On the Waterfront

In 1954, Columbia Pictures released the motion picture "On The Waterfront" starring Marlon Brando, filmed in Hoboken, New Jersey. In the film, is the memorable quote: "I coulda been a contender. I coulda been somebody, instead of a bum." Unlike Brando's role as Terry Malloy, elevated blood pressure is a serious contender for chronic diseases like ischemic heart disease and chronic kidney disease. Ironically, the role of Terry Malloy was originally written for the actor John Garfield who died quite young at age 39, presumably from ischemic heart disease.

In this issue of *Advances in Chronic Kidney Disease*, many aspects of hypertension have been examined as it relates to the kidney. More than 50 years ago (just a few short years before the debut of "On The Waterfront"), Irvine Page proposed the "mosaic theory of hypertension"[1] (Fig 1). If the mosaic were adapted to hypertension and CKD, it might take on features depicted by Figure 2.

The importance of the kidney in high blood pressure is exemplified in the "victim or villain" terminology, which, in one phrase, places the kidneys in the roles of both the perpetrator and, at the same time, the prey of forces which regulate the pressures associated with blood flow. Reading these contributions increases our appreciation for the healthy kidney to produce, excrete, or balance a myriad of chemicals, cytokines, salts, vitamins, and nutrients with constant attention to the preservation of the interior milieu.[2] A waterfront is a scene of bustling activity, accents, and exchanges. The series focused in this issue on hypertension and CKD begins the convoy of information with a positioning of the role of hypertension in worldwide attributable cardiovascular risk, and then moors elevated blood pressure to a series of CKD complications.

We now hope that with a scaffold of elevated blood pressure as a risk factor framed by Ken Jamerson and Ray Townsend, readers will see the size of the net cast by hypertension across the globe. The factors relating to hypertension in end stage kidney disease (ESKD) is adroitly piloted by Rajiv Agarwal, and the influence of elevated blood pressure on cardiovascular disease (CVD) and graft survival after successful transplantation as anchored by Mario Rubin bears further testimony to the ubiquity of blood pressure elevation in patients with a spectrum of kidney dysfunction.

Although we typically answer the question of "What is the most frequent comorbidity associated with ESKD?"

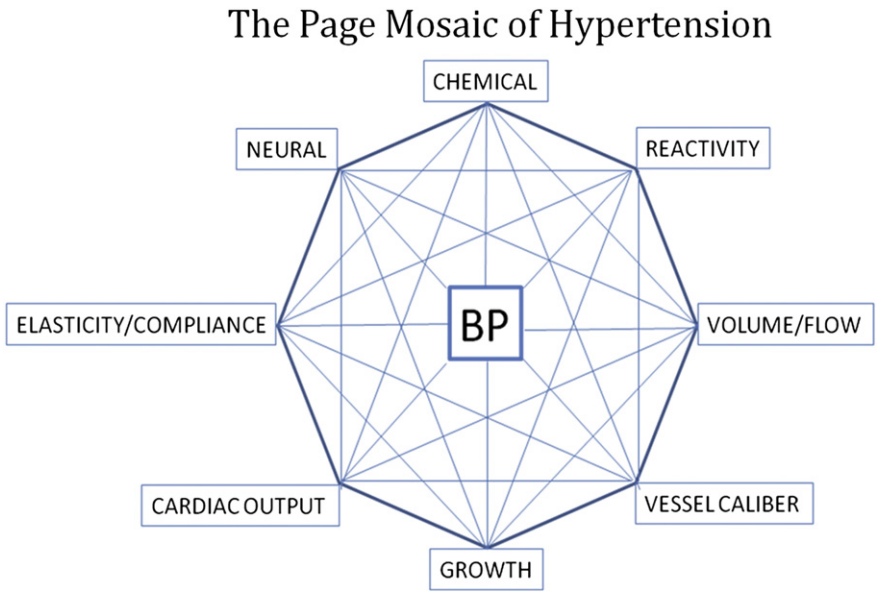

Figure 1. Page Mosaic of Hypertension, developed by Irvine Page in the early 1950s. This model recognized the significant diversity of influences on blood pressure. A major feature is the inter-relatedness of each factor. For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article. The Mosaic Theory of Arterial Hypertension: Its Interpretation, published in Perspectives in Biology and Medicine, 1967;10:325–333. Adapted and reprinted by permission of The Johns Hopkins University Press.

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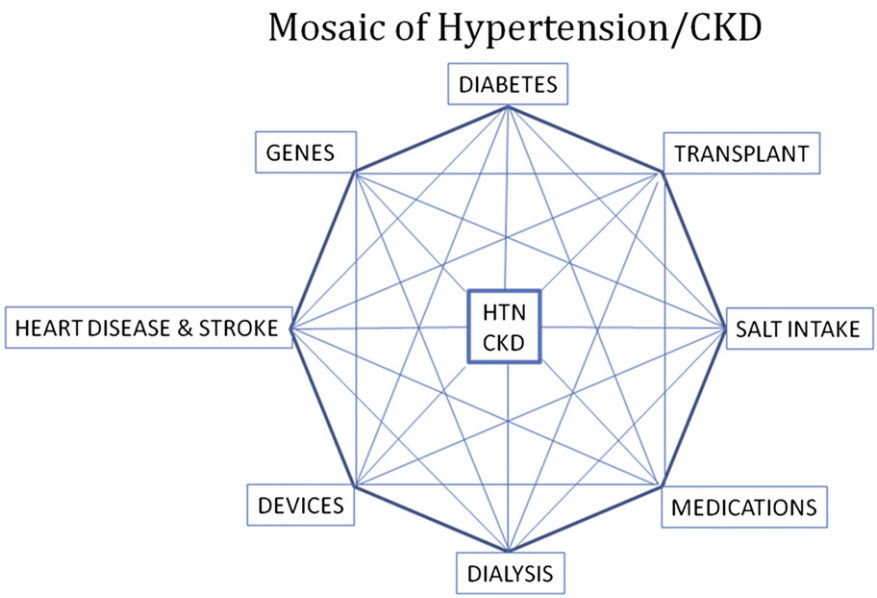

Figure 2. Remodeling the Page Mosaic. There is a shift in emphasis to model hypertension and chronic kidney disease. For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.

with "diabetes," the second leading comorbidty is hypertension, and elevated blood pressure is a frequent co-conspirator with diabetes increasing its prevalence. In our experience with the Chronic Renal Insufficiency Cohort, about 7 out of 8 patients with diminished kidney function suffer from high blood pressure.[3] Luis Ruilope covers the wharf of high blood pressure in CKD that is not characterized by diabetes, whereas Robert Toto navigates us skillfully through the state-of-the-art of diabetic hypertension in CKD.

As outlined in the sections by Domenic Sica, impaired kidney function forces us to consider carefully our choice of medications, the dosages we use, and the potential for enhanced adverse occurrences, particularly rapid worsening of kidney function and elevated potassium levels. Also, there is leveraging of the importance of the kidney sympathetic nervous system (there are no renal parasympathetics) by virtue of catheter-based neural ablation accomplished through the renal arteries.[4]

With so much knowledge regarding the pathophysiology in CKD, and so many drug and device interventions available, what questions remain in this field? There are several things remaining to ponder, as outlined in Table 1, and this only scratches the surface. A visit to Web site www.clinicaltrials.gov and entering the search term "hypertension AND kidney disease" will provide for at least a full night's reading (456 hits when accessed October 4, 2010). Thus, what's in the hypertension and CKD pipeline now? There is a new initiative just beginning to enroll across the United States called the Systolic Pressure Intervention Trial which will address optimal systolic blood pressure for both kidney and cognitive function preservation (among other questions) in more than 9000 adults in the United States. Hopefully, Systolic

Table 1. Some Questions in Hypertension and Chronic Kidney Disease

What is "ischemic nephropathy" and how do we evaluate and manage it?
Which blood pressure aspect (systolic, diastolic, pulse pressure, mean arterial pressure) gives us the best insight into recognizing risk for, or consequence of, kidney damage?
As new genes are implicated in CKD development and progression, how do we "connect the dots" between the gene product(s), blood pressure, and kidney function with plausible pathophysiology?
How well do we assess longitudinal kidney function? Do our formulae (which were developed in cross-sectional studies) perform adequately when measured repeatedly?
How long do interventions on the carotid sinus or the kidney artery (via radio frequency ablation) persist?
What drives the continued loss of kidney function when on an optimal regimen with good blood pressure, lipid, and general CVD risk factor control?
Can drug therapy for hypertension prevent the onset of kidney function impairment?
What role do things like the noninvasive measurement of arterial compliance and central blood pressure profile play in the evaluation and management of hypertension and kidney function?
Will it be possible someday to accurately measure the number of functioning nephrons with a noninvasive procedure or biomarker?
What is the goal blood pressure to aim for in hypertensive patients with CKD, and is it different when significant sub-clinical or clinical CVD is already present?

Pressure Intervention Trial will bring us closer to answers for some of the questions we have proposed. In the meantime, it remains our vigilant responsibility to find elevated blood pressure and decreased kidney function through careful screening efforts like those characterized by the Kidney Early Evaluation Program (KEEP),[5] while we continue to scan the horizon for more tools and more effective usage of existing resources to steer around the many obstacles, visible and submerged, that elevate blood pressure and damage kidney function which reduces the quality of life, and the longevity of our patients.

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References

1. Page IH. The mosaic theory of arterial hypertension—its interpretation. *Perspect Biol Med.* 1967;10:325-333.
2. Noble D. Claude Bernard, the first systems biologist, and the future of physiology. *Exp Physiol.* 2008;93:16-26.
3. Muntner P, Anderson A, Charleston J, et al. Hypertension awareness, treatment, and control in adults with chronic kidney disease: results from the Chronic Renal Insufficiency Cohort (CRIC) study. *Am J Kidney Dis.* 2010;55:441-451.
4. Krum H, Schlaich M, Whitbourn R, et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet.* 2009;373:1275-1281.
5. Kalaitzidis R, Li S, Wang C, Chen SC, McCullough PA, Bakris GL. Hypertension in early-stage kidney disease: an update from the Kidney Early Evaluation Program (KEEP). *Am J Kidney Dis.* 2009; 53:S22-S31.