OBESITY is now a common occurrence in modern society. Barely one-third of Americans fall into the normal weight range, and 32% of the population has been classified as obese (9). The obesity epidemic is permeating into the childhood years, with 16.3% of children in the United States being above the 95th percentile for the body mass index (BMI), resulting in comorbidities such as the metabolic syndrome emerging before adulthood (8, 15). Much attention has focused on the metabolic and cardiovascular pathologies associated with increased adiposity, but obesity is also associated with a wide range of respiratory diseases, including asthma, sleep apnea, and chronic obstructive pulmonary disease (COPD) (7). Obesity can stress the respiratory system through multiple mechanisms from the imposition of mechanical constraints to the release of circulating factors from adipose stores. In this series of nine reviews in the Highlighted Topic series on “Pulmonary Physiology and Pathophysiology in Obesity,” we explore the effects of obesity on lung mechanics, respiratory control, and sleep apnea as well as the impact of adipokines, lung inflammation, and oxidative stress and their contribution to airway hyperresponsiveness and the development of a distinct asthma phenotype.

The first review is by Salome, King, and Berend (11) in the January 2010 issue and discusses how even in the absence of respiratory disease, obese individuals are more likely to experience respiratory symptoms such as breathlessness, particularly during exertion or exercise. Although the effects of obesity on residual volume and total lung capacity are not dramatic, there is a clear reduction in functional residual capacity that is exponentially related to BMI. The distribution of fat is an important consideration, with the largest deficits in pulmonary function associated with abdominal or thoracic fat deposition. Obesity is characterized by a stiffening of the respiratory system and a reduction in total lung compliance. However, the effects on forced expiratory volume in 1 s and forced expiratory vital capacity are small, and there is no direct effect on airway obstruction in healthy individuals. Given the emerging evidence relating obesity to asthma (see below), it will be important to determine the independent effects of obesity on bronchoconstriction and how they interact in asthmatic conditions.

Although the majority of obese individuals maintain eucapnia, the second review, by Piper and Grunstein (10), focuses on a subset of severely obese individuals who retain hypercapnia, a condition known as obesity hypoventilation syndrome (OHS). The mechanisms that lead to a compensatory failure of respiration in some severely obese individuals remain a subject of ongoing debate despite >50 yr of research since the original description of the syndrome by Burwell (2) in 1956. Both impaired respiratory mechanics and reduced respiratory drive likely contribute to OHS, and these factors may, in fact, be linked by the ability of excess adipose tissue to both stress respiratory muscle performance and release adipokines that can impact the neural control of respiration. Progress in this area to uncover the underlying mechanisms has been hampered by the often confounding presence of sleep-disordered breathing, which accentuates hypercapnia and hypoxemia during the night.

Comparable with OHS, obstructive sleep apnea is largely considered to result from both neural and mechanical effects on the upper airway as a consequence of obesity and is the basis for the third review, by Schwartz, Patil, Squier, Schneider, Kirkness, and Smith (12) in the February 2010 issue. The polysomnographic characterization of obstructive sleep apnea in the 1960s (3) had the effect of shifting the focus of respiratory researcher away from OHS to the upper airway. Although the upper airway has been an extremely difficult structure to study, and there are limited relevant preclinical models, considerable progress has been made over the last three decades. Obesity places a mechanical stress on the upper airway due to adipose deposition around the pharynx and by reductions in lung volume that decreases upper airway tractions. In an analogous manner to how the pancreas produces more insulin under conditions of metabolic stress in obesity to stabilize blood glucose levels, the upper airway activates compensatory neural reflexes to stabilize the upper airway. And just as type 2 diabetes develops when insulin secretion is no longer effective at countering insulin resistance, sleep apnea develops when neural compensatory reflexes can no longer resist the mechanical loads on the upper airway. Much new research is focusing on a multitude of factors, such as adipokines and inflammatory cytokines that are upregulated by obesity and likely have secondary effects on the neural control of the upper airway.

In the fourth review, Arens and Muzumdar (1) discuss how, historically, adenotonsillar hypertrophy has been the predominant cause of sleep apnea in children. However, the current epidemic in obesity is now reaching back into pediatric populations to create a new phenotype of obesity-related sleep apnea. Since obese children with sleep apnea also have a very high incidence of adenotonsillar hypertrophy, it has been difficult to isolate and characterize the obese sleep apneic phenotype, and treatment strategies are complex and require input from multiple subspecialties. An extremely concerning aspect of the emergence of apparent “adult sleep apnea” in children is the potential for enhanced metabolic and cardiovas-
The March 2010 issue focuses on how obesity impacts on pulmonary diseases such as COPD and asthma. The fifth review in the series, by Sood (14), stresses that the relationship between obesity and pulmonary disease is associated with changes in cytokines secreted by the adipocytes (known as adipokines). Two important adipokines, leptin and adiponectin, exhibit increases and decreases, respectively, with increasing BMI and may be further modulated in the presence of pulmonary disease. Although leptin is primarily considered a proinflammatory adipokine and adiponectin an anti-inflammatory adipokine, their association with pulmonary disease is somewhat inconsistent: high leptin and low adiponectin predict asthma, whereas low leptin and high adiponectin are associated with stable COPD. Whether adipokines are part of a causal pathway linking obesity and pulmonary disease or are simply acting as biomarkers is a fertile area for future research.

In the sixth review, Mancuso (6) highlights that adipokines, acute-phase reactants, and lipids that are secreted from adipocytes in the presence of obesity can exacerbate the inflammatory responses that occur in lung diseases. While most recent attention has focused on the exacerbation of asthma in obesity, increased adiposity may also increase the susceptibility to inflammation associated with respiratory infections, particulate matter exposure, and chronic bronchitis.

The clinical literature examining whether obesity can accentuate airway hyperresponsiveness, a defining characteristic of asthma, is largely inconclusive, although confounding effects of using BMI rather than fat mass, gender, and type of bronchoconstrictive agent may account for the inconsistencies. In contrast, the seventh review, by Shore (13), underscores that in controlled animal studies, a cause-and-effect relationship exists between obesity and airway hyperresponsiveness, and changes in adipokines (including TNF-α, leptin, and adiponectin) represent plausible mechanistic pathways.

The eighth review, by Lugogo, Kraft, and Dixon (5), highlights that obesity in asthmatics is associated with more severe disease, as manifested by increased exacerbations and decreased responsiveness to medication. It is possible that obese asthmatics may exhibit a distinct phenotype that could arise through a number of putative mechanisms, including gastrointestinal reflux disease, sleep apnea, elevations in inflammatory cytokines, and altered circulating levels of adipokines. Weight loss through diet or bariatric surgery can improve asthma, possibly through the action of reducing oxidative stress. Although there is no clear evidence as yet that obese asthmatics exhibit greater oxidative stress, Holguin and Fitzpatrick (4), in the final review, emphasize that oxidative stress in asthmatics may accentuate airway inflammation by reducing the effectiveness of steroid therapy in the setting of severe asthma.

In conclusion, we hope that this series of nine mini-review articles, which by nature are not intended to be comprehensive, will succinctly summarize what is known about the relationship of obesity to pulmonary physiology and pathophysiology. Clearly there is a growing interest in the role that obesity plays in initiating and exacerbating pulmonary disease. These review articles will provide insight into the mechanisms by which increased adiposity can impact pulmonary physiology and pathophysiology and, importantly, highlight questions and areas of research as a focus for future studies.

REFERENCES