THE ROUTINE TREATMENT OF EARLY SYPHILIS

(Paper read by DAVID WATSON, M.B., C.M., at a meeting of the Scottish branch of the M.S.S.V.D. at Stirling on March 25th, 1931).

That it is advisable for each clinic to have a basis on which the routine treatment of cases is built will, I think, be generally admitted. Not of course a basis from which there can be no variation, but one which will make the compilation of statistics and the comparison of results possible, so that we may be able to arrive at a reasoned estimate of what constitutes the best treatment available for the cure of early syphilis.

In approaching this subject, I think we cannot do better than to consider the recommendations of Colonel Harrison, Dr. Lees and Dr. Snodgrass as shown below:

One Scheme suggested by Colonel Harrison in "Practitioner" of February, 1931

1st Unit of the Course.—Ten injections of 9I4 beginning with .45, ending with .75, totalling 6.3 gm., along with 9 injections of .32 gm. bismuth, totalling 2.88 gm. bismuth, and iodide of potash for 3 weeks. Spread over 13 weeks. The complete course recommended consists of four of these units with intervals of 2 months.

Totals.—9I4 = 40 injections — 25.2 gm.; Bismuth, 36 injections — 11.52 gm.; Iodide of potash, 63 drams. Time, 18 months.

Treatment recommended by Dr. Lees,* provided the Wassermann is negative at the end of the first course and remains so:

During First Three Months.—Eight injections of 9I4 and 9 injections of bismuth, or 7 injections of mercury.

During Second Three Months.—Four injections of 9I4 and 8 injections of bismuth, or 7 injections of mercury.

During Third Three Months.—Five injections of 9I4 and 8 injections of bismuth, or 8 injections of mercury.

During Fourth Three Months.—Five injections of 9I4 and 8 injections of bismuth, or 8 injections of mercury.

Thus during the first year there are given 22 injections of 9I4 totalling 11.1 gm., and 33 injections of bismuth totalling 13 gm. In addition for 14 days following each course 15 to 20 gm. of potassium of iodide, t.i.d.—totalling 42 drams of K.I.

* "Diagnosis and Treatment of Venereal Diseases" (E. and S. Livingstone, 1927).
ROUTINE TREATMENT OF EARLY SYPHILIS

During the Second Year.—2·25 gm. 914 (5 injections) and 12·6 gm. bismuth, or 32 gr. of mercury.

Totals : 914, 27 injections, 13·35 gm. Bismuth, 57 injections, 26·6 gm. Potassium iodide, 82 drams. Time, 2 years.

Treatment recommended by Dr. Snodgrass and used in some Glasgow clinics :—

First Course.—Ten injections of 914 totalling 5·85 gm.; 12 injections of bismuth totalling 2·4 gm. Potassium iodide is given concurrently with the injections—15 gr. t.i.d. for 14 weeks, totalling 73 drams. The injections are spread over 99 days. There is then an interval of 4 to 6 months, during which Hutchinson’s pills are given (Hydrarg. cum Cret. gr. i, P. Epicac. Co. gr. i, t.i.d.). The above course is then repeated.

Totals : 914, 20 injections, 11·7 gm.; bismuth, 24 injections, 4·8 gm.; potassium iodide, 146 drams; mercury by mouth, 5 to 6 drams; opium, 90 to 108 gr. Time about 18 months.

In examining these schemes one finds a considerable disparity in each of the three drugs used in treatment, but the most important is that affecting 914.

Colonel Harrison is the most prominent exponent in this country of attempting the radical cure of early syphilis by pushing 914 combined with a modicum of bismuth. In the article to which I have referred he states that his programme of treatment until 1928 was as follows :—

1st Unit of the Course.—Ten injections of 914 beginning with .45 and ending with .75—totalling 6·3 gm. 914, along with nine injections of .32 gm. bismuth, totalling 2·88, and potassium iodide for three weeks during the course.

A second identical unit was given after two months’ interval in sero-negative primary syphilis.

In an early secondary case two additional course units of treatment, each consisting of three .6 injections and two .75, with corresponding bismuth.

The result of this scheme seems to have been, broadly, 10 per cent. of relapses, and he goes on to say : “I have interpreted these results as meaning that the minimum amount of treatment to be given to a sero-negative primary case is three full courses such as first outlined (i.e., 30 injections), and that for one which becomes sero-positive, whether still primary or now secondary, at least one further course is necessary.” (This is the scheme which is outlined above.) “Where the eradication of syphilis from a community is desired there must be a unanimous determination to administer to every
case of early syphilis not less than the amount of treatment just mentioned,” says Colonel Harrison.

At this point in his article, therefore, he is recommending—nay, insisting on—for a case of early secondary syphilis 40 injections, totalling 25.2 gm. 914, and 36 injections of bismuth, totalling 11.52 gm.

This, to me, is an appalling amount of 914 to suggest as the basis of a routine scheme of treatment, and the only justification would be its outstanding success as a cure for syphilis in comparison with other methods. Even then it would be liable to severe criticism because of the danger of death and disease associated with the treatment itself.

But that it failed in being effective, Colonel Harrison admits when he says: “Being dissatisfied with the immediate results of the scheme of treatment outlined above, I have attempted to improve it.” And if we consider the table given on p. 198 of the “Practitioner,” which shows that of 167 cases of early secondary syphilis 33.5 per cent. were positive after the first course of the series of injections, I think we will be able to understand his dissatisfaction.

In trying to improve his methods, Colonel Harrison at first increased the intensity of the course. He says: “With the same amount of bismuth,—8.75 gm. 914 was administered in 92 days . . . the immediate effects of the course, in terms of negative sero reactions, was no better and the incidence of toxic effects became uncomfortably high.”

I would, with all respect, suggest to Colonel Harrison that he might now have begun to suspect that with 914 he was not going to achieve his purpose.

The improved course which Colonel Harrison substituted 2 1/2 years ago, consisted of:—

First Course—Bismuth.—32 gm. per week from first to sixty-fourth day.

914.—Nine injections of from .45 to .9 gm., spread over 120 days, totalling 6.75 gm.

For sero-positive early syphilis, four such courses are given, a total of 27 gm. 914 and 11.52 gm. bismuth.

Colonel Harrison gives a table comparing the results of the old and the new courses. In this table there are 287 early syphilis cases on the old system, of which 25 per cent. were positive or doubtful at the end of the
ROUTINE TREATMENT OF EARLY SYPHILIS

first ten injections, and on the new there were 136, of which 8 per cent. were unsatisfactory.

This shows a very great improvement, and the probable explanation is that the new course extends to 120 days against 92 in the old, with but the slight increase of .45 gm. of 914.

Can it be that this indicates the turn of the tide?

Colonel Harrison mentions that the incidence of jaundice was increased with the new course—doubtless this was due to the .9's of 914.

If we were to rely on the clinical experience of those who are treating syphilis, I have little doubt that the consensus of opinion would be that the risks of excessive 914 treatment were greater than the risks of future trouble from the disease after moderate treatment; but in this connection we have to admit that the late ill-effects of syphilis may not come under our observation to any great extent even in a long experience, and we have to harken to the warnings of physicians on the subject. On the other hand, we can reply that these late symptoms, if recognised early enough, are still amenable to treatment, and there is certainly no evidence yet available, either from my own practice or from the literature on the subject, which impresses me with the need to increase the risks of the early treatment which I practise.

In this connection, might I suggest to physicians that in cases of jaundice, dermatitis and nephritis of unexplained origin, they might consider the possibility of arseno-benzine toxæmia, as this may have occurred in a patient attending a clinic who has suppressed this information. No physician fails to suspect syphilis as a possible cause of cardio-vascular or nerve disease, but arseno-benzine poisoning might easily escape their consideration in these other conditions.

Turning to the scheme of Dr. Lees, we find something more moderate, but still, I think, subject to similar criticism, though of course in minor degree. It seems to me that an unnecessary amount of 914 is suggested, and the same applies to the scheme of Dr. Snodgrass so far as the amount of 914 is concerned, although that is somewhat less even than Dr. Lees' total.

With regard to the bismuth, you will notice that 36 injections totalling 11.5 gm. are given in Colonel Harrison's scheme, 57 injections totalling 26.6 gm. in
that of Dr. Lees, and 24 injections totalling 4·8 gm. in Dr. Snodgrass'. But Dr. Snodgrass' bismuth deficiency is counterbalanced by the addition of 5 to 6 drams of mercury to be given by mouth.

I entirely agree with Dr. Lees in his use of a large quantity of bismuth if mercury is rejected. However much or little 9/4 is adopted, it must be buttressed by a sufficiency of either bismuth or mercury.

So far as potassium iodide is concerned, the quantities in the three schemes are 63, 84 and 146 drams respectively.

In considering the principles upon which a scheme should be constructed, we have to study safety as well as efficiency. Here I put safety first. There is supposed to be, if not an element of cowardice, at least an absence of heroism in the adoption of such a motto. But there is no room for heroism of this sort in medicine. We have no right to adopt any method of treatment which has such definite elements of risk as are attached to even the mildest of the above schemes without the most careful deliberation.

I am told there were three known deaths in Glasgow last year from arseno-benzine poisoning.

The mortality from treatment is, of course, a small, but by no means a negligible, proportion of the total number treated. With regard to the morbidity, while the vast majority of cases of dermatitis, jaundice and nephriti apparently recover, we know that there is some lasting damage done to the tissues in every case developing symptoms and probably also in many cases that pass unrecognised.

I maintain that our first aim should be to eliminate these risks, or at least to reduce them to the lowest attainable level.

Efficiency we must strive for, but it must be sought after a judicial survey of all the known and ascertainable facts.

In attempting to determine the comparative value of remedies there are three points which it might be well to remember:

(1) We must endeavour to evaluate the real powers of each of the antisyphilitic remedies from experience in practice and by experiment in animals.
(2) We must realise the limitations of each and carefully weigh their dangers.
(3) We must try to discover how the deficiencies of
one can be overcome to the best advantage by the use of another, both by combination and in sequence.

Colonel E. T. Burke (B.M.J. 21/2/31) has formulated an ingenious method for estimating the total therapeutic value of any given scheme of treatment. The method might be of value if only we had the correct figures with which to start the equation. Three short extracts will give us an idea of his theme.

He writes (1) : "The only satisfactory way in which standardisation can be brought about is by taking into account the chemo-therapeutic indices of the various agents." (2) "The chemo-therapeutic index is expressed as the maximal tolerated dose per kilo divided by the minimal curative dose per kilo." (3) "Upon some standard animal experimentally infected it is necessary to make out the chemo-therapeutic indices of the various chemical agents."

I think we will admit all of this is a very desirable, indeed a very necessary, preliminary, but it would only be the first stage. Not only do we need the therapeutic index of each of the agents separately, we need to know what they would be in all possible combinations and sequences, and then would come the real task of determining how closely and safely these results were obtainable in man. A large order indeed, but one which I hope will eventually be completed.

When we come to speak of the therapy of syphilis precedence must be given to 914.

Primarily, 914 is a spirochaeticide destroying the organisms circulating in the blood stream and in vascular tissues more easily and rapidly than any other drug we know. In doing this it clears up almost all syphilitic lesions, and the more vascular the lesions are the more rapidly it effects their disappearance. It is, however, impossible in man to exterminate all the spirochaetes in the system by the use of 914; it has been tried as a sole method of treatment for syphilis and it has proved a failure. It fails because it does not succeed in penetrating certain tissues in sufficient concentration to destroy the spirochaete. In particular it is ineffectual in the brain and spinal cord. With regard to the dense tissues it seems to be impracticable sufficiently to saturate the system, and to maintain this saturation for the adequate period.
The original conception of Erhlich that one dose of 606 would cure by destroying all spirochætes has, of course, been abandoned, but this aim still seems to dominate the efforts of most workers in that they continue trying to administer the maximum bearable quantity of 914 in the hope of thus curing syphilis.

If we turn to the history of the treatment of syphilis by mercury we find a state of matters not unlike what is happening with 914 to-day. It was seen that mercury did have an effect on the lesions of syphilis, and it was only natural for the physicians to push mercury to its extreme limits in the hope of rapidly curing the disease. We have now learned, so far as mercury is concerned, how to use it with advantage to the patient and at the same time to avoid all risk to life or health. Can we say the same with regard to our use of 914? If not, are we going to allow a century or more to elapse before we can?

Personally I recognise the limitations, as well as the powers, of 914. I realise fully its dangers, which I think it not only needless to accept, but quite useless to incur in the search for increased efficiency.

I would suggest that the legitimate function of 914 can be secured by a moderate course well within the limits of safety, and that the protection of the system from the possible recrudescence of the inaccessible spirochætes over a prolonged period can be attained by arranging to best advantage the combinations and sequences of the curative drugs. Among these, of course 914 takes first place, but the others play an essential and hardly less important part and require, in my view, a consideration which they are not receiving.

Bismuth ranks next to 914 as a spirochæticide. Either bismuth or mercury must be associated with the 914, but I prefer the combination with mercury. I will be glad to hear for what reasons bismuth displaced mercury for use with the more effective spirochæticide 914, and the results which have followed its adoption. It has been suggested that it increases the activity of the 914, but in my experience it is not nearly so useful for this purpose as mercury given by the mouth, and so I prefer to retain bismuth as a subsequent course if required. A possible exception to this statement might be found in cases in which it may be impossible or unwise to give
ROUTINE TREATMENT OF EARLY SYPHILIS

ordinary doses of 9I4 and in which there is a call for the most active antispirochäeticidal treatment owing to the presence of lesions.

My own experience of bismuth in combination with 9I4 was a short one, too short to be decisive, but the results were not encouraging compared with my established routine. A less serious objection I found was the increased attendances required. I hesitated to continue the weekly injections of .4 gm. to .6 gm. as used by Dr. Lees, owing to the occasional appearance of stomatitis, and bi-weekly injections are impracticable.

K.I.—I am decidedly sceptical of the need for iodide of potash now that we have 9I4.

It is supposed to promote absorption of inflammatory products, and thus lay the spirochaetes more open to attack. But does it really do so in early syphilis?

Sir Jonathan Hutchinson, who had a high opinion of the value of K.I. in treating tertiary syphilis, says: "In the early days of syphilis the iodide of potassium is comparatively powerless, and mercury should always be used. Thus the induration of a primary sore will resist the influence of the former, but disappears at once when mercury is given."

I do not come across cases of early syphilis where 9I4 with mercury by the mouth fails to ensure the rapid disappearance of the syphilitic lesions, and that being so I see no need for iodide as part of a routine, especially when symptoms of iodism may be so annoying.

Mercury.—Since the introduction of 9I4, and later of bismuth, little attention has been paid to mercury. Hardly any experimental work of importance has been done. Clinically it faded into the background when it was seen that 9I4 so quickly cleared up lesions and banished their spirochaetes, and finally since the recognition of bismuth it has almost disappeared. But I believe that I have preponderating clinical evidence in favour of mercury by the mouth in combination with 9I4—evidence sufficiently strong to suggest that it is the most reliable method of treatment at our command. I commend this as a question well worthy of experimental investigation.

Intramuscular injections of mercury I have never favoured, and my experience of their use is limited. I have been impressed with their disadvantages, namely,
their slow and variable rates of absorption, the accompanying pain and the possibility of encystment. Furthermore, I doubt whether grey oil injected intramuscularly has the same beneficial effect on the liver, etc., as Hydrarg. cum Cret. by the mouth. The latter seems usually to stimulate a feeling of general well-being.

The total amount of mercury administered by injection, as an alternative to bismuth, in the course suggested by Dr. Lees is 62 gr., and I have seen no scheme in which more than that quantity is recommended, while I use 720 gr. given by the mouth. It is difficult to compare these quantities owing to the different methods of administration. In estimating the amount of mercury circulating in the blood, I know no reason for believing that the oral route is not accompanied by the optimum amount of absorption, and certainly the clinical results have given me complete satisfaction.

Sir Jonathan Hutchinson in his 1909 edition, which I can warmly recommend not only as most informative but as delightful reading, gives a reasoned examination of the different methods of administering mercury, and the conclusions he reached to me still are convincing. He says: “I do not recommend for general adoption any other method of treatment than that by small doses administered by the mouth and continued for a very long period.”

There is a report of the Medical Research Council entitled “The Effects of Treatment on the Wassermann,” by Ernest Glynn and others, published in 1926, to which I must briefly refer, as in it the use of mercury is condemned.

This paper, however, has little bearing on the question we are reviewing to-day, as it relates to late as well as early syphilis, and the amount of treatment given was insufficient, both as regards the 914 and the mercury.

The report had, I think, an unfortunate effect in belittling the importance of the mercury by the mouth given along with the 914 injections, and conclusions were drawn and generalisations made with regard to the oral administration of mercury which I think were quite unjustified by the evidence.

Colonel Harrison, in the article I have so freely quoted, makes one or two derogatory references to mercury prescribed orally. Thus he speaks in disparaging terms
ROUTINE TREATMENT OF EARLY SYPHILIS

of those who continue the treatment with the "feeble mercury by mouth for the traditional two years after the serum reactions have become negative." He repeats later: "If not cured by the energetic treatment of the first course, it is unlikely that the surviving spirochaetes will succumb to the feeble attack of a few mercury pills."

And, again, speaking of treatment with mercury for two years, Colonel Harrison says: "The most that this is likely to do is to keep the serum reactions negative and everybody concerned in a fool's paradise." This last strikes me as rather a paradoxical statement. Does it really matter once the reactions are negative whether they are kept so by mercury or 914? The mistake Colonel Harrison makes is, I think, that he undervalues the mercury, exalts the 914 and fails to grasp the merits of the combination of the two.

My own methods and results are as follows:—

The first course consists of eight injections of 914, beginning with three .45's, the other five being .6's; this equals 4.35 gm., and it is spread over ten weeks. Concurrently 4 gr. Hydrarg. cum Cret. per day are being taken for three months, then two to three weeks' rest and a Wassermann—i.e., in 105 to 112 days.

A second course of five injections, six to eight weeks later, is recommended, but it is optional if the Wassermann is negative. The total 914 would then be 6.9 gm.

In women .45 gm. is the usual dose throughout, and in men .6 gm. is not exceeded, but even in men, according to physique, it may be restricted to .45 gm.

The essential feature of my practice is the combination of mercury by mouth with the 914, and its continuance in a dosage of 4 gr. grey powder per day throughout at least two years. The concurrent use of mercury by the mouth with arsenic increases the potency of the latter without increasing its toxicity. It could indeed be inferred quite reasonably that by stimulating the excretory functions it decreases the risk of arsenical poisoning. It is given in the form of Tab. Hydrarg. cum Cret. gr. ii night and morning to all adults, and only discontinued for two to three weeks in each period of four months to allow of blood for a Wassermann test being withdrawn, or while a course of bismuth is being administered. The condition of the teeth has to be supervised, but when this is
satisfactory it is very seldom indeed that I have to
countenance the stoppage of this dosage for more than a
day or two. Occasionally it may be advantageous, until
intestinal tolerance has been established, to add a few
grains of Creta preparata to each dose. This I prefer
to the constant use of Dover's powder. Some have
believed that opium assisted the action of mercury, but
I know of no grounds for this belief and I do see objection
to the long-continued use of opium, even in small doses,
which have a disconcerting way of mounting up to a
considerable total. But I do not wish to exaggerate my
criticism of Dover's powder, except when it is used for
long periods. If mercury had to be stopped on account
of diarrhoea for more than a day or so, I would certainly
continue on Dover's powder if necessary rather than cut
out the mercury for many days.

From this course of treatment, which to extremists in
the use of 914 must seem a very mild one, I expect
results as good as any I know of or have read about, and
this makes me critical of more dangerous schemes.

Thus I expect every case of early syphilis to be free
from all symptoms within a few weeks of starting
treatment, and to continue so throughout the period of
observation. I expect less than 5 per cent. to be positive
at the end of the first course, and only in exceptional
instances do I anticipate their failure to remain per-
manently negative after the first year's treatment.

In the time at my disposal since I undertook this
enquiry I have been able to collect statistics relating
only to 145 cases of primary and early secondary syphilis
treated on these lines, and only 50 of them so far have
completed two years or more of treatment. I am,
therefore, offering the 145 only as an indication of what
effect is produced on the Wassermann by the first course,
and the result is as follows:—

<table>
<thead>
<tr>
<th>Total Cases</th>
<th>Negative after First Course</th>
<th>Positive or Doubtful after First Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>145</td>
<td>139</td>
<td>6 = 4.1 per cent. positive or doubtful after the first course</td>
</tr>
</tbody>
</table>

286
ROUTINE TREATMENT OF EARLY SYPHILIS

Cases which received two or more years of treatment:

<table>
<thead>
<tr>
<th>Total Cases</th>
<th>Negative after First Course</th>
<th>Positive after First Course</th>
<th>Reverted Later</th>
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<tbody>
<tr>
<td>50</td>
<td>49</td>
<td>1 = 2%</td>
<td>4 = 8 per cent. reverted.</td>
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</tbody>
</table>

There were thus five of the fifty who required a prolongation of their 914 treatment, i.e., 10 per cent. Two of these five were ultimately negative for over two years, one was transferred to another clinic, and two were lost sight of before they had been negative for the full two years.

These results are very much what experience had led me to expect.

This course of treatment has been carried out for a dozen years or more at the clinics with which I have been associated, and it is only within the last year or two that bismuth has been used in Glasgow to any large extent at the expense of oral mercury.

I was pleased to see Dr. Peters demonstrate, a few days ago, that there had been in the Glasgow district a decline of from 750 congenital syphilitic births to 250 during the past seven years, and that there had been no increase, but rather a decrease, in asylum cases of G.P.I. in the past decade.

My own contact with patients who in years gone by had such a course of treatment does not shake my confidence in its permanent success, and therefore not only do I refuse to increase the risks of treatment—not to speak of the expense of it—but I have no hesitation in recommending others to do likewise.

It may be taken as a sign of weakness on my part that any optional second course of 914 is recommended at all in view of the results I obtained, and continue to obtain, without it. To that charge I can only plead guilty. It is just a partial surrender, perhaps against my better judgment, to the insistent clamour in the medical literature for more and more 914.

I greatly regret being in opposition to Colonel Harrison and his large number of followers, but I can only say
that I sincerely and conscientiously believe that I would be failing in my duty if I did not raise a protest, however feeble it may prove, against teaching which I believe to be dangerous and erroneous.