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Effect of Viral Infections on Pulmonary Function in Patients with Chronic Obstructive Pulmonary Diseases

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The effect of 100 separate viral infections of the respiratory tract on pulmonary function was evaluated prospectively over an eight-year period in 84 patients with chronic obstructive pulmonary diseases and in eight normal subjects. Some viral infections were associated with small acute declines in forced vital capacity and/or 1-sec forced expiratory volume of 25–300 ml. These declines were detectable only during the 90-day period after infection. The greatest abnormalities of pulmonary function followed infections with influenza virus, and the mean acute changes in 1-sec forced expiratory volume (−118.5 ml) were significantly greater than expected (−15.2 ml; $P = 0.03$). Smaller, statistically insignificant declines followed infections with parainfluenza virus, rhinovirus, adenovirus, and respiratory syncytial virus, and no changes were detectable after infections with coronavirus, herpes simplex virus, *Mycoplasma pneumoniae*, and *Haemophilus influenzae*. Long-term effects of influenza or other viral infections on the course of chronic obstructive pulmonary disease were not detected in this study population.

The hypothesis that viral infections of the respiratory tract may contribute to progressive deterioration of airway function in patients with chronic bronchitis, emphysema, and other chronic obstructive pulmonary diseases (COPD) has intrigued investigators for several years [1–5]. Evidence supporting this hypothesis includes the well-documented association between viral infections and acute exacerbations of bronchitis in patients with COPD [5–12], as well as the recent reports that transient alterations in the function of small airways may occur in normal adults after acute viral infections of the respiratory tract [13–19].

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Informed consent was obtained from the patients in this study, and the guidelines for human experimentation of the University of Utah College of Medicine Human Experimentation Review Committee were followed in the conduct of this research.

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In a recent study of live attenuated vaccine for influenza virus, Zeck et al. [20] reported that patients with COPD were more likely to develop transient deterioration of pulmonary function after infection than were normal adults. Unfortunately, except for the limited and inconclusive study of Stenhouse [6], there have been no adequate prospective studies of the associations between natural viral infections and changes in pulmonary function in patients with COPD.

In studying the association between infections and deterioration of pulmonary function, many investigators have equated infections with clinical "exacerbations" [6, 21–26]. This failure to define adequately the specific infectious etiology of each exacerbation may explain the generally conflicting results of these studies. Leeder [3] has speculated that exacerbations associated with certain viral infections, such as influenza, might have considerably more effect on pulmonary function than would exacerbations associated with allergic reactions or environmental factors.

In 1967 we initiated a long-term prospective study of the effect of bacterial, viral, and mycoplasmal infections on the clinical course and rate of deterioration of pulmonary function in patients with COPD [27]. The acute and long-term effects of 100 separate viral infections of the respiratory

tract on forced vital capacity (FVC) and 1-sec forced expiratory volumes (FEV_1) are assessed in this report.

Materials and Methods

Study population. The study population consisted of 92 subjects who were observed for a mean of 4.4 years (range, two to eight years) during the period 1967–1975. Eight subjects were considered to be normal, 66 had functional evidence of obstructive pulmonary disease upon entry into the study (FEV_1/FVC ratio of <0.70), and the remaining 18 had a history consistent with the clinical diagnosis of chronic bronchitis [25] and/or mild air flow obstruction detectable only by a reduced rate of midexpiratory flow. Ten subjects whose primary diagnosis was asthma were excluded from these analyses because of the wide variability in their performance on pulmonary function tests. A detailed description of the criteria used for selection of our study patients and their clinical characteristics has been previously published [27].

Patients were examined in the clinic about every three months (mean, 4.14 visits/year) and were questioned regarding recent acute respiratory illnesses, immunizations, antimicrobial therapy, and disease status. During each clinic visit, pulmonary function was assessed by spirometry, serum was obtained for antibody studies, and throat swabs, nasal washes, and sputum specimens were collected for isolation of viruses, mycoplasmas, and bacteria. This regular schedule of surveillance was augmented by weekly telephone calls to each subject and instructions to call the investigators at the first signs of an acute respiratory illness. When such illnesses occurred, a nurse visited the home to obtain samples of respiratory tract secretions for culture.

Pulmonary function testing. Spirometry was performed before and after the administration of an aerosol bronchodilator (Bronkometer®; Breon Labs, New York, N.Y.) using established procedures [28]. Determinations of FVC and FEV_1 were made from the largest FVC of two or three spirograms. Only data taken after administration of the bronchodilator were analyzed because these values represented the patients' maximal values on a given day; in addition, they were significantly less variable over long periods than were data taken before administration of the bronchodilator in the individual subjects ($P < 0.01$ by signed rank test). The data were screened for the presence of spirometric values ± 3 SD from the regression lines for individual subjects, as suggested by Fletcher et al. [25]. Values outside of this range were examined for procedural errors, such as miscalculations, and evidence of inconsistency with the individual subject's clinical course. Data that were obviously in error were discarded. Fewer than 0.6% of measurements were discarded by this procedure.

Microbiological studies. Throat swabs were placed in viral transport medium, which consisted of veal infusion broth (Difco, Detroit, Mich.) containing 1% bovine serum albumin, penicillin (100 units/ml), and streptomycin (100 μg/ml). Secretions present in the upper nasopharynx were collected for viral culture by washing each nostril with 5 ml of 0.85% NaCl and mixing the wash with an equal volume of viral transport medium. When available, sputum samples were also obtained for bacterial and viral culture. Sputum samples and specimens for viral culture were kept at 4 C until inoculation onto appropriate media or tissue culture cells. Inoculation of specimens was generally completed within 6 hr of collection.

Sputum, throat, and nasal wash specimens were inoculated onto human embryonic lung (WI-38) cell cultures for isolation of rhinoviruses and herpes simplex viruses. Cell cultures were incubated at 33 C on a roller-tube apparatus and examined daily for evidence of viral CPE. Isolates from cultures exhibiting typical CPE were further characterized by testing for acid lability and chloroform sensitivity [29].

Tests for the presence of CF antibody to respiratory viruses, *Mycoplasma pneumoniae*, and *Haemophilus influenzae* were performed with the microtiter procedure [30]. Adenovirus antigen, parainfluenza virus antigens of types 1, 2, and 3, and guinea pig complement were obtained from Flow Laboratories (Inglewood, Calif.). Soluble CF antigens of influenza types A and B, respiratory syncytial virus, and *M. pneumoniae* were obtained from Microbiological Associates (Los Angeles, Calif.). Coronavirus 229E antigen was prepared from infected WI-38 cells with use of the technique of Kapikian et al. [31]. *H. influenzae* group CF antigen was prepared from American Type Culture Collection strain no. 19418 with the technique of Tunevall [32]. HAI antigens were

prepared and tests for the presence of antibody to coronavirus OC-43 were performed by the technique of Kaye and Dowdle [33]. Because of the known cross-reactivity between parainfluenza virus types 1, 2, and 3, the antigen that produced the highest rise in antibody titer was designated as the infecting agent.

For purposes of data analysis, the date of infection with rhinovirus and herpes simplex virus was considered the date of isolation of the virus, regardless of the presence or absence of illness. Infection with all of the other viruses, *M. pneumoniae*, and *H. influenzae* was based on demonstration of a fourfold or greater rise in antibody titer between consecutive sera. Only serologic rises associated with an acute respiratory illness in the interval between the taking of sera were included in the analysis, and the date that the patient first noted symptoms was chosen as the date of the viral or bacterial infection. When two or more illnesses occurred in an interval between consecutive sera, the illness most compatible with the type of viral infection was chosen. For example, a rise in titer of antibody to influenza virus would be associated with a febrile lower respiratory tract illness in January rather than with a mild upper respiratory tract illness in March.

Statistical methods. The empirical randomization or Monte Carlo method was used to determine whether changes in pulmonary function after an event (in this case, infection with influenza virus) could be explained by chance variation [34]. To explain the methods used in this analysis, we will use an example in which we are interested in comparing the mean FEV_1 in the six-month period before an influenza viral infection (the event) to the mean FEV_1 in the three-month period immediately thereafter. For each patient for whom such observations exist, the mean value for all tests conducted in the six-month period before the event and the mean for all tests done in the three-month period after the event are calculated. A real difference for the patient is given by "after mean" minus "before mean." If more than one event occurs for the patient, "before and after means" are obtained by taking the mean of the means before the events and the mean of the means after the events. The mean of the real difference ($\bar{D}_r$) for FEV_1 is calculated for all patients who have real differences following influenza viral infections.

To determine the statistical significance of $\bar{D}_r$, we chose to compare it to a simulated distribution. (Either a *t*-test or signed rank tests could be used to test the hypothesis of "no-change," but because some decline is expected over time, a test using a simulated "expected change" was derived.) Pseudoevents for each patient are created at random on a Univac 1108 computer (Sperry Univac, St. Paul, Minn.); if a patient had a given number of real influenza viral infections, the same number of simulated random pseudoinfections are created for that patient. The same process is performed with simulated infections as with real infections: for each patient the mean of the FEV_1 means before the simulated infections and the mean of the FEV_1 means after the simulated infections are determined. A simulated difference for the patient is given by "after mean" minus "before mean." These values are averaged for all patients who had influenza viral infections and the required FEV_1 observations, and, as was done with the real data, a mean of the simulated difference ($\bar{D}_s$) is calculated.

A single $\bar{D}_s$ is not enough to make a comparison with the value given by the real data, $\bar{D}_r$. Conceptually the whole simulation process could be repeated to obtain a million or some other great number of $\bar{D}_s$ values. They could be put in ascending order and by counting how many values were $\leqslant \bar{D}_r$, one could very precisely determine the likelihood of obtaining as aberrant a value as $\bar{D}_r$, if in fact $\bar{D}_r$ came from the random distribution. The cost per simulation has to be balanced against the need for precision to determine the actual number of simulations. We have chosen 199 simulations. A number of sets of 199 simulations have been repeated, and stability in results was observed. Using the computer capability to make repeated calculations of $\bar{D}_s$ with different random numbers, one may calculate an empirical *P* value for $\bar{D}_r$. The null hypothesis is that $\bar{D}_r$ is from the same random distribution as $\bar{D}_s$ and that the *P* value (one-tailed) is the proportion of values $\leqslant \bar{D}_r$. The empirical or estimated *P* value is obtained by calculating 199 values of $\bar{D}_s$, which are ordered to include $\bar{D}_r$ from its most negative to its most positive value. Thus, if the greatest decline in pulmonary function out of the 200 values is given by the real data, $P = 0.005$. If the next to greatest is given by $\bar{D}_r$, $P = 0.01$, and so forth.

To make the simulation feasible and lend stability to the observations, only patients with five or

more observations of pulmonary function over at least two years were included. To add further stability, infections were eliminated from the analysis if the distribution of 199 simulated differences contained <10 different values. To facilitate the computations and to have the data correspond to what we believe usually happens, whenever an infection and a pulmonary function observation occurred on the same date, we assumed that the infection preceded the observation.

Periods other than the three months immediately after the event were also of interest. Comparisons using the mean during the six months before the event were also made with the mean during three to six months after, six to nine months after, and so forth, up to and including 15–18 months after the event.

Results

Acute respiratory illness was associated with influenza viral infection on 38 occasions in 35 individuals. The data from 15 individuals were eliminated from the analysis because there were insufficient data from pulmonary function tests to permit statistical evaluation. In addition, normal subjects and those with asthma were excluded so that the results would reflect a population with chronic bronchitis and/or emphysema.

The changes in FVC and FEV_1 that followed influenza viral infection on 17 occasions in 14 individuals are presented in figure 1. Each point on the graph represents the difference between real and simulated values ($\bar{D}_r - \bar{D}_s$) for the differences between the mean of all tests done in the six-month interval before viral infection and the mean of all tests done during each of the indicated three-month intervals after viral infection. The mean real change in FEV_1 during the first 90 days after influenza was −118.5 ml ($\bar{D}_r$), which was significantly greater than the calculated mean simulated change of −15.2 ml ($\bar{D}_s$) ($P = 0.03$). Real changes after the eight infections that were analyzed during this interval ranged from −306 ml to +58 ml. For seven of the eight infections, real declines in FEV_1 were greater than simulated values, and for six of the infections, real declines were >100 ml. The adverse effect of influenza viral infection on FEV_1 appears to be transient, as the difference between real and simulated values in the three- to six-month interval after infection was only −38 ml, and tests done between six and nine months after infection revealed no differences between real and simulated values. Changes in FVC after infection were of similar magnitude and tended to parallel the changes in FEV_1; however, they were more variable, and the changes were not statistically significant ($P = 0.075$). Analysis of spirome-

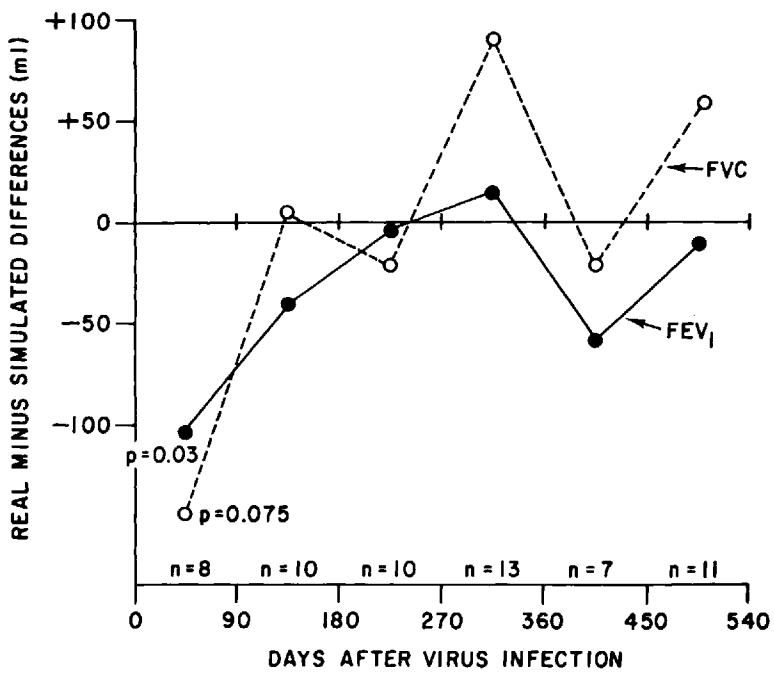

Figure 1. Real minus simulated values ($\bar{D}_r - \bar{D}_s$) for differences in 1-sec forced expiratory volumes (FEV_1) and forced vital capacity (FVC) between the six-month interval before influenza viral infections and the three-month intervals after infection. Seventeen infections occurred in 14 subjects. Normal subjects were excluded from this analysis. Twelve of the 14 subjects had a diagnosis of chronic bronchitis with emphysema, and two had a primary diagnosis of chronic bronchitis with bronchiectasis [27].

tric tests done up to 18 months after infection failed to detect a long-term adverse effect of influenza viral infection.

As was observed after influenza viral infections, adverse effects of other viral infections, when detected, were confined to the 90-day interval after infection. The changes in FVC and FEV_1 that were detected in the 90-day interval after infections with influenza virus, other respiratory viruses, *M. pneumoniae*, and *H. influenzae* are shown in table 1. The greatest (and only statistically significant) acute decline in FEV_1 was detected after influenza viral infections. Infections with adenovirus and respiratory syncytial virus each occurred in three individuals and were associated with moderate differences (−59.9 and −40.2 ml) between real and simulated values during the 90 days after infection. Infections with parainfluenza virus occurred on 11 occasions and were associated with real minus simulated differences in FEV_1 of −26.4 ml. Infections with rhinovirus, coronavirus, herpes virus, *M. pneumoniae*, and *H. influenzae* had no apparent effect on FEV_1. In this analysis we excluded normal subjects and those with asthma. When asthmatics were included in the analysis, an increased adverse effect of rhinovirus infection was detected ($\bar{D}_r - \bar{D}_s = -44$ ml in 90-day interval after infection). Changes in FVC after viral infections tended to parallel changes in FEV_1, except that rhinoviruses were associated with greater changes in FVC (−65.4 ml). In no instance were changes in FVC statistically significant.

A comparison of the mean real difference ($\bar{D}_r$) in FEV_1 and FVC between tests done in the six-month interval before influenza and the three-month interval after influenza viral infection was done for subjects classified according to $alpha_1$-antitrypsin phenotype; degree of airway reactivity, defined as [FEV_1 after bronchodilator/FEV_1 before bronchodilator] × 100; and smoking status (table 2). Three normal subjects were included in this analysis to provide additional numbers for comparison. The mean changes for these three were FEV_1, −91 ml, and FVC, −99 ml, and their exclusion from the analysis did not qualitatively alter the results.

Subjects with normal $alpha_1$-antitrypsin phenotypes had smaller changes in FEV_1 and greater changes in FVC than did subjects who were heterozygous for the deficiency. Subjects with high airway reactivity (defined as ≥10% improvement with bronchodilator) had greater declines in FEV_1 than did subjects with low airway reactivity, whereas the opposite was true for FVC. The most consistent associations were seen with smoking. Individuals who smoked throughout the study had greater declines in both FVC and FEV_1 after influenza than did those who had never smoked or who were former smokers. In no instances were these differences in patient groups significant when analyzed by analysis of variance or the Kruskal-Wallis test [35].

Discussion

The complex of lung diseases variously termed chronic bronchitis, emphysema, or COPD represents an important cause of morbidity and mortal-

Table 1. Real minus simulated values ($\bar{D}_r - \bar{D}_s$) for mean differences in 1-sec forced expiratory volumes (FEV_1) and forced vital capacity (FVC) between the six-month interval before infection and the three-month interval after infection, according to type of infection.

Pathogen	No. of infections	No. of patients	$\bar{D}_r - \bar{D}_s$	
			FEV_1 (ml)	FVC (ml)
Influenza virus	8	8	−103.3*	−145.4
Adenovirus	3	3	−59.9	−187.9
Respiratory syncytial virus	3	3	−40.2	−10.3
Parainfluenza virus	11	7	−26.4	−93.7
Rhinovirus	29	22	−2.6	−65.4
Herpesvirus	29	20	−3.6	+8.9
Coronavirus	8	8	+2	+31.2
Mycoplasma pneumoniae	2	2	+26.2	+68
Haemophilus influenzae	11	11	+54.	+32

NOTE. Normal subjects and patients with asthma were not included in the analysis.
* $P < 0.05$.

Table 2. Mean real difference ($\bar{D}_r$) in 1-sec forced expiratory volumes (FEV_1) and forced vital capacity (FVC) between the six-month interval before influenza viral infection and the three-month interval after infection, according to patient group, with three normal subjects included in the analysis.

Characteristic of patient group	No. of events	No. of patients	$\bar{D}_r$	
			FEV_1 (ml)	FVC (ml)
$Alpha_1$-antitrypsin				
Normal	8	8	−96	−173
Abnormal	3	3	−151	−102
Smoking status				
Never	4	4	−94	−69
Past	3	3	−72	−185
Present	4	4	−157	−216
Airway reactivity*				
High (≥110)	3	3	−130	−64
Low (<110)	8	8	−104	−187

* Defined as: (FEV_1 after bronchodilator/FEV_1 before bronchodilator) × 100.

ity. Smoking, air pollution, lung infections, and various host susceptibility factors have all been considered as possible causes, but their relative importance is still being debated [2, 3, 25]. Opinions of investigators differ on how to define the population to be studied, how to identify lung infections, and which pulmonary function tests to use. Statistical analysis is particularly difficult and must include consideration of the effects of variable, intermittent, and constant factors throughout a disease course of >30 years [23, 25]. These difficulties are considered in the following discussion of our findings.

Spirometric tests of pulmonary function are not ideal for monitoring the natural history of COPD. Tager et al. [36] have shown that in patients with COPD the variability in FEV_1 between consecutive tests on the same day may exceed the yearly rate of change, and Fletcher et al. [25] have estimated that at least 50% of the observed rate of decline of FEV_1 over an eight-year period could be accounted for by variability of the test. We analyzed only data taken after administration of a bronchodilator because these values were less variable. Also we were most interested in the long-term effects of viral infections and wished to reduce the variability induced by acute bronchospastic effects of viral infections. Nevertheless, because of the relative insensitivity of spirometric tests, detection of small changes in FEV_1 or FVC after specific viral infections is likely to be difficult, and our failure to detect statistically significant long-term changes in pulmonary function after viral infections should not be interpreted as proof that viral infections were without adverse effect.

Measurement of midexpiratory flow rates and newer tests of the function of small airways may be more sensitive for detecting the effects of viral infections on pulmonary function in normal adults [15–17, 19]. However, these tests are apparently of little value in detecting changes after viral infections [17] or in following the course of the illness in patients with established obstruction of airways [37, 38]. Thus, despite the recognized difficulties with spirometric tests, most investigators still rely on them for measuring the progress of COPD [23–25].

Bates described the difficulties in assessing the short- and long-term effects of environmental and infectious factors on the course of COPD when he commented that "statistical handling of follow-up data of this kind appears to be a relatively undeveloped science (or art)" [23]. We explored several approaches to the calculation of expected values for changes in pulmonary function for individuals, which could then be compared with observed values. The most direct method was to calculate the least-squares line of best fit for all the individuals' test values for the duration of the study. This method was sensitive to acute changes in function, but was not expected to detect long-term changes. The most complex method for calculating the expected rate of decline of function for each individual was the derivation of an equation based on a step-down regression analysis of the effect of 22 independent variables on the rate of decline of pulmonary function [27]. This equation

was able to explain only 25% of the observed variation in individuals and was therefore discarded. The qualitative results of these various analyses were quite similar: acute changes in pulmonary function were seen after some viral infections; influenza viral infections were associated with the greatest acute changes; and there was no convincing evidence for long-term (greater than six months) changes as a result of viral infections.

We finally selected the empirical randomization method for estimation of expected values and calculations of significance because of its conceptual simplicity and because of our apprehension about assumptions required for any of the more widely used methods: paired *t*-test, signed rank test, or deviation from regression. This method allowed us to compare intervals surrounding specific viral infections with control intervals in the same patient, thus avoiding the problem of varying rates of decline of pulmonary function in subjects with different underlying diseases [27]. It should be noted that the control intervals used in the empirical randomization analysis were selected only to be free of infections with the particular virus under analysis, and that other respiratory illnesses and viral infections occurred throughout these control intervals. We tried a separate empirical randomization analysis in which simulated events were used only when they occurred in a six-month interval that had not been associated with any known viral infection. This analysis led to somewhat greater differences between $\bar{D}_r$ and $\bar{D}_s$, but because many fewer control intervals were available, there was no effect on the statistical significance. There were other arbitrary, but we hope reasonable, choices made regarding the specific ways the simulation approach was used. We used a six-month period to obtain the mean pulmonary function before the event of interest, despite use of three-month intervals after the event, because we felt a six-month interval before would lend greater stability to our base-line measurements.

On the basis of a statistical analysis designed to be conservative, statistically significant changes in FEV_1 were found only during the 90-day period after influenza viral infections. Although acute changes after infections with parainfluenza virus, respiratory syncytial virus, adenovirus, and rhinovirus were not statistically significant, we have elected to discuss their possible importance because the changes were consistently in the direction of an adverse effect. Because small numbers of observations and the inherent variability of the spirometric tests used made statistical analysis in these subgroups difficult, any conclusions based on data obtained in these virus-infected groups must be interpreted with caution.

Most investigators have equated infection in patients with COPD with a clinical diagnosis of chest illness or exacerbation [25]. It is now generally agreed that respiratory viruses are the most frequent causes of acute respiratory illnesses in patients with COPD [6–12] and that pneumococcal and *H. influenzae* infections also occasionally contribute as primary or secondary invaders [1, 39]. However, because at least 50% of such illnesses cannot be associated with a known infectious agent [7–9], we elected to study only those illnesses that were associated with laboratory-proven viral infections. By confining our analysis to specific viral infections, we were able to demonstrate that infections with influenza viruses were more likely to have adverse effects in patients with COPD than were infections with most of the other common respiratory viruses.

Of the common respiratory viruses, influenza viruses most consistently infect and cause histologic abnormalities of the lower respiratory tract [2]. Therefore it is not surprising that we found influenza viral infections to be associated with the greatest, and only significant, changes in FEV_1 and FVC. The acute declines of 100–300 ml observed after influenza viral infection were similar to those described by Johanson et al. [15] in normal adults, and also to those described by Zeck et al. [20] after vaccination with live influenza virus in patients with COPD. Adenoviral infections were observed in only three individuals, and two of these experienced acute declines of FVC and FEV_1 that were similar in severity to those after influenza viral infection. Adenoviruses are also capable of invading the lower respiratory tract, and Kennedy et al. [40] have described acute declines in FVC and indirect maximal breathing capacity in military recruits during acute adenoviral infections on the respiratory tract.

Smaller acute declines in FVC and FEV_1 in some individuals were associated with infections with the parainfluenza viruses. These viruses typically affect the lower respiratory tract during primary infections in childhood, whereas reinfections in normal adults usually are confined to the

upper respiratory tract [41]. Gross et al. [10] have reported that in patients with COPD parainfluenza virus may be associated with viremia and persistence of the virus in pulmonary secretions for two to five months, findings which suggest an unusual pathogenic potential for this virus in patients with COPD. We found that infection with respiratory syncytial virus was uncommon in patients with COPD, but we did observe some acute adverse effects of infection with respiratory syncytial virus in our patients. Other investigators have suggested that respiratory syncytial virus may be a more frequent cause of acute respiratory illness in patients with COPD than in normal adults [7, 8].

Infections with rhinovirus and coronavirus were among the most common causes of acute respiratory illnesses in this study. Except for the subpopulation of asthmatics, rhinoviral infections were not associated with appreciable adverse effects on FEV_1, and changes in FVC after rhinoviral infection were small (−65 ml) and not statistically significant. Transient abnormalities of the function of small airways, which have been described in normal adults after rhinovirus infections [13, 14, 17], indicate the potential for these viruses to invade the lower respiratory tract. We noted that cough and increased sputum production were often associated with rhinoviral infections, but the spirometric tests used in this study did not detect adverse effects on pulmonary function. We were not surprised to find that coronaviruses had no adverse effects on pulmonary function because these viruses are even less damaging to ciliated tracheal epithelial cells than are rhinoviruses [31].

According to Gump et al. [5], herpes simplex virus may be associated with acute exacerbations in patients with COPD. We also isolated this virus more often during illness than during asymptomatic intervals. However, we were unable to detect any acute changes in pulmonary function after infections with herpes virus.

Our analysis of the relative effect of influenza viral infections in different patient subgroups provided data that, although not statistically significant, were often consistent with current hypotheses about the pathogenesis of chronic lung disease. Subjects with reactive airways were found to develop somewhat greater declines in FEV_1 after influenza viral infection than those whose pulmonary function did not improve after bronchodilators. Virus infections can precipitate attacks of asthma [12], and Empey et al. [42] have recently shown that respiratory tract infections (presumably viral) can increase the sensitivity of the normal lung to the bronchospastic effects of histamine and to nonspecific irritants. Our data are consistent with the hypothesis that patients with hyperreactive airways may be more sensitive to further bronchospastic effects of viral infections. Because smoking has been associated with an increased rate of pulmonary deterioration in susceptible patients with underlying reactive airways [27, 43], we expected to confirm the report of Fridy et al. [14] that smokers experience greater adverse effects of viral infections on lung function than nonsmokers. We found that this was true for both FEV_1 and FVC for up to three months after influenza viral infections. We also observed that acute changes in FEV_1 were greater after influenza viral infection in subjects who had abnormal $alpha_1$-antitrypsin phenotype than in those who had a normal phenotype. A possible combined adverse effect of low-level $alpha_1$-antitrypsin activity and infection on lung function has been suggested by Morse [44].

We have recently reported our analysis of the association of multiple variables with the rate of decline of pulmonary function in this patient population [27]. Variables associated with more rapid rates of decline included degree of exposure to cigarette smoke, degree of airway reactivity, and frequency of acute lower respiratory tract illness. Unfortunately, the numbers of patients were not sufficient to permit inclusion of specific viral infections in this multivariate analysis.

When abnormalities in pulmonary function were observed after viral infections of the respiratory tract in patients with COPD, they were transient and not detectable in the 90-day period after infection. The clinical importance of these acute and transient changes depends on the severity of the underlying disease. Most acute viral infections in patients with mild COPD do not alter appreciably either the quality or the duration of life. However, acute respiratory illnesses were the most common cause of death in the study of patients with COPD reported by Diener and Burrows [45], and it is well known that influenza viral infections can be lethal for patients with chronic lung disease [2]. The explanation appears to be

that an acute fall in FVC of 300 ml can be tolerated well by normal adults but may be fatal for a patient with advanced COPD.

For the study group as a whole, we were unable to detect any long-term (greater than three months) adverse effects of influenza or other viral infections in patients with COPD. Marked long-term abnormalities have recently been described in a patient who recovered from influenza virus–associated adult respiratory distress syndrome [46], and long-term sequelae have been described after influenza viral infections in children [47]. Because of the inherent variability in the spirometric tests used, we must temper the negative results of this study with a recognition that future studies using more sensitive techniques and a larger, more intensively studied population may ultimately demonstrate adverse long-term effects of viral infections.

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