12. Gotfried MH, Danziger LH, Rodvold KA. Steady-state plasma and intrapulmonary concentrations of levofloxacin and ciprofloxacin in healthy adult subjects. *Chest* 2001;119:1114–1122.
13. Dunbar LM, Wunderink RG, Habib MP, Smith LG, Tennenberg AM, Khashab MM, Wiesinger BA, Xiang JX, Zadeikis N, Kahn JB. High-dose, short-course levofloxacin for community-acquired pneumonia: a new treatment paradigm. *Clin Infect Dis* 2003;37:752–760.
14. Preston SL, Drusano GL, Berman AL, Fowler CL, Chow AT, Dornseif B, Reichl V, Natarajan J, Corrado M. Pharmacodynamics of levofloxacin: a new paradigm for early clinical trials. *JAMA* 1998;279:125–129.
15. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. *Clin Infect Dis* 1998;26:1–10.
16. Wright DH, Brown GH, Peterson ML, Rotschafer JC. Application of fluoroquinolone pharmacodynamics. *J Antimicrob Chemother* 2000;46: 669–683.

DOI: 10.1164/rccm.2309013

Smoking

A Neglected Cause of Glucocorticoid Resistance in Asthma

Glucocorticoids are currently the most effective antiinflammatory therapy for asthma. Numerous well controlled studies using invasive and noninvasive methods have convincingly demonstrated that these drugs effectively suppress airway inflammation, which is associated with an improvement in symptoms, lung function, and airway responsiveness. Studies examining drug effects in asthma, however, are generally performed in nonsmoking subjects to ensure that the well known harmful effects of smoking on the lower airways do not bias the results. Since up to one third of asthmatics are current smokers (1), an important part of the asthmatic population is thus excluded from these studies. It is therefore not surprising that the effects of smoking on asthmatic airway inflammation and its response to glucocorticoids have remained unnoticed for many years.

Pedersen and coworkers (2) were the first to observe in an uncontrolled study that smoking subjects with asthma responded less well to inhaled corticosteroid treatment with respect to symptoms and lung function than their never-smoking counterparts. They postulated that smoking could perhaps impair the actions of corticosteroids. Chalmers and coworkers (3) confirmed this observation in a double blind placebo-controlled study in which they demonstrated that patients with asthma who actively smoked failed to show an improvement in lung function, bronchial hyperresponsiveness, and sputum eosinophilia after three weeks of high-dose inhaled corticosteroids. With this study a previously ignored problem came on the scene.

In this issue of the *Journal* (pp. 1308–1311), Chaudhuri and colleagues (4) have further explored the issue of diminished sensitivity to glucocorticoids by smoking in asthma by comparing the efficacy of high-dose oral corticosteroids among current smokers, never-smokers, and ex-smokers with chronic stable asthma, and showed a significant improvement in peak expiratory flow, forced expiratory volume in 1 second, and asthma control score in never-smokers, no response in asthmatic smokers, and a partial response in ex-smokers. Apart from smoking history, the patients in the three groups did not differ with respect to demographic characteristics, lung function, or asthma severity, suggesting that smoking was the only cause of impaired glucocorticoid response.

Smoking as a cause of steroid-resistance is a new concept with important impact on our understanding of asthma pathophysiology, prognosis, and treatment. Epidemiological studies had already revealed that smoking is associated with more severe asthma (5), a more rapid decline in lung function (6), more severe exacerbations (7), and even fatal attacks (8). This has, however, always been attributed to proinflammatory effects and airway remodeling by smoking (9). Impaired sensitivity to glucocorticoids as a consequence of smoking has thus far been ignored as a cause of increased morbidity and mortality from asthma, but might indeed be one of the most important contributing factors.

The fundamental question pertinent to the study of Chaudhuri and coworkers is whether or not smokers with asthma represent a separate phenotype of asthmatics with a different type of inflammation that is insensitive to glucocorticoids. From a previous study by the same group it appeared that the type of airway inflammation in smokers differs from that in nonsmokers, being characterized by neutrophils, rather than eosinophils (10). This could either mean that smoking induces a distinct type of asthma that is characterized by neutrophilic inflammation, or that smoking alters the characteristic eosinophilic infiltrate of preexisting asthma into neutrophilic inflammation. Whether smoking can induce adult-onset asthma is still a controversial issue (5, 11), and prospective studies investigating the effects of smoking on airway inflammation in existing asthma are yet to come.

An intriguing finding of the study by Chaudhuri and coworkers is the partial response to glucocorticoids in the group of ex-smokers. This could indicate that steroid-responsiveness recurs after smoking cessation, and that steroid-insensitivity is a reversible phenomenon. The mechanism of steroid-insensitivity in smokers is still unclear. Based on new insights into the mode of action of glucocorticoids, however, the most likely mechanism is that oxidative stress reduces histone deactelylase expression and activity, which is necessary for adequate inhibition of cytokine production by glucocorticoids (12). Reducing oxidative stress could then lead to a recovery of glucocorticoid action.

Alternatively, the partial response to glucocorticoids in ex-smokers could also be attributed to a bias in patient characteristics. The duration of asthma and the number of pack years in smokers and ex-smokers suggests another possibility: asthma may have been manifested in the ex-smokers before they began to smoke, whereas asthma in the current smokers started long after the onset of smoking. If airway inflammation in the ex-smokers was initially eosinophilic in nature, and inflammation in current smokers was neutrophilic from the start, then the partial response to glucocorticoids in ex-smokers is not a reflection of restored glucocorticoid sensitivity. Instead, the partial response reflects the expression of a partial, but irreversible, loss of antiinflammatory actions of glucocorticoids in an originally steroid-sensitive disease. This would in fact represent an unfavorable message.

How does chronic obstructive pulmonary disease (COPD) fit into this picture? Chaudhuri and coworkers (4) have clearly chosen to define asthma as a functional abnormality of the airways with a reversibility in forced expiratory volume in 1 second of more than 15%, as opposed to the irreversible airflow limitation of COPD. Recent evidence, however, indicates that patients with similar fixed airflow limitation but distict clinical histories for either asthma or COPD have different pathologic characteristics in the airway mucosa (13). Accordingly, a definition based on functional abnormalities may be challenged. The study by

Chaudhuri and colleagues adds to this skepticism by showing that reversible airflow limitation *per se* does not predict the response to antiinflammatory treatment. Alternative definitions of asthma and COPD based on clinical history, airway pathology, and response to antiinflammatory treatment are worth consideration.

What are the clinical implications of the study by Chaudhuri and coworkers? It confirms that smokers with asthma are more difficult to treat than nonsmoking patients, and emphasizes that asthma is not always steroid-sensitive. The prevalence of steroid-resistance in the asthmatic population is not certain, but is probably much higher than previously estimated. Glucocorticoid insensitivity poses a significant therapeutic problem in a large proportion of patients with asthma, which stresses the need for new antiinflammatory treatments.

Taken together, this report by Chaudhuri and colleagues represents an important step in several areas of asthma research. Not only does it provide new insight into the effects of smoking in asthma, it also contributes to a better definition of the different clinical subtypes of asthma, and provides a fascinating *in vivo* illustration of newly discovered molecular mechanisms of steroid-resistance in asthma. It is now time to further explore the interaction of smoking and eosinophilic airway inflammation, to examine whether or not steroid-sensitivity can be regained after smoking cessation and, finally, to find the definitive answer to the question as to whether smoking is a risk factor for adult-onset asthma. In the meantime, all our efforts must be given to encourage the patient with asthma not to smoke.

Conflict of Interest Statement: E.H.B. serves on a Scientific Adversary Board for Merck Sharp and Dome and has received research funding from AstraZeneca.

Elisabeth H. Bel, M.D., Ph.D.
Department of Pulmonary Diseases
Leiden University Medical Center
Leiden, The Netherlands

References

1. Precht DH, Keiding L, Madsen M. Smoking patterns among adolescents with asthma attending upper secondary schools: a community-based study. *Pediatrics* 2003;111:e562–e568.
2. Pedersen B, Dahl R, Karlstrom R, Peterson CG, Venge P. Eosinophil and neutrophil activity in asthma in a one-year trial with inhaled budesonide: the impact of smoking. *Am J Respir Crit Care Med* 1996; 153:1519–1529.
3. Chalmers GW, Macleod KJ, Little SA, Thomson LJ, McSharry CP, Thomson NC. Influence of cigarette smoking on inhaled corticosteroid treatment in mild asthma. *Thorax* 2002;57:226–230.
4. Chaudhuri R, Livingston E, McMahon AD, Thomson L, Borland W, Thomson NC. Cigarette smoking impairs the therapeutic response to oral corticosteroids in chronic asthma. *Am J Respir Crit Care Med* 2003; 168:1308–1311.
5. Siroux V, Pin I, Oryszczyn MP, Le Moual N, Kauffmann F. Relationships of active smoking to asthma and asthma severity in the EGEA study: epidemiological study on the Genetics and Environment of Asthma. *Eur Respir J* 2000;15:470–477.
6. Lange P, Parner J, Vestbo J, Schnohr P, Jensen G. A 15-year follow-up study of ventilatory function in adults with asthma. *N Engl J Med* 1998; 339:1194–1200.
7. Silverman RA, Boudreaux ED, Woodruff PG, Clark S, Camargo CA Jr. Cigarette smoking among asthmatic adults presenting to 64 emergency departments. *Chest* 2003;123:1472–1479.
8. Marquette CH, Saulnier F, Leroy O, Wallaert B, Chopin C, Demarcq JM, Durocher A, Tonnel AB. Long-term prognosis of near-fatal asthma: a 6-year follow-up study of 145 asthmatic patients who underwent mechanical ventilation for a near-fatal attack of asthma. *Am Rev Respir Dis* 1992;146:76–81.
9. Maestrelli P, Saetta M, Mapp CE, Fabbri LM. Remodeling in response to infection and injury. Airway inflammation and hypersecretion of mucus in smoking subjects with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;164:S76–S80.
10. Chalmers GW, MacLeod KJ, Thomson L, Little SA, McSharry C, Thomson NC. Smoking and airway inflammation in patients with mild asthma. *Chest* 2001;120:1917–1922.
11. Sparrow D, O'Connor GT, Basner RC, Rosner B, Weiss ST. Predictors of the new onset of wheezing among middle-aged and older men. The Normative Aging Study. *Am Rev Respir Dis* 1993;147:367–371.
12. Ito K, Lim S, Caramori G, Chung KF, Barnes PJ, Adcock IM. Cigarette smoking reduces histone deacetylase 2 expression, enhances cytokine expression, and inhibits glucocorticoid actions in alveolar macrophages. *FASEB J* 2001;15:1110–1112.
13. Fabbri LM, Romagnoli M, Corbetta L, Casoni G, Busljetic K, Turato G, Ligabue G, Ciaccia A, Saetta M, Papi A. Differences in airway inflammation in patients with fixed airflow obstruction due to asthma or chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2003;167:418–424.

DOI: 10.1164/rccm.2309009

Development of Fluoroquinolones as First-line Drugs for Tuberculosis—at Long Last!

In 1985 in the *Journal*, Tsukamura and colleagues (1) reported their experience treating 19 patients with chronic, drug-resistant tuberculosis with the novel fluoroquinolone antibiotic, ofloxacin. A majority of patients had some bacteriologic response to treatment, and five became sputum-culture–negative. Importantly, the drug that was given for 6 to 9 months was well tolerated. Subsequently, a number of investigators reported similar results with both ofloxacin and another fluoroquinolone, ciprofloxacin. No randomized clinical trials, however, of a fluoroquinolone for drug-resistant tuberculosis have ever been undertaken.

Despite increasing use of fluoroquinolones for drug-resistant tuberculosis, the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC) in their 1993 statement on the treatment of tuberculosis only noted that these drugs might be potentially effective for the treatment of drug-resistant disease (2). In the updated guidelines on tuberculosis treatment published earlier this year, fluoroquinolones were designated as preferred agents for the treatment of multidrug-resistant tuberculosis but were specifically considered not to be first-line agents (3). This is because the few randomized, controlled trials of fluoroquinolones for drug-susceptible tuberculosis that have been conducted have not demonstrated a benefit.

Today, however, nearly 20 years after Tsukamura and colleagues' report (1), there is great interest in the potential of fluoroquinolones to significantly improve the treatment of drug-susceptible tuberculosis. A number of factors have contributed to this interest.

A recent study conducted by the Tuberculosis Research Centre in Chennai, India, that did not have a standard control group randomized patients with newly diagnosed pulmonary tuberculosis to one of four ofloxacin-containing regimens (4). Rates of 2-month sputum culture conversion, a marker of the sterilizing activity of tuberculosis drug regimens (5), ranged from 92–98%. This compares to an expected rate of approximately 80% with standard four-drug treatment (6). Rates of relapse during the 2 years following completion of treatment were 2% and 4% in