Claude Bernard is considered by many to be the father of modern physiology and medicine. In his 1865 book, An Introduction to the Study of Experimental Medicine, Bernard introduced the scientific method to the field of medicine and thereby initiated the concept of evidenced-based medicine. In this approach, physiological research focuses on finding solutions for clinical problems through hypothesis-driven research. In this regard, the interaction between clinician and scientist is critical. Bernard clearly understood this when he stated, “The experimenter who does not know what he is looking for will not understand what he finds.” Today, 150 years later, the discoveries made through physiological research have transformed medical practice, and in many respects physiology is medicine. In his invited editorial in this issue of Physiology, Dr. Jeff Sands emphasizes the role of renal physiology in the advances made in clinical nephrology. Sands refers to the recommendations of the Kidney Research National Dialogue initiated by the National Institute of Diabetes and Digestive and Kidney Diseases, which identified research objectives that would improve basic knowledge of kidney physiology and thereby impact the treatment of kidney disease. Along this line, several review articles in this issue of Physiology illustrate how targeted physiological research has and will continue to transform medicine.

Research in renal physiology has provided considerable insight into the complexity and limits of kidney circulatory adaptations in response to reductions in blood flow. It has been demonstrated that occlusive renovascular disease caused by atherosclerotic renal artery stenosis elicits complex pathophysiological responses that eventually lead to loss of kidney function. In their review (6), Saad and colleagues emphasize that reductions in oxygen related to vascular disease ultimately trigger inflammatory injury that continues to drive scarring in the kidney even after restoration of main vessel blood patency. Several randomized prospective clinical trials have shown that stent revascularization alone in patients with atherosclerotic renal artery stenosis provides little additional benefit to medical therapy once these inflammatory processes have developed and solidified. Experimental data now support developing adjunctive cell-based measures to support angiogenesis and promote anti-inflammatory renal repair mechanisms. Modifying the inflammatory response using mesenchymal stem cell therapy in the kidney offers the potential to recover small vessels and limit kidney injury. These data support the use of cell-based therapy to protect injured kidneys and prevent progression to advanced kidney failure.

Research in renal physiology has also shown that macrophages play a key role in both normal and diseased kidneys. Macrophages are involved in the clearance of cellular debris, tissue immune-surveillance, and cellular repair. These cells display considerable phenotypic diversity, and thus their roles in the development, progression, and resolution of a broad range of kidney diseases are equally diverse. For example, pathophysiological changes in some disease states induce pro-inflammatory macrophages that further exacerbate tissue injury, inflammation, and subsequent fibrosis. In contrast, physiological changes may also induce anti-inflammatory macrophages that mediate kidney repair and regeneration. In their review (2), Cao et al. summarize the diverse roles of different macrophage phenotypes in kidney injury, inflammation, and fibrosis in various acute and chronic kidney diseases. Understanding what alterations of the kidney microenvironment occur and how these factors control macrophage phenotype and functions may unveil novel therapeutic targets to limit injury and restore function in kidney disease.

Research in renal physiology has also provided mechanistic insight into autosomal-dominant polycystic kidney disease (ADPKD), which is the most common inherited kidney disease. More than half of affected patients develop kidney failure requiring dialysis or kidney transplantation due to the development of multiple kidney cysts. In addition, ADPKD affects other organs such as the heart, liver, and brain, which can lead to life-threatening conditions. In their review (7), Saiigusa and Bell discuss how physiological research has provided a better understanding of cyst development, including the role of primary cilia and polycystins in ADPKD. An approved treatment for ADPKD is currently unavailable, but research has revealed several potential therapeutic targets that may slow disease progression. Indeed, several drugs are currently being tested in human clinical trials. Such treatments will significantly reduce the overall mortality rate in people with ADPKD.

Physiological research has also impacted other areas of medicine. By the year 2030, 20% of the population in the United States will be over the age of 65. This demographic change will result in a greater incidence of chronic diseases that will require substantial investments in health care. Aging is accompanied by the onset of sarcopenia, the age-related loss of muscle mass, which negatively impacts both muscle strength and endurance, in addition to creating a higher risk for the development of chronic metabolic diseases. Mitochondria are essential organelles for skeletal muscle health and exhibit age-related changes that may underlie sarcopenia. In their review (3), Carter and colleagues discuss physiological research exploring the cellular and molecular mechanisms that connect age-related mitochondrial changes to sarcopenia. Age-related decrements in mitochondrial quality may reflect changes in the molecular pathways responsible for both mitochondrial synthesis (biogenesis) and degradation/repair (mitophagy). Physical inactivity in old age may impact these molecular pathways, leading to diminished mitochondrial quality. It is well known that aerobic exercise induces both mitochondrial biogenesis and mitophagy, thereby improving mitochondrial quality. Older individuals who participate in aerobic exercise stimulate mitochondrial adaptations that improve muscle function and quality of life. However, it is unclear how age-related mitochondrial biogenesis and mitophagy interact with sarcopenia. Improved mitochondrial quality...
could lead to improved muscle physiology and metabolism in old age.

There is an alarming rise in maternal obesity and poor diet during pregnancy that has a detrimental impact on development of the fetal cardiovascular system. However, the in utero relationships between maternal body composition, placental adaptations, and fetal cardiovascular development are not well understood. In their review (5), Roberts et al. summarize what is known about maternal metabolic status and its impact on placental function and cardiovascular health outcomes in the offspring. Mechanistic insight gained from physiological studies in animal models can inform future clinical management of human pregnancies complicated by maternal obesity. Specifically, early detection of placental insufficiency in at-risk women will allow for intervention during pregnancy to improve fetal cardiovascular health and long-term outcome. In addition, identifying children at an increased risk for cardiovascular disease in later life should lead to more effective monitoring and possible therapeutic interventions, which should reduce the public health burden associated with the increased incidence of obesity.

Omega fatty acids, also called polyunsaturated fatty acids, are essential in our diets, serving as components of membrane phospholipids, precursors of hormones, and signaling molecules that affect gene expression. Omega fatty acids are present in all living cells of organisms ranging from bacteria to humans. Current evidence points to specific physiological roles of each omega fatty acid rather than to any ubiquitous effect of this fatty acid class. Understanding the physiological roles of omega fatty acids in animals, particularly in species undergoing dramatic temporal shifts in their physiological state, such as hibernators, may help to gain insights into their roles in human physiology and health. In their review (1), Arnold and colleagues discuss evidence from animal models that explore pathways by which specific omega fatty acids exert different physiological effects. Beneficial effects of certain omega fatty acids, namely omega-3 fatty acids, on the cardiovascular system or neural function in humans are well known. However, studying their function in diverse animal models can help to identify tradeoffs between costs and benefits of upregulated cellular content of individual omega fatty acids. This research may lead to a better understanding of the physiological consequence of uptake of foods that are enriched with, or depleted of, specific omega fatty acids.

The intestinal mucosal barrier must provide both a defense against invading pathogens and recognition of trillions of microbes that comprise the microbiota. A number of pattern-recognition receptors, including the NOD-like receptor (NLR) family of proteins, are expressed by cells within the intestinal mucosa. As pattern-recognition receptors, NLR proteins in the intestinal mucosa play important roles in detecting invading pathogens and mounting an immune response against these microbes. At the same time, NLRs balance signals provided by commensal microbes with immune responses from the barrier cells within the mucosa. In their review (4), Claes and colleagues discuss the role of these NLRs in gastrointestinal homeostasis, and how mutations in some NLR proteins are associated with the pathophysiology of inflammatory bowel disease (IBD). Therefore, a better understanding of the physiology of mucosal NLR proteins may lead to the discovery of novel therapeutic targets for IBD.

No conflicts of interest, financial or otherwise, are declared by the author(s).

References