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SALT IN HYPERTENSION AND THE EFFECTS OF DIURETICS

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Shortly after hypertension was recognized as a clinical disorder Ambard & Beaujard (1) in 1904 proposed that it was due to a failure to adapt to an excess of salt in the diet. In this country Allen (2) was the first to carry out careful dietary studies showing that severe restriction of salt in the diet reduced blood pressure in about 60% of hypertensive patients. Allen, like the French before him, believed that hypertension was due to an unknown renal defect with respect to the excretion of salt. His work was not generally accepted, however, and it was not until 25 years later that the dietary treatment of hypertension was finally popularized by Kempner (3) with his so-called rice-and-fruit diet. Whereas Kempner believed the antihypertensive effect of the diet was due primarily to protein restriction it was later demonstrated conclusively by Murphy (4) and by Watkin et al (5) that it was due to the extremely low sodium content of the diet. These clinical reports called attention to the importance of salt in the maintenance of hypertension, which in recent years has received additional strong support from epidemiological studies.

DIETARY SALT AND BLOOD PRESSURE IN UNACCULTURATED SOCIETIES

In our society there is a direct relationship between blood pressure and age. Blood pressure rises with advancing age and as a result the prevalence of hypertension also increases with age. However, surveys in unacculturated peoples in remote areas of the world have indicated that hypertension is rare or absent and that blood pressure need not rise with age. Prior and his

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associates (6) were the first to supply evidence that the low occurrence of hypertension in unacculturated peoples was due to greatly reduced salt intake. He compared two Cook Islands societies, the relatively unacculturated Pukapukans and the more acculturated Raratongans. In the former, urine sodium excretion was low and hypertension was uncommon. Among Raratongans, however, sodium excretion was considerably higher as was the occurrence of hypertension.

The relationship between sodium in the diet and height of blood pressure in unacculturated peoples has been confirmed by a number of investigators. In their investigation of six Solomon Island societies, Page and his associates (7) found a rise of blood pressure with age in the three most in contact with Western society and no rise in the three most unassimilated peoples. The differences correlated best with the intake of salt, the ingestion of which was considerably greater in the more acculturated populations. Maddocks (8) studied five populations in New Guinea. He found the sodium to potassium ratio to be much higher in the coastal dwelling people than in their more primitive neighbors of the New Guinea highlands. Hypertension was nearly absent among the highlanders and blood pressure did not rise with age. In the coastal dwelling populations, however, blood pressure rose with age and hypertension was common. Sinnet & Whyte (9) confirmed the rarity of hypertension in New Guinea highlanders and found their urinary 24-hr sodium excretion to average only 15 meq. By comparison, the urinary sodium excretion of Americans is about 200 meq per day. Oliver and his associates (10) found no rise of blood pressure with age among the Yanomamo Indians of Brazil. Their 24-hr excretion of sodium averaged only 1 meq. Plasma renin activity and aldosterone excretion were markedly elevated by our standards of normalcy which probably reflected a reduced extracellular volume secondary to the extremely low salt intake.

Both the clinical studies and the investigations of unacculturated peoples supply strong evidence that salt (more specifically sodium) plays an important role in the pathogenesis and maintenance of hypertension. Two important questions are left unanswered: (*a*) what is the mechanism by which salt produces hypertension and (*b*) why does only a fraction of our population become hypertensive when all ingest essentially the same amount of salt in the diet?

MECHANISM OF SALT-INDUCED HYPERTENSION

The mechanism by which salt promotes hypertension is unknown but there is considerable evidence to support Allen's thesis that a renal defect in salt handling is importantly involved. The evidence is derived from various lines of experimental evidence which are reviewed below.

The importance of the extracellular fluid volume (ECF) including plasma volume (PV) in experimental renovascular hypertension was first pointed out in 1953 by Ledingham (11) and by his associates Floyer & Richardson (12). Floyer & Richardson found that the relationship between the blood volume and the capacitance vessels was an important determinant of blood pressure levels in parabiotic rats with experimental hypertension. Ledingham (13) observed the following sequence of hemodynamic events during the development of renovascular hypertension: (*a*) retention of salt and water, (*b*) expansion of ECF and PV, (*c*) rise in central venous and right heart pressure, (*d*) increase in cardiac output presumably due to the Starling effect, and (*e*) rise in blood pressure. The elevated pressure brought about a diuresis with prevention of further expansion of ECF. Surprisingly, after several weeks total peripheral resistance rose and cardiac output returned to normal. The process that had begun as a high output hypertension evolved with time into a high resistance type resembling that seen in most forms of chronic hypertension. Ledingham postulated that the protracted increase in cardiac output caused vasoconstriction by inducing autoregulation of the resistance vessels. When this occurred cardiac output returned to normal because of the increased afterload.

The early sequence of events resulting in an increased cardiac output follows logically from the expansion in ECF and PV and requires no additional explanation. The direct relationship between blood pressure and the capacity of the kidney to excrete salt and water (pressure diuresis) can be clearly demonstrated in the isolated perfused kidney (14), although in the intact organism the relationship may be somewhat obscured by other influences. It is more difficult to explain the late rise in total peripheral resistance. If it is due to autoregulation why is its appearance so delayed? Autoregulation of the resistance vessels as we know it is characterized by a rapid response. Perhaps, it is better at this juncture to accept the fact of the slow resetting of total peripheral resistance and cardiac output but to leave unexplained its causation. Teleologically, the hypertension observed by Ledingham in renovascular hypertension appears to be a defense against the development of an excessive increase in ECF by meeting the need of the kidney for a higher perfusion pressure.

Ledingham's observations were soon confirmed by others using different experimental approaches. Licorice produces sodium retention and hypertension. Borst (15) postulated that the elevated blood pressure results from circulatory adjustments that occur in response to an increase in ECF. In human volunteers fed large amounts of licorice he observed a rise in central venous pressure and in cardiac output associated with the development of hypertension. The resulting pressure diuresis prevented the development of edema.

Guyton et al (16) produced a continued expansion of ECF by salt and water loading of dogs whose renal mass was reduced surgically. They observed the same sequence of events that had been described by Ledingham with an increase in cardiac output followed later by a rise of total peripheral resistance and a return of cardiac output to normal. Guyton concluded that the common denominator in the development of almost all forms of chronic hypertension is the intrinsic functional capacity of the kidney to excrete a salt and water load and prevent an overexpansion of ECF.

Several other observations lend support to this hypothesis. First, reduction of blood pressure with antihypertensive agents other than diuretics frequently results in an expansion of ECF and PV (17, 18). This expansion could result from reduction of blood pressure to below the level at which the kidney can maintain homeostasis of the ECF. Second, studies on the salt-restricted rice-and-fruit diet revealed that the fall in blood pressure was accompanied by a reduction of approximately 15% in ECF (4, 5). Third, the administration of thiazide diuretics also results in a fall of about 15% in ECF which is maintained over the long term and quickly rebounds when the diuretic is stopped (19). Fourth, as is described in more detail later, administration of thiazide diuretics continuously in hypertensive patients results first in a fall in cardiac output and blood pressure and a slight rise in total peripheral resistance. After several weeks, however, the total peripheral resistance falls and the cardiac output rises while blood pressure remains down (20). Tobian (21) has called this effect of the thiazide diuretics *reverse autoregulation* to indicate that long-term contraction of ECF results in opposite hemodynamic changes to that observed by Ledingham, Borst, and Guyton.

There are, of course, other possible mechanisms by which excessive salt in the diet may result in hypertension. Tobian (22) has found that the sodium and water content is increased in small arteries, thereby thickening the wall and possibly increasing total peripheral resistance. Haddy (23) has reviewed the evidence for the role of intracellular sodium in increasing smooth muscle tone. An increase in sodium within the muscle cell activates APTase and releases free ionic calcium which in turn triggers contraction. As yet, however, there is little evidence to support the role of intracellular sodium in the pathogenesis of essential hypertension, although an increase in the content of sodium has been reported in the leucocytes of hypertensive patients (24, 25).

Expansion of ECF and PV also has been shown to increase blood pressure responsiveness to pressor stimuli while reduction in ECF has the opposite effect (26, 27). These latter influences may play a role in supporting or aggravating the hypertension. Folkow et al have supplied evidence which

indicates that frequently repeated hypertensive insults from neurogenic causes can result in structural thickening of the arteriolar walls with a consequent increase in total peripheral resistance (28). Such pressor reactions will be exaggerated when the ECF and PV are expanded.

THE GENETIC SUBSTRATE

Genetic factors play an important role in the development of essential hypertension in both man and in spontaneous hypertension in rats. Dahl (29), a strong proponent of the high-salt theory of hypertension, developed by selective inbreeding two strains of rats. One, a salt-sensitive or "S" strain, exhibited hypertension with salt feeding; the other strain remained normotensive despite a high salt intake ("R" strain). Bianchi (30) developed similar strains of rats. Both investigators independently tested the hypothesis that the basic cause of the hypertension was a renal defect in the excretion of excess dietary sodium. Both (30, 31) found that replacing the kidneys of "R" animals with the kidneys of "S" rats led to hypertension in the latter when they are fed a high-salt diet. The corollary also was true; transplantation of kidneys of "R" rats into "S" animals prevented the development of hypertension in the latter.

These crucial experiments in the rat provide strong evidence that the kidney is the seat of the genetic fault in salt handling that leads to spontaneous hypertension in the rat. Recently, Tobian (32) has supplied further evidence implicating the kidney in rats with spontaneous hypertension. He perfused the isolated kidneys of Dahl "S" and "R" rats with blood at different levels of perfusion pressure. These experiments were carried out in young rats while the "S" animals were still in the prehypertensive stage. At every level of perfusion pressure the "R" kidneys excreted more sodium and water than did the "S" strain. Comparable urine volumes and sodium excretion rates were obtained only when the perfusion pressure was raised significantly higher in the "S" kidneys than in the "R" strain.

What is the nature of the genetic renal defect in the "S" rats that demands a higher perfusion pressure in order to maintain homeostasis of the ECF in response to a high salt intake? The explanation has proven to be remarkably elusive. None of the well-known sodium and water control mechanisms such as the renin-angiotensin-aldosterone system or antidiuretic hormone are sufficient to account for the excretory deficiency (16). Perhaps there is a structural or functional alteration of renal tubular cells or a change in the counter exchange gradient or involvement of the poorly understood "third factor" in the control of sodium excretion. Any explanations at this point must be purely hypothetical. It is also unknown at this time whether a similar renal defect exists in humans with essential hypertension.

MECHANISM OF ANTIHYPERTENSIVE ACTION OF DIURETICS

As originally proposed by Dustan (33) and by Wilson & Freis (19), the antihypertensive effect of the thiazide diuretics was dependent on a reduction in ECF including PV. Wilson and I observed reduction in ECF for as long as 6 months of continuous treatment with chlorothiazide. When the diuretic was discontinued following long-term treatment, there was a prompt return of ECF to or above pretreatment levels. Both groups of investigators observed a reduction in cardiac output and a rise in total peripheral vascular resistance during short-term treatment with chlorothiazide. These results seemed consistent with a direct volume depleting effect with resulting decrease in venous return and cardiac output.

It was not long after, however, that Conway & Lauwers (34) reported differing hemodynamic effects during long-term treatment with chlorothiazide. Although they confirmed the acute reductions in ECF and cardiac output, Conway & Lauwers reported a return of both ECF and cardiac output to essentially control levels after several weeks of continuous treatment. These authors postulated that chlorothiazide reduced blood pressure by volume depletion during short-term administration and by a vasodilator action in the chronic phase of treatment. The development of diazoxide at this time, which is a chemically related vasodilator agent, lent further support to their proposal. This dual view of the antihypertensive action of the thiazide diuretics is currently accepted in most pharmacological textbooks.

Later investigators, however, were able to confirm only part of the observations of Conway & Lauwers. They confirmed that the reduction of cardiac output returned toward normal after several weeks whereas total peripheral resistance was reduced (20). On the other hand, Conway & Lauwers's claim of a return of ECF to normal has not been corroborated. Tarazi et al (35) found that ECF and PV remained reduced as did Leth (36) even after many months of continuous treatment. Recently, Shah et al (37) in this laboratory confirmed that whereas ECF remained reduced during long-term treatment cardiac output returned toward normal after four to six weeks of treatment and total peripheral resistance fell.

Both the acute and chronic effects of thiazides on volume and central hemodynamics appear to have been finally clarified. The explanation for the delayed reduction in total peripheral resistance, however, is still unclear. That it is due to a vasodilator effect of the thiazide diuretics seems unlikely for several reasons. First, a direct vasodilator action of the diuretic thiazides similar to that seen with diazoxide has not been convincingly demonstrated. Second, nonthiazide diuretics such as chlorthalidone ticrynafen and the

loop diuretics also will reduce blood pressure providing they are given in sufficient doses to maintain a reduction in ECF. A continued reduction in ECF appears to be essential for the antihypertensive effect. Third, it seems unlikely that the thiazides would reduce blood pressure by one mechanism initially and by another completely different mechanism later on. Fourth, it has been shown above that diets severely restricted in sodium also reduce ECF and PV by the same percentage as the diuretics. It seems reasonable to assume that the mechanism of the antihypertensive effect both short and long term is similar in the case of both salt restriction and diuretics and is probably volume dependent.

Recognizing both these considerations and the findings of Ledingham, Borst, and Guyton in experimental forms of hypertension, Tobian (22) has proposed the concept of *reverse autoregulation* to explain the long-term effects diuretics. This concept would apply equally well to low-sodium diets. In the experimental hypertensions the expansion of ECF leads initially to an increase in cardiac output and rise in blood pressure. After several weeks the total peripheral resistance rises presumably due to autoregulation of the resistance vessels while cardiac output falls back to normal. According to Tobian the reverse occurs with continued administration of diuretics. The reduction in ECF and PV results initially in a reduction of cardiac output. After several weeks, however, the resistance vessels "autoregulate" to reduce the total peripheral resistance, and the decreased afterload on the left ventricle permits cardiac output to rise toward the pretreatment level.

The above hypothesis provides a single unifying concept to explain the sequence of hemodynamic events that result in either a rise of blood pressure with excess salt and water loading in susceptible individuals or a reduction in blood pressure with salt and water excretion induced by diuretics. The hemodynamic changes found after short- and long-term thiazide administration are, in fact, the mirror image of the sequential changes that occur during the induction of the experimental hypertensions.

There are other possible mechanisms that can be invoked to explain the antihypertensive effects of diuretics. Following chlorothiazide the pressor response to infused norepinephrine or angiotension II is reduced while the depressor response to trimethaphan is enhanced (26, 27). Normal pressor responsiveness to norepinephrine is restored by reexpansion of plasma volume with salt-free dextran (38) suggesting that the reduced pressor responsiveness after diuretics is secondary to decreased volume.

The baroreceptor mechanism also may contribute to the antihypertensive response to thiazide diuretics. Both aging and chronic hypertension result in structural changes that reduce the distensibility of the carotid artery and aortic arch. Baroreceptor responses to either pressor or depressor stimuli tend to become less brisk and effective (39, 40). Moderate decrease in PV

may not be adequately buffered in the presence of stiff carotid arteries. This could explain the observation that young normotensive subjects respond to chlorothiazide with an increase in heart rate but no fall in blood pressure suggesting a brisk baroreceptor response (41) whereas elderly normal subjects show some reduction of blood pressure without much change in heart rate (42). Such faulty buffering may be due to the reduced compliance of the large arteries in the presence of aging or hypertension.

Still another hypothesis concerning the antihypertensive effect of thiazide diuretics involves the loss of either sodium alone (43) or of sodium and water in vascular smooth muscle. However, Tobian et al (44) could find no change in the electrolyte composition of small arteries or of their water content after chlorothiazide. Also, no changes in the electrolyte concentration of the tissues were found by other investigators in intact (45) or nephrectomized (46) animals following this drug. Furthermore, the early studies in man indicated that the net sodium loss could be accounted for by the loss of extracellular fluid volume alone and that sodium and water were lost from this space in isotonic proportion (19). More recently, diuretic-unresponsive hypertensive patients in chronic renal failure who required maintenance hemodialysis were treated with thiazides alternating with placebos at monthly intervals (47). In the absence of a diuretic effect there was no significant fall in blood pressure with the diuretic. These authors concluded that natriuresis is essential for the antihypertensive action of the diuretics and that there was no evidence for a direct vasodilator effect.

THE "CAMEL'S HUMP" EFFECT

When the thiazide diuretics are administered continuously the reduction in ECF and PV is essentially complete after 48 to 72 hr. The total loss is approximately 2 liters of ECF with associated PV (19) and this reduction is approximately maintained without further losses for as long as the diuretic is maintained (19, 35). Apparently, compensatory mechanisms come into play to prevent further losses of ECF. Such mechanisms appear to be those that usually operate during dehydration or dietary sodium restriction. The renin-angiotensin-aldosterone system is activated because of the volume depletion with elevations of plasma renin activity and aldosterone excretion rates. The fall in blood pressure and therefore renal perfusion pressure also will contribute to the arrest of further salt and water loss, and there may be other still unknown forces involved.

Hypertensive patients are able to function quite normally with this degree of reduction of ECF as do patients on the rice-and-fruit "no-salt" diet. Similarly, unacculturated peoples with restricted salt intake exhibit great physical stamina and strength. Thus, the approximately 2 liters of ECF

depleted by diuretics and "no-salt" diets does not seem to be essential for the health and well-being of the individual.

What is the purpose of this excess ECF and why does man have a salt craving? Perhaps the excess ECF serves a function similar to the camel's hump. It represents a reserve of several liters of isotonic fluid that can be drawn on in any condition that would result in either blood loss or dehydration due to diarrheal diseases, water deprivation, or other causes.

CONCLUSIONS

Whatever its mechanism the habit of eating salt in excess and, thereby, maintaining a chronic expansion of ECF appears to lead to the development of hypertension in susceptible individuals. While the nature of the susceptibility has still not been determined in man the available evidence in spontaneously hypertensive rats suggests that it involves a defect in the salt and water excretory capacity of the kidney. The defect appears to be inherited and it probably worsens with age.

Diuretics lower blood pressure by enhancing the salt and water excretory capacity of the kidney which, in turn, results in a reduction in ECF. The sequence of hemodynamic events following institution of diuretics is complex. The initial fall in blood pressure is associated with a decrease in cardiac output and a rise in total peripheral resistance. With continued treatment this condition is reversed with a decline of resistance and a return of output toward normal. The delayed fall in resistance does not appear to be due to any direct vasodilator action of the diuretic but rather to a still undermined cardiovascular adjustment to a prolonged decrease in ECF.

Literature Cited

1. Ambard, L., Beaujard, E. 1904. Causes de l'hypertension arterielle. *Arch. Intern. Med.* 1:520–33
2. Allen, F. M. 1925. *Treatment of Kidney Disease and High Blood Pressure.* Morristown, NJ: The Psychiatric Inst. 206 pp.
3. Kempner, W. 1948. Treatment of hypertensive vascular disease with rice diet. *Am. J. Med.* 4:545–77
4. Murphy, R. J. F. 1950. The effect of "rice diet" on plasma volume and extracellular fluid space in hypertensive subjects. *J. Clin. Invest.* 29:912–17
5. Watkin, D. M., Fraeb, H. F., Hatch, F. T., Gutman, A. B. 1950. Effects of diet in essential hypertension. II. Results with unmodified Kempner rice diet in fifty hospitalized patients. *Am J. Med.* 9:441–93
6. Prior, A. M., Evans, J. G., Harvey, H. P. B., Davidson, F., Lindsey, M. 1968. Sodium intake and blood pressure in two Polynesian populations. *N. Engl. J. Med.* 279:515–20
7. Page, L. B., Danion, A., Moellering, R. C. Jr. 1974. Antecedents of cardiovascular disease in six Solomon Islands societies. *Circulation* 49:1132–46
8. Maddocks, I. 1967. Blood pressure in Melanesians. *Med. J. Aust.* 1:1123–26
9. Sinnet, P. F., Whyte, H. M. 1973. Epidemiological studies in a total highland population, Tukisenta, New Guinea. Cardiovascular disease and relevant clinical, electrocardiographic, radiological and biochemical findings. *J. Chronic Dis.* 26:265–90
10. Oliver, W. J., Cohen, E. L., Neel, J. V. 1975. Blood pressure, sodium intake and sodium related hormones in the

Yanomamo Indians, a "no-salt" culture. *Circulation* 52:146–51
11. Ledingham, J. M. 1953. Distribution of water, sodium and potassium in heart and skeletal muscle in experimental renal hypertension in rats. *Clin. Sci.* 12:337–49
12. Floyer, M. S., Richardson, P. C. 1961. Mechanism of arterial hypertension. Role of capacity and resistance vessels. *Lancet* 1:253–55
13. Ledingham, J. M., Cohen, R. D. 1963. The role of the heart in the pathogenesis of renal hypertension. *Lancet* 2:979–81
14. Selkurt, E. D. 1951. Effects of pulse pressure and mean arterial pressure modifications on renal hemodynamics and electrolyte and water excretion. *Circulation* 4:541–56
15. Borst, J. G. G., Borst, DeG. A. 1963. Hypertension explained by Starling's theory of circulatory homeostasis. *Lancet* 1:677–82
16. Guyton, A. C., Coleman, T. G., Cowley, A. W., Manning, R. D. Jr., Norman, R. A., Ferguson, J. D. 1974. A systems analysis approach to understanding long-range arterial blood pressure control and hypertension. *Circ. Res.* 35:159–76
17. Hansen, J. 1968. Alpha methyldopa (Aldomet) in the treatment of hypertension. The effects of blood volume, exchangeable sodium, body weight and blood pressure. *Acta Med. Scand.* 183:323–27
18. Hammer, J., Ulrych, M., Freis, E. D. 1971. Hemodynamic and therapeutic effects of guancydine in hypertension. *Clin. Pharmacol. Ther.* 12:78–90
19. Wilson, I. M., Freis, E. D. 1959. Relationship between plasma and extracellular fluid volume depletion and the antihypertensive effect of chlorothiazide. *Circulation* 20:1028–36
20. Lund-Johansen, P. 1970. Hemodynamic changes in long-term diuretic therapy of essential hypertension. *Acta Med. Scand.* 187:509–18
21. Tobian, L. 1974. How sodium and the kidney relate to the hypertensive arteriole. *Fed. Proc.* 33:138–42
22. Tobian, L., Binion, J. 1952. Tissue cations and water in arterial hypertension. *Circulation* 5:754–58
23. Haddy, F. J. 1974. Local control of vascular resistance as related to hypertension. *Arch. Intern. Med.* 133:916–31
24. Edmondson, R. P., Thomas, R. D., Hilton, P. J., Patrick, J., Jones, N. F. 1975. Abnormal leucocyte composition and sodium transport in essential hypertension. *Lancet* 1:1003–5
25. Araoye, M. A., Khatri, I. M., Yao, L. L., Freis, E. D. 1978. Intracellular sodium in hypertensive patients. *Clin. Res.* 26:53A (Abstr.)
26. Wanko, A., Freis, E. D. 1958. Altered vascular responsiveness following chlorothiazide or mercurial diuresis in normotensive subjects. *Circulation* 18:792 (Abstr.)
27. Reid, W. D., Laragh, J. H. 1965. Sodium and potassium intake, blood pressure and pressor response to angiotensin. *Proc. Soc. Exp. Biol. Med.* 120:26–29
28. Folkow, B., Hallback, M., Lundgren, Y., Sivertsson, R., Weiss, L. 1973. Importance of adaptive changes in vascular design for establishment of primary hypertension studies in man and in spontaneously hypertensive rats. *Circ. Res.* 33: Suppl. I, pp. 1–2
29. Dahl, L. K. 1972. Salt and hypertension. *Am. J. Clin. Nutr.* 25:231–44
30. Bianchi, G., Fox, U., DiFrancesco, G. F., Giovannetti, A. M., Pagetti, D. 1974. Blood pressure changes produced by kidney cross-transplantation between spontaneously hypertensive rats (SHR) and normotensive rats (NR). *Clin. Sci. Mol. Med.* 47:435–38
31. Dahl, L. K., Heine, M., Thompson, K. 1974. Genetic influence of the kidneys on blood pressure. Evidence from chronic renal homografts in rats with opposite predispositions to hypertension. *Circ. Res.* 40:94–101
32. Tobian, L., Lange, J., Azar, J. T., Koop, D., Coffee, K. 1977. Reduction of intrinsic natriuretic capacity in kidneys of Dahl hypertension-prone rats. *Circulation.* III:240 (Abstr.)
33. Dustan, H. P., Cumming, G. R., Corcoran, A. C., Page, I. H. 1959. A mechanism of chlorothiazide enhanced effectiveness of antihypertensive ganglioplegic drugs. *Circulation* 19:360–65
34. Conway, J., Lauwers, P. 1960. Hemodynamic and hypotensive effects of long term therapy with chlorothiazide. *Circulation* 21:21–27
35. Tarazi, R. C., Dustan, H. P., Frohlich, E. D. 1970. Long-term thiazide therapy in essential hypertension. *Circulation* 41:709–17
36. Leth, A. 1970. Changes in plasma and extracellular fluid volumes in patients with essential hypertension during long term treatment with hydrochlorothiazide. *Circulation* 42:479–85

37. Shah, S., Khatri, I., Freis, E. D. 1978. Mechanism of antihypertensive effect of thiazide diuretics. *Am. Heart J.* 95:611–18
38. Merrill, J. P., Gumond-Baldo, A., Giordano, C. 1958. The effect of chlorothiazide on norepinephrine response in human hypertension. *Clin. Res.* 6:230 (Abstr.)
39. Freis, E. D. 1961. Valsalva maneuver. In *Symposium on the Pathogenesis of Essential Hypertension.* Prague: State Med. Publ. House. 229 pp.
40. Finnerty, F. A. Jr., Tuckman, J., Hajjar, G. C. 1959. Changes in heart rate during levarterenal infusion; an index of arterial elasticity. *Circ. Res.* 7:565–70
41. Freis, E. D., Wanko, A., Wilson, I. M., Parrish, A. E. 1958. Chlorothiazide in hypertensive and normotensive patients. *Ann. NY Acad. Sci.* 71:450–55
42. Hoobler, S. 1966. Antihypertensive effects of diuretics. In *Antihypertensive Therapy. Principles and Practice,* ed. F. Gross. Heidelberg: Springer. 632 pp.
43. Friedman, S. M., Nakashima, M., Friedman, C. L. 1960. Relation of saluretic and hypotensive effects in the rat. *Am. J. Physiol.* 198:148–52
44. Tobian, L., Janecek, J., Foker, J., Ferreira, D. 1962. Effect of chlorothiazide on renal juxtaglomerular cells and tissue electrolytes. *Am. J. Physiol.* 202:905–8
45. Weller, J. M., Haight, A. S. 1963. Effect of chlorothiazide on blood pressure and electrolytes of normotensive and hypertensive rats. *Proc. Soc. Exp. Biol. Med.* 112:820–25
46. Orbison, J. L. 1962. Failure of chlorothiazide to influence tissue electrolytes in hypertensive and non-hypertensive nephrectomized dogs. *Proc. Soc. Exp. Biol. Med.* 110:161–64
47. Bennett, W. M., McDonald, W. J., Kuehnel, E., Hartnett, M. N., Porter, G. A. 1977. Do diuretics have antihypertensive [redacted] independent of natriuresis? *harmacol. Ther.* 22:499–504