THE INTRAMUSCULAR OR SUBCUTANEOUS INJECTION OF NEO-SALVARSAN.

BY

L. W. HARRISON, LIEUTENANT-COLONEL R.A.M.C.,
OFFICER IN CHARGE AND LECTURER IN VENEREAL DISEASES,
MILITARY HOSPITAL, ROCHESTER ROW;

C. F. WHITE, MAJOR R.A.M.C.;

AND

C. H. MILLS, M.R.C.S., L.R.C.P.,
SURGEON TO ST. PAUL'S HOSPITAL.

THE intravenous administration of the arsenical compounds which are now used for the treatment of syphilis is hedged around with many obvious difficulties which seriously limit their use. It is true that certain compounds, such as neo-salvarsan and substitutes, galyi, and luargol, can be administered in concentrated solution with comparatively little trouble, but the precision demanded by the operation and the odd chance that the patient may display alarming symptoms immediately afterwards are deterrents to the practitioner carrying out these injections in his private consulting-room. It is clear, therefore, that if the hypodermic method proved therapeutically as effective as the intravenous, and could be freed from the disadvantages of local pain and reaction, it would simplify the arsenical therapy of syphilis and extend its use.

Previous to the investigation detailed below there were some grounds for supposing that the hypodermic injection of neo-salvarsan might prove therapeutically more effective than the intravenous injection of salvarsan. For example, (a) Wechselmann and Eicke¹ have stated that they can effect more with deep subcutaneous injections of neo-salvarsan than with intravenous injections of salvarsan, though we cannot remember any publication in which the point has been proved by statistics. (b) Various workers have indicated their impression that when the perfected salvarsan of to-day is given intravenously it is too quickly absorbed and excreted to produce its full effect.

Thus Gennerich² stated that latterly he had found it necessary, in order to produce the same effect, to administer more salvarsan than formerly on account of the greater speed of excretion of the present-day preparation.

(c) Scholtz³ commences his course of treatment by administering four small doses of salvarsan intravenously on the first two days, on the principle that it is not so necessary to ensure the presence of as large a quantity of salvarsan as possible in the circulation at one moment as the continuous action of some salvarsan over as long a time as possible.

(d) Neo-salvarsan is more soluble and quickly excreted than salvarsan, and many good authorities (with whom we agree) hold that, when administered intravenously, it is not so effective as the older preparation.

It is probable, therefore, that it is an advantage to ensure slower absorption, as would be done by hypodermic injection. It is, of course, possible with regard to the latter that if, as we now believe, the effect of hypodermic injection is better, it is because the derivative of the arsenical preparation which is produced by the subcutaneous tissues is more effective than that which results from intravenous injection.

In order to compare the effects of the two methods we have treated two parallel series of cases of syphilis (a) by intravenous injections of salvarsan (or "substitutes"), and (b) by deep subcutaneous or intramuscular injections of neo-salvarsan (or "substitutes").

The investigation was carried out in two separate hospitals, and the remedies used were (1) salvarsan, kharsivan, arsenobenzol, and arsenobillon for intravenous injection; and (2) neo-salvarsan, novarsenobenzol, and novarsenobillon for subcutaneous. Since the results obtained by salvarsan agreed substantially with those by each of its substitutes—and the same applies to neo-salvarsan and its substitutes—we have combined them in each series, and, to avoid repetition, will refer to them as intravenous salvarsan and subcutaneous neo-salvarsan respectively.

The cases in the intravenous series were as far as possible similar to those in the subcutaneous.

The best comparison between the two series would be

obtained by observing them for a prolonged period afterwards, but this would be impracticable at present, and we have based our comparison on the results of Wassermann tests carried out at the end of each course of treatment. For the tests we are indebted to Captains A. Dawson and McWhirter, R.A.M.C., and to Mr. N. Clarke, Military Hospital, Rochester Row.

The treatment administered to the respective series consisted of 2.8 grams salvarsan intravenously and from 3.9 to 4.2 grams neo-salvarsan (equivalent to from 2.6 to 2.8 grams salvarsan), subcutaneously, as shown below. In addition, seven injections of mercury at weekly intervals were administered to every case.

TABLE I.—Cases Treated and Doses.

Days of Treatment.	Intravenous Salvarsan Series. Doses of Salvarsan in Grams.	Subcutaneous Neo-salvarsan Series. Doses of Neo-salvarsan in Grams.
1st	0.3 to 251 cases	0.45 to 139 cases; 0.6 to 23 cases.
4th	0.3 "	—
8th	0.3 "	0.45 to 99 cases; 0.6 to 62 cases.
15th	—	0.6 to 161 cases.
22nd	0.4 to 251 cases	0.6 "
29th	0.5 "	0.6 "
36th	—	0.6 "
43rd	0.5 to 251 cases	0.6 "
50th	0.5 "	—
	2.8 grams to 251 cases.	4.2 grams to 22 cases. 4.05 grams to 40 cases. 3.9 grams to 99 cases.

The results obtained in the two hospitals agreed substantially with one another and have been combined. Table II shows the results obtained by the different methods of treatment in different stages of syphilis. The secondary cases in each series contained a substantial proportion of patients who had either suffered from syphilis for at least three months before commencing treatment, or, having been under treatment before, had relapsed. As is well known, such cases are much more difficult to influence from the point of view of the Wassermann reaction. Stage for stage, the cases in both series were, as far as possible, similar, but, if anything, the subcutaneous series contained a larger proportion of these advanced secondary cases.

A study of the table shows that in the primary and secondary stages the results were distinctly better in the subcutaneous series than in the intravenous.

With regard to the tertiary cases, the intravenous apparently gave slightly better results, but the number of patients treated was so small and the results so indifferent in each series that a judgement could be formed only from a much larger number of cases treated for a longer period of time.

In almost all of the subcutaneous series the Wassermann test was applied weekly, and Table III shows the results obtained one week after the fourth injection, and at the end of the course.

Table III is interesting in showing how much more quickly the Wassermann reaction is influenced in the primary than in the secondary and tertiary stages.

In 126 cases (including a number not mentioned in the tables because they had not completed the full course) the *Spirochaeta pallida* was found in one lesion or another before the first injection, and in 123 of these it could not be found twenty-four hours later, though no antiseptic had been applied to the lesion. In one of the cases where the spirochaete was found twenty-four hours after injection the initial dose was 0.3 gram, in another it was 0.4 gram, and in the third it was 0.6 gram. In no case were spirochaetes found forty-eight hours after the first injection. Spirochaetes are found in at least the same proportion of cases twenty-four hours after the intravenous injection of 0.3 gram salvarsan.

In some other cases we have failed to find spirochaetes after a subcutaneous injection of 0.2 gram neo-salvarsan.

We have similarly examined seventeen cases after intramuscular injections of galyi (0.3 gram in two cases and

TABLE II.—Showing the Wassermann Reaction after the Injection of 2.8 grams Salvarsan Intravenously and after the Subcutaneous Injection of 4.2 grams Neo-salvarsan, or Less, respectively.

Stage of Disease.	Method.	No. of Cases.	Wassermann Reactions at End of Course.							
			Actuals.				Percentages.			
			+	±	±	—	+	±	±	—
Primary ...	Subcutaneous ...	67	0	0	3	64	0	0	4.4	95.5
	Intravenous ...	79	3	6	4	66	3.7	7.5	5.0	83.5
Secondary ...	Subcutaneous ...	76	11	4	7	54	14.4	5.2	9.2	71.0
	Intravenous ...	141	35	16	8	82	24.8	11.3	5.6	58.1
Tertiary ...	Subcutaneous ...	18	10	3	1	4	55.5	16.6	5.5	22.2
	Intravenous ...	31	18	1	3	9	58.0	3.2	9.6	29.0

Interpretation of symbols: + = Positive reaction; ± = doubtful reaction, nearer positive than negative; ± = doubtful reaction, nearer negative than positive; — = negative reaction.

Notes.—22 received 4.2 grams neo-salvarsan (equivalent to 2.8 grams salvarsan); 40 received 4.05 grams neo-salvarsan (equivalent to 2.7 grams salvarsan); 59 received 3.9 grams neo-salvarsan (equivalent to 2.6 grams salvarsan). All cases in each series received one weekly injection of mercury gr. 1.

0.4 gram in the remainder), and have found the *Spirochaeta pallida* twenty-four hours after the injection in fifteen. In two of these cases spirochaetes were found after the second injection a week later, out of a total of four which received a second injection. In the remainder of the cases the course was continued with neo-salvarsan, and, owing to their comparatively feeble effect on spirochaetes, we have discontinued intramuscular injections of galyl.

Although clinical observations are not so valid for purposes of comparison, being open to the objection that they may be biased, we think it right to say that we early formed a strong impression that the subcutaneous injection of neo-salvarsan influenced syphilitic lesions more rapidly than did intravenous salvarsan. Our judgement in this respect may have some weight from the fact that our experience of the results of intravenous injections is based on some thousands of cases. We have now given over fifteen hundred subcutaneous or intramuscular injections of neo-salvarsan.

TECHNIQUE.

A disadvantage of subcutaneous or intramuscular injections is the pain and local swelling which they may cause, and we have been at some considerable trouble to eliminate these.

According to patients' accounts of it the pain was negligible in many cases. In others it caused considerable discomfort for a week or more, making the patient lame and preventing his sleeping on the same side. At its worst it was not nearly so severe as an injection of salvarsan, but might be compared to a bad mercurial or a calomel injection. In fact, a number of patients complained more of the mercurial injection than the arsenical. We have not been requested by any patient to change over to the intravenous method.

Methods Tested.

We think we have now succeeded in making the injections tolerably free from discomfort, but since others may

wish to improve on our technique an account of the methods we have tried up to date may assist them. They are as follows:

1.

Intramuscular injections in very small bulk. The remedy was dissolved in the ampoule itself in 10 to 15 minims of distilled water and injected into the gluteus medius muscle. This caused a fair amount of pain with some lameness afterwards. Accompanied, however, by a hypodermic injection of morphine gr. $\frac{1}{3}$ into a different site, it has generally proved almost as comfortable as any of the following.

2.

Deep subcutaneous injection of the same solution as in (1), the injection being made on to the fascia covering the gluteus medius muscle. This was on the whole less painful immediately afterwards but often caused the formation of a tender lump at the site of the injection some days later.

3.

Similar to (2) but preceded some hours previously by an injection of quinine and urea into the site. This was not a great improvement.

4.

Similar to (2), but the neo-salvarsan was dissolved in a saturated solution of chloretone. The later reactions from this injection were troublesome. Large swellings formed, and in three cases sterile abscesses followed. These were aspirated and the fluid examined. It contained leucocytes, but no micro-organisms or arsenic.

5.

Intramuscular and deep subcutaneous injections of concentrated solutions of neo-salvarsan emulsified in "creo-camp" cream of a melting point of 22°C. On the whole this was an improvement. There was pain for some hours afterwards, which kept the patients awake, but as a general rule the patients could allow the site of the injection to be massaged vigorously the following and subsequent days. The discomfort was rather less than that

TABLE III.—Showing the Wassermann Reaction after the Fourth and after the Seventh Injection of a Course of Seven Subcutaneous Injections of Neo-salvarsan.

Stage.	No. of Cases.	Wassermann Reactions.															
		Actuals.								Percentages.							
		After Fourth Injection.				After Seventh Injection.				After Fourth Injection.				After Seventh Injection.			
		+	±	±	—	+	±	±	—	+	±	±	—	+	±	±	—
Primary with negative Wassermann reaction	39	0	0	0	39	0	0	0	39	0	0	0	100	0	0	0	100
Primary with positive Wassermann reaction	28	10	1	5	12	0	0	3	25	35.7	3.5	17.8	42.8	0	0	10.7	89.2
Secondary ...	74	41	9	7	17	10	4	7	53	55.4	12.1	9.4	22.9	13.5	5.4	9.4	71.6
Tertiary ...	18	14	1	1	2	10	3	1	4	77.7	5.5	5.5	11.1	55.5	16.6	5.5	22.2

Symbols the same as in Table II.

which follows an intramuscular injection of galy. After a few days a dull aching pain was experienced which lasted for a week or longer.

6.

Similar to (5), but to overcome the immediate pain the injection was accompanied by a hypodermic injection of morphine into a different site. The results were successful in a few cases but on the whole uncertain, the later reaction being still rather troublesome.

7.

The solution of neo-salvarsan in glucose and stovaine solution with the addition of guaiacol, as recommended recently by Balzer and Beauxais-Lagrave.⁴ These authors recommend a dose of 0.2 gram neo-salvarsan at one time, and in this amount the injection is practically painless. The disadvantage is that the injections have to be repeated more frequently. In a dose of 0.6 gram the local reaction was rather similar to that of (5) and (6). It is claimed by the authors of the glucose, guaiacol, stovaine mixture that the neo-salvarsan in it remains unchanged though exposed to the air. We have injected it a week after our own preparation without untoward effect. A similar preparation of uncertain age which was supplied to us by Messrs. May and Baker in a convenient form, ready for injection, was safely administered three weeks after receipt. It shares with the creo-camph mixture the disadvantage that unless prepared in the syringe itself it is rather wasteful of neo-salvarsan, since a fairly substantial proportion of the mixture sticks to the sides of the mixing vessel, and more than the required dose has to be made up to allow of this.

8.

Injection of 0.6 gram neo-salvarsan dissolved in 1 c.cm. of a 4 per cent. solution of stovaine, and made up to 2 c.cm. with creo-camph cream melting at 15° C.* (Burroughs, Wellcome, and Co., special formula).

This has proved the most comfortable injection up to the present. In some cases it has been accompanied by a hypodermic injection of morphine gr. $\frac{1}{2}$. This has been sufficient to overcome the dull ache in the site of the injection, which may last for about six hours afterwards.

The solution is effected by dissolving the neo-salvarsan in the syringe, the creo-camph is added, and the mixture well shaken.

The injection is made about a point three finger-breadths below the crest of the ilium on a line joining the tuber ischii with a point on the crest of the ilium which is perpendicularly above the great trochanter when the patient is upright. The detached needle is driven into the muscle vertically to the skin.

The general reaction which follows an intramuscular injection of neo-salvarsan is much less than after an intravenous, and we have not experienced any cases of vasomotor disturbance—flushing, constriction of the throat and chest, etc.—such as sometimes follow an intravenous injection. The tonic effect is greater when the injection is intramuscular than when the remedy is administered intravenously. It will be remembered that in the early days, when salvarsan was administered intramuscularly, the tonic effect was a pronounced feature in all reports on the subject.

CONCLUSIONS.

1. The intramuscular or subcutaneous injection of neo-salvarsan, novarsenobenzol, or novarsenobillon is superior in immediate therapeutic effect to that of the intravenous injection of salvarsan, kharsivan, arsenobenzol, or arsenobillon.

2. Spirochaetes disappear from syphilitic lesions just as rapidly after the first intramuscular as after the first intravenous injection, and the Wassermann reaction is more quickly influenced.

3. Solution of the dose of neo-salvarsan in 1 c.cm. of 4 per cent. stovaine and emulsion in creo-camph cream eliminates discomfort sufficiently to make the intramuscular injection of neo-salvarsan practicable for routine use.

REFERENCES.

¹ Berl. Klin. Woch., March, 1914. ² Munch. med. Woch., March 10th, 1914. ³ Lehrbuch der Haut- und Geschlecht-Krankheiten, p. 417. ⁴ Le Bulletin Medical, February 17th, 1917.

* Since the above was written we have given a number of injections in which the creo-camph was replaced by campho-phénique, with, so far, encouraging results.

THE LIFE-HISTORY OF BACTERIA.

[WITH SPECIAL PLATES.]

BY

EDWARD C. HORT, F.R.C.P. EDIN.,

DIRECTOR OF THE CONSTANCE TROTTER RESEARCHES; HONORARY
PHYSICIAN TO THE ADDINGTON PARK WAR HOSPITAL; AND
DIRECTOR OF THE BACTERIOLOGICAL LABORATORY,
ADDINGTON PARK.

ACCORDING to current bacteriological theory the "lower" bacteria, whether living a parasitic or a saprophytic existence, are unicellular organisms which are only capable—apart, in certain cases, from endospore formation of a special type—of reproducing themselves by a simple process of transverse binary fission into two equal parts.

In previous publications¹ on the life-history of bacteria I have brought forward evidence which strongly suggested, if it did no more, that the life-cycle of certain of the "lower" bacteria is one of great complexity. From this evidence the conclusion was difficult to escape that under parasitic conditions simple binary fission is probably only one of many phases in the bacterial cycle, which includes an invisible, or almost invisible, filterable stage, and that this also applies to laboratory cultures of organisms of certain diseases. In passing, I may note that my observations in 1914 in typhus fever, and, later, in the same disease,* in cerebro-spinal fever, in scarlet fever, and in measles, as to the existence in the infected body fluids of filterable infective viruses, and of growth from these of non-filterable bacteria, have since been confirmed in the case of laboratory cultures of the azotobacteria by Löhnis² in the summer of 1916. This observer, however, has recorded no details of his filtration experiments, and does not state if his cultures were from single colonies, or from single organisms, or if he carried out direct observations of growth from single individuals on the warm stage.

In the present communication I propose to present further pictorial evidence of the complicated life-history of the enteric group of bacteria in so far as this can be studied in laboratory media as opposed to the more natural milieu of infected tissues and body fluids. And to morphological studies of the members of the enteric group I have also added observations on a single strain of a coliform bacillus.

The strains of organisms of the enteric group examined are as follows, their source being also indicated:

- B. typhosus*.—4 strains. Strain 1, Lister Institute. Strains 2, 3, 4, carrier strains, Addington.
- B. paratyphosus A.*—3 strains. Strain 1, Lister Institute. Strains 2, 3, carrier strains, Addington.
- B. paratyphosus B.*—5 strains. Strain 1, Lister Institute. Strains 2, 3, 4, 5, carrier strains, Addington.
- B. Shiga-Kruse*.—1 strain. Lister Institute.
- B. Y of Hiss*.—5 strains. Strain 1, Lister Institute. Strains 2, 3, 4, 5, carrier strains, Addington.
- B. Flexner*.—3 strains. Strain 1, Lister Institute. Strains 2, 3, carrier strains, Addington.

In Charts 1 to 8 will be seen the results obtained by study of dried film preparations from young cultures from single colonies, whilst in Chart 9, A, B, C, will be seen growth of living organisms from single individuals studied on the warm stage.

All the strains of organisms shown were obtained from the Lister Institute, except the coliform organism.

It is not possible to reproduce here evidence that the morphological results noted in the case of all the strains enumerated above are identical with the results shown in the drawings and photographs of the selected strains. I must be content, therefore, with stating that the essential results were the same in all cases, approximately 1,000 films having been examined. The organisms which I have chosen in order to illustrate my points here are the *B. typhosus* of Eberth, the *B. dysenteriae* of Shiga-Kruse, the *B. dysenteriae* Y of Hiss, and a bacillus of the coliform group.

In order to reduce the chances of error to the minimum, I have, in addition to rigid precautions against contamination to be described later, submitted each strain of the organisms of the enteric group to searching identification

* Microphotographic evidence of growth from filterable virus to non-filterable bacteria in typhus fever, together with experimental evidence of pathogenicity at each stage, as well as evidence of complexity of life-history of the enteric organisms, was presented³ to the Royal Microscopical Society in November, 1916.