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Circulation and Fluid Volume Control

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1. INTRODUCTION

1.1. The Kidney, Circulation, and Integrative Physiology

The kidney and circulation provide an especially rich source of examples of integrative physiology. The regulation of blood pressure (BP), for example, involves many disparate tissues, ranging from the heart and vasculature to the brain, adrenal gland, and kidney. BP regulation also involves multiple layers of physiological organization—from the biophysics of renal transport to the regulation of flows and resistances to the overall architecture of the fluid volume control system. The value of a truly "integrative" approach is evident from the many properties and features of such systems that could not have been discovered even by the most detailed examination of their individual components.

As we begin this century and millennium, technological advancements are not only leading to new avenues of investigation and additional layers of knowledge, but also an explosive growth in physiological information and literature. The task of integrating the information—forming a comprehensive understanding of each system and the interactions between systems—will be a major challenge. Meeting this challenge will require new efforts and new approaches, but also an awareness of what has been done and what is possible.

1.2. Arthur C. Guyton's Systems Analysis of Circulatory Dynamics and Their Control

To instill a sense of what has and can be done, we can do no better than revisit some of our greatest successes. It is therefore both appropriate and timely to dedicate this chapter to the memory of Arthur C. Guyton (1919–2003) *(1–3)*, exceptional in each of his many roles as scientist, inventor, teacher, and mentor, and one of the most accomplished and truly integrative physiologists of the past century. Although widely respected for his *Textbook of Medical Physiology*, he also made a number of seminal contributions to cardiovascular physiology (Table 1) and effectively fathered the modern-day field of quantitative physiological systems analysis *(4–7)*.

Guyton's "quantitative systems analysis" approach not only led him to consider the most important aspects of various components of circulatory control, but especially how they fit together and interacted. Thus, to him, cardiac output represented the outcome of an interac-

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Table 1
Selected Accomplishments of Arthur C. Guyton

Influential books published

- *Textbook of Medical Physiology* (10 editions) and related texts.
- *Circulatory Physiology: Cardiac Output and Its Regulation* (1973).
- *Circulatory Physiology II: Dynamics and Control of the Body Fluids* (1975).
- *Circulatory Physiology III: Arterial Pressure and Hypertension* (1980).

Important concepts and ideas championed by Dr. Guyton

- Dominant role of the kidney, pressure natriuresis, and the renal body fluid feedback mechanism in long-term blood pressure control.
- Interstitial fluid dynamics, including concept of a negative interstitial fluid pressure.
- Role of venous return and mean circulatory filling pressure in regulating cardiac output.
- Safety factor for pulmonary edema.
- Whole body autoregulation.
- Graphical analysis of physiological regulation (especially cardiac output and blood pressure).
- Quantitative computer modeling of physiological systems.

tion of venous return and cardiac function, total peripheral resistance represented, in part, a consequence of the effects of the effects of BP on tissue blood flow (i.e., autoregulation), and the long-term BP level itself represented an interplay between renal perfusion pressure and renal excretory function. Once revolutionary ideas, these and other concepts have proven their value over time and now penetrate the very fabric of modern cardiovascular physiology.

The quantitative nature of Guyton's systems analysis was conspicuously manifest in a "large circulatory model" (Fig. 1) in which several hundred equations were used to quantify different components of the circulation and their control. Although model parameters were largely based on empirical values, the overall architecture of the model was based on insight and intuition, trial and error, and repeated comparison and testing against experimental data. In addition to its ability to simulate the behaviour of the cardiovascular system (e.g., refs. *8* and *9*), each version of the model essentially represented an explicitly stated theory or hypothesis: "How would a circulatory system of this design behave?" As Dr. Guyton pointed out, the most helpful contribution of the model was when it failed to correctly predict an empirical outcome, since that clearly indicated a limitation in our understanding of the system.

Dr. Guyton's influence lives on, his theories permeating our text books, his approach embedded in the careers and research programs of the many scientists who trained in his department and laboratory. Nevertheless, in an era of rapid advances in highly focused areas of cellular physiology, molecular biology, and genetics, there has perhaps never been greater need for his desire and ability to integrate the pieces into a quantitative and comprehensive model of the whole. In the remainder of this chapter, we focus on two concepts of cardiovascular regulation that arose from Guyton's systems analysis and remain fundamentally important today. These are the dominant role of the renal body fluid feedback mechanism in setting the long-term BP level, and the concept of "whole body autoregulation," by which

the total peripheral resistance is considered to be, in part, a response to the BP level (and not the other way around). If nothing else, this review may serve to illustrate the role of an integrative approach in understanding physiological systems, and the contribution of "quantitative systems analysis" to this end.

2. THE RENAL BODY-FLUID FEEDBACK MECHANISM

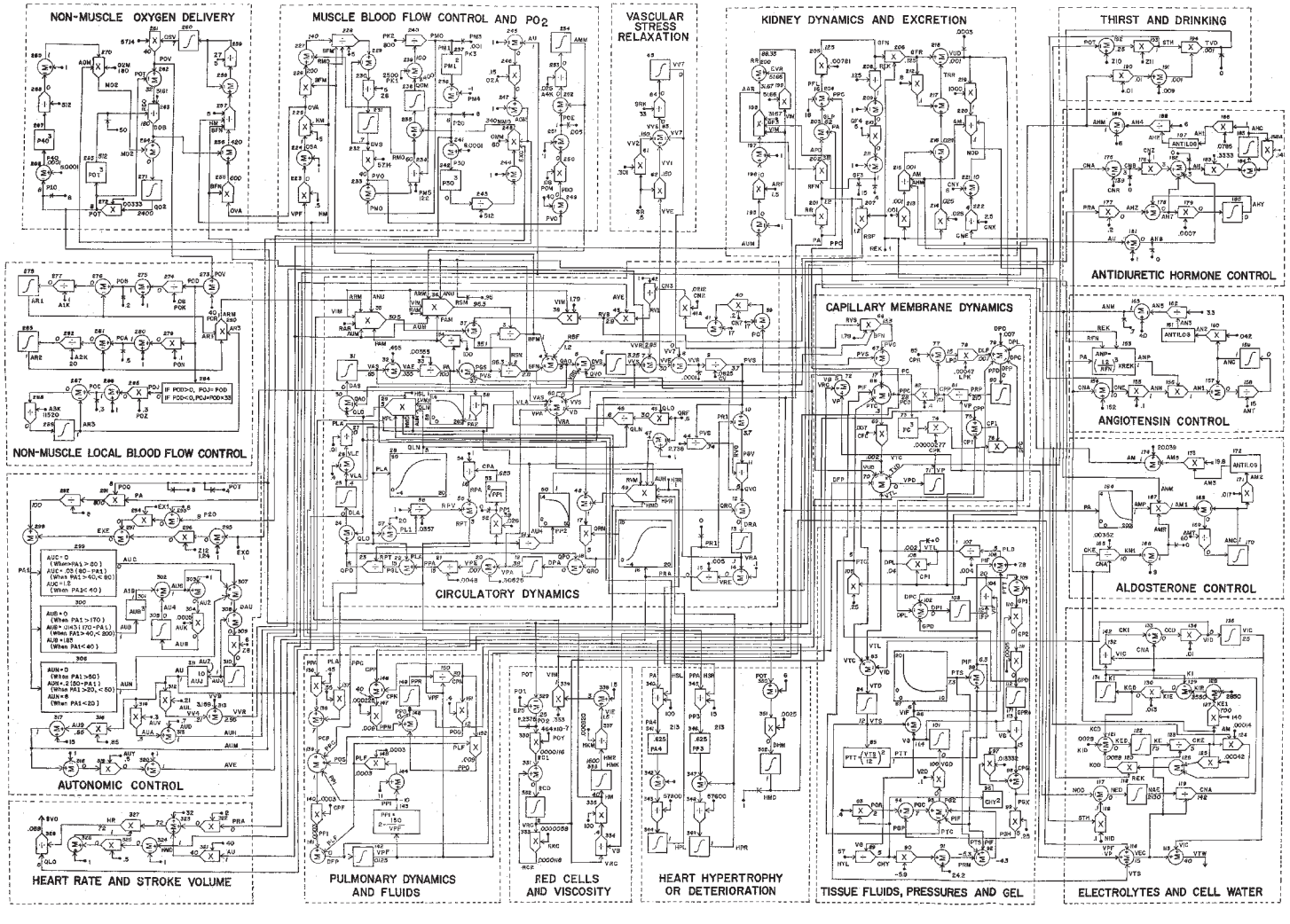
Of the various concepts championed by Guyton, perhaps the most influential was the dominance of the kidney in setting the long-term BP level. The basis for this concept was the renal body-fluid feedback mechanism (RBFFM) illustrated in Fig. 2. At the heart of the RBFFM lies the "pressure natriuresis relationship," which describes the link between BP, salt intake, and salt excretion.

The *acute* pressure natriuresis relationship is determined in isolated kidneys (e.g., refs. *10* and *11*), anesthetized animals (e.g., ref. *12*), or conscious animals (e.g., ref. *13*) by varying the renal perfusion pressure and observing the resultant change in the rate of renal salt excretion. As shown in Fig. 3, acute manipulations of renal perfusion pressure elicit a corresponding change in the renal excretion of salt and water, with increases in BP causing increased sodium excretion (i.e., natriuresis) and reductions in BP causing reduced sodium excretion or even complete cessation of urine flow at low BP levels. The mechanisms underlying this phenomena have been reviewed elsewhere *(14,15)*.

It is important to realize that the acute pressure–natriuresis relationship also predicts the long-term level of BP that would arise for a given level of salt intake if the acute relationship was fixed and did not change with time. However, the acute pressure–natriuresis relationship is not fixed. It changes in response to many factors including changes in dietary salt intake. Thus, another approach is used to assess the chronic relationship between BP, salt intake, and renal salt excretion.

The chronic pressure–natriuresis relationship is measured in a different manner by imposing a level of salt intake on a subject for several days until salt balance is established (i.e., until the rate of salt intake is matched by the rate of renal salt excretion) and then measuring the resultant BP level. This process is repeated for a variety of salt intakes, each level of salt intake contributing one point to the chronic pressure–natriuresis relationship, also known as the "chronic renal function curve" (Fig. 3). In contrast to the acute pressure–natriuresis mechanism, which represents a property of the renal tissues that can be demonstrated even in isolated perfused kidneys, the chronic pressure–natriuresis relationship represents the performance of the entire RBFFM at equilibrium: that is, after the many control mechanisms affecting renal function and BP have exerted their influence, after salt balance has been established, and after BP has stabilized. Because the chronic renal function curve describes the pressure–natriuresis relationship when salt intake and renal salt excretion are equal, the *y*-axis on a chronic renal function curve simultaneously represents both salt intake and salt excretion.

Several characteristics of the renal function curve are of fundamental importance. First, on each curve there is an equilibrium point corresponding to the one level of BP that can maintain salt excretion at the level of salt intake. In Fig. 3, this is represented by point A in the case of either the acute or chronic renal function curve at normal salt intake, point B in the case of the acute renal function curve under the condition of high salt intake, and point C in the case of the chronic renal function curve at high salt intake. BPs above the equilibrium


NON-MUSCLE OXYGEN DELIVERY
MUSCLE BLOOD FLOW CONTROL AND PO_2
VASCULAR STRESS RELAXATION
KIDNEY DYNAMICS AND EXCRETION
THIRST AND DRINKING
ANTIDIURETIC HORMONE CONTROL
ANGIOTENSIN CONTROL
ALDOSTERONE CONTROL
NON-MUSCLE LOCAL BLOOD FLOW CONTROL
CAPILLARY MEMBRANE DYNAMICS
CIRCULATORY DYNAMICS
AUTONOMIC CONTROL
HEART RATE AND STROKE VOLUME
PULMONARY DYNAMICS AND FLUIDS
RED CELLS AND VISCOSITY
HEART HYPERTROPHY OR DETERIORATION
TISSUE FLUIDS, PRESSURES AND GEL
ELECTROLYTES AND CELL WATER

level will raise renal salt excretion above the rate of salt intake leading to a slow and progressive fall in of extracellular fluid (ECF) volume and cardiac output (Fig. 2). Given sufficient time, these changes would return the BP to the equilibrium level at which salt balance would again be achieved. Conversely, BP levels below the equilibrium value will lead to salt retention and a slow rise in cardiac output which, in time, would slowly raise the BP back to the equilibrium level. In this manner, one can appreciate the principle of how the RBFFM operates as a negative feedback controller of the equilibrium BP level (Fig. 2). It is important to note that this equilibrium BP level is set only by the shape and position of the chronic renal function curve and the level of salt intake *(4)*.

A second important characteristic of the renal function curve is its slope. Although the acute pressure–natriuresis relationship is relatively shallow, the slope of the chronic renal function curve is remarkably steep in most individuals (Fig. 3). The steepness of the chronic renal function curve reflects the property of salt insensitivity—a lack of change of the long-term BP level despite changes in salt intake. The steepness of the chronic renal function curve, relative to the acute pressure–natriuresis relationship, is thought to be largely the result of the actions of the renin-angiotensin system (RAS *[16–18]*). This system acts to facilitate salt excretion at high levels of salt intake, and facilitate salt retention at low levels of salt intake, thereby allowing salt balance to be re-established with little or no change in the equilibrium BP level. These effects of the RAS are time-dependent and require an intact circulation, and are therefore not apparent in the acute pressure–natriuresis curve of isolated kidneys. In chronic situations in which the RAS is unresponsive to a change in salt intake, BP becomes salt sensitive, corresponding to a renal function curve with a shallow slope, reminiscent of the acute pressure–natriuresis relationship.

A third and final characteristic of the chronic renal function curve to mention is its position along the BP axis. Repositioning the curve along the BP axis shifts the equilibrium BP level that the system will defend. A shift of the curve to the left lowers the equilibrium BP level, causing increased salt excretion until BP reaches the new equilibrium level, whereas shifting the curve to the right will produce a state of hypertension (Fig. 4). In the case of a curve with a shallow slope (salt sensitivity), hypertension can also be produced by increasing the level of salt intake (moving the equilibrium BP point along the curve to the right). In some cases, hypertension may be associated with a combination of a rightward shift and reduced slope of the renal function curve (Fig. 4).

Fig. 1. *(continued from facing page)* Guyton's large circulatory model *(5)*. The core of the large circulatory model consisted of equations calculating the pressures, volumes, and flows within different segments of the heart and circulation. Each additional section added to the complexity and realism of the control system. For example, an autonomic control section allowed cardiovascular dynamics to be affected by reflex adjustments of sympathetic tone (e.g., baroreflex), sections on renal dynamics and excretion and thirst and drinking allowed circulatory volumes to be governed by sodium and water balance. Other sections added specific fluid compartments, regional circulations, and additional control mechanisms (e.g., antidiuretic hormone, angiotensin, and aldosterone systems). Atrial natriuretic peptide was included in the 1992 version of the model. (From ref. *5* with permission.)

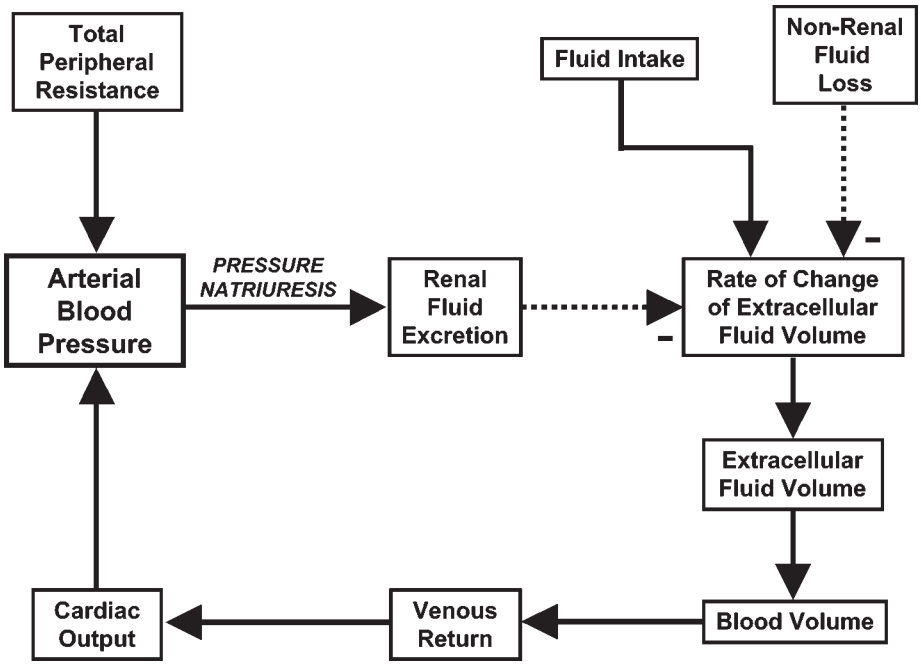


Fig. 2. Regulation of the long-term level of arterial blood pressure by the renal body-fluid feedback mechanism. (Modified from ref. *4*.)

3. DOMINANCE OF THE RBFFM IN CONTROLLING THE LONG-TERM BP LEVEL: ITS IMPLICATIONS AND SIGNIFICANCE

3.1. Effectiveness of the RBFFM as a BP Controller

Of the many feedback mechanisms affecting BP, the RBFFM is believed to be the most powerful, capable of dominating all other mechanisms *(4,5)*. The dominance of this mechanism in controlling the long-term BP level arises from the cumulative, progressive nature of its actions. As long as the BP remains above the equilibrium level predicted by the chronic renal function curve, renal sodium excretion will remain high. Because the ensuing loss of ECF volume is progressive, the longer the arterial pressure remains above the renal set point, the greater the loss of ECF volume will be. Thus, the RBFFM is unusual among BP regulatory mechanisms in that its effectiveness grows with time. Given sufficient time, the RBFFM should theoretically be capable of completely correcting any perturbation in BP. This ability to completely correct a disturbance in arterial pressure is what Guyton often referred to as the "infinite gain" of the RBFFM, "gain" being a control systems term for the power or effectiveness of a regulatory mechanism.

The power of the RBFFM in BP control has many important implications for long-term BP control and hypertension. Several are discussed here.

3.1.1. Predictive Value of the Chronic Pressure–Natriuresis Relationship

A conclusion reached by Guyton's systems analysis is that at equilibrium (i.e., salt and water balance), the long-term BP level is solely determined by the value predicted by the intersection of the chronic pressure–natriuresis relationship and the level of salt intake (Fig. 3 *[4]*). In many respects, this principle is self-evident because this is the only BP level at

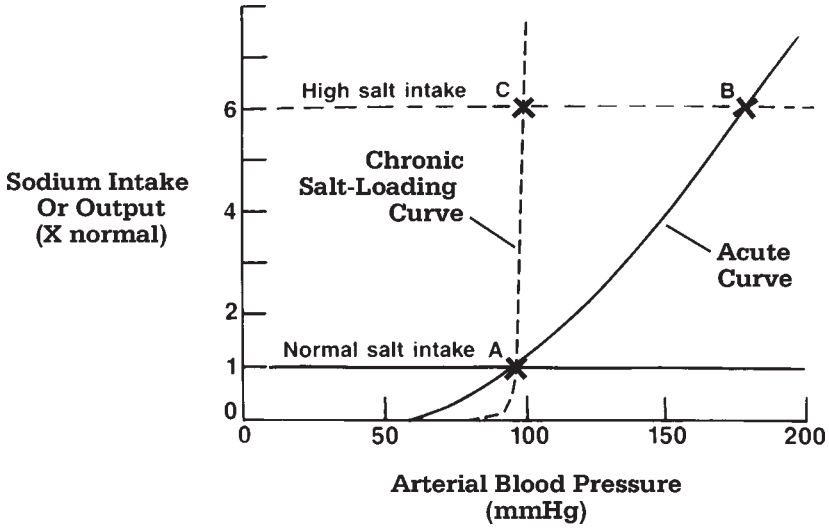


Fig. 3. The acute and chronic pressure–natriuresis relationships. The solid curve (acute curve) illustrates typical changes in salt excretion that quickly arise following acute changes in renal perfusion pressure in an isolated kidney. The dashed curve (chronic salt loading curve) indicates the long-term blood pressure level associated with salt balance (i.e., salt excretion = salt intake) at various levels of salt intake in intact animals. The solid and dashed horizontal lines indicate normal and six times the normal levels of salt intake, respectively. Point A indicates the equilibrium point (the blood pressure level at which salt balance can be achieved) for both the acute and chronic pressure–natriuresis relationships under conditions of normal salt intake. Points B and C indicate the equilibrium point for the acute and chronic pressure–natriuresis relationships, respectively, when salt intake is six times the normal. (Modified from ref. *4*.)

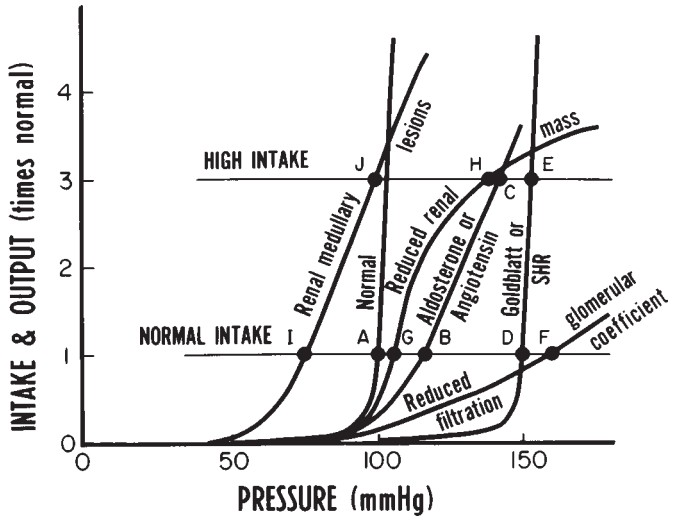


Fig. 4. Effect of hypertension on the chronic renal function curve. Four different kinds of renal function curve associated with hypertension (reduced renal mass, aldosterone or angiotensin infusion, Goldblatt hypertension [i.e,. renal stenosis] or spontaneously hypertensive rats, and reduced glomerular filtration coefficient) and one form associated with hypotension (owing to renal medullary lesions) are compared with the normal curve. Equilibrium points for normal and elevated (three times normal) levels of salt intake are indicated on each curve. (From Guyton ref. *4* with permission.)

which salt balance can be achieved. Any other BP level will lead to a change in salt and water balance that will slowly drive the BP back to the predicted level. Thus, a shift in the chronic pressure–natriuresis relationship will lead to a change in the long-term BP level. In turn, any change in the long-term BP level can be considered to reflect an underlying shift of the chronic renal function curve (assuming salt intake is approximately constant).

3.1.2. Dominant Role of the Chronic Pressure–Natriuresis Relationship in Hypertension

A closely related implication is the prediction that hypertension must reflect a change in the chronic renal function curve. Thus, Guyton was well known for championing the concept of the "dominant role played by the kidney in hypertension." Support for his view of the dominant role of the kidney and RBFFM in causing hypertension comes from several sources of which we mention just a few.

3.1.2.1. Support for the Dominant Role of the Kidney and Pressure–Natriuresis Mechanism

Shortly after Guyton's prediction of a dominant role of the kidney in BP control was published, his prediction was tested by transplantation studies in various genetically hypertensive rat strains (SHR, SHRSP, Dahl, Milan, Prague) *(19–21)*. Recent studies have refined the approach further, circumventing potential pitfalls such as rejection phenomena, the need for immunosuppressants, and the use of indirect methods of BP assessment *(22)*. In such experiments, the BP level of animals receiving a transplanted kidney was shown to be strongly influenced by the BP level of the donor animal: implantation of a hypertensive kidney elevated the BP level of normotensive animals, whereas implantation of a normotensive kidney reduced the BP of hypertensive animals. This general finding has also been supported by transplantation studies in humans *(23,24)*. Recent studies have utilized the transplantation approach to define the contribution of the kidney to the hypertension associated with a considerably smaller number of hypertensive alleles located on a segment of rat chromosome-1 *(25,26)*. The role of the kidney in human genetic hypertension has been supported by observations of altered renal handling of sodium by hypertensive kidneys *(27)* and by our recent understanding of genetic disorders that directly affect renal transport mechanisms and lead to hypertension *(28–30)*.

The kidney is also directly implicated in many well-known forms of acquired hypertension, including that associated with renal stenosis (Goldblatt hypertension), ureteral obstruction, renal wrap hypertension, reduced renal mass, infusion of various substances into the renal artery (e.g., ref. *31*) or medulla (e.g., ref. *32*), and a various renal pathologies. The involvement of the kidney in acquired forms of BP change has also been demonstrated using the transplantation approach. For example, the persistent correction of hypertension induced by high doses of an angiotensin-converting enzyme inhibitor in genetically hypertensive rats has recently been shown to be transferable to untreated rats by renal transplantation *(33)*.

Above all else, support for a dominant role of the kidney and renal function curve in setting the BP level in hypertension has come from a series of studies in which a resetting of the chronic renal function curve to higher pressures has been found to be a consistent feature of all models of hypertension examined (Fig. 4) *(34)*. Again, this once controversial concept appears almost self-evident, since without a resetting of the chronic renal function curve, hypertension would result in an increased rate of renal fluid and water excretion until BP returned to normal.

In summary, the concept of the dominant role of the kidney (or RBFFM, or pressure natriuresis relationship) in hypertension is supported by a wide variety of data. In its most

basic form, this principle simply means that all forms of hypertension must include a mechanism that allows the renal function curve to be reset so that normal sodium and fluid balance can be maintained at the elevated level of BP.

3.1.3. Non-Causes of Hypertension

A third important implication has to do with the "non-causes" of hypertension. Based on the principles discussed previously, non-causes would include any factor that failed to affect the chronic renal function curve (assuming salt intake remains approximately normal). A particularly important example is that this would exclude a contribution from changes in vascular resistance that fail to influence the renal circulation (or chronic renal function curve). Thus, although an increase in the resistance of the renal microcirculation, renal artery, or aorta above the kidney (Guyton's "resistance axis of hypertension" *[35]*) will shift the renal function curve rightward, resulting in a higher long-term BP level, an increase in the resistance to other parts of the arterial circulation do not directly affect the renal function curve, and are therefore presumed to be unable to influence the long-term BP level.

A comparison of the predicted effects of doubling vascular resistance in renal vs nonrenal circulations is provided in computer simulations of Figs. 5 and 6. Doubling the nonrenal vascular resistance transiently raises the BP level but rapidly leads to compensatory mechanisms, including suppression of the RAS and sympathetic system and marked increases in renal salt and water excretion (Fig. 5). Consequently, the long-term BP is unchanged despite the initial doubling of resistance in the nonrenal vasculature. This result fits well with the example frequently given by Guyton of war veterans who had undergone amputation of all four limbs (thereby elevating their peripheral resistance by approx 20%) yet lacked hypertension. In marked contrast, doubling of the renal vascular resistance results in a prompt marked elevation of BP mediated initially by a rise in angiotensin-II and subsequently by increases in fluid volumes and cardiac output (Fig. 6). As discussed in a later section, these responses are facilitated by the phenomena of whole body autoregulation.

A dramatic example also occurs in the presence of a large arteriovenous (AV) fistula (e.g., a communication between the abdominal aorta and vena cava). The creation of a large AV fistula is associated with a profound fall in peripheral resistance and BP. With time, however, renal salt and water retention leads to elevation of cardiac output and a restoration of BP to approximately normal despite the maintenance of a profoundly reduced peripheral resistance *(36)*. This demonstrates the ability of the RBFFM to control BP without regard for the level of peripheral resistance. In rats with abdominal AV fistulas, treatment with deoxycorticosterone acetate and salt (DOCA salt) can produce considerable hypertension despite the fact that peripheral resistance remained well below the level seen in control rats *(37)*. Thus, although hypertension is typically accompanied by an elevation of vascular resistance, it is not actually required for hypertension to occur. Indeed, as discussed in the subsequent section on whole body autoregulation, Guyton's system analysis led to a second provocative conclusion that vascular resistance was largely a consequence, and not a cause, of the long-term BP level.

3.1.4. The Important Role of Nonrenal Tissues in Hypertension

An important misconception is that by acknowledging a dominant role for the kidney in long-term BP control we are excluding a role for other tissues. On the contrary, the important role played by the kidney actually empowers other tissues with the ability to influence the long-term BP level *(4,5,38)*. The only caveat to this is that to do so, nonrenal tissues must in some way reset renal function to agree with the new pressure level. That is, nonrenal

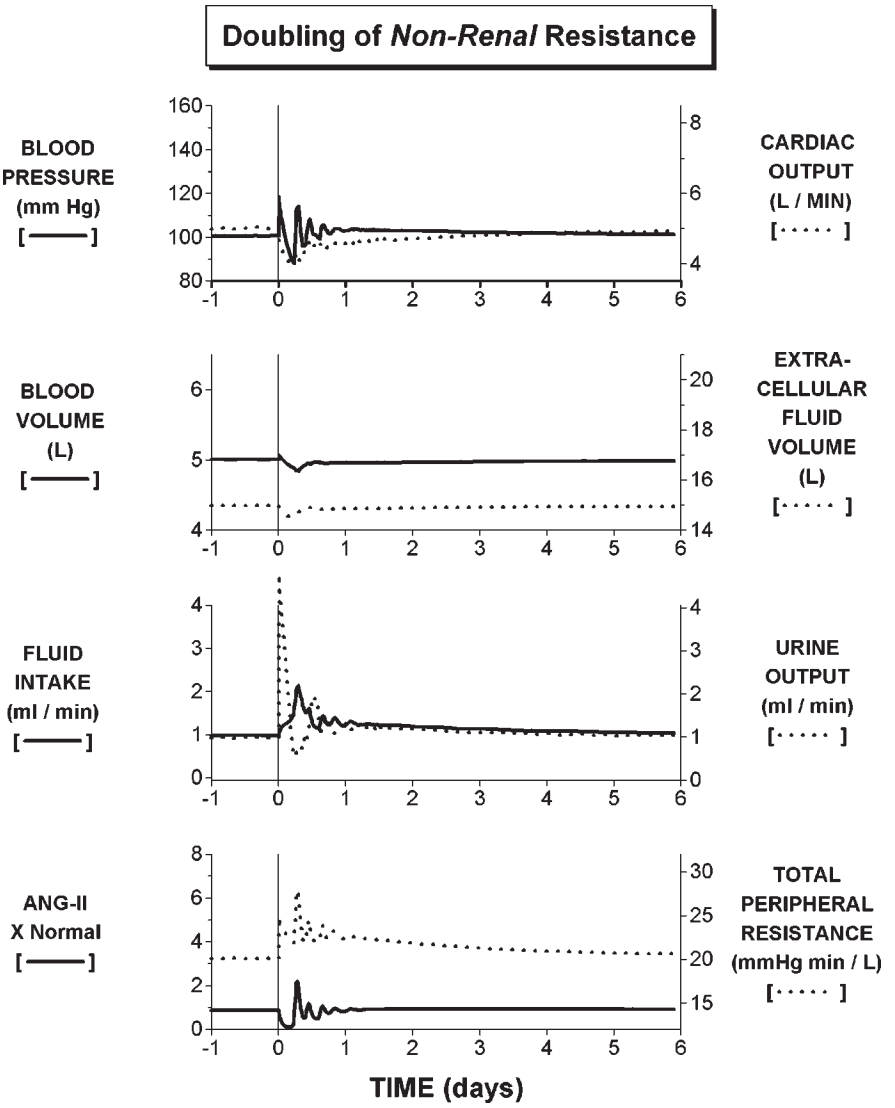


Fig. 5. Computer simulation of the response to doubling of the vascular resistance in all vascular beds other than the renal circulation. The increase in nonrenal resistance evokes a transient rise in blood pressure, which is rapidly compensated for, resulting in no change in the long-term blood pressure level. The simulation was run using the 1992 version of Guyton's large circulatory model.

tissues must, in some manner, affect the chronic renal function curve. The adrenal gland, for example, is a well-appreciated example in which a nonrenal tissue (in this case, via aldosterone) can influence the long-term BP level through their influence on the kidney. The case for an influence of the central nervous system (CNS) on the RBFFM is discussed next.

3.1.4.1. Role of Neural Mechanisms

Guyton spent much of his early research career investigating neural mechanisms of BP control *(38).* In a 1972 review of his systems analysis of the cardiovascular system *(5),* he

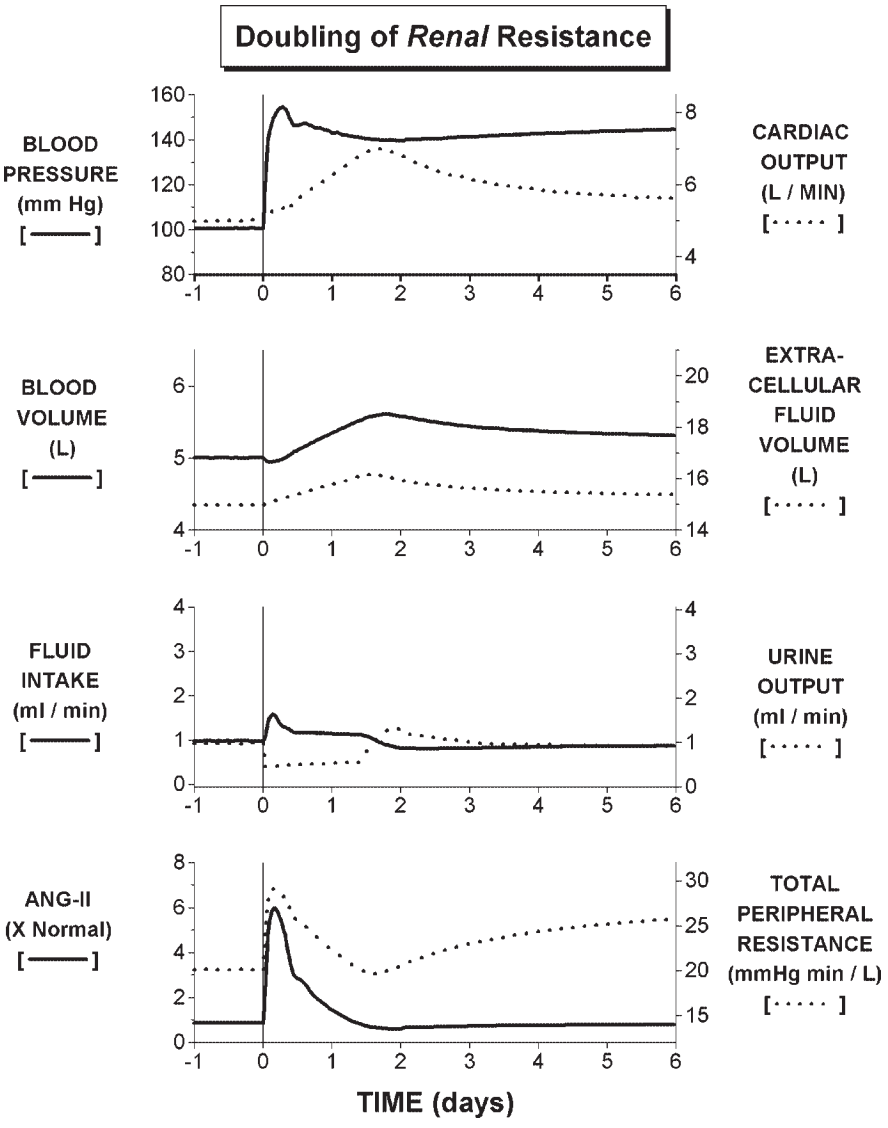


Fig. 6. Computer simulation of the response to doubling the renal vascular resistance. The increase in renal (afferent arteriolar) vascular resistance evokes a prompt and sustained rise in blood pressure, which is accompanied by volume loading and whole body autoregulation of blood flow. The simulation was run using the 1992 version of Guyton's large circulatory model.

pointed out the potential for the CNS to influence the renal body fluid feedback control of the long-term BP level through several pathways including the renal sympathetic nerves. The physiology of the renal nerves and their role in hypertension has subsequently been widely investigated *(39–41)*.

3.1.4.1.1. Effects of the Renal Nerves on Renal Function. As illustrated in Fig. 7, renal nerve activity has three direct actions on the kidney that may influence the long-term BP level. First, renal nerve activity facilitates and/or directly stimulates the release of renin from the

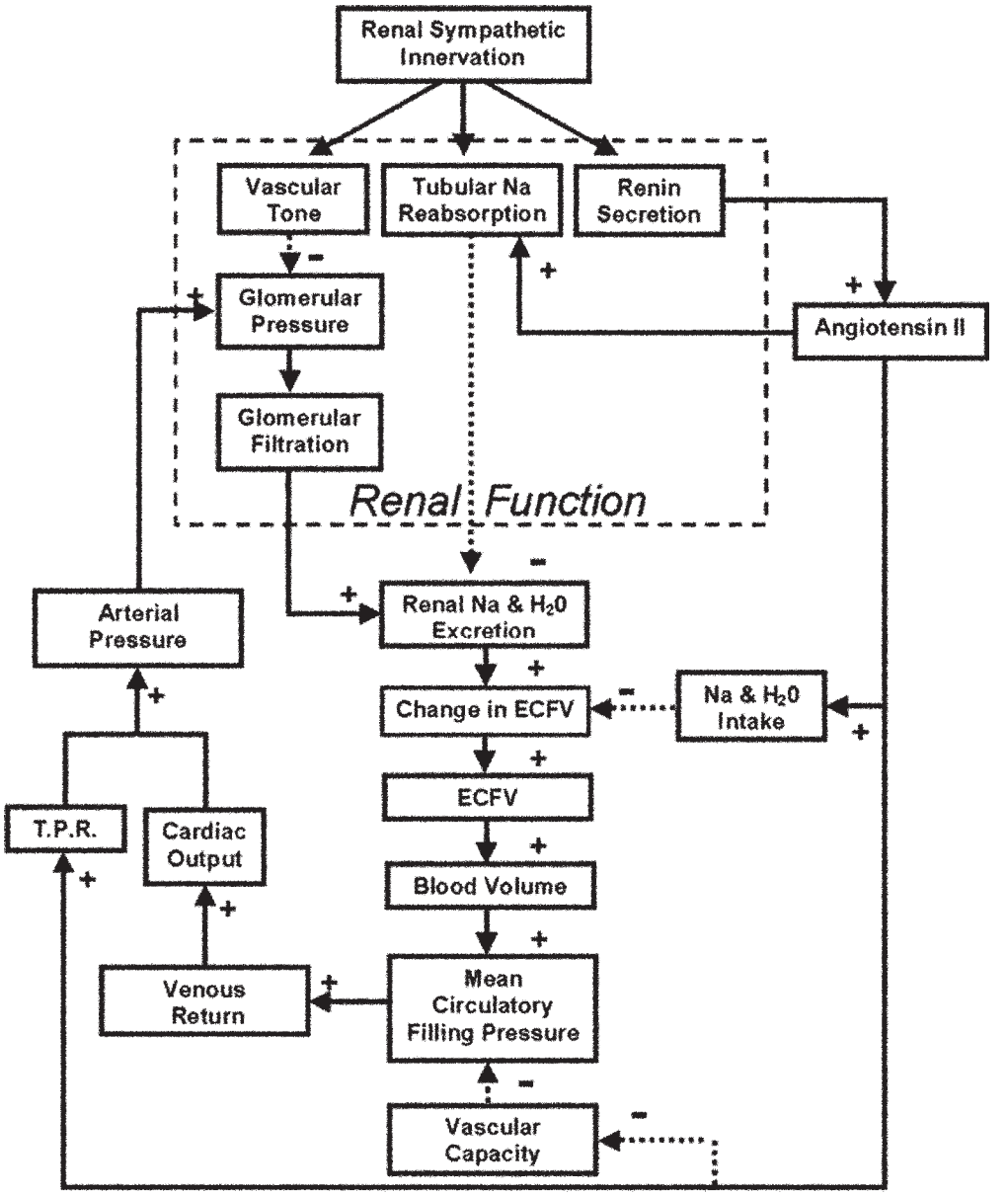


Fig. 7. Effects of the renal sympathetic nerves on renal function and blood pressure control. (Modified from ref. *96*).

granular cells of the juxtaglomerular apparatus. This can influence the long-term BP level through the formation of angiotensin peptides such as angiotensin-II, whose actions include vasoconstriction, reduced renal sodium excretion, and a stimulus for the secretion of aldosterone, itself a potent antinatriuretic hormone. Second, renal nerve activity can directly stimulate the tubular reabsorption of sodium, thereby promoting an increase in ECF volume and BP. Third, renal nerve activity can evoke renal vasoconstriction (e.g., ref. 41), thereby diminishing the rate of glomerular filtration and increasing the rate of tubular reabsorption of salt and water (via reduced peritubular capillary pressures).

3.1.4.1.2. Effect of the Renal Nerves on the Pressure–Natriuresis Mechanism. The effect of the renal nerves on renal salt excretion represents a shift of the acute pressure–natriuresis relationship along the BP axis. For example, increases in renal sympathetic nerve activity (RSNA) shift the pressure–natriuresis relationship rightward along the BP axis *(42,43)*. Overtime, a sustained shift would be expected to promote renal salt retention and fluid volume expansion until BP rises to meet the new set point level. In this manner, the sympathetic system could direct the kidneys to shift the BP level to a higher level. Once the new equilibrium BP level were achieved, renal salt excretion would return to normal, and salt balance would again be achieved despite the sustained shift of the pressure–natriuresis relationship.

It is interesting to consider that little or no change in the rate of renal sodium excretion would occur if the pressure–natriuresis relationship and BP were to both shift at the same time and by a similar amount. This may occur in fact occur during the course of the transient fluctuations in BP and RSNA that occur throughout the day. Although experimentally imposed changes in renal perfusion pressure leads to corresponding changes in renal salt and water excretion (i.e., pressure natriuresis) in anesthetized animals (e.g., ref. *12*) and conscious animals (e.g., ref. *13*), spontaneous fluctuations in BP in conscious animals are generally not associated with corresponding changes in renal salt and water excretion *(13,44)*. However, spontaneous fluctuations in BP do lead to pressure–natriuresis in denervated kidneys *(13,44)*, and pressure–natriuresis associated with arousal is amplified following autonomic blockade *(45)*. These results suggest that RSNA may act to reset the pressure–natriuresis relationship, thereby minimizing changes in renal salt excretion associated with transient changes in BP. Such an arrangement is presumed to be highly advantageous in wild populations in which dietary salt intake is limited, and its conservation directly impacts on survival and reproduction.

3.1.4.1.3. The Renal Nerves and the Long-Term BP Level. Two important parameters define the ability of the renal nerves to influence the long-term BP level: the magnitude of their effect on the pressure–natriuresis mechanism and how well it is sustained with time. The renal nerves normally provide a considerable restraint on renal sodium excretion as evidenced by the up to threefold increase in renal sodium excretion that can be produced by reflex unloading of RSNA in conscious animals *(46–49)*. If such an effect were well sustained, renal denervation would be expected to have a profound effect on the long-term BP level. However, in conscious dogs in which one of the two kidneys is chronically denervated, the 24-h sodium excretion of the denervated kidney is typically no more than about 12% greater than that of the innervated kidney (50–54). This is far less than the threefold difference seen following acute reductions in RSNA, and suggests that the renal nerves are most effective in mediating short-term resetting of the pressure–natriuresis relationship. Nevertheless, even a modest effect on sodium excretion, if sustained, is expected to have significant consequences for the long-term BP level.

The impact of the renal nerves on long-term BP control has been investigated by studying the consequences of renal denervation. Whereas comparison of chronic renal-denervated and sham-operated animals has generally not revealed differences in the BP level under control conditions, there have been several exceptions *(55,56)*. In a recent comparison of renal-denervated and sham-operated rats, for example, renal denervation was associated with significantly (approx 8–10 mmHg) lower 24-h telemetered BP level *(55)*. In hypertension, renal denervation has been shown to reduce the final level of BP achieved in several models including spontaneously hypertensive rats *(57,58)*, obesity-induced hypertension in dogs *(59)*, and phenol-induced hypertension *(60,61)*. Renal denervation has been reported to pre-

vent salt-loading hypertension in rabbits *(62)*, and increases in BP caused by central infusion of angiotensin-II in rats maintained on a high salt diet *(63)*, although it does not appear to greatly impact on salt-induced hypertension in the Dahl rat model *(64,65)*. Renal denervation was reported to reduce the final BP level in the two-kidney one-clip and one-kidney one-clip rat Goldblatt model *(66,67),* although negative results for the one-kidney one-clip model have also been reported *(68,69).*

In addition to the role played by renal sympathetic fibers, renal afferent (sensory) fibers are thought to provide critical contributions in several models including the one-kidney one-clip Goldblatt hypertension *(70)* and phenol-induced hypertension models *(60,61).* It is notable that in man, lumbar sympathectomy was employed for many years as a method with which to relieve hypertension. Although the surgery resulted in a pronounced initial decrease in BP, follow-up studies demonstrated the effects to be poorly sustained (possibly because of reinnervation) and the approach was abandoned *(71).*

4. WHOLE BODY AUTOREGULATION

Whole body autoregulation is an important concept that explains the role of tissue blood flow in setting the total peripheral resistance (TPR). The concept of blood flow autoregulation is most widely understood in the context of the local or regional circulations whereby mechanisms intrinsic to the tissue or organ make adjustments to the local vascular resistance such that: (a) blood flow occurs at a level that is appropriate for the metabolic needs of the organ or tissue, and (b) this level of blood flow is held relatively constant despite moderate increases or decreases in the perfusion pressure. Alternately, autoregulation can also be identified as a positive correlation between an imposed change in BP or flow and the resultant change in vascular resistance, the increase in resistance serving to restrain the increase in blood flow that would otherwise occur. Autoregulatory adjustments of local vascular resistance can be clearly demonstrated in isolated tissues *(72)* and, to some extent, even in isolated vessels (e.g., ref. *73*). Although autoregulation is presumed to involve myogenic control of the vascular smooth muscle in combination with feedback provided by local metabolism, metabolites, or oxygen delivery *(74–76)*, the mechanisms contributing to blood flow autoregulation vary from tissue to tissue and remain incompletely understood.

Because autoregulation influences the control of vascular resistance in virtually all tissues within the systemic circulation (it is absent in the pulmonary circulation), it is not surprising that autoregulation should be evident in the pressure-resistance and flow-resistance relationships of the entire circulation. In dogs and rats in which reflexes and other regulatory systems have been disabled, progressive expansion of the blood volume leads to increases in cardiac output (CO) and BP, which are accompanied by an increase in the TPR, whereas withdrawal of blood leads to reductions in CO and BP that are accompanied by a fall in TPR *(76–81).* Such changes in TPR reflect the underlying whole body autoregulation of blood flow: essentially the summation of the local autoregulatory efforts in different tissues and organs to sustain local blood flow at a normal and appropriate level despite changes in the BP.

Whole body autoregulation is not apparent during acute manipulations of BP or CO in the normal circulation in which circulatory reflexes (e.g., baroreflexes) and other regulatory mechanisms remain intact (e.g., ref. *80*). Indeed, in such circumstances, manipulations of BP or CO lead to changes in TPR in the opposite direction, reflecting the dominance of other mechanisms, including the passive effects of BP on resistance vessels (e.g., increased distending pres-

sure lowers resistance) and control mechanisms such as the baroreflex that adjust vascular resistance in an effort to hold BP near the normal level (e.g., elevated BP evoking reflex vasodilation). In time, however, local autoregulatory mechanisms become increasingly evident in circulatory control. In conscious, chronically instrumented dogs in which blood withdrawal was used to lower BP by 25% for at least 8 h, whole body autoregulatory increases in TPR became apparent within 1 to 7 h following the reduction in BP *(80).* In dogs made salt sensitive by reducing renal mass to 30% of normal, whole body autoregulatory adjustments of TPR slowly became apparent over several days of volume loading with saline (Fig. 8 *[82,83]*).

In considering the time course of whole body autoregulation, it is important to keep in mind that it is only one of a number of mechanisms that may simultaneously influence vascular resistance. At any point in time, the relationship between CO and TPR will reflect the summation of the effects of mechanisms promoting a positive (e.g., autoregulation) vs negative relationship (e.g., baroreflex, pressure-induced distension) in all the regions of the system circulation. Thus, the transition from negative to positive CO–TPR relationships reflects the shifting effectiveness of the underlying mechanisms, with autoregulation becoming more effective (and circulatory reflexes becoming less effective *[4]*), with time.

The precise contribution of whole body autoregulation in setting the long-term level of TPR is difficult to assess for several reasons. First, as discussed previously, relationships between flow and resistance represent the net effect of a number of control mechanisms, not only autoregulation. Second, the effectiveness of autoregulation and other phenomena affecting blood flow are often time-dependent. And third, because there is no selective way of blocking autoregulation, the phenomena is difficult to manipulate experimentally. Despite these limitations, several forms of indirect evidence suggest autoregulation is important in setting the long-term level of tissue blood flow and vascular resistance. In patients and rats in which there is a narrowing (coarctation) of a segment of the aorta, the BP is considerably higher above the coarctation than it is below. Nevertheless, blood flow above and below the coarctation are similar *(84–86)* suggesting that local autoregulatory mechanisms have the capability of adjusting tissue blood flow to appropriate levels even in the face of large and chronic changes in the BP level. Such long-term forms of blood flow autoregulation appear to include a component of altered structural vascular resistance in which the number and caliber of blood vessels is affected. Indeed, this may be the explanation for the increases in structural vascular resistance and rarefaction *(87)* of blood vessels in hypertension subjects, and for the normalizing of vascular resistance in regional vasculatures in which BP has been lowered by restriction of the arterial supply *(88).*

5. WHOLE BODY AUTOREGULATION: IMPLICATIONS AND SIGNIFICANCE

The concept of whole body autoregulation of blood flow has several important implications for circulatory control, which are briefly discussed next.

5.1. Autoregulation May Contribute to the Elevated Level of Vascular Resistance in Salt-Loading Hypertension

In studies of conscious, chronically instrumented dogs in which salt sensitivity was induced by reducing renal mass to 30% of normal *(82,83)*, whole body autoregulation of TPR slowly became apparent over several days. As shown in Fig. 8, a sustained infusion of saline resulted in a prompt rise in BP that was initially mediated by an increase in CO *(82).* Subse-

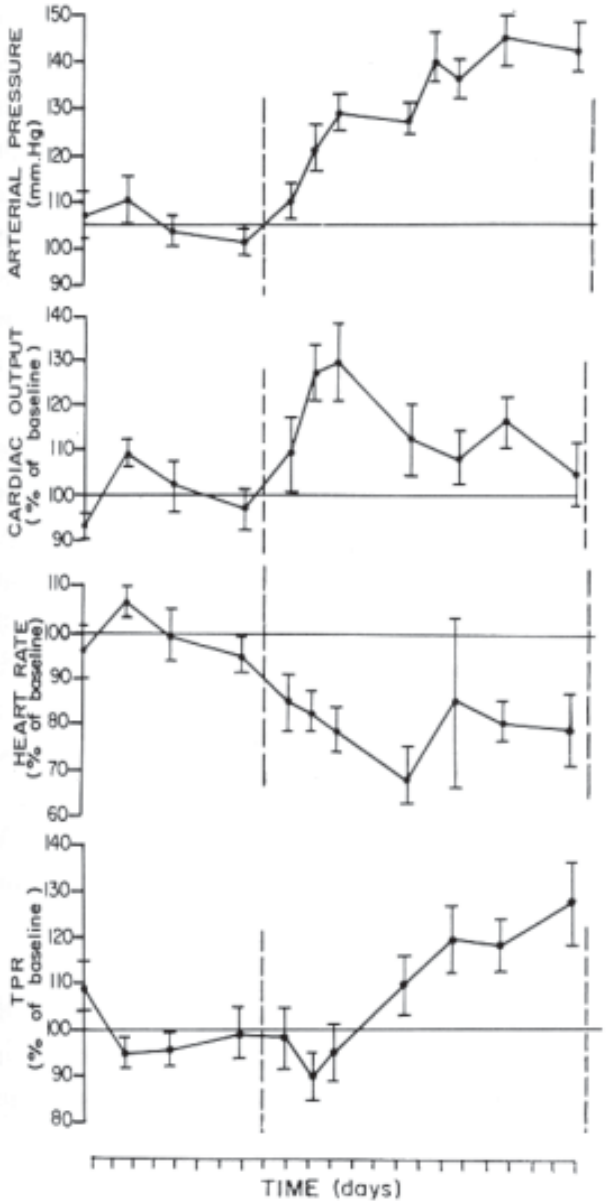


Fig. 8. Time course of hemodynamic effects induced by volume loading in salt-sensitive dogs. Volume loading consisted of an infusion of isotonic saline (191 mL/kg/d). Salt sensitivity was induced by reducing renal mass to approximately one-third of normal. TPR, total peripheral resistance. (From ref. *82* with permission.)

quently, peripheral resistance slowly rose (whole body autoregulation) and CO progressively fell (the predicted effect of increased TPR to decrease venous return and CO *[6]*), such that the increase in BP was eventually sustained by the increase in TPR. Similarly, in the Dahl strain of genetically salt-sensitive rats, salt loading led to hypertension that was initially caused by an increase in CO but eventually sustained by slow increases in TPR *(89–92)*. Slow increases in TPR were also observed to occur during salt loading in dogs made salt

sensitive by a chronic infusion of angiotensin-II *(93,94)*. In regular (i.e., salt-insensitive) dogs and in the Dahl strain of salt-resistant rats, although salt loading does not lead to an increase in BP, it does produce an initial rise in CO counter-balanced by a fall in TPR *(89,90,94)*. In time, CO and TPR returned to normal levels *(89,91,92)* as one might expect to occur in the presence of whole body autoregulation but a normal (salt-insensitive) renal function curve.

Although a general discussion of the role of whole body autoregulation in essentially hypertension is well beyond the scope of this chapter, it is worth noting that a very slow transition from elevated CO to elevated peripheral resistance has been described in a number of longitudinal hemodynamic studies of patients with essential hypertension (see, e.g., Table 1 in ref. *95*). Thus, one view of the increased TPR that accompanies hypertension is that, as is the case with volume loading, it is an essential response to the elevated BP in order to prevent the over perfusion of the tissues that would otherwise occur. The precise mechanisms by which whole body autoregulation may occur remain to be worked out and strongly merit further study.

5.2. Autoregulation Does Not Cause Long-Term Changes in BP or Hypertension

Because whole body autoregulation of blood flow is an important determinant of TPR, whole body autoregulation may be presumed to have an important effect on the long-term BP level. However, this is generally thought not to be the case. As discussed previously, the RBFFM is the dominant controller of the long-term BP level. As shown in Fig. 2, TPR (and therefore autoregulation) lies outside of the main feedback loop of the RBFFM. Consequently, the RBFFM is expected to act to regulate the long-term BP level irrespective of the level of TPR. In other words, the RBFFM sets the long-term level of BP, the product of CO and TPR; whole body autoregulation is simply responsible for adjusting the balance of CO and TPR in a manner that provides an appropriate level of tissue perfusion.

5.3. Autoregulation Prevents the Large Changes in ECF Volume, Blood Volume, and Cardiac Output Otherwise Required to Achieve a Change in BP

Although whole body autoregulation of TPR does not directly influence the long-term BP level, it strongly influences which combination of TPR and CO will be used to achieve a given BP level, and the extent of fluid accumulation required to achieve the increase in CO. To illustrate this role of whole body autoregulation, we have used Guyton's large circulatory model to simulate the response to volume loading caused by a sixfold increase in salt intake in a salt-sensitive individual (caused by reduced renal mass) in the presence and absence of blood-flow autoregulation (Figs. 9 and 10). The simulation demonstrates a valuable benefit of mathematical modeling: the ability to conduct experiments on the model that we (so far) have no way of conducting in real life.

In the presence of normal autoregulation (Fig. 9), a high level of salt intake leads to an increase in fluid volumes (blood volume and ECF volume) associated with a rise in CO and BP and a fall in TPR (pressure-induced distension of the vasculature). In time, however, TPR progressively rises (whole body autoregulation), leading to reductions in the volume loading and CO required to sustain the elevated BP level. Thus, in the long-term, the increase in salt intake leads to salt-sensitive hypertension with rather minor changes in fluid volumes or cardiac output.

In contrast, Fig. 10 shows the results of the same simulation repeated with blood-flow autoregulation removed. In this situation, increases in fluid volumes, CO, and BP occur

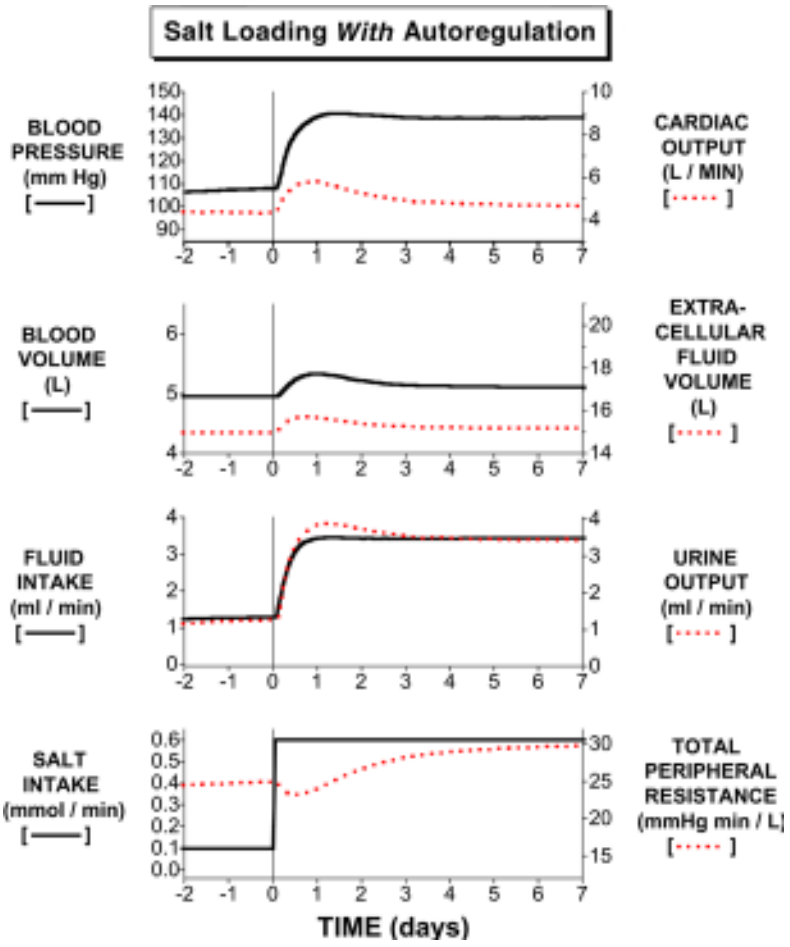


Fig. 9. Computer simulation of the hemodynamic response to volume loading in salt-sensitive subjects with blood-flow autoregulation intact. The simulation was run using the 1992 version of Guyton's large circulatory model. Salt sensitivity was created by reducing renal mass to 30% of normal. Volume loading was commenced at time 0 by increasing salt intake to six times the normal levels. The progressive increase in total peripheral resistance (whole body autoregulation) slowly reduces the volume loading and cardiac output required to sustain blood pressure at the new equilibrium level.

without any increase in TPR (which in fact falls, largely because of unopposed pressure-induced distension of the vasculature). In the absence of an increase in TPR, marked increases in fluid volumes and CO are required to elevate the BP toward the equilibrium level. Indeed, equilibrium is not achieved within the time course of this simulation: by the end of 1 wk on salt, fluid volumes, CO, and BP continue to rise, and BP has not yet reached the equilibrium level that it achieved in the presence of autoregulation (Fig. 9).

This simulation illustrates that whole body autoregulation does more than ensure that regional blood flow occurs at a rate that meets the metabolic needs of the tissues. When fluid volumes are changed, it also serves to minimize the changes in fluid volume and cardiac output that are required to affect the long-term BP level. Because the ability of changes in

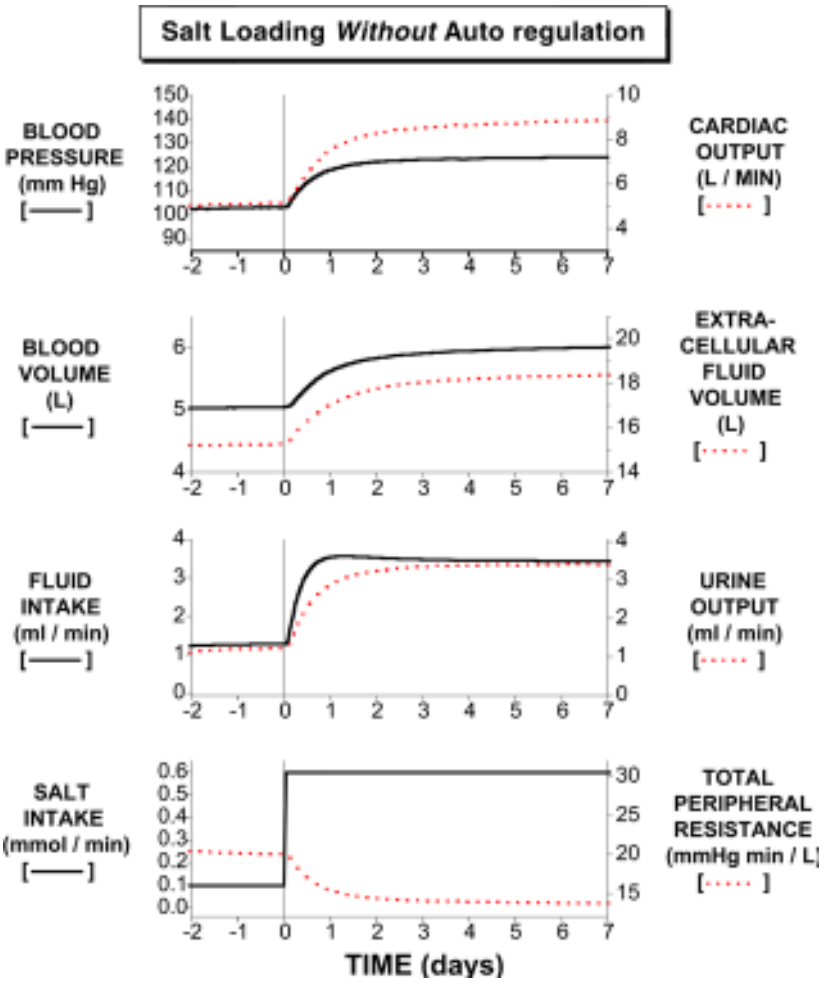


Fig. 10. Repeat of the computer simulation of the response to volume loading shown in Fig. 9 after disabling mechanisms of blood-flow autoregulation. In the absence of autoregulation, the rise in blood pressure induces a sustained fall in total peripheral resistance. Blood pressure does not reach the new equilibrium level associated with the high salt intake during the course of the simulation despite marked and progressive increases in fluid volumes and cardiac output.

fluid volumes to affect BP lies at the heart of the RBFFM (Fig. 2), one can readily appreciate the importance of whole body autoregulation in allowing the RBFFM to regulate the long-term BP level in a highly effective manner without the need for the large changes in fluid volumes that would otherwise be necessary.

6. CONCLUSION

In this chapter we have touched on just two of the concepts that were developed and championed by Arthur C. Guyton, a founder of modern quantitative integrative physiology. Looking at the diagram of his large circulatory model (Fig. 1), it is hard to deny that his approach was integrative. However, perhaps the greatest evidence of his integrative approach

was its achievements: concepts and principles (e.g., Table 1) critical to the understanding of the system, yet largely unexpected from previous studies of the individual components.

Perhaps what we can take most from Guyton's work is the understanding, even respect, for the multitude of control mechanisms that are simultaneously at work in physiological systems, with each mechanism providing a unique contribution to overall control. With this in mind, it is easy to understand Guyton's emphasis on the need to consider the behavior of entire systems (as systems do take on characteristics that are not apparent upon examination of their components) and the use of a quantitative approach at all levels of physiological organization (because not all control mechanisms are of equal importance, and because the importance of individual mechanisms changes with time and circumstance). We hope that such lessons will be helpful in advancing our understanding of physiological systems in the future.

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