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Links Between Dietary Salt Intake, Renal Salt Handling, Blood Pressure, and Cardiovascular Diseases

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Meneton, Pierre, Xavier Jeunemaitre, Hugh E. de Wardener, and Graham A. MacGregor. Links Between Dietary Salt Intake, Renal Salt Handling, Blood Pressure, and Cardiovascular Diseases. *Physiol Rev* 85: 679–715, 2005; doi:10.1152/physrev.00056.2003.—Epidemiological, migration, intervention, and genetic studies in humans and animals provide very strong evidence of a causal link between high salt intake and high blood pressure. The mechanisms by which dietary salt increases arterial pressure are not fully understood, but they seem related to the inability of the kidneys to excrete large amounts of salt. From an evolutionary viewpoint, the human species is adapted to ingest and excrete <1 g of salt per day, at least 10 times less than the average values currently observed in industrialized and urbanized countries. Independent of the rise in blood pressure, dietary salt also increases cardiac left ventricular mass, arterial thickness and stiffness, the incidence of strokes, and the severity of cardiac failure. Thus chronic exposure to a high-salt diet appears to be a major factor involved in the frequent occurrence of hypertension and cardiovascular diseases in human populations.

I. INTRODUCTION

The understanding of hypertension and cardiovascular diseases is very difficult to achieve. These are multifactorial diseases, meaning that they cannot be ascribed to a single gene or environmental factor; rather, they arise from the combined action of many genes, environmental factors, and risk-conferring behaviors. The genes that contribute to multifactorial diseases are notoriously difficult to identify, because they typically exert small effects on the disease risk; in addition, the magnitude of these effects is likely to be modified by other unrelated genes as well as by environmental factors. As a result, susceptibility loci or environmental risk factors identified in one population cannot be always replicated in other populations (189). Despite these difficulties, a century of epidemiological and clinical research and one decade of genetic investigation in humans and animals have provided remarkable insights on the relationships existing between dietary salt (throughout the review, salt stands for sodium chloride), renal salt handling, and blood pressure. The evidence points to a causal link between a chronically high salt intake and the development of hypertension when the kidneys have a reduced ability to excrete salt.

The data also suggest that chronic high salt intake increases cardiovascular morbidity and mortality both by its influences on blood pressure and by pressure-independent effects on the blood vessels and heart. Thus it seems beyond doubt that chronic high salt intake participates in the high prevalence of hypertension and cardiovascular diseases in human populations.

II. SALT INTAKE AND BLOOD PRESSURE

A. Relation of Habitual Salt Intake to Blood Pressure

For several million years the evolutionary ancestors of humans ate a diet that contained <1 g salt/day (38, 88). This implies that present-day humans are genetically programmed to a salt intake of that amount. The deliberate addition of salt to food only began ~5,000–10,000 years ago at the beginning of agriculture and farming so that the present consumption of ~10 g/day on average is, in evolutionary terms, relatively recent. The earliest comment that relates dietary salt to blood pressure is that of a Chinese physician Huang Ti Nei Ching Su Wein (~1,700 BC) who stated from the translation by Wan Ping (AD 762) "therefore if large amounts of salt are taken, the pulse will stiffen and harden." Twentieth century epidemiological evidence on the relation of dietary salt to blood pressure varies between the clear-cut absence of hypertension in populations who absorb <3 g/day to the high incidence of hypertension in populations that consume >20 g/day (hypertension is defined throughout the review as a systolic and/or diastolic pressure over 140/90 mmHg). The relation of dietary salt to blood pressure in populations lying between these two extremes has been more difficult to define. The reasons are not only the range of salt intake between individuals is narrower but also, in contrast to the relative steadiness of body weight for example, the existence of large fluctuations in day-to-day salt intake within individuals. Nevertheless, it appears clearly that in populations on a salt intake >3 g/day, the proportion of individuals with hypertension rises with age, and the phenomenon is more pronounced when the salt intake is higher.

Approximately 40 nonacculturated tribes have been recorded which consumed <3 g salt/day (80). Their blood pressure did not rise with age (Fig. 1*A*). They lived, or still live, in South America, Africa, the Pacific, and the Arctic. The most striking example are the Yanomamo Indians on the border between Venezuela and Brazil (231, 265). They have a mean salt intake of <0.5 g/day, and at the age of 50 years, the blood pressure of men is only 100/64 mmHg. This lack of rise of blood pressure with age is not due to a peaceful Arcadian existence accompanying "the certainty of behaviour in a society ruled by ritual and taboo," in contrast to the "uncertainties of Western Societies in which life is a series of individual choices" (279). On the contrary, the Yanomamo have a culture that encourages aggression and a life of chronic warfare with violence and tension (50). They probably represent the ultimate human example of the overriding importance of dietary salt on blood pressure. There are two other nonacculturated tribes, which demonstrate that it is not the absence of acculturation per se that is responsible for the lack of rise of blood pressure with age in the populations consuming a low intake of salt. The Quash'Qai in Iran are nomadic herdsmen who inhabit an area that contains many natural surface deposits of salt (268). Mean salt excretion is 11 g/day in men and 9 g/day in women. Blood pressure in this nonacculturated society, which consumes the same levels of salt as those of economically developed societies, increases with age. The situation was similar in an area of Northern Kashmir that was unexposed to Western influences of industrialization, diet, and economy but in which the inhabitants also ate a relatively high salt intake (246). The high salt intake was due to their custom of drinking boiled tea to which they added various amounts of salt. Dietary surveys of the mean salt intake in three villages varied between 9.9 and 10.1 g/day with a wide range between individuals of 4.4–20.5 g/day. Both the systolic and diastolic pressure correlated significantly with the individual salt intake.

Between 1950 and 1960, the Japanese became aware that their incidence of cerebral hemorrhage was greater than in any other population, even greater than in African Americans (164, 313–315). The incidence of cerebral thrombosis in Japan, however, was one of the lowest in the world. It emerged that the prevalence of cerebral hemorrhage had a regional distribution that paralleled the dietary intake of salt and the blood pressure. The salt intake in the north of the main island, which had the highest prevalence of cerebral hemorrhage, was 27 g/day (with individual levels up to 60 g/day), and between the ages of 50 and 60 years, 70% of the population had a raised blood pressure (systolic and/or diastolic over 150/90 mmHg). In the south, which had a much lower prevalence of cerebral hemorrhage, the salt intake was 14 g/day, and between the ages of 50 and 60 years, only 10% of the population had a raised blood pressure.

The relationship of dietary salt to blood pressure in populations that consume >3 g/day and <20 g/day is intermediary between the situations described above. It has been difficult to find out whether there is a relationship between dietary salt and blood pressure if all populations, whatever the salt intake, are included. The overriding difficulty is the normal day-to-day within-individual variation (up to 10-fold fluctuations) in the amount of salt excreted in the urine, which reflects changes in dietary salt (225, 331). This difficulty is most relevant in the large number of populations that consume ~10 g salt/day. Re-

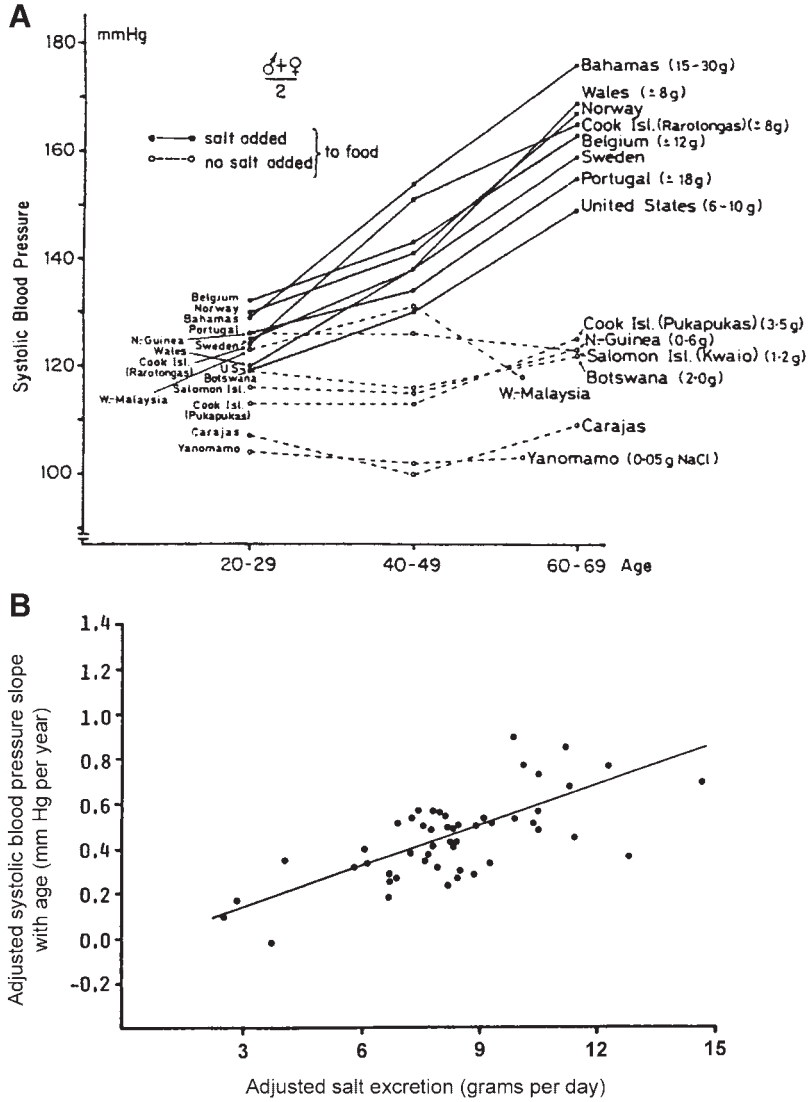

FIG. 1. *A*: systolic blood pressure change with age in various populations according to their habitual daily salt intake. [Adapted from Joossens (178).] *B*: relation of salt excretion to the slope of the rise in systolic blood pressure with age in 52 centers of the INTERSALT study. [Adapted from Elliott et al. (90).]

gression coefficients, which calculate relationships, are seriously underestimated in the presence of such large fluctuations within-individual variability in the independent variable (e.g., salt excretion), an effect known as regression dilution (202, 300). In other words, large within-subject variations mask the detection of differences between subjects. To minimize this effect, it is necessary to use large numbers of 24-h urine collections, and to obtain a true estimate of urinary salt excretion, it is necessary to collect at least half a dozen 24-h urine collections, which is impractical. The first attempt to relate the dietary intake of salt to the incidence of hypertension, which included populations on a moderate salt intake, was put forward by Meneely and Dahl (68). The data came from a total of five populations in only two of which was the intake of salt between 3 and 15 g/day. In addition to the smallness of the number of observations, information on the age of subjects and the definition of hypertension were unclear. Nevertheless, it is interesting that the relation of the salt intake to the blood pressure of these five populations was distributed along a straight line. Ten years later, Gliebermann (117) described the relation of the blood pressure of men aged 50–55 years to their salt intake in 27 populations (117). In 20 populations, dietary salt was >3 and <15 g/day, blood pressure appeared to rise with the salt intake, and the results lay between those obtained in subjects whose salt intake was <3 or >15 g/day. But the assessment of salt intake was haphazard, and no precautions had been taken to ensure that the measurement of blood pressure, the selection of the subjects, and the collection of urine were uniform. More importantly, the effect of several known confounding variables had not been taken into account such as potassium intake, body weight, and alcohol intake. The third set of populations studied was INTERSALT, an international epidemiological comparative study that began in 1981 (165). To remedy the drawbacks of the previous studies, standard methods were applied across a variety

of populations, major confounding variables were studied simultaneously, and sufficient numbers were included to evaluate relationships in individuals. Altogether 10,079 subjects were involved in 52 centers worldwide. Each center recruited 200 men and women aged 20–59 years separated by age and sex into 8 equal 10-year groups. Urine samples were sent to a central laboratory. The study design allowed the relation between 24-h salt excretion and the blood pressure to be examined both in the 10,079 individuals within centers and across the 52 centers of study. Initial calculations found that salt excretion was significantly related to blood pressure in individuals but not across centers. On the other hand, salt excretion across centers was related to the slope of blood pressure with age (Fig. 1*B*). Various calculations included the finding that, after adjustment for age, sex, body mass index, and alcohol, a 5.7 g/day lower salt intake between the ages of 25 and 59 years was associated with a 9 mmHg lower rise of systolic pressure. As, however, an inquiry into the relationship of salt intake to the slope of the rise in blood pressure with age had not been anticipated in the original objectives of the INTERSALT study, some authorities considered this finding to be of doubtful importance (359). Subsequently, further calculations of the results to correct for the previous incomplete correction for the regression dilution problems posed by the day-to-day variations in individual salt excretion estimated the effect of a median salt excretion higher by 5.7 g/day. Over a 30-yr period (comparing age 55 to age 25) in cross population analyses there was a difference of 10 mmHg in systolic pressure and 6 mmHg in diastolic pressure (90). It was also found that higher salt excretions were associated with substantially greater differences in blood pressure in middle age compared with young adulthood. Another very large international epidemiological comparative study that has tested the relationship between 24-h urinary sodium excretion and blood pressure is the still ongoing CARDIAC (Cardiovascular Diseases and Alimentary Comparison) study (410). Overseen by the World Health Organization, very similar to the INTERSALT study in its settings, this study has so far examined the relation between 24-h sodium excretion and blood pressure in at least 3,681 men and 3,653 women aged 50–54 years from 60 centers in 25 countries worldwide. Cross-center correlation analyses showed that systolic blood pressure and diastolic blood pressure were positively associated with 24-h sodium excretion in both men and women, but the association was significant only in the men (410). The analysis of 2,212 women aged 48–56 years showed that after adjustment for age, body mass index, and 24-h urinary potassium excretion, 24-h sodium excretion was positively and significantly associated with systolic and with diastolic blood pressure in postmenopausal women (409). The associations were not significant in premenopausal women. Cross-center correlation analyses of the 21 centers, which had data on menopausal status indicated that 24-h sodium excretion was positively associated with systolic and with diastolic blood pressure in both pre- and postmenopausal women, but again this positive association was only significant in postmenopausal women. This suggests a tendency for salt sensitivity to increase at menopause (409).

Regional differences in habitual salt intake and blood pressure within a population have been documented. In Newfoundland, a survey of salt intake revealed that a county in the center of the island had a typical salt intake varying between 6.7 and 7.3 g/day. In contrast, the salt intake varied between 8.4 and 8.8 g/day in a relatively isolated coastal community where the diet traditionally contained a large quantity of salt (102). This difference in salt intake was accompanied by parallel changes in the incidence of hypertension defined as a diastolic pressure >100 mmHg. In individuals aged between 55 and 75 years, the incidence of hypertension in the inland community was 15% while it was 27% in the coastal community. Forty-five years before, a study was undertaken in Brazil on the dietary habits of two adjoining nonacculturated tribes, the Mundurucu and the Caraja. The Mundurucu had moved from a savannah-like forest to a Franciscan mission on the Cururu river where they had access to salt (80). Otherwise there was no substantial change in their diet. The Caraja lived on a nearby river and continued to eat their traditional low-salt diet. There was a rise in blood pressure with age in the men of the Mundurucu and a similar but not significant trend in the women. The blood pressure of the Caraja did not rise with age. Similar evidence has been obtained among the Solomon Islanders (267). In those tribes, which lived away from the coast and had a salt intake below 2 g/day, only 1% of the population had a raised blood pressure (systolic and/or diastolic over 140/90 mmHg). In two tribes with salt intakes between 3 and 8 g/day, 3% of the population had a raised blood pressure. In one tribe, which lived on the coast and cooked in "copious amounts of seawater" and had a salt intake between 9 and 15 g/day, 8% of the population had a raised blood pressure.

Migratory studies provide also evidences for a relation between habitual salt intake and blood pressure. There are several cases of groups of individuals from low salt-eating countries whose blood pressure rises when a change in their circumstances causes them to eat more salt. One good example was a carefully controlled study from Kenya where subsistence farmers ate a low-salt/high-potassium diet (282). Some of the farmers migrated to an urban community where they underwent a marked increase in salt intake with a fall of potassium intake to levels similar to the diet in Westernized countries (283). Blood pressure in these migrants rose after a few months (+6.9/6.2 mmHg for systolic and diastolic), whereas it did not increase in a control group who did not migrate.

Another example of the effect of life-style changes including dietary sodium intake on blood pressure is that of the Yi people, an ethnic minority living in southwestern China. Blood pressure rose very little with increasing age (0.13 and 0.23 mmHg/yer for systolic and diastolic, respectively) in the Yi farmers who lived in their natural remote mountainous environment and consumed a sodium-poor diet. In contrast, Yi migrants and Han people who lived in urban areas consumed a sodium-rich diet and experienced a much greater increase in blood pressure with progressive aging (0.33 and 0.33 mmHg/yr for systolic and diastolic, respectively) (147). In a sample of 417 recent migrants (Yi) or native (Han) men living in the urban areas, a positive and statistically significant relationship was found between sodium intake and blood pressure (150). These findings suggest that changes in life-style, including higher intake of dietary sodium, contribute to the higher blood pressure among Yi migrants.

B. Exceptions to the General Finding That Habitual Salt Intake Controls Blood Pressure

There is a 30-year study in 144 Italian nuns and 138 controls who were living in the vicinity of the convent (368, 369). All the activities of the nuns are performed in strict isolation from urban life and in near absolute silence. Over the years the urinary salt excretion of the two groups was similar (7.5–8.0 g/day). The blood pressure of the control group rose, whereas the blood pressure of the nuns did not change. At the end of 30 years, the difference in blood pressure between the two groups was 30/15 mmHg. These results suggest that the hypertensive effect of dietary salt can be avoided by living in a stress-free monastic environment characterized by silence, meditation, and isolation from society. It is noticeable, however, that though the first account of these nuns appeared ~10 years ago, these observations do not appear to have been confirmed. A nonacculturated tribe, the Kuna Indians, who live in the isolated San Bas Island chain off the Caribbean coast of Panama, also appears to be an exception. They have no rise in blood pressure yet a dietary assessment indicates that the consumption of salt was probably >8 g/day (156). It has to be stressed that this assessment was mainly based on a rough measurement of salt excretion and each subject's recollection of how many teaspoons of salt they had added to their food. The relative isolation of the Kuna could have facilitated the occurrence of a founder effect or a genetic shift that might explain their protection from hypertension; thus they may provide an attractive population for examining the genetic mechanisms involved in salt sensitivity.

C. Effect of Acute Changes in Salt Intake on Blood Pressure

Studies in humans on the effect of an acute change in salt intake on blood pressure have been carried out for the past 100 years. For the first 50 years they were undertaken on patients with hypertension and subsequently on both hypertensive patients and normal subjects.

The hypotensive effect of lowering the intake of salt in hypertensive patients was first demonstrated by Ambard and Beaujard in 1904 (9). At that time, presumably because of Bright's observation that in patients with severe overt renal disease the blood pressure is raised, the generally accepted view was that hypertension, even when there was no rise in blood urea or proteinuria, was due to protein intoxication. Ambard and Beaujard (9) varied the salt and protein content of the diet fed to six hypertensive patients. They performed 24-h metabolic balances by measuring the salt content of the food and the urine. They found that when the salt intake was suddenly reduced the patients went into negative salt balance and the blood pressure fell, even if the protein intake was raised. Inversely, an increase of the salt intake triggered a positive salt balance and an elevation of blood pressure even in the presence of a decreased protein intake, showing that it was salt and not the protein content of the diet that primarily affected blood pressure. Subsequently a few French physicians advocated the use of a reduced intake of salt for hypertension while most Germans claimed that such a maneuver was ineffective. In 1931, however, Volhard (381) in a textbook on medicine confirmed that a low intake of salt could lower the blood pressure of hypertensive patients with renal involvement. In the 1920s Houghton (158) and Allen and Sherill (7) in the United States, against a general background of disbelief, published the results of reducing the intake of salt below 2 g and 0.5 g on 10 and 180 hypertensive patients, respectively. Among Allen and Sherrill's patients, the blood pressure was restored to normal in 19%, and in 42% there was some lowering of the pressure and relief of some associated symptoms; complete failure to change the blood pressure occurred in 14%. In spite of these results, the connection between salt intake, as opposed to protein intake in causing the blood pressure to rise, continued to be denied. In 1945, one of the foremost authorities on hypertension stated that any hypotensive results that had been obtained with salt restriction were due not to the restriction but to "rest in bed and the psychotherapy of constant attention." The position was finally clarified by Kempner in 1948 (188) who used a 2,000-calorie rice and fruit diet which contained 5 g fat, 20 g protein, and <0.5 g salt on 500 hypertensive patients. Among these patients, 229 had some evidence of "renal involvement." The diet had a "beneficial" effect on 62% of the 500 patients, i.e., there was a decrease in mean arterial pressure

of at least 20 mmHg. A reduction in heart size with a change in the transverse diameter of 18% or more, a change in the electrocardiogram T wave from completely inverted to upright, and a disappearance of severe retinopathy were also observed. The diet was slightly less effective (56%) when there was some renal involvement. The probable reason that Kempner's paper had such an impact was that it was visually so compelling and that it confirmed several previous similar studies. There were blood pressure charts showing relentless falls in blood pressure, chest x-rays of reductions in heart size, echocardiograms showing T-wave inversions reverting to normal and photographs of retina showing loss of edema, hemorrhages, and exudes. Kempner himself believed that the diet's effectiveness was the rigid restriction of protein intake. It is ironic, therefore, that he is now remembered as the person who most convincingly established that a high blood pressure can often be lowered by a low-salt diet. Kempner's results were confirmed by the Medical Research Council in the United Kingdom (387). The outstanding revelation that at that time, in spite of its considerable drawbacks, this unpleasant diet was the only known therapeutic measure that could lower blood pressure in more than 50% of patients with hypertension. There do not appear to have been any attempts made to make the diet more appealing. Instead, it was stressed that even if the blood pressure was controlled, a sudden rise in dietary salt still caused an immediate rise in blood pressure. It is not surprising therefore that, when oral diuretics were developed in mid 1950s, they were considered to be a satisfactory alternative to Kempner's diet. The idea that lowering salt intake might reduce blood pressure was not revived until the 1970s. In view of the difficulties of lowering salt intake below 1 g/day and the implacable dreariness of such a diet, reducing salt intake to ~5 g/day was now studied. The first double-blind controlled study of moderate salt restriction was performed in the 1980s in a group of unselected patients with mild to moderate hypertension (229). It clearly demonstrated that a reduction in salt intake from ~10 to 5 g/day for 4 wk induced a substantial fall in blood pressure equivalent to that seen with a diuretic. This was followed by many further trials. In some, however, the duration of low salt intakes was of short duration, e.g., 5 days, the reduction in salt intake was relatively small, e.g., <1 g/day, urinary salt excretion was inadequately monitored or the conditions were not random or double blind. In only 16 trials there was a random allocation to the experimental condition, no concomitant intervention in either group, and a dietary salt reduction which induced a reduction in 24-h salt excretion >2.9 g/day (3.0–6.7 g) for at least 4 wk. In these cases, systolic and diastolic blood pressure in 658 patients fell by 4.2/2.4 ± 0.4/0.3 mmHg (143). Weighted linear regression analysis showed a dose-response relationship between the change in urinary salt and blood pressure and that a reduction of 5.8 g/day in salt intake predicts a fall in blood pressure of 6.1/3.5 mmHg.

The effect of an acute reduction in salt intake on blood pressure of normotensive individuals has been studied, as it was in hypertensive patients, in many trials in which the conditions were not suitable. Furthermore, to add to the difficulties, the effect on normotensive individuals appears to be less than in hypertensive patients. Nevertheless, in 10 randomly controlled trials representing 2,104 normotensive individuals in whom the reduction in 24-h salt excretion was greater than 2.3 g/day (2.3–6.8 g), systolic and diastolic blood pressure fell by 1.6/0.6 ± 0.3/0.2 mmHg (143). There too, weighted linear regression analysis showed a dose-response relationship between the changes in urinary salt and blood pressure. A reduction of 5.8 g/day in salt intake predicts a fall in blood pressure of 2.7/0.9 mmHg. The most recent randomized trial included both normotensive and hypertensive individuals and was the most meticulous in the manner with which the dietary salt intake was monitored. It was a multicentered trial that studied the effect of three levels of dietary salt intake on 412 individuals whose blood pressure exceeded 120/80 mmHg (305). One diet contained 8 g/day salt, another diet 6 g, and the third diet 4 g. Each intake of salt was maintained for 30 days. The outstanding feature of the trial was the provision to the participants of all their food, including snacks and cooked meals, and taste tests were performed to ensure that the diets were palatable. The participants' adherence to the diet was monitored, not only by measuring the salt content of 24-h urine at the end of each period on a fixed salt intake, but also their daily food diaries were inspected and they ate their weekday lunches or dinners "on site." In addition to studying the effect of the three dietary salt intakes on blood pressure when the participants were otherwise on their habitual diet, the effect of the various salt intakes was also studied on a diet rich in vegetables, fruits, and low-fat dairy products. This diet by itself, known as a "Dietary Approaches to Stop Hypertension (DASH)" diet, reduces blood pressure (13). There was a very significant difference in systolic pressure (−6.7 mmHg) and of diastolic pressure (−3.5 mmHg) between participants on the 8 g/day diet and those on the 4 g/day (Fig. 2*A*). The pressures were all significantly lower on the DASH diet. There was a greater reduction in systolic pressure when blood pressure was initially high and in women, but most importantly the blood pressure-lowering effect of reducing the salt intake was observed in all categories of the population, in particular in normotensive as well as in hypertensive people (Fig. 2*B*). This observation, which confirms the previous studies, is very important for the public health issue. Indeed, it is known that most of the deaths related to high blood pressure occur in normotensive individuals with moderately elevated pressure (systolic and/or diastolic be-

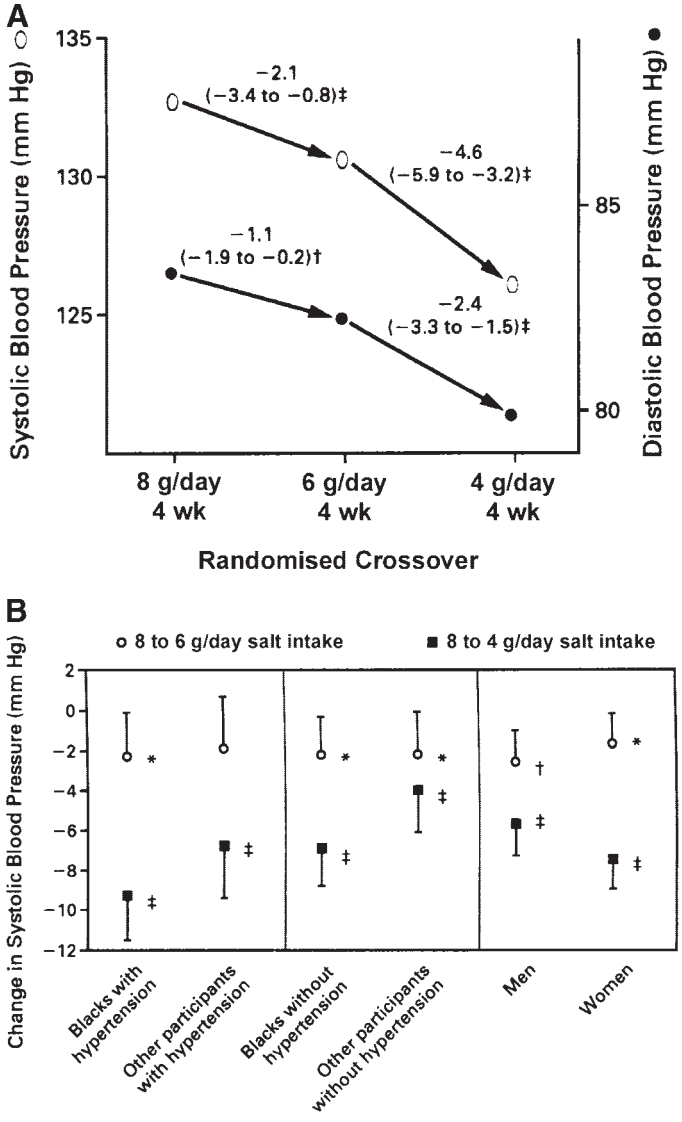

FIG. 2. *A*: effect on systolic and diastolic blood pressure of varying dietary salt intake in a randomized controlled trial in 412 participants with an otherwise regular Western diet. *B*: changes in systolic blood pressure in various subgroups of participants. The error bars represent 95% confidence limits of the changes in systolic blood pressure for each subgroup. *$P \leq 0.05$. †$P \leq 0.01$. ‡$P \leq 0.001$. [Adapted from Sacks et al. (305).]

tween 120/80 and 140/90 mmHg) and not in hypertensive people because the number of these latter in the population is much smaller even though their individual risk is higher (380).

The effect of a reduction in dietary salt intake has also been studied in 476 newborn babies randomized into one of two groups (112). One had a normal salt intake and the other a lower intake for 6 mo. The salt intake of the normal-salt group was almost three times that of the lower-salt group. There was a progressive and increasing difference in blood pressure between the two groups so that at 6 mo of age it was significantly higher in that on the higher salt intake (+2.2 mmHg). At 6 mo, all babies reverted to their normal salt intake. A number were reinvestigated when they were 15 year old, and it was found that the blood pressure difference had persisted though both groups had eaten the same diet for the preceding 14.5 yr. In another study but in only 23 infants, the dietary salt intake was reduced from 0.5 to 0.1 g/100 kcal. The blood pressure at 4 and 8 mo was greater in those on the higher salt intake, but the difference was not significant (396). It is likely that this negative finding was due to the small numbers involved and the reported finding that within-individual blood pressure varied widely. In four studies on the effect of lowering the salt intake on blood pressure in children, the significance of the results has been greatly influenced by the number of participants (77). In the largest group (750 children), a reduction in salt intake of 2 g for 6 mo induced a significant fall in blood pressure (91). In the elderly, there is one study in 47 previously untreated individuals, mean age 66.8 ± 5.3 yr with a range of 60–78 yr, with systolic and diastolic blood pressure varying between 123/64 and 205/120 mmHg (47). When the salt intake was reduced from 10.2 to 5.4 g/day, there was a fall of 7.2 mmHg in systolic pressure and 3.2 mmHg in diastolic pressure. The fall in blood pressure was not associated with age, baseline blood pressure, or habitual salt intake. In dialyzed patients with end-stage renal disease, who are particularly exposed to the development of hypertension, restricting salt intake to 5 g/day allows a remarkable control of high blood pressure in most patients, without any need for an antihypertensive drug treatment (328).

There are some reports on the effect on blood pressure of normotensive individuals of acutely raising the salt intake. One was a nonacculturated tribe in Papua, New Guinea in which the habitual salt intake was 0.6 g/day (294). Two groups, each of five individuals, were given diets with a raised dietary intake of salt for 10 days. In one group the urinary salt excretion rose to 7.5 g/day and in the other it rose to 15 g/day. On the lower rise in salt intake, there was an increase in blood pressure that was not significant, but on the higher salt intake, there was a significant rise in both systolic and diastolic pressure from 92/56 to 102/60 mmHg. There do not appear to be any studies of the effect of a prolonged increase in salt intake on blood pressure in normotensive humans previously accustomed to a low intake of salt. Dietary salt has been increased for relatively short periods in young adults on their normal high-salt diet (8.7 g/day). This has rarely induced a change in blood pressure. In four of five studies, increases in salt intake for up to 4 wk in young and middle aged (<47 yr) normotensive subjects did not cause a rise in blood pressure (77, 226).

D. Prolonged Reductions in Salt Intake and Blood Pressure

One of the most clear-cut examples of the effect of reducing the salt intake on the blood pressure of a community occurred in Portugal, which is notorious for its high consumption of salt (103). The trial was carried out in two communities within the same district, each with ~800 inhabitants who had salt intakes of ~21 g/day and a 30% incidence of hypertension. In the intervention community there was a vigorous, widespread health education effort to reduce the intake of salt especially from those foods that had previously been identified as the major sources of salt. The reduction in salt intake in one of the communities to 12 g/day was associated with a highly significant difference in blood pressure. By the end of the second year, there was a small rise in systolic pressure in the control community and a significant fall in both systolic and diastolic pressure in the community on the low salt intake, the difference between the two villages reached 13/6 mmHg. The fall in blood pressure involved the whole community, normotensives and hypertensive individuals alike, and the response did not differ between the young and the old or between men and women. Those with the greatest fall in salt excretion tended significantly to be also those who showed the greatest fall in blood pressure. Another long-term trial was carried out in Tianjin in China as part of a community-based intervention program to reduce noncommunicable diseases (367). This intervention was based on examinations of independent cross-sectional population samples in 1989 (1,719 persons) and 1992 (2,304 persons) in the intervention and matched reference areas. Food weighing and consecutive 3-day food records were used to measure dietary intake. The mean reduction in salt intake was 1.3 g/day in men and 0.7 g/day in women in the intervention area from 1989 to 1992. During the same period, the sodium intake increased significantly in men of the reference area. The reduction was significant in men ($P = 0.001$) and near significance in women ($P = 0.05$). This reduction in salt intake was similar in different educational and occupational groups, suggesting that the intervention had reached the whole community. In the intervention area, the mean systolic blood pressure decreased by 3 mmHg for the total population and by 2 mmHg for normotensive people. The decrease in systolic blood pressure was significant for both hypertensive and normotensive subjects. A third example of a long-term trial is the intervention that took place in two Belgian towns of 12,000 and 8,000 inhabitants, situated within 50 km of each other (345). The low salt intervention in one of the towns was mainly directed at women and implemented through mass media techniques. Cross-sectional random sampling at baseline and at 5 yr examined a total of 2,211 subjects. No significant difference was observed in the evolution of mean systolic and diastolic pressures that declined to the same extent in the two towns during the trial. The reduction in salt intake was considerably smaller than in the Portuguese trial but of the same order of magnitude than in the Chinese trial. In women of the intervention town, 24-h urinary salt excretion decreased by 1.5 g, whereas in the control town it rose by 0.5 g. This negative result may be explained by the small reduction in salt consumption that would be insufficient to observe a net effect on blood pressure in the Belgian environment, whereas such reduction was high enough to demonstrate an effect in the Chinese environment. In Japan between 1955 and 1989, as a result of a wide-ranging endeavour by public health authorities, the average salt consumption of the whole country fell from 13.5 to 12.1 g/day. In those localities where the salt intake was highest, as in the province of Akita in the north of the country, the intake of salt fell from 18 to 14 g/day. A gradual fall in blood pressure and a marked decline in mortality accompanied the reduction in salt consumption from strokes. In particular, there was a considerable gradual fall in blood pressure that occurred between 1957 and 1973 in each of the yearly intakes into three grades of school children aged between 12 and 15 yr (315).

E. Salt Intake and Blood Pressure in Other Mammalian Species

The available data in other terrestrial mammalian species confirm largely the existing relationship between habitual salt intake and blood pressure levels. Thus, in natural populations of genetically nonselected animals absorbing chronically varying amounts of salt for long periods of time, blood pressure appears to increase with the magnitude of the salt intake. For example, in groups of young adult rats fed different amounts of salt in their diet (0.15, 2.8, 5.6, 7.8, or 9.8%) with free access to distilled water, the average blood pressure after 9 mo increased proportionally to the salt content of the diet (19). The individual blood pressure values of the rats were quite scattered and overlapped from one group to another illustrating the large variation that exists in the susceptibility of each animal to the salt intake. This shows that the relationship between the habitual salt intake and blood pressure is essentially valid on a population and not individual basis. A similar study has been performed in pigs fed a diet containing either 0.5 or 3% salt for 8 mo after weaning with free access to pure water. The average diastolic and systolic blood pressures became progressively higher from the second to the eighth month in the group of pigs with the high salt intake (62). In baboons, adding 4% of salt to the diet resulted in increased blood pressure levels after 1 yr of exposure performed either from birth, during the sexual maturation, or in adults (55).

The effect on systolic and diastolic blood pressures was observed in males and females and was substantially accentuated in the adults when the exposure time to the high salt intake was increased from 1 to 2.5 yr. In addition, at the termination of the experiment, the interruption of the high salt intake after 1 yr of exposure was accompanied by a return of blood pressure levels to normal in a few months. In African green monkeys, a gradual increase of dietary salt from 0 to 6% over a 1-yr period showed that, as a group, this primate species responds to salt intake with elevated systolic and diastolic blood pressures (344). Like in rats, significant individual variations in salt sensitivity were observed that tended to be consistent on the different salt diets, suggesting the involvement of the genetic makeup. In a colony of adult chimpanzees, our closest relatives on a genetic viewpoint, in a study where the salt intake was progressively increased for 20 mo from 0 to 15 g/day, both diastolic and systolic pressures became elevated compared with the group control (79). Moreover, when the salt was removed from the diet, blood pressure levels fell back to the values of the control group after 6 mo. It was also obvious that some chimpanzees reacted more than others to these changes of the salt intake; ~60% of the cohort became hypertensive, whereas 40% remained resistant to high salt intake.

III. MECHANISMS BY WHICH HABITUAL SALT INTAKE CONTROLS BLOOD PRESSURE

A. Central Role of the Kidneys

The primary functional disturbances that link salt intake to the arterial pressure lie in the kidneys. In several hereditary strains of hypertensive rats, renal cross-transplantation experiments with normotensive strains have shown that the rise in arterial pressure is due to abnormal kidneys (33, 69, 70, 125, 153, 250, 290). When a kidney from a normotensive rat is inserted into a young bilaterally nephrectomized hypertensive rat, the blood pressure of the hypertensive rat does not rise, and conversely, when a kidney from a young hypertensive rat (before it has developed hypertension) is inserted into a bilaterally nephrectomized normotensive rat, the blood pressure of the normotensive rat will rise. Similarly the high blood pressure of patients with essential hypertension and terminal nephrosclerosis became normal (over a mean follow-up of 4.5 yr) when, following bilateral nephrectomy, they were transplanted with a kidney from a young normotensive donor (67). The finding that the blood pressure of a bilaterally nephrectomized hypertensive rat does not rise when cross-transplanted with a kidney from a normotensive rat, and the comparable results which have been observed in humans with essential hypertension, indicate that whatever functional abnormalities may occur at other sites, the primary disturbance that initiates the rise in blood pressure in these hereditary forms of hypertension resides in the kidneys.

The primacy of the kidneys in the regulation of blood pressure has been confirmed by the experimental and conceptual work developed by Guyton (133) on the pressure natriuresis and diuresis response. The body has several systems for controlling blood pressure, which largely differ in their time of activation after the pressure suddenly becomes abnormal. Some systems based on neural receptors react within seconds while others like the hormonal systems respond within minutes. But the system whose contribution is by far the greatest is the kidney-fluid volume system, which reacts within hours or days. This system, which is able to restore the pressure to its exact original level, operates as follows. When the arterial pressure rises above normal, the excess pressure causes the kidneys to excrete more water and salt in the urine than are entering the body. Therefore, the extracellular and blood volumes decrease. This causes the heart to pump less blood, and the arterial pressure falls. Conversely, when the pressure falls below normal, the incoming salt and water overbalance the excreted fluid, and the pressure rises.

B. Links Between an Inadequate Renal Capacity to Excrete a High Salt Intake and Hypertension

In normotensive first degree relatives of patients with essential hypertension, compared with control subjects, volume expansion with saline leads to a lower rate of sodium excretion and a rise in blood pressure (126–128, 397). The effect on the blood pressure of a person's habitual salt intake, as measured by 24-h urinary sodium excretion, has also been studied in normotensive offspring of two hypertensive parents, one hypertensive parent, and two normotensive parents (379). Twenty-four-hour urinary sodium excretion was similar in the three groups, but while there was a positive association between urinary sodium excretion and systolic pressure in the offspring of hypertensive parents, no such association was apparent in the offspring of two normotensive parents. In the spontaneously hypertensive rat (SHR), sodium is retained between 4–6 wk of age when the sodium excretion of the SHR is significantly less than that of the control, the Wistar-Kyoto (WKY) rat (253, 371). Urinary sodium excretion has also been monitored during the development of hypertension in the Milan hypertensive rat. At 24 days, there is a statistically significant retention of sodium associated with a transient fall in urinary excretion of sodium but accompanied by an increased fecal content of sodium. The overall result, however, is an average retention of ~2.5 mmol sodium (31, 139).

It should be mentioned that in normal humans the kidney's capacity to excrete sodium declines with age,

and smaller increases in salt intake induce a rise in arterial pressure (30, 227). There is an accelerating fall in glomerular filtration rate (GFR) with age which begins around the age of 30 yr (215, 302). At the age of 80 yr, the fall in GFR is ~40%. Individual variations are wide, and in one longitudinal study of 254 subjects who were followed serially for 8 or more years, one-third had no fall in GFR. The overall deterioration in GFR is more marked in blacks (245). The redistribution in GFR with age is accompanied by a decline in the number of functioning nephrons and is associated with the progressive development of glomerulosclerosis which eventually leads to glomerular obsolescence (185, 224). As there is generally no decline in salt consumption with age, sodium balance is maintained by raising fractional excretion of sodium. This is achieved, in part, by increasing the circulating concentrations of atrial natriuretic peptide, reducing plasma renin and aldosterone, and raising the blood pressure (263, 374). It is probable that the gradual rise in blood pressure that occurs with age in all populations on diets that contain more than 60 mmol sodium/day is due, in part, to these senescent involutional changes in renal structure superimposed on one or more primary renal structural and functional abnormalities (48). In the normal rat, GFR begins to decrease at 3 mo with a mean fall of ~30% at 24 mo (63).

An increase in GFR increases the rate of delivery of tubular fluid to the macula densa, the cells of which then signal the adjoining afferent arteriole to constrict. This reduces the filtration rate and the delivery of tubular fluid to the macula densa and reduces urinary sodium excretion (136). In the normal animal, the sensitivity and reactivity of tubuloglomerular feedback increases when there is a need to conserve sodium, as in hemorrhage and dehydration (186, 276), and diminishes when there is a prolonged need to increase sodium excretion, as in chronic salt loading (135, 322) and DOCA administration (248, 321). In the 6-wk-old SHR when there is most evidence of sodium retention, tubuloglomerular feedback is increased (82, 280). This paradoxical increase that should enhance sodium reabsorption is independent of the associated rise in blood pressure. Conversely, if the SHR is chronically salt loaded, the resultant fall in tubuloglomerular feedback is less than in the salt-loaded WKY rat. By measuring tubuloglomerular feedback activity when perfusing the tubule with harvested tubular fluid from SHR and control rats, one group has demonstrated that the increase in tubuloglomerular feedback activity in the SHR is due to the defective action of a feedback inhibitory substance in the tubule fluid (378). The situation is similar in the Milan hypertensive strain rat. At 3.5–5 wk when the Milan hypertensive strain rat is in a state of slight volume expansion, tubuloglomerular feedback activity is appropriately absent. Two weeks later, however, when the blood pressure starts to rise, tubuloglomerular feedback increases inappropriately to high levels, so diminishing the kidney's ability to excrete sodium (237).

Disturbances of renal circulation in essential hypertension and hereditary strains of hypertensive rats may participate to the kidney's incapacity to excrete sodium. Investigation of renal hemodynamics in normotensive children of hypertensive parents has yielded inconsistent results, but the majority suggests that increased vascular resistance precedes the development of hypertension (116, 157, 377). In the SHR, renal blood flow and GFR are reduced before the rise in blood pressure (83). The kidney of immature prehypertensive SHR demonstrates a blunted pressure natriuresis that worsens with maturity so that by the age of 10–20 wk an increase in perfusion pressure of 54 mmHg gives rise to only a fourfold rise in sodium excretion compared with a ninefold increase in controls (297). Medullary hemodynamics in the SHR are abnormal (65). Measurements of papillary blood flow from the third to the sixteenth week show that whereas cortical and total blood flow in the SHR and WKY rat are similar, papillary blood flow in the SHR, at 6–9 wk onwards, is consistently less than in the WKY rat. Roman and Kaldunski (298) suggested that the increased medullary vascular tone prevents the normal increase in renal interstitial pressure upon which the mechanism of pressure natriuresis depends and that the decreased papillary blood flow in the 6- to 9-wk old rat would enhance sodium reabsorption (298). There is much evidence in the SHR that the circulatory disturbances described are related to local disturbances of arachidonic acid metabolism, particularly cytochrome *P*-450-dependent monooxygenase activity. The observation by Sacerdoti et al. (304) of higher levels of both cytochrome *P*-450 and its products in microsomal fractions from 5- to 13-wk-old SHR kidneys compared with WKY rat impelled them to study the effect of renal cytochrome *P*-450 depletion on the blood pressure of the SHR. Treatment with stannous chloride for 4 days caused a reduction of the blood pressure of 7-wk-old SHR that was maintained for at least 7 wk and was associated with a natriuresis and reduction in the renal content of cytochrome *P*-450 and its arachidonic acid metabolites (stannous chloride stimulates renal heme oxygenase production and so reduces the availability of heme for the formation of other hemoproteins including cytochrome *P*-450 monooxygenases). Stannous chloride did not affect the blood pressure of 20-wk-old hypertensive SHR or WKY rats. The same investigators administered stannous chloride to SHR from 5 to 13 wk of age and found that the development of hypertension was prevented during treatment and for 7 wk thereafter (93). There is also evidence of enhanced renal vascular tone and reactivity in the Dahl salt-sensitive rat, which both precede and accompany the rise in arterial pressure. The impaired pressure natriuresis is due principally to a defect in the sensitivity of the tubule to alter sodium reabsorp-

tion in response to changes in interstitial pressure (295, 296). In the Dahl salt-sensitive rat, in contrast to the SHR, one factor responsible for the development of salt-induced hypertension is an inability to increase vasodilatory nitric oxide production (54). In addition, there is also an absence of vasodilatation to atrial natriuretic peptide and nitroprusside, and an increased vasoconstrictive response to norepinephrine and angiotensin II (334).

Most hypotheses on how dietary salt increases the blood pressure incorporate the premise that the initial rise in arterial pressure is associated with an increase in extracellular fluid volume (Fig. 3). In view of the impaired ability to excrete sodium in normotensive children of hypertensive parents (397) and in young prehypertensive genetically hypertensive rats (31), this premise is theoretically reasonable, but measurements of the extracellular fluid volume in hypertension are inconsistent. Beretta-Piccoli and co-workers (27, 28) found a significant correlation between exchangeable sodium, related to body surface, in men but not in women, but in hypertensive men below the age of 36 years exchangeable sodium was significantly decreased. In the SHR, the extracellular volume or exchangeable sodium is significantly greater than in the WKY rat (139, 253, 371). In the Milan hypertensive rat however, exchangeable sodium is not significantly different from that of the Milan normotensive rat (31, 139). Perhaps the most striking evidence in favor of the proposition that in hypertension there is a state of continuous correction of a slightly expanded extracellular fluid volume is the exaggerated natriuretic response of normotensive children of hypertensive parents, to a rapid infusion of saline. In these groups, rapid volume expansion leads to the phenomenon of accelerated natriuresis, which does not occur in normotensive children of normotensive parents (398). Such a response is well documented in circumstances in which there is a tightly controlled state of volume expansion. It occurs in normal individuals given aldosterone, even when it may not be possible to detect an increase in extracellular volume, in primary hyperaldosteronism (36, 301); it also occurs in established hypertension and in the SHR (25, 399). In addition, the reduced levels of plasma renin (238), the raised levels of atrial natriuretic hormone (397), and the increase in the plasma's capacity to inhibit Na^+-K^+-ATPase (76) are consistent with an increase in extracellular fluid volume.

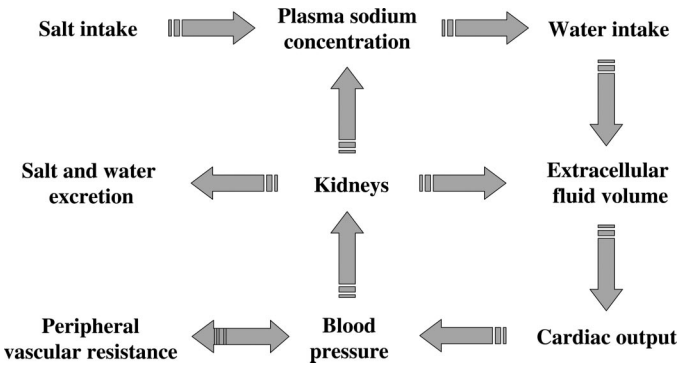

FIG. 3. Links between dietary salt intake and blood pressure. The sequential steps by which salt intake influences arterial blood pressure are shown. They include an effect on plasma sodium concentration and extracellular fluid volume. The greater rise in plasma sodium, which occurs in hypertensive-prone subjects, is due to a defect in the kidney's ability to excrete salt and to regulate extracellular fluid volume. [Adapted from de Wardener and MacGregor (78).]

Based on experiments on 70% of nephrectomized dogs given large amounts of saline intravenously daily for 2 wk, Guyton and co-workers (59, 233) suggested that volume expansion raises the blood pressure by the autoregulatory effect on resistance vessels of the increase in blood flow which accompanies an associated persistent increase in cardiac output. Nevertheless, this slight increase in cardiac output is usually unmeasurable (134). In addition, cardiac output in essential hypertension is normal, even when there is hypervolemia (306, 365). Furthermore, there are several observations that demonstrate that cardiac output does not control the blood pressure. Dialysis patients loaded with saline develop a rise in peripheral resistance without an increase in cardiac output (190), hypertension can occur in a patient with mitral stenosis and a low cardiac output, and after raising the blood pressure of a dog with metapyrone for 6 wk there was no evidence of circulatory autoregulation (372).

Others have proposed that the pressor mechanism induced by dietary salt in essential hypertension and the SHR is, in part, due to an increase in the plasma's capacity to inhibit Na^+-K^+-ATPase, which raises the blood pressure by inhibiting the sodium-calcium exchange pump in vascular smooth muscle (39, 76). This hypothesis is based on the demonstration that in normal dogs acute volume expansion increases the plasma's capacity to inhibit Na^+-K^+-ATPase and that this increase is also detectable in essential hypertension, the SHR, and the Milan hypertensive rat. The nature of the substance responsible for the Na^+-K^+-ATPase inhibition in hypertension has been difficult to elucidate. One study in 27 untreated patients with essential hypertension has demonstrated that plasma marinobufagenin immunoreactivity, which rises with acute volume expansion, is raised in essential hypertension (17, 119). A variable increase in plasma ouabain immunoreactivity, and of ouabain extracted from plasma, has also been reported in essential hypertension though volume expansion does not raise plasma ouabain (119, 234).

Another hypothesis on the origin of the rise in arterial pressure that is initiated by an impaired ability to excrete sodium suggests that an associated increase in extracellular volume is responsible for the documented increase in the right and left (pulmonary wedge) pressures in the auricles. It was proposed that this increase in pressure

induced an increase in afferent stimuli from the auricular walls to the hypothalamus and was thus responsible for the observed hypothalamic changes that lead to the documented pressor increase in sympathetic activity (75).

A body of evidence also suggests that the pressor and other harmful effects of dietary salt are due in part to a rise in plasma sodium. An acute experimental increase in plasma sodium in animals can raise the blood pressure, in spite of a fall in extracellular volume (106, 107). And a substantial acute increase in cerebrospinal fluid (CSF) sodium (+15 mM) induced in dogs by infusing hypertonic saline into the third ventricle raises the blood pressure within minutes (11), whereas a prolonged infusion which only raises the CSF sodium by ~4–5 mM may take 6–10 days to raise the blood pressure (327). In cultured vascular smooth muscle, an increase in sodium concentration of 2–10 mM increases mRNA expression of many hypertrophy-related factors and the number of AT_1 receptors; again, some of these changes take several days (130). In both normotensive and hypertensive humans, acute changes in salt intake are accompanied by parallel changes in plasma sodium (144, 146, 152, 177, 187, 226, 299, 308, 357). In hypertensive individuals, an acute increase in salt intake raises CSF sodium (121, 187).

There do not appear to be any direct observations on plasma sodium in large groups of humans whose habitual dietary intake of sodium is known. But it is possible that in normal circumstances such a rise may be difficult to detect for a rise in plasma osmolarity of only 1.6 ± 11% (which is equivalent to a change in plasma sodium of <1%) will stimulate the thirst center in the hypothalamus of the rat (101). The coefficient of variation for contemporary methods of detection of sodium is <1.5% (45). The close relation that exists between dietary sodium and urine volume in normal and hypertensive humans suggests that it is due to its effect on plasma sodium's control of thirst (145). The suggestion that in essential hypertension and the SHR there is a rise in plasma osmolarity (sufficient to affect the hypothalamus) is also consistent with the finding that in both these forms of hypertension, there is evidence which, though it suggests a state of continuous correction of a slightly expanded extracellular fluid volume (36, 301, 398, 399), which would tend to lower vasopressin secretion, yet both plasma and urinary arginine vasopressin are raised (75). This is consistent with a rise in plasma sodium. There are two studies in which the sodium concentration of the blood has been measured in a large number of hypertensives and controls. In one study the sodium concentration distribution curve in the patients with essential hypertension was shifted by ~2 mM towards the higher value (193); in the other study there was a strong positive association between sodium and systolic pressure in the hypertensives and no relationship in the normotensive subjects (385). There is one study in the SHR and WKY rats in which plasma sodium was measured at 1- to 2-h intervals throughout the 24 h (94). Plasma sodium was ~1–3 mmol/kg greater in the SHR than in the WKY rat throughout the 24 h. Overall therefore, acute experimental increases in plasma or CSF sodium concentration >5 mmol/kg can raise the blood pressure, independent of the extracellular fluid volume. The rate of rise in the blood pressure in such experiments is related to the extent of the rise in sodium concentration. It is proposed that with the 1- to 3-mmol/kg rise in sodium concentration that appear to occur in hypertension, the delay is likely to be considerably longer and that such an increase in plasma sodium not only tends to increase the extracellular fluid volume but may itself be a primary factor in the pressor effect of dietary salt (78).

C. Genetic Aspects of Renal Salt Handling

With the use of association or linkage studies and positional cloning during the last decade, over 20 genes associated with essential hypertension or responsible for rare Mendelian diseases with high or low blood pressure have been identified in humans to date (213). Remarkably, most of these genes encode proteins that either mediate or are involved in the control of renal sodium handling, i.e., ion channels and transporters or regulatory pathways that control their activity (Fig. 4). Moreover, it appears from these studies that mutations increasing renal sodium reabsorption raise blood pressure, whereas those diminishing sodium reabsorption lower blood pressure. More than 20 genome-wide searches for genes regulating blood pressure have also been reported (239). Quantitative trait loci have been suggested on almost all chromosomes with a poor replication from one study to another. As a result, although several genes encoding proteins that exert a direct or indirect effect on sodium homeostasis are located within the loci that seem the more convincing (1q, 2p, 2q, 4q, 6q, 12q, 17q), no particular common polymorphism or haplotype has been yet characterized by using this approach. Another approach that could help for the identification of the genes involved in the renal response to varied salt intake is the use of microarrays, although the technique is clearly limited by the availability of human samples (22).

Gene targeting experiments in the mouse have confirmed and extended the findings in humans. Over 30 genes have been reported to date, among the few thousands that have been mutated by homologous recombination, for which inactivating or activating mutations trigger a chronic change of blood pressure in adult mice (243). The vast majority of these genes encode for renal ion channels and transporters or for components of hor-

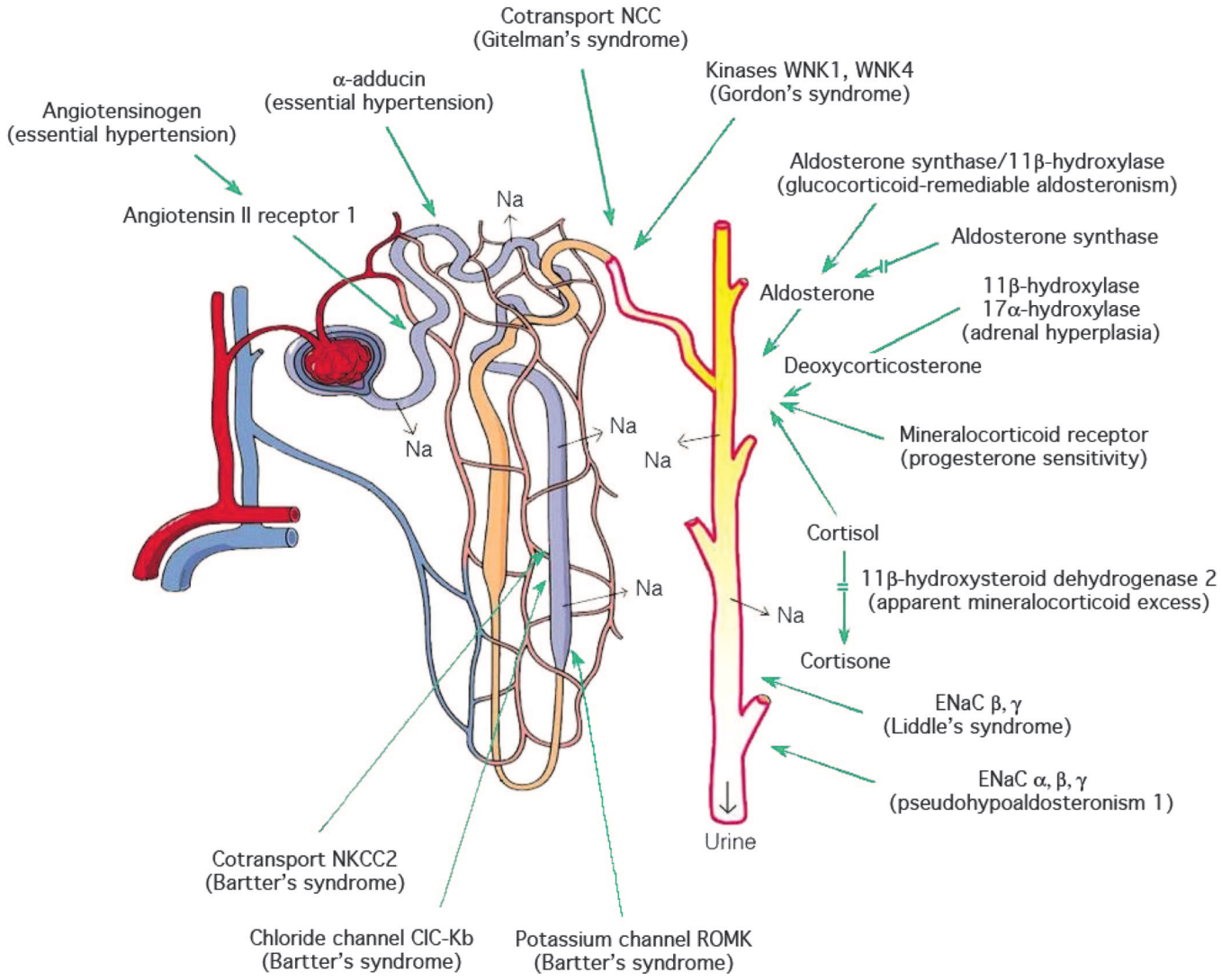

FIG. 4. Mutations and polymorphisms altering blood pressure levels in humans. They have been identified in rare Mendelian forms of hypertension or hypotension or have been linked to essential hypertension. Most of them are present in genes involved directly or indirectly in renal sodium handling, i.e., genes coding for tubular sodium transport systems or for proteins belonging to regulatory pathways. [Adapted from Lifton et al. (213).]

monal or paracrine systems that are known to participate in the regulation of renal sodium reabsorption. All the genes described as being involved in blood pressure control in humans are also found to regulate blood pressure in mice, indicating the high evolutionary conservation of the underlying molecular mechanisms. Like in humans, blood pressure levels appear to not be determined by the preponderant action of a few genes but rather by a large number of genes each having a relatively small effect. Overall, the currently available genetic data in humans and mice strongly reinforce the concept that regulation of extracellular fluid volume by the kidneys is the major blood pressure control mechanism in the long term and stress the crucial role of tubular sodium transport in this process (133).

1. α-Adducin

Adducin is a cytoskeletal protein interacting with the inner face of the plasma membrane that could modulate the activity of sodium transport systems like the Na^+-K^+-ATPase in the tubular renal cells (373). Several concordant studies have established a relation between the gene encoding the adducin α-subunit and salt sensitivity and blood pressure, even though its effect is probably mild at the population level (32). In a study involving French and Italian hypertensive sib pairs, significant linkage was found between several markers surrounding the α-adducin locus and essential hypertension (49). A positive association was found when the genotype frequencies of the G460W polymorphism of the α-adducin gene were com-

pared in 190 hypertensive patients and 126 controls. This effect may be due to epistatic interactions with other loci, especially the angiotensin I converting enzyme I/D polymorphism (346). The blood pressure response to the chronic administration of hydrochlorothiazide was also significantly more important in subjects bearing the 460W allele, suggesting that this variant could predispose to salt sensitivity and to hypertension (49). A better response to hydrochlorothiazide in subjects bearing the α-adducin 460W allele, as well as a significant cardiovascular benefit, was suggested by the retrospective analysis of a large cohort (287). The association of the 460W allele with low-renin status was recently confirmed in a multicenter international study investigating intermediate phenotypes in hypertension (124). Moreover, in this study, the systolic blood pressure response to changes in dietary sodium was significantly greater in subjects homozygous for the 460W allele (25 $\pm$ 4 mmHg) compared with subjects heterozygous for 460W (12 $\pm$ 2 mmHg) or homozygous for the 460G allele (14 $\pm$ 1 mmHg). It is interesting to note that one (2p14) of the six chromosomal regions significantly linked to blood pressure in the HERITAGE Family Study contains the β-adducin gene (291) that has been shown to be a modulator of a missense mutation in the α-adducin gene (412). Homozygous β-adducin-deficient mice have been generated. They display a sharp decrease of α-adducin and a lesser reduction in γ-adducin levels and have higher systolic blood pressure, diastolic pressure, and pulse pressure compared with wild-type controls (236). In the Milan hypertensive rat strain, there is an increase in Na^+-K^+-ATPase activity which may be related to an abnormality of the adducin gene (35). In the same strain, Bianchi et al. (34) found a mutation in two of the genes that code for adducin. The interaction of these missense mutations could explain up to 50% of blood pressure differences between the Milan hypertensive and its normotensive control. Adducin is involved in the assembly of actin and inactin and actin binding proteins, which are coupled to a variety of transmembrane proteins including most ion transport molecules in epithelial cells. One such coupling is to the Na^+-K^+-ATPase α_1-catalytic subunit. Interestingly, the activity of the enzyme in 5- to 8-wk-old SHR is significantly higher in dissected proximal tubules but significantly lower in the thick ascending limb of the loop of Henle than in the WKY rat, although these differences are no longer present at 20 wk (110). Gurich and Beach (131) have also demonstrated an abnormality in G protein control of Na^+-K^+-ATPase in suspensions of SHR renal proximal tubules and suggest that this could increase sodium reabsorption. In the Dahl salt-sensitive hypertensive male rat, there is a functional mutation of the α_1 Na^+-K^+-ATPase subunit in the form of a leucine substitution for glutamine leading to a 3:1 sodium-potassium transport ratio instead of the normal 3:2 ratio in the normotensive salt-resistant rat (154). This change would lead to an excess of sodium ions reabsorbed by the tubule for each potassium ion transported.

2. Epithelial sodium channel

The amiloride-sensitive epithelial sodium channel (ENaC) is the rate-limiting step of salt reabsorption in the terminal part of the nephron. The three genes encoding the α-, β- and γ-ENaC subunits have been found to harbor mutations or polymorphisms related to gain or loss of function of the channel, increased or decreased sodium reabsorption in the terminal part of the nephron, and high or low blood pressure. Gain of function mutations have been found in β- and γ-subunits and are associated with a rare clinical phenotype of low renin form of dominant hypertension with suppressed aldosterone secretion (known as Liddle's syndrome) in which the severity of hypertension is worsened by high salt intake and improved by salt restriction or by amiloride treatment alone (210). These mutations have been described originally as truncations or frame-shifts deleting a critical proline-rich region of the cytosolic tail that interacts with a regulatory protein called Nedd4 (2) and later as missense mutations of critical amino acids in this proline-rich region (138). Truncations as well as missense and splice-site mutations in any of the three genes encoding ENaC subunits that result in a loss of function of the channel provoke pseudohypoaldosteronism type I, an inherited and recessive hypotensive disorder characterized by salt wasting, elevated plasma renin activity, and aldosterone level and unresponsiveness to mineralocorticoids (51, 352). The presence of gain or loss of function mutations in the genes coding for the ENaC subunits suggests the possibility of the existence of more subtle polymorphisms in these genes that might modify ENaC activity, especially in salt-sensitive patients. Several groups have screened for mutations in the genes encoding β- and γ-ENaC subunits among patients with essential hypertension in various ethnic populations. In a series of more than 400 hypertensive subjects, seven missense mutations were found in the gene coding for the β-ENaC subunit, almost all of them in patients of African descent (277). Whereas these variants led to no significant increase in sodium current after expression in *Xenopus* oocytes, data obtained in human B lymphocytes (354) suggest that at least one of them (T594M) could have an effect on sodium reabsorption. In a case-control study involving black residents in London, a significant increase of the 594M frequency was found in the 206 hypertensive patients (8.3%) compared with the normotensive subjects (2.1%), the statistical significance persisting after adjustment for sex and body mass index (18). In the subset of patients in whom plasma renin activity was measured, the T594M polymorphism was also associated with a low renin profile, suggesting that it could raise blood pressure in affected people by increas-

ing renal tubular sodium reabsorption. The association between this polymorphism and blood pressure was not replicated in a case-control study performed in 519 hypertensive patients and 514 normotensive individuals of African ancestry (262). Several polymorphisms have also been detected in the γ-ENaC subunit. Four neutral polymorphisms have been found in the third exon of the gene (T387C, T474C, C549T) and in the last exon (C1990G), but they had similar frequencies in 453 hypertensive and 245 normotensive Caucasian subjects as well as in patients with low-renin profile (278). All these polymorphisms in the genes encoding β- and γ-ENaC subunits have not been shown to have a demonstrable effect in the in vitro expression systems used to examine ENaC activity (277, 278). Polymorphisms in the promoter region of the γ-ENaC gene have also been identified, one of them G(−173)A is associated with enhanced in vitro promoter activities and blood pressure in a large Japanese cohort (168). It remains therefore possible that some of the ENaC polymorphisms might be associated with higher ENaC activity in vivo and contribute to ethnic differences in sodium retention and the subsequent risk of developing low renin hypertension (10, 286). It is worth noting that a sib pair linkage study performed on 286 white families from the general population in Australia showed significant linkage between systolic blood pressure and microsatellites at chromosome 16p12, located in the vicinity of the genes encoding the β- and γ-subunits of ENaC (404). The analysis of the α-ENaC subunit in Caucasian hypertensive subjects showed an interesting missense polymorphism (W493R) located in the extracellular loop of the subunit and in a rather well-conserved sequence not far from the amino acids responsible for the sensitivity to amiloride. However, in Caucasians, this polymorphism was found at similar allele frequency in hypertensive and normotensive individuals and did not change the amiloride-sensitive current when expressed in *Xenopus* oocytes (64). Another common coding polymorphism in the α-ENaC gene (T663A) has been described, but conflicting results have been reported concerning its association with essential hypertension (10, 355). The expression of T663A in oocytes has been associated with higher currents and higher levels of cell surface expression of ENaC, suggesting that it might affect channel trafficking (310). Other polymorphisms in the α-ENaC promoter region have been identified and studied, especially in a Japanese population (169). One of them (G2139A) has been suggested to be associated with higher in vitro promoter activities and with blood pressure levels. Other noncoding polymorphisms have been described on each ENaC subunit. Most of them have not been convincingly linked to hypertension or to salt sensitivity (281). The truncation of the β-subunit found in the original Liddle pedigree was reproduced in the mouse using gene targeting and Cre/loxP techniques (285). Under normal salt diet, these mice have a blood pressure not different from wild-type mice despite evidence for chronic hypervolemia such as increased sodium reabsorption in distal colon and low plasma aldosterone. Under high-salt diet, the mice develop hypokalemic metabolic alkalosis, high blood pressure, and cardiac hypertrophy, thus reproducing to a large extent the human syndrome. A mouse model for pseudohypoaldosteronism type 1 has also been generated by disrupting the gene encoding the β-subunit (284). On a normal salt intake, β-subunit-deficient mice exhibit elevated plasma aldosterone level and compensated metabolic acidosis compared with wild-type mice, but no change in blood pressure. When fed a low-salt diet, these mice develop features of an acute pseudohypoaldosteronism type 1 with weight loss, salt wasting in the urine, hyperkalemia, and decreased blood pressure, and they are unable to survive more than a few weeks after the dietary switch. Interestingly, the α-subunit has been specifically inactivated in the collecting duct leaving intact ENaC expression in the late distal convoluted tubule and connecting tubule (303). In these conditions, the animals survive well and are able to maintain sodium and potassium balance, even when challenged by salt restriction, water deprivation, or potassium loading. This shows that the expression of ENaC in the collecting duct is not necessary for achieving sodium and potassium balance in mice and that more proximal ENaC containing segments (late distal convoluted tubule and connecting tubule) are probably more important for maintaining the balance. This point is coherent with the regulation of the distribution pattern of ENaC in the late portion of the distal convoluted tubule down to the medullary collecting duct in response to variations in dietary salt intake. Indeed, when mice are fed a low-salt diet in the physiological range, the translocation of the β- and γ-subunits from intracellular membranous dispersed sites to the apical plasma membrane takes place mainly in the late part of the distal convoluted tubule and in the connecting tubule, the collecting duct being practically not affected (216).

3. Aldosterone synthesis and signaling

Mutations in several enzymes involved in the synthesis of aldosterone or other steroids that activate the mineralocorticoid receptor have been identified. Glucocorticoid remediable aldosteronism has been shown to result from a chimera gene placing the aldosterone synthase (CYP11B2, the rate-limiting enzyme for aldosterone biosynthesis in adrenal glomerulosa) under the control of an adrenocorticotropic hormone-dependent promoter (212). As a consequence, adrenocorticotropic hormone-regulated CYP11B2 is aberrantly expressed in the adrenal fasciculata where it continuously produces aldosterone, resulting in salt retention and hypertension with suppressed secretion of renin. Inactivating mutations of

CYP11B2 lead to impaired aldosterone biosynthesis with salt wasting and hypotension (247, 271). The gene encoding CYP11B2 is located on chromosome 8q in a region that has shown suggestive evidence for linkage with systolic blood pressure in the Quebec Family Study (292). It has been tested for its possible association with essential hypertension (42, 74, 192) and primary aldosteronism (252). A polymorphism (C344T) in the promoter region of the gene, located in a binding site for the steroid synthesis promoting transcription factor SF-1, could modulate the expression of the gene. Indeed, although angiotensin II and potassium utilize a CRE-like *cis*-element and a different SF-1 binding site to regulate the expression of the gene in vitro (58), the C344T polymorphism has been associated with variations in plasma aldosterone (42, 141) or in the plasma aldosterone-to-renin ratio (73), suggesting that it could favor sodium retention and high blood pressure. However, contradictory results have been obtained according to the populations and the biochemical and clinical parameters studied (60, 142, 198, 325, 364). Several mutations in the mineralocorticoid receptor have been described. Truncations and frame-shift mutations resulting in a partial loss of function of the receptor are responsible for the autosomal dominant form of pseudohypoaldosteronism type I (114, 312). Rare missense mutations have also been described in the DNA-binding domain and in the ligand-binding domain of the receptor (311). The partial loss of mineralocorticoid function that impairs renal sodium reabsorption in pseudohypoaldosteronism type I subjects can be corrected by a salt-rich diet that renders the patients asymptomatic with no obvious phenotype. This nutritional adaptation and/or the presence of modifier genes probably explain the large variability of the phenotype within families (293). Unexpectedly, one particular activating mutation of the mineralocorticoid receptor was found in a family with early-onset hypertension that was markedly aggravated during pregnancy (113). This missense mutation (S810L), which occurs in the aldosterone-binding domain of the receptor, leads in fact to a minimal but permanent constitutive activation of the receptor and to a change in the affinity of the receptor for a number of steroids that normally bind, but do not activate, the receptor. This was in particular the case for spironolactone, which is converted into a rather potent agonist, and for progesterone, thus accounting for the remarkably severe presentation of the phenotype during pregnancy (113). Further in vitro studies have shown the strong affinity of cortisone and 11-dehydrocorticosterone for the L810 mutant receptor, suggesting that hypertension occurring in men and nonpregnant women is likely cortisone related (289). This mutation, however, seems rare as it was not found in a series of 400 women with pregnancy-induced hypertension. The 11β-hydroxysteroid dehydrogenase type II (11β-HSD2) ensures the specificity of in vivo mineralocorticoid receptor activation by aldosterone by metabolizing the excess of cortisol to cortisone. Inactivating mutations of the 11β-HSD2 are responsible of the apparent mineralocorticoid excess, a rare recessive but severe form of hypertension (109, 254, 349). Mutations in the 11β-HSD2 gene affect the activity of the enzyme and thereby lead to increased renal concentrations of cortisol and corticosterone that are powerful agonists of the mineralocorticoid receptor in contrast to cortisone. Thus affected patients are characterized by high values of the cortisol-to-cortisone ratio in plasma and urine and by arterial hypertension, mimicking a primary aldosteronism or a Liddle's syndrome (348). Compared with this condition in which aldosterone and renin are at very low or undetectable levels, apparent mineralocorticoid excess subjects are usually diagnosed in primary infancy with more severe hypertension and more severe hypokalemia (403). However, missense mutations with milder effects have been described in the 11β-HSD2 gene, which result in mild low renin form of hypertension (201, 402). The prevalence of apparent mineralocorticoid excess is low but could be more frequent in some consanguineous populations (209, 288). Salt-sensitive hypertension has been associated with reduced 11β-HSD2 activity (100, 222). The activity of the enzyme, assessed by the urinary ratio of cortisol to cortisone metabolites, was associated in normotensive men with an *Alu* I polymorphism in exon 3, and blood pressure changes to salt maneuvers were associated with a polymorphic microsatellite marker located in intron 1 of the gene. In Italian hypertensive subjects, the shorter CA repeat length was associated with increased changes in blood pressure following a rapid intravenous saline infusion and subsequent furosemide-induced diuresis (3). However, despite its location on chromosome 16q, a region that has been linked to essential hypertension, there is no strong argument in the literature to relate polymorphisms of the 11β-HSD2 gene and blood pressure in the general population. In particular, Brand et al. (43) showed no linkage between hypertension and the 11β-HSD2 locus in 347 sibling pairs. A single polymorphism (G534A) was identified in exon 3, which did not change the encoded amino acid sequence. The same authors also conducted a case-control study on 370 hypertensive subjects with a positive family history of hypertension and 783 French subjects with hypertension with or without a family history of hypertension, compared with 313 normotensive control subjects (43). No positive association with hypertension was found with the G534A polymorphism, suggesting that this gene does not contribute substantially to essential hypertension in Caucasians. Inherited deficiencies of the enzymes involved in cortisol synthesis such as the 11β-hydroxylase and 17α-hydroxylase trigger an overproduction of 21-hydroxylated steroids (deoxycorticosterone and corticosterone) that are potent activators of the mineralocorticoid receptor, with consequent hypertension (180, 395). Two

mouse models have been generated with targeted mutations of aldosterone synthesis and signaling pathways. Mineralocorticoid receptor-deficient mice die in the second week after birth, showing symptoms of pseudohypoaldosteronism with hyponatremia, hyperkalemia, high renal salt wasting, and a strongly activated renin-angiotensin-aldosterone system. The activity of ENaC is strongly reduced in colon and kidneys. Daily subcutaneous injections of isotonic salt solution until weaning and continued oral NaCl supply lead to survival of the homozygous mice. The salt-rescued mice display almost no renal ENaC activity, a strongly enhanced fractional renal excretion of sodium, hyperkalemia, and a persistently strongly activated renin-angiotensin-aldosterone system (29). Homozygous 11β-HSD2-deficient mice appear normal at birth, although approximately one-half of them show motor weakness and die within 48 h. Survivors are markedly hypertensive and exhibit hypokalemia, hypotonic polyuria, and apparent mineralocorticoid activity of corticosterone. The epithelium of the distal parts of the nephron shows striking hypertrophy and hyperplasia that do not readily reverse with mineralocorticoid receptor antagonism. Thus 11β-HSD2-deficient mice display a phenotype directly comparable to the syndrome of apparent mineralocorticoid excess in humans with inactivating mutations of the 11β-HSD2 gene (194). In addition, these mice have an endothelial dysfunction, demonstrated by enhanced norepinephrine-mediated contraction of thoracic aortic rings, that may also contribute to hypertension (137).

4. Aldosterone-induced and ENaC interacting proteins

The serine/threonine serum and glucocorticoid-regulated kinase (SGK1) mediates in part the effects of aldosterone and other hormonal (insulin) and nonhormonal regulators (osmolarity) on sodium transport in the colon and distal nephron. In particular, aldosterone-activated mineralocorticoid receptor induces the synthesis of SGK1 that in turn modulates the activity of channels such as ENaC (272). In a recent study that involved monozygotic (126 pairs) and dizygotic (70 pairs) normotensive twins and their parents, a significant linkage of the SGK1 gene locus to diastolic blood pressure ($P < 0.0002$) and a suggestive evidence for linkage for systolic blood pressure ($P < 0.04$) were found (46). Two single nucleotide polymorphisms at the SGK1 gene were also associated with blood pressure levels, an effect confirmed in an independent sample of 260 young normotensive men (46). The regulation of ENaC activity also involves the ubiquitin-protein ligase called Nedd4–2 (neural precursor cell-expressed, developmentally downregulated gene 4 isoform 2), which negatively controls the expression of the channel at the cell surface (182). Its central importance is suggested by the gain-of-function mutations observed in Liddle's syndrome, that all disturb the interaction between the COOH-terminal PY motif of either β- or γ-ENaC subunits and Nedd4–2, although this interaction has been demonstrated in heterologous expression systems (oocytes mainly) and not in the native distal nephron (347). Another argument comes from the location of the Nedd4–2 gene on chromosome 18q21 (53) in a region of linkage with essential hypertension (15, 196) and with an autosomal dominant orthostatic hypotensive disorder (81). In a systematic screening of the genomic sequence of the human Nedd4–2 gene, Foulakdou et al. (105) found a rare (2 cases out of 852 hypertensive subjects) genetic variant in exon 15 (105). This missense mutation (P355L) modifies the capability of the protein to be phosphorylated by SGK1 and therefore is expected to display weaker interaction with ENaC. Even though the two patients had end-stage renal disease, no further argument allowed for the speculation on its possible pathogenic role. In animals, homozygous SGK1-deficient mice display renal water and electrolyte excretion indistinguishable from that of wild-type mice on a standard salt intake. However, dietary salt restriction reveals an impaired ability of these mice to adequately decrease sodium excretion despite increases in plasma aldosterone levels and proximal tubular sodium and fluid reabsorption and decreases in blood pressure and glomerular filtration rate (407).

5. Sodium-chloride cotransport

Gitelman's syndrome, a rare disorder characterized by mild volume depletion, hypotension, and activation of the renin-angiotensin-aldosterone axis together with hypokalemia, hypomagnesemia, and hypocalciuria has been associated with loss of function mutations of the gene encoding sodium-chloride cotransport (NCC) (206, 338). A number of inactivating mutations have now been identified, including truncations and missense mutations. Most appear to involve the intracellular and COOH-terminal domain of NCC and cause in vitro decreased functional expression with processing disturbances in delivering the matured protein to the cell surface (197, 205). By studying a large Amish kindred with Gitelman's syndrome, the NCC genotype was found to be a significant predictor of blood pressure levels, with homozygous mutant family members having significantly lower age- and gender-adjusted systolic and diastolic blood pressures than those of their wild-type relatives. Moreover, both homozygous and heterozygous subjects had significantly higher 24-h urinary sodium output than did wild-type subjects, presumably due to the defective sodium reabsorption in the distal convoluted segment of the nephron where the transporter is expressed, and reflecting a self-selected higher salt intake (66). A series of polymorphisms has been identified in the NCC gene of hypertensive patients and compared with normotensive people

and patients with Gitelman's syndrome. One of these polymorphisms was overrepresented in the homozygous state in the hypertensive subjects compared with controls, suggesting that it may functionally activate NCC and be causally related to or at least increase the risk of developing hypertension (240). Homozygous NCC-deficient mouse strain with a phenotype similar to Gitelman's syndrome have been generated (324). These mice exhibit low rates of urinary calcium excretion and low plasma magnesium concentrations together with some evidence of salt wasting (increased plasma aldosterone) and compensated metabolic alkalosis (increased plasma bicarbonate) (260). Immunocytochemistry studies show that the initial part of the distal convoluted tubule is completely missing in the NCC-deficient mice so that the cortical thick ascending limb characterized by the expression of the sodium-potassium-chloride cotransport NKCC2 is directly in continuity with the late distal convoluted tubule that expresses ENaC (217). Given that NCC normally reabsorbs ~7% of the filtered sodium load along the distal convoluted tubule, the loss of function of the transporter significantly increases sodium delivery to the connecting tubule and collecting duct. As expected according to the increased plasma aldosterone, the amount of ENaC is upregulated in the apical membrane of principal cells along the connecting tubule for increasing sodium reabsorption (217). This compensatory phenomenon is not observed in the collecting duct, suggesting that the increased ENaC-mediated sodium reabsorption in the connecting tubule is sufficient to compensate for NCC inactivation when the mice are fed a normal salt diet (242). These adaptations in the connecting tubule are efficient enough to allow the mice to survive indefinitely on a low-salt diet, and they probably also explain why the renin-angiotensin-aldosterone system is not strongly activated in NCC-deficient mice.

6. With no lysine (WNK) serine-threonine kinases

Activating mutations in two isoforms of the WNK kinase family (WNK1 and WNK4) expressed in the distal part of the nephron have been found in people with Gordon's syndrome (400). This syndrome, also called pseudohypoaldosteronism type II, is a rare Mendelian form of hypertension associating hyperkalemia, low renin, and aldosterone plasma levels and a high sensitivity to small doses of thiazide diuretics that specifically inhibit the NCC transporter (120). The two mutated kinases localize either in the cytoplasmic compartment (WNK1) or in the tight junctions (WNK4) of the tubular cells where they probably contribute to an increased sodium reabsorption by a mechanism that might involve an upregulation of the NCC transporter (401, 411). Interestingly, the WNK4 gene is located in a chromosomal region (17q12–21) that has been linked to blood pressure by several genome scans. This is the case for the study involving French hypertensive sib pairs, French diabetic sib pairs with hypertension, and English families that found significant linkage and association using markers of this region of chromosome 17 (179). The genome-wide scan performed on 1,702 subjects from 332 families selected from the Framingham survey was even more convincing (207). When systolic blood pressure averaged on a 10-yr period and adjusted for age and body mass index was used as a trait, several regions of linkage were found on chromosomes 5, 10, and 17. Two regions were suggested on chromosome 17, with the one located on 17q12–21 giving the most promising multipoint lod score (4.7). The first results, however, do not suggest a significant association between polymorphisms in the WNK4 gene and essential hypertension (342). Several other candidate genes are located within this region, among them those coding for the angiotensin I converting enzyme and the growth hormones, the carbonic anhydrase IV, the isoform 1 of the chloride-bicarbonate exchanger, and the phenylethanolamine *N*-methyltransferase.

7. Sodium-potassium-chloride cotransport (NKCC2), potassium (ROMK1) and chloride (ClC-Kb) channels

Loss of function mutations in NKCC2, ROMK1, and ClC-Kb have been associated with Bartter's syndrome (335–337), a rare clinical disorder characterized by severe salt wasting and low blood pressure despite elevated plasma renin activity and aldosterone concentration (23). These three genes are all expressed in the thick ascending limb of Henle's loop where they are involved either directly (NKCC2) or indirectly (ROMK1 and ClC-Kb) in sodium reabsorption. It is interesting to observe that despite aldosterone-dependent compensatory mechanisms involving NCC and ENaC and taking place in downstream nephron segments, the salt wasting and hypotension are somewhat more marked in Bartter's syndrome than in Gitelman's syndrome and pseudohypoaldosteronism type I. Recently, a common missense mutation (T481S) has been identified in the human ClC-Kb gene (171). After heterologous transfection of this variant in *Xenopus* oocytes, a strong activation of the chloride current (20-fold increase) was demonstrated. In a following study, the same authors analyzed the prevalence of the mutation and its functional significance in blood pressure regulation (172). The prevalence of the mutation was significantly higher in African than European subjects (22 vs. 12%) and was significantly associated with hypertension. Homozygous NKCC2-deficient mice have many similarities to patients with Bartter's syndrome. These mice display signs of dehydration (increased hematocrit) as early as 1 day after birth. They fail to thrive and usually die before weaning. After 1 wk, they exhibit hyperkalemic metabolic

acidosis, hydronephrosis, and an upregulation of the renin-angiotensin system as observed in some human perinatal cases of Bartter's syndrome. When treated with indomethacin, some mice can survive to the adult stage but then exhibit severe polyuria and hydronephrosis, hypokalemic metabolic alkalosis, and hypercalciuria (361). In addition, they are hypotensive on a normal-salt diet and do not survive on a low-salt diet. Thus the absence of NKCC2 in homozygous mutant mice causes polyuria and low blood pressure that cannot be compensated elsewhere along the nephron. In contrast, heterozygous mutant mice can compensate entirely for the loss of one copy of the gene and the resulting 50% reduction in renal mRNA expression of NKCC2, apparently by restoring the protein level to near normal in the apical membrane; they are identical to wild-type mice considering blood pressure, blood gas, electrolytes, creatinine, plasma renin concentration, urine volume and osmolality, ability to concentrate and dilute urine, and response to furosemide (360). Homozygous ROMK1-deficient mice also develop hydronephrosis and are severely dehydrated; most of them die before 3 wk of age. The mice that survived beyond weaning grow to adulthood and show features of Bartter's syndrome such as metabolic acidosis, elevated blood concentrations of sodium and chloride, reduced blood pressure, polydipsia, polyuria, and poor urinary concentrating ability. Whole kidney GFR is sharply reduced, apparently as a result of hydronephrosis, and fractional excretion of electrolytes is elevated. Single-nephron GFR is relatively normal, absorption of sodium in the thick ascending limb of Henle's loop is reduced but not eliminated, and tubuloglomerular feedback is severely impaired (219).

8. Sodium/proton exchanger 3 (NHE3)

Most of the filtered sodium load is reabsorbed in the proximal convoluted tubule, and mutations or polymorphisms in genes encoding proximal sodium transport systems may significantly alter extracellular fluid volume and blood pressure. Although such mutation or polymorphism has not been described to date in humans, some evidence of a possible relationship between proximal sodium reabsorption and blood pressure sensitivity to dietary salt intake has been reported (56, 84). The sodium/proton exchanger activity is raised in erythrocytes and lymphocytes in ~50% of patients with essential hypertension (118, 326, 388). The cause of the increased sodium/proton exchanger activity in essential hypertension has not been linked to a genetic abnormality (214), nor does it appear to be due to some generalized metabolic disturbance, for an increase in sodium/proton exchanger activity has been found in immortalized lymphoblasts from some hypertensive patients (333). It has been suggested that the enhanced sodium/proton exchanger activity in primary hypertension would be best explained by altered intracellular regulation secondary to some other intracellular disturbance (333). In the kidney, apical membrane vesicles from young prehypertensive Milan hypertensive rats and SHR demonstrate an increased sodium uptake via sodium/proton exchange (208, 249, 270). It is also relevant that transgenic mice overexpressing the sodium/proton exchanger, including in their renal tubules, become transiently hypertensive during salt loading (199). These mutant mice have a reduced fractional excretion of sodium excretion, plasma renin activity, and aldosterone. A mouse model with a targeted disruption of the NHE3 gene directly shows the importance of proximal sodium reabsorption in the long-term control of blood pressure. On a normal salt diet, NHE3-deficient mice are hypotensive, hyperkalemic, and acidotic (323). The large reduction of fluid reabsorption in the proximal convoluted tubule overloads downstream segments of the nephron, which develop compensatory responses to increase distal sodium and bicarbonate reabsorption (384). Thus, in parallel to a strong activation of the renin-angiotensin-aldosterone system, ENaC γ-subunit abundance is higher in the kidneys of these mice (44). But the main renal compensatory mechanism seems to be the decrease in single-nephron GFR, which is mediated in part by the activation of the tubuloglomerular feedback system (221, 405). Nevertheless, these adaptive processes are insufficient to fully compensate for the large reduction of proximal sodium reabsorption, and NHE3-deficient mice display significant urinary salt wasting and cannot survive on a low-salt diet (204). It can be also mentioned that in contrast to NCC and NKCC2, which are specifically expressed in the kidneys, NHE3 is strongly expressed along the intestine where the exchanger normally mediates sodium and bicarbonate reabsorption in parallel with the apical chloride/bicarbonate exchanger (329). It is therefore not surprising that NHE3-deficient mice have intestinal defects resulting in diarrhea and marked increase in the volume content of the distal segments of the intestine despite the presence of a number of compensatory mechanisms occurring to limit fluid wasting in the feces (323). For example, mRNAs encoding ENaC β- and γ-subunits are upregulated, and transepithelial amiloride-sensitive sodium current is sharply increased in the distal colon in parallel to the very high plasma aldosterone level. Of some interest, it is also interesting to mention the sodium/bicarbonate transporter SLC4A5 as a possible candidate gene for hypertension (317). In the Family Blood Pressure Program, it was one of the eight candidate genes lying in the interval on chromosome 2 that consistently displayed linkage with blood pressure (21). A total of 82 SNPs within the 8 positional candidates were genotyped in 4,595 individuals from African, white, and Mexican American sib-ships. SLC4A5 was the only gene that maintained statistical significance after multiple comparisons adjustment, especially in the African American sib-ships. Fur-

ther characterization of the function of this gene is necessary to understand the possible mechanisms by which it may influence blood pressure regulation.

9. Renin-angiotensin system

Angiotensinogen (AGT) is mainly synthesized in the liver and is the unique known substrate for renin. Plasma AGT concentration is within a range where its variations directly affect the angiotensin I production rate. Indeed, plasma AGT levels are around the K_m of renin and, therefore, it is logical to suspect that a chronic state of increased plasma AGT might increase angiotensin I and facilitate hypertension and/or cardiovascular diseases. The role of AGT in human hypertension has been suspected in an epidemiological study where a strong correlation was found between plasma AGT concentration and blood pressure (383) and in an older study that described elevated plasma AGT levels in the offspring of hypertensive patients (95). The first molecular insights suggesting a role of the AGT gene in essential hypertension came from the testing of a highly polymorphic microsatellite marker in 379 sib pairs, which showed an excess of AGT allele sharing in severely hypertensive sib pairs and in men (175). Other linkage studies have since been reported with controversial results (173). Altogether, these results probably highlight the modest effect of the AGT locus in the overall population and the difficulty of identifying susceptibility genes by linkage analysis in complex diseases. Among the 15 polymorphisms initially identified, two of them leading to amino acid changes, T174M and M235T, were found to be associated with hypertension and with plasma AGT concentration (175). This association between plasma AGT level and the M235T genotype was further confirmed in white children (40). In this study, a strong and independent relationship of serum AGT with body mass index and race was also observed. The threonine residue at position 235 is in complete linkage disequilibrium with another nucleotide substitution (G->A) at position −6 in the promoter of the gene, both alleles being indistinguishable (174). This variant is associated in vitro with an increased expression of the AGT gene and probably explains the association with increased plasma AGT (163). However, the true biological effect may be more complex since other polymorphisms, C-532T, C-18T, A-20C, and T+31C, are also in linkage disequilibrium with G-6A and M235T and might play a role in the variation of transcription of the gene (166, 170, 269, 318). Recent data suggest that the AGT genotype, in addition to identifying individuals likely to have or to develop hypertension, also influences the blood pressure response to nonpharmacological therapy. In the Trials of Hypertension Prevention Phase II (TOHP-II), both sodium reduction and weight loss were tested in a randomized trial as blood pressure-lowering strategies (366). Participants were typed for the G-6A polymorphism. As only 3% of African-American participants had the GG genotype, the genetic association analysis was performed in Caucasians only. In the usual care group, the AA genotype was associated with a higher 3-year incidence of hypertension compared with GA or GG genotypes. In the salt reduction and weight loss intervention groups, this AA genotype was also associated with a larger reduction in blood pressure compared with GA and GG genotypes (161). The same polymorphism G-6A was tested with the blood pressure response to the DASH diet, which is another dietary approach that lowers blood pressure (13). After 8 wk, net systolic and diastolic blood pressure response to the DASH diet was significantly greatest in individuals with the AA genotype (−6.93/−3.68 mmHg) and less in those with the GG genotype (−2.80/0.20 mmHg). This confirms that AGT is involved in the individual responsiveness to dietary factors, including salt, that influence blood pressure (358). The angiotensin II G-coupled receptor type 1 (AT1R), which mediates most of the effects of the renin-angiotensin system on sodium reabsorption in the proximal nephron and on aldosterone secretion in the adrenals, is an obvious candidate gene for essential hypertension. No mutation in the coding region of the AT1R gene was detected in 60 probands of hypertensive families (41) and in 20 cases of tumoral primary aldosteronism (72). There was also no evidence for linkage between a micro-satellite marker of the AT1R gene and blood pressure in a hypertensive sib-pair study (41). However, an informative diallelic marker A1166C present in the 3′-untranslated region of the AT1R gene was found more frequently in 206 hypertensive subjects than in 298 normotensive controls (41). Other polymorphisms have been described, especially in the promoter region of the AT1R gene, but none of them has shown evidence for an association with hypertension in a large Caucasian population-based sample (413). The AT1R receptor locus has also been linked to blood pressure. A first sib-pair study suggested a linkage with a micro-satellite marker at the AT1R locus and an association with the A1166C polymorphism (181). In the Finnish Twin Cohort Study (273), a limited number of pairs with early-onset phenotype (mean age at discovery 38.3 yr) were studied to diminish the effect of possible confounding factors. Only 47 sib pairs were studied, 36 dizygotic twins and 11 nontwin siblings. Genotyping was deepened in the regions of suggestive linkage with the addition of all available family members of the 47 probands (total of 138 subjects). Despite these relatively small numbers, several regions gave a maximum likelihood score >1.5 (1q, 2q, 22q, and Xp). The most significant result was obtained on chromosome 3q21–25 (maximum likelihood score = 3.38 on the entire sample). This region contains the AT1R gene, and the stronger result was obtained with the intragenic CA repeat at this locus.

An analysis of candidate genes in a German population, using blood pressure as a quantitative trait, has also suggested linkage with the AT1R gene (256). Interestingly, the expression of the AT1R gene is regulated according to salt intake, particularly in the brain, aorta, and kidney (353). An association and linkage were found between blood pressure response to infused angiotensin II and the AT1R locus in a large series of hypertensive siblings on a low-sodium diet (382). The mouse models generated by homologous recombination clearly confirm the involvement of the renin-angiotensin system in the long-term control of blood pressure (132). In particular, mouse strains with one, two, three, or four functional copies of the angiotensinogen gene demonstrate the causal link between angiotensinogen plasma concentration and blood pressure (340). Such a link between the number of functional gene copies and blood pressure is also observed for the angiotensin II receptor type 1 (167, 203). In contrast, the number of functional copies of the angiotensin-converting enzyme gene does not appear to be related to blood pressure, probably due to compensatory changes in angiotensin I levels that keep constant angiotensin II production (195, 362). The role of angiotensin II receptor type 2 (AT2R) remains unclear, although it is possible that this receptor type may have an hypotensive effect antagonist to the hypertensive effect of AT1R as suggested by the observed hypertension in homozygous AT2R-deficient mice (129). Interestingly, compared with wild-type mice, blood pressure of homozygous AT1R-deficient mice is very sensitive to changes in dietary salt intake, whereas the hypertension displayed by homozygous AT2R-deficient mice is not salt sensitive (129, 232).

10. Other regulatory systems

The data obtained in genetically modified mouse strains suggest that several other regulatory systems are directly involved in the long-term control of blood pressure. In particular, the dopaminergic system and the natriuretic systems seem to play a major role in the complex physiological network that has evolved to regulate the urinary excretion of salt, sodium balance, and blood pressure.

Dopamine is an important regulator of renal sodium excretion and is synthesized within the proximal tubule (162). There are five genetically distinct dopamine receptors (D_1-D_5) of which three are expressed in the proximal tubule. The D_1 receptor inhibits the Na^+-K^+-ATPase and sodium/proton exchanger, while the D_2 and D_3 receptors have no effect on the sodium/proton exchanger. Thus activation of the D_1 receptor results in an increase in natriuresis and diuresis and a stimulation of renal renin release. In contrast, inhibition of the D_1 receptor leads to sodium retention and simultaneously produces a low renin state. In hereditary hypertension in humans and the rat, there is a defect in the renal dopamine pathway, which probably contributes to the kidney's impaired ability to excrete sodium, but the elements of the pathway which are abnormal differ. Although basal production of dopamine in essential hypertension is normal, the increase in urinary dopamine that occurs in response to salt loading is attenuated or reversed (57, 140). This abnormal response also occurs in the normotensive relatives of hypertensive patients (309). The fault may be in the tubular uptake of L-DOPA or its subsequent decarboxylation by aromatic amine decarboxylase. The enhanced response of patients with essential hypertension to an exogenous D_{1A} dopamine receptor agonist is consistent with a state of increased receptor activity that could reflect a deficiency of dopamine (155, 330). The effect of D_{1A} receptor loss on blood pressure is evident in heterozygous and homozygous null mice that both develop hypertension (4). The D_3 receptor, which is located in juxtaglomerular cells, also seems to be an important regulator of sodium transport and blood pressure. Homozygous or heterozygous D_3-deficient mice exhibit a decrease in urinary and sodium excretion rate when volume expanded. These mice also have elevated blood pressure and high renin activity, suggesting an inhibitory role of the D_3 receptor on renin release (14). The hypertension in D_3 receptor-deficient mice can be blocked by administration of an angiotensin II receptor type 1 antagonist, further indicating a link between the D_3 receptor and the renin-angiotensin system. Recently, the generation of mice lacking the D_2 receptor has produced evidence for the involvement of this receptor subtype in sodium handling and blood pressure control. A high-salt diet causes a significant increase in systolic blood pressure in homozygous D_2-deficient mice but not in wild-type mice (376). The absence of a functional D_2 receptor is also associated with higher level of sodium retention when the animals are fed a high-salt diet. These results suggest that the D_2 receptor promotes urinary sodium excretion and could participate in sodium-dependent blood pressure elevation. In the SHR, basal urinary dopamine production is normal, but the rise following salt loading is greater in the SHR than in the WKY rat (350). Nevertheless, the SHR is unable to eliminate an acute sodium load as efficiently as the WKY rat, and also exhibits a poor response to exogenous L-DOPA, dopamine, or fenoldam, a D_{1A} receptor agonist (52, 98). The D_{1A} receptor from the proximal collecting duct of the SHR shows structural homology with receptors from the WKY rat, and there is no evidence of defective binding of dopamine to the D_{1A} receptor (191, 332). This suggests that the abnormal dopamine response to salt loading in the SHR may be a posttranslocational modification such as glycooxylation of the D_{1A} receptor or more probably there is a defect distal to the D_{1A} receptor. In both the Dahl salt-sensitive and Dahl salt-resistant rat, salt loading increases urinary dopamine ex-

cretion, and there is also a blunted natriuretic response to exogenous dopamine compared with the Sprague-Dawley rat. In the Dahl salt-sensitive rat, however, the impaired natriuretic response to salt loading is accompanied by evidence of defective coupling between the D_{1A} receptor and adenylcyclase (96, 261). A G protein-coupled receptor kinase, GRK4, has been shown to be a major regulator of dopamine receptors in the kidney (386). Several coding polymorphisms have been identified, that increase the enzyme activity and result in the phosphorylation and uncoupling of the D_1 dopamine receptor from its G protein and effector complexes in the renal proximal tubule (97). In addition, expressing the A142V variant but not the wild-type GRK4 gene in transgenic mice produces hypertension and impairs the diuretic and natriuretic effects of D_1-like agonist stimulation (97). A positive association with essential hypertension justifies further replication and analysis in relation to renal salt handling (341).

Several peptides synthesized in the heart, the gastrointestinal tract, the kidney, and/or the central nervous system induce a natriuretic effect associated with a decrease in blood pressure (104). This is the case for atriopeptin-A (ANP), atriopeptin-B (BNP), and uroguanylin derived, respectively, from the myocardium and the gastrointestinal tract. These peptides are also produced locally in the kidneys where they could participate in intrarenal mechanisms that regulate tubular sodium transport and thus contribute to the natriuresis elicited by high dietary salt intake. Among the three receptor subtypes that implement the effect of atriopeptins, the guanylcyclase natriuretic peptide receptor A (NPRA) seems to be directly involved in blood pressure control. The existence of a linear relationship between the number of functional NPRA gene copies and blood pressure has been demonstrated in mice (264). Homozygous mice lacking atriopeptin-A have slightly increased blood pressure and develop a marked hypertension on an intermediate salt diet, similar to heterozygous null mice on a high-salt diet (176, 241). The targeted disruption of the NPRA gene also leads to the development of hypertension in homozygous null mice, but the elevation of blood pressure is not sensitive to dietary salt intake (218). Recently, homozygous mice lacking uroguanylin have been generated; these mice have an impaired capacity to excrete salt in urine when subjected to oral salt loads and display an increased blood pressure that is independent of the level of dietary salt intake (220). These findings establish the existence of an endocrine axis linking together the gastrointestinal tract and the kidneys via uroguanylin serving as a natriuretic hormone produced by the stomach and/or intestine and released into the circulatory system when excess salt is ingested. Another natriuretic system is based on the γ-melanocyte-stimulating hormone (γ-MSH) produced from proopiomelanocortin (POMC) by prohormone convertase 2 (PC2) in the pituitary gland (160). The synthesis of POMC and PC2 is induced by a high dietary salt intake, thus increasing the release of γ-MSH into the circulation; γ-MSH promotes urinary salt excretion via the melanocortin receptor type 3 (MC3R) expressed in the kidneys. The natriuretic role of γ-MSH has been demonstrated in homozygous mice lacking either PC2 or MC3R, which develop a marked hypertension when fed a high-salt diet (259).

D. Salt Sensitivity

In humans, the response of the blood pressure to an acute change in salt intake, or a diuretic, has been used to determine what is referred to as salt sensitivity. Those individuals in whom a severe abrupt change in salt intake or excretion causes the least change in arterial pressure are termed salt resistant, whereas those in whom these maneuvers induce large changes in blood pressure are referred to as salt sensitive. Various protocols have been used. Weinberger et al. (393) defined sodium sensitivity as a 10 mmHg, or greater, fall in mean blood pressure from the level recorded after a 4-h infusion of 2 liters saline, compared with the level measured after 1 day on a 10 mmol/day sodium diet, during which three oral doses of furosemide are given. Using these criteria, Weinberger et al. (393) found that 51% of hypertensives and 26% of normotensives were sodium sensitive. One difficulty, however, is that in about one-third of subjects, on repetition of the test, salt responsiveness is not reproducible (390). The distribution of salt sensitivity and resistance in normal and hypertensive subjects is bell shaped, and in both the proportion of individuals who become salt sensitive increases with age. Familial resemblance to acute and chronic salt challenges has been reported, but the genetic basis of salt sensitivity, which is likely to be related to the genetics of hypertension, remains poorly known (24, 223). For example, in 44 families of identical twin children who participated in a sodium restriction protocol (less than or equal to 4.3 g/day salt for a period of 12 wk), mother-offspring resemblance in blood pressure change with sodium restriction was significant both for systolic ($r = 0.31$, $P < 0.001$) and diastolic ($r = 0.20$, $P < 0.05$) pressure (244). Sibling-sibling and twin-twin resemblance was also highly significant, thus demonstrating significant familial resemblance in blood pressure change with sodium restriction in normotensive persons. Other studies have been performed in sib pairs but often using acute salt-loading or salt-depleting pharmaceutical maneuvers that might not represent the physiological adaptations to chronic changes in salt intake (392). Salt-sensitive individuals have a variety of other changes including a set which suggests that salt sensitivity may occur particularly in certain individuals who have the highest blood volumes (183). In these subjects basal

plasma renin and aldosterone levels are at the lower level, and sodium retention induces the least renin and aldosterone response (356). Barba et al. (20) found that those individuals whose blood pressure increased the most on a high sodium intake have also the least reduction in fractional proximal sodium reabsorption.

IV. EVOLUTIONARY VIEWPOINT

Observation and intervention studies in humans and animals support the view that the excess of salt in our diet is a major environmental factor participating in the development of hypertension and cardiovascular diseases. This finding is coherent with our knowledge on the environment in which the genetic makeup of terrestrial mammalian species has evolved for dozens of millions of years. The food consumed by terrestrial mammals, including primates, never contained a lot of salt. Indeed, except for rare cases, plants contain only traces of salt, and the consumption of very large amounts of fruits, roots, leaves, or seeds does not bring much salt in the organism. For omnivorous and carnivorous species, the occasional or regular absorption of meat increases salt intake, but in limited proportions because the eaten meat corresponds most often to the sodium-poor intracellular medium and not to the sodium-rich extracellular medium that is generally lost when the animal is killed or cooked. For example, a chimpanzee in Gabon or a Yanomamo Indian in Amazon, who eats almost exclusively plants, ingests 0.06–0.6 g/day salt. The diet of a Bushman in Botswana or of an Eskimo in Alaska, that contains >50% of meat, brings 1–2 g/day salt to the organism (80). It is only during the last 10,000 years that adding large amounts of salt in food became a habit in humans. This dietary change probably started at the beginning of agriculture and farming with the need of preserving food for long periods of time in settled human communities. Nowadays, the average consumption of salt in industrialized countries is ~10 g/day per person as determined by urinary 24-h excretion (89). The average consumption of salt in developing countries is very variable from <1 g in acculturated populations to ~10 g/day per person in urban centers. In these urban centers and in industrialized countries, the average consumption of 10 g hides in fact a large interindividual dispersion from <2 to >20 g salt per day. In parallel to these dietary modifications, our genes have not evolved very much during the last 10,000 yr. We know that, given the low spontaneous mutation rate of nuclear DNA in mammals, no significant accumulation of mutations or polymorphisms can arise in such a short period of time for adapting a species to a new environment. Therefore, we can affirm that our genetic makeup is still adapted to a low salt intake that has been the rule for the dozens million years during which the mammalian evolution took place. During this evolution, the species, including the human species, have accumulated mutations and polymorphisms to survive with a salt-poor diet in an environment where organisms were often exposed to life-threatening dehydrating situations due to temperature-induced sweating and infectious diarrheas. This discrepancy between our genes and our present-time diet would explain the harmful effects of a high-salt diet on the development of hypertension and cardiovascular diseases (87). It is therefore not so surprising that the genes identified in humans and mice as controllers of blood pressure are precisely genes involved in renal sodium handling. Equally revealing are the facts that the mutations increasing renal sodium reabsorption raise blood pressure and conversely those diminishing sodium reabsorption lower blood pressure and that the phenotypic expression of the mutations occurring in these genes is often dependent on the salt intake. These findings definitively establish that renal sodium handling, which physiologically matches variations in dietary sodium intake, is the central mechanism for long-term control of blood pressure in mammalian terrestrial species. They also point to these genes that have accumulated mutations and polymorphisms for adapting the organisms to the low-salt diet during the evolution of terrestrial mammals.

V. CONSEQUENCES FOR PUBLIC HEALTH

From the available data, it appears clearly that there exists a positive relationship between dietary salt intake and blood pressure levels. Because there is an exponential relationship between blood pressure levels and the individual risk of developing cardiovascular diseases such as myocardial infarcts or strokes (230), salt intake should affect the prevalence of cardiovascular diseases (see Fig. 5). This effect can be calculated: a reduction of daily salt intake from 12 to 9 g would translate into a decrease of 16 and 22% in the prevalence of myocardial infarcts and strokes, respectively (202). Several epidemiological, prospective, and intervention studies have assessed directly the relationship between salt intake and cardiovascular diseases. The first insights obtained concerned the strong relationship existing between salt intake and stroke mortality in different populations (Fig. 4*A*). A decade ago, a very significant positive correlation was observed between urinary sodium excretion and death from strokes in 12 European populations that had participated to the INTERSALT study (275). In the same study, multivariate analyses in 25 populations worldwide showed no significant relation between either the systolic or the diastolic pressure and stroke mortality, but there was a significant relationship between stroke mortality and sodium excretion in men and urinary sodium-to-potassium ratio in women (408). Another multiple regression analysis be-

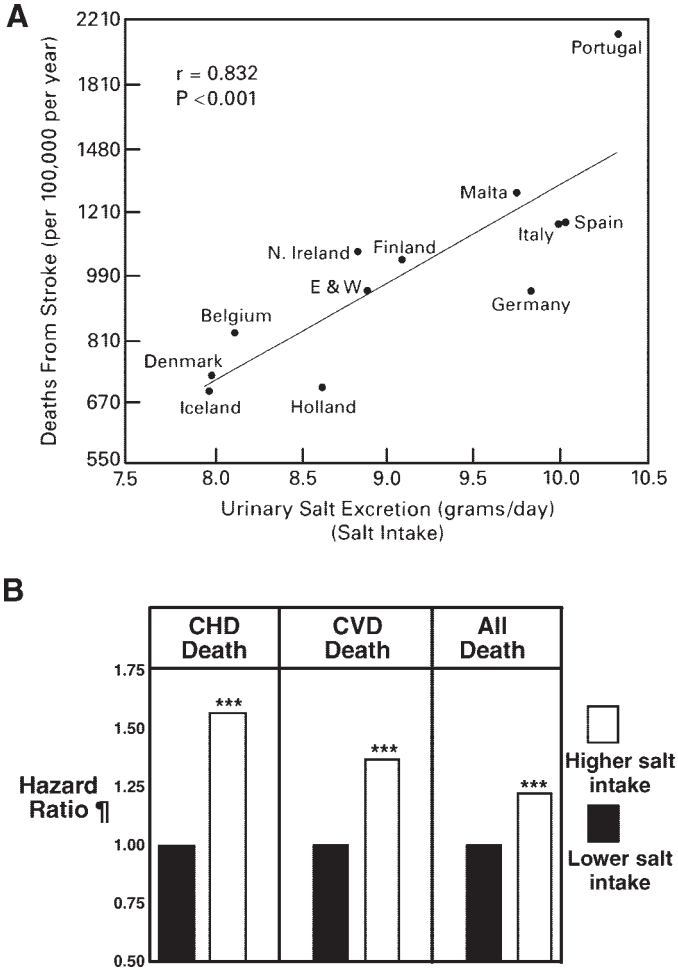

FIG. 5. *A*: relation between urinary sodium excretion and death from stroke in 12 European populations from the Intersalt study. [Adapted from Perry and Beevers (275).] *B*: increased risk of death related to a 6 g/day increase in salt intake (n = 2,436). ***$P < 0.001$ compared with lower salt intake. ¶Adjusted for age, study year, smoking, serum total and high-density lipoprotein cholesterol, systolic blood pressure, and body mass index. [Adapted from Tuomilehto et al. (375).]

tween stroke mortality and dietary variables among 58 populations in 17 countries demonstrated that 24-h urinary sodium excretion was associated independently, significantly, and positively with stroke mortality rates, together with saturated fatty acids and alcohol (316). More recently, an examination of data from the National Health and Nutrition Examination Survey I Epidemiological Follow-up Study (15,000 participants followed in average for 19 yr) found a consistent and positive relationship between dietary sodium intake and risk of cardiovascular diseases and mortality in overweight people (149). A 5.7 g higher daily salt intake was associated with a 32% increase in stroke incidence, a 89% increase in stroke mortality, a 44% increase in coronary heart disease mortality, and a 61% increase in cardiovascular disease mortality in the overweight group (body mass index >27 kg/m^2). Dietary sodium intake was not significantly associated with risk of cardiovascular disease in participants with a normal weight. Another prospective study performed in 29,079 Japanese with the use of a validated food frequency questionnaire reported significant positive associations between sodium intake and death from ischemic stroke (hazard ratio 3.22) and intracerebral hemorrhage (HR 3.85) in men and borderline associations (HR 1.70 and 2.10, respectively) in women (255). More convincingly, because avoiding potential inaccuracy 24-h dietary recall on nutrient intake for estimating the habitual salt intake, a prospective Finnish cohort study conducted in 1,173 men and 1,263 women aged 25–64 yr confirmed these findings (375). The hazard ratios for coronary heart disease and cardiovascular disease mortality associated with a 5.7-g increase in 24-h urinary sodium excretion were 1.51 and 1.45, respectively (Fig. 4*B*). There too, the hazard ratio for cardiovascular disease mortality was 1.23 in normal-weight men while it was 1.44 for overweight men. This suggests that dietary salt increased indeed the risk of subsequent cardiovascular disease, especially in those who are overweight. A direct link between dietary salt reduction and a decrease in the occurrence of cardiovascular events has been observed in the Trial of Nonpharmacological Interventions in the Elderly (TONE). This randomized controlled trial was conducted in 975 hypertensives, aged 60–80 yr, who underwent a reduction of 2.5 g in daily salt intake, a loss of 5 kg in body weight, or both interventions (394). After 29 mo, systolic and diastolic blood pressures were reduced, respectively, by 3.4 and 1.9 mmHg by the reduction in salt intake, 4.0 and 1.1 mmHg by the decrease in body weight, and 5.3 and 3.4 mmHg by the combined interventions. Although the trial was not powered for assessing morbidity and mortality, the percentage of participants exempt of cardiovascular events after 29 mo increased from 24.4 to 37.8% after the reduction in salt intake, 26.2 to 39.2% after the loss in body weight, and 16.3 to 43.6% after the combined interventions. There are two studies published by the same investigative team that have been cited as providing evidence for an inverse relationship between habitual salt intake and myocardial infarction (5, 6). The data on sodium excretion or on sodium intake are however considerably flawed, bringing serious doubts on the validity of these analyses (61, 228). In the first study was reported the presence of a significant inverse association between urinary sodium excretion and incidence of myocardial infarction in a prospective cohort study conducted in 2,937 treated hypertensive patients. But 24-h urine collections were made after 5 days of voluntary salt restriction after patients have been instructed to refrain from habitual salt intake to classify them accordingly to the degree of stimulation of their renin-angiotensin system. In these conditions, the 24-h urinary sodium excretion collections obviously do not reflect the patient's habitual salt intakes. Furthermore, as shown by the creatinine urinary excre-

tion and creatinine clearance, inaccurate urine collections did occur in many that have been included into spurious sodium excretion quartiles and not into true sodium intake quartiles. The second study examined the relationship between dietary sodium intake and mortality from cardiovascular disease in the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study. The investigators found an inverse relationship between sodium intake and mortality from cardiovascular diseases but a positive relationship between sodium-to-calorie ratio and mortality from cardiovascular diseases. Besides not excluding participants with a baseline history of cardiovascular diseases and those who were already on a low-sodium diet due to their health concerns at baseline, they included sodium intake, caloric intake, and sodium-to-calorie ratio as continuous variables in the same multivariate model. Given that an interaction term was included in their analysis model, it is not possible to interpret the main effect of sodium intake alone on the outcomes of interest (151). That could explain the inconsistency of the association between the two indicators of sodium intake (sodium alone and sodium-to-calorie ratio) and mortality from cardiovascular diseases, which may reflect the heterogeneity of the relationship in individuals with different body weights. In addition, measurement of salt intake relying on 24-h dietary recall on nutrient intake is likely to have been partly inaccurate (92, 184). Indeed, the lowest quartile of daily salt intake in both men and women, calorie intake, was 50% lower than the national recommended daily dietary allowance, close to a near-starvation diet. Despite that, women with this extraordinary low calorie intake were on average 4 kg heavier than those in the higher salt intake quartile, who were apparently eating twice as many calories.

In addition to raising blood pressure, dietary salt seems also to have several other damaging effects on the cardiovascular system, which are independent of the raised blood pressure (414). A high dietary intake of salt increases the mass of cardiac left ventricle, thickens and stiffens conduit arteries, narrows resistance arteries including the coronaries and the renal arteries, and increases the sensitivity of platelets to aggregation, all effects that can further increase the cardiovascular risk by themselves. In normotensive subjects cardiac left ventricular mass and diastolic filling are correlated with urinary sodium excretion (86) and in subjects followed up to 8 years the initial left ventricular mass and wall thickness are related to the subsequent development of hypertension (200). Independent of the blood pressure, there is a relation between left ventricular mass and cardiovascular mortality and morbidity (200, 274, 319). In patients with essential hypertension and in hypertensive diabetic patients, 24-h urinary sodium excretion is an independent determinant for relative wall thickness and is a more powerful determinant than the blood pressure (71, 115, 320). Reducing the dietary intake of salt in essential hypertension diminishes the left ventricular mass (99, 211). In the Treatment of Mild Hypertension Study Group, lowering the salt intake was the only factor that was significantly correlated with a reduction of left ventricular mass (85). In the vessels, a moderate reduction in salt intake in normotensive and hypertensive subjects reduces the stiffness and thickness of the arterial wall of conduit arteries (16, 111). Independently of the blood pressure, a high dietary intake of salt increases the stiffness of conduit arteries and the activity of resistance arteries that become both hypertrophied (307, 339). It must be recalled that the stiffness of conduit arteries measured as an increase in pulse wave velocity and pulse pressure is a strong well-established independent predictor of cardiovascular risk (12, 37). Salt intake also influences platelet aggregation in normal men and women with or without a family history of hypertension and in patients with essential hypertension (122, 123). These dietary salt-induced changes in platelet reactivity may participate directly to the link between salt intake, thrombotic strokes, and myocardial infarction. The genetic basis of the blood pressure independent effects of dietary salt is still evasive, but a few insights are available. A Dutch study found that, on a high-sodium diet, hypertensive patients homozygous for the C allele of the A1166C polymorphism in the AT1R gene had an increased renal and vascular sensitivity to angiotensin II compared with the other genotypes (343). The A1166C polymorphism has also been associated with aortic stiffness (26), left ventricular mass (266), coronary vasoconstriction (8), and myocardial infarction in interaction with the angiotensin I-converting enzyme insertion/deletion polymorphism (370). More recently, it has been suggested that this polymorphism could affect autonomic modulation of heart rate, depending on dietary sodium (351).

Congestive heart failure is the end product of several harmful consequences of dietary salt (108). There is systolic contractile dysfunction due in part to the salt-induced hypertension, the hydrostatic effect of which increases the size of the muscle mass. Salt ingestion also increases cardiac muscle hypertrophy and is responsible for excess deposition of collagen and fibrous tissue. In addition, salt-induced thickening of the coronary arteries impairs coronary perfusion that can be detected as an inadequate reserve of coronary blood flow (159, 235). Some older patients develop diastolic dysfunction as manifested by impaired ventricular filling, a consequence again of the collagen deposition and fibrosis of the ventricular wall. Myocardial function is further impaired by the increase in cardiac output that results in part from the salt-induced rise in right auricular pressure. The gain in weight associated with the salt and water retention that accompanies heart failure also increases cardiac work. In an evaluation of risk factors for congestive heart failure in

the First National Health and Nutrition Examination Survey Epidemiological Follow-up Study, a higher intake of dietary sodium has been found to be a strong independent risk factor for congestive heart failure in overweight persons (148). The relative risk of congestive heart failure among overweight participants was 1.43 for those whose salt intake was >6.5 g/day compared with those whose intake was <2.9 g/day. Unfortunately, although reducing salt intake in patients with overt heart failure is often used and seems to lead to a clinical improvement similar to that which occurs with diuretics, there has, as yet, been no controlled trial of salt restriction in heart failure.

It is obvious from the available data in humans and in animals that individuals vary in their sensitivity to high salt intake. The magnitude of the reduction in blood pressure resulting from a lowering of dietary sodium varies among different population subgroups. The proportion of salt-sensitive and salt-resistant individuals has varied from one study to another based on the definition of salt sensitivity and the methods used to assess its presence or absence (389). There is little evidence that these immediate responses of the blood pressure to such sudden and drastic changes in salt status indicate how the blood pressure of a normotensive individual will respond to a lifetime's exposure to the prevaling high dietary content of salt. Nevertheless, several prospective cohort studies have suggested that salt sensitivity increases the risk of cardiovascular disease and all-cause mortality. In 156 hypertensive patients followed for an average of 7.3 yr, 62 were found salt-sensitive when salt sensitivity was defined as a difference of >10% in mean blood pressure between a low- and high-salt diet (1–3 vs. 12–15 g/day). With this criteria, salt sensitivity was associated with a threefold increase (RR = 3.05; 95% CI: 1.34–6.89) in the risk of cardiovascular disease (251). In a cohort of 278 hypertensive and 430 normotensive participants followed for up to 27 yr, salt sensitivity, determined at baseline by an individual's blood pressure response to sodium loading and depletion, was associated with a 73% increase (RR = 1.73; 95% CI: 1.02–2.94) in all-cause mortality (391). Due to the difficulties of performing such studies, population-based investigations to assess the frequency of salt sensitivity in the general population have not been yet conducted. On the basis of the available data, however, a majority of hypertensive and normotensive people respond to sodium reduction. Therefore, one could expect that salt sensitivity is a common phenomenon in human populations. From the analysis of the data on the genetic basis of blood pressure control, it appears that at least several dozen genes with modest individual effects are intervening in the regulation of blood pressure. The sensitivity of an individual will depend on the functional interactions between these genes and on the interactions with several environmental factors. This combinatory determination of blood pressure will preclude any realistic genetic diagnostic of individual sensitivity in a foreseeable future, analogously to the determination of people prone to obesity, diabetes type 2 or cigarette smoking-induced cancers. In consequence, the only practical answer that can be brought is that for the general population decreasing cigarette smoking and salt intake would reduce the incidence of lung cancers, hypertension, and cardiovascular diseases. It is important to realize that the individual sensitivity is not at the present time an operational tool in the strategies aimed to improve public health.

The evidence of a causal link between chronic high salt intake, high blood pressure, and cardiovascular diseases is very strong. Based on epidemiological, migration, intervention, treatment trials, evolutionary, and most importantly on genetic studies in humans as well as in animals, the evidence is more robust than for any other dietary variables considered to be important in the prevention of cardiovascular diseases. A long-term randomized trial of salt reduction with a focus on cardiovascular morbidity and mortality is not being seriously considered by any agency, governmental or nongovernmental, national or international, and in fact, nothing guarantees that it will be done for reasons of costs and practicality (including sample size, problems of blinding and confounding). Like with many other issues in public health, reasoned decisions need to be taken based on the weight of scientific and medical evidence in hand. Accordingly, all government-appointed bodies and nutrition experts who have considered the evidence have recommended a reduction in salt intake from the current average consumption of 10–12 g to an expected intake of 5–6 g/day (1, 257, 258, 363, 406).

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