standard deviation, and in the case of the females 3.59 times the standard deviation. Preliminary measurements of the cross section areas of a small number of the bones show that there is no significant difference between the healed rachitic and normal bones. While the array of results forms a somewhat skewed distribution curve, it is nevertheless probable that the differences in tensile strength between the roentgenologically healed bones and the controls are significant. Further studies are in progress.

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The Effect of Renin on the Cardiac Output.

EUGENE SOMKIN.* (Introduced by B. S. Oppenheimer.)

From the Laboratories, Mt. Sinai Hospital, New York City.

Since the original description of a pressor substance (renin) in the kidney by Tigerstedt and Bergmann there has been considerable speculation on the possible rôle that renin may play in the production and maintenance of experimental hypertension. As the pressor effect of renin can be obtained in perfused surviving organs and it has no effect on the isolated perfused heart,[1, 2, 3] it has been generally assumed that an increase in the cardiac output plays little or no part in the elevation of the blood pressure. Hessel[4] states that renin produces no increase in the cardiac output in dogs but gives no experimental data. The present study was carried out to determine what, if any, effect renin has on the cardiac output. Several determinations were made with tyramine hydrochloride, a drug which gives a pressor response similar to that of renin.

Method. The cardiac output was determined in one female and five male dogs by the use of the Fick principle following the method of Marshall.[5] All experiments were carried out in the morning under basal conditions. With the exception of three preliminary experiments the dogs received from 2.5 to 3.5 mg of morphine sul-

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1 Tigerstedt, R., and Bergman, P. G., *Skand. Arch. Physiol.*, 1898, **8**, 223.

2 Hill, W. H. Phillip, and Andrus, Cowles E., PROC. SOC. EXP. BIOL. AND MED., 1940, **44**, 213.

3 Friedman, B., Abramson, D. I., and Marx, W., *Am. J. Physiol.*, 1938, **124**, 285.

4 Hessel, G., *Klin. Wohnschn.*, 1938, **17**, 843.

5 Marshall, E. K., *Am. J. Physiol.*, 1926, **77**, 459.

phate per kilogram intravenously, from 1½ to 2½ hours before the start of the experiment. The oxygen consumption was measured with a clinical spirometer, using a Blalock dog mask.[6] Blood pressure was taken by an auscultatory method previously described.[7] Blood samples of one cc were analyzed for total oxygen with the Van Slyke apparatus using the Van Slyke and McNeil technic.[8] A standard correction was made for the nitrogen content of the blood. Room and animal temperatures were taken at the beginning and end of the experiment. A typical experiment was carried out in the following manner. The oxygen consumption was first taken for eight minutes as a check on the state of relaxation of the animal. This was followed by a control cardiac output determination. Mixed venous blood samples from the heart were taken before the arterial samples and sometimes also afterward. Then 5 cc of renin (prepared after the method of Friedman and his collaborators[3]) was injected intravenously. Mixed venous samples were taken at various intervals after the establishment of a definite pressor effect. In a small number of experiments from 3½ to 5 mg of tyramine hydrochloride were injected in place of renin. One determination of the cardiac output was made after an injection of 3.8 cc of a purified renin.†

Seventeen determinations of the cardiac output were carried out after 12 injections of renin and of these the greatest increase was 14% in 2 instances. Nine determinations of the cardiac output were carried out after 5 injections of tyramine. In 3 instances the increase was greater than 10%, namely 15%, 26%, and 31%. Figures 1 and 2 show that there is no significant relationship between the change in cardiac output, the time of venous sampling and the height of the pressor response. The pulse rate was almost always slowed at the peak of the pressor effect, later becoming more rapid than the resting rate. Respiration usually became more shallow at the peak of the pressor effect. This latter effect was noticed only after renin.

Discussion. A comparison of the basal cardiac output in each dog from day to day with those of Marshall[5] in unanesthetized dogs shows a greater degree of variation in this series. This is probably due to the fact that no attempt was made to train the animals, while

[6] Blalock, A., *J. Lab. and Clin. Med.*, 1927, **12**, 378.

[7] Friedman, Ben, Somkin, E., and Oppenheimer, E. T., *Am. J. Physiol.*, 1940, **128**, 481.

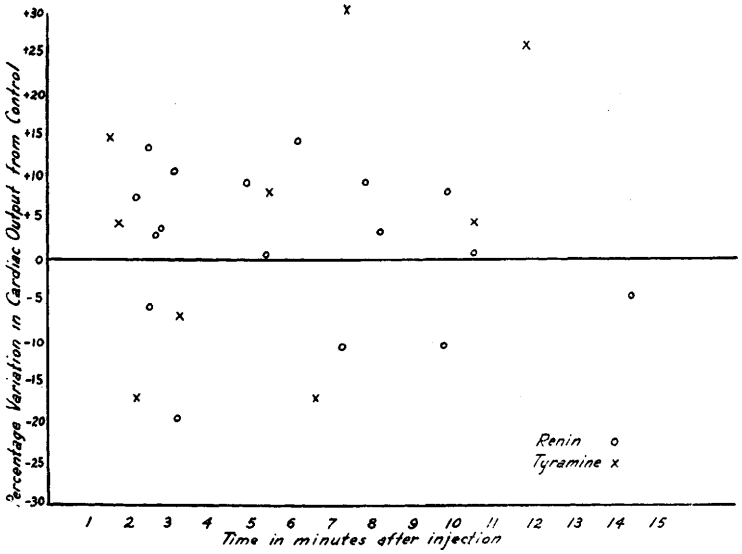
[8] Peters, J. P., and Van Slyke, D. D., *Quantitative Clinical Chemistry*, 1931, Vol. 2, p. 321.

† I am indebted to Dr. I. H. Page for this sample of renin.

the dose of morphine was so light that at times the dogs were somewhat excited. When ever the dog actually struggled the experiment was discontinued. As these were acute experiments it was felt that small daily variations in the basal cardiac output could have no effect on the results. An adequate check on the constancy of the control cardiac output was the fact that mixed venous samples taken on many occasions before and after the arterial sample invariably checked. Any change from the basal state while blood samples were being taken was indicated by reference to the first oxygen consumption period. There were minor variations in the cardiac output after the injection of renin, but they were not significant. Harrison and his coworkers[9] considered a deviation of ±10% to be within the limits of error of the method. The greatest increase (14%) was obtained after the injection of a large dose of a purified renin which gave a tremendous rise in the blood pressure (128). The only other increase of cardiac output above 10% (also 14%) was due solely to a change in the oxygen consumption. In all of the other instances there was no rise although the pressor response was adequate. A possible explanation of the drop in output found in one case (19.6%) may be that the renin used was a crude unstandardized suspension which contained many other substances.

Figure 1

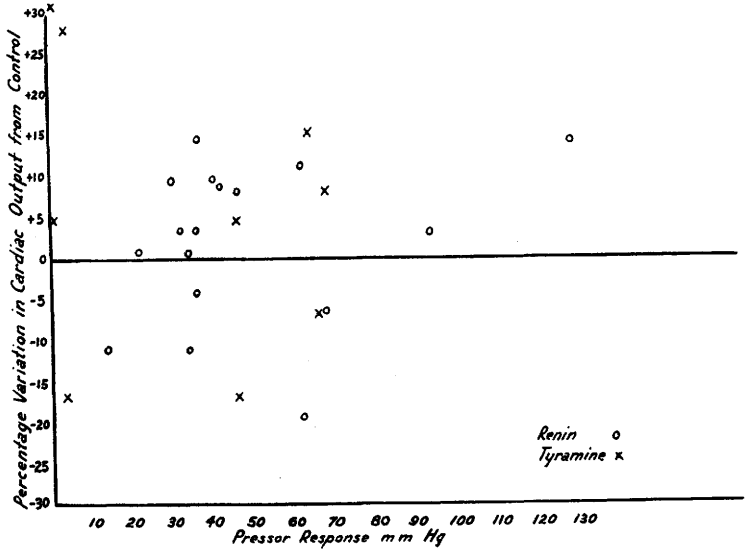
RELATIONSHIP BETWEEN THE % VARIATION IN CARDIAC OUTPUT AND TIME OF VENOUS SAMPLING



9 Pilcher, Cobb, Wilson, Charles P., and Harrison, Tinsley R., *Am. Heart J.*, 1926-7, **2**, 618.

Figure II

RELATIONSHIP BETWEEN THE % VARIATION IN CARDIAC OUTPUT AND PRESSOR RESPONSE



There is an increasing amount of evidence to show that by injecting renin one can reproduce many of the physiological changes found in experimental and clinical hypertension. Hill and Pickering[10] found that a continuous infusion of renin gives a pressor effect which is well maintained for hours and that after stopping the flow, the blood pressure takes from 1 to 4 hours to return to normal. This is similar to the slow drop in blood pressure in the hypertensive animal after the removal of the ischemic kidney. Landis, Montgomery and Sparkman[11] showed that renin is the only pressor substance which does not lower the skin temperature. In the essential hypertension of human beings the skin temperature is normal. Smith and his collaborators have demonstrated that in essential hypertension and after the injection of renin it is the efferent arteriole of the glomerulus which is chiefly affected,[12] and Holman and Page[13] found that there was no change in cardiac output in dogs made hypertensive by the method of renal ischemia. Thus the fact that renin does not affect the cardiac output is an ad-

10 Hill, Janet R., and Pickering, G. W., *Clinical Science*, 1939, **4**, 201.

11 Landis, E. M., Montgomery, H., and Sparkman, L. D., *J. Clin. Invest.*, 1938, **17**, 189.

12 Smith, H. W., *Annual Review of Physiol.*, 1939, **1**, 503.

13 Holman, D. V., and Page, I. H., *Am. Heart J.*, 1938, **16**, 321.

ditional bit of evidence that this substance may be of significance in the production of experimental hypertension.

Previous reports on the effect of tyramine on the cardiac output are meager. Dale and Dixon[14] and Tainter[15] using the cardiometer reported an increased output but they give no data and base their opinion on the increased amplitude of cardiac pulsation which, however, cannot be used as an index of increased stroke volume, for this change may be demonstrated in a mechanical system with a fixed output, by increasing the peripheral resistance. Chen and Meek[16] in addition to the above method carried out two experiments with the teleroentgenogram. They report their results with this method to be inconclusive, as the variations fell within the limits of error. From the results obtained, using the Fick principle, tyramine would appear to have no direct effect on the cardiac output. The large increases which occurred in two instances were certainly secondary as they appeared only after the blood pressure had returned to normal.

Summary. 1. The cardiac output per minute of intact dogs anesthetized with 2.5 to 3.5 mg of morphine sulphate per kilogram was determined according to the Fick principle before and after the intravenous injection of renin and of tyramine. 2. On using a dosage of renin and of tyramine sufficient to give a good pressor effect, the cardiac output was not found to be significantly changed.

I wish to thank Drs. B. S. Oppenheimer and B. Friedman for their interest and criticism of this work.

[14] Dale, H. H., and Dixon, W. E., *J. Physiol.*, 1908, **39**, 25.

[15] Tainter, M. L., *J. Pharm. and Exp. Therap.*, 1927, **30**, 163.

[16] Chen, K. K., and Meek, W. J., *J. Pharm. and Exp. Therap.*, 1926, **28**, 59.