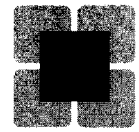

WILLIAM S. WILKE, MD, EDITOR

PROGRESSION OF RENAL DISEASE: CAUSES, POTENTIAL THERAPIES

Studies during the past five years indicate that both the pathogenesis and prevention of progressive renal failure are much more complex than previously thought. The tendency of chronic renal insufficiency to progress to end-stage renal failure at a variable rate has long been observed, and the variable rate of progression was attributed to the diversity of the initial insult. While this initial insult may have an influence, it now appears that several additional mechanisms are responsible for worsening nephron loss. Some of the better-understood causative factors and potential therapies for preventing progression of renal disease are described.

GLOMERULAR HYPERTENSION

Glomerular hypertension is thought to be one of the more important mechanisms in renal disease progression. Various experimental models of progressive renal disease (renal ablation, streptozocin diabetes, experimental glomerulonephritis) are characterized by an increase in transcapillary hydrostatic pressure (Pgc), proteinuria, glomerular hypertrophy, and glomerular sclerosis. Maneuvers (dietary protein restriction, antihypertensive therapy, and sodium chloride restriction) that lower the Pgc toward normal reduce the rate of progression of sclerosis and azotemia. The increase of Pgc is thought to be due to afferent arteriolar vasodilation, possibly mediated by prostaglandin or atrial natriuretic hormone. This increase in Pgc is often accompanied by an increase in glomerular capillary blood flow and single-nephron filtration rate. Several experimental maneuvers are known to alter these glomerular hemodynamics and alter the course of progressive disease in the remnant kidney model.

Administration of angiotensin converting enzyme (ACE) inhibitor agents and dietary protein restriction suppress the glomerular hemodynamic change and thus reduce the extent of later glomerular structural change (Hostetter et al. Kidney Int 1986; 30:509–517) (Brenner. Am J Physiol 1985; 249:F324–327). Conversely, high dietary protein and use of corticosteroids increase both glomerular hypertension and sclerosis.

How the altered glomerular hemodynamics produce glomerular injury is not known. Two possible mechanisms include trapping of proteins in mesangial cells due to increased flow through the mesangial matrix and increased glomerular filtration of plasma proteins, which may damage glomerular epithelial cells.

SYSTEMIC HYPERTENSION

Systemic hypertension affects the kidney adversely and is often responsible for accelerated progression of renal insufficiency in humans and animals with underlying renal disease (Anderson et al. J Clin Invest 1985; 76:612–619). The mechanism may be due to increased glomerular hypertension or to hypertension-induced vascular sclerosis with ischemic glomerulosclerosis. In rats with remnant kidneys and in humans with renal disease, lowering systemic blood pressure is associated with inhibition of the rate of progression of azotemia.

Newer studies have shown that mechanisms other than glomerular hypertension or hyperperfusion may be responsible for progression. For example, *thromboxane inhibitors* suppress glomerular injury without changing glomerular hemodynamics. *ACE inhibitors* reduce glomerular sclerosis in the puromycin model without affecting the hemodynamic pattern (Yoshida et al. Kidney Int 1988; 33:855–867). Since angiotensin-II is known to increase the passage of circulating macromolecules into mesangial cells, to cause increased glomerular pressure via increased efferent arteriolar construction, and to enhance mesangial cell contraction, it is likely that the beneficial effects of ACE-inhibition on progressive sclerosis are multifactorial.

INTRAGLOMERULAR COAGULATION

Intraglomerular coagulation may contribute to progression. Administration of warfarin or heparin reduces sclerosis in rats subjected to subtotal nephrectomy. Because these drugs affect clotting, it is thought that local activation of the clotting process may play a role in sclerosis—possibly through complement activation of the clotting cascade.

Heparin reduces glomerulosclerosis without altering hemodynamics. However, the benefit of heparin may not be due entirely to anticoagulant activity. Evidence for this derives from experiments in which N-desulfated heparin, which is devoid of anticoagulant effects, also reduces glomerular lesions in rats with a remnant kidney.

This beneficial effect of heparin may result from its known antiproliferative effect. This may be of importance because several forms of renal disease have associated *mesangial hypercellularity*. Such mesangial cellularity could be mediated by growth factor enhancing peptides (interleukins), by the physical effects of enhanced glomerular mesangial flows, or from mesangial migration of monocytes with release of monokines (interleukin I) locally.

HYPERLIPIDEMIA

High serum lipid levels, frequently present in various renal diseases, may contribute to progressive sclerosis. Mechanisms include: an effect of lipoproteins upon mesangial cell proliferation and collagen production, lipid-induced adherence of monocytes to endothelial cells, and lipid-induced changes in basement membrane permeability as a result of neutralizing the negative charge on the membrane.

Reduction of cholesterol by drugs (mevinolin or clofibrate) in rats with subtotal nephrectomy and obese Zucker rats decreases focal glomerulosclerosis (Keane WF et al. Am J Clin Nutr 1988; 47:157–160). Dietary protein restriction results in lower serum lipids. Thus, protein restriction may mediate protection against progressive sclerosis via its lipid-lowering effects.

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IDENTIFY MALIGNANT HYPERTHERMIA SUSCEPTIBILITY TO AVERT LIFE-THREATENING EPISODES

Malignant hyperthermia became well known in 1960 when Australian physicians described a 21-year-old student who survived an episode. Ten of his relatives had died as a direct consequence of ether anesthesia. The mortality rate for malignant hyperthermia was more than 60% until intravenous dantrolene sodium therapy became available for widespread use in 1979 and drastically reduced mortality. However, some mortality does occur if malignant hyperthermia susceptibility is not detected before surgery. Thus, the key is to detect susceptible patients prior to surgery so that an episode can be prevented or aborted with proper treatment.

CHARACTERISTICS

Malignant hyperthermia is an autosomal dominant muscle disease that manifests in susceptible persons when they are exposed to general anesthesia. Potent volatile anesthetics (eg, halogenated agents) or succinylcholine produce increased aerobic and anaerobic metabolism, rapidly increasing temperature, systemic acidosis, and frequently muscle rigidity in susceptible persons. This metabolic storm usually includes tachycardia, signs of general circulatory and metabolic stress, and increased muscle permeability that leads to increases in serum electrolytes, creatine kinase, and myoglobin. The mechanisms of metabolic storm are not fully understood, but abnormal calcium control may trigger the event in both excitable and nonexcitable cells.

INCIDENCE

The estimated frequency of susceptibility is 1 of 15,000 children and 1 of 50,000 adults who undergo general anesthesia. Surprisingly, 23% of malignant hyperthermia-susceptible patients have a history of previous uneventful general anesthesia. Susceptibility in the black population is only one-tenth that of the Caucasian population.

DIAGNOSIS AND TREATMENT

The best treatment is prevention. Genetic counseling and diagnostic tests are crucial for those who have had unusual anesthetic complications or who have one or more family members with a history of malignant hyperthermia. All susceptible people should wear a medical alert bracelet. The diagnostic test for malignant hyper-