SIXTEEN MONTHS' EXPERIENCE OF SALVARSAN.

BY

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We have been using salvarsan since October, 1910, when Professor Ehrlich kindly placed some at our disposal for experimental purposes. From the first we have been much impressed by its effect on syphilitic lesions, and we venture to present the following synopsis of our results.

We have treated altogether 92 patients, almost all of whom were private patients. Eleven of them received two injections, and one patient three injections, making a total of 105 injections in all. Seventy-four of our patients received intravenous injections, and 18 were treated intramuscularly. Of the latter, 5 received an injection of the neutral emulsion, and in 13 the salvarsan was injected rubbed up in sterile olive oil.

Of the 11 patients who had two injections, 8 had two intravenous injections, 1 had two intramuscular administrations, and 2 had an intramuscular and an intravenous injection. One of these had an intramuscular injection in neutral emulsion, followed ten months later by an intravenous dose; and the other had an intravenous injection, followed about eight weeks later by an intramuscular injection in oil.

The patient to whom we administered three injections received them all intravenously.

The Sex of the Patients and the Stage of the Disease.

Eighty-three of our patients were male and 9 female; 41 were in the primary and secondary stages, 45 were in the tertiary stage; there were 2 cases of incipient general paralysis of the insane, 2 of locomotor ataxia, 1 of sclerosis of the cord following transverse myelitis, and 1 of congenital syphilis.

Dosage.

As a rule we administered a full dose of 0.6 gram; 5 of our patients received 0.5, 4 received 0.45 gram, for the initial dose; one 0.4 gram, and 9 received an initial dose of 0.3 gram. Of those receiving two doses, 7 received 0.6 followed by 0.3, one received 0.45 followed by 0.3, three received 0.6 followed by 0.6 gram. The patient who received three injections had 0.3 gram on each occasion.

The Reaction.

Intramuscular injections in neutral emulsion are very painful, and require to be followed by the administration of morphine. Intramuscular injections in oil are not very painful at the time of administration, but in three or four days there is sometimes considerable swelling with redness and tenderness on pressure over the site of the injection.

There has been much discussion as to the reaction which follows an intravenous injection. We have fortunately never seen any of these alarming reactions of which so much has been made by some of the critics of salvarsan, and we attribute our immunity to the careful preparation of our patients, the technique of the administration, the after-treatment of the patient, and the fact that we make our solution with saline solution freshly prepared and sterilized immediately before each operation.

The evening before treatment each patient receives a purgative; in the morning breakfast is restricted to a cup of tea or cocoa and a slice of toast, and about five hours afterwards the dose is administered. After the injection the patient is returned to a warm bed and receives nothing except a sip of water for four or five hours. By following this line of treatment we have found that some of our patients have had no reaction at all more than a little sickness or a slight looseness of the bowels. We still hold that in some measure the reaction is related to the acuteness of the disease, and we should expect a patient with a florid secondary eruption to give a more severe reaction than an old tertiary case with an ulcer of the leg; but we have never seen any of these fulminating reactions with

frequently repeated rigors, hyperpyrexia, and profound and alarming prostration.

Elimination of Arsenic.

After an intravenous injection arsenic is discoverable in the first urine voided. A dose of 0.3 gram administered intravenously disappears completely from the urine on an average in four to five days, while a full dose of 0.6 gram is eliminated in from seven to nine days. Some of the arsenic is undoubtedly eliminated by the gastro-intestinal mucosa, as we have discovered it in the stomach contents after vomiting.

In comparison with this rapid elimination the persistence of arsenic in the system after an intramuscular injection is very remarkable. We have found definite traces of arsenic in the urine of a patient twelve weeks after an intramuscular dose of 0.3 gram in olive oil. In this case the patient was a man of feeble physique and slow metabolism, but in all cases we have found that whereas a dose of salvarsan given intravenously is rapidly discharged from the system, the disappearance of an intramuscular dose is a matter of weeks, and may be months.

The Effect on the Lesions.

Primary Sore.—In some cases the effect on the primary sore is almost immediate, there being a definite improvement visible the day after the injection. An ulcerated chancre will cicatrize in from four to seven days, but if the chancre is a large one and the induration very considerable, ten to twelve days may be required for its healing. In some cases the induration will persist for a few weeks after an injection, though the superjacent and surrounding tissues appear normal. In all cases our experience has been that the primary sore is more rapidly influenced by salvarsan than by mercury.

Secondary Lesions.—The effect of salvarsan varies with the nature and type of the secondary lesion. The roseolar eruption will disappear within a week after an intravenous dose, and we have seen an almost equally rapid result follow an intramuscular dose. The maculo-papular eruption, however, recedes somewhat more slowly, but, as a rule, has disappeared in from ten to twenty-one days. No lesions yield more quickly than the mucous patch and the condyloma. Many mucous patches will disappear from the buccal pouches and the isthmus of the fauces in forty-eight hours, and condylomata will wither up in two to three days. The characteristic headache of the secondary stage vanishes in most cases within twenty-four hours; but in a recent case of a young lady with an extragenital chancre there was an attack of periostitis of the frontal bones three days after the injection. The generalized adenitis is the slowest of the secondary symptoms to recede; it may persist for several weeks after all other outward symptoms have disappeared.

Tertiary Stage.—In this stage salvarsan is of great value, and will cause ulcers that have resisted the action of mercury and the iodides to heal up rapidly. For this reason it has been suggested, especially by the French school, that salvarsan is a cicatrizing rather than a spirillicidal agent. But the truth probably is that it combines both properties. The difficulty of causing advanced ulcerative processes in the mouth and throat to yield to treatment is well known. Here salvarsan is of supreme value, and among the cases which we shall quote shortly we have a remarkable example of this fact. Syphilitic affections of the organs of special sense are also much benefited by salvarsan. Two of our cases had syphilitic iritis at the time of injection, and quickly got rid of it; while in one case there was an extraordinary improvement in the hearing of a patient, who, the day after the injection, was able to hear the church bells, which she had been unable to do for many months before. Unfortunately, however, this improvement was not permanent.

Parasyphilitic Disease.—Our experience has been that salvarsan can produce a marked amelioration of symptoms. In the two cases of incipient general paralysis we have treated there was for a time an improvement in the speech of the patients, but this was not maintained. One of the patients was able to return to work for several weeks after receiving an intravenous injection, but he subsequently relapsed. In tabes, salvarsan has in our experience of two cases been more effective, and has caused the disappearance

of lancinating pains, gastric crises, and at the same time improved the patient's power of balancing himself.

We are not sanguine enough to persuade ourselves that salvarsan can restore to its original condition a degenerated neuron; but there is no remedy known to us which has that beneficent property, and the impotence of salvarsan in this direction is not peculiar. But we are convinced that if every case of syphilis in its early stages were treated vigorously with salvarsan there would be fewer patients who would drift into the living death of general paralysis or the crippling ataxia of tabes.

The Effect of Salvarsan on the Wassermann Reaction.

In the Wassermann reaction we have a guide of considerable value as to the adequacy of antisyphilitic treatment. In some cases a single full dose will convert a positive into a negative reaction in three weeks to a month from the time of its administration.

In one of our earliest cases, where the patient received 0.45 of a gram intramuscularly, the Wassermann reaction became negative and remained so for nearly nine months. During these months the patient had no other treatment but was kept under regular observation. A clinical relapse, evidenced by some periostitis, coincided with a return of the reaction to positive. He then received an intravenous injection of 0.6 gram followed by a series of intramuscular injections of grey oil, and the Wassermann reaction became negative again.

In some cases a single injection of salvarsan will not convert a positive into a negative reaction, but a second injection will bring about this change. In our experience a rapid change from the positive to the negative is more likely to occur if the patient, in addition to salvarsan, has had either a preliminary or a subsequent course of vigorous treatment with mercurial inunction or injections. This fact supports the practice which we invariably follow now—namely, a combined treatment with salvarsan and mercury.

The General Effects of Salvarsan.

As salvarsan is an arsenical compound we would expect to find its administration followed by some of the tonic effects of that drug, and our experience has been that there has always ensued a considerable improvement in the patient's general health. The skin becomes clearer, the lips and conjunctivae become more red, and there is almost always an increase in the patient's weight and a remarkable sense of well-being.

Contraindications.

We have denied salvarsan treatment to only two patients who were referred to us for treatment. One was a case in which severe glycosuria complicated the syphilitic condition, and the other was a patient with an extensive weeping eczema.

We have administered it, of course with all due precautions, to two patients with well-compensated mitral incompetence, to two pregnant women, and to a patient passing 5 grains of sugar in the ounce of urine. These patients did not cause us an extra amount of anxiety, and were all greatly benefited by the treatment.

Dangers.

There is an unfortunate idea about, even in professional circles, that salvarsan is a very dangerous remedy, whose use may lead to fatal results and serious disaster to the optic nerve. Like all potent remedies, salvarsan, if improperly administered, may bring about death; but we are firmly convinced that the dangers of its use have been grossly exaggerated. It is a hard thing to suggest that international politics can produce prejudice against a scientific discovery, but we cannot forget that reports of disaster from the use of salvarsan emanated from France before a single dose of salvarsan had been administered in that country. And, further, more fatal accidents would seem to have followed its use in France than anywhere else.

The fatal accidents have been due either to large overdoses, the choice of unsuitable cases, or errors in technique.

In the first 40,000 injections there were 23 deaths, or 0.05 per cent. It has been estimated by Browning and Mackenzie that over one million doses have now been administered, and the mortality per cent. is infinitesimal.

As with the administration of anaesthetics, so with salvarsan: careful administration reduces the danger to a minimum; careless or haphazard administration means disaster. The consensus of the best recent opinion is that salvarsan has not the slightest deleterious effect upon the optic nerve.

The Question of Relapses.

Syphilis is a disease which, under any form of treatment, is characterized by long periods of quiescence and unexpected relapses. Of the cases we have treated, excluding those in which the nervous system was affected, three only have shown any further symptoms after the injection of salvarsan. These facts alone we regard as a proof of the supreme value of the remedy as an antisyphilitic.

Since June of last year we have followed the routine practice of reinforcing the action of salvarsan by following it with a course of inunction with mercury or the intramuscular injection of grey oil. Our reason for this was not any distrust of the remedy, but a recognition of the principle that in dealing with a serious malady, such as syphilis, it is best to make assurance doubly sure. It must not be forgotten that a spirochaete may be lodged in a thrombosed blood vessel or surrounded by fibrous tissue in such a way that an intravenous dose of salvarsan cannot reach it. This spirochaete may lie dormant for a long time before resuming activity, but if the salvarsan injection is followed by mercurial treatment the mercury may ferret out the concealed micro-organism and destroy it. We regard the combined treatment as the best.

General.

Every case treated has responded to salvarsan. In only one—a case of ulceration affecting the cartilage of the nose—was this response delayed. In this case we had given an intramuscular injection in oil, and absorption was very slow; but on administering potassium iodide, which had been previously given without result, there was a rapid improvement, and a second intramuscular injection completed the healing process.

In two cases there was a very slight herpetic outbreak after the injection. One was after an intramuscular injection in neutral solution, and was characterized by the appearance about three weeks later of a few abortive herpetic vesicles in the temporal region. The other occurred about a week after an intravenous injection and affected the chin. It also was very slight.

The following cases will suffice to indicate the remarkable properties of salvarsan:

CASE I.

A ship's captain, aged 51, sent by Dr. Popert, of Southport. Primary infection twenty-seven years ago. When seen by us he had been suffering from extensive ulceration of palate and throat for nearly a year. He had had much treatment with mercury and potassium iodide, and in January, 1911, had received in London an intramuscular injection of salvarsan.

On examination he presented the appearance of a man in the last stages of malignant disease. He was much emaciated, his complexion was a dirty sallow colour, his lips were pale, and he was extremely feeble. The fetor of his breath was intense, and pervaded the whole room. There was extensive ulceration of the palate and posterior pharyngeal wall. Swallowing was extremely painful.

On September 11th, 1911, he received an intravenous injection of 0.6 gram of salvarsan. The following day he expectorated a piece of necrosed bone measuring about 1 in. by $\frac{3}{4}$ in. On September 13th the ulceration of the palate had assumed a healthier appearance, he could swallow with more ease, and felt better. On this day we excised the encapsulated remainder of the intramuscular injection which had been administered in London eight months before. This consisted of a mass of necrosed tissue situated between the inner border of the left scapula and the vertebral column. It measured about 3 in. by 2 in., and the walls of the capsule, which consisted of necrotic muscle fibres, were about $\frac{3}{4}$ in. thick. The contents of the cavity were 1 to 1½ drachms of emulsion of salvarsan. This case illustrates one of the disadvantages of the intramuscular method of injecting salvarsan, and the fact that the salvarsan emulsion was lying encysted there explains why he had derived little, if any, benefit from that injection. The following day he passed out of our care into that of Dr. Popert, who kindly reported on November 23rd that the patient had made an uninterrupted recovery, the ulceration of the palate and pharyngeal wall had healed, the only defect being a tiny hole through the soft palate.

This was a case in which both mercury and potassium iodide had failed, and where salvarsan, too, had been administered without benefit through encapsulation of the

injection. We believe that in this case the intravenous injection of salvarsan saved the patient's life.

CASE II.

A doctor, aged 34, sent to us by Mr. Craig Dun. The primary infection was in January, 1908, and, in spite of treatment carefully carried out from the beginning, there was early ulceration and repeated relapses. He had been treated with hydrarg. cum creta by the mouth and intramuscular injections of grey oil in the most thorough fashion, but, in spite of this, his history was one of constant relapses, and from the time of infection he was rarely free from some manifestation of the disease. He was referred to us in March, 1911. His chief symptom then was nocturnal headache, sufficiently severe to prevent him from sleeping, with boring pains in the bones of the face, also worse at night. He gave a well-marked positive Wassermann reaction.

On March 27th, 1911, at 12.30 p.m., we administered an intravenous injection of salvarsan. He kindly made notes for us of his subsequent progress, from which a quotation may be of interest:

"At 6 p.m. and 9 p.m. the bowels were moved. The usual headache, which started between 8 p.m. and 10 p.m., never arrived, and I fell asleep waiting for it. March 28th. Woke this morning with sense of relief; ate breakfast, and swallowed with no discomfort whatever."

It seems almost like a fairy tale, but from that day till December, 1911, when we last saw the patient, he had no further headache nor any other symptoms of syphilis. In May he gave a negative Wassermann reaction, but it had changed to a slight positive in December, 1911, and on that account we gave him another full injection of 0.6 gram.

He promised to let us know at once should there be any further symptoms, and, as we have not heard from him, we take it no symptom has appeared.

CASE III.

A ship's captain, aged 43. Primary twelve years ago, and had had no objective symptoms for eleven years. About fifteen months before he was seen by us he had a temporary paresis of the right arm and of his speech centre. When seen by us in October, 1911, the knee-jerks were absent; he had lancinating pains in the legs, the Argyll Robertson pupil, and the other cardinal symptoms of locomotor ataxia. Wassermann reaction positive. On October 21st he received an intravenous injection of 0.6 gram.

On October 25th he volunteered the statement that he felt much better, and was more certain of his legs. He had had no lancinating pains since the day after the injection. He had to return to sea, and was instructed to carry out mercurial inunction. On December 27th he returned, and reported that he felt very much better. He had lost all pains in the legs, though there had been a slight return after he had been exposed for forty-eight hours on the bridge in a storm. His speech had improved, his gait was better, he had more control over his limbs, and said "he could dance the Highland fling." Wassermann reaction being, however, still positive, we gave him on January 2nd, 1912, another injection of 0.6 gram.

CONCLUSIONS.

1. In salvarsan we have a unique and potent remedy for the lesions of syphilis.
2. It is a remedy that is efficacious at every stage of the disease.
3. It can bring about healing in lesions that have resisted mercury and the iodides.
4. The ideal treatment is a combination of salvarsan and mercurial treatment, beginning with an intravenous injection of salvarsan, and following it with vigorous mercurial treatment, and, if necessary, repeating the salvarsan injection. Treatment should be controlled throughout by the Wassermann reaction.
5. If properly administered to suitable patients there is no more danger attendant upon the administration of salvarsan than on the use of any other powerful remedy.
6. The intravenous injection is better than the intramuscular one.
7. Though Ehrlich's original idea of accomplishing the complete destruction of every spirochaete in the body by a single injection has not been fulfilled, he has given us in salvarsan the most powerful antisyphilitic remedy that has been discovered in our time.

THE Australian Institute of Tropical Medicine has been granted an increased endowment by the Commonwealth Government. A grant of £4,000 a year has been made from January 1st, 1912. This will permit the immediate erection of new laboratories and the enlargement of the staff, thus enabling the institute to widen the scope of its work.

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CASES OF CHRONIC PURPURA WITH AND WITHOUT CUTANEOUS LESIONS.*

BY

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THE existence of purpura haemorrhagica as an acute transient disease is well known and recognized. Another type—a chronic form in which the lesions continue for months or relapse again and again—has attracted less attention among English writers,† and it is the object of the following paper to record three of these rarer cases.

The occurrence of such cases has been recognized, particularly by French physicians, ever since a paper on the subject by Racle in 1844.¹ Bensaude and Rivet, who had been making observations for some years, summed up their experience in a most excellent paper in 1905.² They recorded the histories of 14 cases personally observed, and of 20 other cases which they had collected from medical literature. The continued form is the rarer, the intermittent the more common; in the latter the attacks are sometimes preceded for months or years by frequent isolated haemorrhages. The duration of such cases may be as great as twenty years, and the intervals between the crises may vary from a few months to, in one case, seventeen years. The termination is variable; 5 of Bensaude and Rivet's own cases and 4 of those they collected ended in death.

As regards diagnosis, Bensaude and Rivet point out that whereas haemophilia is congenital and hereditary, chronic purpura haemorrhagica is neither. In haemophilia the blood shows a considerable diminution in coagulability, but the clot once formed contracts; in chronic purpura haemorrhagica coagulation takes place normally, but the clot does not contract. Further, in haemophilia there is no considerable diminution in the number of blood platelets; in purpura haemorrhagica this is a marked feature.

E. H., aged 46, was admitted as an in-patient at the Bristol Royal Infirmary on January 24th, 1902, under the care of Dr. Shingleton Smith, to whom I am indebted for permission to record the case. She was suffering from pains in the stomach and limbs and bleeding from the mouth. There was no family history of bleeding. Fourteen years previously she had had bleeding from the mouth and a purpuric rash on the skin, an attack which came to an end in about a week. Since that time she had repeatedly suffered in the same way, having had, as far as she could remember, an attack every year. The present one had begun two days previously with bleeding from the nose and mouth, and spots on the trunk and limbs. On examination, it was found that there were numerous discrete purpuric spots scattered over the whole surface of the body; they were mostly small, but on the deltoid region of the right arm many confluent spots made a discoloured area as large as a five-shilling piece. Numerous petechiae were present on the inner surface of the lips, on the fauces, and on the posterior pharyngeal wall. There was no vomiting, and no blood with the motions. The abdomen was normal and the liver and spleen were not enlarged. The urine contained a trace of albumen, but no blood. No fever was present. The patient rapidly got well, and went out in a little over a week. I have ascertained lately that the attacks recurred at intervals during the following five years and then ceased. The disease thus lasted for nineteen years.

J. B., aged 17, was admitted to the Bristol Royal Infirmary under my care on October 3rd, 1904, suffering from pneumonia of four days' duration. No previous illness of any note had occurred; and, in particular, he had never suffered from bleeding, nor was there any family history of bleeding. The lower lobe of the left lung was found to be consolidated. The temperature fell by crisis on the seventh day, and the pulmonary condition rapidly cleared up. During the fever the urine contained a trace of albumen, but no blood. On October 10th the boy vomited, had pains in the cervical region of the spine, and was found to be unable to straighten either arm—a condition caused apparently by contracture of the flexors of the elbow-joints. The biceps and triceps jerks could not be obtained, the knee-jerks and plantar reflexes were normal. The flexion of the arms lasted a week, until October 17th, and then slowly disappeared. On October 23rd an extensive purpuric eruption appeared on the legs and thighs, and the lower end of the right thigh became tender on palpation, but was not swollen. No leucocytosis was present. On October 25th there was some abdominal pain and vomiting, and the urine became smoky in colour and contained blood corpuscles. No renal casts were present. The purpuric rash slowly faded, no fresh spots appeared, and the urine contained, day by day, less blood, so

* A paper read at a meeting of the Bath and Bristol Branch on October 25th, 1911.

† For example, it is not mentioned by Mackenzie in Allbutt's System.