CHRONIC AIRWAY DISEASE: THE INFECTION CONNECTION

STEPHEN B. GREENBERG and (*by invitation*) ROBERT L. ATMAR

HOUSTON, TEXAS

INTRODUCTION

Chronic airway diseases including asthma, chronic bronchitis and emphysema have been increasing in importance as causes of morbidity and mortality in the United States and throughout the world (1). The number of persons with chronic bronchitis and emphysema has risen sharply over the past 20 years and is thought to be 14–16 million individuals. A 40% increase in cases has been diagnosed since 1980 (2). Medical care costs, both direct and indirect, are estimated to be approximately 24 billion dollars per year (3).

Chronic obstructive pulmonary disease (COPD) is currently the fourth most common cause of death, accounting for over 100,000 deaths each year (4). Although age-adjusted death rates from all causes have declined significantly over the past 45 years, COPD deaths per 100,000 population have risen 4-fold. In the past 15 years, the death rate from COPD in males has remained high and unchanged, while the rate in women has doubled.

Asthma affects approximately 14 million individuals in this country, with increases in prevalence being reported in the inner cities (1,5). Children under 18 years of age account for 2/3 of all cases. Although deaths from severe asthma have not changed appreciably, morbidity continues to be significant with increased utilization of health care, especially for urban minority populations (6). The estimated cost of asthma care in the United States is over $10 billion per year (1,7). Recent studies have suggested that childhood asthma and/or respiratory infections can alter maximal growth in lung function and may lead to the development of COPD as an adult (8,9).

BRIEF HISTORY OF CHRONIC AIRWAY DISEASE

Both acute and chronic lung diseases have been appreciated by physicians for over 2,000 years. One of the first descriptions of asthma

Supported in part by contracts NO1-A1-15103 and NO-A1-65298 of NIAID.

Address correspondence to: Stephen B. Greenberg, M.D., Department of Medicine, Baylor College of Medicine, One Baylor Plaza, 559E, Houston, Texas 77030.

($\alpha\sigma\theta\mu\alpha$) was given by Aretaeus The Cappadocian, who lived around the time of Galen, in the 2nd century A.D. (10). In the 17th century, Thomas Willis described asthma as "a most terrible disease" whose "morbitic" cause or nature is "either in the muscular fibers themselves," or "in the branches or nervous slips, or lastly with the brain" (11).

Although not the first physician to relate morbid anatomy to clinical medicine, René Laennec was the first to relate physical changes in the chest to what was found in the lungs at autopsy. In his Treatise on Diseases of the Chest (1821), he described "bronchitis" and "emphysema" and connected what he heard and saw during physical examination with pathologic changes in the lung after death (12).

By the late 19th century, there was a sophisticated understanding of the epidemiology, morbid anatomy and clinical course of asthma, chronic bronchitis and emphysema. In his first edition (1892) of The Principles and Practice of Medicine, William Osler provided a well-developed description of these conditions as they were understood at the time (13). Osler described the differences between acute and chronic bronchitis: the importance of age, climate, and season, as well as the role of acute infection on exacerbations. Osler wrote: "This affection may follow repeated attacks of acute bronchitis . . . It is frequent in the aged; the young rarely are affected. Climate and season have an important influence. It is the winter cough of the old man, which recurs with regularity as the weather gets cold and changeable." Although his understanding of the etiology of asthma was less well-developed, he could appreciate the possible interaction of inflammatory responses, environmental stimuli and predisposition to asthmatic attacks. He thought asthma was a "neurotic affection, characterized by hyperaemia and turgescence of the mucosa of the smaller bronchial tubes and a peculiar exudate of mucin" (13).

Over the next 60 years, increasing industrial air pollution and rates of cigarette smoking were correlated with a steady rise in the prevalence of chronic bronchitis and emphysema (14,15). The observations by Hogg, Macklem and Thurlbeck 30 years ago pinpointed the small airways 2mm or less in diameter as the sites of increased airway resistance in COPD (16). Over the next 20 years, several longitudinal studies defined the natural history of chronic bronchitis and emphysema and related the rising morbidity and mortality to external environmental factors, especially cigarette smoking (17,18).

Since 1900, the major risk factors for COPD and asthma have been thought to combine both genetic predisposition with environmental pollution and/or allergen exposure (19,20). Many studies have proposed a genetic component underlying the development of COPD (21).

Family studies have demonstrated a clustering of cases, an increased incidence in relatives of cases compared to relatives of controls, significant correlations in lung function between parents and children, and similar pulmonary function in monozygotic and dizygotic twins. Family aggregation studies and twin studies have also suggested a genetic basis for asthma. Recent studies are focusing on identifying genes that are important for a predisposition (22).

At approximately the same time that the role of cigarette smoking and allergens were being defined as important cofactors in bronchitis and asthma, an increasing awareness of respiratory infection in the natural history of these diseases was developing (23). One of the earliest studies to link respiratory infection to exacerbations of bronchitis was reported in the early 1950s (24). Dr. C. H. Stuart-Harris cultured patients with acute exacerbations of chronic bronchitis for respiratory bacterial pathogens and influenzavirus and performed serologic tests to document recent influenzavirus infections. Although bacteria such as *Streptococcus pneumoniae* and a *Haemophilus influenzae* were thought to be important in those acute exacerbations, these sentinel studies also demonstrated the importance of influenzavirus infections in exacerbations. The conclusion of this paper was prophetic: "The viewpoint thus reached is that in chronic bronchitis there is essentially a failure of defense of the lower respiratory tract against invasion by nasopharyngeal organisms. The repetitive attacks of respiratory viruses to which we are all subject may play a large part in bringing about this state of affairs." During the past 45 years, studies have confirmed Dr. Stuart-Harris's findings and have provided newer insights into the interaction between respiratory viruses and chronic airway disease (25–35).

ROLE OF RESPIRATORY VIRUSES IN COPD EXACERBATIONS

Eleven longitudinal studies of respiratory viral infections in COPD patients have reported a wide range of viral-associated exacerbations (36–45). Only three were controlled studies and only one attempted coronavirus identification (Table 1). The study by C. Smith demonstrated that rhinovirus, influenzavirus and RSV infections were the most common viruses associated with exacerbations. No significant effect on long-term pulmonary function was detected, although increased pneumonias were noted in those with lower baseline FEV_1 (33,39).

TABLE 1
Respiratory Tract Viral Infectious and Exacerbations in Adult COPD Patients

Dates of Studies	No. of Studies	Duration (months)	No. of Subjects	% RTVI + Exacerbations	Top Three RTVI's Identified
1965–76†	11	9–84	8–199	0–64%	Influenzavirus, rhinovirus, RSV
1983–85*	1	16	62	27%	Influenzavirus, rhinovirus, parainfluenza
1991–95‡	1	26	62	19%	Parainfluenza, coronavirus, rhinovirus

† Only 3 were controlled, and one attempted coronavirus identification.
* Longitudinal.
‡ Longitudinal and controlled.

PLAN OF STUDY

To clarify the importance of respiratory viruses in COPD morbidity and mortality, we studied two cohorts of COPD patients in prospective longitudinal studies. The criteria for COPD were as defined by the American Thoracic Society (46). Baseline evaluations included history, physical examination, routine spirometry and blood for future serologic studies. Patients were contacted every 2 weeks and asked about new respiratory symptoms. Those with acute illnesses were seen as soon as possible and nasal secretions and throat swabs for viral cultures obtained, as well as an acute phase serum. All subjects were offered annual influenzavirus vaccine every fall and over 70% were immunized yearly.

Upper respiratory tract illnesses (URTI) had symptoms of rhinitis and/or pharyngitis. Lower respiratory tract infections (LRTI) were defined by increased cough and sputum production or increased wheezing.

RESULTS

From 1983 to 1985, 62 patients were followed through two winter seasons for an average of 16 months. Twenty-seven percent of acute respiratory illnesses had a respiratory viral infection detected by either tissue culture isolation or serologic rise. Of the patients followed from 1991–95 for an average of 26 months, 19% of acute respiratory illnesses had a respiratory viral infection detected (47). In COPD patients with initial FEV_1 <50%, a significant increase in morbidity and mortality was noted over the duration of the study. Visits to the emergency center and admissions to the hospital were increased in

patients with moderate to severe COPD. The most frequently detected viruses were influenzavirus, rhinovirus, and parainfluenzavirus. Age-matched control patients without lung disease were followed concurrently in the latter study and had a similar distribution of viral infections, but fewer visits to the emergency center and hospitalizations. In both studies, ≈80% of the virus-associated illnesses, as well as the hospitalizations, occurred from October through March of each year. During the study, half the patients with a baseline FEV_1, <50% had at least one hospitalization and 28% had an episode of pneumonia.

ROLE OF RESPIRATORY VIRUSES IN ASTHMATIC ADULTS

In children, the majority of wheezing episodes and asthma exacerbations have been associated with respiratory viruses: rhinoviruses, coronaviruses, and parainfluenza viruses being most commonly identified (48–50). In adult asthmatics, the frequency of exacerbations associated with respiratory viral infections has ranged from 0% to 44% (51–54). We have completed two prospective studies in adults with asthma who obtained their medical care in an urban public teaching hospital (Table 2) (55). In the longitudinal study 29 adults with asthma were followed for viral infection during two fall and winter seasons. In a parallel, cross-sectional study, adults with asthma coming to the emergency center at Ben Taub General Hospital were evaluated for respiratory viral infections. Similar methods of evaluation, virus cultures and serologic studies were performed as in the COPD studies. However, RT-PCR assays for picornavirus, coronavirus and/or influenzavirus were performed on respiratory samples from these acutely ill patients.

Picornaviruses and parainfluenzaviruses were the most common

TABLE 2
Respiratory Tract Viral Infections and Illnesses in Adult Asthmatic Patients

Dates of Studies	No. of Studies	Duration (months)	No. of Subjects	% RTVI + Exacerbations	Most Common RTVI's
1970–94†	8	6–18	8–138	0–57%	Influenzavirus, rhinovirus, parainfluenzavirus
1991–94* (longitudinal)	1	20	29	44%	Rhinovirus, parainfluenzavirus, influenzavirus
1992–94* (emergency center)	1	18	122	55%	Rhinovirus, coronavirus, influenzavirus

† Only one study looked for coronavirus infections.
* Adapted from Atmar R, et al. Arch Int Med 1998 (in press).

causes of respiratory tract viral infections (RTVI) documented in the longitudinal study. In the emergency center study, picornavirus and coronavirus infections were the most common RTVIs identified. Approximately 75% of the picornavirus and coronavirus infections were identified only by RT-PCR. Of the respiratory illnesses reported, 41% in the longitudinal study and 55% in the emergency center study had an associated respiratory virus identified. In both studies, 55% of the emergency center visits had a virus identified and almost half of the hospitalizations had a respiratory virus identified. There were no deaths in the hospitalized patients.

ROLE OF RESPIRATORY VIRAL INFECTIONS IN HOSPITALIZATION OF HIGH RISK PATIENTS

Drs. Paul Glezen, Robert Couch and colleagues have recently completed a study evaluating the role of respiratory viral infections associated with all acute respiratory conditions resulting in hospitalization among persons with chronic underlying conditions (56–58). Over 1,000 admissions for acute respiratory conditions were cultured for respiratory viruses from 1991 to 1995. They represent a parallel population of patients to the COPD and asthma study cohorts previously described (56). Respiratory syncytial virus was the most common respiratory virus detected, especially in children <5 years of age. Among patients aged 55 and older, 20% had a virus detected with the most common being coronavirus, influenzavirus and parainfluenzavirus. More than 50% of these hospitalized patients had asthma or COPD. This study supports an important role for acute respiratory viral infections in the hospitalization of patients with underlying chronic airway disease.

EFFECTS OF RESPIRATORY TRACT VIRAL INFECTIONS ON AIRWAY OBSTRUCTION

There are several proposed mechanisms for how respiratory viruses could lead to the development of airway obstruction and hyperresponsiveness (59). Direct infection of the lower airways has been reported for influenza, parainfluenza and respiratory syncytial viruses. Rhinoviruses may also infect the lower respiratory tract in children and adults (50). Bronchial inflammation could be increased following these respiratory viral infections. Increased airway responsiveness has been observed following virus challenge in atopic or asthmatic volunteers (61). Animal models of respiratory infections have demonstrated enhanced parasympathetic effect signals, increased neuropeptidase release and decreased nitric oxide (NO) production (62). Virus-infected

animals show bronchiolar wall edema and inflammatory cell infiltration with bronchiolar narrowing due to airway lumen plugging (63,64).

Cytokines are important contributors to the inflammatory process in asthma patients (65,66). These mediators of inflammation are found in the epithelial cells of the airway, as well as in mast cells, eosinophils, T-lymphocytes and macrophages. The increased expression of genes that encode inflammatory proteins is regulated by transcription factors. One transcription factor, nuclear factor-κB (NF-kappa B), appears to be particularly important. Respiratory viruses such as rhinovirus, influenzaviruses and adenovirus have been shown to activate NF-κB which could lead to the production of pro-inflammatory cytokines. Recent studies have reported the activation of NF-κB in human nasal epithelial cells in vivo following rhinovirus infection (67). A better understanding of how cellular transcription factors are effected by respiratory viruses could provide a basis for newer strategies in treatment of asthma and COPD.

CONCLUSIONS

The morbidity and mortality in patients with asthma and COPD is significant (Figure 1). In adults without risk factors, respiratory viral infections usually lead to an upper respiratory tract illness with lower respiratory tract symptoms and signs occurring in a significant subgroup. Most cases are treated as outpatients with no short-term or

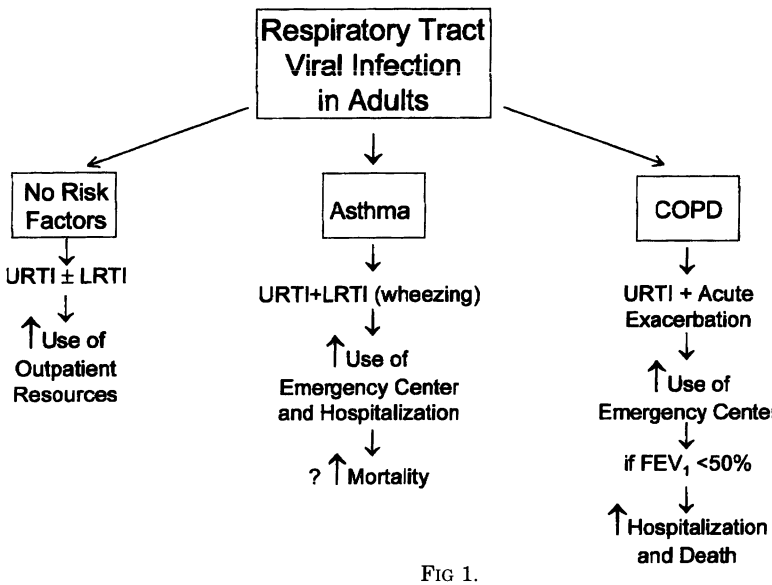

FIG 1.

TABLE 3
Respiratory Tract Viral Infections in COPD and Asthmatic Adult Patients: Longitudinal Studies in Houston, Texas

Study Population	COPD+Asthma	COPD	Asthma*
Years of the Study	1983–85	1991–95	1991–94
Relative Frequency of Respiratory Viral Infections	1) Influenzavirus 2) Rhinovirus 3) Parainfluenzavirus 4) RSV 5) Coronavirus 6) Adenovirus	1) Parainfluenzavirus 2) Coronavirus 3) Rhinovirus 4) Influenzavirus 5) RSV 6) Adenovirus	1) Rhinovirus 2) Parainfluenzavirus 3) Coronavirus 4) Influenzavirus 5) Adenovirus

* Used PCR in addition to cell culture and serology.

long-term sequelae. In adults with asthma, respiratory viruses often lead to both upper and lower respiratory signs and symptoms. In urban centers, these asthmatic adults will often utilize emergency departments for acute care and many will require hospitalization. A portion of the deaths reported in hospitalized patients with severe asthma is probably related to acute respiratory viral infections. In COPD patients, respiratory viral infections lead to URTI syndromes with accompanying acute exacerbations (increased shortness of breath, sputum production, and cough). In our population of urban patients, there was an increased use of emergency center care by acutely ill COPD patients. For those patients with moderate to severe chronic obstruction (FEV_1 <50% of predicted), there was an increased frequency of hospitalization and death compared with age-related controls. From our longitudinal studies of asthma and COPD patients in Houston, Texas, we have demonstrated the importance of rhinovirus, coronavirus and parainfluenzavirus as causes of illness in a heavily influenza-vaccinated cohort of patients (Table 3). The importance of rhinovirus and coronavirus was documented in asthmatic patients when newer PCR technology was applied to clinical samples. Future interventions and strategies for prevention should be based on understanding how these viruses interact with potential bacterial pathogens and the host-immune response.

REFERENCES

1. Health, United States, 1998 report compiled by The Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System, and U.S. Bureau of the Census.
2. Mannino DM, Brown C, Giovino GA. Obstructive lung disease deaths in the United States from 1979 through 1993. An analysis using multiple-cause mortality data. Am J Respir Crit Care Med 1997;156(3 Pt 1):814–818.
3. Adams PF, Marano MA. Current estimates from The National Health Interview

Survey, 1994. National Center for Health Statistics. Vital Health Stat 1995;10(193).
4. Cunningham A, Robinson BS, Myint SH, Ward ME, Tyrrell DA, Holgate ST. The relationship between upper respiratory infections and hospital admissions for asthma: a time-trend analysis. Am J Respir Crit Care Med 1996;154(3 Pt 1):654–660.
5. Sheffer AL, ed. Global initiative for asthma. NHLBI/WHO workshop report. NIH, NHLBI. Publication no. 95–3659, January 1995.
6. Lang DM, Polansky M. Patterns of asthma mortality in Philadelphia from 1969 to 1991. N Engl J Med 1994;331(23):1542–1546.
7. Weiss KB, Gergen PJ, Crain EF. Inner-city asthma. The epidemiology of an emerging US public health concern. Chest 1992;101(Suppl):362S–367S.
8. Shaheen SO, Barker DJ, Shiell AW, Crocker FJ, Wield GA, Holgate ST. The relationship between pneumonia in early childhood and impaired lung function in late adult life. Am J Respir Crit Care Med 1994;149(3 Pt 1):616–619.
9. Shaheen SO, Barker DJ, Holgate ST. Do lower respiratory tract infections in early childhood cause chronic obstructive pulmonary disease? Am J Respir Crit Care Med 1995;151(5):1649–1652.
10. Major RH. Classic Descriptions of Disease, 3rd edition. Charles C Thomas, publisher, p. 576.
11. Major RH. Classic Descriptions of Disease, 3rd edition, Charles C Thomas, publisher, p. 578.
12. Laennec RTH. A Treatise on the Diseases of the Chest (John Forbes, trans.). New York, Hafner, 1962.
13. Osler W. The Principles and Practice of Medicine, 1st edition, New York, Appleton & Co., 1892, pp. 490–503.
14. Burrows B, Niden AH, Fletcher CM, Jones NL. Clinical types of chronic obstructive lung disease in London and Chicago. Am Rev Respir Dis 1964;90:14–27.
15. Fletcher C, Peto R. The natural history of chronic airflow obstruction. Br Med J 1977;1(6077).1645–1648.
16. Hogg JC, Macklem PT, Thurlbeck WM. Site and nature of airway obstruction in chronic obstructive lung disease. N Engl J Med 1968;278(25):1355–60.
17. Burrows B, Bloom JW, Traver GA, Cline MG. The course and prognosis of different forms of chronic airways obstruction in a sample from the general population. N Engl J Med 1987;317(21):1309–14.
18. Burrows B, Martinez FD, Halonen M, Barbee RA, Cline MG. Association of asthma with serum IgE levels and skin-test reactivity to allergens. N Engl J Med 1989;320(5):271–277.
19. Weiss ST, O'Connor GT, Sparrow D. The role of allergy and airway responsiveness in the natural history of chronic airflow obstruction. In: Weiss ST, Sparrow (eds). The Relationship of Airways Responsiveness and Atopy to the Development of the Obstructive Airways Diseases. New York, Raven, 1989, pp. 181–240.
20. Wardlaw AJ. The role of air pollution in asthma. Clin Exp Allergy 23(2):81–96, 1993.
21. Sandford AJ, Weir TD, Pare PD. Genetic risk factors for chronic obstructive pulmonary disease. Eur Respir J 1997;10(6):1380–1391.
22. Manion P. Genetics of asthma: a review. Chest 1997;112(5):1397–1408.
23. Fox JP. Viral contributions to chronic obstructive respiratory disease. Possible mechanism and approaches to detection. Yale J Biol Med 1968;40(5):484–494.
24. Stuart-Harris CH, Pownall M, Scothorne CM, Franks Z. The factor of infection in chronic bronchitis. Quart J Med 1953;86:121–132.
25. Buscho RO, Saxtan D, Shultz PS, Finch E, Mufson MA. Infections with viruses and Mycoplasma pneumoniae during exacerbations of chronic bronchitis. J Infect Dis 1978;137:377–383.

26. Carrilli AB, Gold RS, Gordon W. A virologic study of chronic bronchitis. N Engl J Med 1964;270:123–127.
27. Cherry JD, Taylor-Robinson D, Willers H, Stenhouse AC. A search for mycoplasma infections in patients with chronic bronchitis. Thorax 1971;26(1):62–67.
28. Wiselka MJ, Kent J, Cookson JB, Nicholson KG. Impact of respiratory virus infection in patients with chronic chest disease. Epidemiol Infect 1993;111:337–346.
29. Horn E, Gregg I. Role of viral infection and host factors in acute episodes of asthma and chronic bronchitis. Chest 1973;63:Suppl:44S–48S.
30. Monto A, Higgins MW, Ross HW. The Tecumseh study of respiratory illness. VIII. Acute infection in chronic respiratory disease and comparison groups. Am Rev Respir Dis 1975;111(1):27–36.
31. Monto AS, Bryan ER. Susceptibility to rhinovirus infection in chronic bronchitis. Am Rev Respir Dis 1978;118(6):1101–1103.
32. Mufson MA, Webb PA, Kennedy H, Gill V, Chanock RM. Etiology of upper-respiratory-tract illnesses among civilian adults. JAMA 1966;195(1):1–7.
33. Smith CB, Golden CA, Kanner RE, Renzetti AD Jr. Association of viral and Mycoplasma pneumoniae infections with acute respiratory illness in patients with chronic obstructive pulmonary diseases. Am Rev Respir Dis 1980;121(2):225–232.
34. Smith CB, Kanner RE, Golden CA, Klauber MR, Renzetti AD Jr. Effect of viral infections on pulmonary function in patients with chronic obstructive pulmonary diseases. J Infect Dis 1980;141(3):271–280.
35. Fisher M, Akhtar AJ, Calder MA, Moffat MA, Stewart SM, Zealley H, Crofton JW. Pilot study of factors associated with exacerbations in chronic bronchitis. Br Med J 1969;4(677):187–192.
36. Eadie MB, Scott EJ, Grist NR. Virological studies in chronic bronchitis. Brit Med J 1966;2:671–673.
37. Lamy ME, Pouthier-Simon F, Debacker-Willame E. Respiratory viral infections in hospital patients with chronic bronchitis. Observations during periods of exacerbation and quiescence. Chest 1973;63(3):336–341.
38. Gump DW, Phillips CA, Forsyth BR, McIntosh K, Lamborn KR, Stouch WH. Role of infection in chronic bronchitis. Am Rev Respir Dis 1976;113(4):465–74.
39. Smith CB, Golden C, Klauber MR, Kanner R, Renzetti A. Interactions between viruses and bacteria in patients with chronic bronchitis. J Infect Dis 1976;134(6):552–561.
40. McNamara MJ, Phillips IA, Williams OB. Viral and Mycoplasma pneumoniae infections in exacerbations of chronic lung disease. Am Rev Respir Dis 1969;100(1):19–24.
41. Lambert HP, Stern H. Infective factors in exacerbations of bronchitis and asthma. Br Med J 1972;3(822):323–327.
42. Sommerville RG. Respiratory syncytial virus in acute exacerbations of chronic bronchitis. Lancet 1963;14:1247–1248.
43. Stark JE, Heath RB, Curwen MP. Infection with influenza and parainfluenza viruses in chronic bronchitis. Thorax 1965;20:124–127.
44. Stenhouse AC. Viral antibody levels and clinical status in acute exacerbations of chronic bronchitis: a controlled prospective study. Br Med J 1968;3(613):287–290.
45. Stenhouse AC. Rhinovirus infection in acute exacerbations of chronic bronchitis: A controlled prospective study. Br. med J 1967;3:461–463.
46. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. Am J Respir Crite Care Med 1995;152(5 PT 2):S77–S121.

47. Atmar RL, Allen M, Greenberg SB. Duration of acute respiratory illnesses (ARIs) and viral infection in subjects with and without COPD (abstract). Clin Infect Dis 1996;23(4):878.
48. Berkovich S, Millian SJ, Snyder RD. The association of viral and mycoplasma infections with recurrence of wheezing in the asthmatic child. Ann Allergy 1970;28(2):43–9.
49. McIntosh K, Ellis EF, Hoffman LS, Lybass TG, Eller JJ, Fulginiti VA. The association of viral and bacterial respiratory infections with exacerbations of wheezing in young asthmatic children. J Pediatr 1973;82(4):578–90.
50. Horn ME, Brain EA, Gregg I, Inglis JM, Yealland SJ, Taylor P. Respiratory viral infection and wheezy bronchitis in childhood. Thorax 1979;34(1):23–8.
51. Clarke CW. Relationship of bacterial and viral infections to exacerbations of asthma. Thorax 1979;34(3):344–347.
52. Huhti E, Mokka T, Nikoskelainen J, Halonen P. Association of viral and mycoplasma infections with exacerbations of asthma. Ann Allergy 1974;33(3):145–149.
53. Nicholson KG, Kent J, Ireland DC. Respiratory viruses and exacerbations of asthma in adults. BMJ 1993;307(6910):982–6.
54. Pattemore PK, Johnston SL, Bardin PG. Viruses as precipitants of asthma symptoms. I. Epidemiology. Clin Exp Allergy 1992;22(3):325–336.
55. Atmar RL, Guy E, Guntupalli KK, Zimmerman JL, Bandi VD, Baxter BD, Greenberg SB. Respiratory viral infections in inner city asthmatic adults. Arch Intern Med Dec. 1998 (in press).
56. Glezen WP, Atmar RL, Falcao O, Couch RB. Respiratory virus infections in patients hospitalized with acute respiratory conditions (abstract). Clin Infect Dis 1996;23(4):878.
57. Greenberg SB, Atmar RL, Glezen WP. Spectrum of clinical illnesses due to "common cold" viruses in hospitalized patients (abstract). Clin Infect Dis 1997;25(2):356.
58. Drews AL, Atmar RL, Glezen WP, Baxter BD, Piedra PA, Greenberg SB. Dual respiratory virus infections. Clin Infect Dis 1997;25(6):1421–1429.
59. Folkerts G, Busse WW, Nijkamp FP, Sorkness R, Gern JE. Virus-induced airway hyperresponsiveness and asthma. Am J Respir Crit Care Med 1998;157:1708–1720.
60. Hudgel DW, Langston L Jr, Selner JC, McIntosh K. Viral and bacterial infections in adults with chronic asthma. Am Rev Respir Dis 1979;120(2):393–397.
61. Lemanske RJ Jr, Dick EC, Swenson CA, Vrtis RF, Busse WW. Rhinovirus upper respiratory infection increases airway hyperreactivity and late asthmatic reactions. J Clin Invest 1989;83(1):1–10.
62. Folkerts G, van der Linde HJ, Nijkamp FP. Virus-induced airway hyperresponsiveness in guinea pigs is related to a deficiency in nitric oxide. J Clin Invest 1995;95(1):26–30.
63. Folkerts G, Verheyen A, Nijkamp FP. Viral infection in guinea pigs induces a sustained non-specific airway hyperresponsiveness and morphological changes of the respiratory tract. Eur J Pharmacol 1992;228(2–3):121–130.
64. Folkerts G, Nijkamp FP. Virus-induced airway hyperresponsiveness. Role of inflammatory cells and mediators. Am J Respir Crit Care Med 1995;151(5):1666–1674.
65. Hegele RG, Hayashi S, Hogg JC, Pare PD. Mechanisms of airway narrowing and hyperresponsiveness in viral respiratory tract infections. Am J Respir Crit Care Med 1995;151(5):1659–1665.
66. Zhu Z, Tang W, Ray A, Wu Y, Einarsson O, Landry ML, Gwaltney J Jr, Ellas JA. Rhinovirus stimulation of interleukin-6 in vivo and in vitro. Evidence for nuclear factor kappa B-dependent transcriptional activation. J Clin Invest 1996;97(2):421–430.
67. Barnes PJ, Adcock IM. NF-κB: a pivotal role in asthma and a new target for therapy. Trends Pharmacol Sci 1997;18(2):46–50.

DISCUSSION

Duma, Ormond Beach: Can you put Chlamydia and Mycoplasma in perspective as well? Where might they fit into your observations?

Greenberg: Chlamydia and Mycoplasma pneumoniae have been candidate agents in terms of causing or stimulating exacerbations of COPD and/or asthma. We have, in these same studies, gone after that as an etiology and, in fact, in conjunction with Dr. Thomas Grayston at The University of Washington, have sent our sera out to him to be done for Chlamydia and Atmar has failed to detect either Chlamydia pneumoniae or Mycoplasma pneumoniae infections in our asthma patients by PCR. Not all of the COPD subjects have had the PCR performance for Chlamydia pneumoniae and Mycoplasma pneumoniae, so although we have not found them to be significant pathogens, other groups have reported that they are important in COPD and asthma.

Duma: The reason why I ask, obviously, is because it has important implications in terms of practice. Antibiotics are strongly recommended by pharmaceutical industries. Everybody is detailing them to treat this particular problem, in terms of chronic bronchitis or asthma, bringing into play Mycoplasma and Chlamydia.

Greenberg: Although I didn't mention it and it was not a major part of our prospective study, we looked at all of the exacerbations in COPD patients as to whether they received antibiotics by their physicians. We were not the primary care-givers for that decision. We looked at the duration of symptoms with or without antibiotics and virus-associated infections and nonvirus-associated infections. We could not demonstrate any benefit of antibiotics in those patients who received them for an exacerbation of chronic bronchitis. As a rule, we call these individuals every two days and have a good idea as to the duration of illness. In general, when our chronic bronchitic patients got an acute respiratory viral infection, it was two weeks until they started feeling better.

Ingram, Atlanta: Many years ago we set out to prospectively study the influence of infectious respiratory illness on the airways of smokers versus non-smokers, trying to get some insight into the early part of the story that you are evolving now. It turns out we got a rhinovirus by culture on one subject and we were told by the CDC, who were collaborating with us on the study, that we had to be enormously lucky to have gotten that because there were so many serotypes. This positive culture allowed us to identify by serology several other rhinovirus infections using that serotype. The technical question is, with the new PCR techniques, does that no longer require luck? Can you rule out a rhinovirus infection by a negative PCR?

Greenberg: At this point in time, Doctor Ingram, I would say PCR is as sensitive as you are going to get for detection. What we are finding, and others have found in similar studies, is that PCR will double your frequency of detection of rhinoviruses, especially in adults. It appears that you can isolate the rhinovirus by tissue culture in children with wheezy asthmatic episodes much more easily than in adults. Up until the PCR was available for adults, rhinovirus seemed to be less important than they now appear to be. The other agent that we have found to be important are coronoviruses. The PCR has dramatically helped us since there is not an easy way to detect them by tissue culture.

Woodward, Baltimore: Down the road, is there any chance for developing an attenuated aerosolized strain comprising your three or four strains to immunize against?

Greenberg: The problem as I see it with the development of an aerosolized or attenuated virus is, as you know, that there are numerous serotypes of rhinovirus and finding a common antigen that might be protective or lead to a common immune response has eluded us.You might do it with coronovirus where there are only one or two serotypes, and it could be done for parainfluenza virus. Rhinoviruses are a major problem in terms of developing a vaccine.

Douglas, Princeton: Steve, congratulations on a really fine paper further documenting this connection which many of us have believed for a long time. Were the numbers studied long enough to discern differences among the viruses and the propensity for this association? We think of influenza virus as producing much more destructive histological changes in the lower respiratory tract than coronovirus or rhinovirus. I wonder if your numbers were probably too small to see those differences, but I am curious as to whether that occurred. Secondly, you didn't really talk about secondary bacterial infections. Could the mediator of destructive change be a secondary bacterial infection in spite of the antibiotic data that you presented? What do those data look like?

Greenberg: Let me answer both questions, Doctor Douglas. Thank you. What I was trying to allude to is that we had a highly vaccinated population, both in the asthmatics and COPD patients. Over 70% were getting the annual influenza vaccine. We actually showed that if you got the influenza vaccine, it didn't completely prevent infection. However, we had very few, if any, serious illnesses or hospitalizations in those who got the influenza vaccine. We think we have shifted the population of viruses in this group so that rhinovirus, coronovirus, and parainfluenza viruses appear to be more important. As far as the interaction with viruses and bacteria is concerned, we are actually in the midst of our second year of a longitudinal study following a group of chronic bronchitic patients whom we are culturing for a nontypeable Hemophils influenza infection and Streptoccus pneumoniae. With each exacerbation we are culturing these patients for both viruses and bacteria. The question of virus-bacterial interaction in chronic bronchitis is complex. I am not able at this point to say whether the viruses stimulate the bacteria to grow or, if the bacteria that are chronically present change the ability of viruses to set off an inflammatory reaction.

Dupont, Houston: I think the observation that these viruses are commonly found in patients with chronic pulmonary complications is of potential value in trying to understand pathogenesis, but I wonder how secure are you that these viruses are causing disease and are not there as some secondary factor? Do they produce an immune response to the viruses, for example?

Greenberg: We know on several points that these viruses cause disease. In the longitudinal studies we cultured these people every three months when they weren't sick. We have a baseline of virus cultures in people who are well. We have found about a 1–2% virus recovery when someone says he is ill. This may reflect a chronic infection or a chronic shedding from a previous recent illness. This 1–2% is much lower than what we recorded during the actual illness episodes. We did serologic studies and we found that many of the infections with acute and convalescent sera showed significant rises in specific virus antibody.