REVISION

The Cell Membrane and Central Nervous System in Hypertension

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It is important to know the cause of hypertension. This importance is documented by the extensive literature that has appeared over the past half century in attempts to characterize the mechanism responsible for the arterial pressure elevation. In addition to the goal of understanding mechanisms as an end in itself, this information leads to development of therapeutic tools which are more effective as antihypertensive measures.

Much progress in the quest of this mechanism over the past three decades can be attributed to a concept introduced by Irvine Page in his *Mosaic Theory* [1]. This theory is based on the interaction of the many systems that regulate arterial pressure (Figure 1). It emphasized the fact that no individual regulatory system operates in a vacuum. An abnormality in one regulatory system causes chnges in the others. However, as valuable as this concept has been, it is not a specific hypothesis for which evidence can be generated to prove or disprove its validity. For the purpose of formulating specific, testable hypotheses, I have organized the concept of the mechanism of hypertension according to the outline depicted in Figure 2.

The outline is comprised of *initiating factors* that act through a *sequence of events* that lead to a *final common pathway* responsible for the arterial pressure elevation. The initiating factor is easily defined because it is the intervention introduced by the investigator. The final common pathway is a readily measurable parameter, and it is usually found to be an increase in total peripheral resistance, which indicates that there has been a vascular change. There remain the unknowns in the «black box» that contains the pathophysiological events by which the intervention causes the vascular change. It should be possible for the investigator to develop specific, testable hypotheses regarding this sequence of events.

The hypothesis evaluated in the current review deals with the problem at two levels. At one level,

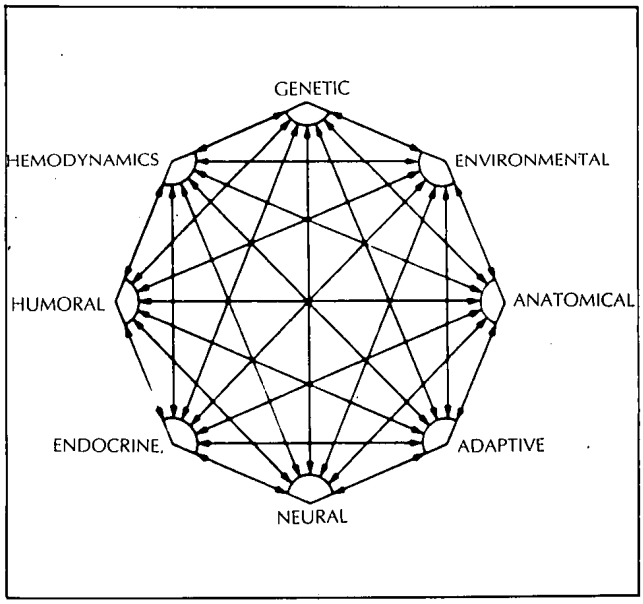

Fig. 1.—The Mosaic Theory of hypertension proposed by Page. Multiple factors depicted around the perimeter of the figure interact in the pathogenesis of hypertension.

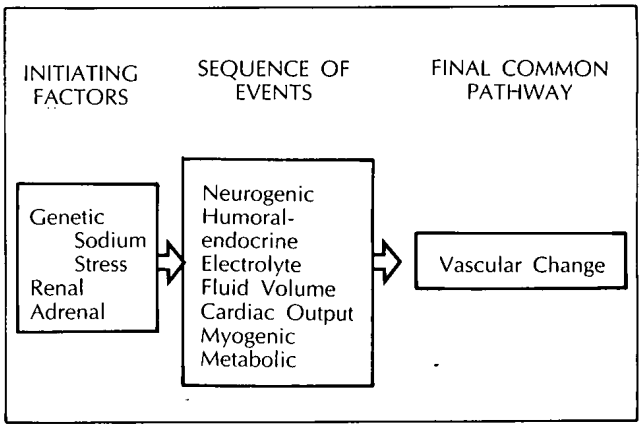

Fig. 2.—Organization of the processes leading to an elevation in arterial pressure in hypertension. Current research is focused on the sequence of events leading from the initiating factor to the vascular change.

we hypothesize that there is in hypertension a generailzed fault in cell membranes. At the other level, we hypothesize that this membrane fault in cells of a pressure-regulating center of the brain is responsible for the arterial pressure elevation. The purpose of this review is to present evidence bearing on these two components of the mechanism.

Most of our evidence is based on observations made on animals in which mineralocorticoid excess was used as the initiating factor to produce the hypertension. Observations made by ourselves and others suggest that the membrane and central nervous system abnormalities may also play a role in renal and in genetic models of hypertension.

Seven years ago, we introduced the pig as a model of mineralocorticoid hypertension [2]. It proved to be a desirable animal for these studies, not only because of its size, but also because of the rapid and consistent blood pressure elevation with which the animal responded to the mineralocorticoid excess (Figure 3). In dealing with the cause of this pressure elevation, we considered three possible mechanisms. First we postulated that the mineralocorticoid might act directly on vascular smooth muscle. This possibility was supported by our observation that, as early as two days following the initiation of treatment with mineralocorticoid, there was an increase in vascular reactivity to vasoconstrictor agents [3]. However, in studies carried out on isolated vascular smooth muscle, we failed to observe any direct action of the mineralocorticoid on this tissue [4]. Evidence to be cited later in this review convince us that the increase in vascular reactivity observed in this model of hypertension was not produced by direct action of the mineralocorticoid on this tissue. The second hypothesis, based on fluid retention, increase in cardiac output, and whole-body vascular autoregulation, also failed to receive experimental support in our studies. However, the third hypothesis, based on a resetting of a pressure regulating center in the brain, received strong support which will be documented in the section of this review dealing with the central nervous system.

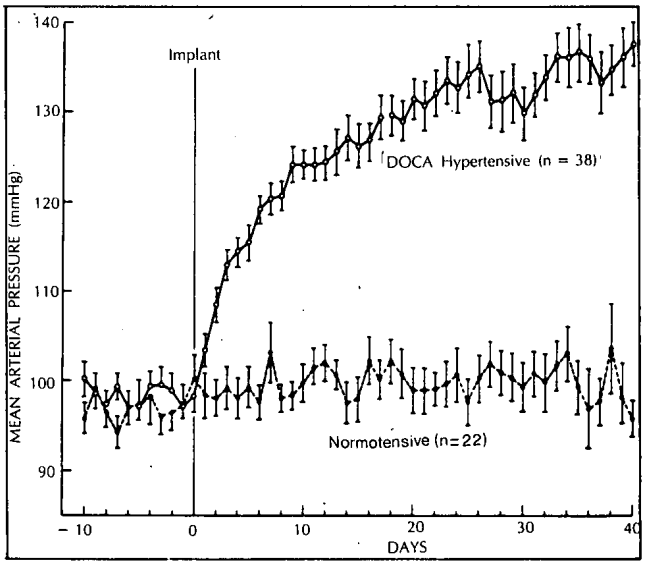

Fig. 3.—Average mean arterial pressure of 38 young male pigs implanted with deoxycorticosterone acetate (DOCA; 100 mg/kg) compared to 22 control pigs with sham implants. Each point represents the mean ± SEM. Reproduced from Bohr [46] by courtesy of the Editors of Hypertension.

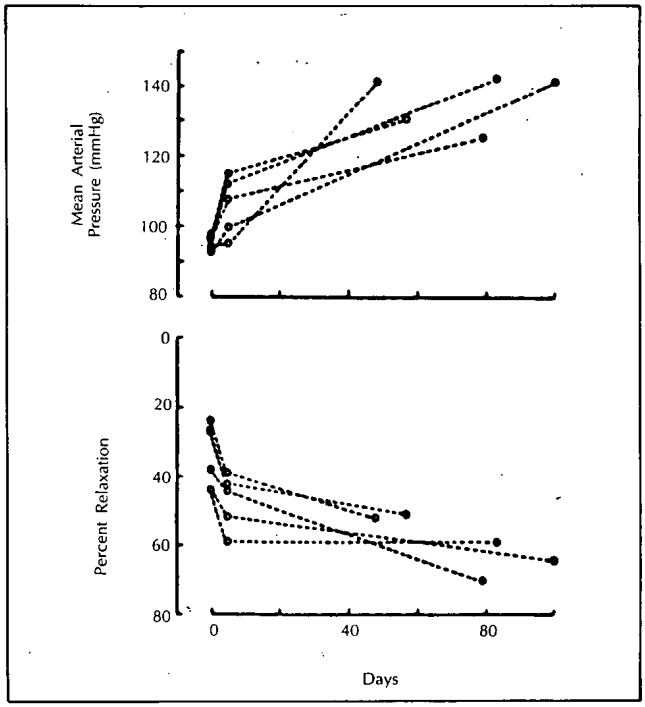

Fig. 4.—Temporal relationships between the rise in blood pressure and the magnitude of potassium-induced relaxation in the DOCA-hypertensive pig. Arteries from a small segment of the tail were isolated before implantation of Silasticstrips impregnated with DOCA, at 3 to 5 days postimplantation of Silastic strips impregnated with DOCA, at 3 to 5 days postimplantation and at the time of termination of the pigs. Pigs implanted with DOCA showed an increase in the magnitude of potassium-induced relaxation at 3 to 5 days postimplant, and a further increase in the magnitude of potassium-induced relaxation that paralleled the rise in mean arterial pressure. Reproduced from Webb [18] by courtesy of the Editors of Hypertension.

A. Cell Membrane Changes in Hypertension

A major impetus for the attention given to the possible membrane abnormality associated with hypertension appeared in one issue of The New England Journal of Medicine in 1980 when two substantial studies presented evidence for membrane abnormalities in red blood cells in patients with essential hypertension. Canessa et al. [5] described an abnormality in the Na^+/Li^+ countertransport system, whereas Garay et al. [6] described a difference in the Na^+/K^+ contransport system. Importance was assigned to these findings because of the role that

they might play as «markers» for the disease. Mechanistically, these findings were of interest because it was unlikely that a membrane abnormality in the red blood cell could itself cause an elevated arterial pressure. Hence, because of the association of this finding with an elevated arterial pressure, it was postulated that the membrane defect might be a generalized abnormality occurring in many body tissues in hypertension including those responsible for the pressure elevation. Extensive studies since that time in experimental and clinical hypertension have resulted in findings that are compatible with this interpretation. Recently, both major journals dealing with hypertension had lead editorials [7, 8] that focused on membrane abnormalities in hypertension.

Membrane properties of vascular smooth muscle may have direct relevance to the pathogenesis of hypertension. Friedman [9] and Jones and his collaborators [10, 11] have observed that the membrane of vascular smooth muscle, from various types of hypertensive rats, is more permeable to monovalent ions than is that from normotensive controls. Constrictor agonists cause a greater membrane depolarization [12] and a greater potassium efflux [10] in the vascular smooth muscle from the hypertensive rat. There is substantial evidence that, in hypertension, this membrane is more permeable to calcium [13-15].

Two types of observations from our laboratory have served as evidence of an increase in membrane permeability to sodium in vascular smooth muscle from hypertensive animals. The first of these is based on studies of potassium-induced relaxation. Potassium relaxation in vascular smooth muscle is a response observed following contraction of vascular smooth muscle in a potassium-free bath when potassium is added back to the bath. The resultant relaxation is caused by hyperactivity of the electrogenic sodium pump, which causes membrane hyperpolarization and hence a decrease in membrane excitability an relaxation [16]. The basis for this pump stimulation is that, during the period in the potassium-free solution, the sodium pump which is dependent on extracellular potassium is inactive. When potassium is returned to the bath, the pump is turned on and the pump is hyperactive because it is stimulated by the elevated concentration of intracellular sodium which ha accumulated during the period when the pump was turned off. The degree of pump stimulation, reflected in the magnitude of the potassium-induced relaxation, depends on the concentration of intracellular sodium that has accumulated [17]. Since this concentration is determined by the rate at which sodium has leaked into the cell, while the sodium extrusion pump was turned off, the magnitude of potassium relaxation is a measure of membrane permeability to sodium. Figure 4 indicates that, in the pig tail artery, the magnitude of the potassium relaxation increases as the arterial pressure rises in response to mineralocorticoid administration [18]. This observation is compatible with the interpretation that there is an increase in membrane permeability to sodium in vascular smooth muscle of the DOCA-hypertensive pig. We have reported similar evidence for elevated membrane permeability to sodium in the spontaneously hypertensive [19] and renal hypertensive rat [20].

A second type of evidence also depends on the rate of entrance of sodium into the cell during periods of inactivation of the sodium extrusion pump [21, 22]. Smooth muscle of the rat aorta contracts upon inactivation of the sodium pump with ouabain. The magnitude of this contraction depends on the rate of intracellular sodium accumulation, and this contraction is greater in the aorta from DOCA-hypertensive or from spontaneously hypertensive rats than it is in the aorta from normotensive control animals. As is evident in Figure 5, if sodium entry is increased with the sodium ionophore, monens in, in the aorta from the control normotensive rat, its response to ouabain can be made to simulate that of the untreated aorta from the DOCA-hypertensive rat. Conversely, if the membrane permeability of the smooth muscle cells of the aorta from the DOCA-hypertensive rat is decreased by treatment with amiloride, the response to ouabain of this smooth muscle then resembles that of the control. Clearly the magnitude of the contractile response to ouabain, which is greater in VSM from the hypertensive animal, reflects the rate of entry of sodium into the cell.

Jones [11], using direct isotope flux studies, has

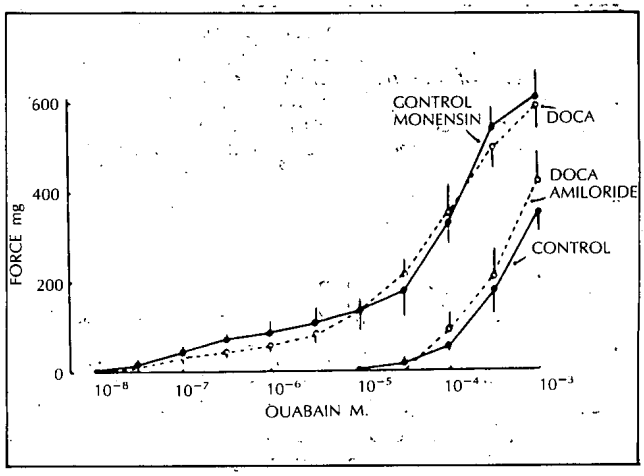

Fig. 5.—Contraction in response to ouabain; influence of the Na^+ flux. Force development in response to ouabain with various Na^+ manipulations. Sensitivity to ouabain reflects the rate of sodium entry into the cell. Reproduced from Moreland, et al. [22] by courtesy of the Editors of Hypertension.

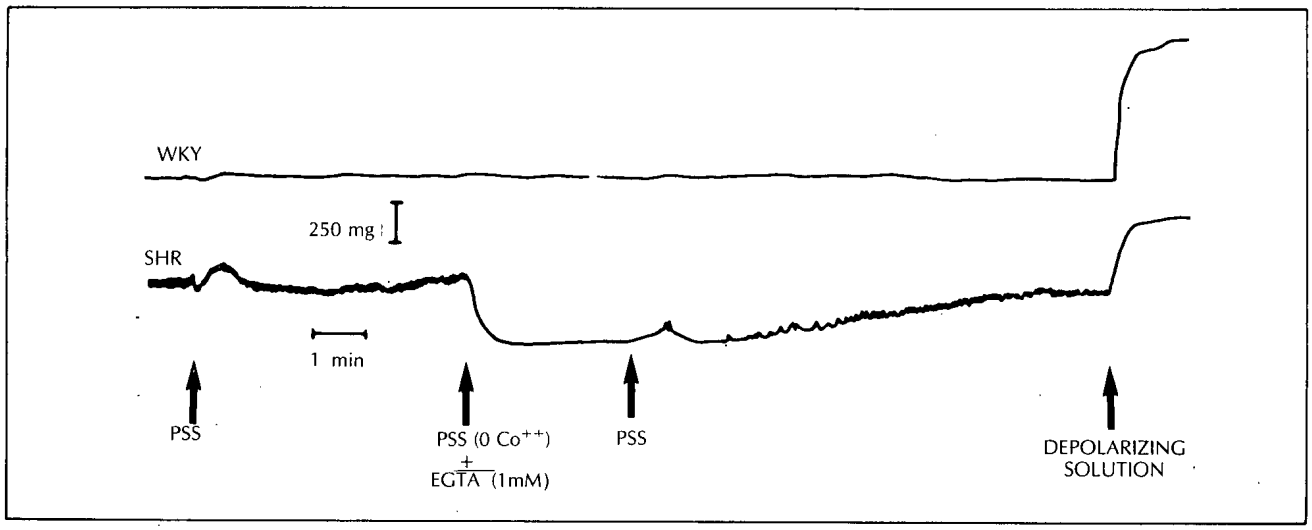

Fig. 6.—Isometric force recordings of isolated basilar artery rings from a normotensive (top tracing) and hypertensive (bottom tracing) rat. Basilar arteries from SHR (but rarely those from WKY) were characterized by spontaneous activity which was inhibited following washing with PSS containing no added Ca^{++}, and with EGTA (1 mM). The spontaneous activity, typically small amplitude oscillations superimposed on a tonic contraction, returned upon washing tissues in normal PSS. Rings from both arteries contract in response to high potassium depolarizing solution. From Winsquist and Bohr [23] by courtesy of the Editors of Hypertension.

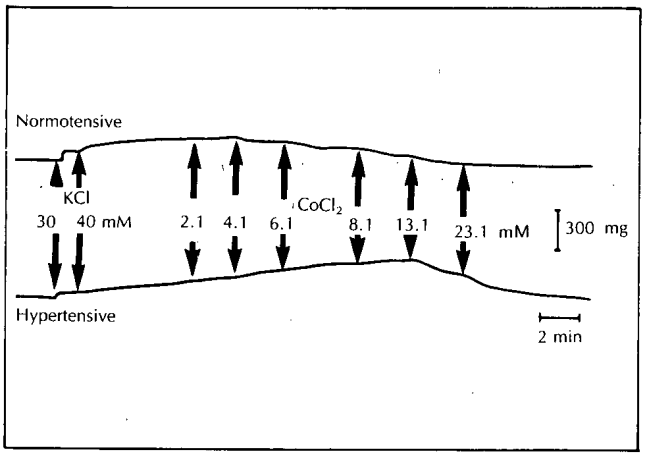

Fig. 7.—Effect of Ca^{++} concentration on contractile response to 40 mM KCl. Maximum contraction of smooth muscle from the femoral artery of the normotensive rat occurred at a Ca^{++} concentration of 2.1 mM, that from de DOCA-hypertensive rat at 8.1 mM. High concentrations of Ca^{++} were required to depress the response of the smooth muscle from the hypertensive rat. Reproduced from Holloway, et al. [25] by courtesy of the Editors of Springer-Verlag.

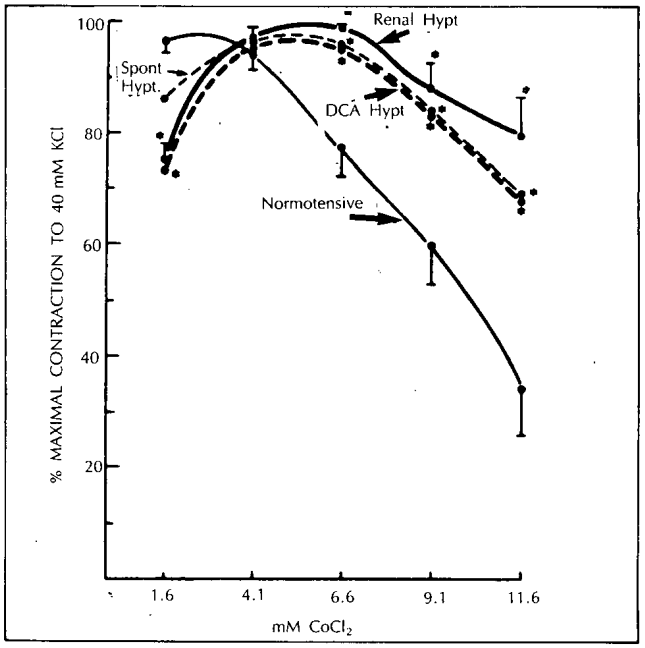

Fig. 8.—Normalized average of responses to 40 mM KCl at various calcium concentrations. The greatest response of strips (eight or nine each group) from the normotensive rats was 1.6 mM Ca^{++}, from the spontaneosly hypertensive rats it was 4.1 mM and from the DOCA- and renal hypertensive rats it was 6.6 mM. Brackets indicate SE, and an asterisk indicated a significant difference from normotensive value and $p < 0.05$. Reproduced from Holloway and Bohr [2-6] by courtesy of the Editors of Circulation Research.

observed an increase in membrane permeability to sodium, potassium, and to chloride in the smooth muscle cell membrane from the hypertensive rat.

There is also a faulty relationship between the vascular smooth muscle cell membrane and the divalent cation, calcium. Perhaps the most relevant evidence of this is an increase in membrane permeability to calcium, illustrated in Figure 6 [23]. This figure depicts the recording of tension from strips of basilar artery smooth muscle, one from a genetically hypertensive rat (SHR), and the other from a normotensive control (WKY). The level of intracellular free calcium is reflected in the contraction (spontaneous tone) of these muscle strips. When calcium is removed from the environment of

the muscles, nothing happens to the recorded tension of the muscle from the control animal, whereas that from the hypertensive animal relaxes. If the physiologic concentration of calcium is reintroduced into the bath (PSS) that from the hypertensive animal contracts, whereas that from the normotensive animal remains completely relaxed. This observation suggests that there are leak channels through which effective concentrations of calcium can enter the cell to cause a level of spontaneous myogenic tone in the smooth muscle from the hypertensive rat; in that from the WKY the leak is not sufficient to cause a contraction. As shown on the right-hand side of the tracing, potential-operated channels can be opened by membrane depolarization with KCl so that muscle from the normotensive control contracts as well as does that from the hypertensive animal.

We have also reported a more subtle but possiblymore basic defect of the relationship between calcium and cell membrane function. As the concentration of calcium outside of the cell increases, the membrane becomes more «stable». In a functional setting, this stability is reflected in a relaxation of vascular smooth muscle [24]. Comparative studies of vascular smooth muscle from normotensive and hypertensive animals indicate that a higher concentration of calcium is required to «stabilize» the cells from a hypertensive animal than is required to «stabilize» the membrane obtained from a normotensive control [25]. Such a study is illustrated in Figure 7, and has been observed to occur in smooth muscle from mineralocorticoid-, renal-, and spontaneously hypertensive rats (Figure 8,26). These observations are compatible with the hypothesis that there are fewer calcium binding sites on the membrane of vascular smooth muscle from the hypertensive animal, hence a higher concentration of calcium is required to produce this effect in the membrane.

This conclusion is also supported by observations made in a different type of study (Unpublished observations by Lamb and Webb). When, following exposure to a calcium-free and potassium-free solution (Figure 9), calcium is added back to the bath, the muscle will contract because sufficient calcium can pass through the cell membrane. The rate of this contraction reflects the rate of entry of calcium into the cell. This rate of contraction is more rapid in vascular smooth muscle from the hypertensive animal than it is in that from the normotensive control. Evidence that this rate of contraction is slowed by the amount of calcium bound to the membrane is supported by the observation that, when all the calcium is removed from the membrane with EGTA, then the rate of contraction of vascular smooth muscle from either normotensive or hypertensive rats is much more

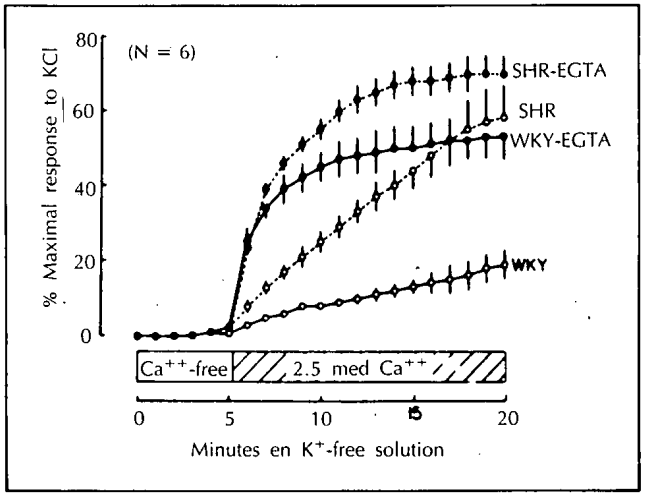

Fig. 9.—Calcium, EGTA, and contractile responses to potassium-free solution in aortic strips from spontaneosly hypertensive rats (SHR)and normotensive Wistar-Kyoto (WKY) rats. Open symbols: Aortic strips from SHR and WKY rats were incubated in calcium-free, potassium-free solution for five minutes. Following this interval, the bath concentration of calcium was increased to 2.5 mM. Aortic strips from SHR developed force at a faster rate than did those from WKY rats. Closed symbols: Aortic strips from SHR and WKY rats were incubated in calcium-free, potassium-free, solution containing 1.0 mM EGTA for four minutes. Following this incubation, the strips were placed in calcium-free, potassium-free solution for one minute. At the end of this interval, 2.5 mM Ca^{++} was added to the bath. Under these conditions the rate of force development was very rapid and that by aortic strips from SHR was not statistically different from that by aortic strips rom WKY rats. Values are mean ± SEM. Reproduced from Bohr and Webb [47] by courtesy of the Editors of the American Journal of Medicine.

rapid. With this experimental paradigm the more rapid contraction of the muscle from the hypertensive animal argues that there is less calcium bound to the membrane of this muscle.

Jones and Hart [27] have used potassium efflux as a measure of the membrane «stabilizing» effect of calcium. They reported that any concentration of calcium, the efflux of potassium from vascular smooth muscle from hypertensive animals was greater than that from the control. Membranes of vascular smooth muscle [28] and other tissues [29, 30] from hypertensive rats bind less calcium than do those from normotensive controls. This deficiency may be the cause of increased membrane permeability in hypertension.

Evidence that the membrane fault may be generalized is found in the observations that the red bllod cell membrane from the spontaneously hypertensive rat is more permeable to sodium and potassium than is that from the normotensive control [31]. More recently, similar abnormalities have been found in the lymphocyte from the hypertensive animal [32]. Sodium and potassium fluxes are greater and the intracellular free calcium content,

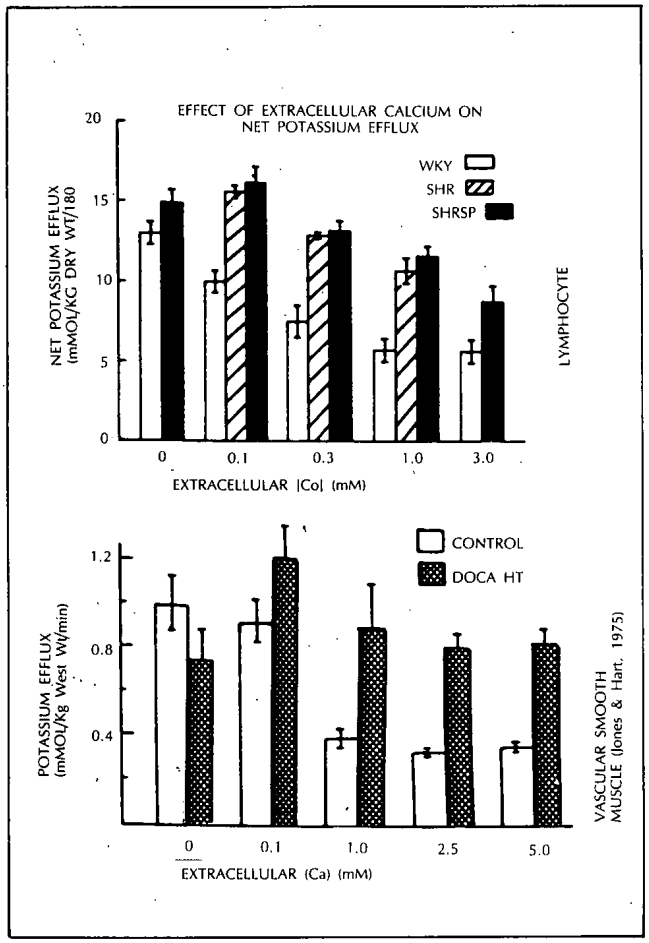

*Fig. 10.—Upper graph: Effects of varying external calcium concentration on net potassium efflux in lymphocytes from WKY, SHR and SHRSP. Number of rats used: WKY, 7; SHR, 4; SHRSP, 6. Bars indicate standard error of the mean: **$p < 0.01$, compared to WKY. Net potassium efflux at 0 mM external calcium concentration in lymphocytes from SHRSP was not significantly different from value at 0.1 mM. Reproduced from Furspan and Bohr [33] by courtesy of the Editors of Hypertension. Lower Graph: Similar study of the effect of varying external calcium concentration on potassium efflux from aorta of normotensive and DOCA-hypertensive rats. Plotted from data presented by Jones and Hart [27] by courtesy of the Editors of Circulation Research.*

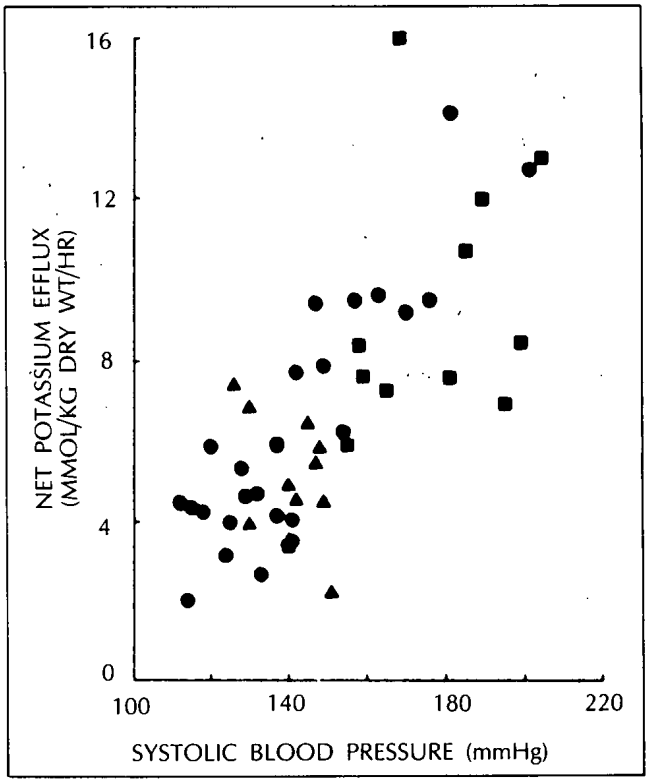

Fig. 11—Correlation between potassium efflux and blood pressure in the F2 population (circles), backcross with WKY (triangls) and SHRSP (squares). The correlation coefficient, $r = 0.86$, is highly significant, $p < 0.001$.

determined by the quin 2 technique, is elevated in lymphocytes from the hypertensive rat [33].

The similarity of hypertensive changes in the membranes of lymphocytes and vascular smooth muscle is demonstrated in Figure 10. This figure depicts results of studies that we have recently carried out on lymphocytes [33], which parallel studies carried out by Jones and Hart [27] in vascular smooth muscle over ten years ago. Three characteristics of this similarity are relevant. 1) In both tissues, as the concentration of extracellular calcium is increased, the potassium efflux is decreased. This observation reflects membrane «stabilization» by calcium. 2) At every calcium concentration, potassium efflux of tissues from the hypertensive animals is greater than that of the normotensive control. This observation is compatible with the hypothesis that in hypertension the membrane is less stabilized by calcium because it has fewer calcium binding sites. 3) Finally, as the calcium concentration is increased from zero to 0.1 mM, the potassium efflux in the normal tissue is depressed, but that from the hypertensive animal is not. This may be interpreted as reflecting the inadequacy of the population of calcium binding sites on the membrane from the hypertensive animal. The slightly enhanced potassium efflux from the c ells of these animals at 0.1 compared to that of zero mM may reflect calcium entry into the cell and activation of the calcium-dependent potassium efflux channel. These similar observations made on the membrane of two different types of tissues from two different types of hypertension are supportive of the hypothesis that a fundamental fault in the membrane in hypertension is a generalized inadequacy of calcium binding sites.

We have recently carried out studies to determine the relevance of the relationship between these lymphocyte membrane changes and the elevated arterial pressure in hypertensive rats. To do this we employed genetic tools [34] in which we crossed SHRSP with WKY rats and studied the traits of blood

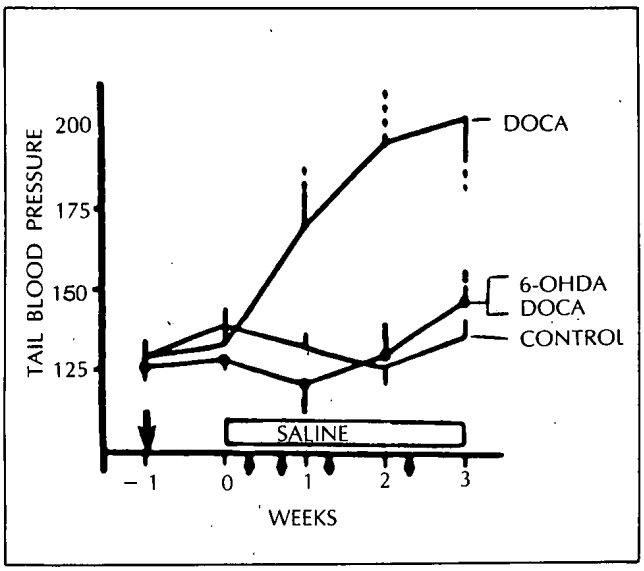

Fig. 12.—Effect of central 6-hydroxydopamine (6-OHDA) on DOCA-hypertension. Mean tail blood pressure was measure at weekly intervals. Intracerebral ventricular injections of 6-OHDA or the saline-ascorbic vehicle were made at the large arrows above the abscissa. From week 1 to week 4, 1 % saline was provided as the only source of drinking watr and subcutaneous injections of DOCA or saline were made at 3 to 7 day intervals as indicated by the small arrows under the abscissa. Reproduced from Lamprech, et a. [37] *bu courtesy of the Editors of tje Journal of Neural Transmission.*

pressure and sodium and potassium fluxes in the segregating generations (F2 and backcrosses between F1 and WKY and backcrosses between F1 and SHRSP). In these segregating generations, th genes have been shuffled so that if the abnormal membrane traits were unrelated to the arterial pressure elevation, these two traits should not appear in the same rat. On the other hand, if the membrane and blood pressure traits were related, it would be expected that rats with higher pressures should have the membrane traits displayed by the parent SHRSPs. There was no correlation between blood pressure and the increased sodium permeability, yet as is evident in Figure 11 that there is a strong correlation between the elevated blood pressure and the increased potassium flux. We hypothesize that this relationship is based on a primary membrane fault of impaired calcium binding. This impairment permits an increase in calcium permeability (referred to earlier), and a resultant increase in intracellular free calcium concentration [33]. In the case of the lymphocyte, the elevated intracellular calcium concentration stimulates the calcium-dependent potassium efflux channel, whereas in the vascular smooth muscle cell, the elevated intracellular calcium concentration causes an enhanced vascular smooth muscle contraction that results in an increased total peripheral resistance.

B. The Central Nervous System

Early evidence of the essential role played by the central nervous system in the development of mineralocorticoid hypertension was reported by Haeusler et al. [35]. They observed that, following the administration of the neurotoxin, 6-hydroxydopamine into the lateral cerebral ventricle of the rat, these animals failed to respond to the standard DOCA-salt treatment with the development of hypertension. More recently, there has been extensive documentation in Brody's laboratory [36] that a discreet lesion in the anterioventral third ventrical (AV3V region) of the rat brain prevented the development of both the DOCA-salt and renal hypertensions. Figure 12 depicts the results of the study by Lamprecht et al. [37], demonstrating that the central administration of 6-hydroxydopamine prevents the development of DOCA-salt hypertension in the rat. We have repeated and confirmed these observations. We have also observed that, following central treatment with 6-hydroxydopamine, the animal not only fails to develope hypertension, but also fails to undergo the increases in sensitivity of vascular smooth muscle characteristic of DOCA-salt hypertension.

This observation supports our earlier statement that the mineralocorticoid does not act directly on the vascular smooth muscle to produce its increase in sensitivity. It appears that a central action of the mineralocorticoid initiates a process, either neurogenic or humoral, which affects the sensitivity of peripheral vascular smooth muscle. Following central treatment with 6-hydroxydopamine, the «pressure regulating center» is no longer capable of effecting this peripheral vascular change.

Recent investigators [38, 39] have confirmed this central role of mineralocorticoids using a different experimental approach. Chronic central infusion of a mineralocorticoid at a very slow rate into the lateral cerebral ventricle of the rat results in hypertension. Infused peripherally at this same rate the mineralocorticoid does not alter blood pressure. Not only does arterial pressure rise in response to this central administration, but the peripheral vasculature undergoes sensitivity changes comparable to those observed with the classical administration of large peripheral doses of the mineralocorticoid.

Finally, in a recent study we have observed [40] that the high sodium intake required for the production of standard mineralocorticoid excess hypertension in the rat, also is effective through a central action. In these studies, observations were made on four groups of animals. Two received the standard peripheral dose of DOCA required to produce hypertension, whereas the other two served as controls. One of each of these two pairs of groups received a chronic

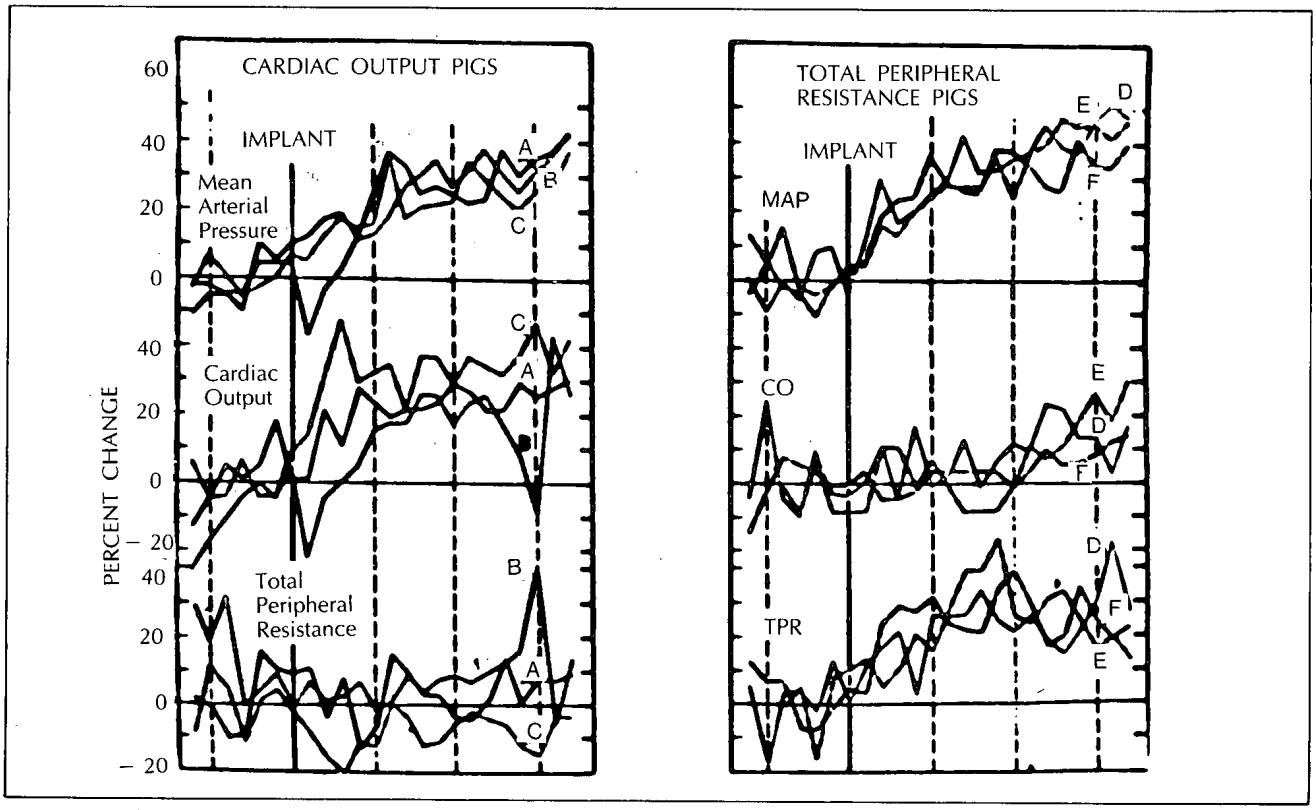

Fig. 13.—Individual hemodynamics of si DOCA-treated pigs. Percent changes in mean arterial pressure (MAP), cardiac output (CO), toal peripheral resistance (TPR), are shown individually for DOCA-treated pigs. Pigs A, B and C (left-hand panel) were selected as examples of animals in which the increase in MAP is caused predominantly by rises in CO. In pigs D, E, and F (right-hand panel) the hypertension is caused primarily by elevations in TPR. In interpreting these graphs it must be recognized that CO normally rises and TPR normally falls in these growing animals. Reproduced from Miller, et al. [41] by courtesy of the Editors of Hypertension.

infusion of isotonic sodium chloride into the lateral cerebral ventricle, whereas the other received a chronic infusion of a hypertonic (600 mM) sodium chloride solution. Of these four groups, the only one to develop hypertension was the DOCA treated group that received a chronic infusion of hypertonic salt solutions centrally. Sensitivity studies were also carried out on vascular smooth muscle from these four groups and it was found that the animals receiving hypertonic sodium chloride centrally demonstrated the changes in vascular smooth muscle sensitivity observed in classical DOCA-salt hypertension. We concluded that both the mineralocorticoid and the sodium acted centrally to cause the hypertension and vascular changes.

Several lines of evidence developed in our large animal models of hypertension, have supported the involvement of the central nervous sytem in the pathogenesis of mineralocorticoid hypertension. For instance in our hemodynamics studies of the evolution of mineralocorticoid hypertension in the pig, we observed a very consistent chronologic pattern for the development of the increase in arterial pressure (Figure 2). However, we observed that in some pigs this pressure elevation was due to an increase in cardiac output, whereas in others it was due to an increase in total peripheral resistance [41] This is evident in Figure 13, which demonstrates the hemodynamic changes of three pigs whose pressure increase was caused by an increase in cardiac output, and another three in which the pressure rose because of an increase in total peripheral resistance. In no case was the pressure elevation initiated by an increase in cardiac output, followed by an increase in total peripheral resistance. This sequence would have been expected if whole body autoregulation were responsible for the increase in total peripheral resistance. We concluded that the pressure elevation resulted from a «resetting» of a central pressure regulating mechanism and hypothesize that this center had access to efferent pathways that could increased either cardiac output or total peripheral resistance to meet the requirements of the altered set point.

Other evidence suggesting the central action of DOCA in the production of hypertension is based on observations that it has parallel actions on other centrally regulated processes. In the sheep [42], as illustrated in Figure 14, and also in the pig [43], an increase in water intake (thirst) parallels the increase

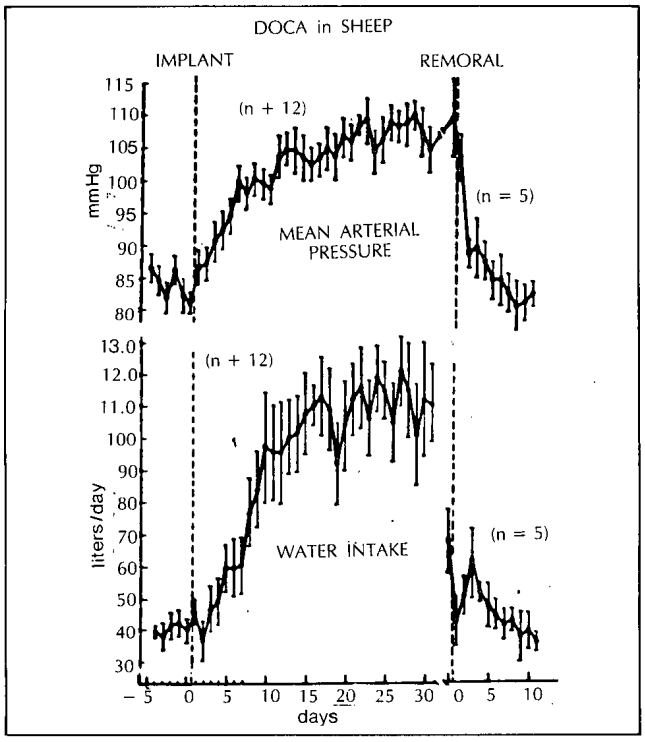

Fig. 14.—Deoxycorticosterone acetate (DOCA) administration, changes arterial pressure and water intake in parallel. Data are expressed as mean ± SEM for the numbers of sheep indicated.

in mean arterial pressure and reverses rapidly to normal following the end of DOCA treatment. Figure 15 demonstrates that both of these centrally regulated changes are dependent on sodium.

Yet another central mechanism, the salt appetite [44], undergoes changes that parallel those in blood pressure. When the normotensive sheep is given a choice of alfalfa pellets which contain only 6 mEq/Kg. of sodium chloride, or alfalfa pellets that have been sprayed with a sodium chloride solution so that they contain 200 mEq/Kg., the normal sheep chooses to eat only half as much salty as unsalty food. However, when DOCA is administered, the choice of food changes as hypertension develops so that by the end of two or three weeks the animal eats three times as much salty as unsalty alfalfa pellets. This choice rapidly reverts to a control pattern following the end of DOCA treatment.

DOCA and Intracellular Sodium

Changes that we have observed in intracellular sodium concentration in the red blood of the pig [45] treated with DOCA contribute to our hypothesis regarding the mechanism of action of DOCA in producing hypertension. Whereas the normal intercellular sodium concentration in the red blood cell of the pig is approximately 5 mEq/L, this value

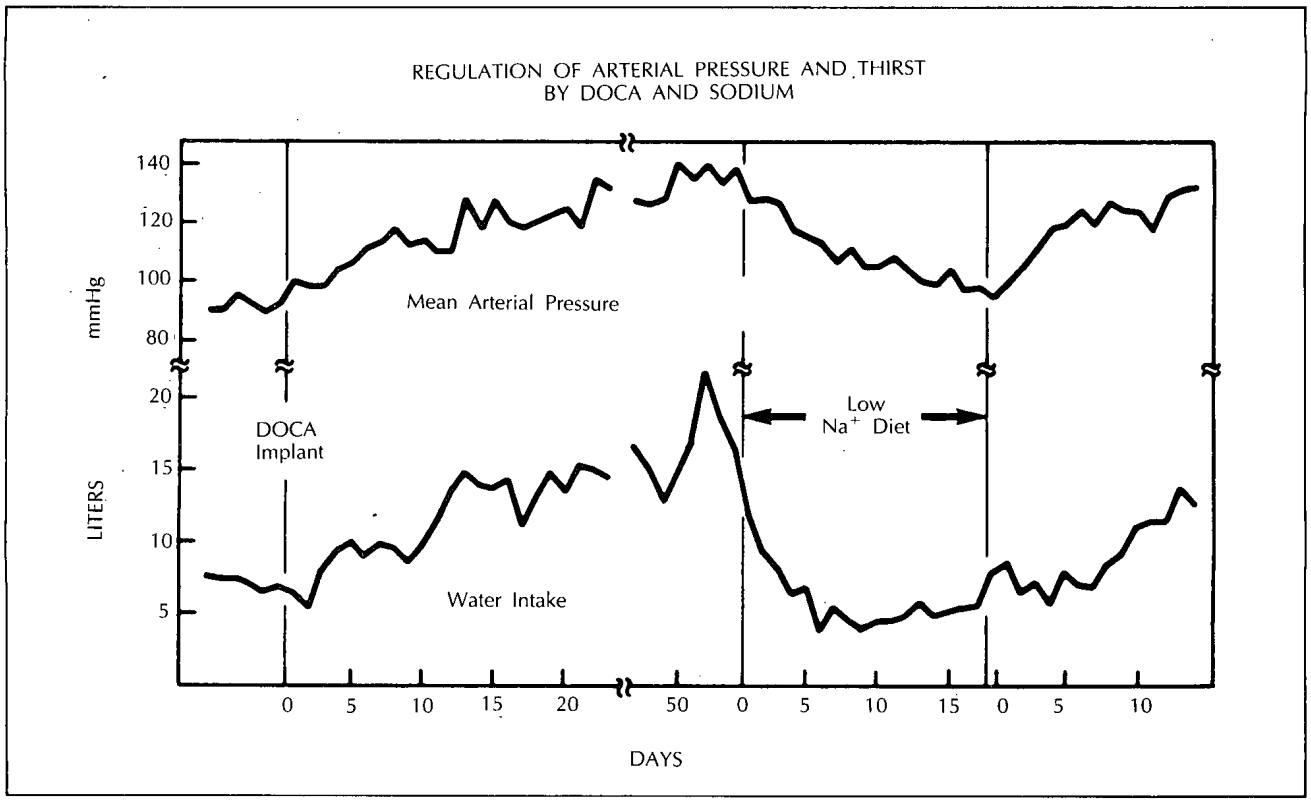

Fig. 15.—Desoxycorticosterone acetate (DOCA) administration in the pig caused parallel increases in mean arterial pressure and thirst. These changes were reversed when the dietary sodium intake was decreased from 200 to 20 mEq per day.

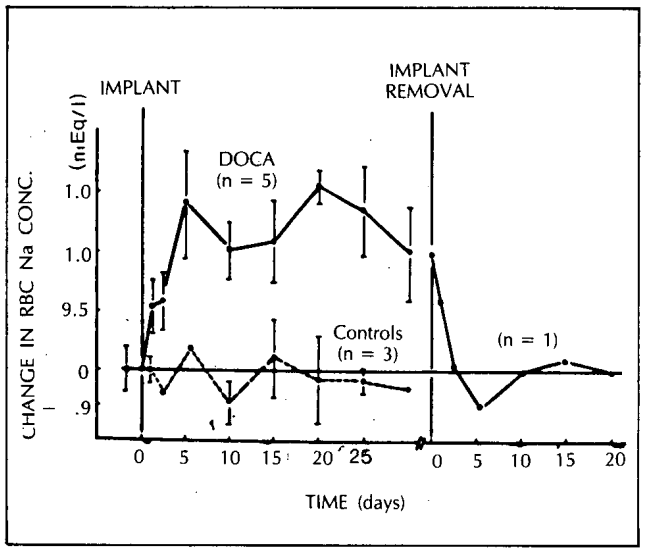

Fig. 16.—Effect of DOCA administration on red blood cell sodium content. Control values for sodium content of RBC was approximately 5 mEq per liter. The reversable change produced by DOCA amounted to a 30 % increase.

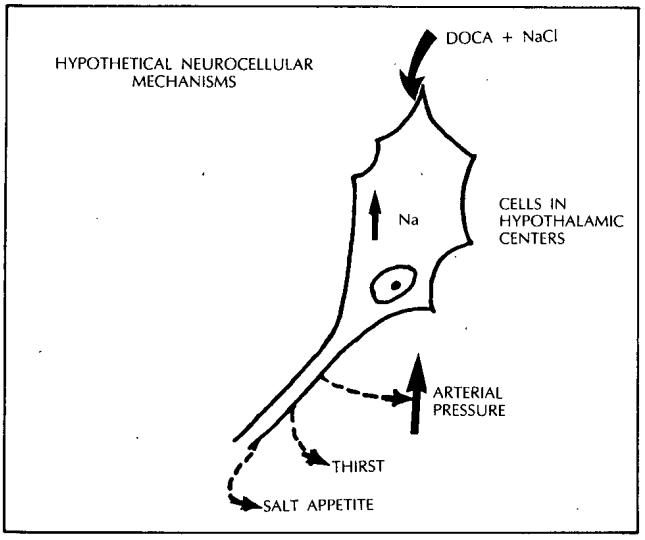

Fig. 17.—Hypothetical change produced by DOCA and NaCl in cells of brain regulatory centers for blood pressure, thirst and salt appetite. It is hypothesized that these paramenters are reset by an increase in intracellular sodium produced by this intervention.

increases approximately 30 % within five days of treatment with DOCA (Figure 16). The value rapidly returns to control levels following the end of DOCA treatment.

These observations have led to our hypothesis that DOCA plus NaCl cause an increase in intracellular sodium concentration of specific hypothalamic regulatory centers as it does in the red blood cell. This increase in intracellular sodium concentration is responsible for resetting centers so that there is an increase in arterial pressure, thirst and salt appetite (Figure 17).

I believe that this hypothesis is compatible with and supportive of the Mosaic Theory of Page. This theory depicts the involvement of several initiating factors and regulatory systems in the mechanism responsible for hypertension. Our hypothesis proposed that various initiating factors can cause specific cell membrane changes, and since these changes may occur in various regulatory centers, they may be reflected in altered function of the involved regulated systems.

References

1. Page IH: Pathogenesis of arterial hypertension. *Jr Am Med Assn* 140:451-458, 1949.
2. Mitchell J and Bohr DF: Experimental hypertension in the pig. In: *Handbook of Hypertension,* vol 4, Experimental and Genetic Models of Hypertension. W de Jong (ed), Elsevier Science Publishers, DV, pp 147-174, 1984.
3. Berecek KH and Bohr DF: Whole body vascular reactivity during the development of deoxycorticosterone acetate hypertension in the pig. *Circ Res* 42:764-711, 1978.
4. Koehler MF, Webb RC, Jones AW and Bohr DF: In vitro effects of desoxycorticosterone on vascular smooth muscle. *Am J Physiol (Heart Circ Physiol* 6):H197-H203, 1979.
5. Canessa M, Adragna N, Soloman HS, Connolly TM and Tosteson DC: Increased sodium-lithium countertransport in red cells of patients with essential hypertension. *N Engl J Med* 302:772-776, 1980.
6. Garay RP, Elghozi JL, Dagher G and Meyer P: Laboratory distinction between essential and secondary hypertension by measurement of erythrocyte cation fluxes. *N Engl J Med* 302:769-771, 1980.
7. Postnov YV and Orlov SN: Cell membrane alteration as a source of primary hypertension. *J Hypertension* 2:1-6, 1984.
8. Blaustein MP: Sodium transport and hypertension: Where are we going? *Hypertension* 6:445-453, 1984.
9. Friedman SM: Evidence of enhanced sodium transport in the tail artery of the spontaneously hypertensive rat. *Hypertension* 1:572-582, 1979.
10. Jones AW: Altered ion transport in vascular smooth muscle from spontaneously hypertensive rats: Influences of aldosterone, norepinepherine, and angiotensin. *Circ Res* 33:563-572, 1973.
11. Jones AW and Miller LA: Ion transport in tonic and phasic vascular smooth muscle and changes during deoxycorticosterone hypertension. *Blood Vessels* 15:83-92, 1978.
12. Hermsmeyer K: Electrogenesis of increased norepinepherine sensitivity of arterial vascular muscle in hypertension. *Circ Res* 38:362-367, 1976.
13. Noon JP, Rice PJ and Baldassani RJ: Calcium leakage as a cause of high resting tension in vascular smooth muscle from spontaneously hypertensive rat. *Proc Natl Acad Sci USA* 75:1605-1607, 1978.
14. Suzuki A, Yanagawa T and Tajiri T: Effects of some smooth muscle relaxants on the tonus and on the actions of contractile agents in isolated aorta of SHRSP. *Jap Heart J* 20(Suppl I):219-221, 1979.
15. Ross PV and Bohr DF: Resting and stimulated calcium influx in aortae of hypertensive rats. *Fed Proc* 43:649, 1984.
16. Bonaccorsi A, Hermsmeyer K, Aprigliano O, Smith CB and Bohr DF: Mechanism of potassium relaxation of arterial muscle. *Blood Vessels* 14:261-276, 1977.
17. Webb RC and Bohr DF: Potassium-induced relaxation as an indicator of Na^+-K^+ ATPase activity in vascular smooth muscle. *Blood Vessels* 15:198-207, 1978.

18. Webb RC: Potassium relaxation of vascular smooth muscle from DOCA hypertensive pigs. *Hypertension* 4:609-619, 1982.
19. Webb RC and Bohr DF: Potassium relaxation of vascular smooth muscle from spontaneously hypertensive rats. *Blood Vessels* 16:71-79, 1979.
20. Cohen DM and Bohr DF: Renal vascular potassium relaxation in two-kidney, one-clip hypertensive rats. *The Physiologist* 24:6, 1981.
21. Moreland RS, Lamb FS, Webb RC and Bohr DF: Functional evidence for increased sodium permeability in aortas from DOCA hypertensive rats. *Hypertension* 6:(Suppl I) I-86-I-94, 1984.
22. Moreland RS, Major RC and Webb RC: Contractile responses to ouabain and K^+-free solution in aorta from hypertensive rats. *Am J Physiol* 250 *(Heart Circ Physiol* 19):H612-H619, 1986.
23. Winquist RJ and Bohr DF: Structural and functional changes in cerebral arteries from spontaneously hypertensive rats. *Hypertension* 5:292-297, 1983.
24. Webb RC and Bohr DF: Mechanism of membrane stabilization by calcium in vascular smooth muscle. *Am J Physiol* 235 *(Cell Physiol* 4):C227-C232, 1978.
25. Holloway ET, Sitrin MD and Bohr DF: Calcium dependence of vascular smooth muscle from normotensive and hypertensive rats. In: *Hypertension* '72, J Genest and E Koiw, eds. Springer-Verlag, Berlin, pp 400-408, 1972.
26. Holloway ET and Bohr DF: Reactivity of vascular smooth muscle in hypertensive rats. *Circ Res* 33:678-685, 1973.
27. Jones AW and Hart RG: Altered ion transport in aortic smooth muscle during deoxycorticosterone acetate hypertension in rat. *Circ Res* 37:333-341, 1975.
28. Kwan CY, Belbeck L and Daniel EE: Abnormal biochemistry of vascular smooth muscle plasma membrane as an important factor in the initiation and maintenance of hypertension in rats. *Blood Vessels* 16:259-268, 1979.
29. Postnov YV and Orlov SN: Evidence of altered calcium accumulation and calcium binding by the membranes of adipocytes in spontaneously hypertensive rats. *Pflugers Arch* 385:85-89, 1980.
30. Devynck MA, Pernollet MG, Nunez AM and Meyer P: Calcium binding alteration in plasma membrane from various tissues of spontaneously hypertensive rats. *Clin Exp Hyper* 3:797-808 1981.
31. Van de Ven CJM and Bohr DF: Intrinsic difference in erythrocyte membrane in spontaneously hypertensive rats characterized by Na^+ and K^+ fluxes. Pflugers Arch 399:74-78, 1983.
32. Furspan PB and Bohr DF: Lymphocyte abnormalities in three types of hypertension in rat. *Hypertension* 7:860-866, 1985.
33. Furspan PB and Bohr DF: Calcium related abnormalities in lymphocytes from genetically hypertensive rats. *Hypertension* (in press), 1985.
34. Furspan PB, Jokelainen PT, Sing CF an Bohr DF: Genetic relationship between lymphocyte membrane abnormality and blood pressure in spontaneously hypertensive stroke prone and Wistar Kyoto rats. (Submitted) 1986.
35. Haeusler G, Finch L and Thoenen H: Central adrenergic neurons and the initiation and development of experimental hypertension. *Experientia* 28:1200, 1972.
36. Brody MJ, Fink GD, Buggy J, Haywood JR, Gordon FJ and Johnson AK: The role of the anteroventral third ventricle (AV3V) region in experimental hypertension. *Circ Res* 43(Suppl I):I-2-I-13, 1978.
37. Lamprecht F, Richardson JST, Williams RB and Kopin IJ: 6-Hydroxydopamine destruction of central adrenergic neurons prevents or reverses developing DOCA-salt hypertension in rats. *Jr Neural Transm* 40:149-158, 1977.
38. Gómez Sánchez EP: Introcerebroventricular infusion of aldosterone induces hypertension in rats. *Endocrinology* 118:819-823, 1986.
39. Thompson LP, Lamb F, Kaynard A and Webb RC: Blood pressure changes and vascular response to ouabain in centrally infused mineralocorticoid hypertensive rats. *The Physiologist* 28:270, 1985.
40. Soltis EE and Bohr DF: Central action of sodium chloride on blood pressure and vascular responsiveness in the rat. *Hypertension* 8(Suppl I): I-52-I-55, 1986.
41. Miller AW, Bohr DF, Schork AM and Terris JM: Hemodynamic responses to DOCA in young pigs. *Hypertension* 1:591-597, 1979.
42. Mitchell J, Ling WD and Bohr DF: Deoxycorticosterone acetate hypertension in sheep. *J Hypertension* 2:473-478, 1984.
43. Grekin RJ, Terris JM and Bohr DF: Electrolyte and hormonal effects of deoxycorticosterone acetate in young pigs. Hypertension 2:326-332 1980.
44. Bohr DF, Hamlin MN and Webb RC: Salt appetite and thirst during deoxycorticosterone acetate (DOCA) hypertension in the sheep (unpublished observation).
45. Guthe CC, Harris AL, Thio B, Moreland RS and Borh DF: Red blood cell sodium in the DOCA hypertensive pig. *Hypertension* 5(Suppl V):V-105-V-109, 1983.
46. Bohr DF: What makes the pressure go up? A hypothesis. *Hypertension* 3 (suppl. II): II-160-II-165, 1981.
47. Bohr DF and Webb RC: Vascular smooth muscle function and its changes in hypertension. *Amer Jr Med* 77:3-16, 1984.