THE TREATMENT OF SYPHILIS BY SALVARSAN (DIOXY-DIAMIDO-ARSENO-BENZOL).

OBSERVATIONS UPON FORTY-FOUR CASES.

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SINCE November 28th, 1910, I have treated 44 selected cases of syphilis with the Ehrlich-Hata preparation. These include, for the most part, cases of chancre alone, cases of chancre *plus* early secondary manifestations, secondary lesions, and 11 tertiary lesions. Thirty-four cases were treated by the intramuscular injection of a neutral suspension of the drug, 10 cases by the intravenous method.

CASE I.—A male, aged 40, with a primary chancre of penis, "bullet" buboes in groin, a papular rash over the trunk and limbs, and a number of mucous patches in the mouth. Spirochaetes were present. This, the first case treated, was given a small dose, 0.4 gram, injected into the buttocks, half into each side. The chancre showed signs of softening within twenty-four hours; in forty-eight it was markedly diminished in size. The rash began to fade on the fourth day, and by the twentieth day had completely disappeared; the chancre had gone by the seventh day.

CASE II.—This patient was injected with the remainder of the capsule, amounting to 0.2 gram. A male, aged 28, with large ulcerating chancre, shotty glands in groins (spirochaetes had been previously demonstrated). Within a week the chancre and glands had entirely disappeared. The patient was discharged on the fourteenth day.

Following these, a number of other primary cases were treated with full doses of salvarsan (0.6 gram). The result was consistently the same as regards the gross primary and early secondary symptoms, as instanced by the rapid disappearance of the chancre, and of the adenitis, and the healing of the mouth and throat lesions.

A number of secondary cases were now treated, with similar success—condylomata, mucous patches, ulcers of the fauces, venereal warts on the vulvae, etc., disappearing with wonderful rapidity.

The effect on the rash on all our cases injected intramuscularly has not been so striking as on the more localized lesions; it tends to fade slowly, there being no appreciable diminution until the fourth or fifth day, or later. In two cases in which a full dose was given, an increase in the intensity of the rash was observed some twelve hours after the injection. Herxheimer has noted this in some cases, and attributes it to too small dosage.

The tertiary lesions treated included many gummatous ulcerations of the skin, a syphilitic infiltration of the lips, producing great thickening and induration, with stenosis of mouth, and a perforating ulcer of the hard palate.

It would be wearisome and unnecessary repetition to fully detail each case, but notes on a few of the more striking ones may be interesting.

CASE VII.—Male, aged 37, was admitted to the Lock Ward at Brownlow Hill Infirmary on August 7th, 1910, with a primary chancre of penis, contracted in May, 1910. He had been continually on mercury and iodides up to the beginning of November, when mercurial treatment was stopped, owing to salivation and general debility. The chancre had then disappeared, but he was still covered with a deeply pigmented papular rash. There were several superficial ulcers on the soft palate and fauces. His voice was hoarse and rasping; he was unable to swallow solid food, owing to pain from involvement of the lower part of the pharynx in the ulcerative process. In addition he suffered from stomatitis and soreness of the gums, with marked emaciation.

On December 15th he was injected with 0.6 gram of salvarsan. In forty-eight hours there was a marked improvement in the voice. The patient volunteered that he could speak and swallow without pain or difficulty. The rash began to show signs of fading on the sixth day. He put on flesh rapidly, and the ulceration of the mouth and fauces disappeared. In three weeks the rash had entirely gone, except for some deep-seated pigmentation, and he was discharged on January 21st and resumed his work as a labourer.

CASE XXXI.—Male, aged 38, had a number of healed scars on the trunk and limbs, periosteal nodes on the tibiae, and a marked gummatous infiltration of the lips. The condition had been present for nineteen years, the patient undergoing nine operations at various hospitals in London and the provinces, in order to overcome the contracture produced by a general thickening around the mouth. He had been on mercury and iodides for months at a time, with no benefit. His speech was greatly interfered with, both lips being greatly thickened and uniformly indurated.

On December 29th, 1910, 0.6 gram of salvarsan was injected into the muscles of the buttock. In a few days a marked softening of the tissues was evident. The lips began to be more pliable and elastic, and to diminish in size. As this proceeded, various operation scars became evident, two of which formed tight bands at each angle of the mouth. The orifice of the latter became more patent, and the patient was able to show his teeth. These bands have now been divided by operation, and the patient can use his mouth for all normal purposes.

CASE XXXIII.—Male, aged 29, contracted venereal disease in the army, 1900; he had suffered from ulcers on the right leg since May, 1910. He had had no previous treatment. There were two extensive serpiginous, deeply excavated ulcers on the lower third of the leg, the floor showing the usual yellow slough. These ulcers were surrounded by four smaller ones of a similar nature.

Injected on February 3rd intramuscularly with 0.6 gram of salvarsan. Signs of healthy healing were evident in a few days, and on February 21st the crater-like cavities had entirely filled up, and the growing edges of the skin completely fused. The leg is now entirely healed over (February 23rd).

CASE XXXVIII.—Female, single, aged 46, had had ulcerated legs for the past two and a half years. She gave no history of syphilis, but examination shows a very extensive irregular ulcer on the outer side of the right leg, surrounded by eight smaller ones in shape and appearance typical of a syphilitic lesion. There were no other evidences of syphilis.

Injected intramuscularly on January 21st, 1911, with 0.6 gram of salvarsan. Complete healing resulted in four weeks' time. This patient was in hospital for twelve weeks eighteen months ago for the same complaint, but left before healing took place.

It would perhaps be unwise to draw any definite conclusion at this early stage, but I can certainly, and without exaggeration, state that in all the cases treated by us with salvarsan it has been our experience, as regards the primary lesions treated, to see rapid improvement, with complete disappearance of the chancre in *all* cases before the fourteenth day, and in most cases earlier than this. Secondary manifestations have also disappeared very rapidly.

Nearly all the tertiary cases have shown marked improvement, gummatous ulceration of the skin, lesions of mucous membrane of the mouth, etc., healing in a most satisfactory manner. In only one case has the reaction been somewhat disappointing—a case of perforation of the hard palate, the necrosis extending to the septum nasi. This looks much healthier than before, but the necrosis of the septum still persists, and a further injection has recently been given.

Furthermore, in a number of the most chronic cases which had been under mercury and iodides for months with no perceptible improvement, the injection of salvarsan has been followed by rapid reaction. Almost immediately the chronic lesions seem to assume a healthier look; healthy granulations spring up; deep crater-like ulcers of the skin fill up from the bottom, with a rapid ingrowth from the margins, the patient puts on flesh rapidly, and the general metabolism improves. How much of this may be due to "suggestion" time alone can tell.

With regard to the choice of methods—intramuscular or intravenous injection—we have had as good results with the former as with the latter in the tertiary stages. In the primary and early secondary stages the intravenous method produces a more rapid disappearance of the lesions.

The intravenous injection has been performed in nine cases by exposing one of the veins near the elbow by dissection under cocaine, the cannula being introduced well into the lumen of the vessel. In the last case, as the veins were prominent and the skin thin, the needle was inserted directly into the vein.

The solution must be prepared with great care.

Fifty c.c.m. of sterile normal saline solution, made from distilled water is put into a graduated sterile flask of 500 c.c.m. capacity; to this the salvarsan is added, and a yellow solution results on shaking. A 15 per cent. sterile solution of sodium hydrate is now added, drop by drop, at first producing a precipitate, the flask being vigorously shaken from time to time. When from 25 to 30 drops have been added a golden yellow solution results. This is diluted up to 400 c.c.m. by the addition of more saline and is ready for use. The solution is kept at a temperature of 104° to 105° F.

We have used, up to the present, the ordinary transfusion apparatus, but Messrs. Sumner and Co. are making for me a special vessel on the principle of the Dewar's flask, which will retain an even temperature for some considerable time.

A column of normal saline solution is first allowed to flow into the vein, followed by the solution of "606," which is strained through sterile gauze. Finally, saline is again allowed to flow.

By this method no portion of the solution can enter the tissues at the point of injection.

It is important that distilled water should be used for making the solution. Tap water produces a fine suspension. We have had no untoward occurrences. There is always a rise of temperature followed by headache and vomiting, and in some cases rigors and diarrhoea.

The condition of the patient is a cause for anxiety at first, but within twenty-four hours all symptoms clear up. In men 0.4 gram, and in women 0.3 gram doses diluted in saline solution have been given.

The intramuscular method has the disadvantage that great pain follows the injection, which may persist for several days, and in some cases weeks. In two cases sterile abscesses occurred at the site of the injection. No culture could be obtained from them, neither could any arsenic be demonstrated. The reaction as regards pain, temperature, headache, vomiting, etc., seems to be much less in women than in men.

In conclusion, I owe much to my house-surgeon, Dr. W. Messer, for his help in assisting me and making notes on the cases. I have also to thank Dr. Stopford Taylor and Dr. R. W. MacKenna for supplying me with some tubes of salvarsan before it was obtainable in this country; also Dr. Moore Alexander for isolating the spirochaete in doubtful cases.

THE CURATIVE EFFECT OF SALVARSAN IN FRAMBOESIA.

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I STATED in my first communication in the BRITISH MEDICAL JOURNAL of February 18th, 1911, page 360, that the injection of 18 cases of yaws with salvarsan at the St. Augustine Yaws Hospital, Trinidad, on January 4th and 11th, was followed by immediate and wonderful improvement. I subsequently injected 3 cases, and I am now (February 18th) able to give the results in these 21 cases. Each received only one injection.

Cured	...	...	13, or 61.9 per cent.
Nearly cured	...	...	3, or 14.3 per cent.
Stationary	...	...	5, or 23.8 per cent.

The shortest period taken to cure was thirteen days, and the longest twenty-eight days.

I find that salvarsan has no effect on yaws tubercles of the nostrils (tubercles situated at the junction of the mucous membrane of the nose and the skin). This failure was noticed in two cases treated by salvarsan and in one treated by serum.

The cases of yaws injected with serum taken from recovering salvarsan cases on the fourth or fifth day all improved for two or three weeks. Some remain stationary, and others have got worse. I believe that if yaws cases were injected with serum every seven or ten days they would be cured with three or four injections.

I injected a goat that had two kids a month old, with 0.3 gram ($\frac{1}{2}$ grains) of salvarsan, and the milk was given to two children in the female ward. Improvement began in the children on the third day, and continued slowly and surely for fourteen days. The goat was borrowed for two weeks, and was sent back to the owner. I intend injecting a cow, and using the milk on a more extensive scale. If my experiment with a goat is verified by others (using more salvarsan than I did) it means a complete overthrow of the theory of Professor Ehrlich, for it must be the salvarsan itself which produces the antibody, and it is probably of the nature of a ferment.

My further experiments with serum are not connected with salvarsan. I put blisters on some yaws cases and used the serum—dose 16 c.cm. for adults—to inject, each case getting his own serum. The object of this experiment was to see if the blistered surface secreted a beneficial substance. I got no results.

I put blisters on some cases cured of yaws by ordinary means, and used the serum on four yaws cases. There was a slight improvement, which did not last for more than a week.

I tried cacodylate of soda, arsacetin, orsudan, atoxyl, and soamin. I find that only orsudan and soamin are of some benefit in yaws. A 9-grain injection (adult dose)

was given once a week. The formula given for soamin is the same as for atoxyl, and I am at a loss to account for the failure of atoxyl, a failure previously recorded by Professor Castellani in Ceylon.

I had salolized capsules prepared by the dispenser and filled with 1 grain of methylene blue and an inert substance. The capsules were gummed and powdered with salol, and allowed to dry. This was done three times. When given to patients and healthy persons, four hours elapsed before the urine was discoloured, so I conclude that absorption takes place in the bowels. I am now trying soamin in these personally tested capsules, and so far as the experiment has gone, it acts well. I will try salvarsan in this way, when a supply comes from England. I suggest the use of tested salolized capsules made with a double end, the small compartment containing 1 grain of methylene blue. On filling such a capsule with a drug, the discoloration of the urine would exactly indicate when absorption began.

It is my intention to try 1 per cent. injections of the hydrochloride of quinine and urea before injecting with salvarsan intramuscularly so as to mitigate the pain by producing local anaesthesia.

SUMMARY.

Salvarsan is the best drug for use in yaws. I have no doubt that this fact has been discovered in every yaws hospital. The experiments in Trinidad have contributed to knowledge in four directions:

1. The serum of cases recovering under salvarsan has been shown to have a curative effect.
2. Nostril yaws tubercles are not affected by salvarsan nor by serum.
3. The milk of a goat injected with salvarsan has a curative effect.
4. Soamin and orsudan are the only organic compounds—excluding salvarsan, of course—that cause some benefit in yaws.

Full details of all my experiments are recorded and communicated to the Acting Surgeon-General of the Colony. My thanks are due to him and others for their appreciation and encouragement. Further experiments will be undertaken.

THE SCIENCE COMMITTEE OF THE British Medical Association.

OBSERVATIONS ON THE OCCURRENCE OF FLUID IN THE ABDOMINAL CAVITY IN PREGNANT RABBITS.

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THE presence of free fluid in the abdominal cavity of the pregnant rabbit has been noticed in the course of research by several observers, but as far as we are aware no special observations have been made with regard to the nature of the fluid present nor to the possible cause of its occurrence. It has occurred to us that some such observations may be of value, especially in relation to the work done by one of us (C. B.) on the pathology of cardiac dropsy.

Relative Frequency.—The relative frequency of free fluid in the peritoneal cavity has been estimated in a series of pregnant and non-pregnant animals:

(a) Non-pregnant: Ten non-pregnant animals were examined, 4 males and 6 females, and although the intestines were moist in all cases, in only 2 was a measurable quantity of free fluid obtained, and in these 2 cases (1 male and 1 female) the quantity was very small, as indicated below.

(b) Pregnant: In 16 pregnant animals examined, we only failed in 2 cases to obtain a measurable quantity of fluid. This gives the following percentages of cases with free fluid:

- (a) Non-pregnant, 20 per cent. (probably is much smaller).
- (b) Pregnant, 87.5 per cent.