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Hypertension: Perspectives

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I. Introduction

IT was intended that this be a broad but concise review and critique of several factors that relate to hypertension in people and laboratory animals. The appropriate literature is so vast that an "in depth" review might relate more properly and more adequately to any single phase of this broad subject. Some such impressive reviews have been included in the REFERENCES.

We have emphasized the interactions of several interesting physiological systems that relate to modulation of blood pressure, to anticipation of heritable hypertension, and to prevention and treatment of essential hypertension before degenerative cardiovascular obsolescence can take its toll. We regret that several omissions were necessary; two were intended to keep form and substance within reasonable bounds: first, the scarce reference in text to investigators by name and by published work; and second, data pertaining to the ever-changing physiology of the heart and vascular system induced by the pathogenesis and treatment of hypertension. Third, we regret the omission of items that the reader thinks should have been included but are not, for one reason or another.

A. Cardiovascular Development

Perhaps it would be perceptive to recall briefly the purpose and phylogenetic development of the cardiovascular system. The lowly amoeba, single cell organisms, are bathed in a relatively vast volume of water of essentially constant composition in which they can move about. This body of water provides the dual function of bringing nutriment to the cell and removing its excreted metabolic products. The amusing multicellular but primitive hydra introduce a pulsatile movement of the organism as a whole to assure an exchange of fluid of relatively constant composition between their gastrovascular cavity and the environment. The starfish have a still more complex but open water-vascular system, with a central pulsatile pumping portion to perfuse and sustain a constant fluid environment of cells that make up their attractive structure and more complex, coordinated functions. Our own closed blood-perfused cardiovascular system retains the pulsatile pump feature but requires many complementary organs and tissues, the structure and variable function of which are basic to the same needs of unicellular organisms—to provide nutriment and to remove excrement. These systems are redundant, but they can act independently. Their interactions are supportive when balanced.

II. Genetic Control of Blood Pressure

A. Variability

The total response of many variable factors to the need to sustain an adequate arterial pulsatile pressure, greater (but not necessarily so) in some people than in others, seems better understood today. Indeed, those factors differ in degree (quantitatively) and balance rather than kind in the hypertensive and normotensive person. If one assumes a Gaussian distribution of diastolic and systolic pressure with respect to age, from an actuarial (life expectancy) standpoint, then adults whose blood pressure is 90 diastolic and 120 mm Hg systolic or lower, respectively, might be considered normotensive and those with higher values as increasingly hypertensive. For our American population the distribution curve seems likely to be shifted toward the hypertensive side, since the kidney is developed to conserve sodium and we are inclined to use salt as a condiment rather than as an essential component of our diet.

B. Heritable Influence

Whereas the genetic control of biological structure and function is awesome, its reproducibility is not invariable. Even homozygotic twins are only more similar to each other than to either parent or to brothers and sisters. Variability within the genetic control of structure and function is the basis for natural selection, i.e., for the reproductive adaptation to environmental change over generations. Variability must be provided adequately within the integrative actions of biological systems for adaptation, for change, and for homeostasis. Under prevailing conditions it is not remarkable that some members of different species should have and pass to their progeny a higher blood pressure than the norm for that population. This was the conceptual basis from which a hypertensive strain of rabbits (7) and several such strains of rats (40, 71, 296, 374) were developed that have been very useful for research on hypertension. They were developed not so much to model human essential hypertension (261) as to represent physiological correlates thereof that are reproduced genetically.

The reproductively sustained predilection to hypertension is a measurement, a sign, that something is different.

In the Dahl S and R rats the difference is the salt-induced sensitivity (S) and resistance (R) to the development of hypertension (72, 78).

Heritable (familial) influences on blood pressure are also well established in humans (22, 229, 266, 276, 343, 351). For instance, at one time it was thought that the difference between the incidence and severity of hypertension was higher among blacks than whites (63, 67, 238, 239, 405) because of nutrition or to a greater intake of salt (205, 257). While such an environmental element seems to obtain, this does not account entirely for that racial difference; that predilection appears to be heritable (258, 420), as well.

Familial correlation between mother and neonate for both systolic and diastolic pressures has been reported to obtain within the first few days of delivery (445). By 6 months of age a statistical significance was noted between the greater difference in systolic pressures of monozygotic twins compared to such values for dizygotic twins (235).

From studies on many children from age 6 years through adolescence, weight (and in some studies height) and blood pressure track through adolescence in both girls and boys (101, 184, 324). The relationship of blood pressure of parents to that of siblings and adopted children in the same household suggests that environmental factors are real but less evident than heritable ones (41, 61, 159).

C. Environmental Influence

There are many examples of environmental factors in the development and expression of hypertension. For instance, the prevalence of hypertension and its sequellae can be related to the amount of salt consumed (278). On the whole, weight, height, and blood pressure seem correlated positively (101, 209, 225). Compared to normotensive children, hypertensive children (50) [like hypertensive rats (176)] respond to stress with a greater elevation of blood pressure that was increased by salt loading (105). Families who migrated from Tokelan Island, an atoll in the South Pacific, to New Zealand were studied. There was an increase in blood pressure, especially among the men, in comparison with their arterial pressure before migration and with that of family members who remained behind. Obesity was one of the factors in the increased arterial pressure, but others obtained as well. Systolic pressure was increased to the greatest extent. This was interpreted to indicate a genetic predisposition to hypertension in such adults that found increased expression when the environment was changed (423). This is somewhat similar to the hypertensive response of the Dahl S rat to salt (72).

This relationship of weight or size to blood pressure is provocative. Is blood pressure greater in heavier, larger children to adolescence for reasons associated with obesity and hypertension? Or, are they bigger children because of a more substantial perfusion of tissues to meet their essential requirements? We are inclined to believe that both are important considerations; in the first instance the greater blood pressure is responsive to need, and in the second it is conducive to growth, i.e., it is causal. Similarly, in hypertensive children plasma renin activity and aldosterone excretion associated with low or high sodium excretion (287) may be causal in the first instance and effect (responsive) in the second instance. (More about renin is presented later in text.)

The foregoing information indicates that, some individuals, some families, and some populations handle environmental factors that pertain to the maintenance of blood pressure excessively as compared to what would be normal for others. What is the incidence? Aside from hypertension secondary to histomorphic evidence of impaired function, to what can such difference be related? What are the concomitant changes? Why do they occur? What can be done about it? When? What difference does it make?

The incidence of hypertension in the adult human population is about 20% (377), although the definition of hypertensive blood pressure varies (316). So great an incidence suggests that a genetic basis for the higher than usual blood pressure may be multifactorial—not a single causal factor.

III. Neurogenic Considerations

This multifactorial point of view is supported by the individual characteristics of the several strains of hypertensive rats that have been developed. Thus, at one extreme the Dahl S and R rats are essentially normotensive until the S rats are exposed to a much higher (8%) than normal (0.4%) salt intake whereupon very high blood pressures develop rapidly (71). On the other hand, these salt-sensitive rats do not respond impressively to emotional stress (75) as the Okamoto-Kyoto spontaneously hypertensive rats do. They are not "spontaneously hypertensive." Hypertension is induced (by high salt intake) in the genetically prone strain (S) but not in rats (R) that are not so predisposed.

Young Dahl S rats (10 to 14 weeks) manifest an increased neurogenic vasoconstriction during the increase in blood pressure in response to a high salt intake; this is reported to account for as much as 50% of the increased vascular constriction. This effect is not observed in the R strain rats, and can be blocked in the S strain by sympathetic denervation of the vascular bed (hind quarters) being measured (394). The salt-sensitive (S) strain is reported to have a higher hypothalamic and plasma norepinephrine content than the R salt-resistant strain. In response to a high salt diet, brain-stem norepinephrine increased in the S strain and decreased in the R strain (196). After 6-hydroxydopamine sympathectomy, the Dahl S strain rats do not develop the typical salt-induced hypertension (395). This sympathetic component to the hypertension developed in the S strain finds peripheral

expression in the greater quantification of α_1- and α_2-adrenergic receptors in their kidneys than in the R strain. This greater number of α-receptors is exaggerated in the S rats by high salt intake, and the increase is reported to anticipate the increase in blood pressure. That this is a genetic modality gains credence from the greater incidence of α_2-receptors in the spontaneously hypertensive (SH) rats, but not in their normotensive (WKY) counterparts or in the Grollman (neurogenic) or DOCA/Na hypertensive rats. The induced increase in Dahl S α_2-receptors can be prevented by the selective α_2 inhibitor, yohimbine (314).

A. Behavioral Correlates

The Kyoto SH rats are so responsive to stress that they should be handled carefully (176, 439). Simply changing from single-unit housing to several SH rats in a cage is sufficient to increase their blood pressure promptly. Group housing of their normotensive WKY Wistar genetic counterparts did not induce hypertension (240). The SH rat is more aggressive than the normotensive Wistar rat from which it was derived (295, 334). A transient increase in plasma renin level may attend the response to stress (358), but the renin level is not elevated characteristically in the young SH rat (220). The New Zealand strain (GHR) (368, 373) and the Milan strain (MHS) (39) are still other strains of SH rats; their blood pressure becomes hypertensive rapidly and the histomorphic signs at the end of their shorter life span are those of hypertension.

As in rats, when adolescents having labile hypertension or normotensive adolescents with a genetic risk of hypertension were compared with normotensive adolescents of normotensive parentage (control subjects), their response to stress (mental arithmetic) was significantly greater than that of the control subjects as measured by sustained, increased heart rate, increased diastolic pressure, and elevated plasma catecholamine. The normotensive adolescents at genetic risk fell into two groups, low and high responders. The response of the labile hypertensive group of adolescents was the greatest (105).

B. Central Sympathetic Involvement

Other studies have indicated an exaggerated central sympathetic involvement in the genesis and maintenance of hypertension in the rat (53, 349). Posterior hypothalamic spontaneous activity was greater in the young (9 weeks) SH rat than the corresponding WKY rats. Graded electrical stimulation of the posterior hypothalamus elicited greater sympathetic neural firing and aortic blood pressure elevation in the SH than the WKY rats. Likewise, the reduction in aortic pressure after ganglionic blockade with pentolinium was greater in the SH rat. Increased vascular receptor sensitivity was not responsible for the greater response to hypothalamic stimulation in the sense that intravenous norepinephrine evoked almost equal pressor responses in both SH and WKY rats (53).

Aside from the inconsistency of reports, just the scope or complexity of central sympathetic involvement is suggested by the following. From both histomorphic and pharmacological evidence, it has been proposed that two central adrenergic centers exist that have opposing effects on the cardiovascular system; one is an excitatory hypothalamic center and the other, a bulbar inhibitory system (174, 175). An imbalance of the two has been suggested to trigger the initiation of hypertension. It should be mentioned (96) that the endorphin-enkephalin system may play a role in hypertension, perhaps through the mediation of the autonomic system. A careful study of the reduced response of several vascular beds of unanesthetized, unrestrained SH and WKY rats showed no differences in their adrenergic control of vasoconstriction. Whether the two strains would have responded similarly to salt or expanded volume stress was not reported (411).

It will be recalled that the number of renal α_2-receptors in the SH and Dahl S rats was greater than for WKY or Dahl R rats and that their number was increased by increased salt intake before the increased blood pressure, as though they mediated an increased renal hypertensive action (314). The reciprocal of that efferent mediation of central α_2-adrenergic effect to the kidney was the moderation of hypertension that attended the denervation or unclipping of the one-kidney, one-clip Goldblatt hypertensive rat (208). The most attractive interpretation of these results, since there was no change in sodium or water balance or in plasma renin activity, was a reduction in afferent sympathetic impulses from the kidney resulting in a diminished adrenergic effect on systemic blood pressure (425).

The young stroke-prone spontaneously hypertensive rats (SpSH) have an elevated concentration of plasma norepinephrine and an enhanced neuronal uptake of norepinephrine during early hypertension (348). Chemical sympathectomy (6-hydroxydopamine) obtunds (89) and renal denervation delays (348) development of hypertension in young SpSH rats. In the established phase, 6-hydroxydopamine did not prevent the further rise in blood pressure of SpSH rats (393).

C. Adrenergic Response to Salt Intake

Under the influence of salt loading, plasma norepinephrine and systemic blood pressure increased in the SpSH rat. In the corresponding WKY rats, salt loading decreased plasma norepinephrine (90). Therefore, salt loading enhanced sympathetic activity of the SpSH rat. In SH and WKY rats H^3-norepinephrine uptake by the heart was similar, but its turnover was less in the SH than the WKY rats (246).

A demonstrably exaggerated adrenergic response to sodium deprivation or volume expansion was obtained in

young adult humans with borderline hypertension as compared with normotensive control subjects. This was indicated by significantly greater plasma norepinephrine concentrations in both supine and upright positions, increased 24-hour urinary excretion of normetanephrine, and increased plasma renin activity in the hypertensive group (335).

The norepinephrine response to tilting and to low sodium intake was essentially the same in low and high renin hypertensive patients, but the plasma renin response to tilt was greater in the high renin group, as though there was a difference in the sensitivity of juxtaglomerular β-adrenoreceptors in the two groups to similar adrenergic stimulation (280, 281). In another series of hypertensive patients, 70% of the high renin patients had elevated catecholamines as compared to 14% in the normal and low renin patients (83). Other evidence for sympathetic nervous system involvement particularly in the high renin patients was greater heart rates, increased cardiac output, and sensitivity to the β-adrenergic blocking agent, propranolol (278, 396).

Borderline hypertensive patients who have increased orthostatic diastolic pressure and increased cardiac output and heart rate by tilt test can be expected to develop sustained hypertension, disappearance of the orthostatic cardiac effects, and a rapid increase in weight gain. This was determined in a 48-month follow-up study of 23 young men (312).

Variations in salt intake can influence plasma catecholamine levels (without affecting blood pressure) in normotensive human subjects (no family history of hypertension) under conditions of high, medium, and low sodium balance. In recent studies, supine norepinephrine plasma concentration was highest at low sodium intake (289, 339). Sympathetic nervous system activity appears to decrease with sodium loading in normal subjects (3, 247) and to increase in borderline hypertensive patients independent of the renin system (182, 210, 253).

Baroreflex sensitivity reflecting autonomic nervous system activity differs in normotensive and hypertensive rats and people. At 4 to 6 weeks baroreflex sensitivity was essentially the same in SH and WKY rats. After 12 to 20 weeks baroreflex sensitivity had not changed in the SH rats (remained depressed), whereas in the WKY strain it had increased two- to threefold (384). Likewise, its responsiveness was impaired in borderline hypertensive patients (421). The baroreflex could be altered in borderline hypertensive rats by the use of propranolol (394) or neostigmine (413) or a combination of the two, as though the aberration represented an altered balance between sympathetic and parasympathetic systems.

Perhaps it should be stated at this point that an adrenergic basis for a genetic predilection to hypertension is not above controversy. In part, this is because of the difficulty of establishing neurochemical correlates of behavior, the uncertain reliability of present methodology, and the difficulties relevant to sampling and ultimately assessing cause or effect. With allowance for these seeming vagaries, a neurogenic basis for early manifestations of heritable hypertension in some patients seems attractive.

IV. Salt and Water Balance

The kidney with its multiple functions is evidently a determinant of the complexity and severity of hypertension, with few exceptions such as pheochromocytoma. Reduction of the blood supply to the kidney directly by renal artery clamping (152) or by the more general embarrassment of structure and function, perimetric constriction (302), was sufficient to focus an everlasting interest in the increasingly fine discrimination of the multiple functions of the kidney in hypertension. Normally, these functions relate to the long-term infinite gain accommodation of volume and pressure within the arterial system to the purpose (168), homeostasis.

A. Relation of Salt to Hypertension, Historical

Ambard and Beaujard (10) reported in 1904 that an increased blood pressure attended a high chloride retention (salt intake) in patients with reduced renal function. Short-term, excessively high salt intake sufficient to induce evident fluid retention can increase blood pressure in normotensive humans and rats, but not invariably (162, 257, 263, 284, 313, 345). Epidemiological and long-term studies in humans and rats relating high-salt consumption to high blood pressure are available (27, 74, 216, 251, 303, 325, 342, 371). More relevant to therapy are the strict dietary studies of Allen (8) first, then Kempner (213) 20 years later. The former related the salt effect to impaired renal function, and, while the latter's treatment for reduction of hypertensive blood pressure is usually attributed to salt reduction by others (160), his meticulous display of data is well worth study from a broader perspective.

B. Relation of Hypertension to Salt and Water Excretion

An exaggerated salt and water excretion by the kidney of the hypertensive patient compared to the normal subject has been confirmed repeatedly since the report in 1946 (107), but the studies have been difficult to interpret. Although glomerular function was restricted somewhat in the hypertensive patients compared to normotensive control subjects in that study, the ratio of urine to plasma chloride indicated a greater chloride as well as water excretion in the former patients, a reduced glomerulotubular balance of function. Other renal clearance studies with 5% saline venoclysis reported the excretion of salt and water to be correlated with blood pressure (188), more of the same, seemingly. A revealing study indicated that, whereas an exaggerated sodium output could be induced in hypertensive but not in

normotensive patients (on a regular hospital diet) by the venoclysis of 2.5% saline at 12 ml/min for 1 hour, the rate of natriuretic response in the normotensive patients could be increased to that of the hypertensive patients by prolonging the venoclysis for 2 hours, i.e., by sodium and volume expansion. Consistent with the concept of difference in contribution of volume to pressure, the venoclysis of even a small volume of hypotonic saline increased sodium excretion in the hypertensive patient but did not do so in the normotensive person, or in the volume-depleted hypertensive subject, unless the venoclysis was sustained for 2 hours or more (25). Although the "exaggerated natriuresis" from relatively small saline loading that does not distort pressure-volume relationships in the hypertensive patient has been attributed to a dose-related impairment in distal sodium reabsorption (329), the aforementioned experiments with corresponding normovolemic, normotensive subjects and volume-depleted hypertensive patients support the view that the volume-expanded hypertensive pressure, not reduced reabsorption, is responsible for this so-called pressure natriuresis (157, 185).

Whereas an exaggerated natriuresis was induced in anesthetized SH rats (but not in matched WKY strain) by a single gastric normal saline load (2% of body weight), the same volume of saline administered intravenously over a period of 60 minutes induced essentially identical natriuresis in both strains. The arterial blood pressure and Na:K urinary excretion ratios were higher in the SH than the WKY rats but did not change during saline loading, and the ^{22}Na plasma concentration at equilibrium in both groups after gastrointestinal (GI) absorption was about one-half that when administered intravenously. The equivalent natriuresis of the two strains at the greater (intravenous) volume expansion makes it appear that the volume expansion of the WKY rats after GI absorption was less than in the SH rat. This was consistent with their finding that when the extent of intravenous volume expansion was 1% instead of 2% of body weight the SH rats responded with a significantly greater natriuresis at 1% than did the WKY rats (431a). These results are consistent with a decreased corticomedullary osmotic and sodium concentration gradient that varied inversely with flow through the nephron. This in turn might be accounted for in various ways to be discussed later in this review (i.e., sodium hormone, prostaglandins, kallikrein-kinins). Emphasis in experiments such as these but conducted in Grollman, or Goldblatt, or mineralocorticoid-induced hypertension in the rat (161, 357) has centered on volume expansion rather than renal function, which may be a reason for the ambiguity in this literature (29). The glomerular function of the Milan spontaneously hypertensive rat is considerably lower than that of their normotensive counterpart before the establishment of hypertension. When they become hypertensive, they manifest an exaggerated natriuretic response to salt loading compared to their normotensive counterpart (38), as would be expected from either a pressure-induced or a reduced reabsorptive glomerulotubular imbalance.

A chronic high salt intake over a period of 3 months exaggerated the hypertension of the SH rats under conditions where the blood pressure of the corresponding WKY rats remained unchanged (64). Elsewhere, the blood pressure increase that attended 8% salt intake for 4¼ months to rats was attended by a significant increase in extracellular (inulin) space. Both increased pressure and inulin space could be prevented by administering a thiazide saluretic agent with the 8% salt diet (408).

C. Age and Response of Blood Pressure to Salt Loading

The onset of the arterial pressor response to high salt (sodium) feeding in conscious, unrestrained SH rats monitored for direct aortic pressures was more complex (315). Young SH rats, 4 to 5 months old, responded to a 7-day dietary sodium stress test with marked retention of sodium (and water) but no elevation of arterial pressure and no change in an observed, inverse correlation linking their blood pressure to sodium balance. SH rats 9 to 11 months old given the same test showed sodium retention similar to the young rats, but, in addition, a substantial elevation of arterial pressure was accompanied by an increase in the correlation value relating pressure to balance. The latter suggested the pressor effect was predominantly sodium-balance dependent even though the actual retention of sodium in the older SH rats was no greater than that observed in the young rats. Thus, arterial pressor sensitivity to retention of sodium (during excessive salt consumption) increases with age in this rat. These results suggest an age-dependent reduction in cardiovascular compliance possibly coupled with deterioration of renal management of sodium in the SH rat (158, 248, 344, 366). Such results seem consistent with a prior report that normal young or old WKY rats had greater urine flow and sodium excretion rates than the corresponding SH rats when subjected to a 15-minute 2.5% i.v. saline load (at 0.01 ml/min/100 g of body weight). Response of SH and WKY rats to isotonic salt load was similar to the greater effect of hypertonic salt loading. Potassium excretion was inversely related to sodium output in response to salt loading, except in the young (9 weeks) SH rats where the sodium and potassium excretion rates responded similarly. Glomerular filtration rate (inulin clearance) and the number and distribution of glomeruli was not sufficiently different in the two strains (and with respect to previous data on Wistar rats) to account for the differences, with one reservation; the number of glomeruli in the young (9 weeks) but not the older (18 to 30 weeks) SH rats was less than expected. In the aggregate, these data were interpreted to indicate a lesser sodium reabsorption in the distal portion of the nephron that may or may not relate to the level of aldosterone modulation of the sodium-potassium inter-

action at that site (106). These data, together with the fact that sodium and water output in the control phase of these experiments was less in the SH than WKY rats, suggest a greater countercurrent medullary conservation of sodium or greater aldosterone effect in the distal portion of the nephron of the SH rats as alternative considerations. Arrested renal development or deteriorating function, depending on whether one had in mind a genetic or a secondary (degenerative) basis, would be consistent with the relationship of salt intake and output to hypertension, as has been reviewed (106).

From a different point of view, Dahl et al., interpreted their parabiotic and renal homograft transplant preparations between his S and R rat strains as indicating that kidneys "... in the R strain have a more powerful antihypertensive influence, whereas those of the S strain are more hypertensinogenic" (73, 74). Although Dahl et al. proposed some humoral factor to account for the increased blood pressure in the Rs rats and the lesser hypertension in the Sr parabiotic rats of the Rs or Sr combinations, only their interpretation of the blood pressure data was presented to support the presence of such a stable, diffusible substance in either the parabiotic or transplant S/R renal preparations (76, 78). In a clinical study, plasma of hypertensive subjects was reported to contain a pressor factor that increased during salt loading and was not noted in normotensive subjects (272). Alternatively, a vasoactive polypeptide has been reported to have been isolated from urine of normotensive and secondary hypertensive (normotensive family history) patients. Patients with primary hypertension had little or none in their urine (432).

D. Kidney and Response of Blood Pressure to Salt Loading

Is renal function arrested in the older SH rat or "overdeveloped" for its natural role of salt and water conservation? It seems more likely that the renal tubular mechanism for sodium and chloride reabsorption is overdeveloped in the SH rat, and that the site of difference is the ascending limb of the loop of Henle. This interpretation is more consistent with the impression that the young SH rat has a normal renin hypertension, as mentioned previously (220). (An exaggerated positive adrenergic and/or renin response to saluresis in the rat may be the reason that antihypertensive doses of thiazides in these animals need be higher than in hypertensive humans.)

The thesis that the kidney is primarily responsible for the short-term (169, 387) as well as long-term hypertensive response to salt loading is convincing. Reasonable salt intake alone will not cause short-term salt-loading hypertension in the normal animal or person (not predisposed genetically to hypertension), for the animal or person will simply excrete the salt load. It has been proposed that a "kidney factor" of uncertain structure released by salt loading is responsible for this phenomenon (85).

V. The Renin, Angiotensin, Aldosterone Axis

Alternatively, an aberration of function, or of structure and function seems accountable for the differences in salt handling by the SH and WKY rats noted in previous paragraphs. Then too, it was previously mentioned that glomerular filtration in the Milan hypertensive rat was inherently less than its normotensive counterpart and so was the size of their kidneys (38). Unless there was a commensurate reduction in proximal tubular function, this could result in greater proximal reabsorption of sodium and an expansion of volume with elevation of blood pressure until sodium filtration and excretion were brought into more favorable balance at a higher filtration rate, as by the intermediation of the macula densa tubuloglomerular feedback mechanism (30).

A. Renal Artery Stenosis and Plasma Renin Activity

The hypertension of renal artery stenosis is the human prototype of that Goldblatt induced by partially clamping or constricting the renal artery of laboratory animals (152). If the obstruction, stenosis, in patients is embolic in origin, the onset and development of hypertension may be sudden, rapid, and severe. Hypertension from such a cause can be relieved by removing the lesioned kidney. Recently, some stenotic lesions of the renal artery have been amenable to less radical resolution (224, 350) and the blood pressure returned to normotensive levels with good to fair response in some 70% of cases. An elevation of plasma renin activity in the renal veins of the stenotic kidney (stenotic/normal kidney ratio greater than 2.0) is considered to anticipate a favorable response to appropriate surgery (179, 268). Renal venous renin ratio correlated positively with the pressure gradient across the stenosis and with the count of granular cells in the juxtaglomerular (JG) apparatus.

B. Renin, General Considerations

In 1898, Tigerstedt and Bergman reported that something in a saline extract of kidney caused an elevation of blood pressure. They called it renin (402).

The proteolytic enzyme, renin, is stored in the JG cells of the renal cortex (79, 211, 372). There exists a large, less active molecular form that has the same enzymatic and immunological characteristics found in certain renal tumors, for example, and referred to as big renin or possibly prorenin (80, 354). Renin is derived from a renin substrate that is produced in the liver from which it is distributed to the kidney and to other organs (114, 136). Renin and angiotensin presence and action in the brain seems to be independent of the renal renin-angiotensin system (14, 135, 282).

Renin is released from the JG apparatus of the kidney into the adjacent afferent glomerular arteriole in response to intrarenal baroreceptor influence in the affer-

ent arteriole and elsewhere (117, 321, 346), to osmolality sensed by the corresponding macula densa of the distal tubule (30), to β-adrenergic innervation, and to still other factors (104, 202, 211, 308, 409, 444). Tumors in the JG apparatus have been described that release inappropriate amounts of renin that induces severe hypertension (336, 347, 415).

C. Angiotensins, General Considerations

In the blood, renin cleaves an inactive α_2-globulin substrate from the liver (angiotensinogen) to yield a decapeptide, angiotensin I. Pressor response to injection of renin or to renal artery constriction in trained dogs can be blocked or reversed, and renin activity lowered, by a specific renin antiserum for 24 hours after a single injection (170). So many peptides have been shown to have sufficient activity as renin antagonists (170, 214) that this seems a feasible area for development. In turn, a converting enzyme (52) (also known as kininase II) removes the two terminal amino acids of angiotensin I (215) to yield the octapeptide, angiotensin II, which is the most potent natural pressor substance. As kininase II, the converting enzyme degrades kinins (102), such as bradykinin, the most potent vasodilator known at the time (116), to inactive substances. This converting enzyme is present in many organs including lungs, kidney, testes, and brain.

Angiotensin II stimulates contractions of the heart and vascular musculature (46, 219, 381) and increases aldosterone production (226, 254), hypothalamic adrenergic activity (103, 109, 376), and the thirst-antidiuretic hormone axis for water balance regulation (109, 360).

Vasopressin secretion, which is elevated in SH rats (69, 273), can be further increased (eight-fold) concomitant with an acute increase in blood pressure after the intracerebroventricular injection of a converting enzyme inhibitor, captopril. In the WKY rat such injections did not increase blood pressure but did increase vasopressin secretion three-fold (68). This suggests a greater sensitivity of the SH rat to vasopressin release, or a more likely greater vascular compliance of the WKY (normal, control) rats. Since angiotensin II increases vasopressin secretion (212), the investigators suggest that captopril may increase brain kinins or stimulate the release of brain prostaglandins since both types of compounds can cause increased vasopressin release (337, 437). (The control injections of isoosmotic pH 2 mannitol solution was without effect.)

Under sustained high renin hypertension, an angiotensin II peptide blocking agent, such as saralasin, P113, (1-sar-8-ala-angiotensin II) (189, 383), or a nonpeptide, smaller, orally active converting enzyme inhibitor, such as captopril (SQ14225) (D-3-mercapto-2-methylpropanoyl-L-proline) (16, 59, 124, 141, 178), or MK-421 (N-[(S)-1-carboxy-3-phenylpropyl]-L-alanine-L-proline) (163, 310, 392), lowers hypertensive blood pressure and blocks the stimulatory effect of angiotensin I on aldosterone release from the adrenal cortex. Whereas they are effective under conditions of high renin activity in the rat, they may or may not be hypotensive in animals and humans having lower (normal) plasma renin activity (118, 142, 233).

A converting enzyme inhibitor or angiotensin blocking agent would be expected to increase plasma renin activity whether normal or high before therapy (24, 194), and to decrease aldosterone blood levels in high renin hypertension, at least acutely. Since potassium is the stronger stimulus to aldosterone secretion (133, 186), hyperkalemia would seem unlikely in the absence of severe renal damage.

D. Identity of Converting Enzyme with Kininase II

It would be expected that an angiotensin converting enzyme inhibitor might be ineffective in normal renin hypertension (24, 194). This is not invariably so (24, 398). Where such therapy has reduced blood pressure in normal renin hypertension, it has been thought to be due to blocking degradation of bradykinin; the potent vasodilator was thought to be responsible for blood pressure reduction directly, or by increasing salt and water excretion, and/or by the release of prostaglandins (191, 200, 270, 271, 274, 389–391, 419).

In quite a different situation the action of converting enzyme inhibitor to inhibit kinin degradation has been demonstrated. Administration by infusion of the inhibitor teprotide to pregnant, nephrectomized rabbits significantly increased uterine and placenta blood flow (6). When such nephrectomized, pregnant rabbits were placed on a sustained infusion of an angiotensin II antagonist (saralasin) and then given injections of the converting enzyme inhibitor, both uterine blood flow and immunoreactive prostaglandin GE_2 level increased therein unless the animal received kinin antibodies before administration of the converting enzyme inhibitor. In these experiments, systemic blood pressure and blood flow were not altered (355).

E. Angiotensin II and III on Aldosterone Release

Whereas it is tempting to end the discussion of the angiotensins with angiotensin II since it is so active, this would be somewhat analogous to discussing the metabolism of dihydroxyphenylalanine with the β-hydroxylation of dopamine to norepinephrine without mentioning the N-methyl derivative, epinephrine, and the differences between the latter two compounds. Thus, the des-aspartyl derivatives of angiotensins I and II are active, the latter heptapeptide being identified in the literature as angiotensin III. Since angiotensin III is considerably more lipophylic than angiotensin II, it is not surprising that their binding characteristics should be different (154), even as they have some of the same attributes. Thus, angiotensin III is reported to be more active than angiotensin II in stimulating aldosterone release (43). Angiotensin III releases prostaglandin from blood vessels

in vitro (47) and stimulates tyrosine hydroxylase in some tissues in vitro (48).

F. Aldosterone, General Considerations

Whereas the renin-angiotensin aspect of the overall renin-angiotensin-aldosterone system is immediately responsive to change, the action of aldosterone introduces a more sustained role in sodium regulation. Aldosterone, characterized in 1954 (369), was identified as the adrenocortical hormone responsible for salt-retaining activity previously noted to occur in the urine of patients with cardiac decompensation (370), cirrhosis (60), or nephrosis (256). These conditions account for the bound and free high aldosterone plasma levels by impairment of metabolism of aldosterone in liver (66) and reduced renal elimination (288). In addition to the activity of ACTH and angiotensin II, a third steroidogenic aldosterone-stimulating factor has been identified and studied (341, 359). It has been determined to be a high molecular weight glycoprotein isolated from normal human urine and localized in the anterior pituitary. It stimulates the release of aldosterone in vivo and in vitro and a smaller fraction of the molecule is active in vitro.

In primary hyperaldosteronism of adrenocortical tumor, sodium retention may be sufficient to cause plasma renin activity to be low. This causal inverse relationship between high-aldosterone–low-renin activity has been clearly demonstrated by steady state aldosterone dose-response studies in adrenalectomized dogs (441). In severe and malignant hypertension the renal excretion of aldosterone is increased (144, 227). This is attributed to increased renin-angiotensin activity (134).

Whereas aldosterone modulation of sodium balance by the exchange of sodium and potassium across the distal portion of the nephron is important, there was little effect of the steroid on plasma sodium concentration in the aforementioned steady state aldosterone dose-response studies in adrenalectomized dogs. Plasma potassium varied inversely with changes in aldosterone steady state over a considerable range of rates, but plasma sodium only changed (decreased) when aldosterone rate of infusion was less than normal. Plasma renin activity increased as aldosterone infusion fell below normal and went to zero as aldosterone rates became slightly in excess of normal. Arterial pressure increased as aldosterone level rose above normal but did not fall below normal at subnormal aldosterone levels, probably due to activation of the renin-angiotensin system under these conditions (441). As a corollary, renin secretion is increased under conditions of sodium depletion (142) or hemorrhage (117, 321, 346), as if to sustain arterial pressure.

Aside from the relationship of aldosterone to renin-angiotensin, the action of the mineralocorticoid on exchange of sodium reabsorption and potassium excretion in the distal cortical portion of the nephron (165) is more evident than understandable. ^{3}H-Aldosterone-protein complexes have been isolated from both nuclear and cytosol fractions of rat kidneys (98, 183, 388). Spironolactone inhibited the formation of the complexes at concentrations that block aldosterone action on sodium transport (388). Delay in onset of action, characteristic of aldosterone, has been accounted for by the time it is presumed to take for the several reactions to be completed; perhaps time for synthesis of a protein carrier for sodium transport, or alteration of membrane permeability.

In attempting to analyze this course of events, it has been found that in the adrenalectomized rat actinomycin-D blocked the effect of added aldosterone and so increased sodium excretion. The ribonucleic acid synthesis inhibitor, actinomycin-D, did not alter concurrent potassium excretion (430). This separation of action of aldosterone on sodium and potassium transport has been noted in another study (26). Aldosterone does not affect sodium-potassium-ATPase (62).

These several studies suggest a facilitatory role of aldosterone for sodium transport from lumen into cells of the more distal portion of the nephron, analogous to the effect of antidiuretic hormone on back diffusion of water. Whereas water diffuses into a medullary medium of high osmolar concentration, maintenance of isosmolar monovalent cation concentration within these cells requires a sodium-potassium exchange on the lumenal side, even as the Na-K-ATPase of the interstitially oriented cell membrane serves to sustain an approximation of the normal, intracellular high-potassium–low-sodium concentration. Evidence presented to this point in text indicates that when increased lumenal sodium reaches the distal cortical portion of the nephron it should trigger the macula densa, in approximation with the juxtaglomerular renin-releasing cells, to stimulate increased aldosterone availability by way of the renin-angiotonin-aldosterone axis. In this way salt may be conserved (reabsorption is facilitated) even when that seems inappropriate, as in the instance of increased renin release attending saluretic therapy by the thiazides and loop diuretics.

VI. Redundancy of Adrenergic and Renin-Angiotensin-Aldosterone Systems

The two systems, adrenergic and renin-angiotensin-aldosterone, are redundant with respect to their effects on heart rate and systemic arterial pressure. They are not alike but redundant, even as each serves purposes peculiar to itself. They are redundant, as the renal effect of angiotensin on glomerular filtration and its central effect on antidiuretic hormone serve to conserve salt and water (14, 282, 442). They are dissimilar in that, whereas water restriction increases renin and antidiuretic hormone (ADH) plasma concentrations, increased hydration raises plasma renin still further as ADH levels return to normal (42b). Intraventricular administration of angiotensin II into anesthetized cats induces elevated blood pressure and tachycardia that can be essentially abol-

ished by transection of the spinal cord at C_1 (376). Other studies indicate that angiotensin facilitates or supports the release of norepinephrine from neurons (31). Conversely, β-adrenergic stimulation of the JG apparatus increases the release of renin (308).

VII. Kallikrein-Kinin System

By way of review (57, 58), kinins are derived enzymatically from inactive kininogens by the actions of kininogenases, serine proteinases. There are two kinds of kininogens, low molecular weight and high molecular weight, found in plasma and numerous tissues. There are two categories of kininogenases, plasma and glandular kallikreins. Bradykinin is derived from high molecular weight kininogen by plasma kallikrein and from both low and high molecular weight kininogens by glandular kallikrein. Whereas plasma kallikrein plays a role in coagulation and fibrinolysis, glandular kallikrein relates more to specific organ functions, such as will be discussed with respect to the kidney. Whereas bradykinin is a most potent vasodilator, some of the effects elicited by a glandular kallikrein may be by renin activation and by prostaglandin release (2). Kinins are readily inactivated by two groups of kininases, exopeptidases and endopeptidases that differ as to site of hydrolysis of the kinin molecule. The best known of these, an endopeptidase, is a peptidyl dipeptidase familiar as kininase II or angiotensin I converting enzyme.

A significant negative correlation between the level of plasma renin activity and blood kinin concentration seems to exist. According to a "deprivation theory" of hypertension, the elevated blood pressure caused by the renin and adrenergic systems was because these systems were opposed by an inadequate production of vasodilatory substances. It is an attractive, rational thesis but the extreme activity of the kinins together with the vagaries that have plagued these assays have contributed to the difficulty of assessing this literature.

A. Relation to Hypertension

In 1934 Elliott and Nuzum (100) reported urinary kallikrein to be less in hypertensive than normotensive individuals. This was confirmed by others (236, 252). The decreased excretion of kallikrein was interpreted to suggest that the hypertension was due to decreased vasodilator production. An increased awareness of the effect of renal pathology, age, race, diet, aldosterone level, and the like on kallikrein excretion developed and a lack of uniformity with which such studies were reported have made this thesis of uncertain significance, other than its contributing to the evidence that urinary kinins are generated in the kidney (108, 292, 385). A recent, seemingly well controlled study confirmed a previous indication that no significant difference obtained between excretion of urinary kallikrein by normotensive and hypertensive individuals. No relationship thereof to aldosterone or plasma renin levels was found after salt restriction (230).

B. Interaction with the Renin, Angiotensin, Aldosterone System

The kallikrein-kinin system and the renin-angiotensin-aldosterone system are related in several ways. Kallikrein and renin are stored in the cells lining the distal convoluted tubules from the JG apparatus (where renin is synthesized) to the collecting duct (298, 352) of the renal cortex. Moreover, kallikrein can activate renin conversion from prorenin (353, 440). The "converting enzyme," which hydrolyzes the decapeptide angiotensin I to the octapeptide angiotensin II, apparently is the same or is much the same as kininase II, which degrades the nonapeptide, bradykinin (102) (formed from the decapeptide, kallidin, by an aminopeptidase). Plasma renin activity and plasma bradykinin change concurrently and in the same purposeful (but actually opposite) direction in response to changes in sodium chloride balance (255, 267, 434). Interestingly, pancreatic kallikrein (free from trypsin, chymotrypsin, cathepsin D, and converting enzyme) released from pretreated human plasma protein fraction IV-4 is a pressor substance identical with angiotensin II. It was inhibited by an angiotensin II antagonist, not by converting enzyme inhibitor. Whereas the pressor substance was released at pH 4.0 to 6.0, depressor substance(s) were released at alkaline pH to 8.0. The investigators proposed a one-enzyme system capable of eliciting pressor or depressor activity from plasma, depending on a pH-sensitive "kinin-tensin enzyme system" (17).

In patients having essential hypertension, renal vein kinin concentration was not significantly correlated with renal vein renin activity, although both activities were significantly higher than those of normal individuals. After upright tilting, kinin concentration in renal venous blood decreased significantly while renin activity therein increased. Moreover, in patients with unilateral renal artery stenosis the venous plasma kinin output of the contralateral kidney (that had suppressed renin release) was higher than from the kidney with arterial stenosis (190) as though this were a homeostatic measure. These results support a reciprocal functional relationship between the two systems. Another communication has characterized malignant hypertension as a syndrome associated with low plasma kininogen and kinin potentiating factor (9).

Two other types of studies relevant to the interrelationship of the renin-angiotensin and the kallikrein systems may be of interest. First, an 8-year follow-up study in children showed an inverse relationship between blood pressure and urinary excretion of kallikrein (447). Second, urinary kallikrein excretion was similar in young normotensive S and R rats of the Dahl strain that had not been exposed to a high salt intake. On the other hand, kallikrein output was lower in the hypertensive S rats exposed to a high salt diet than in the similarly managed normotensive R strain at the time the hypertensive rats developed proteinuria, as though the reduc-

tion was secondary to renal damage and not a causal factor in the development of hypertension (385).

VIII. Integration of Renal Cortical Functions, Proximal and Distal Segments of the Nephron; Juxtaglomerular (JG) Apparatus and the Macula Densa

One more thought is presented before closing considerations of an interaction of the renin and kallikrein systems. Ordinarily, one is inclined to think of the proximal and distal segments of the nephron as though they were at separate poles of the kidney—albeit in the cortex—that they are only related in sequence as collections of more or less related contiguous structures (glomeruli, proximal convoluted tubules, the loop of Henle, and the structures distal thereto). Actually, the cortical representation of a nephron from afferent arteriole to collecting duct seems to function as a single integrated unit by virtue of the JG apparatus, the macula densa, and its adjacent special cells that bind them together structurally as well as functionally. On this basis, these complex structures become a functional unit of the renal cortex with its (their) own feedback and reciprocal systems for modulation of function. However, the extent to which the renin-angiotensin system is involved in renal autoregulation in animals having a macula densa (other than reduction in glomerular filtration rate) remains controversial (218).

IX. Prostaglandins (PG)

The trail of renal vasodilatory materials seemingly led to the kinins in the cortex and the prostaglandins in the medulla of the kidney until prostacyclin (PGI_2) came along, as will be developed (234).

A. Renomedullary Interstitial Cells, Site of Synthesis and Storage

Prostaglandin synthesis, as revealed by prostaglandin synthetase activity, was highest in the (rabbit) renal papilla, less in the outer medulla, and least in the cortex (228). The renomedullary interstitial cells responsible for most of the prostaglandin synthesis have been shown to possess pseudopodia that bring them in contact with the vasa recta, with the thick ascending limb of the loop of Henle, and with the collecting duct as judged by the high prostaglandin dehydrogenase activity of these latter structures (290). These fibroblast-like cells possess granules that contain prostaglandins (291). Arachidonic acid, from which prostaglandins are synthesized, seems to be stored in these droplets isolated from the papilla (323). Grown in tissue culture, these cells synthesize PGE_2, PGA_2, and $PGF_{2\alpha}$, the three prostaglandins of the renal medulla (283).

B. Systemic Plasma Concentration, Response to Sodium Loading

A systemic effect of PGA did not seem likely to contribute as by "deprivation" to blood pressure elevation, even if it was generated in the walls of the vessels (PGE_2 probably does not get into the systemic circulation sufficiently to be effective because of its rapid destruction in the lungs). However, high sodium intake caused systemic PGA_2 plasma concentration to fall and low sodium intake caused PGA_2 systemic plasma concentration to rise (231, 232, 450). This was more suggestive of a local vasoregulatory role at the site of release of the prostaglandins, as in the renal medulla. The observation that PGA_2 was all but undetectable in the blood of anephric patients also suggested that its origin was mostly renal (449). Nevertheless, unilateral renal artery constriction in dogs and humans increased renin activity in blood from that kidney and the resulting increased systemic angiotensin II increased PGE activity of venous blood from the contralateral kidney (88, 305, 318).

C. Relation to Renal Medullary Countercurrent Systems

It will be recalled that whereas the cortex of the kidney is "aerobic," the medulla is considered to have a lower oxygen tension, is "anaerobic." This may be occasioned by the necessarily long loops of the vasa recta, as the countercurrent exchange system of these vessels complements the countercurrent multiplier system of adjacent loops of Henle.

A local vasodilatory effect of increased prostaglandin release deep in the renal medulla might be expected to increase blood flow in the vasa recta (which is a small fraction of renal blood flow ordinarily) without necessarily altering pressure in the cortical vessels. The effect of such (increased) medullary renal vasodilation [as has been demonstrated in perfused, isolated kidney of the dog (195)] might be thought to decrease the effective countercurrent osmotic gradient within the vasa recta and in turn reduce, by diffusion, the gradient of the countercurrent multiplier system of the loop of Henle. The net "wash out" result would be to increase the apparent effectiveness of glomerular filtration on salt excretion and to reduce the effectiveness of the dependent antidiuretic hormone modulation of water back diffusion, resulting in an increased excretion of salt and water.

Conversely, an impaired production of PGE_2 has been reported to attend hypertension, as though it contributed (by "deprivation") to a direct systemic increase in vasoconstrictor tone (397). It seems tenable that reduced prostaglandin synthesis would contribute to volume expansion hypertension by way of increased medullary sodium gradient and a commensurate increase in fluid retention. Consistent with this thought, prostaglandin dehydrogenase activity (PG inactivation) was greater in the thick ascending limb of the loop of Henle and the medullary portion of the collecting duct during dehydration than hydration (290). When PGE_1 was perfused through isolated collecting ducts of the rabbit, it substantially inhibited the effect of the antidiuretic hormone on

water reabsorption, in that it inhibited water reabsorption per se (156).

D. Interaction of Prostaglandins and Renin-Angiotensin System

A vasodilatory effect with increased excretion of sodium, chloride, potassium, and water and without involving renin release can be demonstrated by the injection of PGE_1 into the renal artery (164, 199, 243, 416). However, renal vasoconstriction induced by the injection of angiotensin II into the renal artery (5) or stimulation of renal nerves to the afferent arterioles (94) can cause a fall in renal blood flow resulting in a release of prostaglandin-like vasodilatory substance into the renal vein.

Conversely, arachidonic acid, PGE_2, PGD_2, and PGI_2 (prostacyclin) participate in baroreceptor, macula densa, and α-adrenergic (but not β-adrenergic) renin release (145–147, 259, 285, 361, 425, 443). Blockade of prostaglandin synthesis by indomethacin decreases plasma renin activity (88, 338, 443) and blunts the increased renin secretion that attends hypotensive hemorrhage (361) or suprarenal aortic constriction (42a). Whereas isoproterenol (β_1-adrenergic)-induced renin release is independent of the prostaglandin system, propranolol plus indomethacin given together abolish the renin response to a low salt diet and to upright posture (131).

Of the prostaglandins, prostacyclin (PGI_2) is unique in being the most potent vasodilator (187, 275, 300, 426) and is formed from arachidonic acid in the renal vascular tree, particularly in the cortex and at the site of renin synthesis and storage (293, 399). Whereas PGE_2 is avidly extracted by pulmonary, renal, and hepatic tissue, PGI_2 is not (148). Consequently, PGI_2 has been suggested to be a potential circulating hormone (148, 275, 300); whether for renin release or in its own role as vasodilator is not as clear as is interest in the compound. Recently, however, reports of unaccountably longer action of prostacyclin than would be anticipated has led to the conjecture that a metabolite of PGI_2, 6-keto-PGE_1, may be responsible for some effects attributed to PGI_2 including renin release (327, 328, 433). Lack of an effect of PGI_2-specific antibodies injected into normotensive and spontaneously hypertensive rats may discount a role of circulating PGI_2 in systemic vasomotor regulation (299).

Prostaglandins have been implicated in renin malignant hypertension in rats by virtue of the attenuation by indomethacin of a rise in blood pressure induced by aortic ligation and a concomitant lowering of the elevated plasma renin activity (197, 198). On the other hand, there was no difference in prostaglandin excretion in the New Zealand and the Lyon strains of hypertensive rats from that of control rats that would suggest that these compounds played a primary role in these genetically hypertensive animals (32, 91). Concentration of PGE_2 was reported to be 60% lower in the renal papilla of the Dahl S rat than its normotensive R counterpart. A high linoleic diet brought up available arachidonic acid sufficiently to increase PGE_2 content of the papilla to "normal" in the S rat, delayed the development of hypertension in response to a high salt diet, and decreased the rise in blood pressure. The normotensive R rat also responded to the linoleic diet with an increased prostaglandin synthesis and under comparable circumstances always had a higher papillary prostaglandin concentration than the S strain (406). PGE_2 excretion was decreased in prehypertensive S rats compared to R rats as though it were involved in initiating hypertension (386). However, in adult rats there was no real difference in the response of SH, WKY, or Sprague-Dawley renovascular hypertension to PGI_2 (97). A difference between young (6 weeks) and older (18 weeks) SH rats stimulated by angiotensin II or arachadonic acid was the increase in thromboxane (TXA_2) production in young rats and in PGI_2 in the older animals (362, 363) as though they related to initiation and stabilization of elevated blood pressure, respectively.

E. Prostaglandin Depletion and Inhibition of Synthesis

That the prostaglandin synthetase inhibitor, indomethacin, can block prostaglandin release without affecting cortical blood flow (260) is reassuring of the foregoing associations. That an angiotensin II antagonist can block the effect of angiotensin (286) on prostaglandin release seems consistent, likewise. So does the observation that, in the rat, when prostaglandin synthetase-blocking concentrations of indomethacin are infused into the renal artery at rates that do not alter medullary plasma flow, the sodium and chloride concentration gradient increases some twofold (132).

However, the evidence that the stimulatory effect of angiotensin (5) or bradykinin (262) on the renal vascular response attributed to prostaglandins does not persist (increased medullary and inner cortical blood flow) makes it difficult to know whether one is dealing with a sustained action of prostaglandins or with their exhaustion. It is also difficult to know whether their purpose is for a sustained low level of medullary blood flow or for an induced response to substantial changes in systemic, hence renal, arterial blood pressure in response to stress (400) that call for changes in the capacity of the medulla to influence salt and water balance. Interpretation is made more difficult by differences in onset and duration of action of PGE_2 and PGA_2 and by the (increased) sensitivity of aldosterone release to PGA (111).

F. Furosemide and Indomethacin Interaction

On the strength that acute systemic volume depletion by sodium intake restriction might induce an elevation of PGA activity, there has been some exploration of whether the antihypertensive effect of furosemide might be due to an effect on prostaglandin release. The loop diuretic, furosemide, decreases hypertensive blood pressure and increases salt and water excretion, as do saluretic agents generally. It is reported that the prostaglandin

synthetase inhibitor, indomethacin, was capable of obtunding or preventing the hypotensive effect of furosemide when they were administered together. The natriuretic effect of the diuretic agent was decreased, likewise. Indomethacin, per se, had a slight effect on blood pressure (elevation) but no effect on sodium excretion in this small group of normotensive and hypertensive patients (309). This would seem to tie the antihypertensive effect of the potent diuretic agent, furosemide, to the prostaglandins, and perhaps it does, but the specificity of this pharmacodynamic interaction may be more seeming than real. Furosemide is reported to increase urinary excretion of PGE_2 in normotensive and hypertensive patients (1, 330).

There are aspects of the comparative pharmacology of furosemide that need to be developed in connection with the prostaglandins—its saluretic and antihypertensive effects. Furosemide (with and without indomethacin) at the dosage used in the aforementioned experiment (309) should have reduced the sodium, chloride, and urea concentration gradients from cortex to inner medulla (i.e., reduced osmotic gradient); this is the case at least in the canine kidney (143). Since the pseudopodia of the renomedullary interstitial cells responsible for the prostaglandins are in juxtaposition with the loop of Henle and the collecting tubules as well as the vasa recta (323), it seems reasonable to speculate that the increased excretion of PGE_2 reported above (1, 330) might be simply a washout, a reduction of prostaglandins in the medulla. This would have the same general effect (to increase blood pressure) as reduced prostaglandin synthesis by indomethacin. In other words, part of the inherent antihypertensive effect of furosemide might be offset by reduced medullary prostaglandin content, an effect in addition to the well known increase in renin release induced by saluretic agents, including furosemide. One more fact would be consistent with this speculation. Where thiazides and furosemide have been carefully compared as antihypertensive agents, the thiazides are more effective in lowering hypertensive blood pressure (15, 18, 113), yet they are less potent saluretic agents.

Is the fact that the thiazides do not affect the concentration gradient of the medulla (23), are not "loop diuretics" like furosemide and ethacynic acid (36, 54, 143), relevant to their greater antihypertensive effect? In this context the question is tenable. The thiazides work in the renal cortex, not the medulla (37). The thiazide antihypertensive effect would not be negated by indomethacin if the latter's inhibition of the antihypertensive effect of furosemide related specifically, not generally, to prostaglandin synthesis in the renal medulla. A recent clinical report indicated that indomethacin did not influence either the pharmacokinetics of hydrochlorothiazide or its effect on sodium, potassium, chloride excretion, or urine volume (429).

That thiazides induce an increase in renin output from the cortical JG cells has been known for many years (407). Could it be that the renin release by thiazides is mediated by a cortical prostaglandin, by prostacyclin—perhaps a local vasorenal renin activation? One could carry the speculation a step further if the furosemide-induced renin release was by the same cortical prostacyclin-mediated release of renin. Actually, it is conceivable that this mechanism could account for the observations that the antihypertensive effects of the β-adrenergic inhibitor, propranolol (95), and the essentially different saluretic thiazide could be obtunded by the administration of indomethacin (242, 424).

Such a conjecture could account for the decreased renovascular resistance by the corticovascular release of prostacyclin as an alternative to a thiazide effect on kallikrein. Kallikrein excretion was reported to be increased by hydrochlorothiazide from subnormal (hypertensive) levels to normal along with the decreased systemic blood pressure and reduced renovascular resistance (294).

A bothersome aspect of the indomethacin clinical data mentioned above (424) was the modest increase in weight of the patients when given indomethacin plus propranolol or thiazide, and its return to prior level when indomethacin was withdrawn. To be sure, the increased weight (interpreted here as volume expansion) coincident with indomethacin administration might be attributed to reduced prostaglandin influence on sodium and water excretion.

Another way of looking at the indomethacin experiments mentioned above is that even if neither propranolol nor hydrochlorothiazide had anything to do with prostaglandins per se, inhibition of PG synthesis might be anticipated to cause sufficient salt and water retention to obtund the antihypertensive effect of either type of drug. This indomethacin-induced weight gain was the same as the weight loss induced by sustained thiazide administration concurrent with blood pressure reduction and was somewhat less in the propranolol/indomethacin trials. In another context (431b), the difference that obtains between the antihypertensive effects has been thought to be due to thiazides having a more sustained duration of action than furosemide.

G. Excessive Renal Production and Bartter's Syndrome

That indomethacin can inhibit prostaglandin synthesis, can decrease excretion of sodium, and reduce plasma renin activity seems established (49, 92, 309). Thus, initial fluid retention and elevation of blood pressure are listed among its adverse reactions. On the other hand, in Bartter's syndrome, which includes hyperreninism and hyperaldosteronism (150, 177) (but not hypertension), indomethacin was effective in correcting the abnormality. In a recent report of siblings where much the same syndrome was attended by hypertension, the administration of indomethacin was required to normalize the plasma electrolyte picture and to complete the control of

blood pressure (81). Likewise, resistance to endogenous norepinephrine in Bartter's syndrome is reported to be reduced by indomethacin (365). Thus, excessive renal prostaglandin production was considered to be a part of the syndrome.

In Bartter's syndrome a circulating prostaglandin with the characteristics of prostacyclin, insensitivity to angiotensin, and a platelet defect correctable with indomethacin would favor PGI_2 rather than PGE_2 (382). However, in Bartter's syndrome an increased excretion of PGE_2 and of a metabolite of PGI_2, 6-keto $PGF_{1\alpha}$, has been reported (167).

X. Natriuretic Hormone

One more factor or group of factors considered to relate to hypertension has been reviewed (85, 250) as the natriuretic hormone or antinatriferic factor (222). Blood from volume-expanded rats (153), dogs, (51) and some patients (222) contains a low (500) molecular weight (and a higher weight, possibly precursor, substance) (166) that increases the renal excretion of sodium when injected into another animal. This increased sodium excretion is likely due to decreased reabsorption thereof by the nephron.

Whereas this activity was found in volume-expanded rats but not in normal control subjects (153), natriuretic activity is said to be present in both normal and hypertensive patients. The activity is as much as 24 times as great in hypertensive as in normotensive persons, however (86). Reasoning from their own data and Dahl's hypothesis that his salt-sensitive hypertensive rats were responding to a humoral substance (76), deWardener et al. have suggested that essential hypertension is due to inherited variability to excrete sodium. Difficulty in excreting sodium would be anticipated to expand volume and thusly stimulate a circulating sodium transport inhibitor. By inhibiting sodium-potassium dependent ATPase, it would decrease sodium transport across cell membranes, including vascular musculature and renal sodium reabsorption (87). The inhibition of sodium-potassium exchange in arteriolar musculature would be expected to increase intracellular sodium which would increase calcium and the tonus of the contractile elements (44, 332). This, in turn, would be anticipated to increase blood pressure if the calcium effect were sufficiently general and sustained.

A recent paper (250) describes a direct correlation between the ability of plasma from normotensive and hypertensive patients to stimulate glucose-6-phosphate dehydrogenase and blood pressure. Glucose-6-phosphatase activity of renal slices was considered an inverse correlate of Na-K-ATPase activity of the renal slice bioassay, hence the presence of a circulating sodium transport inhibitor.

Another interesting recent observation (320) was that when leukocytes from normotensive persons were incubated in plasma from hypertensive patients they acquired a ouabain-demonstrable impairment of Na-K-ATPase that was present in leukocytes from the donor hypertensive subjects. Leukocytes from normotensive subjects incubated in plasma from other normotensive individuals were not altered in this manner. This study does recall the Dahl parabiotic experiments with S and R rats mentioned previously (76) as a possibly analogous situation.

A. Relation to Na-K-ATPase

The effect has been attributed to inhibition of the sodium-potassium-dependent ATPase pump (173, 223, 249, 279) which is generally held to be responsible for maintaining the Na-K balance across the cell membrane—not just in the cells of the renal tubules, but more generally in vascular musculature and neuronal cells. Whereas the inhibition of sodium reabsorption is conceived to depress salt and water accumulation (reabsorption) by the nephron, inhibition of the ubiquitous membrane sodium-potassium ATPase might tend to increase intracellular sodium and induce increased vascular tonus (vasoconstriction). Where such a sodium hormone comes from, what it is, and its significance, are subjects of active investigation. The importance of such a circulating sodium transport inhibitor conceptually and the many associations that need be made should be kept in mind as one reads section XI.

XI. Cell Membrane: Sodium, Potassium Flux and Hypertension

A. Importance as Prognostic Aid in Hypertension

Today, the study of sodium and potassium flux across cell membranes of normotensive and hypertensive patients and animals has assumed immediate importance, although studies on the permeability of human erythrocytes to sodium and potassium go back at least 20 years (378). Their practical importance derives from the more general need to develop procedures for affirming the diagnosis of early essential hypertension. Still more desirable would be a reliable way of anticipating who among young normotensive children (of especially hypertensive parentage) is likely to become hypertensive. From the earliest days of thiazide antihypertensive therapy, the fact that the compounds were saluretic and so increased salt and water excretion left tenable the question of whether these drugs had some additional antihypertensive effect and whether there was a direct action of the saluretic thiazides on the vasculature as well as the increased excretion of salt and water that affected tonus of the arteriolar musculature, directly or indirectly (123, 264, 322, 404).

B. Relation of Sodium to Vascular Muscle Tonus

A detailed consideration of the relationship of sodium to arterial contractility and reactivity at a fundamental level may be found in other excellent reviews (126, 127).

The relationship of intracellular sodium to tonus of the vascular smooth muscle has been set forth clearly by the

concordant measurement in dogs of increased arterial vasoconstriction, decreased plasma sodium, and increased plasma potassium (determined with Na^+ and K^+ ion-specific electrodes) following intravenous injection of norepinephrine. The response of sodium movement into the vascular musculature with rise in arterial pressure occurred in a dose-response relationship in response to norepinephrine, and was demonstrated to follow epinephrine and vasopressin injection also. The vasodilation induced by acetylcholine or histamine was attended by increased sodium plasma concentration (129). The relationship of intracellular to extracellular sodium concentration to vascular smooth muscle activation can be demonstrated in vitro (128) and in vivo. For instance, resistance to blood flow decreased over a period of about 5 minutes in small vessels of the dog foreleg during transient local elevation of sodium concentration without altering systemic blood pressure. This was attributed to a reduction in difference in sodium concentration on the two sides of the cell membrane until equilibrium was reestablished (171). While these studies relating the ionic basis of electrical activity to tonus of vascular smooth muscle preceded by many years the work on sodium flux and concentration in erythrocytes and leukocytes of hypertensive and normotensive individuals, they are entirely relevant and deserve to be reviewed (125) in this context.

C. *Erythrocytes*

Whereas the sodium hormone interest has suggested that such an agent affects the critical sodium-potassium dependent ATPase, as mentioned in the foregoing section, other effort has centered on sodium-potassium co-transport and on sodium-sodium or sodium-lithium counter-transport—other characteristics of the cell membrane. This work has been done in the readily available erythrocyte or leukocyte, which has the virtue of not being particularly burdensome to the patient.

It may be relevant that the microviscosity of hydrophobic areas of erythrocyte membrane of SH rats is said to be increased compared to normal WKY rats. This characteristic of the spontaneously hypertensive rat is not seen in DOCA or renal clip renal hypertensive rats and so has been suggested to be of genetic origin, relating to monovalent cation transport and perhaps to calcium binding ability of the inner surface of the cell membrane (297). More relevant is the report that abnormal sodium extrusion from erythrocytes is compatible in humans with the expression of a single gene transmitted according to an autosomic dominant mode. That this is a genetic marker was affirmed in SH rats and H-prone-Na^+ sensitive Sabra rats. Actually, the reduction in net sodium flux when the rats were salt loaded was present before they developed a significant elevation of blood pressure (82).

1. Sodium-Lithium Counter-transport. The sodium-lithium counter-transport is ouabain-insensitive and has been likened to the Na^+-H^+ exchange at the renal brush border (20, 379). It is not statistically different in erythrocytes of normotensive and hypertensive Caucasian patients in the sense that sodium, potassium, and water content of the cells are not different (55). However, the maximum rate of sodium-stimulated lithium counter-transport was more than twofold greater in hypertensive male patients (diastolic >90 mm Hg) than in normotensive subjects, male or female, or in hypertensive female patients. In a small group of relatives of patients with essential hypertension there was a statistically greater mean value of lithium efflux than among the relatives of normotensive subjects. Counter-transport in red cells from several forms of secondary hypertension was not different from the mean values of the normotensive group (55, 56). The sodium-lithium transport system was reported recently to be increased in normotensive sons of hypertensive parents (435). What these studies might be interpreted to indicate is that the cell membrane of the male patient with essential hypertension is particularly sensitive to sodium-sodium counter-transport, that it may be heritable, that it anticipates, but is not due to, hypertension, and that there may be an endocrinological basis for this feature. Interestingly, the endocrinological basis may be better supported than the genetic factor by the report that the transport system was much higher in pregnant women than in nonpregnant normotensive or hypertensive women. The rise and decline in values was gradual over approximately 3 months. It was not present in placental cord blood (436).

2. Sodium-Potassium Co-transport. Others have described a sodium-potassium co-transport assay for essential hypertension based on Na:K flux ratio in sodium-loaded, potassium-depleted erythrocytes (70, 137–139, 181). Where they have been compared, it is essentially different from the Na-Li counter-transport (56). In Caucasians, a lower sodium-potassium net flux ratio is reported in 96.9% of essential hypertensive erythrocytes than from normotensive subjects (3.5%), or from patients having hypertension secondary to various pathological conditions (7.1%). Some 53.6% of young normotensive subjects born to parents of whom one was hypertensive had abnormally low net Na:K flux ratio; the incidence was 73.7% when both parents were hypertensive. When the Na-K co-transport of Caucasian subjects (in Paris) were compared with Ivory Coast black subjects, the hypertensive white patients had a substantially greater incidence of defective transport than unselected normotensive subjects (39%). The incidence of defective transport in unselected normotensive Ivory Coast Negroes was about the same (79%) as hypertensive white subjects (80%) and the incidence of defective transport among the hypertensive blacks was higher still; this reflects the high genetic propensity to hypertension in that population (140).

Net Na extrusion has been reported to be similar in normotensive subjects and secondary and benign hyper-

tensive subjects; the low net Na:K flux in benign hypertension was due to a greater K influx compared to control K influx per unit of time. However, the low Na:K flux in erythrocytes from patients with accelerated (malignant?) essential hypertension was due to a low Na extrusion rate and the K influx was not significantly different from that in control subjects (138). The difference between the benign and accelerated essential hypertension was attributed to a high net sodium influx in benign hypertension (this can be 20% to 40% greater than in normotensive subjects) and a low net extrusion rate for Na in accelerated hypertension (138). This is an interesting difference that may suggest the superimposition of the effect of pathology or exaggerated hormonal regulation in accelerated cases not ordinarily seen in early (benign) hypertension. The inability of the erythrocyte to extrude sodium normally in benign hypertensive subjects is not ouabain-sensitive (not Na:K ATPase dependent) but is furosemide-sensitive (characteristic of Na/K co-transport). In hypertensive subjects this Na:K co-transport is two or three times less than normal. Interestingly, a partial uncoupling of the furosemide-sensitive Na and K efflux was noted. This association of benign hypertension with a defect in sodium transport that is not ouabain-dependent (not Na-K-ATPase dependent) may indicate that the causal relationship of sodium hormone and Na-K-ATPase to essential hypertension may be too narrowly defined regarding action or scope (incidence). These many interactions may need more precise definition as they become better understood (410).

Sodium ion flux measurements yielded better discrimination than sodium content. BUN levels above 60 mg/100 ml caused a marked increase in intracellular Na^+ and Mg^{++} but not in K^+ (243). In the SH and WKY rats there were no differences in intracellular total sodium content, but intracellular Na^+ and Ca^{++} activity as measured by ion-specific electrodes was significantly higher in the SH than the WKY rats (244). Various other biochemical markers including calcium binding have served to distinguish spontaneously hypertensive rats from their normotensive genetic counterparts (84, 438).

D. Leukocytes

Sodium transport in the leukocyte appears to be correlated with blood pressure in essential hypertension compared with normotensive individuals (99), and in borderline hypertensive and normal subjects that have a family history of hypertension (13). This amounts to an increased intracellular sodium and lesser sodium efflux rate constant, as for erythrocytes. Subjects with high intracellular concentrations of sodium had a significantly greater excretion thereof after sodium loading (11). While these generalizations may be admissible, the variance in the values for sodium concentration reported suggest that further development of such methodology is needed before being accepted for diagnostic or prognostic purposes.

E. Effect of Thiazides

It is of interest and of some importance that the elevated sodium content of leukocytes from hypertensive patients can be reduced to normal by treatment with thiazide diuretics (149, 401) but not by some types of antihypertensive therapy (e.g., methyldopa and hydralazine) that do not increase electrolyte excretion with the exception of reserpine (12, 19). Earlier investigators who found that hydrochlorothiazide induced a greater loss of sodium than water deduced that the loss in vascular muscle tone (decreased hypertensive blood pressure) was due to reduced intracellular sodium content. That the hypotensive thiazide effect related to a reduced difference between intracellular and extracellular sodium concentration was seen when replacement of extracellular fluid with sodium-hypotonic fluid increased blood pressure. When volume was replaced by hypertonic saline the lower intracellular to extracellular sodium concentration ratio was sustained and blood pressure did not rise (130).

F. Na-K-ATPase, an Adaptive Function

Since the ouabain-sensitive Na-K-ATPase-dependent system seems an adaptive function of these cell membranes in patients (319) and Dahl rats (304) and since the Na-K co-transport is furosemide (saluretic) sensitive (422) (neither of them being blood pressure sensitive), it is not entirely clear, yet, whether either transport system is responding to the cells' environment or to the nature of its forebearers, or both. Regardless of this conjecture, the concepts that associate calcium accumulation with sodium in the cells generally, and relate the excitatory function of calcium thusly with increased vascular tone, cardiac activity and nerve conductance, etc. (44, 45), are helpful.

XII. Management of Hypertension

A. Need, General Statement

The more we look for an elevation of blood pressure among people of all ages and the more we lower our base line for normal pressure, the more hypertensive subjects we shall find. Not long ago a systolic pressure of 100 plus your age was considered reasonably normal. Today, pressures of 135/90 mm Hg are likely to command attention. As our means for anticipating, with reasonable precision, those normotensive siblings of hypertensive parentage who are likely to become hypertensive are perfected, another dimension of the problem will be set forth.

Only in the present day is there reasonable agreement as to what is actually a "normal" blood pressure for a child of given age, sex, stature, etc. (203, 331). Clearly, the familial characteristics of blood pressure can be tracked from early childhood to pubescence (207, 364, 446, 448), and into adult life. Elevated blood pressure, for that matter essential hypertension that may justify therapy, can begin early in life (180, 221, 241). For instance,

siblings of severe, essential hypertensive patients were some eight times more likely to have a diastolic pressure over 100 mm Hg by middle age than siblings in a family in which such history did not obtain (317).

A worthy objective is to prevent as well as to arrest or moderate the development of hypertension. The consequences of hypertension have been known much longer than has the treatment for it, both medically (316) and on an actuarial basis (237, 377). Indeed, until effective and safe drugs became available, it was not clear to everyone that lowering hypertensive blood pressure was good for the patient. Today there are excellent studies to the effect that lowering the level of hypertensive blood pressure decreases mortality and morbidity incident to hypertension (192, 326). It has been suggested that a reduction of blood pressure in a general population by 10 mm Hg might be a public health measure as important as treating all blood pressure above 135/90 (428). It has been pointed out that a consistent relationship between blood pressure and serious complications exists through the normal range to high blood pressure levels without showing critical values at which morbidity and mortality suddenly increase (204, 237, 238, 311). Although salt is emphasized herein, other risk factors include overweight, age, sex, cigarette smoking, hypercholesterolemia, diabetes, and left ventricular hypertrophy. The more of these that are combined in the same individual the greater the risk of a cardiovascular accident (155, 204).

B. Basic Aspects

Three basic aspects of the management of hypertension are the following: 1) a public awareness approach to arresting or retarding the development of hypertension; 2) a reliable methodology for anticipating among young people, even children, who is most likely to develop hypertension sooner or later; and 3) proper and adequate use of therapy.

1. Public Awareness Approach. Perhaps the phrase "a public awareness approach" to the management of hypertension may not be the best choice of words. What is meant is an approach not primarily dependent on drug therapy. It serves no purpose to argue whether this is sensible, or that a low salt diet is worthwhile in hypertension (93, 277, 367, 380). If everyone who qualified for therapy today and tomorrow presented himself for patient care, only the more serious cases could be handled as medical problems for lack of physician's time to care for them all. On the other hand, we know from Kempner's work (213) and before, that a "low-salt" diet is an effective way to decrease hypertensive blood pressure—if patient compliance can be relied on. In such excellent reviews as those by Freis (119, 120), by Meneely and Battarbee (265), and by Haddy (172), a moderate view is set forth that reducing salt intake from the 10 or 12 g a day to which we are exposed to 2 g or below would greatly reduce essential hypertension as a public health problem, although it be inadequate to control many hypertensive patients. The GRAS Select Committee has endorsed such a view (356), and the Food and Nutrition Board of the National Research Council recommended that dietary salt restriction, with saluretic therapy as appropriate, was a rational approach (65). Such is a reasonable goal, difficult to reduce to practice today, but attainable tomorrow. Why not today?

"Variety is the spice of life," or so the saying goes, but salt is the spice of foodstuffs—the most important, the most used. It is claimed that hypertensive patients use excessive amounts of salt if not cautioned, but so do many others who are normotensive. Three things are needed to lower sodium chloride intake: 1) There needs to be an ongoing more general awareness that excess salt intake can be as harmful to some individuals as a modest amount is essential to good health. It needs to be put forth convincingly to young people as well as adults. If our work in young and older SH rats can be translated to humans, in most instances vascular compliance in the young probably may be sufficient to accommodate the salt-induced volume expansion without the effect on blood pressure that obtains later in life (315). But the taste for salt is likely to be developed early, even with some infant formulations made palatable to the mother's taste. 2) Whereas it would be unreasonable to expect the food industry to reduce the palatability of their products, in many instances this could be sustained by substituting potassium chloride for part of the sodium chloride and by making use of the many spices and flavoring agents generally available. (Infants, rats, and humans will not thrive if the salt content of the diet is too low.) 3) Table salt having reduced sodium chloride content, such as 50% sodium chloride and 50% potassium chloride, is available in this country. It has been reported that sodium intake could be reduced 40% where this type of formulation replaced regular salt in food preparation (269). As cited in the reviews mentioned above and elsewhere, potassium supplementation of the diet has been shown to affect hypertension favorably in humans and rats (4, 28, 77, 245, 265, 306, 307). Moreover, these measures for salt reduction should be beneficial regardless of whether the consideration is of primary or secondary hypertension, or of genetic or other causal bases.

This approach is the subject of a community-based study on the feasibility and effects of reducing salt intake by the use of a salt mixture consisting of 65% sodium chloride, 25% potassium chloride, and 10% magnesium sulfate in the households of North Karelia, Finland (414) where the salt intake is uncommonly high (206). Previously, this group conducted a similar study of systematic detection, follow-up, and treatment that they reported was effective, and which resulted in favorable changes in morbidity and mortality as well as reduction in the blood pressure status of that population (343).

These general statements about public awareness of hypertension relate to populations such as ours. The response of the hypertensive individuals to these meas-

ures—salt restriction, weight reduction, etc.—may be unpredictable. The individual may or may not respond to reasonable salt restriction or weight reduction. Substituting potassium chloride for salt might be helpful to some but would not be in the best interest of one who has an undetected renal insufficiency. In other words, moderation is a proper principle but being aware of one's cardiovascular-renal status and responding appropriately thereto is a prudent practice. Recently, the question of whether mild hypertension should be treated was authoritatively reviewed (122).

2. Anticipation of Hypertension. As emphasized in the foregoing sections of this review, the importance of developing acceptable, reliable methodology for anticipating who is to become hypertensive cannot be overstated. Salt-balance and salt-loading stress tests have the disadvantage of requiring considerable patient participation. Flux studies on blood cells are acceptably "noninvasive" but are technically more demanding and need further development before the interaction of environment and heredity can be interpreted—but they do hold promise.

3. Therapy. Unquestionably, the greatest advance in the management of hypertension has been the development of usefully safe and effective therapy. To date these agents can be arranged in four general categories:

1. Diverse direct vasodilatory agents (217, 301), drugs that depress the response of vascular musculature to endogenous stimulation as by the adrenergic, renin, or sodium regulatory systems. This objective may be too fundamental to be attainable safely, but there is promise and precedent for such an objective. However, their effectiveness is likely to be offset to some extent by compensatory reflex responses of the cardiovascular moderating systems as well as salt and fluid retention (112).

2. Agents of individual attributes that moderate the adrenergic system from the hypothalamus, the sympathetic ganglia to the end organ and identified by its receptors as α- or β-antagonists. Of these, some of the β-blocking agents have been recently reported to prevent the development of hypertension in the SH rat (110, 151, 333) and to reduce mortality significantly when administered to patients subsequent to a first myocardial infarction in separate, large epidemiological studies (33, 403). This affirms previous smaller studies of such agents (79, 427). Whether they will prevent the development of initial infarcts by prior therapy remains to be established. Substantial, long-term trials have attested to the usefulness of present therapy (21, 120, 121, 193, 375, 412, 417, 418).

3. Inhibitors of the renin system, presently identified as peptide inhibitors of angiotensin II activity (383) or inhibitors of the converting enzyme for angiotensin II production from its precursors (141). For the present, the latter (nonpeptide) converting enzyme inhibitor is the more practical because it is active on oral administration. Aside from characteristics unique to specific compounds, agents from categories 2 and 3 are likely to be complementary when coadministered, because of the interactions of the two systems, as has been discussed. On the other hand, when used singly or together to reduce blood pressure their effectiveness may be offset to some extent by salt and water retention (340), as should be evident from the foregoing literature review.

4. The saluretic agents with their modulation of salt and water balance (35) are basic to the proper use of drugs that lower blood pressure by their effects on the cardiovascular system, for the reason that lowering blood pressure tends to increase the glomerulotubular imbalance that would appear to distinguish many hypertensive from normotensive individuals. Adaptation to the hypertensive role is set variously genetically at the level of the kidney and at the cells or systems responsible for the maintenance of vascular tone. Today it is possible with appropriate saluretic and antikaliuretic drugs to modulate the balance of sodium and potassium more appropriately than can be done with either alone (34).

Finally, primary hypertension is evidently a multifactorial, in most instances genetically based, aberration of the cardiovascular systems in which all control mechanisms interact to sustain a common purpose, homeostasis, even at the expense of more rapid deterioration of the heart and blood vessels—earlier obsolescence. We know this can be prevented by the proper use of agents to produce a more appropriate balance of systems to accomplish the physiological objective of adequate homeostasis at a less devastating blood pressure (375, 417, 418). Whereas it is hoped that primary, essential hypertension can be prevented or slowed in progression from childhood by dietary salt control without the early sustained use of drugs in most cases, the therapeutic management of hypertension, even secondary to renal disease (201), is based on much the same principles as set forth in these perspectives of essential hypertension.

XIII. Summary

One draft of this review started with the sentence, "Hypertension can be made to seem exceedingly complex or terribly simple." To this point most would agree with the first prepositional phrase. The author of a recent excellent review of hypertension (115) might agree that the greater the depth the less the light, with "depth" relating to comprehensive coverage of the vast literature on hypertension and "light" having to do with clarity of concept and principle.

We have alluded to the genetic aspects of essential hypertension as generally little more than a Gaussian distribution of blood pressure by families exaggerated by excess salt consumption. Some families tend to have higher blood pressure than others for one reason or another just as some families tend to be taller or heavier than members of other families. Consequently, a tendency toward hypertension of people or strains of rats has

developed one way or another. Environmental factors such as overeating or high salt intake can exaggerate a genetic or familial predisposition to obesity or to hypertension. Excessive food, fluid intake, and salt (as a condiment) are so much a part of the behavior patterns of cultured societies that they contribute by convenience to the exaggeration of such genetic predispositions.

Weight, height, blood pressure—all three tend to track together from early postnatal life to adolescence, so that cause and effect of their relationship may not be obvious. Even so, it is important that the genetic and environmental factors can be distinguished at this early age. We have discussed the response of normotensive and hypertensive subjects to salt loading. Their differences in sodium flux in erythrocytes and lymphocytes are characteristics that may be developed as tests prognostic of genetic essential hypertension. In the authors' view, this is the most evident important development that remains to be perfected in the diagnosis and management of hypertension.

To indicate a genetic basis for hypertension gives no insight as to why these people develop an elevated blood pressure more rapidly than those who may simply put on excess weight. Several models of hypertensive rats developed by selective mating seem to indicate a greater adrenergic modulation of the cardiovascular-renal system than their normotensive counterparts. In some instances hypertension develops "spontaneously" and on a standard commercial diet, as in the SH rat. In some rats, excess salt in the diet evokes the hypertension, as in the Dahl S strain. Stress, as by frustration (mental) or salt-induced volume expansion (physical) is sufficient to evoke an adrenergic increase in vasoconstrictor activity. Even change in posture of prehypertensive individuals is sufficient to excite a difference from normotensive subjects with respect to induced greater adrenergic and renin activity.

In this text the interactions of autonomic, renin, kinin, and prostaglandin systems have been discussed, particularly with reference to the homeostasis of renal blood pressure and flow and salt and water conservation. It is tempting to think of these opposing potent vasoconstrictor and dilatory systems as analogous to the coordinate function of skeletal muscle flexors and extensors that combine to control the fine movements of the hand of a musician, for example. Excessive function of any part of this redundant combination of systems seems sufficient to be reflected systemically with respect to blood pressure, such as tumors of the JG apparatus, reduced blood flow through a stenosed afferent renal artery, or within the kidney, the pheochromocytoma, Bartter's syndrome, or Conn's hyperaldosteronism.

Although we do not customarily think of many normal interactions of these systems in this way, their common cause seems to be for the physiological economy of salt and water, and for the maintenance of an adequate pulsatile arterial blood pressure. Pressure must be adequate to sustain tissue perfusion regardless of mass or volume and to sustain appropriate salt and water excretion under any of several circumstances where their reabsorption may be excessive, as e.g., by a greater (unbalanced) population of longer than shorter loops of Henle, the function of which may be seen increasingly inappropriate as vascular compliance becomes reduced with age.

Whereas the increased (hypertensive) arteriolar pressure may be adequate to these homeostatic purposes, the pulsatile nature of the pressure-volume relationship would seem an important contributory factor to induced early degenerative obsolescence of the blood vessel walls, as reflected in the greater incidence of cerebral vascular accidents for instance.

Thus, prevention of hypertension as by dietary control of weight and salt intake is definitely important from the standpoint of morbidity and life expectancy for all of us. It seems likely that the genetically predisposed individual may have greater difficulty in controlling blood pressure in this way, especially as he or she becomes older and vascular compliance decreases because of increasing age and elevation of pulsatile blood pressure.

When arterial blood pressure cannot be controlled by weight and volume (salt) regulation, the combined therapeutic modulation of vasoconstriction and volume reduction seems indicated. From the foregoing it is evident that reduced vasoconstriction alone, as by inhibitors of adrenergic control and/or angiotensin production, is likely to be offset by some fluid retention; or that the specific action of a saluretic agent to reduce salt and volume (regardless of whether such agents have a direct effect on vasculature) will be decreased by a tendency toward reflex vasoconstriction. Both forms of therapy, especially in combination, have proven impressively beneficial, but less so for the avoidance of acute coronary deaths. In contrast, the combination of β-blockers and saluretic agents may have some advantage in reducing the incidence of acute cardiac accidents.

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