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THE ACTION AND TOXICITY OF MENISINE AND MENISIDINE

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Previously one of us [Chou, 1935] succeeded in isolating menisine, $C_{19}H_{22}O_3N$, and menisidine, $C_{36}H_{41}O_6N_2$, from Mu-fang-chi. The former melts at 127°C and has a specific rotation $[\alpha]_D^{20}$ +290°, while the latter melts at 176°C and possesses a specific rotation $[\alpha]_D^{20}$ +260°. They do not appear to be related to thunbergin, $C_{20}H_{14}O_9$, and mufangchine, $C_{14}H_{21}O_{11}N_{14}$ [Chen and Chen, 1936]. Although their composition has some resemblance to tetrandrine [Chen and Chen, 1935], their low melting points seem to make them definitely different. The present investigation deals with the pharmacological and toxicological action of menisine and menisidine. For our experiments both crystalline bases were dissolved in theoretical amounts of hydrochloric acid, menisine being monobasic and menisidine dibasic.

EXPERIMENTAL

Emesis. Like tetrandrine [Chen and Chen, 1936] both menisine and menisidine induce vomiting in pigeons. As shown in table 1, the minimal emetic dose of menisine is approximately 40 mg per kg and that of menisidine 90 mg per kg.

Circulation and respiration. Ten frogs were perfused into the inferior vena cava with menisine and menisidine. A concentration of 1.20,000 of menisine produced a gradual decrease of heart rate and its amplitude; one of 1.10,000, periods of bradycardia and stoppage (fig. 1A); and one of 1:5,000, rapid standstill at diastole. With menisidine, similar effects were observed, only stronger concentrations were

required. Thus, a 1:10,000 solution caused reduction of cardiac rate and contraction; and frequently, a 1:5,000, periods of slow beating followed by arrest (fig. 1B)

TABLE 1

Emetic action of menisine and menisidine in pigeons

Drug	Pigeon number	Body weight	Dose	Vomiting occurred
		g	*mg/kg*	
Menisine	1	400	30	0
	2	263	40	+
	3	283	50	+
Menisidine	4	325	50	0
	5	300	60	0
	6	239	80	0
	7	320	90	+
	8	304	100	+

In two etherized cats, intravenous injections of menisine in doses of 5 to 10 mg (total), or menisidine in doses of 10 to 20 mg, resulted in a fall of blood pressure with gradual recovery. During the fall, the heart rate was slowed and the respiratory rate more often diminished than accelerated. Menisidine was about one-half as effective as menisine, gram for gram.

Isolated intestines and uteri. Four strips of isolated rabbits' small intestines were treated with menisine. A concentration of 1:250,000 caused a primary stimulation followed by depression, and one of 1:25,000, pure paralysis. The paralytic action persisted after repeated washings. Upon three other strips of intestines, menisidine showed practically the same effect but with twice the quantity.

Two strips of isolated guinea pig's uterus were studied with menisine. A 1:25,000 solution caused prompt contractions and increase in tone. Upon repeated applications, the stimulation completely disappeared,

Similar results were obtained with menisidine. The response of the uterus to pituitary extract was inhibited by both menisine and menisidine. It is apparent that the two alkaloids have an initial, and later, a paralyzing action on the smooth muscles.

TABLE 2.

Toxicity of menisine and menisidine

Species of animal	Drug	Solution	Dose	No. of animals died/No. of animals used	Minimal lethal dose
		per cent	*mg/kg*		*mg/kg*
Mice	Menisine	1	25	0/3	35
			30	2/5	
			35	3/5	
			40	1/1	
	Menisidine	1	90	1/5	100
			95	2/5	
			100	4/5	
Rats	Menisine	1	10	0/1	20
			15	1/4	
			20	3/4	
			30	1/1	
	Menisidine	1	70	1/4	75
			75	3/3	
			80	3/3	
Guinea pigs	Menisine	2	40	0/3	45
			45	3/4	
			50	1/1	
	Menisidine	2	50	0/1	60
			55	1/4	
			60	3/5	
			65	1/1	

Toxicity. Menisine in doses of 0.2 to 0.5 mg per g injected into the lymph sac, paralyzed and killed frogs in less than 40 minutes. The heart stopped at diastole. Depression was noted with sublethal doses. For menisidine, it required an average dose of 0.75 mg per g to cause paralysis and death.

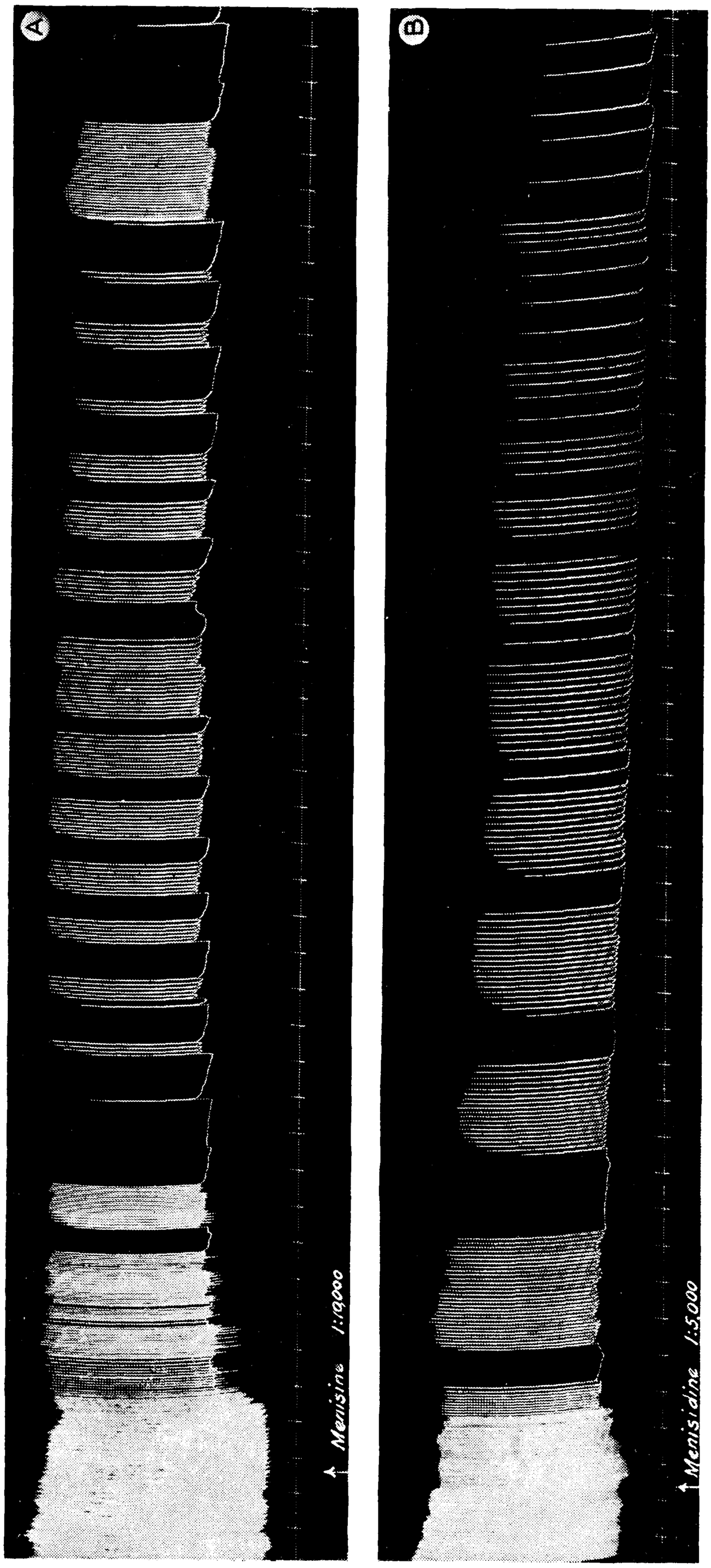

Fig. 1. Action of menisine and menisidine on the frog's heart.

A. Frog No. 552, female, weighing 84 g, decerebrated and pithed, was perfused via the inferior vena cava.

B. Frog No. 554, female, weighing 98 g, decerebrated and pithed, was perfused by the same route.

In higher mammals, the minimal lethal doses of menisine and menisidine by intravenous injection in mice, rats, and guinea pigs were found to be 35 and 100, 20 and 75, and 45 and 60 mg per kg, respectively. Deaths were preceded by clonic convulsions. In each instance, menisidine proved to be less toxic than menisine, gram for gram. It may be interesting to point out that the fatal dose of many other substances is usually smaller in guinea pigs than in mice or rats, but with menisine the reverse is true.

All the above results, including those on emesis, circulation and respiration, and smooth muscle organs, indicate that qualitatively menisine and menisidine have effects similar to those of tetrandrine [Chen and Chen, 1937]. It is not impossible, therefore, that further chemical studies of these substances may similarly reveal close relationship among them.

SUMMARY

1. Menisine and menisidine cause vomiting in pigeons.

2. Menisine and menisidine depress cardiac activity in frogs and cats, and lower arterial blood pressure.

3. Menisine and menisidine produce primary stimulation followed by depression and paralysis of the smooth muscles of isolated rabbits' intestines and guinea pigs' uteri.

4. Fatal doses of menisine and menisidine induce paralysis of limbs in frogs before cardiac arrest. By intravenous injection in mice, rats, and guinea pigs, the minimal lethal doses of menisine and menisidine have been found to be 35 and 100, 20 and 75, 45 and 60 mg per kg, respectively. Clonic convulsions occur before death.

5. The action of menisine and menisidine is qualitatively similar to that of tetrandrine.

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木防已素甲與木防已素乙之作用及毒性

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木防已素甲與木防已素乙能使鴿嘔吐。

木防已素甲與木防已素乙抑制蛙與猫心臟之機能幷低減其動脈血壓。

對於兎之離體小腸與荷蘭猪之離體子宮的平滑肌，木防已素甲與木防已素乙先興奮繼抑制終麻痺之。

木防已素甲與木防已素乙之致死量先使蛙四肢麻痺繼則停止其心臟之機能，於鼷鼠，白鼠與荷蘭猪中，行靜脈注射，木防已素甲與木防已素乙之最低致死量以每體重一公斤計算，順序爲35與100，20與75及45與60公絲。臨死前有陣攣性驚厥，木防已素甲與木防已素乙之作用，從定性上言，與漢防已素同。