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An Organic Antimony Compound with Curative and Prophylactic Activity in Experimental Trypanosomiasis.

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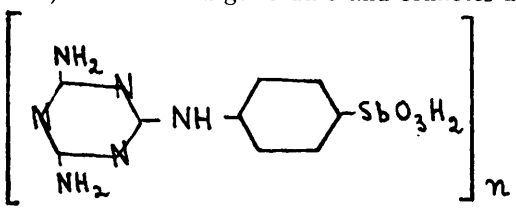
Two types of compounds, both metal free, are known to have a prophylactic effect in trypanosomiasis: the polysulfonated ureide "naphuride" (Synonyms: Bayer 205, Germanine, Moranyl, etc.) and amidines such as pentamidine and stilbamidine.

A third type of prophylactic compound, of the organometallic type, has now been obtained: a sodium salt derived from *p*-(2,4-diamino-1,3,5-triazinyl-6) aminophenylstibonic acid. (Synonym: melaminylphenylstibonic acid) where n is larger than 3 and connotes a



degree of polymerization, which will be discussed elsewhere.

This water soluble compound, containing quinquevalent antimony, was tolerated by 56 out of 56 mice in a single intraperitoneal dose of 2.5 g/kg. A single intraperitoneal dose of 0.0125 g/kg cured definitely without relapse (blood smears examined every second day for 40 days), all of 34 mice from a *T. equiperdum* infection which killed all of 10 untreated control mice within 3 to 5 days. The treatment was performed 24 hours after an intraperitoneal infection, at a time when the experimental animals showed at least one trypanosome per hundred red blood cells. The therapeutic index amounts thus to 200.

The prophylactic effect against a single infection is brought out by the following screening experiment: 5 mice are treated with a single intraperitoneal dose of 0.050 g/kg, polymerized sodium *p*-melaminylphenylstibonate (corresponding to 1/50th of the 100% tolerated dose), and infected 69 days later, together with 5 control mice with *T. equiperdum*. All controls die, within 5 days, of acute trypanosomiasis, whereas all pretreated animals survive and do not take the infection, as proved by daily negative blood examinations continued over 40 days. In this case the mechanism of the prophylactic activity seems to be based on the chemical effect of a drug which is resorbed and eliminated so slowly that a sufficient trypanocidal concentration is maintained in the organism over a considerable length of time. This theory is substantiated by the following observation: The pk of the compound is such that the free stibonic acid is precipitated by CO_2 from solutions of its sodium salt. After intraperitoneal and intramuscular injections of the sodium salt a white deposit of the free acid can be readily seen for many weeks on the surface of the peritoneum and between the muscle fibers.

The prophylactic effect against repeated infection is demonstrated in the next experiment:

105 mice are treated with one single in-

TABLE I.

% animals protected	Days after single treatment	No. of test infections
100	29	1
100	36	2
100	43	3
100	50	4
98	57	5
98	64	6
97	71	7
95	78	8
95	85	9
69	92	10
57	99	11
39	106	12
28	114	13
22	121	14
15	128	15
15	135	16
9	146	17
6	155	18
0	164	19

traperitoneal injection of 0.3 g/kg of polymerized sodium *p*-melaminylphenylstibonate. One month later the animals are given a *T. equiperdum* infection which kills the untreated controls without exception in 3 to 5 days. The test infection is repeated at weekly intervals on the surviving mice found to be free of trypanosomes. Untreated controls are set up at each infection and die without exception within 3 to 5 days. Blood examinations are performed daily on all animals. The results are summarized in Table I.

It is noteworthy that the mice finally breaking down under multiple infections show an atypical form of trypanosomiasis, differing basically from the classical acute blood infection characterized by the number of trypanosomes increasing continuously and progressively until death occurs. The pretreated animals present a chronic infection, of the human and rabbit type, with parasites appearing in and disappearing from the blood at irregular intervals. The post mortem of these chronic cases shows, invariably, an enormously enlarged spleen up to 10 times the weight and size of the normal spleen.

In this last experiment with repeated infections the mechanism of the prophylactic effect may possibly include an immunological factor.

Summary. A new heterocyclic stibonic acid is described, having a pronounced prophylactic effect in the *T. equiperdum* infection of the mouse and which cures this infection with a single intraperitoneal dose representing 1/200th of the maximum (100%) tolerated dose.

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Concentration of Chloride, Sodium and Potassium in Blood of Guinea Pigs Treated with Desoxycorticosterone Acetate.*

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The fibromatogenic effect of estrogens is known from the work of Nelson,[1] Lipschutz and Iglesias.[2,3] Subsequently the antifibromatogenic effect of steroids such as progesterone, testosterone, dihydrotestosterone and desoxycorticosterone has been demonstrated by Lipschutz and others.[4]

Desoxycorticosterone offers special interest clinically because the sex organs were not affected by antifibromatogenic quantities of this steroid, as was the case with the androgens. However, several clinicians[5,6] have described toxic actions in patients treated with therapeutic doses of desoxycorticosterone acetate. Changes in the concentration of the ions of the blood have been found in these patients. Selye and his collaborators[7,8] have induced important modifications of the ionemia with

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