produce convulsions when the drug was infused into the marginal ear vein or the portal vein of rabbits. In all cases a larger amount was required to produce convulsions when administered by the portal route. This evidence seems to establish the fact that metrazol is detoxified rather than excreted and that the liver plays an important rôle in the detoxication process.

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Coronary Occlusion. II. Efficacy of Papaverine Hydrochloride in Treatment of Experimental Cardiac Infarction.

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Papaverine has been suggested repeatedly as a drug of therapeutic value in the treatment of coronary artery disease.[1-4] This recommendation has been based on the thesis that the vaso-dilator action of papaverine would increase local blood flow. The anginal attack is thus relieved, or the ultimate size of the myocardial scar is minimized as a result of the improved nutrition.

Allen and MacLean[4] stated that the pain in peripheral arterial embolization is due not only to the presence of the embolus, but also to the attendant widespread reflex vascular spasm. The extensive ischemia that they observed was more marked than could be accounted for by the occlusion of the main vessel alone. In arterial embolization papaverine is said to have effects analogous to sympathectomy, *i.e.*—relaxation of the vaso-spasm. The use of papaverine has been suggested also in cerebral, pulmonary and mesenteric occlusion.[3,4] Mulinos, Shulman and Mufson[5] found that vaso-spasm of Reynaud's disease was relieved by large doses of papaverine hydrochloride intravenously, doses which did not lower the blood pressure but which resulted in a moderate acceleration of the heart rate.[6] Gruber and Robinson[7] noted that papaverine in small

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3 De Takats, G., *J. A. M. A.*, 1936, **106**, 1003.

4 Allen, E. V., and MacLean, A. R., *Proc. Staff Meet. Mayo Clinic*, 1935, **10**, 216.

5 Mulinos, M. G., Shulman, I., and Mufson, I., *Am. J. Med. Sci.*, 1939, **197**, 793.

6 Mulinos, M. G., and Shulman, I., *J. Pharm. Exp. Therap.*, 1939, **66**, 27.

7 Gruber, C. M., and Robinson, P. I., *J. Pharm. Exp. Therap.*, 1929, **37**, 429.

doses caused an increase in the height of the contractions in the isolated perfused terrapin heart. Macht[8] observed that small doses caused slowed, more powerful contractions of the isolated frog's heart.

Coronary occlusion, whether due to embolus, spasm, or ligation, results in a central area of almost complete ischemia which is surrounded by a halo of myocardial edema and reflexly spastic vessels. These peri-infarctial coronary vessels are of importance because they supply blood to the adjacent myocardium and also because they are potential anastomotic connections with the infarcted area (Wearn[9]). It is to be expected, therefore, that vasodilators which decrease the vaso-spasm should prove beneficial by increasing the anastomotic circulation, and also by lessening the peri-infarctial edema, thus diminishing the ultimate size of the infarct. No experimental work has been done in support of the contention that papaverine exerts such a beneficial effect on the course of occlusive coronary disease. The present study attempts to determine the effect of papaverine upon the size of an experimentally produced myocardial infarct. Gold, Travell and Modell[10] and Fowler, Hurevitz and Smith[11] have made similar studies employing aminophylline as the vasodilator.

Method. Using the method described previously,[12] the left branch of the left anterior descending coronary artery was ligated aseptically in 22 cats under sodium pentobarbital anesthesia. An attempt was made to tie the vessel at the same point in each animal. Standard 3 lead electrocardiograms, white and differential blood counts, and determinations of the sedimentation rate were made pre-operatively, and at intervals in the post-operative life of the cats. Following the ligation alternate cats received 5 mg per kilo of papaverine hydrochloride (1 cc = 30 mg)* intramuscularly twice a day for a period of 2 weeks (Sundays excepted). The interval cats were kept as controls and were treated analogously except for the injections. All the cats remained in good condition until they were sacrificed.

8 Macht, D. I., *Arch. Int. Med.*, 1916, **17**, 786.

9 Wearn, J. T., Harvey Lecture, 1940.

10 Gold, H., Travell, J., and Modell, W., *Am. Ht. J.*, 1937, **14**, 248.

11 Fowler, W. M., Hurevitz, H. M., and Smith, F. M., *Arch. Int. Med.*, 1935, **56**, 1242.

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TABLE I.
Infarct Size and Its Relation to Age of Infarct and Administration of Papaverine.

Treated cats			Untreated cats		
Cat No.	Days	Infarct area, cm^2	Cat No.	Days	Infarct area, cm^2
18	7	0.88	9	24	1.33
29	7	3.19	5	27	1.59
25	14	3.76	3	28	1.62
16	15	2.24	12	29	1.22
13	20	1.76	27	30	0.55
26	20	1.52	10	30	2.06
6	21	2.91	11	30	1.30
14	21	0.80	7	33	1.07
4	29	3.64	8	44	2.15
19	101	0.39	9	47	1.58
			10	50	4.40
			21	56	None seen
10	Avg 25.5	Avg 2.11 $\sigma = 0.363$	12	Avg 35.7	Avg 1.57 $\sigma = 0.324$

From 6 to 102 days after operation, the cats were killed by the intravenous injection of chloroform. The hearts were excised, the infarct delineated with ink and a contact tracing of each infarct was made. The areas of the tracings, shown in Table I, were determined by means of a planimeter. There is no obvious correlation between the size of the infarct and its age.

Results. The treated cats experienced some immediate pain from the injection of the papaverine hydrochloride, which has a pH of 2, but showed no other untoward effects. There was no depression, vomiting, or loss of appetite.

As shown in the Table, the area of infarct averaged 34% larger in the papaverine treated cats than in the uninjected controls. This difference falls well within the average deviation of either series and is consequently considered as accidental. In large part the size of the infarct depends in the different cats upon the anatomical distribution of the coronary vessel which is ligated at the operation. The differences in the area of the infarcts are shown in the Table as a scatter of from 0.39 sq cm to 3.76 sq cm for the papaverine treated cats and of from zero to 4.40 sq cm for the control animals. A larger series might be desirable. However, more data would merely result in lowering of the average deviation of infarct size, without throwing additional light upon the effect of the drug. Our figures indicate that infarct size cannot be used as a criterion of coronary vasodilator action and therefore it is felt that the coronary vasotropic effect of papaverine must be studied by other methods as well. Papaverine is being compared by us with nitroglycerine

and theophylline for its effects upon the electrocardiogram with and without induced anoxemia. The length of time necessary for the recovery of the electrocardiogram and for the return of the white blood cell count and sedimentation time to normal was roughly proportional to the size of the infarct, and independent of the administration of the papaverine. From our failure to demonstrate any reduction in the size of the infarct after coronary ligation, it cannot be concluded that papaverine hydrochloride has no place in the clinical treatment of coronary occlusion or of angina pectoris.

Conclusion. The daily injection of papaverine hydrochloride (5 mg per kilo) into cats for 2 weeks did not alter significantly the size of the infarct resulting from the ligation of the left branch of the left anterior descending coronary artery.

It is suggested that because of the greatly variable amount of cardiac tissue involved in each ligation this method of study is too crude to detect any "clinical" improvement that the drug may have exerted.

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Anaphylactic Shock and Susceptibility to Histamine Poisoning in the Cotton Rat *Sigmodon hispidus littoralis.**

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The Eastern cotton rat *Sigmodon hispidus hispidus* and the Florida cotton rat *Sigmodon hispidus littoralis* have come into prominence as laboratory animals because of their reported susceptibility to the virus of poliomyelitis.[1] [2] The cotton rat is a small rodent and apparently it is capable of adaptation to laboratory life. It is therefore of interest to explore its usefulness for other experimental purposes. Reports on a natural trypanosome infection of the Florida cotton rat,[3] on the susceptibility of this animal to diph-

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3 Culbertson, J. T., *J. Parasit.*, in press.