THOMAS KUHN identified the processes through which new scientific paradigms arise (70). The process begins with “normal science,” where we work within an existing paradigm that defines our scientific approach. But normal science generates anomalies that can only be resolved through a “revolution” that generates a new paradigm to replace the old one. Kuhn defined an anomaly as a “violation of the paradigm-induced expectations that govern normal science” (70). Kuhn’s definition of a paradigm included anything “sufficiently unprecedented to attract an enduring group of adherents away from competing modes of scientific activity” and “sufficiently open ended to leave all sorts of problems for the redefined group of practitioners to resolve” (70). Arthur Guyton and Thomas Coleman’s theory of the role of the kidney in long-term control of arterial pressure and the pathogenesis of hypertension fits nicely with this definition.

Nevertheless, advancement in science is characterized by the replacement of established paradigms with new ones. This is why paradigms are so useful; they allow us to advance our theoretical understanding of, in our case, human biology and medicine, by making it “less wrong.” In this article, we examine the anomalies that could be considered to challenge the “Guytonian paradigm” of the role of the kidney in long-term control of blood pressure. Our intention is not to propose a new paradigm, but to consider where we are in the “Kuhn cycle” that drives paradigm change (70). We particularly highlight the evidence that, except in experimental models associated with extreme volume retention, both renal excretory dysfunction and dysfunction of the systemic vasculature are associated with the development of hypertension.

There is a long history of criticisms of the Guytonian paradigm, dating back to the time soon after the first publications of Guyton, Coleman, and colleagues’ on the subject (36). Moreover, some of these authors have even suggested what might be called alternative paradigms (20, 65, 71, 89). In this respect, it could be argued that we have little new to offer. But...
rather than advocate for or against the Guytonian paradigm, we aim to identify the central questions that should be addressed to advance the field.

**Guytonian Paradigm**

Arthur Guyton described with passion the moment of epiphany, in which he and Thomas Coleman arrived at the interdependent conclusions that define what we will refer to herein as the Guytonian paradigm: 1) that hypertension can only develop if the relationship between arterial pressure and sodium and water excretion is shifted to a higher level of arterial pressure and 2) that the renal body fluid mechanism has infinite gain to control arterial pressure (46). The concept has endured for more than five decades, perhaps in part because it shares many of the characteristics of a good theory outlined by Kuhn (69). That is, the Guytonian paradigm is first accurate in the sense that its consequences are largely in agreement with the results of existing experiments. It has been bolstered by the results of computational modelling, which have allowed the predictions of the paradigm to be compared quantitatively with experimental observations. Generally, the more reliably a particular model is able to simulate experimental observations made under disparate conditions, the greater confidence we can have in the theoretical basis of the model. However, concordance between simulated data and the results of real experiments does not necessarily qualify all elements of the model as different models may provide similar results. Models are wonderful workshops of hypotheses, but not necessarily sponsors of reality. Second, the Guytonian paradigm is also internally consistent and was different from then current concepts, so novel. The great breakaways were the crucial involvement of the kidney in long-term blood pressure control. This conceptual breakthrough was based on unique (albeit initially pathophysiological) long-term experiments demonstrating narrow relations between 1) blood volume and cardiac output, 2) cardiac output and blood pressure, and 3) blood pressure and volume excretion, and the application of comprehensive modelling of these and associated relationships. Third, it also has a broad scope, offering a coherent framework for understanding both physiological control of arterial pressure and the development of hypertension; fourth, is relatively simple, in that its centerpiece comprises only two concepts (see above) (45–47), although they imply several operational features based on modelling alone; and fifth, has been fruitful in the sense that it has driven multiple lines of research over decades. It is disappointing, however, that the mechanisms of pressure natriuresis remain unclear despite the explosive increase in insight into cellular and molecular biology (30), and that progress with regard to understanding the mechanisms of essential hypertension has been limited.

The consequence of the paradigm is that sodium excretion is a monotonous function of arterial pressure. Therefore, the long-term set point of arterial pressure must be at the point of intersection of the pressure natriuresis curve and the daily intake of salt and water (23, 47). That is, arterial pressure varies around an average level that allows maintenance of homeostasis of extracellular fluid volume (Fig. 1). There are several important criticisms of the paradigm set out in Fig. 1.

First, the “acute pressure natriuresis” curve shown schematically in Fig. 1A was derived exclusively from studies of anesthetized animals and isolated perfused kidneys, in which the renal excretory responses to manipulation of renal perfusion pressure could be observed. As previously discussed (11), multiple studies document that anesthesia and surgery induce major changes in multiple regulatory pathways, and that results obtained in anesthetized animals are not necessarily meaningful with regard to sodium homeostasis.

Second, in the “chronic pressure natriuresis curve” depicted schematically in Fig. 1B, the independent and dependent variables are not presented in the conventional way. The data upon which this figure is based were derived from experiments in which both sodium excretion and mean arterial pressure (MAP) were measured at various levels of sodium intake. Yet the independent variable (sodium intake estimated from sodium excretion) is plotted on the ordinate and the dependent variable (MAP) is plotted on the abscissa.

Third, in most of the experimental studies in which this relationship was derived in intact animals, its slope did not...
differ measurably from infinity (22), or was even negative (92), compatible with the notion that arterial blood pressure is not sensitive to salt intake. It could be argued that the absence of a finite slope of the pressure-natriuresis relationship under steady-state conditions is the consequence of a long-term regulatory mechanism operating with infinite gain. Real cellular and systemic mechanisms compatible with such control have not been proposed, but might involve integrative control (activity being a function of the time integral of the error signal) rather than the usual proportional control (activity being a function of the magnitude of the error signal). However, even such a hypothetical, integrative control system would require an initial error signal to initiate regulation. As we discuss below, there is also an important caveat that must be applied to the concept of infinite gain of the renal-body fluid feedback mechanism for the long-term control of arterial pressure (see Misinterpretation 2, below). Moreover, robust increases in sodium excretion with sodium loading may well occur without any increase in blood pressure (see anomaly 1 below).

Nevertheless, provided that some kind of causal relationship between renal arterial pressure and sodium excretion does hold true even for small changes in arterial pressure, the Guytonian paradigm provides an explanation for the development of hypertension when the excretory function of the kidney is impaired. That is, water and electrolyte homeostasis can only be maintained at the cost of chronically increased arterial pressure. In addition to the questionable assumption of a causal relationship between arterial pressure and sodium excretion, it is vital to this concept that 1) baroreceptor reflexes and other extra-renal counter-regulatory blood pressure control mechanisms reset in response to sustained changes in arterial pressure, and 2) renal excretory function does not reset (82). These two concepts are widely accepted, although the degree to which arterial baroreceptors reset has remained a matter of controversy (77, 104). Indeed, the Guytonian paradigm has its critics. As reviewed by Montani and Van Vliet (83), some of these criticisms are based on misinterpretations of Guyton and Coleman’s theory. Our intention is not to review the evidence for a role of the kidney in the pathogenesis of hypertension. For this, we refer the reader to some excellent recent reviews (15, 24). Rather, our intention is to focus on the potential anomalies that might challenge the Guytonian paradigm. But first we will address some misinterpretations of the Guyton-Coleman theory that were not addressed in detail by Montani and Van Vliet, (83) before discussing what we see as true anomalies.

Common Misinterpretations of Guyton and Coleman’s Theory

Misinterpretation 1: initial salt and water retention and increased cardiac output is a necessary prerequisite for development of hypertension. Many of the early studies of Guyton and colleagues and their contemporaries employed models of hypertension induced by maneuvers that severely reduced renal function and/or increased salt and water intake. These models included one-kidney, one clip (1K1C) hypertension in rats (72, 73) and dogs (9, 32), salt-loading in dogs (18, 28) and rats (78) with reduced renal mass, cellophane wrap hypertension in dogs (one kidney, one wrap; 1K1W) (32–34), and a combination of intravenous angiotensin II infusion and salt loading in dogs (68). In the latter model, hypertension could be prevented by servocontrol of total body water, indicating a critical role of extracellular fluid volume expansion (66). In each of these models, hypertension was initiated by salt and water retention and (when measured) increased cardiac output (CO). But over a period of time ranging from days to weeks (depending on the experimental model), total peripheral resistance (TPR) increased and CO fell. Similar observations were made in anephric humans who were overhydrated over a period of weeks (16, 17) (Fig. 2). These observations led to the classical view of so-called “volume-dependent” hypertension, in which a shift in the pressure, natriuresis relationship to the right results in volume retention and so increased CO. Peripheral resistance then increases in response to tissue hyperperfusion, through still ill-defined mechanisms (so-called “whole body autoregulation”), so that hypertension is sustained by increased TPR rather than by increased CO (Fig. 2) (17). Thus this view of the pathogenesis of hypertension conflates two concepts: 1) that hypertension could develop from salt and water retention and 2) that autoregulatory mechanisms could transform a hyperdynamic state into a state of elevated TPR. We will return to the vexed issue of whole body autoregulation later, but first consider the proposition that volume retention represents a common pathway to the development of hypertension.

In contradiction to what some have claimed (e.g., Ref. 65), Guyton himself acknowledged that hypertension need not be associated with an initial increase in CO (17). He accepted that some experimental models of hypertension are associated with well-maintained or even decreased CO during their early phases. His interpretation was that “The contrasting results suggest that if angiotensin or other vasoconstrictors can bring renal perfusion pressure back to normal without changing the blood flow to the other tissues, then the autoregulatory response will not be initiated” (17). In other words, whole body autoregulation is not a necessary element of models of hyper-
tension associated with marked peripheral vasoconstriction. A good example is hypertension induced by chronic infusion of norepinephrine in dogs, which is associated with an initial natriuresis and contraction of extracellular fluid volume (48, 50) (Fig. 3). Here, the pressure natriuresis relationship is shifted to the right. Furthermore, arterial pressure increased more and did not reach a steady state when renal perfusion pressure was servocontrolled to its level before infusion of norepinephrine (48, 50). Nevertheless, because a major effect of norepinephrine is on TPR, the hypertension is associated with contraction of extracellular fluid volume even in its very early stages.

There is also good evidence that renovascular hypertension can develop even when salt and water retention is prevented. In animals on a standard laboratory diet, hypertension induced by constriction of a clip on a single kidney is usually associated with an initial retention of salt and water and, when it has been measured, increased CO. However, others have observed reduced CO during the onset of 1K1C hypertension in dogs (87) and renal wrap hypertension in rabbits (36). Furthermore, 1K1C (19, 101) and 1K1W (27, 38) hypertension still develops in dogs in which sodium intake is restricted to prevent increased extracellular fluid volume. Qi and colleagues (95) also showed development of hypertension in Dahl salt-sensitive rats, when placed on a high-salt diet, even if body weight (and thus total body water) was servocontrolled (95). All of these observations are compatible with a role of the kidney in the development of hypertension but not with an absolute requirement for sodium retention and increased CO.

If the contributions of increased CO and TPR vary in the initial stages of experimental hypertension, it seems plausible that they might also vary in essential hypertension in humans. Indeed, this appears to be the case. In so-called borderline or mild hypertension, relatively high CO has been observed in some but not all reported studies (reviewed by Refs. 79 and 98). This variability is likely real, reflecting the varying contributions of increased vascular tone and increased extracellular fluid volume to the development of hypertension. Consequently, if we are to understand mechanisms mediating the pathogenesis of human essential hypertension, we must consider dysfunction of both renal excretory capacity and peripheral vascular tone. But we also must accept that the hemodynamic profile in established hypertension tells us little, if anything, about the pathway(s) leading to the development of hypertension. Arthur Guyton made this point himself at least 35 years ago (45).

Misinterpretation 2: the concept of “infinite gain” implies that the pressure natriuresis relationship does not reset in response to chronic changes in arterial pressure. The kidneys not only respond to neurohumoral control systems, but they are also the master controllers of one of the most important of these mechanisms: the renin-angiotensin-aldosterone system. Thus changes in arterial pressure alter renal excretory function not just through intrinsic mechanisms (i.e., pressure natriuresis), but also by altering extrinsic (i.e., hormonal and perhaps even neural) control of renal excretory function. Let us assume that changes in extracellular fluid volume necessarily lead to changes in arterial pressure and that small changes in arterial pressure necessarily lead to changes in sodium excretion. We will address these assumptions later (anomalies 1 and 2). Nevertheless, if they hold, the proposed infinite (or near infinite) gain of the renal-body fluid feedback mechanism for the long-term control of arterial pressure would be capable of returning arterial pressure to (or very near) its long-term set point in response to any perturbation that does not influence renal excretory function (48). But this set point is itself determined not just by intrinsic factors within the kidney, but also by the influence of neurohumoral (extrinsic) factors on kidney function. Thus the only way to alter the arterial pressure to which the kidney is exposed without also altering the neurohumoral mechanisms that influence renal excretory function is to block these neurohumoral mechanisms (100). Such maneuvers necessarily open the feedback loops that govern renal control of extracellular fluid volume and thus the long-term set-point of renal control of arterial pressure. Pressure natriuresis and neurohumoral control of sodium excretion can be considered as parallel, but interdependent mechanisms. Consequently, the pressure-natriuresis relationship could only truly have infinite gain if all neurohumoral regulators of renal excretory function were blocked. This caveat reduces the utility of the concepts of infinite gain, and the kidney’s long-

Fig. 3. The “Guytonian pathway” to hypertension during infusion of norepinephrine or some other powerful vasoconstrictor stimulus that also shifts the pressure natriuresis relationship to higher arterial pressure. Initially, the vasoconstrictor stimulus may increase total peripheral resistance to such an extent that the increase in arterial pressure exceeds that required to compensate for the shift in the pressure natriuresis relationship (lines 1 to 2 in A). The resultant natriuresis causes contraction of extracellular fluid volume (B) and so reduced cardiac output. Consequently, arterial pressure falls until a new equilibrium point (line 3 in A) is reached. Redrawn from Hall et al. (48) with permission (Comprehensive Physiology © 2012 Wiley).
term set point of arterial pressure, for our understanding of long-term regulation of arterial pressure.

Under some conditions, renal arterial pressure and neurohumoral control might be expected to influence sodium excretion in opposite directions. This has been addressed experimentally in conscious animals by use of sophisticated and demanding techniques.

Reinhardt and colleagues (97, 100) provided strong evidence that extrinsic (neurohumoral) factors can modulate renal excretory function in the face of chronic changes in renal perfusion pressure. By remote control, they servocontrolled renal arterial pressure in conscious, freely moving dogs, for a period of 4 days, to a level 20% below each dog’s control systemic arterial pressure (e.g., from 115 to 92 mmHg). Total body water and sodium and systemic MAP increased across the first day, but thereafter remained relatively stable, even though the servocontrol of renal artery pressure kept said pressure at 92 mmHg (Fig. 4). They dubbed this mechanism “pressure escape.” This escape from the volume-retaining effects of reduced renal artery pressure could potentially be explained by altered extrinsic control of the kidney. Reinhardt and colleagues observed decreased plasma aldosterone and increased atrial natriuretic peptide concentrations, consistent with a role of extrinsic factors. Notably, volume retention in response to the reduction in renal arterial pressure did not occur when the renin system was blocked (i.e., the 20% reduction in renal arterial pressure did not per se contribute to volume retention). In subsequent studies they showed that the “pressure escape” phenomenon could be prevented by clamping the renin-angiotensin-aldosterone system at baseline levels by continuous intravenous infusion of angiotensin II and aldosterone along with an angiotensin-converting enzyme inhibitor. During continued hormone infusion, sudden release of the vascular clamp reintroduced the pressure escape situation at the expense of a 20% increase in renal arterial pressure. However, the elevated renal artery pressure did not correct the hormone-mediated volume surplus, and blood pressure remained elevated (100).

Mizelle and colleagues (82) performed an experiment similar to that of Reinhardt and colleagues (97, 100), but servocontrolled renal arterial pressure to only one of the two kidneys, to a level ~12 mmHg (~14%) below baseline systemic arterial pressure. Using a split-bladder technique, they performed side-specific urine collections in this well-controlled analogy in dogs of the 2K1C model of renovascular hypertension. Consequently, the two kidneys were exposed to identical (extrinsic) circulating hormones but different levels of arterial pressure. Sodium excretion by the kidney exposed to a lower arterial pressure decreased, but sodium excretion from the kidney exposed to the slightly elevated systemic arterial pressure increased (Fig. 4). Surprisingly, they found that the antinatriuretic effect of the 12-mmHg decrease in renal artery pressure in one kidney was matched precisely by the 4-mmHg increase in systemic pressure and thus pressure to the contralateral kidney, despite the concomitant 2.3-fold increase in plasma renin activity. These changes were maintained at a relatively stable level for the 12 days of the experiment. Thus

![Fig. 4. Extrinsic, but not intrinsic, factors can reset the pressure natriuresis relationship. Left: schematic representation of the findings of Seeliger and colleagues (100). Renal perfusion pressure was reduced bilaterally by 20% of each dog’s control arterial pressure for a 4-day period. This resulted in sodium retention and increased arterial pressure, but a new equilibrium was reached (red line). Inhibition of angiotensin-converting enzyme (ACEI) prevented sodium retention and increased arterial pressure in response to bilateral servocontrol of renal artery pressure (black line). Clamping the renin-angiotensin-aldosterone system by intravenous infusion of low doses of angiotensin II (ANG II) and aldosterone (Aldo), along with ACEI, resulted in continued increases in arterial pressure and total body sodium during bilateral servocontrol of arterial pressure (blue line). Right: schematic representation of the findings of Mizelle and colleagues (82). They reduced perfusion pressure to only one kidney, by ~10 mmHg, so the other kidney was exposed to systemic arterial pressure. Importantly, in this experiment both kidneys were exposed to the same neurohumoral (extrinsic) influences. In this experiment, sodium excretion by the servo-controlled kidney (red line) was reduced for the duration of the experiment, while that to the contralateral kidney was increased (black line), presumably reflecting the level of perfusion pressure each was exposed to. Figures were redrawn and modified from those in the original reports (82, 100) with permission.](http://ajpregu.physiology.org/doi/10.1152/ajpregu.00254.2015)
when extrinsic factors controlling the two kidneys were identical, changes in the intrinsic factors controlling renal function were unable to reset the pressure natriuresis relationship. This result is also remarkable because it shows that in the unper- turbated kidney a minute elevation in arterial pressure is able to override a substantial increase in systemic renin system activity seemingly at odds with the results of the Reinhardt group (see above). However, it aligns with Guyton’s representation of the renal-blood volume pressure control complex as the dominating pressure servocontrol system (45).

Notably, these two unique sets of protocols were carried out under different baseline conditions, particularly with regard to baseline arterial pressure (measured 20–23 h/day) which averaged 115–120 mmHg in the Reinhardt study and 87 mmHg in the Mizelle study, despite similar sodium turnover. Neither study seems to have been repeated by independent parties. More surprisingly, neither protocol seems to have been subjected to computer simulations. Yet regardless of their apparent inconsistencies, the findings of these two studies do allow us to conclude that chronic changes in arterial pressure, that are sufficient to alter the activity of the renin-angiotensin system, will reset the relationship between arterial pressure and renal excretory function. However, there is no support for the idea that direct effects of altered renal perfusion pressure on the kidney can reset this relationship.

Anomalies

Thomas Kuhn (70) proposed that “Discovery commences with the awareness of anomaly, i.e., with the recognition that nature has somehow violated the paradigm-induced expectations that govern normal science. It then continues with a more or less extended exploration of the area of the anomaly. And it closes only when the paradigm theory has been adjusted so that the anomalous has become the expected.” According to this approach, the pathway to a neo-Guytonian paradigm, or a paradigm shift, must begin with the identification of anomalies in the Guytonian paradigm.

Anomaly 1: volume retention and increased CO during salt loading does not necessarily increase arterial pressure. One of the central concepts in Guyton and Coleman’s theory of long-term control of blood pressure is the notion that retention of salt and water (through changes in the so-called mean systemic filling pressure) increases MAP by increasing CO (46, 47). However, there are a number of conditions in which MAP remains remarkably stable in the face of altered extracellular fluid volume and/or CO. One of these is the response to changes in salt intake in “salt-resistant” animals and humans. In humans, plasma volume increases by about 1.5 ml/mmol increase in daily sodium intake (25, 96). Kjolby et al. (64) varied daily sodium intake in dogs across more than an order of magnitude. While they observed considerable changes in plasma volume, arterial pressure changed little in response to altered sodium intake. The maintenance of arterial pressure was possibly due to compensatory changes in the degree of activation of the renin-angiotensin-aldosterone system, since the plasma concentrations of components of this system varied linearly with the logarithm of the intake of sodium. These observations accord with those of Krieger and colleagues, who found that 7 days of high salt intake in previously salt-depleted dogs resulted in retention of salt and water and increased CO but that MAP remained relatively stable due to reduced TPR (67). In contrast, when dogs were salt loaded while receiving a continuous intravenous infusion of angiotensin II, the increased CO was associated with a gradually increasing TPR, so that MAP increased (68). This form of experimental hypertension was completely prevented by servocontrol of total body water (66). Collectively, these observations indicate that there is considerable scope for neurohumoral mechanisms, including the renin-angiotensin-aldosterone system, to maintain MAP at a relatively stable level in the face of altered CO, by altering TPR. Thus, under physiological conditions, small changes in body fluid volume do not necessarily lead to changes in arterial blood pressure.

Evidence that the failure of such compensatory mechanisms might be important in the pathogenesis of hypertension came from studies of Dahl salt-sensitive (SS) and salt-resistant (SR) rats. Greene and colleagues (44) examined the responses to increased salt intake (by intravenous infusion) in Dahl SS and SR rats, with or without servocontrol of body weight (and thus total body water). They found that servocontrol of body weight prevented development of hypertension in SS rats exposed to a high-salt diet. However, when body weight was not servocontrolled, SS and SR rats had similarly increased blood volume, but MAP increased only in SS rats. In a separate protocol, in which CO was measured by thermodilution, increased dietary salt intake was found to increase CO in both SS and SR rats. Importantly, hypertension only developed in SS rats because of failure of a compensatory reduction in TPR (Fig. 5). Thus, while volume retention was a necessary prerequisite for hypertension in the SS rat, salt loaded by either intravenous infusion.
or dietary intake, it appears not to be the critical mediator. Rather, the critical deficit may lie in failure of counterregulatory mechanisms that control vascular tone. This concept has recently been dubbed the “vasodynamics theory” by Kurz and colleagues (71). It has also been central to arguments for a pivotal role of the central nervous system in the development of hypertension (89).

The findings of Greene and colleagues (44) are consistent with those of Ganguli and colleagues who studied anesthetized SS and SR rats 3 days after a high- or low-sodium diet was commenced (40). That is, CO apparently increased in response to increased salt intake in both SS and SR rats, but TPR fell only in SR rats. Simchon and colleagues (102) described changes in arterial pressure, CO, and renal blood flow (RBF) during development and maintenance of hypertension in SS rats on 8% NaCl. They found that the increase in MAP after 4 wk was mediated by increased CO, but at 46 wk CO was subnormal and TPR was elevated. They were unable to detect a significant increase in CO in SR rats, although it certainly tended to be increased at the 4-wk time point. Importantly, in these three sets of experiments (40, 44, 102), volume expansion and increased CO was apparently a requirement for development of hypertension in the SS rat. However, in each case, the critical difference between the SS rat and SR rat appeared to be the response of the resistance vasculature to increased salt intake. This notion also accords with the findings of renal transplantation studies in Dahl rats, indicating roles for both intrarenal and extrarenal factors in salt sensitivity of blood pressure in this model (85). However, it is not consistent with the idea that salt sensitivity of arterial pressure arises from dysfunctional neurohumoral control of renal excretory function (Fig. 1), which would appear to be a critical test of the Guytonian paradigm.

The observations described above raise two important questions: 1) what are the critical loci for the disparate vascular response in SS compared with SR rats, and 2) how relevant are observations in the Dahl rat to our understanding of human essential hypertension? Regarding the first of these questions, it is possible that the kidney represents a major locus for the disparate vascular response in SS compared with SR rats. For example, Simchon and colleagues (102) observed selective renal vasoconstriction (but not systemic vasoconstriction) at the 4-wk time point in SS rats on 8% NaCl. These observations are strikingly similar to those from a recent study of a group of carefully selected patients with mild, uncomplicated hypertension, whose renal vascular conductance was much smaller than that of a control group while the nonrenal vascular conductances were indistinguishable (26). That is, the greater TPR in the patients, compared with control subjects, could be attributed entirely to augmented renal vascular resistance. Thus, while it would be dangerous to extrapolate from studies in the Dahl SS rat to human essential hypertension, these findings indicate that abnormal renal vascular tone and/or renal vascular structure could play a critical role in the pathogenesis of hypertension, not just through its effects on renal excretory function, but also through effects on TPR.

There may also be inherent differences in the nonrenal vasculature between individuals susceptible to hypertension and those not. In anephric patients, volume expansion increased arterial pressure only in individuals who had been hypertensive before nephrectomy (88).

Regarding the second question posed above, it seems likely that vascular dysfunction does play an important role in salt-sensitive hypertension in humans. For example, Schmidlin and colleagues (99) demonstrated similar increases in CO in salt-sensitive and salt-resistant individuals placed on a high-salt diet. Arterial pressure increased in salt-sensitive individuals because, unlike the salt-resistant subjects, TPR did not fall when salt intake was increased (99). Furthermore, Kurz and colleagues (71) recently presented a detailed argument that Mendelian forms of salt-sensitive hypertension could be driven by failure of the counterregulatory vasodilatation that normally occurs when salt intake is chronically increased (71).

The considerations described above do not necessarily require us to reject Guyton and Coleman’s view of the pathogenesis of hypertension, but they certainly do require it to be deployed with some subtlety, a point emphasized by Guyton and his colleagues (45). We accept the concept that hypertension can occur either in the absence or presence of volume expansion. But the critical subtlety, as we see it, is that we must also accept that a combination of altered renal excretory function and altered control of peripheral resistance vessels must be a hallmark of forms of hypertension other than those associated with rapid and frank volume expansion. There are a number of candidate mechanisms that might mediate this altered control of vascular tone, including the sympathetic nervous system (4, 37), multiple signaling cascades mediated by endogenous ouabain-like factors (13, 74), reductions in vascular nitric oxide bioavailability induced by asymmetrical dimethylarginine (99), certain G protein (G$_{12}$-G$_{13}$) signaling cascades (106), and interactions between immune cells, cytokines, and oxidative stress (80).

In conclusion, as pointed out by Guyton and his colleagues (45), the notion that essential hypertension develops initially from salt and water retention, and that increased CO is transformed to increased TPR (Fig. 2), is likely a gross oversimplification of the clinical situation. This concept arose from early studies of models of hypertension characterized by marked fluid retention (e.g., Refs. 16–18), which probably have little direct relevance to human essential hypertension. Moreover, there is strong evidence that arterial pressure can be maintained in the face of increased extracellular fluid volume and CO, and that at least some forms of hypertension are attributable to failure of this compensatory vasodilatation.

**Anomaly 2: day-to-day and hour-to-hour renal regulation of salt and water homeostasis is not driven by changes in arterial pressure.** This issue has been reviewed in detail previously (10, 12, 25, 59, 100), so it will only be discussed briefly. There is now strong evidence that the major driver of day-to-day changes in sodium excretion, in response to day-to-day changes in sodium intake, is the renin-angiotensin-aldosterone system, at least in animals and humans in which this system is intact. That is, acute and chronic changes in salt and water intake, either orally or by intravenous infusion, are usually accompanied by changes in salt and water excretion that maintain salt and water homeostasis, without appreciable changes in arterial pressure. Indeed, natriuresis has even been observed during acute sodium loading in the face of reduced arterial pressure (1). However, acute and chronic changes in sodium intake are accompanied by marked changes in the activity of the renin-angiotensin-aldosterone system, which appears to be the dominant mechanism mediating changes in

---

**References:**

1. Schmidlin, A., and colleagues (99). Demonstrated similar increases in CO in salt-sensitive and salt-resistant individuals placed on a high-salt diet.
2. Kurz, A., and colleagues (71). Recently presented a detailed argument that Mendelian forms of salt-sensitive hypertension could be driven by failure of the counterregulatory vasodilatation that normally occurs when salt intake is chronically increased.
4. Simchon, A., and colleagues (102). Observed selective renal vasoconstriction (but not systemic vasoconstriction) at the 4-wk time point in SS rats on 8% NaCl.
5. Greene, J.A., and colleagues (44). Consistent with those of Ganguli and colleagues who studied anesthetized SS and SR rats 3 days after a high- or low-sodium diet was commenced.
6. Simchon, A., and colleagues (102). Described changes in arterial pressure, CO, and renal blood flow (RBF) during development and maintenance of hypertension in SS rats on 8% NaCl.
sodium and water excretion (12). It is also relevant to note that the phenomenon of “pressure escape,” initially described by Reinhardt and colleagues (97) (vide supra), could be abolished by “clamping” the renin-angiotensin-aldosterone system (100) (Fig. 4). This group also found no significant correlation between spontaneous diurnal variations in arterial blood pressure and the concomitant rates of sodium and volume excretion (100). Thus it appears that neurohumoral mechanisms can readily override the influence of minor changes in renal perfusion pressure on renal excretory function.

All of these observations are consistent with the view that the relationship between blood pressure and natriuresis is exquisitely sensitive to neurohumoral status (Fig. 1). The effects of altered activity of the renin-angiotensin-aldosterone system (or of renal sympathetic nerve activity, atrial natriuretic peptides, or indeed any other regulatory mechanism) may well be considered to be mediated via a shift in the pressure natriuresis relationship. Nevertheless, we also must concede that the major factor that controls short-term changes in salt and water excretion under physiological conditions is neurohumoral status, not renal artery pressure.

Based on the discussion above, and as suggested previously (12, 100), we can envisage multiple lines of defense against the development of salt-sensitive hypertension (Fig. 6). The first line of defense is the response of the kidney to altered neurohumoral influences, including the renin-angiotensin-aldosterone system, which are initiated by volume-dependent mechanisms. This allows sodium and water balance to be achieved, albeit at the expense of some expansion of extracellular fluid volume. The second line of defense is the response of the vasculature to altered neurohumoral influences, which allows compensatory reductions in TPR so that MAP is not increased, even in the face of increased CO. The third line of defense is the pressure natriuresis mechanism, which is engaged when arterial pressure increases, presumably as a result of malfunction of the first two mechanisms. These three mechanisms must operate within some hierarchy. The nature of this hierarchy remains one of the central questions in our understanding of the mechanisms that control blood pressure in the long term, and thus the pathogenesis of hypertension. Nevertheless, it seems reasonable to propose that all three lines of defense must malfunction in order for chronic hypertension to develop.

**Anomaly 3: sodium homeostasis might rely on extrarenal mechanisms.** This concept has been reviewed in detail recently (105). In brief, recent evidence suggests that sodium can be stored in skin and muscle in an osmotically inactive form bound to glycosaminoglycans, providing sinks and sources of free sodium ions under conditions of increases and decreases, respectively, of total body sodium. There is evidence that these storage depots are regulated by a complex interplay between immune cells and the lymphatic system. These concepts represent an anomaly for the Guytonian paradigm, which is based on the underlying assumption that the various components of the extracellular fluid volume are in equilibrium. The presence of osmotically inactive sodium would allow some level of uncoupling of total body sodium from total body water. The apparent existence within the body of mechanisms buffering changes in total body sodium will not, by their buffer capacity alone, change the principles of body fluid regulation.

However, they may well explain how the magnitude of changes in body fluid can deviate quantitatively from those predicted from the physicochemistry of simple electrolyte solutions. The implications of these relatively new findings, for our understanding of the long-term regulation of sodium homeostasis and arterial pressure, must await further research.

**Anomaly 4: the mechanisms underlying “whole body autoregulation” have not been identified.** We have already established that hypertension need not be initiated by volume retention and increased CO (see anomaly 1). There is also evidence that some forms of experimental hypertension can be associated with increased CO, with no evidence of progression toward increased TPR. For example, Fine and colleagues (35) assessed the effects of increased dietary salt intake in rats in which the renin-angiotensin system was clamped by combined intravenous infusion of the angiotensin-converting enzyme inhibitor enalapril and angiotensin II. Arterial pressure, measured telemetrically, increased when the animals were placed on a high-salt diet for 7 days due to increased CO (measured by transit-time ultrasound flowmetry). During the 7-day protocol there was no evidence of increased TPR. On the other hand, progression from increased CO to increased TPR has been observed in many forms of hypertension associated with salt and water retention. These include 1K1C hypertension in the rat (72, 73) and dog (32, 33), 1K1W cellophane wrap hypertension in the dog (34), hypertension in dogs subjected to increased sodium intake with reduced renal mass (18), or during infusion of a low dose of angiotensin II (68). It has also been observed in response to volume loading in anephric patients in some (16), but not all, (63) studies. The only plausible theory to explain this transition relies on the phenomenon of whole body autoregulation (47). That is that the long-term set point of local (and thus total) peripheral resistance is determined by the requirements of the tissues for blood flow. In Guyton and Coleman’s original formulation of the renal-body fluid system for arterial pressure control, it merited...
little discussion as if it was assumed that local autoregulatory mechanisms would naturally respond on a whole body basis (47). Yet this concept remains controversial and poorly defined.

There is also good evidence that whole body autoregulatory mechanisms can operate when arterial pressure is chronically decreased. Until the seminal work of Horace Smirk (29), it was widely believed that pharmacotherapy to reduce arterial pressure would be dangerous because it would lead to tissue ischemia. Smirk was able to show that arterial pressure could be safely lowered in patients with hypertension by pharmacological ganglion blockade (103). This work paved the way for larger clinical trials of antihypertensive therapy that definitively demonstrated the beneficial effects of these drugs. Later studies provided more direct evidence that diuretic agents, in particular, lower arterial pressure through an initial reduction in CO, which is later transformed to a reduction in TPR (21, 39).

So-called borderline or mild hypertension has been of considerable interest to the protagonists of the whole body autoregulatory theory, since it is generally thought to reflect the early stages in the pathogenesis of hypertension. The observation of relatively high CO in patients with borderline hypertension would therefore provide support for the theory. This has been observed in the majority of reported studies (79). However, the observation that the difference in CO between patients with borderline hypertension and controls is abrogated by assuming a sitting position or exercise suggests that abnormally high CO in the recumbent position might have dubious significance (61). Nevertheless, it seems reasonable to propose that volume retention and subsequent whole body autoregulation might contribute to the pathogenesis of human essential hypertension in at least a subset of patients. But what do we mean by “whole body autoregulation” and what are the mechanisms that mediate it?

For our current purposes, we can define autoregulation as any phenomenon that opposes changes in blood flow in response to altered perfusion pressure. At least three mechanisms might mediate whole body autoregulation in response to increased arterial pressure: 1) vasoconstriction, either as a direct response to the increased perfusion pressure or as a longer-term consequence of increased sensitivity of the vasculature to constrictor agents, 2) vascular rarefaction, and 3) vascular hypertrophy or (eutrophic) remodeling of resistance vessels around a smaller lumen. Unfortunately, we currently have very limited understanding of the relative contributions of these mechanisms to whole body autoregulation.

**ACUTE MECHANISMS.** Autoregulation can be observed in most organs and tissues when perfusion pressure is acutely altered. The underlying mechanisms are tissue dependent, although some generalizations can be made. First, acute autoregulatory responses to increased perfusion pressure are largely mediated by the so-called “myogenic response,” whereby stretch of vascular smooth muscle increases cytosolic calcium concentration leading to smooth muscle contraction and thus vasoconstriction. In contrast, metabolic factors likely dominate the response to reduced perfusion pressure, whereby hypoxia itself or accumulation of local metabolites such as adenosine, carbon dioxide, and hydrogen ions drive the vasodilatation. In some organs, such as the kidney, additional mechanisms come into play (62). From a “whole body” point of view, acute autoregulation encompasses mechanisms that maintain adequate oxygen delivery to tissue in the face of changes in either driving pressure or oxygen demand. This is achieved both through a combination of changes in oxygen extraction and the state of dilatation of local resistance vessels (101). Whole body autoregulation has been observed acutely in experimental animals, beginning with the seminal studies of Guyton and Coleman in dogs in which the central nervous system had been destroyed (17) and extending to studies in conscious dogs (81) and rats (55–58) in which cardiovascular reflexes had been blocked. However, for two reasons, such acute mechanisms are unlikely to make much contribution to the transition from increased CO to increased TPR in essential hypertension. First, if the relatively high CO in borderline hypertension were to reflect “over perfusion” of tissues, the arteriovenous oxygen concentration difference in these individuals might be expected to be relatively low, but this has not been observed (79). Second, the time course is all wrong. Acute autoregulatory mechanisms operate over a time course of seconds to hours (41), whereas the transition from increased CO to increased TPR takes days or weeks in experimental hypertension (16, 18, 32–34, 68, 72, 73) and perhaps years in human essential hypertension (79).

**CHRONIC MECHANISMS.** Candidate mechanisms include changes in the sensitivity of the vasculature to vasoactive agents, vascular rarefaction, and vascular remodeling.

Increased sensitivity to vasoconstrictors has been observed in established hypertension (8) as has reduced influence of endothelium-derived vasodilator factors (54). There is also evidence for altered calcium signaling in the vasculature in certain forms of hypertension, perhaps driven by endogenous ouabain-like factors (13, 75, 76, 94) or by increased expression of L-type calcium channels induced by increased arterial transmural pressure (93). An increased propensity of resistance vessels to constrict leads to functional rarefaction (14). Functional rarefaction, in turn, can lead to loss of the microvasculature (structural rarefaction) (14).

Structural rarefaction has been observed in multiple animal models of hypertension, including the spontaneously hypertensive rat (SHR) and reduced renal mass hypertension (42, 52, 78). Evidence of structural rarefaction has also been obtained in established human hypertension (3), borderline essential hypertension (2), high-output borderline hypertension, and in individuals with a familial predisposition toward hypertension (86). Furthermore, computational models predict that rarefaction could make a significant contribution to the increased vascular resistance in established hypertension (43). There is also evidence that antihypertensive pharmacotherapy can reverse rarefaction (6). But is rarefaction an important factor in the hemodynamic alterations in hypertension?

Hallback and colleagues (51) examined the characteristics of the relationships between flow and perfusion pressure in the isolated hindlimb of SHR compared with normotensive controls. Their findings indicated that vascular rarefaction could not adequately explain the alterations in hindlimb pressure-flow relationships in the SHR. Rather, they concluded that the vascular abnormality in the SHR is best explained by structural changes in precapillary resistance vessels, leading to reduced lumen diameter even at maximal vasodilatation (51). Such structural changes amplify the effects of constrictor factors on peripheral resistance and thus arterial pressure. In intact rabbits with 2K2W hypertension Wright, Angus, and Korner provided...
evidence that this “vascular amplifier” makes a major contribution to the enhanced sensitivity of the circulation to constrictor factors and thus maintenance of hypertension (107, 108). Critically, there is evidence that oxidative stress can drive development of vascular hypertrophy (54). However, remodeling of the resistance vasculature has traditionally been viewed as an adaptive response to hypertension, rather than a primary pathogenic event (31).

Unfortunately, most experimental studies of the changes in microvascular (42) and resistance vessel (65) structure and function in hypertension have been performed in animals with established hypertension. Structural rarefaction has been observed within 3 days of commencing a high-salt intake in rats. But these responses were similar in rats with reduced renal mass to those of sham-operated rats who did not develop hypertension (53). Functional evidence of vascular remodeling, consistent with the vascular amplifier concept, has been seen as early as 2 wk after initiation of angiotensin II-dependent hypertension (84). However, to our knowledge, no true time-course studies have been performed. Consequently, we really do not know whether these structural changes occur over a time course consistent with a role in the phenomenon of whole body autoregulation, or whether they simply reflect a structural adaptation to increased arterial pressure. Furthermore, the relative contributions of functional and structural rarefaction, changes in vascular sensitivity to vasoactive agents, and remodeling of resistance vessels remain unknown.

Anomaly 5: the Guytonian paradigm does not allow us to understand the sequence of events that lead to the pathogenesis of hypertension. One argument that is often used to support a critical role of the kidney in long-term control of arterial pressure and the pathogenesis of hypertension can be encapsulated in the statement that “hypertension is always accompanied by a rightward shift in the pressure natriuresis relationship.” While we accept the truth of this statement, we also concede that it represents a tautology. A “rightward shift in the pressure natriuresis relationship” is a physical necessity; the statement reiterates that sodium balance occurs in chronic homeostasis in the face of chronically reduced renal perfusion pressure (see anomaly 1), that hormonal and neural factors, rather than renal perfusion pressure, dominate renal control of extracellular fluid volume (anomaly 2), that nonrenal mechanisms contribute to control of sodium homeostasis (anomaly 3), and that we have little understanding of the mechanisms that mediate whole body autoregulation (anomaly 4), it could be argued that such a statement really only serves to divert out attention from the important questions in the field. We believe these important questions relate to the interrelationships between dysfunction of control of CO by the kidney and venous system and control of TPR by resistance vessels. Our interpretation of the available literature is that essential hypertension must be driven by the interplay between the dysfunction in these two components of the cardiovascular system. A focus on any one of these systems in isolation from the other is unlikely to lead to major advances in the field.

A Way Forward for “Normal Science”

The anomalies associated with Guytonian theory, we have described above, hardly constitute a crisis that in the near future might lead to a new paradigm in our view of the role of the kidney in the pathogenesis of hypertension. However, a number of the experimental results seem to justify that “pressure natriuresis” should be considered as one natriuretic mechanism operating parallel to other control mechanisms. An immediate benefit would be to eliminate the need for the complex explanation that volume-mediated natriuresis, occurring along with concomitant decreases in blood pressure and renin system activity, is due to shifts of the former rather than to deactivation of the latter. The inclusion of parallel actions of multiple hierarchical, primarily independent natriuretic control systems into the concepts of Guyton could be considered an adjustment justifying the label of a “neo-Guytonian” paradigm. Otherwise, the anomalies probably indicate that there is considerable scope for normal science, as defined by Thomas Kuhn (70), to proceed. But how might this normal science best be directed toward a neo-Guytonian paradigm?

The massive research effort in hypertension, in the 20 years since Arthur Guyton’s last published contribution to the field (49), has yielded a wealth of understanding of the molecular mechanisms that influence cardiovascular control and that drive development of hypertension in animal models (60). However, we would argue that they have not got us much closer to understanding the mechanisms that drive the pathogenesis of human essential hypertension. This failure might be partly a result of “the molecular revolution,” which we would argue has led many researchers to focus on their favorite molecule rather than on the broader integrative questions. It is probably also fair to say that interest has dwindled in “the big questions” in the field of hypertension. For some these questions might seem already answered. For others they might seem unanswerable.

We accept the Guytonian principle in so far that hypertension can only occur when renal excretory function is impaired, either through intrinsic changes in the kidney or altered neurohumoral control of the kidney, so that a greater level of arterial pressure is required to assist in the excretion of the daily sodium load. However, intact experimental animals and humans that are not susceptible to hypertension appear able to deal with some level of salt and water retention and increased CO without increased MAP, through neurohumorally mediated reductions in TPR (see anomaly 1). Simultaneously, these neurohumoral mechanisms must also influence renal excretory function in a manner that allows homeostasis of extracellular cellular fluid volume at its new level, without the need for increased arterial pressure. Changes in neurohumoral control of the kidney even appear able to maintain salt and water homeostasis in the face of chronically reduced renal perfusion pressure (see Misinterpretation 2). These observations at least partly break the mechanistic link between altered renal excretory function and the development of hypertension, which are at the heart of the Guyton-Coleman view of the pathogenesis of hypertension. Consequently, we must accept that we really do not understand the sequence of events that might lead from altered renal excretory function to the development of chronic hypertension (anomaly 5). We even have little understanding of the sequence of events that might transform so-called
volume-dependent hypertension into a state of increased TPR (anomaly 4). Elucidation of these issues will probably require a renewed and focused effort in integrative cardiovascular physiology in human subjects. Prospective studies are required, with frequent follow-up, to characterize the sequence of events in the pathogenesis of hypertension. Information regarding systemic and renal hemodynamics, water and electrolyte homeostasis, small and large vessel structure and function, neurohumoral status, and metabolic and immunological functions will be required. Remarkable methodological advances have been made in all of these fields in recent years, including in the use of noninvasive methods, so such a renewed effort would be timely and feasible. Perhaps the greatest challenge in this research effort will be to overcome the confounding effects of pharmacological and nonpharmacological interventions that are, quite rightly, offered soon after clinical diagnosis of hypertension.

Another important activity for advancement in the field is the development of advanced computational models of the long-term control of arterial pressure and the pathogenesis of hypertension (90, 91). Computational models were vital to the initial development of the two central concepts in the Guytonian paradigm: 1) the overriding dominance of the kidney in long-term control of arterial pressure, and 2) the principle of infinite gain of the body fluid mechanism of long-term blood pressure control (45). More recently, alternative models have been developed that can replicate some of the outcomes of the model generated by Guyton, Coleman, and colleagues, but are based on very different assumptions regarding the hierarchy of importance of blood pressure control mechanisms (4, 5). For example, simulations of hypertension induced by angiotensin II and high salt intake by the “neurogenic” model of Averina and colleagues generate hemodynamic profiles that are very similar to those of the Guyton-Coleman model (4, 5). Yet this new model is not based on the assumption of a direct relationship between arterial pressure and sodium excretion, thereby illustrating the point that conceptually different models may provide equally attractive simulation results. The complexity of the control mechanisms dictates that intimate interactions between in vivo and in silico experiments are necessary to identify the most fruitful working hypotheses.

ACKNOWLEDGMENTS

P. Bie’s sabbatical at Monash University was supported by the Faculty of Biomedical and Psychological Sciences, Monash University.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: R.G.E. and P.B. conceived and designed research; R.G.E. performed experiments; R.G.E. drafted manuscript; R.G.E. and P.B. edited and revised manuscript; R.G.E. and P.B. approved final version of manuscript.

REFERENCES

ANOMALIES IN THE GUYTONIAN PARADIGM?

Review

ANOMALIES IN THE GUYTONIAN PARADIGM?


103. Smirk FH. Hypotensive actions of hexamethonium bromide and some of its homologues; their use in high blood-pressure. Lancet 2: 1002–1005, 1942.


