Blood Volume and Aldosterone Secretion in Hypertension and Primary Aldosteronism.* (26736)

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Observation of an expanded extracellular fluid and plasma volume in 2 cases of primary aldosteronism(1) suggested that the hypervolemia might be a useful differential point in its diagnosis, particularly in distinguishing the hypertensive patient in whom the possibility of aldosteronism should be considered.

Case reports. Primary aldosteronism. L.B., a 39-year-old white female, and R.T., a 25-year-old white male, had known hypertension of 14 and 6 years duration respectively. Both had hypernatremic, hypokalemic alkalosis for about 6 years. On admission to hospital blood pressure in both was 220/130 mm Hg. Cardiomegaly, Keith-Wagner Grade II hypertensive retinopathy, and a positive Trousseau sign were observed in each. No edema or congestive heart failure was evident. The mean of 9 urinary aldosterone determinations during sodium intakes higher than 100 mEq was 29 μg/24 hours in L.B. (normal 3-15 μg/24 hours). Mean of 5 urinary aldosterone values in R.T. was 40 μg/24 hours. At operation an 8.4 g left adrenal adenoma in L.B. was removed and, in R.T., a 4.5 g right adrenal adenoma. Two months after excision serum electrolytes were normal in both patients and blood pressure had fallen to 140/90 mm Hg in L.B. and 170/100 in R.T.

Hypertension. Blood pressure, serum electrolytes and serum creatinine determinations are summarized in Table I. Blood volume and urinary aldosterone were determined while sodium intake was in excess of 100 mEq/24 hours. The selected patients had no evidence of congestive failure, edema, or propensity to retain sodium with salt loads. Patient J.M. is of particular interest since during our observation she developed malignant hypertension with papilledema and subsequently died of bacterial pneumonia. The adrenal glands were normal at postmortem examination. Patient M.S. also had malignant hypertension, which did not respond to antihypertensive medications. Postmortem study revealed normal adrenal glands and severe nephrosclerosis.

Methods. Red cell volume was determined by a modification of the $NaCr^{51}O^4$ method of Sterling and Gray(2,3). *Plasma volume* in the cases of primary aldosteronism was measured directly with T-1824(4) or I^{131} human serum albumin(5), thus allowing calculation of true whole blood volume and body hematocrit. Values for whole blood volume in the group of hypertensives (Table II) were calculated from red cell volume and venous hematocrits uncorrected for plasma trapping or for differences between the hematocrit of venous blood and that of the body as a whole. *Extracellular fluid* was determined by volume of dilution (Inulin)(7). Normal values were predicted at 16.2% of body weight. *Urinary aldosterone* was measured by the double isotope derivative technic of Kliman and Peterson(8) after hydrolysis at pH 1 for 24 hours at room temperature. Normal values with sodium intakes above 100 mEq/24 hours in this laboratory are 3-15 μg/24 hours.

Results. Primary aldosteronism (Table II). Preoperative. In patients L.B. and R.T., respectively, a marked expansion of extracellular fluid of 58% and 57%, total

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TABLE I. Blood Volume and Urinary Aldosterone in Hypertension.

Patient, age & sex	Blood pressure, mm Hg	Serum electrolytes (meq/l) Na	K	Cl	CO_2	Serum creatinine, mg/100 ml	Red cell volume Het., %	Pred., l	Obs., l	Dev., %	Total blood vol (Cr^{51})* Pred., l	Obs., l	Dev., %	Urinary aldosterone, μg/24 hr
P.C. 36 ♂	235/170	138	3.5	93.5	29.4	1.9	41.9	1.60	1.27	79	3.40	3.02	89	3.4
R.P. 50 ♂	200/140	145	3.7	99.9	31.4	2.1	39.9	2.53	2.20	87	5.27	5.52	105	3.1
C.D. 37 ♀	160/110	143	4.1	106.0	23.9	1.4	30.0	1.82	.93	51	4.00	3.10	78	13.0
V.M. 56 ♀	220/120	132	3.7	85.0	28.2	2.8								7.7, 9.4
D.C. 6 ♀	170/125	132	4.6	100.0	29.6	1.4								6.4
J.M. 36 ♀	170/120	138	3.1	77.5	33.0	3.7	37.3	1.73	.93	54	3.63	2.50	69	5.4
J.M.† 36 ♀	210/130	118	5.5	79.1	21.1	10.0	30.3		1.09	61	3.63	3.56‡	98	36.0
M.S.† 4 ♀	260/160	146	4.6	113.0	20.6	1.5								28.6

* Predictions based on height and weight according to Wennesland *et al.*(6).
† Malignant phase.
‡ Given 2 units of blood and 250 ml 3% saline day before volume measurement. Urinary aldosterone determined 5 days before blood volume.

TABLE II. Blood Volume Alteration in Primary Aldosteronism.

	Height, cm	Wt, kg	Plasma vol l	%*	Red cell vol (Cr^{51}) l	%*	Total blood vol l	%*	Body het.: Venous het.	ECF (inulin) l	%*	Het., %	Urinary aldosterone, μg/24 hr
L.B., preoperative	165.5	50.2	3.48 (T-1824)	(176)	1.58	(113)	5.06	(145)	.89	13.0	(158)	35.0	29
L.B., postoperative			2.75 (T-1824)	(140)	1.20	(73)	3.95	(111)	.99	10.6	(124)	30.7	5
R.T., preoperative	189.5	75.2	4.37 (I^{131})	(148)	2.22	(99)	6.59	(129)	.94	19.0	(157)	35.8	40
R.T., postoperative			2.94 (I^{131})	(100)	2.14	(97)	5.08	(100)	.91	12.0	(100)	46.1	3

* % of predicted values.

blood volume 45% and 29%, and plasma volume 75% and 48% above predicted normal but with low hematocrits were noted. Serum albumin concentration was 3.7 g/100 ml in L.B. and 4.4 g/100 ml in R.T. Red cell volumes in both patients were *normal*. *Postoperative*. Eight weeks after operation all these measurements had been restored to normal in R.T. In L.B., the restoration was toward normal; total blood volume was but 11% above normal. Postoperative serum albumin concentration was 3.6 g/100 ml in L.B. and 4.6 in R.T. *Hypertensive patients* (*Table I*). Similar measurements performed in 4 patients with essential and in one with malignant hypertension revealed normal-to-decreased total blood volumes. Red cell volume was decreased 51-87% of predicted normal values. However, urinary aldosterone levels had increased to 28.6 (M.S.) and 36.0 (J.M.) in the patients with malignant hypertension, while still normal in the group with essential hypertension (3.1 to 13.0 μg/24 hours).

Discussion. In the 2 cases of primary aldosteronism it appears that the expanded plasma volume is a consequence of an increase in extracellular fluid produced by chronic secretion of excessive aldosterone similar to that seen after continued administration of desoxycorticosterone acetate(9) or aldosterone(10). Red cell volume was normal, and the plasma expansion was thus revealed by the low hematocrit in both cases. Serum albumin concentration in both patients was normal and remained unchanged after removal of the adenomas. Colloid osmotic pressure was strikingly unaltered irrespective of changes in aldosterone secretion. Complete restoration of total blood volume, plasma volume and extracellular fluid without changes in red cell volume occurred in R.T. 2 months after operation. In L.B., total blood volume approached normal values with a 46% fall in plasma volume. Significant anemia resulting from blood loss at operation may have contributed, in part, to the still expanded plasma volume.

In contrast, total blood volume and urinary aldosterone levels in 4 cases of severe essential hypertension were normal or even depressed. Total blood volume and extracellular fluid have been found previously to be normal in hypertension(11,12). Grollman (13) observed increases in extracellular fluid but normal plasma volumes in hypertension. Urinary aldosterone assays in essential hypertension have been found normal(14). Only in malignant hypertension has increased aldosterone secretion been clearly established (15). In one case of transition from essential to malignant hypertension without occurrence of heart failure, urinary aldosterone increased greatly without associated increases in blood volume or changes in plasma electrolytes. The adrenals were not enlarged at the time of postmortem examination. The blood volume in the second case of malignant hypertension was not determined, but urinary aldosterone was increased and there was no indication of hypervolemia, as reflected by a normal hematocrit without serial change and the absence of congestive heart failure.

Thus the demonstration of an expanded plasma volume, which may be indicated by a low hematocrit in a hypertensive patient with hypernatremia and hypokalemia, suggests primary aldosteronism. The hypertensive patients studied also showed a slight decrease in hematocrit, which reflected a true red cell volume deficit and not an expanded plasma volume, as seen in the 2 cases of primary aldosteronism. The differentiation of primary aldosteronism from malignant hypertension might be clarified further by a normal blood volume.

Summary. Two cases of primary aldosteronism were demonstrated to have expanded extracellular fluid, total blood volume, and plasma volume, with restoration toward normal after removal of adrenocortical adenomas. Red cell volumes were normal in both. No increase in urinary aldosterone was observed in 5 patients with essential hypertension. Blood volume was normal or slightly decreased. Increased urinary aldosterone without hypervolemia was observed in 2 patients with malignant hypertension. Thus increased total blood volume in hypertensive patients, due solely to plasma volume and anemia (low hematocrit), should prove a

useful addition to the diagnostic screen for primary aldosteronism.

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Activation of Tremorine by Liver.*† (26737)

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Tremorine (1,4-dipyrollidino-2-butyne) was reported by Everett(1) to produce sustained tremors and parasympathetic-like stimulation in several species of laboratory animals. Since it elicits tremors and other parkinsonian-like signs, Tremorine has been used in routine screening for potential antiparkisonian drugs. The report(2) that an hour elapses before the cat shows typical drug effects after administration of Tremorine (10-20 mg/kg) suggested that Tremorine may have to be biotransformed before it becomes pharmacologically active. Evidence presented here indicates that the liver converts Tremorine to an active form which has pharmacologic properties differing from those of the original product.

Materials and methods. Young adult male Swiss-Webster mice, hamsters weighing 100-150 g, 2-3 kg cats and 5-10 kg dogs were used. Tremorine dihydrochloride‡ was dissolved in pH 7.4 Krebs-phosphate buffer (2 mg/ml) prior to incubation with liver. Homogenates and tissue slices totaling 2-4 g wet weight from the livers of mice, hamsters, or rats were incubated at 37°C for 2 hours in a shaking incubator with 12 ml of buffered Tremorine solution in 250 ml flasks (O_2 gas phase). After incubation filtrates of the solution were injected into animals in doses expressed as equivalents of Tremorine present before incubation.

Time of onset of tremors was measured from injection to time of head and limb tremors of a fully developed intensity as judged by a single observer throughout the study. Five or more mice per group were used in each experiment, except as noted.

Results. Tremorine incubated with mouse liver slices produced tremors within 5 sec after intravenous injection into mice, whereas non-incubated Tremorine required more than 15 min to produce effects (Table I). It

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