A new look at the old mosaic[1]

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The author pays tribute to Dr. Irvine H. Page, whose life was a "mosaic" of key scientific contributions in the field of hypertension and of professional and societal involvement. Important and recent contributions are brought together to confirm the hypothesis, as expressed by Dr. Page in 1937, that the secretions of some endocrine glands, in particular, the adrenal cortex, keep the vascular system in a hyper-reactive state. Evidence is presented to demonstrate that increased peripheral resistance and chronic hypertension are neither due to an increase in cardiac output or plasma or extracellular fluid volume nor arteriosclerotic lesions, but are primarily related to increased arterial sensitivity and responsiveness to pressor agents, such as norepinephrine and angiotensin II. The sodium balance, which is mainly determined by the production of aldosterone in the adrenal cortex, is fundamentally involved in the increased peripheral resistance of hypertension. Since hypertension is the result of disequilibrium between the sympathetic nervous system activity and the state of sensitivity and reactivity of the contractile proteins in the arterial walls, models are proposed based on increased sympathetic nervous system activity, increased activity of the renin-angiotensin system, and a disturbance in aldosterone regulation and sodium transport across cell membranes and which are associated with the increased sensitivity and reactivity of the arterioles.

Index terms: Hypertension • Irvine H. Page Lecture

Cleve Clin Q 51:449–461, Summer 1984

Tribute to Dr. Page

In 1949, Dr. Irvine H. Page proposed what he called the "Mosaic Theory of Hypertension," based on the assumption that "a steady state exists in the circulation in which the important regulatory factors are in equilibrium, maintain-

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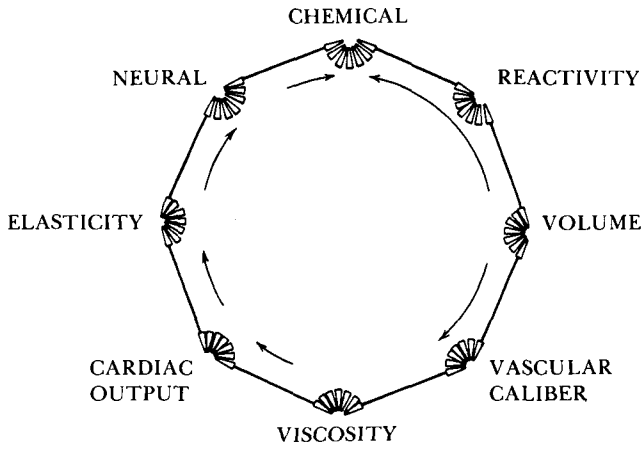

Fig. 1. The Mosaic Theory of Hypertension as first proposed by Page in 1937

ing blood pressure and tissue perfusion at relative constancy adapted to tissue needs."[1] The mosaic (*Fig. 1*) showed what were considered at that time the most important regulatory factors of hypertension. In view of the extraordinary growth of knowledge of all aspects of hypertension, Page[2] has proposed in a recent commentary that the Mosaic Theory might be more appropriately expressed as genetic, environmental (e.g., salt intake, stress, trace metals), anatomic (e.g., coarctation of the aorta), adaptive (intracellular Na^+ and Ca^{2+}), neural (e.g., baroreceptors, area postrema, anteroventral region of the third ventricle), endocrine (e.g., catecholamines, aldosterone), humoral (e.g., angiotensin, prostaglandins), or hemodynamic (e.g., blood volume, cardiac output, viscosity) (*Fig. 2*). Each of these factors can produce a specific type of hypertension because of

1. The renin-angiotensin system (primary reninism, renovascular hypertension, malignant hypertension),
2. The adrenal cortex and aldosterone (primary aldosteronism,* excessive production of cortisol and deoxycorticosterone [Cushing's syndrome]),
3. The adrenal medulla and catecholamines (pheochromocytoma),
4. The thyroid hormone (thyrotoxicosis),
5. Increased plasma volume in terminal renal failure and possibly acute glomerulonephritis,
6. Increased cardiac output in hyperkinetic patients with labile blood pressure,
7. Loss of elasticity of the large vessel (atheroarteriosclerotic) type of hypertension in elderly patients,
8. Proximal resistance to cardiac output (coarctation of the aorta),
9. Loss of renal tissue and of the antihypertensive function of the kidney (atrophic pyelonephritis, polycystic kidney disease),
10. Increase in red cell mass and blood viscosity (polycythemia vera), and
11. Excessive sodium intake in genetically predisposed individuals.

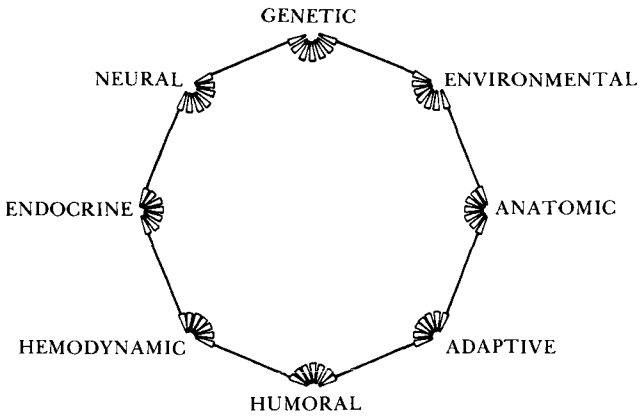

Fig. 2. The Mosaic Theory of Hypertension as reviewed by Page in 1982

How do these factors, or a combination of factors, interact with each other to produce the condition known as primary or idiopathic or essential hypertension, which affects approximately 90% of the large hypertensive population, which itself constitutes about 17% of the total population? The Mosaic Theory of Hypertension, an attempt to answer this question, is a reflection of the life and scientific contributions of Dr. Page.

Figure 3 shows the major aspects of Dr. Page's most productive research career, which started in Munich and continued with Dr. Donald Van Slyke at the Rockefeller Institute for Medical Research. After six years with Dr. Van Slyke, Dr. Page began his leadership career in the field of hypertensive cardiovascular diseases in Indianapolis and later at the Cleveland Clinic. During this period, he trained many soon-to-be leading hypertension experts in the world. His numerous, important contributions in the field of hypertension, atherosclerosis, and brain chemistry are shown in *Figure 4*. His work dealing with the renin-angiotensin system (leading to the discovery of angiotonin simultaneously with the Braun-Menéndez group in Buenos Aires), as well as

* Excessive intake of licorice can produce a similar syndrome due to glycyrrhizic acid—a substance with mineralocorticoid activity.

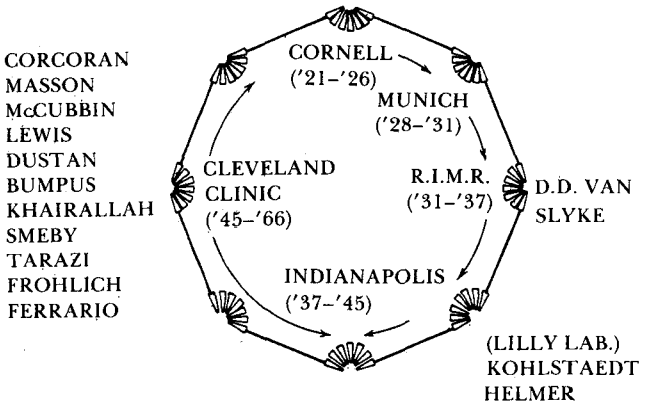

Fig. 3. The mosaic of Page's life

hemodynamics and baroreceptors and the management of hypertension, had a major impact on the history of hypertension research.

Dr. Page also went into the field of atherosclerosis research, studying nonesterified fatty acids, lipoproteins, strokes, and brain chemistry and discovered serotonin. Aside from these tremendous scientific accomplishments, Dr. Page gave us the image of the complete physician by being deeply involved in professional and societal affairs, as editor of *Modern Medicine* with its superb and far-reaching editorials,[3] as the originator of the Coronary Club, as one of the chief instigators of the Institute of Medicine, in the International Society of Hypertension, and with the establishment of the Council for High Blood Pressure Research—probably his most important contribution. He is an example for all of us and provides a lesson to so many of us too often satisfied to remain in our ivory tower and not having the courage to enter the broader picture of the societal aspects of biomedical research and its role in modern society.

Confirmation of Dr. Page's hypothesis

According to Poiseuille's Law, described in 1835, three major hypotheses explain the possible mechanisms of essential hypertension:

1. Increased cardiac output, the initial event leading to elevated blood pressure,
2. Increased blood volume within the arterial system or increased intracellular fluid volume, and
3. Increased arteriolar sensitivity and reactivity, followed by increased wall thickness of the small resistance arterioles. Presently, evidence favors the third theory.

These hypotheses are especially difficult to evaluate because no experimental type of hypertension is the counterpart of essential hypertension in humans. Even spontaneously hypertensive strains of rats differ in some ways from human essential hypertension.[4] Renal experimental hypertension produced by clipping one of the two main arteries by a "figure-of-eight" procedure,

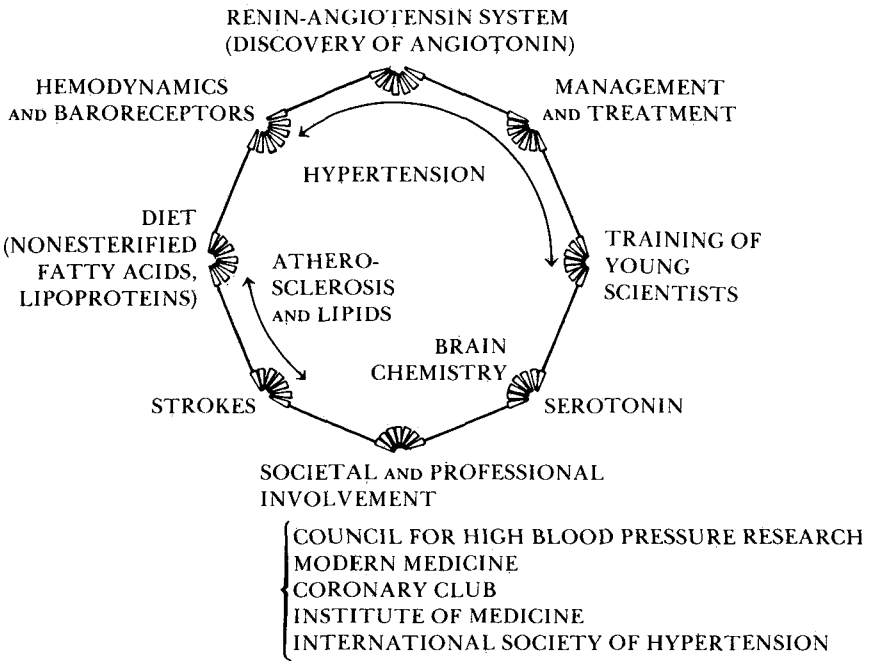

Fig. 4. The mosaic of Page's contributions

cellophane wrapping, or an aortic ligature between the renal arteries in rats has been invaluable for studying the effects of persistent hypertension and its mechanisms, but the only human counterpart is renovascular, not essential, hypertension. Also, experimental hypertension can neither be produced nor maintained in the absence of the adrenal cortex and dietary salt.

According to proponents of the first hypothesis, the initial event leading to essential hypertension is increased cardiac output secondary to excessive neural activity, presumably of hypothalamic origin[5] or to a hyperkinetic heart leading to an increase in arterial wall thickness with a decreased wall-lumen ratio and subsequent increase in peripheral resistance. The hypothesis of thickened arterial walls encroaching on the lumen is based on measurements of the pressure-flow relationship at maximal arterial dilatation. In these experiments, threshold responsiveness to norepinephrine was the same for hypertensive as for normotensive arteries, and hyper-reactivity to norepinephrine was a simple consequence of the increase in the wall mass relative to the lumen.

Objections to the first hypothesis are:

1. The conclusions were mostly based on studies of flow resistance of the arterial vasculature in the isolated hind quarters of eviscerated rats perfused with Tyrode's solution and with a repeated bolus administration of papaverine (1 mg) to achieve maximal dilatation. Perfusion of hind legs with artificial solutions is frequently accompanied by increased capillary permeability with edema and swelling. This can be corrected by adding a dextran type of colloid polymer to increase osmotic pressure of the perfusate and to prevent edema. The increased permeability is one of the major consequences of bilateral adrenalectomy and is probably related to the absence of adrenocortical hormones in the perfusates.[6] In addition, the large amounts of administered papaverine may produce toxic effects in the tonicity and responsiveness of the arterioles. Lais and Brody,[7] who could not confirm the findings of Folkow et al,[5] demonstrated, by perfusion of the hind quarters of spontaneously hypertensive rats with blood instead of Tyrode's solution, a significant reduction in the threshold concentration of norepinephrine needed to elicit a pressor response (less than one third of that required for controls). If there is an increased thickness of the media due to hyperplasia of the resistance arteries with the same threshold responsiveness to norepinephrine in hypertensive arteries as that of normotensive animals, a hyporesponsiveness of the individual smooth muscle cell is obviously indicated.[8] Furthermore, an increased flow resistance reported at maximal dilatation could be explained by a decreased number of arterioles per tissue volume as suggested by Hutchins and Darnell.[9]

2. Hypertrophy of the vascular smooth muscle in the media of arterioles is not necessarily the result of adaptation to an increase in pressure since myocardial hypertrophy can occur without hypertension in sympathectomized spontaneously hypertensive rats[10] and before the onset of hypertension in deoxycorticosterone acetate (DOCA) salt- and aldosterone-treated rats.[11]

3. If the increased thickness of the arterial wall was the initial event leading to hypertension, a progressive increase in mean internal or external diameter and/or in mean wall-lumen ratio of the arterioles would be expected to occur in aged patients with prolonged and severe hypertension, as compared with younger patients or those with milder hypertension. Nevertheless, this does not appear to be so since no significant difference in the parameters of hypertensive patients more than 45 years old were noted when compared to younger patients.[12] According to Friedman,[8] the data of Furuyama,[13] used to support the hypothesis of a primary thickening of the walls of the small arterioles, are based on histologic examinations of arteries larger than 300 μm—vessels that contribute little to the total resistance of the vascular beds. No wall hypertrophy in the resistance arteries of less than 100 μm was present.

4. Many normotensive patients show the same degree of arteriosclerosis, especially in the splanchnic area, as patients who die from hypertension, although the lesions are more frequent and more severe in the latter.[12]

5. The fact that many clinical and experimental hypertensive states revert to a normal blood pressure within minutes or hours after removal of the causal factor is a strong argument against the proposition that arterial structural changes are primarily responsible for increased blood pressure. Clinically, frequent and immediate cure of hypertension is possible within minutes or hours after the removal of a pheochromocytoma or an adrenal adenoma in patients with primary aldosteronism, despite prolonged periods (often for several years) of high cardiac output. Resection of a coarctation of the aorta is often followed immediately by normal blood pressure, despite

the presence of severe arteriosclerotic lesions in the hypertensive region.

6. The two-kidney–one-clip (2K-1C) hypertension in dogs is characterized by an initial increase in cardiac output in the first two to four days after clipping. This is followed by an increase in peripheral resistance. The rise in cardiac output can be prevented by occlusion of the inferior vena cava; however, the increase in peripheral resistance and hypertension develops.[14,15] Cardiac output can be increased in animals by a variety of procedures, but none has succeeded in producing chronic hypertension.[16]

7. Nishiyama et al[17] administered two beta-blockers (propranolol and timolol) at the rate of 0.5 mg/mL each in drinking water to control Wistar-Kyoto and spontaneously hypertensive rats from birth to death. Neither of these beta-blockers, which reduced cardiac output by 30%, had any effect on the course of the development and maintenance of arterial hypertension in the treated, as compared to the untreated, spontaneously hypertensive rats. In addition, no difference in cardiac output in the untreated spontaneously hypertensive rats was noted when compared to the normotensive Wistar-Kyoto rats. These findings indicate that cardiac output has little importance in the development of hypertension in spontaneously hypertensive rats.

8. In the early stages of experimental or clinical hypertension, no structural changes have been detected in small arteries either by light or by electron microscopy.[18]

9. Of the patients with hyperkinetic hearts and high cardiac output as studied by Gorlin,[19] 50% had labile hypertension; the others were normotensive. Evelyn[20,21] has demonstrated in a 30- to 35-year follow-up that patients with labile or borderline hypertension may live more than 30 years without stable "true" hypertension or its severe cardiovascular complications developing.

10. Many pathologic states characterized by high cardiac output (beriberi, thyrotoxicosis, Paget's disease, severe anemia, anxiety states, and even normal pregnancy) are not accompanied by systolodiastolic hypertension. As emphasized by Dustan and Tarazi[22] and Neff et al,[23] high cardiac output in advanced renal failure and secondary to severe anemia seems to have little relationship to hypertension since normotensive patients with similar degrees of renal failure had equally high outputs. Dustan and Tarazi stated that "the feature distinguishing the two groups of uremic patients is peripheral vascular resistance, which is elevated in those with elevated pressures and low in those with normal pressure."[22]

11. One of the most important studies of the hemodynamic factors in patients with early essential hypertension was reported by Safar et al.[24] One hundred and one patients with essential hypertension (mean age, 29 yrs old) were compared to 101 normotensive subjects (mean age, 28 yrs old). The stroke volume and cardiac index were similar in both groups. Blood volume was significantly decreased, but the key finding was the striking increase in total peripheral resistance in the group of young and early essential hypertensive patients when compared with the group of normotensive subjects. Frohlich et al[25] have reported essentially similar results from studies of patients with essential hypertension and a normal-size heart.

Although these data appear to invalidate the first hypothesis, one should still remain receptive to studies seeming to support this theory, especially in view of the recent finding of Hamet et al[26] of a significant increase in weight and deoxyribonucleic acid (DNA) content of the hearts of newly born spontaneously hypertensive rats when compared with Wistar-Kyoto rats, whether in absolute terms or as a ratio to body weight (*Table 1*).

No significant evidence for the second hypothesis (increased plasma or extracellular fluid volume as a primary event in patients with essential hypertension) was demonstrated by Ibsen and Leth,[27] Schalekamp et al,[28] and Tarazi et al.[29–31] Also, most heavy salt eaters have normal blood pressure. Furthermore, Tarazi[30] demonstrated an inverse correlation between blood volume and blood pressure or total peripheral resistance.

Table 1. Heart in newborn spontaneously hypertensive rats*

	Wistar-Kyoto rats	Spontaneously hypertensive rats
Weight (mg)	24.2 ± 0.5	25.0 ± 0.3†
Heart weight/body weight	4.6 ± 0.1	5.5 ± 0.1‡
Total protein (mg)	2.6 ± 0.1	3.0 ± 0.1‡
Protein/100 mg tissue	10.6 ± 0.4	11.3 ± 0.4
Total DNA	81.0 ± 6	113.0 ± 6‡
DNA/100 mg tissue	334.0 ± 18	425.0 ± 20‡

* Data adapted from Hamet et al[26]

† $P < 0.05$

‡ $P < 0.01$

Total body weight in newborn spontaneously hypertensive rats (N = 44) was 4.73 g ± 0.06 versus the total body weight of Wistar-Kyoto rats (N = 46), 5.27 g ± 0.06 ($P < 0.01$).

Onesti et al[32] found that an elevated blood pressure did not develop in half of the anephric patients given salt loads, despite a marked increase in blood volume. Dogs with hypertension induced by metyrapone administration show no correlation between rise in blood pressure and increase in intracellular fluid volume.[33,34] Nevertheless, compelling evidence shows that hypertension is caused primarily by increased arterial sensitivity and responsiveness to pressor agents.

The evidence of increased vascular reactivity in hypertensive states, based on results of studies of systemic circulation, regional vascular beds, or isolated arterial strips is overwhelming. The evidence is clearer from results of studies of precapillary regions, such as in the bulbar conjunctiva[35] and in the nail folds of patients with essential hypertension.[36] Results of these studies show an increased vasomotor activity of the precapillary vessels and of the meta-arteriolar sphincters.

Additional and more important evidence comes from the use of the superior mesenteric artery preparation in the rat.[37] If this preparation is perfused with an artificial medium such as Tyrode's or Krebs' solution, the pressor response to a standard ED_{50} dose of norepinephrine (i.e., the dose that produces half the maximal response) will be an increase in blood pressure. This phenomenon is reproducible over a period of hours. The reactivity of the denervated mesenteric artery preparations from rats with spontaneous hypertension or from renal experimental, renal saline, or DOCA-salt hypertension shows significantly greater responsiveness to the same ED_{50} dose of norepinephrine compared with the response of normal rats given the same preparations.[37-41] Furthermore, an increased pressor response to norepinephrine and other pressor agents can be demonstrated *before* the onset of hypertension in Goldblatt hypertensive animals.[42] Significantly increased reactivity of arterial strips and of the mesenteric artery preparation is also evident before the development of hypertension in the 2K-1C Goldblatt dogs, in DOCA-salt hypertension in rats and pigs, in Grollman hypertensive hamsters, and in hypertensive rabbits with aortic coarctation.[14,15]

The strongest evidence comes from the experiments of Nolla-Panades[43] and from those of Bohr and Berecek.[44,45] The former, using rats made hypertensive by coarctation of the aorta, showed that strips from the arteries protected by the aortic constriction from the increased arterial pressure had the same hyper-responsiveness to pressor agents, such as norepinephrine, as strips from the hypertensive arteries. Bohr and Berecek obtained similar results in pigs made hypertensive by DOCA-salt administration in which the hind leg was protected from systemic hypertension by iliac or femoral occlusion.

Veins also show increased reactivity to pressor agents, both in experimental and human hypertension. Such changes cannot be secondary to increased pressure in the venous system and must, therefore, reflect a basic abnormal hyperreactivity of the entire vasculature.[46,47]

These experiments demonstrate beyond doubt that vascular hyper-reactivity exists in various hypertensive conditions, both experimental and human, and is present in the prehypertensive state. That this could be due to factors other than circulating substances is difficult to believe. This hyper-reactivity is enhanced by high sodium chloride intake and is decreased or prevented by acute and severe restriction or depletion of sodium.[48-51] Enhancement is also caused by vasopressin, angiotensin II, and aldosterone.

If present data point out so strongly that the primary event leading to hypertension is an increased sensitivity and responsiveness of the resistance arterioles to pressor agents, what then is responsible for this fundamental disturbance? I strongly believe that the reason is related to disturbances in aldosterone and related mineralocorticoids and in sodium regulation. Most specifically, the peripheral resistance results from a balance between, on one hand, the activity of the sympathetic nervous system and the circulating concentration of catecholamines, especially norepinephrine, and on the other hand, the state of tonicity, sensitivity, and responsiveness of the contractile proteins of the resistance arterioles.

The evidence linking the adrenal cortex and aldosterone to hypertension is substantiated by the following facts:

1. Hypertension cannot be induced in animals in the absence of adrenal cortex and dietary salt.

2. The excessive production or administration of large amounts of aldosterone, deoxycorticosterone (DOC), 11-OH-DOC, and 18-OH-DOC results in an increase in blood pressure to hypertensive levels. This type of hypertension can be prevented by severe sodium restriction or made more severe by high sodium chloride intake. Administration of the adrenocorticotropic hormone (ACTH) to sheep and rats with saline in drinking fluid results in the rapid develop-

ment of hypertension. Recently, Komanicky and Melby[52] demonstrated, after three weeks of subcutaneous aldosterone infusion by a minipump at 100 μg/day, that hypertension occurred in rats with significant increases in heart and kidney weights, whereas DOCA or saline administered in a similar manner had no similar effect.

3. Several hypertensive syndromes in humans are secondary to pathologic conditions of the adrenal cortex, such as primary aldosteronism, Cushing's syndrome, a hypertensive form of virilizing adrenal hyperplasia, and the 17-hydroxylase deficiency syndrome. The Glasgow group has described many reasons for the similarity in causal mechanisms between primary aldosteronism (whether due to an adenoma or to bilateral hyperplasia) and essential hypertension.[53, 55]

4. Clinically, hypertension often follows long-term administration of glucocorticoid hormones for the treatment of allergic, rheumatic, and dermatologic conditions. The amount of sodium ingested plays an important role. Similarly, the administration of 9α-fluorocortisol, a potent mineralocorticoid used in the treatment of adrenal insufficiency and of orthostatic hypotension, is frequently accompanied by hypertension. Again, the amount of salt in the diet is critical.

5. Results of studies done in the late 1920s and early 1930s on the effects of a bilateral adrenalectomy have demonstrated that the adrenal cortex is essential for the maintenance of blood pressure and vascular tone.[56,57] The fall in blood pressure, culminating in circulatory collapse and death four to six days following the bilateral adrenalectomy, is closely related to severe losses in urinary sodium and decrease in blood volume and with the progressive loss of arterial sensitivity and responsiveness to norepinephrine. This is accompanied by greatly increased capillary permeability. Here, it is of historical interest to quote the statements of two of the great researchers in hypertension at a symposium held in New York City in 1945. Goldblatt stated: "Of the various glands of internal secretion that were investigated, the only one which has been definitely implicated in the genesis and maintenance of experimental renal hypertension is the adrenal. . . . There is clear indication that deprivation of the adrenocortical hormones interferes with the humoral mechanisms of hypertension by reducing the amount of renin substrate in the blood and possibly with the sensitivity of the arterioles to the effect of the hypothetical vasopressor substance."[58] At the same meeting, Page said, "Our view has always been that the adrenal cortex contains some substance which was necessary for the normal reactivity of the blood vessels to be maintained."[59]

Table 2. Plasma aldosterone concentration

	DIDA	Radio-immunoassay
Control subjects	7.5 ± 5 (N = 20)	6.9 ± 4 (N = 69)
Mild essential hypertension		
Normal renin	12 ± 6* (N = 42)	9.7 ± 6* (N = 55)
Low renin	12.7 ± 7* (N = 17)	11.4 ± 5* (N = 26)

* $P < 0.01$ versus control subjects (ng/dL) (mean ± standard deviation)
DIDA = double isotope dilution assay

6. A bilateral adrenalectomy in 2K-1C hypertensive rats reduces blood pressure to control levels, but hypertension returns in all rats that have undergone an adrenalectomy when they are given a 1% sodium chloride solution as drinking fluid.[60]

Since the adrenal cortex, mostly through its secretion of aldosterone, regulates sodium distribution and excretion, evidence of fundamental disturbances of both aldosterone and sodium in hypertension is convincing. A link between disturbances of aldosterone to hypertension can be based on the following facts:

1. A rigorously selected group of patients with mild and stable essential hypertension, and a blood pressure between 140–170 and 90–105 mm Hg and on a controlled sodium and potassium intake of 135 and 90 mmol/day, respectively, were thoroughly studied.† Plasma aldosterone concentration measured in each of two groups of control subjects and of patients with mild and stable essential hypertension, first by a double isotope dilution assay and second by a radioimmunoassay, showed a significant mean increase in hypertensive patients when compared to control subjects[61,62] (*Table 2*).

2. A significant increase in urinary excretion of the 3-oxo conjugate metabolite of aldosterone was observed in patients with essential hypertension.[61–63] Data from Brunner et al[64] appear to confirm these findings.

3. In two-month-old spontaneously hypertensive rats (systolic pressure, 171 mm Hg vs. 115 mm Hg in Wistar-Kyoto rats, [$P < 0.001$]), the basal plasma levels of aldosterone and of corti-

† Including arteriography

costerone were found to be increased with a significantly enhanced response from the administration of ACTH when compared with the Wistar-Kyoto control rats.[65]

4. Stable hypertension in rats results from the constant subcutaneous infusion of aldosterone (100 μg/day for 3 weeks)[52]; Komanicky and Melby also produced hypertension with low-dose infusion of aldosterone for six weeks without the development of hypokalemia or metabolic alkalosis (personal communication).

5. Patients with essential hypertension show a blunted or suppressed aldosterone response due to the stimuli of severe sodium restriction, sodium and volume depletion following furosemide administration, and severe hemorrhage despite a rise in plasma renin activity identical to that seen in control subjects.[66–69]

6. Plasma aldosterone concentration is inappropriately high in an older population in relation to the plasma renin activity and in the younger hypertensive patients with low plasma renin activity levels.

7. The most important finding is probably that reported by Collins et al[70] and Luetscher et al[71] that patients with essential hypertension on a high sodium chloride intake (300 mmol/day) have substantially less suppression of their aldosterone secretion rate, excretion rate, and plasma concentration when compared with control subjects (*Fig. 5, Table 3*). Because of the average sodium chloride content of diets in Western countries, this suggests an inappropriately high aldosterone secretion rate and plasma concentration in relation to the amount of salt ingested.

8. Infusions of angiotensin II at increasing rates are accompanied by a greatly exaggerated plasma aldosterone response in patients with essential hypertension when compared with control subjects.[54]

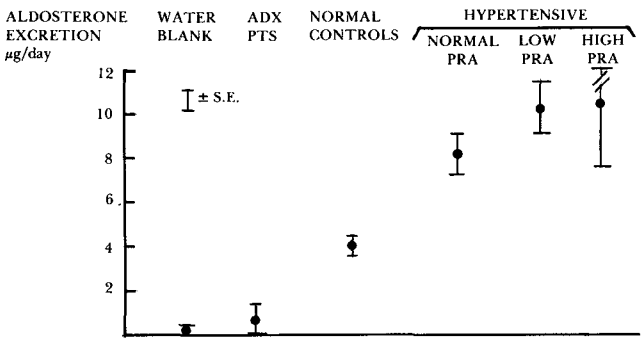

Fig. 5. Effects of high sodium intake (> 300 mmol/day) on aldosterone excretion in patients with mild essential hypertension. *ADX PTS* = adrenalectomized patients, *PRA* = plasma renin activity, and *S.E.* = standard error. (From Luetscher et al,[71] p 287. By permission of the authors and publisher)

Table 3. Effect of salt loading on aldosterone in patients with benign essential hypertension*

	Normal subjects (N = 14)		Benign essential hypertension (N = 25)
Aldosterone			
Secretion rate (μg/day)	102	32	98†
Excretion rate (μg/day)	10.5	3	9.8†
Plasma level (patient supine) (ng %)	4–8	1	4.5
Sodium intake (mmol/day)	120	>300	>300

* Data adapted from Collins et al[70]
† $P < 0.001$

9. The Glasgow group demonstrated that primary aldosteronism due to bilateral nodular hyperplasia of the adrenal cortex is a simple variant of essential hypertension since each condition results in the same biochemical characteristics.[53, 55] Extension of these studies to patients with primary aldosteronism caused by an adrenal adenoma led the authors to the same conclusion for this group.[72]

10. The experiments of Mendlowitz et al[73,74] demonstrated a great contrast in the digital vascular reactivity of control subjects when compared to patients with essential hypertension (*Table 4*). These latter patients showed a selective increased digital reactivity in response to norepinephrine when pretreated by aldosterone in contrast to the absence of change in control subjects. Yet, the control subjects showed digital vascular hyper-reactivity to prednisone in contrast to much lesser changes in patients with essential hypertension.

Table 4. Digital vascular reactivity* in essential hypertension†

	Normotensive subjects (N = 15)	Essential hypertension (N = 15)
Aldosterone (1 mg IM × 3 days)	↑	↑↑↑
Prednisone		
(30 mg/day × 7 days)	↑↑	No change
(100 mg IV)	↑↑	No change

* Response to norepinephrine
† Data adapted from Mendlowitz et al[73,74]
IM = administered intramuscularly, and IV = administered intravenously

Such disturbances in aldosterone regulation may possibly be linked to the defect in the sodium transfer across the cell membrane in patients with essential hypertension, as suggested by the work of Moura and Worcel.[75] The well-established evidence linking sodium to hypertension, the focus of intense interest by researchers, can be summarized as follows:

1. The antihypertensive effectiveness of a severe dietary sodium restriction by itself, by Kempner's rice and fruit diet in 30% to 50% of patients with essential hypertension, and by thiazide diuretics in more than half of patients with essential hypertension has been well demonstrated. As emphasized by Tobian et al[76] and by L. Page,[77] a life-long low sodium chloride intake of less than 60–70 mmol/day is associated with the virtual absence of hypertension even among human subjects susceptible to it.

2. Dahl[78] has conclusively shown that by inbreeding Sprague-Dawley rats, a strain can be produced which is extremely sensitive to small amounts of ingested salt that rapidly develops hypertension, and another strain can be produced which is extremely resistant to large amounts of ingested salt and remains normotensive. Similarly, large amounts of salt fed to humans are followed by significant increases in blood pressure up to hypertensive levels.

3. Populations living on a high salt diet[78–82] have a significantly higher incidence of hypertension, whereas populations living on a low salt diet show virtually no hypertension or any rise of blood pressure with age. The common factor between these populations is not only a low intake of sodium, but also a high potassium content in the diet. The importance of the high potassium intake is not elucidated, although evidence exists suggesting that a high potassium intake has a certain protective effect against the severity of hypertension.

4. Gordon et al[83] have shown a prolonged pressor response in normal rabbits on a high salt diet when cross-transfused with blood from 1K-1C hypertensive rabbits. No such pressor response occurred in the cross-transfused rabbits on a normal diet.

5. The intracellular sodium concentration in red cells, leukocytes, lymphocytes, and thymocytes in patients with essential hypertension is substantially increased. At least five different transport systems have been described for the transfer of sodium across cell membranes: (*a*) passive transfer, (*b*) Na^+-K^+ adenosine triphosphatase pump inhibited by ouabain and by the natriuretic factor recently described by de Wardener and MacGregor,[84] (*c*) the Na^+-K^+ co-transport, which is sensitive to furosemide, (*d*) the Na^+-Li^+ counter-transport, which is inhibited by phloretin, and finally, (*e*) the Na^+-Ca^{2+} counter-transport.[85]

Although a disturbance in sodium transport across cell membranes exists with hypertension, the mechanisms are not yet clear. Presently, a great deal of confusion has developed since results obtained by various groups show either marked overlapping of values between hypertensive and normotensive groups or are directly conflicting. The nature of the disturbances in the sodium transport process is being elucidated, and whether or not these disturbances are associated with an increase in free cytosolic calcium, as suggested by Blaustein[85] to explain the increased sensitivity and responsiveness of the small arterioles, remains to be demonstrated.

The reported effects of aldosterone on the Na^+-K^+ adenosine triphosphatase activity are confused and contradictory. Possibly, the activity of aldosterone on the transport of sodium across cell membranes could be exerted through the Na^+-K^+ co-transport, the Na^+-Li^+ counter-transport, or the Na^+-Ca^{2+} exchange system. Since patients with primary aldosteronism show a markedly increased sodium content in tissues, the mode of action of aldosterone in increasing intracellular sodium transport remains to be clarified.

Haddy et al[86] have demonstrated the inhibition of the Na^+-K^+ adenosine triphosphatase pump in rats with various types of low renin hypertension. This inhibition comes from a circulating heat-stable ouabain-like agent present in plasma and appears to be under the influence of the anteroventral third area of the brain. The suppression of the Na^+-K^+ adenosine triphosphatase pump would result in increased contractile activity and responsiveness to vasoactive agents. De Wardener and MacGregor[84] have also provided recent evidence of a significant increase in a short-acting factor present in plasma from hypertensive patients that inhibits the activity and would lead to increased amounts of sodium in urine and in tissues. The activity of this factor varies inversely with that of glucose-6-phosphate dehydrogenase activity. If these findings are confirmed, they would also explain the renal tubular defect consisting of the inability of the hypertensive kidney to excrete a sodium load at normal pressures and, at the same time, the increased sodium concen-

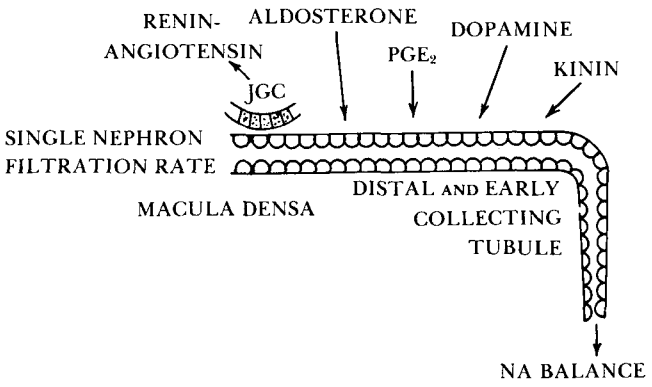

Fig. 6. Some of the factors responsible for the fine adjustment of sodium balance in the distal and early collecting tubule. *JGC* = juxtaglomerular cells.

trations reported in various cells both in the presence of essential and experimental types of hypertension. This hypothesis is attractive since it links together the kidneys and increased arteriolar resistance.

In this mosaic of factors, the kidney plays a most important role as demonstrated by (*a*) the transplantation of a kidney from a hypertensive rat (Dahl's salt-sensitive hypertensive rat or Milan or Okamoto spontaneously hypertensive rats) to a normotensive nephrectomized rat, which leads to hypertension in the latter; (*b*) the reverse experiment of transplanting a kidney from a normotensive rat to a hypertensive nephrectomized rat, which lowers blood pressure to a normal level in the latter; (*c*) the kidney as the source of the renin-angiotensin system, of the antihypertensive factors, prostaglandin E_2 (PGE_2), and the neutral lipid described by Muirhead,[87] and (*d*) the responsibility of the distal tubular area of the nephron for the fine adjusting of sodium homeostasis (*Fig. 6*).

If the assumption that the direct and primary factor involved in hypertension is increased peripheral resistance and that the latter is directly involved with disturbances of aldosterone and of sodium regulation is correct, then hypertension will be the result of a disturbance of the equilibrium between the sympathetic nervous system activity, on the one hand, and the state of sensitivity and reactivity of the contractile proteins in the arteriolar walls, on the other. The factors involved on each side of the balance are illustrated (*Table 5*). The increased peripheral resistance can therefore be expressed in three models:

1. *Model 1*: increased sympathetic nervous system activity and plasma concentrations of norepinephrine such as that seen in pheochromocytoma, neurologic disorders, emotional stresses, and in some patients with essential hypertension.
2. *Model 2*: increased renin-angiotensin system activity with increased plasma levels of plasma renin activity and angiotensin II, such as that seen in renovascular hypertension, malignant hypertension, primary reninism, renal infarcts, and ectopic renin-producing tumors. This model is also accompanied by increased plasma concentration of aldosterone because of a decreased metabolic clearance rate.
3. *Model 3*: increased arteriolar sensitivity and reactivity to norepinephrine and to angiotensin II, such as is postulated in essential hypertension, primary aldosteronism, Cushing's disease, and 17-hydroxylase deficiency syndrome. This model would be associated with disturbances in aldosterone regulation (*Fig. 7*) and in the sodium

Table 5. Factors involved in the arteriolar peripheral resistance

Peripheral Resistance		
Autonomic nervous system		Arteriolar smooth muscle
		Renin-angiotensin system
Central	Peripheral	Aldosterone
Endorphins	Norepinephrine	Na^+ "sensitivity"
Vasopressin	Rate of conjugation	Na^+ renal tubular defect
Baroreceptors	Turnover rate	Na^+ cell membrane transport
Serotonin		Dopamine
Gamma-aminobutyric acid		Natriuretic hormone
Brain*		Prostaglandins
Area postrema		Kallikrein
Tractus solitarius		
Anteroventral region of the third ventricle		

* As derived from Conomy et al[88]

transport system across cell membranes. Such disturbances would render the contractile protein more sensitive and hyper-reactive to a normal or "inappropriate" plasma norepinephrine level.

Many other factors involved in hypertension, such as prostaglandins, kallikrein, and dopamine, are all related in some way to aldosterone or sodium. Similarly, almost all drugs used at the present time for the treatment of hypertensive patients act either by interfering with the sympathetic nervous system activity at various levels, such as reserpine, alpha-methyldopa, alpha- and beta-blocking drugs, guanethidine, ganglionic blockers; increasing sodium excretion, and blunting arterial responsiveness to norepinephrine,[89] such as the thiazides and diuretics; or interfering with renin release or formation of angiotensin II, such as propranolol and the converting enzyme inhibitors. The mode of action of two other antihypertensive drugs, hydralazine and minoxidil, is not well known at the present time.

Conclusion

Dr. Page stated at the end of a lecture in 1937 that

> The chief physiological mechanisms involved in the maintenance of arterial blood pressure are:
>
> 1. Blood volume
> 2. Blood viscosity
> 3. Cardiac output
> 4. Resistance to flow of blood in the blood vessels, chiefly in the arterioles.
>
> The first three have been proved to be normal in patients suffering from essential hypertension and can therefore be dismissed. Increased impedence to blood flow by arterioles which are hypertonic, is generally agreed to be responsible for the elevated arterial pressure.
>
> It has been my working hypothesis that the secretions of some endocrine glands, for example the adrenal cortex, are concerned with the maintenance of the vascular system in a state of reactivity.[90]

In 1982, those of us working in the field agree more strongly now than ever before. This is my tribute to Dr. Page's vision.

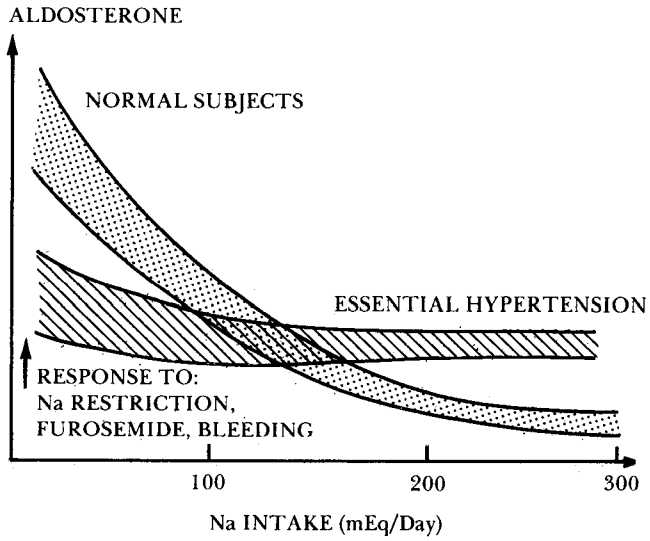

Fig. 7. Disturbances in mineralocorticoid activity, especially aldosterone, in patients with essential hypertension on different salt-intake diets

References

1. Page IH. Pathogenesis of arterial hypertension. JAMA 1949;**140:**451–458.
2. Page IH. The mosaic theory 32 years later. Hypertension 1982;**4:**177.
3. Page IH. Speaking to the doctor: his responsibilities and opportunities. Selected editorials from Modern Medicine. New York, New York Times Media, 1981, pp 1–320.
4. Trippodo NC, Frohlich ED. Similarities of genetic (spontaneous) hypertension: man and rat. Circ Res 1981;**48:**309–319.
5. Folkow B, Hallbäck M, Lundgren Y, Weiss L. Background of increased flow resistance and vascular reactivity in spontaneously hypertensive rats. Acta Physiol Scand 1970;**80:**93–106.
6. Zweifach BW, Shorr E, Black MM. The influence of the adrenal cortex on behavior of terminal vascular bed. Ann NY Acad Sci 1953;**56:**626–633.
7. Lais LT, Brody MJ. Mechanism of vascular hyperresponsiveness in the spontaneously hypertensive rat. Circ Res 1975;**36–37** (suppl 1):216–222.
8. Friedman SM. Arterial contractility and reactivity. [In] Genest J, Koiw E, Kuchel O, eds. Hypertension: Physiopathology and Treatment. New York, McGraw-Hill, 1977, pp 470–484.
9. Hutchins PM, Darnell AE. Observation of a decreased number of small arterioles in spontaneously hypertensive rats. Circ Res 1974;**34–35** (suppl 1):161–165.
10. Gutiletta AF, Benjamin M, Culpepper WS, Oparil S. Myocardial hypertrophy and ventricular performance in the absence of hypertension in spontaneously hypertensive rats. J Mol Cell Cardiol 1978;**10:**689–703.
11. Komanicky P, Melby JC. DOCA produces cardiomegaly without hypertension in the rat (abst). Clin Res 1979;**27:**254A.
12. Moritz AR, Oldt MR. Arteriolar sclerosis in hypertensive and nonhypertensive individuals. Am J Pathol 1937;**13:**679–728.
13. Furuyama M. Histometrical investigations of arteries in reference to arterial hypertension. Tokoku J Exp Med 1962;**76:**388–414.
14. Greenberg S. Vascular responses of the perfused intestine to vasoactive agents during the development of two-kidney,

one-clip Goldblatt hypertension in dogs. Circ Res 1981;**48:**895–906.
15. Greenberg S, Palmer EC, Wilborn WM. Pressure independent hypertrophy of veins and pulmonary arteries of spontaneously hypertensive rats. Characterization of function, structural and histochemical changes. Clin Sci Mol Med 1978; **55** (suppl):31s–36s.
16. Ferrario CM, Page IH. Current views concerning cardiac output in the genesis of experimental hypertension. Circ Res 1978;**43:**821–831.
17. Nishiyama K, Nishiyama A, Pfeffer MA, Frohlich ED. Systemic and regional flow distribution in normotensive and spontaneously hypertensive young rats subjected to lifetime β-adrenergic receptor blockade. Blood Vessels 1978;**15:**333–347.
18. Rojo-Ortega JM, Hatt PY. Histopathology of cardiovascular lesions in hypertension. [In] Genest J, Koiw E, Kuchel O, eds. Hypertension: Physiopathology and Treatment. New York, McGraw-Hill, 1977, pp 910–944.
19. Gorlin R. The hyperkinetic heart syndrome. JAMA 1962;**182:**823–829.
20. Evelyn KA. A long-term study of the national history of essential hypertension. Ann Intern Med 1950;**33:**629–635.
21. Evelyn KA. The natural history of hypertension. Trans Assoc Life Insur Med Dir Am 1970;**53:**84–115.
22. Dustan HP, Tarazi RC. Cardiogenic hypertension. Annu Rev Med 1978;**29:**485–493.
23. Neff MS, Kim KE, Persoff M, Onesti G, Swartz C. Hemodynamics of uremic anemia. Circulation 1971;**43:**876–883.
24. Safar ME, Chau NP, Weiss YA, London GM, Milliez PL. Control of cardiac output in essential hypertension. Am J Cardiol 1976;**38:**332–336.
25. Frohlich ED, Tarazi RC, Dustan HP. Clinical-physiological correlations in the development of hypertensive heart disease. Circulation 1971;**44:**446–455.
26. Hamet P, Kunes J, Fletcher K, Cantin M, Genest J. Hypertrophy and hyperplasia of heart and kidney in newborn SHR. [In] Rascher W, Clough D, Ganten D. Proceedings of the International Symposium on Rats with Spontaneous Hypertension and Related Studies. Heidelberg, W. Germany, F. K. Schattauer, 1982, pp 161–164.
27. Ibsen H, Leth A. Plasma volume and extracellular fluid volume in essential hypertension. Acta Med Scand 1973;**194:**93–96.
28. Schalekamp MA, Lebel M, Beevers DG, Fraser R, Kolsters G, Birkenhager WH. Body-fluid volume in low-renin hypertension. Lancet 1974;**2:**310–311.
29. Tarazi RC, Fouad FM. Hemodynamic characteristics in hypertension. Herz 1978;**3:**245–251.
30. Tarazi RC. Hemodynamic role of extracellular fluid in hypertension. Circ Res 1976;**38**(suppl 2):73–83.
31. Tarazi RC, Dustan HP, Frohlich ED. Relation of plasma to interstitial fluid volume in essential hypertension. Circulation 1969;**40:**357–365.
32. Onesti G, Kim KE, Greco JA, del Guercio ET, Fernandes M, Swartz C. Blood pressure regulation in end-stage renal disease and anephric man. Circ Res 1975;**36**(suppl 1):145–152.
33. Bravo EL, Tarazi RC, Dustan HP. Humoral and hemodynamic characteristics of chronic steroid hypertension in intact conscious dogs (abst). Clin Res 1975;**23:**515A.
34. Bravo EL, Tarazi RC, Dustan HP. Multifactorial analysis of chronic hypertension induced by electrolyte-active steroids in trained, unanesthetized dogs. Circ Res 1977;**40**(suppl 1):140–145.
35. Lee RE, Holze EH. Peripheral vascular hemodynamics in the bulbar conjunctiva of subjects with hypertensive cardiovascular disease. J Clin Invest 1951;**30:**539–546.
36. Greisman SE. The reactivity of the capillary bed of the nailfold to circulating epinephrine and nor-epinephrine in patients with normal blood pressure and with essential hypertension. J Clin Invest 1952;**31:**782–788.
37. McGregor DD, Smirk FH. Vascular responses in mesenteric arteries from genetic and renal hypertensive rats. Am J Physiol 1968;**214:**1429–1433.
38. Collis MG, Alps BJ. The renin-angiotensin system, dietary salt, and increased sensitivity to noradrenaline in mesenteric vasculature preparations from renal/salt hypertensive rats. Cardiovasc Res 1976;**10:**232–235.
39. Collis MG, Alps BJ. Vascular reactivity to noradrenaline, potassium chloride, and angiotensin II in the rat perfused mesenteric vasculature preparation, during the development of renal hypertension. Cardiovasc Res 1975;**9:**118–126.
40. Collis MG, Alps BJ. The involvement of calcium and angiotensin II in vascular reactivity to noradrenaline in renal/salt hypertension. Arch Int Pharmacodyn Ther 1974;**211:**107–114.
41. Beilin LJ, Wade DN, Honour AJ, Cole TJ. Vascular hyperreactivity with sodium loading and with deoxycorticosterone induced hypertension in the rat. Clin Sci 1970;**39:**793–810.
42. Ogden E, Brown LT, Page EW. The increased sensitivity of arterial muscle in the prehypertensive phase of experimental renal hypertension. Am J Physiol 1940;**129:**560–564.
43. Nolla-Panades J. Hypertension and increased hindlimb vascular reactivity in experimental coarctation of the aorta. Circ Res 1963;**12:**3–9.
44. Bohr DF, Berecek KH. Relevance of vascular structural and smooth muscle sensitivity changes in hypertension. Aust NZ J Med 1976;**6** (suppl 2):26–34.
45. Berecek KH, Bohr DF. Whole body vascular reactivity during the development of deoxycorticosterone acetate hypertension in the pig. Circ Res 1978;**42:**764–771.
46. Overbeck HW. Hemodynamics of early experimental renal hypertension in dogs. Circ Res 1972;**31:**653–661.
47. Greenberg S, Bohr DF. Venous smooth muscle in hypertension: enhanced contractility of portal veins from spontaneously hypertensive rats. Circ Res 1975;**36**(suppl 1):208–213.
48. Friedman S. Sodium in blood vessels: a brief review. Blood Vessels 1979;**16:**2–16.
49. Friedman SM, Nakashima M, Mar MA. Morphological assessment of vasoconstriction and vascular hypertrophy in sustained hypertension in the rat. Microvasc Res 1971;**3:**416–425.
50. Friedman SM, Nakashima M, Mar MA. Evidence of enhanced sodium transport in the tail artery of the spontaneously hypertensive rat. Hypertension 1979;**1:**572–582.
51. Reid WD, Laragh JH. Sodium and potassium intake, blood pressure, and pressor response to angiotensin. Proc Soc Exp Biol Med 1965;**120:**26–29.
52. Komanicky P, Melby JC. Hypertensinogenic potencies of aldosterone and deoxycorticosterone in the rat. Hypertension 1982;**4:**140–148.
53. Brown JJ, Lever AF, Robertson JI, et al. Are idiopathic hyperaldosteronism and low-renin hypertension variants of essential hypertension? Ann Clin Biochem 1979;**16:**380–388.
54. Kisch ES, Dluhy RG, Williams GH. Enhanced aldosterone response to angiotensin II in human hypertension. Circ Res 1976;**38:**502–505.
55. Davies DL, Beevers DG, Brown JJ, et al. Aldosterone and

its stimuli in normal and hypertensive man: are essential hypertension and primary aldosteronism without tumour the same condition? J Endocrinol 1979;**81:**79–91.
56. Swingle WW, Remington JW. The role of the adrenal cortex in physiological processes. Physiol Rev 1944;**24:**89–127.
57. Baumann EJ, Kurland S. Changes in the inorganic constituents of blood in suprarenalectomized cats and rabbits. J Biol Chem 1927;**71:**281–302.
58. Goldring W, ed. Experimental Hypertension. Being the Results of a Conference on This Subject Held by the Section of Biology of The New York Academy of Sciences, New York City, Feb 9 and 10, 1945. New York, New York Academy of Sciences, vol 3, 1946, p 13.
59. Goldring, p 28.
60. Floyer MA. The effect of nephrectomy and adrenalectomy upon the blood pressure in hypertensive and normotensive rats. Clin Sci 1951;**10:**405–421.
61. Genest J, Koiw E, Nowaczynski W, Sandor T. Study of a large steroid spectrum in normal subjects and hypertensive patients. Acta Endocrinol 1960;**35:**413–425.
62. Genest J, Nowaczynski W, Kuchel O, Boucher R, Rojo-Ortega JM. The role of the adrenal cortex in human essential hypertension. Mayo Clin Proc 1977;**52:**291–307.
63. Weidmann P, Beretta-Piccoli C, Ziegler WH, Keusch G, Glück Z, Reubi FC. Age versus urinary sodium for judging renin, aldosterone, and catecholamine levels: studies in normal subjects and patients with essential hypertension. Kidney Int 1978;**14:**619–628.
64. Brunner HR, Sealey JE, Laragh JH. Renin subgroups in essential hypertension. Circ Res 1973;**32–33**(suppl 1):99–109.
65. Sowers J, Tuck M, Asp ND, Sollars E. Plasma aldosterone and corticosterone responses to adrenocorticotropin, angiotensin, potassium and stress in spontaneously hypertensive rats. Endocrinology 1981;**108:**1216–1221.
66. Williams GH, Rose LI, Dluhy RG, et al. Abnormal responsiveness of the renin aldosterone system to acute stimulation in patients with essential hypertension. Ann Intern Med 1970;**72:**317–326.
67. Williams GH, Hollenberg NK. Accentuated vascular and endocrine response to SQ 20881 in hypertension. N Engl J Med 1977;**297:**184–188.
68. Williams GH, Cain JP, Dluhy RG, Underwood RH. Studies of the control of plasma aldosterone concentration in normal man. I. Response to posture, acute and chronic volume depletion, and sodium loading. J Clin Invest 1972;**51:**1731–1742.
69. Hollenberg NK, Williams GH. Angiotensin as a renal, adrenal, and cardiovascular hormone: responses to saralasin in normal man and in essential and secondary hypertension. Kidney Int 1979;**15:**29–35.
70. Collins RD, Weinberger MH, Dowdy AJ, Nokes GW, Gonzales CM, Luetscher JA. Abnormally sustained aldosterone secretion during salt loading in patients with various forms of benign hypertension: relation to plasma renin activity. J Clin Invest 1970;**49:**1415–1426.
71. Luetscher JA, Beckerhoff R, Dowdy AJ, Wilkinson R. Incomplete suppression of aldosterone secretion and plasma concentration in hypertensive patients on high sodium intake. [In] Genest J, Koiw E, eds. Hypertension 1972. Berlin, Springer-Verlag, 1972, pp 286–292.
72. Fraser R, Beretta-Piccoli C, Brown JJ, et al. Response of aldosterone and 18-hydroxycorticosterone to angiotensin II in normal subjects and patients with essential hypertension, Conn's syndrome, and nontumorous hyperaldosteronism. Hypertension 1981;**3**(suppl 1):87–92.
73. Mendlowitz M, Naftchi N, Weinreb HL, Gitlow SE. Effect of prednisone on digital vascular reactivity in normotensive and hypertensive subjects. J Appl Physiol 1961;**16:**89–94.
74. Mendlowitz M, Naftchi NE, Bobrow EB, Wolf RL, Gitlow SE. The effect of aldosterone on electrolytes and on digital vascular reactivity to l-norepinephrine in normotensive, hypertensive and hypotensive subjects. Am Heart J 1963;**65:**93–101.
75. Moura AM, Worcel M. Arterial smooth muscle effects of aldosterone ex vivo: action of ionic fluxes. Proceedings of the Ninth Scientific Meeting of the International Society of Hypertension, Mexico City, February 1982.
76. Tobian L, Pumper M, Johnson S, Iwai J. A circulating humoral pressor agent in Dahl S rats with salt hypertension. Clin Sci 1979; **57** (suppl):S345–S347.
77. Page LB. Epidemiologic evidence on the etiology of human hypertension and its possible prevention. Am Heart J 1976;**91:**527–534.
78. Dahl LK. Salt intake and hypertension. [In] Genest J, Koiw E, Kuchel O, eds. Hypertension: Physiopathology and Treatment. New York, McGraw-Hill, 1977, pp 548–559.
79. Dahl LK, Heine M, Tassinari L. Effects of chronic excess salt ingestion. Further demonstration that genetic factors influence the development of hypertension: evidence from experimental hypertension due to cortisone and to adrenal regeneration. J Exp Med 1965;**122:**533–545.
80. Iwai J, Knudsen KD, Dahl LK, Heine M, Leitl G. Genetic influence on the development of renal hypertension in parabiotic rats. Evidence for a humoral factor. J Exp Med 1969;**129:**507–522.
81. Dahl LK, Heine M, Thompson K. Genetic influence of renal homografts on the blood pressure of rats from different strains. Proc Soc Exp Biol Med 1972;**140:**852–857.
82. Dahl LK, Heine M, Thompson K. Genetic influence of the kidneys on blood pressure. Evidence from chronic renal homografts in rats with opposite predispositions to hypertension. Circ Res 1974;**34:**94–101.
83. Gordon DB, Drury DR, Schapiro S. The salt-fed animal as a test object for pressor substances in the blood of hypertensive animals. Am J Physiol 1953;**175:**123–128.
84. de Wardener HE, MacGregor GA. Dahl's hypothesis that a saluretic substance may be responsible for a sustained rise in arterial pressure: its possible role in essential hypertension. Kidney Int 1980;**18:**1–9.
85. Blaustein MP. Sodium ions, calcium ions, blood pressure regulation, and hypertension: a reassessment and a hypothesis. Am J Physiol 1977;**232:**C165–C173.
86. Haddy FJ, Pamnani M, Clough D, Huot S. Role of a humoral sodium-potassium pump inhibitor in experimental low renin hypertension. Life Sci 1982;**30:**571–575.
87. Muirhead EE. The renomedullary antihypertensive system and its putative hormone(s). [In] Genest J, Kuchel O, Cantin M, Hamet P, eds. Hypertension: Physiopathology and Treatment. New York, McGraw-Hill, 2nd ed, 1983, pp 394–407.
88. Conomy JP, Barnes KL, Ferrario CM. The brain and arterial hypertension: new direction in an old relationship (editorial). Neurology 1978;**28:**1203–1205.
89. Aleksandrow D, Wysznacka W, Gajewski J. Influence of chlorothiazide upon arterial responsiveness to nor-epinephrine in hypertensive subjects. N Engl J Med 1959;**261:**1052–1055.
90. Page IH. The nature of hypertension. Bull NY Acad Med 1937;**13:**645–654.