Physiology impacts our lives on a daily basis, and physiologists have the rewarding experience of exploring how life works. Our research reveals life and eventually makes life better through the knowledge we provide. Our journal *Physiology* publishes review articles on a wide range of themes in physiology, and in this issue we introduce three of these themes.

**Physiology is Medicine**

One of the important goals outlined in the 5-year strategic plan of the American Physiological Society (APS) is to enhance human and animal health by disseminating research discoveries and facilitating research and scientific interactions. As pointed out in several recent editorials in *Physiology*, physiologists have traditionally been a critical link between basic research and human medicine (3, 5, 11). Physiologists play an important role in translating scientific discoveries at a molecular, cellular, whole organ, and integrative level to drug discovery and improved patient care. Indeed, physiology is medicine! One of the important themes or goals of articles published in *Physiology* is to highlight the relevance of the discipline of physiology to enhancing human and animal health. Several of the reviews in this issue of *Physiology* describe biological processes that have important physiological and pathophysiological implications.

Physiological adaptations to mechanical forces play an important role in numerous biological processes. For example, cardiac hypertrophy due to increased preload to the heart is a normal response to healthy exercise or pregnancy, which results in an increase in the heart’s muscle mass and pumping ability. In response to diseases such as hypertension or myocardial infarction, unhealthy cardiac hypertrophy or pathological hypertrophy occurs. Pathological hypertrophy also leads to an increase in muscle mass, but the muscle does not increase its pumping ability and instead leads to myocardial fibrosis and in some cases eventual heart failure. Other cell types in the body such as smooth muscle and epithelial cells also respond to mechanical forces under various physiological and pathophysiological conditions. Thus a better understanding of how muscles, cells, and proteins respond to force is of critical importance. Moreover, the ability to explore the molecular mechanisms of these events, in key proteins, is of crucial importance. In their review, Javadi et al. (4) describe how development of single-molecule force spectroscopy has emerged as an important tool to investigate the forces and motions associated with such processes. They suggest that these novel technical approaches can be readily combined with simulations and theoretical studies to provide a well-rounded view of how proteins respond to force at the single-molecule level.

The respiratory and the digestive systems of the body are constantly being exposed to toxins or infectious agents. The respiratory and the digestive tracts utilize novel sensing mechanisms that can evoke changes in local epithelial characteristics or local autonomic reflexes to guard against the exposure of these potentially harmful substances. Obviously, abnormalities in these protective mechanisms could have important pathological consequences. In their review, Tizzano and Finger (12) described how G-protein-coupled receptor molecules and downstream effectors that are used by taste buds are also utilized by chemoresponsive cells of the airways to detect irritants. They also describe the different cell types in the airways that utilize taste-receptor signaling involving PLC2, IP3R3, and TrpM5 to trigger protective mechanisms. These mechanisms include epithelial responses as well as neural responses such as sneezing, coughing, or apnea to respond to dangerous toxins and bacterial infection.

Contraction of the cardiac muscle involves a precise balance of the expression and function of sarco-/endoplasmic reticulum luminal and transmembrane proteins involved in myocyte calcium handling. An imbalance in the activities and/or levels of these proteins can lead to impaired cardiac contractility and cardiac dysfunction. Although the synthesis of the proteins responsible for contractile calcium handling are essential for proper cardiac myocyte function, the location and mechanisms of these processes in cardiac myocytes have yet to be fully elucidated. In this issue of *Physiology*, Glembotski (2) reviews the integrative functions of the sarcoplasmic reticulum of cardiac myocytes in contractile calcium handling, protein synthesis, protein quality control, and the management of proteotoxic stress. The author reports that, in addition to its roles in contraction, the sarcoplasmic reticulum may have important functions in secreted/membrane protein synthesis and folding. He also reviews recent evidence that certain components of the sarcoplasmic reticulum-associated protein synthesis and folding machinery may interact with, and perhaps regulate, sarcoplasmic reticulum-associated calcium-handling proteins.

**Sex Matters**

Physiologists can’t deny it—the bodies of females and males differ across the life span. Thus physiological mechanisms in females and males differ, and differences in these mechanisms affect all aspects of health and disease. Indeed, in 2001, the Institute of Medicine (IOM) advocated that a better understanding of differences in human diseases between males and females, with translation of these differences into clinical practice, requires consideration of sex as an important biological variable in the design of basic research (13). The IOM defines sex as male and female based on the complement of sex chromosomes and presence of reproductive organs and sex steroids; gender refers to a complex psychosocial construct that takes into account biology but also the influences of society and environment.

In clinical practice, sex and gender differences translate into diseases that are distinct to one sex or the other, diseases that show disproportionate incidence or severity in one sex or the other, or diseases in which symptoms present differently in one sex compared with the other. However, acknowledgement of biological sex differences and research into cellular mechanisms of disease by sex are often not attended to by basic scientists, including physiologists. The reasons for these omissions are many and may reflect the long-held dominance of males in leadership roles in science, the perception that studying female animals is “too
complicated” and expensive, lack of clarity about the definitions of sex and gender, or the simple lack of attention to reporting the sex of the experimental material. Fortunately, in the era of personalized medicine and the call by government agencies to increase the rate of translation of results from basic science to clinical reality, these reasons are becoming obsolete. More women are engaged in the scientific workforce, and targeted funding is available to study women and female animals. Definitions of sex and gender as defined by the IOM are being more universally applied, and, finally, scientific journals including the journals of the APS are requiring inclusion of the sex of the biological material in the methods.

With the advent of new leadership in *Physiology*, we are pleased that Dr. Sieck has made the discussion of sex and gender in biological systems an important overarching theme of the journal contributions. We would like to encourage all contributors to consider the possibility that there may be sex and gender differences in your studies and in reports reviewed for preparation of your submission to *Physiology*. If no data are available on sex/gender differences, then at least speculate on possible sex and gender differences in the physiological mechanisms described.

We offer the following examples of how consideration of sex and gender differences might be incorporated into each review article. In the June 2012 issue of *Physiology*, Pearen and Muscat thoroughly discuss the role that orphan nuclear hormone receptors play in metabolism and obesity (10). They note that two receptors of this superfamily are the estrogen-related receptor (ERR)-alpha and -beta. ERR-alpha regulates genes that affect fatty acid metabolism and mitochondrial biogenesis. Knockout of this receptor causes defective mitochondrial oxidative metabolism, especially in skeletal muscle and heart. Whether there are sex differences in the expression of these orphan receptors and whether they have different effects in males and females was not discussed and is likely not known since the majority of work has been done in cells in culture whose sex was not determined in the original studies. Pearen and Muscat also mention that PPAR orphan receptors affect insulin sensitivity and glucose regulation, both glycogen metabolism and gluconeogenesis. Since both men and women often gain weight with aging and natural reductions in sex steroids, it would be interesting to speculate on whether there are sex/gender differences in the contributions these receptors make in glucose homeostasis in males and females.

In another article in the February 2012 issue of *Physiology*, Ariel and Ryan very elegantly discuss mechanisms of neurotransmitter release in the brain (1). Sex differences in brain physiology are widely known. It may be interesting to include information about, or at least speculate about, whether there are sex differences in the mechanisms responsible for synthesis, release, and disposition of neurotransmitters that could either negatively or positively impact brain function in males and females.

When describing results obtained in experimental animals (or in humans), it is not very informative to say “in knockout animals” or “in rats” but to critically review the publication to identify the sex of the animals. Some key questions to consider are: Is viability of the knockout strain the same in females and males? Is expression of the desired knockout phenotype the same in each sex? Similar considerations should be given when quoting studies done in humans: Are data from human studies analyzed with gender as a covariant or dichotomized by gender or sex?

With appropriate attention to detail and desire to strive for scientific excellence, contributors to *Physiology* are in the position to educate their colleagues and to make transformative changes to our understanding of mechanisms in health and disease by incorporating considerations of sex and gender differences in their reviews.

**Responding to Our Environment**

The founding editor of *Physiology* (then called *News In Physiological Sciences*), Professor Knut Schmidt-Nielsen, was an icon in comparative physiology. Throughout his long scientific career, Schmidt-Nielsen made seminal physiological discoveries using animals held under controlled conditions as well as animals living in their natural environments. This strategy of combining laboratory and field studies remains essential in contemporary comparative physiology. Unraveling physiological mechanisms in controlled environments can reveal how animals function, whereas studies on naturally behaving animals in their native habitats provides insight into the selective pressures that have driven the evolution of particular physiological adaptations, i.e., why the animals function the way they do.

Is this classic, time-tested approach to understanding animal function and its evolution relevant for today’s readers of *Physiology*? We certainly feel it is, and we are delighted that “Responding to Our Environment” will be one of the major themes in *Physiology* over the coming years.

An appreciation of the magnificent physiological adaptations that allow animals to perform under adverse environmental conditions, e.g., carp or turtles that tolerate months without oxygen while dormant under the ice in the winter [highlighted in a previous *Physiology* review (7)] or fish that thrive in high-salinity water (highlighted in a recent *Physiology* review). Other animals exploit extraordinary senses as exemplified by flying bats and diving whales that pinpoint their prey in complete darkness by echolocation [to be highlighted in an upcoming *Physiology* review (8)] and elephants that communicate with low-frequency vibrations [highlighted in a previous *Physiology* review (9)]. Other animals are able to withstand, with no ill effects, extreme changes in organ function, such as hibernating mammals whose heart rates fall to just a few beats per minute. We believe that all of these examples will captivate any person with a sincere interest in how the living body functions and, hence, should stimulate curiosity in physiology. However, the quest to understand extraordinary animals is more than an exotic study of rarities, because understanding physiological responses to and tolerances of extreme environments and lifestyles allows us to define the conditions that limit life itself. As such, giraffes that live with extraordinarily high blood pressures lead us to speculate how the mammalian kidney has evolved to withstand hypertension, and the observations that many
animals and even some mammals can supercool or tolerate freezing stimulates the search for natural cryoprotectants that could be used to improve organ storage techniques prior to transplants.

The concept of using particular animals with extraordinary features or adaptations to gain insight into physiological processes is by no means novel and was beautifully formulated by the Danish Nobel laureate Professor August Krogh: “For such a large number of problems there will be some animal of choice or a few such animals on which it can be most conveniently studied” (6). In this original formulation of what is now recognized as the Krogh principle, Krogh made particular reference to Christian Bohr’s intuitive idea to use tortoises for studies on pulmonary gas exchange because the trachea divides into the main bronchi high in the neck of these reptiles, allowing for separate measurements and manipulation of lung gases in each lung. Ironically, exploiting the peculiar respiratory anatomy of tortoises allowed Krogh to show that pulmonary gas exchange occurs by diffusion and diffusion alone, and hence provided experimental evidence that allowed the refusal of active oxygen transport as proposed by Bohr.

The use of natural animal models for advancing biomedicine is more possible now than ever—within the next few years, entire genomes of thousands of animals will be sequenced, and we will no longer be limited to studying the relatively small number of model species currently in use, many of which were originally chosen for convenience rather than by the virtue of possessing any particularly interesting physiological trait.

Although we are convinced that the Krogh principle remains as vital and promising as ever, it is also becoming apparent that studies of animals that have evolved within particular environments over an evolutionary time scale can provide otherwise unattainable insight into the capacity of physiological systems to respond to and adapt to perturbations, and thus may be highly appropriate to address a variety of clinical problems. In addition, although laboratory rodents make up the vast majority of model organisms for most of present-day biomedical research, there is a growing concern that the physiological responses of these animals are far removed from what would be considered “normal” physiology. In fact, multiples generations of laboratory breeding and housing in settings in which exposure to complex environments is minimal, dietary and exercise regimes are highly artificial, and interanimal behavioral interactions are very limited has led to manifestations of subclinical or clinical levels of disease, such as tendencies toward metabolic disorders (e.g., obesity, diabetes), behavioral and nervous system abnormalities, and a relatively low capacity to mount effective responses to a variety of stressors. In this context, it is interesting that Larry Irving (a friend and colleague of Schmidt-Nielsen) maintained that the white rat is not a real animal because it has been housed with ad libitum access to food and water for thousands of generations and hence has lost its ability to survive in nature.

We are currently witnessing a devastating and worldwide decline in the populations of many animal species as well as a rapid increase in the number of species that go extinct. Habitat loss due to urbanization and industrial development, and other human activities such as air pollution and increased greenhouse gas emissions certainly are major contributors to this demise. However, it is also clear that, as scientists, we have the ability to contribute to efforts to slow or even reverse these alarming trends toward species losses, which affect not only animal populations but the ecosystems in which they live and the human populations that interact with and benefit from those ecosystems. Physiologists are in a unique position to develop predictive models for animal responses to environmental changes, be they anthropomorphic in nature or otherwise. Rigorous studies that draw upon both laboratory and field-based techniques are revealing species’ tolerances to environmental change and their ability to rebound from perturbations that threaten their existence. Such information forms the basis of conservation physiology, an emerging, translational discipline that provides the basic sciences that can be applied to management and policy decisions that should help keep our earth’s living resources healthy.

References