THE ACTION OF SALVARSAN AND NEO-SALVARSAN ON THE WASSERMANN REACTION.

By J. E. R. McDONAGH, F.R.C.S.,

SURGEON TO OUT-PATIENTS, LONDON LOCK HOSPITALS, AND CHIEF ASSISTANT, SKIN DEPARTMENT, ST. BARTHOLOMEW'S HOSPITAL.

FROM the beginning of the salvarsan epoch the reports concerning the drug's action on the Wassermann reaction have been very conflicting. This is not surprising, as one had no knowledge as to the time that should elapse between stopping treatment and carrying out the test.

The current opinion for some time was to allow two months to pass from the last day of treatment, and as the majority of cases tested at this period gave a negative reaction, it was considered tentatively that one injection of "606" was sufficient.

Then the observation was made that some cases in the primary stage, giving a negative Wassermann's reaction before treatment, gave a position within a week after an injection, to become negative again two months later.

It was only when so many of these cases developed recurrences, with a reappearance of a positive reaction, that it was recognized that a negative reaction under such circumstances could only signify that the patient was in the latent stage.

Then Gennerich and Milian advised that the blood should be tested at frequent early intervals after each injection, and that so many injections should be given until the reaction was negative on each occasion. Having made some few hundreds of tests with blood withdrawn at frequent intervals after both salvarsan and neo-salvarsan, a brief survey of my results may be of interest.

Primary Stage.

In the primary stage, when the reaction is negative before treatment is commenced, most cases give a positive reaction after; which is most marked about the forty-eighth hour, but commences to show itself about the seventeenth hour. In some cases, on the other hand, the reaction does not become positive until the fifth day. Although it may remain positive for several days, the degree diminishes generally about the third week, till it becomes negative before the eighth. If the reaction is only slightly positive after the injection, it becomes negative much earlier. If the serum is tested in diminishing strengths, to estimate its reagin content, one can estimate how close to the secondary stage the patient is, and roughly how many subsequent injections will be necessary to produce a cure.

If the first injection gives rise to only a weak reaction, then three or four more will undoubtedly suffice to make the reaction permanently negative; if, however, the reaction is strong, then the patient is in the secondary stage, and will require at least 3 grams of salvarsan or neo-salvarsan before the desired effect is obtained.

CASE I.

Intra-urethral chancre, fourteen days' duration, six weeks after intercourse; slight inguinal adenitis; spirochaetes found.

No. of Injection and Result.	24 Hours After.	48 Hours After.	Fifth Day.	Tenth Day.	Fourteenth Day.
First injection ...	-	++	+++	+++	
Second injection (8th day after first) ...	+++	+	++		+++
Third injection (21st day after second) ...	+++	-	+++	+++	
Fourth injection (8th day after third) ...	+++	-	-	+	
Fifth injection (14th day after fourth) ...	-	-	+		
Sixth injection (8th day after fifth) ...	+	-	-		

The reaction was tested on the 7th, 14th, 21st, and 28th days after the last injection, and was negative on each occasion.

CASE II.

Two chancres on penis, two on scrotum; no adenitis; date of infection not clear; spirochaetes found.

No. of Injection and Result.	24 Hours After.	48 Hours After.	Fifth Day.
First injection ...	-	+	++
Second injection (8th day after first) ...	++	+	++
Third injection (8th day after second) ...	++	-	-
Fourth injection (8th day after third) ...	-	-	-

The reaction was tested on the 7th, 14th, 21st, and 28th days after the last injection, and was negative on each occasion.

CASE III.

Chancre, internal canthus of eye; adenitis, preauricular and cervical; date of infection uncertain; spirochaetes found.

No. of Injection and Result.	24 Hours After.	48 Hours After.	Fifth Day.	Tenth Day.	Seventeenth Day.
First injection ...	-	+	++		
Second injection (8th day after first) ...	+++	+++	++	+	
Third injection (17th day after second) ...	++	++	++		
Fourth injection (8th day after third) ...	+	-	-	-	++
Fifth injection (21st day after fourth) ...	-	-	-		

On testing the reaction on the 7th, 14th, 21st, and 28th days after the last injection, it was found to be negative on each occasion.

In the primary stage it is necessary to test the blood forty-eight hours and the fifth day after the first injection, and if positive on either occasion to repeat the injection on the eighth day. Then it is necessary to test the blood weekly and repeat the injections until the Wassermann's reaction is negative on the seventh day after the last injection. When this is the case the patient should only be passed when the blood remains negative, tested weekly, for another month.

Unfortunately, it is rare to get a case so early that the reaction does not become positive as the result of an injection. I have seen such, but think it wiser to give a second injection for safety, and a provocative injection six months or a year later.

Secondary Stage.

When the reaction becomes strongly positive after an injection, and in cases in which it is markedly positive before treatment is commenced, no blood tests need be made until before and after the fourth injection, as in my experience four injections are the minimum likely to be required to produce a permanent negative result.

CASE IV.

Chancre on penis, general adenitis, and headaches at night time.

No. of Injection and Result.	24 Hours After.	48 Hours After.	Fifth Day.
First injection ...	+++	+++	+++
Second injection (8th day after first) ...	+++	+	++
Third injection (8th day after second) ...	+	+	++
Fourth injection (8th day after third) ...	-	-	-

The reaction was also found to be negative on the 7th, 14th, 21st, and 28th days after the last injection.

CASE V.

A typical case of early generalized syphilis, rash, sore throat, etc.

No. of Injection and Result.	24 Hours After.	48 Hours After.	Fifth Day.
First injection	+++	+++	+++
Second injection (8th day after first)	+++	+++	+++
Third injection (8th day after second)	++	+++	+++
Fourth injection (8th day after third)	+++	+++	+
Fifth injection (8th day after fourth)	+	++	-
Sixth injection (8th day after fifth)	-	-	-
Seventh injection (8th day after sixth)	-	-	-

The reaction was also found to be negative on the 10th, 14th, and 28th days after the last injection.

Tertiary Stage.

In the tertiary stage the Wassermann reaction behaves much in the same way as it does in the primary and secondary, except for one peculiar phenomenon which is occasionally to be noted—that is, that a case with a strong positive reaction before treatment may become negative immediately after an injection and remain so from twenty-four to seventy-two hours, and then becomes quite positive again. On repeating the injection the same may happen, but more often it is quite the reverse—namely, that the reaction becomes more positive, an occurrence which is seen in the primary, secondary and latent stages.

CASE VI.

The patient contracted syphilis twenty-five years ago, for which he took mercury off and on for four years. For the past five years he had been troubled with cutaneous gummata, which disappeared under mercury and iodides, to quickly reappear after treatment was discontinued. In 1911 the patient had three intramuscular injections of salvarsan, and he came to me for a Wassermann test just after Christmas. There were no symptoms at the time.

No. of Injection and Result.	24 Hours After.	48 Hours After.	Fifth Day.
First injection	+++	+++	+++
Second injection (8th day after first)	+++	+++	+++
Third injection (8th day after second)	+++	++	+++
Fourth injection (8th day after third)	++	+	+
Fifth injection (8th day after fourth)	-	-	-
Sixth injection (8th day after fifth)	-	-	-

CASE VII.

A man, aged 42, contracted syphilis eighteen years ago, for which he was treated with mercury (pills) internally for three years. A few years later he was much troubled with headaches, which were only relieved by mercury and iodides, and the moment treatment was stopped the headaches commenced again. From time to time the patient had cutaneous gummata and some soft nodes (gummatous pericranitis) on his skull. When he came to me he had a gumma over his frontal bone which had eroded a portion of the external table; headaches were bad, and the patient complained bitterly of losing his memory.

No. of Injection and Result.	24 Hours After.	48 Hours After.	Fifth Day.
First injection	-	-	+++
Second injection (8th day after first)	+++	-	+++
Third injection (28th day after second)	+++	++	+++
Fourth injection (8th day after third)	+++	++	+++
Fifth injection (8th day after fourth)	+++	+	+++
Sixth injection (8th day after fifth)	++	+	-
Seventh injection (8th day after sixth)	+++	++	+
Eighth injection (8th day after seventh)	++	+	-
Ninth injection (8th day after eighth)	+	-	-

On testing the reaction on the 7th, 14th, 21st, and 28th days after the last injection, it was found to be negative on each occasion.

When arriving towards the end of treatment, and when all the reactions are negative, and in cases in which the amount of reagin is normally small—namely, cases of arterio-sclerosis, cerebro-spinal syphilis, syphilitic epilepsy, and hemiplegia—each serum should be tested in gradient increasing strengths.

When a serum is used stronger than normal, controls should never be omitted, showing that it has no haemolytic power on the sheep's blood corpuscles, an occurrence which is not at all uncommon, especially when the serum has been allowed to remain with its corpuscles for a few days. Therefore pipetting off the serum as soon as possible after the blood has been withdrawn is desirable.

It sometimes happens that cases nearing the end of treatment, for instance, after the fourth or fifth injection, give a weak positive reaction only between the third and fourth week, which becomes immediately negative within a few hours of repeating the injection. Therefore, before a patient is finally discharged, a test should be carried out between the twenty-first and twenty-eighth day after the last injection. Such cases usually only require one more injection before the treatment is complete.

Patients who have had syphilis and give a negative Wassermann's reaction are either cured or in the latent stage, which of the two can only be ascertained by giving a provocative injection of salvarsan and then testing the blood.

CASE VIII.

A man aged 29 contracted syphilis five years ago. The attack was very mild, but nevertheless the patient continued his mercury treatment (pills and injections) for four years. A recurrence never appeared. On three different occasions the blood had given a negative Wassermann's reaction, but the patient, being anxious to marry, was desirous of an injection of "606" to make things sure.

No. of Injection and Result.	24 Hours After.	48 Hours After.	Fifth Day.	Fourteenth Day.
First injection	+	+++	-	-
Second injection (8th day after first)	+	+++	++	-
Third injection (8th day after second)	+	+	++	-
Fourth injection (8th day after third)	+	+	+	+
Fifth injection (21st day after fourth)	-	-	-	-
Sixth injection (8th day after fifth)	+	-	-	-
Seventh injection (8th day after sixth)	-	-	-	-

The reaction was also negative on the 7th, 14th, 21st, and 28th days after the last injection.

If the previous treatment has been recent—that is, only a few months back—the appearance of a positive reaction may be delayed, or, as happened in several of my cases, was positive in the forty-eight hours blood, and negative again on the fifth or even third day, to become only definitely positive on each occasion after the second injection. I have had two cases in which the reaction was not positive at all until after the second injection—cases of arterial syphilis.

Not only is the reaction determined by the time of the previous treatment, but also largely by the quality of that treatment. If the treatment has been good, then the occurrence of a positive reaction may also be delayed, and only a few injections are required to produce a permanent negative reaction.

I have seen several patients who had been treated with mercury for three to four years, and who had given a negative Wassermann's reaction on several occasions, give a positive after a provocative injection of salvarsan, and require four to six injections before a permanent negative reaction was obtained. I doubt whether prolonged administration of mercury often cured a case of syphilis. It merely abolished symptoms, drove the patient into the latent stage, from which he might on any future occasion return to the active; or what still more often happened, insidious changes took place in his vessels, which could not be detected clinically until the arterio-sclerosis was

well advanced, or serologically because the amount of reagin circulating in the blood was too small to estimate.

An important group of cases belonging to this latent stage are women who have no symptoms, in whom the Wassermann's reaction is negative, but who, in spite of all, beget syphilitic children, and *ipso facto*, are themselves syphilitic. Such cases will, in my experience, give a positive Wassermann's reaction after a provocative injection of salvarsan, thereby indicating how necessary treatment is.

In cases of cerebro-spinal meningitis, in which the cerebro-spinal fluid gives a positive Wassermann's reaction, repeated injections of salvarsan will convert the positive into a negative reaction and at the same time cause the lymphocytosis to disappear. As the cerebro-spinal fluid is both weak in its reagin content and complement-fixing capacity, it should invariably be tested in increasing strengths.

I have recently had two interesting cases in which before treatment the Wassermann's reaction was negative in the blood and positive in the cerebro-spinal fluid, becoming positive in the former only after treatment.

From the foregoing it can be seen that there is a fallacy in the fourteen-day limit which is advocated now. Cases of latent syphilis, especially after the first injection, may give a negative reaction then and not appear positive on the fourteenth day until after the second injection. Further, cases of primary syphilis and cases nearing their end of treatment not infrequently give a negative reaction on the fourteenth day, but a positive between the seventeenth hour and fifth day, and, in my opinion, so long as an injection has the power of producing a positive reaction, whenever that may be, the disease is not eradicated—until the reaction is negative on every occasion tested.

As an injection of salvarsan will not give rise to a positive reaction in a non-syphilitic, one must regard the occurrence of such as indicative of the presence of disease, and efforts should be made to bring about a cure.

In the primary and secondary stages of syphilis this is possible, but in a large number of tertiary cases it is not, even nine injections being insufficient to change a positive into a negative reaction. Therefore, in the early stages of syphilis salvarsan should be used with the idea of curing the disease, and in some of the late stages of abolishing the symptoms only. This alone will show how imperative it is to diagnose and treat a case of syphilis as early as possible.

One most important point I have noticed in making these various tests—that is, that two individuals in exactly the same stage, with the same lesions, in the one a permanent negative reaction may be obtained after four injections, while in the other six or more may be required.

Another point: A permanent negative reaction is most easily obtained when the treatment is continuous, that is, when the injections of salvarsan follow closely upon one another and when mercury is given simultaneously. For instance, early cases of syphilis which were given one or two injections of salvarsan several months back, have required nearly the number given continuously as presumably would have been required had those previous injections not been given. Therefore, it is of the greatest importance, if a course is going to be started, that it should be persevered with until the desired effect is obtained.

Neo-Salvarsan.

As to neo-salvarsan, the most important point to estimate is whether it is more, or less, powerful than salvarsan. The ease with which it dissolves and the little disturbance following its employment would not alone warrant its use in preference to salvarsan; it must be proved to be more potent in its action.

If films from a primary sore are made at frequent intervals after an injection, and in one case the spirochaetes are found to be absent after seventeen hours, and in another after twenty-four hours, no conclusions can be drawn if the former is found to be the case after neo-salvarsan and the latter after salvarsan, since the time required to kill the spirochaetes varies enormously, and the variation is no doubt caused by the fibrous tissue in the induration preventing a thorough permeation with the drug.

The only means by which one can compare neo-salvarsan with salvarsan is through the medium of the Wassermann's reaction.

I first of all employed weekly injections of neo-salvarsan and tested the blood twenty-four hours, forty-eight hours, and the seventh day after last injection, and found that a negative reaction was obtained after fewer injections, and that some of my tertiary cases which failed to give a negative Wassermann's reaction after seven injections of salvarsan, quickly became negative on using neo-salvarsan.

As my observations of the influence of treatment on Wassermann's reaction have shown me how necessary it is to give the injections following upon one another as soon as possible, much better results are likely to follow neo-salvarsan than salvarsan, because two maximum doses of the former can be given weekly without any ill effect, or three smaller doses. I have used neo-salvarsan—1 gram of which corresponds to 0.6 gram salvarsan—twice weekly, employing doses from 0.9 gram to 1.5 gram, and three times weekly with smaller doses, in all over 200 injections.

When two injections weekly are given the Wassermann's reaction should be tested in the blood withdrawn on the day of injection, and so many injections given till the last blood test is negative. Then the blood should be tested seven, fourteen, twenty-one, and twenty-eight days later. This should also be done when three injections weekly are given.

CONCLUSIONS.

Taking all stages of syphilis, I have found that three to seven injections are necessary to cure most cases of syphilis.

There is no doubt that many cases in the tertiary stage can be cured with neo-salvarsan which failed to be cured with salvarsan.

Liable to change as these conclusions may be, I cannot but admit that the alterations in the Wassermann's reaction as the result of treatment are most constant, and that when tested at short intervals give a much safer guide to regulate treatment than by saying that just so many injections will be required, or, as the old syphilologists used to teach, that a three years' pill treatment was sufficient for all cases alike.

As there is a possibility of fallacy, I advise my patients to have a provocative injection of neo-salvarsan six months or a year after they have been discharged, and the blood tested forty-eight hours, the seventh, fourteenth, twenty-first and twenty-eighth day after that injection. I might finally add that all my cases for some months past have had three to nine injections of salvarsan, given at seven to fourteen days' interval, or three to seven injections of neo-salvarsan, given at not more than seven days' interval, with not a single bad manifestation or a recurrence of symptoms.

THE X-RAY TREATMENT OF GRAVES'S DISEASE.

By WILLIAM H. HOOTON, M.R.C.S., L.R.C.P.,

LEEDS.

THE numerous remedies, ranging from fresh air and forced feeding to a severe surgical operation or the quasi-specific treatment by serum or milk of thyroidectomized animals, indicate by their very multitude the generally unsatisfactory nature of the treatment of exophthalmic goitre. But it is beginning to be seen that we have in the x rays, properly applied, a therapeutic agent of efficacy in the relief of this disease. The Roentgen rays affect the tissues as follows: After a dose has been administered there is a latent period of several days during which no change can be made out; then, if the dose has been a small one, there is increased secretion from glands and increased activity in other structures—for example, the amount of sweat increases and hair grows more rapidly for a time. A full dose, on the other hand, paralyses cell activity, the hair falls, and glandular secretions are diminished. A still larger dose causes inflammation of the superficial structures, which may go on to necrosis, leaving an ulcer often very slow to heal. It is obvious, therefore, that the quantity of rays given must be accurately measured.

It is generally agreed that the symptoms of Graves's disease are due, at least in the first instance, to an unduly great outpouring of the result of thyroid activity into the blood stream. If, then, by administering suitable doses of