

bronchiolitis and recurrent wheeze and asthma, has shown a 50% reduction in the occurrence of recurrent wheeze even after controlling for potential confounding variables (16). One can also speculate that RVs were likely to be responsible for many wheezing events in infants in that study who were not protected by the use of the RSV monoclonal antibody. Prospective trials with antiviral strategies, including potential new vaccines targeting RSV and RV in selected populations at risk, should give us better understanding of the role of viral infections in early life in the causation of childhood asthma.

Conflict of Interest Statement: R.T.S. has served as a consultant for Abbott in the past 3 years and received a total of \$3,600 in fees; he has also given lectures for Abbott in the past 3 years for which he received a total of \$7,700.

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Antibiotic Prophylaxis for Chronic Obstructive Pulmonary Disease Resurrecting an Old Idea

On May 27, 1959, Dr. C. M. Fletcher of the Medical School of London delivered a lecture to the annual meeting of the American Trudeau Society (soon to be renamed the American Thoracic Society) (1). He elaborated an idea regarding the pathogenesis of chronic bronchitis, a condition that likely now would be diagnosed in most such patients as chronic obstructive pulmonary disease (COPD). In what became known as the "British Hypothesis," Fletcher suggested that "atmospheric irritants (chiefly cigarette smoke) produce bronchial hypersecretion in susceptible subjects" and that "recurrent or persistent infection develops and leads to disability from bronchial obstruction." (1). He also stated his belief that antibacterial drugs were capable of prolonging life in severe forms of this condition, and he ended his lecture with a call for more and better research on this subject.

The belief that recurrent respiratory infections played a central role in the pathogenesis of chronic bronchitis led to a number of randomized trials designed to study whether prophylactic antibiotics might prevent exacerbations and disability. These trials, mostly conducted in the 1950s and 1960s, were reviewed in a Cochrane Collaboration metaanalysis (2). Most studies included in the metaanalysis were relatively small, and there was much variation in quality, duration of treatment, and type of antibiotic administered. A summary estimate indicated that antibiotics statistically significantly decreased the likelihood of having an

exacerbation, but the relative reduction was only 9%. In addition, patients in two trials received daily antibiotics during the colder seasons of five consecutive years (3, 4). Compared with placebo, antibiotics had no discernible effect on loss of lung function during that period. As a consequence of these generally disappointing results, the practice of prescribing prophylactic antibiotics for COPD has been largely abandoned during the past 40 years.

In the 1980s, reports first emerged about the beneficial effects of erythromycin, a macrolide antibiotic, in diffuse panbronchiolitis (5, 6). Evidence suggested that the beneficial effects of erythromycin in this disease were not mediated by conventional antibacterial effects, but rather by a variety of antiinflammatory and immunomodulatory actions, which are now better understood (7, 8). Due to observed similarities between diffuse panbronchiolitis and cystic fibrosis, trials of macrolide antibiotics were undertaken in patients with cystic fibrosis (9). As reviewed in another Cochrane Collaboration metaanalysis, these trials (all of which used azithromycin) showed consistent, albeit modest, improvements in lung function and reductions in exacerbation frequency (10). A subsequent trial not included in the metaanalysis also showed a statistically significant reduction in exacerbation risk (11).

In this issue of the *Journal* (pp. 1139-1147), Seemungal and colleagues extend the investigation of macrolides in obstructive

lung diseases to patients with COPD (12). In a single-center, randomized controlled trial, they administered erythromycin (250 mg, twice daily) or placebo for 1 year to 109 patients with moderate to severe COPD (mean FEV₁ = 50% of predicted). The primary outcome was the frequency of exacerbations that required antibiotics, oral corticosteroids, or hospitalization. Erythromycin reduced exacerbation frequency in relative terms by 35% and increased median time to first exacerbation from 89 to 271 days, both differences being statistically significant. There were no statistically significant treatment-related differences in other secondary outcomes, including lung function and selected inflammatory markers obtained from sputum and serum. Lack of an erythromycin effect on inflammatory markers suggests that antimicrobial effects might be the more important mechanism for reducing exacerbations. However, no causal linkage has been established between the inflammatory markers measured in this study and exacerbation frequency. Other, and possibly as yet unidentified, antiinflammatory effects of macrolides might be more clinically relevant.

No significant safety issues related to extended erythromycin use were identified in this trial, but the relatively small sample size (109 patients) and limited follow-up (1 yr) provide insufficient power to detect infrequent but serious side effects. Except for dose-dependent gastrointestinal disorders, macrolides are generally well tolerated, but they are capable of causing serious adverse effects. Macrolides may prolong the electrocardiographic Q-T interval, with consequent risk of lethal tachyarrhythmias (13). This risk may increase with age and from interaction with multiple other drugs. Macrolides may also cause hepatic dysfunction, ototoxicity, and severe allergic reactions. As macrolides are generally administered for only brief periods, little is presently known about the safety of prolonged administration, particularly in older populations.

The effect size reported in this study is impressively large by comparison with the generally modest benefits of most current COPD therapies, but the finding requires confirmation. The literature is replete with examples of initially promising clinical trial results that cannot be confirmed by larger, multicenter studies, a recent example being the use of interferon γ -1b for idiopathic pulmonary fibrosis (14). The National Heart, Lung and Blood Institute-sponsored COPD Clinical Research Network is currently conducting a multicenter randomized clinical trial of 1,130 patients with COPD at high risk for exacerbations (ClinicalTrials.gov identifier NCT00325897). Trial participants receive either daily azithromycin (250 mg) or placebo for 1 year and the primary outcome is time to first exacerbation. This study will presumably either support or refute the findings of Seemungal and colleagues, and perhaps just as importantly, provide a more comprehensive safety assessment.

From a societal standpoint, there are other important implications to chronic antimicrobial therapy in patients with COPD, particularly with regards to emergence of bacterial resistance. In relative terms, diffuse panbronchiolitis and cystic fibrosis affect very small populations, whereas COPD may afflict as many as 10% of adults 40 years of age and older worldwide (15). Macrolide therapy for reduction of exacerbations, assuming that is the only clinical benefit, presumably would be indicated for only a small proportion of patients with COPD at highest risk for exacerbations. But this might still include millions or even tens of millions of patients on a global scale. In this scenario, substantial, widespread emergence of macrolide bacterial resistance is virtually foreordained, with attendant reduction in the antimicrobial usefulness of this drug class (16). Balancing benefit

against harm could pose a dilemma for which there might be no clear answers.

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