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## THE PHARMACOLOGICAL ACTION OF PEIMINE AND PEIMININE.*

BY K. K. CHEN, A. LING CHEN AND T. Q. CHOU.

The crude drug, Pei Mu, has been used in Chinese medicine as an antipyretic, cough sedative, expectorant and lactagogue (1). In combination with other ingredients, it has been advocated for the treatment of difficult labor, retention of placenta, blurring of vision and spider and snake bites.

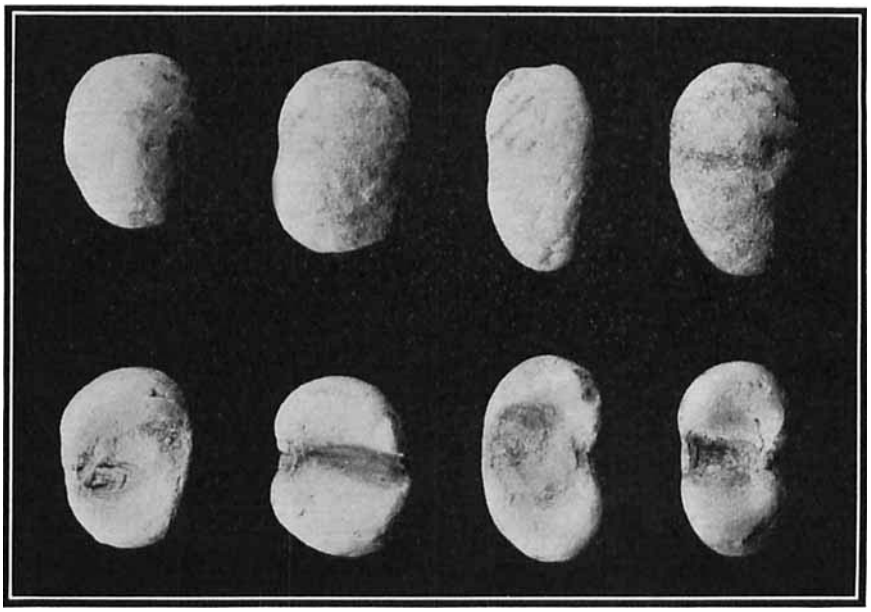

Fig. 1.—Pei Mu from Chekiang Province.

Pei Mu is made of the bulbs or corms of a liliaceous plant which is identified as *Fritillaria roylei* by Stuart (2), but as *F. verticillata*, Willd. *var. Thunbergii*, Bak. in Botanical Nomenclature (3). The corms produced in Chekiang Province are kidney-shaped, as shown in Fig. 1, each weighing on the average 3.5 Gm., and

* From the Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, and the Institute of Materia Medica, National Academy of Peiping, and the Sino-French University, Peiping, China.

measuring 1.9 cm. in width and 2.8 cm. in length. Those grown in Szechuan Province and other localities are different in size and shape. It is possible that in Chinese commerce several varieties or species come under the same name, Pei Mu.

Yagi in 1913 (4) reported the isolation from Pei Mu of a base having the formula $C_{25}H_{41}NO_3.H_2O$ which he named *fritilline*. This substance forms no salts with acids. It is said to depress the respiration and heart action similarly to veratrine.

In contrast to the results of Yagi, Fukuda (5) obtained two different crystalline substances: *verticine*, $C_{18}H_{33}O_2N$ or $C_{19}H_{35}O_2N$, m. p. 224–224.5° C., $[\alpha]_D^{10}$ −10.66°; and *verticilline*, $C_{19}H_{33}O_2N$, m. p. 148–150° C.

In a previous communication (6) one of us (T. Q. C.) described the isolation of two alkaloids from the material of Chekiang origin. Although the two principles

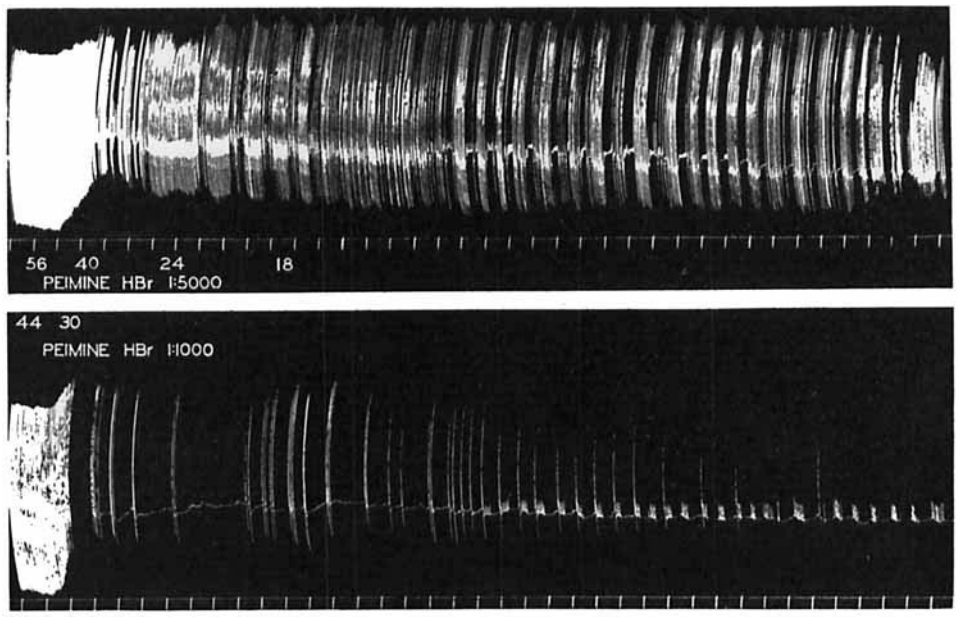


Fig. 2.—Action of Peimine HBr on Frog's Heart. Upper: Frog No. 222, male, weighing 44 Gm., pithed. Lower: Frog No. 219, female, weighing 50 Gm., pithed.

have some resemblance in elementary composition to verticine and verticilline, they do not seem to be entirely identical with the latter, thus justifying the proposal of two new names: *peimine*, $C_{19}H_{30}NO_2$, m. p. 223° C., $[\alpha]_D^{24}$ 0°; and *peiminine*, $C_{18}H_{28}NO_2$, m. p. 135° C., $[\alpha]_D^{24}$ −62.5°.

The present paper deals with the pharmacological effects of peimine and peiminine. The hydrobromides of the two substances were employed in all experiments—peimine HBr melting at 288° C. and peiminine HBr at 292° C.

*A. In Frogs.*—The action of both peimine and peiminine is practically identical. In small frogs (20 to 21 Gm.) doses of 5 to 10 mg. of either substance injected into the lymph sac produced no toxic signs. When perfused through the inferior vena cava, a 0.1 per cent solution of peimine HBr rapidly caused slowing of heart rate, increase in systole and decrease in diastole, soon followed by almost complete

A-V block, as shown in Fig. 2. The ventricle became so depressed that it contracted only at intervals, and gradually the amplitude grew very small. A concentration of 1:5000 reacted in a similar but less effective manner (Fig. 2). Periodicity was the ultimate feature. The results with peiminine are essentially the same.

*B. Toxicity.*—By intravenous injection in mice of a 0.1 per cent solution of either peimine HBr or peiminine HBr, the minimal lethal dose was determined to be 9 mg. per Kg. for each, as summarized in Table I. Violent tonic convulsions occurred before death. Doses as small as 3 or 4 mg. per Kg. also caused convulsive movements which became more pronounced upon stimulation. Those animals that survived showed no apparent injury when observed for 7 to 10 days.

TABLE I.—TOXICITY OF PEIMINE HBR AND PEIMININE HBR IN MICE BY INTRAVENOUS INJECTION (SOLUTION 0.1 PER CENT).

| Drug. | Dose, Mg. per Kg. | Number of Mice Used. | Number of Mice Died. | Minimal Lethal Dose, Mg. per Kg. |
|---|---|---|---|---|
| Peimine HBr | 8 | 5 | 2 | |
| | 9 | 5 | 3 | 9 |
| | 10 | 5 | 4 | |
| Peiminine HBr | 8 | 5 | 1 | |
| | 9 | 5 | 4 | 9 |
| | 10 | 1 | 1 | |
| | 11 | 3 | 2 | |

In rats the toxicity, as tested with peimine HBr, is not so great, although convulsions were noticed with a dose of 5 mg. per Kg., injected intravenously. These animals completely recovered from an amount of 25 mg., but deaths began to occur with a dose of 35 mg. per Kg. No study was made with peiminine in rats.

In rabbits, weakness in the legs, ataxia and tremulous movements occurred following a dose of 10 mg. per Kg., given by vein, of either peimine or peiminine in the form of a hydrobromide.

*C. Other Effects.*—Both peimine and peiminine as hydrobromides in the dosage of 10 or more mg. produced a fall of blood pressure, with prompt recovery, in etherized cats. The amplitude of the respiration diminished slightly as the blood pressure fell.

In rabbits there was a moderate hyperglycemia following the intravenous administration of either peimine or peiminine. Thus one animal had an increase of 71 mg. of sugar per 100 cc. of blood 45 minutes after the injection of 10 mg. of peiminine HBr. The maximal increase in another rabbit with 5 mg. of peiminine HBr was 14 mg. Peimine HBr caused a maximal rise of blood sugar of 23 mg. per 100 cc. of blood in a rabbit with a dose of 10 mg., 22 mg. in another with a dose of 7.5 mg. per Kg. and 18 and 35 mg. in two others with doses of 5 mg. per Kg. each.

A concentration of 1:10,000 of peimine or peiminine HBr inhibited the movements of rabbits' isolated intestines, with gradual recovery.

When applied locally a 1 per cent solution of either substance is slightly bitter to the taste, the action of peimine HBr being somewhat more pronounced. No mydriasis or local anesthesia resulted when the same solution was dropped into rabbits' eyes. Neither peimine nor peiminine stimulated the submaxillary and pancreatic secretions, or increased the urinary output (dogs).

SUMMARY.

The effects produced by peimine and peiminine are practically the same. When perfused through the inferior vena cava in frogs, they induce decrease in the heart rate, complete A-V block and periodicity. They cause a fall of blood pressure (cats), and inhibit the activity of isolated rabbits' intestines. There is a moderate hyperglycemic action in rabbits. The minimal lethal dose to white mice, by intravenous injection, of both peimine and peiminine, is 9 mg. per Kg., death being preceded by tonic convulsions.

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# STUDIES IN PERCOLATION.*

## A. Anomalies Observed in the Percolation of Cinchona.

BY MILTON WRUBLE.

As one of the first tests of the mechanism of percolation, it seemed desirable to learn something about the nature of the extraction as the menstruum passes down from stratum to stratum in the percolator. The ideal way to carry out this test experimentally on a percolator containing 1000 Gm. of drug, would be to segment the drug in layers of 100 Gm. and stop the tincture at the bottom of each segment. To carry out this idea practically it seemed unsatisfactory to devise a means giving even approximate results. Hence, in place of a single percolator, a number of percolators were used, each representing a hypothetical segment of the larger percolator as suggested above.

The unit adopted for the first test of this scheme was that of 100 Gm. and the unit of percolate to be tested that of 100 cc. Inasmuch as 10 cc. were to be removed from each percolate for the tests planned, it was necessary to charge the second percolator with 90 Gm. of drug and to draw 90 cc. of percolate, to charge the third percolator with 80 Gm. of drug and to draw 80 cc. of percolate, etc.

Cinchona was selected for this experiment, not only because its alkaloidal content could be determined quantitatively with a considerable degree of accuracy even in mere traces, but because this drug presented problems in connection with the keeping qualities of both tincture and fluidextract that were worth while investigating.

The drug in question was obtained from J. L. Hopkins & Co., in December 1930, in powdered form, approximately a No. 20 powder.

*Experiment I.*—The 100-Gm. batch was moistened with 75 cc. of 95 p. c. alcohol, and the other batches with equivalent amounts. Each such moistened batch was allowed to stand in a closed container for 6 hours before packing in the per-

* Scientific Section, A. Ph. A., Toronto meeting, 1932.