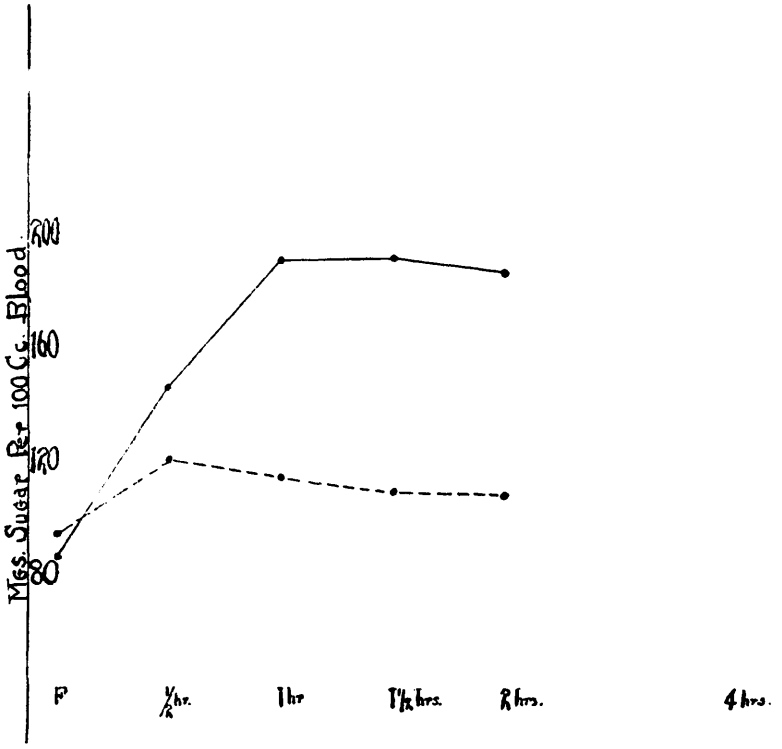


CHART I.

The unbroken line is the average composite curve of the blood sugar determinations on seven dogs following the injection of 10 mgm. morphine sulphate per kilo; the broken line, the composite curve on the same animals under amytal anesthesia and morphine.

4715

## Toxicity of Acetarsone (Stovarsol) and its Calcium and Sodium Salts on Oral Administration to Rabbits and Cats.*

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Acetarsone (acetyl-amino-hydroxy-phenyl arsonic acid) was synthesized in 1921 by Tréufouel and Fourneau[1] after having been pre-

* This report is based on part of an extended cooperative study of the chemotherapy of amebiasis conducted by the Department of Pharmacology of the University of California Medical School and the Pacific Institute of Tropical Medicine, San Francisco.

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[1] Fourneau, E., *Ann. Inst. Pasteur*, 1921, xxxv, 571.

pared earlier by Ehrlich.[2] Levaditi[3] noted the drug was toxic for rabbits in doses of 0.66 gm. per kilo on oral administration, and that it was tolerated in doses of 0.3 to 0.4 gm. per kilo. Since then the drug has been recommended for syphilis, amebiasis, and other protozoan infestations. Conflicting reports have appeared on its therapeutic efficiency and toxicity. Pool,[4] Worms,[5] and Kolle[6] found this compound more toxic than Levaditi originally reported, causing death in rabbits when 0.2 to 0.3 gm. per kilo were given by mouth.

Levaditi and Poole worked on material synthesized by Fourneau. We attempted to find the minimal lethal dose on oral administration to cats and rabbits of the commercially available product, and have also studied the toxicity of its calcium and sodium salts.[7]

The material was powdered and administered in gelatin capsules washed down with water. It was necessary to anesthetize the cats for this procedure. All animals were kept in individual cages, under identical conditions of diet and hygiene, and were observed for at least 30 days following the administration unless death intervened. Those animals dying within the observation period were subjected to post-mortem examination and sections of the principal organs were taken for histological study. Untreated animals were maintained in the laboratory under similar conditions as controls.

Table I shows the results of this study on 35 cats and 56 rabbits. The determination of the minimal lethal dose on oral administration is difficult because of the uncertainty of absorption. The range of toxicity of these compounds indicated by our figures seems reliable except in the case of calcium acetarsone in rabbits. Poole noted that some animals survived very high doses of sodium acetarsone.

In lethal doses animals lost weight markedly. Lethargy, anorexia, abdominal distension, and soft stools were noted. Immediately before death the pupils became constricted, respiration was increased, the abdomen bloated, the muscles relaxed, and on stimulation clonic convulsions were observed.

In animals dying from lethal doses necropsy revealed distension of the stomach, large intestines, and bladder, congestion of the lungs,

[2] Ehrlich, P., and Hata, S., *Die experimentelle Chemotherapie de Spirillosen*, Berlin, J. Springer, 1910.

[3] Levaditi, C., *et al.*, *Ann. Inst. Pasteur*, 1922, xxxvi, 729.

[4] Poole, A. K., *Johns Hopkins Hosp. Bull.*, 1926, xxxviii, 242.

[5] Worms, W., *Deutsche Med. Woch.*, 1925, li, 428.

[6] Kolle, W., *Deutsche Med. Woch.*, 1924, i, 1074.

[7] Supplied by Lilly Research Laboratories.

TABLE I.
*Toxicity of Acetarsone for Rabbits and Cats on Oral Administration.*

| Animal and M.L.D. | Dose in mgm./kg. | No. used | No. lived | No. died | Time of death |
|---|---|---|---|---|---|
| ACETARSONE | | | | | days |
| Arsenic content about 27.2% | | | | | |
| *Rabbits* | 100 | 2 | 2 | 0 | — |
| | 125 | 5 | 3 | 2 | 10, 11 |
| 125-150 mgm./kg. | 150 | 5 | 2 | 3 | 9, 9, 13 |
| 5/10 died | 175 | 5 | 3 | 2 | 4, 12 |
| | 200 | 5 | 1 | 4 | 10, 12, 19, 20 |
| | 225 | 2 | 1 | 1 | 26 |
| *Cats* | 100 | 2 | 2 | 0 | — |
| | 125 | 2 | 2 | 0 | — |
| 150-175 mgm./kg. | 150 | 4 | 3 | 1 | 3 |
| 3/6 died | 175 | 2 | 0 | 2 | 3, 20 |
| | 200 | 3 | 0 | 3 | 10, 20, 29 |
| | 250 | 1 | 0 | 1 | 8 |
| CALCIUM ACETARSONE | | | | | |
| Arsenic content about 23.8% | | | | | |
| *Rabbits* | 75 | 2 | 2 | 0 | — |
| | 100 | 4 | 2 | 2 | 6, 8 |
| Not determined | 125 | 2 | 1 | 1 | 10 |
| | 150 | 5 | 4 | 1 | 9 |
| | 200 | 3 | 1 | 2 | 8, 14 |
| | 250 | 1 | 1 | 0 | — |
| *Cats* | 125 | 2 | 2 | 0 | — |
| | 135 | 3 | 2 | 1 | 3 |
| 135-150 mgm./kg. | 150 | 5 | 2 | 3 | 3, 3, 5 |
| 4/8 died | 200 | 1 | 0 | 1 | 3 |
| SODIUM ACETARSONE | | | | | |
| Arsenic content about 25.3% | | | | | |
| *Rabbits* | 75 | 1 | 1 | 0 | — |
| | 100 | 2 | 2 | 0 | — |
| 150 mgm./kg. | 125 | 5 | 4 | 1 | 14 |
| 2/4 died | 150 | 4 | 2 | 2 | 7, 14 |
| | 200 | 2 | 0 | 2 | 7, 7 |
| | 250 | 1 | 0 | 1 | 7 |
| *Cats* | 100 | 2 | 2 | 0 | — |
| | 125 | 4 | 1 | 3 | 3, 4, 30 |
| 125-150 mgm./kg. | 150 | 3 | 1 | 2 | 3, 22 |
| 5/7 died | 200 | 1 | 0 | 1 | 3 |

liver, and kidneys, and occasional hemorrhages in the kidneys. Microscopic sections[8] showed congestion of the lungs, liver, spleen, and kidneys, with deposition of pigment in these organs. Tubular degeneration of the kidneys with occasional hemorrhages was seen in several sections. Moderate granulation of cardiac fibres was noted. Disorganization of the muscle fibres of the stomach was observed. The liver cells were filled with fat globules. Our findings agree with those of Heitzmann,[9] who also mentions blood cell destruction,

[8] Through the courtesy of the Department of Pathology, University of California Medical School.

[9] Heitzmann, O., *Archiv. f. Derm. u. Syph.*, 1926, clii, 344.

epithelial necrosis, calcification in the kidneys, and fatty deposits in the heart, liver and kidneys.

*Summary:* The minimal lethal dose of commercially available acetarsone administered orally to cats and rabbits is between 125 and 175 mgm. per kg. This is about 4 times the toxicity originally reported by Levaditi for the material prepared by Fourneau. In view of the relatively large number of clinical cases of acetarsone poisoning these experimental findings indicate the necessity of a revision of the recommended therapeutic dose.

The minimal lethal dose of the calcium and sodium salts of acetarsone on oral administration to cats and rabbits seems to be about the same as that of acetarsone.

## 4716

## Osseous Changes Due to Pressure Trauma.

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When a continuous pressure is maintained upon the bone in the alveolar process of the maxilla the resulting trauma is characterized by several histo-pathological changes.

The manner of applying pressure is by means of bands cemented upon the crowns of the teeth. To these spring wire has been previously soldered so that when the appliance is in place the tension may be increased, decreased or changed in direction merely by bending the spring wire. Such appliances have been in place on teeth of monkeys *(Macacus rhesus)* from one day to 8 months and the results have been so striking that this preliminary report seems appropriate.

When the crowns of teeth are separated distally their roots are forced nearer each other. This pressure produces areas of absorption in the alveolar process as well as on the periphery of the roots. Combined with this absorption is a great amount of fibroblastic activity. These changes commence apparently early in the experiment as shown by the examination of the tissues from an animal on which the appliances had been in place only 24 hours.

In one case, where the greatest possible tension was applied in the effort to produce absorption, the alveolar process between the teeth was fractured.