

Cardiovascular Effects of Renin.*

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(Introduced by Soma Weiss.)

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Renin, a pressor protein from the kidney which has been suggested as a cause of clinical hypertension, raises the blood pressure largely through generalized peripheral vasoconstriction.^{1, 2} During the pressor response, no significant changes have been observed in the skin temperature^{3, 4} nor cardiac output⁵ of animals. Hessel⁶ reported the production of permanent hypertension in rabbits by repeated intravenous injections of pig renin.

The effects of renin on human beings have not been extensively studied but it has been shown that hog renin is ineffective^{7, 8} while human renin raises the blood pressure.⁷ Angiotonin, formed by the action of renin on blood globulins, has been shown to increase the arterial and venous pressure and to decrease the heart rate, cardiac output and blood flow in the limbs in human beings.^{9, 10}

Methods. In the present investigation extracts of human and hog kidneys were prepared and assayed by methods described elsewhere.^{11, 12} A rabbit unit has been defined as the amount of renin (expressed as micrograms nitrogen) per kilogram of body weight which would cause an average rise in arterial blood pressure of 30 mm mercury.¹¹ A human unit is similarly defined as the amount of renin per kilogram of body weight required to produce in human beings a rise of 30 mm mercury in systolic arterial pressure. In un-

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6 Hessel, G., *Klin. Wchnschr.*, 1938, **17**, 843.

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anesthetized dogs the blood pressure was measured by direct arterial puncture. In human beings the blood pressure was measured by the auscultatory method, blood flow in the hand or forearm by plethysmographic methods,¹³ the venous pressure by the direct method of Moritz and von Tabora,¹⁴ and cardiac output by the acetylene method.¹⁵ All extracts were injected intravenously, the total dose being given during a period of one minute.

Results. Specificity of Renin. Hog renin was found to be equally active in rabbits and dogs, but inactive in human beings (no pressor response with 13 rabbit units per kg body weight). In order to produce the same rise in blood pressure in dogs as in human beings, 1-3 human units of human renin were required per kg dog. Rabbits required 5-15 times as much human renin per kg as human beings in order to show the same effect. The rise in blood pressure in rabbits was slower and lasted longer after human than after hog renin.

Effect of Repeated Injections of Hog Renin in Rabbits. After a control period of 3 weeks each of two rabbits was given one single daily dose of 2-3 R.U. per kg for 16 days. This treatment did not produce any permanent change in blood pressure. Two other rabbits received 4-6 injections (5-7 R.U. per kg each) daily for 3-4 weeks. During the injection period, the rabbits ate less and one finally refused all food and died at the 22nd day. The kidneys of this animal were grossly and microscopically normal except for a slight thinning of the cortex. During the second half of the injection period the sensitivity of both animals to one rabbit unit had decreased to about one-third of that of untreated rabbits. Doses of 2 R.U./kg and more were often followed by albuminuria. In the electrocardiograms of rabbits receiving repeated doses of renin a marked decrease in the heart rate and an inversion of T₂ or T₃ appeared shortly after large single doses. Similar records on rabbits not receiving daily injections also showed bradycardia as well as auricular premature beats after doses greater than about 5 R.U. Permanent hypertension as reported by Hessel⁶ was not obtained.

Effect of Human Renin on Human Beings. In 14 male persons with normal blood pressure and 6 hypertensive patients, human renin consistently produced a rise in blood pressure which was approximately proportional to the dose of extract administered. In the best extracts, the amount of renin obtained from 0.05 g of human

¹³ Kunkel, P., Stead, E. A., Jr., and Weiss, S., *J. Clin. Invest.*, 1939, **18**, 225.

¹⁴ Moritz, F., and von Tabora, D., *Deutsches Arch. f. klin. Med.*, 1909-10, **98**, 475.

¹⁵ Grollman, A., Friedman, B., Clark, G., and Harrison, T. R., *J. Clin. Invest.*, 1933, **12**, 751.

kidney, injected in one minute, was sufficient per kg body weight to raise the blood pressure 30 mm. The amount of renin recovered from kidneys of patients with severe hypertension was not significantly different from the amount obtained from normal kidneys; similar data have been reported before.^{16, 17} The response began 1 to 2 minutes after the start of the injection, reached a maximum in 4-5 minutes and returned to the previous level in 20 to 30 minutes. Elevation occurred in both systolic and diastolic levels, but at higher dosages the systolic rise was usually greater. The largest dose given was 2.3 human units per kg and it produced a rise of 73 mm systolic and 31 mm diastolic pressure. Six mildly hypertensive patients, when compared with normal persons of similar age, exhibited no consistent increase in sensitivity to the extracts. Slight temporary fullness of the head, tightness of the chest and cold extremities after large doses were the only symptoms experienced. The test for albumin in 2 urine samples was negative. Twenty-seven injections of varying amounts of human renin in one normal person, did not significantly change his pressor response to this material.

With moderate blood pressure elevation a drop in heart rate regularly occurred, in one instance falling from 66 to 40. Electrocardiograms, taken on 9 occasions, showed sinus bradycardia and, in 3 instances, there was a slight increase in the amplitude of the T-waves. The cardiac output in one normal person (3 experiments) showed a decrease of 0.2 liters/minute which was judged to be of no significance. Simultaneously the B.P. rose 42-56 mm systolic and 36-42 mm diastolic and the stroke volume increased 2-9 cc per minute as the pulse rate fell. In 3 experiments the basal metabolic rate did not change significantly. In 2 normal persons the blood flow in the hand at 40°C fell from an average of 27 cc to 3 cc per minute per 100 cc of tissue during a pressor response of 43-67 mm in systolic blood pressure. The volume of the hand decreased after the injection of renin. In 3 persons the forearm blood flow at 32°C did not change or decreased only slightly after renin, whereas adrenalin, 0.4 cc of a solution 1:20,000 intravenously, caused a sharp transitory increase in flow. After renin venous pressures of 3 normal persons rose 8-83 mm water concurrently with rises of 13-54 mm mercury in systolic pressure (5 experiments).

The observations reported here correspond in general with those of other investigators on the action of angiotonin in human beings,

¹⁶ Prinzmetal, M., Friedman, B., and Abramson, D. I., *Ann. Int. Med.*, 1939, **12**, 1604.

¹⁷ Landis, E. M., *Am. J. Med. Sci.*, 1941, **202**, 14.

except that angiotonin is reported to cause a reduction in cardiac output when measured by the ballistocardiographic method.^{9, 10} The acute pressor effect of renin differs from that of adrenalin in its failure to increase the cardiac output, basal metabolic rate¹⁸ and forearm flow. In these respects the action of renin is similar to that of paredrinol¹⁹ but renin produces a more marked decrease in the blood flow of the hand than does paredrinol. The acute effect of renin differs from chronic hypertension in man both by the elevation of venous pressure and the decrease in blood flow in the hand.²⁰

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Duality of Pituitary Gonadotrophins. Effects of FSH-ICSH Mixture on Hypophysectomized Male and Female Rats.*

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The dual nature of the gonadotrophins of pig and sheep pituitaries has been demonstrated beyond question by the preparation of pure ICSH^{† 1, 2, 3} (interstitial cell stimulating or luteinizing hormone) and very active^{4, 5, 6} or biologically pure^{7, 8} FSH[†] (follicle-stimulat-

¹⁸ Grollman, A., *The Cardiac Output of Man in Health and Disease*, Chas. C. Thomas, 1932.

¹⁹ Stead, E. A., Jr., and Kunkel, P., *J. Clin. Invest.*, 1939, **18**, 439.

²⁰ Weiss, S., Publication No. 13, *Blood, Heart and Circulation*, Am. Assn. Adv. Sci., 1940, p. 295.

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† The use of names which clearly indicate a function of a hormone such as follicle stimulating (FSH) or gametotropic on the one side and interstitial cell stimulating (ICSH) or hormonotrophic on the other appears to us preferable to the coinage of a new nomenclature.

¹ Shedlovsky, T., Rothen, A., Greep, R. O., Van Dyke, H. B., and Chow, B. F., *Science*, 1940, **92**, 178.

² Li, C. H., Simpson, M. E., and Evans, H. M., *Endocrinology*, 1940, **27**, 803.

³ Li, C. H., Simpson, M. E., and Evans, H. M., *Science*, 1940, **92**, 355.

⁴ Fraenkel-Conrat, H., Simpson, M. E., and Evans, H. M., *Anales de la Facultad de Medicina* (Montevideo), 1940, **24**, No. 5, 6, 7, 8.

⁵ Fraenkel-Conrat, H., and Simpson, M. E., *Proc. Soc. Exp. Biol. and Med.*, 1940, **45**, 627.

⁶ Jensen, H., Tolksdorf, S., and Bauman, F., *J. Biol. Chem.*, 1940, **135**, 791.

⁷ Greep, R. O., Van Dyke, H. B., and Chow, B. F., *J. Biol. Chem.*, 1940, **133**, 289.

⁸ McShan, W. H., and Meyer, R. K., *J. Biol. Chem.*, 1940, **135**, 473.