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NEPHROLOGY FORUM

Salt, volume, and hypertension: Causation or correlation?

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Case presentations

A 24-year-old man (Patient 1) was first found to be hypertensive (blood pressure, 150/95 mm Hg) at the age of 8 years, when he presented to a physician because of headaches.He was discharged untreated. Approximately 7 years later he again was found to be hypertensive (blood pressure, 180/120 mm Hg) and over succeeding years was treated with varying success with several drugs, including propranolol, atenolol, and indapamide. When he was first seen at age 24 in the Medical Research Council Blood Pressure Unit, his blood pressure was poorly controlled on propranolol (80 mg/day). Treatment was withdrawn and after 4 weeks his blood pressure was 210/106 mm Hg. At that time his 29-year-old brother (Patient 2) also was referred to the Unit with headaches and hypertension (blood pressure, 160/106 mm Hg). Physical examination of both patients was within normal limits except for hypertension. Both patients had normal routine blood studies, and neither had any clinical or biochemical evidence of renal disease or abnormal catecholamine secretion.

The patients' father was apparently severely hypertensive, but no records were available. He had suffered two strokes at the ages of 38 and 45 years, the second of which was fatal. Their mother also has hypertension and has suffered one transient cerebral ischemic attack. Three paternal uncles were hypertensive; all 3 died at relatively early ages (42, 52, and 61 years). Whether any of these relatives had hyperaldosteronism is unknown.

Results of special studies in both patients appear in Table 1. Plasma aldosterone concentration was high (upper limit of normal, 18 ng/dl) and plasma renin concentration low (normal, 10–50 μU/liter) in both cases. Plasma cortisol concentration was normal, suggesting normal ACTH secretion, but interestingly plasma 11-deoxycorticosterone (DOC), another mineralocorticoid, was slightly raised (normal range, 4–16 ng/dl). Electrolyte determination revealed hypokalemia; serum sodium concentration was normal. Total-body sodium and potassium were measured before and after the administration of 2 mg of dexamethasone (0.5 mg four times daily) for 4 weeks. The fall in plasma cortisol concentration to undetectable levels (with dexamethasone) indicated suppression of ACTH secretion to subnormal levels during treatment. This decrease in cortisol levels occurred concurrently with a decrease in the concentrations of plasma aldosterone to low-normal and of plasma DOC to low levels. These hormonal changes were associated with an increase of plasma potassium concentration to normal and a slight fall in plasma sodium concentration. Total-body potassium increased and in each patient total-body sodium fell more than 300 mEq. The decrease was accompanied by a return of blood pressure to the normal range. The biochemical abnormalities and hypertension recurred in 4 weeks after dexamethasone was withdrawn.

Infusion of ACTH while the patients were untreated gave dose-response curves for aldosterone and DOC that were steeper than normal, whereas that for cortisol was normal. The dose-response curve for aldosterone was unaffected by dexamethasone treatment (Fig. 1).

In Patient 1, the side effects of dexamethasone were unacceptable, and he is being treated successfully with amiloride, a potassium-sparing diuretic. Patient 2 remains well-controlled on a low dose of dexamethasone (0.25 mg/day).

Discussion

DR. J. I. S. ROBERTSON (*Clinical Scientist and Consultant Physician, Medical Research Council Blood Pressure Unit, Western Infirmary, Glasgow, Scotland, U.K.*): In this Forum, we shall be considering mainly the body content of sodium but also of potassium in various hypertensive syndromes, especially essential hypertension. Before considering the details, however, I have asked my associate, Dr. Robert Fraser, to describe briefly a rare, but most interesting disease, hypertension resulting from dexamethasone-suppressible aldosterone excess, which provides the springboard of this discussion. Several of my colleagues will contribute to this Forum.

DR. R. FRASER (*Non-clinical Scientist, MRC Blood Pressure Unit, Western Infirmary*): Primary hyperaldosteronism, a hypertensive condition associated with potassium loss and sodium retention, is the result of autonomous oversecretion of the

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Table 1. Biochemical studies in the patients being discussed

	Patient 1		Patient 2	
	Untreated	Treated[a]	Untreated	Treated[a]
Blood pressure *mm Hg*	210/112	134/84	160/106	132/86
Serum K^+ *mEq/liter*	3.3	4.2	3.5	4.2
Total body K^+ *mEq/liter*	3995	4384	4355	4655
Serum Na^+ *mEq/liter*	142	139	141	139
Total body Na^+ *mEq/liter*	4029	3656 (−373)	3817	3494 (−323)
Plasma active renin *μU/ml*	<3	68	<3	49
Plasma aldosterone *ng/dl*	27	4	20	2
Plasma cortisol *μg/dl*	15	<1	13	<1
Plasma DOC *ng/dl*	19	1	21	1

[a] Treatment comprised dexamethasone, 2 mg/day, for 4 weeks.

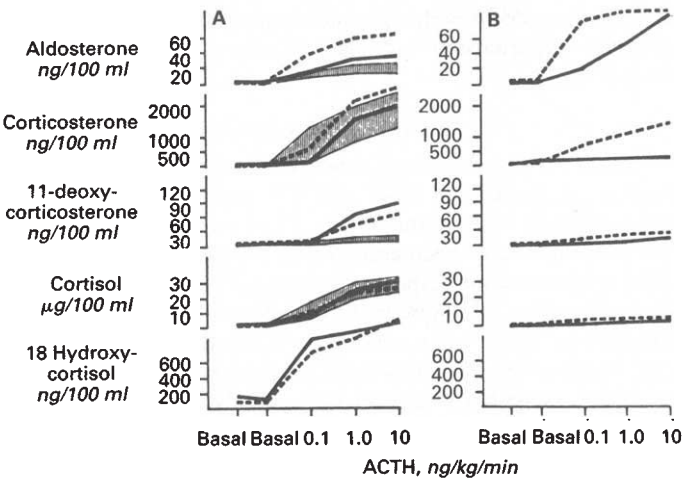

Fig. 1. *Corticosteroid responses to ACTH* (0.1, 1.0 and 10.0 ng/kg/min) *in Patients* 1 (—) *and* 2 (---) *before treatment* (**A**) *and after 4 weeks of dexamethasone* (0.5 mg 4 times daily). (**B**) Shaded areas in A represent responses to ACTH in 8 normal subjects. Values are means ± SD. (Reproduced from Ref. 2.)

mineralocorticoid aldosterone. The rare variant of this disease, dexamethasone-suppressible hyperaldosteronism, originally was described by Sutherland et al in 1966 [1]. Diagnosis is based on the general criteria for primary hyperaldosteronism, that is, high plasma aldosterone concentration or aldosterone secretion rate, low plasma renin concentration and hypokalemia, as well as the special criterion for this disease, sustained correction of blood pressure and biochemical abnormalities by administration of the synthetic glucocorticoid dexamethasone. Dexamethasone suppresses ACTH secretion; aldosterone secretion, which is supersensitive to ACTH infusion in this condition, is also suppressed. As the condition probably is inherited as an autosomal dominant factor, other members of the family are likely to be affected. The patients presented today thus fulfill each of these criteria for diagnosis, and they also illustrate the sodium-dependent nature of the raised blood pressure. We have reported on these patients in detail elsewhere [2].

Assessment of whole-body sodium and potassium could throw important light on the pathogenesis and treatment of human hypertension. Perhaps surprisingly, this approach has interested only a few centers and remains less than fully explored. There are obvious limitations; total-body measurements do not reveal what could be critical aspects of the distribution of electrolytes within the organism. Nevertheless, it is my opinion and that of my colleagues that, despite the reservations, this approach can provide important pathophysiologic insights into human hypertension.

Dr. Robertson: In his presentation of these 2 patients, Dr. Fraser showed data on an unusual, but extremely interesting, familial syndrome in which an excess of aldosterone, which is abnormally dependent on ACTH secretion, leads to hypertension, expansion of exchangeable sodium, and suppression of the renin-angiotensin system. When ACTH secretion is lowered by the administration of dexamethasone, body sodium content falls and, in parallel, arterial pressure decreases. The remarkable correlation between body sodium and blood pressure in this rare syndrome provides us an opportunity to consider body sodium content in relation to other, more common types of hypertension, particularly essential hypertension.

Over the years great interest has been shown in a possible involvement of sodium chloride in the pathogenesis of essential hypertension [3]. First, the rise in blood pressure with age observed in most westernized societies and the high prevalence of hypertension in these populations has been attributed to excessive dietary intake of sodium. Linked with this idea is the suggestion that only a proportion of individuals within a population might be "salt sensitive" and thus might develop hypertension on this basis. Moreover, a "threshold" of sodium intake might exist above which hypertension develops. An obviously related idea, although not a necessary corollary, is that dietary sodium restriction might be effective in reducing arterial pressure. Second, there might be a renal abnormality central to the pathogenesis of hypertension, one that requires that systemic blood pressure be elevated for the preservation of sodium balance. Third, many abnormalities of transmembrane electrolyte transport have been described in essential hypertension. Again, these derangements might be involved in various ways in the pathogenesis of hypertension; these several observations and hypotheses are not necessarily mutually exclusive.

The renin-angiotensin system is also intricately related to sodium balance [4]. Sodium losses stimulate this system; increased renin secretion from the kidney results in a rise in angiotensin II. With many other actions, the increase in angiotensin II helps to sustain arterial pressure and, by promoting aldosterone secretion, restores sodium homeostasis.

More recently, the atrial peptide system has excited intense interest and research [5]. Atrial peptides cause a natriuresis and diuresis, lower arterial pressure, diminish the secretion of renin and aldosterone, and oppose several of the actions of angiotensin II and aldosterone. For these reasons, it has been proposed that the atrial peptide system antagonizes the renin system and is designed to deal promptly with fluid and volume overload. Assessment of the total-body content of sodium (and of potassium) might facilitate insight into these pathogenetic mecha-

nisms and could provide approaches to treatment, not only of essential hypertension but also of other hypertensive syndromes [6].

Methodologic considerations

Measurements have been made both of total exchangeable sodium and potassium (NaE and KE) and total-body sodium and potassium (TBNa and TBK). Total exchangeable sodium and potassium have been assessed by isotope dilution after the administration of the respective isotopes ^{24}Na and ^{43}K followed by equilibration [7]. Total-body potassium has been measured employing a whole-body counter to detect the naturally occurring isotope ^{40}K [8]. Total-body sodium has been measured using the whole-body counter immediately after activation of sodium in vivo by neutron bombardment [9].

Our observations have shown that, as might be expected, TBNa consistently exceeds NaE by some 15% in the middle of the range [10]. This excess probably represents a large pool of nonexchangeable (or very slowly exchangeable) sodium in bone. Our findings in humans are paralleled almost exactly by a similar excess of TBNa over NaE in rats. We showed a close concordance between TBNa measured by neutron bombardment and by chemical analysis following ashing of carcasses [11]. Our findings in humans show that TBK exceeds KE by approximately 5% in the middle of the range [12]. In none of the syndromes studied in humans, such as essential hypertension, renal hypertension, and primary hyperaldosteronism, has evidence been found of variation in the proportion of nonexchangeable sodium or potassium. Thus qualitatively, similar information is obtained whether total-body or exchangeable sodium and potassium are measured.

Serial estimation of body sodium and potassium content in the same person at different stages of the disease, as Dr. Fraser already described for dexamethasone-suppressible hyperaldosteronism, permits the greatest precision of measurement. To compare body sodium and potassium content between different people, however, one must correct for individual variations in body size and shape. Although there is no entirely satisfactory frame of reference, we have found that either body surface area or leanness index (height^3 ÷ weight) is most suitable [10]. Both of these indices give similar values when used to express either body sodium or potassium. In many of the studies of hypertensive patients that I shall present here, total-body or exchangeable sodium or potassium have been expressed as a percentage of the value predicted for a normal individual of similar body size and shape. In an extensive series of normal individuals from Berne, Switzerland, and Glasgow, Scotland, no detectable relationship was found between NaE and arterial pressure [10].

Mineralocorticoid-induced hypertension

The classic form of mineralocorticoid-dependent hypertension in humans is Conn's syndrome [13]. In this disease hypersecretion of aldosterone by an adrenocortical adenoma gives rise to high blood pressure, which is accompanied by sodium retention and potassium depletion. Renin secretion is suppressed, and there is a characteristic and often diagnostic interrelationship between low values for plasma renin and angiotensin II on the one hand and high circulating levels of plasma aldosterone on the other [14]. In this condition more than in any other, if a connection exists between changes in body sodium and arterial pressure, we should find an overall expansion of body sodium content and a positive correlation between body sodium and blood pressure.

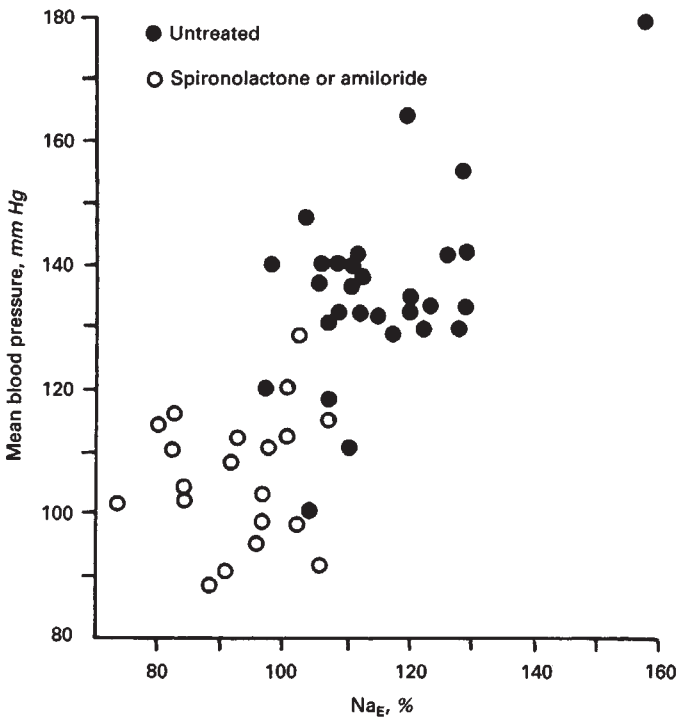

Fig. 2. *Total exchangeable sodium expressed in relation to leanness index (%) plotted against mean arterial pressure* (diastolic + 1/3 pulse pressure) *in 29 patients, all of whom were later proved to have an aldosterone-secreting adenoma.* Solid circles = measurements made without treatment; open circles = measurements made in 20 of these patients after at least one month's treatment with either spironolactone or amiloride. In the untreated patients, mean exchangeable sodium is clearly expanded, and there is a significant positive correlation with arterial pressure. During treatment with the potassium-conserving and natriuretic agents, arterial pressure falls in proportion to the fall in exchangeable sodium. (Reproduced from Ref. 6.)

Indeed, we have confirmed this relationship. In a substantial series of untreated patients with this disease (Fig. 2), both NaE and TBNa were clearly increased; conversely, TBK and KE were decreased [6, 15]. In this series we also found a significant positive correlation between the degree of expansion of body sodium and the level of the arterial pressure. Although not proof, these findings are consistent with a cause-and-effect relationship. We obtained further evidence of a causal relationship by treating patients who had primary aldosteronism with a potassium-conserving and natriuretic agent such as spironolactone or amiloride for at least one month before operation (Fig. 2). Body sodium content decreased concurrently with a fall in arterial pressure [6, 15]. A similar result is achieved by surgical excision of the tumor and consequent correction of the aldosterone excess. Restoration of normal levels of aldosterone also corrects body sodium content, and arterial pressure falls in proportion. The fall of body sodium content with therapy occurs simultaneously with proportional decreases in total-body water, extracellular fluid volume, and plasma volume [6, 15, 16].

Dr. Fraser already has mentioned in the two case presenta-

tions similar relationships between shifts in body sodium content and arterial pressure in dexamethasone-suppressible aldosterone excess. Other, rare syndromes of mineralocorticoid excess similarly show expansion of body sodium content in the untreated state as well as a decrease in arterial pressure in parallel with a fall in body sodium with therapy. Such syndromes include 17-alpha-hydroxylase deficiency and 11-beta-hydroxylase deficiency [6]. In both of these syndromes, cortisol synthesis is defective; consequently ACTH output is excessive and results in overproduction of ACTH-sensitive mineralocorticoids. Similar findings have been described with excessive ingestion of an exogenous mineralocorticoid, licorice [17]. Although body sodium and potassium content are statistically related to arterial pressure in syndromes of mineralocorticoid excess, we should be cautious about concluding that there is a cause-and-effect relationship between these phenomena [15].

"Idiopathic aldosteronism"

I now wish to digress briefly to consider a problem that relates to both mineralocorticoid hypertension and essential hypertension. About 25% of patients with high blood pressure, elevated plasma aldosterone, and low plasma renin levels do not harbor a typical aldosterone-secreting adenoma but have a variety of subtle changes within the adrenal gland [6, 18–22]. Some patients have bilateral micronodular changes in the adrenocortical zona glomerulosa, some have simple hyperplasia of the zona glomerulosa, and some even have histologically normal adrenal glands. This syndrome has been described variously as "idiopathic aldosteronism," "non-tumorous aldosteronism," and "pseudo-primary aldosteronism." Surgical therapy is less effective in lowering blood pressure in this condition than it is in Conn's syndrome.

The nature of this condition has excited considerable argument over the years. In striking contrast to the findings in Conn's syndrome and the other forms of mineralocorticoid excess, body sodium content in this condition is either normal or only marginally elevated [20, 23]. Similarly, our studies disclose no consistent reduction of body potassium content. At present it seems more likely that idiopathic aldosteronism is not a separate entity but a variant of essential hypertension.

Low-renin hypertension

Approximately 25% of patients who apparently have essential hypertension have low levels of plasma renin, often as low as values in patients with aldosterone-secreting adenomas [6, 24, 25]. This observation has led to speculation that an excess of an as-yet-unidentified mineralocorticoid or corticoid might be responsible in this group of patients both for the hypertension and the renin suppression. In most of these patients, however, no such mineralocorticoid excess can be demonstrated. Furthermore, the mean body sodium content is not increased, nor is body potassium content decreased [18, 23]. Consistent with these findings for body sodium and potassium is the finding that neither extracellular fluid nor plasma volume is expanded [26].

Similarities among essential hypertension, low-renin hypertension, and idiopathic aldosteronism

Given the physiologic observations in several hypertensive syndromes, we proposed that low-renin hypertension and idiopathic aldosteronism—and even essential hypertension—might be closely similar one to another [22]; indeed, these three disorders might form a continuum. By contrast, Conn's syndrome appears to be a distinct entity. These notions were reinforced when we examined these various entities. In untreated, tumorous Conn's syndrome, the relationship between plasma aldosterone and plasma angiotensin II was inverse [14, 27], as would be predicted if there were autonomous (or largely autonomous) overproduction of aldosterone, which inhibits renin secretion. In sharp contrast, the correlation between angiotensin II and aldosterone was positive in patients with "idiopathic" aldosterone excess [14, 27]. This observation indicated that in the latter condition, the physiologic relationship between the renin-angiotensin system was more nearly normal, and that angiotensin II probably was still responsible, at least in part, for regulating aldosterone secretion.

Infusion of angiotensin II, which in normal individuals stimulates aldosterone secretion, has little or no effect on aldosterone in true Conn's syndrome. In contrast, however, angiotensin II stimulates aldosterone more briskly in essential hypertension than in subjects with a normal blood pressure. Plasma aldosterone rises even higher in response to angiotensin II in "idiopathic" aldosteronism than in essential hypertension. True tumorous Conn's syndrome and "idiopathic" aldosteronism thus lie at opposite ends of a spectrum with respect to the aldosterone responses to angiotensin II [14, 18, 27, 28].

Orthostasis similarly increases plasma aldosterone concentration in normal subjects and in patients with essential hypertension, low-renin hypertension, or idiopathic aldosteronism. In patients with Conn's syndrome, by contrast, orthostasis usually produces little or no alteration in plasma aldosterone [14, 27]. In normal persons and in patients with essential hypertension (whether with normal or low levels of renin) or "idiopathic" aldosteronism, renin falls progressively with age [14, 23, 27]. Neither we nor any other group has demonstrated a relationship between renin and age in tumorous Conn's syndrome.

These various features have provided a basis for several statistical appraisals, one of which will be discussed in more detail by Dr. Gordon Murray. Such statistical analyses have supported the notion of a basic distinction between Conn's syndrome and the other conditions I mentioned [14]. These observations have led us to conclude that artificial distinctions have been made between essential hypertension, low-renin hypertension, and "idiopathic" aldosteronism because of an over-rigid application of diagnostic criteria that we believe are quite arbitrary [16, 25]. This concept has important pathophysiologic and practical therapeutic implications. Whereas the correct and definitive therapy for Conn's syndrome is removal of the tumor, surgery is not indicated in "idiopathic" aldosterone excess [14, 16].

Renovascular hypertension

I now want to consider a strikingly contrasting hypertensive disease—particularly as it concerns body sodium content—namely, hypertension associated with unilateral renal artery stenosis. Many patients with unilateral renal artery stenosis (that is, with an intact contralateral kidney and renal artery) have normal plasma electrolytes and normal or near-normal body sodium and potassium content [29]. However, in this

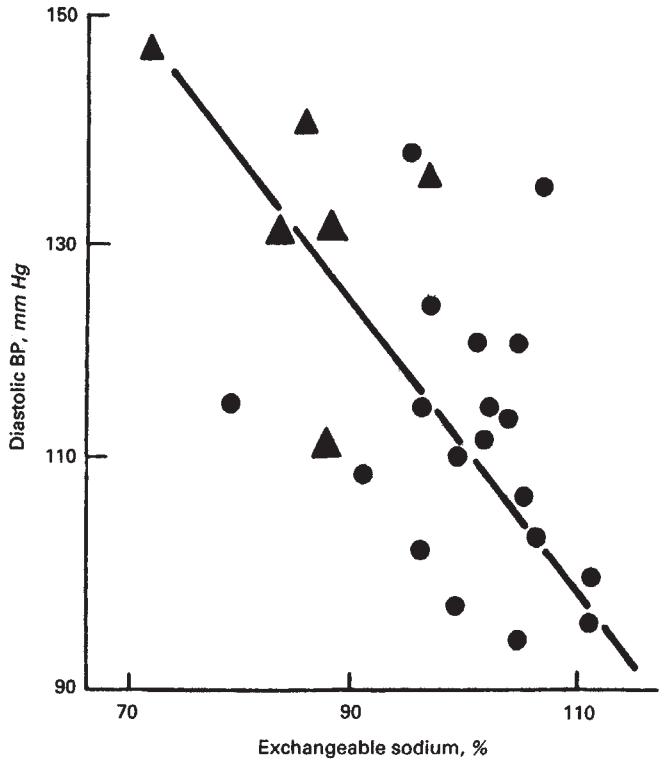

Fig. 3. *Inverse relationship between exchangeable sodium, expressed in terms of body surface area, and diastolic pressure, in patients with unilateral renal artery stenosis.* The 6 patients indicated by triangles had, on the day of exchangeable sodium measurement, plasma sodium concentrations below 135 mEq/liter. r = 0.57; $P < 0.01$. (Reproduced from Ref. 30.)

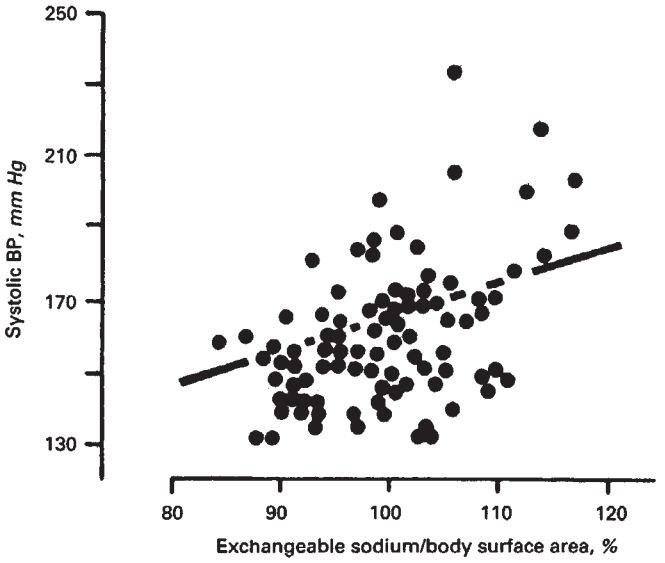

Fig. 4. *Total exchangeable sodium in relation to systolic pressure in untreated patients with essential hypertension* (r = 0.44; $P < 0.001$). (Reproduced from Ref. 6.)

disorder, especially in patients in whom blood pressure rises considerably, renal sodium wasting leads to progressive sodium depletion [29, 30]. Sodium loss can be marked in patients with acute, severe, unilateral renal artery stenosis or occlusion. In its most pronounced form, patients can present with a "hyponatremic hypertensive syndrome," with considerable depletion of body sodium and potassium, hyponatremia and hypokalemia, marked elevation of peripheral plasma renin and angiotensin II, and secondary aldosterone excess [29, 30]. In these circumstances, the severe renal artery lesion provides an intense stimulus to renin secretion; consequently there is a pronounced rise in plasma angiotensin II. Blood pressure increases progressively while sodium is lost from the contralateral normal kidney because of pressure natriuresis and possibly also because of the direct renal action of very high circulating levels of angiotensin II and vasopressin. Secondary aldosteronism ensues, with consequent potassium depletion added to the sodium depletion. Renin secretion is further stimulated by the losses of sodium and potassium. This vicious cycle can be broken by relieving the renal artery stenosis, removing the diseased kidney, or reducing levels of angiotensin II with a converting enzyme inhibitor. In a large series of patients with hypertension associated with unilateral renal artery stenosis, the correlation between arterial pressure and body sodium content was an inverse one, with the most markedly hypertensive patients having substantial sodium depletion [30–32] (Fig. 3). These findings suggest that, when systemic hypertension arises by a mechanism that does not primarily involve sodium retention, there is a tendency toward sodium depletion, with pressure natriuresis as the predominant cause.

Essential hypertension

Next I wish to examine the relationship between the level of arterial pressure and body sodium content in essential hypertension. We already have seen that in normal individuals no correlation exists between body sodium content and the level of systolic or diastolic arterial pressure [10]. In essential hypertension, irrespective of plasma renin level, the mean value for body sodium is also normal [10]. However, in a large series of patients with essential hypertension, although the mean value for exchangeable sodium is close to 100% of predicted normal, a highly significant positive correlation is found between the level of arterial pressure and concomitant exchangeable sodium (Fig. 4). The relationship is more readily apparent in male than in female patients.

One could argue that this relationship between arterial pressure and exchangeable sodium is an artifact, and that in some way it is related to the well-known abnormalities of transmembrane electrolyte transport in essential hypertension, which could interfere with the equilibration of administered isotope necessary for exchangeable sodium measurement. But when we measured total-body sodium by activation analysis (which does not involve the administration or equilibration of isotope), we found the same relationship as with exchangeable sodium. Total-body sodium in essential hypertension is, on average, close to 100% of predicted normal, and a highly significant positive correlation exists between the level of blood pressure, systolic or diastolic, and the value for body sodium content [10].

Despite this overall good correlation, I should emphasize that in young, mildly hypertensive patients, body sodium content is

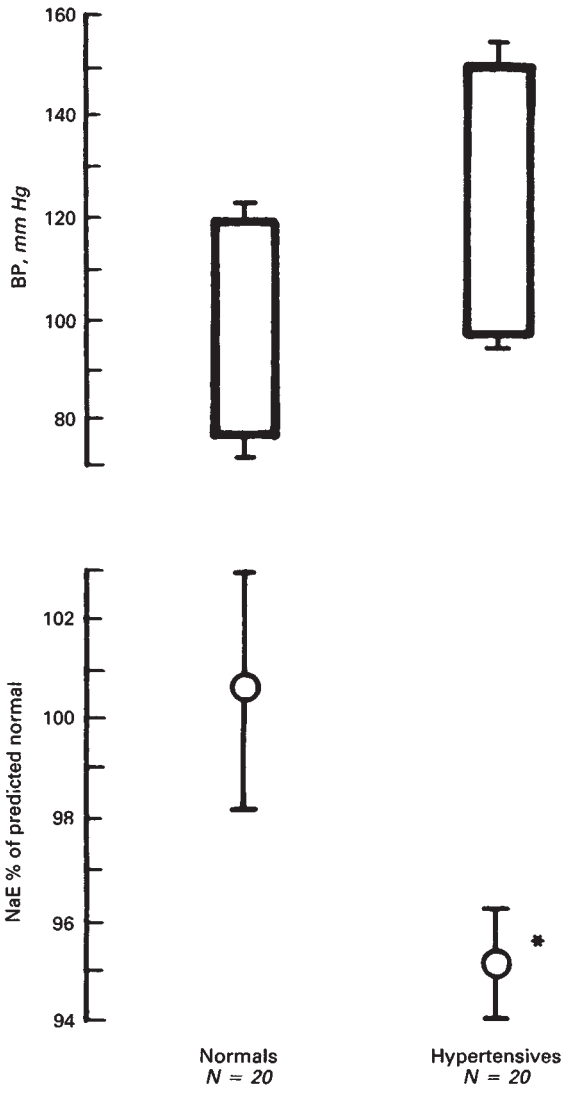

Fig. 5. *Systolic and diastolic blood pressure* (BP) *and exchangeable sodium* (NaE, expressed as percentage of predicted normal value) *in 20 normal subjects and 20 young hypertensives matched for age, gender, and leanness.* Mean ± SD plotted. Exchangeable sodium is significantly lower in the hypertensives ($P < 0.05$). (Data from Refs. 9 and 33. Reproduced from Ref. 33.)

distinctly low. Figure 5 illustrates the values for blood pressure and exchangeable sodium in 20 young hypertensive patients (under 36 years) who were matched for age, weight, gender, and leanness with 20 normotensive individuals. Whereas the normotensive subjects had a normal value for exchangeable sodium, the hypertensives manifested significantly depressed levels of exchangeable sodium [10, 33].

Interpretation of these findings has been difficult. One possibility is that the physiologic changes that occur at different stages of essential hypertension mimic the alterations reflected in the two contrasting diseases, unilateral renal artery stenosis and Conn's syndrome. We could hypothesize that early in essential hypertension the rise in blood pressure is initiated by mechanisms that are independent of sodium retention and that the high blood pressure pushes sodium out of the body in a manner similar to that observed in renovascular hypertension. Later in the course of the disease, possibly as a result of hypertension-induced renal changes, the hypothesis suggests, the high blood pressure becomes sodium dependent because of a tendency to sodium retention.

These speculations imply that dietary sodium restriction in the treatment of hypertension is likely to be more effective in the more severe and chronic cases, in which sodium retention has occurred. I have asked my colleagues, Drs. A. M. Richards and G. D. Murray, to elaborate on these issues. Dr. Richards will review the data on the hypotensive effect of salt restriction, and Dr. Murray will describe our attempts to correlate the findings in several of the entities I described.

Dr. A. M. Richards (*New Zealand Medical Research Council and Wellcome Visiting Clinical Research Fellow, MRC Blood Pressure Unit, Western Infirmary*): Does moderate sodium restriction lower blood pressure? This question was addressed by Grobbee and Hofman, who analyzed data from a total of 584 subjects in 13 trials of moderate sodium restriction in both normotension and hypertension [34]. The mean age of participants in these trials varied from 16 to 60 years. Mean reduction in daily sodium intake varied from 21 to 170 mEq. Initial average systolic and diastolic pressures varied from 103 to 175 mm Hg and 61 to 112 mm Hg respectively. Five of the trials examined normotensive subjects. Hence the authors were able to analyze the effects of a broad range of "moderate" sodium restriction in subjects of different ages who exhibited a broad spectrum of initial blood pressures. A significant fall in arterial pressures was achieved in only 3 of the 13 trials. The mean changes in systolic and diastolic pressures were only −3.6 (range, −0.5 to −10.0) and −2.0 (range, +3.2 to −7.0) mm Hg respectively. Changes in arterial pressure were not related to reductions in daily sodium intake, but rather to initial blood pressures and age: older and more hypertensive subjects were more likely to respond to moderate sodium restriction with a fall in blood pressure. The finding of greater reductions in blood pressure in patients with higher initial blood pressures is consistent, regardless of therapy, in essential hypertension and might, at least in part, reflect regression to the mean. These findings [34] agree with those in the Royal Society of Medicine Services 1986 publication concerning dietary salt and hypertension, in which data from 8 trials of sodium restriction in patients with essential hypertension and a further 8 in normotensive subjects are described [35]. Although most trials have been shorter than 2 months in duration, the results generally lead to the conclusion that modest dietary sodium restriction, at least for relatively brief periods, probably is not effective therapy in itself for hypertension in young and mildly hypertensive patients. This does not detract from its value as an adjunct to antihypertensive pharmacotherapy. A specific subgroup of hypertensive patients with a predictable, clinically significant hypotensive response to sodium restriction might exist, but that group remains to be defined.

A number of studies suggest possible mechanisms that might partly explain the overall disappointing response to sodium restriction in hypertensive patients. Richards et al conducted a detailed study of 12 patients with essential hypertension [36]. Ambulatory continuous intra-arterial pressure recording, together with hourly blood sampling for plasma hormones, were employed over 24 hours. Overall, the group showed no signif-

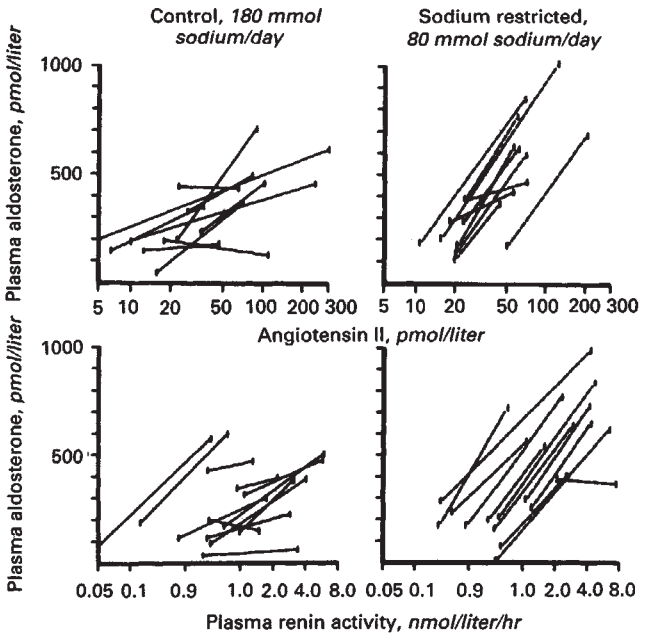

Fig. 6. *Regression lines relating plasma renin activity and angiotensin II* (log scale) *to plasma aldosterone in 12 patients* (n = 10 for angiotensin II) *on a control diet and a sodium-restricted diet.* Each regression line was constructed from 24 hormone samples drawn hourly for 24 hours. Slopes of regression lines increased significantly with sodium restriction overall ($P < 0.01$ for angiotensin II; paired t-test). (Reproduced from Ref. 41.)

icant change in arterial pressures between control and sodium-restricted phases. A close positive correlation was found, however, between individual changes in plasma renin activity and diastolic arterial pressure. That is, subjects with little rise in renin activity during sodium restriction exhibited a fall in diastolic pressure, whereas those with brisk renin responses showed little change or even a rise in pressure. Similar pressure-hormone relationships were seen with plasma angiotensin II and aldosterone values. These data suggest that the hypotensive response to sodium restriction is dictated, at least in part, by the response of the renin-angiotensin-aldosterone system. This concept is supported by Cappucio et al [37]. In a study of 29 patients with essential hypertension, these authors found a significant inverse correlation between blood pressure reductions induced by sodium restriction alone on the one hand, and the additional fall in pressure caused by infusion of the angiotensin II antagonist saralasin, on the other. Similar corroborative data have appeared from other workers [38–40].

The patients we studied demonstrated a uniform rise in plasma aldosterone concentration during modest sodium restriction (80 mEq/day), and a consistent increase in the slope of individual regression lines relating renin and aldosterone (and angiotensin II and aldosterone) over 24 hours [41] (Fig. 6). Conversely, the relationship of renin (or angiotensin II) to arterial pressure was not altered by this degree of sodium restriction. The former finding is consistent with data demonstrating increased aldosterone responses to infused angiotensin II in sodium-depleted subjects [42, 43]. The latter finding contrasts with the findings of decreased pressor responses to infused angiotensin II in marked sodium restriction, however

Table 2. Distribution of Mahalanobis' distance in the three study groups

Variables	Essential hypertension (*median, range*)	Idiopathic aldoteronism (*median, range*)	Conn's syndrome (*median, range*)
Na, K, HCO_3^-	1.9 (0.9–3.7)	2.4 (1.0–5.6)	4.6 (1.8–6.6)
Na, K, HCO_3^-, AII	1.8 (0.3–4.1)	2.6 (1.1–4.0)	5.0 (1.8–8.0)
Na, K, HCO_3^-, NaE, KE	2.2 (0.6–4.5)	3.1 (1.5–5.2)	5.2 (1.9–9.4)
Na, K, HCO_3^-, NaE, KE, AII	2.4 (0.9–4.5)	3.2 (1.6–5.2)	5.4 (1.8–9.7)

[43]. Hence modest sodium restriction (to an intake of approximately 80 mEq sodium/day) may, at least in the short term, cause uniform activation of the renin-angiotensin-aldosterone system and produce increased aldosterone responses to angiotensin II. Still, such sodium restriction might fail to reach the threshold of sodium depletion at which the pressor effects of angiotensin II are reduced. These mechanisms could partially account for the small and inconsistent hypotensive effect of modest sodium restriction in normal subjects and in patients with essential hypertension.

DR. G. D. MURRAY (*Senior Lecturer in Medical Statistics, University of Glasgow*): Dr. Robertson pointed out that the range of values for exchangeable sodium and potassium was similar in "idiopathic aldosteronism" and essential hypertension but differed in Conn's syndrome. Looking at individual variables does not necessarily give a complete picture, however, because it ignores the correlations between those variables. The aim of our study was to examine "idiopathic aldosteronism" and essential hypertension more closely to determine whether the similarity between the two syndromes was still apparent when we analyzed several variables simultaneously [44].

We studied 89 patients with essential hypertension, 22 patients with "idiopathic aldosteronism," and 34 patients with surgically proved Conn's syndrome. The statistical evaluation used Mahalanobis' distance [45], a multivariate statistic that can be thought of as measuring how atypical an individual's set of measurements (NaE, KE, etc.) are relative to a reference population (in our application, the essential hypertension group). This distance takes into account the correlations between variables. For example, a plot of serum potassium (K) against bicarbonate (HCO_3^-) for the 89 patients with essential hypertension revealed a negative correlation. This meant that, although a value of 3.5 mEq/liter for K was not abnormally low for the group, and a value of 25 mEq/liter for HCO_3^- was not abnormally low for the group, the *combination* of these values would be exceptional. A patient with this combination would therefore lie a long way from the group with essential hypertension in terms of Mahalanobis' distance.

We calculated the Mahalanobis distance of each patient from the essential hypertension group for each of a number of sets of variables. The distances for the patients with essential hypertension provided a reference range, and the spread of distances for the patients with "idiopathic aldosteronism" and Conn's syndrome was compared to this reference. The results are summarized in Table 2.

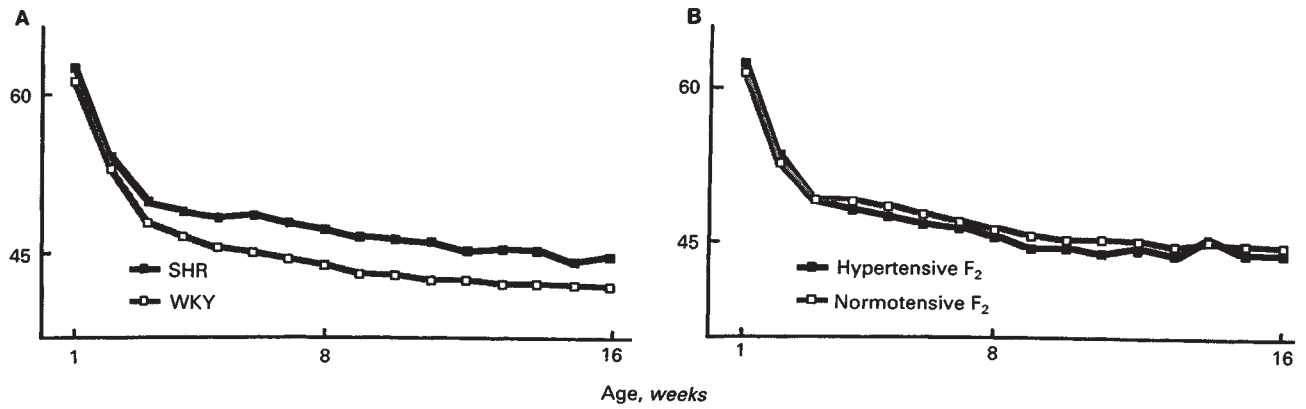

Fig. 7. A *Total-body sodium (mmol/kg) during the first 16 weeks of life of male SHR and WKY.* SHR had significantly higher levels than WKY at each age measured. This difference became significantly greater after about 5–6 weeks of age (see Ref. 51). **B** *Total-body sodium (mmol/kg) during the first 16 weeks of life in male SHR-WKY F_2 rats that at 16 weeks of age are either in the hypertensive* (mean 180 ± 5 mm Hg) *or normotensive* (mean 135 ± 3 mm Hg) *ranges.* No tendency to sodium retention was observed at any time during the development of hypertension, and there was no difference overall between the two groups. (Reproduced from Ref. 51.)

For each set of variables considered, the range of values of Mahalanobis' distance for the group with "idiopathic aldosteronism" is close to that for the group with essential hypertension, whereas many of the values for patients in the group with Conn's adenoma lie well outside the range of values observed in the group with essential hypertension. This further emphasizes the similarity of "idiopathic aldosteronism" with essential hypertension, and the distinction between these conditions and Conn's syndrome.

DR. ROBERTSON: The patients presented by Dr. Fraser are examples of a genetically determined abnormality of aldosterone secretion that results in an increase in total-body sodium and in hypertension. This sodium-dependent form of genetic hypertension appears to be inherited in an autosomal dominant fashion and controlled by a limited number of genes [46]. In contrast, essential hypertension is a disorder in which multiple genetic factors exert a relatively minor direct effect on blood pressure, which is strongly influenced by environmental factors [47]. The relative importance of genetic and environmental factors as causes of abnormal total-body sodium content and abnormal sensitivity of blood pressure to salt intake are unknown. These problems would best be investigated by sequential studies of total-body sodium and blood pressure under strictly controlled environmental circumstances in individual hypertensive patients. The protracted and complex nature of such studies makes them impractical in humans. I have asked Dr. S. B. Harrap to describe the experimental studies in hypertensive rats.

DR. S. B. HARRAP (*Commonwealth Visiting Clinical Research Fellow, MRC Blood Pressure Unit, Western Infirmary*): The availability of the Japanese spontaneously hypertensive rat (SHR), in which genetic factors exert a strong influence on blood pressure [48], provides the opportunity for an examination of the relationship between total-body sodium and blood pressure under standardized environmental conditions. In this way, genetically determined abnormalities of sodium balance can be detected. Early studies noted that a high sodium intake from a young age exacerbated the hypertension in SHR, and the total-body sodium of mature SHR with established hypertension was significantly greater than that in control normotensive rats [49, 50]. Recent sequential and noninvasive studies of total-body sodium in SHR from 1 to 16 weeks of age have helped define changes in total-body sodium during the development of hypertension [51, 52]. At all ages, the total-body sodium (expressed as mEq/kg body weight) is greater in SHR than in control normotensive Wistar-Kyoto (WKY) rats (Fig. 7A). Of particular interest is the exaggeration of this difference in total-body sodium between SHR and WKY at 4 to 6 weeks of age, that is, during the early developmental phase of hypertension. This apparent relative sodium retention is not explained by greater weight gain in WKY and also has been noted in metabolic studies of sodium balance in SHR at this age [53]. These findings suggest that sodium retention might be an important pathogenetic abnormality in SHR hypertension.

No true control strain exists for the SHR, and it is possible that phenotypic differences of total-body sodium between SHR and WKY might be independent of the genetic differences responsible for hypertension. To investigate this problem, detailed cross-breeding studies have been performed in which the genes of SHR and WKY were mixed to produce an F_2 generation. The blood pressure of mature F_2 rats ranges from normotensive to hypertensive levels. If the abnormalities of total-body sodium in SHR play a primarly role in the genetic hypertensive process, one would expect that mature hypertensive F_2 rats would have higher total-body sodium levels than do mature, normotensive F_2 rats. In fact this is not the case. More important, sequential measurements of total-body sodium in these two groups failed to reveal any tendency toward sodium retention in the F_2 rats that eventually became hypertensive, that is, those carrying the hypertensive genes inherited from the SHR (Fig. 7B).

Some basic conclusions can be drawn from these studies. First, the high total-body sodium and sodium retention in the SHR do not appear to be responsible for the hypertension in this strain. This does not, however, exclude an internal redistribution of sodium as important in the hypertensive mechanism of SHR. In addition, these genetic experiments do not negate an environmental effect of sodium on SHR blood pressure. It is

worth noting, however, that mild to moderate sodium restriction does not affect the level of hypertension of SHR [54]. In regard to salt restriction, the SHR contrasts with the Dahl salt-sensitive rat strain, which exhibits a genetic predisposition to changes in blood pressure as a result of alterations in sodium intake [55]. Second, even under strictly defined environmental circumstances, phenotypic differences between hypertensive and normotensive individuals might be quite unrelated to the difference in blood pressure, even if such a link seems obvious and logical. Finally, when considering a multifactorial disease such as essential hypertension, we must consider carefully the complex nature of genetic and environmental interactions as well as the secondary effects of raised blood pressure per se.

DR. ROBERTSON: Dr. Lever will conclude the formal remarks by presenting our views on the alternative hypothesis that explains the relationships among sodium, volume, and hypertension.

DR. A. F. LEVER (*Unit Director, Consultant Physician, MRC Blood Pressure Unit, Western Infirmary*): No salt hypothesis, including one of our own [3], wholly or satisfactorily explains the pathogenesis of essential hypertension. As we have just heard, mineralocorticoids cause hypertension in humans and animals, and it may be that they do so by their sodium-retaining effect. In support of the relationship between volume and hypertension are these observations: (*1*) the degree of sodium retention relates to the rise of arterial pressure in essential hypertension and Conn's syndrome [15, 56]; (*2*) a low-sodium diet in animals injected with mineralocorticoid prevents a rise of blood pressure [57]; and (*3*) in patients with Conn's syndrome, diuretics reduce arterial pressure, and the fall of pressure is related to the fall of NaE [15]. However, arguing against a simple role for increased body sodium is the absence of sodium retention in a small number of patients with Conn's syndrome [15] and the lack of a relationship in time between sodium retention and the rise of blood pressure in this syndrome. Sodium retention may be present long before pressure rises, and pressure actually can be rising when sodium balance is negative [58].

Is mineralocorticoid hypertension a model for essential hypertension in humans? Some electrolyte abnormalities are present in both conditions; others are not. As in Conn's syndrome, NaE relates positively to arterial pressure in essential hypertension, whereas body potassium and plasma potassium relate negatively [56, 59]; also blood pressure can be lowered in essential hypertension by dietary sodium deprivation or by diuretics. Although these observations hint at mineralocorticoid excess or at an abnormality in the metabolism or dietary content of sodium, no known mineralocorticoid is present in excess in essential hypertension (except possibly aldosterone during states of abnormally increased dietary sodium). More important, on average sodium is not retained abnormally in essential hypertension [59]. Indeed, as Dr. Robertson pointed out, a small insignificant expansion found in older patients is balanced by a small significant reduction of NaE in young male patients [56, 59]. In women no relationship between NaE and arterial pressure is apparent, although plasma potassium is inversely related to pressure [56]. These observations are an inadequate basis for a claim that sodium retention is a necessary step in the development of essential hypertension. Guyton and colleagues have suggested that equilibrium could be reached with hypertension and 100% normal NaE because the gain in the pressure-natriuresis mechanism is 100% [60]. In other words, after a period of sodium retention, blood pressure rises and NaE returns exactly to its original value. This does not explain the low level of body sodium in young males with hypertension or the absence of a relationship between NaE and arterial pressure in women [56, 59].

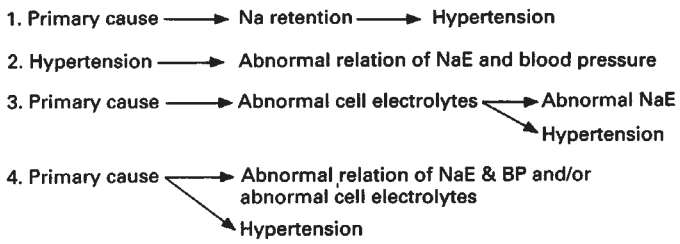

Fig. 8. *Four possible routes to hypertension.*

Four hypotheses relating sodium and hypertension are summarized in Fig. 8. In the *first*, sodium retention is a necessary step in the sequence of events producing hypertension. Evidence suggests that this hypothesis is unlikely. The *second* hypothesis is the reverse of the first: hypertension causes an abnormal relationship between NaE and arterial pressure. The clear relationship between NaE and pressure in older patients, and the absence of such a relationship in younger patients, lends some support for the idea. The finding of abnormal electrolyte transport in the blood cells of normotensive offspring of hypertensive parents makes it unlikely, however, that all electrolyte abnormalities in essential hypertension are a consequence of raised blood pressure.

The *third* hypothesis is based on indirect evidence from many, and sometimes contradictory, reports. One series of experiments hints that a primary abnormality of electrolyte transport or of the cell membrane (leading to a secondary abnormality of electrolyte transport) in blood cells is generalized and that by affecting vascular smooth muscle, this membrane disorder causes vasoconstriction [61–65]. Some have claimed that a circulating agent might affect electrolyte transport and thus ultimately cause essential hypertension [66, 67]. A mechanism of this sort might explain the abnormal relationship between sodium and arterial pressure, and could be either a necessary step (hypothesis 3) or, as the *fourth* hypothesis suggests, an epiphenomenon in the sequence of events causing hypertension. Militating against the first of these suggestions is evidence that the change of cell sodium is insufficient to cause the vasoconstriction [68].

Insulin has been suggested as a pathogenetic agent in essential hypertension [65, 69, 70]. In fact, plasma insulin levels are increased in patients with essential hypertension and in obese patients with raised arterial pressure [70, 71]. Insulin could act directly on sodium balance or it could cause abnormal sodium transport [70]. Another possibility is that it acts not by its electrolyte effect but as a growth factor for vascular smooth muscle [72]. I have argued elsewhere that insulin produces hypertrophy of resistance vessels and thereby raises blood pressure slowly and progressively [65] through the positive-feedback mechanism proposed in the 1950s by Folkow [73].

Excess growth hormone, which is commonly associated with hypertension in humans [74], could act in a similar fashion [65].

In summary, clear evidence exists for an abnormal relationship between arterial pressure and electrolytes in patients with essential hypertension. This disturbance is apparent for the body content of sodium and potassium, for plasma concentrations of sodium and potassium, and for the transport of sodium and other electrolytes in blood cells. Also, the blood pressure of patients with essential hypertension falls more on average than does the pressure of normal subjects during dietary sodium deprivation; patients with hypertension also usually respond well to the sodium depletion produced by diuretics. There is no widely accepted explanation linking these observations. The evidence is insufficient to abandon any of the four hypotheses currently being considered.

Questions and answers

DR. JEROME P. KASSIRER (*Associate Physician-in-Chief, Department of Medicine, New England Medical Center Hospitals*): It appears that we are relinquishing the notion that the total quantity of sodium in the body is causally related to hypertension, and that we are adopting a concept positing that alterations in volume may be an epiphenomenon and that some other kind of mechanism is more important in the genesis of hypertension, particularly in essential hypertension. Do you think the recent observations on calcium in hypertension could represent a similar kind of epiphenomenon?

DR. ROBERTSON: Let me deal with the first part of your question: I still accept the idea that in the later states of essential hypertension there may be a tendency toward sodium retention and volume expansion, that this expansion might contribute to the high blood pressure and that, in these circumstances, sodium restriction might be important in lowering arterial pressure. I think, however, that our data diminish the role for sodium retention, or a tendency thereto, as being important early in the pathogenesis. Data presented at the meeting of the International Society of Hypertension in Heidelberg in 1986 [75] have left me with considerable uncertainties concerning calcium in essential hypertension. Morris and McCarron found that giving calcium carbonate, 1 g daily for 12 weeks, produced an average fall of only 4 mm Hg in standing systolic pressure and yielded no significant changes in standing diastolic or in lying systolic or diastolic pressure. Neither Nowson and Morgan of Melbourne nor Zoccali of Italy [75] found an effect on blood pressure by administering calcium salts to patients with essential hypertension. McCarron's data on calcium in this condition certainly could represent an epiphenomenon. I prefer to regard our data on sodium reduction in mild essential hypertension as a physiologic consequence of the high blood pressure at that stage of the disease. I doubt that this comes strictly under the definition of an epiphenomenon.

DR. KASSIRER: Because compensatory responses might be involved, sodium restriction might not have much of an effect on blood pressure in hypertensive patients. Does that imply that in the diuretic-treated patients, in whom there is a drop in blood pressure, the compensatory mechanisms are not sufficient to counter the effect of the sodium depletion?

DR. RICHARDS: Rather than stating that sodium restriction is ineffective in treating essential hypertension, it is more correct to say that there is a spectrum of response. A clinical trial of sodium restriction in a given patient with essential hypertension is probably still worthwhile, but you probably should not have great expectations for its success as a monotherapy, particularly in young people. With respect to your question about diuretics, I don't think that anybody has compared the kind of sodium loss that is induced by modest dietary sodium restriction to that induced by the standard diuretic regimen.

DR. LEVER: There is another difference: diuretics are usually tested in more severely hypertensive patients than is dietary sodium deprivation. Because blood pressure falls more in hypertensives whose initial blood pressure is higher, the comparison of diuretics with salt depletion is not a comparison of like with like. As Dr. Richards says, it would be useful to produce a comparable reduction of body sodium by the two methods in the same group of patients in a crossover study and then compare the effect on blood pressure.

DR. ROBERTSON: In collaboration with Dr. Manhem, we studied exchangeable sodium in the spontaneously hypertensive rat and the effect of chlorothiazide [76]. Although chlorothiazide significantly reduced blood pressure, that decrease was not paralleled by a comparable lowering of exchangeable sodium.

DR. LEVER: Can lessons be learned from the specificity of a therapeutic agent? Patients with pernicious anemia respond well to B_{12}, but not at all to iron. We infer, correctly, that deficiency of B_{12}, not iron, is responsible for the disease. Essential hypertension is different: patients respond well to a large number of different specific agents—to calcium channel blockers, beta-blockers, alpha$_2$-antagonists, alpha$_1$-antagonists, converting enzyme inhibitors, and diuretics—as well as to a reduction in dietary salt. Because of this variety of therapeutic possibilities, success with dietary salt deprivation no more reveals a primary mechanism (excess dietary salt) than does success with a beta-blocker (overactive beta-agonist mechanism), or success with an ACE inhibitor (overactive renin-angiotensin mechanism). Essential hypertension cannot have 6 primary causes (although there could be 6 links in the chain of events causing the disease). The success of therapists in designing 6 highly effective agents has limited interpretation based on the success of any one agent.

DR. FRASER: Are we certain that the response of blood pressure during sodium chloride restriction is due to the sodium ion alone? Passmore et al, using the DOCA-salt-treated rat model of hypertension, found higher blood pressures in animals given sodium chloride than in those receiving sodium associated with other anions (phosphate, bicarbonate, aspartate, and glycinate) [77]. These authors postulate an important role for the chloride ion. Has anybody looked at the role of the chloride ion in humans?

DR. ROBERTSON: The literature contains occasional case reports of patients with peptic ulcer who, when they ingest large quantities of sodium bicarbonate, develop hypertension with suppression of plasma renin [78]. I know of no direct evidence.

DR. HARRAP: One of the interesting features of essential hypertension is the apparent reduction in total-body sodium in younger patients. Is there any evidence that during the development of "idiopathic aldosteronism," as we now define it, there is a reduction in total-body sodium? If so, might this decrease cause adrenal hyperplasia? Such a finding would go a

long way toward linking these two conditions as part of a continuum.

DR. LEVER: Is it not more likely that young patients with essential hypertension who have subnormal body sodium, older patients with low-renin hypertension, and patients with "idiopathic hyperaldosteronism" are part of a continuum? For reasons we do not understand, does body sodium rise more than normally with age [10, 23] and aldosterone decrease less [79]? As a result, we find in older patients more often different combinations of increased body sodium, decreased renin, and higher-than-normal aldosterone. Low-renin hypertension and so-called "idiopathic aldosteronism" may be two such combinations.

DR. ROBERTSON: The data I showed were from an early study. In a later, more detailed study, we confirmed the previous suggestion that there was indeed a significant, albeit slight, expansion of exchangeable sodium in "idiopathic aldosteronism" as compared with essential hypertension, although it still remained substantially below the average value for Conn's syndrome. This finding agreed with Dr. Lever's observation that "idiopathic aldosteronism," if it belongs to the essential hypertension distribution, is probably a more severe, later stage in which the patient has a tendency toward sodium expansion.

DR. FRASER: Although there are close similarities between the blood pressure-electrolyte relationship and the response of aldosterone to angiotensin II infusion, studies in our Unit show differences in the levels of some steroids, such as 18-hydroxy-11-deoxycorticosterone, between the two conditions (Lasaridis, Lever, Fraser, unpublished data).

DR. KASSIRER: Do patients with non-renin-dependent hypertension respond to dexamethasone?

DR. LEVER: We have tested all our patients suspected of having primary hyperaldosteronism with dexamethasone, but we have not tested so far those with essential hypertension.

DR. RICHARDS: Dr. Lever, if there is a factor causing increased blood pressure, a factor associated with a rise in exchangeable sodium (hypothesis 4, Fig. 8), why should mean body sodium in patients with essential hypertension be only 100% of normal? Why isn't it more than 100%?

DR. LEVER: Perhaps if sodium retention is an epiphenomenon not directly responsible for the blood pressure increase, the simultaneous rise in blood pressure might still tend to restore sodium balance to normal by pressure natriuresis.

DR. FRASER: The physiologic effects of varied sodium intake in early life have been studied in the rat [80]. Salt deprivation led to changes in sodium homeostasis and aldosterone control and possibly also affected blood pressure. Is this evidence of an influence of dietary sodium?

DR. LEVER: For 4 weeks Aviv and coworkers deprived very young normal rats of sodium and then instituted a normal-sodium diet [80]. Predictably, the aldosterone excretion rate increased during the low-sodium period. However, when normal sodium status was restored, aldosterone excretion remained well above the control group. These authors concluded that a relatively irreversible state of hyperaldosteronism could be produced by neonatal salt deprivation. They speculated that this hyperaldosteronism might lead to an elevation of blood pressure. However, no measurements of blood pressure were reported in their paper. We repeated the experiment; to our surprise, systolic pressure rose during the period of sodium deprivation and fell when normal sodium intake was restored. Aldosterone and corticosterone, however, did revert to normal when dietary sodium intake was increased. Why did blood pressure rise in normal young rats eating a low-sodium diet [81, 82]? An explanation suggested by Seymour and colleagues is that dietary sodium deprivation activates the renin mechanism to the point at which its pressor effect more than compensates for the depressor effect of volume depletion [81]. The response of their animals to inhibitors of the renin-angiotensin mechanism lent support for the idea.

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