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Effect of Pentaquine on Cardiovascular System of Unanesthetized Dogs.

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In the course of studies on the chemotherapy of malaria with pentaquine, Craige, Jones, Eichelberger, Alving, Pulman, and Wharton[1] observed that a certain number of patients developed postural hypertension which they believe was caused by the drug. More recently, Freis and Wilkins[2] have summarized the results of a clinical trial of this compound in a group of 17 patients with long standing hypertension. In the majority of their cases the administration of large doses produced lowering of the systolic and diastolic pressure in the supine position, usually associated with postural hypotension. Pentaquine is too toxic for routine treatment of hypertension in man, but it is unknown at the present time whether it might not be possible to obtain less toxic, and more active agents in the group of 8-amino quinolines. The search for such an agent would be made easier if it were possible to use an experimental animal as a test object. For this reason we have investigated the effects of pentaquine on the cardiovascular system of normal unanesthetized dogs, and have obtained results suggesting that such studies can serve as the basis for a screening test for other 8-amino quinolines which may have an action on essential hypertension in man.

Unanesthetized adult dogs were used throughout. Animals were comfortably restrained on a tilt table during the period of observation. Arterial pressure was recorded by an Anderson glass capsule manometer[3] from a cannula inserted in a femoral artery. One per cent procaine was used to anesthetize the skin over the area of the incision.

The response of the cardiovascular system to the following procedures was studied: (a) The effect of the intravenous injection of a range of doses of epinephrine, (b) the effect of the intravenous injection of a range of doses of acetylcholine, (c) the effect of tilting from a horizontal position to an 85° angle, for a period of one minute.

Following control observations the cannulated artery was tied, powdered sulfadiazine shaken into the incision, and the wound closed with linen sutures. Pentaquine* was then administered orally as an aqueous solution 3 times daily at 8 a. m., 12 m. and 5 p. m. After an appropriate period of treatment the observations on the cardiovascular system were repeated, using the opposite femoral artery.

Results. Typical toxic effects were produced in all dogs by the oral administration of doses of pentaquine in excess of 3.75 mg

TABLE I.
Resting Observations on Unanesthetized Dog Before and After Treatment with Pentaquine.

Dose mg/kg	Length of treatment	No. of dogs	Dog showing postural hypotension	Mean pulse rate per min.	Mean arterial pressure mm Hg	
					Diastolic	Systolic
—	—	12	0/12	119	119	171
3.75	4½	6	0/6	135	125	195
7.5	4½	5	2/5	**151**	**103**	146
15.0	2½	6	4/6	139	108	148
30.0	2½	5	4/5	131	95	127

[1] Craige, Jones, Eichelberger, Alving, Pulman, and Wharton, personal communication.

[2] Freis and Wilkins, personal communication.

[3] Anderson, F., *J. Lab. Clin. Med.*, 1941, **26**, 1520.

* All doses of pentaquine used refer to the monophosphate salt.

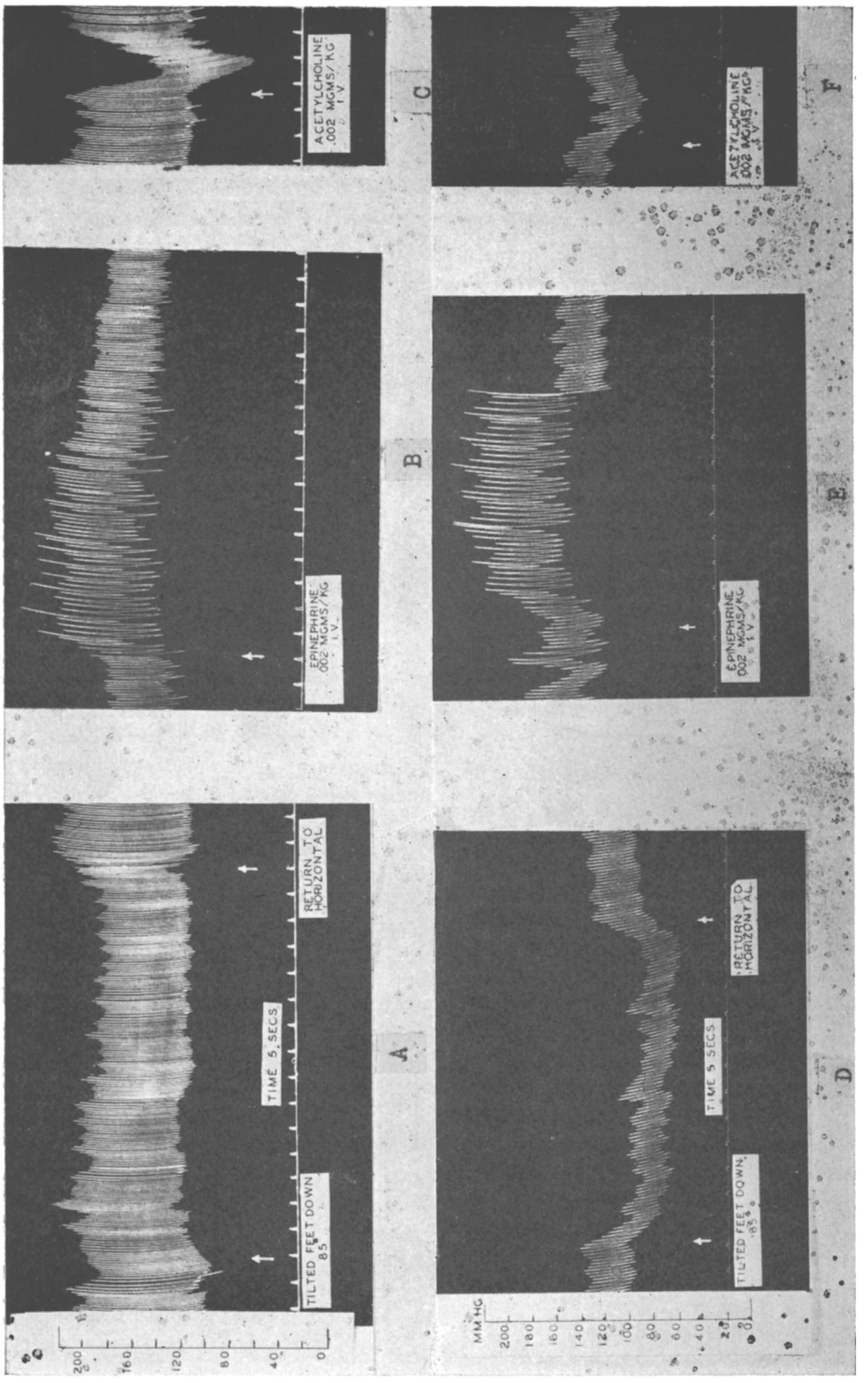

FIG. 1. The effect of pentaquine on response of the cardiovascular system to tilting, epinephrine, and acetylcholine. Fig. A, B, C, responses to an untreated unanesthetized dog. Fig. D, E, F, responses after treatment with pentaquine, 15 mg per kilo per day for 4½ days.

TABLE II.
Effect of Pentaquine on Cardiovascular Responses of Unanesthetized Dogs to Tilting, Epinephrine and Acetylcholine.

		Mean % change from resting observations.								
		Tilting feet down 85° for one minute			I.V. epinephrine 0.002 mg per kilo			I.V. acetylcholine 0.002 mg per kilo		
	No. dogs	Pulse rate	Arterial pressure		Pulse rate	Arterial pressure		Pulse rate	Arterial pressure	
			Systolic	Diastolic		Systolic	Diastolic		Systolic	Diastolic
Untreated controls	12	+16.6	+ 3.1	+ 8.9	—30.8	+31.2	+28.5	+48.0	—26.6	—31.1
Pentaquine 3.75 mg/K/day	6	+ 8.2	— 8.6	— 3.0	—36.5	+36.7	+35.7	+55.5	—29.4	—28.5
" 7.5 " "	5	+19.5	—18.1	— 7.3	—43.6	+36.2	+24.9	+25.1	—19.3	—18.2
" 15.0 " "	6	+23.6	—25.5	—25.8	—43.8	+42.1	+38.1	+21.1	—24.3	—27.8
" 30.0 " "	5	+ 8.9	—29.8	—29.8	—36.2	+48.1	+48.1	+20.1	—19.6	—19.4

per kg per day. These consisted of methemoglobinemia, loss of appetite, and generalized depression. In addition, most animals showed constricted pupils, some endophthalmus, and relaxation of the nictitating membrane.

Table I summarizes observations on the pulse and blood pressure of treated and untreated dogs lying quietly on the tilt table. In general the pulse rate following treatment with pentaquine was more rapid, and both diastolic and systolic arterial pressures were lower than in the control animals. The toxicity of doses of 30 mg per kg per day was such that treatment was limited to a period of 2½ days. On doses of 3.75 mg per kg per day, animals survived at least 2 weeks medication.

Fig. 1 illustrates a representative experiment. Kymograph records, 1-A, B, and C show the response of the circulation of an untreated animal to tilting, epinephrine, and acetylcholine. Kymograph records D, E, and F of Fig. 1 show the response of the circulation, following treatment with pentaquine for 4½ days at a total daily dose of 15 mg per kg.

The most striking effect of pentaquine was the development of postural hypotension, unaccompanied by significant tachycardia. Also characteristic of those animals showing postural hypotension was the failure of acetylcholine to accelerate the pulse.

Table II summarizes the data relating dosage of pentaquine to effect on the cardiovascular system. Insignificant changes were produced by daily doses of 3.75 mg per kg for 4½ days. Doses of 7.5 mg per kg per day produced postural hypotension in part of the animals, and higher doses produced a typical effect in most of the animals.

An important feature of the action of pentaquine was the length of time required for production of the cardiovascular effects. In 3 dogs the repeated intravenous injection of 1 mg per kg of pentaquine was fatal when 10-12 mg per kg had been administered over a period of one hour. Death in such animals was accompanied by generalized convulsions ending in respiratory failure, with-

out evidence of methemoglobin. In none of the 3 dogs thus studied was there a significant change in cardiovascular response to tilting, epinephrine, or acetylcholine. In other animals repeated sublethal doses of pentaquine did not lead to postural hypotension until at least 2½ days of treatment had elapsed.

None of the 6 animals given daily doses of 3.75 mg per kg of pentaquine for 4½ days showed a significant postural hypotension. Treatment of this group of dogs was continued for 4 days longer at which time one of the 6 showed a fall in blood pressure on tilting. It would appear from this that maximal cardiovascular effects from a particular dose might ordinarily be expected by 5 days, if they are to occur at all.

Also characteristic of these cardiovascular actions of pentaquine was a persistence of effect beyond the period of therapy. In some animals postural hypotension was observed for at least 5 days after drug administration had been discontinued. These same phenomena of slow onset, and persistence of action have been observed in man.[1,2]

Discussion. A consideration of the results presented above permits the following provisional analysis: (a) Since epinephrine in pentaquine-treated animals produces at least as great a degree of hypertension as in controls, one must assume that the peripheral sympathetic end organs are intact, (b) since epinephrine produces as much bradycardia the so-called "vagus cut off" mechanism is intact, (c) since acetylcholine still produces a fall in blood pressure the peripheral end organs of the parasympathetic system are unaffected, (d) the inability of the pulse to speed up with a fall in blood pressure either as a result of tilting or acetylcholine suggests that reflexes necessary for maintaining arterial pressure have been altered. These findings therefore taken in conjunction with those of Moe and Seevers[4] suggest that the cardiovascular actions of 8-amino quinolines are produced by a functional impairment of the central sympathetic system.

Conclusions. The repeated administration of high doses of pentaquine produces an effect upon the cardiovascular system such that unanesthetized animals develop a striking postural hypotension. Pentaquine has no effect upon the response of animals to epinephrine, but blocks the tachycardia produced by acetylcholine. It is suggested that these effects are produced by an impairment of the central portion of the sympathetic nervous system.

[4] Moe, G. K., and Seevers, M. H., *Fed. Proc.*, 1946, **5**, 193.

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The Circulatory Action of a Number of Phenylpropylamine Derivatives.*

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Barger and Dale[1] reported that phenethylamine presented the optimal basic chemical structure for sympathomimetic activity. This has been adequately confirmed by the synthesis and pharmacological examination of numerous modifications of the phenethylamine skeleton. A number of derivatives (Table I) in which an ethylamine side chain is separated from the benzene ring by either a keto or hydroxyl group have been made

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[1] Barger, G., and Dale, H. H., *J. Physiol.*, 1910, **41**, 19.