Identifying and understanding basic physiological differences between males and females is the basis of the emerging field of sex-based biology. In the final issue of the Highlighted Topics series, “Genome and Hormones: Gender Differences in Physiology,” featured articles demonstrate the diversity, integration, and depth of investigations needed to understand how sex/gender influence health and affect the diagnosis and treatment of diseases in humans.

The first Highlighted Topics article featured in this issue of the Journal of Applied Physiology, “Association of gender-related LMP2 inactivation with autoimmune pathogenesis,” by Hayashi and Faustman (p. 2804–2815), addresses the contribution of defective LMP2 proteasome subunit with autoimmune disease expression. Insulin-dependent diabetes mellitus (IDDM, also called Type 1 diabetes) is an autoimmune disease. In IDDM, mononuclear infiltration is observed in pancreatic islets, and insulin-producing β-cells are selectively destroyed, resulting in insulin deficiency and hyperglycemia. A strong genetic association exists between certain autoimmune diseases and the expression of certain kinds of major histocompatibility complexes (MHCs). In the nonobese diabetic (NOD) mouse, an animal model of autoimmune diabetes, the cumulative incidence of diabetes by 30 wk age in NOD female mice is 70–80%; in the case of 30-wk-old male mice, diabetes occurs in less than 25% of cohorts. Recent results in NOD mice suggest a hypothesis to explain the role of the MHC in autoimmunity. The MHC genomic region contains many immune response genes that are important for T cell education and antigen presentation by MHC molecules. Two such genes encoding the LMP2 and LMP7 proteasome subunits are located in this high-risk MHC genomic region. The proteasome is a multisubunit complex that mediates the processing or degradation of diverse cellular proteins; thus a proteasome containing an LMP2 subunit is essential for T cell education and proteolytically activates transcription factor (NF)-κB. In this study, Hayashi and Faustman demonstrate that splenocytes from female NOD mice with disease expression were selectively defective in LMP2 expression. The spontaneous defective LMP2 expression in NOD mice is gender biased toward female cohorts and is additionally restricted to select lymphoid and myeloid cells. In female NOD mice, the developmentally controlled lowering LMP2 causes NF-κB inactivation and heightened tumor necrosis factor-α-induced apoptosis. These defects are apparently only after ~7 wk of age. These results suggest a proteasome role in autoimmune progression and a gender developmental and lineage restriction of LMP2 expression that may contribute to the diverse autoimmune characteristics preferentially observed in female NOD mice.

Retrospective clinical studies suggest that gender of donors and/or recipients may influence the outcome of liver transplantation. However, these data are variable, and, to date, no clear consensus has been reached. The second Highlighted Topics article in this issue, “Effects of gender on reduced-size liver ischemia and reperfusion injury,” by Harada and colleagues (p. 2816–2822), reports how gender influences heptocellular viability and survival of mice subjected to hepatic resection in combination with ischemia and reperfusion (I/R). Hepatic resection with concomitant periods of I/R occurs during reduced-size liver transplantation (e.g., split liver or living donor transplantation). This relatively new surgical technique is being used to effectively expand the supply of donors for liver transplantation. However, I/R is thought to reduce the ability of the liver to regenerate and to lead to liver failure. The current study provides evidence that gender may affect the outcome of reduced-size liver transplantation, as 100% of female mice survived reduced-size liver with I/R indefinitely, whereas all male mice had greater initial liver injury and died within 5 days postsurgery. In females, ovariectomy or administration of a selective estrogen antagonist (ICI-182780) to female mice increased liver injury and mortality following reduced-size liver I/R. Conversely, male mice treated with 17β-estradiol exhibited less hepatocellular damage and survived indefinitely. Therefore, 17β-estradiol may contribute to differential survival of female and male animals following liver resection plus I/R. Gender differences in survival were not observed after warm I/R-induced injury of full-size livers or liver resection in the absence of I/R. These findings suggest that the presence of one or more estrogen-mediated pathways limits or attenuates hepatocellular injury induced by reduced-size liver I/R. Results from this study may have implications for treatment of patients undergoing reduced-size liver transplantation.

The third Highlighted Topics article appearing in this issue, “Effects of sex and ovariectomy on responses to platelets in porcine femoral veins,” by Lewis and colleagues (p. 2823–2830), examines how hormones influence interactions of platelets with veins contributing to increased risk of venous thrombosis. Causes of venous thrombosis are multifactorial being defined by Virchow’s triad as changes in the anatomy of the vein wall, blood flow, and coagulability of the blood. Previous studies have shown that hormones alter the content of platelet-derived factors such as 5-hydroxytryptamine, ADP, and prostanoids that cause changes in vascular tone. In the paper by Lewis et al., interactions of
platelets with the venous wall were compared between male and female pigs and between females with and without ovarian hormones. Autologous aggregating platelets in all groups caused relaxations of veins when the endothelium was present and contraction when the endothelium was removed. These contractions were greatest in veins from male pigs. Contractions to 5-hydroxytryptamine and relaxations to ADP, two substances released from platelets, were similar among groups. Therefore, differences in responses to platelets were probably due to a change in amount or type of substance released from the platelets rather than to changes in smooth muscle sensitivity to one substance. When production of prostanoids was inhibited by indomethacin, relaxations to ADP were increased in veins from males and females but not in veins from ovariec-
tomized females. Inhibition of nitric oxide reduced relaxations to ADP only in veins from males. These observations suggest that, in addition to changes in substances released by platelets, production, release, and response to endothelium-derived factors are also under the influence of hormones. Results of this study extend previous observations to show that sex and hormones modulate release of endothelium-derived factors in veins to at least one factor (ADP) released during aggregation of platelets. Therefore, changes in risk of venous thrombosis with initiation of estrogen therapies may reflect combined effects of hormones on platelets and the venous wall.

The final Highlighted Topics article featured in this issue, “Time-dependent hypoxic respiratory responses in female rats are influenced by age and by the estrus cycle,” by Zabka and colleagues (p. 2831–2838), reveals remarkable differences in the way that age affects ventilatory control in female and male rats. This study examined the time-dependent phrenic and hypoglossal nerve responses during and after episodic hypoxia. Serotonin-dependent respiratory plasticity elicited by intermittent hypoxia or chemoafferent neuron activation known as long-term facilitation (LTF) (Mitchell et al. J Appl Physiol 90: 2466–2475, 2001) increased with age in female rats. This is in direct contrast to the response previously shown in middle-aged male rats [Zabka et al. J Physiol (Lond) 531: 509–514, 2001]. Furthermore, LTF increased during diestrus, a phase of the reproductive cycle associated with maximal levels of progesterone and extracellular serotonin concentrations in the brain. Thus circulating sex steroid hor-
mones may modulate serotonin-dependent plasticity in control of respiration. Although the precise physiolog-
ical role of LTF has not been discovered in any species (Mitchell et al. J Appl Physiol 90: 2466–2475, 2001), LTF may play an important role in stabilizing respira-
tory pump and upper airway muscle activity when there is risk of repetitive apnea or hypopnea. Thus diminished LTF in middle-aged male rats mirrors the increased incidence of obstructive sleep apnea in mid-
dle-aged men. In contrast, the progressive increase in LTF in middle-aged female rats suggests the presence of some “protective” mechanism in maintaining upper airway patency, paralleling the observed lower inci-
dence of obstructive sleep apnea in women until meno-
pause. However, without a thorough investigation of serotonin-dependent plasticity and the effects of age and gender in humans, it is premature to conclude that changes in LTF play any sort of causal role in obstruc-
tive sleep apnea. Nevertheless, the parallels are strik-
ing and suggest that future investigations are war-
ranted.