Clinical and other Notes.

"HATA," DIOXY-DIAMIDO-ARSENO-BENZOL.

By LieutEnant-Colonel C. BIRT.

Royal Army Medical Corps.

The German Institute of Chemotherapy, under the direction of Ehrlich [1], has been engaged for years in the study of the curative values of innumerable synthetic organic bodies. As the result of almost countless experiments on animals, a few substances only have given indications of being applicable to general therapeutic use. These are—arsenophenylglycin, trypanosan, and dioxy-diamido-arseno-benzol, known as "Hata" or "606." Ehrlich employs the terms, "organotrope" and "parasitotrope," to express the relative affinity of chemical substances for the tissues of the body and the invading parasite respectively. A preparation may exert a strongly destructive effect in vitro, yet may be powerless when injected into the animal body. Koch's research on the action of mercuric chloride on anthrax may be quoted as an example. If this salt be administered to an infected animal in doses larger than those which are necessary to destroy the bacillus in the test-tube, it has no influence on the infection, but the animal dies of mercurial poisoning. Here, then, the organotrope properties of the sublimate exceed the parasitotrope. Bechhold has made similar observations on the halogen derivatives of phenol, which are germicidal in high dilution, but are useless therapeutically. Hata ascertained that a one in six million solution of methylene blue destroyed in vitro the spirillum of relapsing fever, yet if he injected five hundred times this amount into a mouse infected with this organism the course of the disease was not delayed. On the other hand, a substance may be harmless to a parasite in vitro, while in vivo it may exhibit potent effects. Mesnil found that a 1:12,000 dilution of atoxyl injected into man causes destruction of trypanosomes, although they were unharmed by a saturated solution in vitro. Ehrlich has shown that this action depends on the atoxyl undergoing reduction in the tissues. The product which is formed is highly trypanocidal. Other parasitotrope bodies may act in a different manner. Some basic dyes, pyronine for example, will cure trypanosomiasis when a 1:20,000 to 1:50,000 solution is injected, a dilution far higher than that which will affect the trypanosomes outside the body. In this case the parasites in the animal are not killed, but their nuclei are attacked and their multiplication is arrested. Tryparot is not deadly to paramécia, which can survive in a solution for weeks, but their power of reproduction is suppressed. By cultivating trypanosomes in media containing dyes of the orthokinone series, Werbitski bred a race which was...
remarkable in its wanting blepharoblasts. This characteristic was preserved through twenty generations. If the life of the individual parasite be limited to a few hours only, then this hindrance to reproduction is equivalent to complete disinfection of the body. There is another way by which cure may be effected. Suppose that a chemical preparation be injected into an infected animal by which half the parasites are killed, their dead bodies call forth antibodies which are rapidly elaborated according to the researches of Wassermann, Schelling, Mesnil, and Ehrlich. Hence cure is brought about partly by destruction of the parasites by the chemical agent and partly by the antibodies which speedily appear. Uhlenhuth's work on fowl spirillosis shows that this is no idle fancy. If the spirilla and the arsenical preparation were injected simultaneously, the results were much less favourable than when the remedy was administered a day or two after the appearance of the parasites in the blood. Ehrlich thinks that this underlies an important principle. He would delay treatment in the earlier stages of an infection, and would wait until the invading organism was present in large numbers, for then with an "ictus immunisatorius" he would destroy them in their millions. This corresponds to Nature's method when the crisis, or curative reaction, comes on at the acme of an infection.

Paradoxical as it may appear, a "contrary effect" sometimes may be manifested. A substance highly lethal in vitro may in vivo aid and abet the infection, and may cause an increase in the number of parasites. Hata has seen this "contrary effect" produced in the spirillosis of fowls, and Marks has observed it while treating the proteosoma infection of birds. Ehrlich thus explains this anomaly. It is a not unusual phenomenon that a substance which is inimical to an organism in a large dose is favourable to its growth in a small dose, and in those instances in which a "contrary effect" is observed, the quantity of the chemical reagent which the parasite fixes is so small that it is sufficient to stimulate but not to destroy it. Ehrlich therefore inclines to his "Therapia magna sterilans." He would throw into the body one, and only one, massive dose of the parasitotrope chemical substance which would free it, once and for all, from its invading parasitic foes. His ideal has been attained by the signal success which has been achieved in the treatment of syphilis with dioxy-diamido-arsenobenzol.

\[
\begin{align*}
\text{OH} & \quad \text{As} = \text{As} \quad \text{OH} \\
\text{NH}_2 & \quad \text{NH}_2
\end{align*}
\]

This preparation has been investigated by Ehrlich's co-worker, Hata, and hence is called by his name, or by the number 606. Hata proved that its parasitotrope properties were highly marked. One fiftieth of the dose poisonous to birds is sufficient to cure fowl spirillum fever. It causes the disappearance of the Treponema pallidum in twenty-four hours in the primary lesion of a rabbit which has been induced by
inoculating it with syphilitic virus. Every week the German medical press publishes eloquent testimony of the marvellous action of the remedy. Wechselmann [2], the head of the Skin Department of the Virchow Hospital, Berlin, has used "606" in 503 cases of syphilis. He states that it acts on specific lesions with a rapidity which no other known substance even distantly approaches. Two severe cases of rupia recovered in a fortnight. A phagedenic chancre with roseola was treated with an injection of "Hata." The rash faded four hours afterwards. The sore was healed, and induration had gone in five days. In a case of an immense chancre on the lip with great induration, which had proved refractory to mercury, no trace of the lesion remained twenty days after a dose of "606." A patient with large ulcers on the tonsils and numerous erosions on his penis and scrotum recovered in a fortnight under the remedy.

The secondary patches in the throat and on the labia of a girl disappeared in eight days after one injection of "606." A large gyrate papular syphilide which had remained uninfluenced by five mercurial courses receded in eight days after the administration of "Hata." A rupial eruption of seventeen months' standing, rebellious to many mercury cures, recovered in a fortnight after a dose of "Hata."

A girl underwent the inunction treatment in February. Very severe rupia supervened, sloughing ulcers of her throat prevented her swallowing. Eight days after an injection of "606" her fauces were healed and the rupial sores had cicatrised. Just as incredible is another case of malignant syphilis. Infected seven months, vigorously treated with inunctions and mercurial injections—rupia, phagedenic ulceration of throat, necrosis of nasal bones, joints affected. Very emaciated, fed by oesophageal tube, pulse 120; prognosis very unfavourable. Yet improvement began three days after an injection of "606." Healing of the throat and rupial ulcers was completed in twelve days, and he could swallow; the ozaena disappeared and he gained 8 kilogrammes in a month.

In another example of malignant syphilis which resisted mercury and iodides there was general rupia, sloughing ulcers in the fauces, and extreme weakness. Nevertheless, everything had disappeared three weeks after the administration of "606."

A man developed nervous symptoms, attacks of giddiness and aphasia after infection; notwithstanding energetic mercurial treatment a gumma of his testes and an ulcerating syphilide on his back developed. The gumma had gone and the ulcers had scarred seven days after a dose of "Hata." There was no recurrence of the nervous complications.

Old cases also benefit. A woman in a deplorable condition, with a deep ulcer on the perineum, caused by syphilis contracted in 1905, had benefited little from much mercury, iodide, and Röntgen ray therapy. A fortnight after an injection of "606" the ulcer, which was originally
15 cm. long and 2 cm. deep, had become greatly reduced in size. Cicatrisation was perfect five weeks later.

In another sufferer from old-standing malignant syphilis, absolutely intractable to the usual remedies, there was extensive destruction of the fauces, serpiginous ulceration of the thigh and scalp, nodes, and phagedenic sores on the penis. Twenty-six days after an injection of “Hata” the lesions had become repaired. Pemphigus in infants, the subjects of congenital syphilis, has hitherto been almost invariably fatal. Two out of five treated with “606” survived.

Michaelis [3] reports similar successes in malignant syphilis. He looks upon “606” as being the greatest pharmacological discovery since the introduction of quinine, and he notes that the discovery was made by systematic research and not by good fortune. He has employed it in 71 cases without noticing any evil results.

Pick [12] has an experience of 126 cases. He is astonished at the rapidity of its action. He considers it the best remedy for lues whether benign or malignant.

Spiethoff [13] has seen phagedena of the glands disappear in a week, phimosis and enlarged glands subside in a few hours. He reports on 50 cases.

H. Loeb [4] states, as the result of his own experience, that we possess in “606” a remedy which attacks exclusively the Spirochaeta pallida without damaging the tissues of the body, and that this substance surpasses all other anti-lytic agents in the rapidity and thoroughness of its action.

Treupel. [5] has no doubts of the almost magic action of “Hata.” Secondary lesions often disappear in two days.

A. Gluck [6] has treated 109 cases with “606.” Cleaning of ulcers and softening of induration and; of glands are apparent after twenty-four hours. Early secondaries vanish in three to five days. Lichen aggregatus and condylomata disappear completely within a week.

The greatest living authority on syphilis, Neisser [7], in conjunction with Kuznitzky, has given a pronouncement on the subject which must carry great weight. They mention that though arsenophenyl-glycin has afforded good results, yet it has a greater affinity for trypanosomes than for spirochetes. They have injected “Hata” in 126 cases and they find that the substance is very highly spirochetotropic, and is strikingly feeble in organotropic properties. In almost every instance where manifest syphilis existed the lesions subsided in a startling (verblüffenden) manner. Primary sores lose their hardness and heal. Treponemata in chancres and condylomata disappear in twenty hours. Macular and papular eruptions become stains only in a day or two. Mucous patches go; shotty glands soften and subside; gummata melt away; tertiary ulcers of malignant syphilis clean and are cicatrised in a few days. The paralyses and pains of cerebral lues disappear, sometimes in an hour or so,
A priori Neisser would have believed it impossible that these infiltrations could be absorbed with such rapidity. In short, the specific action of "606" is undoubted. What before was possible only by means of long and intensive treatment with mercury and iodides can now be attained in a few days.

The influence of the new remedy in changing a positive Wassermann reaction into a negative is marked. Neisser observed this in 44 per cent. of his cases; though if the more sensitive Stern's test was applied, 19 per cent. only became negative. Gerome found negative reactions in 60 per cent. of his cases treated with "606"; Schreiber in 80 to 90 per cent., and Wechselmann in 100 per cent. The earliest change noted occurred thirteen days after the injection. Generally twenty to thirty days must elapse before the serum gives a negative response. In Lange's experience, 57 per cent. of 268 cases reacted negatively four to five weeks after the treatment.

Each dose of "Hata" is contained in a glass capsule sealed in vacuo. It is in the form of a strongly acid dichloride. The method adopted for the preparation of the emulsion at the Military Hospital, Rochester Row, S.W., is as follows: 0.6 gramme of "606" is shaken into 30 cc. of sterile water heated to 50° C., contained in a sterile vessel. Solution is effected with the end of a glass rod; 6 cc. of ¹⁄₇ NaOH are slowly added—a lumpy precipitate falls which redissolves in the excess of the alkali. ¹⁄₇ acetic acid, prepared by mixing 1 cc. of glacial acetic acid with 16.6 cc. of sterile water, is dropped in till neutrality is restored—some employ phenol-phthalein, and others litmus as the indicator; 3.25 cc. is the theoretical amount of ¹⁄₇ acid required. The dioxy-diamido-arsenobenzol is again precipitated; but this time in a very fine form, which can pass with ease through the needle of the syringe. By using the exact quantities given above, the "606" becomes suspended in a solution of sodium chloride and acetate, which is isotonic with physiological saline fluid; pain is thereby avoided. The whole is then injected either into the glutei (Michaelis and Neisser) or subcutaneously beneath the scapula (Wechselmann). The sciatic nerves should be avoided. The pain of the injection is trifling at the time, but shortly afterwards may be severe. On the third or fourth day it may be aggravated by the infiltration which is produced. Warm baths and fomentations may relieve this, but morphia is sometimes required. Michaelis insists that the patients should remain in bed two days, but Neisser says that many experience so little discomfort that this is unnecessary. A few hours after the administration, rigors, vomiting, and pyrexia, 39.5° C. to 40° C., are observed. These symptoms, however, soon pass off. Neisser states that 2,500 patients have been treated with "606" without any bad symptoms other than those described. Disorders of vision and optic atrophy, which have caused the disuse of arsacetin, have never been observed. Bohac and Sobotka [8] noted retention of urine and constipation for some days.
in three cases, but Ehrlich [9] ascertained that 132 capsules of the same supply of "606" sent out to five different clinicians caused no similar effects. Hence it may be concluded that "606" in a dose of 0.6 gramme is harmless.

Schreiber [10] has recommended intravenous injection. But Ehrlich thinks that it is desirable that the compound should be fixed in the muscle or subcutaneous tissue. He [14] states that "606" should not be given in advanced degenerations of the nervous system.

Neisser advocates the use of "606" in every case of syphilis where no contra-indication exists. A review of the evidence before us would lead us to believe that we have entered on a new era in the treatment of syphilis.

REFERENCES.


A CASE OF ENTERIC FEVER WITH COMPLICATIONS; OPERATION; RECOVERY.

By Captain W. W. Boyce and Lieutenant A. G. Wells.
Royal Army Medical Corps.

Private E. was admitted to the Station Hospital, Lahore Cantonment, on January 18th, 1910, with symptoms of enteric fever. On the 20th some blood was taken for a bile test, and on the 23rd the test was reported "positive." On the 24th a few spots were noticed, and the abdomen, previously retracted, showed some distension. From this date to the 30th the disease ran a normal course, the temperature gradually falling, till on the latter date it remained 98.4° F. all day. Towards evening on the 31st the patient complained of pain and passed a motion containing a little blood. The pain was colicky in character and came on gradually, but there was no local tenderness or rigidity in the abdomen and no