Basic research in cardiovascular physiology has provided essential answers for a wide spectrum of problems in cardiovascular disease and has led to evidence-based medicine. The cardiovascular system must properly function throughout life, and we owe it to ourselves to maintain this well designed physiological system through exercise, proper nutrition, and stress reduction. In this regard, the discoveries of our physiological community are absolutely critical. This issue of Physiology explores various aspects of cardiovascular physiology and how a healthy cardiovascular system affects our lives.

Worldwide, more people die annually from cardiovascular disease than from any other cause. Exercise is a well documented, safe, inexpensive, and accessible strategy that counteracts the deleterious effects of many risk factors associated with cardiovascular disease, confers sustainable protection against myocardial infarction in animal models, and improves survival following myocardial ischemia in humans. Yet the cellular mechanisms behind these beneficial actions of exercise remain largely undiscovered. In their review (1), Calvert and Lefer discuss the role that endothelial nitric oxide (NO) synthase, endogenous NO, NO metabolites (nitrite and nitrosothiols), and β-adrenergic receptors (β-ARs) play in mediating the cardioprotective effects of exercise following myocardial ischemia-reperfusion injury. A greater understanding of the molecular signaling cascades induced by exercise may lead to therapeutic strategies for patients at risk for cardiovascular diseases or who have already suffered a heart attack or stroke.

Preeclampsia is a spontaneous cardiovascular disease of pregnancy affecting ~7% of pregnancies in the US and is responsible for ~20% of the 13 million pret term births worldwide each year. In their review (3), LaMarca and colleagues discuss the role of immune mechanisms stimulated in response to reductions in uterine perfusion pressure in a rat model of preeclampsia. The ischemic placenta is associated with a dysregulation of natural killer cells, the activation of CD4+ T lymphocytes, and the release of anti-angiogenic and proinflammatory factors such as the soluble VEGF receptor-1 (sFlt-1) and s endoglin, the angiotensin II type-1 receptor autoantibody (AT1-AA), and cytokines such as TNF-α and interleukins 6 and 17. Many of these factors have been shown to stimulate maternal endothelial dysfunction, an increase in circulating and local endothelin (ET-1) and reactive oxygen species (ROS), or enhanced vascular sensitivity to angiotensin II, all of which have been shown to contribute to the decrease in renal function and/or to the hypertension in pregnant animal models of this disease. Understanding the link between immune activation, placental ischemia, endothelial dysfunction, and hypertension during pregnancy should lead to better prediction, prevention, and treatment strategies for women and children affected by this devastating disease.

Beginning in adolescence, men have higher blood pressure than women, and these trends persist into the sixth decade of life. Despite the fact that sex differences in blood pressure have been recognized since the 1940s, current national guidelines recommend the same approach for treating men and women with hypertension. A recent cross-sectional survey found that women with hypertension were more likely than men to be treated and take their medication, yet only 45% of treated women achieved effective blood pressure control compared with 51% of treated men. In their review (6), Zimmerman and Sullivan argue that it is important for the scientific community to better understand the implications of sex differences in blood pressure control. Recent data from both clinical studies and basic science research have revealed important sex differences in the molecular mechanisms that control blood pressure. For example, a comprehensive analysis of 23,574 transcripts in multiple tissues of male and female mice derived from an intercross between inbred mouse strains C57BL/6J and C3H/He revealed that the extent of sexual dimorphism in gene expression was much greater than previously recognized. Thousands of genes were differentially expressed in liver, adipose, and muscle, and hundreds of genes were sexually dimorphic in the brain. A better understanding of the molecular mechanisms driving sexual dimorphisms in vasculature, nervous system, and kidney function, as well as how the individual pathways to control blood pressure interact, is imperative to design and implement more effective and potentially sex-specific, anti-hypertensive treatments.

Renal artery stenosis remains an important cause of secondary hypertension and is associated with increased cardiovascular morbidity and mortality. Salvaging kidney function is a significant challenge in managing renal artery stenosis. Recent studies have identified key processes responsible for kidney injury such as oxidative stress, microvascular damage, inflammation, and fibrogenic pathways. These studies have advanced the notion that interactions among these deleterious pathways amplify renal injury. In their review (2), Eirin and Lerman discuss experimental studies in humans and animal models aimed at developing innovative strategies that have the potential to attenuate the detrimental effects of chronic hypoperfusion in the stenotic kidney and decrease the burden of chronic kidney disease.

When the immune system ceases to recognize the body’s normal constituents, it produces autoantibodies that can be beneficial, helping to destroy unwanted cells and eliminate waste products. However, autoantibodies directed at receptors can interfere with signaling and normal physiological processes that may cause a variety of autoimmune diseases. For physiologists, many basic questions remain. Precisely how these autoantibodies activate receptors is mysterious since they commonly bind far distant from the ligand binding sites. In his review (5), Luft argues new advances are needed into the structural biology of receptor-autoantibody interactions. He discusses how activating autoantibodies directed at beta-adrenergic receptors, alpha-adrenergic receptor, and the angiotensin II (AT1) receptor have been implicated in causing cardiomyopathy, hypertension, preeclampsia, and humorally mediated kidney transplant rejection. The clinical implications of these observations...
are considerable. Improved methods of diagnosis and strategies directed at removal of offending autoantibodies could be developed as therapeutic targets for these devastating diseases.

NO is the principle mediator of penile erection and is released from nerves innervating the corpora cavernosa and small penile arteries when the stimulus for erection occurs. PDE-5 inhibitors are the first-line agents used to treat erectile dysfunction (ED); however, they are no longer effective when NO formation or bioavailability is decreased by oxidative stress. In their review (4), Lasker and colleagues discuss new classes of agents that promote erection. Soluble guanylate cyclase (sGC) stimulators, such as BAY 41-8543, produce normal erectile responses when NO formation is inhibited and the nerves innervating the corpora cavernosa are damaged. Their effectiveness is limited by severe oxidative stress when the heme iron on sGC can be oxidized, rendering the enzyme unresponsive to NO or sGC stimulators. In this case, sGC activators have been developed to increase the catalytic activity of the oxidized enzyme, increase cGMP formation, and promote erection. These new agents have the potential to improve erectile function in patients with ED resulting from diabetes and prostatic surgery.

**References**