Thiazide Effects and Adverse Effects
Insights From Molecular Genetics

David H. Ellison, Johannes Loffing

One of the longest-running debates in clinical medicine shows no sign of disappearing; just when it seems that thiazides have reassumed their role as front-line drugs to treat hypertension, new concerns emerge, leading some to question their role once again. Thiazides are effective antihypertensives with long track records and low cost. The major concerns about their use arise from their tendency to cause hypokalemia, impair glucose tolerance, increase serum cholesterol, and increase serum uric acid. Few medical controversies have generated as much heat, with well-established camps staking out positions that appear resistant to change.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, the largest study of antihypertensive monotherapy ever performed, was intended to identify the best first-line treatment for high-risk hypertensive individuals; however, despite its size and the numerous resulting publications, its implications and authority continue to be disputed. The goal of this review is not to take sides in this debate but rather to inject a distinct, and sometimes neglected, perspective; during the past 15 years, remarkable developments in molecular biology and human genetics have provided substantial insights into the pathogenesis of hypertension and mechanisms and adverse effects of diuretics. Diuretic proponents and antagonists alike often neglect these developments when addressing the topic; it is the purpose of this Brief Review to integrate these developments into the debate with the goal of generating questions that can be addressed scientifically.

How Thiazides Reduce Blood Pressure
Thiazide diuretics were developed during the 1950s, when chemists and physiologists at Merck Sharp and Dohme tested derivatives of sulfonamide-based carbonic anhydrase inhibitors, with the goal of discovering drugs that enhance the excretion of sodium with chloride rather than sodium bicarbonate.

Although these drugs lower arterial pressure effectively, the mechanisms have long perplexed investigators. Thiazides reduce cardiac output acutely by reducing extracellular fluid (ECF) and plasma volume, but ECF volume returns toward baseline during chronic use, and vasodilation supervenes. At steady state, therefore, the predominant effect of thiazides is vasodilation rather than volume contraction. On the basis of this sequence of physiological effects and on the difficulty in detecting any ECF volume depletion during chronic treatment, many authorities suggest that the primary mechanism by which thiazide diuretics reduce arterial pressure involves direct vasodilation, perhaps mediated by alterations in vascular ion transport; others, however, emphasize that salt depletion is necessary, suggesting that vasodilation is secondary to ECF volume contraction. In support of this are studies showing that thiazides are not effective in end stage renal disease.

Significant effort has been directed toward determining the mechanisms by which thiazides dilate blood vessels. One possibility is that the drugs alter membrane ion flux in the vascular smooth muscle. In vitro, thiazides open large-conductance, calcium-activated potassium channels, thereby hyperpolarizing vascular smooth muscle cells and causing vasorelaxation. In vivo, hydrochlorothiazide causes mild dilation of human forearm blood vessels, but this effect is observed at a concentration that is higher than that achieved during oral drug use. The effect appears related, at least in part, to the carbonic anhydrase–inhibiting capacity of hydrochlorothiazide, which alkalinizes the cell. The carbonic anhydrase–inhibiting potency of thiazide diuretics varies between congeners; thus, the vascular effects of these drugs would be expected to vary as well.

Despite the evidence for direct vasodilation, the predominant activity of thiazide diuretics is to inhibit a directly coupled Na-Cl cotransporter (NCC; gene symbol SLC12A3) along the distal convoluted tubule (DCT) of the kidney. The drugs are quite specific inhibitors of this protein, because they do not inhibit the furosemide-sensitive Na-K-2Cl cotransporter or the amiloride-sensitive Na channel. The NCC is expressed by DCT cells of rodents, rabbits, and humans. Although there is some evidence that it may be expressed in bone and intestine, it is not expressed by vascular smooth muscle or cardiac tissue. Mutations in SLC12A3 cause Gitelman syndrome (GS), a syndrome of hypokalemia and
alkalosis. These mutations, which disrupt the function of NCC, reduce arterial pressure by \(\approx 8\) mm Hg, an effect similar to the reduction in arterial pressure that occurs during thiazide treatment of hypertension (see Figure 1). Surprisingly, however, the hypotension in GS is mediated by vasoconstriction and not by ECF volume depletion, although \(\text{SLC}12A3\) is expressed by kidney cells but not by vascular smooth muscle cells. Individuals with GS have upregulation of NO production, reduced peripheral resistance, and vascular smooth muscle cell hypertrophy. Angiotensin II signaling is blunted, with reduced expression of the \(\alpha\)-subunit of the Gq-binding protein, and reduced downstream cellular events, eg, intracellular Ca and inositol triphosphate release. Although potassium deficiency itself has been suggested as contributing to this vasodilatation, this seems unlikely to be the predominant cause, because dietary potassium loading, rather than deficiency, typically dilates vessels and reduces blood pressure. Thus, it seems very likely that blood pressure in GS is low because renal salt wasting in some way causes secondary vasodilatation.

Recently, an additional molecular and genetic discovery has highlighted the impact of disordered renal sodium transport on human vascular responsiveness. Familial hyperkalemic hypertension (FHHt; also called pseudohypoaldosteronism type 2 or Gordon syndrome) is a rare autosomal dominant disease; one of the clinical features is extraordinary sensitivity to the blood pressure–lowering effects of thiazide diuretics. Although in essential hypertension thiazides reduce systolic pressure by 8 to 10 mm Hg, in FHHt, thiazides reduce systolic pressure by as much as 40 mm Hg (see Figure 1). However, like GS, FHHt is a disease of the kidney DCT, resulting in this case from activation of NCC. Yet, the hypertension in FHHt is mediated, at least in part, by enhanced vasoreactivity, because these individuals demonstrate an exaggerated response to a "cold pressor test." Thus, a disease that alters kidney tubule function to engender salt retention leads, at steady state, to vasoconstriction. In this state, the effect of thiazides to reduce arterial pressure is enhanced.

Clearly these observations in genetic syndromes do not exclude a direct effect of thiazides on blood vessels as contributing to their hypotensive effectiveness. However, they do indicate that it is not necessary to invoke direct effects on vascular smooth muscle to explain the vasodilatation that is observed during their use. In view of the fact that the protein product that is dysfunctional in GS and is hyperfunctional in FHHt is not expressed by vascular smooth muscle or endothelial cells, the observations of altered vascular reactivity in these states compel a mechanism by which renal salt loss relaxes blood vessels indirectly; this model is consistent with the concept of reverse whole-body autoregulation, as postulated by Tobian and Shah et al based partly on the work of Manning et al. Acutely, when ECF volume depletion occurs because of salt wasting, cardiac output tends to decline, resulting in reactive vasoconstriction. Chronically, however, cardiac output (tissue perfusion) is regulated according to metabolic needs, and vasodilatation supervenes, returning cardiac output toward baseline; this transforms hypotension from hypovolemic to vasodilatory.

The data discussed so far suggest that thiazides reduce arterial pressure primarily by inhibiting NCC in the kidney, but these conclusions are inferential. A more direct test would be to determine whether thiazide diuretics reduce blood pressure in individuals who lack functional NCC (GS). A hint that such effects might occur in humans is the observation that thiazides do enhance NaCl excretion in GS, albeit to a reduced extent. Although this could reflect incomplete loss of NCC function, most GS mutants are completely inactive. One potential explanation would be that the effects in GS result from carbonic anhydrase inhibition, because thiazides inhibit this enzyme. Another alternative would be an effect in the collecting duct, where thiazides have been shown by some but not other investigators to inhibit salt transport. Consistent with this latter idea, Eladari et al (ASN abstract 2007, unpublished) recently reported thiazide-sensitive NaCl reabsorption in kidneys and isolated collecting ducts of NCC-deficient mice.

**Thiazide-Induced Hypokalemia**

When thiazides were introduced into clinical medicine, relatively high doses were used (\(\geq 150\) mg/d of hydrochlorothiazide), and hypokalemia was common and severe. During the 1970s, the first of several debates about unwanted consequences of thiazides arose. Hypokalemia was deemed hazardous by many investigators; associations with ventricular arrhythmias were especially worrisome. Multiple approaches were developed to prevent or treat hypokalemia, and a series of polemics addressing this issue were published. (One was titled, "Our National Obsession With Potassium," engendering a response, titled, "Our Appropriate Concern About Hypokalemia." It is now recognized that the best
balance between effectiveness and adverse effects is obtained with much smaller doses. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, at 4 years of follow-up, serum K concentration was 0.3 mmol/L lower in individuals who received chlorthalidone 12.5 to 25.0 mg daily than in individuals treated with amlodipine, a drug that is probably metabolically neutral.

Unlike loop diuretics, thiazides do not affect K transport directly; instead, they stimulate K secretion indirectly. Hypokalemia results primarily from increased distal Na and fluid delivery because of upstream transport inhibition coupled with an enhanced aldosterone effect. An underappreciated additional mechanism involves their ability to lower the luminal calcium concentration along distal tubules. This activates epithelial Na channels (which are inhibited by calcium) and favors K secretion. This could be one reason that loop diuretics, which increase distal calcium delivery, generate less hypokalemia. Another reason may be that the compensatory response to loop diuretics derives from increased electroneutral NaCl reabsorption in the DCT, which would not be expected to enhance potassium secretion. Instead, thiazide diuretics induce adaptation primarily along the connecting and collecting tubules, where enhanced electrogenic Na reabsorption stimulates K secretion. Thiazides also enhance K secretion by activating flow-sensitive maxi-K channels; these channels are molecularly distinct from the K secretory channels described above.

Some observational studies have suggested that diuretic-induced hypokalemia may be associated with an increased incidence of arrhythmias, but the data are limited and definitive conclusions have not been reached. Insight into the cardiac risks posed by hypokalemia may be gleaned from individuals with GS. Such individuals live as if they were on maximal doses of thiazide diuretics throughout their lives. The serum potassium concentration of affected individuals averages 2.6 mmol/L, much lower than levels obtained during thiazide treatment, and hypokalemia in GS is typically associated with profound hypomagnesemia. Foglia et al reported that QT intervals were slightly prolonged in approximately half of individuals with GS, but continuous ambulatory electrocardiography and exercise testing were normal. They concluded that the results did not suggest a strong tendency for hypokalemic arrhythmias, although they noted that more profound hypokalemia leading to potentially hazardous arrhythmias might occur under unusual circumstances. A few case reports of GS-associated cardiac rhythm disorders have been published, but surprisingly few; although these data are reassuring, they do not exclude risks related to superimposed disease.

**Thiazide-Induced Hyperglycemia**

Although concern about hypokalemic arrhythmias from thiazide use continues, its preeminence has been replaced by concern about other metabolic adverse effects. Recently, this led the National Heart Lung and Blood Institute to convene a working group to examine mechanisms, consequences, and prevention of diuretic-induced dysglycemia. Their preliminary report summarizes many aspects of the problem, which will not be repeated here. However, the report concludes that hypokalemia is the most likely cause of diuretic-induced hyperglycemia and cites experimental and observational data supporting this conclusion. These data are convincing, but there are indications that nonrenal effects of thiazides may also be involved. The nondiuretic thiazide diazoxide is used treat hypoglycemia, not by inducing hypokalemia, but because it hyperpolarizes the islet cell membrane in the pancreas, inhibiting calcium influx and, thus, the calcium-dependent release of insulin. There is evidence that hydrochlorothiazide, hydroflumethiazide, and indapamide have similar effects although this has been disputed. Alternatively, or additionally, thiazides might increase serum glucose by activating the renin-angiotensin-aldosterone system, perhaps in concert with sympathetic activity. There is evidence that the effects of thiazides on serum glucose can be mitigated by inhibiting the renin-angiotensin-aldosterone axis, which of course also attenuates hypokalemia. To date, it has not been possible to separate the effects of potassium depletion from direct drug-induced hyperglycemia.

Once again, mechanistic insight into the causes of diuretic-induced hyperglycemia might be gleaned from studies of individuals with inherited alterations in NCC; individuals with FHH, who suffer from hyperkalemia, are typically treated with thiazide diuretics, but in this case the diuretics simply reduce the elevated potassium toward normal. Mayan et al reported that thiazides increased plasma glucose in individuals with FHH while reducing K to 4.6 mmol/L; they suggest that this excludes hypokalemia as the cause of the glucose intolerance. In contrast, individuals with GS live life lacking an NCC and develop profound hypokalemia. It has been reported that “hyperglycemia is not observed in GS,” but specific data supporting this contention are limited. Recently, however, Lifton and colleagues analyzed glucose and lipids in 17 individuals with GS and in 9 unaffected relatives, all from a large, previously described Amish family. Subjects were not significantly different in age (mean: 55 years) or gender, but the mean serum [K] of GS subjects was 3.0 mmol/L versus 4.1 mmol/L in unaffected relatives. Surprisingly, there were no significant differences in glucose or insulin during fast, 1 hour, or 2 hours after glucose challenge (Richard Lifton, written communication, 2009) despite the presence of severe and persistent hypokalemia (and strong stimulation of the renin-angiotensin-aldosterone axis). There were also no differences in lipid profiles between the 2 groups. It might be argued that the Amish individuals do not share concomitant risk factors for diabetes mellitus, eg, obesity, that are common in the rest of the US population, and body mass index has been shown to correlate with the magnitude of thiazide-induced hyperglycemia, but demographic factors account for only a small fraction of the risk for hyperglycemia. Thus, the data that exist with respect to the impact of genetic NCC deficiency do not support a dominant role for hypokalemia (or hypomagnesemia) on glucose tolerance. Clearly, these data do not disprove a role for hypokalemia, but they compel the continued search for alternative hypotheses and suggest that it might be possible to develop structurally dissimilar NCC inhibitors that do not affect glucose tolerance. Conversely, if the hyperglycemia results from the intrinsic diuretic effectiveness of the drugs or drug-related
hypokalemia, then alternative approaches to prevent or treat it must be considered.

Thiazide-Induced Structural Kidney Damage

Recently, another potential adverse effect of thiazide treatment has been described. Rats that received thiazides chronically showed evidence of “subtle glomerular injury characterized by periglomerular fibrosis and wrinkling and thickening of the glomerular basement membrane” (see Figure 2A).3 The kidneys showed evidence of oxidative stress as well, and the adverse effects were not mimicked by diet-induced potassium deficiency. The authors speculate that the changes might have resulted from glomerular ischemia; they suggest that diuretic treatment of humans may damage the kidney and “may not be necessary in many patients with chronic kidney disease” to control hypertension.3

The effects of thiazides on kidney structure reported by Reungjui et al3 are similar to effects of thiazide treatment on DCT segments described previously by Loffing et al.72 In those studies, thiazide treatment of rats led to apoptosis of epithelial cells and to a remarkable transformation of the DCT to form a pseudostratified, dedifferentiated epithelium (see Figure 2B).72 Tubules of treated animals contained squamous and degenerating cells and massive lysosomal bodies. Inflammatory cells and layers of fibroblasts surrounded the damaged tubular profiles. Remarkably, the tubular damage was strictly confined to the early DCT (the DCT1), a segment in which the predominant apical sodium entry pathway is the NCC. Damage was not seen along the late DCT (DCT2), a segment that expresses both NCC and the epithelial sodium channel at its apical membrane. Other nephron segments, as well as glomeruli, remained structurally intact, although these segments and glomeruli lie very near to DCT segments and might be susceptible to damage by association. Loffing et al72 considered a variety of explanations for the observed effects of thiazides on the DCT structure. They speculated that blockade of sodium entry into the DCT1 causes cellular toxicity either directly, by lowering the intracellular sodium concentration, or indirectly, by intracellular calcium loading. Cellular entry of calcium along the DCT is strongly stimulated when apical sodium transport is inhibited by acute thiazide application.73

Insight into the consequences of diuretic treatment on kidney tissue of humans can be gleaned from an analysis of individuals with Bartter syndrome (BS) and GS; these syndromes are genetic mimics of effects of loop and thiazide diuretics on kidney tubule transport. BS is characterized by profound juxtaglomerular hyperplasia and secondary glomerular atrophy.74 These changes (see Figure 2C) can appear quite similar to those described during chronic thiazide treatment of rats. Global glomerular sclerosis, focal and segmental glomerulosclerosis, and periglomerular fibrosis have also been reported in some individuals with BS,75 and BS can lead to chronic kidney disease. Unlike BS, however, GS has not been reported to cause chronic kidney disease, although 1 case of end stage renal disease has been reported in a patient with the unusual feature of severe hypocalcemia.76 Kidney biopsies from individuals with GS, although rarely reported, typically show some hyperplasia and hypertrophy of the juxtaglomerular apparatus but not glomerular ischemia or sclerosis.77 Thus, lifelong deficiency of the NCC does not cause substantial renal damage in humans. Although the structural and functional changes in rat kidney reported4,78 are impressive, it is best to be circumspect before imputing similar changes to human use, because effects may differ between species. Our groups22,23,79–81 have provided evidence for species-dependent differences in transport protein expression patterns. In rats, the distribution of basolateral

![Figure 2. Morphological effects of diuretics, BS, and NCC knockout on kidney tissue. Note the structural similarities among A through C. A, Thiazide treatment of rats, from Reference; focal glomerular injury characterized by wrinkling and thickening of the glomerular basement membrane, with splitting of Bowman’s capsule, glomerular collapse, and periglomerular fibrosis (top arrow). Thickening of peritubular basement membrane in the vicinity of the glomerulus (bottom arrow). Original magnification, ×630. B, Thiazide treatment of rats, from Reference; dysplasia and degeneration of DCT segments (D) with peritubular inflammation and fibrosis (bottom arrow), whereas other tubule segments (connecting tubule [CN] and proximal tubule [P]) are structurally intact. Magnification, ×360. C, Kidney from BS patient, from Reference; shows atrophy of one glomerulus (top arrow) and severe juxtaglomerular hyperplasia affecting a second (bottom arrow). Magnification, ×210. D through F, Absence of glomerular changes from control (D), metolazone-treated (for 6 days; E), and NCC-knockout mice (F). A, B, and C were used with permission, 3,72,74.](http://hyper.ahajournals.org/lookup/doi/10.1161/01.hyp.101.06.199)
calcium-extruding pathways is restricted largely to more distal segments of the DCT and connecting tubule; in humans, these transport proteins are expressed along much longer segments. If the cellular toxicity of thiazide diuretics is induced by calcium loading, the expression of calcium exit pathways along much of the DCT may protect human DCT cells from damage. As an example, Loffing et al 17 studied the renal morphology of mice lacking the NCC (see Figure 2D through 2F), mimicking the effects of lifelong thiazide treatment. Those studies showed that DCT segments are markedly shortened and atrophic, with normal architecture beginning at the transition from DCT1 to DCT2.82 Scarring of glomeruli, however, was not described; in follow-up studies, the glomerular morphology of NCC knockout mice was compared with the morphology of mice treated with metolazone for 7 days and with untreated controls. There was no evidence of glomerular fibrosis in any of the groups.

Overall, there is little evidence that thiazide diuretics, when taken by humans chronically at low or moderate doses, increase the risk for chronic kidney disease or structural renal damage. Thiazides are known to reduce glomerular filtration rates (GFRs) functionally; in rats, thiazides reduce GFRs by activating tubuloglomerular feedback.83 In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, an analysis of individuals with baseline estimated GFRs <60 mL/min per 1.73 m\(^2\) found that the GFR after 6 years of treatment was lower with a thiazide diuretic than with amiodipine; it was not, however, lower than with lisinopril,84 a drug usually considered renal protective. Of note, thiazides also reduce proteinuria in hypertensive patients treated with drugs that block the renin-angiotensin system.85,86 Thus, a small decline in GFR does not necessarily imply renal toxicity.

**NCC Deficiency and Essential Hypertension**

A final insight into effects of thiazide diuretics may come from novel genetic approaches. GS and BS are autosomal, recessive, salt-wasting disorders that reduce blood pressure by mutations in salt transport genes along the loop of Henle and DCT. Recently, Lifton et al 87 studied whether a single mutant copy of the GFRs functionally; in rats, thiazides reduce GFRs by activating tubuloglomerular feedback.83 In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, an analysis of individuals with baseline estimated GFRs <60 mL/min per 1.73 m\(^2\) found that the GFR after 6 years of treatment was lower with a thiazide diuretic than with amiodipine; it was not, however, lower than with lisinopril,84 a drug usually considered renal protective. Of note, thiazides also reduce proteinuria in hypertensive patients treated with drugs that block the renin-angiotensin system.85,86 Thus, a small decline in GFR does not necessarily imply renal toxicity.

**NCC Deficiency and Essential Hypertension**

A final insight into effects of thiazide diuretics may come from novel genetic approaches. GS and BS are autosomal, recessive, salt-wasting disorders that reduce blood pressure by mutations in salt transport genes along the loop of Henle and DCT. Recently, Lifton et al 87 studied whether a single mutant copy of the NCC (see Figure 2D through 2F), mimicking the effects of lifelong thiazide treatment. Those studies showed that DCT segments are markedly shortened and atrophic, with normal architecture beginning at the transition from DCT1 to DCT2.82 Scarring of glomeruli, however, was not described; in follow-up studies, the glomerular morphology of NCC knockout mice was compared with the morphology of mice treated with metolazone for 7 days and with untreated controls. There was no evidence of glomerular fibrosis in any of the groups.

Overall, there is little evidence that thiazide diuretics, when taken by humans chronically at low or moderate doses, increase the risk for chronic kidney disease or structural renal damage. Thiazides are known to reduce glomerular filtration rates (GFRs) functionally; in rats, thiazides reduce GFRs by activating tubuloglomerular feedback.83 In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, an analysis of individuals with baseline estimated GFRs <60 mL/min per 1.73 m\(^2\) found that the GFR after 6 years of treatment was lower with a thiazide diuretic than with amiodipine; it was not, however, lower than with lisinopril,84 a drug usually considered renal protective. Of note, thiazides also reduce proteinuria in hypertensive patients treated with drugs that block the renin-angiotensin system.85,86 Thus, a small decline in GFR does not necessarily imply renal toxicity.

**NCC Deficiency and Essential Hypertension**

A final insight into effects of thiazide diuretics may come from novel genetic approaches. GS and BS are autosomal, recessive, salt-wasting disorders that reduce blood pressure by mutations in salt transport genes along the loop of Henle and DCT. Recently, Lifton et al 87 studied whether a single mutant copy of the NCC (see Figure 2D through 2F), mimicking the effects of lifelong thiazide treatment. Those studies showed that DCT segments are markedly shortened and atrophic, with normal architecture beginning at the transition from DCT1 to DCT2.82 Scarring of glomeruli, however, was not described; in follow-up studies, the glomerular morphology of NCC knockout mice was compared with the morphology of mice treated with metolazone for 7 days and with untreated controls. There was no evidence of glomerular fibrosis in any of the groups.

Overall, there is little evidence that thiazide diuretics, when taken by humans chronically at low or moderate doses, increase the risk for chronic kidney disease or structural renal damage. Thiazides are known to reduce glomerular filtration rates (GFRs) functionally; in rats, thiazides reduce GFRs by activating tubuloglomerular feedback.83 In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, an analysis of individuals with baseline estimated GFRs <60 mL/min per 1.73 m\(^2\) found that the GFR after 6 years of treatment was lower with a thiazide diuretic than with amiodipine; it was not, however, lower than with lisinopril,84 a drug usually considered renal protective. Of note, thiazides also reduce proteinuria in hypertensive patients treated with drugs that block the renin-angiotensin system.85,86 Thus, a small decline in GFR does not necessarily imply renal toxicity.

**NCC Deficiency and Essential Hypertension**

A final insight into effects of thiazide diuretics may come from novel genetic approaches. GS and BS are autosomal, recessive, salt-wasting disorders that reduce blood pressure by mutations in salt transport genes along the loop of Henle and DCT. Recently, Lifton et al 87 studied whether a single mutant copy of these genes might lower blood pressure without causing frank disease, thereby protecting individuals from hypertension. Although these observations do not resolve questions about potential salutary or harmful effects of thiazides, they do suggest novel approaches to separate pharmacological and physiological effects of the drugs. Such insights might be used to develop antihypertensive agents that possess only the good, and none of the bad, aspects of diuretics. Although such a goal may never be met fully, even partial success should benefit our patients.

**Sources of Funding**

Experimental work cited in this article was supported in part by the National Institutes of Health (grant DK51496 to D.H.E.), the Department of Veterans’ Affairs (Merit Review to D.H.E.), the Swiss National Science Foundation (to J.L.), the Cloëtta Foundation (to J.L), and the Novartis Research Foundation (to J.L.)

**Disclosures**

None.

**References**


Thiazide Effects and Adverse Effects: Insights From Molecular Genetics
David H. Ellison and Johannes Loffing

*Hypertension*. 2009;54:196-202; originally published online June 29, 2009;
doi: 10.1161/HYPERTENSIONAHA.109.129171

*Hypertension* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/54/2/196

**Permissions:** Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Hypertension* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

**Reprints:** Information about reprints can be found online at:
http://www.lww.com/reprints

**Subscriptions:** Information about subscribing to *Hypertension* is online at:
http://hyper.ahajournals.org//subscriptions/