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Relation of Renin to Human Hypertension with Particular Reference to Eclampsia, Preeclampsia and Acute Glomerulonephritis.*

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The agent responsible for the rise of blood pressure resulting from constriction of the renal artery in experimental animals was first shown by Braun-Menendez *et al.*[1] to be due to the renal enzyme, renin, and their findings have been further extended[2] and confirmed.[3] The present study describes the assay of renin in the blood of patients with various types of hypertension.

Methods. Renin in human blood was determined by the following modification of the method of Leloir *et al.*[4] Fifty cc or more of venous blood, with or without an anticoagulant, were withdrawn from hypertensive patients and placed on ice immediately. After centrifugation, 0.09 g solid sodium chloride was added for each cc of serum or plasma. It was cooled to 5°C and the pH lowered to 2.0 (glass electrode) with 10% hydrochloric acid and left for 2 hours at this temperature in order to destroy hypertensinase. The pH was raised to about 6 with N sodium hydroxide and the solution dialyzed with a little toluol overnight against tap water at 5°C. It was then divided into 2 or, if sufficient amounts of blood had been obtained, 3 equal parts, each part representing about 10 cc of original serum or plasma. To each were added an excess (6 to 8 cc) of hypertensinase-free beef hypertensinogen,[4] 0.5 cc M/2 phosphate buffer at pH 7.3, and 0.2 cc 1:1000 merthiolate (Lilly). The first tube was incubated at 37°C for 4 hours; the second tube was unincubated; the third, which was often omitted, was incubated at 37°C for 4 hours with enough hemolyzed fresh human red blood cells (hypertensinase) to produce a pink color. At the end of incubation the tubes were heated in boiling water for 5 to 10 minutes at about pH 4. Three volumes of 95% ethyl alcohol were then added, the precipitated proteins removed by filtration, the filtrate made slightly acid, and the alcohol removed by evaporation under reduced pressure over boiling water to a volume of 2 or 3 cc. The contents of the flask were taken up in two 5 cc washings with normal saline, adjusted to neutral, and their content of hypertensin assayed in cats under dial anesthesia by the method of Leloir *et al.*[4]

The specificity of the method was indicated by a pressure rise from the intravenous injection of the first tube and a lack of pressor response from the second and third tubes.[4] Other pressor substances such as adrenalin, pituitrin, "spätgift," tyramine, and guanidine are not recovered by this method. The addition of 0.2 cat unit of human renin to human plasma can be recovered by this technic when assayed on a suitable animal preparation.

Results. Significant amounts of renin were found in the blood of 1 patient with eclampsia, 2 with severe preeclampsia, and 1 with fulminating acute glomerulonephritis without convulsions (see Table I and Fig. 1). In 3 cases the hypertension was of sudden onset. In 1 of the preeclamptics it was of more gradual onset, but was superimposed on a previous essential hypertension. The blood was obtained soon after admission to the hospital when the blood pressure was approaching its maximum elevation and before treatment was instituted. In the case of the 4-year-old boy, P.P., with acute glomerulo-

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1 Braun-Menendez, E., Fasciolo, J. C., Leloir, L. F., and Muñoz, J. M., *Rev. Soc. argent. de biol.*, 1939, **15**, 420.

2 Houssay, B. A., *Medicina*, 1941, **1**, 167.

3 Kohlstaedt, K. G., and Page, I. H., PROC. SOC. EXP. BIOL. AND MED., 1940, **43**, 136.

4 Leloir, L. F., Muñoz, J. M., Braun-Menendez, E., and Fasciolo, J. C., *Rev. Soc. argent. de biol.*, 1940, **16**, 635.

TABLE I.
Amount of Renin Recovered from Blood of 3 Patients with Toxemia of Pregnancy and 1 with Acute Glomerulonephritis.

Patient	Blood pressure, mm Hg.	Amt serum tested, cc	Cat units renin recovered	Diagnosis and remarks
P.L.	160/110	11	0.4	Eclampsia
I.D.	158/118	11	0.7	Severe preeclampsia.
L.D.	180/110	9	0.5	Essential hypertension with preeclampsia.
P.P.	248/160	10	2.4	Acute glomerulonephritis, fulminating. B.P. 85/50 24 hrs previously.

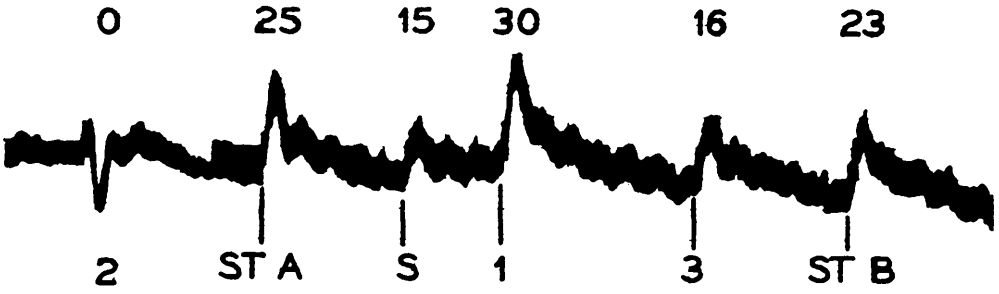

FIG. 1.
Demonstration of Renin in the Plasma of Patient P.P. with Acute Glomerulonephritis. Blood Pressure: 248/160 mm Hg.

Blood pressure curves are those of a cat under dial anesthesia.

The figures above the curves indicate the rise in blood pressure in mm Hg.

2—Response to injection of unincubated control equivalent to 10 cc serum. (See text for preparation of tubes 1, 2, and 3.) After this injection the cannula clotted.

St. A—Response to 0.75 cat unit of standard hypertensin.

S—Response to 10 cc physiological saline.

1—Response to incubated sample equivalent to 5 cc serum. When calculated for renin, this is equivalent to 2.4 cat units of renin per 10 cc serum.

3—Response to sample incubated with hypertensinase. Note that this gives approximately the same rise as the saline control.

St. B—Response to 1.2 cat units of standard hypertensin.

nephritis, which was verified subsequently by autopsy, a therapeutic phlebotomy made possible duplicate determinations of renin in the serum. Renin could be demonstrated in all tests, and large amounts of hypertensinase were necessary to destroy the hypertensin formed. In 5 cases of preeclampsia and in 2 of acute glomerulonephritis where the hypertension was not severe or where it was gradual in onset, no renin was detected in the blood. In 13 patients with chronic hypertension of all degrees of severity associated with chronic glomerulonephritis, chronic pyelonephritis, or of unknown cause (essential hypertension), no renin was found in the blood (Fig. 2).

Discussion. Dell'Oro and Braun-Menendez,[5] using the method of Leloir *et al.*,[4] have shown that renin may be detected in the systemic blood of dogs made hypertensive by means of a Goldblatt clamp during the time when the blood pressure is rising abruptly. Once the pressure has attained its maximum and plateaued, renin is not demonstrable in the systemic blood by this method. It has been claimed that renin can be detected in the blood of hypertensive patients using the isolated rabbit's ear[6] and the toad's hind limb,[7] but the technics as described made little attempt to identify the nature of the constrictor substance. It has only been by the

[5] Dell'Oro, E., and Braun-Menendez, E., *Rev. Soc. argent. de biol.*, 1942, **18**, 65.

[6] Page, I. H., *J. Exp. Med.*, 1940, **72**, 301.

[7] Garreton Silva, A., Croxatto, R., Fuenzalida, O., and Viveros, R., *Rev. med. de Chile*, 1941, **69**, 625.

[8] Houssay, B. A., and Fasciolo, J. C., *Rev. Soc. argent. de biol.*, 1937, **13**, 284.

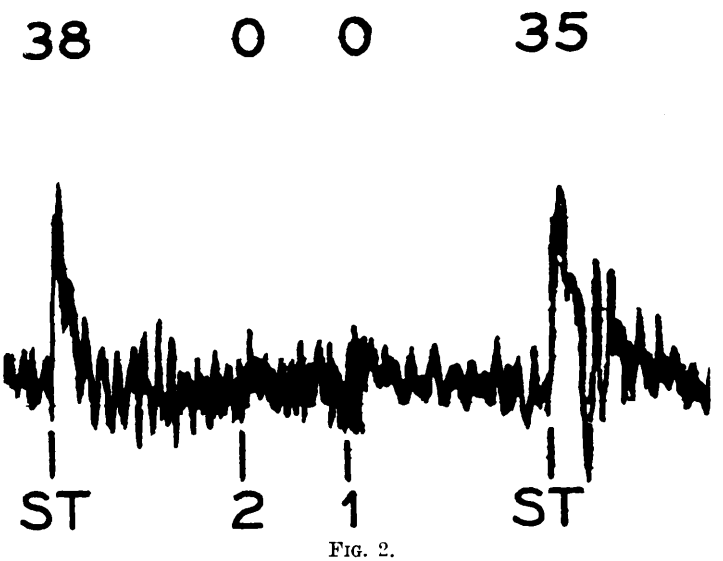

FIG. 2.
Test for the Presence of Renin in the Plasma of Patient B.F. with Essential Hypertension. Blood Pressure: 195/110 mm Hg.
Blood pressure curves are those of a cat under dial anesthesia.
The figures above the curves indicate the rise in blood pressure in mm Hg.
St.—Response to 0.5 cat unit of standard hypertensin.
2—Response to unincubated control equivalent to 10.5 cc plasma. (See text for preparation of tubes 1 and 2.)
1—Response to incubated sample equivalent to 10.5 cc plasma.
N.B. Renin was therefore not demonstrated in the blood of this patient.

use of kidney grafts[8] and cross-circulation experiments[9] that a pressor substance, similar in its pharmacologic properties to renin, has been demonstrated unequivocally in the systemic blood of dogs with chronic Goldblatt hypertension.

In patients we have found renin in the blood in those cases where the hypertension has been severe and explosive in onset, *i.e.*, eclampsia, severe preeclampsia, and fulminating acute glomerulonephritis. In cases of preeclampsia and acute glomerulonephritis with only moderate elevation of blood pressure or where the hypertension has been of gradual onset, and in patients with chronic hypertension with pressures as high as 285 systolic and 180 diastolic, we have been unable to detect renin in the systemic blood.

Summary. 1. Significant amounts of renin have been detected in the blood of 1 patient with eclampsia, 2 with severe preeclampsia, and 1 with fulminating acute glomerulonephritis using a modification of the method of Leloir *et al.*[4] 2. No renin has been found in the blood of patients with milder degrees of toxemia of pregnancy and acute glomerulonephritis, nor of patients with chronic hypertension of all degrees of severity. 3. The relation of these observations to those on animals with experimental renal hypertension is discussed.

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[9] Solandt, D. Y., Nassim, R., and Cowan, C. R., *Lancet*, 1940, **1**, 873.