAB	C		12	3	3	1	S	++					Papules in throat	36	Total 16.05 "914". 26c.c.Cal.cream. 12 wks. pills. 5 wks. Kl.	-	14
1240	19		NAB	C		17	1	1	9							Only one S result in 14 negative results.	-	101		
1561	30	C	NK	C		18	3	3	2	S						6.75NK.12ccCal.cream.12Kl.CSF also S at 18thwk.	-	19		
48	28		NAB	C		26	2	2	1							9.75 NAB. 9c.c.Cal.cream. 4 Kl.	+	14		
89	24		NAB	C		19	2	1	1							10.5NAB.5c.c.Cal.cream.4Kl.28wks.later S	-	37		
184	26	1	NAB	C		12										12.6 NAB. 5c.c.Cal.cream. 28 wks.pills.	+	17		

M 2 (Contd.)

No.	Age	Type	1st. Course.			Intol.	Time of 1st course in wks.	No. of Courses					No. and type of relapses					Clinical Relapses	Week of relapse	Final Blood W. C.S.F.	Time observed in months.
			As.	M.	Kl.			As.	M.	Pills	-6	-12	-18	-24	+24	-6	-12				
309	24	M	NAB	C		10	4	4	5	-	+	-	-	-			6.0NAB. 9cc Cal. cream. 32wks later after 2nd course WR +	-	-	44	
285	25	L	NAB	C		14	2	2	1	+	+						8.55NAB. 12c.c. Cal. cream. 16 weeks pills	+	-	8	
181	28	S	NAB	C		9	2	2	2	+	-	+					8.4NAB. 13c.c. Cal. cream. Relapsed 38 wks. later	+	-	14	
910	20	L	NAB	C		17	3	3	2	+	W	+	+	+			17.1 "914". 32cc Cal. cream. 24wks. pills. 7 Kl.	+	-	25	
420	51	S	NAB	C		17	3	3	2	S	-						6.75NAB. 11c.c. Cal. cream. WR. S in 17th week	-	-	18	
752	28	S	NAB	C		15	3	3	3	-	-	W	-				13.45 "914". 24cc Cal. cream. 24 wks. pills. 3 Kl.	-	-	21	
561	21	S	NAB	C		16	2	2	3	S	S	-	-				8.85NAB. 14cc Cal. cream. WR. S after 35th week	-	-	21	
597	26	M	NAB	C		13	3	1	7	S	-	-	-	-			7.9NAB. 11 cc Cal. cream. 8 wks. pills. S after 25th wk.	-	-	44	
11	19	F	NAB	C		22	2	1		-	S	-	-	-			6.9NAB. 3c.c. Cal. cream - absent 25 weeks.	-	-	29	
202	23	S	NAB	C		7	2	2	3	W	+						11.25NAB. 11c.c. Cal. cream in 34 weeks.	-	-	22	
49	23	L	NAB	C		14	3	3	3	-W	-	-	-	-			- at 8th week. W at 14th week,	-	-	46	
251	23	L	NAB	C		10	3	3	4	-S	-	S	-	-				-	-	49	
113	31	L	NAB	C	+	10	3	3	2	W-	S	S					Total 13.5 NAB. 7c.c. Cal. cream.	S	-	16	
29	30	S	NAB	C	+	8	3	3	4		+	+	-	S			6.00NAB. 3cc. Cal. cream in 8 wks. Absent 34 wks.	-	-	46	
1057	25	M	NAB	C		16	1	1	1	-	W						6.00NAB. 7cc. Cal. cream - then absent 33 weeks.	W	-	11	
1078	44	S	NAB	C		14	1			+							6.45 NAB.	+	-	5	
1094	30	F	NAB	C		15	2	2	5	-	-	S	-	-			6.75 NAB. 12c.c. Cal. cream. Pills 47wks. then S	-	-	27	
1504	29	S	NAB	C		12	4	3	5	S	S	-	S	S			20.1 "914" 16c.c. Cal. cream. 3.7B. 11Kl. 72weeks pills	-	S	33	
1558	32	S	NAB	C	+	18	2	2		+	+						10.4 NAB. 20c.c. Cal. cream. 8 Kl.	+	-	10	
3168	21	S	NK.	B		14	2	2	5	+	+	-	S	-			12.85 NK. 5.2B. 6Kl. Treated first NK rectally 4x.6	-	-	55	
224	18	S	NAB	C		15	2	2	0	W							9.55 NAB. 10c.c. Cal. cream.	W	-	7	
312	26	S	NAB	C		19	2	2		+							7.5 NAB. 12c.c. Cal. cream.	+	-	6	
901	25	M	NAB	C		16	1	1	3	-				S-			8.25NAB. 11c.c. Cal. cream. 42 wks. pills. Then absent 14wks.	-	-	49	
768	24	S	NAB	C		16	2	4	3	-	++S	WSW-	Ulc	er	cheek	48	8.25NAB. 11c.c. Cal. cream then absent 35 weeks. Per-				
													albuminuria			sistent albuminuria for 2 yrs. after next As. 8.25NAB					

F2

No.	Age	Type	1st. Course			Intol. Time in weeks of 1st. course	No. of Courses					No. and type of relapses					Clinical Relapses	Week of relapse	Final W.R.				
			As.	M.	Kl.		As.	M.	Pills	-6	-12	-18	-24	+24	As.	M.			Pills	Blood	C.S.F.	Time observed in months.	
2530	21	S		B			1										3.5 gm. Bi. No. 5.			+	6		
980	43	M	NK	C		1	2	2	2								ulcers, leg scalp rash wrist & knee	33	.75NK. 2c.c. Cal. cream then absent 32 weeks.	-	-	18	
486	29	S	NAB	C		4	3	2									condylomata	45	1.5NAB. 4c.c. Cal. cream then absent 41 weeks.	+		16	
1110	34	S	NAB	C	+	8	2	2	3	+	-	S							2.25 NAB. 7c.c. Cal. cream then absent 15 weeks.	-	S	33	
1267	28	M	NAB	C		2	2	2											.75NAB. 2c.c. Cal. cream then absent 43 weeks.	+		14	
1922	16	F	NAB	C		3	1	1											1.5NAB. 3c.c. Cal. cream then absent 59 weeks.	+		14	
3923	32	M	NK	B		14	1	2											1.65NAB. 3.8 B.	-		7	
3415	38	F	NK	B	+	2	1	1											1.05NK. .4B. 2Kl. then absent for 28 weeks.	+		7	
3634	29	F	NK	B	+	5	2	2										Laryngitis	111	3.30NK. .8B. 4Kl. absent 75wks & again 34 wks	+		27
3845	51	M	NK	B	+	4	2	2										Iritis: condylomata: rash	40	2.25NK. 1.0 B. 5Kl. then absent 36 weeks.	-		29
3930	29	M	NK	BC		12	4	6	3										2.85NK. 1.2B. 6Kl. 22Con. 16wks. pills then relapsed	-		31	
3697	29	F	NK	B	+	17	1	3										S papular rash wrist	95	Skin trouble after 3.45NK. 1.6B. 8 Kl.	S		30
239	27	M	NAB	C		7	3	3	1										4.50NAB. 6c.c. Cal. cream. Left for 33 weeks	S		17	
862	25	S	NAB	C		9	2	2											4.5 NK., NAB. 9cc Cal. cream. Left for 17 weeks	+		7	
1980	31	S	NK	C		23	1	2											4.5NK. 2c.c. Cal. cream. 15Cont. 414.	W		7	
802	25	F	NAB	C	+	12	5	5										Tertiary rash back and chest	70	11.1"914" 19c.c. Cal. cream. 7Kl. 8wks. pills Irreg. attendance. Healthy baby. WR Safter 1st course.	+		39
1260	21	S	NAB	C		9	2	2											4.2NAB. 8c.c. Cal. cream. Left for 34 weeks.	+		10	
1446	30	L	NAB	C		8	2	2	3									CSF S	5.3NAB. 8c.c. Cal. cream. 7 Contra. 20wks. pills After 1st course absent 90 weeks.		S	52	
1607	34	S	NAB	C	+	14	3	3	4										12.0NK. 8cc Cal. cream. 5.15F. 36 wks pills 33Na 5Kl.	-	-	24	
1992	24	M	NK	IR		19	2	2	1	W	S								6.75NK. 28 IBQ. 1.0Bic.	S		10	
2289	31	M	NK	B	+	19	2	3	1		W	+							6.3 NK. 5.0B. 12 Kl. 16 wks. pills.	-		26	
2575	29	M		B		6	2	3	2	S	W								7.7NK. 1.28B. No.5 in P.C. 1.7BL No.5. 1.0B. 6Kl. 16wk. pills	S	-	20	
2798	24	L	NK	B	+	21	1	1	1	+	S								4.50NK. 1.6B. 11 Kl. 12 wks. pills in 21wks.	S		6	
3328	18	M	AB	B	+	14	1	3											3.15NK. 1.0AB. 3.8B. 17 Kl.	+		6	
3269	33	M	AB	B	+	5	3	4	6	+	+	S	+	W					.5AB. 13.95NK. 7.2B. 4Na. li.v. 20 Kl. 56wk. pills	-		41	
4096	18	S	NK	B	+	19	1	1											4.8NK. 2.0B. 11Kl.	+		2	
8	40	S	NAB	C		9	4	4	5	+	-	-							25.05"914". 17cc Cal. cream. 52wks. pills. 4 Kl.	-		29	
1038	29	S	NAB	C		17	2	1	1										8.85NAB. 12cc Cal. cream. 16wks. pills. 4 Kl.	-		18	
1113	29	S	NAB	C		13	3	2	3	W	W	W	S	S	S				12.95"914". 20cc Cal. cream. 32wks. pills. 7 Kl.	S	-	25	
1484	27	L	NAB	C		17	1	1	7										5.65NAB. 12cc Cal. cream. 80wks. pills. 17 Kl.	-	S	41	
1705	29	M	NK	C		16	2	2	4										10.5NK. 12cc Cal. cream. 40wks. pills. 5Kl. 11 IBQ.	-		22	
1731	16	F	NK	C		21	2	2	3	W									7.45NK. 11cc Cal. cream. 89wks. pills. 6Kl. 11BQ. 9B.	-		72	

F2. (Contd.)

No.	Age	Type	1st. Course			Intol.	Time in weeks of 1st course	No. of Courses			No. and type of relapses					Clinical Relapses	Week of relapse	Final W.R.	Time observed in months.
			As.	M.	Kl.			As.	M.	Pills	-6	-12	-18	-24	+24				
1860	23	M	NAB	F		14	1	1	1							5.55NAB. 2.75F.	+	4 $\frac{1}{2}$	
2221	31	L	NK	B	+	19	2	2	7	-	S	-	-	S	-	9.9NK. 3.8B. 8.15Kl. 67 weeks pills.	-	91	
2260	23	L	NK	B	+	15	4	3	7	S	-	S	-	S	-	11.4NK. 3.6B. 25Kl. 45 weeks pills.	-	52	
2420	22	L	NK	B	+	16	3	1	3	WS	W	-	-	S	-	7.4 NK. 1.8B. 17Kl. 20 weeks pills.	-	24	
1789	24	S	NK	C		15	2	2	3	-	-	-	-	-	-	8.3NK. 9ccCal. cream. 2Kl. 56weeks pills. 5IBQ.	-	31	
3216	32	M	NK	B	+	13	1	4	3	+	S	-	-	-	-	5.85NK. 35Kl. 36 weeks pills. 5.2B.	-	21	
3453	28	M	NK	B	+	17	2	2	4	+	-	-	-	-	-	12.15NK. 27Kl. 84 weeks pills. 5.0B.	-	41	
3512	28	S	NK	B	+	19	2	5	3	+	+	W	+	-	S	-	11.1NK. 11Con. 8 $\frac{1}{2}$ C.B. 19Kl. 28wks.pills. 5.8B.	-	S 48
3516	28	L	NK	B	+	15	4	4	7	-	-	-	-	-	+	-	21.3 "914". 47Kl. 80 weeks pills. 8.8B.	-	S 48
4028	30	S	NK	B	+	18	4	6	3	W	+	-	-	S	W	16.35 "914". 39Kl. 20 weeks pills. 7.8 B.	W	- 25	
4118	61	F	NK	B	+	15	2	2	4		W	-	-	-	-	9.9 "914". 24Kl. 52 weeks pills. 4.0B.	-	22	
4205	32	S	NK	B	+	12	3	3	1	-	-	+	+	-	-	10.5 "914". 22Kl. 16 weeks pills. 4.2B.	+	12	
4263	22	S	NS	B	+	15	3	3	4	W	-	W	-	S	-	12.3 "914". 26Kl. 16 weeks pills. 5.0B.	-	16	
4323	26	M	NS	B	+	14	3	3	1		+	-	-	-	-	9.0 "914". 21Kl. 12 weeks pills. 3.2B.	+	13	
4434	32	M	NS	B	+	14	2	2	2	+-	-	-	-	-	-	6.3 "914". 14Kl. 20weeks pills. 2.6B.	-	8	
21	28	L	NAB	C		8	4	4	4	++	+	-	-	-	-	15.00"914". 13ccCal. cream. 9Kl. 32 weeks pills	-	62	
298	22	S	NAB	C		30	2	1	2	-	S	-	-	-	-	6.75"914". 10ccCal. cream. 12 weeks pills.	S	12	
342	31	S	NAB	C	+	17	4	2	2	+	W	-	-	S+	S	11.85"914". 12ccCal. cream. 22Kl. 28weeks pills.	S	36	
355	33	S	NAB	C		27	4	7	9	-	-	-	-	-	-	+ + S W - Thicken- ing of lip: site of chancre		38	
362	31	S	NAB	C		15	4	5	4	-	+	-	-	S	-	17.1"914". 28ccCal. cream. 4Kl. 31wks.pills..45F.	+	41	
904	36	S	NAB	C		15	2	2	3	S	-	-	-	-	-	10.95"914". 19ccCal. cream. 2Kl. 20wks.pills.	-	30	
955	28	M	NAB	C	+	17	1	1	3		-	-	-	-	-	6.45"914". 10ccCal. cream. 11Kl. 36wks. pills. 4.7gm. Na. 1	-	S 25	
1061	20	S	NAB	C	+	17	4	5	8	-	-	+	-	S	-	S-CSF: + -W+W-	-	152	
1269	28	S	NAB	C	+	13	2	2	1	S	+	S	-	-	-	Papular rash on back	S	35	
1284	28	S	NAB	C		15	2	2	3	-	W	-	+	-	-	13.5"914". 22ccCal. cream. 3Kl. 22wks.pills. 64Na. 1	-	S 20	
1383	31	M	NAB	C	+	16	1	1	1	+	-	-	-	-	-	6.15"914". 9ccCal. cream. 2Kl. 4 wks. pills.	+	11	
1420	50	S	NAB	C		15	1	1	1	-	+	-	-	-	-	6.00"914". 12ccCal. cream. 8 Kl. 3 wks. pills.	-	5	
1494	22	S	NAB	C		16	4	1	1		-	-	-	-	-	12.9"914". 11ccCal. cream. 18Kl. 4wks.pills. 10Na. 1	-	S 18	
2349	25	L	NK	B	+	22	3	3	1	+	+	-	-	W	S	11.58"914". 22Kl. 12 wks.pills. 5.0B.	S	28	
2875	26	S		B		3	8	9	6	+	+	+	+	++	W	+ S + S + Indocyclitis	+	43	
3377	19	M	NK	B	+	22	1	2		+	-	-	-	-	-	29.4"914". 52Kl. 100wks.pills. 15.6B. 4gm. Na. 1	+	9	
3396	22	L	NK	B	+	19	6	7	5	+	W	-	+	W	+	29.7"914". 37Kl. 54wks.pills. 38B. 16gm. Na. 1	+	- 56	
1203	24	S	NAB	C	+	15	3	3	2	-	-	+	W	+	S	18.00"914". 34ccCal. cream. 2Kl. 79wks.pills.	-	42	
																Left for 38 wks. after 1stcourse 7.95NAB. 11ccCal. cream.	-	42	
146	24	S	NAB	C	+	10	4	3	4	+	-	-	-	-	-	24.45"914". 27ccCal. cream. 9Kl. 44wks.pills.	-	42	

S E C T I O N III.

THE SERIAL EXAMINATION OF THE BLOOD WASSERMANN
REACTION IN EARLY SYPHILIS.

Pages 95-146.

The serial examination of the Wassermann reaction
of the blood serum in cases of early syphilis.

It was considered desirable to ascertain the course of variation of the Wassermann reaction of the blood serum in cases of early syphilis which were undergoing anti-syphilitic treatment. The kind co-operation of Professor C. H. Browning and Professor E. M. Dunlop in undertaking the great increase of work entailed, has made this examination possible. All Wassermann reactions were performed in Professor Browning's department, in accordance with the technique laid down in Recent Methods in the Diagnosis and Treatment of Syphilis, Browning and Mackenzie, second edition.

An endeavour was made to have the Wassermann reaction of the blood serum of each case done every second week. The cases were treated with the usual course of "914" and Bismuth, and the majority received fifteen grains of potassium iodide thrice daily throughout their course. Naturally a certain amount of variation took place. This is recorded in the appendix at the end of this section. For the sake of clearness the appropriate table of treatment is reproduced here.

Table 1.

Course of treatment administered
to cases of early syphilis.

	"914"	Bismuth metal	Ki gr. <u>xv</u> t.i.d. ac.
1st week	0.45gms.	0.2gms.	Ki
2nd week	0.6 "	0.2 "	Ki
3rd week	0.6 "	0.2 "	Ki
4th week	--	0.2 "	Ki
5th week	0.6 "	0.2 "	Ki
6th week	0.6 "	0.2 "	Ki
7th week	--	0.2 "	Ki
8th week	0.6 "	0.2 "	Ki
9th week	0.6 "	0.2 "	Ki
10th week	--	--	--
11th week	--	--	--
12th week	--	--	--
13th week	0.6 "	0.2 "	Ki
14th week	0.6 "	0.2 "	Ki
15th week	0.6 "	0.2 "	Ki
Total weight in grams.	5.85 "	2.4 "	

A series of 169 cases was thus investigated, and a summary of each case is presented at the end of this section. Twelve of the cases were sero-negative when first seen; these were male primaries with a positive dark ground field. The other 157 cases were sero-positive on first attendance and were distributed as follows:- 36 male, primary W.R. +, and 40 male secondary syphilis; 14 female primary W.R. +, and 67 female secondary syphilis. The material is thus tabulated.

Table 2.

	Males	Females	Total
1. D.G. + W.R. -	12	0	12
1. W.R. +	36	14	40
Secondary	40	67	107
Total	88	81	169

The twelve sero-negative male primaries are considered first.

Five of these defaulted with less than six months treatment. Two received less than 3.5 grams of "914", two received between 3.5 and 5 grams of "914", and eight received between 5 and 6 grams of "914" in the first course. All received bismuth, and eleven received potassium iodide by mouth throughout the course. The final Wassermann reaction of the blood serum was negative in all.

The following cases showed variation in the Wassermann reaction:-

Case No. 2402, age 45, chancre of fourteen days duration, W.R. suspicious at beginning of second week.

Case No. 3454, age 28, chancre of eight days duration, W.R. weak positive at beginning of third week.

Case No. 2935, age 44, chancre of four days duration, W.R. positive at beginning of third, fourth, fifth week, and suspicious at the beginning of the sixth week. This case received between 5 and 6 grams of "914" with 2.4 gms. of Bismuth metal and continuous potassium iodide by mouth as a first course. He attended regularly. No clinical or further serological relapses occurred, and the case was clinically well and serologically negative in respect of

blood and cerebro-spinal fluid at the end of thirty-four months. He received in all 5.7 grams of N.K., 2.4 grams of Bismuth metal, seventeen weeks of fifteen grains of potassium iodide, thrice daily by mouth, and forty weeks of oral mercury.

There is little to comment on in these few cases. Case No. 2935 was the only one which definitely exhibited a rise of the Wassermann reaction to full positive while undergoing treatment, and it subsequently made a good recovery. All cases when last seen were negative, as might be expected.

It might be suggested, in view of case No. 2935, that the frequency of injection and total dosage of "914" should be increased during the first two or three weeks.

An examination of the 157 sero-positive cases is next undertaken. The records show some irregularities in the dates at which the Wassermann reactions were performed, due to an increase to weekly observations at interesting times or to variability in the attendance of the patient. They will accordingly be grouped in "four-weekly" periods. The first twenty weeks of treatment and observation will thus fall into five groups:-

- 1 - 1st - 4th week inclusive
- 2 - 5th - 8th week inclusive
- 3 - 9th -12th week inclusive
- 4 - 13th -16th week inclusive
- 5 - 17th -20th week inclusive

A number of cases defaulted at varying stages of treatment. Where these cases are not specially shown under the time groupings, they will be referred to under the term "group X". The time groups will be referred to under the appropriate figures 1 to 5.

A preliminary table shows the general results; giving the stage of the disease, the sex, the period at which the Wassermann reaction first became negative, or the period at which the case defaulted with a positive W.R., or those cases which were not negative at the end of the first course of treatment.

Table 3.

Time groups of first negative W.R., shown in "4 weekly periods"

Time groups of default if W.R. †, shown in "4 weekly periods", or if W.R. † after first course.

Sex and stage of disease	Total cases	1	2	3	4	5	1	2	3	4	5
M.1.	36	3	14	13	4	1				1	
F.1.	14	2	8	3	1	0					
M.2.	40	0	14	17	5	0			3	1	
F.2.	67	1	22	25	7	1		3	1	4	3
Total cases	157	6	58	58	17	2	0	3	4	6	3

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The main facts brought out by this Table are :- that about one third of all cases of early syphilis treated by the course as outlined in Table 1., show their first negative reaction of the blood serum between the 5th and 8th weeks, and one third between the 9th and 12th weeks.

The other figures are self explanatory.

It is apparent from Table 3 that the Wassermann reaction becomes negative rather earlier in primary syphilis than in secondary syphilis. This is to be expected. The only case of secondary syphilis to become negative in the first four weeks was No. 4572, a female, age 22, a secondary of three months duration, who received 4.6 grams of "914", 2.4 grams of bismuth, and continuous oral potassium iodide in the first course. The case is still under observation and is still negative. Only three cases, all of female secondary syphilis, remained positive after twenty weeks, i.e. after a complete course of treatment. These were :-

Case No. 3396, age 22, Latent, of less than two years standing, received between 6 and 7 grams of N.K. in her first course, along with 2.4 grams of Bismostab and continuous oral potassium iodide. This case has remained Wassermann fast in spite of much treatment for fifteen months, and is still attending. No clinical lesions were ever noted.

Case 3377, age 19, a moderate secondary of two months duration, received a course similar to above, and remained Wassermann fast for nine months when she de-

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faulted. No clinical relapse occurred.

Case No. 3328, age 18, a moderate secondary of five months duration, received between 3.5 and 5 grams of N.K., 2.0 grams of Bismostab and continuous oral potassium iodide. The blood Wassermann became suspicious twice during the course, to relapse in two weeks to positive. She defaulted after six months with the blood Wassermann positive.

The next point of investigation concerned the amount of "914" in grams, administered during the first course of treatment. This quantity, as in previous sections, is expressed in five groups:- 3.5 grams, 3.5 - 5grams, 5 - 6 grams, 6 - 7 grams, more than 7 grams.

The cases are now tabulated in terms of the amount of arsenic in the first course expressed in grams, as noted against the time group when the Wassermann reaction first became negative, or against the amount received when the patient defaulted.

Table 4.

Amount of "914" in grams, in first course X time group of negative W.R., or default when still positive.

Time groups	As. groups.					Total cases
	-3.5	-5	-6	-7	+7	
1	1	2	2	1		6
2	6	6	34	12		58
3	5	5	40	7	1	58
4	1	1	11	2	2	17
5		2				2
Default	2	4	8	2		16
Total Cases	15	20	95	24	3	157

The only value such a table has, is to show the variation in the courses of treatment received by the

cases, which thus exhibits the actual practice of the clinic. It shows clearly that any standard course must receive many modifications according to the needs of the individual patient.

It will be obvious that more interesting information may be obtained by grouping the actual amounts of "914" received by each case at the time when it first became serologically negative. This is shown in the next table. Here the average amount of arsenic received in the "4 weekly periods" is substituted for the time group number. This is essentially Table 2 with quantities of "914" substituted for the time group numbers.

Table 5.

Average quantities of "914" received by cases at the time when they became serologically negative, or defaulted when still serologically positive.

		W.R. Negative.					W.R. Positive.				
		<u>Time groups and equivalent "914".</u>					<u>Time groups and equivalent "914".</u>				
		1	2	3	4	5	1	2	3	4	5
Sex and stage of disease	Total cases	gms. 1.65	gms. 3.45	gms. 4.05	gms. 5.85	gms. 5.85	gms. 1.65	gms. 3.45	gms. 4.05	gms. 5.85	gms. 5.85
M.1.	36	3	14	13	4	1				1	
F.1.	14	2	8	3	1	0					
M.2.	40	0	14	17	5	0			3	1	
F.2.	67	1	22	25	7	1		3	1	4	3
Total cases	157	6	58	58	17	2		3	4	6	3

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It is to be noted that these are average group quantities.

A reference to the preceding table shows that twenty-seven cases received in a course more than 6 grams of "914", usually exceeding 5.85 grams by only a small amount, and that thirty-five cases received less than 5 grams in the course, usually either through default when negative, or through decreased dosage from some other factor, such as intolerance, irregular attendance, or occupation. It must also be noted that a considerable number of Wassermann reactions in each group became negative towards the commencement of that time group. Thus it may safely be stated that two thirds of this group of 157 cases of early syphilis, became serologically negative after receiving between 3 and 4 grams of "914" along with the simultaneous administration of 1.6 or 1.8 grams of bismuth metal, and fifteen grains of potassium iodide thrice daily. From the public health point of view this may be stated in another form. The administration of 4 grams of a "914" substitute along with a heavy metal within a period of twelve weeks, will render the majority of cases of early syphilis non-contageous. This would appear of some importance in view of pending attempts to introduce the legislative control of the treatment of syphilis.

From the aspect of "cure" of the individual case, the question is left open. It is noted that nineteen cases of the 157 required the full course of approximately 6 grams and its concomitants before becoming negative, and that three cases were Wassermann positive after such a course. These numbers, totalling twenty-two, present $12\frac{1}{2}\%$ of the total cases, and it would therefore seem unwise to decrease the total quantity of "914" given in the first course. It may be argued that a smaller quantity of "914" and metal might suffice, as the negative reaction of the blood serum would tend to arrive a few weeks later. This is borne out by cases which default early and return in a clinically and serologically negative state some time later. It may also be argued that the further administration of the less toxic metal would suffice after 4 grams of "914" had thus been administered. In these studies this is not capable of proof, but one feels sure, on clinical grounds, that the relapsed and Wassermann fast cases would increase in percentage, were such methods adopted. The matter will be referred to later when considering Wassermann variation.

A different point arises from a review of these results. Taking into consideration the number of

cases which default, might it not be wiser to concentrate the "914" still further into the earlier weeks of the course of treatment? This question is also raised by the fact that only one case of secondary syphilis treated under this regime became negative during the first four weeks. In any given case, provided that the toxicity is not unduly increased, might not this concentration of a larger percentage of the "914" of the first course into the first four weeks, offer the hope of accelerating the production of the first negative Wassermann, diminishing immediate infectivity and decreasing the ultimate tendency to serological and clinical relapse. It is widely accepted that the longer a Wassermann reaction is permitted to remain positive, the more difficult will it be to create a permanently negative serological state. We note that certain clinics at the present time do concentrate their early dosage. Thus in Edinburgh and Liverpool the first three doses of "914" are all given in eight days. In Edinburgh, the first course is intra-muscular, and the subsequent spacing after the first four injections is comparable with the spacing in this course. In Liverpool, Dr. Ross gives bi-weekly intravenous injections without intermission

until 5.75 grams of "914" have been administered in thirty-nine days. In Portsmouth, Mr. Campbell gives 0.6 grams and 0.9 grams of "914" by the intravenous route in 10 days, followed by three further doses after three weeks rest and four final doses commencing on the 81st day. Col. L. W. Harrison states that he is endeavouring to reduce the total quantity of "914", while beginning to have more faith in the value of larger individual doses.

Unfortunately, no detailed observations are available from these clinics in regard either to the percentage of apparent cures, or to the earliest times at which the serological reactions become negative, and therefore no standards for comparison have been found. In the extensive series of American observations from their grouped clinics, "606" has been the drug of election, and no data are available as to the earliest periods of negativity of the blood Wassermann.

On the whole it is felt that a series of cases should be commenced, for comparative purposes, in which a larger amount of the arsenic should be given in the first four weeks, having all due regard to the individual case requirements and to the manifestations of arsenical intolerance.

The cases are next grouped in relation to the duration of infection and the time group of negative result also expressed as quantity of "914" received.

In the primary cases the duration is stated in days where known; in the secondary cases the duration is given in months.

Table 6.

Male Primary W.R.+

Duration of lesion	Total cases	Time group and equivalent "914" of first negative W.R.					
		1 grams 1.65	2 grams 3.45	3 grams 4.05	4 grams 5.85	5 grams 5.85	X default
-7 days	1		1				
-14 days	8	1	4	1	2		
-21 days	11	0	6	4			1
+21 days	13	2	3	7	1		
Total	33	3	14	12	3		1

Table 6 contd.

Female Primary W.R. †

Duration of lesion	Total cases	Time group and equivalent "914" of first negative W.R.					
		1 grams 1.65	2 grams 3.45	3 grams 4.05	4 grams 5.85	5 grams 5.85	X default
-7 days	1		1				
-14 days	2	1		1			
-21 days	1	1					
+21 days							
Total cases	4	2	1	1			

In these few cases it would appear that the earlier a patient comes for treatment the quicker will the Wassermann reaction become negative, or, in other words, the smaller is the quantity of "914" that will be required to produce a negative serological result. The whole group is, however, too small to permit of any dogmatic deduction, but the tentative conclusion is one that most clinicians feel to be in accordance with their clinical experience.

The cases of secondary syphilis are now similarly examined.

Table 7.

M.2.

Duration of lesion in months	Total cases	Time group and equivalent "914" of first negative W.R.					
		1 grams 1.65	2 grams 3.45	3 grams 4.05	4 grams 5.85	5 grams 5.85	X default
-4	19		8	8	2		1
-8	3			3			
-12	2						2
+12	2			1	1		
Total cases	26		8	12	3		3

Table 7 contd.

F.2.

Duration of lesion in months	Total cases	Time group and equivalent "914" of first negative W.R.					
		1 grams 1.65	2 grams 3.45	3 grams 4.05	4 grams 5.85	5 grams 5.85	X default
-4	28	1	11	12	2	1	1
-8	18		5	5	2		6
-12	4		1	1	2		
+12	1			1			
Total cases	51	1	17	19	6	1	7

It is impossible to draw any definite conclusion from so small a group, but there is to be noted a tendency towards the later time groups as the first expression of a negative Wassermann when the duration of the infection, prior to treatment, increases. In respect of the three female cases which were positive after twenty weeks, the durations, prior to treatment, were two months, five months and more than

one year respectively. Again the only comment to be made is that this seems in accord with clinical experience.

The influence of sex upon the time group at which the Wassermann reaction first becomes negative is next examined.

Table 8.

Sex	Total	Time groups of first negative W.R.					Time groups of default if W.R. †, or if W.R. † after first course.				
		1	2	3	4	5	1	2	3	4	5
M.	76	3	28	30	9	1			3	2	
F.	81	3	30	28	8	1		3	1	4	3
Total	157	6	58	58	17	2		3	4	6	3

It is obvious that, in this series, the question of the sex of the patient has no influence whatever upon the rate of reduction of a positive Wassermann reaction to a negative one.

The cases are next examined in terms of the type of lesion, where definitely known, against the time group of the first negative Wassermann. In primary syphilis the lesions are either termed "Clean", if fairly clean and free from secondary infection, or "Infected", if there be much secondary infection.

Table 9.

M.1.

Type of lesion	Total cases	Time group and equivalent "914" of first negative W.R.					
		1 grams 1.65	2 grams 3.45	3 grams 4.05	4 grams 5.85	5 grams 5.85	X default
Clean	22	2	10	6	2	1	1
Infected	14	1	4	7	2		
Total cases	36	3	14	13	4	1	1

F.1.

Type of lesion	Total cases	Time group and equivalent "914" of first negative W.R.					
		1 grams 1.65	2 grams 3.45	3 grams 4.05	4 grams 5.85	5 grams 5.85	X default
Clean	9	2	6		1		
Infected	5		2	3			
Total cases	14	2	8	3	1		

Such variation as these few figures show, indicates a slightly more favourable early outcome for the case in which there is little secondary infection.

This favourable result may, however, be an expression of a time factor in regard to the duration of the lesion before treatment, for the longer a chancre remains untreated, the greater are its chances of secondary infection. On the other hand, those cases of primary syphilis which either start with a chancreoid type of lesion, or exhibit other secondary venereal infection as apart from the infection of ordinary pyogenic organisms, come early for treatment on account of the severity of the local lesion.

In secondary syphilis the lesions are termed slight, medium, florid or latent on ordinary clinical grounds in accordance with the natural history of the disease, taking into account the duration of the condition.

Table 10.

M 2.

Type of lesion	Total cases	Time group and equivalent "914" of first negative W.R.					
		1 grams 1.65	2 grams 3.45	3 grams 4.05	4 grams 5.85	5 grams 5.85	X default
Slight	23		7	10	3		3
Medium	15		6	7	2		
Florid	1						1
Latent	1		1				
Total cases	40		14	17	5		4

F 2.

Type of lesion	Total cases	Time group and equivalent "914" of first negative W.R.					
		1 grams 1.65	2 grams 3.45	3 grams 4.04	4 grams 5.85	5 grams 5.85	X default
Slight	28		10	11	1		6
Medium	33	1	12	11	4	1	4
Florid	3			2	1		
Latent	3			1	1		1
Total cases	67	1	22	25	7	1	11

The severity of the lesion in secondary syphilis does not appear to influence the time at which the Wassermann reaction becomes negative. It has been noted that the severity of the lesion is quite independent of the time of its existence, and is to be taken as an expression of the severity of the manifestation of the particular type seen. This table, therefore, may reasonably be considered to be free from a time factor in respect of the duration of the disease prior to treatment.

A table is now shown giving the result of the latest Wassermann reaction of the blood serum when such a test was performed after the twenty weeks period of treatment and observations. It is compared with the time at which the first negative result was noted.

Table 11.

Final Wassermann reaction, if taken after twenty weeks, compared with time group of first negative W.R.

Time Group Sex & stage of dis- ease.	1.				2.				3.				4.				5.								
	Total	Final W.R.				Total	Final W.R.				Total	Final W.R.				Total	Final W.R.				Total	Final W.R.			
		-	S	W	+		-	S	W	+		-	S	W	+		-	S	W	+		-	S	W	+
M.1. W.R.+	3	2	0	0	0	14	12	0	0	0	13	11	0	0	0	4	2	0	0	0	1	1	0	0	0
F.1. W.R.+	2	2	0	0	0	8	8	0	0	0	3	3	0	0	0	1	1	0	0	0	0	0	0	0	0
M.2.	0	0	0	0	0	14	11	0	0	0	17	14	0	0	0	5	3	1	0	0	0	0	0	0	0
F.2.	1	1	0	0	0	22	22	0	0	0	25	22	0	0	1	7	6	0	0	1	1	1	0	0	0
Total cases	6	5	0	0	0	58	53	0	0	0	58	50	0	0	1	17	12	1	0	1	2	2	0	0	0

These results are satisfactory. It should be noted, however, that the total time available for the observation of any case in this series only exceeds forty-eight months in four instances. A considerable number have been under observation for about two years.

Only three cases were not negative, and of these only two were positive, female secondaries. The details of these cases are:- Case No. 4205, age 32, general adenitis and healing condylomata, the infection being of seven months

duration. She also had gonorrhoea. The Wassermann reaction only slowly became negative, the successive results being +,+,W,S,S,-. She has attended for twelve months. She received 5.85 grams of N.K., 2.4 grams of Bismostab and continuous oral potassium iodide as a first course. No clinical lesions appeared. The Wassermann reaction was negative at the onset of her second course of injections, but became positive by its end. In this second course she received 4.05 grams N.K., 1.6 grams Bismostab and oral potassium iodide. A repeat of the Wassermann reaction showed a similar positive result. The total time of observation so far, has been twelve months.

Case No. 4323, age 28, of two months duration, showed general adenitis, labial oedema and a small follicular rash. The Wassermann reaction took eleven weeks to become negative. She received 5.85 grams of N.K., 2.6 grams of Bismostab and 15 grains potassium iodide t.i.d. by mouth. No clinical relapse took place. Shortly after she received 6x.45 grams myosalvarsan and thereafter the W.R. was positive. After a further course of 5.85 grams N.K., 2.4 Bi. and Ki., the W.R. was negative - this final

result was obtained subsequent to the closure of the case records, and so the original positive result is allowed to stand. She has been twenty-two months under observation.

These results as a whole are more satisfactory than our average results in the treatment of early syphilis, but no deduction may be made as to the final serological result from the observation of the serial Wassermann reaction.

The next point examined was the rapidity with which a positive serological result was altered to a completely negative one.

Only two examples are noted in which this change (positive to negative) occurred in one week, Case No. 3888 and Case No. 2495, both male cases of secondary syphilis. In several instances the change from positive to negative took place after the two weeks interval, which ordinarily represented the frequency of serological examination, but in the majority the change is a gradual one, and it usually takes from four to six weeks to reverse completely a Wassermann reaction. More accurate timing cannot be made for there are a considerable number of deviations from the two weeks interval. It is apparent that there is no significant difference between the sexes, or

between the primary and secondary stages of infection, as regards the time taken to make the change. This series shows three cases of secondary syphilis in which the condition had been present for more than twelve months. They present no deviation from the normal picture.

It is also of interest to note that the rate of change, in the average case, is much the same no matter in which time group the first approaches towards the negative result are initiated. No appreciable acceleration of the reversal process is associated with its earlier commencement. It would be of interest to attempt to correlate the date of commencement of change and the rate of alteration from positive to negative with early Wassermann relapse, but in this series only two cases have relapsed to the full degree of positive after the period of twenty weeks. These cases have already been described. No. 4323, a female secondary of medium type, showed her first negative at the eleventh week. It took six weeks to drop from positive. No. 4205, a female secondary of slight grade, took eight weeks to become negative at fourteenth week. Three cases of female secondary syphilis remained positive at the end of their first course - cases

No. 3328, 3377 and 3396. In only one was any change noted during the course of treatment, and in that one, No. 3328, although on four occasions the Wassermann was suspicious, on no occasion was a completely negative result recorded.

The correlation of this rate and date of change with late, i.e. second year or over, Wassermann relapse is also of interest, but, as has been shown, only one case had a full positive result when last seen. This case, a female secondary, No. 4205, took eight weeks, starting from the sixth week, to become negative. This may or may not be a significant sign.

One is familiar with the difficulty of Wassermann reduction in latent syphilis of over two years duration, and tertiary syphilis. We have no data to present as regards the rate of reversal. In Venereal Disease Information, January 1933, p.4, Figure V11 indicates the gradual drop in a "four plus" series of 212 late latency cases which underwent considerable treatment. The rate of fall is very gradual, and no cases reached a negative phase. The American figures, however, were made as a result of ordinary routine tests at considerable intervals of time, and the composite results recorded by a statistical method as a continuous line.

No information is to be obtained in respect of any individual case.

The variations of the Wassermann reaction which took place during the course, and the short after period needed to complete twenty weeks is next studied. Tables have been completed to show all variations which occurred in the various groups of syphilis - male and female, primary and secondary. The four grades of the Wassermann returned to us are, in descending order, positive, weak positive, suspicious and negative. These changes are tabulated against the time groups in which they occurred. The cases in which the original Wassermann reaction was negative, and the dark ground positive, are not included.

Table 12.

M.l., W.R.+

Grade of relapse	Time Groups					Totals
	1	2	3	4	5	
- to S	1	1	3		1	6
- to W	1					1
→ to †					1	1
S to W		1				1
S to †						
W to †	4	1				5
Totals	6	3	3		2	14

Table 13.

E.l., W.R.†

Grade of relapse	Time groups					Totals
	1	2	3	4	5	
- to S		1	1			2
- to W						
- to †						
S to W						
S to †						
W to †	1					1
Totals	1	1	1			3

Table 14.

M.2.

Grade of relapse	Time groups					Totals
	1	2	3	4	5	
- to S		1	3		1	5
- to W						
- to †						
S to W		1				1
S to †						
W to †						
Totals		2	3		1	6

Table 15.

F.2.

Grade of relapse	Time groups					Totals
	1	2	3	4	5	
- to S			2	1	1	4
- to W				1		1
- to †						
S to W						
S to †						
W to †	1			1	1	3
Totals	1		2	3	2	8

Table 16.

Totals

Grade of relapse	Time groups					Totals
	1	2	3	4	5	
- to S	1	3	9	1	3	17
- to W	1			1		2
- to †					1	1
S to W		2				2
S to †						
W to †	6	1		1	1	9
Totals	8	6	9	3	5	31

There were 1086 tests performed on this series of 157 cases and the total variations in an upward direction were only thirty-one. This appears to be a small number in such a series. The reading "Suspicious" means a suspicious negative result and has a therapeutic rather than a diagnostic value. If the grade from negative to suspicious be excluded, the total changes are only fourteen in number. Further, some increase in the grade of Wassermann positive is to be expected in the early weeks of treatment, especially in the primary cases. There were seven such changes, of which six occurred in primary syphilis. If these too be excluded, the total changes are only seven in number. Similarly, minor changes in the second time group of four weeks may also be said to be of little importance, and its withdrawal leaves only four later changes.

These four changes were:-

- (1) M.1. W.R. - to + in 17th week. This case, No.3839, was negative in the following week and then defaulted.
- (2) F.2. W to + in 14th week and also in the 18th week.
- (3) This case, No. 3328, defaulted after six months treatment and observation with a full positive Wassermann. No clinical relapse.
- (4) F.2. - to W in the 14th week in case No.3216. This case continued under treatment and observation, became negative and remained so at the end of twenty-one months.

One may conclude that unfavourable minor changes in the Wassermann reaction were extremely uncommon in this series treated in the manner shown in Table 1, provided early increases in positivity in primary syphilis be excluded. Also that minor changes in the Wassermann reaction are of little significance in respect of the expectation of a favourable result at the end of the first course. It is again emphasised that the results in this series at the end of the first course are more favourable than in our total primary and secondary cases at the clinic, and one would have almost welcomed more unfavourable figures in hope of securing aid from their analysis.

The peculiar sudden reversal from negative to full positive, seen once in this series during the course, and twice at other later periods, is completely unexplained. It was confirmed by repetition of the Wassermann test. In no case did the most careful clinical examination elicit any sign, nor did the patients have any symptoms either of particular or of general import. Undoubtedly in the earlier stages of treatment such cases must be regarded as true relapsed syphilis. One feels, however, that no special difficulty will be created, and that a little additional treatment is all that is needed to give

them as good an ultimate chance of cure as their colleagues. This view is not extended to late serological relapses.

Some cases defaulted while still not negative, to return at a later date. These cases are shown in the next table.

Table 17.

Sex & stage of disease.	Case No.	Week of default	W.R. on default	Treatment in As. gms. on default.	Month of return	W.R. on return
M.2.	4079	17th	S.	-6	13th	-
M.2.	3616	9th	S.	-5	40th	-
M.2.	4032	10th	f	-5	23rd	-
F.2.	3528	6th	f	-3	13th	-
F.2.	3347	9th	S.	-5	15th	-
F.2.	3784	14th	W.	-6	26th	-
F.2.	4028	17th	W.	-6	25th	S.
F.2.	4263	15th	W.	-6	16th	-
F.2.	4434	14th	W.	-6	8th	-

This group is interesting, showing the extension of the therapy received. It serves to confirm the statement made earlier in this paper, that from three to four grams of N.K. along with a heavy metal is sufficient to reduce the Wassermann reaction to neg-

ative in the majority of cases. It offers us hope in the case of our numerous defaulters.

The maintenance of a positive Wassermann reaction in face of treatment raises fresh questions. This, noted already, occurred in the cases F.2., 3328 and 3396, without any signs of clinical relapse. Case 3328 defaulted in six months, but case 3396 has received much treatment without Wassermann reversal and is in perfect health after fifty-two months. Her fiance, the cause of her infection, made an ordinary recovery and has not subsequently relapsed.

It raises doubts as to the significance of such a fixed reaction. Many cases are discovered, as part of a routine examination, to have a positive Wassermann and a history of antecedent syphilis, and since the salvarsan era, many of those give a history of fairly adequate treatment at the time of infection. They present no signs of syphilis on clinical examination, and the thought is created that possibly there may be some occasional subsidiary factor in the maintenance of this positive reaction. The life long observation of a group of such cases, combined preferably with post mortem examination, will afford one mode of answering such a question from the clinical stand point.

These somewhat laboriously acquired observations appear upon consideration to justify themselves. A definite idea of the standard early response of the blood Wassermann to a routine mode of treatment has been achieved in respect of early syphilis. This affords a definite standard for comparison with other methods of treatment. This standard response has, so far, not been found of value in the prognosis of the later stages of treatment or observation, but, also so far, the cases under review have been fairly satisfactory from a clinical standpoint. As they have so far been satisfactory, it is not unreasonable to suggest that this recorded behaviour of the Wassermann reaction affords a useful method to aid in the rapid evaluation of other schemes of treatment. Unless an alternative scheme of therapy produces as large a proportion of negative results, as early a commencement of change, as quick a complete reversal from positive to negative, and as few early variations and full serological relapses, it would not appear judicious to continue such treatment. The literature contains much writing concerning the rapidity with which clinical lesions disappear, but relatively little on the serial Wassermann variations in the early stages.

The concrete proposals suggested as a result of this analysis will be found in the section dealing with the suggested future treatment of early syphilis.

An appendix is submitted, giving a summary of each case. This shows sex and stage of the disease, the case number, the age of the patient at the first attendance, the duration of the lesion in days for primary syphilis, or in months for secondary syphilis, the amount of "914" in grams given in the first course, the metal administered concurrently and whether or not potassium iodide was given throughout the course, The total attendance of the patient is then shown in months, a + indicating that the case is still under observation. Then follows a graph of the course of the Wassermann reaction of the blood, in which the abscissae represent the grade of the reaction and the ordinates the time in weeks at which the reaction was performed. The last recorded Wassermann reaction in each case is submitted on the extreme right hand of the graph.

MALES :

PRIMARY SYPHILIS,

D.G + W.R. -

NO.	AGE	DURATION IN WEEKS	TYPE	TREATMENT AS METAL IODIDES	TOTAL ATTENDANCE IN MONTHS	GRADE S.M.P.	TIME IN WEEKS	FINAL W.R.
3519	40	1/2		-3.5 + Bi + Ki	1	+ Z W S Z		
2402	45	1/2		-3.5 + Bi + Ki	1	+ Z W S Z		
3644	32	1/2		-5 + Bi + Ki	5	+ Z W S Z		
4152	25	2 1/2		-5 + Bi + Ki	4	+ Z W S Z		
3454	28	8/365		-6 + Bi + Ki	5	+ Z W S Z		
243+	22	4/365		-6 + Bi + Ki	11	+ Z W S Z		
3815	47	1		-6 + Bi + Ki	6 1/2	+ Z W S Z		
3831	20	2/365		-6 + Bi + Ki	6	+ Z W S Z		
3485	29			-6 + Bi + Ki	15	+ Z W S Z		
3455	23			-6 + Bi + Ki	15	+ Z W S Z		
2935	44	4/365		-6 + Bi + Ki	34	+ Z W S Z		
2685	20	19/365		-6 + Bi + Ki	7 1/2	+ Z W S Z		

MALES: PRIMARY SYPHILIS

W.R. POSITIVE

NO.	AGE	DURATION IN DAYS	TYPE	TREATMENT			TOTAL ATTENDANCE IN MONTHS	GRADE OF W.R.	TIME IN WEEKS.	FINAL W.R.
				AS	METAL	IOOIOES				
3839	38	35	C	-6	+ Bi	+ Ki	5	+	25W	
2486	23	21	C	-6	+ Bi	+ Ki	6	+	25W	
2448	27	30	C	-6	+ Bi	+ Ki	56+	+	29W	
3547	24	7	I	-6	+ Bi	+ Ki	7½	+	25W	
3558	32	10	I	-6	+ Bi	+ Ki	4	+	25W	
3882	50	10	C	-6	+ Bi	+ Ki	28	+	25W	
3843	31		C	-6	+ Bi	+ Ki	27+	+	25W	
3614	23	42	I	-6	+ Bi	+ Ki	27+	+	25W	
3786	39	14	I	-6	+ Bi	+ Ki	21+	+	25W	
3692	22	18	I	-6	+ Bi	+ Ki	16	+	25W	
3927	34	21	I	-6	+ Bi	+ Ki	26+	+	25W	
4327	25	17	C	-6	+ Bi	+ Ki	10+	+	25W	
3919	31	28	I	-6	+ Bi	+ Ki	20+	+	25W	
4328	29	14	C	-6	+ Bi	+ Ki	12+	+	25W	

MALES: PRIMARY SYPHILIS

W.R. POSITIVE

NO.	AGE	DURATION IN DAYS.	TYPE	TREATMENT AS METAL IODIDES	TOTAL ATTENDANCE IN MONTHS.	GRADE of W.R.	TIME IN WEEKS.	FINAL W.R.
4291	22	21	C	-3.5 + Bi + Ki		+		
3793	20	21	I	-3.5 + Bi + Ki		+		
1883	32	19	C	-5 + F + Na'	4	+		
2146	25		C	-5 + F	19	+		
2382	54	21	I	-5 + Bi + Ki	9	+		
3534	34	5	C	-5 + Bi + Ki	7	+		
4155	50	14	I	-5 + Bi + Ki	19+	+		
4163	57	12	C	-5 + Bi + Ki	19+	+		
3531	38	60	C	-6 + Bi	5	+		
3342	26	17	C	-6 + Bi	3 1/2	+		
3329	25	10	C	-6 + Bi	16	+		
3341	32	16	C	-6 + Bi + Ki	49	+		
3598	27	7	I	-6 + Bi + Ki	10 1/2	+		
3483	27	30	I	-6 + Bi + Ki	20	+		

MALES: PRIMARY SYPHILIS

W. R. POSITIVE

NO.	AGE	DURATION IN DAYS	TYPE	TREATMENT AS METAL IODIDES	TOTAL ATTENDANCE IN MONTHS	GRADE OF W.R.	TIME IN WEEKS	FINAL W.R.
3426	33	14	I	-Y + Bi	24	Z4E+		
3373	29	11	C	-Y + Bi	23	Z4E+		
3470	27		I	-Y + Bi + Ki	15	Z4E+		
3628	31	9	C	-Y + Bi + Ki	13	Z4E+		
3241	32	21	C	-Y + Bi + Ki	13	Z4E+		
3406	34	17	C	-Y + Bi + Ki	42+	Z4E+		
3836	43	42	I	-Y + Bi + Ki	33	Z4E+		
3207	41	17	C	+Y + Bi + Ki	24	Z4E+		

FEMALES: PRIMARY SYPHILIS

W.R. POSITIVE

NO.	AGE.	DURATION IN DAYS.	TYPE	TREATMENT AS METAL IODIDES	TOTAL ATTENDANCE IN MONTHS.	GRADE OF W.R.	TIME IN WEEKS.	FINAL W.R.
3387	37		1	-3.5 + Bi + Ki	47+	Z0W+		
4428	21		C	-5 + Bi + Ki	8+	Z0W+		
3494	26	7	C	-5 + Bi + Ki	30+	Z0W+		
3363	40		C	-5 + Bi + Ki	40+	Z0W+		
3908	28	14	C	-6 + Bi + Ki	31+	Z0W+		
3997	21		1	-6 + Bi + Ki	28+	Z0W+		
3668	26	7	1	-6 + Bi + Ki	39+	Z0W+		
4145	40		C	-6 + Bi + Ki	14	Z0W+		
3646	35		C	-6 + Bi + Ki	16	Z0W+		
4115	28		1	-6 + Bi + Ki	18+	Z0W+		
4254	27		1	-6 + Bi + Ki	17+	Z0W+		
4200	39		C	-6 + Bi + Ki	17+	Z0W+		
3041	20	7	C	-6 + Bi + Ki	41	Z0W+		
3345	19		C	-7 + Bi + Ki	52+	Z0W+		

MALES:

SECONDARY SYPHILIS.

NO.	AGE	DURATION IN WEEKS.		TREATMENT.	TOTAL ATTENDANCE IN MONTHS	GRADE of W.R.	TIME IN WEEKS.	FINAL W.R.
		D	T					
2822	28	15	S	-35 + Bi + Ki	2	20+		
4162	55	6	S	-35 + Bi + Ki	19+	20+		
2893	25		M	-5 + Bi + Ki	37	20+		
4084	50		S	-6 + Bi + Ki	5	20+		
4079	53	26	F	-6 + Bi + Ki	13	20+		
3616	41	40	S	-6 + Bi + Ki	40+	20+		
3888	41	9	M	-6 + Bi + Ki	9+	20+		
4224	44		M	-6 + Bi + Ki	6+	20+		
3955	41	5	M	-6 + Bi + Ki	13	20+		
3941	42	17	M	-6 + Bi + Ki	27+	20+		
3881	35		S	-6 + Bi + Ki	27+	20+		
3971	38	6	S	-6 + Bi + Ki	17	20+		
4284	31		M	-6 + Bi + Ki	14+	20+		
3915	33	9	S	-6 + Bi + Ki	10	20+		

MALES:

SECONDARY SYPHILIS.

NO.	AGE	DURATION IN WEEKS	TYPE	TREATMENT AS. METAL IODIDES	TOTAL ATTENDANCE IN MONTHS	GRADE of W.R.	TIME IN WEEKS	FINAL W.R.
3694	21	?	M	- 6 + Bi + Ki	12	20+		
3808	21		S	- 6 + Bi + Ki	17+	20+		
4170	23	9	S	- 6 + Bi + Ki	17	20+		
2495	24		S	- 6 + Bi + Ki	66+	20+		
3940	43	13	S	- 7 + Bi	26+	20+		
3348	30		L	- 7 + Bi	49+	20+		
3386	30		S	- 7 + Bi + Ki	8	20+		
3632	26	3?	S	- 7 + Bi + Ki	5	20+		
3353	28		S	- 7 + Bi + Ki	38+	20+		
3411	23	17	M	- 7 + Bi + Ki	40+	20+		
3586	54	9	M	+ 7 + Bi + Ki	7	20+		
3188	32	14	M	+ 7 + Bi + Ki	47+	20+		

FEMALES :SECONDARY SYPHILIS.

NO.	AGE	DURATION IN WEEKS	TYPE	TREATMENT AS METAL IODIDES	TOTAL ATTENDANCE IN MONTHS	GRADE of W.R.	TIME IN WEEKS	FINAL W.R.
3328	18	5	M	-5 + Bi + Ki	6	Z ₅₂ +		
3545	38	6	M	-5 + Bi	3	Z ₆₂ +		
3647	35	3	S	-5 + Bi + Ki	40+	Z ₆₂ +		
3677	36	8	S	-6 + Bi + Ki	36+	Z ₆₂ +		
3892	28	?	S	-6 + Bi + Ki	29+	Z ₆₂ +		
3912	17	3	S	-6 + Bi + Ki	28+	Z ₆₂ +		
3013	33	?	M	-6 + Bi + Ki	37	Z ₆₂ +		
2583	26	3	S	-6 + Bi + Ki	6	Z ₆₂ +		
3216	32	5	M	-6 + Bi + Ki	21	Z ₆₂ +		
3601	36	2	S	-6 + Bi + Ki	38+	Z ₆₂ +		
3604	42		S	-6 + Bi + Ki	30	Z ₆₂ +		
3588	25		M	-6 + Bi + Ki	8	Z ₆₂ +		
3784	42	5	S	-6 + Bi + Ki	26	Z ₆₂ +		
3825	27	10	S	-6 + Bi + Ki	14	Z ₆₂ +		

FEMALES :SECONDARY SYPHILIS.

NO.	AGE	DURATION IN WEEKS	TYPE	TREATMENT AS METAL IODIDES	TOTAL ATTENDANCE IN MONTHS	GRADE S W Z	TIME IN WEEKS.	FINAL W.R.
4209	27	9	F	-35 + Bi + Ki	19	+ W S Z		
3930	29	4	M	-35 + Bi + Ki	31	+ W S Z		
3923	32		M	-35 + Bi + Ki	7	+ W S Z		
3938	24	30	M	-35 + Bi + Ki	13	+ W S Z		
3697	29	3	F	-35 + Bi + Ki	30	+ W S Z		
3528	18	5	S	-35 + Bi	13	+ W S Z		
3431	20	6?	M	-35 + Bi	22	+ W S Z		
3081	26	7?	M	-35 + Bi + Ki	48	+ W S Z		
2940	31		S	+ Bi	26	+ W S Z		
3711	26	2	S	-5 + Bi + Ki	3	+ W S Z		
3922	20	4	S	-5 + Bi + Ki	22	+ W S Z		
4247	25	5	M	-5 + Bi + Ki	3	+ W S Z		
3347	42	4	S	-5 + Bi	15	+ W S Z		
3487	38	2 1/2	M	-5 + Bi + Ki	3	+ W S Z		

FEMALES:SECONDARY SYPHILIS.

NO.	AGED	DURATION IN WEEKS.	TYPE	TREATMENT.			TOTAL ATTENDANCE IN MONTHS.	GRADE OF W.R.	TIME IN WEEKS.	FINAL W.R.
				AS.	METAL	IODIDES				
3676	44	6	S	-6	+ Bi	+ Ki	7	20E+	20E+	20E+
3740	19	3	M	-6	+ Bi	+ Ki	9 $\frac{1}{2}$	20E+	20E+	20E+
3658	22	?	M	-6	+ Bi	+ Ki	14	20E+	20E+	20E+
4028	30	?	S	-6	+ Bi	+ Ki	25+	20E+	20E+	20E+
4192	50	1 $\frac{1}{2}$	S	-6	+ Bi	+ Ki	19+	20E+	20E+	20E+
4212	44	8	M	-6	+ Bi	+ Ki	17+	20E+	20E+	20E+
4263	29	22	S	-6	+ Bi	+ Ki	16+	20E+	20E+	20E+
4276	29	1 $\frac{1}{2}$	S	-6	+ Bi	+ Ki	15+	20E+	20E+	20E+
4274	28	1 $\frac{1}{2}$	M	-6	+ Bi	+ Ki	15+	20E+	20E+	20E+
4313	27	2	S	-6	+ Bi	+ Ki	14+	20E+	20E+	20E+
4305	30	3	S	-6	+ Bi	+ Ki	13+	20E+	20E+	20E+
4377	32	2 $\frac{1}{2}$	S	-6	+ Bi	+ Ki	11+	20E+	20E+	20E+
4222	31		L	-6	+ Bi	+ Ki	18+	20E+	20E+	20E+
4289	18	3	M	-6	+ Bi	+ Ki	9	20E+	20E+	20E+

FEMALES :SECONDARY SYPHILIS.

NO.	AGE	DURATION IN WEEKS.		TREATMENT AS. METAL IODIDES	TOTAL ATTENDANCE IN MONTHS	GRADE & W.R.	TIME IN WEEKS.	FINAL W.R.
		D	W					
4323	26	2	M	-6 + Bi + Ki	13+	+ W S Z		
4205	32	7	S	-6 + Bi + Ki	12	+ W S Z		
4402	23	1	M	-6 + Bi + Ki	10+	+ W S Z		
4230	22		M	-6 + Bi + Ki	8	+ W S Z		
424	55		M	-6 + Bi + Ki	8	+ W S Z		
4390	36		M	-6 + Bi + Ki	10	+ W S Z		
4427	21	7	M	-6 + Bi + Ki	5	+ W S Z		
4434	32	4	M	-6 + Bi + Ki	8+	+ W S Z		
4418	41		M	-6 + Bi + Ki	9	+ W S Z		
3377	19	2	M	-7 + Bi + Ki	9	+ W S Z		
4401	19	6	S	-7 + Bi + Ki	10+	+ W S Z		
3326	33	3	M	-7 + Bi + Ki	21	+ W S Z		
3870	35	3	S	-7 + Bi + Ki	18	+ W S Z		
3293	30	5	F	-7 + Bi + Ki	20	+ W S Z		

FEMALES:

SECONDARY SYPHILIS.

NO.	AGE	DURATION IN WEEKS.	TYPE	TREATMENT AS. METAL IODIDES	TOTAL ATTENDANCE IN MONTHS	GRADE OF W.R.	TIME IN WEEKS	FINAL W.R.
3396	22		L	-7 + Bi + Ki	52+	+		
3067	36	2	M	-7 + Bi + Ki	57+	+		
3414	28	2	S	-7 + Bi + Ki	45+	+		
3344	33		M	-7 + Bi + Ki	45	+		
3318	27	3	M	-7 + Bi + Ki	4	+		
4518	22	7	M	-6 + Bi + Ki	6	+		
4522	18	1	S	-3 + Bi + Ki	4	+		
4524	30	3	M	-5 + Bi + Ki	5	+		
4552	45	1	S	-6 + Bi + Ki	5	+		
4565	35	2	S	-6 + Bi + Ki	3	+		
4572	22	3	M	-4.5 + Bi + Ki	4	+		

S E C T I O N I V .

THE CEREBRO-SPINAL FLUID IN EARLY SYPHILIS.

Pages 147-188.

Cerebro-Spinal Fluid Examination in
cases of treated early syphilis.

Out of five hundred and seventy cases of treated early syphilis, one hundred and forty-five were subjected to lumbar puncture, and many of these were examined on more than one occasion. Table 1 shows the total numbers of cases in each category of early syphilis, the total number of cases in each category examined by lumbar puncture, and the total numbers in each category in which the Wassermann reaction of the first puncture was negative or not negative.

Table 1.

Sex and stage of disease.	Total cases	Total C.S.F. Examination	W.R.	
			Neg.	Not Neg.
M.1. D.G.+ W.R.-	48	15	14	1
F.1. D.G.+ W.R.-	2	0	0	0
M.1. W.R.+	126	31	30	1
F.1. W.R.+	36	9	6	3
M.2.	172	44	40	4
F.2.	186	46	33	13
Total Cases	570	145	123	22

An appendix is provided at the end of this section showing certain tabulated data concerning those cases which received lumbar puncture.

The routine examination of the cerebro-spinal fluid in our out-patient clinic is accompanied by many difficulties. It is impossible to allow a lengthy rest period after lumbar puncture has been done. Many cases come from a considerable distance for treatment. Many cases, from economic necessity, are unable to take the subsequent day off work. For these reasons a considerable percentage of the patients subsequently develop malaise and a severe headache, and, on their return to the clinic, they regard this as information to be disseminated quickly and widely amongst the other patients. This information acts on many prospective candidates as a most complete vaccination against future lumbar puncture. Also this leads to default. Seven cases, after consenting to lumbar puncture, defaulted before it was done. One might note further, that eight cases never returned after lumbar puncture had been performed, and there is complete ignorance as to what happened to them. For these reasons, anything in the nature of a routine time for suggesting lumbar puncture has hitherto been avoided, a favourable opportunity being

sought in respect of any single patient. There is too, as yet, no general agreement concerning the optimum time for a single puncture in any given case. It was hoped that this haphazard sampling of cases might, on analysis, yield some information of unexpected value, and therefore, up to the closure of these case records, no definite system had been adopted. The practical point which, it is hoped, this section will answer is :- What is the optimum time for performing a lumbar puncture in treated cases of early syphilis ?

As, however, no time for puncture is free from the drawbacks just mentioned, it is desirable to consider briefly anything which will diminish subsequent discomfort and induce a larger number of cases to submit to examination. The important objection raised to the operation by the patient is, of course, subsequent headache, and it may be stated in a sentence here, that many expedients have been tried in order to diminish its incidence and severity. The most important practical points have been found to comprise the usage of a very fine bore needle, and expert handling, whereby the puncture is performed neatly with a single operation avoiding any bruising or tearing of the theca. The small bored needle is criticised on the grounds that its small clean thecal puncture is less liable to

close than the more irregular tear produced by a larger bevel. It can only be repeated, however, that using such a fine needle the later results in the clinic are much more successful. It may also be stated that only time and rest in the prone position relieve the headache, though temporary ease always follows the intravenous administration of 100 c.c. of water, and often accompanies the use of Pyramidon, gr. x, thrice daily in a cachet.

One hundred and forty-five cases received one or more lumbar punctures. All cases were treated, and almost all were treated by the standard type of course as already explained (Section 1, p.10).

The cases are first examined in respect of the week of attendance at which the first puncture was done. One hundred and twenty-three cases showed negative Wassermann reaction when first examined.

Table 2.

C.S.F. which showed a negative Wassermann reaction, grouped in respect of the week of treatment at which lumbar puncture was first done.

Sex and stage of disease.	Week at which puncture done.							Latest week in group 100+
	Earliest week in group-20	-20	20 to 40	40 to 60	60 to 80	80 to 100	+100	
M.1. D.G.+ W.R.-	17	4	0	4	4	1	1	142
M.1. W.R.+	11	4	7	5	1	3	10	255
F.1. W.R.+	16	0	0	0	1	2	3	206
M.2.	17	2	6	6	5	5	16	208
F.2.	13	5	4	3	7	3	11	607
Total cases		15	17	18	18	14	41	

This table calls for no comment at present other than that it shows a great diversity in the times at which the fluid was examined.

Only twenty-two cases showed a Wassermann reaction other than negative on first examination.

Twelve of these fluids gave a suspicious reaction.

Table 3.

Suspicious W.R. of C.S.F. x time when lumbar puncture first performed.

Sex and stage of disease.	Week groups.					
	-20	20-40	40-60	60-80	80-100	100+
M.1. W.R.+	1					
M.2.	1	1	1			
F.2.	2		1	1	1	3

Six fluids gave a weak positive reaction on first examination.

Table 4.

Weak positive W.R. of C.S.F. x time when lumbar puncture first performed.

Sex and stage of disease	Week groups					
	-20	20-40	40-60	60-80	80-100	100+
M.1. D.G.+WR.-						1
F.1. W.R.+			1		1	1
F.2.				1	1	

Four fluids gave a positive reaction on first examination.

Table 5.

Positive W.R. of C.S.F. x time when lumbar puncture first performed.

Sex and stage of disease.	Week groups.					
	-20	20-40	40-60	60-80	80-100	100+
M.2.		1				
F.2.					1	2

These tables are combined in order to show contrasts. For reasons later to be discussed, these cases which gave a suspicious Wassermann reaction are kept separated from those showing a weak positive or positive result, which are combined.

Table 6.

Negative, suspicious and positive C.S.F. x time of puncture.

Case group	Week groups.					
	-20	20-40	40-60	60-80	80-100	100+
Negative	15	17	18	18	14	41
Suspicious	4	1	2	1	1	3
Positive		1	1	1	3	4

The total number of cases is not a great one. It shows, however, that apart from the latest time group there has been a remarkable even time distribution in performing lumbar puncture. The table suggests that suspicious reactions occur more frequently in the early stages of treatment, and that there is a tendency for weak positive results to appear more frequently as time elapses.

The ultimate fate, clinical and serological, of those cases which received lumbar puncture is now considered.

Of the 123 cases giving a negative Wassermann reaction in the cerebro-spinal fluid on first examination, further lumbar puncture was performed on nine. Of these, seven were found again to present a negative Wassermann reaction in the C.S.F. In the other two cases the result was suspicious. These were two cases of secondary syphilis in the female and the details of these cases are:-

Case No. 2221, age 31, a latent secondary syphilis received 9.9 grams of "914", 3.6 grams of Bismuth metal, sixteen weeks of mercury by mouth and potassium iodide by mouth for fifteen weeks before her C.S.F. was found, at the fifty-fifth week, to be negative to the Wassermann reaction. Thereafter she received two injections only,

of metallic Bismuth, and Mercury by mouth for a further fifty-one weeks. At the 128th week the Wassermann reaction of the C.S.F. was suspicious, but later still it was again negative. Numerous examinations were made of the Wassermann reaction of the blood serum. Apart from the original positive result they were all negative except for one between the sixth and the twelfth months, and one just after the twenty-fourth month of attendance, which were suspicious. At no time have there been any clinical signs of disease. She has been under observation for 91 months. She is considered to have neuro-syphilis.

Case No. 955, age 28, a secondary syphilis of moderate severity, received 6.45 grams of "914", 10 c.c. Calomel cream, twenty weeks of oral mercury and ten weeks of potassium iodide before her lumbar puncture, at the forty-fifth week, which showed a negative Wassermann reaction. Thereafter she received additionally sixteen weeks of oral mercury and 4.7 grams Na.I. intravenously. At no time was there any clinical relapse or signs of neuro-syphilis. The Wassermann reaction of the C.S.F. was suspicious at the hundredth week. At no time after becoming negative did the Wassermann reaction of the blood relapse. She attended for twenty-five months.

In none of these 123 cases of early syphilis were any clinical relapses noted. At the time when they were last observed, the Wassermann reaction of the blood serum was negative in one hundred and seventeen cases, suspicious in two cases, weak positive in none and positive in four cases. None of the cases in which the blood serum showed a suspicious or positive Wassermann reaction had a further cerebrospinal fluid examination. None of the cases at any time showed clinical signs of involvement of the nervous system.

The percentage of negative serological results, at the end of observation in these 123 cases, is higher than in the series of 570 cases as a whole. This may be explained by the fact that a number of patients, after satisfactory treatment and a negative blood serum, were subjected to lumbar puncture in an attempt to say that such cases might provisionally be regarded as cured, such patients thus qualifying for admission to this group of 123 cases. Such tests would tend to be performed in the later time groups.

The cases, twenty-two in number, in which the C.S.F. was not negative to the Wassermann test on first examination, are now considered.

In presenting them, the following information is given:-

1. Case groupings. Male or female primary; Dark ground positive; Wassermann reaction negative; (M1 DG+ W.R.-), (F.1 DG+ W.R.-). Male primary or female primary; Wassermann reaction positive; (M.1 W.R.+), (F.1 W.R.+). Male or female secondary syphilis; (M.2), (F.2).
2. Case number.
3. Week at which C.S.F. was first examined.
4. Treatment given in first course. "914" shown to nearest gram by figures. Bi. indicates intramuscular metallic bismuth. Hg. indicates intramuscular mercury. K.l. signifies that oral potassium iodide was given for more than three weeks during the course.
5. Total treatment antecedent to lumbar puncture: this is only indicated by symbols as above in 4. where additional treatment was given. The oral administration of mercury is ignored.
6. Total treatment received by the patient at the clinic.
7. Any clinical relapse or development of signs of neurosyphilis.
8. The total time of attendance of the patient expressed in months.

9. The final Wassermann reaction of the blood serum.
" + " indicates a positive Wassermann reaction, " W " a weak positive, " S " a suspicious result, " - " a negative result.
10. The further results of examination of the cerebrospinal fluid. Any increase in the cell count is noted.

The twelve cases in which the C.S.F. showed a suspicious Wassermann when first examined are now detailed.

Table 7.

Data concerning suspicious results in C.S.F. examination.

Case group.	No. C.S.F.	Week of C.S.F.	Ist. course As. to near-est gm. Metal	Total treatment antecedent to C.S.F.	Total treatment received	Clin. Rel.	Time of attendance in months.	Final W.R. Blood C.S.F.
M.1	1561	18	-7 +Hg.+Kl.			-	19	-
	1504	15	-7 +Hg.		-2L Hg. Bi. Kl.	-	33	- S., S, S.
M.2	1673	20	-6 +Hg.			-	34	-
	2765	40	-4 +Bi.	-6 +Bi +M		-	11	-
F.2	1625	18	-7 +Hg.+Kl.			-	20	-
	1494	18	-7 +Hg.		-13 Hg. Bi. Kl. NaI.	-	18	- S
	2260	46	-6 +Bi.+Kl.	+Hg.	-12, Hg. Bi. Kl.	-	52	-
	1284	62	-7 +Hg.	-14 -Hg.	-Bi. NaI.	-	20	- S
	1110	91	-3 +Hg.			-	33	-
	1484	138	-6 +Hg.		-Hg.	-	41	- S
	1446	145	-4 +Hg.	-6 +Bi +Hg.		-	52	-
	3512	175	-6 +Bi.+Kl.			-	48	- S

The majority of these cases received adequate treatment and were observed for a reasonable period. None developed any clinical signs of disease. None had other than a negative blood Wassermann reaction when last seen. It is striking to note that five out of the eight to receive further lumbar puncture, again showed a suspicious reaction in the C.S.F. to the Wassermann test. The significance of this reaction is not clear. It is concluded in the section dealing with Wassermann relapse in the blood serum, that a reaction of the grade suspicious must be regarded as a "therapeutic positive", and that such cases require further antisyphilitic treatment. In the cases of C.S.F. now under review no clinical disease has been seen up to a period of forty-eight months observation. Although there are no clinical signs, yet the period is too short and the cases too few in number to permit of the deduction that a Wassermann reaction of the grade suspicious is of no importance. The cases are blood Wassermann negative and have received adequate treatment. It is therefore considered desirable that such cases should receive no further treatment, but that they should be kept under observation, and that, from time to time, the cerebrospinal fluid should be examined.

The six cases in which the C.S.F. gave a weak positive reaction to the Wassermann test when first examined are now considered.

Table 8.

Data concerning Weak positive W.R. results in C.S.F. examination.

Case Group.	No.	Week of C.S.F.	Ist. course As. to near-est gm. Metal	Total treatment antecedent to C.S.F.	Total treatment received	Clin. Rel.	Time of attendance in months.	Final W.R. Blood C.S.F.
M.1 DG+ WR-	1530	140	-7 +Hg. +Kl.		-8 +Bi +Kl +Nal.		39	- at 168th week
	826	56	-6 +Hg.	+Hg.		-	28	-
F.1 W.R.	607	94	-7 +Hg.	-8 +Hg.		-	23	-
	352	111	-7 +Hg.	+Hg.		-	27	- at 117th week
	3396	52	-7 +Bi. +Kl.	-9+Bi.+Kl.	-30+Bi+Hg+Kl+Nal.	Shingles	56	- at 230th week
F.2	342	93	-6 +Hg.	-10+Hg.+Kl.	-12 +Hg. +Kl.	-	36	S at 104th week

There is little further to add to this table.

Case No. 3396 showed a Wassermann fast condition of the blood serum for four and a half years in spite of much treatment. Since these notes were compiled a further fifteen months has elapsed and this patient has received much additional treatment. The Wassermann reaction of the blood is now negative and another examination of the C.S.F. also yielded a negative serological result.

So far as these few cases are concerned, the presence of a weak positive Wassermann reaction in the C.S.F. has been transient, and has not been accompanied by any clinical signs of disease.

The four cases in which the C.S.F. yielded a positive Wassermann reaction when first examined are now tabulated.

Table 9.

Data concerning positive W.R. results in C.S.F. examination.

Case Group	No. C.S.F.	Week of C.S.F.	1st. course As. to near-est gm. Metal	Total treatment antecedent to C.S.F.	Total treatment received	Clin. Rel.	Time of attendance in months.	Final W.R. C.S.F.
M.2.	1448	34	SS.	SS +	SS.F. Hg. Nally. Oral	?	13	Blood C.S.F.
F.2.	1789	88	-6 +Hg.	-9+Bi.+Hg.+Kl.		-	62	-
	3516	144 (120 cells)	-6 +Bi +Kl	-10+Bi+Hg+Kl.	-23 +Bi +Kl	-	48 ^A	- + 152nd week, 175 cells. - 199th week, 0 cells.
	1061	124	-7 +Hg.	-14 +Hg. +Kl.	-23+Bi+Hg+Kl	-	132 ^A	+ 124th week - 182nd week W 231st week + 261st week W 293rd week ? 458th week (15 cells)

Case No. 1448, treated with silber salvarsan, defaulted after lumbar puncture to return at the end of thirteen months only to default again. He cannot be regarded as having received adequate treatment. He was not adequately examined clinically on his return after default.

Case No. 1789, age 24, whose syphilis was of three months standing, presented a general adenitis and leucoderma of neck. One notes the often quoted association of leucoderma and C.S.F. abnormality.

Case No. 3516, age 28, with a history of disease of eight months duration, had had a rash, sore throat and loss of hair, but, on examination, presented no clinical signs of disease.

Case No. 1061, a female, age 20, showed slight secondary signs, comprising mucous patches and superficial ulceration of the mouth. She received much treatment, is still under observation, and at her last lumbar puncture showed a cell count of fifteen. In spite of the absence of clinical signs she must be considered as a possible candidate for neuro-syphilis. She has been under observation for one hundred and thirty-two months.

In those cases exhibiting a weak positive or positive Wassermann test of the C.S.F., no clinical relapse was noted.

It is interesting to compare the corresponding blood Wassermann results. These are shown side by side in a table expressing six monthly periods of time.

Table 10.

Case group and number	<u>Time in months.</u>											
	-6	-12	-18	-24	-30	-36	-42	-48	-54	-60	+60	
<u>M.L. DG+ WR-</u> 1530	-						- W	- -				
<u>F.1. W.R.+</u> 826			- W		-							
<u>F.1. W.R.+</u> 607				- W								
<u>F.1. W.R.</u> 352				- W								
<u>F.2.</u> 3396	+	W	- W	W	+	+	+	S+	+	+	+	
<u>F.2.</u> 342	+	W+		S+	S							
<u>M.2.</u> 1448												
<u>F.2.</u> 1719	-					Defaulted	Defaulted		2 cells			
<u>F.2.</u> 3516	-											
<u>F.2.</u> 1061	-		W		+		S	S	+	W	W	
	<u>66</u>	<u>72</u>	<u>78</u>	<u>82</u>	<u>90</u>	<u>96</u>	<u>102</u>	<u>114</u>	<u>120</u>	<u>126</u>	<u>132</u>	
												15cells

It is seen that there is no correlation between the Wassermann results of the blood serum and the cerebro-spinal fluid. Therefore no conjecture may be made from the result of the examination of the one, in respect of the serological result of the other fluid. Note particularly case Nos. 3396, 342 and 1061.

It is regretted that the systematic counting of the cells in the cerebro-spinal fluid has not, for reasons connected with organisation difficulty, been done in all the lumbar punctures. It has been a routine now for some years and it is felt to be of the greatest value, but it is thought unwise to base any personal deductions upon the small number in this series, more particularly as only in one case, No. 1061, has a significant increase, to fifteen, been found in conjunction with a negative Wassermann result. Certain other observations have been made of a comparable nature during the cerebro-spinal fluid examination of cases of late syphilis. Support is given to the expression of opinion in the American Series, "Co-operative Clinical Studies in the Treatment of Syphilis", in Venereal Disease Information, May 1932, p.173, where it is said "In spite of its lack of specificity, the increased cell count is, in the presence of a syphilitic infection, a finding of the utmost importance as an index of involvement of the nervous system

early in the course of the disease". A word of caution is, however, advisable here lest one is tempted to project this pleocytosis on to the patients' future as too strong an unfavourable prognostic omen. Thus Kyrle^{1&2} considers abnormal reactions of the C.S.F. during the first year in primary and secondary syphilis, usually to be of a fleeting nature, and Horgan³ quotes Ravaut as regarding minor C.S.F. changes in the first three years of no particular moment. Yet, as Horgan points out, changes in the third year tend to be diagnostic, and so the prophylactic advantage of becoming acquainted at an earlier date with any minor deviation from the normal is lost.

Similarly, and for similar organisation difficulties, there is only little information to offer concerning the increase or otherwise in the protein content of the C.S.F. This examination has also been more frequently performed of late and it is roughly comparable to the cell increase, provided that the cell increase be to fifteen per c.m.m. or over. The cell count is considered much the more important method of examination. The number of cases examined by Lange's colloidal gold reaction has been too small to permit of any deduction whatever.

1. KYRLE, J. Uber lumbal punktur. Wiener Klin Wchnschr, 1921. No. 15.
2. KYRLE, J. Welchen Wert. Nat die Liquor Kontrolle bei Syphilis, etc. Wiener Klin Wchnschr, 1920. No. 42.
3. HORGAN. Modern Aspects of Syphilis, 1923, p. 50 et seq.

Before proceeding to a discussion of what should be the clinic's future practice, these figures are contrasted, so far as they be comparable, with the information given in the American series. These tables, not otherwise specifically to be referred to, are found in Venereal Disease Information, May 1932, pp. 179-181, and their discussion in June 1932, pp. 221-229 and July 1932 pp. 278, 284, 289 and 292.

Table 11.

Series	Total examination	Total W.R. not neg. and not "Susp."	Suspicious
American	1747	209	-
This series	145	10	12

Table 12.

	American		This Series.		
	Total cases	W.R. not negative	Total cases	W.R. not neg and not susp.	Susp.
Primary sero-neg.	193	15	15	1	
Primary sero-pos.	309	20	40	3	1
Secondary	1245	164	90	6	11

Tables 11 and 12 show extremely similar percentage results in both series.

Table 13.

Series.	C.S.F +	<u>BLOOD W.R. RESULT</u>		
		Negative	Positive	Suspicious
American	228	34	187	-
This series	10	8	2	0

The figures in this series are too few in number to permit of any deduction, yet it is interesting to note the preponderance of positive blood Wassermann results in those cases which presented a positive cerebro-spinal fluid. The American figures were obtained from five large clinics and each clinic indicates a different method by which the Wassermann reaction is to be performed.

The cases are next examined in terms of the persistence of a positive Wassermann reaction of the blood serum during the first six months of treatment, in an attempt to ascertain if such cases are likely to develop neurosyphilis.

Table 14.

Relation of W.R. fastness (for $\frac{6}{12}$ or more) in blood serum to C.S.F. abnormality.

	Abnormal C.S.F.	Wassermann fast
American	228	104
This series		
W.R. + or W	10	2
W.R. Susp.	12	2

The two cases in our series in the positive group in Table 14 were the same two as in the preceding table, although, prior to lumbar puncture, both cases had shown serological variation in the blood serum.

There is now shown the total blood Wassermanns which remained positive for the first six months in the five hundred and seventy cases of early syphilis which attended this clinic.

Table 15.

Early Syphilis x W.R. fast for $\frac{6}{12}$

Total Cases	570
Total W.R. fast for first $\frac{6}{12}$	32

This information is not obtained in the American figures.

The American report states that more than forty per cent of those who show a positive W.R. in the C.S.F. are Wassermann fast (blood), and that the failure of the blood Wassermann reaction in early syphilis to respond in the first six months of treatment is an intimation of the presence of asymptomatic neuro-syphilis. In the cases attending this clinic there is a figure of twenty per cent as regards the first part of this statement, and in respect of the second part, out of thirty-two cases which were Wassermann fast (blood) for the first six months, the W.R. of the C.S.F. was negative in nine, suspicious in two, weak positive or positive in two and not done in nineteen. There is considerable agreement between the two sets of figures although, of course, the numbers of this series are very small.

The American series had 1.7% of clinical neuro-syphilis in early secondary syphilis prior to treatment - always an acute syphilitic meningitis. There are none here - nor would such cases tend to be sent to an outdoor venereal dispensary.

The Americans had a considerable number of C.S.F. persistently abnormal in respect of being themselves Wassermann fast. i.e.

Sero negative primary	2 cases	= 0.6%
Sero positive primary	6 cases	= 1.0%
Early secondary	30 cases	= 1.3%
Late secondary	4 cases	= 6.2%
Total	42 cases	= 1.3%

Here there are no Wassermann fast C.S.F. results and there are only five final suspicious results out of twelve original suspicious cases, all in secondary syphilis, and two suspicious results out of ten original weak positive and positive results, both in cases of secondary syphilis. It is noted that out of twelve original suspicious results, four were in males and eight in females; that out of ten weak positive and positive, two were in males and eight in females, but that six out of the final suspicious results on final lumbar puncture occurred in females, and all occurred in cases of secondary syphilis. But it is again emphasised that a "suspicious" reaction is not considered, and is indeed shown not to be sufficient, to give rise to much apprehension concerning the future of the case.

The Americans found, out of 3,244 cases of early syphilis, 132 cases, or 4.1%, to give evidence of "Neuro-syphilis, clinical or serological". As they examined 1747 by lumbar puncture and found abnormalities in 572, or 32.7%, this statement requires further elucidation, which will appear in their later studies. One can only say that none of our five hundred and seventy patients have so far developed any clinical signs of neuro-syphilis. In view of the inadequacy of the treatment of many - in view of the number of cases of neuro-syphilis the clinic has treated - the fact of this present good fortune can only be stated and appearance of neuro-recurrence must be looked for. Stress is laid on the fact that the cases periodically undergo a thorough medical examination, and it may be pointed out that clinical neuro-syphilis, to a trained observer, does not hide its light under a bushel. Two cases of Bell's paralysis have developed in cases of early syphilis, both to clear up satisfactorily and both to show negative W.R. reactions in the C.S.F.; and there has been one case of numbness and tingling in the forearms, transitory in type, unaccompanied by any C.S.F. abnormalities, possibly related to the administration of "914", but banished by a week's rest, aided by an alkaline diuretic mixture.

The American report states, p. 275, "Even thorough going treatment does not protect, necessarily, against the development of abnormalities in the spinal fluid (much treatment prior to the development of the abnormality had been given in 45.6% of 101 cases who developed abnormal fluids in spite of treatment)."

Out of the ten weak positive and positive W.R. results in this series, nine had had a typical first course, six of these had had further arsenical treatment and might be deemed adequately treated, and in these six the C.S.F. abnormality was found at from one year onwards.

Of the twelve suspicious W.R. results in the C.S.F., nine had had a normal first course, and four had had further "914" treatment. Here, however, the C.S.F. was examined in five cases before the twentieth week - and again the result of the W.R. of the C.S.F. seems to be of little significance.

It is not possible then to advise any special alteration in methods of treatment of early syphilis employed in this clinic with the design of preventing C.S.F. Wassermann changes, and it appears that the incidence of abnormality when taken in conjunction with the end results, clinical and serological, as noted previously, is not sufficiently serious to warrant a search for a change. Other factors

must determine any suggested alterations in treatment.

This same absence of permanent ill effects may be otherwise stated thus: In the experience of this clinic the alterations found in the Wassermann reaction, on examining the cerebro-spinal fluid in early syphilis, are amenable to treatment and are not so far followed by signs of clinical involvement. Some of these alterations in the suspicious series occurred in the first six months, the others at varying times up to the one hundred and seventy-fifth week. In the weak positive and positive series, one was seen under one year, one at one year and the rest at times up to nearly the end of the third year. This would seem to be in accord with those opinions quoted from Kyrle and Horgan - that the earlier changes are not of permanent importance.

One is prepared as a result of the review of this series of cases to state:-

All cases of early syphilis require lumbar puncture at some time in the course of treatment and observation. In addition to the Wassermann reaction, the cell content should be ascertained. There is no need to do lumbar puncture prior to the conclusion of systematic treatment with "914" and metal except in the event of clinical neuro-syphilis.

It is not advisable to do lumbar puncture in cases whose blood Wassermann reaction is strongly positive unless

much treatment has been given, for there is always the minor danger of conveying infection to the cerebro-spinal fluid. Therefore it is definitely suggested that in Wassermann fast (blood) early syphilis, lumbar puncture be not done during the first year except for special reasons which will rarely arise, besides, treatment will, in such cases, naturally be continued.

Although it has been found that changes in the cerebro-spinal fluid which occur during the first two and a half years are amenable to treatment, the fact remains that such cases have received treatment.

It would seem desirable to continue to treat such cases, for although none of this series have developed clinical syphilis, the probability that such early changes may disappear spontaneously, should not be allowed to obscure the possibility of the later development of clinical neuro-syphilis.

It is therefore advised that the cerebro-spinal fluid be examined at a date some six months after the cessation of intravenous and intramuscular treatment. Most cases in this country receive mercury by mouth over a prolonged observational period, and it is suggested that a six months wait after systematic treatment is concluded will, in the first place, allow the full extension of any therapeutic

value from injections received, and, in the second place, will not be long enough to allow the majority of cases to default, for most of the patients who do complete injection treatment are willing to attend for a reasonable period of probation. There are, nevertheless, numerous cases of neuro-syphilis, and of these a number that have been seen received fairly good antecedent treatment in the early stages. There is, therefore, need for a further examination of the cerebro-spinal fluid in all cases of treated early syphilis. The evidence as to the most favourable time when this should be done must, owing to the absence of early neuro-syphilis in this clinic, be deduced from the developed cases of neuro-syphilis and is not presented here. It may be stated, however, that, if an examination of the cerebro-spinal fluid in adequately treated early syphilis were to prove negative at the end of the fifth year, few cases of neuro-syphilis would develop. It should be, however, clearly recognised that only a very small fraction of clinic patients will attend for such a period of time. It then becomes a more debatable matter as to the time at which the first lumbar puncture, which, if negative in results, will often be the last one, should be done. No rigid rule can thus be laid down. In the average young adult, healthy, apparently cured, finished with treatment,

desirous of marriage, desirous of forgetting his past completely, insufficiently educated (one does not desire to rear a race of syphilophobes), two to three years is the maximum time one can expect him to listen to authority's voice. In such cases, it is suggested that the most favourable time for a single puncture is at the end of the second year when, as is the custom in most clinics, treatment is stopped and the idea of "cure" is first presented strongly to the patient's mind. This will allow some time to elapse if very early cerebro-spinal fluid changes may be regarded as transitory, and it will prevent too long a period for any persistent C.S.F. changes to develop into clinical signs. Yet, in Table 6, there is pointed out a tendency for abnormal Wassermann reactions to increase slightly in percentage after the hundredth week, and Tables 7, 8 and 9 show that this is not the expression of gross irregularities in their first course of treatment or in subsequent arsenical treatment. Therefore the adoption of a single puncture at the end of two years must be regarded only as a matter of clinic expediency. At present it will be adopted in our cases, for there can really be little disadvantage to the patient in waiting, under observation, the further six or eight months required to extend the time at which it has been indicated as best to be done.

Efforts will be made to induce the patient to have a further lumbar puncture at the end of the fifth year. The minimum examination of the cerebro-spinal fluid that is considered necessary must be a cell-count and a Wassermann reaction.

Appendix giving details of all cases receiving lumbar punctures.

The cases are shown by sex and stage of disease.

No. = Case number.

Age = Age of patient on first coming to clinic.

1st course - As. = "914". Other varieties of As. stated by initial letters.

Bi. = Metallic bismuth given by intramuscular injection.

Hg. = Mercury given as Calomel cream by intramuscular injection.

Quantities of "914" and Bi. shown in grams; of Hg. in grains.

Kl = gr. 15 potassium iodide t.i.d. :-
time given expressed in weeks.

Total treatment before C.S.F. Symbols as before.

Pills = Hutchinson's Pills, one thrice daily.

Week of C.S.F. is the week in patient's attendance at which lumbar puncture was done.

The other headings are self explanatory.

Male Primary W.R.+ Cerebro-Spinal Examinations, Negative Results.

No.	Age	Lst. Course				Total treatment before C.S.F. Weeks of				More Treatment	Final W.R.			
		As.	Bl.	Hg.	Kl.	As.	Bl.	Hg.	Pills Kl.			C.S.F.		
1648	29	4.85		8						11				
3534	34	4.95	2.0							28				
3562	27	4.65	1.6							139				
1021	20	5.2		10						48				
1671	26	5.4		12						15				
1917	21		34IBQ							47				
2758	34	5.55	2.4bic.		9					255				
2761	28	5.85	2.2		14					107				
3158	29	5.55	2.6							243				
2468	23	5.55	2.8bic		13					26				
3341	32	5.55	2.4bic		3					88				
2448	27	5.55	2.4		10					82				
3927	34	5.85	2.6		14					100				
373	30	6.75		12	1					120				
535	29	6.45		10						94				
785	30	6.55		11	3					55				
1024	24	6.45		10	4					26				
1240	19	6.75		3	3					17				
1155	18	6.75		12	3					22				
1263	20	6.75		11	3					19				
1087	23	6.75		9	3					35				
1570	24	6.3		11	3					24				
1434	24	6.75		10	2					26				
1724	25	6.3		10	3					47				
3200	19	6.0	2.2		1					197				
3836	43	6.0	1.4		5					131				
3406	34	6.3	2.4		14					165				
830	26	6.3		10						56				
89	24	10.5		5	4					148				
1180	28	4.5		8						64				

Male Primary W.R.+ Cerebro-Spinal Examinations, Suspicious Results.

1st. Course				Total treatment before C.S.F.				Weeks of C.S.F.	More Treatment	Final W.R.					
No.	Age	As.	Bi.	Hg.	Kl.	As.	Bi.	Hg.	Pills	Kl.	Weeks of C.S.F.	More Treatment	Bd.	C.S.F.	Final W.R.
1561	30	6.75		12	12						18	+	-	-	-

Male Primary D.G.+ W.R.- C.S.F. negative.

1st. Course				Total treatment before C.S.F.				Weeks of C.S.F.	More Treatment	Final W.R.					
No.	Age	As.	Bi.	Hg.	Kl.	As.	Bi.	Hg.	Pills	Kl.	Weeks of C.S.F.	More Treatment	Bd.	C.S.F.	Final W.R.
1444	38	3		5		4.8		8	8		61	+	-	-	-
929	21	3.5		9	1	6.75		12	24	2	54	+	-	-	-
2121	23	5.4	2.4		3						19	+	-	-	-
2935	44	5.7	2.4		13	5.7	2.4		24	16	87	+	-	-	-
1768	37	5.4		11	1	5.4		11	22	2	42	+	-	-	-
1965	34	5.7		12	2	7.35	.6	12	32	2	142		-	-	-
2685	20	5.55	2.4		15	8.1	3.4		16	20	47	+	-	-	-
1178	31	6.75		9	3	6.75		9	16	3	19	+	-	-	-
984	22	6.45		12	2	6.45		12	20	2	43	+	-	-	-
1251	29	6.75		11	2						18	+	-	-	-
1135	35	6.75		11	3	12.75		15		5	68	+	-	-	-
1309	28	6.75		12	2				4		17	+	-	-	-
2338	30	6.45	2.2		6	9.45	2.6		16	17	73	+	-	-	-
763	28	7.5		12	2	7.5			28	2	74	+	-	-	-

C.S.F. Not negative

1st. Course				W.R. of C.S.F.				Week of C.S.F.	More Treatment	Final W.R.					
No.	Age	As.	Bi.	Hg.	Kl.	As.	Bi.	Hg.	Pills	Kl.	Week of C.S.F.	More Treatment	Bd.	C.S.F.	Final W.R.
1530	22	1.5		4							140	+	-	-	-

Female Primary W.R.t, C.S.F. negative.

No.	1st. Course				Total treatment before C.S.F.				Week of C.S.F.	More Treatment	Final W.R.				
	Age	As.	Bi.	Hg.	Kl.	As.	Bi.	Hg.				Pills	Kl.	Cells	
3587	37	2.1	2.0			2.1	8.8			14		90	+	-	Bd. C.S.F.
2643	26	3.15		+		8.75	3.5	26	9			112	+	-	
3041	20	5.55			8	7.9	1.8	20	15			85	+	+	
3668	26	5.7	2.4		14	9.75	3.8	8	23	10		158	+	-	
3908	28	5.4	2.2		12	11.25	4.6	16	23			66	+	-	
3345	19	6.45	2.4		3	12.15	3.0	116	3			206		-	

C.S.F. not negative.

No.	1st. Course				Total treatment before C.S.F.				W.R. Cells	C.S.F. ment	Week of Treatment	More Final W.R.			
	Age	As.	Bi.	Hg.	Kl.	As.	Bi.	Hg.					Pills	Kl.	
826	28	5.4		7	2			20				56	+	-	
607	25	6.75		12	2	7.65	12	54	2			94	+	-	
352	36	6.15		8	2			64				111		-	six weeks later.

Male Secondary. C.S.F. examination, results negative.

No.	1st Course				Total treatment before C.S.F.				Week of C.S.F.	Cells W.R.	More Treatment	Final W.R.		
	Age	As.	Bi.	Hg.	Kl.	As.	Bi.	Hg.					Pills	Kl.
3461	27	2.55	1.2		6	11.4	5.0		72	25		167	-	-
3291	35	1.7 AB				10.7	3.6		20	16		120	-	-
1376	31	1.95SS			5							27	+	-
1393	19	3		3		8.85		7	12	1		47	+	-
2893	25	4.95	2.2		14							17	+	-
1850	28	3.75	1.6	4½	3	6.9	1.6	4½	4			31	+	-
811	27	6.45		11	2	6.45		11	20	2		60	+	-
157	50	4.5		5	3	4.5		5	8	3		118	+	-
4072	40	5.85	2.4		14	9.9	4.2		48	24		86	+	-
4032	26	5.85	0.8		3	10.35	6.2	8	51	3		91	+	-
3890	34	5.85	2.4	8	13	11.70	4.8		60	26		121	-	-
3655	23	5.85	2.4		14	11.70	4.6		66	25		114	-	-
3881	35	5.85	2.6		15	11.70	5.4		36	29		107	-	-
3616	41	4.8	1.4		10	10.65	3.8		72	22		131	-	-
3481	28	5.55	2.4		3	8.4	2.8		92	3		153	+	-
2495	24	5.7	2.8		14	8.55	3.8		32	14		63	+	-
1792	25	5.7				5.7		8		3		38	+	+
1791	31	5.55				5.55			8			22	+	-
1725	26	5.1		6	3							22	+	-
1702	26	5.55		12	3	5.55		12	24	3		41	+	-

Male Secondary. C.S.F. examination, results not negative.

1448	32	2.15SS			3	3.1SS						661.v.	34	+	+	-	+
2765	19	3.75	1.6		61.v.	5.55	2.4		8			61.v.	40	+	+	-	-
1673	23	5.4		8	3							20	20	+	+	-	-

Male Secondary. C.S.F. examination, results negative.

1st. Course										Total treat. before C.S.F.			Week of C.S.F.		Cells W.R.		More Treatment		Final W.R.	
No.	Age	As.	Bi.	Hg.	Kl.	As.	Bi.	Hg.	Pills	Kl.	C.S.F.	Week	W.R.	Cells	Treat-	ment	W.R.	Final	W.R.	
987	30	5.6		11	2	5.6		11	20	2	57				+					
1169	30	5.25		10	3	13.05		22		4	78				+					
188	22	5.25		7		12.9		16	52	1	142				-					
302	23	5.25		8	8	12.0		17	66	3	141				+					
5346	30	6.0	1.8		2	6.0	1.8		20	2	45				+					
1450	23	6.75		11	3	6.75		11	8	3	50				+					
1280	18	6.75		9	3	6.75		9	4	3	18				+					
1158	34	6.2		11	1	6.2		11	4	1	24				+					
1094	30	6.75		12	6	6.75		12	16	6	40				+					
1123	35	6.75		12	3	12.15		19	16	6	67		0		+					
561	21	6.0		10	1	8.25		14	28	1	84				-					
647	30	6.75		12	3	6.75		12	46	3	69				+					
560	39	6.75		10	2	6.75		10	36	2	97				+					
597	26	6.55		11	2	10.9		11	60	2	91				+					
805	27	6.75		11	2	6.75		11	8	2	208				-					
49	23	6.0		3		16.2		8	36	4	184				-					
251	23	6.0		8		11.15		16	44	1	196				-					
309	24	6.0		9		13.65		16	40		176				+					
43	28	6.0		6		11.25		6	24	5	184				-					
768	24	8.25		11	3	16.5		22	30	5	156				+					
Male Secondary. Results not negative.																				
1504	29	6.3		4	2	6.3		4	4	2	15		W.R.	S				S.	S.	

No.	Female Secondary.				C.S.F. examination, negative results.				Final W.R.						
	Age	1st. Course		Total treatment before C.S.F.		Week of C.S.F.	More Treatment	Ed. C.S.F.							
		As.	Bl.	Hg.	Kl.					As.	Bl.	Hg.	Pills	Kl.	Cells
859	31	4.50		9	1	4.50	9	48	11		68	+	-	-	
1607	34	4.95		8	3	4.95	8	4	3		22	+	-	-	
2575	29	3.75	2.9			7.7	3.9	16	6		79	+	2	-	
3647	35	4.65	2.2		5	4.65	4.8	76	23		172		-	-	
4081	28	5.25	2.4		11	11.1	3.0	24	24	0	82		-	-	
3912	17	5.85	2.4		14	11.70	4.8	36	26		78		-	-	
3892	28	5.85	2.4		3	11.7	5.0	44	8		113		-	-	
3677	36	5.85	2.2		14	10.5	4.0	52	23		116		-	-	
3395	24	5.55	2.8			9.45	4.4	88	4		196		-	-	
2711	27	5.40	2.4		9	10.80	2.6	8	20		87	+	-	-	
2221	31	5.85	2.2		7	9.9	3.6	16	15		55	+	-	-	
														-	S, 4 cells 128 wks.
1657	19	5.55		8	3	5.55	8		3		21	+	-	-	
1705	29	5.55		12	4	5.55	12	8	4		29	+	-	-	
1557	55	5.7		3	3	5.7	3		3		16	+	-	-	
1113	29	5.25		9	3	7.4	9	24	4		78	+	S	-	
233	35	5.55		5	5	7.2	8	12	5		114	+	-	-	
355	33	6.45		9	1	23.25	13.4	76	64		607		-	-	
362	31	6		10	2	15.75	27	27	2		114	+	+	-	
363	26	6.75		9	1	6.75	9	76	1		119	+	-	-	
955	28	6.45		10	10	6.45	10	20	10		45	+	-	-	
														-	S, 100 weeks.
1258	34	6.45		11	3	6.45	11		3		19	+	-	-	
1004	30	6.45		12	1	6.45	12		1		13	+	-	-	
1074	21	6.45		11	4	6.45	11	4	4		18	+	-	-	
643	21	6.15		8	3	7.6	8	24	12		68	+	-	-	
904	36	6.75		11	2	10.95	19	12	2		107	+	-	-	
2740	22	6.05	2.4		15	6.05	2.6	16	15	4	40	+	-	-	
3067	36	6.3	2.6		1	11.85	5.0	52	12		136	+	-	-	
3326	35	6.75	2.4		4	9.0	4.6	32	4		82	+	-	-	
146	24	7.20		5	5	12.15	5	32	4	1	122	+	-	-	
1508	28	7.05		11	3						16	+	-	-	
1090	27	3.00		8	8	3.00	8	28			30	+	-	-	
980	43	3.00		7	2	3.00	8	12	2		77		-	-	
4142	24	1.65	0.8		4	1.65	4.2	8	21	0	72	+	-	-	

Female Secondary. C.S.F. examination, results not negative.

No.	1st. Course				Total treat. before C.S.F.				C.S.F. result W.R.	Cells	Week of C.S.F. treatment	More Treatment	Final W.R.
	Age	As.	Bi.	Hg.	Kl.	As.	Bi.	Hg.					
1446	30	3.5	8	8	5.3	8	8	8	S	145	+	-	-
1789	24	5.15	9	1	8.3	1.0	9	56	+	88	+	-	-
3512	28	5.55	3.0	17	11.1	5.6	19	28	S	175	+	-	-
3516	28	5.55	2.6	13	9.6	4.4	68	23	+	120	+	-	-
									+	175			-
2260	23	5.85	2.2	7	5.85	2.2	16	8	S	46	+	-	-
													-
1484	27	5.65	12	1	5.65	12	72	14	S	138	+	-	-
1284	28	6.75	10		13.50	22	16	3	S	62	+	-	-
1625	23	6.3	9	3					S	18	+	-	-
													-
1494	22	6.75	11	3					S	18	+	-	-
													-
3396	22	6.0	2.4	6	8.55	4.4		11	W	52	+	+	-
										Shingles			-
1061	20	6.45	8	3	13.2	10	50	6	+	124			-
									-	182			-
									W	231			-
									+	261			-
									W	293			-
									?	458			-
342	31	6.15	10	3	22.56	4.2	20	84	W	15			-
													-
													-
													-
													-
1110	34	2.25	7		7.35	18	20	7	S	91	+	+	-
													-
													-

No clinical signs.

S E C T I O N V.

CLINICAL RELAPSES IN PRIMARY AND
SECONDARY SYPHILIS.

Pages 189-220.

Clinical relapses in primary and secondary syphilis.

This section will consider the data relevant to all cases of clinical relapse in the series of five hundred and seventy cases of primary and secondary syphilis which have been subjected to analysis in other respects.

It will exclude all cases which showed variation in the Wassermann reaction of the blood serum, or which showed abnormalities in the cerebro-spinal fluid, unless such cases also exhibited clinical signs of disease. It will also exclude such cases as might be termed a second infection of syphilis, whether such diagnosis was made at the first time the case appeared at the clinic, or at any time subsequent to that date.

The total numbers of clinical relapses occurring in each grade and sex of early syphilis are presented in the following table.

Table 1.

Sex and stage of disease.	<u>Total Cases.</u>		<u>Total Relapses.</u>	
	Male	Female	Male	Female
M1 DG+ W.R.-	48		1	
F1 DG+ W.R.-		2		0
M1 W.R.+	126		3	
F1 W.R.+		36		3
M2	172		7	
F2		186		11
	346	224	11	14
	570		25	

There is then a total of twenty-five cases out of five hundred and seventy, or 4.38%, in which some variety of clinical relapse has been noted.

Out of these twenty-five cases, only eleven received an adequate first course of treatment. Out of the five hundred and seventy cases, three hundred and eighty-six might be said to have received adequate initial treatment. There was thus a percentage of 2.8% of clinical relapse in cases receiving adequate initial treatment. No case receiving less than 5 grams of "914" is considered to have had an adequate initial course of treatment.

The standard course of treatment with the variation in dosage which has been in use in the clinic is shown for information.

Table 2.Variations in dosage of model course.

	Dosage and year introduced						
	"914"			Metal	Potassium iodide		
	1919	1923	1929	C.C. 1919	Bi. gr. 1924	xv. t.i.d. 1919	1924
1st week	.45gm.	.3gm.	.45gm.	1gr.	0.2gm.		Kl.
2nd week	.45	.45	.6	1	0.2		Kl.
3rd week	.75	.6	.6	1	0.2		Kl.
4th week				1	0.2		Kl.
5th week	.75 or .6	.6	.6	1	0.2		Kl.
6th week	.75 or .6	.6	.6	1	0.2		Kl.
7th week				1	0.2		Kl.
8th week	.75	.6	.6	1	0.2		Kl.
9th week	.75	.6	.6	1	0.2		Kl.
10th week						Kl.	Kl.
11th week						Kl.	Kl.
12th week						Kl.	Kl.
13th week	.75	.6	.6	1	0.2		Kl.
14th week	.75	.6	.6	1	0.2		Kl.
15th week	.75	.6	.6	1	0.2		Kl.
Total weight in grams.	6.75	5.55	5.85	12grs.	2.4		

Occasionally in the earlier years 0.9 grams of "914" was given in a single dose. The dose of calomel cream was 1 grain of mercury; the dose of bismuth metal was 0.2 grams.

Tables are next submitted in which all data which might be of assistance have been summarised. These data, originally taken from the clinic case sheet, were, in the first place, set down on case record cards and the tables have been constructed therefrom. As these tables will embody much of the information later to be discussed, a description of their headings is given in detail.

Each table starts with the indication of the stage and sex of the disease.

Thereafter in series the headings are :-

- No. = Case number of the patient.
Year = Year in which the patient first attended.
Age = Age of patient at date of first clinic attendance.
Type = Variety of disease.

In primary syphilis C = a clean chancre free from much secondary infection. I = chancre infected with secondary organisms.

In secondary syphilis S = slight, M = medium, F = florid and L = latent. Such terms apply to the severity of the manifestations, having regard to the duration of the disease and thus having regard to the natural history of the syphilitic process.

1st Course

- Summary of first course of treatment received at the clinic. As. = "914" substance. Figures refer to the nearest gram administered. S.S. = Silber Salvarsan. Hg. = Mercury, as calomel cream, given by intramuscular injection. Figures refer to the number of grains of calomel given and also to the number of injections, as each injection consisted of one grain. F = injections of Flumerin. Bi = intramuscular injections of metallic bismuth. Figures refer to grams administered.

Time of course

- Shows in weeks the duration of the first course.

Absence

- Shows the number of weeks after the first course during which the case was either absent, or during which the only treatment given was mercury by the mouth.

Week of relapse

- Shows the week at which the clinical relapse was noted.

Nature of relapse

- Gives a brief clinical summary of the relapse indicating thereafter, by W.R.+ or -, whether the Wassermann reaction of the blood serum was positive or negative at the time at which the relapse was first noted.

W.R. of Blood

- Gives a history of the various changes in the Wassermann reaction of the blood serum throughout the total attendance of the patient. "+" indicates a positive reaction, "w" indicates a weak positive reaction, "S" indicates a suspicious reaction, "-" indicates a negative reaction. The figures indicate consecutive six-monthly periods up to 24 months, +24 indicates times subsequent to the second year.

Total treatment

- indicates the total treatment administered to the patient at the clinic. The symbols and figures are as in the first course. Na.l. i.v. indicates the intravenous administration of sodium iodide: the figures indicate the weight of sodium iodide given in grams.

Total attendance

- Shows in months the total time during which the case attended the clinic.

Final

- Refers to the last noted observations on the case and Clin. = clinical findings; + indicates a present lesion; - indicates no lesion found.

W.R. Bd.

- Wassermann reaction of blood.

W.R. C.S.F.

- Wassermann reaction of cerebro-spinal fluid.

M 2

Table 4.

No.	Year	Age	Type	1st. Course			Time of course	Absence	Week of relapse	Nature of Relapse	Total Treatment					Na. i.v.	Total attendance	Clin.	Final		
				As.	Hg.	Bi.					-6	-12	-18	-24	+24				As.	Hg.	Bi.
1506	1922	28	S	1.85	SS.		8 12	20	Ulceration of tonsils. W.R.+	-	+	-	S	S	17	3	4.2	55	33	-	S
1750	1923	25	M		F		8 0	8	Condylomata. W.R.+	+					1	3.05F			3		+
1774	1923	21	M		F		4 32	36	Adenitis condylomata.	+					2	3.4	0.8		10		+
1169	1921	30	M	5	10		12 26	38	Mucous patches fauces. W.R.+	-	+	S	-		13	22			22	-	-
1792	1923	25	S		F		8 0	8	Frenal sore. Sp.P.+ W.R.-	-	+		+		9	8+F	2.0		19		+
1298	1922	26	M	7	12		13 11	24	After 1st. injection of 2nd course, syphilitic acne of forehead. ?J.H. reaction. Disappeared in one week.	+	-								11	-	-
768	1920	24	S	8	11		16 35	41 81	Ulcer cheek. W.R.+ Albuminuria + casts for 2 years. W.R.+	-	+	+	S	SW	16	22			53	-	-

F 2

Table 5.

486	1920	29	M	1.5	4		4 41	45	Condylomata. W.R.+	+	+				8	11			16	-	+
980	1921	43	M	.75	2		1 32	33	Ulcers on legs, scaly rash on knee and wrist. W.R.+	+	+	-			3	5			18	-	-
3845	1929	51	M	2.75		1.0	4 36	40	Iritis: condylomata.		+	+	S	-	8		3.4		29	-	-
3697	1928	29	F	3		1.6	17 In- tol.	95	Papular rash on wrists. W.R.+	-	-	+	+	S	3		4.0		30	-	S
3634	1929	29	F	3		.8	5 75+ 34	111	Gumma of larynx.	+	+	+	+		4				27	Defaulted	
802	1920	25	F	4	8		12	78	Tertiary rash back & chest. W.R.+	S	+	+	+	+	11	19			39	-	+
8	1919	40	S	6	6		9	5	Vulvar ulceration. W.R.+	+	-	+	-	-					29	-	-
4402	1931	23	S	6		1.4	15 22	37	Iritis. W.R.- .No V.D.G.	+	-				9		2.8		10	-	-
1269	1921	28	S	7	10		13 22	35	Papular rash. W.R.+	S	+	S			11	19			11	-	S
355	1919	33	S	7	9		27 291	318	Thickening of lip at site of chancre. W.R.+ W.R.+	+				+	25	9	13.4		152	-	-
2875	1926	26	S			0.6	3 40	43	R. iridocyclitis. W.R.+	+	+	+	+	+	29		15.8		72	-	+

There are, then, twenty-five cases outlined in these tables. Certain factors which seem easily to account for the condition of relapse in some of them are now noted.

In six the first course administered was of an unusual or experimental type.

Thus in the cases:-

M1 W.R.+ Case No. 2146.

M2 Case No. 1750.

Case No. 1774.

Case No. 1792.

Here the first treatment given was the intravenous injection of the mercurial preparation flumerin alone, or, in one instance, combined with a small quantity of "914".

In M2 Case No. 1506, Silber Salvarsan, 1.85 grams, was the only treatment given.

In F2 Case No. 2875, 0.6 grams of Bismuth metal given in three injections was the sole treatment received. The case then defaulted.

It is submitted that such cases merely demonstrated the complete inadequacy of their initial treatment.

Two further cases only received a small quantity of "914" spread over a long period as a result of intolerance and irregular attendance.

F2 Case No. 3697, less than three grams "914" in seventeen weeks.

F1 W.R.+ Case No. 2643, less than three grams "914" in fifteen weeks.

Six cases attended for only a short time before defaulting.
These cases received normal treatment during the weeks in
which they attended.

M1 W.R.+ Case No. 1180 attended for nine weeks.
 F1 W.R.+ Case No. 241 attended for five weeks.
 F2 Case No. 486 attended for four weeks.
 Case No. 980 attended for one week.
 Case No. 3845 attended for four weeks.
 Case No. 3634 attended for five weeks.

Again in these two groups the fact of clinical relapse seems definitely correlated with the inadequacy of the original treatment.

The remaining eleven cases of relapse received a satisfactory initial course of treatment. Out of the total of twenty-five clinical relapses, there are thus fourteen cases in which the first course of treatment was extremely deficient. It is difficult to assess this as a percentage of the total number of cases which received inadequate initial treatment. Very many cases not included in the total series of five hundred and seventy defaulted before the completion of their first course and we have no further information concerning them.

There were, however, in this series of 570 cases, 184 which did not receive an adequate first course of treatment. The 14 cases of relapse in this group thus represent a

percentage incidence of 7.6%. This is to be contrasted with the 2.8% of clinical relapse in those cases (386) which received a normal first course of treatment.

There is, in the series of tertiary cases, a considerable number of reasonably early relapses, but this figure can hardly be used for comparison as the patient's information concerning his first treatment is usually quite unreliable.

There is now shown out of this series of 570 cases, all those cases which were observed for more than two years and in which, for various reasons, the total "914" administered is considered inadequate. Such cases were usually ones which defaulted for very lengthy periods and on their return were either found apparently cured clinically and serologically, or, if not so cured, defaulted again before a reasonable amount of treatment could be given. Those cases, then, which in two years or more received less than 6 grams of "914" in all, are now given by sex and stage of disease, with a note as to whether the final Wassermann reaction of the blood was negative or fell into the positive group of reactions.

Table 6.

Cases observed for more than two years which received less than 6 grams "914".

Sex & stage of disease.	Total	Final W.R. of Blood	
		+	-
M1 DG+ W.R.-	0		
F1 DG+ W.R.-	0		
M1 W.R.+	4	1	3
F1 W.R.+	1		1
M2	2		2
F2	7	2	5
Total	14	3	11

There is also shown in a somewhat similar table such cases out of the 570 which, receiving inadequate initial treatment, defaulted for a lengthy period to return with some serological abnormality, and thereafter to receive adequate treatment. A period of twenty-six weeks default was considered necessary to include a case in this category.

Table 7.

Cases defaulting for lengthy times after inadequate treatment, to return with serological abnormality. Thereafter well treated.

Sex & stage of disease.	Total cases	Final W.R.		Final W.R. of CSF. if W.R. neg.	
		+	-	+	-
M1 DG+ W.R.-	1		1	1	
F1 DG+ W.R.-	0				
M1 W.R.+	3	2	1		
F1 W.R.+	0				
M2	4	1	3	1	
F2	6	3	3		2
Total	14	6	8	2	2

In Tables 6 and 7, out of these twenty-eight cases defaulting after inadequate initial treatment, there are seventeen, (three in the sixth table and the whole fourteen of the seventh table), who presented serological abnormality on their return, and only eleven who appeared clinically and serologically cured.

Considering then these cases, and the cases of clinical relapse noted already, it would definitely appear that treatment much short of that outlined in the standard course is inadequate and is liable to be followed by clinical or serological relapse. In the section of this thesis concerning the serial examination of the Wassermann reaction of the

blood serum in cases of early syphilis, it is stated that more than two thirds of all cases of early syphilis show a reversal of a positive blood Wassermann reaction to a negative one within twelve weeks, after receiving between 3 and 4 grams of "914" along with a heavy metal and iodide, administered in the form of the course outlined in this section. This still leaves one third of the cases to take a longer time to show Wassermann reversal, and concomitantly to receive more treatment. If, then, 14 cases of clinical relapse, in those whose initial treatment was much short of the standard course, are found, and if, out of a further 28 cases who defaulted for long periods after inadequate treatment, 17 showed serological abnormality on their return, and since there are only 11 cases of clinical relapse amongst cases receiving an adequate first course of treatment, the conclusion can be drawn from this series of cases that the commonest factor in relapse is inadequate initial treatment. Therefore, if the scheme outlined in Table 2 be used as a model for treatment, it is not safe to administer less than 5 grams of "914" in such a course.

The twenty-five cases as a whole, paying particular attention to those eleven cases which received adequate treatment in their first course, are now examined in an attempt to determine whether bismuth or mercury is the better drug to employ in the treatment of early syphilis in conjunction with a "914" substitute.

Table 8.

Total cases of clinical relapse receiving bismuth or mercury.

Metal	Total relapse	Adequate initial treatment
Bismuth	6	2
Mercury	17	9
No metal	2	0
Totals	25	11

To determine the significance of these figures one must consider various other data such as (1) the year in which treatment was started; (2) the time taken to relapse; (3) the total numbers of cases receiving Hg. or Bi. along with "914"; (4) any special types of treatment.

(1) Year in which relapsed cases first attended, with relapsed cases receiving adequate initial treatment shown separately.

Table 9.

Annual incidence of relapse showing total cases in Hg. and Bi. periods.

Year	Total Relapses	Relapses with adequate initial treatment
1919	3	2
1920	3	2
1921	6	4
1922	2	1
1923	3	285
1924	2	Hg. cases
1925	0	0
1926	1	0
1927	1	1
1928	1	0
1929	2	0
1930	0	255
1931	1	Bi. cases
Totals	25	11

(2) Time taken to show clinical relapse.

Table 10.

Time in months.	Total Relapses.	Adequate initial treatment.
-6/12	7	4
-12/12	11	7
-24/12	3	0
+24/12	4	0
Totals	25	11

(3) Out of the series of 570 cases, there were:-

285 cases treated with Hg. and "914" in the initial course.

255 cases treated with Bi. and "914" in the initial course.

Bismuth was employed in place of Hg. from 1924 onwards. There were 303 cases treated in the Mercury period, and 267 cases treated in the Bismuth period.

(4) Amongst the relapsed cases :-

4 cases received Flumerin only.

1 case received an inadequate amount of Bi. only.

It is seen, then, from Table 6 and these data, that out of 285 "mercury and 914" cases, 17 relapsed, of which 9 had received adequate initial treatment; and that out of 255 "bismuth and 914" cases, 6 relapsed, of which 2 had received adequate initial treatment.

All cases of relapse in those patients who received a normal first course took place within a year. This took place whether bismuth or mercury had been employed in their first course. It is also to be noted that in the clinic as the years progress, there is a diminution in the total number of relapses. This takes effect even if one allows for the greater number of cases in the earlier years, and if one allows a further period of time to permit of late relapses occurring in those cases treated in the later years.

This information may be combined with the aid of Tables 3, 4 and 5 into the following statements :-

A. As regards all cases not treated solely with "914" and metal in their first course :

Out of 285 cases treated with "914" and mercury, 13 relapsed.

Out of 255 cases treated with "914" and bismuth, 5 relapsed.

B. As regards such cases in group A who received an adequate first course of treatment :

Out of 199 cases treated with "914" and Hg., 9 relapsed after a normal first course of "914" and Hg.

Out of 187 cases treated with "914" and Bi., 2 relapsed after a normal first course of "914" and Bi.

Although the figures are small, and although it may reasonably be suggested that there is still time for some late relapses to appear, which would naturally affect the bismuth group, still it is suggested that so far the balance of evidence lies in favour of the use of bismuth rather than mercury as a metla for the treatment of syphilis.

It is now necessary to consider the ultimate fate of the cases of relapse, in order to attempt to determine the late effects created by the preliminary use of bismuth or mercury.

The final clinical and serological results of the cases of clinical relapse are now shown, having regard to the total time of attendance of the patient and whether the total amount of treatment received might be considered adequate or inadequate.

Table 11.

Hg. cases.

Final clinical and serological results in cases of clinical relapse.

Total time of attendance in years	Total treatment	Final clinical result		Final serolog. result W.R.					
		-	+	Blood		C.S.F.			
				W	S	-	+	-	
-2	Adequate	8	2		1	5		3	
	Inadequate	4	2			2		1	
+2	Adequate	4	1			3		3	
	Inadequate		1	1					

Bi. Cases.

Total time of attendance in years	Total treatment	Final clinical result		Final serolog. W.R.			result C.S.F.		
		-	+	+	W	S	-	+	-
-2	Adequate	1					1		
	Inadequate								
+2	Adequate	2					2		
	Inadequate	1	2	2		1			

"914" only.

Total time of attendance in years	Total treatment	Final clinical result		Final serolog. W.R.			result C.S.F.		
		-	+	+	W	S	-	+	-
-2	Adequate								
	Inadequate								
+2	Adequate	2				1	1		1
	Inadequate								

Here, too, the slight bias in favour of bismuth is again exhibited. Four cases originally receiving mercury did not show a negative blood Wassermann reaction after adequate total treatment. No cases of bismuth therapy came into such a category.

The types of clinical relapse are summarised :

At site of chancre	Skin and mucous membranes	Eye signs	Tertiary type of lesions
7	14	4	6

The ultimate fate of those cases showing relapse at the site of the original chancre is shown:

<u>Total</u>	<u>Final W.R.</u>	
	+	-
7	1	6

Thus it would not appear, comparing this figure with the results in Table 11, that relapses at the original site are more difficult to treat successfully than are manifestations in other situations of the body.

The ultimate fate of those cases showing relapses of a tertiary type is shown:

<u>Total</u>	<u>Final W.R.</u>		
	+	S	-
6	2	1	3

Thus from Table 11 it would appear that late relapse - signalised by the tertiary type of lesion - is relatively an unfavourable phenomenon.

The relationship of clinical relapse to the Wassermann reaction of the blood serum is investigated.

At the time of the relapse the blood serum Wassermann reaction was positive in twenty-one cases, not done in one, and negative in three.

These three negative cases showed:-

M 2. Sore at frenum, original site. Sp. P. +; no other signs of infection.

M 2. Syphilitic acneiform rash on forehead at outset of second course of injections.

F 2. Iritis. No rheumatic or gonococcal infection found.

Prior to clinical relapse, five cases had shown a persistently positive Wassermann reaction of the blood serum for at least six months, two for about one year, and five for periods greater than one year. Also, the other thirteen cases had shown a variable condition of the blood Wassermann reaction prior to relapse. Further, thirteen cases after exhibiting clinical relapse showed, during further treatment, variable condition in the Wassermann reaction of the blood sérum.

The total numbers of cases in the series of 570 which remained Wassermann fast for these periods mentioned above, are now shown and compared with the numbers of clinical relapse in the total Wassermann fast cases of these periods.

Table 12.

Time in months during which Wassermann fast.

		6/12	12/12	+12/12
Total cases 570	W.R. fast	32	14	12
Total relapses in W.R.fast 25	Relapses	5	2	5

Although only twelve cases of clinical relapse had originally been Wassermann fast for six months or more, yet a consideration of these with the total number of cases, 58, which remained Wassermann fast for six months or more, indicates quite clearly that, in the treatment of early syphilis, it is most desirable to secure a reversal of the Wassermann reaction at an early date. Nearly half of those who remained Wassermann fast for more than a year showed clinical relapse. It should, however, be pointed out that the majority of these cases were inadequately treated at the outset. Nevertheless, it must be regarded as a most significant feature, if treatment fails to reverse a positive Wassermann reaction of the blood serum. It is strongly suggested that any cases which fail to respond to treatment within the period of a year, be made the subject of a careful clinical study, and subjected to a special intensive course of treatment, varying the type of drugs from those previously employed. The majority of these cases will, of course, not develop further clinical lesions.

Two cases which had been Wassermann fast for over a year were subjected to the most thorough clinical examination, employing in addition the X-rays, blood examination, renal and liver efficiency tests, gastric analysis, the electrocardiograph, skin allergy tests and cerebro-spinal

fluid examination without detecting any clinical abnormality. Neither has, in eight years, shown any clinical signs of relapse.

The grade of severity of the initial lesion in secondary syphilis bears no relation to the tendency to relapse.

Amongst the eighteen cases of relapse in secondary syphilis, eight were slight in their original manifestations, six were medium, and three were florid. This does not show any noticeable percentage deviation from the actual numbers of such grades of severity of the initial lesion in the total series.

No cases of "malignant syphilis" were seen in this clinic. In another place, however, a male case has been watched for twelve years, in whom the natural history of the disease seemed to be unchecked by the most drastic varieties of treatment, and in whom the progression through primary, early and late secondary signs to a series of subcutaneous and skin gummata, was uninterrupted. He never showed intolerance to treatment, and the Wassermann reaction of the blood serum was constantly strongly positive. No signs of neuro-syphilis appeared.

The time elapsing between the initial attendance and the noting of clinical relapse is considered in respect of the final serological result, noting such cases as had received adequate total treatment.

Table 13.

Time in months of occurrence
of relapse.

	Less than 6	6 to 12	12 to 24	More than 24
Total relapses	7	11	4	3
Total "not negatives" at end of observation	3	4	2	2
Total adequately treated and "not negative"	2*	3*	1	0

* Four of these five end reactions were "suspicious".

It is apparent that the later relapses tend to more unfavourable end serological results, but there is little difference provided that the case be properly treated.

The question of the final "cure", or otherwise, of cases showing clinical relapse is now considered.

The lesion in relapsed cases is not less immediately amenable to treatment than is any lesion in untreated syphilis of the same age and same clinical type. Relapse lesions resolve just as quickly as do untreated lesions, and the only difference noted is a tendency for pigmentation to persist longer than it might do in a similar fresh lesion of comparable age.

From tables 3, 4 and 5 it will be observed that out of the twenty-five cases of relapse, two cases defaulted while still showing clinical signs of disease, three had a suspicious Wassermann result when last seen and eight cases finally presented a positive blood Wassermann reaction. These positive cases are shown by stage of disease, adequacy of first course of treatment, adequacy or otherwise of total treatment and duration of observation.

Table 14.

Sex and stage of disease	Case No.	Final W.R.+ results.		Duration of observation in months
		Adequate 1st. course of treatment	Adequate total treatment	
F 1 W.R.+	1919	Yes	No	57
M 2	1750	No	No	3
	1774	No	No	10
	1792	No	Yes	19
F 2	486	No	Yes	16
	3697	No	No	27
	3634	No	Yes	39
	1926	No	Yes	72

Here again is seen the influence of an insufficient first course of treatment. Nos. 1750, 1774 and 1792 only received Flumerin as a first course of treatment. No. 1926 defaulted for forty weeks after 0.6 grams of bismuth metal. None of the others received more than three grams of "914". Here, too, is seen the effect of inadequate total treatment. Thus only two cases of clinical relapse, both of female secondary syphilis, Nos. 3624 and 1926, were observed for more than two years, received adequate total treatment and were finally Wassermann positive.

From Tables 3, 4 and 5 it is seen that thirteen cases of relapse out of twenty-five showed variability in the Wassermann reaction of the blood serum after treatment was continued. As 22% of the total series of 570 cases showed variable Wassermann reactions at some period or another, there is a higher percentage of variation in relapse syphilis. In view of the favourable final outcome when adequate total treatment is given, clinical relapse need only be considered as an indication that the total amount of antisyphilitic treatment in such cases should be increased. It has been found that a complete course of "914" and heavy metal given after a Wassermann reaction of the blood has been negative for six months, has been enough to prevent further serological and clinical relapse. Two cases of a second relapse were seen.

It has been repeatedly said that the most important point in the successful prevention of relapsed early syphilis (apart from any cases of so called malignant syphilis which may appear) lies in the successful administration of an adequate first course of treatment - using the word adequate to imply a course which does not differ greatly from the standard course already explained. There is shown as evidence for this statement, a table concerning those eleven cases which did receive adequate initial treatment, noting whether total treatment was adequate or not, the final serological results and the duration, in months, of the period of observation.

Table 15.

Rate of cases receiving adequate initial treatment.

Group	Case No.	Adequate total treatment	Final result of W.R.		Time observed in months
			Bd.	CSF.	
M1 DG+ W.R.-	1135	yes	-	-	37
M1 W.R.+	830	yes	-	-	14
F1 W.R.+	3041	yes	-	-	41
M2	1169	yes	-	-	22
	1298	no	-	-	11
	768	yes	-	-	53
F2	802	yes	+	-	39
	8	no	-	-	29
	4402	yes ?	-	-	10
	1269	yes	S	-	11
	355	yes	-	-	152

The end results of these cases are much better than in the fourteen others, even allowing for the fact that all but

two received adequate total treatment. The two cases, F2, 802 and F2, 1269, which were not negative, were instances of the tertiary type of relapse. This conclusion supports the contention which has been upheld from other angles of approach, in other sections of this thesis, namely, that the first course of treatment is the most important and that everything should be done to finish this course by preventing intolerance in, and default of, the patient.

Out of the fourteen cases not receiving a reasonably normal first course of treatment, nine eventually received an adequate total amount, but four of these (see Table 14) were not serologically negative when last seen. This, too, seems to lend support to the impression that the commencing weeks of treatment are fundamentally important although, naturally, the total treatment received is of consideration. It seems only logical, however, to expect a certain amount of clinical relapse if the course as outlined in Table 2 is used.

No system of treatment has been described in which clinical relapse does not occur, and it would appear that our present armamentarium is unable completely to inhibit the natural history of syphilis in all cases.

The data so far considered may be briefly summed up :-

(1) There is a slight difference between the anti-syphilitic action of bismuth and mercury when combined with "914".

Bismuth may be used as such difference seems in its favour.

(2) The severity of the initial lesions does not appear to affect the tendency to clinical relapse.

(3) The later the first relapse occurs, the more difficult is it to secure a final negative clinical and serological result.

(4) The tertiary type of cutaneous relapse is more difficult to treat satisfactorily than the secondary type.

(5) A Wassermann fast condition of the blood indicates a state in which relapse tends to occur. This is significant when fastness persists for more than a year.

(6) Relapsed cases treated with adequate total antisyphilitic measures are as likely to yield a final favourable result as are cases of blood W.R. fastness of more than one year's duration comparably treated.

(7) Adequate initial treatment is the factor of greatest importance in the prevention of clinical relapse.

The final question asked is : Can a modification of our standard course be suggested which will diminish the incidence of clinical relapse from the evidence provided in this section ?

In the American clinic investigation as detailed in Venereal Disease Information, July 1932, page 278, the following percentages of clinical relapse are shown :-

Sero negative primary	2.6%
Sero positive primary	2.7%
Secondary, 1st year	2.9%
Secondary, delayed	4.6%

These percentages refer to cases under observation for six months or longer, and are the cases upon which the conclusions were based.

The standard method of treating these cases was by the use of "606", followed by injections of mercury or bismuth.

The authors regard (page 265) relapse as an indication of either the misuse or the failure of arsphenamine, and they consider that the critical point lies "between the fifth and ninth arsphenamine injection". They conclude that the best way to prevent relapse is "to treat the patient continuously without rest periods voluntary or involuntary", but they do not state with what measures nor for how long. They stress the importance of "serologic resistance" as a guide to "the probability of relapse". In these percentages

they excluded the first six months of treatment (page 265), but out of their total cases, "5952 in number, 360, or 6.05%, developed muco-cutaneous relapse". By this standard our percentage, 25 cases out of 570, or 4.38%, compares not unfavourably. In this series, "914" is given in conjunction with a heavy metal, and there are rest periods of from three to six months during which mercury only or potassium iodide only is given by the mouth.

In the American series the various schemes of treatment employed at the different clinics are summarised briefly as under.

- A. Eight injections arsphenamine at weekly intervals, the first three at four day intervals. Then ten injections of bismuth every fifth day. Repeat for four courses.
- B. Injections of arsphenamine alternating with Hg. by inunction or injections of bismuth, continued with short rest periods until blood W.R. has been negative for one year.
- C. Combined neoarsphenamine and bismuth for twenty injections then short alternating courses of bismuth and neoarsphenamine. Then the combined treatment until forty injections of neoarsphenamine are given.

- D. Alternating but continuous treatment with arsphenamine and mercury or bismuth. More heavy metal than in other clinics.
- E. Three daily doses of arsphenamine: then a course of mercury by inunction or bismuth injections followed by a rest period of from three to four months, continued for six or more courses.

There is thus a considerable diversity of methods to compare with the custom of this clinic. None of them appear to offer much improvement, in respect of a diminution of clinical relapse, upon our own. There has not been found recorded detailed evidence whereby to suggest a modification in the scheme of treatment of this clinic designed to lessen the incidence of relapse. The most important fact which they stress is the necessity for continuous treatment.

The conclusions reached in this section appear to indicate the supreme importance of the first course of treatment. In view of the high incidence of default, it would appear advantageous if more of the total quantity of "914" to be given could be concentrated into the earlier weeks of treatment. The implications of this are considered in the section dealing with the suggested modification in the treatment of early syphilis.

S E C T I O N VI.

**INTOLERANCE TO ANTISYPHILITIC TREATMENT WITH
SPECIAL REFERENCE TO EARLY SYPHILIS.**

Pages 221-275.

Intolerance to antisyphilitic treatment with special reference
to early syphilis.

The material to be considered in detail comprises those cases of primary and secondary syphilis, five hundred and seventy in number, which have formed the basis of the other sections of this part of the thesis. For convenience they are again presented in tabular form.

Table 1.

	Male	Female	Total
DG+ W.R.-	48	2	50
Primary W.R.+	126	36	162
Secondary	172	186	358
Total	346	226	570

All complications occurring as a result of treatment have been noted on the main record cards, and tables therefrom have been constructed to show the chief data available for consideration. These are shown at the end of this section.

The accidents resulting from treatment will be analysed in detail in this series, but, in discussing their significance and their prophylaxis, attention will also be given to accidents occurring during treatment in the later stages of

syphilis. The percentage incidence of intolerance in four hundred and seventy-three cases of muco-cutaneous late syphilis was 44%.

A summation of the number of cases which showed intolerance in early syphilis is first given.

Table 2.

Intolerance in early syphilis.

Sex and stage of disease	Total cases	Total cases showing any intolerance	
M.1 DG+ W.R.-	48	10	
M.1 W.R.+	126	28	Total Males = 346 Total 80 = 23.1%
M.2	172	42	
F.1 DG+ W.R.-	2	1	
F.1 W.R.+	36	18	Total fe- males = 224 Total 78 = 28.9%
F.2	186	59	
Total	570	158	= 27.8%
Total, excluding local reactions		151	= 26.4%
Total, excluding local reactions and stomatitis		96	= 16.9%

Figures comparable with these are obtained from the American Series, Venereal Disease Information, July 20, 1932, Table 46, where out of three hundred and fifty-five cases of early syphilis treated with Neo-arsphenamine and a metal, one hundred and seventy-two (48.45%) showed complications of

treatment, and one hundred and forty-one showed arsenical complications. In a series of cases of early syphilis at the "ad hoc" centres of the Corporation of Glasgow, investigated with regard to methods of preventing complications, and presently to be noted, seven hundred and ninety-one cases were observed of which one hundred and eighty-three showed intolerance - a percentage incidence of 23.1%.

The various types of intolerance are next examined. It can be noted from the main summary that one patient might, and frequently did, exhibit more than one type of intolerance, hence the total of these various manifestations is greater than the actual number of cases involved. This is not brought out in the American figures, but with that reservation the figures are compared wherever the headings permit.

Table 3.

Types of intolerance.

	Present series		American series	
Total cases	570	100%	355	100%
Local	6	1.0	2	.56
Nitritoid	1	.17	29	8.17
Fever	2	.34		
Malaise	23	4.0		
Skin	17	2.9	+ in slight skin	
Gastro intestinal	35	6.1	49	13.80
Renal	2	.34		
Slight skin	13	2.28	35	9.86
Jaundice	23	4.0	21	5.92
Dermatitis	6*	1.0	7	1.97
Encephalitis	0			
Stomatitis	55	9.6		

* Three cases were sent to the clinic because they had dermatitis.

The arsenical complications are now tabulated against the "914" substitute used at the time of their occurrence, or last used if the intolerance was delayed. The total number of injections of each "914" substitute given in all the cases of early syphilis is shown along with the percentage incidence

of the reaction in terms of the total injections of the appropriate "914" substitute. Where more than one drug had been given in the course, the complication is shown under each drug. In most instances mercury or bismuth was given in the same course as the "914" substitute.

Table 4.

	Total	AB	SS	NK	NAB	NS	St.	Myo	S	NSS
Nitritoid	1			1						
Fever	2			2						
Malaise	23			17	5	1				
Skin	17	2		10	3	2				
Gastro intestinal	36	1		16	16	2				
Renal	2			2						
Slight skin	13		1	10	1	1				
Jaundice	23			16	8	1				
Dermatitis	6			2	3		1			
Total Complications		3	1	76	36	7				
Total injections given		28	80	3635	2975	637		17		6
Percentage of reactions to injections		%	%	%	%	%				
		10.9	.8	2.09	1.21	1.09				

AB = Arsenobillon
 SS = Silber salvarsan
 NK = Neo kharsivan
 NAB = Novarsenobillon

NS = Neosalvarsan
 St. = Stabilarsan
 MyoS = Myosalvarsan
 NSS = Neosilbersalvarsan

The difference between the percentages of accidents during the use respectively of neokharsivan and novarsenobillon is noteworthy. These percentages, 2.09% for N.K. and 1.21% for N.A.B., are significant when calculated on a statistical basis. Amongst the intolerances noted, it is seen that where N.K. is used there is an increase in skin reactions, whether slight or otherwise, and in jaundice. These are two of the most important accidents which lead to the suspension of further "914" treatment for lengthy periods. In the cases treated with N.K. and N.A.B. bismuth and mercury were employed in fairly equal proportions, and thus the associated metal cannot be implicated in seeking for factors other than the "914" substitute, in the production of these complications. Neokharsivan and novarsenobillon were used exclusively as the sole "914" substitute in the clinic, except for a few unusual cases, for two or three years at a time. There was thus a fairly even division between them from 1919 onwards, which would indicate a reasonable control in respect of any annual variation likely to occur in the nature of the disease itself. Finally the personnel of the clinic has not altered, nor has the technique employed in making the actual injections been changed. From the cases treated, it seems not unreasonable to conclude that novarsenobillon is slightly less productive of toxic effects than neokharsivan. This is a matter of considerable importance in regard to the

routine treatment as carried out in all the Glasgow centres, and the question will be investigated in detail employing all the centres. Here it is only to be noted that out of seven hundred and ninety-one cases of syphilis treated in the "ad hoc" centres, all were given N.K. and the percentage of all types of intolerances noted in the cases was 23.1% (183 cases). This, of course, does not refer to the percentage incidence in respect of the total number of injections of N.K. given to these cases.

The next broad question examined concerns the reaction to the heavy metal employed.

There were nineteen manifestations of bismuth intolerance in two hundred and fifty-five cases treated with bismuth, and twenty-four manifestations of intolerance in two hundred and seventy-five cases treated by mercury. Larger quantities of bismuth metal are given as compared with mercury. The bismuth reactions are all of the nature of gingivitis and stomatitis and most are mild in grade. Amongst the mercury reactions are noted an acute gastro-enteritis and temporary renal damage. The gingivitis and stomatitis produced by mercury is more difficult to heal, and more prone to relapse, than in the case of bismuth intolerance. In eleven cases, mercury treated, removal of all teeth was necessary to permit of treatment being continued. This was only found necessary three times while bismuth was being

employed. In this series the alleged superiority of bismuth in respect of freedom from toxic symptoms is not exhibited, but undoubtedly the degree of disturbance is less severe than when mercury is used.

From time to time short experiments were made in an attempt to diminish the general incidence of ill effects resulting from treatment. It was early realised, however, that such experiments, to be of any value, had to extend over a considerable period and required to be controlled by an equivalent series of cases not so treated. Such varied and uncritical experiments comprised:

One ounce of glucose orally one hour before the intravenous administration of a "914" substitute.

One ounce of glucose orally coincidentally with an intravenous injection of a "914" substitute.

One half pint of milk one hour before the intravenous injection of a "914" substitute.

The dissolving of the dose of "914" substitute in an aqueous solution of sodium thiosulphate.

The continued administration of sulphur in the form of sulphur lozenges or sulph. praecip.

The few cases so treated did well but no conclusions could be drawn therefrom.

In 1929 an attempt was made through the medium of the Corporation Venereal Clinics to secure more definite information. These clinics were selected firstly because their combined totals gave access to a considerable number of cases and secondly because, being under the charge of different medical officers, it was thought that any personal element might more definitely be ruled out. All cases of early syphilis were treated at each clinic under the same regime with a combined course of 5.85 grams of N.K. and 2.4 grams of bismuth metal. Latitude was permitted in the handling of cases of tertiary syphilis. The three clinics were Black Street, Broomielaw and Bellahouston.

Each new case of syphilis on being submitted to treatment, was placed in order of rotation into one of four categories, A, B, C, D, and was kept in that category throughout the duration of the experiment.

Cases in A group received no prophylactic treatment of any kind.

Cases in B group received 1 oz. of glucose by mouth at the time of each injection of N.K.

Cases in C group received their dose of N.K. dissolved in 10 c.c. of water containing 0.6 gram Ametox (sodium thio-sulphate).

Cases in D group received both the one ounce of glucose by mouth, and the 0.6 gram of sodium thiosulphate.

In Black Street clinic the results were as follows :-

	A	B	C	D
Total cases	29	34	31	27
Total complications	6	7	9	10
Jaundice	1	1	3	2

This showed no advantage from any of the methods of prophylaxis.

In the other clinics this scheme was overlooked from time to time, and the resulting figures showed so much variation in the numbers of the four groups, that the figures are scarcely susceptible to analysis, though they also suggest that no benefit was derived from these methods of prophylaxis.

	A	B	C	D
Total cases	247	44	36	35
Total complications	37	13	6	9
Jaundice	9	4	2	0

This experiment was repeated in 1931 but again it proved difficult to insure that a strict rotation was maintained by the various medical officers and their assistants.

The combined figures from Black Street and Bellahouston on this occasion were :-

	A	B	C	D
Total cases	100	68	76	64
Total complications	22	21	24	19
Jaundice	7	4	5	3

Again the conclusion reached was that such methods of prophylaxis were of no value in the prevention of intolerance. Although this method of investigation was very loosely carried out, yet it appears to have been a haphazard sampling of all types of syphilis in the male, and it is justifiable, therefore, to add together the three sets of figures already given. The final table of results thus reads :-

	A	B	C	D
Total cases	376	146	143	126
Total complications	65	41	39	38
Jaundice	17	9	10	5
Percentage of complications to total cases	17.3	28.1	27.2	30.1

The total number of cases here is 791.

It seems impossible to escape from the definite conclusion that neither the oral use of glucose, the intravenous exhibition of sodium thiosulphate nor the combined employment of these two substances influence the incidence of intolerance to antisyphilitic remedies. It may be suggested that although the incidence is unaffected, still one or other method might be of value in reducing the severity of intolerance, but taking jaundice as a typical severe reaction, such is not found to be the case.

These opinions have a certain statistical basis and will therefore receive such support as clinical findings based on this method of approach may merit. It seems, however, not unreasonable as the result of an extensive clinical experience to state some general opinions founded upon clinical observation and deduction but also employing such statistical aid as the detailed analysis of the accidents in this series may afford. In this discussion, while the complications encountered in the present series will be dealt with in detail, the accidents which occur in tertiary syphilis will only generally be considered. It is felt that this subject is of the utmost importance in the handling of the individual case as well as in the bulk treatment of clinic patients, and no apology is thus offered for discussing it at some length. It may be pointed out that anything which adds to the patient's comfort or safety tends to increase the period of his total time of attendance, thus tending to increase the percentage of final apparent cure. Also since there is no doubt but that an increasing number of general practitioners are undertaking the treatment and management of cases of syphilis, it is of great value that rules should be laid down to enable them to handle simply those toxic drugs with the least amount of reaction. It has been noted in cases subsequently referred to the clinic, that there is a tendency on the part of the majority of practitioners to treat their cases with a dosage considered by most

authorities to be inadequate both in number of injections and quantity of single dose administration, and this is partly attributable to the fear of toxic effects. On the other hand the intransigence of a small minority of the doctors, manifested as the continued administration of large doses of "914", leads one to marvel at the powers of resistance to toxic effects on the part of many of their patients.

The discussion will be arranged under the following headings :

- (1) The general health and reactions of the patient: focal sepsis - cutaneous irritability - therapeutic shock - respiratory disease - nervous disease - cardio-vascular disease - renal disease - hepatic disease - alcohol.
- (2) The preparation of the patient and technique of injection - food - water.
- (3) Arsenical reactions.
- (4) Metal reactions.
- (5) The association of intolerance with the final serological results.

(1) The general health and reactions of the patient. A complete examination of the patient is, of course, indicated, but it is less likely to take the form of a perfunctory routine if certain danger points are kept in the forefront.

The search for, and elimination of, focal sepsis is considered of great importance. Such sepsis is not so frequently found in patients with early syphilis for they tend to fall into the younger age groups. It is a very real difficulty amongst the older cases who exhibit tertiary manifestations. Here fall to be noted cases of tooth abscess, sinus disease, tonsil disease, gall bladder disease and appendix disease. It is strongly suggested that the best method of dealing with such cases is, in the first instance, to cause the resolution of the syphilitic lesions with large doses of potassium iodide and small doses of bismuth metal. Thereafter the appropriate measures for dealing with the septic focus can safely be instituted and finally, after convalescence, full antisyphilitic treatment may be commenced.

The following cases illustrate the clinical difficulties which led to these suggestions for dealing with the patients.

A woman, aged 36, whose husband died of G.P.I. presented signs of diffuse vascular cerebro-spinal syphilis, with positive Wassermann serological tests in the blood and cerebro-spinal fluid. Her general health was poor, with dyspepsia and fibrositis as her chief complaints. She tolerated bismuth given by the intramuscular route, but even small doses of "914" (.15 gm.) led to prolonged malaise with nausea, anorexia and itching of the hands and feet. Eventually she was operated on for cholecystitis, and an unhealthy gall bladder and some

gall stones were removed. Thereafter - for four years - she received full treatment with "914", Tryparsamide and metals and showed no intolerance of any kind.

A girl, aged 17, with congenital syphilis was on examination considered to be in good health apart from a syphilitic ulcer of the hard palate and some stigmata of hereditary syphilis. She showed skin irritability to small doses of "914". Various prophylactic experiments failed. Eventually more thorough re-examination showed an infected maxillary antrum. After this had been drained, intolerance to "914" completely ceased.

On the other hand it is unwise not to deal at once with the obvious syphilitic lesion. Thus a male patient with a large nodular tuberoso lesion on the right thigh had unhealthy teeth and gums. He was unwilling to allow complete extraction to be done, and X-ray plates were obtained of the roots of the teeth. By the time those teeth which showed apical abscesses had been removed the syphilitic lesion had ulcerated. It thus took a longer time to heal and left behind a large and distinctive scar.

Cutaneous irritability or "skin allergy" is thought to be one of the most important general factors in leading to intolerance of all types. Indeed this heading, which is

the one commonly referred to by text-books on the treatment of syphilis, should, in the writer's opinion, be widely extended. Cutaneous irritability is only one manifestation of a series of phenomena which appear to be founded upon a common etiological basis. This is suggested by their clinical overlapping in patients, by their joint response to similar therapeutic measures, and possibly by their common tendency to enhance the frequency with which complications follow the use of "914" and bismuth and mercury. Cases which appear to qualify for such a group may show some of the conditions and tendencies seen in the following list:- asthma, hay-fever, food idiosyncrasy, urticaria, moist eczema, scaly dermatitis, hyperchlorhydria, constipation associated with spastic colon or mucous colitis, low blood pressure.

As is well known many of these complaints are found in children diagnosed as suffering from acidosis - many are seen in a familial grouping and a number are associated with the more neurotic type of middle aged patient. All, in this clinic's experience, require care in the administration of salvarsan substitutes and the heavy metals.

Dr. J. C. Alexander has conducted, at the writer's request, a lengthy series of investigations into all cases coming to the clinic to determine whether or not the "patch" test may aid in the recognition of such troublesome cases. He employs a weak watery solution of "914" which is applied

to the arm as a compress in an attempt to produce local reactions. Local reactions have been found in cases which have shown marked arsenical intolerance. As a routine prior to the administration of "914" this test has not been found helpful.

It is well known that cases which have exhibited intolerance to one of the "914" series are rendered more liable to further exhibitions of intolerance if "914" be resumed. This complicates the assessment of the value of prophylactic measures which are designed to aid the underlying abnormality. It is also obvious that if these therapeutic measures are applied in advance of arsenical therapy, and if the case does not show intolerance it then becomes difficult to assign any real value to such antecedent therapy. Nevertheless, after making due allowance for these difficulties, experience has led to the conclusion that attention to elimination by the bowel is the most important factor in the prevention of toxic side effects in cases coming into the various categories just mentioned. The simplest method thought effective is to give a mercurial purge and a saline every five days, and to cut down the total quantity and the carbohydrate amount of the last meal of the day. It is also thought that the regular administration of kaolin and the heavy carbonate of magnesia has been of definite benefit. These lines of therapy are at least consistent with the hypothesis that histamine

production may play an aetiological part in many cases.

Antecedent disease of the respiratory tract should lead to care in the choice of drug and dosage. Chronic bronchitics do not tolerate full doses of "914" well. Cases of pulmonary tuberculosis should not receive iodides, but unless there be a definite febrile state, it has been found that they tolerate "914" in the usual dosage.

A full examination is essential to detect the earliest involvement of the vascular or central nervous system. In such cases the appearance of therapeutic shock may be attended with clinical disaster. Various hypotheses are suggested to explain the origin of the phenomenon of the Jarisch Herxheimer reaction. Thus it may be attributed to the liberation of toxins through the sudden death of numerous spirochaetes, and the consequent allergic reaction on the part of the tissues - attended by serious results should such stress be encountered by the tissues of the brain stem or the finer arteries of the organs of the heart and vessels themselves. Clinical exper-¹ience, however, suggests that, at least in certain cases, the possibility of the liberation of and stimulation to activity of living spirochaetes must be borne in mind. At all events the clinical recognition of therapeutic shock may be met with in all stages of the disease. Careful questioning can

elicit from most cases of early syphilis a short period of increased local activity on the part of the chancre, sometimes only for a few hours, and usually also an increase in the local or general adenitis. So, too, to a more obvious degree in the secondary manifestations. In these stages, however, no dangers have been met with in the immediate exhibition of the most powerful drugs. This also applies to such tertiary cases as exhibit gummatous lesions of the skin, connective tissues and bones. Irreparable damage has been seen, on the other hand, in disease of the vascular and nervous system. One has been called to see three cases of nervous syphilis in the male, cases of tabes dorsalis, tabo-paresis, and syphilitic meningitis. As soon as the diagnosis had been established, a "914" substitute had been given. The results are as follows :

Age	Disease	Dosage	Immediate result	Final result
57	Tabes	.45 N.A.B.	Coma, shallow breathing, rapid feeble pulse.	Stationary condition. Facile
42	Tabo-paresis	.45 N.K.	Coma, leading to broncho-pneumonia	Death in 3 months.
48	Meningitis	.45 N.K.	Lesions of the IVth, VIIth and VIIIth nerves. Raised blood pressure.	These nerve lesions persisted in a modified way.

The immediate treatment comprised a suitable selection from the following methods - lumbar puncture, subcutaneous and intravenous saline, alkali by mouth, venifsection, adrenalin, hypertonic saline (15%).

Clinical experience has also shown that it is unwise to commence treatment with either potassium iodide by mouth or the intravenous use of sodium iodide in neuro-syphilis. This is particularly unsuitable in parenchymatous disease of the nervous system, and an increasing rate of mental deterioration in G.P.I. has been noted following the use of such remedies. This fact does not appear to be so widely recognised because its effects are not dramatic but insidious. It can be readily understood when the action of the iodides in resolving gummatous tissue is recalled. The only safe method of commencing treatment of neuro-syphilis is by the intramuscular injection of mercury or bismuth, and, depending upon the initial signs, such treatment should be continued for from four to six weeks. The initial dose of "914" substitute should be a small one.

In cardio-vascular disease the time of preparation for "914" should be even longer, and many cases in which there is evidence of gross damage to the aorta, the aortic valves or the conducting mechanism may never receive arsenical substitutes. No case of sudden coronary occlusion subsequent to an early injection of "914" has been seen, but notes have

been obtained of a male, aged 37, with signs of atheroma, left ventricle hypertrophy, no albuminuria and no elevation of the blood pressure who died suddenly some thirty hours after 0.6 gram N.K. had been given as his initial treatment. It may be suggested that the effect of therapeutic shock in this case produced an occlusive oedema of the openings of the coronary vessels.

No ill effect has been seen from commencing treatment in cardio-vascular syphilis with the exhibition of potassium iodide by mouth, and the continued use of the iodides has been found of especial benefit in all such lesions.

Pre-existing renal disease has only rarely been seen in this clinic. The few cases encountered have all apparently been of primary vascular origin and have been dealt with along the lines suggested in cardio-vascular disease. All did badly. A history of albuminuria in antecedent pregnancies has not called for any modification of treatment.

It is considered important to ascertain the presence and nature of any previous liver derangement. The immense physiological reserve of the liver must also be borne in mind. Notes have been taken of eleven patients who gave a history of simple jaundice, presumed to be catarrhal in type, before the onset of their syphilitic infection. All received ordinary clinic treatment with "914" and a heavy metal, and all did well.

The general habits and mode of life of the patients has been found to exercise remarkably little effect upon the drug tolerance. Coal miners and clerks, athletes and students, teetotalers and confirmed alcoholics, University graduates and illiterates alike tolerate antisyphilitic remedies. Alcohol is only considered to be of significance when its long continued use has already led to degenerative changes. One case of tabes dorsalis which exhibited very high "914" tolerance was a confirmed morphine addict. Obese people generally take "914" preparations well, but often show local reactions to intramuscular injections of metal. In such cases absorption of the metal is frequently delayed. After completion of a normal course of 2.4 grams of bismuth metal, X-ray examination showed unabsorbed deposits, in one case twenty-two weeks and in another thirty-four weeks later.

These observations may be summed up by stating that a patient cannot be too carefully examined as a preliminary to antisyphilitic treatment. This is of particular importance in clinic work where it is inevitable that some sort of routine treatment must be given to large numbers of comparable cases. The peculiarities of each case, in so far as they are likely to affect treatment, should be simply and shortly noted on the case record in such a manner that they must attract attention on each visit of the patient.

(2) The preparation of the patient and the technique of injection. Clinic experience merely tends to confirm the importance assigned to this part of the management of the case as laid down in all standard text-books. It is particularly thoroughly dealt with by Stokes (page 312 et seq., Modern Clinical Syphology), and no fresh important points have emerged in the experience of this clinic.

It is noteworthy that minor reactions are more common as a result of veni-puncture and intravenous injection when performed by the various series of clinical clerks instead of by experienced individuals. All traces of alcohol should be removed from a syringe prior to intramuscular injection. No water difficulties have been encountered as fresh distilled water has invariably been employed.

Instructions regarding the withholding of food before and after an intravenous injection of a salvarsan substitute, and instructions concerning the after care of the bowel are almost universally disregarded by clinic patients. This is chiefly on account of economic circumstances. Remarkably few ill effects have been seen in consequence.

(3) Arsenical reactions.

The following types of reaction occurred in this series of five hundred and seventy cases of early syphilis.

Nitritoid crisis	1
Rever	2
Malaise	23
Gastro intestinal	35
Slight skin	13
Skin	17
Dermatitis	6
Jaundice	23

Only one case of "nitritoid crisis" is recorded in this series: the Americans noted twenty-nine in three hundred and fifty-five cases of early syphilis. It is obvious that there must be some difference in nomenclature. This series describes twenty-three cases of malaise and none are noted under this heading in the American group - some of these consisted of cases which showed immediate and transitory nausea. Probably these cases are to be compared with the American nitritoid crises. It is also thought that a number of minor exhibitions of this intolerance may not have been reported. The symptoms of "nitritoid crisis" have been met with more frequently in cases of late syphilis and in older individuals. In no case in this clinic has this condition necessitated the permanent stoppage of "914".

As stated the reaction has not infrequently been met with in cases of tertiary syphilis. The following methods have been tried in an attempt to prevent subsequent reactions in susceptible patients.

1. Preliminary injection of a solution of sodium bicarbonate (Jeanselme).
2. Preliminary injection of a solution of sodium iodide.

3. Antecedent injection of atropine, gr. $\frac{1}{70}$. (Milian).
4. Fractional dosage $\frac{1}{10}$ being given, $\frac{9}{10}$ being given forty-five minutes later. (Bezredka and Stokes).
5. Very slow administration.
6. The coincident administration of a few minims of an aqueous solution of $\frac{1}{1000}$ adrenalin hydrochloride.
7. The injection of $\frac{1}{4}$ to $\frac{1}{2}$ c.c. of adrenalin $\frac{1}{1000}$ five minutes before the "914" is given.
8. The simultaneous oral use of Spt. Ammon. Aromat.
9. The administration of "914" with the head at a lower level than the body.
10. Heavy purgation during the twenty-four hours preceding injection.
11. Acid sodium phosphate gr. 20 thrice daily for one week prior to injection in an attempt to alter the p^H of the blood.
12. Alk. Sodium phosphate given as above.

Methods 5, 7 and 10 are thought to be the most helpful. The very slow administration of the dose is usually enough.

Malaise and gastro-intestinal reactions are the most common form of intolerance. Some of these may be due to the associated metal. They have, however, all been attributed to the "914". They are considered to be due chiefly to dietetic indiscretions and occupational strains. Their almost entire absence in private patients is extremely

noteworthy. They rarely entail more than a discussion with the patients concerning diet and attention to the bowels. A mild degree of nausea during the two days following an injection is common towards the end of a course. It is thought that many such minor complaints have not adequately been recorded. The slow administration of the injection is an important feature in securing prophylaxis. Clinical clerks produce more gastro-intestinal reactions than do experienced operators.

Diet must be adequate: patients who are losing weight, a rare event, tend to do badly. Loss of weight is often associated with loss of appetite. This is often seen when there is a mild grade of anaemia. Blaud's pill has been found curative in such cases.

Jaundice. Twenty-three cases occurred in five hundred and seventy patients - a percentage incidence of 4.0%. This is high. It includes all cases with any icteric tint, even transitory, and any case where bile pigments were found in the urine. These twenty-three cases of jaundice took place in seven thousand three hundred and eighty-seven injections of arsenical preparations - an incidence of one case to every three hundred and twenty-one injections. In the "ad hoc" centres, out of seven hundred and ninety-one cases there were forty-one cases of jaundice - a percentage of 5.1%. This is even higher.

Wile and Sams¹ note 1.35% incidence of jaundice in 4,126 cases of early syphilis, but quote Clement-Simon and Vulliemoz, who, in 1,100 cases, noted 5% jaundice.

Jaundice occurs most frequently some eight to twelve weeks after the completion of a course of "914", but has been seen as early as the fourth week during the course of treatment.

The distribution by sex, stage of disease and the number of the course of injections of "914" in which jaundice took place is shown.

Table 5.

Incidence of Jaundice

Course of treatment when
jaundice occurred.

Sex and stage of disease	1st course	2nd course	Total cases
M1 DG+ W.R.-	4	0	48
F1 DG+ W.R.-	0	0	2
M1 W.R.+	6	0	126
F1 W.R.+	3	0	36
M2	7	1	172
F2	2	0	186

Total cases of jaundice in males ■ 18

Total cases of jaundice in females ■ 5

All cases with one exception occur in relation to the first course of treatment. The higher incidence in males is possibly related to work, diet and alcohol.

The severity of the degree of jaundice was:

- 12 cases - very slight - transient - well in six weeks.
- 8 cases - moderate severity - six to eight weeks.
- 1 case - severe - six months till restored to former health.
- 2 cases - very severe - one died: acute yellow atrophy of liver; one developed subsequent severe haemolytic anaemia.

It is difficult to recognise the initial stages of arsenical jaundice. It may be ushered in by a prodromal period of some four to ten days during which the patient may complain of loss of appetite, slight nausea, heaviness in limbs and head, lassitude, irritability of disposition, disinclination for physical or mental effort with inability to concentrate, a mild degree of insomnia and sometimes a disturbance of the bowel. As however the commonest toxic reaction to arsenic is a gastro-intestinal one or a feeling of malaise, it is difficult to assess the prognosis in any single case thus complaining. The continued disinclination for sustained effort is considered the most important diagnostic complaint amongst those enumerated. Also of importance is

the significance of a statement of distaste for fat or fried food. This has been seen on five occasions, in which the clinical signs of jaundice appeared later.

The cessation of antisypilitic treatment; a fat free diet; the exhibition of mercurial and saline purges; the intravenous administration of sodium thiosulphate and the use of an alkaline mixture with liq. pancreaticus have been tried in the hope of preventing the appearance of jaundice with, it is thought, a certain measure of success, but the prevalence of the gastro-intestinal reaction which does not lead to jaundice, makes any assessment extremely difficult.

Attempts have been made to find some indication of liver insufficiency antecedent to the clinical diagnosis of excess bile in the blood stream. But the functional liver capacity is so great that it is difficult to get a sign of positive value at a period much earlier than that when clinical examination of the patient and of the urine gives all the requisite information.

Some simple attempts to investigate liver function have been made. Thus in investigating the pigmentary functions of the liver, Dr. A. A. Charteris carried out the Van den Bergh reaction on the blood serum of seventeen cases with symptoms which might have led to jaundice. In no case did an immediate delayed or biphasic reaction appear. Two cases subsequently developed jaundice. Eight sera were tested by

Fouchet's reaction: all were negative; none developed jaundice. A number of urines have been tested for Ehrlich's aldehyde reaction - this is known to give a positive response for urinary urobilin before the development of jaundice. But in this series the results were negative and no jaundice developed.

On the whole it is thought that an extended use of Ehrlich's aldehyde reaction might be tried. It is easily performed and so suitable for the ordinary routine of a clinic.

It is considered important to ascertain the presence and nature of any antecedent liver derangement. One should, however, bear in mind the recuperative power of the liver. Notes have been taken of eleven patients who gave a history suggestive of simple catarrhal jaundice before their syphilitic infection. All received ordinary clinic treatment with "914" and all did well.

*

It has been suggested that early jaundice i.e. in the fourth week after treatment has been started, is an expression of the syphilitic process rather than a toxic manifestation, and so the continuation of treatment has been advised. This has not hitherto been practised in this clinic.

The cause of the more common later jaundice, i.e. eight to twelve weeks after the end of a course, has been variously

ascribed to epidemic catarrhal jaundice, syphilis or "914".
1
Stokes considers epidemic catarrhal jaundice of common occurrence and describes prodromal symptoms which enable such a diagnosis to be made. These symptoms, urticaria, arthritic pains and epigastric pain were not present in any case in this series. To regard these cases of jaundice as syphilitic, after Milian, seems unreasonable. The Wassermann reaction of the blood serum was negative except in one instance; and no further syphilitic phenomena appeared at that period. In no case - this is significant - was the final clinical examination or serological blood Wassermann result other than negative, although in many cases no further "914" substitute was given. The cases simply suggest a catarrhal jaundice due to arsenical poisoning. Their response to treatment is analogous.

Skin intolerance in arsenical therapy is now considered.

The following reactions occurred. The figures are taken from Table 4 and show the drug given at, or prior to, the time of the accident.

1. STOKES, J. H. Modern Clinical Syphology. p.795.

	Total React- ions.	Drug given at time of reaction					
		A.B.	S.S.	N.K.	N.A.B.	N.S.	Stab.
Slight skin	13		1	10	1	1	
Skin	17	2		10	3	2	
Dermatitis	6			2*	3*		1*
Totals	36	2	1	22	7	3	1
Total injections of drug given		28	80	3635	2975	637	0
Percentage of skin reactions to injections.		4.27	1.25	.57	.23	.45	-

* One case which received N.K., one case which received N.A.B., and one case which received Stabilarisan were sent to this clinic because they had dermatitis. They are therefore not included in the percentage incidence occurring in this clinic.

For convenience the definitions of the various grades of skin reaction described in the appendix are here given:

- Slight skin - those cases which presented prolonged itching of one or more parts, or urticaria or erythema persisting for seven days, or a small isolated patch of dermatitis without constitutional disturbance, not lasting more than two weeks.
- Skin - an isolated patch or patches of dermatitis, without constitutional disturbance, lasting for more than two weeks.
- Dermatitis - those cases with generalised dermatitis accompanied by any constitutional disturbance.

Arsenobillon yielded 4.27% reactions in twenty-eight injections. Although no cases of dermatitis were met, yet this high incidence, in conjunction with the high incidence of intolerance seen when AB. was used in late syphilis, was one of the chief factors which determined the general use of "914" substitute rather than "606" in this clinic.

Silber-salvarsan showed 1.25% reactions in eighty injections. S.S. was never a drug of election and has only been employed experimentally in early syphilis.

Neokharsivan yielded .57% reactions in 3,635 injections. Novarsenobillon yielded .23% reactions in 2,975 injections. As has already been pointed out in this section, the incidence of complications is higher when NK is used than when NAB is employed. This holds for all types of arsenical reactions. It is maintained in the severer intolerances such as jaundice and skin reactions. The difference between .57% and .23% is of statistical significance. The spread of all associated factors between NK and NAB seems on an equal basis. The conclusion seems obvious that NAB is less toxic than NK.

Neo-salvarsan showed .45% reactions in 637 injections. In view of the small total number of injections given, its relative significance to NK and NAB is not discussed.

The subject of skin intolerance to arsenicals is one about which much has been written and it is difficult to condense the experience and experiments of this clinic usefully

without entering on numerous controversial points. It has been decided to deal with skin intolerance briefly from a clinical standpoint and to discuss very shortly certain points concerned with :A. Etiology; B. Prophylaxis; C. Correlation with end clinical and serological results.

A. Etiology. Patients with greasy seborrhoeic skins seem more prone to skin intolerance. Patients who suffer from chronic low grade focal sepsis appear to fall into two categories. The majority of cases improve under the tonic effect of arsenic: in a few there seems an increased liability to skin reactions. This is more noticeable in the older tertiary cases. In two cases where septic foci were dealt with, tooth abscess and a large carbuncle, skin intolerance immediately followed upon surgical treatment. No undue intolerance was seen in treating large septic ulcers. Broadly speaking there is correspondence between the type of case likely to react unfavourably to iodide and to arsenic. One curious case was noticed in which the skin intolerance was associated with a mild attack of scurvy. The patient was a man of 62 years of age who lived in a model lodging house on a diet of tea and bread. Attempts have been made to search for a specific factor in the skin. Dr. Mearns conducted a lengthy series of experiments with the intra dermal injections of agar. Dr. Murdoch attempted the investigation of skin allergy

by painting the skin with various aniline dyes. Dr. J. C. Alexander tried the "patch" test using watery solutions of "914". By each method it could be shown that some patients who had had dermatitis, slight or severe, had unduly sensitive skins. No information was gained as to the type of case likely to lead to skin complications.

An analysis of the usual diet, regulation of the bowel, alcoholic habits, urine, blood pressure, and state of the arteries was made by the writer in forty cases of various grades of skin intolerance in tertiary syphilis. It was hoped that some common underlying feature such as defective elimination by bowel or kidney, or some metabolic error might be disclosed. It certainly appeared that many of these cases were extremely careless in their habits, and that intestinal stasis was of fairly common occurrence, though when an equivalent group of people fully treated but free from skin intolerance were questioned on this point, little difference was found. Such difference as appeared indicated greater intestinal stasis on the part of the intolerant patients.

B. Prophylaxis. Methods designed to secure prophylaxis are very difficult indeed to appraise. It is a problem of the first importance. In view of the differences between the incidence of intolerance in the various drugs in this clinic

it is obvious that experimental work should be carefully controlled by an equivalent number of cases unprotected using the drugs under investigation. Further, as the incidence is small the numbers of cases must be large. This clinic has no such experiments to offer. The matter has been referred to earlier in this section in connection with the Corporation treatment centres. It is merely suggested in connection with the normal routine of the clinic, that the "914" must be freshly made up in distilled water and given very slowly. The methods of prophylaxis used in connection with the nitritoid crisis (pages 244 -45) were employed in a number of tertiary cases. They have no assessable value in regard to the prevention of skin intolerance. Recognition and removal of possible etiological factors is essential.

C. Correlation with end clinical and serological results.

The following results were obtained in this series of skin intolerance :

Table 6.

Sex and stage of disease	Total all cases	<u>Slight skin</u>			<u>Skin</u>			<u>Dermatitis</u>		
		Final W.R.			Final W.R.			Final W.R.		
		Total	-	+	Total	-	+	Total	-	+
M1 DG+ W.R.-	1	0	0	0	1	1	0	0	0	0
F1 DG+ W.R.-	0	0	0	0	0	0	0	0	0	0
M1 W.R.+	9	5	4	1	2	2	0	2	2	0
F1 W.R.+	3	0	0	0	3	2	1	0	0	0
M2	7	2	2	0	3	3	0	2	2	0
F2	16	6	6	0	8	7	1	2	1	1
Totals	36	13	12	1	17	15	2	6	5	1

Thus out of thirty-six cases, four showed an unfavourable end result - a percentage incidence of 11.1%. This is in all cases irrespective of the total time of attendance, and compares with a gross percentage of 16.6% unsatisfactory end results in five hundred and seventy cases of early syphilis. This slightly more favourable outcome, noted in cases with skin tolerance, is also seen when the end results in all types of intolerance are investigated and will later be considered.

There were four cases which were finally not serologically negative.

M1 W.R.+	Case No. 3977.	W.R.+	6-7 grams "914" in first course. No additional treatment.
F1 W.R.+	Case No. 3255.	W.R.+	Less than 3.5 grams "914" in first course. More "914" given later.
F2	Case No. 1789.	W.R.-	C.S.F.+ 5-6 grams "914" More "914" given
	Case No. 1922.	W.R.+	Partial first course only, less than 3.5 grams "914".

It need only be stated here that skin intolerance is certainly not associated with an increased percentage of unfavourable end results. The implication will be discussed at the end of this section.

It is now considered whether intolerance is the result of overdosage by continued weight of treatment or the expression of a sharp reaction to a single large dose.

In the cases thus reviewed the maximum dose was 0.95 gram of "914". The usual dose was 0.6 gram. Practically all the intolerances of importance were not subsequent to the first or second doses but appeared after a total of several grams of "914" had been given. They are due to the accumulated effect of several injections and the reactions to mercury and bismuth (chiefly stomatitis) are the expression of storage of metal.

(4) Metal reactions are now considered.

The following reactions were noted in 570 cases of early syphilis.

	Total	Hg.	Bi.
Stomatitis	43	24	19
Renal	2	2	0
Skin	1	1	0
Gastro-intestinal	?	?	0
Percentage incidence	8.07%	4.74%	3.33%

Prophylaxis is all important in the prevention of gingivitis and stomatitis. Many of the cases have never owned a toothbrush and do not want to own one. The normal uncared for mouth in the average Glasgow clinic patient is a dreadful mixture of carious, dirty, broken teeth and septic gums. Where time permits a preliminary cleansing is always advised. Chalk and a toothbrush: tincture of myrrh after the use of peroxide of hydrogen: tincture of iodine: a weak solution of Condy's fluid are generally sufficient. An attempt to

prevent mercurial mouth reactions was made in one hundred and fifty cases of tertiary syphilis. Each case took sixty grains of precipitated sulphur each night, varying the amount slightly if too marked a laxative effect was noted. The incidence of mercurialism in this series was 10.2%, indicating that this method had no prophylactic value. The best routine prophylaxis apart from local treatment of the mouth is secured by attention to the bowel. This seems to aid regular elimination of the metallic deposits in the hip muscles. It is noted that the earliest signs of gingivitis appear either at the site of the central incisors, or near still buried wisdom teeth. As a precursor an unpleasant foetid metallic odour of the breath is of prognostic help. In such cases if treatment be stopped, and if in addition to the local measures detailed for prophylaxis, salines, sulphur, intramine or sodium thiosulphate be used, the onset of gingivitis is often prevented.

It is to be remembered that the hip muscles contain depots of unabsorbed mercury or bismuth and, even though treatment be stopped, absorption of metal continues to take place. Thus in one male case of tertiary syphilis, after nine injections of one grain of calomel cream produced a foetid breath, there was an interval of ten weeks before true gingivitis was observed.

Once gingivitis or stomatitis is established, much time is required to effect a cure. It takes longer to secure a healthy mouth if mercury is the toxic agent than if bismuth has been employed. Little can be done for the patient apart from attention to the bowel, light diet and an alkaline diuretic mixture. Local cleanliness does not materially shorten the time or course of the intolerance. A very variable dose has been noted as productive of intolerance, and undoubtedly some people are unduly sensitive. In one case a blue marginal line was noted after the third injection of mercury; in another after the fourth injection of 0.2 gram of bismuth metal. These cases proved equally susceptible to further injection of the same metal, but the mercury toxic patient was able to tolerate bismuth.

Acute forms of bismuth intolerance have not been seen in early syphilis. Acute varieties of mercurial poisoning with renal and gastro-intestinal disturbance have followed the use of intravenous mercurials and have not been seen when the intra-muscular route is used. The renal cases showed enormous numbers of tube casts in the urine. There seems to be no need to employ the intravenous route for the administration of mercury. No undoubted cases of skin intolerance due to metal have been seen in early syphilis. In one instance a generalised scarlatiniform rash of eight days duration, in which there was no itching, was considered

due to mercury, but the patient was also receiving neokhar-sivan and the diagnosis remains in doubt.

The incidence of metal intolerance in tertiary cases is high. Their mouths are even more septic to start with - the patients are older. Their eliminating powers are poorer. They receive larger quantities of metal owing to their chronic disease. A severe case of ulceration of the left tonsil with bismuth pigmentation in the ulcer and its margins, as well as a general bismuth stomatitis, was seen in a case of latent neuro-syphilis (who rejoiced in the historic name of Koch). Two indubitable mercury skin rashes and two bismuth skin rashes were noted in tertiary muco-cutaneous syphilis at periods when the influence of any other drug could be excluded. They were urticarial in type, tending to scarlatiniform though rather more blotchy in appearance. They rapidly disappeared. The only treatment given was an alkaline diuretic mixture and a saline purge. No after ill effects were noted and after a short rest period, metallic tolerance seemed again complete.

(5) The association of intolerance with the final serologic-al results is now investigated.

There were five hundred and seventy cases of early syphilis: 16.6% when last seen were not serologically negative: 27.8% showed intolerance.

There were one hundred and fifty-eight cases of intolerance: 27.8%. Eighteen of these cases, or 11.3%, when last

seen were not serologically negative.

This suggests that the effective therapeutic dose lies near to the limits of toxicity.

One hundred and seventy-eight cases were treated and observed for more than two years. Twenty-two cases, or 12.4%, were not negative serologically when last examined. In these cases there were fifty-three cases, or 29.7%, which showed intolerance.

This is, of course, a selected group of cases which has received considerably more treatment than the rest of the series. Hence the percentage of serological failures is lower, and, in view of the increased treatment, the percentage of intolerance is slightly higher than the whole average percentage. The suggestion is made, in view of the relatively small increase in intolerance, that this is chiefly a feature of the initial course of treatment and analysis confirms this. Only thirty-eight cases exhibited intolerance in courses other than the first one, and of these thirty-eight, eleven also showed intolerance in their first course of treatment.

An analysis of the accidents in the eighteen cases which were finally not serologically negative is given and compared with the total incidence of reactions.

Table 7.

	Total Reactions	Reactions in unfavourable final results.
Local	6	0
Nitritoid	1	0
Fever	2	0
Malaise	23	3
Skin	17	2
Gastro-intestinal	35	4
Renal	2	0
Slight skin	13	1
Jaundice	23	0
Dermatitis	6	0
Stomatitis	43	7

Here it is noted that no surviving case of jaundice (one died) failed finally to appear cured.

This apparent increase in the favourable end result in the presence of intolerance is important and merits consideration from another angle. It is an aspect of treatment that does not seem to have claimed much of the literature and no comparable series appears to be described. Tables are accordingly shown giving the total occurrence of intolerance, and the total final unfavourable end Wassermanns by sex and stage of the disease.

Table 8.

Sex and stage of disease	Total Intolerances	Total final unfav- ourable W.R. of blood
M1 DG+ W.R.-	10	0
F1 DG+ W.R.-	1	0
M1 W.R.+	28	3
F1 W.R.+	18	1
M2	42	6
F2	59	8
Totals	158	18

Thus it is seen that out of one hundred and fifty-eight cases of intolerance, eighteen, or 11.3%, were not serologically negative when last seen. This includes all cases with or without two years of observation, and is to be compared with the figure 16.6% which represents the total incidence of unfavourable end results in the five hundred and seventy cases of early syphilis.

If those cases of intolerance which were so severe as to lead to a complete cessation of further "914" therapy be examined, the results are even more striking.

Table 9.

Sex and stage of disease	Total cases of intolerance receiving no more "914"	Total unfavourable end results
M1 DG+ W.R.-	9	0
F1 DG+ W.R.-	0	0
M1 W.R.+	20	2
F1 W.R.+	11	0
M2	30	2
F2	31	3
Totals	101	7

Here the percentage of unfavourable end results is only 7%. This represents the most successful treatment group in this series. Such cases were chiefly examples of arsenical intolerance. In many of the milder grades, treatment with "914" was not continued because the patient showed at or near the time of the intolerance a negative Wassermann result in the blood serum. Further, the percentage of relapsed Wassermann reactions in this series was very low indeed, being only 3%. When this is added to the final 7% of unfavourable results, making 10%, it is in striking contrast to the general incidence of some 25% of Wassermann variation and fastness. A certain amount of Wassermann variation had taken place in these one hundred and one intolerant cases prior to the intolerance, amounting to an additional 5%. Thus the non-

continuance of "914" therapy is not only an expression of the fear of further toxicity, but is a realisation of the attainment of a reasonably stable negative clinical and serological state.

The results of this section show that intolerance is a common feature in modern antisyphilitic treatment. Apart from general care in examining, selecting and preparing suitable cases for treatment, specific methods of preventing intolerance are lacking. Research on this matter is probably one of the most urgently required needs concerning the management of syphilis. Intolerance lessens the total amount of treatment received, and the total attendance of the patient. Intolerance does not, however, necessarily lead to unfavourable end results. On the contrary, individual intolerance in some cases seems to coincide with maximum therapeutic efficiency. Therefore increase in the average power of tolerance in a group of patients should lead to an increase in the amount of "914" and metal to be given with correspondingly increased therapeutic benefit.

Tables of Intolerances occurring in 570 cases of early syphilis.

An explanation of the various headings is given:-

"No." expresses the case number of the patient.

"Age" gives the age of the patient on first attendance.

The next fourteen groups of letters indicate the drug or drugs administered at the time when intolerance was noted, and the figures 1, 2, 3 show the number of the course or courses during which intolerance occurred. The letters indicate drugs by the usual contractions but are enumerated for reference.

AB.	-	Arsenobillon
SS.	-	Silbersalvarsan
NK.	-	Neokharsivan
NAB.	-	Novarsanobillon
St.	-	Stabilarsan
Hg.	-	Calomel cream
Bi.	-	Any metallic bismuth
Con.	-	Contraluesin
Con. Bi.	-	Contraluesin - bismuth
Other Bi.	-	Bismuth preparations other than metallic bismuth.
Kl.	-	Potassium iodide.
Na.1	-	Sodium iodide administered by intravenous route.

The next twelve headings show the nature of the intolerance, and the figures 1 to 4 indicate the severity of the condition. 1 and 2 are both to be regarded as slight, 3 and 4 as severe degrees.

"Local" includes all disabilities referable to the site of injection, such as painful arm following an intravenous injection or a painful hip following an intramuscular injection.

"Nitritoid" indicates the syndrome commonly termed the "nitritoid crisis". These are signs and symptoms immediately following the administration of salvarsan or a salvarsan substitute, which resemble the effect of an overdose of Amyl Nitrite.

"Fever" indicates those cases which showed, or produced evidence of having had, a rise in temperature subsequent to the administration of a salvarsan substitute.

"Malaise" indicates those cases which gave a history of headache, pains in the muscles and joints, loss of appetite, loss of well-being, when such symptoms were considered a sequel to antisyphilitic treatment.

"Slight skin" indicates those cases which presented prolonged itching of one or more parts, or urticaria or erythema persisting for seven days, or a small isolated patch of dermatitis without constitutional disturbance, not lasting for more than two weeks. If the condition lasted longer than two weeks it is termed "Skin".

"Gastro-intestinal" indicates those cases with disturbance of the bowel, or nausea, or vomiting or gastric pain. A very mild degree of nausea would be included under the heading "Malaise".

"Renal" indicates those cases with albuminuria found on more than a single occasion, not attributed to a syphilitic process and those cases showing haematuria or tube casts considered to be the sequel to antisyphilitic treatment.

"Jaundice" indicates those cases with the clinical signs of jaundice no matter how transient.

"Dermatitis" indicates those cases with generalised skin dermatitis accompanied by any constitutional disturbance.

"Encephalitis" indicates those cases which showed cerebral signs suggestive of endarteritis. None were seen, but the heading is inserted for completeness.

"Stomatitis" indicates those cases with mercurial or bismuth gingivitis, stomatitis or ulceration in the mouth.

Occasionally thereafter a short note is appended on the case.

The next heading "As. group" - arsenic group - indicates the amount of salvarsan substitute received during the first course. This is expressed in grams.

"More treatment" indicates that the case received further antisyphilitic treatment subsequent to the intolerance.

"More arsenic" indicates that the case received further injections of a "914" substitute.

"W.R. Blood" gives the final result of the Wassermann reaction of the blood serum.

"W.R. C.S.F." gives the final result of the Wassermann reaction of the cerebro-spinal fluid where done.

The headings adopted for the classification of manifestations of intolerance have been based on those used by Stokes in his text-book, Modern Clinical Syphilology, page 300 et seq. This affords a certain measure of comparison.

M1 DG+ W.R.-

No.	Age	AB.	SS.	NK.	NAB.	NS.	St.	Hg.	Bi.	Con.	Con. Bi.	Other Bi.	Kl.	Na.1	Flumerin	Local	Nitritoid	Fever	Malaise	Skin	Gastro-intestinal	Renal	Slight skin	Jaundice	Dermatitis	Encephalitis	Stomatitis	As. Group	More treatment	More As.	Blood	Final W.R.	C.S.F.		
1032	34				1				1														2				3.5	1		-					
3644	32			1					1				1												1		to 5								
3815	47			1					1				1							1								1							
2222	42			3					1				1					1							1		-6	1							
2935	44			1					1				1											1				1							
889	27			1	1			1																1				1							
1178	31				1			1																1				1							
1165	30				1			1																1				1							
1325	37				1			1													1							-7	1	+					
2338	30			1					1				1						2									1							
Fl DG+ W.R.-																																			
3363				2					2																			-5	1						
M1 W.R.+																																			
1941	22			1											1									1					1						
3427	31			1					12												2				1				1	+					
3934	46			1					1										1									-3.5	1	1					
4291	22				1				1				1																1	1					
1641	22			1				1															1						1	1					
1291	26				1			1																1					1						
1830	28				1			1																2					1						
2382	54			1					1				1															-5	1						
3562	27			1					1																				1						
1180	28		2																					2				3	sent & der-	1					
4216	59				2				2				2												1				1	1					
4322	56			1					1				1																1						
3996	27			1					1				1												3			sent & der-	1						
3483	27			1					1				1											1				1							
3342	26			1					1						1						1							-6	1						
3158	29			1					1																				1	1					
2021	30			1											1														1	1					
1240	19				1			1																					1						
1087	23				1			1																					1						
1434	24				1			1																					1						
1331	23			3					3																				1						
1629	21			1				1																					1						
1724	25				1			1																					1	1					
3373	29			1					1																				1						
3836	43			2					2				2																1						
3686	34			1					1																				1						
3977	23			1					1				1																3						
184	26				2			2																						1	1	1	+		

M2

No.	Age	AB.	SS.	NK.	NAB.	NS.	St.	Hg.	Bi.	Con.	Con. Bi.	Other Bi.	Kl.	Na.1	Flamerin	Local	Nitritoid	Fever	Malaise	Skin	Gastro-intestinal	Renal	Slight skin	Jaundice	Dermatitis	Encephalitis	Stomatitis	As. group	More treatment	More As.	Final Blood W.R.	C.S.F.		
4162	55			1					1										2		2													
3291		1							1												1													
3320	35	1		2					2				2								1			2										
1750	25														1												1							
1448	32		3												5	1																		
1304	25				13			13													1						1							
1393	19				12			13													1						1							
976	23		1		1			1																2										
1673	23		1					1																			1							
1785	66		1																					2										
902	24		1		1			1																			3							
157	50				1			1																	1									
247	33				2			2														1												
4190	33			1		1			1				1											1										
4101	40			1					1				1																					
4365	21				2	1			12				1																					
4392	28					1			1										1															
4284	31					1																		1										
4278	31					2																												
3915	33		1						1																1									
4072	40		2			2			2				2												1									
3941	42		1						1				1												1									
3807	33		1						1																									
2649	29		2						2																									
1792	25														1												1							
1791	31			2											2																			
1725	26		1					1																			1							
1702	26				12			1							2												1							
1220	33				1			1																			1							
987	30		1		1			1																	1									
1169	30				3			3																										
328	26				1			1																			1							
3386	30		1						1				1														1							
113	31				3			3																			1							
29	30				3			3																			1							
1550	32				1			1																			1							
1450	23				1			1																	1									
1280	18				1			1																			1							
647	30				1			1																			1							
1123	35				2			2																			1							
1158	34				1			1																			1							
1527	38				1			1																										

-3.5

-5

-6

-7

Sick after catching no protection.

F2. (Contd.)

No.	Age	AB.	SS.	NK.	NAB.	NS.	St.	Hg.	Bi.	Con.	Con. Bi.	Other Bi.	Kl.	Na.1	Flumerin	Local	Nitritoid	Fever	Malaise	Skin	Gastro-intestinal	Renal	Slight skin	Jaundice	Dermatitis	Encephalitis	Stomatitis	As. group	More treatment	More As.	Blood	Final W.R.	C.S.F.
1789	24			1				1												1	1							1	1	-	-	+	
4402	23					1					1											1						1	1	-	-	-	
4081	28			1				1				1														1		1	1	-	-	-	
3516	28			2				2				2							1									1	1	-	-	S	
4276	29					2		2				2								2								1	1	-	-	-	
2062	28			1						1											1							1	1	-	-	-	
3825	27			1				1				1													4	Ulcerative			1	W			
4028	30			1				1				1														1		1	1	-	-	-	
3013	33			1.2				1.2							2					2								-6	1	-	-	-	
2350	32			2				2				2											2					1	1	-	-	-	
4222	31			1		1		1				1														1		1	1	-	-	-	
4205	32			1		1		1				1							1							1		1	1	+	-	-	
3676	44			1				1				1											2					1	-	-	-	-	
4241	55			1		1		1				1							2									1	-	-	-	-	
4187	56			1		1		1				1							2									1	1	-	-	-	
1557	55			1				1												1	1							1	-	-	-	-	
651	22				1			1											1									1	-	-	-	-	
396	22			2															3									1	-	-	-	-	
1625	23			1				1																		1	Shingles after lumbar puncture	1	-	-	-	-	
643	21				1			1													1							1	-	-	-	-	
1061	20				1			1																			3	4 courses all	1	-	-	-	
1074	21			1				1																			1	minor intol.	-7	1	-	-	-
1269	28			1				1																			1	1	1	S	-	-	
1383	31			1				1																		2		1	1	+	-	-	
769	36			1				1											1									1	-	-	-	-	
904	36			1	1			1													1							1	1	-	-	-	
1203	24			1				1																		1		+7	1	1	-	-	-
146	24			3				3													1							1	1	-	-	-	

F2.

No.	Age	AB.	SS.	NK.	NAB.	NS.	St.	Hg.	Bi.	Con.	Con. Bi.	Other Bi.	Kl.	Na.1	Flumerin	Local	Nitritoid	Fever	Malaise	Skin	Gastro-intestinal	Renal	Slight skin	Jaundice	Dermatitis	Encephalitis	Stomatitis	As. group	More treatment	More As.	Blood	Final W.R.	C.S.F.
3042	23			1	1								1					1										1	1	-	-		
3938	24			1					1				1							1							1		1	1	-	-	
4142	24			1					1				1				1									1		1	1	-	-		
3431	20			2					2														2						1	1	-	-	
3697	29			1					1				1							3								1	1	-	-		
3081	26			1					1				1										2						1	1	-	-	
4209	27			1					1				1							2								1	1	-	-		
1090	27				1			1												2								-3.5	1	1	-	-	
1267	28				1			1																		1		1	1	-	-		
3930	29			1					1				1			2			1									1	1	-	-		
1813	34			1											1								1					1	1	-	-		
4088	30			1					1													1						1	1	-	-		
1140	34				1.2			1.2											1.1									1	1	-	-	3	
3990	50			1					1				1											2				1	1	-	-		
1922	16				1			1																	2	1		1	1	-	-	+	
1446	30				2																1							1	1	-	-		
1410	47				1			1					1								1							1	1	-	-		
1607	34			1				1													1						1	1	-	-			
3647	35			1					1										1								1	1	-	-			
4014	30						1																		4		Sent e der-		1	1	-	-	
3365	29			1					1														1					-5	1	1	-	-	
802	25				1			1																			1	1	-	-			
1763	27							1																			1	1	-	-			
3922	20			1					1				1						1									1	1	-	-		
1114	24				1			1																			1	1	-	-			
4096	18			1					1				1														1	1	-	-	?		
1657	19			1				1																			1	1	-	-			
3912	17			2					2				2			1												1	1	-	-		
3395	24			3					3										1									-6	1	1	-	-	
2420	22			1					1				1														1	1	-	-			
2932	23			1							1																1	1	-	-			

Some Chemotherapeutic Studies

Part III

Sections VII to XI

S E C T I O N VII.

LATENT SYPHILIS.

Pages 276-335.

L A T E N T S Y P H I L I S .

This section will consider the problems raised by those cases, male and female, which, having on their first arrival at the clinic a positive Wassermann reaction in the blood serum, with or without a history of antecedent syphilitic infection, present no clinical signs of disease and in whom, if infection be admitted, it has been present for more than two years. In some cases the cerebro-spinal fluid, on being examined at or near the onset of treatment or observation, presents a positive reaction to the Wassermann test. Such cases have been termed asymptomatic neuro-syphilis and have been excluded. It is a matter for discussion whether or not these cases should not here be dealt with, but they have been rejected in order to enable this series of cases to be compared with a somewhat similar group examined by a number of American investigators, and described in Venereal Disease Information, August 1932, pp. 317 - 331, and September 1932, pp. 351 - 364. Since reference will frequently be made to these papers they will be referred to henceforth as V.D.I., quoting the appropriate page.

The material consisted chiefly of ex-soldiers who desired to know if they were cured, and the husbands, wives and consorts of cases which attended the clinic, mostly with known syphilitic disease.

Certain further criteria in selecting the cases require explanation. Latency occurs as a natural phenomenon in hereditary as well as in acquired syphilis. Every care has been taken to exclude cases of hereditary disease wherever the history, facies, bones, teeth or eyes have in any way been suggestive.

Six female cases have been seen who have given birth to a syphilitic child and in whom history, examination and blood Wassermann have all been negative. Almkvist¹ records five cases out of sixty-three in which no clinical or serological evidence of syphilis was obtained. Such cases have been included by the Americans, V.D.I., p. 319. They are excluded in this series. The reason for their exclusion must be stated. Latency takes various forms. Thus, even in the first two years following infection, shorter or longer latent

1. ALMKVIST, J. Wein Klin. Wchnschr., Vienna, 1929. XLII. 97.

intervals may be encountered - such cases are more amenable to treatment than those which have completed the early cycle of clinical phenomena and have settled down to the long interval preceding the onset of tertiary signs.

Further the Americans, V.D.I., p.319, have included an unspecified number of cases without a positive Wassermann reaction of the blood "on the basis of a clear-cut history of infection inadequately treated". This seems to be unreasonable. Thus at our clinic there are numerous cases in the primary and secondary stages of syphilitic infection which, while undergoing treatment, show negative clinical and serological pictures. Many such cases default in early stages of treatment. No known standard of inadequacy of treatment can be set up, and numerous cases are recorded as apparently cured subsequent to a very small amount of treatment. Such negative cases then should receive further treatment, if the story of infection be less than two years old, but should not be included in a latent series. For similar reasons, cases showing a suspicious or weak positive Wassermann reaction of the blood serum, and of comparable age, have also been rejected. These groups of cases may reappear at the

clinic during or after the first two years following infection. If they appear during the first two years, the results of treatment are definitely more favourable than in the later time groups. During the first two years they should be regarded as latent secondary syphilis. The American report does not make this point clear, and groups all cases of latency as early, "occurring in the first four years of disease", V.D.I., p. 319, or late, "occurring after the first four years of disease", V.D.I., p. 320.

For these reasons then, none of our cases, treated or untreated, which give a history of antecedent syphilis have been included unless the date of their infection occurred more than two years before coming to the clinic.

In the selection of latent cases it must be obvious that the most careful clinical examination is required. Certain clinical conditions require special note. These are:- changes in the tongue, enlargement of the lymph glands, cardio-vascular syphilis, neuro-syphilis.

The tongue should be carefully examined in all cases. Many late syphilitics present, as their sole clinical phenomenon, a glossitis, atrophic in type, or a leucoplakia.

1

This point is also stressed by Milian in his examination of the latent syphilitic.

A generalised and typical adenitis in which the glands are small, discrete, painless and of rubber-like consistency, is almost universal in early syphilis. It is the last of the clinical signs to disappear, whether spontaneously or as the result of treatment. In many cases traces of glandular enlargement remain. Generalised adenitis is not a common feature of late syphilis, and it is to be stated that in active late skin lesions it is the exception rather than the rule. Apart from syphilis, enlarged glands are quite a common occurrence - they may be felt in healthy individuals who do hard manual work. They may occur in many cases of various types of disease seen in the medical wards of a general hospital, and in such cases they are usually felt in the groin and the neck. Enlargement of the lymph glands two or more years after the onset of syphilitic infection should only rarely be interpreted as a sign of active syphilitic disease.

The question of the early recognition of cardiovascular disease is a very difficult one. One must remember the fortuitous association of a positive Wasser-

mann reaction along with non-syphilitic cardiac lesions. Many of the older cases will show essential hypertension along with cardiac enlargement, determined either by percussion or by X-ray examination, or else suggestive symptoms such as "a dull ache across the sternum. . . .
 . . . sometimes ascribed to syphilis", to quote Lewis .
 Accentuation of the second aortic sound cannot be accepted (vide V.D.I., p. 321), as of any special syphilitic significance when in association with a positive Wassermann reaction of the blood.

Evidence of cardiac failure and cardiac asthma may be accepted as being syphilitic in nature, in the absence of other known causes, but syphilitic myocardial lesions, apart from an increase in interstitial fibrous tissue, are not common. (Lewis, loc. cit. p.213). Cases with any suspicious signs of syphilitic vascular disease have been excluded. Only one of this series has a definite history of rheumatism and this one, a female, presented an uncomplicated mitral stenosis with no sign of active rheumatic infection. In order to err on the safe side, several cases have been omitted which might reasonably be termed essential hypertension. A few cases in which a moderate degree of arterio sclerosis, without elevation of the

1. LEWIS, T., Diseases of the Heart, 1933, p. 221.

blood pressure, was present have been included.

The diagnosis of early **neuro-syphilis** is also a difficult question. Any case presenting any abnormality in the cerebro-spinal fluid has been set aside. Minor variations in the strength of the response of the deep tendon reflexes are not considered to be significant of syphilitic disease of the central nervous system. Variation is seen, for example, from time to time in the knee jerk in normal individuals, and in cases in medical wards. So, too, slight pupillary irregularities in position, shape, size, and response to light, and on accommodation, are not to be considered pathognomonic in absence of any other clinical phenomena. In older persons a certain amount of tremor, probably associated with senile changes in the mid-brain, is of common occurrence and need not be referred to syphilitic vascular lesions.

Adopting these criteria of choice, the series to be presented comprises 239 cases - 146 males and 93 females.

The question to be asked at the outset is important and far reaching. Is the treatment of latent syphilis a necessary or an advisable procedure ?

An answer is sought along several lines.

(1) Is an untreated case of latent syphilis more liable

to late clinical syphilis than a treated one ?

(2) Are cases of latent syphilis contagious ?

(3) Does hereditary transmission occur in latent syphilis ?

(1) Is an untreated case of latent syphilis more liable to late clinical syphilis than a treated one ?

Clinical latency is a normal feature of the natural history of syphilis - it is the typical state in the quiescent period preceding the tertiary manifestations, and it may extend for many years. There are, at this clinic, numerous examples of late skin syphilis with apparently complete latency over thirty years and more. The present tendency to employ arsenicals and metals whenever a lesion is noted, or whenever an abnormal serological test is discovered, has quite obscured our knowledge of this natural history of syphilis. It is known from case records that the earlier manifestations of disease are not so florid as in the past. This point is emphasised by many writers and seems to be independent of the facts of the earlier recognition of infection and the modern methods of treatment. It is

impossible to say what may be the sequence of events in the untreated latent case, or whether any natural variation has occurred in the course of treatment.

Since, however, each case of late clinical syphilis has once been latent, there is a strong a priori claim to treatment.

Information as to the fate of a number of cases, observed over a long period of time and securing little or no treatment, is required.

There is of course the series described by Bruusgaard,¹ dealing with 2181 cases of primary and secondary syphilis, observed in Oslo between the years 1891 - 1916. They received only small amounts of mercury and iodide by mouth or no treatment at all. In 1925-27, 473 of these cases were traced. Of these 164 had died and 34 deaths might be deemed due to syphilis. Of the others, 37% had developed an active lesion, 14% showed a persistent positive Wassermann reaction of the blood and 27% appeared to be cured. No other comparable series has been described in the literature. If it is assumed then, that 27% of primary and secondary syphilis is self-

1. BRUUSGAARD, E. Uber das Schicksal der nicht spezifisch behandelten Luetiker. Arch. f. Dermat. u. Syph. 1929. CLVII. 309.

limiting or self-curative, we are not entitled to extend this figure to cases which, when they appear at the clinic, have a positive Wassermann reaction of the blood, and thus to argue that 27% of them will remain healthy or even show later negative serological reactions. It is to be hoped that the 14% described by Bruusgaard as having only a positive blood Wassermann, will not receive treatment and that their end results will be duly noted.

If Bruusgaard's figure of 27% be accepted as the indication of self-limiting syphilitic infection, it will be shown in this section that approximately 80% of cases of latent syphilis, treated and observed for more than two years, are clinically and serologically negative. This appears to be a final argument in favour of treatment of latent syphilis in the interests of the individual.

Another method of approach to the question is found in the post-mortem examination of an unselected series of cases.

Thus Warthin¹ describes 43.7% as the incidence of latent syphilis for the decade 1910-1920, and 25.7% for the decade 1920-1930, in the post-mortems conducted in

1. WARTHIN, A.S. S Med. J. Birmingham, 1931. XXIV. 273.

University Hospital, Ann Arbor. The total number of autopsies, he states, was sixteen hundred and seventy-five. The smaller percentage in the later decade may be correlated with improvement in the treatment of cases of early syphilis. If these figures be accepted, they show on the one hand that a large number of syphilitic infections apparently remain latent throughout life, but on the other hand that treatment reduces the incidence of post-mortem syphilitic lesions.

(2) Are cases of latent syphilis contagious ?

Finger¹ and Jordan and Arthur¹ state it as an observed clinical fact that marital infection has been observed. V.D.I., p. 328, states that "it is impossible to tell if infection of the marital partner occurred during outspoken early syphilis or during latency", but eventually, p. 329, concludes that "the danger is considerable".

In the present series no unequivocal case of infection of a consort during the latent period has been noted. The criteria allowing of such a diagnosis are difficult to attain. It would entail an initial negative clinical and serological examination of the consort, subsequent positive findings and the exclusion of any other source

1. Venereal Disease Information, September, 1930. p. 414.

of infection.

Experimental evidence is adduced to show that latent syphilis may be infectious.

Thus Hamburger¹ describes the transmission of disease from the lymph nodes of a latent syphilitic child to a rabbit. Such a case, though here quoted, involves a definition of latency other than that of the cases of this series, but its insertion is not unjust for in this sense latency in hereditary disease is very comparable to that of acquired syphilis.

Kertesz^{2&3} states that he examined the spermatic fluid from a series of latent male syphilitics and found spirochaetes in 25%. Further, the vitreous body of a rabbit's eye was inoculated with spermatic fluid and in 50% specific tissue changes were discovered.

It must be concluded that treatment is indicated in latent syphilis to diminish the probability of conveying infection to other persons.

In further support of this opinion, information is submitted concerning the presence of syphilis in the consorts of these cases of latent syphilis, 239 in number,

1. HAMBURGER, R. Monatschr. f. kinder., Leipzig, 1929. XLII. 198.
2. KERTESZ, G. Med. J.& Rec., New York, 1930. CXXXI. 472.
3. KERTESZ, G. Med. J.& Rec., New York, 1930. CXXXII. 136.

attending the clinic, in Table 1.

Table 1.

Infection of Consorts in latent syphilis.

		1.	2.	3.	4.
	Total	Infected	Probably Infected	Probably Healthy	Healthy
Males	138	42	16	10	3
Females	79	27	20	5	6

The criteria adopted in the various columns are defined:

1. Infected - Cases examined at clinic and showing signs of syphilis or giving a story of syphilis and a positive Wassermann reaction of the blood.

2. Probably infected - Cases not examined but giving a definite record of disease or of treatment for syphilis and, at the time of questioning, a positive Wassermann reaction of the blood performed elsewhere.

3. Probably Healthy - Cases not examined, with no history of disease and the report that the blood Wassermann is negative.

4. Healthy - Cases examined in this clinic in which there were no signs of disease, no story of antecedent disease and a negative Wassermann of the blood.

In many husbands and wives included in this table, infection must have been transmitted through the marital partner at a date more than two years after the original infection was contracted. In view of the fact, later to be elaborated, that 27.6% of all latent cases at this clinic gave no history suggestive of clinical primary or secondary syphilis, it seems reasonable to conclude that some cases of contagion during latency must have occurred.

(3) Does hereditary transmission occur in latent syphilis ?

Here the evidence in favour of treatment of latent syphilis is absolutely indisputable.

The table in V.D.I., p. 329, is quoted :-

"The influence of latent syphilis on the product of conception"

Table VIII.

	Total pregnancies.	Outcome of pregnancy, per cent				
		Child healthy non-syphilitic	Child living congenital syphilis	Died in infancy	Mis-carr- iage or still- birth	In- duced abor- tion.
This series. . . .	1,467	16.9	11.1	18.4	48.9	4.5
Jean's compilation from the literature, syphilitic women.	2,000-4,000	16.6	24.0	30.2	30.3	-
Jean's normal women.	1,712	76.0	-	15.0	9.7	-

1

Jean's figures of syphilitic women include some with active syphilitic lesions. This table does not state that the pregnancies occurred in women only during latent periods and does not exclude pregnancies taking place at the outset of the syphilitic process, nor does it exclude pregnancies occurring during the first two years of the course of the disease.

The present series of 239 cases have been questioned to ascertain the outcome of pregnancy occurring more than two years after the onset of the disease, if infection be admitted. It is suggested that this will give a more accurate figure for true latent syphilis.

Table 2.

Pregnancies in latent syphilis more than two years after primary infection.

	Total children	Died young.	Known healthy	Known syphilitic.	Miscarr- iages known	Marriages of six years duration with no pregnancies.
<u>Males</u> 116	152	26	16	22	3	23
<u>Females</u> 79	167	29	23	38	58	7

1. JEANS, P.C. Syphilis and its relation to infant mortality. Aus. J. Syph., 1919. III. 114.

The children in the column "Known healthy" and "Known syphilitic", have been examined at this clinic. The state of the remaining children is not known. Many of them were adolescents or grown up, and presumably most were healthy. The number of miscarriages is, of course, not included in the first column "Total children".

This table speaks for itself. It need only be pointed out that out of 99 children examined at the clinic, 60 were found to have hereditary syphilis.

By way of contrast, the results of pregnancies in cases of latent syphilis attending this clinic are shown after adequate treatment had been given.

Table 3.

Pregnancies in latent syphilitics after adequate treatment.

	Known healthy	Known syphilitic	Miscarriages
Males	7	0	4
Females	11	0	3

All the children in the table were examined in this clinic. In spite of small numbers this shows conclusively the value of treatment of the latent syphilitic. Pregnancies occurring during the first six months of treatment are not shown in Table 3.

It is submitted that on this ground alone an overwhelming case is made out for the treatment of the latent syphilitic.

It is considered then, that the treatment of latent syphilis is advisable for the three reasons discussed.

(1) It lessens the incidence of late syphilitic lesions in the individual. (2) It prevents infection of marital partners. (3) It prevents hereditary syphilis.

The treatment of latent syphilis.

There has been little to guide one in the literature, and general principles of a type applicable to the treatment of late muco-cutaneous lesions have been applied. It was felt that in absence of any recorded data, treatment should only be continued for a period of a few months after the reversal of the positive Wassermann reaction, and that thereafter the patient should be kept under observation. In the majority of cases mercury was then prescribed in the form of Hutchinson's pill, but this was rather with the intention of inducing the patient to return at regular intervals, than with the hope of securing much therapeutic benefit. Unless there were any contra-indications, the routine treatment consisted

of the standard course of "914" and heavy metal as laid down in the section on Early Syphilis. For convenience a copy of the table of treatment is appended.

Variations in dosage of model course.

	"914"			Metal		Potassium Iodide gr. xv. t.i.d.	
	Dosage and year introduced			C.C.	Bi.		
	1919	1923	1929	1919	1924	1919	1924
1st week	.45gm.	.3 gm.	.45gm.	1 gr.	0.2gm.		Ki
2nd week	.45gm.	.45gm.	.6 gm.	1 gr.	0.2gm.		Ki
3rd week	.75gm.	.6 gm.	.6 gm.	1 gr.	0.2gm.		Ki
4th week				1 gr.	0.2gm.		Ki
5th week	.75 or .6 gm.	.6 gm.	.6 gm.	1 gr.	0.2gm.		Ki
6th week	.75 or .6 gm.	.6 gm.	.6 gm.	1 gr.	0.2gm.		Ki
7th week				1 gr.	0.2gm.		Ki
8th week	.75gm.	.6 gm.	.6 gm.	1 gr.	0.2gm.		Ki
9th week	.75gm.	.6 gm.	.6 gm.	1 gr.	0.2gm.		Ki
10th week						Ki	Ki
11th week						Ki	Ki
12th week						Ki	Ki
13th week	.75gm.	.6 gm.	.6 gm.	1 gr.	0.2gm.		Ki
14th week	.75gm.	.6 gm.	.6 gm.	1 gr.	0.2gm.		Ki
15th week	.75gm.	.6 gm.	.6 gm.	1 gr.	0.2gm.		Ki
Total weight in grams	6.75	5.55	5.85	12 gr.	2.4		

The dose of calomel cream was 1 grain of mercury; the dose of bismuth metal was 0.2 grams. Occasionally in the earlier years 0.9 grams of "914" was given in a single dose.

Further courses of treatment were given after periods of four to six months. In a considerable percentage of the more elderly cases these intercurrent periods were prolonged, and the patient received a series of intramuscular injections of mercury or bismuth without any concomitant "914" being administered.

It may be objected that one course of "914" is not enough under any circumstances, and that this relatively small amount of treatment may tend to the appearance of neuro syphilis. Thus Naegeli¹ holds that intensive and repeated treatment is indicated, though he produces no evidence in support of this statement. It will be shown later that the percentage incidence of neuro-syphilis is low in treated latent cases, and that only one case has developed when a negative Wassermann test was obtained from the cerebro-spinal fluid at the time of the patient's first coming to the clinic.

The cases are deemed to have had adequate treatment when they have received the equivalent of two courses of combined "914" and metal, and have been observed for one year from the end of the second course. Some cases which

1. NAEGELI, O. Schweiz. med. Wehnschr. Basel, 1929.
LIX. 697.

showed negative Wassermann tests at the end of the first course received no further injections of "914" and remained serologically negative. These are included in the term "adequate" if the time period is correct.

Cases other than these are termed inadequately treated.

The result of the case is called satisfactory if the final clinical and serological result is negative. If the end result does not fall into this category the case is termed "unsatisfactory".

Table 4.

Results of treatment showing adequate (A) and inadequate (I) treatment, satisfactory (S) and unsatisfactory(U) results.

Treatment	Adequate		Inadequate	
	S.	U.	S.	U.
Males	39	42	15	50
Females	29	31	5	28
Totals	68	73	20	78

In this preliminary table an end Wassermann reading of "suspicious" has been termed unsatisfactory.

Out of the seventy-eight cases receiving inadequate treatment and showing unsatisfactory results, sixty-four attended for less than one year.

This table shows that:-

- (1) Of one hundred and forty-one cases receiving adequate treatment, 48.2% showed a satisfactory result and 51.8% showed an unsatisfactory result.
- (2) Of ninety-eight cases receiving inadequate treatment, 20.4% showed a satisfactory result and 79.6% showed an unsatisfactory result.

These figures are only presented to stress one point considered to be of some importance. It will be noted that a small number of these cases can be adequately treated and yet be slightly under a two years period of observation. These cases which have completed a full two years of treatment and observation will be considered in greater detail. The results are better in every way, and this is considered to indicate the fact that a number of serological reactions in well treated cases show a reversal from positive or weak positive to negative with the lapse of time.

The comparable figures are one hundred and five cases observed for more than two years of which fifty-three or 50% showed a satisfactory result, but if "suspicious" end Wassermanns be termed satisfactory, the percentage rises to 62.8%.

In V.D.I., pp. 357-359, the composite results of five clinics are described. The percentages of satisfactory results vary from 60.2% in a clinic which gives "continuous arsphenamine in the early months - alternating with courses of mercury by inunction or an insoluble bismuth salt", to 17.5% in a clinic which gives "intensive short courses (3 daily doses) of arsphenamine, followed by a course of mercury by inunction or an insoluble bismuth salt - followed by an average rest period of 4 - 6 months. Continued for 4 to 6 or more such courses." The average percentage of satisfactory results is given as 51.7%.

The 105 cases observed for more than two years are next examined and the next three tables now presented show the details of all these cases - giving details of male, female and total cases.

An explanation is given of the headings of the tables.

No. of As. Inj. - Number of injections of "914" given throughout the period of observation.

Metal - Column indicating the administration of mercury or bismuth by intramuscular injection.

M. - Much metal and indicates more than twenty injections.

L. - Little metal and indicates twenty or fewer injections.

The total number of cases in each group is then shown.

Satisfactory indicates that the final clinical observation and serological tests are negative. Under this heading are shown separately the total number of cases, the number of clinical relapses, and any serological relapses giving the grade of serological change as "+" - positive, "w" - weak positive, and "s" - suspicious. Then follows a column indicating the cases which when last observed showed a "suspicious" reaction of the Wassermann test on the blood serum. The next main heading "unsatisfactory" shows the state of the blood Wassermann, whether + or w (weak positive) when last noted, the clinical relapses and the number of cases which exhibited an unchanged positive reaction of the Wassermann of the blood serum throughout the two years and are termed "W.R. fast".

Table 5.

Males observed for more than two years.

No. of As.Inj.	Metal	Total cases	Satisfactory.				Result.							
			Total Satis.	Clin. Rel.	Sero.Rel.		Final W.R. Susp.	Clin. Rel.	Unsatisfactory.					
					+	w			w	+	W.R.Fast	Total Unsats.		
0	Much	1	1											
	Little	5	4		1				1					1
1 - 4	Much	1											1	
	Little	2	1						1		1			1
5 -10	Much	4	3				1							
	Little	6	2				2		1		1		1	2
11 -20	Much	6	4		1								2	
	Little	10	4	1	1	1	2				1	3	3	4
21 -30	Much	17	6		5	1	2				4	5	5	9
	Little	1										1	1	1
31 -40	Much	4	2		2						1	1	1	2
	Little													
40	Much	4	2		2		1		1		1			1
	Little	1										1	1	1
		62	29	1	10	2	2	8	2	7	18	15		25

Table 6.

Females observed for more than two years.

No. of As.Inj.	Metal	Total cases	Satisfactory						Result						
			Total Satis.	Clin. Rel.	Sero.Rel.		Final W.R. Susp.	Clin. Rel.	Unsatisfactory		Total Unsats.				
					+	w			+	w					
0	Much	3					1	1	1						
	Little														
1 - 4	Much	1	1												
	Little	1	1			1									
5 -10	Much	4	2	1	2		1			1					1
	Little	4	3			1				1					1
11 -20	Much	8	4			1	1			1			1		3
	Little	5	5			1	2								
21 -30	Much	12	7		1	5	1			1			2	2	4
	Little	1	1												
31 -40	Much														
	Little														
40	Much	4					1			1			3	2	3
	Little														
		43	24	1	3	7	4		1	5		7	7	5	14

Table 7.

Male and female cases observed for more than two years.

No. of As.Inj.	Total Metal cases	Satisfactory				Result			
		Total satis.	Clin. Rel.	Sero.Rel.		Final W.R. Susp.	Clin. Rel.	Unsatisfactory	
				+	w s			w	+ W.R.Fast
0	Much 4	1			1		1	1	2
1 - 4	Little 5	4		1				1	1
	Much 2	1				1			1
	Little 3	2		1				1	1
5 - 10	Much 8	5		0	2		1		1
	Little 10	5		1	2		2	1	3
11 - 20	Much 14	8		1	1		2	3	5
	Little 15	9		2	2		1	3	4
21 - 30	Much 29	13		6	3		5	8	13
	Little 2	1						1	1
31 - 40	Much 4	2		2			1	1	2
	Little								
40	Much 8	2		2	2		4	2	4
	Little 1						1	1	1
	105	53		13	13		14	24	39

The broad conclusion shown by these tables is that out of one hundred and five cases observed for more than two years, fifty-three or 50% were clinically and serologically negative at the last time of observation, and that thirteen or 12.4% showed only a suspicious Wassermann reaction of the blood serum, making a total of sixty-six or 62.8% apparently cured. A survey of the tables indicates that this percentage of favourable results has been compiled from cases receiving very varying amounts of treatment. Thus some received no arsenicals, others received more than forty injections. Some received fewer than twenty injections of metal, others received as many as two hundred injections of a heavy metal. The reason for this great variation becomes apparent when it is recalled that treatment is suspended a few months after a favourable serological Wassermann result has been achieved. This is further indicated by the small number of cases in the smaller treatment groups which showed Wassermann relapse, and conversely Wassermann relapse in those cases eventually presenting a successful outcome, becomes more frequent in the larger treatment groups. The information contained in these tables may thus be regrouped to indicate what proportion of cases of latent syph-

illis are likely to give a favourable response to graded amounts of treatment.

Table 8.

Treatment received	Cases	Favourable results:
1. Up to 1 course	105	23 = 21.9%
2. 1 to 2 courses	73	20 = 19%
3. 2 to 3 courses	44	17 = 16.1%
4. 3 to 4 courses	13	2 = 1.9%
5. More than 4 courses	9	4 = 3.8%

Total=57.0%

From this it may be broadly stated that if three courses of ten injections of "914" equivalent to 5.5 grams of "914" per course, and three courses of bismuth comprising twelve injections or 2.4 grains of bismuth metal in each course be given to cases of latent syphilis, 57% of those so treated will appear clinically and serologically cured after the lapse of two years. It is interesting to note that this figure is closely comparable to those figures attained in the American series. In V.D.I., p.359, are given the corresponding figures for the five co-operating clinics termed A, B, C, D, E.

"Table XIII - V. D. I., p. 359".

Results of treatment of latent syphilis by clinics limited to patients observed for two or more years.

	Patients	Results Satisfactory
Clinic D	176	60.2
Clinic A	271	55.3
Clinic B	386	55.2
Clinic C	66	53.0
Clinic E	114	17.5
Total	1,013	51.7

In order to consider comparative methods of treatment the standard methods of treatment of these clinics are abstracted from V.D.I., p. 358.

Plan of treatment in the five co-operating clinics.

"Table XII - V. D. I., p. 358."

CLINIC A . . . Treatment intermittent; a combined course of arsphenamine plus a soluble mercurial or bismuth salt; followed by a course of mercury by inunction or a soluble bismuth salt; followed by an average rest period of two months. A minimum of four such courses.

- CLINIC B . . . Treatment continuous; courses of arsphenamine alternating with mercury by inunction or an insoluble bismuth salt; continued until blood Wassermann reaction has become and has remained negative for one year, or, in Wassermann fast cases, arbitrarily for two years.
- CLINIC C . . . Treatment continuous; courses of arsphenamine or bismarsen alternating with mercury by inunction or an insoluble bismuth salt. A minimum of three such courses.
- CLINIC D . . . Treatment continuous during early months; courses of arsphenamine alternating with courses of mercury by inunction or an insoluble bismuth salt. As compared with other clinics, less total arsphenamine and much more heavy metal. After the first year, often gives courses of mercury or bismuth, separated by rest periods over a period of many years.
- CLINIC E . . . Treatment intermittent; intensive short courses (3 daily doses) of arsphenamine; followed by a course of mercury by inunction or an insoluble bismuth salt; followed by an average rest period of three to four months. Continued for four to six or more such courses.

The similarity of results is as striking as the varied manners in which they have been achieved. On the whole, the best American figures show a predominance of metal treatment while the worst figures are gained by intensive

short courses of arsphenamine. This series has been treated by "914" compounds and not by the "606" series, and it is interesting to note that cases have not apparently suffered therefrom.

In view of the importance attached to mercurial and bismuth treatment in the American series, the 105 cases in Table 7 are regrouped to show the effects of much arsenic (more than ten injections), little arsenic (ten or fewer injections), much metal (more than twenty injections) and little metal (twenty or fewer injections).

Table 9.

	Total	Satis. Result	W.R. "susp"	Final Results		
				W.R. w.	W.R. +	W.R. Fast
Little As. x Little M.	18	11	2	1	3	2
Little As. x Much M.	14	7	3	3	1	0
Much As. x Little M.	18	10	2	1	5	5
Much As. x Much M.	55	25	6	8	16	13

These figures are confusing. At first sight they offer no help in the choice of methods of treatment, but they require interpretation in the light of Table 8 which indicates that an early favourable result is withdrawn

from further treatment and that a persistently Wassermann positive case will receive much As. and much metal. A consideration of the two tables does not appear to bear out the American contention, implicit in their quoted tables and explicit in V.D.I., p. 364, that large amounts of heavy metal are an essential feature in treatment.

A further observation may be suggested from a consideration of Table 8. In view of the fairly small amounts of treatment, 21.9% - 19% - 16.1% in series, in view too of Bruusgaard's statement that 27% of untreated syphilis is spontaneously cured or self limited, it seems reasonable to suggest that the broad natural tendency of latent syphilis is towards arrest or even cure. This is further shown in this series by the absence of clinical and serological relapse after two years' observation.

Before giving a final opinion as to the amount of treatment advisable for cases of latent syphilis, the unfavourable results must be considered, and thereafter some special factors which might or might not have a bearing upon the general results.

From Table 8, it is seen that out of 105 cases treated and observed for at least two years, twenty-five or 23.9% had a positive Wassermann reaction of the blood

serum, and 14 or 13.3% a weak positive result when last observed - a total of 39 or 37.1% of unfavourable results. These cases, like those showing satisfactory results are now also given, graded in accordance with the total amount of treatment received.

Table 10.

Group	Treatment received	Cases	Final serological result	
			+	W.R. Fast
1.	Up to 1 course	105	9	2
2.	1 to 2 courses	73	9	6
3.	2 to 3 courses	44	14	8
4.	3 to 4 courses	13	2	1
5.	More than 4 courses	9	5	3

The final cases occurring in groups 1 and 2 comprised defaulters or a few patients who were intolerant of arsenic. Those in groups 3, 4 and 5 might be deemed to have had a reasonable amount of therapy. It should be noted that the average case of latent syphilis - presenting no lesions and feeling perfectly well, will only allow some three courses or so of treatment and thereafter prefers to make the best of his serological state instead of

submitting to an indefinite prolongation of what seems to him rather a painful and pointless course of action. It is next noted that out of twenty-five cases which, when last seen, were Wassermann positive, no fewer than twenty or 19% of the total 105 cases observed for more than two years were Wassermann fast throughout their whole time of attendance. The record was achieved by a female case who has remained Wassermann fast for 137 months in spite of very large doses of every type of anti-syphilitic drug. Out of these twenty (19%) of Wassermann fast cases, twelve remained fast after adequate treatment, and three cases out of nine which received very large amounts of treatment, persistently showed a positive Wassermann reaction of the blood serum.

It would appear that some 11% of latent syphilis remains Wassermann fast no matter how much treatment is given. It should be noted that all these cases were clinically well, and have been so for observed periods varying from two to eleven years. On this ground then, a certain percentage of failures by this type of therapy seems inevitable and from Tables 10 and 8 it may be suggested that a case of latent syphilis which does not show signs of clinical relapse, which has not shown any tendency towards variation of a positive Wassermann reaction, which has received the equivalent of three

courses of "914" and heavy metal, and which has been treated and observed for two years, might reasonably be kept solely under observation provided that there is no contingency of pregnancy occurring.

On the other hand since only five out of the final twenty-five positive Wassermann results showed any variation in the blood serum Wassermann reactions, and since (Table 7) twenty-two out of fifty-three satisfactory cases showed Wassermann relapse at some period in the two years, chiefly after receiving fairly large amounts of treatment, any temporary reversal of a positive serologic test should be considered a good omen, and treatment should be continued for as many years as may be necessary to induce a permanent negative serological result, or as may be permitted by the patient.

Certain other factors which might affect the validity of these hypotheses are now considered. The age of the syphilitic infection when the patient is first seen at the clinic is investigated.

The duration of the infection is thus examined next.

Table 11.

The duration of the syphilitic infection.

	Total	Less than four years	Less than ten years	Less than twenty years	More than twenty years	no known infection
Males	146	25	38	42	21	20
Females	93	16	18	14	0	45
Total	239	41	56	56	21	65

Thus out of 239 cases, 65 or 27.6% gave no history suggestive of primary or secondary syphilis. Undoubtedly patients suffering from venereal disease frequently give false information or withhold relevant data, but this percentage must indicate clearly that a considerable number of early infections produce no local reaction, or, at any rate, such slight local reaction as to escape the patient's observation. It will be shown in the section dealing with syphilis of the nervous system, that a considerable number of cases give no history of primary or secondary disease. Here it may be stated that no case of the sixty-five male and female patients giving no history of early syphilis, has developed signs of neuro-

syphilis. Of these sixty-five cases, twenty-eight received an inadequate amount of treatment; four of those were observed for more than two years.

The point is worthy of mention from another angle - namely that symptomless early syphilis does not necessarily lead to neuro-syphilis.

It will be noted from Table 11 that the percentage of unknown early infections is higher in female patients - forty-five out of ninety-three cases or 48.3%. The corresponding figure for the male cases is 13.7%. This is especially important with regard to potential pregnancy. Maternal syphilitic infection is accepted as the commonest factor in hereditary syphilis. Indeed the question as to whether a woman may give birth to a syphilitic child and remain uninfected herself is denied by many observers. In this connection it is worthy of note that six women attending this clinic have given birth to syphilitic children but have themselves presented no signs of syphilis either clinically, serologically or in respect of their history.

When the result of pregnancy in latent syphilitic females is correlated with this absence of history in 48.3% of them, it becomes obvious that a routine examin-

ation of the blood by the Wassermann test is essential wherever any suspicion of syphilis is entertained, and its extended routine application might well clear up a number of apparent clinical puzzles.

It may next be asked whether this symptomless syphilis prejudices the individual's future to an extent greater than in these cases giving a history of early disease, for it may be suggested that the patient's failure to react to the syphilitic infection indicates an increased unfavourable prognosis. The series of cases here dealt with is not large enough to base a firm opinion thereon, but the actual results are as under:-

Table 12.

Final results of cases receiving adequate treatment in terms of known and unknown early disease.

	Known infection		No. known infection		Total
	Final result Sat.	Final result Unsat.	Final result Sat.	Final result Unsat.	
Males	34	38	5	4	81
Females	16	16	13	15	60
Totals	50	54	18	19	141

Although the series is a small one, yet there is no evidence to suggest that latent syphilis with no antecedent history of infection is more difficult to treat successfully than cases in which a definite history of early syphilitic infection is obtained.

It has been suggested that in such symptomless latent syphilis, the factor lies with the strain of spirochaetes rather than in the immunity reaction of the patient. If this be so, one might expect to find this lack of early signs in both husband and wife. Such is the case in eight couples out of this series.

The age of the syphilitic infection is now considered in terms of treatment and final result.

Table 13.

The age of the latent syphilitic infection in terms of the outcome of treatment.

FEMALES

Treatment	Result	Total cases	Age of infection in years				
			Less than 4	5 to 10	11 to 20	More than 20	Unknown
Adequate	Sat.	29	3	8	5	-	13
Adequate	Unsat.	31	4	6	6	-	15
Inadequate	Sat.	5	2	0	0	-	3
Inadequate	Unsat.	28	7	4	3	-	14
Totals		93	16	18	14	-	45

MALES

Treatment	Result	Total cases	Age of infection in years				
			Less than 4	5 to 10	11 to 20	More than 20	Unknown
Adequate	Sat.	39	11	11	7	5	5
Adequate	Unsat.	42	4	10	18	6	4
Inadequate	Sat.	15	6	4	4	0	1
Inadequate	Unsat.	50	4	13	13	10	10
Totals		146	25	38	42	21	20

Table 14.

MALE and FEMALE combined.

Treatment	Result	Total cases	Age of infection in years				
			Less than 4	5 to 10	11 to 20	More than 20	Unknown
Adequate	Sat.	68	14	19	12	5	18
Adequate	Unsat.	73	8	16	24	6	19
Inadequate	Sat.	20	8	4	4	0	4
Inadequate	Unsat.	78	11	17	16	10	24
Totals		239	41	56	56	21	65

In this table a final Wassermann result of suspicious is considered an unsatisfactory result.

An inspection of the combined table of males and females indicates a more favourable outcome for early latency i.e. latency of less than four years duration. There may appear too, a slightly more favourable outcome in the case of those whose infection is not more than ten years old, but the indications are slight, and the numbers of cases are small. Still this table suggests the importance of pursuing, vigorously, treatment in the case of those whose latency is of shorter duration. It might appear that this table offers a counter argument to the

suggestion brought by the earlier figures examined in this section, namely that there is a spontaneous tendency to arrest or cure in many cases of latent syphilitics, but the later time periods merely indicate those cases in which the Wassermann reaction was found positive at the clinic and are comparable with the cases which compose Bruusgaard's 14% of Wassermann positives.

A comparison of the age of the patient and the result of treatment is now made.

Table 15.

Age groups x results of treatment.

MALES.

Satisfactory results

Treatment	Total cases	Age in years									
		-20	-25	-30	-35	-40	-45	-50	-55	-60	+60
Adequate	39		4	6	8	10	4	5	1	1	
Inadequate	15		2	4	3	3	2	1			
<u>FEMALES.</u>											
Adequate	29		1	6	5	6	7	4			
Inadequate	5		1			2	1				1
Totals	88	0	8	16	16	21	14	9	1	1	1

Table 16.

MALES

Unsatisfactory results (either relapse or W.R.fast)

Treatment	Total cases	Age in years.									
		-20	-25	-30	-35	-40	-45	-50	-55	-60	+60
Adequate	42			3	10	11	8	7	2		1
Inadequate	50		2	7	10	8	5	8		2	3
<u>FEMALES</u>											
Adequate	31		4	4	9	6	3	4	5	1	
Inadequate	28		8	3	6	4	3	1	1	1	1
Totals	151	0	14	17	35	29	19	21	8	4	4

This table is merely of interest in showing the age of incidence of arrival at the clinic of cases of latent syphilis.

A curious point emerged on analysis, namely that if a female knows that she has a primary infection, she tends to come at an earlier date than does a male, whereas when there is no knowledge of primary disease the period of latency prior to coming to the clinic, tends to be longer in the female.

The age groups of those cases male and female which received adequate treatment are shown separately.

Table 17.MALE and FEMALE

Adequate treatment.

Result	Total cases	Age in years.									
		-20	-25	-30	-35	-40	-45	-50	-55	-60	+60
Satis.	68		5	12	13	16	11	9	1	1	
Unsatis.	73		4	17	19	17	11	11	7	1	1

Here there is seen a slightly more favourable outcome up to thirty years of age. This is probably only correlated with the age of latency and is not an expression of the actual age of the case. A similar absence of an age factor in treatment results is noticed in the section on Early Syphilis.

No other change of note is seen - the figures in the -55 years group are too small to be conclusive.

One interesting observation may be made - out of 239 cases, 156 were under forty years of age, and out of 93 females. 65 were under forty years of age. All of these cases are still young and are still subject to the heavy strains of work of all kinds; for all, there is a reasonable prospect of children. This large proportion of relatively young cases of latent syphilis is merely another

argument in favour of treatment.

The question of the final results is now considered in terms of antecedent treatment - this treatment has been given at or near the onset of disease in every case.

Table 18.

Effects of previous treatment on results.

<u>MALES</u>			Previous treatment						
Treatment	Result	Total	No Treat- ment	Medi- cinal	"Inject- ion"	Metal Injs.	Arsenical		
							-10 inj.	+10 inj.	not known
Adequate	Satis.	39	19	6	2	2	6	3	1
Inadequate	Satis.	15	5	3			3	3	1
Adequate	Unsat.	42	21	12	1	1	3	3	1
Inadequate	Unsat.	50	26	6	2	3	7	5	1
<u>Females</u>									
Adequate	Satis.	29	21	2			1	3	2
Inadequate	Satis.	5	3	1		1			
Adequate	Unsat.	31	26	2			2	1	
Inadequate	Unsat.	28	21	4			2	1	

It is rather surprising that nineteen cases had received more than ten injections of some arsenical preparation, while it is less so to note that twenty-four had received fewer than ten injections and six an unknown amount. At the other end of the scale stand one hundred and forty-two cases out of two hundred and thirty-nine who had received no treatment at all. In none of these one hundred and forty-two cases had any tertiary manifestation appeared. The percentage is higher in the female, 76% against 55.4% in the male. This is surely an argument in favour of the statement that syphilis runs a more benign course in the female than in the male.

If the fact of previous arsenical injections be compared with the outcome in adequately treated cases, it is found, though the numbers are small, that of sixty-eight satisfactory results, six had had more than ten injections of arsenicals, and of seventy-three unsatisfactory results four had had more than ten injections of arsenical preparations. At any rate the earlier treatment did not prejudice a satisfactory result.

Clinical Relapse in Latent Syphilis.

It is difficult, while observing the well-being of a series of individuals undergoing anti-syphilitic treatment, of whom a considerable proportion are over the age of forty, to state with accuracy how many of the various lesions seen from time to time are to be ascribed to syphilis and how many may be due to other factors, degenerative, infective or nutritional. It would appear reasonable to omit pneumonias and erysipelas from a list of syphilitic relapses, but the question is much more difficult to answer in the case of an obstinate secondary anaemia or a progressive arterial degeneration. In order to provide as complete data as possible, a list is now appended giving certain details concerning all cases in which any dubiety might exist, with a note as to the conclusion reached. The cases are shown in series by sex, paying attention to whether treatment was adequate or inadequate and whether the final result was satisfactory or unsatisfactory.

Development of disease while undergoing anti-syphilitic treatment.

MALES.

Cases receiving adequate treatment and showing a satisfactory result.

<u>Case No.</u>	<u>Years since primary</u>	<u>Age</u>	<u>Lesion</u>	<u>Time appearance after first attendance in months:</u>	<u>Due to Syphilis.</u>
674	16	47	Recurrent herpes of penis. C.S.F. negative.	26	No.
2827	19	39	Hyper-thyroidism. Well two years later.	10	<u>Yes.</u>
1544	10	54	Stricture of urethra. No evidence of G.C.	6	No.
1797	12	35	Eczema right ear. Adenitis.	4	<u>Yes.</u>
2831	?	39	Fibrosis of lung. Later T.B.	12	No.
4086	3	37	Secondary anaemia.	4	No.

Cases receiving adequate treatment and showing a final Unsatisfactory result.

1568	23	48	Corneal Ulcer.	101	<u>Yes.</u>
1811	14	40	Fixed pupils. Peripheral neuritis. C.S.F. negative.	12	No.
2496	12	36	Psoriiform rash not changed by treatment.	4	No.
1219	10	35	G.P.I. C.S.F. - at out-set, + in	37	<u>Yes.</u>

<u>Case No.</u>	<u>Years since primary</u>	<u>Age.</u>	<u>Lesion.</u>	<u>Time appearance after first attendance in months,</u>	<u>Due to Syphilis</u>
2075	19	41	Peripheral neuritis.	12	No.
3888	14	41	Persistent headache. No C.S.F.	6	<u>Yes.</u>
1549	2	38	Nerve deafness. No C.S.F.	13	<u>Yes.</u>
1194	22	42	Giddiness (Vascular?) C.S.F. -	10	<u>Yes.</u>
3834	10	31	Gumma of larynx.	11	<u>Yes.</u>
3961	30	46	Phlebitis.	10	No.
3384	30	48	Fibrosis of lung.	14	<u>Yes.</u>

Cases receiving inadequate treatment and showing satisfactory results.

NONE.

Cases receiving inadequate treatment and showing a final unsatisfactory result.

932	?	35	Tabes Dorsalis. No C.S.F.	53	<u>Yes.</u>
1920	5	43	Papular rash.	3	<u>Yes.</u>
2988	24	45	Herpes zoster. C.S.F. -	5	No.
2256	10	31	Eczema right hip. Lamp- lighter's irritation.	5	No.

<u>Case No.</u>	<u>Years since primary</u>	<u>Age</u>	<u>Lesion.</u>	<u>Time appearance after first attendance in months.</u>	<u>Due to Syph-ilis.</u>
4280	13	35	Neuritis ? fibrositic.	8	No.
3491	?	49	Achlorhydria and Stasis.	22	No.

FEMALES.

Cases receiving adequate treatment and showing a final satisfactory result.

1745	?	35	C.S.F. "S".	80	No.
1606	?	29	Ulceration of legs. Varicose element.	16	<u>Yes.</u>
3438	10	36	Papular rash. Ala nasi.	40	<u>Yes.</u>

Cases receiving adequate treatment and showing a final unsatisfactory result.

3811	8	47	Gumma of clavicle.	34	<u>Yes.</u>
3893	?	43	Variable glycosuria.	12	<u>Yes.</u>
1395	9	32	Osteo arthritis. Knee.	7	<u>Yes.</u>
2212	3	27	Gumma of sternum.	6	<u>Yes.</u>
1207	?	30	C.S.F. -, then C.S.F. +	6	<u>Yes.</u>
1975	?	57	Vascular degeneration also alcoholic.	12	<u>Yes.</u>

Cases receiving inadequate treatment and showing satisfactory results.

NONE.

Cases receiving inadequate treatment and showing an unsatisfactory result.

<u>Case No.</u>	<u>Years since primary</u>	<u>Age</u>	<u>Lesion.</u>	<u>Time appearance after first attendance in months.</u>	<u>Due to Syph- ilis.</u>
2129	?	40	Tremor of hand. C.S.F. -.	18	No.
3146	?	56	Sluggish pupils. Later C.S.F. -.	4	No.

From these observations the following is constructed.

Clinical Relapsessin Latent Syphilis.

Total cases	Type of Relapse.			
	Skin and Mucous Membranes.	Cardio Vascular	Nervous system.	Organs
239	8	2	5	4
	3.9%	.9%	2.4%	1.7%

Total Cases

239

Total Relapses

19

= 8.9%

In examining these figures, it is to be noted that fourteen of these nineteen relapses occurred within two years, and that, of our one hundred and five cases observed for more than two years, five cases showed relapse after two years, equivalent to 5%.

The American figures from the individual clinics as recorded in V.D.I., p. 359, are given for comparison.

Total Relapse by Clinics in patients observed for two years or more.

	Patients	Clinical Relapse
Clinic D	176	3.4
Clinic A	271	3.0
Clinic B	386	6.7
Clinic C	66	10.7
Clinic E	114	--
Total	1,013	4.6

While the American series gives the percentage of clinical relapse in 1,013 cases observed for two or more years, relapses seen in the total cases grouped according to the quantities of arsenic and heavy metal received,

V.D.I., p. 363, are given in series as 10.6%, 6.5%, 10.3%, 13.3% - a very significant difference, which probably indicates the total incidence of relapse. With these figures the percentage 8.9, of this series compares favourably.

There seems little to be gained by further subdividing our cases of clinical relapse to indicate the various amounts of treatment given before relapse took place. From the lists provided may be seen the numbers of relapse that occurred, in terms of the adequacy of treatment received and the final outcome - and it is apparent from the relative numbers that clinical relapse is of bad omen in that, though generally curable in its manifestations, there is a slightly greater tendency towards a final unfavourable outcome, even in spite of adequate treatment.

It is, however, interesting to examine in greater detail the five cases which showed clinical relapse two or more years after their first attendance at this clinic. The cases are summarised:

1568 - A man of 48 years of age, infected twenty-three years ago, received adequate treatment at this clinic and after an absence of twenty-nine weeks returned in the one hundred and first month of

his period of observation with a corneal ulcer of right eye - thought to be syphilitic by this clinic and by the Glasgow Eye Infirmary. He had attended regularly; there were no gaps in his treatment and he was not a Wassermann fast case.

- 932 - A male, aged 35, had no knowledge of primary infection. There was no initial examination of the cerebro-spinal fluid. After three injections of N.K. = 1.2 grams and three injections of calomel cream, he defaulted for fifty-two months. He then reappeared with developed tabes dorsalis.
- 1219 - A male, aged 35, with a history of infection ten years earlier, presented a negative clinical and serological picture of both blood and C.S.F. He had one period of default of thirty weeks after his second course on injections. He was not W.R. fast. He received 25.95 grams of "914", 49 injections of heavy metal and 66 grams of intravenous Nat. G.P.I. steadily developed after the third year and after sixty-three months attendance he was admitted to a mental hospital. The C.S.F.

became positive to the Wassermann test.

3811 - A female, aged 47, had a primary lesion not treated eight years earlier. She attended regularly, received adequate treatment, was not W.R. fast, but showed at the thirty-fourth month a gumma at the right sterno clavicular junction. Observation subsequent to the period when these case records were closed, indicates a negative clinical and serological result for the past eleven months in response to further treatment.

3438. - A female, aged 36, with no history of infection developed a small papular rash in the right ala nasi during the fortieth month of observation at the clinic. She attended regularly, received adequate treatment, was not W.R. fast, and has presented a final satisfactory clinical and serological result.

These cases are on the whole well treated ones. It is considered that their incidence is not sufficiently high to justify the indefinite prolongation of treatment in all patients. It is noted that none of the cases

were Wassermann fast. It is thought that after adequate treatment, as laid down, has been given and if a negative clinical and serological picture is obtained, the individual is then sufficiently safeguarded by regular periods of observation.

Cerebro-spinal fluid examination in latent syphilis.

It is regretted that, for reasons fully explained in the section on early syphilis, only a small number of cases have been examined on or near the date of first attendance.

Forty-three out of two hundred and thirty-nine cases on examination, showed a negative Wassermann reaction in the C.S.F. and seven gave a "suspicious" Wassermann reading, subsequently to show negative tests. Of these fifty, forty-nine remained without clinical signs of nervous involvement, one developed neuro-syphilis - case number 1219, which in three years became a general paralytic.

This case of G.P.I. developing three years after a negative clinical and serological examination, and thirteen years after the primary infection, is particularly

interesting and particularly disappointing. It is widely held that not only in latent syphilis, but in late muco-cutaneous and visceral active syphilis, an initial negative examination of the C.S.F. is sufficient to allow of a favourable nervous prognosis. V.D.I., p. 330, states "A negative spinal fluid . . . is a practical guaranty against the subsequent development of neuro-syphilis (excepting a more or less purely vascular involvement)". Our series admittedly shows only one such case, but this out of fifty negative C.S.F. cases is comparable to our total incidence of neuro-syphilis which is 2.4%. Even though this series is small it does not bear out the American contention. Still it has to be noted that the American statement is based upon the examination of the C.S.F. made in 1,013 cases out of a total in their latent series of 1,936 patients.

It is apparent that further efforts must be made in our clinic to secure the early examination of the cerebro-spinal fluid in a larger percentage of cases of latent syphilis.

Wassermann fast cases of latent syphilis.

In this series of 239 there are twenty cases which have shown no variation from the initial positive Wasser-

mann reaction, which when last seen have still been Wassermann fast and have been observed for two years or more. These comprised five out of ninety-three females and fifteen out of one hundred and forty-six males. Three male cases defaulted after a few weeks of treatment. One case returned in four years with tabes dorsalis and one case returned in two years with a papular rash. The remaining seventeen cases received adequate treatment throughout the period of observation and none showed any signs of clinical relapse. As there were seventeen cases of relapse amongst a total of one hundred and forty-one cases adequately treated, this is rather unexpected. No factor common to all of these seventeen cases has been noted. They included males and females of varying ages, of varying duration of latency, of varying stories in respect of the type of early infection, married and single, parous and non-parous, and they exhibited a general diversity in bodies and mental build.

This lack of clinical relapse may be merely a coincidence or it may be of significance. No mention of the point is found in the American series, nor are Bruusgaard's 14% of Wassermann positives in untreated syphilis comparable. It is strongly suggested, however, that such cases are suitable for detailed serological

investigation, for the complete absence of clinical phenomena must raise some doubt as to the interpretation of the significance of this continually positive serologic result as a syphilitic manifestation. There is, too, some further justification for the opinion already offered, that after adequate treatment for two years, Wassermann fast latent syphilis may only require observation and not further treatment. V.D.I., p. 360 suggests that a Wassermann fast condition is induced by intensive arsenical therapy, and diminished by intensive metal therapy. In this series, seven out of the twenty cases received twenty or fewer injections of metal, and two received ten or fewer injections of "914". There is little evidence here, for or against the American conclusion, and it is to be recalled that the standard treatment administered in this series was the combined administration of "914" and heavy metal, the "914" being given in an interrupted manner.

It may be supposed that cases were sent to this clinic for treatment because of being Wassermann fast, and that our material does not thus represent an average sample. This is not so. As already pointed out, none of the cases had been treated prior to reporting at this clinic, except in the early stages of infection. The

material comprised chiefly ex-soldiers, who wished to know if they were cured, and the husbands, wives and consorts of cases already attending the clinic mostly for known and active lesions, and it has been shown in this section that initial treatment does not prejudice a final favourable outcome.

S E C T I O N VIII.

TERTIARY MUCO-CUTANEOUS SYPHILIS.

Pages 336-377.

Tertiary Muco-Cutaneous Syphilis.

This section deals with the results of treatment in certain cases of late syphilis which attended the Western Infirmary clinic for the first time between the beginning of January 1919, and the end of December 1931, provided that they attended long enough to allow of further serological examination. In order to avoid discussion as to questions of diagnosis, only such cases are included as have shown a skin or mucous membrane lesion typically syphilitic in nature, in association with a positive or weak positive Wassermann reaction of the blood serum, and in which, if a history of primary infection is obtained, it has been at least two years earlier. Cases with signs of central nervous involvement or those which, though without clinical signs of neuro-syphilis, had a positive or weak positive Wassermann reaction in the cerebrospinal fluid, have been excluded. Cases with obvious cardiovascular disease have also been excluded - the cardiovascular condition determines their prognosis.

It has been found impossible to present by any statistical method the results of the treatment of the cardiovascular or neuro-syphilitic cases. Such cases are not adapted to minute analysis on a purely out-patient basis. Their lesions very frequently progress in spite of serologically negative results. They require, from time to time,

periods of in-patient treatment and observation. They default in large numbers, and no information is available to state whether this default is due to increased illness or to a feeling of well-being. As the last noted serological test and clinical examination affords no clue to their condition during default, it is only possible to assess those who have attended for lengthy periods. The clinical progress of such lesions demands much time for observation before reaching conclusions - a five year period is necessary - and therefore the smallness of the numbers attending for such a period, is in itself a barrier to accurate conclusions. It can only be stated as a clinical opinion that the prognosis in cardio-vascular syphilis with symptoms is very bad. It is thought that five years represents the average expectation of life. In regard to neuro-syphilis, some brilliant "cures" or arrests appear in vascular cerebro-spinal syphilis, in circumscribed gummata, in meningitis and occasionally in tabes dorsalis. Apart from these exceptions the outlook is generally considered bad. Many cases are known to be stabilised, but at such a low mental and bodily level that life can only be a burden to themselves and their attendants. The position of the treatment of neuro-syphilis is quite unsatisfactory, and is most inadequately dealt with by the literature which tends to confine itself to the thorough investigation and follow up of a few cases. Only general paralysis of

the insane has been adequately dealt with. There is need for a co-ordinated scheme embracing both in-patient and out-patient treatment of a large series of cases over a prolonged period of time. An adequate "follow up" system is also indispensable. This alone will permit of the accumulation of sufficient data to assess not only the chances of arrest of any type of neural disease, but also the methods of therapy which should be employed. Such a programme involving large numbers of the less well to do men and women can only be carried out through the co-operation of the municipal authorities.

Cases which showed lesions affecting any of the internal viscera - liver, kidney, stomach etc. - have been excluded. Cases with bone or joint involvement have also been omitted. In such cases the clinical response to treatment has been found to be considerable, and many cases of gummatous osteitis have involved subjacent structures e.g. brain and liver. Hereditary syphilis is not here considered. There is thus left a group of cases in which the histological lesion, the gumma, has apparently affected only the skin and subcutaneous tissues, and such cases will be divided into three sub-groups - those showing skin rashes, those with ulceration and those with sub-cutaneous gummata. These groups of cases, in the first place, represent the largest

amount of late syphilis which comes to the clinic. In the second place they are important in that no vital systems or organs are affected, or likely to become affected, and so the prognosis of an individual case after treatment is strictly that of the progress of the syphilitic infection.

It is of interest merely to note the total numbers of each class of case which have attended this clinic during the time period mentioned - and attended sufficiently long to permit of some further clinical or serological note being made.

Tertiary muco-cutaneous connective tissue syphilis	473
Cardio-vascular syphilis	118
Neuro-syphilis	276
Bone and joint syphilis	43
Visceral syphilis	47
Latent syphilis	<u>239</u>
	1196

The problems raised immediately in considering the treatment of such a series of cases of late muco-cutaneous syphilis are varied, and a little reflection shows them to be of quite a different nature from the problems raised by the treatment of early syphilis. The aim of ultimate sterilisation with clinical and serological cure becomes

ideal rather than practical. So many cases are elderly or middle-aged; so many cases have already shown metabolic degeneration, chronic infective processes, senile changes in the main systems, that it is obviously unwise to push treatment to a marked degree. Further, in many of the cases under review the attack of the spirochaete is relatively a mild one. In only two out of the four hundred and seventy-three cases in this series has cardio-vascular disease of syphilitic nature appeared as a later complication. In one case only did a cerebro-spinal fluid show a reversal from negative to positive. Thus these cases exhibit almost entirely a series of skin and subcutaneous tissue lesions. In many instances there have been lengthy periods of good health subsequent to the initial infection, extending as long as thirty-seven years. In most cases a further skin manifestation is the only relapse that is to be anticipated, and such lesions are easily controlled by small amounts of therapy. The considered results of an extensive clinical experience lead to the suggestion that, in the vast majority of cases of syphilis, the nature of the late manifestations of disease is determined during, at most, the first two years of infection. It is emphasised that alike in cardio-vascular, neuro-, visceral, cutaneous and bone late syphilis, there is remarkably little tendency for one type to spill over into another. A

considerable number of cases undoubtedly present evidence of the multiplicity of attack of syphilis, in that many systems are affected, but such cases are usually recognised as such on their first appearance, and have probably received their wide flung dissemination in the early years.

There never can be a regime for the treatment of tertiary muco-cutaneous lesions. The individual must be considered in respect of his general condition, his occupation, his age, his habits, the length of latency of the quiescent periods, the number and frequency of his syphilitic attacks and his general response to treatment. For this reason then no system, no standard course, has been devised comparable to that employed in early syphilis. There has been a general tendency to commence with the oral use of iodide and the intramuscular injection of a heavy metal and subsequently to proceed to the use of "914". A trial of "606" yielded too many toxic results. In many cases with wide spread and active lesions early use of "914" and metal was made in order to inhibit further tissue damage. This particularly applied to ulcer cases. In the early years of the clinic enthusiasm gained the upper hand, and some cases were extensively, and sometimes intensively, treated in an attempt to secure not only clinical well-being, but a permanently negative blood Wassermann. The main fact which compelled rationalisation of this enthusiasm was the return of numerous defaulters who received only a

small amount of treatment, sufficient to cause resolution of their lesions. These cases remained absent for 2 - 3 - 4 - 5 years, and returned to the clinic from the most casual motives of curiosity as to the state of their blood Wassermann reaction. As they proved almost universally to be clinically healthy on examination, in spite of a positive serological test, they compelled the reconsideration of the optimum total amount of therapy which should be given. There has thus been a revision of the earlier thorough methods of treatment. A certain number of cases, both male and female, are always desirous of continuing with treatment in order to attain a permanently negative blood Wassermann result, and, where no contra-indication exists, such cases have had much and varied treatment. As is to be shown, the end results do not justify this - either in regard to the actual treatment of a small group of cases, or in respect of its application to the total population of the clinic. This analysis is carried out in the hope of securing information as to the average amount of treatment required by the average case to produce a clinically negative state, in which clinical progression or relapse is unlikely to occur. The relationship of a permanently positive Wassermann reaction in the blood serum to this state of clinical well-being will also be considered.

The cases number 473 and are subdivided into the following categories:-

Table 1.

Total cases of muco-cutaneous tertiary syphilis.

	<u>Male</u>	<u>Female</u>	<u>Total</u>
Ulceration	133	129	262
Skin rashes	44	49	93
Subcutaneous gummata	76	42	118
Totals	253	220	473

One hundred and eighty of these cases were treated and observed for more than two years. Their distribution is shown.

Table 2.

Total cases of muco-cutaneous tertiary syphilis observed for more than two years.

	<u>Male</u>	<u>Female</u>	<u>Total</u>
Ulceration	45	58	103
Skin rashes	10	19	29
Subcutaneous gummata	30	18	48
Totals	85	95	180

It is interesting to note the slightly better attendance on the part of the female patient; 43% attended for more

than two years as compared with 33% of males.

Tables have been constructed to show the total amount of treatment received by each case. The amount of "914" given is shown by the number of actual injections received by each case. Apart from an initial dose of .45 gram, the usual dose given was 0.6 gram. The total numbers are subdivided into those cases which received 0 injections, 1 to 4, 5 to 10, 11 to 20, 21 to 30, 31 to 40 and more than 40 injections of "914". No discrimination has been made between bismuth and mercury. The analysis of the results in early syphilis shows that bismuth is at least as good as mercury in its antisyphilitic action, and is less toxic. Bismuth has been used since 1924. The usual injection has been 0.2 gram of bismuth metal or its equivalent. Before 1924 mercury was used. The dose was 1 c.c. of calomel cream. An arbitrary line has been drawn between those cases receiving twenty or fewer injections of metal, and those cases receiving more than twenty injections. The groups have been called "Little" and "Much" with reference to the number of injections of metal received. The cases have then further been subdivided according to sex, type of lesion, duration of treatment (under or over two years), and the final serological result. The end result has been termed negative if clinical and serological examination was negative when last performed, and in the tables are shown the numbers and grade of Wassermann

relapse. The second end result is termed suspicious. Such cases exhibited a suspicious Wassermann reaction of the blood serum when last seen. No further information is tabulated, but it is to be noted that no cases of clinical relapse were seen in this small section, and no cases of positive Wassermann reaction were found in the cerebrospinal fluid. The third end result is termed unsatisfactory. It is indicated by +, includes positive and weak positive Wassermann results, and here is shown the state of the Wassermann reaction when last noted and the numbers of cases which were Wassermann fast throughout the whole period of observation.

These tables are submitted as an appendix to this section. A table is shown giving the summary of the results.

Table 3.

Results of treatment of 473 cases of late muco-cutaneous syphilis.

No. of injs. "914" metal		Less than 2 years attendance					More than 2 years attendance				
		Total	-	S	+	W.R. fast	Total	-	S	+ or w	W.R. fast
0	M	5	0	2	3	2	0	0	0	0	
	L	12	1	0	11	10	2	1	0	1	
1-4	M	6	0	2	4	2	1	0	0	1	
	L	24	1	0	23	22	3	2	0	1	
5-10	M	13	3	0	10	5	17	5	3	9	
	L	165	24	5	136	121	19	9	3	7	
11-20	M	24	5	1	18	13	38	14	4	20	
	L	38	6	3	29	28	21	9	3	9	
21-30	M	2	0	1	1	1	37	14	2	21	
	L	3	1	0	2	2	2	0	0	2	
31-40	M	1	0	0	1	0	26	9	4	13	
	L	0	0	0	0	0	0	0	0	0	
40+	M	0	0	0	0	0	14	4	1	9	
	L	0	0	0	0	0	0	0	0	0	
Totals		293	41	14	238	206	180	67	20	93	

It will be recalled that in this table under the heading metal, M means much or more than twenty injections, L means little or less than twenty injections. The headings -, S, + indicate the results of the last blood Wassermann test. W.R. fast indicates those cases which showed no variation from an initial positive Wassermann reaction of the blood serum.

The broad general result given by this table is:-
 293 cases were treated and observed for less than two years.
 41 of these cases when last seen were clinically and serologically negative = 13.5%.
 180 cases were treated and observed for more than two years.
 67 of these cases when last seen were clinically and serologically negative = 37.2%.

Before discussing the tables in detail with reference to the types of treatment received, it is desired to point out the importance of time in connection with the achieving of successful results.

Thus, from Table 3, in those cases with less than two years observation:
 62 received from 11 to 20 injections of "914" and 11, or 17%, were negative.

While in those cases with more than two years observation:
 59 received from 11 to 20 injections of "914" and 23, or 39%, were negative.

This is considered an important fact. It illustrates statistically what is felt, on clinical grounds, to be a useful observation. In late syphilis the benefit of combined treatment with "914" and a heavy metal is projected into the ensuing months. This appears to hold good for almost any amount of treatment however small it may be. Thus the percentages of apparent cures increase greatly with the lapse of time when any two quantities of treatment are compared. Undoubtedly a number of those cases observed for more than two years ceased to receive any further treatment because they became negative, and so tend to swell the percentage of favourable end results. Yet intensive treatment has very rarely been adopted in this clinic for tertiary syphilis and tends to be adopted just as much in those cases which defaulted within two years. The case records of the longer observed patients show numerous instances of Wassermann reversal 4 - 6 - 8 months subsequent to the conclusion of a course of injections. Such patients were, at most, receiving mercury by the oral route, and it is thought that the conclusion, reached in the section dealing with early syphilis, that mercury by mouth is of very low anti-syphilitic action, is valid here. The kindly effect of this time factor is thought to be of great value for those cases which default after a moderate amount of treatment.

The cases are now arranged in four groups to show the results when much metal (more than twenty injections), little metal (less than twenty injections), much arsenic (more than twenty injections), and little arsenic (less than twenty injections) have been used.

Table 4.

Results in cases grouped by quantities of treatment received.

	Period of observation							
	Less than 2 years				More than 2 years			
	Total	-	S	+	Total	-	S	+
Much As. x much metal	3	0	1	2	77	27	7	43
Little As. x much metal	48	8	5	35	56	19	7	30
Much As. x little metal	3	1	0	2	2	0	0	2
Little As. x little metal	239	32	8	199	45	21	6	18
Totals	293	41	14	238	180	67	20	93

Those cases attending for more than two years are considered in detail:

Total	180	-	Negative	<u>37.2%</u>
Much arsenic x much metal	77	-	Negative	<u>35.0%</u>
Little arsenic x much metal	56	-	Negative	<u>34.0%</u>
Little arsenic x little metal	45	-	Negative	<u>46.6%</u>

This seems to afford a contradictory series of percentage results in that the most successful group is that of the

cases which received little arsenic and little metal. On reflection it is obvious, however, that cases which, with such a small amount of therapy, do not become Wassermann negative and attend for more than two years, will tend to receive more treatment and so appear in the "much" groups. This can be demonstrated by showing the percentage of variable Wassermann reactions of the blood serum which occurred in those cases in the three treatment groups which finally achieved a successful end result.

Table 5.

Percentage of variable Wassermann reactions in treatment groups observed for more than two years.

	Total cases	Total finally negative	Percentage of variable W.R. in final negative results.
Much As. x much metal	77	27	73%
Little As. x much metal	56	19	63%
Little As. x little metal	45	21	33%

This definitely shows that Wassermann relapse has been interpreted as an indication for further treatment.

The broad conclusions that may be drawn are, however, rather striking and were quite unrealised until this analysis was undertaken, however much they may prove to be in accord with clinical feeling.

(1) Out of a mixed group of 180 cases of tertiary mucocutaneous syphilis treated and observed for more than two years, 19 or 10% were found to be rendered clinically and serologically negative with less than twenty injections of a "914" preparation and less than twenty injections of heavy metal.

(2) Out of a mixed group of 180 cases of tertiary mucocutaneous syphilis treated and observed for more than two years, 161 or 90% were not rendered clinically and serologically negative with less than twenty injections of a "914" preparation and less than twenty injections of heavy metal. Further treatment with "914" and metal secured a favourable end serological result in 29.8% or nearly one third of this residual figure.

This is quite an intelligible result. It appears obvious that increased quantities of treatment should bring about an increase in the percentage of favourable results. There seems no doubt but that the prolonged continuance of treatment would still further increase the percentage of apparently cured individuals. It is, however, obviously impossible to continue to treat individuals throughout their lives, and the next inquiry is directed to ascertain, if possible, at what stage of treatment the proportion of favourable end results becomes such that more treatment is unlikely to

produce a satisfactory increase in the percentage of end results. To determine this the numbers of those cases attending for over two years are so presented as to show the total numbers passing through each of the groups of treatment, noting such cases as ceased further treatment, and noting whether or not they were serologically negative. There were 180 cases.

Table 6.

Final results in cases observed for more than 2 years according to the amount of "914" treatment given.

Total cases	No. of injs. of "914"	Final W.R. result ceased attending	-	+
180	0	1	1	1
178	1-4	2	2	2
174	5-10	14	22	22
138	11-20	23	36	36
79	21-30	14	25	25
40	31-40	9	30	30
14	40+	4	10	10

It is seen from this table that the percentage of serological failures tends to rise after the group receiving 11 to 20 injections of "914". That is to say, it becomes increasingly difficult thereafter to secure an equal percentage of serological success even if more treatment be administered. Obviously these groups receiving the greater

amounts of treatment must contain increasing percentages of Wassermann fast or Wassermann variable cases.

But Table 6 primarily shows the effect of arsenical therapy. It is necessary to examine the results in a similar manner using, as indications for the total numbers of cases, those figures which give respectively the totals of the patients receiving "much" or "little" metal.

The next table shows the information derived from those cases which received much metal i.e. more than twenty injections of bismuth or mercury.

Table 7.

Final results in cases observed for more than two years and receiving much metal. "914" injections shown.

Total cases	No. of inj. of "914"	Final Result	
		-	+
133	0	0	0
133	1-4	0	1
132	5-10	5	12
115	11-20	14	24
77	21-30	14	23
40	31-40	9	19
14	40+	4	10

Here arsenic groups 5 to 10, 11 to 20 and 21 to 30 show almost equal chances of attaining an end negative serological

result. This negative result appears therefore as a function of larger amounts of metal.

When those cases receiving little metal, i.e. less than twenty injections, are tabulated, the results shown are:-

Table 8.

Final results in cases observed for more than two years and receiving "little" metal. "914" injections shown.

Total cases	No. of injs. of "914"	Final Result.	
47	0	-	+
		1	1
45	1-4	2	1
42	5-10	9	12
21	11-20	9	10
2	21-30	0	2

The best results are seen in the arsenic groups 1-4, 5-10 and 11-20 injections. The percentages of successful results are actually higher and less "914" is required, though the total numbers are small, than in those cases where much metal is employed. This seems anomalous, and can only be explained by reference to the individual record cards. It is then seen that in this group - little metal- are included (1) cases which rapidly became negative with a small amount of treatment, to remain only under observation thereafter.

(2) a few cases which defaulted for a long period after small amounts of treatment, and on their return were

clinically and serologically negative.

(3) a few cases which were treated with "606" instead of with "914" and did well.

The best percentage of end therapeutic results in the normal cases is thus found in those patients receiving some twenty injections of "914" and more than twenty injections of metal. This is also in accord with clinical judgment which places considerable value on the prolonged use of bismuth metal given by means of the intramuscular route.

Certain other factors which may compel a modification of the interpretation of these results are now to be dealt with.

These factors are clinical relapse, Wassermann fast cases, intolerance, sex and type of lesion. Consideration will also be given to the question as to whether increased clinical and serological well-being is associated with treatment in excess of the quantities just mentioned.

Those cases which showed clinical relapse are now considered. It is pointed out that all cases with initial cerebro-spinal fluid abnormality are excluded from this series. Only one case showed an alteration from initial negative Wassermann reaction in the C.S.F. to a subsequent positive result. No clinical lesions were found. Cardio-vascular disease appeared to be definitely found as a

progression of disease (or relapse) in only two cases, one male and one female. A number of cases with rheumatic history developed auricular fibrillation - a number of cases showed hypertension and a number showed myocarditis and subsequent failure. Such cases are not regarded as syphilitic. There was a considerable amount of disease, such as bronchitis, tuberculosis, cancer, cirrhosis, which was not considered specific.

Ten cases of skin relapse were seen in four hundred and seventy-three cases. This represents a percentage incidence of 2.1%. Details are submitted concerning these cases.

Skin Relapse.

<u>Sex</u>	<u>Type of original lesion.</u>	<u>Case No.</u>	<u>Relapse lesion.</u>	<u>Treatment prior to relapse.</u>		<u>Duration of (a) observation, (b) default in weeks.</u>	
				<u>"914" metal</u>		<u>(a)</u>	<u>(b)</u>
M.	G.	2934	Ulcer tendo achilles.	11-20	L	227	206
M.	G.	3367	Ulcer of leg.	5-10	L	117	100
F.	R.	4376	Gumma tonsil.	0	L	28	26
F.	G.	979	Gumma right foot.	5-10	L	72	66
F.	U.	716	Alopecia.	5-10	L	26	14
F.	U.	2914	Ulceration		K.l.	8	0
F.	U.	1990	Ulcers hand and foot.	0	L	6	0
F.	U.	1590	Ulcer left knee.	5-10	L	8	0
F.	U.	2279	Gumma behind ear.	1-4	L	72	70
F.	U.	3002	Ulcer tibia.	11-20	M	185	44

G = subcutaneous gumma. R = rash. U = ulcer.

It will be noted that only two of these cases received more than one course, 5.85 grams of "914", and only one of these received more than twenty injections of metal. Skin relapse then in this series is practically unknown if adequate initial treatment be given. Most cases of relapse had a considerable period of default until the appearance of a lesion caused them to return to the clinic. It is noteworthy that all these cases of clinical relapse showed an unfavourable end serological result. The lesions of relapse were easily amenable to treatment. No systemic damage appeared with or after the relapse lesions.

The Wassermann fast cases are now examined.

Out of the one hundred and eighty cases treated and observed for more than two years, there were sixty cases which remained consistently Wassermann fast - a percentage of $33\frac{1}{3}\%$. The total percentage of unfavourable end results in these one hundred and eighty cases was 62.8%. It is thus seen that roughly one third of the cases show apparent serological cure; one third show Wassermann relapse and one third are Wassermann fast. When those cases which received twenty one to thirty injections of "914" and more than twenty injections of metal are examined (Table 3), it is seen that out of thirty-seven, fourteen were finally negative, twenty-three were not, and, of these, seventeen were Wassermann fast. Here the

percentage of Wassermann fast cases rises steeply. But if treatment be continued it falls again. Thus forty cases received more than thirty injections of "914" and more than twenty injections of metal. Of these, thirteen were finally negative, twenty-seven were not and seven were Wassermann fast.

These figures illustrate the simple conclusions that with a small amount of treatment a considerable number of cases will show Wassermann reversal. Amongst the residue will be Wassermann fast cases. Three "courses" of "914", equivalent to some seventeen grams, and more than thirty injections of metal will not, as a rule, serve to reverse a resistant Wassermann fast serum. If further treatment be given, equivalent to some additional eleven grams of "914" and twenty injections of heavy metal, the chances of Wassermann reversal are much improved. When the small percentage of clinical relapse is noted (none was seen if the case got more than twenty injections of "914"), when the high incidence, 44%, of intolerance is considered, the end does not justify the means. It is accordingly advised that, provided there be no abnormality in the cerebro-spinal fluid, Wassermann fast cases of muco-cutaneous tertiary syphilis should only exceptionally receive treatment on account of the persistent maintenance of a positive Wassermann reaction in the blood serum.

The incidence of intolerance is very high. It is 44% of the four hundred and seventy-three cases of this series as compared with 27.8% in five hundred and seventy cases of early syphilis. The two main reactions are stomatitis and minor skin intolerance. There is also a considerable amount of malaise subsequent to "914" injection. One death from septicaemia was noted. It was considered that a mild skin intolerance had lowered this patient's power of resistance to infection. On the whole, the incidence of intolerance rises with the age of the patient. Intolerance is sufficiently frequent throughout this series, and sufficiently severe, to demand consideration when schemes of treatment are being planned. The risk of its occurrence must be definitely weighed up as a negative factor when assessing the need for further treatment in any individual case.

The influence of sex and type of lesion are now considered.

The end results of all cases are now shown, indicating the sex, the duration of observation and the nature of the initial lesion, rash, subcutaneous gumma or ulcer. The following tables give the total numbers of cases in each category and the end serological result.

Female.Table 9.

Nature of initial lesion	Period of observation							
	Less than 2 years				More than 2 years			
	Total	-	s	+	Total	-	s	+
Rash	31	8	3	20	18	11	0	7
Gumma	23	1	1	21	19	11	1	7
Ulcer	71	7	2	62	58	22	7	29
Totals	125	16	6	103	95	44	8	43

Male.

Nature of initial lesion	Period of observation							
	Less than 2 years				More than 2 years			
	Total	-	s	+	Total	-	s	+
Rash	34	9	5	20	10	3	3	4
Gumma	46	8	1	37	30	6	5	19
Ulcer	88	8	2	78	45	14	4	27
Totals	168	25	8	135	85	23	12	50

One hundred and twenty-five cases of females received treatment for less than two years. Of these, 16 or 12.8% were serologically negative when last seen.

Ninety-five cases of females received treatment, and were observed for more than two years. Of these, 44 or 46.3% were negative when last seen.

One hundred and sixty-eight cases of males received treatment for less than two years. Of these, 25 or 14.9% were negative when last seen.

Eighty-five cases of males received treatment and were observed for more than two years. Of these, 23 or 27% were negative when last seen.

Thus it appears in this series that not only do females attend in greater proportion than males for two years or more, but that they also have a greater chance of becoming clinically and serologically negative if they do attend. The difference between 46.3% females and 27% males must be considered significant in spite of the small numbers. This is in accord with clinical experience which permits the definite statement that all the three types of lesion here dealt with, rash, ulcer, gumma, are clinically less severe and less extensive in the female than are corresponding lesions in the male. It has been asserted that lesions in the female are more prone to appear at or near the time of the menopause. No data are available from the case records to show whether or not any given case was at this age period. Some information may be obtained from the age incidence at which the lesions appeared. The figures for male and female are shown in the following table.

Table 10.

Age in years of incidence of tertiary muco-cutaneous lesions.

	-20	21-30	31-40	41-50	51-60	61-70	70+	Total
Male	1	31	84	83	62	14	3	278
Female	2	41	82	71	39	6	1	242

In this table are included a number of cases which have not been included otherwise in this series as there is no record of a Wassermann test performed subsequently to the initial one. The cases are otherwise comparable.

When the incidence in the female age group 41-50 is compared firstly with the numbers in the age groups immediately above and below in its own sex, and secondly with the corresponding age groups in the male, there is no evidence to suggest that the female climacteric is unduly prone to clinical manifestations of tertiary syphilis. It is to be noted that the female tends to come at an earlier age than does the male. This fact coupled with the longer attendance of the female may be thought partially to explain the better percentage of end results in the female. But an examination of the Early Syphilis records shows that the female tends to acquire syphilis at a slightly younger age than does the male. Hence one would naturally look for an earlier age group for female late syphilis.

There seems little doubt but that late muco-cutaneous syphilis is more amenable, serologically, to treatment in the female than it is in the male. The female is more prone to clinical relapse.

The type of lesion has no effect upon the ultimate end serological result. Allowing for the differences between the sexes, rashes, gummata and ulcers do equally well. There is a slightly worse percentage result in the case of ulceration but this cannot be deemed of significance. This is interesting, because the cases with open ulceration require more attention in respect of daily dressing of the ulcer. They are seen more often and, doubtless for this reason, a clinical impression had been created that ulcer cases did not respond so well to treatment as did those cases in which the skin was unbroken. The actual facts correct this impression.

This analysis of four hundred and seventy-three cases of muco-cutaneous tertiary syphilis has only been carried out on simple broad lines. Nevertheless the results permit the deduction of a number of equally broad and simple conclusions.

The first point is to note the unsatisfactory outcome in respect of blood Wassermann results as compared with the results achieved in early syphilis.

After two years treatment and observation, some 62.8% of tertiary muco-cutaneous syphilis is not Wassermann negative;

after two years treatment and observation, some 10.5% of early syphilis is not Wassermann negative. The moral is obvious. It is already known. It requires constant repetition. The only curable stage of the syphilitic infection is the early one, and all efforts must be made to improve the methods of therapy of the first two years.

With regard to tertiary syphilis itself, it is noted that the lesions are rapidly amenable to anti-syphilitic treatment: that progression to neuro-syphilis or cardiovascular syphilis is rare: that clinical skin relapse (2.1%) is an expression of small amounts of treatment and has not been seen when 11.7 grams of "914" and a corresponding amount of metal (not less than 5 grams of Bi. metal) has been given. Even intensive treatment will encounter some 20% of Wassermann fast cases, and with small or moderate amounts of treatment the percentage of Wassermann fast results rises to $33\frac{1}{3}\%$. It has further been ascertained, from a comparison of groups of cases receiving identical treatment but observed respectively for less than two years and more than two years, that there is a therapeutic projection forwards. This means that a Wassermann reversal from positive to negative not infrequently occurs some months after the cessation of treatment. Finally it is noted that the incidence of intolerance is higher than in early syphilis - 44% as compared with 28.9%.

Accordingly it is suggested that where the risks of the production of marital infection or of hereditary syphilis are not in question, the individual will achieve adequate protection and will not be unduly submitted to toxic effects if he receives:

Two courses of ten injections of "914" $\frac{1}{2}$ 11.7 grams and thirty injections of bismuth metal $\frac{1}{2}$ 7 - 8 grams, along with considerable quantities of potassium iodide by mouth. Such treatment might be given in one year.

A case so treated has a thirty per cent chance of being Wassermann negative at the end of two years, a thirty per cent chance of being Wassermann fast. His relapse incidence is less than 1%. If the cerebro-spinal fluid was negative at the outset, it is most improbable that neuro-syphilis will develop. The further treatment of such a case is not likely to modify, in a favourable direction, his chances of developing cardio-vascular disease. Finally, it is stated that treatment considerably in excess of this amount will still leave 20% of Wassermann fast cases. No additional benefit appears to accrue. If prolonged and intensive treatment be carried out over a series of years (not under five), it is considered that the chance of achieving a permanently negative blood Wassermann is still less than 50%. Should a patient who is otherwise healthy, under the age of forty, and in circumstances of work and economic surroundings

which permit of reasonable care of his person, desire this intensive treatment, it is legitimate to carry it out, but only after a full explanation of the attendant risks.

MALES - ULCERS. UNDER 2 YEARS OBSERVATION.

Injs. of As. Metal	Total all cases	Satisfactory end result		Susp. end Result	Unsatisfactory end result	
		Sero. relapse Total + W S	Initial Weak + W.R.		Total	W.R. when last seen + W
0	M 1			1		
	L 7	1			6	6
1-4	M 2				2	2
	L 13				13	13
5-10	M 3				3	3
	L 39	3	1	1	35	35
11-20	M 10	2	1		8	8
	L 8	1			7	6
21-30	M 1				1	1
	L 3	1	1		2	2
31-40	M 1				1	1
	L					
40+	M					
	L					

MALES - ULCERS. OVER 2 YEARS OBSERVATION.

Injs. of As. Metal	Total all Cases	Satisfactory end result			Susp. end Result	Unsatisfactory end result		
		Total	Sero. relapse	Initial Weak + W.R.		Total	W.R. when last seen + W	Initial Weak + W.R.
0								
1-4	1	1	1	1				
5-10	5	3	1	1	1	4	4	4
11-20	11	3	1	1	1	1	1	1
21-30	6	3	1	1		8	6	2
	9	2				3	3	3
31-40	5	1	1	1	2	7	6	1
40 +	3	1	1	1				
						2	2	2

MALES - RASHES. OVER 2 YEARS OBSERVATION.

Injs. of As. Metal	Total all cases	Satisfactory end result		Susp. end Result Total	Unsatisfactory end result				
		Sero. relapse + W S	Initial Weak + W.R.		Total	W.R. when last seen + W	Initial Weak + W.R.	Fast	
0									
1-4	1				1		1		
5-10	2			1	1		1		1
	1								
11-20	3			2					
21-30	3				1		1		1
31-40									
40 +									

MALES - SUBCUTANEOUS GUMMA. UNDER 2 YEARS OBSERVATION.

Injs. of As. Metal	Total all cases	<u>Satisfactory end result</u>			<u>Susp. end Result</u>		<u>Unsatisfactory end result</u>		
		Total + W	Sero. relapse W S	Initial Weak + W.R.	Total	end Result	Total	W.R. when last seen + W	Initial Weak + W.R. Fast
0	1						1	1	1
	3						3	2	1
1-4	2						2	1	1
	1						1	1	1
	3						3	2	1
5-10	26	5	1	3			21	20	1
	1	1		1					
11-20	8	2	1				6	6	5
	1								
21-30						1			
31-40									
40 +									

FEMALE - ULCERS. OVER 2 YEARS OBSERVATION.

Injs. of As. Metal	Total all cases	Satisfactory end result			Initial Weak + W.R.			Susp. end Result			Unsatisfactory end result		
		Total	sero. relapse + W S	Initial Weak + W.R.	Total	Result	Total	W.R. when last seen + W	Initial Weak + W.R.	Total	W.R. when last seen + W	Initial Weak + W.R.	Fast
0	M L	1	1										
1-4	M L	1	1										
5-10	M L	7	4	1 2	3	3	3	3	3				3
11-20	M L	10	2	1 1	1	7	7	7	7				7
21-30	M L	16	6	3	1	9	8	1	1				7
31-40	M L	10	5	2 2	2	3	2	1	1				1
40 +	M L	7	2	2	1	4	1	3	3				3

FEMALES - RASHES. UNDER 2 YEARS OBSERVATION.

Injs. of As.	Metal	Total all cases	Satisfactory end result			Initial Weak + W.R.	Susp. end Result Total	Unsatisfactory end result			
			sero. +	W	S			W.R. when last seen + W	Initial Weak + W.R.	Fast	
0	M	1						1	1	1	
	L										
1-4	M	2					2				
	L	1						1	1	1	
5-10	M	1						1		1	
	L	19	5	1			1	13	11	2	11
11-20	M	4	2					1	1	1	1
	L	3	1					2	2	2	2
21-30	M										
	L										
31-40	M										
	L										
40 +	M										
	L										

FEMALES - RASHES. OVER 2 YEARS OBSERVATION.

Injs. of As. Metal	Total all cases	Satisfactory end result			Initial Weak + W.R.	Susp. end Result Total	Unsatisfactory end result			
		sero. relapse + W S	W S	W S			W.R. when last seen + W	Initial Weak + W.R.	W.R. Fast	
0										
1-4										
5-10	3	1	1	1		2	1	1	1	1
11-20	3	3	1							
21-30	5	5	1			5	4	1		4
31-40	2	2	1	1						
40 +										

FEMALE - SUBCUTANEOUS GUMMATA. UNDER 2 YEARS OBSERVATION.

Injs. of As. Metal	Total all cases	Satisfactory end result		Initial Weak + W.R.		Susp. end Result Total	Unsatisfactory end result	
		Total +	sero. relapse W S	Initial Weak + W.R.	W.R. when last seen + W		Total	Initial Weak + W.R. Fast
0								
	1						1	1
1-4	2						2	1 1 1 1
	1						1	1
5-10	15						13	11 2 11
11-20	4						4	4
21-30								
31-40								
40 +								

FEMALES - SUBCUTANEOUS GUMMATA. OVER 2 YEARS OBSERVATION.

Injs. of As. Metal	Total all cases	Satisfactory end result			Initial Weak + W.R.	Susp. end Result Total	Unsatisfactory end result		
		sero. relapse + Total	W S	Initial Weak + W.R.			W.R. when last seen + Total	Initial Weak + W.R.	Fast
0									
M									
L									
1-4	1						1	1	1
M									
L									
5-10	4	3	1				1	1	
M									
L									
11-20	6	4	1	1			1	1	
M									
L									
21-30	2	2	2						
M									
L									
31-40	2	1						1	
M									
L									
40 +	3						3	2	1
M									
L									

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SECTION IX.

IODIDES.

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IODIDES.

This section will deal with a series of experiments carried out in an attempt to determine the most advantageous methods of employing iodine in the treatment of syphilis.

This work was undertaken because, on reviewing the literature, it was found that very few clinical studies of recent date had been published. The modern text books exhibit a remarkable unanimity in their advice. Thus Harrison, Hazen, Clarkson, White, Jeanselme, Rolleston, Browning and McKenzie, Browning and Watson, Osler and McRae suggest that the potassium salt be given orally in doses of ten to fifteen grains thrice daily over short periods of time, and indicate that the special value of the drug is to be found at the outset of the treatment of tertiary cutaneous lesions, and during the intervals between courses of treatment by the arsenical substitutes and the heavy metals. In the pharmacological and therapeutic text books such as those of Poulison, Cushny, Hale White, and Bruce and Dilling, similar advice is offered.

A search was therefore made of the earlier literature in order to determine the clinical foundations upon which such views were founded. The earliest reference which has so far been traced is that found in an

article by Jacques Coster¹ in 1823, where the following paragraph occurs:-

"M. Biett, profiting by the opinion expressed by M. Coindet of Geneva on the supposed value of potassium iodide against inflammatory lesions of a syphilitic nature, made a great many observations in the Hospital Saint-Louis in cases of venereal ulcer. He is the first, I believe, who has combined iodine with mercury in this sort of affection. Brera², a celebrated professor of Padua, published a book containing the results of investigations made by him in a hospital in that city, over a period of two years".

Many early references are to be found in the volume "Iodothérapie" written by A.A. Boinet and published in 1855. There, p.5, he definitely states that M. Coindet of Geneva delivered the first paper on 25th July, 1820, on the use of iodine in goitrous cases. This followed upon the demonstration of iodine in sea water, in burnt sponges and in burnt sea-weed. Buisson³ in 1825 wrote a thesis on the use of iodine in syphilis.

1. COSTER, J. Arch gen. de Med. Paris. Volume 2. 1823.
2. BRERA. Saggio clin. Sull'iodio etc. Padova, 1822,
(quoted by Coster)
3. BUISSON. Thésés de la Fac. de Paris No. 223.
(quoted by Boinet)

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Numerous papers in all countries rapidly followed upon these discoveries, but the first man to establish a regime for the systematic employment of the potassium salt appears to be William Wallace, a surgeon in Dublin. His cases, one hundred and forty-two in number, were observed during the years 1832-1836, and his observations were published in the second volume of the Lancet, 1836. These lectures on the treatment of syphilis are extraordinarily interesting, are replete with sound clinical understanding and are most logically expressed. For the late venereal ulcer he advises thirty grains of potassium iodide in plenty of water, with or without the addition of syrup, to be given daily in three doses until the urine reacts very strongly and to be continued if no complications arise. Patients must show an increase of appetite and a feeling of well being. The drug is most suitable in those cases which do not tolerate mercury well. He describes the ordinary features of iodism, and notes two cases corresponding to iodine cachexia in which emaciation, trembling, sleeplessness and other signs of hyperthyroidism became apparent.

Ricord¹, hearing of Wallace's work, soon carried out his principles in France, and his widespread reputation has perhaps obscured the pride of place to which Wallace is justly entitled. No better work than that

1. BOINET Iodothérapie, p.128. RICORD, Bull de therap. 1837. xii. 241.

of Wallace has been noted though Fournier, in his treatise on syphilis, somewhat elaborates it. There: after no important changes took place, if one excepts the occasional use of sodium iodide in place of the potassium salt, until about 1912 when, in America, a series of experiments were made with various organic compounds of iodine for oral administration. These experiments, partly carried out by McLean¹, were reviewed by him, and their results were considered inferior in value to those obtained by the simple inorganic salts, while Barker and Sprunt² more fully endorsed this view.

McLean employed (1) iodised proteins such as iodalbumin and iodoglucosin and (2) iodised fats and fatty acids such as iodipin (a combination of iodine chloride and oil of sesame) and also sajodin, the calcium soap of a fatty acid obtained by iodising erucic acid with iodo-behenic acid. His conclusions stated that they had no specific action; were not well utilised and must be split up to be utilised; that the second group

1. McLEAN. Arch. Internal Medicine. 1915. Vol.XV. 92.

2. BARKER and SPRUNT. Therap. Gazette, Detroit. 1922. Vol. XLVI, pp.539-45.

might be helpful where the long continued action of iodine is wanted; and that toxic side effects might arise from by-products released of the nature of fats or fatty acids.

As Barker and Sprunt's paper is the latest clinical survey of the position that was obtained, their main points are briefly summarised. No change is noted from Wallace's dosage. Potassium iodide is the most popular salt. Pure iodine is very irritating. The salts are slowly absorbed from the stomach, rapidly from the small intestine, and less so from the large bowel. Alkaline salts appear most rapidly in the secretions. Organic compounds are less rapidly absorbed and excreted. Iodism occurs more rapidly when the kidney is damaged. Iodine does not effect the general metabolism but through the thyroid gland may produce emaciation, atrophy of mammae and testes and death.

A short survey was then made of the work and theories of the pharmacologists in an attempt to find a rational basis for clinical experimentation. This proved most disappointing.

Thus Binz¹ C. and Hinz² consider that the oxidising property of nascent iodine, which renders the walls of the blood vessels more permeable and stimulates a lymphocytosis, is the essential mode of action. But T. Sollmann³ states that there is no evidence that elementary iodine can be liberated from iodide or iodate in the H ion concentration known to exist in the body.

Or again, while Muller and Inada⁴ assert that the underlying factor is a change in the viscosity of the blood caused by the iodine, Determann⁵ denies any change in the viscosity of the blood under the administration of iodides.

Lehndorf⁶ suggests that a fall in the blood pressure after iodide administration may be in some way accountable, but thirteen years earlier Stockman and Charteris⁷ showed that no fall in the blood pressure took place.

1. BINZ. Arch.f. Exper.Path.U. Pharmak.1894. XXX10.185.
2. HINZ. Virchow's Arch. f.Path.Anat.1899.ch.44.
3. SOLLMANN, I.J. of Phar. and Exp. Ther. 1917. IX. p.209.
4. MULLER, O. and INADA, R. Deutsch med. Wchnschr. 1904. XXX. 1751
5. DETERMANN. Deutsch. med. Wchnschr. 1908. XXXIV. 871.
6. LEHNDORF, A. Arch.f. Exper. Path. U. Pharmakve. 1914. IXXVI. 224.
7. STOCKMAN, R. and CHARTERIS, F. Brit. Med. J. 1901. 11 1520.
11

Much work was done by Jobling and Petersen¹, and according to them blood serum has an antitryptic action due to the normal presence of the ferment antitrypsin. This ferment inhibiting action is said to be brought about by lipoidal combinations formed with compounds of the unsaturated fatty acids. The action of iodide is to combine with these unsaturated fatty acids thus diminishing the antitryptic effect of serum. Then autolysis of gummatous tissue can take place with resultant absorption. It is a fact that gummatous tissues along with cancerous, tuberculous and suppurating tissues, show from two to three times as much iodine as is found in the corresponding healthy organs. This was found, according to Jobling and Petersen, by Loeb, Jacobi, Van Den Velden and others. Holler², confirming this, stated that the greatest accumulation was in tuberculous tissue.

It might here be noted that in normal tissues the highest percentage is stated to be found in the thyroid gland, lesser percentages in the blood and skin and none in fat or bone .

1. JOBLING and PETERSEN. Arch. Int.Med. 1911.
 2. HOLLER, G. Klin. Wehnschr. 1923. 1692.

1

Pouls¹son and many others indicate that potassium iodide administered orally appears in the blood stream in the form of sodium iodide and potassium chloride, and it is stated that the potassium chloride particularly exerts an osmotic or "salt action" which partly explains its influence in "promoting the absorption of morbid deposits and exudates". All clinicians, however, note that sodium iodide given orally acts comparably upon gummata when given in a dosage equivalent to the potassium salt. A theoretical objection to the long continued use of iodide is raised by Barker and Sprunt² who suggest that it may interfere with the natural defensive mechanisms of the body, and that cases treated with iodides always relapse, but they themselves, and indeed all clinicians, do not propose to treat syphilis by iodine alone. Further, syphilis can hardly be classed as a self-limiting or spontaneously curing disease. It will also be shown later that iodides per se have no local anti-spirochaetal action.

1. POULSSON. Text-book of Pharmacology and Therapeutics, p. 390.

2. BARKER, L.F. and SPRUNT, T.P. Ther. Gaz. Detroit, 1922. XVI. 539.

The literature was then examined to ascertain if more definite information could be obtained concerning the fate of the iodides after their administration. Sollmann¹ states that iodide always circulates unchanged in the form of sodium iodide: that the more toxic iodate is never formed: that in H. ion concentration of the body fluids no liberation of free iodine takes place: and that iodine given orally exists solely in the blood in the form of iodide. He considers that there should be no therapeutic difference between potassium and sodium iodide given orally.

Krahulik and Pilcher² investigated the relative rates of absorption and excretion of the iodides of strontium, sodium and potassium. Strontium iodide contains the greatest percentage of iodine. They found that strontium did not delay absorption or excretion, and that the rate of absorption of iodine from strontium compounds was greatest. This difference was immaterial, and there is therefore no value in adopting the more unusual strontium salt.

1. SOLLMANN, T. J. *Phar. and Exp. Ther.* 1917. 9. 209.
2. KRAHULIK and PILCHER. *Arch. Int. Med.* 1918. 21. 176.

The most exhaustive experimental work was done by Osborne, E.D.¹ without, however, any clinical observations. This paper must be more fully summarised:-

- A. Administration by mouth of one, five and twenty grams of sodium or potassium iodide.
- (1) NaI. excreted faster in first hour than KI.
Of Importance in relation to absorption.
 - (2) No appreciable difference in the amounts of iodine excreted after either NaI. or KI.
Individual variation.
 - (3) Urinary concentration highest between second and fourth hours. Amount of urine does not appear to influence amount of iodine excreted.
 - (4) NaI. and KI. both eliminated in 96 hours.
 - (5) During second twenty four hour period same percentage of iodine excreted regardless of drug or dose.
- No iodine in stool. 96% excretion by urinary tract. Meals have no influence on rate of excretion. Less irritation if taken half an hour before food.

Nal. better tolerated than KI.

B. Comparative rates of elimination following the oral and intravenous administration of Nal. in doses of five, ten and twenty grams.

(1) No difference in rate of elimination either after oral or intravenous route - large doses eliminated as rapidly as small doses.

(2) Rapid adjustment of body fluids to the intravenous administration of hypertonic solutions.

5 grams - iodine in urine rises at once.

10 grams - iodine in urine rises more slowly.

20 grams - iodine in urine rises slowly for sixty minutes and then to maximum in fourth hour.

(3) No accumulation from large oral doses of 30-40 grams daily.

C. Rectal administration:-

Maximal efficiency 3-10 grams daily in three doses, 16.9 to 43.3% of iodine given excreted in urine. Thirty grams gives rectal irritation.

As 96% iodine is orally absorbed and only 20% rectally, 10 grams rectally is equivalent to 2-3 grams orally.

D. Blood Serum. Na, K, and l concentrations, after oral administration of 1-5-20 grams.

- (1) NaI. Blood serum rise of Na. proportional to dose: No change in K.
- (2) KI. Not a rise in K. content, but Na. rise is proportional as in (1).
- (3) l. Equivalent to dose given. If dose 1-5 grams highest concentration in one hour - if 20 grams highest concentration in two hours.

E. Blood Serum. Na, K, and l concentrations after intra-venous administration of 10 grams of NaI.

- (1) Na. high for 12 hours: normal in 48 hours.
- (2) K. No change.
- (3) l. 43 in one hour. 7.1 in 24 hours.

Thus 9-15 grams given orally in three doses in the day is equivalent to 10 grams given in a single dose by the intravenous route, and also the oral dose gives a more uniform concentration while the intravenous route shows peaks of high concentration and rapid decline.

F. Iodine content of Blood Serum protein.

- (1) Only traces of l after oral NaI.
- (2) 7 - 26% of iodine after KI. orally.
- (3) 6 - 99% of iodine after NaI. intra-venously.

G. Only traces of iodine in blood serum lipoids.

Many other papers have been investigated, but nothing of material consequence was discovered.

It is strange to note that few pharmacologists have been able to resist the lure of the iodides, and so the literature is colossal. As an instance of the persevering curiosity of the human mind one might quote that literature which deals with the action of the fumes of iodine in the treatment of syphilis. Boinet on the action of burnt sponges in scrofula is omitted.

Bargues¹ 1913, concludes that fumes of iodine influence the healthy tissues and exert an anti-syphilitic action.

Petzer, Grahot and Cottin² 1918, conclude that there is an antisyphilitic action but that other methods of administration are more effective.

Luckhart et al³ 1920 investigated the physiological action of the fumes of iodine and concluded:-

1. The skin absorbs iodine which appears in the urine.
2. The iodine content of the thyroid gland is increased.

1. BARGUES, J.A.M.A. (abst.) 1913 July, 26. 311.

2. PETZER, GRAHOT and COTTIN. J.A.M.A. (abst.) 1918. Nov. 30. p. 1863.

3. LUCKHART, KOCH, SCHROEDER and WEILAND. J. Phar. and Exp. Ther. 1920 XV. 1. 1. 20.

3. Iodine fumes are absorbed by the respiratory tract and the excess appears in the urine.
4. If indiscreetly given dyspnoea follows from inflammatory reaction.
5. Death follows by acute pulmonary oedema.

On this melancholy note the subject of fumes may be concluded.

In April, 1923, the writer commenced experiments with the intra-venous administration of sodium iodide under the misapprehension that this was an original idea. By December, 1923, the error was discovered, and the following references fall to be noted in connection with the intravenous use of iodide in the treatment of syphilis.

1917. ENGENDER¹. His conclusions are stated in detail.

1. After intravenous injection of Nal. in man, even in large doses, there is almost complete failure of appearance of the known symptoms of Iodism of the skin and mucous membrane.

2. On the other hand the risks of thyrotoxic disturbances are notably increased. For the most

1. ENGENDER. Munch. Med. Wchnschr. 1917. IXIV. 760-762.

part these are of a slight nature such as palpitation, tremor, malaise, etc.

3. However, the syndrome may appear such as was experimentally caused in dogs by Klose and fully answers clinically to Basedow's disease. With febrile disturbance comes increase and strengthening of the heart's action of the pulse and respiration, excretion of albumen and severe attacks of faintness (in cases with latent thyroid cachexia tendency).

4. In consideration of these chances, and in view of the progressive increase of dosage and the gradual habitation to the drug, I do not think it advisable in the treatment of syphilis to give, by intravenous injection, larger doses of iodide than are usually employed.

5. However, special cases are forthcoming (there is need of special care in the selection of these and of careful clinical observation) in which by an intensive iodine course of treatment by means of the 10% Nal. solution of Klemperer great therapeutic benefits may be expected.

6. Injections of Nal. sometimes influence specific processes after Hg. Kl. and salvarsan, at least for the moment, have reached their highest

usefulness. Further also the Wassermann reaction and leucoplakia of the mouth (with W.R.+) may be influenced. Also there seems to be a notable result in cases of obstinate psoriasis.

7. My investigations have not reached the special cases of "Innere Lues" which Klemperer thinks particularly suited for intravenous iodine treatment.

1918. R.C. HOWARD¹. This is the report of an obstinate case of laryngeal syphilis which received 125 massive doses of sodium iodide by intravenous injection, 54 doses of salvarsan and many hundred intra-muscular injections of mercury. The case did well.

1919. F.J.DEVOTA². A case of tabes dorsalis received three injections of thirty grains of sodium iodide dissolved in four ounces of normal saline. Shooting pains in the legs were relieved.

1922. F.J.FARNELL³. His first reference given is 1922. Arch. Neur. and Psych., 7-729. Sodium iodide intravenous administration. This journal could not be obtained, and in Journal Nerve and Mental

1. HOWARD, R.C. Am.J. Syph. 1918. 11. 850-862.
2. DEVOTA, F.J. Lancet. 1919. 1. 339.
3. FARNELL, F.J. Arch.Neur.and Psych.1922, 7-729.
Jour.Neur. and Ment.Dis.1922,LV.112.
New York Med.J. 1923. Sept.5. 290.

Dis., 1922, LV. 112, also not obtained, the author's abstract (obtained) states:-

"SUMMARY. Iodine in the form of an iodide can be given in hypertonic form intravenously.

Iodides when given into the blood stream in hypertonic form have a tendency to reduce the idiosyncrasy towards iodism.

Iodides introduced into the blood stream appear to re-adjust systematic fungus disturbances (oidiomycosis) very rapidly.

Iodides intravenously in concentrated form appear to help materially the action of salvarsan upon the diseased tissue and cell. Potassium iodide produced local thrombosis.

Iodides introduced into the blood stream in hypertonic solution probably have some influence upon reducing the edema, hyperaemia, etc., of the brain in increased brain bulk disorders."

The second reference is New York Med.J. and Med. Pce. 1923, Sept.5, p.290. In the treatment of syphilitic alopecia areata and lesions referable to the bone or periosteum or both, intravenous injections of hypertonic sodium iodide solutions have been given with good results. The intravenous

method is considered superior to the oral method because the tissue reaction is quicker and the salt reaches the tissue more rapidly than it could by absorption. A 10% solution is used. This is boiled for ten minutes, cooled and injected immediately by gravity, ten minutes being required to make the injection. The solution should be made up fresh for each treatment. A hypertonic solution is said to produce immediate rise in intra-cerebral pressure, then immediate and sustained fall (probably quoting Osborne).

1923. ISACSON¹ reports that, after the intravenous administration of fifteen grains of sodium iodide, dermatitis, headache, nausea and chill ensued for three days. Subsequently 2 gm. NaI orally produced no ill effect.

Various observers investigated the penetration of iodine into the cerebro-spinal fluid after different methods of administration, Catton² giving potassium iodide by the mouth found no penetration in a few cases.

1. ISACSON, L. New York Med. J. 1923, Sept.5, 322.
2. CATTON, J.A.M.A. 1916. LXVLL. 1369.

H.G. Mehrtens¹ was only able to detect iodine in the cerebro-spinal fluid in cases of meningitis.

But Osborne², using a more delicate method³, found:-

1. Traces of iodine in normal individuals in the C.S.F.
2. Iodine content increased after administration of iodide by oral, rectal, or intravenous route.
3. Greatest concentration after intravenous administration.
4. Iodine content after intravenous administration follows a curve.
5. Neuro-syphilitic tissue takes up more iodine than normal and particularly in cases of meningitis.

Again Cohen⁴ injected 50 c.c. of 10% KI. in ten cases. At intervals of from twelve to sixty minutes cerebro-spinal fluid was withdrawn and examined. The results confirm earlier observers and do not agree with Osborne's findings. The tuberculous, syphilitic and meningococcal diseases gave positive results; other diseases, tabes, disseminated sclerosis,

1. MEHRTENS, H.G. Calif. State. J. Med. 1918. 16. 306.
2. OSBORNE, E.D. J.A.M.A. 1921. 76. 1384.
3. KENDALL. Jour. Amer. Chem. Soc., 1912. XXXIV, 894-909; Biol. Chem., 1914. XIX, 251-256, and 1920. XLIII, 149-159.
4. COHEN, H. Lancet, 1924. 1. 127.

meningismus and "normals" gave negative results.

As the matter seemed contradictory, and as Kendall's method was a delicate one for estimating the presence of small amounts of iodine in organic material, an investigation was carried out by Professor David Campbell and the writer¹, with the objects of (1) confirming the actual facts of penetration or otherwise of iodine into the cerebro-spinal fluid, and (2) attempting to correlate any findings with the type of disease and any treatment administered. This paper confirms the main observations made by Osborne and may be summarised by exhibiting Table 1 from p. 357.

Table 1.

Number of Cases.	Kl. or NaI. administered.	Time of withdrawal of cerebro-spinal fluid after administration of last dose of iodide.	Milligrams per 100c.c of cerebro-spinal fluid (average amount).
19	Nil	<u>hours.</u>	Nil or mere trace.
12	Single dose 2-4 grams by mouth	1	0.08
17	1.5 grams thrice daily by mouth	1	0.38
17	1-8 grams intravenously	$\frac{1}{2}$	0.08
24	1-8 grams intravenously	1	0.28
8	10 grams intravenously	6-7	2.03
6	10 grams intravenously	18	0.20

1. CAMPBELL, D. and SNODGRASS, W.R. J. Pharm, and Exp. Ther. 1926. XXVII. 355.

This demonstrates that iodine can penetrate into the cerebro-spinal fluid, that an increase can be produced and maintained by regular oral administration of the simple potassium salt, and that the intravenous route may be used to increase the concentration of iodine in a marked way.

The significance of the high concentration of iodine in those eight cases, in whom lumbar puncture was performed 6-7 hours after the administration of ten grams of sodium iodide by the intravenous route, bears a different interpretation depending on the hypertonicity of the injection, and is later discussed in connection with its therapeutic application.

The figures given in the table represent the average of all cases whether suffering from disease of the central nervous system or not. To determine whether such disease had any effect on the concentration of iodine in the cerebro-spinal fluid, the cases were divided into five groups. (a) Those suffering from cerebro-spinal syphilis. In this group were included not only cases showing clinical evidence of organic changes, but also those in which the cerebro-spinal fluid gave a positive reaction to the Wassermann test at least two years

after a verified syphilitic infection.

(b) Doubtful cases, in which, with an antecedent syphilitic history, there were no objective or subjective signs of disease of the central nervous system, but in which the Wassermann reaction was suspicious, or positive, but within two years of the primary infection. (c) Cases of syphilis without any involvement of the central nervous system. (d) Cases of gross non-syphilitic nervous disease, such as spastic paraplegia, ataxic paraplegia and disseminated sclerosis. (e) Normal individuals.

Comparison of the amounts of iodine in the cerebro-spinal fluid in these five groups, whether iodide was given intravenously or by the mouth, showed that there was no essential difference. Disease of the central nervous system did not, in our experience, affect the passage of iodine into the spinal fluid. Our highest result, 5.5 mgm. of iodine in 100c.c., was found in a case of syphilis, where there was no clinical evidence of disease of the central nervous system, and where the Wassermann reaction of the spinal fluid was negative, while the next highest was 3.8 mgm. in an undoubted case

of cerebro-spinal syphilis. Osborne; in one of his cases which had marked syphilitic meningeal involvement, found as much as 42.308 mgm. of iodine per 100c.c. of spinal fluid, and, while suggesting that the meninges may be more permeable to iodine compounds when there is meningitis present, inclines to the view that tissue actively involved by syphilis takes up more iodine than normal tissue. Our clinical material was derived from an outpatient department and accordingly we had no opportunity of making observations on any case of gross meningeal affection. But our failure to obtain any great amount of iodine in the spinal fluid of cases suffering from other forms of syphilitic disease of the central nervous system, suggests that it is damage to the meninges, rather than increased affinity of syphilitic tissue for iodine, which is responsible for rendering the cerebro-spinal fluid more accessible to foreign chemical substances.

These cases have subsequently been examined to ascertain if any correlation exists between the amount of iodine present in the cerebro-spinal fluid and whether or not the cases were, at that time, receiving anti-syphilitic treatment with "914" and

a heavy metal. No such correlation exists. In other words, the presence of small quantities of arsenic, mercury or bismuth in the body does not influence the concentration of iodine in the cerebro-spinal fluid. Sex also did not affect the results.

The second part of this section is concerned with a great many experiments performed by the writer on some seventeen hundred and fifty cases of syphilis over a period of nine years. The number of experiments performed extends into the thousands, and it is quite impracticable to provide detailed protocols in each case. The main headings of investigation are given. These are then repeated with additional subheadings and thereafter a short discussion of the work done and the results is submitted. The preparations of iodide used have been almost exclusively the potassium salt for oral administration, and the sodium salt for intravenous injection. These preparations were employed as a result of the preceding review of the literature.

The main headings of investigation will be :

- I. Method of administration of iodide.
- II. Maximum dosage in respect of a single dose and of continued administration of iodide.

- III. Intolerance to iodides.
 - IV. The effect of iodide upon *Sp. Pallida* and the primary chancre.
 - V. The effect of iodide upon the secondary manifestations of syphilis.
 - VI. The action of iodide on tertiary skin and subcutaneous manifestations.
 - VII. The effect of iodide upon certain other tertiary signs and symptoms.
 - VIII. The use of iodides in latent syphilis.
 - IX. The effect of iodide upon the Wassermann reaction of the blood serum and cerebro-spinal fluid.
-

I. Methods of administration of iodide.

A. Potassium iodide by oral route:

Solution in water up to 50%
strength.

Solution in milk up to 50%
strength.

} before and
after food.

Tablet form given before food.

Tablet form given after food.

B. Sodium iodide by intravenous route:

Isotonic solution in water.

Hypertonic solution in water from

1% to $33\frac{1}{3}\%$.

Hypertonic solution in normal saline

from 1% to $33\frac{1}{3}\%$.

C. Sodium or potassium iodide per rectum:

Potassium salt in various aqueous

dilutions up to 20%.

Sodium salt in various aqueous

dilutions up to 30%.

I.A. Mode of administration of potassium iodide
by oral route:

It was found that the majority of cases tolerate well any percentage strength of potassium iodide, whether water or milk be used as a solvent, and whether the mixture be given before or after food. No flavouring agent was found which either finally disguised the taste of the mixture or diminished any tendency to iodism. In a proportion of cases the administration of potassium iodide after food produced dyspepsia lasting for an hour or so and such cases usually complained of some degree of dyspepsia after each dose. In all

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cases so complaining, if the mixture was given before food the dyspepsia ceased. A number of patients objected to the taste of the watery solution with or without flavouring agents. In such cases the salt, dissolved in water, was added to half a glass of milk and taken before food. In no case did this fail to secure regular taking of the iodide. The clinic routine is now to give the salt dissolved in water to be taken in additional water immediately before food.

Tablets of potassium iodide were not found suitable if a single dose greater than thirty grains was desired. Dyspepsia usually followed. This could be minimised or abolished if a large quantity, a half to one pint of water was taken at the same time as the tablets.

I.B. Mode of administration of sodium iodide by intravenous route:

Isotonic aqueous solutions of NaI. were first employed. No literature was then available and experiments were carried on with a steadily increasing percentage of the aqueous solution of the sodium salt. If the strength of solution be from 15% to $33\frac{1}{3}\%$, there is an

advantage in that smaller quantities of fluid require to be given and the whole operation can be carried out with one large syringe.

Percentages of 15% and higher, however, frequently cause sudden and transitory severe burning pain over the deltoid region in the injected arm, with transitory flushing of the face and a feeling of vertigo. This would appear to be due to the hypertonicity of the solution, for similar complaints were found when aqueous solutions of sodium chloride of similar percentage strength were tested. Solutions of Na.l of 15% or over, also tend to produce thrombosis in the vein; a comparable result was found when Na. Cl. was used. Eventually it was determined that a 10% aqueous solution was safe and painless. It is easily measured into various dosages and easily administered by a syringe. Repeated use of the gravity method using a needle and funnel tends to thrombosis of the vein. No advantage accrued from using normal saline as a solvent and it merely complicates the calculation of the percentage strengths and the consequent amount of Na.l given.

I.C. Mode of administration of iodide per rectum:

The potassium salt of iodine is not suitable for rectal administration in a watery concentration of more than 5% - 10%. It then becomes irritating and may cause pain and diarrhoea. The sodium salt may be given in percentages up to 20%. A higher percentage produces local pain and a burning sensation. A 10% aqueous solution is well tolerated but must be given slowly.

II. Maximum dosage which can be given in respect of a single dose and continued administration without intolerance:

- A. Potassium iodide given orally.
- B. Sodium iodide given by intravenous route.
- C. Combined oral potassium iodide and intravenous sodium iodide.

II.A. Dosage of oral potassium iodide:

Idiosyncrasy occurs and two cases have been seen in which iodism on every occasion followed a dosage varied from two grains to ninety grains. No method was found of overcoming this phenomenon. In both cases the skin showed a negative result to repeated applications of the "patch" test employing

5% potassium iodide as the irritant. A number of cases showed initial intolerance, later to be referred to, but the majority of cases can tolerate, as a single oral dose, anything from one forty-eighth of a grain to two hundred and forty grains. Intolerance was only once seen when the initial dose was more than thirty grains.

In three cases fifteen grains of potassium iodide thrice daily before food has been given continuously for eighteen months. No ill effects have been observed. Several cases have received a similar dosage for more than one year and no ill effects have been noted. Many cases have taken this dosage for six months, and to a few the taste of iodide became so obnoxious that the mixture was stopped. Such cases complained of loss of appetite.

II.B. Dosage of intravenous sodium iodide:

Idiosyncrasy was noted in one patient only. This case could tolerate the oral administration of potassium iodide but was unable to take half a gram of sodium iodide well diluted without iodism appearing within twelve hours. All

other cases showed no intolerance, and the only technical reasons for cessation of intravenous therapy consisted in local thrombosis or, through faulty technique, the escape of hypertonic solution into the subcutaneous tissues with resulting severe local discomfort.

The maximum single dose given was 22 grams in 10% aqueous solution. No further increase was made for no increased therapeutic effect could be visualised from a larger dosage.

The daily administration of intravenous sodium iodide was only limited by the availability of the veins. One case received 10 grams of sodium iodide daily for three weeks with no untoward results.

II.C. Dosage of combined oral and intravenous iodides:

One patient received by the oral route 90 grains of potassium iodide four times a day and 10 grams of sodium iodide daily by the intravenous route for fourteen days without ill effect.

The tolerance of the average patient is thus extremely high to single oral and intravenous administration and to lengthy periods

of regular dosage. Full advantage therefore could be taken of this factor in therapeutic experiments.

III. Intolerance to iodides: iodism:

It is not necessary to describe here the various clinical phenomena of iodism. The mildest grades noted as indicative of such a condition were (1) slight watering of nose or eyes or both. (2) a slight transient or persistent erythema, usually of the face or neck. Only once was a pustular iodide rash seen. No cases of iodine cachexia, mild or severe were noted.

Iodism is of common occurrence if the oral route be used. It appeared in about 12% of those cases whose initial dose was 5 grains or less: in about $7\frac{1}{2}\%$ of those whose initial dose was from 10 to 30 grains: in less than 1% if the initial dose was more than 30 grains.

Iodism usually appeared within the first week of treatment. In a number of cases where no intolerance had been noted at the outset, intolerance, while on a constant dosage, appeared at a later date. Almost all such cases had some intercurrent disease not attributable either to syphilis or iodide. Such conditions were gall stones, cholecystitis, secondary anaemia and pleurisy with effusion. No attempt was made in such cases to re-establish tolerance. Intolerance was thrice noted when a large dose was reduced. No other factor was determined. This was considered an exceptional and curious fact and a number of experiments were made by the sudden reduction of dosage in the hope of inducing intolerance in other cases. All failed.

Intolerance could usually, but not always, be overcome by increasing the oral dosage - it was found that an increase to thirty grains thrice daily before food gave the best results. A smaller dosage was less reliable. The gradual increase of the dosage by two or three grains was not helpful. The administration of a large single dose of sodium iodide by the intravenous route was definitely the best way of stopping intolerance. Various quantities

were tried - varying from one half to ten grams. Four to six grams is sufficient to stop iodism. One to two grams is not. It is now a routine practice in cases of iodide intolerance to give either four or six grams of sodium iodide by the intravenous route and to tell the patient to continue with the oral mixture. This method and dosage has been completely successful in ninety-eight cases. It has failed once.

Apart from one case which exhibited idiosyncrasy to intravenous sodium iodide, no case of initial intolerance to the intravenous route has been found with an initial quantity varying from a half to twenty-two grams. If daily injections of sodium iodide be given it is found that a small percentage of cases complain after a time of restlessness and sleeplessness. In such cases cessation of treatment led, shortly, to a return of sleep. No intolerance has been seen when injections are given at weekly intervals.

Generally it is considered that intolerance is more apt to appear in cases with greasy skins, which may or may not show seborrhoeic conditions. In three out of ten such cases showing intolerance which were investigated, there was hyperchlorhydria. It is thought that where there is much initial sepsis, as in large

infected tertiary lesions, there is an increased tendency to intolerance. Sex is not considered to influence the incidence, nor is the age of the patient. The age of the syphilitic infection has no bearing upon the incidence of intolerance. Concomitant treatment with "606", "914", mercury or bismuth is not considered to predispose to iodism. Iodide appears in the saliva, but is chiefly excreted by the kidney. Syphilitic disease of the mouth or of the kidney, and cystitis (non syphilitic) did not appear to increase the incidence of iodism.

IV. The effect of iodide upon Sp. Pallida and the primary chancre:

- A. Local - hypotonic and hypertonic solution.
- B. Oral - ten to thirty grains thrice daily.
- C. Intravenous - two to ten grams of sodium iodide.
- D. Combined oral and intravenous - B + C.
- E. Rectal.

Local applications of sodium or potassium iodide temporarily decrease the number of Sp. Pall., but only if hypertonic solutions be employed. Hypertonic saline has a similar action.

In vitro Sp. Pall. is destroyed by all hypertonic solutions: it is not materially affected by isotonic solutions of sodium or potassium iodide.

Oral, intravenous, and rectal administration carried out singly, and in the case of oral and intravenous routes by combination, for periods of one to three days, did not reduce materially the number or the mobility of Sp. Pall.

Boinet in his book "Iodothérapie", recounts that the prolonged administration of oral iodide leads to the earlier resolution of the chancre, but not to an inhibition of secondary phenomena.

No period of treatment with iodide alone extended beyond three days. No change in the ulcer or in its secondary infection was noted in that time with any of the methods of administration described.

V. The effect of iodide upon the secondary manifestations:

A. Mucous membrane lesions:

Effect on Sp. Pall.,

resolution,

pigmentation.

by:

- (1) Local application - isotonic and hypertonic solutions.
- (2) Oral administration of potassium iodide in doses up to 120 grains four hourly.
- (3) Intravenous injection of sodium iodide in dosage up to twenty grams - single injection or daily injections.

- (4) Combined oral and intravenous administration.
 (5) Rectal administration of aqueous solutions
 of sodium iodide.

B. Skin rashes:

Effect on resolution
 pigmentation.

- | | | |
|-----------------------------------|---|------------|
| (1) Local |) | |
| (2) Oral |) | |
| (3) Intravenous |) | As in V.A. |
| (4) Combined oral and intravenous |) | |
| (5) Rectal |) | |

C. Adenitis:

Effects on resolution

- | | | |
|------------------------------------|---|------------|
| (1) Oral |) | |
| (2) Intravenous |) | |
| (3) Combined oral and intra venous |) | As in V.A. |
| (4) Rectal |) | |

No experiment was continued longer than one week.
 Ordinary anti-syphilitic treatment was then commenced.
 This was considered advisable in the interests of the
 patient. The conclusions, therefore, are only of
 short range, and appear as chiefly negative in result.

No method of administration altered the Spirochaete
 content of moist lesions, except the local application

of hypertonic solution. Here too sodium chloride in hypertonic aqueous solution was equally efficacious.

No effect was seen in one week upon the resolution of moist lesions, the involution of rashes or the resolution of adenitis. Very large doses were given by the oral route; 120 grains four hourly, and by the intravenous route, 10 grams daily.

Some effect was produced upon the persistence of pigmentation in secondary syphilis. An individual lesion, other than simple roseolar spots, shows three stages in its life history. There is a short stage of efflorescence, lasting from three to seven days; a longer stage of florescence lasting from seven to about thirty days, and a still longer stage of deflorescence lasting from fourteen days to several months. The deeper the lesion is situated in the skin, or the more the lesion protrudes, as in large flat papular rashes, the longer the process takes. Further, the longer the process the longer will pigmentation persist, particularly in deep skin lesions and definite staining has been seen eighteen months after the onset of the lesion. These facts were determined, partly by observation of treated secondary syphilis, but chiefly by piecing together the statements of a large number of cases seen at different stages in their secondary infection.

The administration of "914" or "914" and a heavy metal alters the normal course of events. It aborts efflorescence and any rash spots not fully out quickly disappear. Allowance must be made for the Jarisch Herxheimer reaction. It cuts short the stages of florescence and deflorescence, but it seems to have less effect upon the prolongation of pigmentary changes. The nature of this pigmentation is not known. Professor J.S. Young examined sections from a case and showed that it was not due to Iron deposition from haemoglobin, nor due to mercury. In any case it is chemically indistinguishable from the pigmentation of an untreated patient in whom natural resolution occurs. If, however, the oral administration of potassium iodide be maintained throughout the first course of anti-syphilitic treatment there is no doubt, clinically, but that the production of pigmentation is diminished and, if it be produced, its duration is appreciably diminished. An attempt was made to follow out the end result of such cases but the numbers of apparently cured and relapsed cases do not show any significant factor. The available evidence could not be construed into the suggestion that the administration of iodide aided, through its resolvent action, the more thorough destruction of skin deposits

of spirochaetes by facilitating the action of "914" or a heavy metal.

VI. The action of iodide on tertiary skin and subcutaneous manifestations:

A. Skin and mucous membrane rashes.

B. Ulceration.

C. Subcutaneous gummata.

(1) Oral potassium iodide:

gr.¹/48 t.i.d. to gr. 90 four hourly.

(2) Intravenous sodium iodide:

A half gram to twenty two grams daily or weekly injections.

(3) Combined oral and intravenous administration:

(4) Rectal administration:

One gram to ten grams of sodium iodide given daily or weekly.

A great many experiments were made. The main conclusions are stated.

VI. A.B.C. (1) Oral potassium iodide: Most attention has been given to this method of administration, for it is obvious that the intravenous route will only be employed by clinics and a few specialists. The simple oral administration of iodide must remain the most

convenient and popular method of administration. Certain factors were shown to have no effect in hastening or retarding resolution of all skin lesions.

These were the sex of the patient, the age of the patient, the state of general health of the patient and the occupation. Occupation is specially noted, for quite a number of tertiary lesions appear in the neighbourhood of body sites subjected to the trauma of work, e.g. rash on the outer side of thigh - lamp-lighter; front of thigh - shoemaker; prepatellar region - charwomen; shoulder - gamekeeper.

Chronic alcoholism does not delay resolution.

A varicose condition of the adjacent veins always delayed resolution: indeed several ulcers in the lower third of the legs required months of dressing and treatment of various kinds.

The site of the lesion was of little importance, though those lesions in regions where there was a good deal of loose subcutaneous tissue seemed to show slightly quicker resolution and generally the more vascular parts show quicker resolution. The size of the lesion was naturally of the greatest importance, and in many cases the size is an expression of the duration of the lesion. The duration of the lesion apart from the increase in its

natural growth (or a size factor) did not affect the time of resolution. Multiple lesions behaved as did similar single lesions of corresponding type. In a few cases only the lesions when first seen had commenced spontaneous resolution - such showed no differences from the response to treatment of fully active conditions.

Subcutaneous gummata, with unbroken skin, disappeared most quickly of all types of lesions. Then came the nodular rashes (the tuberosa syphilide), provided also that the skin was unbroken. Next in order of rapidity of resolution were rashes in which the hyperplastic element was reduced to a minimum, such as those of a psoriaform type: then simple ulcers, fairly free from secondary infection: then skin rashes in which superficial ulceration had appeared, where though the unbroken skin element quickly resolved, the ulcerated portions were often slow to heal. Large chronic infected syphilitic ulcers, especially if varicosity indicated poor circulation, definitely took the longest time to resolve and to heal. There were also seen in this slowly healing group a number of osseous gummata. In one male case, where thirty five tumours were felt on the long flat bones, three months iodide treatment failed to make any impression. In this case X-ray examination, histological examination, serological tests and a conjugal

infection confirmed the diagnosis of syphilis.

Some curious cases of individual resistance or lack of response to iodide were seen. These were all noted while using a dosage of less than fifteen grains thrice daily, and such cases usually responded normally to an increase in the dose. In four cases the dose of iodide was not increased but the patient was given five grains of thyroid extract twice daily. Three weeks of this treatment produced no acceleration of the rate of resolution. In one case an eighth of a grain of para: thyroid extract combined with five grains of potassium iodide thrice daily, failed to accelerate the process of resolution in two weeks. In every case in which it was tried, the interpolation of a single intravenous injection of four, six, or eight grams of sodium iodide produced a temporary increase in the rate of resolution. This was considered to have passed off in one week. These observations led to a series of experiments with single doses of potassium iodide, varying from one to two hundred and forty grains, given orally. From this it was concluded that iodide exerts a rough quantitative action, but does not initiate a healing process which can then continue spontaneously. This action of the single dose of iodide was considered to increase pro: portionately while the dose was raised from one grain

to thirty grains. Thereafter little accrued benefit seemed to be derived from larger single doses. These observations were considered of great importance in reaching a decision as to the optimum dosage. It appears likely that, if a single dose of one hundred and twenty grains given orally is no better than one of thirty grains, repeated dosage of the larger quantities will also fail to show increased benefit, and such is, in fact, the conclusion drawn from the various experiments with the regularly repeated administration of various quantities of potassium iodide. These observations cannot give an answer to the question of the mode of action of the iodides, but at least they do not conflict with the hypothesis expressed by Jobling and Petersen (see p.384).

The regular administration of various quantities of iodide was then experimented with. The dose was given in water thrice daily before food. Out patients cannot be trusted to take any medicine more frequently than this and indeed in many cases considerable doubt existed as to whether the prescribed dose was properly taken.

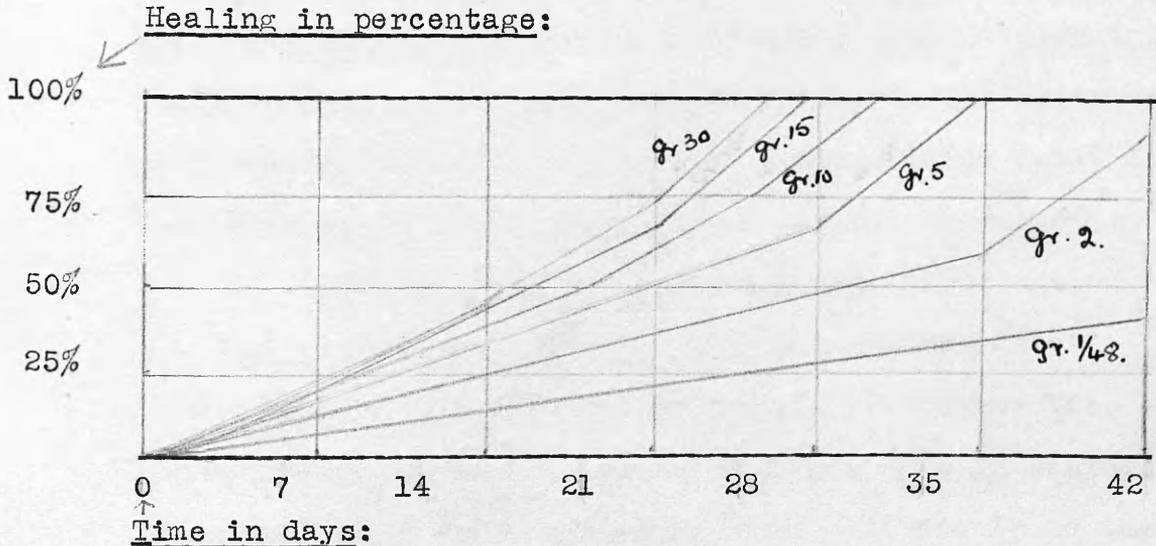
The following quantities were tried:
 gr. $\frac{1}{48}$, gr. $\frac{1}{24}$, gr.1, gr.2, gr.3, gr.5, gr. $7\frac{1}{2}$, gr.10,
 gr.15, gr.20, gr.25, gr.30, gr.45, gr.60, gr.90.

It is curious that such a small quantity as $\frac{1}{48}$ of a grain thrice daily should initiate and maintain resolution of gummata. It was tried in five cases, and in four, where there was no sepsis, improvement slowly and steadily took place over periods of from three to six weeks. The rate of resolution appeared to increase with each increase in dosage up to fifteen grains. Thereafter it was considered that only a slight additional benefit was obtained with dosage of twenty or thirty grains and that none was seen in the higher ranges.

It should here be noted that in visceral syphilis, particularly if there be gummatous involvement of the liver, the larger doses, 45 to 90 grains, are considered helpful. One lascar, with hepatitis, in the medical wards, showed no clinical improvement on a dosage of twenty grains six hourly, but quickly improved on sixty grains every four hours.

It is difficult to make accurate statistical comparisons of these various dosages, for the size of the lesion and the amount of secondary infection are confounding factors. Also the definition of "resolution" is not easy. It was considered to indicate a condition wherein the underlying tissue, at the site of the lesion, could not be differentiated from healthy tissue by palpation, but, even here, allowance had to be made for scar tissue.

An attempt is made to exhibit the comparative results in the form of a rough graph in which the ordinates represent time in days and the abscissae degrees of resolution in percentages from 0 to the completed stage.



Certain abnormal cases, cases with varicose ulcers, and grossly septic cases are not included. In many cases "914" and heavy metal were given before complete resolution occurred. These curves thus have been compiled in the face of known errors, but nevertheless represent a reasonably accurate result of the comparative values of the different quantities of potassium iodide. Such errors as do occur are spread fairly uniformly throughout the series. The conclusion seems obvious - and has been already stated by William Wallace in his

original paper - that the optimum dose is fifteen to thirty grains of potassium iodide given thrice daily. Further, in view of the observations noted that a single dose of potassium iodide had a quantitative effect on resolution and that no increase in this effect was seen when the dose was increased beyond thirty grains, it seemed im:
:probable that further experimentation could modify this conclusion. Also since fifteen grains thrice daily was practically equivalent to thirty grains thrice daily in the rate at which it produced resolution, it was con:
:sidered advantageous to employ the smaller dosage. An attempt was then made to determine whether the repetition of the dose was necessary, or whether the single daily administration of a single dose of fifteen grains could be considered adequate. It was found that definitely better results were achieved when the dose was repeated three times. This seems to agree with Osborne's observation that the highest urinary concen:
:tration is noted at from two to four hours after a dose of any quantity. Thus a repetition of the iodide became advisable. In view of this observation five cases received fifteen grains of potassium iodide every two hours, day and night. All responded well, but no acceleration was seen in the rate of absorption as

compared with those cases receiving fifteen grains thrice daily. So far then, clinical observation suggests quite definitely that there is no advantage in increasing the iodine concentration of the blood serum beyond the point reached by fifteen or thirty grains, and no advantage in reaching this concentration more frequently than three times in the twenty-four hours. But there is one disturbing observation already recorded, namely that in any case, the interpolation of a single intravenous injection of four, six or eight grams of sodium iodide appeared, temporarily, to hasten resolution. Accordingly a number of cases taking fifteen grains of potassium iodide thrice daily were given a single oral dose of ninety or one hundred and twenty or two hundred and forty grains. Here too this interpolation of the single large oral dose seemed to produce acceleration of resolution for a short time. It is to be noted that as described the continued administration of the larger doses did not yield corresponding benefit. Since the optimum dosage appeared to be fifteen or thirty grains thrice daily, the temporary value of the single large dose can be restricted to those few cases in which resolution is unduly slow, or to those cases in which unfavourable factors, already noted, are present. This is now the routine practice of the clinic but the intravenous

route is employed for the single large dose and therefore where the maximum iodide effect is wanted, a single injection of four or six grams of 10% aqueous solution of sodium iodide is given, combined with the oral administration of fifteen grains of potassium iodide thrice daily before food. The daily injection of intravenous iodide combined with the oral administration of potassium iodide did not appear to offer any further improvement. It is considered that the experiments here discussed are shown to have definite conclusions, and that no further useful evidence can be obtained by this method of experimentation.

VI. A.B.C. (2) (p.33) Intravenous sodium iodide:

It has been explained that tolerance is high and a 10% aqueous solution is safe and easy to give. The effect of potassium iodide by the mouth has just been described. Therefore although the earliest experiments were made independently of the oral use of the potassium salt, it was soon realised that the difficulties of administration demanded a definite superiority for the method if any practical result was to be achieved. The general conclusions just described in connection with oral potassium iodide, as to the factors which influence the resolution of gummatous lesions, were reached in the case of the intravenous route when

sodium iodide was employed. In this case however only forty seven cases were utilised for experimentation while in the case of potassium iodide by mouth seven hundred and forty three cases were experimented on. These general conclusions therefore have not such a mass of experimental proof.

The quantities used were one, two, three, four, six, eight and ten grams, at weekly and daily intervals. It was concluded that the weekly injection of any dose of sodium iodide was inferior to the repeated oral administration of fifteen grains of potassium iodide. It was thought that an increased clinical benefit was seen when a dosage greater than six or possibly eight grams was given. The daily administration of an injection of sodium iodide yielded good results and there seemed, in these cases, no increased benefit from giving a quantity larger than four or six grams. Yet the results were in no way superior to the oral route of administration and the technical difficulties much greater. Osborne (as quoted p387) indicates that there is no difference in the rate of elimination whether the oral or intravenous route be used, or whether a large or a small dose be given. A daily injection of four grams is equivalent in clinical effect to fifteen

grains given thrice daily by the oral route. It is suggested on the basis of these clinical studies that the value of iodide in a case of syphilis is concerned with the fact that a regular oral dose produces a regularly repeated rise in the iodine content of the blood serum. No experiments have been made giving several injections of sodium iodide during the course of twenty four hours - no theoretical advantage could appear to accrue therewith in view of the rapid rise in the blood serum content which Osborne states follows the use of the potassium salt by mouth.

During the course of these experiments the question was raised as to whether the fact that the solutions were hypertonic had any bearing on the results - accordingly 90 or 100c.c. of 15% aqueous solution of sodium chloride were given on three successive days to four patients, each of whom showed a tertiary skin lesion with no ulcerated areas. The curious fact was brought out that, at the end of a week, a slight degree of clinical improvement was noted in each patient. This was definitely less than was to be expected had sodium iodide been used, still each case, when first seen, had not commenced any retrograde changes. No further experiments were made along these lines, for

the changes though interesting, did not appear to be of therapeutic importance.

VI. A.B.C.(3) (p.33) Combined oral and intravenous iodides:

The outcome of these combined methods has necessarily been indicated in the discussion on the oral use of potassium iodide. It is to the effect that a weekly injection of four, six, or eight grams acts as a temporary adjuvant to the regular oral administration of fifteen grains thrice daily. No increased benefit followed the use of a larger quantity by the intravenous route.

VI. A.B.C.(4) (p.33) Rectal administration:

One, five, ten and twelve grams of sodium iodide in 10% aqueous solution were employed daily or at weekly intervals. This method of administration is not necessary. Therapeutic results are, however, achieved and the maximum benefit seemed to be obtained from the daily employment of ten or twelve grams. Rectal irritation was complained of after one week in one case receiving a daily injection of ten grams in 10% aqueous solution. Only twelve cases were used for this variety of experiment.

Summary of suggested use of iodides in the treatment of tertiary muco-cutaneous lesions.

- (1) Give fifteen grains of potassium iodide well diluted in water thrice daily before food:
- (2) If intolerance to iodine is met with give an intravenous injection of four grams of 10% aqueous solution of sodium iodide and continue the use of the oral potassium iodide:
- (3) If resolution appears unduly delayed give, at weekly intervals, an injection of six or eight grams of 10% aqueous solution of sodium iodide and continue to employ the potassium salt by mouth in fifteen grain doses thrice daily.

These conclusions were reached by experimentation with iodide, unaccompanied by the employment of either "914" or a heavy metal. In subsequent cases anti-syphilitic treatment was employed using "914" and Hg. or Bi. Undoubtedly lesions heal very much more quickly under the combined influence of all these drugs, but a variation of the quantities of potassium iodide maintaining the usual course of treatment with "914" and Hg. or Bi. did not lead to any different conclusions. Conclusions were difficult to draw

concerning the value of iodide in conjunction with these other drugs as the other drugs themselves, exert such a rapid and powerful resolutive effect upon tertiary skin lesions.

VII. The effect of iodide upon certain other tertiary symptoms and signs.

Pains, sleeplessness, anaemia, loss of appetite:

These symptoms were all relieved quickly by the use of iodide alone. Even two grains of potassium iodide thrice daily alleviated the night pains of syphilitic periostitis of the tibia. In three weeks time, giving fifteen grains of potassium iodide thrice daily before food, and no other therapy, in one case the haemoglobin rose from 65% to 83% and the R.B. cells from 4,100,000 to 4,580,000. An increased sense of well being was almost universally experienced by all cases.

Some observations on the clinical effect produced by iodides on neuro syphilis will be found in section IX.

VIII. The use of iodides in latent syphilis.

A. Continued use of potassium iodide with no other drug:

B. Continuation of iodide throughout course of "914" and metal:

C. Intravenous sodium iodide.

Latent syphilis is defined as a condition in which the Wassermann reaction of the blood serum is positive: in which no clinical signs of syphilis are found, and in which, if a definite history of primary or secondary infection be obtained, it is of at least two years duration.

Three cases received fifteen grains of potassium iodide thrice daily for eighteen months. No clinical relapse occurred: no alteration from a positive blood Wassermann was noted.

The continuation of fifteen grains of potassium iodide thrice daily throughout the whole periods when "914" and metal (Hg. or Bi.) were given did not lead to a greater percentage of final favourable serological results. This cannot be considered as a properly controlled statement, for although many cases did not receive iodide along with other drugs, small quantities of inter-current iodide therapy were given to almost every case.

The use of intravenous sodium iodide was not made in a systematic manner and a table showing the actual quantities given to all these cases, male or female, treated and observed for more than two years is therefore subjoined.

The cases are subdivided according to whether the total treatment given was adequate or inadequate (see section on Latent Syphilis) and the final serological result was negative (satisfactory) or not negative (unsatisfactory). The amount of sodium iodide administered is shown in grams.

Nal. in latent syphilis observed for two years or longer.

Total amount of intravenous Nal. in grams.

Treatment:	Result	0	1 to 20	21 to 50	51 to 75	76 to 100	More than 100.
Adequate	Sat.	35	2	5	3	0	1
Inadequate	Sat.	6	0	0	0	0	0
Adequate	Unsat.	29	4	6	5	2	1
Inadequate	Unsat.	5	1	0	1	0	0

No definite conclusions of value can be drawn from this table. The increase in the numbers of cases getting intravenous sodium iodide which, after receiving adequate treatment, finally showed an unsatisfactory serological result is probably due to attempts to reverse the positive Wassermann reaction by all available methods of therapy. It is however suggested that this indicates that intravenous sodium iodide is not of much benefit in securing a final negative serological result in latent syphilis.

IX. Effect of iodide upon the Wassermann reaction of the blood serum.

A. Early Syphilis:

B. Late and congenital syphilis:

IX. A. Effect of iodide upon the Wassermann reaction in the blood serum in early syphilis:

After 1923 i.e. after the replacement by bismuth of mercury as the heavy metal to be given concomitantly with "914", the standard course in early syphilis consisted of ten injections of "914" equivalent to 5.85 grams, and twelve intramuscular injections of bismuth metal equivalent to 2.4 grams of metal. Normally potassium iodide was given in a dose of fifteen grains thrice daily for three weeks during a rest period between the eighth and tenth weeks. It was considered theoretically possible that the continued administration of potassium iodide throughout the whole course might be of advantage. This view was based upon the known action of iodide on gummatous tissue. It was thought that the continued use of iodide might prevent the formation of gummatous deposits in the tissues and, by facilitating the access of anti-syphilitic drugs, lessen the tendency to late serological and clinical relapse. Should this prove the case the therapeutic value of such

a proceeding would be obvious. A careful search through the literature failed to bring out any comparable experiment. Such an experiment requires much time to enable any definite conclusions to be drawn, and it is felt that at least five years observation is necessary. Only a few cases have remained under observation for such a period, and therefore statistical evidence is scanty. This answer is quite inconclusive for almost all cases observed for such a time did well whether the treatment consisted of "914" and Hg. or of "914" and Bi., or of "914" and Bi. and Kl.

An analysis was then made of those cases which had been under observation for two years. At the end of this period a preliminary attempt is always made to determine whether or not a case can be termed "cured" and if it be thought "cured" no further treatment is given. There was a very slight improvement in the percentage of satisfactory serological end results in early syphilis, male and female, when iodide was used continuously with "914" and Bi. This was noted as compared with those cases in which "914" and Bi only were employed and also in comparison with the cases treated with "914" and Hg. It is not considered to be a significant figure, because firstly, the numbers are

small, and secondly, these cases, on the whole, have tended to receive more complete courses of "914" and metal since they occurred in the later years.

Finally the cases were analysed in an attempt to ascertain if the continuous use of iodide throughout the first course of treatment produced a greater percentage of negative serological results at the end of this first course. No such improvement was found.

In 1929 this method of employment of iodide was suggested as a routine in the standard treatment of all the "ad hoc" venereal centres attached to the Corporation of Glasgow. In 1931, Dr. A.S. McLachlan, from Bellahouston clinic, reported that in his opinion the continuous employment of iodide led to an increase in arsenical intolerance, chiefly of a mild type. No details were given. The intolerances occurring in the Western Infirmary were therefore subjected to analysis to determine if such was the case. This analysis proved to be laborious owing to the system of case records, but it can be definitely stated that the continuous use of iodide does not increase either the incidence or the severity of arsenical, mercury or bismuth intolerance in this series of cases.

It is therefore concluded, that the continuous use of iodide throughout treatment with "914" and a heavy metal is not shown to be of value, either in the production of a negative serological test at the end of the first course, at the end of two years, or at the end of five years.

A number of cases of early syphilis on completion of their standard treatment, and on attaining a repeatedly negative Wassermann reaction of the blood, were given a series of intravenous injections of sodium iodide at weekly intervals with the idea of thus aiding in the maintenance of a "cured" condition by preventing any gummatous tissue formation. Twenty four cases were so treated, receiving from twenty seven to one hundred and four grams of NaI. All cases did well but no deduction is made therefrom.

IX. B. Effect of iodide on the Wassermann reaction of the blood serum in late and congenital syphilis.

Potassium iodide by mouth: No Wassermann improvement followed the administration of fifteen grains of potassium iodide thrice daily for periods of twelve to fifteen months in eleven cases of tertiary syphilis - nor for periods of eight to twelve months in thirty seven cases. In one case the Wassermann reaction of

the blood serum changed from positive to negative after nine months during which nothing but potassium iodide was given. It shortly relapsed again to positive. Hundreds of cases received potassium iodide for periods of three to four months without any serological change, except in a small percentage (1.6%). Such favourable changes were only temporary, and can easily be attributed to the antecedent antisyphilitic treatment which they had received. The percentage of such favourable changes did not differ from that seen after rest periods of comparable length during which no treatment was administered.

The intravenous use of sodium iodide: An extensive series of experiments was made employing this drug at weekly intervals both in conjunction with anti-syphilitic drugs and as the sole intercurrent treatment. The results achieved were somewhat varied and can best be expressed in a table. This table shows the type of syphilitic lesion, the sex of the patient, the amount in grams of Nal. given, whether it was given alone or in conjunction with "914" or a heavy metal, and the serological reaction immediately subsequent to the course of intravenous sodium iodide. It is to be remembered that each experiment merely represents one "course" of

treatment in the clinical history of a case. Many cases received more than one such course.

Type of disease:	Sex:	Quantity of NaI. in gms.	"914" and Metal also given:		No other treatment given:	
			End +	Wassermann -	End +	Wassermann -
Skin and sub-cutaneous tertiary syphilis:	Male	-100	18	1	9	0
		-150	23	2	6	1
		+150	14	1	4	0
	Female	-100	13	1	7	1
		-150	15	2	8	0
		+150	13	4	3	0
Neuro-Syphilis:	Male	-100	14	1	12	1
		-150	16	0	7	0
		+150	14	1	7	0
	Female	-100	10	0	10	0
		-150	3	0	11	1
		+150	2	0	5	0
Con-genital Syphilis:	Male	-100	6	0	2	1
		-150	4	0	0	0
		+150	2	0	2	1
	Female	-100	3	0	0	0
		-150	5	0	3	0
		+150	4	1	1	0

In the tertiary skin and subcutaneous lesions and in the congenital cases, the number of favourable results seems to be slightly in excess of those cases not so treated. The serological improvement was only temporary, and did not seem to affect the final outcome of the case to any great extent. It is considered a definite principle that in treating late syphilis, treatment should only be prolonged beyond two years if serological improvement is detected at any time during the first two years, and the patient desires it (section on late syphilis). It is suggested that a course of intravenous sodium iodide should be given along with "914" with or without a heavy metal at some period during the second year of treatment if no serological improvement has hitherto been seen. But as the final serological result is not materially affected there seems no need to introduce this method of therapy during the earlier stages of treatment.

With respect to the cases of neuro-syphilis, a similar temporary improvement is noted in the immediate Wassermann reactions. It should be pointed out however, that the serological reactions of the blood and cerebrospinal fluid are not considered of such prognostic importance in neuro and cardio vascular syphilis as in the other late manifestations of syphilitic disease.

Many cases of neuro-syphilis progress clinically in spite of negative serological tests. Therefore, in connection with the use of intravenous sodium iodide, the question of clinical benefit has to be noted. It is definitely thought that its employment is followed by an increased feeling of wellbeing in a considerable proportion of cases, and that many subjective phenomena are temporarily improved. Improvement has been noted in respect of the cessation of pain, ability to walk, less inco-ordination, tremor, and clearer speech. The best results are obtained when "914" is given concurrently. It is thought that sodium iodide may advantageously be used at some stage or another in the treatment of most cases of neuro-syphilis, but it should not be employed in the earlier stages in case of setting up the Jarisch Heixheimer reaction.

A further series of experiments was made with the use of hypertonic aqueous solutions of sodium iodide in an attempt to facilitate the entrance of arsenic into the cerebro-spinal fluid. As no account of any similar experiments has been discovered in the literature, the argument and details concerning these cases will be presented in greater detail.

Spinal drainage has been employed in an attempt to increase the penetration of drugs, such as salvarsan, into the cerebro-spinal fluid, and thereby to enhance its therapeutic effect in the treatment of neuro-syphilis. Thus Gilpin and Early¹ in 1916, after the administration of arsphenamin by the intravenous route, later removed by lumbar puncture a quantity of cerebro-spinal fluid. They reported satisfactory clinical results. For patients attending clinics it is not always possible to secure in-patient accommodation, and some substitute for lumbar puncture is desirable.

A method was suggested by Corbus, O'Connor et al², in 1928. This consisted in the administration of 100c.c. of 15% aqueous solution of sodium chloride by intravenous injection six hours before the administration of neo-arsphenamin. The rationale of this procedure is derived from a study of the following points:

1. GILPIN, S.F. and EARLY, T.B. "Drainage of cerebro-spinal fluid as a factor in the treatment of nervous syphilis". J.A.M.A. 66. 260-262. January, 1916.
2. CORBUS, B.C. O'CONNOR, V.J., LINCOLN, MARY C., GARDNER, STELLA M., "Spinal drainage without lumbar puncture." J.A.M.A. 78. 264-266. January 28, 1922.

Weed and McKibben¹, in 1919, showed that the intravenous injection of hypertonic saline solution caused an initial rise in the pressure of the cerebro-spinal fluid, and a subsequent fall, often to zero. Foley and Putnam² confirmed this. Foley³ states that this fall in pressure disturbs the normal circulation of the cerebro-spinal fluid so much that intraventricular absorption of fluid occurs through the choroid plexuses and ependyma. Presumably this is a result of an effort to maintain the blood serum at its normal specific gravity. Restoration of the spinal fluid begins about the sixth hour after injection of the hypertonic saline, and the normal pressure is restored one to three hours later. If then, salvarsan be given about the sixth hour, there should be a greater degree of absorption of arsenic from the blood stream than ordinarily occurs.

Corbus found in the treatment of thirty patients that arsenic did penetrate into the cerebro-spinal fluid in twenty eight cases, and that, clinically and serologically, the results of this method were encouraging.

1. WEED, L.H. and MCKIBBEN, P.S. "Pressure changes in the cerebro-spinal fluid following intravenous injection of solutions of various concentrations". AM.J.Phys. 48. 512-30. May, 1919.
2. FOLEY, F.E.B. and PUTNAM, T.J. "The effect of salt ingestion on cerebro-spinal fluid pressure and brain volume". Am.J.Phys. 53. 464-76. October, 1920.
3. FOLEY, F.E.B. "Clinical uses of salt solution in conditions of increased intracranial tension". Surg.Gynec. & Obst. 33. 126-136. August, 1921.

In the course of investigations conducted with Dr. David Campbell¹ into the penetration of iodine into the cerebro-spinal fluid, it was found that, if sodium iodide was given in aqueous solution either orally or by the intravenous route, penetration did occur into the cerebro-spinal fluid. The degree of concentration in the cerebro-spinal fluid was not parallel with that of the blood stream in which case concentration is greatest at an early time. In the cerebro-spinal fluid the iodine concentration was definitely higher six hours after injection than it was a half, one, or two hours after administration.

With these facts in mind an attempt was made to perform drainage without lumbar puncture, using the principle set out by Corbus, but employing a hypertonic solution of sodium iodide in place of the simple saline. It was hoped that additional benefit would be derived from the iodide and, with certain precautions, this method would appear practicable in the case of out-patients.

The technique was as follows: At 11.30 a.m. each patient received, by intravenous injection, 100c.c. of

1. CAMPBELL, D. & SNODGRASS, W.R. "The penetration of iodine into the cerebro-spinal fluid". *Journal of Phar. & Exper. Ther.* 1926. XXVII. 355.

distilled water containing 10 grams of sodium iodide and 5 grams of sodium chloride to increase the hypertonic effect. Patients were then sent home, preferably to bed. They returned at 5.30 p.m. for an intravenous injection of neo-kharsivan, usually 0.6 gram, and thereafter were again sent home to bed with instructions to stay there for twenty four hours in any case, or forty eight hours if malaise, headache, or fever appeared. No case required to spend more than twenty four hours in bed.

The results of treatment are set out in the following table. All the cases were male. Six cases were investigated.

Case No.:	Clinical condition:	Previous treatment with salvarsan substitute:	Wassermann reaction, before treatment:		No. of injns. of N.K. and	Wassermann reaction, after treatment:	
			Bd. C.S.F.	Nal.		Bd. C.S.F.	Nal.
1186	Advanced tabes	Yes	+	+	8	S.	+W
1808	Ataxia paraplegia	mercurial only	S	+	7	-	+
1891	Spastic paraplegia	Yes	-	S	9	-	-
2072	Tabes with 3rd nerve involve: ment	mercurial only	+	+	8	+W	S
2189	Cerebro-spinal syph. with mental impairment	No treatment	+	+	8	+	-
2166	Latent Syphilis Asthma	mercurial only	+	-	4	0	0

Clinical improvement took place in the first five cases. Treatment was stopped in No. 2166 owing to the persistent severity of his asthma. It had been hoped that the iodide might have helped the asthmatic conditions. It is quite noteworthy that in each completed case some serological improvement took place and, with the exception of No. 1808, it was the first favourable change recorded.

No.2072 developed jaundice immediately after his 8th injection. He was admitted as an in-patient. The jaundice ran a mild course and, under treatment, completely disappeared in five weeks.

These cases have been kept under observation for over a year. The improvement, both clinical and serological, was only of a temporary character as was to be expected having regard to the clinical condition. In all cases further treatment with antisyphilitic remedies was continued.

In view of the fact that a definite, though temporary, improvement took place in the serological reactions, and that this was accompanied by clinical improvement, it is suggested that this method deserves a trial in selected cases. The serological improvement is noteworthy, since one would not anticipate any change of this nature after so short a course of treatment in advanced neurosyphilis.

S E C T I O N X .

THE METHODS TO BE EMPLOYED IN THE
INVESTIGATION OF NEW SUBSTANCES
DESIGNED FOR THE TREATMENT
OF SYPHILIS.

Pages 448-464.

The Methods to be employed in the Investigation
of New Substances designed for the Treatment of Syphilis.

In the Western Infirmary Clinic a number of new drugs have been examined and reported on, in respect of their use in the treatment of syphilis. Such preparations have usually come through the courtesy of the Medical Research Council or of Professor C. H. Browning.

A list of these drugs is given:

<u>Arsenic</u>	<u>Mercury</u>	<u>Bismuth</u>	<u>Iodine</u>
Acetyl sal- varsan	Flumerin Merkon	Contraluesin bismuth Bismuthyl saccharic acid	Sodium iodide by the intra- venous route.
Arcetan	Contraluesin	Bismuthyl saccharic acid sodium salt	
Halarsol	Avenyl	Bismuthyl gluconic acid.	
Myo salvar- san.			

The purpose of this section is not to assess the value of any one of these drugs, but to set forth the methods considered necessary for the investigation of any new substance designed for the treatment of syphilis.

Information as to the modes of procedure may be derived from the study of the clinical records of the earliest use of the drugs commonly employed, but these records fail to detail the preliminary steps, and it is obvious that each experimenter more or less devises his technique as he goes along. It is astonishing that no paper has been found which clearly sets forth the minimum necessary precautions. The matter is

discussed by Stokes in his text-book, Modern Clinical Syphilology, pp. 134-5, but no detailed advice is given although a number of safeguards are indicated. It is accordingly felt that the experience gained through the handling of the various preparations enumerated, is worthy of being put on record. This experience is limited to drugs analogous to known and tried anti-syphilitic remedies. In no case has the chemical formula or preliminary animal experiments suggested a new departure in the method of attack on the spirochaete. This is important, for, should remedies be proposed, of a chemical composition different in structure from those already in use, or with a suggested mode of action different to that of the arsenicals and heavy metals, showing a corresponding variation in toxic side effects, it is at least conceivable that a further series of methods would require to be devised.

The method of approach to the clinician:- Most reputable manufacturers in the country now submit their new preparations to the Medical Research Council which, in turn, submits them to a Therapeutic Trials sub-committee. Should the drug be then approved, an invitation is extended to various clinicians to make a report thereon. This should be the only method of approach. The Medical Research Council at the present time will only consider remedies of British manufacture and, from time to time, requests have been received

for a clinical report on drugs of foreign origin. Some of these have been accepted, provided that the criteria, later to be described, have been considered adequate.

Substances for clinical test should only be submitted to large, well-equipped clinics with a competent laboratory working in association, and such work should not be undertaken by any single physician remote from such laboratory guidance and the corrective advice of his colleagues.

Any investigation should only be undertaken provided that full liberty of publishing, or not publishing, any or all results, favourable or unfavourable, in any manner whatsoever be explicitly granted. This is worthy of mention for our department has been approached in various undesirable ways. Thus it has been requested (1) only to publish favourable results; (2) to send our completed investigations, good or bad, to the manufacturer for publication in a brochure of the firm; (3) to investigate to a limited point and to that only. One of the preparations coming under this head, which was refused, became extensively advertised for a time in the lay and medical press, subsequently to drop deservedly out of existence.

An adequate supply of material must be provided. Usually only a small quantity is required when a report is unfavourable, but if good results are anticipated, sufficient to treat fully any desired number of cases must be forthcoming. Before the Medical Research Council took up the duty of the

preliminary investigation of the drugs, difficulty was experienced in this matter, particularly in respect of drugs of foreign origin.

Adequate time must also be demanded. The very first experiments in toxicity require patient observation, and the commercial urge to get on the market should be counteracted in advance.

The preparation itself :- Manufacturers will naturally not divulge the secrets of preparation, but no drug should be accepted unless the chemical composition and, preferably, the structural formula be submitted. In some cases the structural formula may still be a matter for final proof, but in such cases an approximate indication should be given, or at least the affinities of the remedy. The manufacturer should be prepared to state publicly the composition of the drug as far as it is known. Again a debt is owing to the Medical Research Council, for, prior to its action, the most evasive replies had been received to questions under this heading.

The stability of a preparation should be known. A report in all cases is desirable as to the time at which deterioration may be looked for, and an account of any naked eye changes to be expected.

Finally, full data as to modes of preparation and administration must be to hand. These are to be suggested on

the theoretical grounds afforded by animal experimentation.

Animal experiments :- The criteria for these are well known but inferences as to their transference to man are difficult. Most of the drugs handled have been tried upon mice, and knowledge is desired on the following points:

- (1) The lethal dose, and mode of death.
- (2) The toxic manifestations both early and late to sub-lethal dosage.
- (3) The particular effect upon any special tissues especially the liver and excretory organs.
- (4) Any means of preventing or treating such reactions.
- (5) The therapeutic index of the preparation in injections with known organisms as compared with preparations in clinical use.
- (6) The question of the presence or absence of relapse in the animal.

There are few clinicians competent adequately to assess the experimental results both in animals and man, and great reliance is placed on the experienced opinion of a laboratory worker discussing the clinical and toxic value of the new preparation on the type of animal with which he is familiar, in terms of preparations previously examined.

Points to be investigated in man :-

The following order of investigation should be adopted:

- (1) Toxicity - early and late, with which is associated elimination and storage of the drug.
- (2) Clinical effect on late skin syphilis or sub-cutaneous gummata.
- (3) Serological effect on late Wassermann positive syphilis.
- (4) Clinical and bacteriological effect upon early syphilis.
- (5) Serological effect upon early syphilis.
- (6) Relapse, clinical and serological, will at this stage fall to be considered.

These points will be discussed separately in detail, but a preliminary short discussion of the reasons for these headings is given.

It is obvious that the whole question of toxicity must be first settled. While late toxic results are being looked for, the actual effect upon syphilitic lesions may be experimented with. It is unfair to subject early syphilis, the most curable stage of the disease, to the action of preparations of whose therapeutic value one is completely ignorant, but no undue risks are experienced in late skin syphilis through a delay of three or four weeks. Granted a low toxicity and a therapeutic action upon gummata, it is again only reasonable to try the extended use of the preparation in

cases of late syphilis in an attempt to reverse the Wassermann reaction of the blood serum. So many cases cannot be reversed with ordinary measures of treatment, so much uncertainty attends the treatment of any single case, that an absence of Wassermann change in one or two experimental cases is not to be taken as an indication for giving up further experiments, and any minor changes in the reaction should be hopefully regarded. It is most strongly urged, however, that no serological experiments be conducted in the first stages of investigation on cases of early syphilis. Experience was necessary to prove the truth of this, and we have two cases of secondary syphilis, treated at the onset with a new mercurial drug inadequately assessed, which have become Wassermann fast and have resisted for years all varieties of recognised therapy. There is no reason to suppose that they would have proved thus obstinate had ordinary methods been applied in the first instance. Experiments upon the primary and secondary clinical phenomena should then be undertaken, and these should include notes on the action upon spirochaetes in the chancre. The value of known antisyphilitic remedies seems roughly proportional to the rapidity of their action upon early lesions, and, if the new drugs should exert a definite action upon such lesions, but if that action is notably slower than that of known drugs of comparable type, it is unjust to submit early syphilis to the effect of the prolonged

administration of the new preparation unaccompanied by known remedies. Lastly comes the question of prolonged observations upon cases of early syphilis treated solely with the new preparation, to determine the question of clinical or serological relapse. As many writers hold that relapsed syphilis is more difficult to cure, all cases treated at the outset with a new drug should receive, as early as practicable thereafter, a full course of ordinary treatment, and only after very thorough proof of the early value of the new preparation, should the period of observation between its employment and further routine treatment be gradually extended. It is considered that a scheme of this nature would adequately safeguard the individual, and the only drawback would appear to be an increase in the time taken to appraise the value of the remedy under consideration.

(1) Toxicity:

I. Intramuscular and subcutaneous administration.

As an initial dose $\frac{1}{20}$ th of the dose deduced for man from animal experiments is employed. This initial dose is either given to one of the staff or to a male case of latent syphilis who has received a great deal of treatment and who volunteers after the matter is explained to him. A case experienced in treatment is advisable. His responses to various injections are known and he knows how to assess the local discomforts of a new drug. Unless the manufacturer

advises a suitable vehicle, the following methods of administration are employed in turn.

- (a) Aqueous solution, at first isotonic, then up to 20% solution, or aqueous suspension.
- (b) Aqueous solution or suspension as in (a) with the addition of 2% to 4% glucose. This sometimes lessens local pain.
- (c) Solution or suspension in olive oil containing a trace of phenol.
- (d) Admixture with a basis of creosote and camphor (B.W.&Co.)

In no case should the bulk of the initial dose exceed four cubic centimetres.

The following reactions should be looked for:

- (A) Pain, local or referred. This is the most common obstacle to further experimentation. In its appraisal the experienced patient is particularly valuable. It may be immediate but is more common some ten to twenty-four hours later. If immediate, it is usually at the site of injection. Various vehicles may be tried in an attempt to abolish local painful reactions, but unless a preparation may be given in practically a painless manner, it can never be generally employed in clinic treatment. Patients will simply default.
- (B) Necrosis. This occurs more readily after subcutaneous injections, and if arsenical and mercurial preparations are

used. It is less common with bismuth compounds. Hence it is preferable to give the initial doses by deep intramuscular injection. There are notes of two preparations which could be tolerated by either intramuscular or intravenous administration but, for the above reason, could not be given by the subcutaneous route. Great caution should be exercised in choosing the subcutaneous route, and a very small initial dose should be tried.

On one occasion, after a series of bismuth injections a painless swelling appeared on one hip with slight redness of the skin. Aspiration showed a sterile thick fluid composed of bismuth and necrotic tissue. Its early stages should have been detected by careful palpation when the deep tenderness and resistance which were present in the other hip would have been noted. Cessation of treatment led to gradual absorption of the material from the other hip.

(C) General toxic effects due to the action of arsenic, bismuth or mercury. These are of the same type as are experienced with the ordinary preparations in current use. They may, more conveniently, be referred to in connection with intravenous administration, where they are liable to occur at an earlier date in the trial of a drug which will be eventually unsuitable. It is noted that the intramuscular administration of arsenic is more prone to give minor skin reactions than any other form of intolerance, and that a

bismuth or mercurial stomatitis is the commonest reaction to the heavy metal.

The urine is tested with osmic acid in an attempt to determine the elimination of arsenical preparations. The addition of one drop of osmic acid to a test tube filled with freshly passed urine gives a blackish precipitate in presence of minute traces of arsenic. Caution is advised in the further administration of arsenical compounds, should this test be positive at the end of a week. It has been found to be so in the exhibition of one preparation of arsenic which was later determined to be unsuitable for human use.

Malaise or gastro-intestinal disturbance, appearing after a few arsenical injections have been given, leads to the examination of the urine by Erlich's aldehyde reaction for an excess of urobilin and to the Van den Berg reaction being performed on the blood serum. A positive test leads to the cessation of treatment in such a case, and, unless the clinical effect on lesions be noteworthy, to the cessation of further use of the drug.

If no signs of intolerance appear, it is advised that a rest period of at least three months be allowed whenever the total amount given of the available arsenic in the new preparation be approximately equal to the amount of arsenic in four grams of "914". This allows time for development of

the later complications such as jaundice and dermatitis. Neither of these late toxic results have been met with in the series of experiments.

In respect of bismuth and mercury, the progress of elimination should be controlled by the use of the X-rays. Great variations in the X-ray picture have followed the employment of ordinary metallic bismuth. Thus, a distinct shadow has been seen as late as eighteen weeks after the administration of 2.4 grams of bismuth metal spread over a period of thirteen weeks. On the whole, metal given in oily solution or suspension appears to be absorbed rather more quickly than if given in watery solution or suspension.

II. Intravenous administration.

Here the initial dose given is $1/20$ th of the deduced therapeutic dose for man. Only one bismuth compound has been given in this manner, and, in the administration of arsenical and mercurial preparations, initial dosage should always bear in mind acute-toxic manifestations. Acute vomiting, diarrhoea, fever, malaise have followed on an attempt to raise a small dose of an arsenical preparation to a therapeutic level. Acute mercurial poisoning with vomiting, colic and diarrhoea marked by blood and mucus has been noted. The tolerance of a group of individuals is not the tolerance of any one member of that group, and it is necessary to increase the initial trial dose ($1/20$ th of the estimated initial therapeutic

dose) with caution. It is advisable after a quantity has been reached which is considered such as might serve for an ordinary initial injection of therapeutic value, to try the effect of this dose upon a number of cases.

In considering the possible later toxic manifestations when intramuscular injections are used, or the earlier ones in intravenous experimentation, special attention must be given to the effect on the kidneys. Albuminuria with granular tube casts has been seen following experiments with one arsenical compound and one mercury compound. The granular tube casts continued to appear in the urine for some weeks; the albumin for some months. In both cases treatment was immediately stopped on the appearance of a trace of albumin in the urine. In neither case had any antecedent toxic phenomenon appeared. It marks the need for caution and the gradual increase of the dosage.

(2) Clinical effect on late skin syphilis or subcutaneous gummata.

If material is available, lesions which are free from secondary infection should be chosen. It is well to have some idea of the average response of such lesions to recognised therapeutic remedies. These times are useful to bear in mind as an approximate means of testing the efficiency of the new preparation. Stress is not laid on this aspect of

experimentation for the rapidity with which almost all the new preparations produced their clinical effect in late muco-cutaneous syphilis is somewhat noteworthy.

(3) Serological effect upon late Wassermann positive syphilis.

Observations on any change towards a reversal of a positive serological blood reaction will naturally proceed as tests for toxicity and clinical efficiency are made. Cases which tolerate the drug well may then continue to receive treatment until a full dosage is given. This has been stated to be, for arsenical compounds, the arsenical equivalent of 4 grams of "914". For bismuth and mercury by the intramuscular route a very large quantity may be given before salivation indicates approaching over-dosage. Little stress is to be laid on the failure of any preparation to produce serological change in the dosage permitted by one course.

When a preparation of bismuth or mercury is under examination, it is quite legitimate at this stage to employ it in conjunction with a "914" salvarsan substitute. It is unreasonable to expect Wassermann reversal from single courses of heavy metal given alone.

(4) Clinical and bacteriological effect upon early syphilis.

These observations call for particular care in judgment. Almost all the preparations tested showed a rapid sterilising

effect on the chancre or on mucous patches, and almost all showed a power of rapidly causing primary and secondary lesions to resolve. These are often specious promises. Clinical relapse has been noted as early as four weeks subsequent to the disappearance of a lesion - it has also been seen during the exhibition of a new mercurial which originally induced rapid healing. It has not infrequently followed some six to ten weeks after the cessation of a new remedy - seen alike with arsenical, bismuth and mercurial preparations. These phenomena have greatly impressed the writer firstly with the activity of Sp. Pall. and secondly with the power of the known and widely used antisyphilitic remedies. It must be a definite rule on the completion of experimental therapy to subject the patient to as nearly normal a course of ordinary combined "914" and heavy metal as possible.

(5) Serological effect upon early syphilis.

This should be investigated by the serial examination of the Wassermann reaction of the blood serum at fortnightly intervals. It has been shown elsewhere in this thesis that, employing the standard course laid down in this clinic, two thirds of all cases of early syphilis show a reversal of a positive Wassermann to negative between the eighth and the twelfth weeks of treatment. It is thought that if no

serological change be met with by the end of the twelfth week of experimentation with a drug, it should be discontinued.

Clinical experience has shown, and the detailed analysis in this thesis supports the view, that the earlier a Wassermann reaction is converted from positive to negative, the better will be the ultimate clinical and serological outcome. For this reason remedies designed for use in early syphilis must be powerful enough to produce reasonably rapid serological change. Early serological relapse within six months is of bad omen. It is of bad omen when ordinary methods of therapy are employed. If serological relapse occurs during experimentation with new remedies (it has once been seen), it should be an indication that the drug is not suitable for use by itself. A bismuth or mercury compound might then be tried in conjunction with "914". An arsenical compound should be abandoned. Finally, late serological relapse, after one year, should be looked for. This serological change is of worse prognostic importance than is earlier relapse. It is very difficult to assess the role played in the initial stages by the new remedy which will be only one item in such a patient's total treatment. Still, the whole experience of this clinic lays emphasis on the importance of the first course of treatment, and on its projection into the after history of the patient. Accordingly

any such late serological relapse must lead to a careful reevaluation of the role played by any new drug in the initial stages of treatment.

Suggestions for improvement in the Methods of the
Treatment of Early Syphilis.

This section is the fons et origo of the whole of this thesis. It was hoped that a long range experiment with a standard model course of treatment might yield valuable information. It was felt that such a course, adequately observed and recorded, might also serve in some measure to afford criteria for the evaluation of any future lines of therapy.

The conclusions drawn from the review of the sections dealing with latent syphilis and tertiary muco-cutaneous syphilis emphasise the importance of treatment in the early stages. It is with the greatest diffidence that the word "cure" may be employed in these later categories of disease. Although a number of cases, 50.0% in latent syphilis and 37.2% in tertiary muco-cutaneous syphilis, do appear to be, at any rate temporarily, cured in respect of prolonged absence of clinical or serological evidence to the contrary, yet such "cures" are arrived at by the most varied methods of treatment and the most varied amounts of therapy. No guiding principles to achieve "cure" can be laid down and the clinician appears to do well if he can state a minimum therapy which seems likely to obviate clinical disease for

the ensuing few years, although a permanently negative serological state is apparently as far distant as it was at the onset. To sum up, chronic syphilis cannot, with any certainty, be cured, and thus any given individual must undergo life-long observation. If such were the outlook in early syphilis, it would be indeed a waste of energy elaborating further schemes in face of such fundamental difficulties. However the results of the analyses in the preceding sections, which deal with the varied aspects of the group of cases of early syphilis at this clinic, offer a distinct measure of hope. Even as it is, a very considerable percentage of those cases treated and carefully observed for two years and longer, appear to be "cured" and so, pending the arrival of fresh remedies, the proper use of such drugs as are at present at our disposal becomes the most vital problem.

An attempt, therefore, will now be made to present the facts brought out in the preceding sections that seem important in arriving at an appreciation of the factors responsible for the results achieved by this standard course. Thereafter arguments and evidence in favour of a suggested new course will be elaborated.

In view of the many aspects of treatment and their results to be considered, it is suggested that the reader, at this point, might advantageously read the synopsis of

this section (provided in the separate volume of synopses). This will serve as a guide to the statements now to be appended and will obviate a certain amount of cross reference.

In the first place there is again submitted a copy of the table showing the model course employed and the variations in dosage which have occurred.

Table 1.Variations in dosage of model course.

	"914"			Metal.		Potassium Iodide.	
	Dosage and year introduced.			C.C.	Bi.	gr. xv. t.i.d.	
	1919	1923	1929	1919	1924	1919	1924
1st week	.45gm.	.3gm.	.45gm.	1gr.	0.2gm.		Kl.
2nd week	.45	.45	.6	1	0.2		Kl.
3rd week	.75	.6	.6	1	0.2		Kl.
4th week				1	0.2		Kl.
5th week	.75 or .6	.6	.6	1	0.2		Kl.
6th week	.75 or .6	.6	.6	1	0.2		Kl.
7th week				1	0.2		Kl.
8th week	.75	.6	.6	1	0.2		Kl.
9th week	.75	.6	.6	1	0.2		Kl.
10th week						Kl.	Kl.
11th week						Kl.	Kl.
12th week						Kl.	Kl.
13th week	.75	.6	.6	1	0.2		Kl.
14th week	.75	.6	.6	1	0.2		Kl.
15th week	.75	.6	.6	1	0.2		Kl.
Total weight in grams	6.75	5.55	5.85	12grs.	2.4		

The dose of calomel cream was 1 grain of mercury; the dose of bismuth metal was 0.2 grams. Occasionally in the earlier years 0.9 gram of "914" was given in a single dose.

The method employed may be described as the combined administration of "914" and a heavy metal, with a uniform number of injections, and a uniform time grouping in which short periods of intermission occur. Five hundred and seventy cases of early syphilis were so treated, observed and recorded.

Cardinal principles considered to be of importance in the suggested new course :-

In view of the results achieved in the present series of cases, the following points are thought to be worthy of consideration in modifying the existing methods of treatment.

- A. The importance of the first course of treatment.
- B. The importance of adequate total treatment of the patient.
- C. The need for increased concentration of treatment in the earlier weeks of the first course.

These main principles will later be explained and upheld.

Criteria for evaluating any course of treatment.

It is well to state now such criteria as have been found necessary in evaluating the results of treatment in the present series. Such criteria are obviously applicable to any course of treatment. Freedom from clinical and

serological relapse is of importance. In this series 4.38% of clinical relapse, and 24.5% of serological relapse took place. Although satisfactory end results can be achieved in the great majority of relapsed cases with further adequate treatment, it is quite obviously a treatment ideal that relapse should be cut down to a minimum. It is thought, in view of the small incidence of clinical as compared with serological relapse, that the latter should be considered of importance in assessing the value of a new course of treatment, and in the section concerned with the experimental use of new remedies for the treatment of syphilis, it is considered that serum Wassermann relapse, early or late, is of great importance in assessing the value of a new drug.

Where fresh combinations of old remedies are to be suggested, as in the present case, the section dealing with Wassermann variation in the blood serum indicates that Wassermann relapse is the most important single criterion. This seems reasonable because not only is the incidence of Wassermann relapse some six times as common as that of clinical relapse, but also serological relapse is the precursor of the clinical condition.

In the serial examination of the Wassermann reaction, it was found that almost two thirds of the cases after receiving 4.00 grams of "914" + metal, in accordance with the

model course, showed a negative blood Wassermann between the eighth and the twelfth weeks. It would appear highly desirable to attempt to increase the proportion of early Wassermann reversals.

The reduction of intolerance to the administration of antisyphilitic remedies is of the greatest importance. It has been shown in the section on Intolerance that various methods of prophylaxis, including glucose, sodium thiosulphate and their combination are ineffective in securing either a reduction of the total amount of intolerance or a modification of its severity. Attention to the general points of preparation of the patient and the treatment of focal sepsis laid down in this section, is the most that can be usefully predicated. It is also noted that the dose of maximum therapeutic efficiency lies near the limits of toxicity. The best percentage of end results is seen in these cases adequately treated which have shown arsenical intolerance.

Research on methods for the prevention of intolerance is most urgently required. It might greatly enhance the effective value of the drugs presently employed by facilitating the employment of larger dosage. Intolerance may lead to the cessation of treatment. It is also one factor in the production of default.

The question of default must be considered of importance in assessing the value of any course of treatment.

In addition to being an expression of the general efficiency of the clinic, or of the vagrant occupations of the patient, it is also related to the drugs used. The production of pain or discomfort, even apart from general intolerance, increases the incidence of default. These points require consideration in building up new schemes or employing new drugs.

It should be stated that a certain proportion of cases, failing legislative control, will always default. These people, devoid of regard for themselves or for others, will inevitably fail under a voluntary system. It is doubtful whether legislation could compel them to attend or whether their ingenuity could not adequately cope with any threat to their freedom of action. In view of the damage they cause themselves and other people, the experiment appears worthy of trial, but it is to be remembered that it is easier to make legislation than to repeal it. The rest of the problem should not exist. A careful explanation of the nature of the disease, the duration of treatment and the probable consequences of untreated syphilis should be given to the patient on his first two appearances at the clinic. Thereafter the patient's confidence may gradually be gained, and his attendance secured. A system of repeated letters to defaulters has proved of immense value in securing the return of absentees. Finally, the adequate provision of

travelling cards to allow men to pursue their work in various parts of the country, secures the continuity of treatment in a considerable proportion.

Adequate time for observation of the results of treatment is essential. Short distance conclusions are valueless. Two years is the minimum period permissible before reaching, even tentatively, any conclusion. In this series of cases 178 were observed for more than two years: six cases of serological relapse occurred after observed freedom from relapse for more than two years. This figure, though small, is of importance. It follows that at least two years must elapse before a case treated by a new drug or new method, may be counted provisionally as showing a satisfactory result. Undoubtedly unfavourable results may appear with new methods of treatment in a shorter time and so demand a revision of the scheme of treatment.

Finally, an adequate number of cases is essential to permit of any valid conclusions. Those cases which will inevitably default before two years have elapsed will yield valuable information but only in an unfavourable direction. At least one hundred cases observed for at least two years is essential to permit of a preliminary survey of the value of any new scheme of therapy. In view of the present incidence of early syphilis in Glasgow, this number will take three or more years to attain. It is advisable, therefore,

for statistical investigation, that all early cases of syphilis attending the Glasgow venereal centres should receive a uniform type of treatment.

Results obtained with standard course.

These are shown with the intention :- (1) of stressing the importance of the first course of treatment.

(2) of stressing the importance of adequate total treatment.

(3) of indicating the value of a time factor in the first course.

Adequate total treatment prior to 1923 implies at least six months observation while taking mercury pills, and usually half a course of "914" and Hg. after the blood Wassermann is negative. Subsequent to 1923 it implies at least one course of "914" and metal, and six months observation while taking mercury pills after the blood Wassermann is negative.

1. Total cases = 570.

When last seen, 16.6% were not clinically and serologically negative. 83.4% were clinically and serologically negative.

These figures have no value in assessing the results of treatment.

2. Total cases observed for two years or more = 178.

When last seen, 11.2% were not both clinically and serologically negative; 88.8% were both clinically and serologically negative.

These results may be said to have an assessable value. They show the percentage of cases apparently "cured". They do not include all cases which received adequate total treatment. They are subdivided into percentages of final "positives" and "negatives" in accordance with the adequacy or inadequacy of the first course of treatment (not less than 5 grams of "914" in fourteen weeks is termed adequate), and the adequacy or inadequacy of the total treatment received.

	<u>Total cases</u>	<u>Positive</u>	<u>Negative</u>
A. Adequate first course: adequate total treatment.	129	15 11.6%	114 88.4%
B. Adequate first course: inadequate total treatment.	12	0 0%	12 100%
C. Inadequate first course: adequate total treatment.	33	3 9%	30 91%
D. Inadequate first course: inadequate total treatment.	4	4 100%	0 0%

The figures indicate (1) the importance of an adequate first course and (2) the fact that adequate total treatment is not only of importance in maintaining the effect of an adequate first course, but in making up for its deficiencies.

These figures may be combined to show :-

Adequate first course	141 cases,	10.6% positive. 89.4% negative.
Adequate total treatment.	162 cases,	11.1% positive. 88.9% negative.

Cases in groups B and D usually showed long periods of default.

3. Further evidence is provided to show the importance of an adequate first course of treatment.

(1) Serological results immediately after first course of treatment :

	<u>Cases</u>	<u>+</u>	<u>weak +</u>	<u>S</u>
Adequate first course	376	11.1%	4.7%	9.3%
Inadequate first course	194	29.7%	4.6%	5.7%

(2) Final results observed in all cases receiving inadequate total treatment:

	<u>Cases</u>	<u>Final W.R.</u>	
		<u>+</u>	<u>-</u>
Adequate first course	177	11.4%	88.6%
Inadequate first course	115	40.0%	60.0%

This offers, then, a distinct measure of hope that an adequate first course, even in face of early subsequent

default, will afford a very considerable degree of protection to the individual.

These results indicate that if this model course be adopted not less than 5 grams of "914" and metal should be given, and that such a course is of considerable value. The results also show the importance of adequate total treatment i.e. the further administration of at least 5 grams of "914" and metal.

4. Further evidence in support of adequate total treatment is submitted. The reader is again reminded that this adequate total treatment implies at least one additional course of "914" and metal and the prolonged use of mercury by the oral route, subsequent to a negative blood Wassermann reaction.

Seventeen cases showed clinical or serological relapse after an adequate first course but no adequate total treatment, and after a period of at least twelve months during which they remained both clinically and serologically negative.

Unquestionably many cases remained clinically and serologically free from evidence of disease although only one adequate course of treatment was given. Many such are noted in this series, but an even larger number must be found in the ranks of the defaulters. There is, however,

no method of determining at the outset of treatment whether a case will or will not be easily "cured". Relapse, clinical and serological, calls for a considerable increase in total therapy, and it is quite impracticable to assume that a single course of treatment is sufficient if followed by regular clinical and serological examination. Further, there are numerous cases amongst the cardio-vascular and neuro-syphilitic groups who received a first course of treatment which was adequate, but no follow up courses of treatment.

5. The influence of time as a factor is considered.

(1) With the lapse of time there is a continued improvement after cessation of anti-syphilitic treatment, if an adequate first course be given.

This seems clearly shown by the following figures:-

	<u>Cases</u>	<u>Not negat- ive at end of first course.</u>	<u>Percentage of those re- ceiving no further treat- ment and finally not neg- ative.</u>
Adequate first course	376	25.1%	12.4%
Inadequate first course	194	40.0%	40.0%

The two percentages 40% are not, of course, composed of the same individuals. This result is thought to bear some relation to the amount of metal given with "914".

It is to be emphasised that, to take advantage of the therapeutic value of an adequate first course, adequate total treatment must be given.

(2) The time occupied by the first course of treatment.

Allowing a deviation of two weeks in either direction from the normal period of sixteen weeks at which the informative Wassermann reaction of the blood is taken, there are three group periods.

(a) Less than fourteen weeks :- Most cases here also received an inadequate first course through intolerance or default. The results are bad. Some cases received full treatment, usually to enable men to get away to distant work. Such cases did well and did not show undue toxicity.

(b) Fourteen to eighteen weeks. This is the standard group. In some cases the full amount of arsenic was not given. Such cases did proportionately badly.

(c) More than eighteen weeks. Cases falling into this group usually showed minor grades of default or intolerance. They did not show as high a proportion of immediately favourable results as did the cases in group (b).

It is not considered advisable to discuss these headings in terms of percentages, for, as indicated, there are so many other factors to take into account. It is, however, definitely thought that reduction of the normal time limit for administration of an adequate first course does not

yield inferior early or late end results, and that any increase in the time period does not give as high a proportion of immediate favourable serological results as does the standard time group.

(3) The section dealing with the serial examination of the blood Wassermann showed :-

that 1/3 of the cases altered from + to - between the 5th and the 8th weeks.

that 1/3 of the cases altered from + to - between the 9th and the 12th weeks.

This selected group of cases showed better results than did the average of the whole series. It is obviously desirable to facilitate the early reduction of the Wassermann reaction of the blood serum from positive to negative.

6. The type of heavy metal employed.

Adequate total treatment and adequate first course.

As. + Hg.	172 cases	86.2% finally negative.
		13.8% finally positive.
As. + Bi.	184 cases	91.4% finally negative.
		8.6% finally positive.

This shows a slight bias in favour of Bismuth.

Intolerance

Hg.	= 4.74%	Bi.	= 3.33%
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This percentage difference is insignificant, but clinically

Hg. intolerance was more severe, more intractable and led to longer periods of cessation of treatment than did bismuth intolerance.

The value of mercury given by the oral route is difficult to assess. It is irregularly taken as shown by the times at which many cases return; often it is not taken at all. The anti-syphilitic effect cannot be statistically presented from this series of cases. It is thought to be only of slight value.

7. Default as a factor.

All figures hitherto given indicate the bad effect of default before (a) adequate first course and (b) adequate total treatment is given. They cannot show the effect of various short periods of default at all periods of treatment. This cannot be statistically presented. It is definitely thought to be a factor of major importance in increasing the percentage of unfavourable end serological results.

8. Intolerance to arsenic as a factor.

One hundred and one cases showed intolerance and received no further injections of "914" after their toxic manifestations, either (1) on account of intolerance or (2) because they remained clinically and serologically negative. Seven cases were finally not clinically or serolog-

ically negative . This group of cases gives the most favourable end result of all groups studied. This suggests that the maximum therapeutic dose lies near the toxic dose.

9. Iodide.

The administration of fifteen grains of potassium iodide thrice daily throughout the whole course of treatment does not increase the percentage of favourable results (1) at the end of the first course (2) at the end of the total treatment, whether adequate or inadequate (3) at the end of two or three years of observation. It does not decrease the percentage of favourable end results.

The broad conclusions reached from these data confirm the importance of the cardinal points suggested at the outset. Details concerning the new course of treatment may be said to comprise, if "914" and metal be given in combination :-

- (1) not less than 5 grams "914" in a course.
- (2) a course should take less than fifteen weeks.
- (3) bismuth should be used as the metal.
- (4) the continuous use of potassium iodide is not advised.
- (5) the total treatment given should not be less than the amount presently defined as adequate.

Further evidence is desired before coming to decisions involving principles of therapy.

An attempt was made to ascertain the various methods of treatment employed in other clinics, and a request for information was sent out to a number of British Venereal Treatment Centres. The following questions were asked :-

- I. What was your standard treatment for early syphilis in 1921 ?
- II. What was your standard treatment for early syphilis in 1931 ?
- III. What were the reasons which led to the change, if any change has been made ?

Replies were received from the following centres:

Dundee	-	Dr. Averill
Edinburgh	-	Mr. Lees
St. Thomas	-	Col. Harrison
Newcastle-on-Tyne	-	Sir Robert Bolam
Liverpool	-	Dr. Ross
Portsmouth	-	Mr. Campbell
Whitechapel	-	Dr. Anwyll Davis
London Lock	-	Dr. Abraham
Salford	-	Dr. Burke

Thanks are due to these gentlemen for their courtesy in answering and for the trouble they have taken in explaining their methods.

It must be pointed out that where 1931 has seen a change from 1921, the reasons given in the letter for making such a change are naturally only briefly stated. So different are these schemes in respect of initial dose of "914",

frequency of dosage, total dosage in first course and number of subsequent courses of "914", and so varied is the use made of the heavy metals, that comparison becomes very difficult.

There are subjoined two tables. Table 2 shows the general lines of treatment given in 1931 in primary sero-negative syphilis and the chief divergences from 1921 therapy, and Table 3 shows similar information for early syphilis sero-positive. The headings are obvious. These tables are approximately accurate paraphrases of the individual clinic's methods.

Table 2.

Primary Sero-negative Syphilis.

Clinic	1931			1921			
	No. of injs.	"914" gms.	Time in wks.	Metal	Type of treatment	Subsequent Treatment	
Newcastle	7	3.9	12	Hg.	Comb-ined.	Hg. injs.	Less "914" and less Hg.
Dundee	9	4.8	14	Bi.	"	Repeat	Less "914" No metal
Whitechapel	20	7.5	13	Bi.	"	Repeat twice	Less "914" No metal
St. Thomas	15	3.0	12	Bi.	"		More "914" (6.3). Hg.
Edinburgh	8	4.2	8	Bi.	"	3 such courses = 9-10gm. Bi. = 20-25	"914" as before. Hg.
London Lock	?	5 to 6	?	Bi.	"	1 course "914" then Bi.	1 course "914" then 2 years Hg. intramusc.
Portsmouth	3	2.1 in 10 dys. off 3/52					
	3	2.1 in 10dys.					
	4	2.4					
	=						
	10	6.6	12	?	?	?	?
Liverpool	10	4.5	6	Bi.	Comb-ined	2 more	More "914"
Salford	18	Stab. 10.35	24	Bi.	Tandem	Variable	Combined "914" and Hg. 3 courses.

Table 3.

Primary Sero-positive Syphilis.

Clinic	1931				1921		
	No. of injs.	"914" gms.	Time in wks.	Metal	Type of treatment	Subsequent Treatment	
Newcastle	7	3.9	12	Hg.	Comb-ined	8 x "914" = 3.6gms. 12 gr. Hg.	More "914" More Hg.
Dundee	9	4.8	14	Bi.	"	Repeat	Less "914" No metal
Whitechapel	20	7.5	13	Bi.	"	Repeat twice	Less "914" No metal
St. Thomas	5	3.0	12	Bi.	"	?	More "914" (6.3). Hg.
Edinburgh	8	4.2	8	Bi.	"	"914" = 14gm. Bi. = 25.3gm.	Hg. smaller total.
		Injs. on 1st, 8th & 15th days					
London Lock		5-6		Bi.	"	2 more courses. More Hg.	5-6gms. 9Kl. and repeat. 2 years intramuscul.
Portsmouth	3	2.1	in 10 days; off 3/52.				
	3	2.1	in 10 days then	?	?	?	?
	4	2.4					
	=						
	10	6.6	12				
Liverpool	10	4.5	6	Bi.	Comb-ined	2 or more courses	More "914"
Salford	22	Stab. 2.75	34	Bi	Tandem	Varied	Continued "914" and Hg 3 courses.

These tables require further classification and arrangement. It will be advantageous to exhibit the comparable data shown by the methods employed in this clinic.

The type of treatment employed in the various clinics.

A. Combined "914" and metal given intermittently, showing average amount of "914" per week for first course, and the associated metal.

<u>St. Thomas H.P.</u>	.25	grams	for	12	weeks	+	Bi.
<u>Dundee</u>	.31	"	"	12	"	+	Bi.
<u>Newcastle</u>	.31	"	"	12	"	+	Hg.
<u>Glasgow</u>	.39	"	"	15	"	+	Bi.
<u>Whitechapel</u>	.57	"	"	13	"	+	Bi.

B. Combined "914" + metal, intermittent, but short initial intensive biweekly treatment.

Edinburgh .52 grams for 8 weeks + Bi.

C. Intensive "914" combined with metal, given biweekly.

Liverpool .75 grams for 6 weeks + Bi.
soon repeats course.

D. "Tandem" treatment: "914" followed by Bi. followed by "914" followed by Bi.

Salford .39 grams Stab. for 5 weeks then Bi. et sequitur.

E. Irregular: short intensive courses with rest periods.

Portsmouth .50 grams for 13 weeks + Bi.

There is now shown the total treatment received by the average case of primary sero-positive syphilis which becomes Wassermann negative after the first course of injections and remains so. The total time during which this treatment is given is indicated.

Centre	<u>Metal</u>			<u>Time of treatment in months</u>
	<u>"914"</u> <u>in grams.</u>	<u>Bi.</u> <u>in grams.</u>	<u>Hg.</u> <u>in grains.</u>	
Glasgow	11.7	4.8	much oral	24
Salford	12.75	1.92	-	7
Newcastle	7.5	-	23	16
Whitechapel	22.5	12.0	-	12
Dundee	9.6	7.2	-	? 11
Edinburgh	12 to 14	25 to 30	-	24
Liverpool	17.1	10.8	-	14
London Lock	10 ?	?	-	?
St. Thomas	12.0	12.8	-	?

St. Thomas's Hospital uses Bisoxy. Salford uses Bivatyl.

The other clinics state that they use bismuth metal.

It is now possible to describe the methods of treatment used in this clinic in comparison with those of the other representative centres. Glasgow employs "914" and a heavy metal given in combination and given in an interrupted manner. The dosage, 5.85 grams, of "914" given in the first course is, relatively, fairly high. The total "914" administered, 11.70 grams, represents a medium quantity. With respect to the heavy metal, bismuth, both in the initial course and in the total treatment, the quantity given is low. Exceptionally high use is made of mercury by the oral route and this clinic probably gives more potassium iodide than do most.

In contrast to our weekly intervals between injections, it is to be noted that Edinburgh gives three injections in the first ten days, and that Liverpool adopts a highly concentrated bi-weekly method of treatment. Salford stands alone in the use of the tandem mode of employing "914" and bismuth. Portsmouth relies on short intensive courses of treatment with rest periods. Unfortunately details of the results achieved by the other clinics are lacking. Dr. Ross, of Liverpool, is enthusiastic concerning his concentrated methods and states "Under this scheme we have never had a positive C.S.F. in any so treated case."

Other comments which merit attention, as being the result of considerable clinical experience, are :-

Dr. Abraham, London Lock - "In the last year or two, I have not been so keen on giving so much arsenic."

Dr. Lees, Edinburgh - "Prolonged saturation with both drugs is necessary", referring to "914" and bismuth.

Col. Harrison, St. Thomas - "I have very little confidence of the ability of 0.45 to penetrate at all deeply; also before and during the war, I found that 3 x 0.6 grams "606" achieved more than did 6 x 0.30 grams."

Dr. Davis, Whitechapel - "(1) Insufficiency of treatment with arsenobenzenes destroys the patients' natural immunity and leaves them possibly in a worse state than before.

(2) Relapses after insufficient treatment are most resistant"

The absence of recorded results makes it difficult to appraise these various schemes. It is now considered in this clinic that the first course of treatment, often the last unfortunately, is the most vital. It is also considered that an increased concentration is desired in the earlier weeks of this first course. This is a simple extension of the principle that the first course is most important. The experiences of Edinburgh and Liverpool suggest that bi-weekly injection of "914" and metal will be advised in the suggested scheme.

These clinic methods of treatment also suggest that more importance should be attached to the use of continuous treatment.

It is not possible to ignore the careful analysis by five of the large clinics in America, and in their conclusions they state, Venereal Disease Information, July 1932, pages 273-274 :-

"5. "Cures do occur on minimal amounts of treatment, as, for example, little* arsphenamine and little* heavy metal.

"6. Contrasted with this, however, is the vastly greater efficiency of prolonged and vigorous treatment with much* of each drug.

"7. When continuously administered, much treatment is twice as effective as little treatment; when intermittently given, five times as effective; when irregularly given, four times. This statement is confirmed in the main by the incidence of relapse, including all forms of serologic resistance (except fixed positives in the "much" treatment category under the continuous scheme of treatment).

"8. Prolongation and increased mass of treatment can to some extent compensate the disadvantage of those patients who have not had continuous treatment.

*Little = 20 or fewer injections. Much = more than 20.

"9. Early muco-cutaneous relapse occurred in 15% of those who received little arsphenamine (that is, 19 or less injections) and in only 2% of those who received 20 or more injections.

"10. Central nervous system syphilis is almost three times as common in those who received little as in those who got much arsphenamine.

"11. Late syphilis as relapse, excepting cardio-vascular syphilis, is entirely absent from the "much arsphenamine" group.

"12. Progression in the cardio-vascular system, however, occurs approximately as frequently in those who receive much, as in those who receive little treatment.

"13. The same general relations apply to those who receive much as compared with those who receive little heavy metal.

"14. No evidence appears from the statistical analyses that mass of treatment is in any way injurious to the patient with respect to the outcome of his infection."

The gross figure of final unsatisfactory results in the American series is 26.6% (V.D.I., page 276) : our corresponding figure is 16.6%. Their standard of "cure" is stricter (See Section on Primary and Secondary Syphilis). The percentage figure of failure in their most favourably treated group is 13.1%: our corresponding figure in the cases adequately

treated and observed for two years is 10.5% (See Section on Primary and Secondary Syphilis). Again their standard of cure is stricter.

There seems no need for this clinic to abandon the combined use of "914" and metal for the consecutive use of "606" and metal which is in accordance with American treatment. On the other hand, it is felt that (1) the principle of continuous treatment must definitely be accepted. (2) "Much" treatment, i.e. more than 20 injections of arsenic and 20 injections of metal, is definitely desirable. The American conclusions admit of no other interpretation.

It is to be remembered that "606" rather than "914" has been the drug of election in these American clinics. In this connection it is to be noted that none of the British centres employ "606". An experiment was made in this clinic with the use of "606" to determine primarily whether it would prove too toxic for routine use in an out-patient clinic whose clientele consisted chiefly of working class men. Dr. J. C. Alexander was good enough to give the injections. The drug employed was arsenobillon. Standard precautions were adopted. Sixty-four cases were treated. Five hundred and thirty injections of AB. were given. Out of the sixty-four patients, eleven showed mild toxic reactions, one collapsed after the sixth injection and five developed jaundice. The favourable serological results seen (for example, six negative

blood Wassermanns were found at the end of a course in twenty-eight cases of neuro-syphilis which were positive at the outset), cannot compensate for the toxic effects. Default was common. It is not advisable to use "606" in this outpatient clinic in place of "914".

The arguments founded on the various data submitted may now be usefully recapitulated and summed up :-

- (1) The first course should be of "914" and metal given in combination.
- (2) The metal should be bismuth.
- (3) The quantity of "914" in a course must not be less than 5 grams.
- (4) Concentration of treatment should take place during the earlier weeks.
- (5) Such concentration can conveniently take the form of bi-weekly injections of "914" and bismuth.
- (6) The total treatment which can be considered adequate must include more than two courses of not less than 5 grams of "914" in each course.
- (7) The principle of continuous treatment must be adopted.
- (8) The administration of mercury by the oral route cannot be considered adequate to maintain the principle of continuous treatment.

The question is now subjected to general discussion to determine details.

In this clinic serological disaster tends to wait on the early defaulters - those who receive less than the

standard course. Exceptions, of course, occur. May it not also be reasonably urged that those cases finally serologically uncured and yet well treated by our standards, contain, apart from the variations in the syphilitic virus, a proportion of individuals who have received insufficient therapy ? But since these cases comprise the patients whose total therapy tends to be the largest in amount - through virtue of their serological difficulties - it seems reasonable again to suggest that one cause for the lack of success may be that the first course of treatment has proved inadequate. The fact that practically none of our cases were Wassermann fast throughout, brings each and all into the category of Wassermann relapse syphilis, and this has been shown to be an expression primarily of inadequate initial treatment. The more one reflects on this problem, the more one becomes convinced that the first course of treatment is by far and away the most vital factor in the patient's after history. And it must be remembered that, with all precautions, early default is relatively common. Now 6.00 grams of "914" represents a rough maximum for any single course of treatment at any clinic. More is apparently considered too toxic. No clinic written to in Great Britain which uses less "914" than this one does, has indicated its percentage of favourable results. The dosage appears smaller solely because fears are expressed on account of the toxic effect of "914". We

have never seen late permanent damage in our cases as the result of early toxicity. The total percentage of the incidence of arsenical intolerance does not exceed that experienced by the Americans when "914" was employed in comparable dosage. Such cases as died did not receive large doses of "914". The American conclusion that large doses of arsphenamine did not injure "the patient with respect to the outcome of his infection", is of the greatest importance. Prior to the institution of the standard course at this clinic, totals of 9, 10 and 11 grams of "914" with single doses as large as 0.9 gram were given. No better end results were seen in these few cases, but also no increased liability to early or late intolerance was experienced. It is, however, felt that six grams of "914" in a single course is about as much as an average case can safely tolerate. The experience of all the other centres must be allowed due weight. It is suggested then that no increase in a total dosage of 6.00 grams in a course be employed.

In this clinic it has been noted that undue increase of the time period leads to worse results, but that no worse results followed on shortening of the time period of the first course, provided at least 5 grams "914" be given. The experience of Liverpool under Dr. Ross is most striking, and shows that bi-weekly injections of "914" need not entail undue intolerance. Early bi-weekly treatment for a short period is

seen in Edinburgh.

Rest periods are a feature of all the courses from the various centres. They are cut down to a minimum in Liverpool and greatly extended in Newcastle. In the early days of this clinic, weekly injections of 0.6 gram or 0.75 gram were given without interval for thirteen, fourteen and fifteen weeks, and no apparent ill effects were seen. Provided, then, that the total length of the course be not prolonged sufficiently to allow of the theoretical objection that it may damage permanently the liver, it is suggested that no lengthy rest periods be employed during the course of "914". It is most strongly urged that the clinical experience of this clinic, the analysis of its cases, the percentage of its defaulters alike call for an intensification of treatment during the early weeks. Accordingly the following scheme is suggested :-

1st day	0.45 gram "914"	
4th day	0.60 " "	
8th day	0.45 " "	
12th day	0.60 " "	
15th day	0.45 " "	
19th day	0.60 " "	= 3.15gms.
26th day	0.60 " "	
33rd day	0.60 " "	
40th day	0.60 " "	
47th day	0.60 " "	

Total 5.55 grams in 47 days.

By this method 3.15 grams of "914" would be administered

in nineteen days by bi-weekly injections. This should prove sufficient to act as a primary saturation quantity with depth of penetration. It should not prove unduly toxic to the average patient, though this must be one of the earliest criteria to be assessed. The next four injections are of 0.6 gram given at weekly intervals. It is hoped that intolerance will thus be minimised. Nothing less than 0.6 gram seems of utility, and there is plenty of experience in our records which asserts that 0.75 gram is not required for sterilisation. There are no rest periods longer than seven days. The total quantity of "914" given is in the neighbourhood of six grams.

The theoretical considerations which led to the adoption of the combined use of "914" and metal are unchanged. Our results appear to be equivalent to those of the American series in which "606" and metal are used consecutively. There seems no reason to adopt the consecutive use of these drugs, and Salford as yet adduces no evidence in support of its methods. There also seems no reason to revert to the use of mercury. At present bismuth seems equally efficacious and less toxic. The standard course employed in this clinic entails 2.4 grams of Bi. metal in fifteen weeks. This is well below the tolerance of the average patient - and the average patient is not careful respecting the toilette of his mouth. In tertiary syphilis, weekly injections of

0.2 gram have been given for fifty-two weeks consecutively without ill effect or, on the other hand, 0.4 gram Bi. metal has successfully been given for twenty consecutive weeks. The writer, at the British Medical Association meeting in 1931, advocated some experiments with regard to ascertaining the body tolerance to bismuth metal given by the intramuscular route. These figures just quoted indicate ordinary routine clinic experience. There may also be quoted some unusual examples of therapy to indicate the high tolerance of the average individual to bismuth:-

Male, aged 37, tertiary syphilis - 0.2 gram Bi. metal daily for 28 days = 5.6 grams in four weeks.

Male, aged 29, secondary syphilis - 0.4 gram Bi. metal thrice weekly for ten weeks = 12 grams in ten weeks.

Male, aged 24, primary syphilis - 0.5 gram Bi. metal twice weekly for ten weeks = 10 grams in ten weeks.

In the latter two cases, "914" was also employed.

No one advocates reliance upon bismuth as the main therapeutic agent of the first few weeks. Primary, secondary and tertiary lesions alike heal more slowly than when "914" is administered. Numerous isolated papers point to relapses, serological and clinical, when bismuth is used as the sole anti-syphilitic drug. Undoubtedly its value lies in its slow and prolonged action, and its benefit is to be seen in the later periods of therapy. There seems little advantage in increasing greatly the total quantity of bismuth in the first course, but, on the other hand, it appears wise to

increase the quantity in the later injections of the course in order that, after the effect of the more transitory "914" has passed off, the tissues may contain depots of bismuth metal and its anti-syphilitic action may be prolonged. It is a matter of clinical experience here that, unlike the short, sharp, quantitative action of a dose of potassium iodide on late cutaneous syphilis, a single dose of bismuth metal will continue to exert a resolutive effect which is prolonged over a period of some weeks.

Accordingly the following employment of bismuth is suggested in conjunction with "914" :-

1st day	0.2	gram	bismuth	metal
4th day	0.2	"	"	"
8th day	0.2	"	"	"
12th day	0.2	"	"	"
15th day	0.2	"	"	"
19th day	0.2	"	"	"
26th day	0.2	"	"	"
33rd day	0.4	"	"	"
40th day	0.4	"	"	"
47th day.. . . .	0.4	"	"	"

Total = 2.6 grams in 47 days.

It may be objected that this new quantity of 2.6grams of bismuth metal differs only slightly from the old figure of 2.4 grams. It is pointed out that this new quantity is administered in 47 days; the old in 105 days. Further, more metal will shortly be given in pursuance of the principle of continuous treatment.

It is reasonable here to point out that there are three main classes of bismuth preparation (1) bismuth metal (2) complex inorganic or organic bismuth salts (3) bismuth preparations in which other elements, judged to be of a remedial nature, are associated e.g. iodo-bismuthate of quinine. Extensive experimentation with these classes of bismuth preparations seemed, in tertiary cutaneous syphilis, to yield fairly comparable results in respect of the rapidity of healing of the lesions, and the obstinacy of the persistence of Wassermann positive blood sera. It is definitely thought that at present no advantage accrues from the use of other than simple metal preparations in the treatment of early syphilis.

The combined first course suggested now becomes:-

1st day	.	.	.	0.45	gram	"914"	+	0.2	gram	bismuth	metal
4th day	.	.	.	0.60	"	"	+	0.2	"	"	"
8th day	.	.	.	0.45	"	"	+	0.2	"	"	"
12th day	.	.	.	0.60	"	"	+	0.2	"	"	"
15th day	.	.	.	0.45	"	"	+	0.2	"	"	"
19th day	.	.	.	0.60	"	"	+	0.2	"	"	"
26th day	.	.	.	0.60	"	"	+	0.2	"	"	"
33rd day	.	.	.	0.60	"	"	+	0.4	"	"	"
40th day	.	.	.	0.60	"	"	+	0.4	"	"	"
47th day	.	.	.	0.60	"	"	+	0.4	"	"	"
				<hr/>							
				5.55 grams				2.6 grams			

Let it be assumed that the clinical and serological results are negative after such a course, whether the blood Wassermann was initially positive or not. What should then be done ? There is no doubt but that this is insufficient

treatment. The experience of the clinicians expressed as a symposium in the American Journal of Syphilis, 1924, confirms this. Our clinic has seen a considerable number of cases of tertiary syphilis in which short dated but intensive treatment with "606" was administered in the early stages of disease, during the war period. Dr. Lees speaks of the need for the "prolonged saturation with both drugs". The recent American analysis, V.D.I., July 1932, most emphatically supports the principle of continuous treatment, and definitely upholds the superior value of continuous amounts of even small dosage in contrast with the intermittent supply of large quantities of anti-syphilitic remedies. From 1923 onwards this principle was recognised in this clinic and an effort was made to comply with it by giving orally as much mercury as, in bygone days, Jonathan Hutchinson deemed sufficient to effect a cure unaided by other remedies. There emerges no evidence out of the analysis of the cases of this clinic in support of high value for oral mercury as a subsequent method of treatment. However effective oral mercury may be when given alone and at the outset, and the early histories of the tertiary cases attest its frequent failure, it seems to be of little if any use in the treatment of cases which are Wassermann fast and which show serological relapse. Numerous cases of Wassermann fast tertiary syphilis, their lesions healed with "914" and intramuscular injection of

metal, have taken these pills for two years on end. Only an infrequent serological improvement, usually of a highly temporary nature, has been noted. It is felt that the oral use of mercury should be discontinued. One possible exception remains - as a placebo and a means of inducing patients to keep in touch with the clinic, it may be of value. The use of mercury by inunction is a different matter. It is found at this clinic to be of value in the treatment of congenital syphilis in young children. It is regularly employed at Aix and in America. It cannot be adequately given by the self ministrations of the uneducated working class, desirous of home privacy and fearful of betraying their disease. It requires a staff of trained rubbers. It is not practicable here. Intravenous injection of soluble mercurials have a rapid healing effect. They are toxic: they are evanescent in action. The major serological tragedies in this clinic have followed when they were employed without associated treatment. Mercury salicylate by intravenous injection was tried in extenso in five cases of tertiary syphilis without serological benefit. As a routine mode of therapy suitable for large clinics, the intravenous route seems inadvisable. The intramuscular injection of preparations such as calomel cream and gray oil falls into a different category. There are living at the present time many more cases whose apparent cure is due to such substances

than to the newcomer bismuth. It appears to be a mistake to forego entirely the use of mercury in the routine treatment of early syphilis, and its intramuscular use is accordingly advocated as part of the subsequent continuous treatment of early syphilis. It seems inadvisable, for reasons already adduced, to allow it to replace bismuth as the standard drug in the combined course. Its accurate employment will be discussed later.

In this clinic from 1924 onwards, standard practice has been to give one course of combined "914" and metal after the Wassermann of the blood at the end of the preceding course, and the Wassermann of the blood taken prior to the administration of this course, are alike negative. If this were adhered to it would therefore entail a minimum of two courses for any one case. It has been considered that two courses is not enough. The interval between the first two courses has varied from four to six months. Latterly there has been a tendency to shorten this interval. It is felt that it should definitely be shortened to such a period as will reasonably allow one to conclude that late arsenical intolerance is not likely to appear. Jaundice has been seen on several occasions at the twelfth week after the completion of a course of arsenical injections. So, too, skin complications have appeared at comparable dates. On the other hand, should serological relapse occur, the quicker it is recognised and treated, the better appears the ultimate issue. Dr. Ross

advocates a rest interval of three months after his first intensive course. Here it is suggested that an interval of four months will almost definitely exclude jaundice and skin intolerance. But if the Wassermann reaction of the blood be positive at the end of the third month after treatment, then the next course should be commenced. The very emphatic American pronouncement on the value of continuous treatment is backed by such abundant and careful statistical inquiry, that it is felt it cannot be ignored. It is not proved, nor is it even often suggested that the intercurrent use of bismuth or mercury increases the incidence of arsenical intolerance. Accordingly, it is proposed that after a rest of one month, during which therapeutic benefit may be expected from the depots of bismuth in the tissues, treatment be resumed and that eight weekly injections of one grain of calomel be given. Should mercury lead to local discomfort of a definite degree, then bismuth might be substituted. During this time potassium iodide, gr. 15, thrice daily might be administered. Its value in the resolution of gummatous tissue demands its employment. It is harmless. Its continuous use has, however, been shown to bring no additional therapeutic benefit. After this course, an interval of one month completes the four months period suggested as the interval advised between the two main courses of treatment. It is suggested that the second course be an exact replica of the first one. There do not appear

any fresh reasons as a result of the progress of time in the individual case to alter its composition. If the case be already cured it matters not what system be employed. If the case be not cured its treated life has extended to some six and a half months. It would still seem amenable to shock methods.

Much energy has been wasted in the subdivision of different grades of early syphilitic infection for different therapeutic regimes. This has always been considered hair-splitting and quite unjustified by the known vagaries of the syphilitic virus. No explanation has ever been afforded as to why one case may appear cured after two or three injections while a second, after much treatment, moves steadily along the path ending in cardio-vascular syphilis and a third becomes a candidate for tabes dorsalis. There must be something in the soil on which the virus falls. Analogous questions can be asked in respect of every infection. Why should one case of acute rheumatism, of tuberculosis, of dysentery, of malaria rapidly appear cured and another not? In face of such unanswered questions nothing but a broad subdivision of cases need be discussed. Is it wise to separate, for therapeutic purposes, cases of early syphilis into the two groups Wassermann negative and Wassermann positive in accordance with the reaction shown by the blood serum before treatment is commenced? Most clinics make this distinction

in their replies to the questionnaire. It is definitely considered that no such distinction should be drawn. Indubitably, sero-negative primary syphilis affords in this clinic, as in others, the best chances of cure. In this clinic it yields the smallest percentage of Wassermann and clinical relapse. Yet the ultimate results cannot be definitely predicated. We have notes of one male case which, after 6.75 grams of NAB., 11 grains of mercury and fifteen months of oral mercury, showed a suspicious Wassermann reaction of the blood more than two years after his initial appearance and after being continuously negative. A suspicious Wassermann reaction has been shown to be a "therapeutic positive". It is impossible to legislate for the exceptional case, but legislation should make exceptional cases unusual. Provided that no undue intolerance is met with, it is definitely suggested that in all cases of early syphilis a third course of "914" and bismuth be given, and that the interval between the second and third courses be increased to six months if the Wassermann of the blood remain negative. This principle may be extended by stating that each case of early syphilis shall receive two complete courses of "914" and bismuth after the blood Wassermann has become negative. The principle of continuous treatment should still be upheld, and accordingly, it is proposed that after six weeks rest, subsequent to the second course of injection of "914" and bismuth,

there be given ten injections of calomel cream at weekly intervals, bismuth again being substituted if local discomfort be met. Thereafter a rest period of eight weeks supervenes until the onset of the third course.

By this time the case which has responded well to treatment and shown no intolerance has received 16.65 grams of "914", 7.8 grams of bismuth and 18 grains of mercury in a total time period of some fourteen and a half months.

This exhibits an increase in our total "914" dosage. It does not yet equal the total given by Liverpool or Whitechapel in their routines. The total quantity of bismuth is 7.8 grams, which is still less than Edinburgh, St. Thomas or Liverpool employ, but there is an additional amount of 18 grains of mercury. Our time is shortened. It is felt that the total amount of treatment administered in this continuous yet intensive manner should be sufficient. This is highly speculative, but the proper after handling of such cases is even more a matter for philosophic conjecture. All cases should be observed for at least two years, and at the expiry of this time should have an examination made of the cell content and the Wassermann reaction of the cerebrospinal fluid. During the intervening nine and a half months regular Wassermann tests of the blood serum should be made. It is permissible to allow these amounts to be regulated by factors not strictly therapeutic. Such might be the willingness of the patient to continue regular weekly treatment.

This is a real difficulty as few cases wish to come once a week during the greater part of their second year's attendance. During these ten and a half months potassium iodide, in the usual dosage of 15 grains thrice daily, might also be employed frequently.

It should be pointed out that this clinic does not discharge cases of treated early syphilis. A yearly blood test and a yearly examination is requested in the hope that this may assist in assessing the permanent value of the therapy given.

It is impossible to discuss treatment in detail of such cases as, under this regime, show clinical or serological relapse. Beyond stating the general view that two courses of treatment should be given after the blood Wassermann has become negative, no details can usefully be given. The individual problems which arise must be dealt with individually.

A word of caution is necessary. It is that this is not a cast-iron regime like a Procrustean bed into which all must be fitted. Yet, as in healthy young adults the natural history of the first two years of syphilitic infection runs a comparable course, so there may reasonably be suggested a standard therapeutic method of attack. The greatest individual latitude is obviously permitted.

It is hoped that with such a regime clinical relapse will be less frequent, but unless its incidence be greatly increased

this aspect of relapse will be too infrequent to permit of assessment of the value of the regime within a reasonable time. In other words, it will take too long to accumulate sufficient clinical relapses to lead to an unfavourable view of this method of treatment. The standard should be Wassermann relapse in all its grades and at all times. Unless during the two years observation of the case the total serological relapses, and particularly those relapses which occur during the second year of observation and treatment, be diminished, as compared with the present regime, further changes in methods must be adopted. It is also urged that sufficient cases receive this course of treatment to permit of analysis, and it is thought that a minimum of one hundred cases observed for at least two years should be investigated.

One interesting aspect of treatment merits a short notice. Gennerich noted that there was a remarkable lack of subsequent neuro-syphilis in such cases as developed one of the exanthemata during their primary or secondary stages of syphilitic infection. It has occurred to the writer, as to many others, that the introduction of one or two "protein shocks" during the acute stages of disease, or even after therapy is completed, might act as a substitute for the natural exanthem. Such practice has been carried out in isolated cases. It is, however, quite impracticable as a routine measure in large out-patient clinics.

As an appendix to this section there is submitted the complete details of the proposed scheme of treatment.

Doubtless the reader has repeatedly lost his way to, and in this section in figures and tables: doubtless, too, many side tracks, interesting in themselves but not particularly germane to the main purpose, have been encountered. His indulgence is begged, and he can be assured that the labour of compilation, analysis and construction greatly outweighs his own brief trials.

