

FURTHER OBSERVATIONS ON THE TREATMENT OF YAWS WITH CASTELLANI'S MIXTURE

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TWO PLATES

Salvarsan and neosalvarsan are, without doubt, the specific remedies for frambœsia; but the high price and shortage of these drugs brought about by the war, the lack of hospital facilities in districts where the disease prevails, and the fact that patients often refuse any kind of injection treatment are some of the considerations that led Castellani, (1, 2) in 1915, in Ceylon, and us in the following experiments to use his formula in place of the drugs. The formula consists of:

	Quantity.
Tartar emetic.....grams.....	0.065
Sodium salicylate.....do.....	0.65
Potassium iodide.....do.....	4
Sodium bicarbonate.....do.....	1
Water.....do.....	30

The above is given in one dose, diluted in 4 ounces of water, thrice daily, for adults and for children over 14 years of age, half doses to children 8 to 14 years of age, one-third doses or less to younger children, and not more than half doses to Europeans. According to Castellani the preparations of antimony, which were first introduced in the treatment of yaws by Brault in 1911, have a beneficial effect, but their action is slow. Sodium salicylate apparently hastens the disappearance of the thick yellow crusts, due to secondary pyogenic infections. Potassium iodide potentiates tartar emetic, but its great drawback is that the good effects are obtained only by using doses that often give rise to iodism. This and the emetic action of the antimony and potassium tartrate are diminished by the addition of sodium bicarbonate. The formula is pharmaceutically a very inelegant one; it is cloudy and has a sediment due to the formation of antimony

oxide. The sediment, however, disappears when each dose is diluted with four times the amount of water or when 8 cubic centimeters of glycerin are added to the formula.

Castellani tried this formula in eleven cases given in the doses mentioned for from ten to fifteen days, followed by from five to ten days of rest, then another course for another five or ten or fifteen days. His results were very satisfactory in recent and fairly recent cases, in which the disease had started three to twelve months previously. In chronic cases the results were much less satisfactory. Very mild symptoms of iodism were observed in three cases, but were not sufficiently severe to necessitate stopping the treatment or decreasing the doses. No symptoms pointing to any depressing action on the heart were noted.

Spaar⁽⁵⁾ obtained excellent results with this treatment in three cases, the patients recovering in two or three weeks.

We have used this treatment in more than 43 cases, including 7 in the Philippine General Hospital, 14 in Parañaque, and 22 in Las Piñas. The cases in the Philippine General Hospital were all discharged completely cured.

With the exception of four, all our cases presented, more or less moderately, one or several of the following symptoms during the treatment: General malaise, weakness, slight fever, nausea, vomiting, gastralgia, diarrhoea, pharyngitis, ptialism, intense coryza, lachrymation, congestion of the conjunctiva, cephalalgia, and insomnia. One case also presented slight induration or nodules of the skin of the face and ears, and another presented erythematous patches in various parts of the body. However, we did not observe in those cases who were under our immediate supervision furunculosis, acne, purpura, nor œdema of the eyelids, face, and larynx. The method of administration followed by us brings about gradual saturation of the body. We gave on the first day one-third dose three times; on the second day, one dose twice; and on the subsequent days, one dose three times daily. We adopted this dosage in order to ascertain the susceptibility and gradually to establish tolerance in the patient. The number of doses necessary to effect a cure varied from 15 to 80, and the time elapsing from the commencement of the treatment till complete recovery was from five to twenty-seven days.

Of the 14 cases of Parañaque, 10 showed complete recovery, while the remaining 4 showed only improvement of the symptoms. Seven of the Las Piñas cases discontinued the treatment early, 3 showed improvement of symptoms, 3 proved refractory, and 9 recovered completely. To summarize: Of the 36 cases that continued the treatment, 24 completely recovered, 7 showed im-

provement of symptoms, 7 showed no improvement at all, and 5 had relapses in from two to five months after the lesions had entirely healed.

The details of the cases treated and the results of the treatment are given in the subjoined protocols:

Case I.—M. P., female, 45 years old, a native of Bulacan. The duration of the infection was about nine months. The lesions consisted mainly of granulomatous ulcers on the labia majora and a few papillomatous growths about the nasal fossæ and the left angle of the mouth. The growth was covered with a thick yellowish crust. The ulcerations on both labia excreted a purulent fetid material. The general appearance of the growth simulated "granuloma pudendi." The patient received 44 doses of Castellani's mixture in nineteen days, and sixteen days later the lesions were completely healed.

Case II.—F. P., female, 24 years old. The infection was of six months' duration. The lesions consisted of warty growths on the forehead, face, neck, abdomen, and genitals. The mother yaw was an ulcer with irregular borders, 2 centimeters in diameter, on the anterior surface of the left ankle. The patient entered the hospital to obtain relief from pain in the bones and joints. The joints of the fingers and hands were swollen and painful. She received 23 doses in ten days and left the hospital after fifteen days with complete disappearance of arthritic pain and cicatrization of the lesions.

Case III.—C. F., male, 30 years, married, denied having had venereal diseases. The duration of the infection was one year and four months. The patient thought that he had contracted the disease from his children, who had yaws. The primary lesion appeared as a bed bug bite on the left thigh. On scratching the skin over it, the lesion gradually increased in size to about 10 centimeters in diameter. Two months later eruptions appeared all over the body, but after a year they disappeared without treatment. Last January he was admitted to the hospital, complaining of pain in the bones. He presented extensive ulcerations on the soles of both feet. The Wassermann test was negative. The patient was given 15 doses in eleven days. He left the hospital completely cured.

Case IV.—E. Y., female, 19 years old, contracted yaws six months ago. She said she had had yaws when she was 12 years old. The scars were plainly visible on the face and on other parts of the body. She had an ulcer on the anterior aspect of the right leg, which measured 3 centimeters in diameter and 1 centimeter deep. The edges were irregular, and the base was formed by necrotic tissue and exposed bone. Wassermann reaction was positive. The patient was given 5 drops of saturated solution of potassium iodide and 5 milligrams of protoiodide of mercury three times daily. Aseptic dressing was applied to the ulcer. She experienced no improvement from this treatment. Castellani's formula was then given three times daily, and 25 per cent protargol ointment was applied locally. After 54 doses the ulcer completely healed, although the pain in the bones persisted for some time.

Case V.—M. Santa Ana, male, 38 years old. The duration of the illness was five months. The lesions consisted of granulomatous growths of varying size, whose summits were covered with yellow crusts. They were distributed on the scalp, forehead, chin, neck, shoulder, back, and buttocks. The lesions appeared in crops, accompanied by severe pain in the bones and

swelling of all the joints. The bones of the fingers were markedly enlarged. He took 24 doses, and after nine days in the hospital the symptoms disappeared and the lesions healed.

Case VI.—S. P., 17 years old, male, had yaws for a month. There were papules covered with a yellowish crust in the right nostril, and there were also scars. The patient entered the hospital on account of pain in the bones and swelling in the joints. He said he had had a similar attack one year ago. He took 14 doses in six days. The treatment caused amelioration of the pain and of the lesions.

Case VII.—A. M., male, 40 years old, contracted yaws four years ago. He came for treatment of an old ulcer on the right forearm. It measured about 4 centimeters in diameter. The edges were irregular and elevated, and the base was covered with yellowish purulent material. The patient stayed in the hospital twenty-seven days, during which time he took 80 doses. The ulcer had completely healed when he was discharged from the hospital.

Case VIII.—L. S., male, 31 years old, had yaws for one year and four months. The lesions were granulomatous nodules of from 1 to 1.5 centimeters in diameter. They were found on the neck and chest. The face showed numerous pigmented scars. The patient was given 10 drops of a saturated solution of potassium iodide three times daily for nine months. The iodide produced only insignificant improvement of the eruptions on the face. Castellani's mixture was then given, and in five days the lesions completely healed.

Case IX.—F. C., female, 40 years old. The patient said she had had an eruption eight years ago. She came for treatment of an ulcer on the right external malleolus. The ulcer was of five months' duration. It was about 4 centimeters in diameter and was covered with fetid whitish material; the border was elevated. The ulcer completely healed after the patient had taken 39 doses in a period of fifteen days.

Case X.—F. de G., 40 years old, male, had yaws for one year. The lesion appeared as an abrasion of the skin of the forehead. It later developed into an ulcer. There were four ulcers on the forehead, from 5 to 10 centimeters in diameter, at the time of treatment. The edges were elevated and granular. Castellani's treatment caused complete cicatrization of the ulcers.

Case XI.—C. S., female, 16 years old, was ill for four months. At first she had a febrile pain in the joint and itching of the skin over the left knee. The skin then became covered with a yellow crust, which she thought was scabies. Later small papules appeared around the lesion on the knee. These spread in two weeks all over the body and assumed the characteristic appearance of the manifestation of yaws. The patient believed she had contracted the disease from a visitor who had the same disease. She took 47 doses in eighteen days, and the lesions completely disappeared.

Case XII.—J. F., 34 years old, was the mother of case XI. She had yaws for three months. The lesions consisted of granulomatous papules on the face and hands and of scaly eruptions on the forearm. The latter were arranged in the form of islands 3 to 4 centimeters in diameter. She was admitted with case XI. After 41 doses, given in sixteen days, she recovered completely.

Case XIII.—J. T., 27 years old, married, female, had yaws for three months. The mother yaw was found on the left middle finger. Seven days later granulomatous papules appeared on the face and other parts of the

body. She complained of pain in the bones and joints, but no swelling was found. She stayed in the hospital twenty-three days and took 66 doses. When she was discharged, all the eruptions had completely healed. The last three cases were relatives living in one house. Their infection seems to originate from the visitor mentioned in case XI.

Case XIV.—F. O., male, 8 years old. He developed secondary yaws nine months ago. On examination there were found secondary lesions, especially on the penis and about the anus, and an ulcer with granulomatous, irregular border on the left internal malleolus. The diagnosis was tertiary yaws. Thirty doses produced complete cicatrization of the ulcers.

Case XV.—E. C., female, 42 years old, had yaws in 1898. At the time of the examination she presented an ulcer on the posterior surface of the right forearm below the elbow. The surface of the ulcer was granular and was covered with fetid, purulent grayish secretion. It measured about 8 centimeters in its longest, and 5 centimeters in its shortest, diameter. It began as an induration of about 0.5 centimeter. It gradually increased in diameter to about 3 centimeters. The diagnosis was tertiary yaws. The ulcer healed without local treatment after the patient had received 30 doses of Castellani's mixture.

Case XVI.—I. P., female, 30 years old, had had yaws at the age of 7 years. About three years ago she was hit on the right knee. A nodule appeared on this knee. Later it became an ulcer with deep, irregular borders and fetid yellowish gray secretion. The joint was swollen and painful, incapacitating the patient for walking. The diagnosis was tertiary yaws. She was given 36 doses of Castellani's mixture, and the ulcer completely healed.

The treatment of Castellani undoubtedly exerts a curative influence on the various manifestations of frambœsia. In six or seven days of treatment the granuloma takes on a livid appearance, becomes surrounded by a pinkish halo, and begins to flatten. The crust dries and gradually disappears, leaving a macule that eventually disappears. In deep and extensive ulcers cicatrization takes place gradually and concentrically, the entire process lasting from fifteen to thirty days. Pain in the bones, pain and swelling of the joints, and pruritus are relieved early in the treatment, although sometimes the pain in the bones and joints recurs even after complete healing of the lesions.

The relapses and incomplete recovery observed in some cases are to be ascribed to an incomplete medication, due to the suspension of treatment before the destruction of *Spirochæta pertenue* was complete. Some of our cases discontinued the treatment after the disappearance of granulomata and ulcers; while others, who were not under our direct supervision, could take only a few doses irregularly. We were not able to supply the patients with the adequate amount of the medicine, because the experiments were carried out in neighboring towns, where we had to distribute the preparation gratis. On the whole, the

patients do not seem to object to this treatment; on the contrary, they willingly submit themselves after they are convinced of its gratifying results.

Our results confirm the conclusion of Castellani that the diverse manifestations of frambœsia heal under the influence of his treatment. The cure of recent infections by this preparation is nearly as marvelous as that by salvarsan and neosalvarsan. We cannot assert as yet whether or not the cure is permanent, since only a limited number of cases remained under our observation for a long time. We believe, however, that the continuation of the treatment after the lesions have healed (from five to ten days' treatment with intermissions of from ten to fifteen days) will insure a permanent cure.

The tendency of the mixture to cause emesis and iodism is not a serious objection to its routine employment, because these untoward effects are slight and may be easily corrected. If emesis, gastralgia, and diarrhœa are troublesome, they can be prevented by merely increasing the sodium bicarbonate or by giving, fifteen minutes before each dose, 4 cubic centimeters of paregoric or 1 centigram of codeine. Other untoward effects, which are apparently due to vasomotor disturbances, such as œdema, lachrymation, coryza, congestion of the conjunctiva, etc., are readily overcome by epinephrine. According to Milian, (3, 4) this drug also gives excellent results in iodism and cerebral symptoms associated with the use of arsenobenzol. He strongly advocates the administration of massive doses of the drug, for example, 3 milligrams per orem twice daily, and if this fails, 1 or 2 milligrams injected subcutaneously or intramuscularly.

In the administration of Castellani's mixture it is always important to bear in mind the possible presence of the larval form of hyperthyroidism and also the greater susceptibility of children to iodides, for large doses may give rise to alarming and very unpleasant side effects.

Frambœsia, though not a grave malady quod vitam, has a tendency to relapse, running a highly chronic course extending for years, and gives rise to rheumatoid pains, osseous deformities, extensive ulceration (which may serve as a portal of secondary infection), and deforming cicatrices, which not only are disfiguring but often more or less seriously incapacitate the patients, school children and adults alike. Admitting that it is not a source of high mortality, it is, however, decidedly a cause of high morbidity, entailing material loss to the individual and to the community.

Frambæsia is one of the common diseases in the Philippine Islands and is widely distributed. It is impossible to estimate the extent of infection, but it is undoubtedly of considerable importance. The establishment of ambulatory or provisional hospitals in the larger infested districts for the adequate administration of salvarsan would be the ideal method of suppressing this disease. This being impossible under present conditions, the general use of Castellani's treatment, under suitable administration, offers a practicable means of combating the disease.

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ILLUSTRATIONS

PLATE I. YAWS

- FIG. 1. Case VIII, before treatment.
- 2. Case VIII, five days after treatment.
- 3. Case XIII, before treatment.
- 4. Case XIII, after 41 doses given in sixteen days.

PLATE II. YAWS

- FIG. 1. Case XV, before treatment.
- 2. Case XV, after 30 doses of the mixture.
- 3. Case XVI, before treatment.
- 4. Case XVI, after 36 doses of the mixture.



Fig. 1. Case VIII, before treatment.

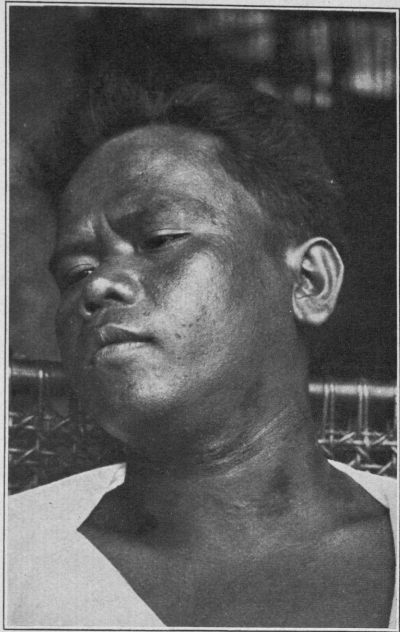


Fig. 2. Case VIII, five days after treatment.



Fig. 3. Case XIII, before treatment.



Fig. 4. Case XIII, after 41 doses given in sixteen days.

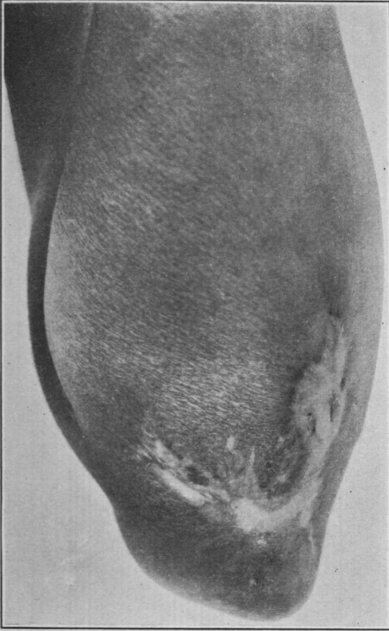


Fig. 1. Case XV, before treatment.



Fig. 2. Case XV, after 30 doses of the mixture.

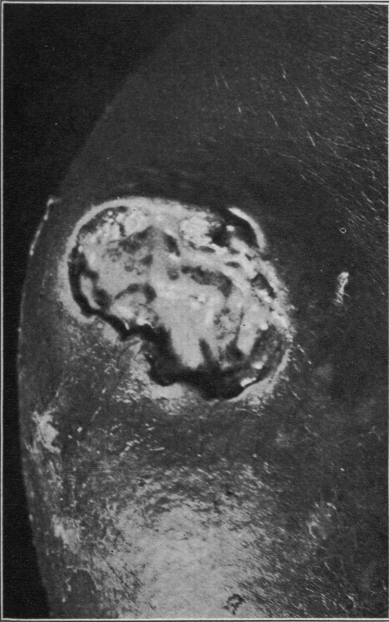


Fig. 3. Case XVI, before treatment.

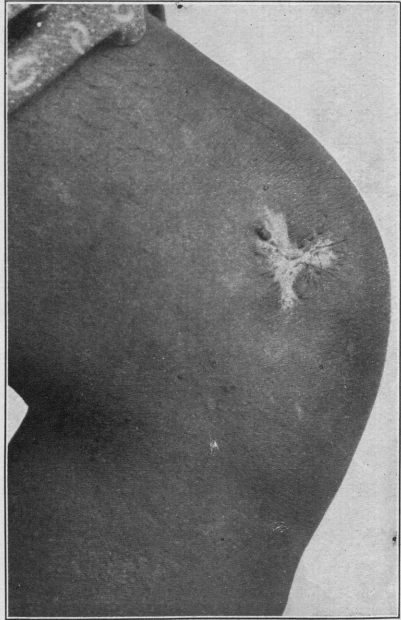


Fig. 4. Case XVI, after 36 doses of the mixture.