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Understanding the contribution of Guyton's large circulatory model to long-term control of arterial pressure

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With the publication in 1972 of a large computer model of circulatory control, Guyton and colleagues challenged the then prevailing views on how blood pressure and cardiac output were controlled. At that time, it was widely accepted that the heart controlled cardiac output and that peripheral resistance controlled arterial blood pressure. By incorporating the empirically demonstrated concepts of blood flow autoregulation and the pressure–natriuresis relationship into their mathematical model, Guyton and colleagues were able to develop a number of revolutionary concepts. Guyton's circulatory model was particularly instrumental in exploring the linkage between blood pressure and sodium balance and in demonstrating an overriding importance of renal salt and water balance in setting the long-term blood pressure level. In both the model and experimental data, any long-lasting imbalance between salt intake and salt excretion leads to a progressive alteration of the degree of filling of the vascular system and thus to parallel changes in blood pressure. In turn, changes in blood pressure alter sodium excretion, opposing the initial salt imbalance. Although Guyton's model does not include the most recent cardiovascular discoveries, the concepts underlying the basic functioning of the cardiovascular system can serve as a well-built basis for the development of new, large and integrative cardiovascular models.

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A short history of the development of Guyton's model

In 1972, Guyton, Coleman and Granger published a detailed description of a large computer model of circulatory control (Guyton *et al.* 1972). The model consisted of several hundred mathematical equations aiming primarily at understanding the long-term regulation of blood pressure (BP) and cardiac output (CO). In the late 1950s, when Guyton started to be quite prolific in the field of physiology, considerable controversy existed concerning the regulation of these major cardiovascular variables. The two prevailing views in cardiovascular control were: (a) that the heart controls CO (cardiocentric view); and (b) that vascular resistance controls BP (vasculocentric view).

The early contributions of Guyton (Guyton *et al.* 1959) challenged the cardiocentric view. Guyton used a circuit analysis based on simple physical laws of pressure–flow and pressure–volume relationships to dissect the major factors affecting the return of blood to the heart. Later, after investigating the manner in which the heart function is coupled to venous circulation, Guyton established the now classical graphical analysis of CO and venous return (Guyton *et al.* 1973), the principles of which were incorporated into his 1972 model and remain today a powerful didactic tool to explain CO regulation in a steady-state situation. While more advanced models of cardiac function have subsequently been developed (e.g. pressure–volume analysis), the coupling of the heart with the venous circulation remains a core feature of modern circulatory models.

Guyton and colleagues' investigation of the linkage between the regulation of extracellular fluid volume (ECFV) and that of BP also strongly challenged the vasculocentric viewpoint. Extending traditional models consisting of circulatory pressures, flows and resistances, they added circulatory volumes and compliances and linked them to sources of fluid entry (absorption of salt and water by the digestive tract) and loss (chiefly salt and water excretion by the kidney). Analysis of the model's behaviour revealed an overriding importance of the relative filling of

the vascular system in the feedback regulation of the long-term BP level. Any sustained imbalance between salt intake and salt excretion caused a change in the degree of filling of the vascular system and, in turn, parallel alterations in BP. This effect was opposed by the demonstrated ability of changes in BP to cause corresponding alterations in renal sodium excretion, the so-called acute pressure–natriuresis relationship (PNR). Consequently, the long-term mean BP was found to represent the one BP level at which these effects were balanced, i.e. the one pressure level at which salt balance (intake = output) could be achieved. Thus, Guyton and colleagues came to realize that BP regulation was intimately linked with fluid volume regulation, and that the long-term BP was controlled at a level predicted by the PNR and not by the vascular resistance *per se*.

With the 1972 publication of the large circulatory model, Guyton and colleagues paved the way to new thinking in the regulation of cardiovascular dynamics. The model was written in FORTRAN and ran initially on a large minicomputer (first on a PDP 9, from Digital Equipment Corporation, then in the mid-1970s on a PDP 11/70). It was later transferred into the personal computer environment (Montani *et al.* 1989*a*,*b*), where it could be made freely available to the scientific community. Following 1972, Guyton continued to revise the model, mainly by developing the kidney components and incorporating more recent cardiovascular discoveries. However, the main features of the 1972 version (e.g. pressure–natriuresis relationship, blood flow autoregulation) remained as core concepts of the model. Guyton made very few additions to his model after his retirement in 1989 at the age of 70. He died in 2003, leaving behind the most recent version of his model dating from 1992.

Why does the kidney play a dominant role in long-term blood pressure control?

In Guyton's model, control of BP and sodium balance are tightly linked via the acute pressure–natriuresis relationship, a concept so central to the regulation of sodium excretion that the many other factors and mechanisms that influence sodium excretion were considered by Guyton to act chiefly by modifying this relationship (Guyton, 1980). Based on this concept, one can understand the general renal body fluid feedback mechanism (Guyton *et al.* 1972; Guyton, 1980, 1990; Hall *et al.* 1986*a*) as illustrated in the block-diagram of Fig. 1. Any imbalance between intake and output of salt will lead to a cascade of events that oppose the initial disturbance, a

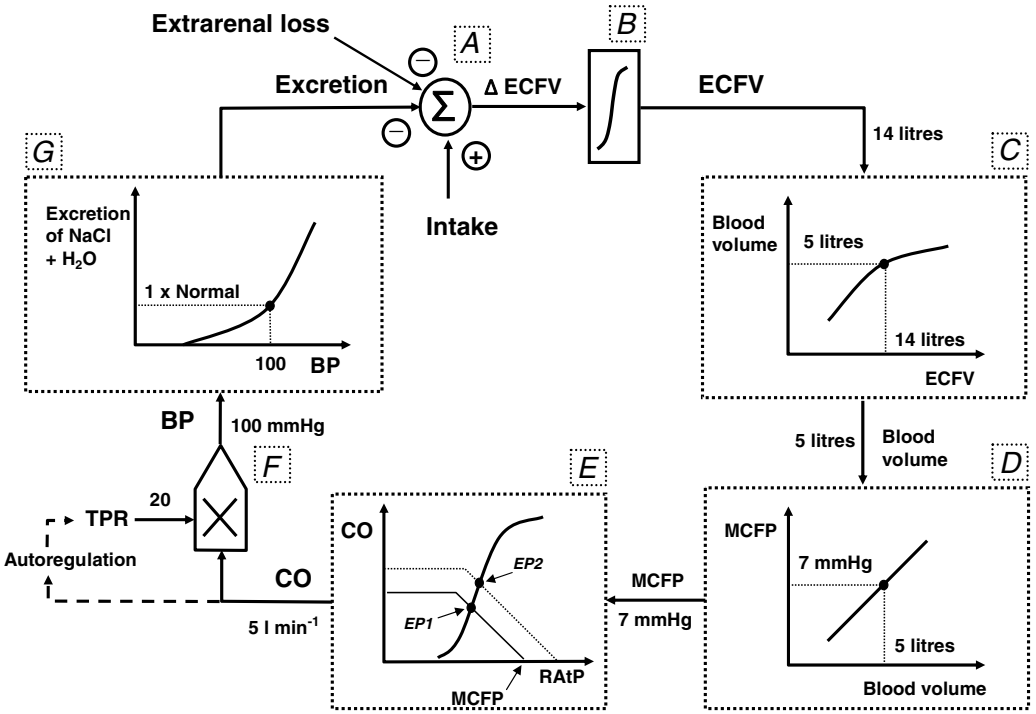

Figure 1. The renal body fluid feedback mechanism for control of blood volume and extracellular fluid volume in the face of large changes in salt intake

See text for a detailed explanation of each block (*A*–*G*) of the block-diagram. Abbreviations: ECFV, extracellular fluid volume; MCFP, mean circulatory filling pressure; RAtP, right atrial pressure; CO, cardiac output; EP, equilibrium point; TPR, total peripheral resistance; and BP, blood pressure.

classical negative feedback loop. For example, if salt intake is greater than salt excretion (Fig. 1*A*), there is a positive rate of change of the ECFV (ΔECFV) which, integrated over time (Fig. 1*B*), results in an increase in ECFV and, in turn, to an increase in blood volume (Fig. 1*C*). The greater blood volume increases mean circulatory filling pressure (MCFP, which represents the degree of filling of the whole circulation, relating blood volume to vascular capacity), as shown by the relationship depicted in Fig. 1*D*. This results in a right and upward shift of the equilibrium point (Fig. 1*E*) in Guyton's classic graphical analysis of the cardiac function curve and the venous return curve (Guyton *et al.* 1973), yielding both an increase in right atrial pressure and an increase in venous return. The resulting increase in cardiac output raises BP (Fig. 1*F*). In turn, by way of the acute pressure–natriuresis mechanism, the higher BP increases salt output (Fig. 1*G*), which opposes the effects of the initial increase in salt intake. Being dependent on fluid volume changes, this system is inherently slow (hours or days). However, because the underlying changes in fluid volume accumulate over time until BP reaches a point at which salt balance is achieved, this feedback system is extremely effective. Theoretically, if given a sufficient period of time, such a system could completely correct any error in salt balance or blood pressure.

It should be noted that the acute pressure–natriuresis curve (PNC) depicted in Fig. 1*G* and Fig. 2*A* is not immovable, but can be modulated by a number of factors and conditions including changes in salt intake. For example, it becomes steeper and is shifted to the left during high salt intake (Fig. 2*B*). Conversely, during low salt intake, the PNC becomes flatter and is shifted to the right. Joining the equilibrium points at the various salt intakes now reveals a very steep steady-state relationship with little change in BP (the chronic pressure–natriuresis relationship or 'renal function curve'). That is, BP has become relatively salt insensitive. Various neurohormonal mechanisms contribute to the adjustment of the acute PNC with varying salt intakes, such as sympathetic activity, natriuretic and antinatriuretic hormones. Above all, modulation of the renin–angiotensin system (RAS) plays a crucial role in the adaptation to changes in salt intake, with suppression of the RAS at high salt intake facilitating sodium excretion and stimulation of the RAS at low salt intake contributing to sodium conservation (Montani & Van Vliet, 2004). In summary, the great sensitivity of the acute PNC to neurohumoral modulation can explain how sodium balance can be defended with little or no change in BP.

Several lines of evidence are consistent with the central role of the kidney in long-term BP control, as follows.

- First, inability to modulate the pressure–natriuresis curve leads to salt sensitivity. Indeed, dramatic salt-induced changes in BP occur when the RAS is blocked with an angiotensin-converting enzyme inhibitor or when circulating angiotensin II levels are fixed with an intravenous infusion of angiotensin II (Hall *et al.* 1980).
- Second, most renal transplantation studies support the notion that the kidney is a major determinant of long-term BP (Rettig, 1993). This concept is reinforced by a recent study in an experimental model of kidney cross-transplantation in the mouse, which shows that

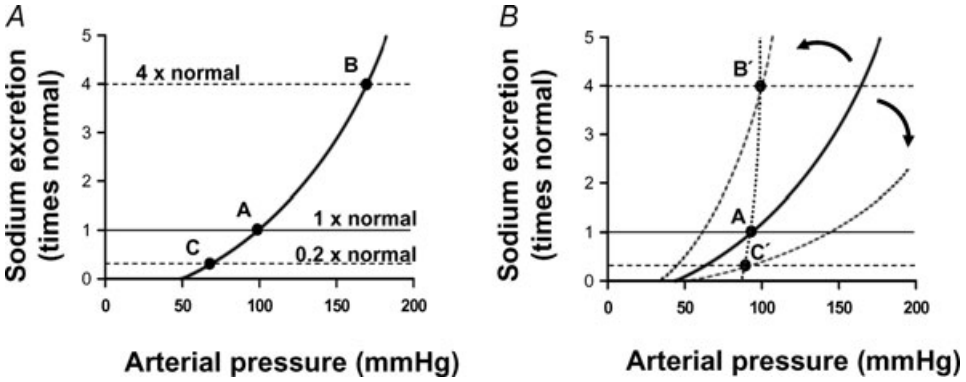

Figure 2. The concept of the acute pressure–natriuresis relationship and how adjustments of this relationship facilitate sodium balance during sustained changes in salt intake
Equilibrium is reached at the intersection between the acute pressure–natriuresis curve (PNC) and the corresponding level of salt excretion that matches salt intake. *A*, with a fixed PNC, equilibrium for the three depicted levels of salt intake (1 × normal, 4 × normal and 0.2 × normal) would be reached at points A, B and C, respectively, yielding considerable salt sensitivity. *B*, after adjustments of the PNC with varying salt intakes (left-shift with steepening at high-salt intake, right-shift with flattening at low-salt intake), joining the intersection points (B′, A and C′) reveals an almost vertical chronic pressure–natriuresis relationship (see dotted line), i.e. the chronic renal function curve. The modulation of the acute PNC during alterations in salt intakes thus allows the body to achieve sodium balance with minimal changes in arterial pressure.

angiotensin II causes hypertension through its receptors in the kidney (Crowley *et al.* 2006).

- Third, in various experimental models of hormone-induced hypertension [e.g. due to infusion of aldosterone (Hall *et al.* 1984*b*), angiotensin II (Hall *et al.* 1984*a*), vasopressin (Hall *et al.* 1986*b*) or noradrenaline (Hall *et al.* 1988)], shielding the kidney from the hormone-induced increase in BP (i.e. holding renal perfusion pressure near control levels) leads to marked fluid retention that persists throughout the infusion period despite larges increases in ECFV and severe systemic hypertension.
- Fourth, experiments in dogs instrumented for separate monitoring of left and right kidney functions have shown that the acute pressure–natriuresis relationship does not reset during long-term changes in arterial pressure (Mizelle *et al.* 1993).
- Finally, support for the role of BP in the control of sodium balance comes from genetic studies. Many genes have been identified to be associated with essential hypertension or responsible for rare monogenic diseases that are characterized by low or high blood pressures (Lifton *et al.* 2001; Mullins *et al.* 2006). Intriguingly, most of these genes encode proteins that are directly involved with renal sodium handling. Mutations that favour renal sodium reabsorption increase BP, whereas mutations that diminish tubular sodium reabsorption tend to decrease BP. Changes in BP seem thus to be a homeostatic mechanism to achieve sodium balance in the face of excessive or deficient salt reabsorption.

Some common misconceptions in understanding Guyton's model

Guyton limited the size of his model to several hundred equations in order to focus on the mechanisms that were most important in long-term control of BP and fluid volumes. Nevertheless, understanding his model requires that a number of components and concepts must be kept in mind simultaneously. This inherent complexity has occasionally led to misconceptions and apparent paradoxes that are worth clarifying.

Misconception 1: a primary renal dysfunction is at the origin of all forms of hypertension. According to Guyton's analysis of BP regulation, any long-lasting alteration in BP requires a shift of the PNR (assuming salt intake is constant). However, a shift of the PNR does not need to be the primary event in the cascade of changes leading to hypertension; it can also be secondary to non-renal influences. Indeed, Guyton's model allows one to simulate many forms of hypertension of extrarenal origin, including a mineralocorticoid-producing tumour, coarctation of the aorta or even sympathetic overactivity. However, the model predicts that, whatever the cause of hypertension, it must in the end somehow modify the kidney's ability to excrete salt and water for a given level of BP; otherwise, the hypertension would lead to an increased excretion of salt and water through the PNR, ultimately returning BP to regular levels. Even the escape to the sodium-retaining effects of servo-controlled low renal perfusion pressure (Reinhardt *et al.* 1994), an experiment often suggested to challenge Guyton's body fluid feedback mechanism, can be explained by a leftward shift of the PNC as a consequence of volume expansion, systemic hypertension, suppression of antinatriuretic factors and stimulation of natriuretic factors (Montani & Van Vliet, 2007). Furthermore, in many instances, overt changes in BP are not required to achieve sodium balance. Indeed, a number of autocrine and paracrine factors generated within the kidney itself can influence renal sodium excretion. However, conceptually, these short-loop feedbacks are equivalent to a shift of the PNC.

Misconception 2: Guyton's model dismisses the role of the central nervous system in long-term blood-pressure regulation. Although Guyton's model contains only a rudimentary representation of central nervous system (CNS) function (limited to basic cardiovascular reflexes, such as baroreceptors, chemoreceptors and central ischaemic reflex), Guyton left open a possible role of the CNS in long-term BP control. In his original 1972 description of his system's analysis and model, he noted suggestions by earlier authors that neurogenic hypertension could be mediated through a nervous influence on renal function. Subsequently, he provided analyses and model simulations illustrating how sustained hypertension could be induced by activation of sympathetic nerves throughout the body, or to the kidney alone, but that such effects did not occur if the sympathetic outflow to the kidney was excluded (figures 35-1 through 35-3 of Guyton, 1980).

In Guyton's model, the direct effects of sympathetic stimulation are limited to renal effects, constriction of the vasculature and to increasing heart performance. The model does not exclude the possibility that sympathetic stimulation of non-renal tissues could also alter kidney function by other mechanisms, including an influence on circulating mediators (e.g. endothelin, digitalis glycosides and immune system components). It is also very possible that the CNS could alter renal function and BP by mechanisms other than sympathetic activation. Indeed, the CNS is known to release a number of substances that influence renal function (vasopressin, adrenocorticotrophic hormone, γ-melanocyte-stimulating hormone and digitalis glycosides) and others may remain to be identified. However, whatever the role of the CNS, Guyton's analyses suggest that any influence on the long-term BP level would imply a final pathway acting on the kidney.

Misconception 3: changes in mean arterial pressure must be linked to changes in total blood volume. Although the analysis of Fig. 1 shows that ECFV and blood volume are essential components of long-term regulation of BP, a more careful examination reveals that the BP is not a function of total blood volume *per se* but of the 'volume in excess' in the vascular tree (i.e. the distending volume in excess of the resting size of the vasculature), particularly in the arterial tree. This concept is analogous to the concept of effective arterial blood volume used by others (Schrier, 1990). With this in mind, one can easily see why the renal body fluid feedback mechanism also applies to hypertension models characterized by a low blood volume, such as noradrenaline-induced hypertension (Hall *et al.* 1988) or administration of angiotensin II at higher doses (Carroll *et al.* 1984).

On the one hand, one would expect noradrenaline or angiotensin to promote sodium retention by acting directly on the kidney and thereby increasing total blood volume. On the other hand, both agents are also strong vasoconstrictors that increase BP rapidly, leading to initial natriuresis and thus to a decrease in blood volume. In parallel, these vasoconstrictor agents decrease vascular capacitance, permitting the maintenance of a high BP value with a low blood volume. Simulation of these hypertensive states with Guyton's model reveals a state of overfilling of the circulation, with increased MCFP and arterial volume in excess despite a decreased total blood volume.

Misconception 4: whole body blood flow autoregulation is the cause of volume-loading hypertension. Auto regulation is the ability of an organ or tissue to adjust its blood flow by local mechanisms, in accordance with local needs, and is often evident in the relative consistency of tissue blood flow despite changes in perfusion pressure. In the intact circulation, volume-loading elevates CO and thus BP. The resulting overperfusion of the tissues leads then to secondary autoregulatory changes in vascular resistance (Coleman & Guyton, 1969). Unfortunately, this 'whole body' form of autoregulation is often misinterpreted as the cause of systemic hypertension during volume-loading. However, autoregulation lies outside of the main feedback loop of the renal body fluid feedback mechanism, as shown in Fig. 1. Consequently, the renal body fluid feedback mechanism is expected to act to regulate the long-term BP level in order to achieve sodium balance irrespective of the level of total peripheral resistance. By opposing pressure-induced distension of arterioles, autoregulation greatly reduces the change in ECFV, blood volume and CO that would otherwise be required to increase BP in order to achieve sodium balance (Guyton *et al.* 1988). Thus, autoregulation converts an initial high-CO hypertension into a high-resistance hypertension, thus allowing the renal body fluid feedback mechanism to regulate the long-term BP level in a highly effective manner without the need for the large changes in fluid volumes.

The relevance of Guyton's model to modern cardiovascular physiology

Guyton was a pioneer of 'quantitative systems analysis', and his body of work clearly illustrated the power of such an approach when combined with physiological experimentation. It is important to stress that, while model building does involve insight and intuition, trial and error, the underlying components and parameters of Guyton's model were based on empirical data. Indeed, Guyton did not discover or invent the PNR or tissue blood flow autoregulation or the Frank–Starling relationship; his contribution was in bringing these well-described phenomena together in a manner that revealed remarkable insights about their role in cardiovascular regulation. Such insights led to countless cycles of experimentation, model refinement, further experimentation and so on. 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.

Guyton's model was initially developed in the sixties when computing power was poor and computer memory was scarce and expensive. Simplifications were mandatory to accommodate a large number of cardiovascular relationships. Shortcuts in solving equations were also required in order to run months of simulated experiments in a reasonable computing time. Over the years, the model evolved, the kidney acquired more details and atrial natriuretic peptide was included, but the core of the model and the basic concepts remained untouched. Although Guyton's model focuses on steady-state analysis and does not include the most recent cardiovascular discoveries, many of the principles contained in the original model have been incorporated by others into advanced models that elaborate on individual components or provide a more comprehensive representation of the entire circulation and its control by various influences, including the CNS (Karaaslan *et al.* 2005; Abram *et al.* 2007). Thus, Guyton's contributions continue to serve as a firm foundation on which contemporary cardiovascular modellers can build.

References

Abram SR, Hodnett BL, Summers RL, Coleman TG & Hester RL (2007). Quantitative Circulatory Physiology: an integrative mathematical model of human physiology for medical education. *Adv Physiol Educ* **31,** 202–210.

Carroll RG, Lohmeier TE & Brown AJ (1984). Chronic angiotensin II infusion decreases renal norepinephrine overflow in conscious dogs. *Hypertension* **6,** 675–681.

Coleman TG & Guyton AC (1969). Hypertension caused by salt loading in the dog. 3. Onset transients of cardiac output and other circulatory variables. *Circ Res* **25,** 153–160.

Crowley SD, Gurley SB, Herrera MJ, Ruiz P, Griffiths R, Kumar AP, Kim HS, Smithies O, Le TH & Coffman TM (2006). Angiotensin II causes hypertension and cardiac hypertrophy through its receptors in the kidney. *Proc Natl Acad Sci USA* **103,** 17985–17990.

Guyton AC (1980). *Circulatory Physiology III. Arterial Pressure and Hypertension.* W. B. Saunders Company, Philadelphia, London, Toronto.

Guyton AC (1990). Long-term arterial pressure control: an analysis from animal experiments and computer and graphic models. *Am J Physiol Regul Integr Comp Physiol* **259,** R865–R877.

Guyton AC, Abernathy B, Langston JB, Kaufmann BN & Fairchild HM (1959). Relative importance of venous and arterial resistances in controlling venous return and cardiac output. *Am J Physiol* **196,** 1008–1014.

Guyton AC, Coleman TG & Granger HJ (1972). Circulation: overall regulation. *Annu Rev Physiol* **34,** 13–46.

Guyton AC, Jones CE & Coleman TG (ed.) (1973). *Circulatory Physiology: Cardiac Output and its Regulation*, 2nd edn. W. B. Saunders Company, Philadelphia, London, Toronto.

Guyton AC, Montani JP, Hall JE & Manning RD Jr (1988). Computer models for designing hypertension experiments and studying concepts. *Am J Med Sci* **295,** 320–326.

Hall JE, Granger JP, Hester RL, Coleman TG, Smith MJ Jr & Cross RB (1984*a*). Mechanisms of escape from sodium retention during angiotensin II hypertension. *Am J Physiol Renal Physiol* **246,** F627–F634.

Hall JE, Granger JP, Hester RL & Montani JP (1986*a*). Mechanisms of sodium balance in hypertension: role of pressure natriuresis. *J Hypertens Suppl* **4,** S57–S65.

Hall JE, Granger JP, Smith MJ Jr & Premen AJ (1984*b*). Role of renal hemodynamics and arterial pressure in aldosterone "escape". *Hypertension* **6,** I183–I192.

Hall JE, Guyton AC, Smith MJ Jr & Coleman TG (1980). Blood pressure and renal function during chronic changes in sodium intake: role of angiotensin. *Am J Physiol Renal Physiol* **239,** F271–F280.

Hall JE, Mizelle HL, Woods LL & Montani JP (1988). Pressure natriuresis and control of arterial pressure during chronic norepinephrine infusion. *J Hypertens* **6,** 723–731.

Hall JE, Montani JP, Woods LL & Mizelle HL (1986*b*). Renal escape from vasopressin: role of pressure diuresis. *Am J Physiol Renal Physiol* **250,** F907–F916.

Karaaslan F, Denizhan Y, Kayserilioglu A & Gulcur HO(2005). Long-term mathematical model involving renal sympathetic nerve activity, arterial pressure, and sodium excretion. *Ann Biomed Eng* **33,** 1607–1630.

Lifton RP, Gharavi AG & Geller DS (2001). Molecular mechanisms of human hypertension. *Cell* **104,** 545–556.

Mizelle HL, Montani JP, Hester RL, Didlake RH & Hall JE(1993). Role of pressure natriuresis in long-term control of renal electrolyte excretion. *Hypertension* **22,** 102–110.

Montani JP, Adair TH, Summers RL, Coleman TG & Guyton AC (1989*a*). A simulation support system for solving large physiological models on microcomputers. *Int J Biomed Comput* **24,** 41–54.

Montani JP, Adair TH, Summers RL, Coleman TG & Guyton AC (1989*b*). Physiological modeling and simulation methodology: from the mainframe to the microcomputer. *J Miss Acad Sci* **34,** 15–24.

Montani JP & Van Vliet BN (2004). General physiology and pathophysiology of the renin-angiotensin system. In *Handbook of Experimental Pharmacology*, vol. 163/1, *Angiotensin*, ed. Unger T & Scholkens BA, pp. 3–29. Springer Verlag, Berlin.

Montani JP & Van Vliet BN (2007). Integrative renal regulation of sodium excretion. In *Sodium in Health and Disease*, ed. Burnier M, pp. 175–199. Informa Healthcare, New York.

Mullins LJ, Bailey MA & Mullins JJ (2006). Hypertension, kidney, and transgenics: a fresh perspective. *Physiol Rev* **86,** 709–746.

Reinhardt HW, Corea M, Boemke W, Pettker R, Rothermund L, Scholz A, Schwietzer G & Persson PB (1994). Resetting of 24-h sodium and water balance during 4 days of servo-controlled reduction of renal perfusion pressure. *Am J Physiol Heart Circ Physiol* **266,** H650–H657.

Rettig R (1993). Does the kidney play a role in the aetiology of primary hypertension? Evidence from renal transplantation studies in rats and humans. *J Hum Hypertens* **7,** 177–180.

Schrier RW (1990). Body fluid volume regulation in health and disease: a unifying hypothesis. *Ann Intern Med* **113,** 155–159.