of the drug was dropped on the heart, the rate was slowed, and notching, observed in the control record, disappeared. When the heart is washed with physiologic saline the effects of trichlorethylene are removed. If more than 1 cc of the drug is used, the heart continues to slow and stops in about 5 min. Washing with physiologic saline does not then revive the heart.

Since the electrocardiogram is a better record of the condition of the myocardium and conducting mechanism of the heart, it was decided to use this method next. Rabbits (4) were used for these experiments, and trichlorethylene was administered by inhalation. When the control records were made the rabbits were in a basal-like state,[5] and the drug was administered while they were still in this state. One rabbit was anesthetized every day for a week to study the effect of repeated anesthetizations. In the rabbits not previously treated with trichlorethylene, the drug produced arrhythmias and marked slowing. In the rabbit anesthetized each day for a week, T wave changes were noted on the electrocardiogram taken at the end of the period in addition to those mentioned above.

Experiments were also carried out to determine the effect of trichlorethylene on human and frog capillaries. These were visualized with a capillary microscope and measured with a micrometer. The capillaries of the parietal peritoneum were visualized in the case of the frogs, whereas those of the nail bed of the ring finger of the left hand were used in the case of the human experiments. Capillary loops were observed in all instances in order to study both the arterial and venous divisions. Trichlorethylene was administered by inhalation. Tests were carried out on 6 different human subjects and on 6 different frogs. The results were alike. Constriction of the arterial side of the capillary loops occurred. The degree of constriction was approximately 50%.

All of the aforementioned experiments are being extended and further work is being done.

It was concluded that: (a) trichlorethylene causes vasoconstriction of the arterial division of capillary loops both in humans and frogs; (b) it does not produce permanent injury to the heart unless it is given in large quantities (frog) or repeatedly (rabbit).

[5] Wereh, S. C., *J. Lab. Clin. Med.*, 1941, **26**, 725.

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Trypanocidal Activity and Arsenic Content of Rat Blood Following Intravenous Administration of Mapharsen.

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Fractional dose therapy of rat trypanosomiasis has shown the trypanocidal action of mapharsen *in vivo* to be of relatively short duration.[1] The brief trypanocidal activity of rabbit serum after administration of the related trivalent arsenical, reduced tryparsamide, is also indicative of this fact.[2] On the contrary, arsenic has been found in the

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[1] Swinyard, A. E., Hirschfelder, A. D., and Wright, H. N., *J. Pharm. Exp. Therap.*, 1942, **75**, 367.

[2] Murgatroyd, F., Russel, H., and Yorke, W., *Ann. Trop. Med. Parasit.*, 1934, **28**, 227.

blood and tissues of rats for relatively long periods after mapharsen injection.[3] This study was concerned with an investigation of the apparent lack of parallelism between these two factors.

The procedure consisted in determining the minimum trypanocidal concentration (M.T.C.) of the blood arsenic of rats at various intervals after intravenous injection of the maximum tolerated dose (12.5 mg/kg) of mapharsen and comparing this with the M.T.C. of the uninjected drug. The blood samples were taken at ¼, ½, 1, 4, 8, 12, 18, 24, 36, 48 or 240 hr after injection, heparin being used as an anticoagulant. The arsenic content was determined by the A.O.A.C. Gutzeit method,[4] and was expressed as μg (γ) of mapharsen per cc of blood. The M.T.C. was determined by a modification of the method of Murgatroyd *et al.*,[2] and Hawking *et al.*,[5] sterile technic being used throughout. A series of dilutions of the blood was made, on the basis of arsenic content, with a medium consisting of 1 part of heparinized rat blood and 2 parts of Locke's solution (0.2% glucose). The tubes were then inoculated with a dilute suspension of *Trypanosoma equiperdum* from infected rats and incubated for 18 hr at 37°C. After incubation, cultures which showed no motile organisms in microscopic cover-glass preparations were injected intraperitoneally into young rats, which were observed for septicemia and death for 30 days. As the study was extended, mice were substituted for rats, and found satisfactory in this infectivity test. The minimum concentration of arsenic rendering cultures noninfective was taken as the M.T.C. *(in vivo)*. The M.T.C. of uninjected mapharsen *(in vitro)* was determined simultaneously in each case, using the same diluting medium and the same inoculum of parasites. The mean M.T.C.'s *in vivo* and *in vitro* for any interval were considered different only if they exceeded a significant value (±1:2.018 million) calculated statistically from results on duplicate determinations on mapharsen made on 10 occasions.

The trypanocidal activity of the blood, exceedingly high at first, decreased steadily and disappeared after 24 to 36 hr. The trypanocidal period could be divided into 3 phases:

1. A period of extremely high activity for ½ to 1 hr during which the activity of the blood arsenic did not differ significantly from that of the drug itself, the decrease in activity being due entirely to a decreasing arsenic content. At ½ hr the arsenic content of the blood was 24.45γ per cc. (1:35,419) or 13.8% of the theoretical content immediately after injection. The M.T.C. *in vivo* was 1:11.1 million (m), the M.T.C. *in vitro* being 1:12.2 m.

2. A period of intermediate activity, to about 8 hr, during which the decreasing activity was due both to a decrease in the activity of the arsenic present and to a further decrease in the blood arsenic level. At 8 hr the blood arsenic level was 9.13γ per cc (1:109,509). The M.T.C. *in vivo* was 1:0.34 m, the *in vitro* value being 1:7.5 m.

3. A period of low activity during which the trypanocidal activity of the blood continued to decrease in spite of an increase in the arsenic content. At 12 hr the arsenic level was 11.34γ per cc (1:88,086), the M.T.C. *in vivo* being 1:0.12 m as compared with an *in vitro* value of 1:12.2 m. At 24 hr these values were 19.48, 1:0.055 m, and 1:10.9 m respectively. At 36 and 48 hr the blood was non-trypanocidal in spite of a substantial arsenic content. Arsenic was still present, but inactive, at 240 hr. Wright[3] has shown that the rise in blood arsenic at later intervals is due to a return of arsenic from the tissues. Since this returning arsenic is non-trypanocidal and since the incubation of mapharsen with blood produces a much slower decrease in activity than that occurring *in vivo*, it appears that the tissues play a major role in inactivation of the drug.

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[3] Wright, H. N., unpublished data.

[4] *Methods of Analysis, Association of Official Agricultural Chemists*, 4th Ed., 1935.

[5] Hawking, F., Hennelly, T. J., and Quastel, J. H., *J. Pharm. Exp. Therap.*, 1937, **59**, 157; 1938, **64**, 147.