THE importance of the calcium ion in muscle contractility and in the optimal functions of the cardiovascular and neurological systems has been recognized since the time of Ringer. A huge body of research data has been generated investigating various facets of the control of blood pressure, including the role of calcium in the biochemistry and physiology of contractile proteins. Interests have been renewed over the past decade on the role of calcium in genetic hypertension at the molecular as well as the organ or whole organism level. Many recent observations on this subject in humans with essential hypertension and in the rat model of spontaneous hypertension are of potential scientific and clinical interest. This review is an attempt to critically analyze the pertinent available data with the following objectives in mind:

1. To present the evidence for and against the role of calcium deficiency in genetic hypertension
2. To integrate the information on this subject under a working hypothesis
3. To define the important issues that need to be resolved
4. To suggest some areas and approaches of research that may fill in the gaps of our knowledge of the potential role of calcium in the pathogenesis of genetic hypertension

Evidence of Calcium Deficiency in Genetic Hypertension

Recent clinical\textsuperscript{1,3} and animal studies\textsuperscript{15-26} suggest a role of calcium deficiency in genetic hypertension. As the following list shows, the data can be grouped into six categories, which will be reviewed and discussed:

1. Hypercalciuria
   a. Hypertensive subjects\textsuperscript{1-3}
   b. Spontaneously hypertensive rats (SHR)\textsuperscript{15, 24, 26}

2. Reduced serum ionized calcium levels
   a. Hypertensive subjects\textsuperscript{3-27}
   b. SHR\textsuperscript{15-18}

3. Increased serum parathyroid hormone (PTH) levels
   a. Hypertensive subjects\textsuperscript{1, 3}
   b. SHR\textsuperscript{15, 18}

4. Decreased intestinal calcium absorption
   a. SHR\textsuperscript{10}

5. Low calcium intake associated with higher blood pressure
   a. Humans\textsuperscript{5-11}
   b. Animals\textsuperscript{20-23}

6. Oral calcium loading associated with reduced blood pressure
   a. Humans\textsuperscript{12-14}
   b. SHR and other animal models\textsuperscript{15, 23-26}

The presumed evidence falls into two broader categories: calcium deficiency and the inverse relationship between calcium intake and blood pressure; however, a cause and effect relationship cannot be established from inferences using indirect and often imprecise indices of calcium balance\textsuperscript{3-15} or from the mere association between reduced calcium intake (based on diet recall) and higher blood pressure.\textsuperscript{5-11} For example, in a study that directly measured external calcium balance, the adult SHR were found to retain more calcium than their normotensive controls, the Wistar-Kyoto rats (WKY).\textsuperscript{26} Because many confounding variables are not excluded in epidemiological studies, interpretation is difficult, as is exemplified by analyses of the first National Health and Nutrition Examination Survey (1971-1973) data by two independent groups of investigators,\textsuperscript{8, 28} which drew different conclusions.

Hypercalciuria

Hypercalciuria has been demonstrated in humans with essential hypertension\textsuperscript{1-3} and in adult SHR, as compared with their controls, the WKY.\textsuperscript{15, 24, 26} Not all forms of hypercalciuria are indicative of a calcium deficiency. In these studies, the role of hypercalciuria,\textsuperscript{2} the nonfasted status,\textsuperscript{3} and the higher sodium intake present only in hypertensive subjects\textsuperscript{3, 29} were never excluded as possible causes or contributing factors. At least in the SHR, the hypercalciuria was found to be absorptive and entirely dependent on food or calcium intake. When standard clearance techniques
were used, no detectable renal calcium leak could be demonstrated after an overnight fast either in the parathyroid intact state or after parathyroidectomy. Had it not been for the reduced sodium excretion rate, the lower calcium clearance rate in the SHR would imply enhanced renal calcium reabsorption, not tubular wastage. Furthermore, when directly measured, calcium balance and skeletal calcium deposits were found to be increased in the SHR.

**Reduced Serum Ionized Calcium Levels**

Serum ionized calcium levels have been found to be reduced in hypertensive subjects and SHR. It is unclear if these data truly reflect total body calcium economy because these studies did not exclude the role of respiratory alkalosis, fasting versus feeding, and differences in extracellular fluid volume status. For example, while total serum calcium concentration was not different from that in controls, serum phosphorus levels were reduced in the hypertensive patients, which is consistent with the interpretation of acute hyperventilation. The role of feeding is best illustrated by the increased serum ionized calcium levels found in the SHR when they were fed at midnight, shortly after a heavy calcium intake, since the rats are nocturnal animals.

**Increased Serum Parathyroid Hormone Levels**

Serum immunoreactive PTH levels have been reported to be increased in hypertensive subjects but the specificity and reliability of these findings referable to calcium homeostasis will remain uncertain unless and until the role of volume expansion and the status of magnesium balance are also defined. For example, when 24-hour urinary cyclic AMP excretion was evaluated, the SHR actually had decreased rates of excretion. In general, the literature is replete with observations in which ionized calcium and PTH levels could not be used to accurately predict calcium balance. Despite calcium deficits from increased resorption, increased serum ionized calcium and decreased PTH concentrations generally are seen, for example, in PO depletion and immobilization.

**Decreased Intestinal Calcium Absorption**

Decreased calcium absorption was recently described, based on recirculation perfusion studies across small intestinal segments of the anesthetized SHR or on experiments using isolated, everted duodenal sacs. Extrapolated to the entire intestine, these results would predict calcium malabsorption but clearly do not prove the presence of calcium deficiency. Conversely, virtually opposite results have been reported using essentially the same two techniques. This gross discrepancy in results has remained unexplained. Furthermore, in the natural, conscious physiological state, overall net calcium absorption along the entire intestine, as determined by balance studies or by the excretion of orally administered 44Ca, has been found to be increased in the SHR. In situ duodenal 44Ca uptake in conscious SHR was also found to be greater than that found in the control WKY. The bulk of the experimental findings is therefore incompatible with the notion of calcium malabsorption in the SHR. In the prehypertensive SHR, a similar hyperabsorptive phenomenon has been suggested by preliminary studies.

**Low Calcium Intake and Higher Blood Pressure**

Several laboratories have noted higher blood pressure in normotensive and hypertensive rats during long-term dietary calcium deprivation. There are, however, problems with the interpretation of these data. In addition to the obvious inference that calcium deficiency may lead to hypertension, there are other unexcluded factors, such as marked weight loss, growth retardation, severe secondary hyperparathyroidism, and magnesium depletion, which invariably accompanied long-term calcium deficiency. The PTH and magnesium depletion are well-known variables of vascular resistance and systemic blood pressure. Indeed, preliminary observations with mild calcium restriction within the physiological range failed to show an elevation in blood pressure despite 50% reduction in calcium balance as long as normal growth was maintained.

**Oral Calcium Loading and Reduced Blood Pressure**

The sixth line of evidence is the association observed by several epidemiological surveys between reduced intake of dairy products and higher blood pressure, though the latter was generally within the normal range. All these studies are open to the following criticisms. First, the method of dietary recall by questionnaires is obviously fraught with problems of accuracy and reliability. Second, factors that influence preference or avoidance of dairy products may independently affect blood pressure. Conceivably, the conscious reduction in milk and cheese consumption, for example, was the consequence of obesity, which was present in one study and which is known to be correlated with higher blood pressure. Third, differences in other nutrients and ions like potassium could not be eliminated in these population studies, which could affect blood pressure independently of calcium. It is well known that potassium supplement is natriuretic and antihypertensive and that potassium deficiency has the opposite effects.

Fourth, "soft" water is not necessarily lower in calcium alone. If magnesium and potassium were similarly affected, a relative deficiency of these other ions is just as likely to contribute to the higher blood pressure as is calcium deficiency. Fifth, and most crucial of all, epidemiological surveys can at best establish an association. Even if the other reservations could be removed, a causal role has yet to be proven.

Finally, and perhaps theoretically the strongest support for the postulate of calcium deficiency in genetic hypertension, oral calcium loading has been found to be associated with a decline in blood pressure in hu-
Doubts were raised, with that in controls that were matched for age, sex, amount of calcium was accompanied by a slight but significant reduction in blood pressure as compared with that in controls that were matched for age, sex, strain, and species. Doubts were raised, however, by the findings that long-term intraperitoneal calcium injections, which achieved a comparable magnitude of hypercalcemia, could not reproduce these results.

Perhaps more importantly, when the reduction in PO$_4$ balance that accompanied oral calcium loading was prevented, the antihypertensive effect was also abolished, which suggests that reduced PO$_4$ balance rather than increased calcium balance is the mediator. Direct and unequivocal effects of PO$_4$ deficiency on vascular resistance have recently received additional support. Nonetheless, preliminary clinical trials suggested an overall 6.5 mm Hg fall in standing systolic blood pressure in about 30 hypertensive patients treated for 8 weeks with 1 g of calcium supplement, which is arguably a nonpharmacological dose. Even if these effects proved to be statistically significant and extended to diastolic blood pressure, whether they are mediated by the mechanism of augmenting calcium balance would remain an issue. Actually, a small and initial natriuresis would have been missed without serial sodium balance data in the early phase of calcium supplementation, as was observed during the first week of instituting dietary calcium supplement. In addition, a small reduction in PO$_4$ balance would not be detectable by merely measuring outpatient serum and urine PO$_4$ at 2- to 4-week intervals, unless PO$_4$ intake and output (in the stool and urine) were quantified. Conceivably, long-term changes in PTH levels may produce effects on blood pressure that are very different from that of the acute vasodilation and hypotension.

It should be noted that preliminary findings suggest that other maneuvers that increased calcium balance without reducing PO$_4$ balance, as was produced by the administration of 1,25 dihydroxy-vitamin D$_3$ or magnesium supplements, failed to attenuate the severity of hypertension in the SHR or reduce the blood pressure in the WKY rats. Initial trials in hypertensive subjects also failed to document any antihypertensive effects with 1,25 dihydroxy-vitamin D$_3$ administration. Taken together, the available clinical and experimental data do not at present justify the conclusion that genetic hypertension is characterized by deficits in calcium. Until this conclusion is firmly established, it would be premature, in our opinion, to base therapeutic decisions on such incomplete and equivocal findings. Furthermore, an equally impressive if not more solid body of evidence has been accumulated, which offers a cogent argument for the role of calcium excess in the genesis or the maintenance (or both) of the hypertensive state, and will be summarized in the succeeding pages.

Evidence of the Calcium Excess in Hypertension
Observations implicating a role of calcium excess in hypertension can be divided into the following six categories:

1. Vasoconstrictive and hypertensive effects of acute hypercalcemia have been produced by calcium injections.
2. Chronic hypercalcemia from vitamin D overdose or hyperparathyroidism, or both, has been associated with hypertension.
3. Decreased contractility of vascular smooth muscle by calcium-channel antagonists and other vasodilators has been associated with reduced cytoplasmic free calcium or with $^{45}$Ca fluxes predictive of such a reduction.
4. Increased cytosolic free calcium has been observed in the platelets of hypertensive men and lymphocytes of SHR.
5. Increased intracellular calcium content of adipocytes has been found in hypertensive patients and SHR. Increased calcium balance has been found in SHR.

Vasoconstrictive and Hypertensive Effects of Acute Hypercalcemia
Current concepts suggest that the final common pathway for the control of vascular reactivity and, ultimately, peripheral vascular resistance lies at the level of the vascular smooth muscle cell. Contracture of the smooth muscle cell depends on the interaction, attachment, and cycling of cross bridges between the actin and myosin filaments, the contractile proteins. The mechanical process is therefore initiated by a rise in cytosolic free calcium concentration. Thus, regardless of the precise pathogenetic factors mediating the hypertension, be they neural, humoral, cardiac, metabolic, myogenic, or any combination thereof, a common denominator at the cellular level is an alteration in free calcium concentration in the muscle cells.

Increases in extracellular fluid calcium concentration (e.g., acute hypercalcemia as produced by intravenous calcium administration) have been found on numerous occasions to be associated with systemic hypertension and increased peripheral vascular resistance, which is consistent with the prediction by the current concepts. These vasoconstrictive effects can be attributed to increased contractility of vascular smooth muscle in response to presumably elevated cytoplasmic calcium concentrations. Indirect and direct $^{45}$Ca flux measurements in response to high potassium depolarization, noradrenaline stimulation, and their blockade by lanthanum or calcium channel antagonists have firmly established the role of increased cytosolic free calcium in mediating the excitation-contraction coupling of myocytes in isolated venous or intact vascular beds, regardless of whether the increment is derived from extracellular calcium or intracellular calcium pools. In contrast, many vasodilatory and antihypertensive agents were found to exert their effects by interference with the calcium-dependent mechanisms or by a reduction in cytoplasmic ionized calcium concentration.
Chronic Hypercalcemia

The clinical literature is also replete with instances of hypertension in sustained hypercalcemic states, caused by vitamin D overdose or hyperparathyroidism. A positive correlation between serum calcium levels and systolic, as well as diastolic, blood pressure was also recently reported in a large series involving Belgian army recruits.

Decreased Contractility of Vascular Smooth Muscle

Decreased contractility of vascular smooth muscle in response to a variety of vasodilatory and antihypertensive agents, such as adenosine, \( \beta \)-adrenergic blocking agents, \( \beta_{1} \)-adrenergic blocking agents, hydralazine and calcium channel antagonists, generally is associated with a reduction in cytoplasmic free calcium, if measured directly or with alterations in \( ^{40} \) Ca fluxes that would predict such a reduction. On the other hand, the increased vascular reactivity observed in SHR, \( ^{93,94} \) has been attributed to the membrane leakiness to calcium, similar to that for sodium, potassium, and chloride, \( ^{97} \) although, as will be discussed, the evidence for defective membrane calcium regulation is largely indirect.

Increased Cytosolic Free Calcium

Measurements of peripheral blood elements such as platelets in hypertensive patients and lymphocytes in SHR, using fluorescence signals of quin 2, a calcium chelating dye, have also revealed increased intracellular free calcium concentration. More importantly, patients with borderline hypertension were found to have mildly elevated calcium levels, which were intermediate in value between the normotensive and the frankly hypertensive subjects. Furthermore, long-term treatment of the hypertension with thiazide diuretics and \( \beta \)-adrenergic blocking agents was found to restore the cytosolic free calcium to normal. These investigators also obtained a significant correlation between blood pressure and platelet intracellular calcium concentration. These results confirmed but extended the observed association between reduced force generation by adenosine in ferret portal vein strips and the reduced cytoplasmic free calcium concentration, as determined by aqueorin, a bioluminescent protein. They also corroborated the calcium flux data across coronary arteries in adenosine-treated dogs and reinforced the results of calcium uptake in adenosine-treated intact and cultured vascular smooth muscle cells.

Increased Intracellular Calcium Content of Adipocytes

Kinetic studies using \( ^{45} \)Ca fluxes suggested that the two slowly exchanging intracellular calcium pools in adipocytes are enlarged in SHR, \( ^{35} \) regardless of whether the animals had previously been adrenalectomized or rendered normotensive by peripheral immunosuppression. Similar results have also been reported in the adipose tissue of hypertensive patients by this laboratory. These findings are further indications that the derangements in calcium metabolism in genetic hypertension tend to be characterized by intracellular calcium excess rather than deficiency. Since the SHR subjected to sympathectomy had maintained normal blood pressure from the fourth through the ninth week (the time of study), the increased intracellular calcium pools were unlikely to be the consequence of hypertension. In this connection, the persistence of the hypercalciuria in hydralazine-treated adult SHR reinforced the concept that disturbances in calcium metabolism in genetic hypertension are not secondary to untreated hypertension.

Increased Calcium Balance

As was mentioned earlier, when complete external calcium balance was measured directly, the adult SHR were found to retain more calcium than were the control WKY. This finding was true for both sexes and clearly attributable to intestinal hyperabsorption of calcium. Skeletal calcium accumulation was also increased in the hypertensive animal. Preliminary studies in \( 3/4 \)-week-old normotensive SHR also revealed similar balance results, which indicates that these changes precede the onset of hypertension and that they may conceivably play a role in the subsequent elevation of blood pressure. Absorption of \( ^{45} \)Ca in the conscious intact animal, as measured by urinary recovery, was also increased in the SHR which supports our group’s findings.

Calcium deposition in bone has also been shown to be higher in SHR, \( ^{26} \) as have the calcium contents in the tail artery and aorta of hypertensive rats. Thus, the weight of the presently available evidence on the issue of disturbances in calcium metabolism favors the view that intracellular calcium is abnormally elevated in the hypertensive state, at least in tissues studied thus far. At least three possible and not necessarily mutually exclusive explanations may partly reconcile the apparent paradox between parenteral and oral calcium loading, on the one hand, and the conflicting results obtained using different indices of calcium balance and metabolism, on the other hand: 1) generalized membrane defects in calcium regulation, 2) role of PTH, and 3) membrane stabilizing effect of high calcium levels.

Membrane Defects in Calcium Regulation

The observations of reduced serum ionized calcium and elevated PTH levels by some though not all investigators are not necessarily incompatible with intracellular calcium excess if one accepts the hypothesis of a membrane defect in calcium regulation in genetic hypertension. In the most simplistic scheme, too much calcium is distributed inside the cytosol as free ionic calcium owing to a combination of increased leakiness across the plasma membrane, decreased effectiveness of the extrusion mechanism(s) (or incomplete compensation by the calcium-dependent ATPase), reduced capacity for buffering cytosolic calcium, or increased calcium release by intracellular organelles, such as the mitochondria, endoplasmic reticulum, or sarcoplasmic reticulum. This hypothesis does not address or depend on the issue of whether the derangements in calcium
transport are causes for or effects of the hypertension, if they are related at all. Emerging evidence tends to argue against the second possibility, however, since many of these changes predate the onset of hypertension. The direct observations consistent with this membrane hypothesis are tabulated in the following list and will be briefly summarized.

1. Duodenal epithelium: increased calcium absorption.
2. Renal epithelium: increased calcium reabsorption.
3. Lymphocytes of SHR and platelets of men with essential hypertension: increased cytosolic free calcium.
4. Red blood cells
   a. Increased passive influx and permeability.
   b. Decreased ATP-dependent calcium extrusion.
   c. Decreased $^{45}$Ca binding to inner membrane.
5. Adipocytes
   a. Decreased endoplasmic reticular $^{45}$Ca uptake.
   b. Increased mitochondrial $^{45}$Ca uptake.
   c. Increased intracellular fluid calcium pool.
6. Arteries
   a. Increased $^{45}$Ca uptake (aortic strip).
   b. Increased calcium accumulation in tail artery and aorta.
7. Vascular smooth muscle
   a. Decreased microsomal $^{45}$Ca uptake.
   b. Increased sarcolemmal $^{45}$Ca influx.
   c. Decreased binding of $^{45}$Ca to inner membrane.
   d. Increased calcium-dependent ATPase in microsome.
8. Cardiac myocyte
   a. Decreased sarcoplasmic reticulum $^{45}$Ca uptake.
   b. Decreased microsomal $^{45}$Ca uptake.

Despite conflicting data, duodenal calcium transport in situ and in vitro has been found to be increased, which corroborates the net calcium absorption results reported by balance studies. Tubular calcium reabsorption was found to be increased, a difference that recently was demonstrated to be independent of PTH levels, changes in ultrafilterable calcium levels, and sodium and calcium excretion rates. Cytosolic free Ca calcium has been shown to be increased in platelets of hypertensive men and lymphocytes of SHR, as previously mentioned. Disturbances in calcium fluxes and permeability have been reported in a variety of plasma membranes of the SHR, including erythrocytes, adipocytes, and myocytes. For instance, passive influx of $^{45}$Ca across ATP-depleted erythrocytes was found to be abnormally increased as early as 3 weeks of age in SHR. Decreases in ATP-dependent calcium extrusion, as reflected by lanthanum-sensitive, calcium-dependent ATP hydrolysis, also was observed, which is consistent with reduced calcium pump activity. Binding of $^{45}$Ca to inner surface of plasma membrane was reduced in erythrocytes of SHR and hypertensive subjects. Together, these data suggest that if there were no counter-regulatory mechanisms, cytosolic calcium in these tissues ought to be increased in genetic hypertension, as was found in platelets and lymphocytes, which, as far as we know, are the only tissues directly studied thus far.

As previously mentioned, the intracellular calcium pool in adipocytes of SHR and hypertensive man has been found to be enlarged and was associated with reduced endoplasmic reticulum $^{45}$Ca uptake. Total calcium content was found to be increased in the tail arteries and aorta of hypertensive rats, and short-term flux studies also demonstrated an increased rate of $^{45}$Ca uptake, which was presumably caused by increased passive leakage. In vascular smooth muscle membrane vesicles preparations, similar decreases in $^{45}$Ca uptake by the microsomal fraction and by the inner surface of plasma membrane have been documented in the SHR and have been associated with increased influx across the sarcolemma. The latter could also be substantiated in 3-week-old SHR before any demonstrable hypertension was apparent.

Decreases in $^{45}$Ca uptake by sarcoplasmic reticulum and by the microsomes have been reported in the cardiac muscle cells of the SHR. One, though not the only, inference of these findings is decreased sequestration of calcium by intracellular buffers and, presumably, a consequent increase in cytosolic calcium. To the best of our knowledge, direct measurements in the vascular smooth or cardiac muscle with cardiac-selective microelectrodes or quin 2, or both, to compare the SHR and normotensive control have not been published. If confirmed, these changes clearly could provide a cellular basis for increased muscle contractility, vascular reactivity, and resistance ultimately leading to systemic hypertension.

While the present state of our knowledge is fragmentary and at times conflicting or even confusing, there appears to be a consensus that fundamental defects exist in calcium homeostasis in the SHR and, probably, in human essential hypertension. The basic abnormalities have yet to be defined, and a lot more information is needed at the cellular and organ level before one can objectively and adequately address the controversial issue of calcium supplementation in essential hypertension, its scientific rationale, if any, and its potential therapeutic benefits.

**Role of Parathyroid Hormone in Hypertension**

The second possible explanation for the apparent paradox in the effects on pressure between oral and parenteral calcium loading is the role of changes in PTH levels, as the following list briefly enumerates.

1. Excess PTH
   a. Primary hyperparathyroidism is often associated with hypertension in humans that resolved following surgical repairs.
   b. Long-term PTH administration has been shown to increase arterial blood pressure in humans and rats.
2. Parathyroidectomy was found to attenuate hypertension, which reappeared following parathyroid gland autotransplantation.
3. PTH has been shown to act as an endogenous calcium ionophore across vascular and other tissues.

It should be quickly stated that the effects of short-term and long-term PTH administration are probably very different. In the short term, PTH or its biologically active fragments have been found to...
produce a marked but transient vasodilatation, and the hypotensive effects last only a few minutes.\textsuperscript{30, 114, 124-127} Much as the biochemical mechanism is poorly defined, the physiological relevance of this short-lived effect in the clinical setting is obscure. In contrast, long-term administration of PTH to humans\textsuperscript{113} and rats\textsuperscript{114} was reportedly associated with sustained hypertension. This finding constitutes the first line of evidence suggesting that PTH plays a role in hypertension. In these situations, relative hypercalcemia was invariably present. Therefore, the separate effects of excess PTH and elevated serum calcium concentration could not be differentiated, as was often the case with primary hyperparathyroidism in clinical settings.\textsuperscript{37, 40, 41, 112} Primary hyperparathyroidism, occurring either in nature or in experiments, cannot be equated to a mere increase in serum PTH and serum calcium, since many other metabolic derangements are known to coexist, including changes in metabolism of calcium, PO\textsubscript{4}, magnesium, and vitamin D. Nevertheless, it is generally true that the combination of PTH excess and hypercalcemia is accompanied by hypertension. Resolution of the hypertension has indeed been reported following surgical parathyroidectomy, although the precise mechanism was not defined in these clinical cases.\textsuperscript{37, 40}

Parathyroidectomy has been found to attenuate the magnitude of hypertension in SHR\textsuperscript{36, 115, 118} and in deoxycorticosterone acetate-salt treated rats.\textsuperscript{116, 117} However, the role of the concomitant hypocalcemia, as a result of the long-term absence of PTH,\textsuperscript{36, 115-117} or that of oral calcium loading\textsuperscript{118} could not be dissociated. In the rats, retarded growth invariably follows parathyroidectomy,\textsuperscript{36} which per se could modify the hypertension. Nevertheless, the combination of PTH deficiency and hypocalcemia appears to be frequently associated with hypertension, which is the opposite picture of the pressure and biochemical changes seen in primary hyperparathyroidism and discussed above. When the parathyroid gland was autotransplanted back to the SHR that had undergone parathyroidectomy, elevated systolic blood pressure indeed reappeared.\textsuperscript{36}

In a variety of tissues, including rat aorta,\textsuperscript{119} cardiac cells,\textsuperscript{119} erythrocytes,\textsuperscript{120} and renal tubular cells,\textsuperscript{121, 122} intracellular calcium uptake by isotopic or quin 2 techniques has been found to be elevated by PTH, as if the hormone acted as a natural or endogenous calcium ionophore\textsuperscript{123} with calcium and cyclic AMP serving as the two intracellular secondary messengers. If a short-term rise in cytoplasmic calcium is the ultimate trigger to initiate contraction,\textsuperscript{56, 73-76, 78, 94} then the increased influx of calcium facilitated by PTH should enhance vascular tone and reactivity, which would increase resistance and blood pressure.

The accentuation by long-term PTH administration of the hypertension induced by deoxycorticosterone acetate and salt administration,\textsuperscript{116} the blunted vascular reactivity,\textsuperscript{117} and the reduced calcium content after parathyroidectomy\textsuperscript{115} are all consistent with the hypothesis that PTH exerts an ionophoretic and therefore a permissive effect on the vasoconstrictive and hypertensive action of extracellular fluid calcium.\textsuperscript{123} According to this postulate, increased calcium entry alone ought to enhance smooth muscle contractility and increase the blood pressure; PTH facilitates calcium influx and potentiates the effect of hypercalcemia as in clinical and experimental hyperparathyroidism. The absence of PTH, coupled with hypocalcemia, would produce the opposite effects. When endogenous PTH is suppressed by oral calcium loading, two opposing effects are at play; functional hypoparathyroidism tends to diminish and mild hypercalcemia tends to enhance muscle contractility. According to this postulate, the net effect favors an attenuated vascular reactivity, expressed as a reduction in blood pressure, as was found in many clinical\textsuperscript{12-14} and animal studies.\textsuperscript{13, 23-26} This concept is further supported by the hypotensive effect of oral magnesium loading (0.96% vs the normal 0.21% magnesium diet), which is similar to that of calcium loading in deoxycorticosterone acetate hypertension.\textsuperscript{36} It must be emphasized that not all studies evaluating the effects of magnesium loading produced these findings,\textsuperscript{28, 128} and even if confirmed, the mechanism may lie in membrane competition between calcium and magnesium,\textsuperscript{97} rather than PTH suppression.

On the other hand, acute hypercalcemia resulting from intravenous calcium infusion elevates systemic arterial blood pressure, presumably because the net balance of the two opposite actions is tilted in favor of hypercalcemia. Although much of the published literature could be accommodated by this interpretation, not every piece of conflicting data could be so resolved. For example, it remains to be explained why in parathyroidectomized SHR, an antihypertensive effect of oral calcium loading was still evident, when compared with identically treated rats fed a normal calcium diet.\textsuperscript{97} Furthermore, this hypothesis would not explain the absence of a blood pressure difference between intact and parathyroidectomized rats fed the same normal calcium diet\textsuperscript{97} or the lack of a hypotensive effect with magnesium supplementation in intact SHR that demonstrated augmented calcium absorption and calcium balance.\textsuperscript{35} Clearly, if PTH modulates the rate of transmembrane calcium fluxes and if the final signal to vascular smooth muscle contraction is a transient rise in cytosolic free calcium, this hypothesis can only be tested directly by applying a calcium-selective micro-electrode to accessible vascular tissues. Alternatively, changes in PO\textsubscript{4} balance and extracellular fluid volume status may indeed play a role in the antihypertensive effects of oral calcium loading. The role of alterations of PO\textsubscript{4}, sodium, and possibly magnesium balance must be specifically and appropriately evaluated in future clinical and animal trials to study the mechanism whereby oral calcium supplements, unique among all attempted maneuvers that promote greater calcium retention, produce an antihypertensive effect.

**Dual Effects of Calcium**

The third possibility that could resolve much of the existing controversy is the concept that the calcium ion
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exerts more than one biochemical effect on vascular reactivity. For example, more than 2 decades ago Bohr* suggested that the "membrane excitation" of rabbit aorta, corresponding to the fast component of contractile responses to epinephrine, may actually be reduced by a medium high in calcium (>3 mM), whereas the "coupling" process, corresponding to the slow component of the force development, is dependent on an optimal concentration of calcium in the medium (around 1.0 mM). Bohr termed the reduction in force development the membrane stabilization effect of calcium. The thesis gained further support in subsequent experiments by Webb and Bohr,\(^{77, 85}\) which compared the relaxing effects of calcium and potassium in helical strips of rat tail artery after norepinephrine stimulation. The membrane stabilization effects of these two ions were attenuated by ouabain, reduced temperature, and media low in sodium and potassium concentrations, which is consistent with either stimulation of the Na, K-ATPase or reduction in ion conductance. In this context, it is conceivable that calcium supplementation may exert a similar membrane stabilization effect.

These results must be interpreted with caution, however, since these levels of hypercalcemia (3–20 mM of ionized calcium) are rarely experienced in pathophysiological conditions that are compatible with life. In fact, in a medium with a calcium level below 4.0 mM, contraction was directly related to calcium concentrations.\(^ {77}\) In the original experiments, within the first 10 minutes of withdrawing calcium from the bathing solution, the fast component of the force contractile response was reduced before is registered a 15% increase.\(^ {56}\) In addition, the vascular strip preparation had to be previously stimulated by epinephrine\(^ {56}\) or norepinephrine.\(^ {77}\) Finally, the calcium concentration in the medium was always increased in stepwise fashion, so that without an appropriate time control lasting a full hour between two maneuvers, it is not clear whether the reduced contraction observed was necessarily associated with the further increment in calcium concentration.

All these reservations must be borne in mind when extrapolating their results to the interpretation of data concerning the role of calcium in hypertension. Although potentially interesting, it is uncertain that these experiments are clinically relevant when other manipulations achieving similar degrees of hypercalcemia failed to reduce the blood pressure. Again, intracellular free calcium measurement in response to all these maneuvers would be invaluable to assess this theoretical explanation.

Conclusions

More research clearly is needed to define the direction and nature of disturbances in calcium metabolism in genetic hypertension. Based on analyses of the available literature, we favor the view that cytosolic free calcium concentrations are abnormally increased, regardless of what extracellular fluid biochemical indices would suggest. The underlying mechanism is not defined but, hypothetically, is most likely related to a generalized defect in membrane calcium regulation\(^ {105}\) that is genetically transmitted rather than acquired as a consequence of the hypertension. The precise relation, if any, of altered membrane permeabilities to other ions,\(^ {129}\) in particular sodium,\(^ {130–135}\) is not clear.

As shown in Figure 1, a plausible working hypothesis could integrate the concepts of Dahl,\(^ {130}\) de Wardener and MacGregor,\(^ {134}\) Bianchi and co-workers,\(^ {136–138}\) Blaustein and Hamlyn,\(^ {130}\) and others.\(^ {130, 135, 139, 140}\) This model suggests that, in genetic hypertension, the renal tubule is abnormally sodium retentive before the onset of hypertension.\(^ {136–140}\) Which expands the intrathoracic blood volume\(^ {134}\) and ultimately increases cellular sodium content.\(^ {131}\) If this pathophysiological sequence of events is proved correct, then circulating inhibitors for Na, K-ATPase would be increased and sodium transport would be reduced.\(^ {130, 134, 135}\) The sodium pump inhibition may partially offset the intrinsic renal defect in sodium retention, but across a variety of vascular tissues, intracellular sodium content would increase, norepinephrine release would be enhanced while natriuresis would be reduced.\(^ {130}\) An additional cellular mechanism involves the reduced transcellular sodium gradient (caused by increased cytosolic sodium) and a reduced calcium extrusion by the Na-Ca exchange mechanism. Such a formulation would provide a theoretical basis for some of the intracellular and membrane calcium abnormalities in SHR. Presently, however, the existence and the role of this exchange mechanism in vascular smooth muscle cell are poorly documented\(^ {131–134}\) and have been seriously questioned.\(^ {78, 98}\)

![Figure 1. A hypothetical model for genetic hypertension.](http://hyper.ahajournals.org/Download/...)

ECF = extracellular fluid; ANF = atrial natriuretic factor; PTH = parathyroid hormone.
This model is intended to accommodate the role of many potential and well-established factors, other than calcium, in the pathogenesis of genetic hypertension. Clearly, the challenge to basic and clinical investigators alike is a better in vitro and in vivo understanding of the chronology of, mechanisms for, and relationships between the abnormalities in membrane regulation of the various ions. To achieve this, we need studies employing newer tools such as calcium-sensitive dyes, ion-selective microelectrodes, better tissue culture techniques for vascular smooth muscle cells, and more sophisticated approaches in protein biochemistry and molecular biology. Until additional information derived from these sources is made available, the role of calcium in the pathogenesis or maintenance of hypertension will remain incompletely understood.

Acknowledgment

The authors thank Lorraine Butler for her secretarial support.

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Hypertension. 1985;7:657-667
doi: 10.1161/01.HYP.7.5.657

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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