International Journal of Obesity (2008) 32, S35–S47

0307-0565/08 $32.00
www.nature.com/ijo

ORIGINAL ARTICLE

The time course of salt-induced hypertension, and why it matters

BN Van Vliet[1] and J-P Montani[2]

[1]*Division of BioMedical Sciences, Faculty of Medicine, Memorial University of Newfoundland, St. John's, Newfoundland, Canada and* [2]*Institute of Physiology, University of Fribourg, Fribourg, Switzerland*

The epidemiology of salt-induced hypertension has been explored in detail in animal studies, in some cases involving exposures to excess dietary salt for much of the animal's lifespan. The results of these studies demonstrate the presence of two distinct time courses of the blood pressure response to a high salt intake: an acute (rapid) blood pressure response occurring over days to weeks, and a slow and progressive blood pressure response that develops over extremely long periods of time, amounting to a significant fraction of the lifespan in normal individuals. The acute form of salt sensitivity is well known in humans, having often been demonstrated as a fall in blood pressure during the period of salt restriction. The slow and progressive form of salt sensitivity has been demonstrated directly in rats and chimpanzees and is also evident in analyses of human cross-population data as a salt dependency of age-associated changes of blood pressure. This slow and progressive component of salt-induced hypertension may be attributable, at least in part, to a progressive rise in the acute salt sensitivity of blood pressure during sustained exposure to high salt. However, a progressively irreversible or 'self sustaining' component of salt-induced hypertension has also been demonstrated in rat studies. This irreversible component has not been completely characterized, but its presence raises the possibility that blood pressure responses to salt restriction may not fully reveal the contribution of salt to blood pressure or the epidemiology of hypertension. These various components of salt sensitivity (acute vs slow, reversible vs irreversible) should be considered in any comprehensive explanation of the effects of salt on blood pressure and especially in experimental studies of the genetic and physiological mechanisms underlying salt-induced hypertension.
International Journal of Obesity (2008) **32**, S35–S47; doi:10.1038/ijo.2008.205

Keywords: dietary sodium; dietary salt; salt sensitive; hypertension; blood pressure

Introduction

Cardiovascular disease is now considered an epidemic because of the human and financial burden it presents. In countries such as Canada, it is responsible for more than half of total mortality above the age of 50 years.[1] Hypertension is a major risk factor for cardiovascular disease and, although most hypertension have no obvious direct cause, dietary salt (or sodium) has been suggested to be an important etiological factor.[2–5] In addition to its effects on blood pressure, excess salt intake has been demonstrated to have blood pressure-independent effects on the heart and blood vessels.[6–11] Thus, the consequences of excess salt intake and benefits of salt restriction are becoming increasingly clear,[12,13] and it is highly appropriate to consider salt in this symposium on 'dysfunctional' foods.

Correspondence: Dr BN Van Vliet, Division of BioMedical Sciences, Faculty of Medicine, Memorial University of Newfoundland, St. John's, Newfoundland, Canada A1B 3V6.
E-mail: vanvliet@mun.ca

Analysis of the diet of economically undeveloped 'hunter-gatherer' human societies suggests that our Paleolithic ancestors evolved on a diet containing relatively modest amounts of sodium ($<50\,mmol\,day^{-1}$).[14] In contrast, average sodium intakes of 100–200 mmol per day are common in contemporary Western societies (Figure 1), the precise level varying by country, year and among individuals (intakes tending to be higher in male participants and young adults). Recent estimates of average sodium intake (mmol Na per day in adult male participant/female participant) include 179/131 in America,[15] 170/117 in Finland[16] and 156/116 in Canada.[17] It should be kept in mind that the distribution of intakes is skewed and that values well above the mean occur in certain sub-populations and individuals. For example, in the 1988–1994 National Health and Nutrition Examination Survey, the median sodium intake among young (19–30 years old) male non-Hispanic American blacks was estimated to be 202 mmol per day, with the 90th and 99th percentiles reaching 303 and 410 mmol day^{-1}, respectively.[18] Clearly, sodium intake in contemporary Western societies exceeds that of our ancestors, and by an extreme amount in many individuals.

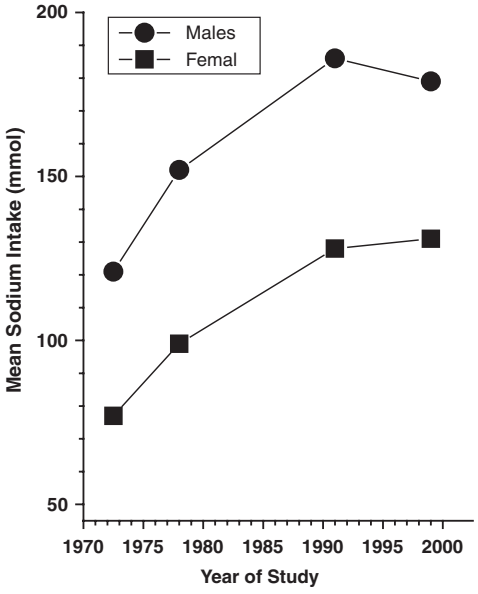

Figure 1 Estimated daily sodium intakes in the adult US population (male participants and female participants, 20–74 years of age) over the past three decades. Data are from the National Health and Nutrition Examination Surveys[15] and represent estimates based on food sources and sodium used in food preparation, but not salt added to the food at the table.

The purpose of this review is to develop a general picture of how dietary salt may influence blood pressure in humans, relying heavily on fundamental characteristics of salt-induced hypertension revealed in the animal literature. Although one needs to be familiar with only a small number of studies to appreciate how the effects of salt may be manifested, these key studies are distributed among a vast literature spanning more than half a century and are easily overlooked. The main emphasis of this review is that salt affects blood pressure in (at least) two distinct ways, one being a relatively acute effect spanning days or weeks and the other occurring over a much longer time span (decades in humans). It is our belief that distinguishing these two forms of salt sensitivity is the first and the most important step in understanding the impact of salt on blood pressure, in addressing the mechanisms underlying this effect, and in considering how to best reduce the impact of salt on our health.

Acute salt sensitivity of blood pressure

Salt-induced increases in blood pressure have often been observed to occur within a period of several days to weeks, a time course approximately paralleling the re-establishment of salt balance. Herein, we refer to salt-induced changes of this time course as 'acute' to distinguish them from much slower salt-induced effects discussed in subsequent sections. Acute salt sensitivity of blood pressure has been

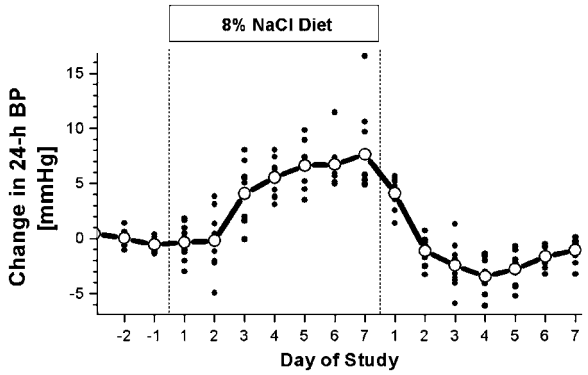

Figure 2 Time course of changes in 24-h mean arterial pressure (BP) during a 7-day exposure to a high-salt (8% NaCl) diet in male Sprague–Dawley rats. Open circles represent the mean of 11 animals. The small filled circles represent the results of individual animals. The diet during the control and recovery period contained 0.15% NaCl (BN Van Vliet, unpublished).

demonstrated in experiments involving a number of species including chickens,[19,20] dogs,[21–24] green monkeys,[25] mice,[26] pigs,[27] rabbits,[28,29] rats[30–34] and spider monkeys.[25,35] An example of the time course of the blood pressure response to a high-salt diet in regular Sprague–Dawley rats is shown in Figure 2. In the case of humans, salt loading has long been known to be capable of affecting blood pressure on this time scale.[36,37] However, 'normal' salt intake is already quite high in many individuals in Western societies, and a moderate salt restriction is associated with a fall in blood pressure in some individuals (for example, Figure 3). A recent meta-analysis of salt-restriction trials affirmed that the blood pressure response to salt restriction is 'dose-dependent', more pronounced for systolic than diastolic pressure, and greater in hypertensive than normotensive individuals.[12] The degree of blood pressure response to salt loading and restriction has been widely used to classify individuals as salt sensitive or salt resistant[38,39] and to investigate the characteristics associated with these states.[40–42]

Acute salt sensitivity and the steady-state relationship between salt intake and blood pressure

A theoretical framework for understanding acute salt sensitivity arose as part of a systems analysis of the regulation of blood pressure and fluid volume conducted by Arthur Guyton and co-workers.[43–49] In their analysis, salt sensitivity of blood pressure was defined in terms of the steady-state relationship between blood pressure and salt excretion (Figure 4), the so-called 'chronic pressure–natriuresis relationship' (also known in older literature as the 'renal function curve'). This relationship is usually assessed by imposing a level of salt intake on a subject for several days until salt balance is established (excretion ≈ intake) and then measuring the resultant levels of blood pressure and renal salt excretion. This process is repeated for one or more additional levels of salt intake, each level of salt intake

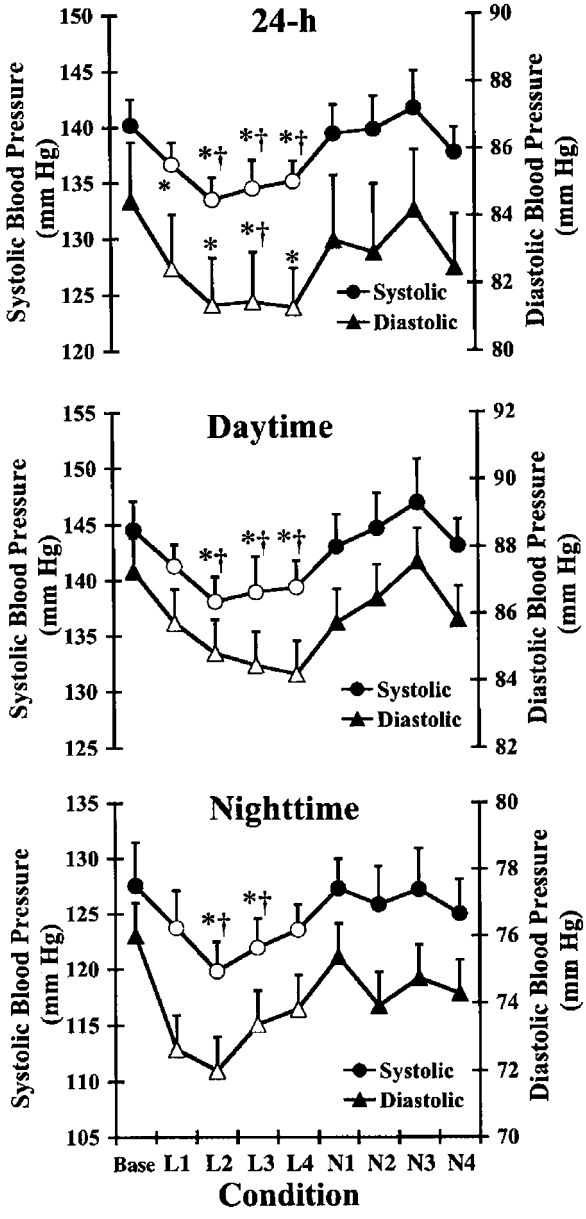

Figure 3 Time course of ambulatory blood pressure response during 4 weeks of dietary sodium restriction in humans. Data are averages from 12 individuals of either sex over 50 years of age (mean age ~64 years). From Gates *et al.*[105] with permission. *$P<0.05$ for baseline vs low salt (L1–L4). †$P<0.05$ for low salt (L1–L4) vs corresponding normal salt (N1–N4).

contributing an additional point on the curve. As 'steady-state' conditions are specified, the relationship represents the performance of the entire system after the various control mechanisms that affect renal function and blood pressure have exerted their influence, after salt balance has been established and after blood pressure has stabilized.[44] When the chronic pressure–natriuresis relationship is plotted in this traditional manner (that is, with blood pressure on the *x* axis[44]), the salt sensitivity of blood pressure

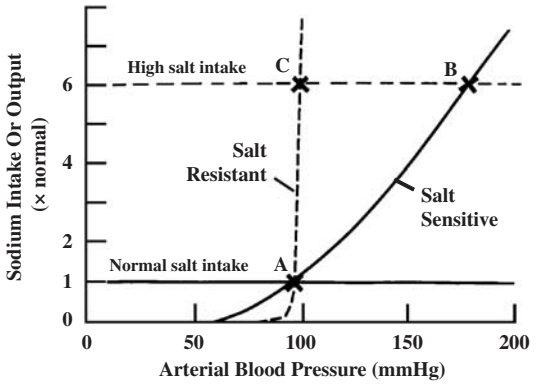

Figure 4 Effect of salt sensitivity vs resistance of blood pressure on chronic pressure–natriuresis curves. The curves represent the relationship between salt intake and blood pressure under steady-state conditions (at which point salt intake and excretion are highly similar). In individuals in which the re-establishment of salt balance at a new level of salt intake is associated with a corresponding change in the steady-state level of blood pressure ('salt-sensitive' individuals, solid curve), the relationship is characterized by a shallow slope over at least some part of its range. In contrast, the relationship is relatively steep in salt-resistant individuals in which changes in salt balance are accompanied by little change in the steady-state blood pressure level. Modified from Guyton.[44]

is inversely proportional to the slope of the relationship. Thus, a chronic pressure–natriuresis relationship with shallow slope predicts that the re-establishment of salt balance at a higher level of intake will be accompanied by an increase in the blood pressure level. Conversely, a relatively steep slope of the relationship indicates a state in which blood pressure is relatively salt resistant (Figure 4).

The shape and slope of the chronic pressure–natriuresis relationship is influenced by a number of factors, essentially all regulatory mechanisms that influence the steady-state level of blood pressure and/or renal sodium excretion. One mechanism of particular importance is the influence of renal perfusion pressure (that is, blood pressure) on renal sodium excretion, a phenomenon referred to as 'pressure–natriuresis.'[50–52] This phenomenon refers to the increase in urinary sodium excretion induced by an elevation of renal perfusion pressure and the corresponding fall in urinary sodium excretion that can be produced by reducing renal perfusion pressure. This relationship between renal perfusion pressure and urinary sodium excretion (the acute pressure–natriuresis relationship) is often used to define the salt-excreting capacity of the kidney at a given point of time and has been assessed in isolated perfused kidneys[53,54] as well as those of intact anesthetized[55] and conscious animals.[56] Pressure–natriuresis provides an important mechanistic link between blood pressure and salt excretion, and contributes to the regulation of both of these variables. Nevertheless, our blood pressure would be markedly sensitive to the level of salt intake if this were the only mechanism regulating renal sodium excretion. This is because the short-term pressure–natriuresis relationship has a slope or sensitivity that is relatively modest, such that a considerable change in blood

pressure would be required to adjust urinary sodium excretion to meet a new level of sodium intake.

The reason for the salt balance being usually re-established without large changes in blood pressure is that additional mechanisms normally help adjust renal sodium excretion to meet the new level of intake with minimal volume changes and without the need to rely on the effect of a large change in blood pressure on sodium excretion.[44,48] Ultimately, understanding the acute salt sensitivity of blood pressure amounts to understanding the factors that restrict or impair the normal adjustment of renal excretory capacity during a change in salt intake (thereby resulting in larger volume and pressure changes). For example, the renin–angiotensin–aldosterone system is a powerful modulator of the acute pressure–natriuresis relationship, and its participation is thought to be important in maintaining a relative salt resistance of blood pressure.[48,57,58] Treatments that prevent or limit the response of this system (for example, administration of a mineralocorticoid agonist such as desoxycorticosterone acetate, infusion of exogenous angiotensin II or removal of kidney mass, which limits the upper range of renal salt-excreting capacity) have often been used to increase the acute salt sensitivity of experimental animals. In a similar manner, the impairment of any other system that normally contributes to the ability of renal sodium excretion to adapt to a new level of salt intake (for example, atrial natriuretic peptide,[59] sympathetic activity[60–63] and nitric oxide[64]) is also expected to promote salt sensitivity of blood pressure.

Progressive salt-induced hypertension

In contrast with acute salt sensitivity of blood pressure, a fundamentally different effect of salt on blood pressure has been directly demonstrated in a small number of animal studies. The distinguishing feature of this effect of salt on blood pressure is its slow and progressive time course, often developing on a time scale corresponding with a considerable fraction of the animal's lifespan.

Evidence for progressive salt-induced hypertension in rats

Much of our current understanding of the time course of the slow and progressive phase of salt-induced hypertension comes from a series of systematic investigations of the subject by Meneely and colleagues in the 1950s.[65–67] In their experiments, the effects of dietary salt were investigated in more than 600 male outbred (Sprague–Dawley) rats followed over their lifespan (up to 30 months). Although many levels of dietary salt were investigated, results obtained for a moderately high salt (2.8% NaCl) diet and control (0.15% NaCl) diet are of particular relevance. The 2.8% NaCl diet was considered to be roughly comparable with a 14 g NaCl (240 mmol Na) intake in humans (assuming a 500 g dry weight daily food intake).[65–67] Such an intake is above the average sodium intake in Western societies but nevertheless

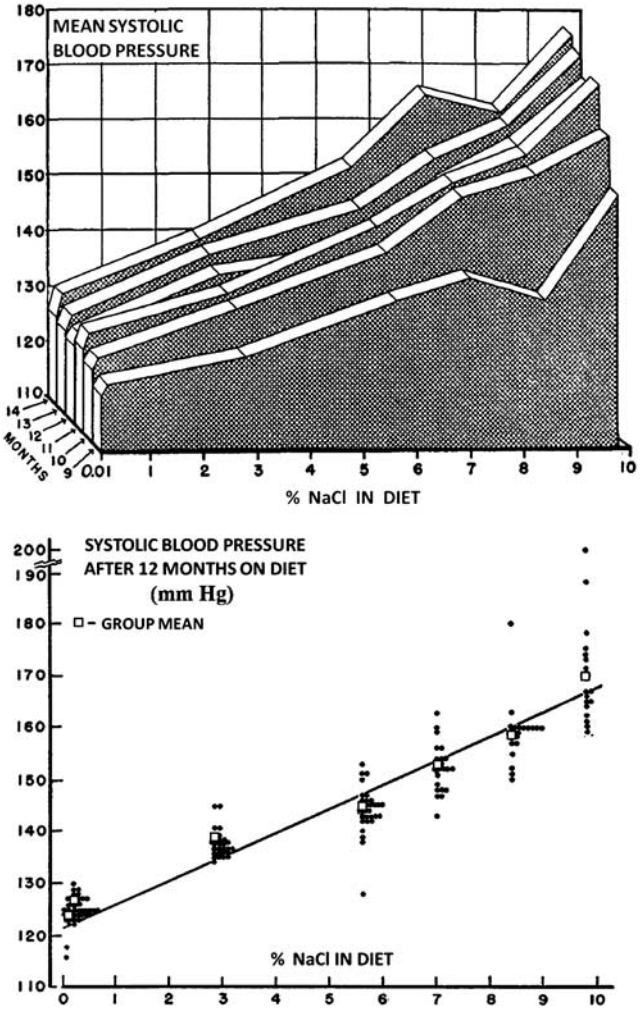

Figure 5 Time course and dose dependency of the effects of excess dietary salt on tail systolic blood pressure in rats (male outbred rats, Sprague–Dawley) exposed to a high-salt diet for up to 14 months. Top: interaction between time (8–14 months) and dose (0.01–9.8% NaCl in diet). Bottom: responses of individual rats at 12 months of high salt exposure. Reproduced (with minor modification) from Meneely *et al.*[66] with permission (copyright 1953, The Rockefeller University Press).

corresponds with the normal level of sodium intakes in many individuals (for example, it corresponds with the sodium intake of $\geqslant 5\%$ of the American population as a whole and with the intake of $\sim 25\%$ of young American male individuals[18]). Using the same assumptions, the 0.15% NaCl control diet corresponds with a 0.75 g NaCl (13 mmol Na) intake; that is, within the range of levels found in hunter-gatherer societies.[14]

Meneely's studies demonstrated that, over time, an excess dietary salt intake led to dose-dependent increases in blood pressure, renal and vascular damage, left ventricular hypertrophy, abnormal electrocardiograms and premature mortality. The effects of salt on tail-cuff systolic blood pressure were time dependent, requiring many months for hypertension to become evident on the moderately high (2.8%) salt diet

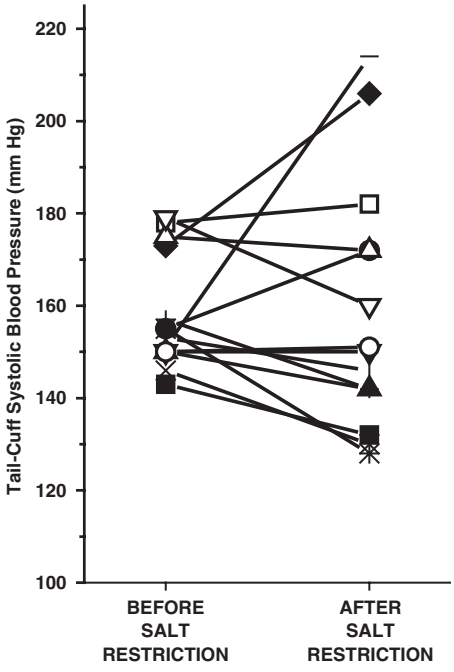

Figure 6 Effects of salt restriction on tail systolic pressure in rats (female Sprague–Dawley) with long-standing salt-induced hypertension. Hypertension was originally induced by 12–13 months of an 8% salt diet. Salt restriction consisted of 2 months on a very low salt diet (0.025% NaCl) followed by an additional 2 months on a regular salt diet (0.5–0.75% NaCl). Systolic pressure in rats maintained on a normal salt diet is approximately 130 mm Hg. Data from Dahl.[69]

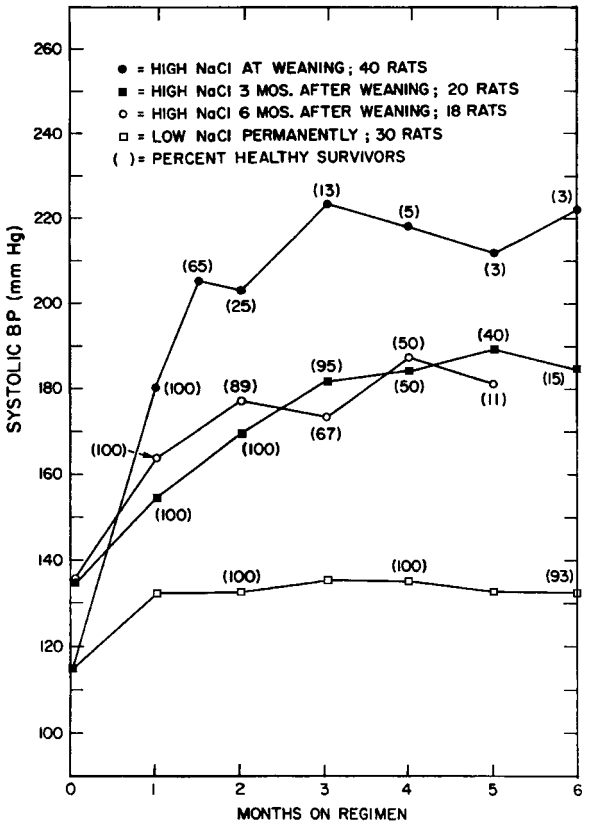

Figure 7 Time course of tail systolic pressure responses to an 8% NaCl diet in the Dahl-S strain of salt-sensitive rats. The greatest response is for rats starting with high salt at weaning. Less response is seen in rats started on high salt 3 and 6 months after weaning. The lowest curve illustrates the data of control animals maintained on a regular salt diet. From Dahl *et al.*[72] with permission.

(Figure 5). However, given sufficient time (12 months or more), the blood pressure of virtually all animals was affected (Figure 5).

A similar interaction between dose and time was also evident for other variables such as heart weight and mortality.[67] In contrast with the early appearance of cardiac hypertrophy in rats exposed to very high salt levels, cardiac weights in the 2.8% NaCl group remained normal until the later stages of life, with cardiac hypertrophy becoming evident only among rats surviving for at least 20 months. Similarly, the effect on mortality was also delayed in the 2.8% NaCl group, becoming evident only after ~16 months of age, whereas mortality occurred earlier at higher salt levels.

A number of additional observations of the effects of a high dietary salt intake (typically 8% NaCl) on tail systolic blood pressure of Sprague–Dawley rats were performed by Lewis Dahl.[68–71] In addition to confirming Meneely's observation of progressive salt-induced hypertension, Dahl also observed that the responses to excess salt were greater in males than in females and greater in young rats (for example, at weaning) than in old. Dahl[69] also provided an important observation concerning the reversibility of salt-induced hypertension in female Sprague–Dawley rats made hypertensive by feeding a high-salt diet (8% NaCl or 11.6% sea salt containing 7.3% NaCl) for 12–13 months. When these rats were subjected to a 4-month period of salt restriction (2 months of 0.025% NaCl feed followed by 2 months of regular (0.5–0.75% NaCl) feed), the fall in blood pressure varied markedly between individuals, with the hypertension, in many animals, being virtually unaffected by salt restriction at this point (Figure 6). On average, the change in systolic blood pressure of the group was negligible (Figure 6), and in no case did the systolic pressure fall to a level typical of control animals[69] ($\leqslant$130 mm Hg).

In subsequent studies, Lewis Dahl selectively bred Sprague–Dawley rats for the trait of progressive salt-induced hypertension. After many generations of selective breeding, the resultant strain of rats ('Dahl-S' or 'DS' rats) exhibited a heightened and accelerated progression of salt-induced hypertension[72] (Figure 7). Dahl also selectively bred a separate strain of rats (Dahl-R rats) the blood pressure of which was resistant to the effects of a high-salt diet. However, subsequent studies have demonstrated that in these 'salt-resistant' rats (as in several other experimental models[6–11]), a high-salt diet can lead to structural changes in the heart and vasculature despite the absence of any effect

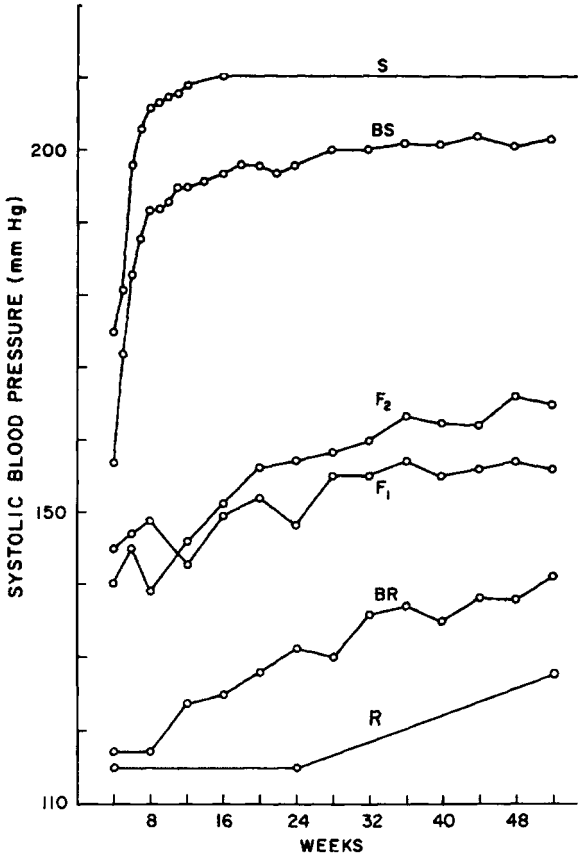

Figure 8 Time course of hypertension induced by a high-salt (8%) diet in Dahl salt-sensitive rats (S), Dahl salt-resistant rats (R) and the progeny of cross-breeding (F1 = S × R; F2 = F1 × F1; BS = S × F1; BR = R × F1). Reproduced from Knudsen *et al.*[73] (copyright 1970, The Rockefeller University Press).

on blood pressure.[11] Cross-breeding of the salt-sensitive and salt-resistance strains results in a full spectrum of rates of progressive salt-induced hypertension[73] (Figure 8).

Dahl's studies helped establish the concept that blood pressure is genetically determined and continue to serve as an important illustration of the interaction between the genetic and environmental determinants of blood pressure. Descendents of Dahl's original strains are still widely used, particularly for investigation of the mechanisms underlying salt sensitivity of blood pressure. These rats are currently available as inbred (JR, also known as Rapp) and genetically homogenous (MCW) strains. A number of congenic/consomic variations are also available for the MCW strain.[74] In addition, a Sabra strain of salt-sensitive and salt-resistant rats was also developed in a manner similar to that of the Dahl strains.[75,76] Although the swift progression of salt-induced hypertension in these specialized strains greatly facilitates investigation of the mechanisms underlying salt-induced hypertension, it is important to keep in mind how slow the effects of excess salt are in the ordinary rats from which these strains were originally derived. That is, in regular outbred rats, hypertension and cardiovascular

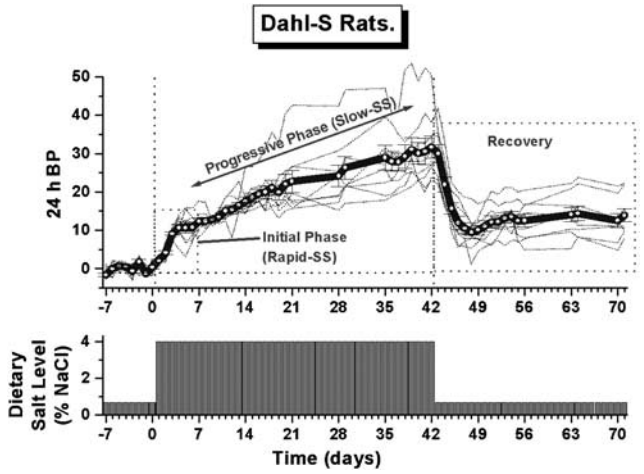

Figure 9 Detailed time course of blood pressure response to a 4% salt diet in Dahl salt-sensitive rats. The time course suggests the presence of two distinct phases, one rapid (acute salt sensitivity) and the other, slow (progressive salt-induced hypertension). Data up to day 42 are from Van Vliet *et al.*[34] Recovery data are from BN Van Vliet (unpublished).

morbidity produced by moderately high levels of salt intake are slow phenomena that develop progressively on a time scale approaching that of the animal's lifespan (Figure 5).

Components of salt-induced hypertension in Dahl salt-sensitive rats

Although acute salt sensitivity and progressive salt-induced hypertension occur on quite different time scales, the distinction between them has seldom been formally made or explored. This is not surprising as relatively few studies have investigated the very slow and progressive effects of salt on blood pressure, and those that have made use of intermittent measurements of blood pressure incapable of revealing rapid events that might accompany a change in salt intake. Furthermore, when progressive salt-induced hypertension has been investigated in the highly salt-sensitive Dahl-S rat model on very high salt (8%) diets, the time course of its progressive phase of salt-induced hypertension is often so accelerated that it is difficult to distinguish from any initial acute response.

To explore the distinction between acute salt sensitivity and progressive salt-induced hypertension, the detailed time course of salt-induced changes in blood pressure was investigated in the Dahl-S salt-sensitive rat strain.[34] In this series of experiments, the rate of progressive salt-induced hypertension was slowed by using older rats (and subsequently, also hybrid rats) in which the rate of progressive blood pressure changes is known to be reduced and by limiting dietary salt to moderately high (4% NaCl) levels. In this manner, it was hoped that the slow and progressive increase in blood pressure could be clearly distinguished from any initial changes in blood pressure that might occur.

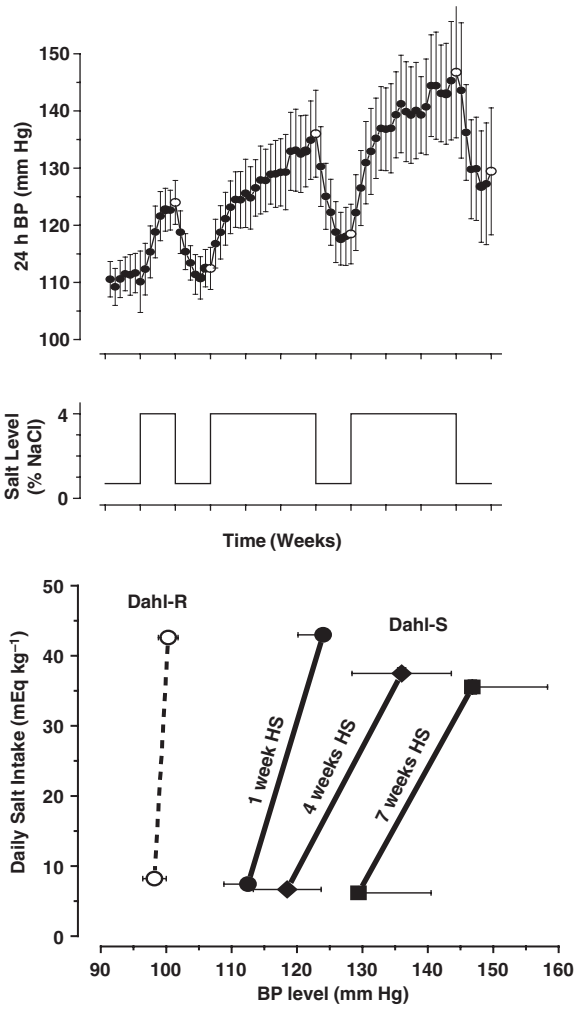

Figure 10 Top: progressive irreversibility of the progressive phase of salt-induced hypertension in Dahl salt-sensitive (Dahl-S) rats. Bottom: the corresponding chronic pressure–natriuresis relationship. The relationship in Dahl-S rats has a shallow slope, relative to Dahl salt-resistant rats (Dahl-R). Continued exposure to high (4%) salt leads to a further reduction in slope and a progressive rightward shift of the relationship to higher blood pressure levels. From Van Vliet *et al.*[34] (copyright to Lippincott, Williams and Wilkins, 2006).

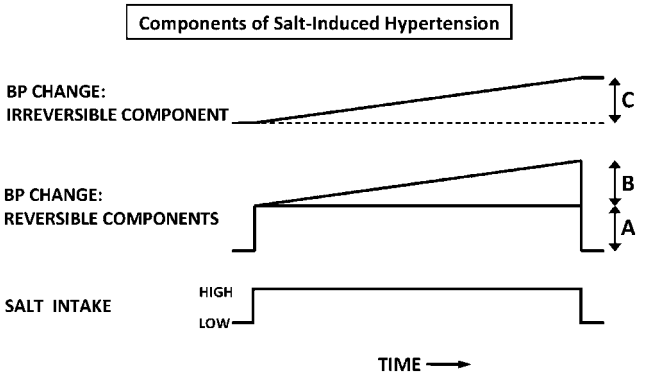

Figure 11 Illustration of the possible components of salt-induced hypertension (acute vs progressive, reversible vs irreversible) based on studies in the Dahl-S rat strain.[98] The components consist of salt-induced increases in blood pressure due to (A) pre-existing acute salt sensitivity (reversible), (B) a salt-induced increase in acute salt sensitivity (reversible) and (C) a progressive and irreversible salt-induced increase in the blood pressure level.

As shown in Figure 9, Dahl-S rats exhibited two distinct phases in the time course of salt-induced changes in their blood pressure. The first phase required approximately 4 days for blood pressure to stabilize at its new value and corresponds well with the examples of acute salt sensitivity discussed above (for example, Figure 2). The second phase began by the end of the first week of high-salt exposure, with blood pressure rising slowly and progressively with time. Two distinct phases were also apparent in hybrid rats.[34] In this case, however, the initial salt-induced blood pressure response was relatively consistent among the hybrid rats, whereas the slow progression of salt-induced hypertension varied markedly between individuals. This difference in the variation of these two phases suggests that they are controlled by distinct genetic and physiological mechanisms.

It is notable in these experiments that while blood pressure did fall when salt intake was returned to the control level, the blood pressure did not return all the way to the baseline. Thus, these Dahl-S rats exhibited a 'self-sustaining' form of salt-induced hypertension similar to that described by Lewis Dahl[69] in Sprague–Dawley rats (Figure 6, see above). An irreversibility of salt-induced hypertension has also been described for hybrids of the Dahl-S strain, for which the degree of the reversal of hypertension (induced by 4.5 weeks of 8% NaCl diet) varied markedly between individuals.[77] When reversibility of salt-induced changes in blood pressure was investigated as a function of time in Dahl-S rats,[34] a progressively irreversible component was observed, developing in parallel with the slow rise in blood pressure (Figure 10, top). Graphical analysis of this data (Figure 10, bottom) revealed that although the acute response to a change in salt intake corresponded with an altered slope of the chronic pressure–natriuresis relationship, the slower phase of salt-induced hypertension was quite different and consisted of a progressive (and irreversible) rightward shift of this relationship to higher blood pressure levels and a further reduction in its slope. These results emphasize that the acute and progressive forms of salt-induced changes in blood pressure are distinct and likely involve different underlying mechanisms.

In summary, results obtained using the Dahl strain of genetically salt-sensitive rats illustrate that up to three components of salt-induced hypertension can be distinguished (Figure 11). One component (labeled A in Figure 11) is simply the increase in blood pressure that will occur when individuals with acute salt sensitivity of blood pressure consume a high dietary salt intake. This is presumed to be a reversible component that is responsive to salt restriction.

A second component (labeled B in Figure 11) is the increase in blood pressure caused by a progressive induced worsening of acute salt sensitivity. This component is also presumed to be reversible and responsive to salt restriction. A final component (labeled C in Figure 11) is the salt-induced increase in blood pressure that is both progressive and irreversible. Being irreversible, this component would not be revealed by acute salt-restriction studies.

Evidence for progressive salt-induced hypertension in primates

The results of a small number of long-term studies suggest that primates may also exhibit the slow and progressive effects of salt on blood pressure that have earlier been described in rats.

A slow and progressive effect of salt intake on blood pressure is evident in a study of salt-induced hypertension in baboons.[78] The increased salt intake ($\sim 1.5\,g\,kg^{-1}$ body weight per day vs $\sim 0.06\,g\,kg^{-1}\,day^{-1}$ in controls) was achieved by adding salt to both the feed and the drinking water. Blood pressures were found to be significantly increased by salt in each of the three experimental groups investigated. The progressive nature of the hypertension was evident in the increase in blood pressure during the final year of a 2.5-year exposure to high salt intake (from 3 to 5.5 years of age, systolic/diastolic pressure in the last year increased from 166/104 to 187/107 in males and 148/92 to 154/94 in females).[78]

Far more graphic evidence of an effect of excess salt intake to cause a progressive increase in blood pressure was subsequently reported in chimpanzees by Denton *et al.*[79] (Figure 12). In this study, the blood pressure of chimpanzees (~ 50 kg, either sex, various ages) maintained on a regular low-salt diet (vegetables and fruits, associated with urinary sodium excretion $\leqslant 25$ mmol Na per day) remained stable over a 20-month period, whereas blood pressure rose progressively with time in individuals receiving a daily salt supplement of ~ 256 mmol Na per day (Figure 12). Systolic pressure and pulse pressure were affected to a far greater degree than were diastolic or mean blood pressure (Figure 12). In chimpanzees maintained on a monkey chow containing 0.24% Na for which daily sodium consumption was estimated to be 100–200 mmol per day (see comments in Denton *et al.*[79]), blood pressure was reported to rise progressively with age at a rate of ~ 1.8 mm Hg per year over their 30- to 40-year lifespan.[80]

Recently, the results of two additional protocols confirm the impact of long-term (8–24 months) changes in dietary salt on blood pressure in chimpanzees.[81] As with the earlier study, the effects appeared greater in the case of systolic than diastolic pressure. The magnitude of the effect amounted to ~ 9 mm Hg (or slightly higher) in systolic pressure for each 100 mmol day^{-1} change in sodium intake (8.9 mm Hg per 100 mmol (unadjusted difference from the control group) for a change from 248 to 126 mmol day^{-1}, 9.2 mm Hg per 100 mmol for a change from 35 to 120 mmol day^{-1} and 13.3 mm Hg per 100 mmol for a change from 75 to 35 mmol day^{-1}). Regression analysis suggested that in this case, larger effects of salt on blood pressure were associated with female sex, higher body weight and higher baseline blood pressure levels.

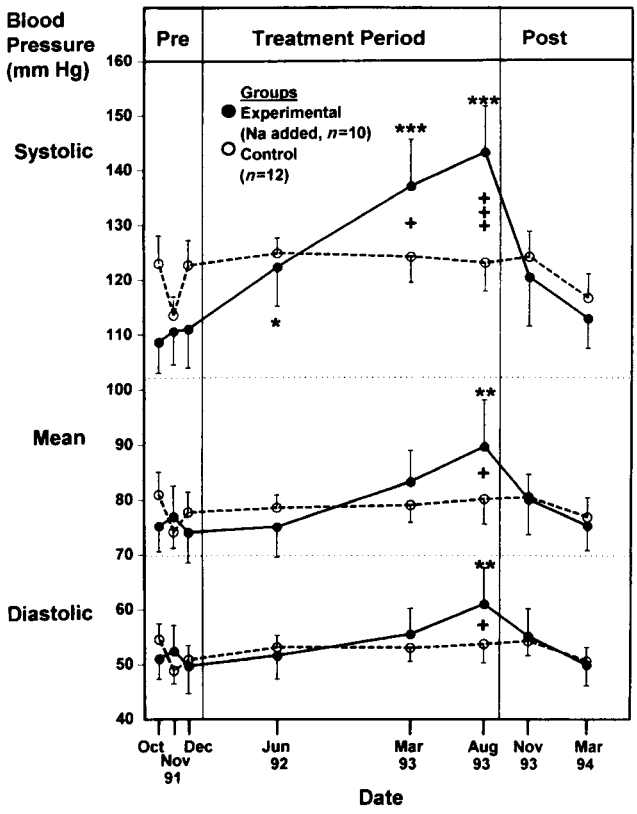

Figure 12 Salt-induced increases in blood pressure over a 20-month period in chimpanzees. The diet of the experimental group (filled symbols) was supplemented with ~ 256 mmol Na per day. Control animals maintained on a regular fruit diet (open symbols) exhibited no change in blood pressure. From Denton *et al.*[79] with permission (copyright 1995, Macmillan Publishers Ltd, Nature Publishing Group). *($P<0.05$), **($P<0.01$), and ***($P<0.001$) indicate significant differences from the initial baseline. +($P<0.05$) and ++($P<0.001$) indicate significant differences between the control and experimental group.

The above observations confirm in two primate species that a high salt intake can cause a slow and progressive form of salt-induced hypertension similar to that which had previously been described in rats (see above). The observation of this phenomenon in chimpanzees establishes this effect of salt in a species that is similar to humans not only genetically, but also in terms of nutrition (both likely to consume a similar low-sodium high-potassium diet under wild conditions), size (chimpanzees are approximately two-thirds of human size) and lifespan (that of chimpanzees is 50–75% of that in humans).

Evidence for progressive salt-induced hypertension in other animals

A few studies have been published concerning the long-term effects of excess salt consumption on blood pressure in

species and strains other than those noted above. Dahl[68] investigated the effect of excess dietary salt administered to Beagles over a 4-year period. In this study, systolic blood pressure of dogs maintained on drinking water containing 1% NaCl or a diet supplemented with 2 or 6% NaCl did not differ from that of a control group.[68] This finding is consistent with the suggestion that, as a species, the dog is relatively capable of accommodating large dietary salt loads.[82] Although dogs have been widely used for the study of salt-loading hypertension, such studies have relied on special measures to cause or promote salt sensitivity (as are also often used in other species), such as an extreme salt load ($\geqslant 2\,g\,kg^{-1}\,day^{-1}$) provided alone or in combination with salted drinking water, reduced renal mass or administration of a mineralocorticoid.[21,22,24]

In other species, the long-term effects of excess salt have not been investigated in detail in the few studies that have appeared, conclusions are limited because of the short duration of salt exposure, the lack of time course data or the reliance on special measures to induce or amplify salt sensitivity of blood pressure. In rabbits, for example, addition of $5\,g\,day^{-1}$ NaCl for 8 months was associated with significant increases in blood pressure, but the time course data presented suggest that the increase in blood pressure was not progressive, with blood pressure stabilizing within the first 6 weeks or so.[28] In chickens, the addition of salt (0.9 or 1.2%) to drinking water was shown to raise the blood pressure level, but each intervention was limited to a 3- to 4-week period.[20]

Although the salt sensitivity of blood pressure has been described in a number of knockout mouse models, and in response to experimental treatments (for example, desoxycorticosterone acetate), the long-term effects of excess salt do not appear to have been well investigated in 'normal' mice and the few relevant studies that have been conducted have been limited to the C57Bl/6J inbred strain. In 3-month-old male C57Bl/6J mice outfitted with blood pressure telemeters, switching to an 8% salt diet caused the mean arterial pressure level to promptly increase 6 mm Hg, but the peak increase occurred on the second day of salt and did not progress beyond this point over the following 6-week period[26] or after a total of 14 weeks on 8% salt in subsequent studies.[83]

Evidence for progressive salt-induced hypertension in humans

As described above, under highly controlled conditions, animal studies have directly demonstrated that an increased dietary salt intake alone is sufficient to cause an increased blood pressure, cardiovascular target organ damage and premature death. Importantly, the effects of salt on blood pressure appear to be of two forms: (i) an acute salt sensitivity of blood pressure with a time course of days to weeks, approximately paralleling the re-establishment of salt balance and (ii) a progressive salt-induced hypertension that normally develops over a long time period corresponding to a significant fraction of the animal's lifespan. We have already alluded to the presence of an acute form of salt sensitivity of blood pressure in some human individuals (Figure 3). Is the slow and progressive form of salt-induced hypertension directly observed in animals also present in humans?

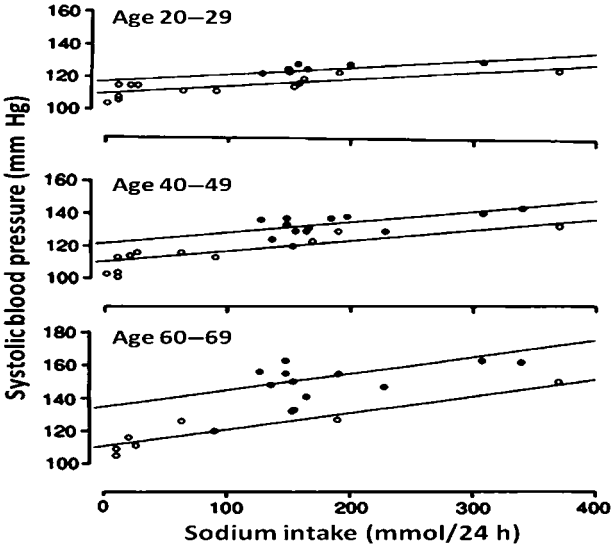

Figure 13 The relationship between systolic blood pressure and sodium intake in analyses of large cross-population data sets in humans. The relationship is plotted for different age ranges (top to bottom graphs) and different levels of economic development (developed = upper lines with solid symbols; undeveloped = lower lines with open symbols). From Law *et al.*[84] with permission.

The effect of salt to cause a slow and progressive increase in blood pressure in humans has not been investigated directly. However, a strong support for the effect of salt to promote age-associated increases in human blood pressure has come from detailed analyses of cross-population data. The first major analysis was of a collection of previously published cross-cultural data involving a total of 47 000 individuals across 24 communities.[84] The data were used to construct a regression model relating blood pressure to salt intake, including the effects of age and economic development (Figure 13). Some of the major conclusions of the analysis were

(i) there was a highly significant association between sodium intake and blood pressure;
(ii) the effect of sodium increased with age, the effect on systolic pressure rising from 5 mm Hg per 100 mmol Na intake at ages 20–29 years to 10.3 mm Hg per 100 mmol at ages 60–69 years (the corresponding diastolic effect being 2.6 and 4.3 mm Hg per 100 mmol Na, respectively). These effects increased ~50% in individuals of the upper 5th percentile of the blood pressure distribution and were reduced by ~50% in individuals of the lower 5th percentile of blood pressure;

(iii) the effect of sodium on blood pressure was similar in economically developed and undeveloped cultures and
(iv) economic development was associated with an additional sodium-independent effect of age on blood pressure.

An additional support for the effect of dietary salt on age-associated increases in blood pressure has come from the analysis of blood pressure and urinary sodium excretion data collected in 10 074 individuals in 52 centers in 32 countries during the course of the INTERSALT study.[85] Analyses of these data revealed that, in addition to a general association of blood pressure with salt intake, the rise in systolic blood pressure with age between the third and sixth decades of life increases in a sodium-dependent manner amounting to 10–11 mm Hg for each 100 mmol increment in sodium intake. The corresponding increase in diastolic pressure over 30 years amounted to 6 mm Hg per 100 mmol.

These two analyses suggest that the progressive form of salt-induced hypertension that has been directly observed in animal studies is also present in human populations and that, as in animals, its progression occurs over a sizable fraction of the lifespan of the species. Depending on the analysis used, dietary salt appears to cause a progressive increase in systolic pressure by 0.13–0.35 mm Hg per year for each 100 mmol of sodium intake. At a sodium intake typical of Western societies (for example, 180 mmol Na per day), this would correspond with a 10–25 mm Hg increase in systolic blood pressure between 20 and 60 years of age. It is important to realize that such estimates are for the average effect in a population, with greater and lesser responses expected among individuals. Furthermore, it is quite possible that this slow and progressive effect of sodium may extend into the later decades of life, leading to an even greater total effect of the lifetime exposure to sodium on the blood pressure of the elderly.

Mechanisms underlying the slow and progressive effects of salt on blood pressure

The results of both animal and human studies suggest that excess dietary salt intake promotes a progressive salt-induced increase in blood pressure over the lifespan of the individual, one that is so very slow that it can easily be mistaken for the well-known effect of aging on blood pressure.[86] There is little consensus, however, concerning the mechanisms by which salt may promote this slow and progressive increase in blood pressure. In humans, the acute blood pressure response to salt restriction increases with age,[87–89] and this age-dependent increase in acute salt sensitivity has been suggested to account for the association of salt intake with age-dependent blood pressure changes.[90] However, the observed effects of long-term salt exposure on blood pressure in rats suggest that progressive salt-induced hypertension can also include an irreversible or 'self sustaining' component. In regular Sprague–Dawley rats fed a high-salt diet for 12–13 months (and also in the Dahl-S salt-sensitive and hybrid rat strains fed a high-salt diet for shorter periods of time[34,77]), blood pressure remained partially elevated at the end of the exposure period despite the lowering of dietary salt to low levels (Figure 6). There is little information on the reversibility of such long-term salt-induced hypertension in other animal studies. In Denton's study of chimpanzees,[79] salt-induced increases in blood pressure produced by feeding a high-salt diet over 20 months (~5% of the animal's lifespan) appeared to be reversible, suggesting that the progressive hypertension may have simply been due to increases in the acute salt sensitivity of blood pressure. At this point, it remains unclear whether the irreversible component of progressive salt-induced hypertension varies from species to species or whether it may simply vary with the extent and duration of exposure to excess salt (for example, possibly being pronounced in regular rats exposed to high-salt diets for ~40% of their lifespan[69] but absent in chimpanzees exposed to high-salt diets for ~5% of their lifespan[79]). This is an especially important matter in humans, in which our vulnerability to salt is often evaluated in terms of the acute response to salt restriction. As observed by Dahl many years ago, the production of self-sustaining hypertension by salt feeding '…suggests that the lack of response to (acute) salt restriction does not rule out an etiological relationship between salt intake and the development of hypertension'.[71] Unfortunately, because of the long time frame and tremendous resources that would be required, the reversibility of long-standing salt-induced hypertension is unlikely to be investigated directly in humans.

A large number of specific mechanisms have been implicated in the cascade of events underlying the slow and progressive forms of salt-induced hypertension,[62–64,91,92] and this broad subject is beyond the scope of the current review. However, it is worth pointing out that a variety of renal structural changes have been associated with the progressive form of salt-induced hypertension and likely contribute to its irreversible component.[93–95] In particular, an increase in the resistance of the preglomerular renal vasculature would be expected to account for a rightward shift of the chronic pressure–natriuresis curve in the manner that has been associated with progressive salt-induced hypertension.[44,96] A variety of subtle forms of renal injury, including inflammation and modest structural changes, have also been associated with the development of acute salt sensitivity in response to experimental interventions.[97,98] It is possible that similar changes could contribute to the increase in acute salt sensitivity associated with aging in humans,[87–89] or that which accompanies progressive salt-induced hypertension in Dahl-S rats.[34]

Finally, it is also worth considering the potential contribution of salt-induced changes in vascular dynamics to the slow and progressive effects of salt on blood pressure. As the observed effects of salt on blood pressure are often more pronounced for systolic and pulse pressure than diastolic pressure (for example, Figure 12), it is possible that this effect of salt on blood pressure could be due, in part, to a reduction

in large artery compliance and its attendant effects on wave propagation and arterial pressure pulses. High salt intake has been associated with stiffening of the large central arteries in both animals[99] and humans.[100,101] If a component of this were due to structural changes that were not rapidly reversible (that is, similar to those that have been associated with hypertension and aging[102–104]), this could contribute to the effect of salt to cause a slow and irreversible increase in blood pressure.

Summary and conclusions

In addition to the relatively rapid effects of salt on blood pressure that occur with a time course similar to the re-establishment of salt balance, salt also has actions that are so remarkably slow that they may require a sizable fraction of the lifespan of an individual to become evident. These slow actions of salt could easily be mistaken for simply an effect of aging and it is indeed possible that they represent a salt dependency of the mechanisms underlying age-associated blood pressure changes. Both rapid and slow effects of salt will each contribute to the burden of salt-induced hypertension, and both effects should be considered in any comprehensive explanation of the epidemiology of salt-induced hypertension. The demonstration of an irreversible component of progressive salt-induced hypertension in rat studies is of particular interest for several reasons including the unique mechanisms that may underlie this component, the inherent difficulty in demonstrating such a component in long-lived species such as humans, and its implications for dealing with salt-induced hypertension (since once manifested, this component could not be reversed by salt restriction). Finally, it is important that these multiple components of salt sensitivity (rapid vs slow, reversible vs irreversible) be distinguished in mechanistic studies, as they are likely to have different genetic and physiological explanations. Such distinctions may be made by simple considerations in the design and timing of salt exposure protocols (for example, Figures 9 and 10).

Acknowledgements

We thank Diane Gilmore, Jennica Gilmore and Linda Chafe for their assistance in the preparation of the paper. This study was supported by a grant from the Canadian Institutes of Health Research (no. 64440).

Conflict of interest

Bruce N Van Vliet has received a grant from the Canadian Institute of Health Research. Jean-Pierre Montani has declared no financial interests.

References

1 Hamet P. The burden of blood pressure: where are we and where should we go? *Can J Cardiol* 2000; **16**: 1483–1487.
2 Fodor JG, Whitmore B, Leenen F, Larochelle P. Lifestyle modifications to prevent and control hypertension. 5. Recommendations on dietary salt. Canadian Hypertension Society, Canadian Coalition for High Blood Pressure Prevention and Control, Laboratory Centre for Disease Control at Health Canada, Heart and Stroke Foundation of Canada. *CMAJ* 1999; **160** (9 Suppl): S29–S34.
3 Kaplan NM. *Clinical hypertension/Norman M. Kaplan; with a chapter by Ellin Lieberman* 7th edn Williams & Willkins: Baltimore, 1998.
4 MacGregor GA, de Wardener HE. *Salt, Diet & Health*. Cambridge University Press: Cambridge, 1998.
5 Meneton P, Jeunemaitre X, de Wardener HE, MacGregor GA. Links between dietary salt intake, renal salt handling, blood pressure, and cardiovascular diseases. *Physiol Rev* 2005; **85**: 679–715.
6 Frohlich ED, Chien Y, Sesoko S, Pegram BL. Relationship between dietary sodium intake, hemodynamics, and cardiac mass in SHR and WKY rats. *Am J Physiol* 1993; **264** (1 Part 2): R30–R34.
7 Khan NJ, Hampton JA, Lacher DA, Rapp JP, Gohara AF, Goldblatt PJ. Morphometric evaluation of the renal arterial system of Dahl salt-sensitive and salt-resistant rats on a high salt diet. I. Interlobar and arcuate arteries. *Lab Invest* 1987; **57**: 714–723.
8 Kihara M, Utagawa N, Mano M, Nara Y, Horie R, Yamori Y. Biochemical aspects of salt-induced, pressure-independent left ventricular hypertrophy in rats. *Heart Vessels* 1985; **1**: 212–215.
9 MacLeod AB, Vasdev S, Smeda JS. The role of blood pressure and aldosterone in the production of hemorrhagic stroke in captopril-treated hypertensive rats. *Stroke* 1997; **28**: 1821–1828.
10 Simon G, Jaeckel M, Illyes G. Development of structural vascular changes in salt-fed rats. *Am J Hypertens* 2003; **16**: 488–493.
11 Tobian L, Hanlon S. High sodium chloride diets injure arteries and raise mortality without changing blood pressure. *Hypertension* 1990; **15** (6 Part 2): 900–903.
12 He FJ, MacGregor GA. Effect of longer-term modest salt reduction on blood pressure. *Cochrane Database Syst Rev* 2004; Issue 1: CD004937. DOI: 10.1002/14651858.CD004937.
13 Penner SB, Campbell NRC, Chockalingam A, Zarnke K, Van Vliet B. Dietary sodium and cardiovascular outcomes: a rational approach. *Can J Cardiol* 2007; **23**: 567–572.
14 Eaton SB, Konner M. Paleolithic nutrition: a consideration if its nature and current implications. *NEJM* 1985; **312**: 283–289.
15 Briefel RR, Johnson CL. Secular trends in dietary sodium intake in the United States. *Annu Rev Nutr* 2004; **24**: 401–431.
16 Reinivu H, Valsta LM, Laatikainen T, Tuomilehto J, Pietinen P. Sodium in the Finnish diet: II. Trends in dietary sodium intake and comparison between intake and 24-h excretion of sodium. *Euro J Clin Nutr* 2006; **60**: 1160–1167.
17 Canadian Community Health Survey, Cycle 2.2, Nutrition. Nutrient intakes from food. Provincial, regional and national summary tables, volume 1, 2004.
18 Panel on dietary reference intakes for electrolytes and water. *Dietary reference intakes for water, potassium, sodium, chloride, and sulfate*. National Academies Press: Washington, DC, USA, 2004. Appendix D.
19 Krakower CA, Heino HE. Relationship of growth and nutrition to cardiorenal changes induced in birds by a high salt intake. *Arch Pathol* 1947; **44**: 143–162.
20 Lenel R, Katz LN, Robard S. Arterial hypertension in the chicken. *Am J Physiol* 1948; **152**: 557–562.
21 Coleman TG, Guyton AC. Hypertension caused by salt loading in the dog. III. Onset transients of cardiac output and other circulatory variables. *Circ Res* 1969; **25**: 153–160.
22 Constantopoulos G, Genest J, Kusumoto M, Rojo-Ortega JM. Water, cations, and norepinephrine content of cardiovascular

tissues of unilaterally nephrectomized dogs treated with deoxycorticosterone and NaCl. *Can J Physiol Pharmacol* 1975; **53**: 866–872.
23 Manning Jr RD, Coleman TG, Guyton AC, Norman Jr RA, McCaa RE. Essential role of mean circulatory filling pressure in salt-induced hypertension. *Am J Physiol* 1979; **236**: R40–R47.
24 Vogel JA. Salt induced hypertension in the dog. *Am J Physiol* 1966; **210**: 186–190.
25 Srinivasan SR, Dalferes Jr ER, Wolf RH, Radhakrishnamurthy B, Foster TA, Berenson GS. Variability in blood pressure response to dietary sodium intake among African green monkeys (*Cercopithecus aethiops*). *Am J Clin Nutr* 1984; **39**: 792–796.
26 Leonard AM, Chafe LL, Montani J-P, Van Vliet BN. Increased salt sensitivity in eNOS knockout mice. *Am J Hypertens* 2006; **12**: 1264–1269.
27 Corbett WT, Kuller LH, Blaine EH, Damico FJ. Utilization of swine to study the risk factor of an elevated salt diet on blood pressure. *Am J Clin Nutr* 1979; **32**: 2068–2075.
28 Fukuda TR. L'hypertension par le sel chez les lapins et ses relations avec la glande surrenale. *L'Union Med Canada* 1951; **80**: 1278–1281.
29 Weinstock M, Borosh M. Low baroreflex sensitivity predisposes to salt-sensitive hypertension in the rabbit. *Am J Physiol* 1993; **264** (2 Part 2): H505–H511.
30 Huang BS, Van Vliet BN, Leenen FHH. Increases in CSF [Na^+] precede the increases in blood pressure in Dahl S rats and SHR on high salt diet. *Am J Physiol (Heart Circ Physiol)* 2004; **287**: H1160–H1166.
31 Osborn JW, Hornfeldt BJ. Arterial baroreceptor denervation impairs long-term regulation of arterial pressure during dietary salt loading. *Am J Physiol* 1998; **275**: H1558–H1566.
32 Qi N, Rapp JP, Brand PH, Metting PJ, Britton SL. Body fluid expansion is not essential for salt-induced hypertension in SS/Jr rats. *Am J Physiol* 1999; **277** (5 Part 2): R1392–R1400.
33 Sapirstein LA, Brandt WL, Drury DR. Production of hypertension in the rat by substituting hypertonic sodium chloride solutions for drinking water. *Proc Soc Exp Biol Med* 1950; **73**: 82–85.
34 Van Vliet BN, Chafe LL, Halfyard S, Leonard AM. Distinct rapid and slow phases of salt-induced hypertension in Dahl salt-sensitive rats. *J Hypertens* 2006; **24**: 1599–1606.
35 Srinivasan SR, Berenson GS, Radhakrishnamurthy B, Dalferes Jr ER, Underwood D, Foster TA. Effects of dietary sodium and sucrose on the induction of hypertension in spider monkeys. *Am J Clin Nutr* 1980; **33**: 561–569.
36 McDonough J, Wilhelmj CM. The effect of excess salt intake on human blood pressure. *Am J Dig Dis Nutr* 1954; **21**: 180–181.
37 McQuarrie I, Thompson WH, Anderson JA. Effects of excessive ingestion of sodium and potassium salts on carbohydrate metabolism and blood pressure in diabetic children. *J Nutr* 1936; **11**: 77–101.
38 Fujita T, Henry WL, Bartter FC, Lake CR, Delea CS. Factors influencing blood pressure in salt-sensitive patients with hypertension. *Am J Med* 1980; **69**: 334–344.
39 Kawasaki T, Delea CS, Bartter FC, Smith H. The effect of high-sodium and low-sodium intakes on blood pressure and other related variables in human subjects with idiopathic hypertension. *Am J Med* 1978; **64**: 193–198.
40 Franco V, Oparil S. Salt sensitivity, a determinant of blood pressure, cardiovascular disease and survival. *J Am Coll Nutr* 2006; **25** (3 Suppl): 247S–255S.
41 Weinberger MH. Salt sensitivity of blood pressure in humans. *Hypertension* 1996; **27**: 481–490.
42 Weinberger MH. Pathogenesis of salt sensitivity of blood pressure. *Curr Hypertens Rep* 2006; **8**: 166–170.
43 Guyton AC, Coleman TG, Granger HJ. Circulation: overall regulation. *Ann Rev Physiol* 1972; **34**: 13–46.
44 Guyton AC. *Circulatory Physiology III. Arterial pressure and hypertension*. WB Saunders and Co: Toronto, 1980.
45 Guyton AC. Renal function curve—a key to understanding the pathogenesis of hypertension. *Hypertension* 1987; **10**: 1–6.
46 Guyton AC. Renal function curves and control of body fluids and arterial pressure. *Acta Physiol Scand Suppl* 1990; **591**: 107–113.
47 Guyton AC. Kidneys and fluids in pressure regulation. Small volume but large pressure changes. *Hypertension* 1992; **19** (1 Suppl): I2–I8.
48 Montani JP, VanVliet BN. Integrative renal regulation of sodium excretion. In: Burnier M (ed). *Sodium in Health and Disease*. Informa Health Care: New York, 2008, pp 175–199.
49 Van Vliet BN, Montani JP. Circulation and fluid volume control. In: Walz, W (ed) *Integrative Physiology in the Proteomics and Post-Genomics Age*. Humana Press, New Jersey, 2005, pp 43–66.
50 Cowley Jr AW. Long-term control of arterial blood pressure. *Physiol Rev* 1992; **72**: 231–300.
51 Granger JP, Alexander BT, Llinas M. Mechanisms of pressure natriuresis. *Curr Hypertens Rep* 2002; **4**: 152–159.
52 McDonough AA, Leong PK, Yang LE. Mechanisms of pressure natriuresis: how blood pressure regulates renal sodium transport. *Ann NY Acad Sci* 2003; **986**: 669–677.
53 Selkurt EE. Effect of pulse pressure and mean arterial pressure on modification on renal haemodynamics and electrolyte water excretion. *Circulation* 1951; **4**: 541–551.
54 Starling EH, Verney EB. The excretion of urine as studied in the isolated kidney. *Proc R Soc Lond* 1925; **97**: 321–363.
55 Evans RG, Szenasi G, Anderson WP. Effects of *N*-nitro-L-arginine on pressure natriuresis in anesthetized rabbits. *Clin Exp Pharmacol Physiol* 1995; **22**: 94–101.
56 Nafz B, Ehmke H, Wagner CD, Kirchheim HR, Persson PB. Blood pressure variability and urine flow in the conscious dog. *Am J Physiol* 1998; **274** (4 Part 2): F680–F686.
57 Hall JE, Guyton AC, Mizelle HL. Role of the renin–angiotensin system in control of sodium excretion and arterial pressure. *Acta Physiol Scand Suppl* 1990; **591**: 48–62.
58 Hall JE. The renin–angiotensin system: renal actions and blood pressure regulation. *Compr Ther* 1991; **17**: 8–17.
59 Melo LG, Veress AT, Chong CK, Pang SC, Flynn TG, Sonnenberg H. Salt-sensitive hypertension in ANP knockout mice: potential role of abnormal plasma renin activity. *Am J Physiol* 1998; **274** (1 Part 2): R255–R261.
60 Ehmke H, Persson PB, Seyfarth M, Kirchheim HR. Neurogenic control of pressure natriuresis in conscious dogs. *Am J Physiol* 1990; **259**: F466–F473.
61 Golin R, Genovesi S, Castoldi G, Wijnmaalen P, Protasoni G, Zanchetti A *et al*. Role of the renal nerves and angiotensin II in the renal function curve. *Arch Ital Biol* 1999; **137**: 289–297.
62 Huang BS, Amin S, Leenen FHH. The central role of the brain in salt-sensitive hypertension. *Curr Opin Cardiol* 2006; **21**: 295–304.
63 Leenen FH, Ruzicka M, Huang BS. The brain and salt-sensitive hypertension. *Curr Hypertens Rep* 2002; **4**: 129–135.
64 Manning RD, Hu L, Tan DY, Meng S. Role of abnormal nitric oxide systems in salt sensitive hypertension. *Am J Hypertens* 2001; **14**: 68S–73S.
65 Ball COT, Meneely GR. Observations on dietary sodium chloride. *J Am Diet Assoc* 1957; **33**: 366–370.
66 Meneely GR, Tucker RG, Darby WJ, Auerbach SH. Chronic sodium chloride toxicity in the albino rat. II. Occurrence of hypertension and of a syndrome of edema and renal failure. *J Exp Med* 1953; **98**: 71–80.
67 Tucker RG, Ball COT, Darby WJ, Early WR, Kory RC, Youmans JB *et al*. Chronic sodium chloride toxicity in the albino rat. III. Maturity characteristics, survivorship, and organ weights. *J Gerontol* 1957; **12**: 182–189.
68 Dahl LK. Effects of chronic excess salt feeding. Elevation of plasma cholesterol in rats and dogs. *J Exp Med* 1960; **112**: 635–651.
69 Dahl LK. Effects of chronic excess salt feeding. Induction of self-sustaining hypertension in rats. *J Exp Med* 1961; **114**: 231–236.

70 Dahl LK, Heine M. Effects of chronic excess salt feeding. Enhanced hypertensinogenic effect of sea salt over sodium chloride. *J Exp Med* 1961; **113**: 1067–1076.
71 Dahl LK, Schackow E. Effects of chronic excess salt ingestion: experimental hypertension in the rat. *Can Med Assoc J* 1964; **90**: 155–160.
72 Dahl LK, Knudsen KD, Heine MA, Leitl GJ. Effects of chronic excess salt ingestion. Modification of experimental hypertension in the rat by variations in the diet. *Circ Res* 1968; **22**: 11–18.
73 Knudsen KD, Dahl LK, Thompson K, Iwai J, Heine M, Leitl G. Effects of chronic excess salt ingestion. Inheritance of hypertension in the rat. *J Exp Med* 1970; **132**: 976–1000.
74 Mattson DL, Kunert MP, Kaldunski ML, Greene AS, Roman RJ, Jacob HJ *et al*. Influence of diet and genetics on hypertension and renal disease in Dahl salt-sensitive rats. *Physiol Genomics* 2004; **16**: 194–203.
75 Ben-Ishay D, Kobrin I, Saliternick-Vardi R, Feurstein G, Zamir N. The Sabra hypertension prone (H) and hypertension resistant (N) rat strain. *Paroi Arterielle* 1980; **6**: 157–159.
76 Yagil C, Katni G, Rubattu S, Stolpe C, Kreutz R, Lindpaintner K *et al*. Development, genotype and phenotype of a new colony of the Sabra hypertension prone (SBH/y) and resistant (SBN/y) rat model of salt sensitivity and resistance. *J Hypertens* 1996; **14**: 1175–1182.
77 Cowley Jr AW, Stoll M, Greene AS, Kaldunski ML, Roman RJ, Tonellato PJ *et al*. Genetically defined risk of salt sensitivity in an intercross of Brown Norway and Dahl S rats. *Physiol Genomics* 2000; **2**: 107–115.
78 Cherchovich GM, Capek K, Jefremova Z, Pohlova I, Jelinek J. High salt intake and blood pressure in lower primates (*Papio hamadryas*). *J Appl Physiol* 1976; **40**: 601–604.
79 Denton D, Weisinger R, Mundy NI, Wickings EJ, Dixson A, Moisson P *et al*. The effect of increased salt intake on blood pressure of chimpanzees. *Nat Med* 1995; **1**: 1009–1016.
80 Eichberg JW, Shade RE. Normal' blood pressure in chimpanzees. *J Med Primatol* 1987; **16**: 317–321.
81 Elliott P, Walker LL, Little MP, Blair-West JR, Shade RE, Lee DR *et al*. Change in salt intake affects blood pressure of chimpanzees: implications for human populations. *Circulation* 2007; **116**: 1563–1568.
82 Ladd M, Raisz LG. Response of the normal dog to dietary sodium chloride. *Am J Physiol* 1949; **159**: 149–152.
83 Ryan S, Halfyard S, Van Vliet BN. iNOS knockout mice do not have increased salt sensitivity. Proceedings of the Satellite meeting of the International Society of Hypertension on Salt and Hypertension, Nagoya, Japan, Oct 2006.
84 Law MR, Frost CD, Wald NJ. By how much does dietary salt reduction lower blood pressure? I. Analysis of observational data among populations. *BMJ* 1991; **302**: 811–815.
85 Elliott P, Stamler J, Nichols R, Dyer AR, Stamler R, Kesteloot H *et al*. Intersalt revisited: further analyses of 24 h sodium excretion and blood pressure within and across populations. *BMJ* 1996; **312**: 1249–1253.
86 Staessen J, Amery A, Fagard R. Isolated systolic hypertension in the elderly. *J Hypertens* 1990; **8**: 393–405.
87 Miller JZ, Weinberger MH, Daugherty SA, Fineberg NS, Christian JC, Grim CE. Heterogeneity of blood pressure response to dietary sodium restriction in normotensive adults. *J Chronic Dis* 1987; **40**: 245–250.
88 Myers J, Morgan T. The effect of sodium intake on the blood pressure related to age and sex. *Clin Exp Hypertens A* 1983; **5**: 99–118.
89 Weinberger MH, Fineberg NS. Sodium and volume sensitivity of blood pressure. Age and pressure change over time. *Hypertension* 1991; **18**: 67–71.
90 Law MR, Frost CD, Wald NJ. By how much does dietary salt reduction lower blood pressure? III—Analysis of data from trials of salt reduction. *BMJ* 1991; **302**: 819–824.
91 Majid DSA, Kopkan L. Nitric oxide and superoxide interactions in the kidney and their implication in the development of salt-sensitive hypertension. *Clin Exp Pharmacol Physiol* 2007; **34**: 946–952.
92 Rodriguez-Iturbe B, Romero F, Johnson RJ. Pathophysiological mechanisms of salt dependent hypertension. *Am J Kidney Dis* 2007; **50**: 655–672.
93 Chen PY, St John PL, Kirk KA, Abrahamson DR, Sanders PW. Hypertensive nephrosclerosis in the Dahl/Rapp rat. Initial sites of injury and effect of dietary L-arginine supplementation. *Lab Invest* 1993; **68**: 174–184.
94 Jaffé D, Sutherland LE, Barker DM, Dahl LK. Effects of chronic excess salt ingestion. Morphologic findings in kidneys of rats with differing genetic susceptibilities to hypertension. *Arch Pathol* 1970; **90**: 1–16.
95 Rapp JP, Dene H. Development and characteristics of inbred strains of Dahl salt-sensitive and salt-resistant rats. *Hypertension* 1985; **7** (3 Part 1): 340–349.
96 Kimura G, Brenner BM. Implications of the linear pressure–natriuresis relationship and importance of sodium sensitivity in hypertension. *J Hypertens* 1997; **15**: 1055–1061.
97 Rodríguez-Iturbe B, Pons H, Quiroz Y, Gordon K, Rincón J, Chávez M *et al*. Mycophenolate mofetil prevents salt-sensitive hypertension resulting from angiotensin II exposure. *Kidney Int* 2001; **59**: 2222–2232.
98 Quiroz Y, Pons H, Gordon KL, Rincón J, Chávez M, Parra G *et al*. Mycophenolate mofetil prevents salt-sensitive hypertension resulting from nitric oxide synthesis inhibition. *Am J Physiol Renal Physiol* 2001; **281**: F38–F47.
99 Et-Taouil K, Schiavi P, Lévy BI, Plante GE. Sodium intake, large artery stiffness, and proteoglycans in the spontaneously hypertensive rat. *Hypertension* 2001; **38**: 1172–1176.
100 Avolio AP, Deng FQ, Li WQ, Luo YF, Huang ZD, Xing LF *et al*. Effects of aging on arterial distensibility in populations with high and low prevalence of hypertension: comparison between urban and rural communities in China. *Circulation* 1985; **71**: 202–210.
101 Polónia J, Maldonado J, Ramos R, Bertoquini S, Duro M, Almeida C *et al*. Estimation of salt intake by urinary sodium excretion in a Portuguese adult population and its relationship to arterial stiffness. *Rev Port Cardiol* 2006; **25**: 801–817.
102 Greenwald SE. Ageing of the conduit arteries. *J Pathol* 2007; **211**: 157–172.
103 McEniery CM, Wilkinson IB, Avolio AP. Age, hypertension and arterial function. *Clin Exp Pharmacol Physiol* 2007; **34**: 665–671.
104 O'Rourke MF. Arterial aging: pathophysiological principles. *Vasc Med* 2007; **12**: 329–341.
105 Gates PE, Tanaka H, Hiatt WR, Seals DR. Dietary sodium restriction rapidly improves large elastic artery compliance in older adults with systolic hypertension. *Hypertension* 2004; **44**: 35–41.