Clinical and other Notes.

PRELIMINARY NOTE ON THIRTY-SIX CASES OF SYPHILIS TREATED WITH DIOXY - DIAMIDO - ARSENO - BENZOL ("HATA," OR "606").

BY MAJOR T. W. GIBBARD AND CAPTAIN L. W. HARRISON.
Royal Army Medical Corps.

In the October number of this Journal Lieutenant-Colonel Birt gave an account of Ehrlich's new remedy for syphilis which must have excited considerable interest and speculation.

The chemical composition of this latest preparation and the results which some other workers have obtained with it have been sufficiently detailed by Lieutenant-Colonel Birt. We propose to record only our own observations, which are necessarily somewhat incomplete, on account of the short time which has elapsed since we commenced to use the drug, but they have been so striking and so much in accord with those of other observers that they may perhaps serve to supplement Lieutenant-Colonel Birt's paper on the subject.

The new remedy is not yet on the market, but, by the kindness of Professor Ehrlich, we were supplied with a small quantity of "606" in July, and were able to commence using it early in September.

"Hata," or "606," is put up in vacuo in glass capsules, the weight of its contents being marked on each capsule. The dose which we have commonly used has been 0·6 gramme, though in some cases, especially the later ones, 0·7 gramme has been given.

At first we prepared the drug for injection as follows:

For 0·6 gramme "Hata" 30 cc. of sterile distilled water, at a temperature of about 55° C., were placed in a porcelain capsule, which, in its turn, was put in a water bath at about the same temperature, and the yellow powder slowly sprinkled into it with fairly vigorous stirring. To the resulting bright yellow acid solution 6 cc. of normal NaOH solution were slowly added with vigorous stirring. A flocculent precipitate formed which redisolved, and the result was a strongly alkaline brownish-yellow solution. Three drops of 0·5 per cent. alcoholic solution of phenolphthalein were then added, and the solution became deep crimson. Normal acetic acid was then run in till the crimson colour just disappeared (indicating neutrality); while the acid was being added a fine precipitate formed. Finally the capsule contained about 40 cc. of fluid containing a fine yellow salt in suspension, which was injected subcutaneously between the scapula, 20 cc. on each side of the spinal column. The resulting tumours were then dispersed by massage.

In later cases we have modified this technique by discontinuing the
use of phenolphthalein in favour of litmus paper as an indicator, reducing the bulk of the injection by using 25 cc. of water in the first place, and injecting the suspended salt under the skin overlying the pectoral muscles. We consider that these slight modifications, especially that regarding the site of the injection which is not pressed upon when the patient is lying in bed, have the advantage of causing less discomfort.

Further investigation will decide whether this is the best form in which to administer "606." Having such a small supply, we judged it best to adhere to the plan which we found fairly satisfactory, without wasting the drug in experiments to discover a better method. It is a disadvantage that the bulk of the injection is so large, but the fluid is more nearly isotonic in its contents of sodium acetate and sodium chloride than when a smaller quantity of water is used.

In addition to the examination for evidence of syphilis, by clinical signs, microscopic examination for Spirochaeta pallida in certain cases, and the test for the Wassermann reaction, the patient, previous to injection, in each case is examined as to the state of his vision, fundus oculi, heart, lungs and kidneys, and his weight is taken. The immediate result of the injection has been some local pain and tenderness, the former being frequently referred to the front of the chest or point of one shoulder, and sometimes accompanied by a sense of constriction of the chest. This pain gave way, in an hour or so, to a rather persistent ache, which appeared in most cases to become aggravated at the end of forty-eight hours, when a reaction, varying in severity with different patients, set in and lasted for about two days. In all the cases, except the one related below, all material discomfort had disappeared in from five to seven days. In one patient, a case of gummatous hepatitis, the reaction was considerably more severe. The whole back became oedematous and there was severe pain, especially in the night, at the site of injection. This reaction lasted for about ten days; it is difficult to account for its exceptional severity, but the patient differed in his circumstances from the others of our series in the fact that he had been allowed a large quantity of fruit daily, and it is possible that at the time of the injection his blood coagulability was abnormally low. Possibly the fact that this patient was suffering from a certain amount of portal obstruction may help to explain the severe oedema.

In another case a faint circinate erythema appeared on the trunk twenty-four hours after the injection; this, however, disappeared by the following day.

The temperature has generally been febrile for four days. The highest temperature recorded was 103·4° F. in our first case. In none of the others did it rise higher than 102·2° F. A curious feature has been the slight increase of fever which occurred in most of our cases between forty-eight and seventy-two hours after the injection, at which period the average temperature was 100·2° F. The majority of our
patients suffered from insomnia for four days; this could not altogether be attributed to the discomfort in the back, since it occurred in some of the cases where there was very little pain.

An injection of morphia \( \frac{1}{6} \) gr. on each of the first three evenings, when required, has been sufficient to mitigate the discomforts immediately attendant on the injection. We have not noted any of the untoward symptoms recorded by some other observers, such as delirium, suppression of urine, and obstinate constipation.

Regarding the effect on the clinical manifestations of the disease, we can only endorse what has been already published as to the marvellous rapidity with which the drug acts. Most of us are aware of the length of time which elapses before a primary sore heals, or an ulcerated mouth and throat are clear of patches, even under vigorous local and general mercurial treatment, so that the following results will give some idea of the effect of "606" in this direction. We may mention that, beyond the use of a simple mouth wash of lead and alum, and a normal saline dressing to primary sores, no other local application was used, except in the case of iritis. Needless to say, no mercury was administered.

In nine cases of primary sore, all treated in the early stage, the chancre had completely healed in an average of eight days, the maximum being fourteen days and the minimum, one day. In each of these cases *S. pallida*, sometimes in great numbers, was demonstrated previously, by microscopic examination; in no case was it possible to demonstrate them, even by dark-ground illumination, forty-eight hours after the injection, and in most of the cases none could be found twenty-four hours subsequent to the injection. In one case where, previously to the injection, the spirochaetes were so numerous that thirty-two were counted in a single field, none could be found on carefully searching two slides twenty-four hours after the injection.

In seventeen cases extensive superficial ulceration of the mouth and throat had completely healed in an average of six days, the minimum being three days and the maximum fifteen days, the latter a case in which the throat had healed in eight days, but a deep ulcer at the angle of the mouth took a further week before it was completely covered with epithelium.

In three cases condylomata had completely disappeared in an average of four days, and spirochaetes, abundantly present in each case previously, could not be found forty-eight hours after the injection.

In four cases suffering from generalised skin eruption the rash had completely disappeared in an average of seven days. In this connection it is interesting to note that in some of our cases the stains of recent rashes rapidly disappeared completely, or almost completely, after the injection.

The following cases, related in more detail, illustrate the effects of
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this remedy when mercury had more or less failed to arrest the course of the disease.

Private II.: Contracted syphilis, April, 1910; received nine injections of mercury, commencing with three of calomel, \( \frac{3}{4} \) gr. each, till July 2nd; commenced second course September 19th; admitted September 28th, after two injections, suffering from ulceration of the tonsils and ulceration between all the toes of both feet, in which numerous *S. pallida* were demonstrated.

September 30th.—Injection of "Hata," 0'6 gramme.

October 1st.—A few spirochaetes recovered from ulcers between toes.

October 2nd.—No spirochaetes found in two slides examined under dark-ground illumination.

October 4th.—Ulcers between toes healed.

October 6th.—No clinical signs of syphilis. Wassermann reaction, strongly positive on admission, still positive (October 13th).

Police Constable B.: Contracted syphilis June, 1910; treated with injections of calomel, \( \frac{3}{4} \) gr., and mercurial cream (Hg. gr. i).

July 20.—Syphilitic iritis of left eye, which cleared up with injections of mercurial cream and the usual treatment for iritis; weekly injections of mercurial cream (Hg. gr. i) throughout August.

September 5th.—Severe recurrence of iritis in the left eye; injection of calomel, \( \frac{3}{4} \) gr.

September 7th.—Eye much worse; vision of left eye reduced to hand movements; two large, well-defined, yellowish-red nodules on iris, extending from ciliary to pupillary border, the portions of the iris affected being firmly adherent to the lens, though atropine drops (gr. iv, ad \( \frac{3}{2} \)) have been used every four hours for two days, and the usual treatment for iritis adopted. Deposits of lymph on the posterior surface of cornea render it impossible to see the fundus oculi. Ciliary congestion not very marked, tension normal, no pain. Vision of right eye 2/6, otherwise normal. Injection of "Hata," 0'6 gramme given.

September 8th.—Slept very little on account of throbbing pain in left eye, which is so severe this morning as to necessitate a hypodermic injection of morphia. Marked circumcorneal congestion; in fact the whole conjunctiva is acutely congested. Tension slightly raised, but not sufficiently to account for the pain. Shortly after the morphia the pain passed away and did not return.

September 9th.—Atropine drops (gr. iv ad \( \frac{3}{2} \)) resumed three times a day, also hot boric lotion was applied frequently.

September 10th.—Nodules on iris much smaller, and circumcorneal congestion less marked. Counts fingers at a distance of three feet.

September 17th.—Vision, right eye 2/6, left eye 5/60. Nodules on iris scarcely visible except by oblique illumination in dark room.

September 20th.—Vision of left eye 5/6; synechiae persist. Atropine drops reduced to once daily; no ciliary congestion.
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October 3rd.—Vision of left eye $\frac{4}{10}$ (under atropine).
October 11th.—Vision, R. $\frac{6}{12}$, reads D. 6 at 18 inches; L. $\frac{6}{12}$ and reads D. 6 at 18 inches.
Wassermann reaction on admission negative to original method, but positive to Stern’s modification.
October 11th.—Wassermann reaction negative to original but showed a trace of deviation when tested by Stern’s modification.

The very weak reaction to the Wassermann test on admission may possibly be explained by the fact that the recent mercurial treatment of the patient had so strictly localised the spirochetes that the substances resulting from their activity were not given off into the general circulation in sufficient quantity to determine a positive reaction to the original method, which is less delicate than Stern’s modification.

Private M.: Contracted syphilis February, 1909. Treated with injections of mercurial cream and potassium iodide, having had 12 gr. of metallic mercury by injection, the last being given on August 22nd, 1910. Admitted September 8th, 1910, with deep punched-out ulcer with unhealthy oedematous base on extensor surface of right forearm, measuring 2$\frac{1}{4}$ inches by 1$\frac{1}{4}$ inches; three small ulcers near this, and a punched-out ulcer on back of neck, measuring 1$\frac{1}{2}$ inches by 1$\frac{1}{4}$ inches. None of the ulcers show any signs of healing. Arms and legs show many stains and cicatrices of previous ulcers. Superficial ulceration of tongue involving whole of right side, from tip to base. Injection of “Hata” (0·6 gm.).

September 11th.—Ulcer on arm almost level with surface, and shows a healing margin.
September 12th.—The previously ulcerated portion of tongue is now covered with new epithelium, and the ulcers on the neck and forearm show healthy margins with advancing line of new epithelium all round each.
September 18th.—Ulcer on arm now 1$\frac{1}{4}$ in. by 1$\frac{1}{2}$ in., that on neck $\frac{5}{8}$ in. by $\frac{1}{4}$ in.

September 30th.—Ulcer on neck practically well; requires no further dressing. That on arm almost healed.

In this case it was obvious that the active process underlying the ulceration ceased within forty-eight hours of the injection, and the later progress was simply that of two large healing ulcers and three trivial ones.

The following notes illustrate the effect of “Hata” in ordinary cases of syphilis:

Private W.: Admitted August 28th, 1910, with a slightly indurated chancre round the urinary meatus, in which numerous $S. pallida$ were found; papular rash on body and arms; mucous patches on both tonsils and behind last molar tooth on right side. Gonorrhoea also present.
September 3rd.—Injection of “Hata” (0·6 gramme).
September 4th.—Rash and mucous patches less marked; no spirochetes could be found in the sore.
September 7th.—Throat and mouth quite well. Five fading spots on the body were the only evidence of a rash having existed.
September 10th.—Sore healed. No clinical sign of syphilis. No gonorrhoeal discharge, and urine shows no mucus or threads. (Has had no irrigations since the injection.)

Wassermann reaction strongly positive on admission.

September 27th.—Wassermann reaction + by original method, still positive to Stern's modification. Further investigation of the serum reaction temporarily stopped, as the case was transferred on discharge to another station, and, owing to some error, the serum was not sent to be tested.

Gunner A.: Admitted September 2nd, 1910, with sore behind the corona in which S. pallida found. Generalised maculo-papular rash.

September 5th.—Injection of “Hata,” 0·6 gramme.

September 6th.—Rash much fainter.

September 7th.—Rash now discrete, in fact on the arms only faint staining is to be seen.

September 9th.—Very faint staining the only signs of a rash having existed.

September 11th.—Sore healed.

September 12th.—Staining of rash has disappeared. No clinical signs of syphilis.

Wassermann reaction: On admission strongly positive.

September 27th.—Weakly positive to both methods.

October 12th.—Negative to original and to Stern's modification.

Private B.: Admitted September 2nd, 1910, with extensive ulceration of pharynx and tonsils; four condylomata on scrotum, in which numbers of S. pallida found, and six similar lesions on inner side of upper third of the left thigh. A few papules on the body.

September 5th.—Injection of “Hata,” 0·6 gramme.

September 6th.—Condylomata no longer present, and no spirochaetes could be found. Marked improvement in throat.

September 12th.—Throat quite well; no clinical signs of syphilis, and even the stains of a previous rash on his arms have disappeared.

Wassermann reaction, positive on admission, was negative to original and to Stern's modification on October 13th.

Private G.: Admitted October 5th, 1910, with sore on fraenum in which S. pallida found. Macular rash on abdomen, chest, and legs. Injection of “Hata,” 0·6 gramme.

October 6th.—Sore quite healed.

October 8th.—Eruption on limbs very indistinct.

October 9th.—No clinical signs of syphilis.

Wassermann reaction, strongly positive on admission, shows no change at present (October 13th).

As a side-effect of the clinical results above related, the remainder of the patients under treatment in the same ward as these special cases have requested us, at one time and another, to administer the remedy to them.
also, notwithstanding the fact that it must have been clear to them that the injection gave rise to some discomfort for a few days.

Regarding the test of these patients' sera for the Wassermann reaction subsequently to the injection, it is impossible, at present, to make any definite statement, as sufficient time has not yet elapsed since many of the cases received the injection. At a future date we hope to publish a more complete report on this part of the investigation, as well as on the occurrence or not of relapses in our cases. Meantime, a study of the subjoined table appears to show that no very great change in the reaction occurs for about two weeks; after that time it seems to become progressively weaker and to die out eventually.

We may mention that the test was conducted in a roughly quantitative manner in the case of the original method, as well as in that of Stern's modification. In the former case, the estimate was made by using the standard amount of complement (equivalent to 0.1 cc.) and also double that quantity, and in the latter, by using two different quantities of extract, one being twice the amount of the other.

**Table.—Analysis of Results of Tests for the Wassermann Reaction at Various Lengths of Time after Injection of “606.”**

<table>
<thead>
<tr>
<th>Number of weeks after injection</th>
<th>Number of cases originally positive</th>
<th>Number in which the reaction became markedly weaker or ±</th>
<th>Number in which reaction became completely negative</th>
<th>Number of cases originally negative or ±</th>
<th>Number of these in which reaction remained or became completely negative</th>
<th>Number in which reaction changed to positive</th>
<th>Test by Stern's method failed from lack of complement in patient's serum</th>
</tr>
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<tbody>
<tr>
<td>1–2</td>
<td>8</td>
<td>6</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>1*</td>
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<tr>
<td>2–3</td>
<td>9</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>1*</td>
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<tr>
<td>3–4</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>0</td>
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<tr>
<td>4–5</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
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<tr>
<td>5–6</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
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<td>0</td>
<td>0</td>
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</table>

As Tested by Stern's Modification.

<table>
<thead>
<tr>
<th>Number of weeks after injection</th>
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</tr>
</thead>
<tbody>
<tr>
<td>1–2</td>
<td>10</td>
<td>8</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1*</td>
</tr>
<tr>
<td>2–3</td>
<td>11</td>
<td>7</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1*</td>
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<tr>
<td>3–4</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
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<td>4–5</td>
<td>3</td>
<td>2</td>
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<td>1</td>
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<td>5–6</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</table>

* These results were given by same patient's serum.
† Reaction very strong.
‡ Reaction very weak.

In this table the column headed "Number of cases in which the reaction became markedly weaker or ±" is to be interpreted as follows: "Became markedly weaker" means, in the case of the original method, that the sera deviated the double amount of complement before the injection, but only the standard amount later. In the case of Stern's
modification, that deviation originally occurred with the smaller amount of extract, but that later the tube only in which the larger amount of extract was present showed deviation. "Became ±" means that, with the standard amount of complement or the larger amount of extract, according to the method, some hæmolysis occurred in the tube. We are aware that to include these ± cases under this heading, and to place similar results obtained before the injection under the heading of "negative," is not strictly fair to the remedy, but it eliminates the only possible question of bias in its favour from the point of view of the Wassermann test.

In one case the reaction, originally negative, became strongly positive a week later, and, again, was found to be considerably weakened after twenty days.

Our observations, which confirm those of other workers, justify us in concluding that in "606" Ehrlich has given to the world a remedy which has a profoundly specific effect in syphilis. The importance to the Army of a drug by which we can reduce the stay in hospital to the extent indicated in the above records, may, in view of the large number of admissions for syphilis, be safely left to the imagination of our readers. If "Hata" justifies its present promise of being capable of effecting a cure with one or, at the most, a few injections, its distinguished elaborator will have conferred a benefit on humanity which has not been equalled since the discovery of antiseptics.

We desire to acknowledge our great indebtedness to Lieut.-Colonel Birt for his invaluable advice and assistance in preparing the first doses for injection; to Major Profeit for the very careful manner in which he has recorded the progress of many of the cases; and to Captain A. D. Jameson for kindly obtaining specimens of blood serum from those cases which were transferred to Aldershot on discharge from hospital.

A CASE OF MALIGNANT ENDOCARDITIS TREATED BY "VACCINE"—RECOVERY.

BY CAPTAIN H. A. EMERSON.
Royal Army Medical Corps.

WITH A NOTE ON THE BACTERIA PRESENT, BY MAJOR W. S. HARRISON.
Royal Army Medical Corps.

PRIVATE G. K. was admitted to the Military Hospital, Canterbury, on January 29th, 1910, suffering from tonsillitis. The disease followed a mild course, and there was no suppuration; he was discharged apparently well on February 8th.

On February 17th he was again admitted with symptoms of "gastritis," which were attributed at the time to his having eaten winkles two days previously. The gastritis passed off, but two days after admission
Preliminary Note on Thirty-Six Cases of Syphilis Treated with Droxy - Diamido - Arseno - Benzol ("Hata," or "606")
T. W. Gibbard and L. W. Harrison

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