following 2 or 3 weeks of observation.

Summary. A new method of blood oxygenation by gas dispersion was tested by subjecting dogs, under local anesthesia and morphine sedation, to conditions of complete anoxic anoxia by substituting pure nitrogen for air as the respiratory gas for about one hour. If a *minimum* blood flow of approximately 40 ml/kg/min was maintained, the animals survived the experiment without loss of consciousness, and recovered completely without exhibiting any neurological signs of anoxic damage.

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A Method with Perfused Feline Hearts of Quantitatively Comparing Drugs with Coronary Vasodilating Activity. (17874)

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Hearts perfused by the method of Langendorff(1) have long been employed for detecting coronary vasodilating action in new compounds. This type of assay would appear to suffer particularly from two limitations: 1. The coronary dilating effects are brief and are difficult to quantitate, so that careful comparisons between congeners are impossible; 2. In many experiments the coronary flow initially is so rapid as to make any further augmentation difficult of attaining. To be assured one is obtaining a primary coronary dilating action, increases in flow must occur without changes in the cardiac rate or the amplitude of the myocardial contractions.

Method. It was found that the proper concentration of a suitable vasoconstrictor in the fluid perfusing the heart would significantly diminish the coronary flow, sometimes by as much as 50%, without altering the rate or the amplitude of the contractions. Originally for this purpose we employed surgical Pituitrin in a concentration varying from .005 to .075 unit per ml. We found it unsatisfactory for 2 reasons: 1. Many hearts proved entirely insensitive to its constrictive effect; 2. Not infrequently its predominant action was a positive inotropic effect with little change in the coronary flow. 2-naphthyl-(1')-methyl-imidazoline hydrochloride (Privine) yielded better results. Its addition to the recycled perfusion fluid in a concentration of from 1 to 2 γ/ml usually caused in hearts exhibiting a fast initial flow (greater than 15 ml/min) a progressive reduction in the flow up to as much as 50% without altering the rate or amplitude of the contractions. In hearts with slow initial flow (from 10-15 ml/min) relatively high concentrations of Privine (up to 5 γ/ml) usually failed to reduce it further. This proved no disadvantage since such hearts responded directly to coronary dilators. Fig. 1 and 2 illustrate this action by histamine and sodium nitrite respectively. Obviously it is needless to study by this procedure any drugs that do not exhibit a brief augmentation of the coronary flow after single injections of suitable doses directly into the cannula just above the aorta.

Discussion. The higher doses of Privine not infrequently exerted a mild, positive inotropic effect, later followed by irregularities. The last were most common with "irritable" hearts that had exhibited from the beginning a relatively high rate with occasional extra systoles. The coronary constrictive action of Privine would appear weak not only on the basis of the data presented but also on the basis of Meier's work with cats *in vivo* (2). He found Privine invariably augmented the coronary flow, presumably because the elevated blood pressure following its admin-

1. Langendorff, O., *Arch. ges. Physiol.*, 1895, v61, 291.

2. Meier, R., personal communication.

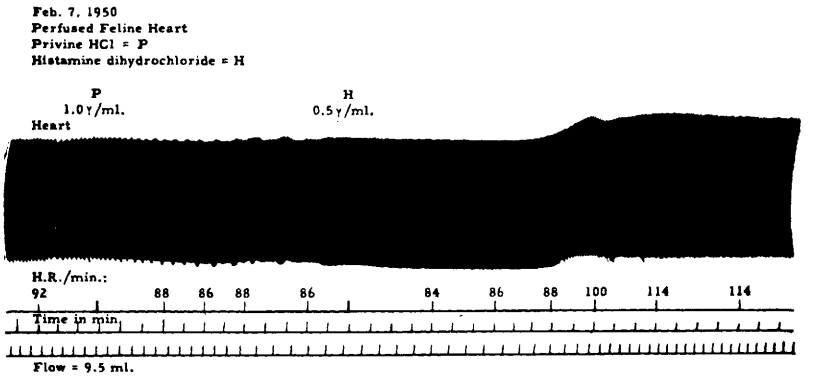

FIG. 1.

Each mark on the flow line indicates passage of a volume of 9.5 ml through the coronary circulation. The rapid initial flow was diminished by addition of 1 γ/ml of Privine to the perfusion fluid. The addition of 0.5 γ/ml of histamine dihydrochloride to the perfusion fluid not only restored the coronary flow but elevated it even above the control rate. The moderate tachycardia it induced could not alone account for the marked change in flow.

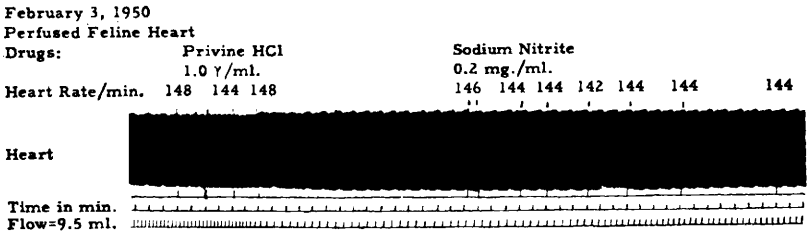

FIG. 2.

Each mark on the flow line indicates passage of 9.5 ml through the coronary circulation. The rapid initial flow was diminished by addition of 1 γ/ml of Privine to the perfusion fluid. The effect of the latter drug was subsequently antagonized by the addition to the perfusion fluid of 200 γ/ml of sodium nitrite.

istration was more than sufficient to offset its slight coronary constrictive action. It would be desirable to know the mechanism of Privine's action, as that would permit a better evaluation of the dilator action of drugs that antagonize it, but for the present one can only state that known coronary dilators do antagonize it. Since it produces constriction more consistently than Pituitrin, it would appear to act closer to the final link in the enzymatic chain of reactions terminating in the contractile response of the vascular musculature.

The method herein presented would appear best suited for a study of the action of a drug upon "tone" of the coronary vessels. Whether a drug effecting an increased coronary flow by this mechanism would be suited for clinical trial must, of course, depend upon its toxicity and general systemic effects. The possible value of this method of selecting a coronary dilator can only be settled after an extensive clinical trial of drugs causing dilatation under the conditions described.

Summary. The use of Privine has been described for inhibiting the coronary flow of feline hearts perfused by the method of Langendorff. This permits a quantitative evaluation of the activity of coronary vasodilators in that majority of perfused hearts that exhibit such a rapid spontaneous coronary flow that its augmentation is difficult, if not impossible. Under the conditions described the Privine does not alter the cardiac rate or the amplitude of the myocardial excursions.

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