induced NO (F_ENO) may identify the problem. Compliance may be improved by giving the ICS as a combination with a LABA that gives symptom relief. Compliance with OCS may be measured by suppression of plasma cortisol and the expected concentration of prednisone/prednisolone in the plasma. There are several factors that may make asthma more difficult to control, including exposure to high, ambient levels of allergens or unidentified occupational agents. Severe rhinosinusitis may make asthma more difficult to control; upper airway disease should be vigorously treated. Drugs such as beta-adrenergic blockers, aspirin, and other cyclooxygenase (COX) inhibitors may worsen asthma. Some women develop severe premenstrual worsening of asthma, which is unresponsive to corticosteroids and requires treatment with progesterone or gonadotropin-releasing factors. Few systemic diseases make asthma more difficult to control, but hyper- and hypothyroidism may increase asthma symptoms and should be investigated if suspected.

Bronchial biopsy studies in refractory asthma may show the typical eosinophilic pattern of inflammation, whereas others have a predominantly neutrophilic pattern. There may be an increase in T_H1 cells, T_H17 cells, and CD8 lymphocytes compared to mild asthma and increased expression of TNF-α. Structural changes in the airway, including fibrosis, angiogenesis, and airway smooth-muscle thickening, are more commonly seen in these patients.

Corticosteroid-Resistant Asthma A few patients with asthma show a poor response to corticosteroid therapy and may have various molecular abnormalities that impair the anti-inflammatory action of corticosteroids. Complete resistance to corticosteroids is extremely uncommon and affects less than 1 in 1000 patients. It is defined by a failure to respond to a high dose of oral prednisone/prednisolone (40 mg once daily over 2 weeks), ideally with a 2-week run-in with matched placebo. More common is reduced responsiveness to corticosteroids where control of asthma requires OCS (corticosteroid-dependent asthma). In patients with poor responsiveness to corticosteroids, there is a reduction in the response of circulating monocytes and lymphocytes to the anti-inflammatory effects of corticosteroids in vitro and reduced skin blanching in response to topical corticosteroids. There are several mechanisms that have been described, including an increase in the alternatively spliced form of the glucocorticoid receptor (GR)-β, an abnormal pattern of histone acetylation in response to corticosteroids, a defect in IL-10 production, and a reduction in HDAC2 activity (as in COPD). These observations suggest that there are likely to be heterogeneous mechanisms for corticosteroid resistance; whether these mechanisms are genetically determined has yet to be decided.

Brittle Asthma Some patients show chaotic variations in lung function despite taking appropriate therapy. Some show a persistent pattern of variability and may require oral corticosteroids or, at times, continuous infusion of β_2-agonists (type 1 brittle asthma), whereas others have generally normal or near-normal lung function but precipitous, unpredictable falls in lung function that may result in death (type 2 brittle asthma). These latter patients are difficult to manage because they do not respond well to corticosteroids, and the worsening of asthma does not reverse well with inhaled bronchodilators. The most effective therapy is subcutaneous epinephrine, which suggests that the worsening is likely to be a localized airway anaphylactic reaction with edema. In some of these patients, there may be allergy to specific foods. These patients should be taught to self-administer epinephrine and should carry a medical warning accordingly.

TREATMENT REFRACTORY ASTHMA

Refractory asthma is difficult to control, by definition. It is important to check compliance and the correct use of inhalers and to identify and eliminate any underlying triggers. Low doses of theophylline may be helpful in some patients, and theophylline withdrawal has been found to worsen in many patients. Most of these patients will require maintenance treatment with oral corticosteroids, and the minimal dose that achieves satisfactory control should be determined by careful dose titration. Steroid-sparing therapies are rarely effective. In some patients with allergic asthma, omalizumab is effective, particularly when there are frequent exacerbations. Anti-TNF therapy is not effective in severe asthma and should not be used. A few patients may benefit from infusions of β_2-agonists. New therapies are needed for these patients, who currently consume a disproportionate amount of health care spending.

Aspirin-Sensitive Asthma A small proportion (1–5%) of asthmatics become worse with aspirin and other COX inhibitors, although this is much more commonly seen in severe cases and in patients with frequent hospital admission. Aspirin-sensitive asthma is a well-defined phenotype of asthma that is usually preceded by perennial rhinitis and nasal polyps in nonatopic patients with a late onset of the disease. Aspirin, even in small doses, characteristically provokes rhinorrhea, conjunctival injection, facial flushing, and wheezing. There is a genetic predisposition to increased production of cysteinyl-leukotrienes with functional polymorphism of *cys*-leukotriene C_4 synthase. Asthma is triggered by COX inhibitors but is persistent even in their absence. All nonselective COX inhibitors should be avoided, but selective COX2 inhibitors are safe to use when an anti-inflammatory analgesic is needed. Aspirin-sensitive asthma responds to usual therapy with ICS. Although antileukotrienes should be effective in these patients, they are no more effective than in allergic asthma. Occasionally, aspirin desensitization is necessary, but this should only be undertaken in specialized centers.

Asthma in the Elderly Asthma may start at any age, including in elderly patients. The principles of management are the same as in other asthmatics, but side effects of therapy may be a problem, including muscle tremor with β_2-agonists and more systemic side effects with ICS. Comorbidities are more frequent in this age group, and interactions with drugs such as β_2-blockers, COX inhibitors, and agents that may affect theophylline metabolism need to be considered. COPD is more likely in elderly patients and may coexist with asthma. A trial of OCS may be very useful in documenting the steroid responsiveness of asthma.

Pregnancy Approximately one-third of asthmatic patients who are pregnant improve during the course of a pregnancy, one-third deteriorate, and one-third are unchanged. It is important to maintain good control of asthma because poor control may have adverse effects on fetal development. Compliance may be a problem because there is often concern about the effects of antiasthma medications on fetal development. The drugs that have been used for many years in asthma therapy have now been shown to be safe and without teratogenic potential. These drugs include SABA, ICS, and theophylline; there is less safety information about newer classes of drugs such as LABA, antileukotrienes, and anti-IgE. If an OCS is needed, it is better to use prednisone rather than prednisolone because it cannot be converted to the active prednisolone by the fetal liver, thus protecting the fetus from systemic effects of the corticosteroid. There is no contraindication to breast-feeding when patients are using these drugs.

Cigarette Smoking Approximately 20% of asthmatics smoke, which may adversely affect asthma in several ways. Smoking asthmatics have more severe disease, more frequent hospital admissions, a faster decline in lung function, and a higher risk of death from asthma than nonsmoking asthmatics. There is evidence that smoking interferes with the anti-inflammatory actions of corticosteroids by reducing HDAC2, necessitating higher doses for asthma control. Smoking cessation improves lung function and reduces the steroid resistance, and thus, vigorous smoking cessation strategies should be used. Some patients report a temporary worsening of asthma when they first stop smoking, possibly due to the loss of the bronchodilating effect of NO in cigarette smoke.

Surgery If asthma is well controlled, there is no contraindication to general anesthesia and intubation. Patients who are treated with OCS will have adrenal suppression and should be treated with an increased dose of OCS immediately prior to surgery. Patients with FEV_1 <80%