sis. The right ventricle dilated and irregular heart action was seen for several minutes. A loud systolic murmur was heard post-operatively. The dog was well for 12 hours, but was found dead the next morning. Post mortem examination revealed a patent functioning anastomosis of 1 cm diameter.

Discussion. The acute experiments described above demonstrate that the venous pressure may operate as *vis a tergo* to pump at least some of the venous return through the lungs without benefit of right ventricular action. This illustrates anew the remarkably low resistance of the pulmonary circuit. Obstruction to outflow through the pulmonary artery results in a momentary damming of blood in the great veins until the venous pressure rises to levels of about 12 cm saline. A transmission to the venous presure of some of the pulse from the distended right ventricle continues because of the resulting equivalent of a functional tricuspid regurgitation. However, it is unlikely that this participates in the development of an increased pressure in the right auricle because of the large distensible venous reservoir in free communication with the atrium.

In the chronic experiments with production of the atrio-pulmonary shunt, a functional tricuspid regurgitation is produced because of the flow of some of the output of the right ventricle via the pulmonary artery anastomosis to the right atrium. The amount of this regurgitation has not been determined. Under normal circumstances the anastomosis results in a flow from ventricle to pulmonary artery to atrium, especially during the heightened pressure of ventricular systole. The possibility must be considered that some blood passes from atrium to pulmonary artery during diastole when the pulmonary diastolic pressure is low, and especially during atrial systole before ventricular contraction occurs. Production of a stenosis or complete occlusion of the pulmonary artery central to the anastomosis forces the flow of blood from atrium directly to the pulmonary artery.

Summary. 1. An anastomosis was made between the right atrial appendage and the main pulmonary artery.

2. In acute experiments, the venous pressure was demonstrated to drive venous return through the lungs without benefit of the pumping action of the right ventricle.

3. In chronic experiments, the anastomosis acts similarly to a tricuspid insufficiency. No deleterious effects were seen in the course of two months observations on such dogs.

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17083 P. A New Imidazoline Derivative with Marked Adrenolytic Properties.

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Intense interest in efforts to combat the adrenergic predominance associated with various vascular dyscrasias has resulted in the development of numerous agents of diverse chemical structure, including the hydrochloride of 2- [N-p'-tolyl-N-(m'-hydroxyphenyl) - aminomethyl] - imidazoline (C-7337).[1-3]

Toxicity. The acute LD_{50} values (20 rats per group) are as follows: Intravenous, 75 mg,* subcutaneous, 275 mg, oral, 1250 mg. A brief report of chronic toxicity studies in dogs has been made.[4]

Specific Sympathetic Blocking Effects 1.

[1] Marxer, A., and Miescher, K., to be published.

[2] Meier, R., *New York Academy of Sciences*, 1947, in press.

[3] Meier, R., *Farmacoterapia Actual*, 1948, **44**, 84.

* All doses mg or μg/kg intravenously unless stipulated otherwise.

[4] Warren, M. R., Woodbury, R. A., and Trapold, J. H., *Fed. Proc.*, 1949, **8**, 343.

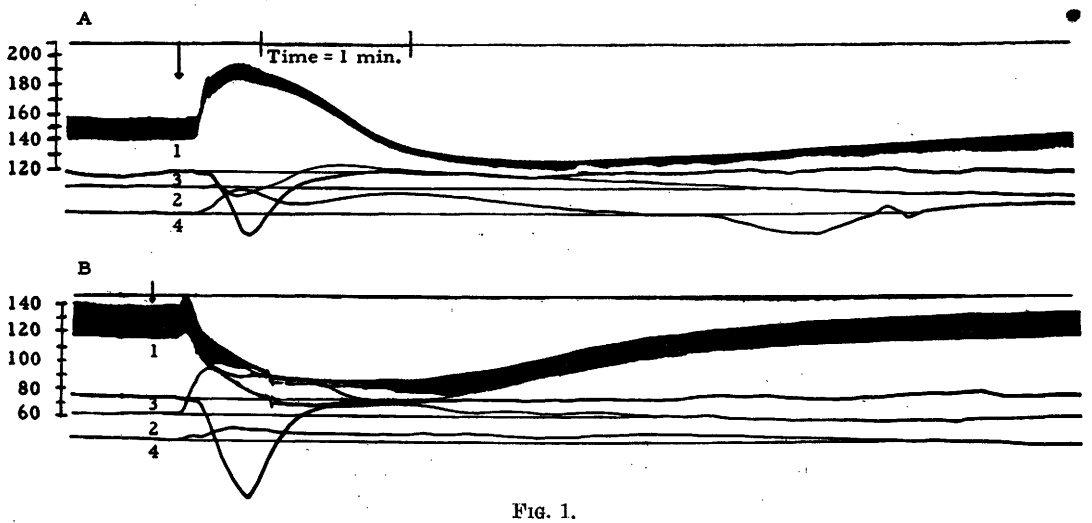

FIG. 1.

A. Cat under Dial anesthesia (70 mg/kg). The effects of 5 μg epinephrine intravenously (injected at arrow) are demonstrated on 1) blood pressure, 2) flow in mesenteric artery, 3) flow in renal artery, and 4) flow in femoral artery. Flow rates were determined with the Rein Thermostromuhr. B. Same animal 30 min. after 1 mg C-7337 subcutaneously. Note chief effect is "epinephrine reversal." Flow rates qualitatively the same as in A. Time = 1 minute.

In mice the LD_{100} of epinephrine subcutaneously injected is 7.5 mg. C-7337, 0.03 mg injected subcutaneously half an hour before the epinephrine, permitted a 20% survival; 0.1 mg administered in the same manner protected 40% against the lethal dose of epinephrine; after C 0.3 mg there was 100% survival.

2. The rise of blood pressure after epinephrine (0.1-10 μg) was diminished in cats, dogs and rabbits (Dial anesthesia) by doses of 0.01-0.03 mg C-7337 intravenously or subcutaneously and completely inhibited in cats and dogs by 0.1 mg intravenously or subcutaneously. The typical "epinephrine reversal" was produced in cats and dogs by doses of 0.1-1.0 mg intravenously or subcutaneously (Fig. 1). The epinephrine reversal was also observed in rats and guinea pigs and in the spinal cat. Despite this inversion, the typical effect of epinephrine on blood flow in the renal and femoral arteries remained qualitatively unchanged (Fig. 1).

3. The sustained vasoconstriction produced by constant arterial perfusion of the posterior extremities of the rabbit with epinephrine (10^{-7}) was decreased 21% by 10^{-8} C-7337, 50% by 10^{-7} and 90-100% by 10^{-6} (Fig. 2).

4. The contractile action of epinephrine (2 μg) on the nongravid rabbit uterus *in vivo* was almost entirely obliterated by 100 μg of C-7337.

5. The relaxing effect of epinephrine (5×10^{-7}) on the isolated ileum of the rabbit was diminished approximately 50% by 5×10^{-7} C-7337 and about 65% by 5×10^{-6} C-7337.

6. The minimal doses of C-7337 required to eliminate salivation in the cat were 50 μg for adrenolysis (3 μg epinephrine) and 700 μg for sympatholysis (10 second faradization of cervical sympathetic nerve).

The adrenolytic effect of C-7337 (50 μg) against 3 μg of epinephrine as a sialogogue was complete, but this blocking effect could be partially broken through by 10 or 15 μg of epinephrine.

7. As a rule higher doses of C-7337 were required to produce an adrenolytic and sympatholytic effect upon the nictitating membrane than upon blood pressure and the salivary gland. The retraction of the nictitating membrane produced by epinephrine (10 μg) was almost completely inhibited by 1.0 mg C-7337; after 10 seconds of faradization it was eliminated by 17.7 mg C-7337.

8. Epinephrine hyperglycemia (50 μg) in rabbits was not prevented with doses of 0.15

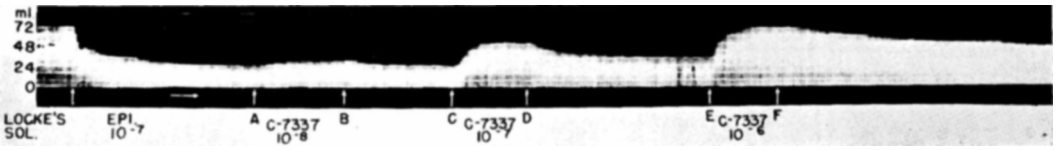

FIG. 2.

Rabbit, hind limbs continuously perfused with Locke's solution containing epinephrine, 10^{-7}. Each vertical line represents an interval of 10 seconds during which the varying rates of flow were registered in milliliters; normal flow was approximately 75 ml per 10 seconds whereas epinephrine, 10^{-7}, reduced this rate to approximately 25 to 30 ml per 10 seconds. From A to B, perfusion with C-7337, 10^{-8}; from C to D, C-7337, 10^{-7}; from E to F, C-7337, 10^{-6} concentration. Note the increasing antagonism of epinephrine's vasoconstrictor action following gradually increased concentrations of C-7337.

to 15 mg C-7337 subcutaneously.

9. The adrenolytic effects of adequate amounts of C-7337 (1 to 3 mg) on the vasopressor response to epinephrine (2 μg) were observed also after absorption following ileal intubation in the cat and dog.

Miscellaneous Features. 1. C-7337 was invariably hypotensive in all species examined (rabbit, cat, dog, rat, guinea pig) and in any dose which produced adrenolytic effects after the conventional, reasonably rapid injection. The hypotensive effect was more marked with increasing dosage and endured—depending on the dose employed—for 2 to 3 hours or more. After intravenous injection the fall in blood pressure was more pronounced than after subcutaneous injection.

2. C-7337 in a concentration of 10^{-6} decreased the coronary flow of the isolated perfused heart of the rabbit 25%, the rate 8% and the amplitude 17%. The corresponding reductions for the feline heart were 30%, 12% and 13%.

3. The isolated vessels of the hind limb of the rabbit showed no reaction to concentrations of C-7337 up to 10^{-5}.

4. No direct myotropic stimulating effect was observed in respect to the bronchi of the rabbit, nictitating membrane of the cat, isolated ilea of the rabbit and guinea pig or intact ileum of the dog. As opposed to the majority of adrenolytic substances, C-7337 has no contractile action upon the isolated uterus of the guinea pig or the uterus *in vivo* of the rabbit.

5. No sialogogic (cholinergic) effect was evident in the cat even with a dose of 27.5 mg of C-7337, whereas faradization of the chorda tympani nerve consistently resulted in salivation.

6. Warburg studies have indicated that C-7337 did not appreciably interfere with feline cardiac respiration until concentrations approaching 500 μg/ml had been reached. At this concentration there was a 12.5% decrease in cumulative oxygen consumption after 4 hours.[5]

Conclusions. The compound 2- [N-p'-tolyl-N-(m'-hydroxyphenyl) -aminomethyl] -imidazoline HCl, (C-7337), is a potent adrenolytic agent but much less active as a sympatholytic drug. It is effective orally.[6]

[5] Herrold, E. A., Cameron, A., Earl, A., Roth, F., Smith, J., Smith, N., Sorensen, E., and Craver, B. N., *Fed. Proc.*, 1949, **8**, 302.

[6] Grimson, K., Chittum, J. R., and Longino, F. H., *Fed. Proc.*, 1949, **8**, 61.

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