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PHARMACOLOGICAL ACTION OF FRITIMINE

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Previously one of us [Chou, 1932] reported the isolation of two bases, peimine and peiminine, from the Pei Mu of Chekiang Province. Later an entirely different alkaloid, fritimine, $C_{38}H_{62}N_2O_3$, was obtained by the same author from the Pei Mu of Szechuan Province [Chou, 1933]. Although both specimens of Pei Mu may be considered the bulbs of *Fritillaria royale* or *F. verticillata var. Thunbergii,* it is not likely that they belong to the same species. This may account for the difference in alkaloidal constituents. Similarly, Yagi [1913] reported the isolation of fritilline and Fukuda [1929] that of verticine and verticilline, from Pei Mu. It is probable that the Chinese drug Pei Mu includes several species of liliaceous plants. A careful identification of their botanical origin is urgently needed.

The pharmacological results of peimine and peiminine have been presented elsewhere [Chen, Chen and Chou, 1933]. The present communication deals with the effects of fritimine in animals For experiments, the base, m.p. 167°C, was dissolved in a least amount of $N/10$ hydrochloric acid, and diluted to the desired strength.

The action of fritimine on blood pressure in etherized cats is that of depression. A dose of 4.2 mg/kg produced a prolonged fall of pressure as shown in fig. 1 The respiration diminished as the blood pressure began to drop, but promptly recovered, although the pressure remained at a low level. Similar results were observed in another animal with twice the amount of the alkaloid.

In rabbits, fritimine in the dosage of 7.5 mg/kg or more, injected intravenously, causes an increase of blood sugar as determined by the

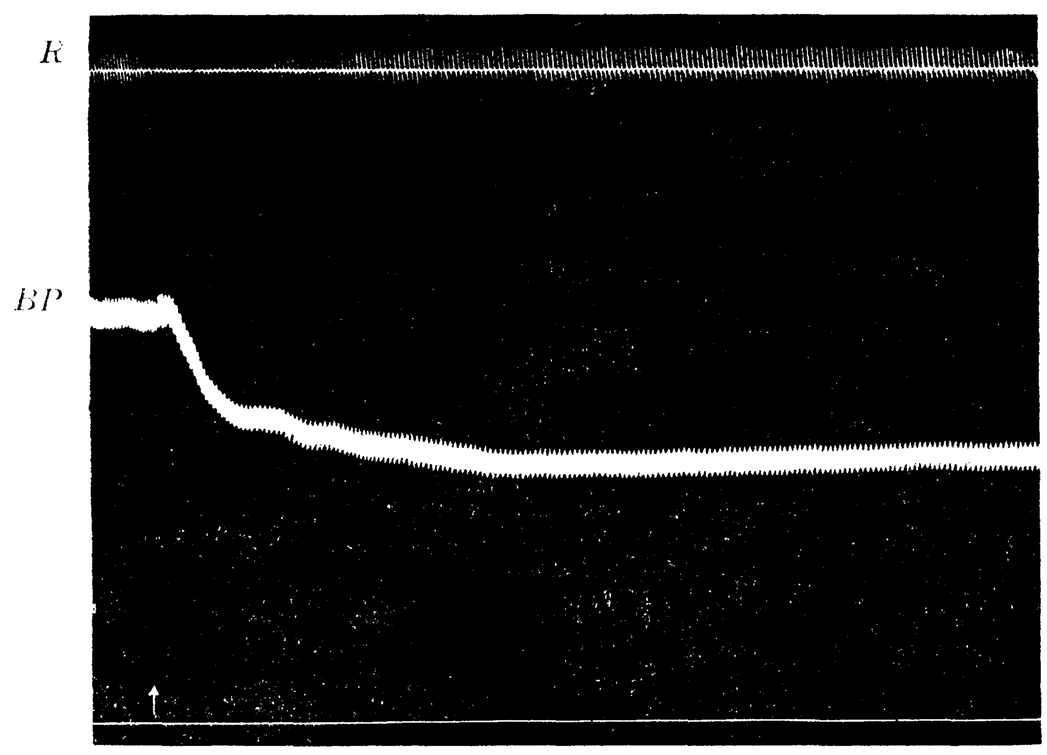

Fig. 1. Action of fritimine on blood pressure (BP) and respiration (R). Cat, male, 2.388 kg, etherized, was injected intravenously with 10 mg of fritimine. Notice the prolonged fall of blood pressure.

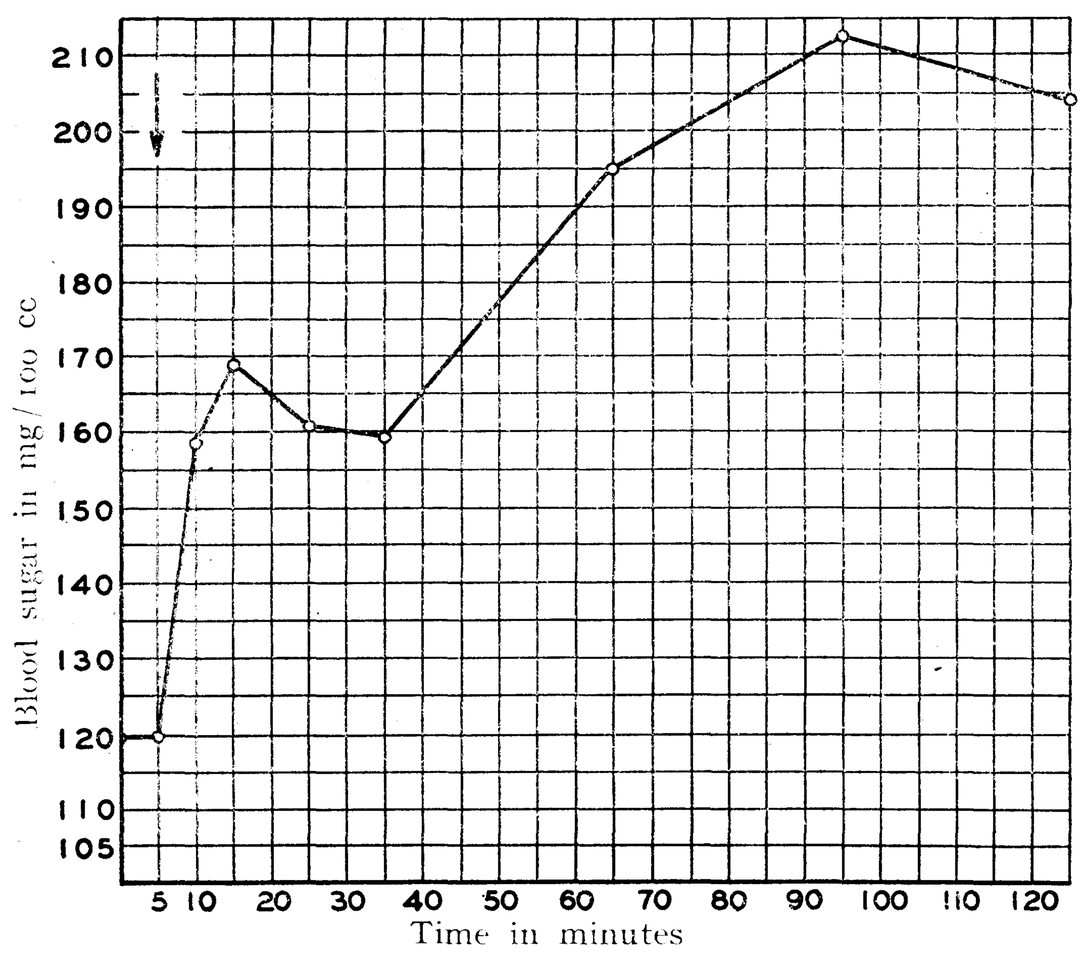

Fig. 2. Fritimine hyperglycemia.

Rabbit, female, 2.44 kg, was injected intravenously with 10 mg of fritimine per kg of body weight. The animal had convulsions 5 minutes after the injection, but survived.

Hagedorn-Jensen method [1923]. The hyperglycemia usually lasts longer than 2 1/2 hours. Fig. 2 may be taken as representative of the experiments. It should be noted that two hours after the injection, the blood sugar was still 80 mg/100 cc above the original concentration.

A 1 per cent solution of fritimine when applied locally to the rabbit's eyes does not cause mydriasis.

The minimal lethal dose of fritimine as the base in white mice by intravenous injection was determined to be 40 mg/kg (table 1). The substance is therefore less toxic than peimine or peiminine [Chen, Chen and Chou, 1933]. Tonic and then clonic convulsions occur with sublethal doses and become more severe with fatal doses. Rigor supervenes as soon as the mouse dies of fritimine poisoning, for the body of the animal is uniformly stiff when the heart stops.

Rabbits appear to be more susceptible to fritimine. The minimal lethal dose of this base by intravenous injection probably lies between

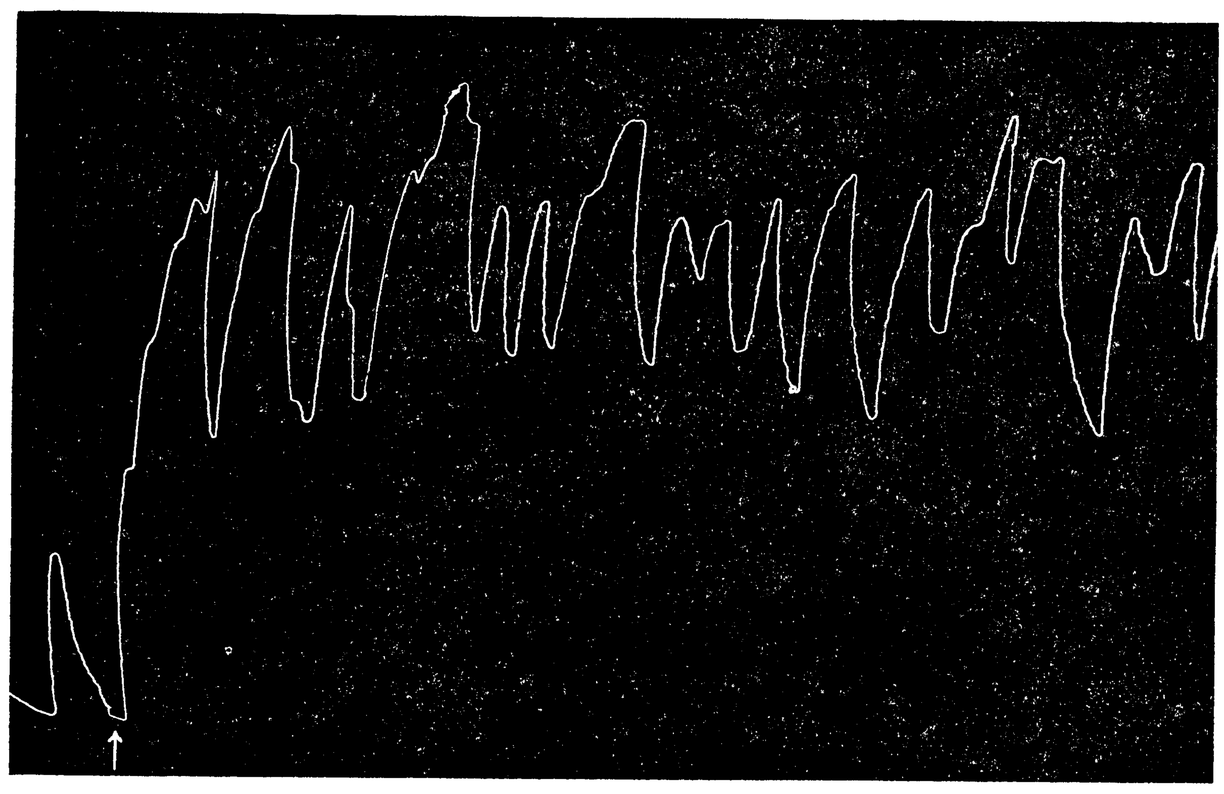

Fig. 3. Action of fritimine on isolated guinea pig's uterus.

A strip of the right horn was immersed in Locke-Ringer's solution, maintained at 38°C. At arrow, fritimine was added to the bath to a concentration of 1:50,000.

TABLE 1.

Toxicity of fritimine in white mice

Dose as base	Number of mice used	Number of mice died	Minimal lethal dose
mg/kg			*mg/kg*
25	1	0	
35	5	1	
40	5	4	40
50	1	1	

TABLE 2

Toxicity of fritimine in rabbits

Rabbit number	Sex	Body weight	Dose as base	Results
		kg	*mg/kg*	
1	M	2.95	7.5	Hyperglycemia, recovered
2	F	2.09	10	Convulsions, hyperglycemia, recovered
3	M	1.85	12	Convulsions, rapid breathing, legs paralysed, died in 6 hours
4	M	1.90	14	Convulsions, legs paralyzed, recovered in 5 hours
5	M	1.99	15	Convulsions, died in 17 minutes
6	F	1.91	16	Convulsions, legs paralyzed, recovered in 5 hours

12 and 15 mg/kg (table 2). Tonic convulsions take place with an amount of 10 mg/kg or higher doses. Both front and hind legs are extended, and among surviving animals complete recovery occurs in about 5 hours.

Fritimine contracts and increases the tone of the isolated guinea pig's uterus (fig. 3) in concentrations varying from 1:167,000 to 1:50,000. Of special interest is its action on the isolated rabbit's small intestines —being definitely inhibitory (fig. 4). It does not antagonize the effect of physostigmine or barium chloride. The inhibition is not likely due to the stimulation of the sympathetic nervous system on account of the depressor action and lack of mydriasis. Nor is it due to the parasympathetic paralysis, because physostigmine produces its

usual response. The same can be said for the muscular paralysis since barium chloride is effective after fritimine. The limited quantity of the alkaloid at our disposal prevented us from further exploration. It is obvious, therefore, that additional work will be necessary, particularly with reference to ganglionic structures, before the site of action of fritimine can be precisely analyzed.

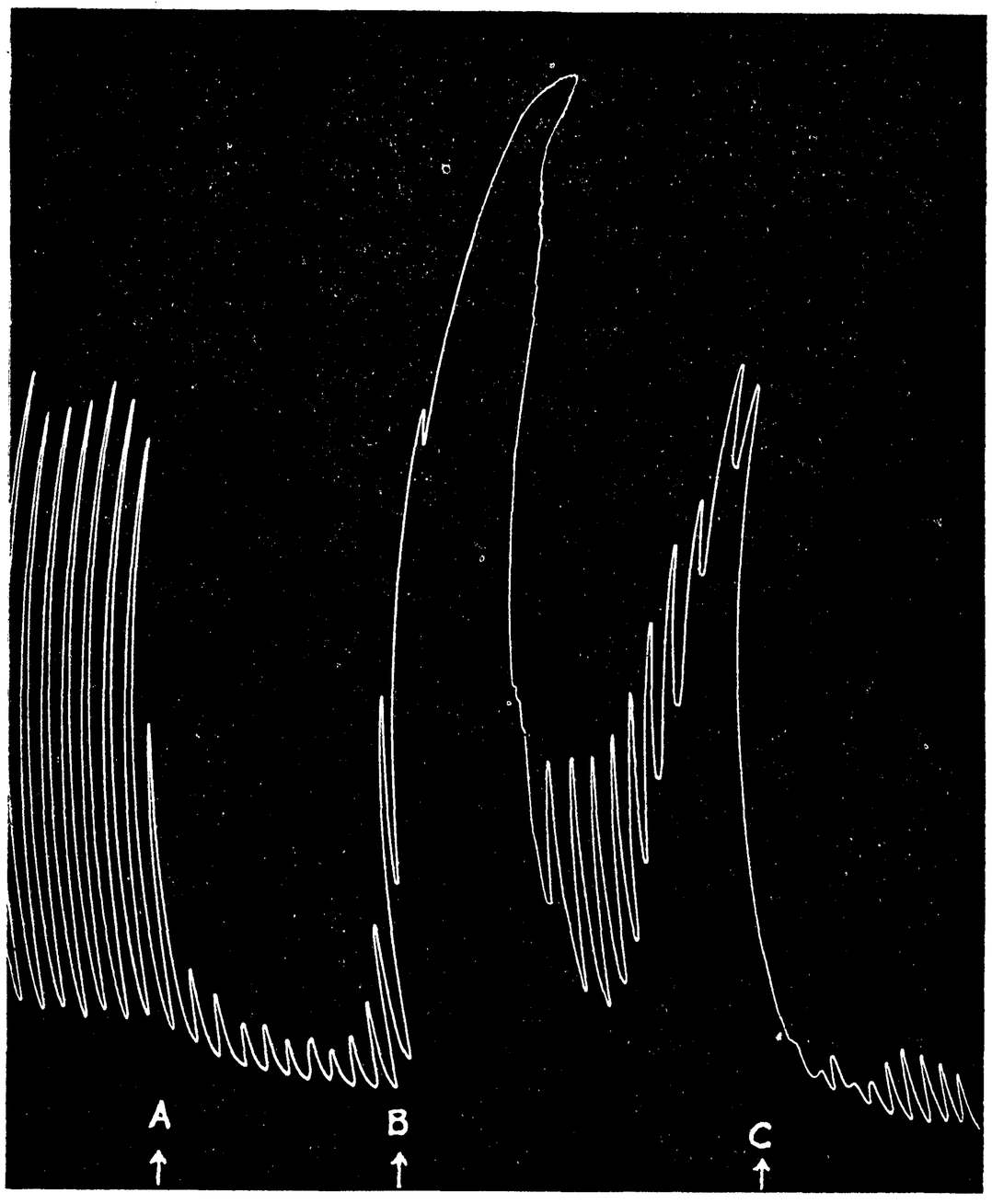

Fig. 4. Action of fritimine on isolated rabbit's small intestines.

A strip was immersed in Locke-Ringer's solution, maintained at 38°C. At A, fritimine was added to the bath to make a concentration of 1 : 100,000. At B, physostigmine salicylate was introduced without washing—the concentration being 1 : 100,000. At C, adrenaline chloride was super-imposed —the concentration being 1 : 2,500,000.

SUMMARY

Fritimine, an alkaloid of the Pei Mu of Szechuan Province, lowers blood pressure in anesthetized cats, temporarily depresses respiration, increases blood sugar in rabbits, contracts the isolated guinea pig's uterus, and inhibits the isolated rabbit's small intestines. The minimal lethal dose of the base in white mice by intravenous injection has been found to be 40 mg/kg. Deaths are preceded by convulsions and immediately followed by rigor. Fritimine is more toxic to rabbits.

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貝母素丙之作用

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趙承嘏於川貝母中提出貝母素丙（Fritimine）已載本誌（第七卷第一期）。此素能降低猫之血壓，暫抑呼吸，增加兎之血糖，收縮離主體的荷蘭猪子宮。及阻止離主體的兎腸之蠕動。其最小殺鼷鼠量爲每公斤體重用四十公絲。死前有痙攣。死後身卽硬。貝母素丙於家兎爲尤毒。