The Lung Division of the NHLBI convened a workshop on obesity and asthma on July 15 and 16, 2003. Drs. Patricia Noel and Virginia Taggart, the workshop organizers, sought to examine current research on the role of obesity in the onset and persistence of asthma, as well as the mechanistic basis for this association. An additional goal of the workshop was to describe barriers in conducting research in this area and to identify the most promising opportunities for future research.

EPIDEMIOLOGY OF ASTHMA AND OBESITY

Asthma is defined by episodic airflow obstruction, increased airways responsiveness, and airway inflammation characterized by infiltration with eosinophils and T lymphocytes, particularly CD4+ T lymphocytes that express T helper (Th) cell type 2 cytokines such as interleukin (IL)-4, IL-5, and IL-13. The histopathologic appearance of the airways includes denudation of the airway epithelium, thickening of the basement membrane, mucus production, and airway smooth muscle hypertrophy. Although asthma is a chronic, often lifelong disease that affects humans of all ages, the onset of the disease occurs primarily in early childhood. Fifty percent of all male asthma cases are diagnosed by age three, and 50% of all female cases are diagnosed by age eight (1). From 1980 to 1996, data from the National Center for Health Statistics demonstrate an increase in self-reported asthma prevalence of 74% (2). Although this increase has occurred in children and young adults of all ages, it has been most pronounced in children 5 years or younger. This increase has been most marked in minority populations, particularly African Americans and Puerto Rican Hispanics. There has been substantial morbidity and cost to this epidemic as asthma is the most common chronic condition for days lost from school (3).

In addition to the asthma epidemic, there is an obesity epidemic in the United States. One-third of all 16-year-old children in the United States are overweight, and 15% are obese. Cross-sectional studies indicate an increased prevalence of asthma in the obese (4–7). The incidence of asthma among children and young adults of all ages, it has been most pronounced in children 5 years or younger. This increase has been most marked in minority populations, particularly African Americans and Puerto Rican Hispanics. There has been substantial morbidity and cost to this epidemic as asthma is the number one cause of hospitalizations in children as well as the most common chronic condition for days lost from school (3). At the present time, medications and healthcare utilization for childhood asthma costs approximately $10 billion per year.

In addition to the asthma epidemic, there is an obesity epidemic in the United States. One-third of all 16-year-old children in the United States are overweight, and 15% are obese. Cross-sectional studies indicate an increased prevalence of asthma in the obese (4–7). Although it is possible that this association is the result of reduced exercise by subjects with asthma leading to the obese (4–7). Although it is possible that this association is the result of reduced exercise by subjects with asthma leading to obesity, longitudinal studies (8–10), which indicate that obesity antedates asthma, suggest that this is not the case. An important aspect of these epidemiologic data is that the impact of obesity on asthma is much stronger in females than males. For example, the incidence of asthma after the age of 11 years is five- to sevenfold higher in female children who become obese versus those who remain lean, whereas no such relationship exists for males (8). Further understanding of this sex difference may help elucidate the basis for the relationship between these two health conditions. This relationship between asthma and obesity has been reviewed recently (11).

OBESITY AND AIRWAY RESPONSIVENESS

Although the relationship between obesity and asthma is reasonably clear, the relationship between obesity and airway responsiveness is less so. In an initial report, Schachter and coworkers (12) found a relationship between obesity and asthma occurrence; however, they found no relationship between obesity and an increase in airway responsiveness. Data on white adults between the ages of 17 and 73 years from three large epidemiologic studies in New South Wales, Australia, from 1971 were examined. In this population, asthma risk was significantly increased (odds ratio 2.04, p = 0.048), but there was no increase in airway responsiveness to histamine (odds ratio 2.87, p = 0.78). In a large cross-sectional, population-based study in Anqing, China, extremes of body mass index (BMI), either very low or very high, were associated with a 2.5-fold increase in symptomatic airway hyperresponsiveness (6). The effects were seen in both males and females and in both extremes of the BMI distribution. In longitudinal data from the Normative Aging Study, there was also an association between BMI and increased airway hyperresponsiveness with a reported odds ratio of 7 (13). Thus, the data in the literature is conflicting as to whether airway hyperresponsiveness is increased by obesity.

OBESITY AND ALLERGY

There is at least one article examining data from the National Health and Nutrition Examination Survey that suggests that obesity is associated with an increase in skin test reactivity but not peripheral blood eosinophils. IgE levels were not measured in this study (7). There is only one other report of cross-sectional data showing a relationship between BMI and an increase in skin test reactivity (14). There has been only one attempt to link the increase in obesity to the increase in asthma wheezing prevalence. Figueroa-Munoz and coworkers (15) used data from a National Study of Health and Growth in the United Kingdom to examine if obesity preceded the increase in asthma and wheezing. In their initial report on data from this population, the investigators show a strong relationship between BMI and asthma occurrence cross-sectionally. In a subsequent report, the investigators suggest that this cross-sectional association may not have been temporally related (16). This latter report can be criticized.
because it is primarily a repeated cross-sectional qualitative analysis rather than a true longitudinal analysis, it did not use all the available data, and it did not clearly show that BMI values actually antedated the asthma wheeze determinations. Issues of selection in the data make this article a less than optimal test of this particular hypothesis. As is commonly seen in complex traits like asthma, there are multiple obesity phenotypes. For example, central adiposity is linked with insulin resistance, whereas centrifugal or gluteal adiposity is not. These phenotypes differ with respect to their relationship to birth weight and to activation of the sympathetic nervous system (SNS). To date, no attention has been given to elucidating the obesity phenotypes that are linked to asthma or the asthma phenotypes that are linked to obesity.

Given that asthma is a disease of young children, it is possible that in utero events are contributing to the relationship between obesity and asthma. For example, birth weight appears to impact the development of both asthma (5) and obesity (17). Low birth weight is associated with a higher subsequent incidence of asthma, whereas high birth weight is associated with a higher subsequent incidence of obesity. There are data indicating that maternal caloric intake during pregnancy in humans, animal-rearing temperature (i.e., the cage temperature that mother and neonate are kept at), and human fetal hyperinsulinemia impact the development of obesity. However, there are few data as to the impact of these factors on asthma and no data as to their impact on the relationship between obesity and asthma.

**OBESITY AND LEPTIN**

Leptin is a hormone produced by adipocytes that acts in the hypothalamus to signal satiety and to increase basal metabolic rate. Serum leptin is increased in obesity (18). The role of leptin in the relationship between obesity and asthma is unknown. Leptin receptors are expressed outside the hypothalamus, and peripheral effects of leptin on many organs and tissues, including the lung and hematopoietic cells, have been reported. For example, leptin stimulates surfactant synthesis in fetal lung cells (19, 20), as well as proliferation of tracheal epithelial cells (21), and mice that lack dysanapsis leptin have markedly reduced lung size (22). Given that larger lungs and smaller airways are potentially important in the etiology of asthma (23), understanding the role of leptin in fetal lung development may prove to be very important (10).

Leptin is a member of the IL-6 family of cytokines, and hematopoietic cells respond to leptin with proliferative responses as well as altered cytokine production. In general, the overall response to leptin is to stimulate a Th1 cytokine profile: peritoneal macrophages pretreated with leptin generate increased amounts of IL-12 in response to endotoxin (24), whereas in CD4+ T cells, leptin increases Th1 and suppresses Th2 cytokine production (25). Starvation and malnutrition are associated with immune dysfunction, and leptin administration reverses the immunosuppressive effects of acute starvation in animal models (25). Leptin also reverses the impairments in T cell proliferation and cytokine release that are observed in humans with congenital leptin deficiency (26). In addition to its effects on immune cell function, leptin also has effects on inflammation such as promotion of the release of tumor necrosis factor-α and IL-6 from endotoxin-treated macrophages and lymphocytes. Consistent with these effects, leptin enhances ozone-induced airway hyper-responsiveness and increases ozone-induced neutrophil influx and eotaxin release into bronchoalveolar lavage fluid in mice (27). In contrast, fasting, which reduces serum leptin, attenuates ozone-induced inflammation. Finally, obesity per se is associated with systemic inflammation including elevations in peripheral blood leukocytes, which causes an increase in serum levels of C-reactive protein, proinflammatory cytokines, such as tumor necrosis factor-α and IL-6, and cell adhesion markers, and markers of lipid peroxidation (28–31). Greater understanding of the similarities and differences between the inflammatory characteristic of obesity and asthma might aid in understanding the impact of obesity on asthma.

An additional effect of leptin that could have important implications for asthma is its ability to activate the SNS, an effect that appears to occur at the level of the hypothalamus in animal models (32). Leptin increases activity in sympathetic nerves in the kidney, brown adipose tissue, hind limbs, and adrenal medulla (33). The impact of leptin on the activity of sympathetic nerves in lung is not known, but increased sympathetic activation of the adrenal medulla could lead to release of catecholamines that would be expected to impact lung function.

Although serum leptin is increased in obesity, there is resistance to the effects of peripherally administered leptin on eating behavior and on sympathetic activity to brown fat in rodent models of obesity (34, 35). In contrast, renal sympathetic activity is preserved in obese mice (36), suggesting the possibility of selective leptin resistance. Whether there is also resistance to the effects of leptin in the lung or on immune function is unknown, but such resistance might be expected to polarize to a Th2 response and to reduce lung size in developing children, conditions that could be expected to impact the development of asthma. In the brain, the mechanism of leptin resistance is via upregulation of suppressor of cytokine signaling 3, a phosphatase that limits leptin receptor signaling (37). Suppressor of cytokine signaling 3 limits IFN-γ signaling (38), which might enhance Th2 cytokine signaling.

**MECHANICAL FACTORS**

In obese individuals, airway smooth muscles are likely to be unloaded (have less tension) in part because obese individuals have a decreased FRC and in part because obese individuals assume a breathing pattern with higher frequencies and lower Vt that lean control individuals. Decreased FRC shortens muscle length and hence decreases tension. Tidal stretch of airway smooth muscle is an extremely potent bronchodilator: stretch of airway smooth muscle detaches cross bridges, leading to reduced force generation and reduced shortening (39). The reduction in cross bridges also makes the muscle less stiff. Thus, in the obese individual with a reduced FRC and a decreased Vt, it is easy to create a downward spiral, wherein less stretch leads to greater stiffness making the muscle even harder to stretch and resulting in increased airway shortening and airway hyperresponsiveness. These mechanical effects have been observed in the massively obese. The extent to which these changes occur in subjects over a wide range of body weight and age is an important research question. Understanding whether there are age- or sex-related differences in these mechanical factors and how different patterns of obesity and breathing produce these effects would be worthwhile.

**FEMALE SEX STEROID HORMONES**

The clear-cut sex differences in the epidemiology of obesity and its impact on asthma suggest that female sex hormones may be contributing to the increased risk of asthma in obesity. Aromatase, the enzyme responsible for converting androgens to estrogens, is found in adipose tissue. Therefore, it is reasonable to hypothesize that obesity increases estrogen and is associated with early menarche (40) and delayed puberty in males (41). The risk of developing asthma in girls who gain weight is also
particular enzymes (42). It is unclear how estrogen might impact the development of asthma, but both estrogen and progesterone have been shown to increase IL-4 in peripheral blood mononuclear cells (43), and there may be other effects on immune or inflammatory cells. It is also possible that there are ERs on airway smooth muscle or other airway cells and that estrogen directly impacts airway function. If so, it will be important to understand how ER expression and signal transduction are regulated in these cells.

SNS ACTIVITY

Although human airway smooth muscle is not sympathetically innervated (46), other cells in the airways that may impact airway function are goblet cells and mucus glands (47). Moreover, smooth muscle cells do express β-2adrenergic receptors, respond to β-agonists with increases in cAMP formation and relaxation, and are likely to be influenced by catecholamines of medullary origin. There are changes in sympathetic activity with obesity that appear to be organ specific. In animal models of obesity, baseline renal sympathetic activity is increased, whereas activation in brown fat is reduced (48). This should be contrasted with the leptin-induced increase in SNS activity in brown fat noted earlier. In contrast, 24-hour urinary epinephrine levels indicate decreased adrenal medullary function associated with obesity or a high-fat diet in humans and animals (49, 50). The observations that adrenal medullary function is reduced in obesity and that SNS activity is decreased in asthma suggests that changes in sympathetic activity may be the link between these two syndromes but much remains to be established. For example, there are no data on the impact of obesity on sympathetic outflow to the lung. Furthermore, little is known about 24-hour urinary norepinephrine and epinephrine levels in asthma relative to normal levels. Greater attention to the physiologic changes seen in obesity as applied to the subject with asthma might provide an insight into the mechanistic interrelationship between these two conditions.

In rodents, sympathetic activation of brown fat appears to play an important role in increasing thermogenesis and basal metabolism via activation of uncoupling proteins. All three types of β-adrenergic receptors, β₁, β₂, and β₃, are expressed in adipose tissue. Moreover, in rodent models of obesity, there are deficits in β₂ and β-receptor expression in brown and white adipose tissues, as well as deficits in β₁ and β₂ coupling, as indicated by cAMP formation in response to receptor-specific agonists (51). In contrast, β₂-receptors are unaffected. The β₂-receptor is the primary β-receptor expressed in the lung, but there are tissue-specific differences in β-receptor regulation, and the impact of obesity on β-receptor expression in the lung is unknown.

The classical pathway by which β-receptors activate cells is activation of G proteins leading to adenylyl cyclase activation, cAMP formation, and protein kinase A activation. However, β-receptors can also activate the mitogen-activated protein kinase pathway. Activation of the extracellular regulated kinase mitogen-activated protein kinases by β-receptor activation requires Src family kinase (c-Src) and appears to occur as a result of G protein–coupled receptor kinase phosphorylation of the receptor, consequent β-arrestin binding, and recruitment of cytoplasmic activator of the c-Src to β-arrestin. In contrast, the β₂-receptor directly recruits c-Src (52). In adipocytes, p38 mitogen-activated protein kinase is also activated by β₂-agonists and appears to be required for the ability of these agents to induce uncoupling protein 1 (53). The role of these nonclassical pathways of β-receptor activation in asthma and in the relationship between obesity and asthma is unexplored but warrants exploration.

Environmental factors such as maternal diet, stress, physical activity, and cage temperature play a major role in SNS development in utero and in the ability of model organisms such as the mouse to respond to environmental stress. These factors play a role in SNS development in utero (54). As discussed previously, intrauterine growth impacts the subsequent development of obesity. Similarly, SNS activity tends to be impaired in infants with in utero growth retardation, and it remains unclear what effect prematurity has on SNS development. A better understanding of diet, child diet, maternal and child exercise, and their impact on SNS function might help elucidate joint or overlapping mechanisms (54, 55).

GENETICS

Linkage analysis has identified several linkage peaks with chromosomal regions that are shared for obesity and asthma phenotypes (11). 2P, 5Q, 6P, 7P, and 12Q all contain regions with loci common to both complex phenotypes. The testing of candidate genes and their role in both the SNS and inflammatory pathways provides unique opportunity to look for shared genes as well as shared environmental exposures that may be common to these two complex traits. In addition to linkage, specific candidate genes deserve careful attention. For example, the β₂-adrenergic receptor polymorphisms may be important in understanding airway smooth muscle cell function as well as fat cell and immune and inflammatory cell functions.

SLEEP-DISORDERED BREATHING

Sleep-disordered breathing is characterized by recurrent episodes of upper airway obstruction (apneas and hypopneas) and is often associated with abnormal gas exchange, snoring, and sleep disruption. The prevalence of this condition is 1 to 3% in children, 2 to 10% in the middle aged, and greater than 25% in the elderly. Importantly, the prevalence of snoring and sleep-disordered breathing is higher among subjects with asthma than among those without asthma (56), and asthma is a risk factor for sleep-disordered breathing in children (57). Moreover, in subjects with both asthma and sleep-disordered breathing, there can be an improvement in asthma symptoms on treatment with nasal continuous positive airway pressure (58). Sleep-disordered breathing and asthma share some common risk factors, including African American race, prematurity, and obesity: 50% of the obese have sleep apnea syndrome, and among those with sleep apnea, 40% are obese (59, 60). Other common risk factors are allergy and lower respiratory infections. The mechanistic basis for the association between asthma and sleep-disordered breathing is unclear. The two phenotypes may overlap because of the common occurrence of the two complex traits. It may also be that hormonal changes, changes in neural tone to the airways, gastroesophageal reflux, alterations in breathing pattern leading to altered smooth muscle tone, or hypoxemia contribute.

CONCLUSIONS

Clearly, both asthma and obesity are common conditions, and both are major public health problems. Moreover, obesity appears
to increase the risk of asthma. Both disorders may share common genetic and environmental causes. There are mechanical, developmental, hormonal, signal transduction, and immunologic reasons for their effects. The workshop developed a total of 10 complex recommendations to further research in this area.

RESEARCH RECOMMENDATIONS FROM THE OBESITY AND ASTHMA WORKSHOP, NHLBI

1. More information, including better phenotyping and more longitudinal cohort studies, is required to determine what is the attributable risk for developing asthma given obesity and in sorting out cause–effect relationships between asthma and obesity. For example, do treatments for asthma, such as β-agonists or inhaled glucocorticoids, predispose to obesity? Obesity, like asthma, is very heterogeneous, and it will be important to understand which of the various obesity phenotypes are linked to asthma. Ethnic differences in obesity and asthma phenotypes may help strengthen such associations. Given the apparent importance of obesity in the development of asthma, can ongoing studies of cardiovascular disease or weight reduction (Cardia, Lookahead) be used to determine the impact on asthma by collecting asthma outcomes measurements? Can more use be made of gastric reduction surgery patients in terms of evaluating how weight reduction improves asthma?

2. It is clear that the impact of obesity in asthma is more pronounced in females than in males. Understanding this sex difference may help elucidate the mechanistic basis for the relationship between these two syndromes. In this context, it is important to understand what role estrogen is playing. What are the effects of estrogen on eating centers in the brain? Which cells in the airways express ERs and how is ER expression and signal transduction regulated? Does ER signaling interact with other signaling pathways of relevance to asthma? Does estrogen influence airway inflammation? Are there interactions between leptin and estrogen in the brain, in the adipose tissue, or in the airways? Are there interactions between estrogen and the SNS?

3. There is decreased adrenal medullary activity in obesity, as evidenced by 24-hour urine epinephrine levels. However, the decreased SNS activation does not affect all innervated organs. Renal SNS is increased in obesity. How is sympathetic outflow to the lung affected in obesity? How does this impact the development of asthma symptoms? Is there a potential link between obesity-related changes in SNS activation and asthma? How is sympathetic innervation of the lung regulated developmentally, and does obesity impact innervation? How do polymorphisms of the β-adrenergic receptors influence the relationship between obesity and asthma? Is the impact of β-receptor polymorphisms in airway smooth muscle, fat cells, and immune/inflammatory cells the same? Do exercise, diet, and polymorphisms of the β-receptor interact to predict which obese individuals get asthma? Are there differences in response to sympathetic activation in the lungs of obese versus nonobese? Are the signal transduction pathways (protein kinase A, extracellular regulated kinase, p38) activated by β-agonists affected by obesity? What is the relationship of 24-hour urinary norepinephrine and epinephrine levels to asthma and its phenotypes? Can this phenotype for SNS activity be used to assess environmental factors and genetic factors influencing obesity and asthma?

4. Besides leptin, there are other hormones produced from fat cells, including resistin, adiponectin, and tumor necrosis factor-α, as well as other hormones that are affected by obesity such as the renin–angiotensin system. It may be important to determine what effect, if any, these hormones have on the lung or on inflammatory/immune responses and to determine if these are relevant to asthma.

5. Evidence suggests that obesity is an inflammatory state. Are there similarities in the inflammation produced by obesity and asthma? Do they have a common etiology?

6. Little is known about how intrauterine and early life relate to development of obesity and asthma. What dietary, environmental, or genetic factors influence the development of obesity? If so, what is the mechanistic basis for this relationship? Which phenotypes, such as birth weight corrected for gestational age and birth length, growth in the first year of life, serial ultrasounds during fetal development, best predict the development of asthma and/or obesity in early childhood? Given that preterm birth appears to influence the development of both asthma and obesity, are there genes linked to preterm birth that may influence the development of these conditions?

7. Genome-wide scans have identified regions linked to asthma and to obesity, some of which overlap. There are also common candidate genes, including, but not limited to, the β-receptor, the glucocorticoid receptor, transforming growth factor-β, and peroxisome proliferator–activated receptor–γ. Functional genomics of mediators, genes, and pathways that are likely to participate in both obesity and asthma and interactions between these pathways may help elucidate the mechanistic basis for the relationship between these conditions. Understanding how diet, exercise, and other environmental factors interact with these genes may also help determine risk.

8. Obesity provides an important load to the respiratory system and alters lung volumes and the pattern of breathing, both of which can affect airway smooth muscle shortening. How does obesity impact the loading of airway smooth muscle including the frequency of deep inspirations? Are there age- or sex-related differences in deep inspirations or in the impact of deep inspirations on airway function? Do these vary with obesity? How does obesity impact airway
development and are these effects sex specific? Does breathing at low lung volumes over long periods of time, as occurs in obesity, cause remodeling of the airways?

9. There appear to be important interactions not only between asthma and obesity but also between asthma and sleep and obesity and sleep. Measurement of sleep phenotypes (polysomnograms, sleep questionnaires, diet, exercise, sleep deprivation) in ongoing longitudinal asthma cohort studies and measurement of asthma phenotypes (asthma questionnaires, lung function testing, skin testing, IgE levels) in ongoing sleep studies may help elucidate these relationships. Further understanding of the mechanistic basis for the impact of sleep on asthma may also help clarify the relationship between obesity and asthma. Can one separate the effects of obesity and sleep on respiratory mechanics? Are the same mechanisms operating in obese patients with sleep apnea and obese subjects with asthma in terms of airway mechanics?

10. Many participants emphasized that cross-discipline collaboration between investigators interested in asthma and those interested in obesity would likely accelerate progress in this area.

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