WHY DO THIAZIDE DIURETICS LOWER BLOOD PRESSURE IN ESSENTIAL HYPERTENSION?[1,2]

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This review must have an aura of apology about it, since it does not deliver the genuine nugget which is our goal. Oral diuretics, such as the thiazides or chlorthalidone, will indubitably lower the blood pressure of most patients with essential hypertension (1, 2). There are more than a hundred medical articles attesting to this. Since the author treats hypertensive patients, he can abundantly confirm these reports. In moderately large doses, these drugs by themselves will drop the blood pressure of most patients with primary hypertension. Furthermore, these drugs enhance the antihypertensive effect of all other hypotensive drugs. In this review an attempt will be made to explain this important drug effect, but the ultimate explanation is still lacking (hence, the apology).

The pure effect of these drugs can best be brought out when they are used alone. If the diuretic agents are taken daily by mouth at a dose level which produces a half maximal or three-fourths maximal diuresis, the blood pressure of hypertensive patients gradually begins to drop, and after two weeks it is often 30 mm lower in systolic pressure and 20 mm lower in diastolic pressure. With continued administration of the drug, the blood pressure is maintained at the lower level almost indefinitely. Very little tolerance to the drug is seen. Additional antihypertensive drugs can be subsequently added to the regimen and their effect is enhanced in the presence of the thiazide medication.

When the thiazides are first administered, they have their usual diuretic action and there is an increased excretion of sodium and water. In some parts of the renal tubule, there is a diminished reabsorption of filtered sodium and water, which leads to the diuresis. The mechanism here is in dispute. Dirks et al. (3) have noted in micropuncture studies of dog kidney that inulin concentrations in proximal tubular fluid are the same in thiazide-treated dogs as in nontreated controls. This would suggest that the actual "diuresis" is not occurring in the proximal convoluted tubule. On the other hand, Ullrich (4), using the split-oil-droplet technique in micropuncture studies, finds that thiazide diuretics greatly diminish the reabsorption of sodium and water from segments of proximal convoluted tubule. There is a way to reconcile partially these seemingly opposite views. It is quite possible

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that the thiazide diuretics do inhibit sodium reabsorption in the proximal tubule. With continuing glomerular filtration, this would tend to increase the amount of fluid remaining in the proximal tubule and would distend the tubule and increase its cross-sectional area. Gertz (5), Rector (6), and Windhager (7) have each put forth data indicating that an increase in the cross-sectional area of the proximal tubule enhances sodium reabsorption in that tubule. Hence, if the initial effect of the thiazide is to inhibit sodium reabsorption, the subsequent distention of the proximal tubule would tend to have the opposite effect, and one effect might cancel out the other. This could reconcile the seemingly opposite findings of Dirks and Ullrich. It is also possible that the volume-depleting tendency of the diuretic has the effect of enhancing proximal reabsorption of sodium. This effect would tend to cancel out a direct inhibitory action on sodium reabsorption in the proximal tubule. Further down the nephron, particularly in the distal convoluted tubule, the effect of the thiazide in inhibiting sodium reabsorption becomes manifest and a diuresis occurs. The effect of the thiazide on the ascending limb of the loop of Henle is not known for certain. However, it seems likely that the thiazide drugs do not strongly inhibit sodium reabsorption in the ascending limb as do ethacrynic acid or furosemide. A recent detailed review of the diuretic action of these drugs by Baer & Beyer is available (8).

When the thiazides are given daily to man, the sodium diuresis occurs and causes a lowering of the volume of blood and extracellular fluid (9–11). There is a concomitant decrease in the cardiac output (12). The drop in extracellular fluid volume stimulates an increased rate of renin release (13) and increases sympathetic outflow (14). During this phase, patients often complain of lightheadedness on standing, and excessive fatigue. These unwanted side effects can be avoided if the dose of thiazide is started at a low level and gradually increased over a four-week period. After about a week of continuous treatment, an adaptation begins. The diuretic effect of the drug gradually diminishes and a positive sodium balance makes its appearance. Cardiac output comes back to normal. The extracellular fluid volume and blood volume begin to increase and within six months are almost back to normal pretreatment levels (10, 11). It is not certain that these volumes actually do reach pretreatment levels, since there are fairly large errors in the method of estimating them. However, Bourgoignie et al. (15) have shown that the plasma renin levels are high during the early phase of thiazide administration and come back into the normal range after six weeks of treatment. This constitutes evidence that the extracellular volumes are being repleted to a large extent. Again, there is also a fairly large error in the renin method and one can't be sure that renin secretion returns completely to normal. We fed some normal rats chlorothiazide for five weeks and found that the treated animals had a significantly higher juxtaglomerular count than did the untreated controls (16). This would indicate that some slight volume deficit remains, even after prolonged treatment with thiazide. Conway & Lauwers felt that body water remained diminished during the chronic administration

of thiazide, even though extracellular fluid volume had returned almost to normal (10). Moreover, patients seem to lose about 1.2 kg of weight after taking thiazides for six to eight weeks (17). This weight is promptly regained when the drug is discontinued. The thiosulfate space, which provides an estimate of extracellular fluid volume, was also diminished about 1.1 liters, on the average, in patients taking thiazides for six to eight weeks (17). This corresponds very well with the 1.2 kg weight loss and indicates a drop in extracellular fluid volume. Winer (17) also found an average drop of 137 mEq in total exchangeable sodium in these same patients after taking thiazides for six to eight weeks. This figure would also roughly fit in with the loss of a liter of extracellular fluid and the loss of a kilogram of body weight. The plasma volume in these patients was also decreased 155 ml on the average, a drop of 6 per cent. This lowering of plasma volume would tend to potentiate the action of other hypotensive drugs which act by increasing the volume in the veins and venules. Hypotensive drugs of this type would include the ganglionic blockers, guanethidine, and bethanidine.

The arterial pressure of patients with essential hypertension goes down when thiazides cause an early drop in blood volume and extracellular fluid volume. However, it stays down when these volumes come back to near normal. Moreover, the same thiazide given in a similar manner to a normotensive subject also temporarily lowers blood volume and extracellular fluid volume, but not blood pressure. The enhancement of sodium excretion by thiazides is seemingly a key part of their antihypertensive action. When Winer (17, 18) added 20 g of salt per day to the diet of hypertensive patients who had been on thiazide medication for one to eight months, this was enough to overcome the negative sodium balance and completely abolished the antihypertensive effect of the thiazides. When only 6 to 12 g of salt were added, the hypotensive effect of the thiazides continued unabated. Evidently the diuretic drugs could overcome the repleting effect of this smaller amount of salt.

Whereas 20 g of salt per day could negate the blood pressure-lowering effect of thiazides, expansion of plasma volume with 500 cc of a 6 per cent dextran in glucose solution could not. This amount of dextran solution was used to expand the plasma volume of hypertensive subjects who had taken thiazides for several months. It enlarged plasma volume to a level about 161 ml greater than that which existed before thiazide therapy was begun. This expansion with dextran was able to overcome about 28 per cent of the total drop in systolic pressure that had occurred as a result of thiazide therapy (17). Thus, in these patients the thiazide had reduced systolic pressure about 32 mm Hg on the average. At this point, expansion with dextran solution raised the systolic pressure only 9 mm Hg on the average, thus reversing only a small fraction of the hypotensive effect of the thiazide. Moreover, the expansion with dextran did not significantly raise the diastolic pressure at all in these hypertensive patients taking thiazides. These results would suggest that hypertensive patients on long-term thiazide therapy have a slight de-

crease in blood volume. The dextran infusion can correct this, but nevertheless the diastolic pressure does not rise and the systolic pressure rises only slightly. Thus, the hypotensive effects of the thiazides are only slightly overcome by a temporary normalization of blood volume. However, they can be completely overcome by massive salt repletion. One can infer from this that the effect of the thiazides on sodium economy is at the root of their antihypertensive action, which is essentially a decrease in peripheral resistance. Continuous thiazide medication also produces a negative potassium balance of about 165 mEq, but this diminution of body potassium is not decisive in the lowering of blood pressure (17). The concentration of sodium in the plasma of hypertensive patients receiving thiazides is normal (17).

It is not likely that a diuretic thiazide acts as an immediate, direct vasodilating drug in the lowering of blood pressure. If it did, one would expect it to lower blood pressure in normotensive subjects, and this does not occur. Since hypertensive subjects have an increased content of sodium in the arterial wall (19, 20), it would seem to be an attractive idea that the thiazides through their sodium diuresis correct this compositional abnormality. However, three studies in rats have produced no evidence that thiazides reduce the content of sodium in the arterial wall. Our own study concerned the walls of mesenteric arterioles in normal rats (16). Daniel found that thiazides produced no lowering in the amount of sodium in the aortic wall of rats with deoxycorticosterone hypertension (21). Weller & Haight also found no effect of thiazides on the sodium of aortic wall (22). However, it is still possible that thiazides have a favorable effect on human essential hypertension and that this secondarily causes a decrease in the sodium content of arterial wall. This point has not as yet been investigated. The evidence which we do have indicates that thiazides do not directly lower sodium in arterial wall.

Two areas may provide clues to the secret of thiazide efficacy. The first of these relates to the fact that an extremely low intake of sodium can alleviate the manifestations of essential hypertension. Ambard and Beaujard (53) were the first to advocate the use of salt-free diets in the treatment of hypertension. This therapeutic maneuver was rediscovered by Allen (54) in the early twenties. After lapsing into a temporary medical obscurity, this approach was again revived by Kempner (55) with his advocacy of a rice diet. Grollman et al. correctly suspected that the main benefits of the rice diet lay in its extremely low content of sodium (23).

Diets very low in sodium content usually lower the blood pressure in patients with hypertension, frequently bringing it down into the normal range. Corcoran, Taylor & Page (24) showed that a few hypertensive patients will show a reduction in blood pressure if the sodium intake is restricted to 300-400 mg per day. However, most of their patients did not show any sizable reduction of blood pressure unless the sodium intake was down to 200 mg per day or less. With an intake of 100 mg of sodium per day, the average reduction of blood pressure is about 29 mm Hg in systolic pressure and 16 mm Hg in diastolic pressure (25). The urinary excretion of sodium becomes progres-

sively lower for the first seven days on the lowered intake of sodium (26). If kidney function is reasonably good, the adult patient usually comes into sodium balance after one to two weeks, despite extremely low intakes of sodium (26). In addition to lowering the blood pressure, these sodium-restricted diets may result in resolution of hemorrhages, exudates, and papilledema in the optic fundus; in a reduction in heart size toward normal dimensions; in a disappearance of electrocardiographic abnormalities; and in a prolongation of life (27). At a level of 100 mg of sodium in the daily diet, a decrease in the total exchangeable sodium of adult humans occurs, amounting to about 1 to 20 per cent (28, 29). Instituting a rice diet will result in an average decrease in plasma volume of 10.2 per cent (310 ml of plasma), an average decrease in blood volume of 14.6 per cent (815 ml of blood), and an average decrease in interstitial fluid volume of 11.8 per cent (1655 ml) (30). The extracellular sodium on this diet decreased 163 mEq, on the average (30). This is very similar to the sodium deficit in Winer's hypertensive patients on long-term treatment with thiazide (17). After three weeks of the low-salt diet, the plasma and interstitial fluid volume reach a constant level. The decrease in blood volume can easily be compensated by a contraction of smooth muscle in the walls of veins. Thus, the evidence suggests that the reduction in blood pressure is brought about mainly by a generalized decrease in peripheral resistance. The concentration of sodium in the plasma remains virtually unchanged on this diet in most people with benign hypertension. Most people on the diet show no evidence of sodium depletion (26): they respond to a sodium load with an immediate increase of sodium excretion in the urine, which would not be the case in true sodium depletion (31). In a diet composed mainly of rice, the addition of 10 g of salt per day usually abolishes the hypotensive effect, proving that the low-sodium feature is of predominant importance in this respect (24, 25). It is the restriction of sodium and not of chloride that produces the hypotensive effect (23, 26). Some patients with severe hypertensive disease become quite depleted of sodium and extracellular fluid on the low-sodium diet without any reduction in blood pressure (26). On the other hand, excellent hypotensive effects may be obtained in benign hypertensive patients with good renal function who easily go into sodium balance without any clinical evidence of sodium depletion. With a low-salt diet, sodium balance may be achieved in a week at a slightly lowered level of total exchangeable sodium, but the blood pressure may continue to decline for several weeks while adaptation to the diet is going on (26). The amount of "desalting" of the body and the lowering of blood pressure often correlate rather poorly (26, 29). The drop in blood pressure has to do more with some adaptation to a low intake of sodium than simply to the "desalting" process (26).

The thiazide diuretics probably act through the same mechanism as does the low-salt diet. With the thiazides, there is an initial depletion of sodium. But, with continued administration of them, an adaptation or "escape" takes place so that the drugs cease to deplete the body of sodium. In fact,

there is a considerable amount of repletion of body sodium toward normal. Nevertheless, there is a continued effect of the thiazide with some slight degree of sodium and volume depletion (17). When the thiazides are abruptly discontinued, a weight gain with sodium retention occurs. Some adaptation to the low-salt diet rather than the actual desalting is associated with a drop in blood pressure. In like manner, it is probably a similar adaptation to thiazides which brings about the drop in arterial pressure and peripheral resistance.

Along these lines, Ulrych et al. (32) noted that an infusion of 6 per cent dextran in saline into hypertensive subjects caused an exaggerated rise in venous pressure, compared to normotensive subjects. This presumably led to the higher cardiac output which occurred in hypertensive subjects following the infusion. Furthermore, this higher cardiac output correlated with and probably accounts for the extra-fast sodium excretion which occurs in hypertensives following a saline infusion. The fact that the dextran-saline infusion caused an extra-large rise in venous pressure in hypertensives suggests that their capacity vessels do not undergo normal reflex dilatation when the vascular system is overdistended. The institution of a low salt intake in hypertensive subjects may provide for some slack in this train of events, since it abolishes the fast excretion of sodium after a sodium load (33, 34). In a similar manner, thiazides may also provide some slack in the capacity vessels. This would tend to diminish cardiac output and promote a tendency toward a lower blood pressure (35, 36).

A second important area of interest is the influence of the thiazide diuretics on the sympathetic nervous system. A number of investigators have found that acute and chronic treatment with thiazide diuretics diminishes the peripheral constrictor response to norepinephrine (37, 38). Winer, however, did not find such a difference in response in human hypertensives (18). The acute intravenous administration of chlorothiazide does not block the constrictor action of either norepinephrine or angiotensin II when these substances are administered as an infusion at the same time as an infusion of thiazide (39, 40). This would suggest that the diuretic aspect of the thiazide drugs is necessary for blunting the vasoconstrictor action of norepinephrine. Thiazides continue to alter the action of catecholamines even after five weeks. This was clearly shown by Eckstein, Wendling & Abboud (41) in dogs. After these dogs had received chlorothiazide for five weeks, they had a definitely diminished vasoconstrictor response to norepinephrine and this diminished response was also apparent after ganglion blockade. In these thiazide-treated dogs, norepinephrine did not have its usual reflex effect of slowing the heart rate and dropping the cardiac output. It appeared that chlorothiazide had reduced the effectiveness of the cardioinhibitory reflexes. When hexamethonium was given in order to block the cardiac reflexes, the control dogs then had the same absence of cardioinhibitory reflexes as the thiazide-treated dogs. These data give strong support to the view that chronic thiazide administration blunts the cardioinhibitory reflexes.

Preziosi et al. (42) gave relatively small doses of chlorothiazide into one

femoral artery of a dog and, after a few minutes, noted that stimulation of the lumbar sympathetic chain did not produce the usual vasoconstrictor response in that particular hindlimb. The effect of nerve stimulation was completely abolished and continued so for about three hours. During this time, an intra-arterial infusion of epinephrine was still effective in producing a peripheral vasoconstriction.

Aoki & Brody (56) of the Iowa School of Medicine gave thiazides for two weeks to rats with renal hypertension (figure-of-eight ligature on the lone remaining kidney). This thiazide-treated group had about 50 per cent more traffic of nerve impulses along the lumbar sympathetic chain than did a non-treated hypertensive group. Moreover, the treatment of these hypertensive rats with thiazide diminished the vasoconstrictor response to sympathetic nerve stimulation even though it did not diminish the vasoconstrictor response to intra-arterial norepinephrine. Since the thiazides increased the number of sympathetic nerve impulses and at the same time diminished the vasoconstrictor effect of each nerve impulse, the two influences tended to counteract one another and the arterial pressure of the hypertensive rats did not change. These investigators speculate that the thiazides reduce the amount of norepinephrine liberated with each nerve impulse. Moreover, in these same hypertensive rats thiazide treatment did not alter the rise in arterial pressure after asphyxia or carotid occlusion even though it did cause a greater increase in sympathetic nerve traffic in response to these stimuli. Again, if the nerve traffic is greater and the pressor response is unchanged, one can infer that the thiazides diminish the amount of norepinephrine released with each sympathetic nerve impulse. Thiazides did not change the vasoconstrictor effect of injected norepinephrine in this hypertensive rat preparation. In human hypertensive subjects Mendlowitz et al. did observe that thiazides caused a decrease in digital vascular reactivity to intra-arterial injections of norepinephrine (43).

The thiazide diuretics have an effect on another hypertension syndrome, the specific hypertensive disease of pregnancy known as pre-eclampsia. Almost everyone agrees that a large intake of salt predisposes pregnant women to pre-eclampsia. Early in the course of pre-eclampsia there is usually an excessive gain in weight as a result of the accumulation of edema fluid. In the normal progression of the disease, the weight gain is followed by hypertension and albuminuria. If the excessive gain in weight can be prevented by a drastic restriction of salt intake, the subsequent hypertension and albuminuria may be averted. Finnerty & Bepko (44) and Fallis et al. (45) have independently established that treatment of the edema phase of pre-eclampsia with thiazide diuretics during the middle and last trimesters of pregnancy prevents the expected rise in blood pressure and largely abolishes the syndrome of pre-eclampsia. Such treatment can prevent many maternal deaths. Moreover, fetal mortality is also greatly reduced with this use of thiazide diuretics (44). These drugs probably act like a low salt intake in preventing an excessive edema of pregnancy which is the early sign of pre-eclampsia.

Thiazides are also efficacious in treating certain types of experimental hypertension. In the hypertension which appears during the active absorption of parenteral deoxycorticosterone, thiazide diuretics were found to lower blood pressure (21, 46). Fregly & Gennaro (47) found on the other hand, that thiazide diuretics actually cause the blood pressure of rats to rise more quickly during the administration of deoxycorticosterone than it did in control rats receiving only the deoxycorticosterone.

After a prolonged exposure to deoxycorticosterone, rats may remain permanently hypertensive even though no more deoxycorticosterone is given. This is known as "metacorticoid" or "postdeoxycorticosterone" hypertension. In this type of hypertension, two investigators have independently noted that the thiazides will bring about a distinct drop in blood pressure, reminiscent of its effect in human essential hypertension (47, 48).

In rats made hypertensive by placing a figure-of-8 ligature around one kidney and excising the other, Scriabine et al. noted a drop in blood pressure after administering a thiazide diuretic (49). Weller & Haight studied this same type of hypertensive rat. They also noted some drops in blood pressure after thiazide, but the effect was inconsistent (22).

In another type of experimental hypertension produced in rats by narrowing one renal artery and leaving the opposite kidney intact, the author found that giving a thiazide diuretic produced no drop in blood pressure whatsoever (50). This was not unexpected since a diet extremely low in sodium is also ineffective in lowering the blood pressure in this type of hypertension.

Thiazide diuretics are able to increase urine osmolality and decrease urine volume in patients with diabetes insipidus of either pituitary or nephrogenic origin. Sodium depletion is thought to be somehow responsible for this effect (51). Whether this effect relates to the antihypertensive effect of the thiazides is a moot point.

Thiazide diuretics can change the electrolyte composition of many tissues in the body, including the intestine and pancreas (52). Grollman & Dahr (52) speculate that this compositional alteration in the intestine may predispose to the small intestinal ulcers and obstruction which appear in some patients taking thiazides. They also speculate that the electrolyte abnormalities in the pancreas may be partially responsible for the pancreatitis and the diabetes which occasionally occur in patients taking thiazides.

Summary statement: The action of thiazides in lowering arterial pressure is still mysterious. Their diuretic action tends to produce a slightly lowered blood volume. This would by itself tend to reduce cardiac output and arterial pressure. Moreover, it would also potentiate the action of any other drugs such as ganglionic blockers or guanethidine, which increase the volume of the veins and venules. More importantly, thiazides also tend to decrease body sodium and extracellular fluid volume. This tendency to sodium depletion brings about adaptive responses in the kidney, so that the body sodium content is diminished only a little. Yet this tendency to sodium depletion and

the adaptation to it somehow oppose the fundamental hypertensive diathesis in essential hypertension and produce a widening of systemic arterioles and a decrease in peripheral resistance. Some of the decrease in resistance may be related to a diminished effect of the sympathetic nervous system. At any rate, the tendency to sodium depletion may be involved in the antihypertensive action, since the eating of really large quantities of salt can abolish the antihypertensive effect of the thiazides.

LITERATURE CITED

1. Freis, E. D., and Wilson, I. M., *Med. Ann. District Columbia*, **26**, 468 (1957)
2. Bowlus, W. E., and Langford, H. G., *Clin. Pharmacol. Therap.*, **5**, 708 (1964)
3. Dirks, J. H., Cirksena, W. J., and Berliner, R. W., *Abstracts of the General Sessions and Symposia, Intern. Congr. Nephrol., Sept. 25–30, 1966*, 80–81
4. Ullrich, K. J., Micropuncture Studies on Saluretic Sulfonamides, *Ann. N. Y. Acad. Sci.* (1966, In press)
5. Gertz, K. H., Mangos, J. A., Braun, G., and Pagel, H. D., *Arch. Ges. Physiol.*, **285**, 360 (1965)
6. Rector, F. C., Jr., Brunner, F. P., and Seldin, D. W., *J. Clin. Invest.*, **45**, 590, 630 (1966)
7. Windhager, E. E., Hierholzer, K., and Wiederholt, M., *Federation Proc.*, **25**, 459 (1966)
8. Baer, J. E., and Beyer, K. H., *Ann. Rev. Pharmacol.*, **6**, 261 (1966)
9. Wilson, I. M., and Fries, E. D., *Circulation*, **20**, 1028 (1959)
10. Conway, J., and Lauwers, P., *Circulation*, **21**, 21 (1960)
11. Gifford, R. W., Jr., Mattox, V. R., Orvis, A. L., Sones, D. A., and Rosevear, J. W., *Circulation*, **24**, 1197 (1961)
12. Aleksandrow, D., Wyszancka, W., and Gajewski, J., *New Engl. J. Med.*, **260**, 51 (1959)
13. Winer, B. M., *J. Clin. Invest.*, **42**, 994 (1963)
14. Seriu, Y., *Japan. Circulation J.*, 29, 433 (1965)
15. Bourgoignie, J., Catanzaro, F. J., and Perry, H. M., *Clin. Res.*, **14**, 446 (1966)
16. Tobian, L., Janecek, J., Foker, J., and Ferreira, D., *Am. J. Physiol.*, **202**, 905 (1962)
17. Winer, B. M., *Circulation*, **23**, 211 (1961)
18. Winer, B. M., *Circulation*, **24**, 788 (1961)
19. Tobian, L. and Binion, J. T., *Circulation*, **5**, 754 (1952)
20. Tobian, L., Janecek, J., Tomboulian, A., and Ferreira, D., *J. Clin. Invest.*, **40**, 1922 (1961)
21. Daniel, E. E., *Circulation Res.*, **11**, 941 (1962)
22. Weller, J. M., and Haight, A. S., *Proc. Soc. Exptl. Biol. Med.*, **112**, 820 (1963)
23. Grollman, A., Harrison T. R., Mason, F. M., Baxter, J., Crampton, J., and Reischsman, F., *J. Am. Med. Assoc.*, **129**, 533 (1945)
24. Corcoran, A. C., Taylor, R. D., and Page, I. H., *Circulation*, **3**, 1 (1951)
25. Watkin, D. M., Froeb, H. F., Hatch, F. T., and Gutman, A. B., *Am. J. Med.*, **9**, 441 (1950)
26. Dole, V. P., Dahl, L. K., Cotzias, G. C., Eder, H. A., and Krebs, M. E., *J. Clin. Invest.*, **29**, 1189 (1950)
27. Newborg, B., and Kempner, W., *Am. J. Med.*, **19**, 33 (1955)
28. Dole, V. P., Dahl, L. K., Cotzias, G. C., Dziewiatkowski, D. D., and Harris, C., *J. Clin. Invest.*, **30**, 584 (1951)
29. Dahl, L. K., Stahl, B. G., and Cotzias, G. C., *J. Clin. Invest.*, **33**, 1397 (1954)
30. Murphy, R. J. F., *J. Clin. Invest.*, **29**, 912 (1950)
31. Strauss, M. B., Lamdin, E., Smith, W. P., and Bleifer, D. J., *Arch. Internal Med.*, **102**, 527 (1958)
32. Ulrych, M., Hofman, J., and Hejl, Z., *Am. Heart J.*, **68**, 193 (1964)
33. Hollander, W., and Judson, W. E., *J. Clin. Invest.*, **36**, 1460 (1957)
34. Baldwin, D. S., Giggs, A. W., Goldring, W., Hulet, W. H., and Chaiss, H., *Am. J. Med.*, **24**, 893 (1958)
35. Freis, E. D., *Physiol. Rev.*, **40**, 27 (1960)
36. Floyer, M. A., and Richardson, P. C., *Lancet*, **I**, 253 (1961)
37. Freis, E. D., Wanko, A., Schnaper, H. W., and Frohlich, E. D., *J. Clin. Invest.*, **39**, 1277 (1960)
38. Feisal, K. A., Eckstein, J. W., Horsley,

A. W., and Keasling, H. H., *J. Appl. Physiol.*, **16,** 549 (1961)
39. Silah, J. G., Jones, R. E., Bashour, F. A., and Kaplan, N. M., *Am. Heart J.*, **69,** 301 (1965)
40. Greene, M. A., Boltax, A. J., Niv, M., and Rogow, E., *Am. J. Med. Sci.*, **246,** 575 (1963)
41. Eckstein, J. W., Wendling, M. G., and Abboud, F. M., *Circulation Res.*, **18,** Suppl. 1, 48 (1966)
42. Preziosi, P., De Schaepdryver, A. F., Marmo, E., and Miehle, E., *Arch. Intern. Pharmacodyn.*, **131,** 14 (1961)
43. Mendlowitz, M., Naftchi, N., Gitlow, S. E., Weinreb, H. L., and Wolf, R. L., *Ann. N. Y. Acad. Sci.*, **88,** 964 (1960)
44. Finnerty, F. A., and Bepko, F. J., *J. Am. Med. Assoc.*, **195,** 429 (1966)
45. Fallis, N. E., Plauche, W. C., Mosey, L. M., and Langford, H. G., *Am. J. Obstet. Gynecol.*, **88,** 502 (1964)
46. Friedman, S. M., Nakashima, M., and Friedman, C. L., *Am. J. Physiol.*, **198,** 148 (1960)
47. Fregly, M. J., and Gennaro, J. F., Jr., *Can. J. Physiol. Pharmacol.*, **43,** 521–30 (1965)
48. Stanton, H. C., and White, J. B., *Arch. Intern. Pharmacodyn.*, **154,** 351 (1965)
49. Scriabine, A., Korol, B., Kondratas, B., Yu, M., P'An, S. Y., and Schneider, J. A., *Proc. Soc. Exptl. Biol. Med.*, **107,** 864 (1961)
50. Tobian, L., and Coffee, K., *Proc. Soc. Exptl. Biol. Med.*, **115,** 196 (1964)
51. Earley, L. E., and Orloff, J., *J. Clin. Invest.*, **41,** 1988 (1962)
52. Grollman, A. G., and Dahr, A. S., *Texas Rept. Biol. Med.*, **24,** 164 (1966)
53. Ambard, L., and Beaujard, E., *Sem. Méd. Paris*, **25,** 133 (1905)
54. Allen, F. M., and Sherrill, J. W., *J. Metab. Res.*, **2,** 429 (1922)
55. Kempner, W., *N. Carolina Med. J.*, **5,** 125 (1944)
56. Aoki, V. S., and Brody, M. J., *The Pharmacologist*, **8,** 215 (1966)

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