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SYNERGISM BETWEEN RESPIRATORY VIRUSES AND BACTERIA**

Many studies concerning the etiology of acute and chronic diseases of the respiratory tract have been triggered by outbreaks of epidemic influenza in man. Parsons,[1] in his report of the influenza pandemic of 1889-90, summarizes the evidence for and against the many hypotheses concerning its etiology which had been considered over the centuries.

Shortly before this pandemic, several groups of organisms associated with acute upper and lower respiratory tract infections had been identified. These included, among others, *Diplococcus pneumoniae, Streptococcus viridans, Streptococcus hemolyticus,* and *Friedlander's bacillus.* Different investigators, particularly in Germany, isolated the above organisms from the secretions of the respiratory tract, lungs, or blood of patients having influenza and ascribed a primary etiological role to them.[2] Pfeiffer isolated the bacillus which bears his name from the secretions and tissues of patients suffering from or dying of influenza.[3] Following his report, the frequent close association of *Pfeiffer's bacillus* with human influenza infections was widely confirmed by others, and this organism came to be considered generally as the specific cause of epidemic influenza.[4,5]

With the world-wide outbreak of influenza in 1918, an opportunity presented itself to investigate with improved methods and design the etiological role of *Pfeiffer's bacillus* in this disease. Its primary causative role was soon questioned, for outbreaks of influenza during the summer months of 1918 occurred, from which cases the influenza bacillus could not be isolated. Jordan,[6] the British Ministry of Health,[7] and David and Robert Thomson,[8,9] reviewed the bacteriological findings from thousands of published reports made during the 1890 and 1918 pandemics and other lesser influenza outbreaks. In summarizing the available evidence, bacterial organisms in epidemic influenza were relegated to the etiological role of secondary invaders acting alone or in symbiotic fashion to produce the often severe complications.

A few years before the 1918 pandemic of influenza several studies were reported which suggested that epidemic influenza and the common cold may be due to viruses. During this outbreak many studies were carried out

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employing man and animals in an effort to demonstrate filter-passing agents in the respiratory tract secretions and blood of individuals suffering from influenza or from the lungs of patients dying of the disease. The experiments for the most part were negative. Those few studies on human volunteers which were considered to show the presence of virus were poorly planned and no significance could be attached to them. Nevertheless, the view persisted and increased that a virus was probably the etiological agent of influenza and the common cold in man, as well as influenza in horses and swine, and distemper in dogs and cats.[6-10]

EXPERIMENTAL ANIMAL STUDIES

Distemper virus and bacteria

In a series of well-controlled experiments, Laidlaw and Dunkin[11-13] demonstrated the virus etiology of canine distemper. They showed conclusively that *B. bronchisepticus,* a long-recognized bacillus regularly isolated from secretions, was actually a secondary invader and was primarily responsible for the purulent complications. They also succeeded in transmitting the virus infection to ferrets, which in the absence of *B. bronchisepticus* showed none of the severe complications of the combined infection. While the distemper virus was never considered to be the cause of influenza, the uncomplicated illness in the ferret resembled the illness produced by human strains of influenza virus.

Influenza viruses and bacteria

Following the isolation of swine influenza virus by Shope[14] and human strains by Smith, Andrewes, and Laidlaw,[15] and Francis,[16] numerous investigations have been undertaken to determine the relationship of these viruses and certain bacteria to the pathogenesis of respiratory diseases.[17]

Shope and associates[14] observed that the intranasal inoculation of the swine influenza virus alone into susceptible pigs produced only a mild febrile illness of short duration. Also, the intranasal inoculation of *H. influenzae suis* alone produced little or no disease. Combining the virus and bacillus resulted in a more severe illness, which was clinically and pathologically identical with the natural disease. Elkeles[18] established that young swine are susceptible to the WS strain of human influenza virus. When the human virus and *H. influenzae* of porcine or human origin were given in combination, a more severe disease resulted than that caused by the virus alone. Shope and Francis[19] confirmed Elkeles' observations and showed that the mixture of human strains of influenza virus and *H. influenzae suis* produced a disease in swine undistinguishable from swine influenza. How-

ever, Mote and Fothergill,[20] employing swine, studied the pathogenesis of combined infections using swine influenza virus, the PR8 strain of human origin, and several human strains of *H. influenzae*. They could not clearly establish a symbiotic or synergistic effect, nor were they successful in establishing *H. influenzae* strains of human origin in the respiratory tract of swine.

Shope[21,22] in classical experiments demonstrated that the swine lungworm, *Metastrongylus*, serves as a vector for swine influenza virus. The virus was shown to persist in the lungworm larvae in a masked non-infective form. In order to render the virus infectious a provocative stress had to be applied to the swine harboring it. The most successful stimulus for activation of swine influenza was multiple intramuscular injections of *H. influenzae suis*. Swine prepared for the ingestion of lungworms carrying virus were refractory to the provocation during the summer months and relatively refractory in September and October, and most susceptible during the first four months of the year. The provocative conditions which activate the masked virus and thus set off natural epizootic outbreaks of swine influenza were postulated to be meteorological and physical influences in the environment. Nayak and associates[23] were interested in learning if the primary inflammatory reaction provoked by the lungworm alone would intensify the pathological process of swine influenza. They found that the swine lungworm did enhance experimental swine influenza. The infection in the animals with worm infestations had a more severe clinical course, more extensive pathology and a higher mortality than did animals with influenza virus alone. These authors cite the studies of Underdahl who showed that migrating larvae of the helminth *Ascaris suum* also enhanced the pathology of swine influenza tenfold.

Bang[24] found that by combining the swine influenza virus and *H. influenzae suis* more severe and fatal infections could be produced in the chick embryo. The resulting infection appeared to have a selective effect on the lungs not produced by either alone. Two strains of human influenza virus combined with *H. influenzae suis* did not result in fatal infections in the chick embryo. Employing fertile eggs, Buddingh[25-28] has studied extensively combined infections produced by influenza virus type C and *H. influenzae* type B. The amniotic route was used. Influenza type C was readily propagated without apparent infection or injury to the embryo. Introduction of *H. influenzae* into the amniotic cavity of influenza infected embryos readily resulted in death and inflammatory lesions, particularly purulent sinusitis, pharyngitis and tracheobronchitis. The increased growth of *H. influenza* in the virus-infected egg was considered to be due to the fact that the virus interferes with "natural" bacteriocidal or bacteriostatic substances.

Janssen and associates[29] demonstrated the synergistic effect of PR8 influenza virus and *Staphylococcus aureus* in embryonated chicken eggs, as indicated by increased deaths of the embryos in the group receiving the combined inocula. The synergistic effect was not observed when the bacterium was given first. Neutralization of the virus by immune serum also abolised the synergistic action. Janssen[30] and associates also studied the synergistic activity between the PR8 influenza virus and *Staphylococcus aureus* in the guinea pig. The virus and organisms were administered as aerosols. Death occurred in higher numbers in animals with the combined infection than with the virus alone. Synergistic effects were observed only in animals receiving the staphylococcus within 24 hours after onset of virus infection.

Smorodintseff and associates[31] studied combined influenza and bacterial infections in mice. The pulmonary infections due to *Streptococcus hemolyticus, Diplococcus pneumoniae,* and *Pfeiffer's bacillus* were greatly enhanced when the organisms were given to mice previously infected with the influenza virus. They considered that the virus acted to suppress the natural resistance of the tissues in the air passages. Francis and associates[32] observed that combined pulmonary infections in mice employing *H. influenzae* and PR8 influenza virus resulted in an exaggerated disease and increase in mortality in animals receiving the virus and bacteria. To a lesser extent the same effect was observed when strains of staphylococcus and *Streptococcus hemolyticus* were used. Cook, Francis, and Kendrick[33] also have shown that combined infections, employing influenza A virus (Asian strain) and staphylococcus in the chick embryo, were significantly more severe than those produced by either agent alone.

Harford and associates[34-36] have made detailed investigations of combined infection employing the PR8 influenza virus and *Diplococcus pneumoniae* type I in mice. Quantitating the dosage, they observed that influenza virus infections rendered the lungs more susceptible to infection with bacteria. The importance of edema fluid in the lung for the establishment of bacterial growth was demonstrated. Treatment of the secondary infection with sulfonamides was effective in preventing death, compared to untreated animals. Gerone and associates[37] also studied combined infections in mice with PR8 influenza virus and *Diplococcus pneumoniae.* The mice were infected by breathing aerosols of PR8 virus or bacteria. Sublethal doses of influenza virus were given, followed after several days by nonlethal doses of pneumococci. Eighty per cent of the mice exposed to the combined agents died, while only 11 per cent of mice exposed to influenza virus alone succumbed. No mice died that had been exposed to aerosols of pneumococci alone. As an interval of three days after the onset of virus

infection is necessary to effect an increased mortality due to the pneumococcus, the viral lesion was considered important in the pathogenesis of the superimposed bacterial lesion.

Experimental infections caused by the influenza virus alone and in combination with group C hemolytic streptococci have been reported. Brightman[38] observed that the predominating organisms in the nasopharynx of ferrets were staphylococci, gram-negative cocci and diphtheroid organisms. In some animals group C hemolytic streptococci could be isolated. He found that group C streptococcal infections could not be produced in ferrets by intranasal inoculation alone. Also, ferrets inoculated with influenza virus alone had only mild illnesses. When both virus and streptococci were given simultaneously, severe infection with bacterial invasion of the blood stream resulted. Brightman also noted that ferrets which had recovered from virus infections were immune to further infection by the combination of virus and streptococcus. He concluded that the role of the streptococcus appeared to be that of a secondary invader. Glover[39] found also that influenza A infection in the ferret rendered it much more susceptible to secondary infection with *Streptococcus hemolyticus* group C. Bacterial infection could be established as long as seven days after the onset of the virus infection. The virus-bacteria infected animals shed large numbers of streptococci into the environment and infected ferrets in adjoining cages. Streptococcal infection could not be established in the absence of virus infection.

Schwab and associates[40-42] studied mixed infections due to PR8 influenza virus and *Streptococcus hemolyticus* group C in mice and monkeys. In mice they found that mixtures of virus and streptococci given intranasally produced more severe infections than either agent alone. Employing the *Macaca mulatta* the same observations were made, namely, that virus or bacteria alone when given intranasally produced relatively mild infection. On the other hand, healthy monkeys given PR8 influenza virus intranasally, and followed in 4 to 17 days by streptococci, developed severe bacterial infections. Their conclusions were that the virus infection predisposes to secondary bacterial invasion.

Influenza viruses and bacterial lung infections in man

The increased incidence of bacterial pneumonias and deaths during influenza outbreaks is now universally recognized. Since methods have been available for isolation and identification, the influenza viruses have been frequently associated with bacterial pneumonias occurring during influenzal outbreaks.[43-68] In nonfatal cases viruses have been isolated frequently from bronchial secretions. Employing both isolation and serological procedures,

as many as 50 per cent of bacterial pneumonias yield evidence of an underlying virus infection. While the majority of bacterial pneumonias are due to *Diplococcus pneumoniae*, fulminating fatal infections due to *Staphylococcus aureus* not infrequently occur. Less frequently isolated bacteria from bacterial pneumonias occurring during influenza outbreaks are *H. influenzae, Friedlander's bacillus,* and *Streptococcus hemolyticus.* Hers[48] and Stuart-Harris[62,63] have summarized the pathogenesis and pathology of human influenza including bacterial complications. The early destruction of the tracheal, bronchial, and alveolar lining cells by the virus, leading to a tracheitis, bronchitis, bronchiolitis, and alveolitis is similar to that seen in the experimental disease in animals.

With respect to onset in man, the virus infection is recognized generally to precede by a day to a few days or longer the onset of the bacterial complication. In discussing the association of secondary bacterial infections with virus lesions, Burnet[64] states:

> It is only in the field of respiratory infections that the effect of a primary viral infection in facilitating serious secondary bacterial infection is fully substantiated. . . . There seems to be no reason to believe that any type of synergism exists between special strains of virus and bacteria. The damage done by the virus to the epithelial lining of the respiratory tract with associated functional and chemical changes simply changes the local environment, making it a suitable ecological niche for any of a variety of pathogenic bacteria. What happens depends on the numbers and types of bacteria which are present in or can reach the respiratory passages of the individual.

NEWER RESPIRATORY DISEASE VIRUSES IN MAN

The viral etiology of acute respiratory diseases in man has broadened greatly during the past 15 years. Dozens of new viral types, falling into several immunologically distinct groups, have been identified. These include the adenoviruses, the parainfluenza viruses, the respiratory syncytial viruses, the reoviruses and the picornoviruses, including Coxsackie A and B, the ECHO viruses, and rhinoviruses. Also during this period, the etiological agent (*Mycoplasma pneumoniae*) of primary atypical pneumonia was identified. With improvements in isolation procedures, herpes simplex viruses are not infrequently isolated. As is the case with influenza virus types A and B, each group produces a wide spectrum of clinical illnesses varying from mild unapparent infections, the afebrile common cold, to febrile nasopharyngitis, tonsillitis, laryngitis (croup), tracheitis, bronchitis, bronchiolitis, and pneumonitis. The distribution of these viruses is world wide. While their prevalence varies, the different groups operate simultaneously in families and communities to produce the wide variety of clinical illnesses seen during the respiratory disease season. All age groups

are susceptible. While respiratory virus tract infections are more severe in infants and children, mild to moderately severe infections in adults have been reported. In 1962[65] a conference concerned itself with the epidemiological aspects and relative role of the many groups of new viruses, as well as the influenza viruses and the mycoplasmas in the etiology of acute upper and lower respiratory tract infections in man. More recently, monographs by Stuart-Harris,[66] Tyrrell,[66] Andrewes,[67] and Hamre[68] summarize the immense amount of information concerning respiratory tract infections caused by the newer viruses.

Reports appear reguarly of studies concerning the etiological role of these and other known viral agents and the clinical characteristics of the respiratory illnesses caused by them in different population groups and communities.[69-81] Other reports are concerned with a specific virus group, such as the rhinoviruses,[68] respiratory syncytial viruses,[82-92] mycoplasmas,[93-101] parainfluenza viruses,[102-105] and adenoviruses.[106-109] It is estimated that from 70 to 75 per cent of all acute upper and lower respiratory tract infections in all age groups are caused by a virus or *Mycoplasma pneumoniae*. New strains of known viral groups and additional new groups of viruses associated with respiratory tract infections are being identified. The multitude of possibilities for becoming infected with viruses, indeed, makes the epidemiology of acute respiratory tract infections complex.[110-113]

Colonization and dissemination of bacteria and viruses from upper respiratory passages in apes and man

Before viruses associated with the common cold were isolated, numerous observations were made concerning the increased number and dissemination of pathogenic organisms from the upper air passages of individuals suffering from colds.[10] Dochez and associates[114-116] over a period of years made a series of studies on the transmission of the "common cold symptoms" to anthropoid apes including the chimpanzee. They observed that the "common cold symptoms" of man could be readily transmitted to apes in contact with the "keeper" having the cold. They also noted that the bacterial flora of the upper respiratory passages of apes were very similar to that found in man. Under controlled conditions of quarantine, Dochez and associates were successful in transmitting "colds" from human beings to chimpanzees by the intranasal injection of filtered nasal washings from human patients in about half of the animals. On occasions, experimental colds were successfully transmitted from chimpanzee to chimpanzee. Of great importance to the investigators was the change or increase in numbers of potential bacterial pathogens in the throat flora. Coincidental with the appearance of symptoms, there appeared increased numbers of pneu-

mococci, *Streptococcus hemolyticus,* and *Pfeiffer's bacillus,* which spread widely over the nasopharyngeal membranes. From their studies, Dochez and associates concluded that the most important significance of viruses (common cold and influenza) was their capacity to incite activity on the part of the more dangerous pathogenic organisms which infect the upper respiratory tract.

Several studies have shown that the membranes of the nose and throats of newborn infants are sterile at birth.[117-121] Shortly after delivery aerobic organisms, particularly nonhemolytic streptococci, could be cultured in increasing numbers. These were similar to those found in the nose and throats of the mothers and attending personnel. The mechanism of acquisition was considered to be by aerial dissemination of infectious droplets. On occasions several days after birth potential pathogens, pneumococci, hemolytic streptococci, and *Staphylococcus aureus* could be recovered, but usually did not persist.

It is well known that severe staphylococcal infections can occur in hospital nurseries leading to serious illness and death. In a study of the spread of *Staphylococcus aureus* in nurseries, Eichenwald[122] found that some babies developing a stuffy nose often contaminated their environment to a high degree with staphlyococci, which spread to other infants and occasionally to attending personnel. Such disseminators of bacteria were referred to as "cloud babies." The "cloud factor" found to be present in a high proportion of the infants was adenovirus type 2 or ECHO virus type 20, which appeared to promote the dissemination of the staphylococci without producing illness except for a stuffy nose. The cloud baby, or the stuffy nose syndrome, represents an unusual example of viral-bacterial interaction to promote the dissemination of the bacteria without enhancement of the infection.

Since procedures for identifying the newer respiratory disease viruses in man have been available, only a few studies have been made of bacterial-viral relationships. Wulff and associates[123] made a study of the etiology of respiratory illnesses in 114 infants and children. Sixty viruses were isolated from 58 patients. Respiratory syncytial and influenza B viruses comprised 55 per cent of the isolates. Other viruses were parainfluenza viruses types 1, 2, and 3, adenoviruses, mumps virus, and two virus strains not identified. Fourteen of the 18 RS viruses, six influenza viruses, and the parainfluenza viruses had associated upper and lower respiratory tract infections. Cultures of the nasopharynx yielded pneumococci from half the patients and *H. influenzae* from a third. About two thirds yielded both organisms. Cherry and associates[124] made a study of 73 hospitalized infants and children with acute respiratory illness. From eleven cases with rhinovirus in-

fections, all but one had lower respiratory tract illness including eight with pneumonia. Bacterial pathogens (*H. influenzae, Diplococcus pneumoniae,* and hemolytic streptococcus) were isolated only from the cases with underlying rhinovirus infections. As all cases on admission had cough and coryza, the authors postulate that the virus infections occurred first and predisposed the young children to more serious bacterial infections. Later studies by Nichol and Cherry[125] were made on 69 additional hospitalized children with respiratory infections and 28 control children without respiratory illness. Viral infections (adenovirus and parinfluenza viruses) were noted in 62 per cent of the patients and in 38 per cent of the controls. Multiple infections (bacterial-viral and viral-viral) occurred in 35 per cent of the infected group and only 7 per cent of the control group. The cases with multiple infections, viral-bacterial, had more severe illnesses, the bacterial organisms being hemolytic streptococci, pneumococci, and *Staphylococcus aureus.*

Viruses as a cause of acute episodes in chronic bronchitis

Recent studies have shown that secretions from the lower respiratory tract of adults free of bronchitis are sterile.[126-128] The factors which cause alteration in the mucous membranes and bronchial wall tissues to allow retention and growth of bacteria in chronic bronchitis are not well understood. Recent studies suggest that some of the newer respiratory disease viruses may be important. The first reports[129,130] of studies of the role of viruses as a cause of chronic bronchitis revealed no association. However, several subsequent investigators have identified a variety of respiratory disease viruses in association with acute febrile illnesses in patients with chronic bronchitis. Viruses that have been isolated or identified by serological procedures included influenza A2, B and C, adenoviruses, respiratory syncytial virus, parainfluenza viruses, psittacosis, herpes simplex, and more recently the rhinoviruses.[131-136] Furthermore, mycoplasma agents have recently been identified in 19 per cent of patients with chronic lung disease, some under treatment for tuberculosis.[137] These studies are of great importance with respect to the etiology of chronic bronchitis and should be continued.[138] The finding that viruses are responsible for acute exacerbations in the chronic bronchitic adds significantly to an increasing body of evidence that bacteria probably do not play a primary or initiating role in the pathogenesis of chronic bronchitis.

Histopathology of pulmonary virus infections in man

The histopathology of influenza virus infections in man and animals has been described repeatedly and is well known.[48,62,68] Less is known concern-

ing the pulmonary changes provoked by the more recently isolated groups of respiratory disease viruses and *Mycoplasma pneumoniae*. This is due to the fact that they have not been readily adaptable for study in experimental animals. However, knowledge of the histopathology of pulmonary lesions caused by a number of different viruses is available from the study of cases coming to autopsy. While reports of fatal infections are few, pathological changes in the respiratory tract of man due to adenoviruses,[139-141] parainfluenza viruses,[108] respiratory syncytial virus,[142] herpes simplex viruses,[143] varicella viruses,[144] and reoviruses[145] have been reported. Likewise, the histopathology of pulmonary infections due to measles virus, Coxsackie viruses and *Mycoplasma pneumoniae* have been described in current textbooks of pathology.

The pulmonary changes caused by the above groups of viruses and the mycoplasmas resemble in general those caused by the influenza viruses. In brief, there is an extensive inflammatory reaction of the walls of the trachea, bronchi, bronchioles, and the respiratory portion of the lungs. The mucous membrane cells, including ciliated and mucus secreting goblet cells, are partially or completely destroyed by the viruses growing in them. The submucosal, peribronchial and perivascular tissues are edematous and thickened with exudate cells. Because the viruses grow in the mucous membrane cells of the bronchial tree, the inflammatory reaction in the peribronchial area is more intense than in the respiratory portion of the lungs. The alveoli in the vicinity of the inflamed terminal and respiratory bronchioles contain more exudate than those in the peripheral parts of the lung, giving a patchy appearance to the pneumonitis. The patchy pneumonic involvement with increased vascular and bronchial markings is usually seen in the chest roentgenograms. During the convalescent period the pneumonitis resolves, but the increased perivascular and peribronchial markings may persist for weeks to months, indicating possible residual scarring.[144] The bronchiolitic lesions caused by the known viral agents resemble those described in fatal cases of acute bronchiolitis before procedures were available for virus identification.[146,147]

Virus infections in the pathogenesis of chronic bronchitis in man

Chronic bronchitis is frequently associated with chronic obstructive lung disease. The latter and emphysema have long been associated. The pathogenesis of chronic bronchitic lesions is not completely elucidated. On the basis of available evidence, repeated viral infections involving the smaller bronchi, bronchioles, and adjacent alveolar tissue with or without secondary changes brought about by bacterial infections should be considered an important cause. A number of investigators conclude that bronchial and

bronchiolar lesions characteristic of viral infections lead to constriction of the luminae, increased pulmonary pressure, air trapping, and eventually rupture of the alveolar walls, to give the picture of emphysema.[148-155]

DISCUSSION AND SUMMARY

Studies of experimentally produced mixed pulmonary infections in animals demonstrate a synergistic action between viruses and bacteria. In most of the investigations, strains of influenza virus along with a variety of bacteria were employed. It was shown that neither virus nor bacterium produced as serious an infection as when the agents were used in combination. Inoculation of the virus had to precede the introduction of the bacterium to provoke a syngergistic action or potentiation of the combined infection. Potentiation of the combined infection was not observed when bacteria were given first. The mechanism by which the influenza virus renders the pulmonary system more susceptible to superimposed bacterial infection is explained on the basis of the specific pathological changes it provokes. The virus grows in the mucous membrane cells lining the air passages and alveolar spaces. In so doing, it destroys them and elicits an inflammatory reaction. The pulmonary eliminatory mechanism is destroyed and the lungs become susceptible to implantation and growth of bacteria.[48]

Experimental studies of mixed viral and bacterial pulmonary infections reported to date have been essentially acute in nature. Chronic residual changes in the lungs brought about by such dual infections have not been investigated. Thus, the development of animal models for the study of biological agents, viruses and bacteria alone and in combination, in the pathogenesis of chronic bronchitis and emphysema is important. Many laboratory animals and certain domestic animals have acute and chronic respiratory tract illnesses caused by viruses and bacteria related to those which infect man. The importance of using naturally occurring infections of animals to elucidate infections in man is stressed by Smith[156] who stated:

> All species of domestic animals have their respiratory diseases and it would seem that if this enormous material involving a variety of hosts and still a greater variety of microorganisms could be brought together . . . . . the causes of human respiratory infections would literally drop into our laps.

Smith's objective is also the primary goal of this conference.

With respect to influenza infections in man, there is considerable evidence that the underlying virus infection potentiates bacterial complications. Studies have been reported which suggest that certain of the newer respiratory disease viruses potentiate certain bacterial infections in infants and children. The majority of acute respiratory tract infections in all age groups of man are now recognized as being due to viruses and *Mycoplasma pneu-*

moniae. The respiratory tract pathology provoked by these agents resembles that produced by the influenza viruses. Strains from the newer respiratory disease virus group and the mycoplasmas have been shown to be the cause of acute febrile episodes in patients with chronic bronchitis and emphysema. It is suggested that these recurring respiratory infections throughout man's lifetime may cause significant enough pathological change in the pulmonary airway structure to contribute to the pathogenesis of chronic bronchitis and emphysema. However, the part respiratory virus and mycoplasma infections play in the pathogenesis and pathology of chronic bronchitis and emphysema is yet to be determined. With procedures available for the identification of these agents, they should be included along with bacteriological analyses in prospective studies of the role of biological agents in the pathogenesis of chronic bronchitis in man. In the light of available evidence, the finding of bacteria alone in the respiratory tract secretions does not exclude the many possibilities that an underlying virus infection was present or had taken place.[63-66,75]

Other factors, of course, must be considered in the etiology of chronic bronchitis and emphysema. Inhaliation of air pollutants (gases), smoking, and alteration in the pulmonary blood supply, can result in changes in lung structure.[157-159] Those who smoke and/or live in polluted atmospheres are at the same time experiencing viral and mycoplasma, and/or bacterial respiratory tract infections which may be potentiated by these chemical irritants. While animal models for the study of the etiology of chronic bronchitis and emphysema are important, the study of the causes of these diseases as they occur in man must not be neglected.

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