Hypertension and Dietary Electrolyte Intake

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"Can that which is unsavory be eaten without salt?" This question was directed by Job at none other than God, who also had other important problems to ponder. The question posed in this review is whether essential hypertension is induced and/or sustained by an unnecessarily high salt intake, and whether the role of other dietary components, particularly calcium, potassium, and alcohol, may be as important in blood pressure regulation. Current thinking about the association between blood pressure, obesity and regional body fat distribution is also considered.

INTRODUCTION

Cardiovascular disease is the commonest cause of death worldwide and hypertension is a major risk factor.[1] The incidence of hypertension is about 20% with an upward trend in both men and women, so that in the sixth to seventh decade of life, about half of subjects in developed nations have the condition. The blood pressure of a population is distributed in a unimodal fashion so that the definition of hypertension is necessarily arbitrary. Blood pressure values considered in the hypertensive range and deemed worthy of treatment values have been decreasing over the years. Salt restriction as a form of treatment for hypertension was introduced at the beginning of the century when chloride could first be measured. Interestingly almost 100 years later, the merits of the salt hypothesis and the utility of its application are still being debated. The controversy is not without emotion. Editorials entitled "*the salt saga*,"[2] "*spice on the salt debate*,"[3] "*a salty issue*,"[4] and a recent commentary "*the (political) science of salt*"[5] are representative of the continuing debate.

EPIDEMIOLOGICAL EVIDENCE

Ecological studies have demonstrated an association between average salt consumption and blood pressure levels in populations with differing lifestyles.[6] In several developing countries where the average daily salt consumption is < 3g, blood pressure does not rise with age, and hypertension is virtually non-existent,[7,8,9] whereas in populations with a typically Western lifestyle, both salt intake (8 - 10g/day) and the prevalence of hypertension is far higher.[10,11] The INTERSALT study which included an examination of 10 074 participants from 52 centres in 32 countries, using standardized methodology, demonstrated a positive association between sodium excretion and median blood pressure when the data from all centres were included. However, when four distinctly disparate populations with very low sodium excretion values were excluded, the association no longer remained.[12] A simultaneously published Scottish report[13] on 7 354 men and women found only a weak positive correlation between urinary sodium excretion and blood pressure and concluded that sodium had no evident independent role in determining hypertension. These two large studies do not provide compelling evidence that salt intake causes hypertension. A subsequent analysis of the Intersalt data applying more expansive corrections for "regression dilution bias" estimated stronger positive association between urinary sodium excretion and blood pressure,[14] however such post-hoc reanalyses have been the subject of much criticism.[15]

It has been argued that giving advice to the general public to reduce salt intake is justified if health benefits are gained by individuals who are "salt sensitive," while those who are salt-resistant are not harmed. However, a cohort study of 2 937 mildly and moderately hypertensive men which investigated

the effects of a low salt intake on cardiovascular disease over an average of 3.8 years of follow-up, demonstrated a significant, inverse association between baseline 24 h urinary sodium excretion (anithypertensive therapy was discontinued for 3 to 4 weeks before providing a urine collection) and myocardial infarction, independent of several known coronary heart disease risk factors.[16] The downfalls of observational studies with regard to unmeasured confounder variables and the imprecision of the potential confounders which are measured are well known and may have contributed to the occurrence of this surprising finding.[17]

Nevertheless, the findings of a much larger cohort study also provided some disconcerting results for the advocates of salt restriction.[18] The first National Health and Nutrition Examination Survey (NHANES I) established baseline information during 1971-75 in a representative sample of 20 729 American adults aged 25-75 years. Over half of the sample underwent medical examination and nutritional examination based on 24h recall. Based on 20 years of follow-up, sodium intake at baseline was significantly inversely associated with both all-cause and cardiovascular mortality. However, when sodium intake was expressed as a function of energy intake (sodium/kcal), a direct association between sodium intake and all-cause and cardiovascular mortality was found. The authors interpreted their results cautiously and concluded that the data did not provide support regarding either an increased or decreased salt intake. The validity of a single 24 h dietary recall method to assess habitual salt intake has been questioned. High intra- (45 %) and inter- (45 – 56 %) subject variability for reporting of non-discretionary salt sources has implications for the reliability of food record estimates. Indeed, it has been estimated that 81 days of dietary recording would be required to estimate an individual's intake within 10 % of the observed mean.[19] Seven-day recording of food intake is generally considered to be the maximum time feasible for data collection – the observed 95th percentile confidence intervals of sodium intake in the study of Mattes *et al.*,[19] based on 7-day records, were 1 540 to 5 478 mg/24 h (i.e salt intake of 3.8 – 13.7g/24 h), which encompasses practically the entire intake range for the general population. The authors concluded that at least five 7-day collection periods would be required to estimate intake with a reasonable level of confidence.[19]

Migration studies provide information on the effects of moving from a low-salt to a high-salt environment. The Kuna Indians in Panama, in whom hypertension was previously rare and in whom blood pressure was shown not to increase with age, have recently been revisited by Hollenberg *et al.*[20] Kuna people living in three different environments were identified; those remaining in villages; those who have migrated to a suburban area; and those living in urban Panama City. Through trading and other societal forces, the salt intake of the Kuna has increased in the past 50 years to at least as much, if not more, than that of industrialized societies, regardless of where they live. Nevertheless, distinctly different blood pressure patterns were identified across the three populations. Village-dwelling Kuna were found to still have a very low incidence of hypertension, irrespective of age, whereas in the Panama City-dwelling population blood pressure rose markedly with age, and a prevalence of hypertension greater than 40 % was found in subjects aged 60 + years. Suburban-dwelling Kuna had blood pressure profiles in-between. These findings suggest that increases in blood pressure associated with increasing urbanization cannot be explained by an increased salt intake alone.

Intervention trials which have been conducted in normotensive and hypertensive subjects in order to assess the overall efficacy of sodium restriction in reducing blood pressure have been described in meta-analyses[21,22,23,24,25,26] An average reduction in sodium intake of 100 mmol/24 h is associated with decreases in systolic and diastolic blood pressures of 5.4 and 6.5 mmol Hg, respectively.[26] These estimates were confirmed in a review by Cutler *et al.*[24] in which the findings of 23 randomized controlled trials, including 1 536 subjects, were analyzed. The median reduction in urinary sodium in the trials was 74 mmol/24 h. After weighting for sample size, the reductions in systolic and diastolic blood pressure averaged 4.9 and 2.6 mm Hg, respectively in hypertensive subjects, and 1.7 and 1.0 mm Hg respectively in non-hypertensives. Similarly, a review of 13 randomized trials including 584 subjects, found that a mean reduction in sodium intake of 78mmol/24 h was associated with a decrease in blood pressure averaging 3.6 mm Hg for systolic blood pressure and

2.0 mm Hg for diastolic pressure.[25] Scatterplots from Midgley *et al.*[27] show the association between net changes in urinary sodium excretion and changes in blood pressure for hypertensive and normotensive subjects (Figure 1). It has been suggested that a moderate salt restriction would result in a left shift of the blood pressure distribution curve in a community and therefore a considerable reduction of cardiovascular morbidity and mortality.[28] However, Midgley *et al.*[27] concluded that while dietary salt restriction may be considered for older hypertensive subjects, there was little support for universal dietary salt restriction.

SALT SENSITIVITY

Blood pressure is a function of flow and resistance. The kidneys are responsible for managing the electrolyte and water content in the body, since the kidneys excrete almost all ingested electrolytes and much of the water consumed daily. Volume content is tightly controlled by the regulation of sodium (and thereby chloride) excretion. A relationship between renal salt and water excretion and blood pressure can be created for any level of blood pressure and is termed the renal pressure-natriuresis or diuresis relationship. As initially shown by Selkurt and developed by Guyton, all forms of hypertension in animal models tested to date, feature a shift in the pressure-natriuresis relationship to the right, so that a higher level of pressure is required to excrete any given amount of salt and water. The topic has recently been reviewed by Cowley.[29] The salt-sensitivity of any form of hypertension is a function of the steepness of the pressure-natriuresis relationship. In normotensive individuals, the relationship between salt and water intake (and excretion) is very steep, so that little change in blood pressure occurs when salt and water intake (and excretion) are modified over a large range. Fairly flat pressure-natriuresis curves indicate salt-sensitivity since blood pressure is significantly influenced by salt intake. Steep pressure-natriuresis curves indicate that blood pressure, even if elevated, is little influenced by salt.

The salt-blood pressure hypothesis states that excessive salt intake leads to an increase in blood pressure in genetically susceptible persons and, if the high intake is maintained over the long term, ultimately leads to sustained hypertension.[30] The hypothesis regards salt as the essential factor; however, the influence of supraphysiological salt intake interacts with both genetic predisposition as well as other environmental factors.[31,32,33,34] Salt sensitivity can be defined as a rise in blood pressure occurring during salt administration and/or a fall in blood pressure when salt is taken away exceeding the magnitude of directionally-appropriate, random fluctuations in blood pressure. Salt-sensitivity is an intermediate BP phenotype that has been shown to be reversible with weight loss. Definitions of salt-sensitivity in response to salt loading or salt depletion have been arbitrary and varied, but are generally in the region of a 5 mm Hg increase in mean arterial pressure with salt loading. Blood pressure response to salt should be seen as a continuum, taking into account an individual's baseline random variability in blood pressure.[35]

On a per mm Hg basis, sodium raises systolic more than diastolic blood pressure. In the US, the greater susceptibility of African-Americans than whites to hypertension and pressure-related target-organ damage has been linked to a higher prevalence of salt sensitivity (though at least 50% of white hypertensives are also salt-sensitive), lower urinary potassium excretion, lower plasma renin activity, and higher circulating levels of immunoreactive parathyroid hormone and 1,25 dihydroxyvitamin D.[36] Studies conducted in South Africa[37,38] have also suggested diminished activity of the sodium-potassium ATPase pump in black hypertensives. Both black South Africans and African-Americans manifest higher average BP responses to calcium antagonists than to ACE inhibitors, an observation consistent with the thesis that hypertension amongst these groups is often salt-sensitive.[39,40] Indeed, data from Weir *et al.*[41] documented that in hypertensive African-Americans salt-sensitivity predicted a much less effective BP-lowering response to an ACE inhibitor than to a calcium antagonist. However, it has been shown that the salt-induced reduction of the ACE inhibitor BP response in African-Americans can be overcome by increasing ACE-inhibitor doseage.[40] Based on findings from their studies of Africans in Nigeria, Jamaica and the United States, Cooper *et al.* cautioned against the "destructive" use of racial or genetic characteristics to explain the marked differences in hypertension among different groups of people.[42] About 40 – 50 % of the increased risk found in African-Americans (33 %) compared to Nigerians (7 %) is explained by differences in body weight, "poor diet", and lack of exercise.

PATHOPHYSIOLOGY

As well as its association with blood pressure levels, salt sensitivity has also been linked to abnormal renal hemodynamics (reduced renal plasma flow, raised intraglomerular capillary pressure, increased filtration fraction) and increased urinary protein excretion during dietary salt loading. These changes, if sustained over time, could lead to glomerular injury, premature glomerular senescence, and ultimately to clinically detectable renal insufficiency. Salt may cause vascular injury independent of its pressor effect as per capita sodium consumption in European countries has been linked directly to stroke risk, independent of BP level.[43] In Japanese subjects, salt sensitive hypertension has been shown to predict an increased risk of cardiovascular events.[44] The association between salt sensitivity and insulin sensitivity is less clear; hyperglycemic and hyperinsulinemic responses have been shown in young white salt sensitive, however not in a sample of rural black Zimbabweans.[45]

SALT APPETITE

The average dietary sodium intake of Americans adults is 3 289 mg/day (equivalent to a salt intake of about 8 g/day),[46] which greatly exceeds the estimated minimum requirements of healthy non-pregnant, non-lactating adults of about 500 mg/day[47] and exceeds the US National High Blood Pressure Education Program[48] recommended intake for adults of no more than 2 400 mg sodium (about 6 g salt) per day. Studies of the sources of dietary sodium estimate that about three-quarters of intake comes from food processing, 10 – 11 % is naturally occurring (inherent) in foods, about 15 % is discretionary (half of which is contributed by table salt and half by added salt in cooking), while less than one percent is provided by water.[19,49,50,51] National dietary survey data from the NHANES II study which used a 24-hour recall method has demonstrated that the main sources of sodium in the American diet are provided by grain products, including bread, which contributes about a quarter of total intake.[52]

The question arises why humans consume sodium in quantities which far exceed physiological requirements and whether a "salt appetite" manifests in certain individuals, as a result of either genetic programming or learned taste through exposure to high salt intakes. As Mattes[53] points out, cultural practices may contribute to salt intake patterns. For instance, a 10-fold difference in sodium intake has been reported between two Solomon Island populations which has been attributed to the one group's practice of steaming foods with fresh water whereas the other group cooked with sea water.[8]

A salty taste involves the passage of sodium through a specific ion channel in the apical membrane of receptor cells.[54] The channel can be blocked with amiloride, a potassium-sparing diuretic. Lithium, which can pass through readily is salty, whereas other cations such as potassium, which do not fit, do not taste salty. The specificity explains the difficulty in finding an acceptable salt substitute. It has been proposed that a diminished perception of saltiness taste exists in old age, which results in an increased salt consumption.[55] However, Drewnowski and colleagues found no such evidence in studies of young and older subjects.[56] Long-term adherence to a diet low in sodium can lead to a sensory shift in taste whereby both normotensive[57] and hypertensive[58] persons develop an increased acceptance of low-salt foods. Support for a salt appetite, defined as "a strong motivation to seek, obtain and ingest sodium," originates largely from a case study in which a strong craving for salt was observed in a child with undiagnosed Addison's disease,[59] as well as reports of self-medication by the ingestion of liquorice, which possesses mineralocorticoid properties, in individuals with salt-wasting pathologies.[60,61] However, salt-craving has only been described as being present in about 15 % of patients with Addison's disease[62] and sodium depletion in humans is not accompanied by a strong and consistent craving for salt.[63] In summary, there is little evidence supporting a relation between either taste sensitivity or hedonic responses to salt and blood pressure.[53]

OTHER DIETARY FACTORS: CALCIUM, MAGNESIUM, AND POTASSIUM

Dietary factors other than sodium which have been shown to influence blood pressure include potassium, magnesium, calcium and alcohol.[64] In 1984, using data from the first NHANES study in the United States, it was demonstrated that a diet low in calcium and potassium resulted in an increase in systolic blood pressure, the likelihood of hypertension, or both.[65] A low intake of dairy products, followed by a similarly low consumption of fruit and vegetables, was the dietary pattern most

predictive of hypertension. Further, the benefit of consuming dairy products, fruits and vegetables was independent of age, race, sex or body weight.

The validity of these observational data has recently been confirmed by a randomized controlled trial, Dietary Approaches to Stop Hypertension (DASH).[66] In a group of 459 adults with systolic blood pressures below 160 mm Hg and diastolic pressures of 80 – 95 mm Hg, subjects fed a diet rich in fruit and vegetables for 8 weeks significantly reduced systolic and diastolic blood pressure by 2.8 and 1.1 mm Hg more, respectively, than subjects on a typical American diet. Subjects randomized to a "combination" diet, rich in fruit, vegetables and low-fat dairy products, and with a reduced saturated and total fat intake (See Table 1) had an even greater reduction in both systolic and diastolic blood pressure (5.5 and 3.0 mm Hg, respectively). In subjects who were hypertensive the effects were more marked; the fruit and vegetable-rich diet resulted in reductions of systolic and diastolic blood pressure of 3.5 and 2.1 mm Hg, respectively, while the combination diet resulted in corresponding reductions of 11.4 and 5.5 mm Hg, respectively. It was estimated that a population-wide reduction in systolic or diastolic blood pressure of the magnitude observed with the combination diet would reduce incident coronary heart disease by approximately 15 % and stroke by about 27 %.

Meta-analyses of randomized controlled trials of blood pressure and calcium levels in 2 412 adults and 2 459 pregnant women provide evidence that both normotensive and hypertensive individuals may experience reductions in blood pressure when calcium is increased.[67,68] Further, the provision of a high calcium diet to salt-sensitive subjects whose systems are acutely loaded with salt prevents the expression of salt sensitivity.[69,70] However, not all the evidence is consistent. In Pima Indians, a population at very high risk for diabetes and other cardiovascular risk factors, calcium supplementation did not lower blood pressure.[71] Conversely, among three Chinese populations, the pressor effect of a high salt intake was found only in those with a low calcium intake.[72] Similarly, in African-American adolescents, calcium supplementation of 1.5 g/day in a randomized trial resulted in a reduction in diastolic blood pressure only in subjects with habitual dietary calcium intakes in the lowest two tertiles (-4.9 and -2.3 mmHg, respectively); no change was found in systolic blood pressure across all tertiles of calcium intake.[73] Levey *et al.*[74] have suggested that the ratio of sodium to calcium in the diet may be more important than absolute intake of either mineral. Further, there may be a threshold above which benefit is not enhanced. A study of mildly hypertensive patients on a restricted sodium intake did not achieve further blood pressure lowering by calcium supplementation.[75] Similarly, supplementation of calcium did not further enhance the blood pressure-lowering effect of a high potassium diet in women who had a low habitual intake of potassium, calcium and magnesium.[76]

Observations that lower urinary magnesium excretion or low erythrocyte magnesium concentrations are found in subjects with higher blood pressure in different population groups prompted studies to investigate the effect of magnesium supplementation on blood pressure.[77] Magnesium sulfate has effective hypotensive properties when rapidly infused, however there is little evidence for its role in blood pressure regulation. In randomized controlled trials, dietary magnesium supplements did not lower blood pressure of hypertensives, but only in those whose potassium levels were depleted by diuretics.[78,79]

Regarding dietary potassium intake, findings in 38 normotensive men were recently reported by Morris *et al.*[80] Subjects were assigned a basal diet low in sodium (15 mmol/d) and marginally deficient in potassium (30 mmol/d) for six weeks; 250 mmol/d of sodium chloride was added to the diet during the last four weeks, accompanied by potassium supplementation as potassium bicarbonate ($KHCO_3$) to either mid- or high-normal (70, or 120 mmol/d, respectively) levels throughout the last three weeks. On the low potassium intake, salt loading induced a mean rise in BP only in African-American men. Moderate potassium supplementation attenuated salt-sensitivity similarly in African-American and white subjects, while supplementation to 120 mmol/d suppressed the frequency and severity of salt-sensitivity to levels similar to those in whites. The authors concluded that in normotensive African-American men but not white men, marginally deficient dietary potassium evokes salt-sensitivity, but potassium supplementation attenuates this in a dose-dependent manner. The relatively high doses of $KHCO_3$ were well tolerated.

Dietary salt intake as high as 400 – 600 mmol/d failed to induce a rise in BP in either African-American or white normotensive men when

dietary potassium intake was adjusted for potassium losses.[81,82,83,84] The dietary potassium intake required for protection against the pressor effect of salt has yet to be determined. Morris and colleagues[81] have proposed that a "normal" dietary intake of potassium may not be sufficient to suppress expression of salt sensitivity in many normotensive African-Americans as well as in some normotensive whites. In the US, dietary intake of potassium has been found to be lower in urban African-American than whites.[85,86] Many of the studies which have demonstrated ethnic differences in blood pressure response to dietary sodium chloride loading (i.e. salt sensitivity) have not taken into account differences in baseline potassium intake. Finally, supplemental dietary chloride has been shown to have its own pressor effect, as demonstrated in two studies of genetic rat models of hypertension[87,88] even when given as potassium chloride.[89] Potassium bicarbonate ($KHCO_3$), on the other hand, has a hypocalciuric, calcium-retaining effect.[89,90,91] Potassium-rich sources of food such as fruit and vegetables contain little chloride; in addition, the abundance of K^+ and $HCO3^-$ -yielding anions in these foods contributes to their hypocalciuric and calcium-retaining effects.[92]

GENETICS

Over 20 years ago, we observed a genetic influence on the responses to salt intake [93] and coined the term salt sensitivity and resistance of blood pressure [94]. The kidney is the final common pathway in blood pressure regulation and ultimately determines the setpoint for pressure-natriuresis. Salt sensitivity features low plasma renin activity, evidence for volume expansion, exaggerated acute natriuresis with blunted longer-term sodium excretion, is more common in black subjects, the elderly, and in obesity-related hypertension [95,96]. The causes for salt sensitivity (or resistance to salt) are not known for certain. However, the mechanisms of salt sensitivity and resistance must operate by influencing the setting (rightward-leftward) or slope (sensitive-resistance) of the pressure-natriuresis relationship [97]. Guyton and colleagues developed a cybernetic system of blood pressure regulation, based an multiple differential equations [98]. The physiological determinants are candidate genes responsible for enzymes, transporters, ion channels, receptors, hormones, binding proteins etc. These candidates can now be viewed in terms of a metabolic control analyses for salt handling and blood pressure regulation [99].

The "fine tuning" of sodium reabsorption takes place in the distal tubule and collecting duct. Sodium molecules enter from the lumen via the epithelium (amiloride sensitive) sodium channel (ENaC). The channel consists of three subunits, all of which display mutations [100]. Mutations in two (b and g) subunits are responsible for a monogenic hypertension termed Liddle syndrome. The channels are inserted into the membrane through the action of aldosterone-inducible proteins. A recently described example is the protein SGK [101]. The channel subunits are removed by NEDD4, a transfer protein which makes the subunits available degradation by ubiquitin. Aldosterone itself is synthesized through the action of aldosterone synthase. The aldosterone synthase gene, together with the 11-b hydroxylase gene, can form a chimeric gene responsible for glucocorticoid-remediable aldosteronism [120]. Aldosterone, and not cortisol, must be able to occupy the mineralocorticoid receptor. To protect the receptor from cortisol, the enzyme 11-b hydroxysteroid dehydrogenase 2 (11ßHSD2) must function properly. Failure of the gene to produce a functioning enzyme causes a monogenic form of hypertension termed apparent mineralocorticoid excess. The mineralocorticoid receptor gene can feature both activating and deactivating mutations causing either hypo or hypertension (Lifton RP, personal communication). On the basilar side of the cell, the sodium pump is regulated in part by adducin, a cytoskeletal protein implicated in salt sensitive hypertension. Finally, gene loci for Gordon´s syndrome have been described. This syndrome features salt sensitivity and acid-base disturbance. Affected persons have mild hyperchloremic metabolic acidosis. In short, a series of genes function in an interrelated fashion to produce a system providing for sodium reabsorption. All of these genes are recognized candidates for salt sensitivity and hypertension. Indeed, we and others have already studied some of them.

Sharma et al. have recruited and phenotyped 250 normotensive men in terms of salt sensitivity and has also obtained DNA from the parents. Numerous publications have accrued from this work. Most relevant to this discussion is the finding that variation in the 11b HSD2 gene is associated with an intermediary phenotype in corticosteroid excretion and salt sensitivity [102].

Sharma has also performed studies on the GNB3 gene [103,104], angiotensinogen-leptin interactions, and the atrial natriuretic peptide gene [105].

CONCLUSIONS

The available evidence suggests that dietary advice for the prevention and management of hypertension needs to address changes in dietary patterns as a whole, rather than focusing on one or more specific nutrients. It appears that the most beneficial dietary pattern is the DASH "combination" diet which is low in total and saturated fat and alcohol (and reduced in total energy, if the subject is obese), and high in fiber, potassium, calcium and magnesium, and moderately high in protein. In terms of foods, this translates into a diet which is rich in fruit and vegetables and low-fat dairy foods. The Sixth US Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VI)[48] have recommended a series of lifestyle modifications which offer the potential for the prevention of hypertension, as well as a reduction in blood pressure in subjects who already have essential hypertension. They list, in order of priority, weight reduction, followed by moderation of alcohol intake, increased physical activity, moderation of dietary salt intake, and an adequate intake of dietary potassium and calcium. In addition, cessation of smoking and reduced intake of saturated fat and cholesterol were recommended for lowered overall risk of cardiovascular disease. The Report of the JNC VI acknowledged the difficulty in achieving and maintaining lifestyle changes and encouraged a systematic team approach, utilizing health-care professionals and community resources wherever possible, so as to provide necessary education, support and follow-up.

The question of advocating salt reduction for the nonhypertensive population as a major public-health policy is a complicated matter. Recent research holds promise for a greater understanding of the mechanisms related to the expression of salt sensitivity; it is conceivable that the future identification of markers for salt sensitivity will allow preventive interventions to be more appropriately directed to those groups at greatest risk of hypertension. A recent study has suggested that physicians are less likely to provide specific guidelines with respect to diet than they were ten years ago.[106] We are left with perhaps the soundest advice of all for our patients, their families and ourselves – instead of "eat less salt," we should simplify the advice to "eat less" (period!).

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