From the Editor
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Why Are We Here?
Why is there a Council on the Kidney in Cardiovascular Disease? Obviously, there must be some relationship between the kidney, the vasculature, and the heart! We all recognize the link between hypertension and kidney disease, as well as the role the kidney likely plays in the pathogenesis of most forms of hypertension.

Hypertension is a leading risk factor for heart attack and stroke, making our existence completely clear. However, this “dance” between the heart and kidney is accompanied by music from the levels of glucose and lipids in the blood, a chorus conducted by adipose tissue and the endocrine pancreas. As we learn more, the orchestra accompanying our players continues to expand.

This issue of the newsletter summarizes some recent publications regarding that clustering of risk factors, often called the metabolic syndrome, the insulin resistance syndrome, or, my personal favorite, syndrome X. I like the latter because it sounds like something from a cartoon or a bad science fiction movie. You can almost hear the Cold War villains or contemporary terrorists discussing the use of “Syndrome X” for their next attack on an unsuspecting population. Perhaps the Department of Defense should increase research funding for the major killers...

Enough of that; I will get back to the business at hand. This clustering of cardiovascular and kidney risk factors was employed in the design of an early intervention program approximately a decade ago. The Kidney Early Evaluation Program (KEEP™) is maturing and showing its value as both a clinical intervention and a population research tool.

The American Heart Association will sponsor a symposium on Obesity, Lifestyle, and Cardiovascular Disease, January 18–20, 2006, in Washington, DC. More information can be found at www.americanheart.org/presenter.jhtml?identifier=3029186.

Please let me know if there are other controversies or issues you would like to see addressed in these pages. Once again, the best way to reach me is by e-mail at phlane@unmc.edu.

KEEP It Simple Screening
The Kidney Early Evaluation Program™ (KEEP) of the National Kidney Foundation (NKF) is a screening program targeted at adults with a personal history of diabetes or hypertension or with a family history of diabetes, hypertension or kidney disease. Physician counseling is provided to participants who undergo evaluation of blood pressure, body mass index, urine albumin, blood creatinine, blood hemoglobin and family history. Approximately 5 percent of KEEP participants have elevated creatinine levels, and more than half have chronic kidney disease (CKD), defined as an estimated glomerular filtration rate (GFR) >60 with microalbuminuria or an estimated GFR <60.

Overall, 25 percent of KEEP participants self-report diabetes, while another 7 percent have abnormal screening values for glucose. More than half report hypertension, while another 5 percent to 9 percent have elevated blood pressure readings. More than three-quarters of participants are obese, while only 13 percent have ever smoked.

The KEEP Annual Data Report 2005 was recently published as a supplement to the American Journal of Kidney Disease, 2005:46 (Suppl 3). It provides graphic descriptions of the interrelationships between CKD and risk factors for cardiovascular disease in the KEEP™ participants and the latest NHANES population.

Cardiovascular risk factors include a self-reported personal history of diabetes, body mass index >25, a history of smoking, anemia using sex-specific criteria and hypertension. Overall, more than 70 percent of KEEP™ participants have two or more cardiovascular risk factors. If no evidence of CKD is present, approximately 60 percent of those screened fall into this category. Microalbuminuria, with normal or mild reductions in GFR, increases the prevalence of multiple risk factors to more than 75 percent. Reductions in GFR below 60 increase the prevalence of clustered risk factors to approximately 85 percent.

Cardiovascular disease is the most important cause of death in patients with late-stage CKD; however, even in earlier stages these people are likely to have multiple cardiovascular risk factors that should be identified for intervention. Expanding the KEEP™ program’s screening strategy may help reduce the burden of cardiovascular and kidney disease.
The Syndrome X Files

The “metabolic syndrome” is a lot like pornography; it is hard to define, but we all know it when we see it. Alternatively known as the “insulin resistance syndrome” or “syndrome X,” this entity represents a clustering of risk factors for cardiovascular disease (CVD). ICD-9 code 277.7, “dysmetabolic syndrome X,” is defined as “a specific group of metabolic disorders that are related to the state of insulin resistance without elevated blood sugars; often related to elevated cholesterol and triglycerides, obesity, cardiovascular disease, and high blood pressure.”

Two major specific definitions of the metabolic syndrome, the ATP III and the WHO (see table), are used in most research studies. While there is much overlap between these definitions, there are distinct differences as well. Microalbuminuria, an established marker of risk for kidney and cardiovascular disease, is included in the WHO criteria but not those of the ATP III.

With the ATP III definition, patients can be classified as having “metabolic syndrome” without evidence of abnormal glucose metabolism. There are also ambiguities in these definitions that make patient classification difficult.

Whatever definition is used, there is no question that this clustering of findings predicts risk of future cardiovascular disease and type 2 diabetes mellitus. This fact is hardly surprising since abnormalities of glucose are included in both definitions, although only required in the WHO criteria. Thus, mild abnormalities of glucose control predict more severe future dysregulation. In general, most of these criteria are independent predictors of cardiovascular and kidney disease risk as well. We must now consider what “value” is added to the diagnosis of “metabolic syndrome” versus consideration of the individual risk factors.

The “metabolic syndrome” concept was unified via the central mechanism of insulin resistance by Reaven in 1988, who suggested that compensatory hyperinsulinemia could predispose patients to hypertension, hyperlipidemia, and diabetes. More than 4,000 subsequent publications have assessed this cluster of findings as a multivariate cardiovascular risk factor, in general confirming the relationship to CVD. As discussed by Kahn et al (Diabetes Care 28:2289, 2005), the sheer volume of work on this entity and the existence of an ICD-9 code suggest that it is a well-established clinical diagnosis. This joint statement of the American Diabetes Association and the European Association for the Study of Diabetes then reviews the literature regarding the “syndrome” and concludes that there is little “value added” by making this diagnosis. The CVD risk associated with “metabolic syndrome” is generally no greater than the sum of its parts, and there is no treatment for the “syndrome” aside from treatment for its individual components. The American Heart Association and National Heart, Lung, and Blood Institute have recently published a joint scientific statement recommending diagnosis of the metabolic syndrome so that therapies can be directed at reducing all of these risk factors simultaneously (Circulation 112:e285, 2005). This paper argues that this cluster of signs and symptoms is clinically useful for determination of long-term cardiovascular risk above and beyond individual risk factors.

The bottom line: risk factors for CVD, including kidney problems, cluster, perhaps because of related causes. If a patient has one of these risk factors, searching for other modifiable risk factors is imperative. Many of these risk factors can be treated simultaneously with lifestyle modifications that address the entire cluster of signs and symptoms. Finally, both position papers agree that the cause(s), natural history, and treatment(s) for this entity require further research.

The AHA/NHLBI position paper can be accessed at http://circ.ahajournals.org/cgi/content/full/112/17/2735. The ADA/EASD joint statement by Kahn et al can be found at http://care.diabetesjournals.org/cgi/content/full/28/9/2289.