Infection, the Environment and Chronic Bronchitis

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Recent studies in Britain and the USA have provided strong evidence for the concept that chronic bronchitis is caused largely by environmental agencies. In Britain, cigarette smoking, air pollution, and the circumstances of life in industrial communities are thought to be the principal causative factors, although the manner of their interaction remains obscure. In other European countries and the USA the great influence of cigarette smoking has also been recognised but the role of atmospheric pollutants has sometimes been difficult to elucidate. Such conclusions have resulted as much from comparative studies in different populations as by intensive study in any one country. In Europe, the Bronchitis Conferences held at Groningen in the Netherlands have done much to stimulate comparative studies, as was emphasised by that held in 1969 (Bronchitis III, 1971). The epidemiological approach leading to these conclusions has not, however, always been understood by clinicians used to dealing with observations on individual patients and who have been impressed by the influence of factors such as infection.

Infection, by bacteria or viruses, has long been recognised as a component of the micro-environment with a considerable effect on the progress of airways diseases. It is a subject that has been difficult to quantitate or to study experimentally as was shown by the symposium on the development of animal model systems held at La Jolla in 1967. The role of infection in chronic bronchitis has been reviewed previously (Stuart-Harris, 1965, 1966, 1968) and in this article concepts of infection will be examined in relation to the natural history of chronic bronchitis and its associated physiological abnormalities.

It is first necessary to note the relationship between chronic bronchitis and the associated conditions of airways obstruction and emphysema. The average patient may be pictured as a man at the intersection of three apparently separate states (Fig. 1). State A is that of chronic productive cough occurring on most days for at least three months in the year and for at least two successive years—chronic bronchitis. Its morbid basis is hypersecretion of mucus by goblet cells and mucosal glands, the latter becoming hyperplastic. State B is generalised airways obstruction causing increased airways resistance and
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Fig. 1. Chronic bronchitis and emphysema. Circle A—Chronic bronchitis defined as chronic productive cough = hypersecretion mucus. Circle B—Airways obstruction (generalised) with spirometric decrease of forced expiratory volume (reversible or irreversible). Circle C—Emphysema—destruction of alveolar walls with increase in air beyond the terminal airways.

defined as a reduction of the forced expiratory volume in one second (FEV$_{1.0}$) and in the ratio of the latter to the forced vital capacity. Its mechanism is unknown, although it may be reversible (asthmatic) or irreversible. State C is a morbid increase in the intrapulmonary content of air beyond the terminal airways and associated destruction of the alveolar walls—emphysema. Its recognition during life is extremely difficult, except when advanced, and it is believed to exist in several different forms. The course of the patient so described varies because the airways obstruction may remain remarkably stable for long periods or may increase steadily, or suddenly. It rarely lessens to any considerable extent. Deterioration of pulmonary function beyond a certain stage brings the patient into respiratory and then congestive heart failure. Although improvement can occur even at this late stage, recurrence is a constant threat and eventually leads to the inevitable termination.

THE BACTERIAL AND VIRAL FLORA OF THE LOWER RESPIRATORY TRACT

Although there is much information on the flora of the upper respiratory tract, relatively little is known about the bacteria and viruses that occur in the lower respiratory tract. Nasopharyngeal secretion certainly finds its way below the
larynx during sleep; the disposal of inhaled organisms has been studied experimentally in animals as it cannot be followed in man. Cleansing of the lower respiratory tract by phagocytosis, ciliary action, and movement of the mucus blanket is a most active process. Yet it occurs silently because the volume of mucus secretion in health rarely exceeds that which can be disposed of without coughing. Inhalation of gases, chemical aerosols, or dusty particles and changes in temperature or humidity can readily disturb this cleansing mechanism. Thus, hypersecretion of mucus resulting from environmental changes causes coughing and also allows organisms from the upper respiratory tract to lodge and multiply in the airways.

In both early and late chronic bronchitis the sputum contains aerobes such as *Micrococcus catarrhalis*, viridans, and non-haemolytic streptococci—the normal commensals of the nasopharynx. Potentially pathogenic species such as pneumococci, *Haemophilus influenzae*, staphylococci, haemolytic streptococci, and coliform bacilli are also present in a percentage of specimens that varies with the phase of illness. Three circumstances form a powerful argument for the view that these organisms actively cause inflammatory changes. First, the proportion of specimens yielding pneumococci and *H. influenzae* is greater when the sputum is purulent or collected during acute exacerbations of illness. This has been shown by many observers and most recently in Edinburgh by Fisher *et al.* (1969) and in the USA by Jenne *et al.* (1970). A quantitative increase in both organisms during acute illnesses was also observed in chronic bronchitic patients by Cooper *et al.* (1961).

Secondly, agglutinins and precipitins against *H. influenzae* are found much more often in sera from patients with chronic bronchitis than from asthmatics or control subjects (Glynn, 1959; Burns and May, 1967). Specific immunoglobulin titres against pneumococci and *H. influenzae* also increase during exacerbations of illness (Reichek *et al.*, 1970) and strongly suggest active infection by those organisms. Thirdly, treatment with antibiotics undoubtedly reduces the volume and leucocyte content of sputum during exacerbations and in ordinary health; the organisms increase in number and the sputum volume increases when treatment is discontinued.

It may be concluded that bacterial infection of the lower respiratory tract is a definite accompaniment of chronic bronchitis and is particularly obvious during exacerbations of illness. Miller and Jones (1964) found that in transport workers, who were only minimally affected in terms of ventilatory function, those who produced sputum when requested had much the same bacterial flora as hospital patients. The infected sputum of these early cases makes it difficult to believe that infection always develops as a secondary phenomenon. Infection can conceivably be the chicken rather than the egg, so far as mucus
hypersecretion is concerned. Yet it is impossible to deny that other environmental agencies, in particular cigarette smoking, also appear to act at an early stage of the disease.

Viruses, unlike bacteria, are found only transiently in the upper respiratory tract, except for herpes virus and certain adenoviruses that persist in a latent fashion. The myxoviruses (influenza, para-influenza, respiratory syncytial virus, and the coronaviruses) and the common cold rhinoviruses are present only during episodes of respiratory illness and disappear from the throat as antibodies develop locally in nasal secretions and in the serum. Studies on patients with chronic bronchitis have shown that viruses can be recovered from the throat and sometimes from the sputum during acute exacerbations of illness but are found infrequently during the quiescent phase. Rhinoviruses (Eadie et al., 1966; Stenhouse, 1967) are the viruses most frequently encountered in the nasopharynx or sputum but all of the known groups of respiratory viruses have been found by serological studies, and sometimes by isolation, to infect patients with chronic bronchitis (Ross et al., 1966; Stenhouse, 1968). Although such viruses may be causing lesions only in the upper respiratory tract, it is more likely that they also multiply in the lower airways, thus accounting for the greatly increased number of deaths of patients with chronic bronchitis during influenza epidemics such as the recent Hong Kong influenza in 1969–70. This effect is too constant a finding to be a casual relationship. The evidence that respiratory viruses can cause cell damage and necrosis in the respiratory epithelium suggests that occasionally a particular viral infection, such as an attack of influenza, may actually play a primary role in initiating chronic bronchitis. Yet, because of their transience, viruses cannot play an enduring role in provoking continued mucus hypersecretion.

MYCOPLASMAS AND CHRONIC BRONCHITIS
Recent attention has been given to the possibility that pleuro-pneumonia-like organisms, the mycoplasmas, may be important pathogens. In animals, mycoplasmas are frequently involved in chronic illnesses, particularly of the respiratory tract. M. gallisepticum causes chronic respiratory disease in chickens (Fabricant, 1969) and M. pulmonis has a significant role in chronic respiratory disease in mice (Tully, 1969). Until recently the only mycoplasma found to be pathogenic for the respiratory tract in man was M. pneumoniae causing primary atypical pneumonia. Serological changes suggesting that it may cause exacerbations of illness in chronic bronchitis were found in Sheffield by Stenhouse (1968) and by Hers and Masurel (1967) in the Netherlands. However, this species does not appear to be a persistent inhabitant of the lower respiratory tract in man as is the case in the animal species already.
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mentioned. Working with specimens collected by Stenhouse in Sheffield, Dr. D. Taylor-Robinson and colleagues at the MRC Common Cold Research Unit at Salisbury have recently examined the whole question of mycoplasmas in relation to chronic bronchitis in man (Cherry et al., 1971).

Studies were made on bronchial aspirates collected by bronchoscopic examination from 42 patients, 22 with established chronic bronchitis, and 20 suspected of having bronchial carcinoma. These specimens were cultured on both solid and liquid media suitable for the growth of mycoplasmas (Manchee and Taylor-Robinson, 1968). Five isolations were made, four of M. salivarium and one of M. orale Type 1. The latter and two of the M. salivarium strains isolated were recovered from the non-bronchitic patients. They were more often found in throat swabs than in bronchial aspirates.

Nasal and throat swabs and sputum were examined repeatedly from 26 patients attending a clinic for bronchitis. Eleven isolations were made from 38 specimens collected during acute illnesses and six from 12 specimens during quiescence; 205 serum samples were collected during quiescence and during exacerbations of respiratory illness from these and from 24 more patients with chronic bronchitis. These sera were studied using M. salivarium, M. hominis, M. orale Type 1 and M. pneumoniae antigens. They showed 30 instances of rises of antibody, measured by the metabolic-inhibition test of Taylor-Robinson et al. (1966) and Purcell et al. (1966). Twenty-five instances occurred during or after an acute respiratory illness and only five occurred at other times. Rises in antibody titre were detected against mycoplasma species not always recovered from the patient. Taylor-Robinson and his colleagues consider that these serological findings indicate increased mycoplasma activity at times of acute illness caused either by viruses or bacteria because mycoplasmas other than M. pneumoniae have rarely, if ever, been found to be the cause of human respiratory illness, and chickens, chronically infected with M. gallisepticum, develop antibody rises during infection by avian bronchitis virus.

**Generalised Airways Obstruction and Infection**

The precise mechanism and origin of airways obstruction affecting the overall ventilatory function of the lungs are still obscure. There is no doubt that ordinary spirometric values are normal in some patients with symptoms of chronic bronchitis. However, studies such as those of Bates et al. (1968) suggest that even then focal areas of small airways disease may exist and cause a disturbance of ventilation and perfusion ratios. Furthermore, apparently healthy persons examined during field studies are found to have low volumes by forced expiration, suggesting that a loss of FEV has occurred silently without sputum production and often without breathlessness (Fig. 2). It is likely,
therefore, that generalised airways obstruction may develop in the absence of hypersecretion of mucus. Yet prospective studies indicate that ventilatory function declines with the passage of time at a faster rate in patients with chronic bronchitis than in normal subjects. Thus, Howard (1967) studied 125 clinic patients for an average of 7.1 years and found a regression coefficient of −0.0834 litres per year of the FEV₀.₇₅. A group of healthy persons of similar age had a regression of −0.034 litres per year (Howard, 1970) and many other observers have found similar values in health. A study of the effects of prophylactic antibiotic therapy (Report of MRC Working Party, 1966) also showed that a mean value of decrease of the FEV₁.₀ by 0.082 litres per year was to be expected among patients with chronic bronchitis.

Granted that patients undergo a deterioration of ventilatory function at a faster rate than healthy persons, it might be expected that a correlation would be observed between the rate of decline of function in individual patients and some environmental factor. Howard (1967) found among his patients that a great deal of variation existed between individuals. Many lost FEV at a slow, steady pace apparently unrelated to acute illnesses, whereas some exhibited sharp falls in the FEV within a period of six months’ observation. Among 21 such steep falls in 19 patients, only 10 occurred in relation to an illness that, however mild, could possibly be regarded as an acute exacerbation. Six of the losses of ventilatory function occurred without any symptomatic change. Only a slight overall relationship was found between the numbers of

Fig. 2. Distribution of the MBC in men in industry (232 men). (Courtesy Arch. Environ. Hlth.)

SYMPTOMS OF CHRONIC BRONCHITIS
NO COUGH OR SPUTUM

MBC (FEV₀.₇₅ X 40) litres/min

NUMBER OF MEN

Fig. 2. Distribution of the MBC in men in industry (232 men). (Courtesy Arch. Environ. Hlth.)
exacerbations of illness and changes in FEV. As these exacerbations were regarded as an indication for antibiotic treatment, there was little objective evidence that infection was a dominant factor in the progression of generalised airways obstruction.

A seven year study of healthy men and of others with symptoms of early chronic bronchitis among transport workers in London has recently been reported (Fletcher et al., 1971). This study was carried out when the smoke pollution in London air was undergoing a rapid decrease. The physiological status of the men was immeasurably better than hospital patients. Among 3,013 men aged 30 to 59 at entry to the study in 1961, the mean FEV$_{1.0}$ was 3.29 litres. The mean FEV at each six-monthly survey of the population showed a decline for the first two years of the study, followed by an unexpected plateau between 1963 and 1965 (Fig. 3). From 1966 onwards the mean FEV resumed its fall, and by 1968 values were obtained which suggested that the overall rate of decline had not differed greatly from that expected on the basis of the experience in 1961 and 1962. The rate of decline of FEV was examined by multiple regression analysis. The frequency of chest illnesses, the frequency of production of purulent specimens and the presence of antibodies to *H.*

![Fig. 3. Deviation of mean FEV at each survey from the mean linear regression of FEV on time. Each large closed circle represents mean of all deviations of individual readings from each man’s linear regression of FEV on time. The small dots represent mean deviations of each individual observer’s readings from the linear regressions at each survey. s = summer; w = winter. (Courtesy the authors and editors of Bronchitis III, Third International Symposium, Groningen.)](image-url)
*influenzae* were unrelated to the rate of decline of FEV. As with Howard's study of more advanced patients, there was no clear evidence that recurrent infection played a part in the development of airways obstruction. However, the volume of morning sputum was related to the rate of decline, and so was cigarette smoking. Non-smokers and those who had never smoked had the lowest, and cigarette smokers had the highest rate of decline. When a comparison was made of the frequency of chest illnesses in smokers and non-smokers, it was found that there was an increased frequency in smokers and also a greater frequency in those with, than those without sputum. Increased tendency to chest illnesses occurred with increase in volume of morning sputum.

Thus, it could be said that sputum production and volume and chest illnesses were related to each other and that sputum volume was related to the rate of decline of FEV although no statistical association existed between chest illnesses and the rate of decline of FEV. Thus, airways obstruction shown by a reduced FEV/FVC ratio appeared to increase the liability to chest illnesses in these men independently of the volume of sputum. The degree of airways obstruction rather than its speed of development appeared to be related to the occurrence of chest illnesses and these, in other studies, have been shown to be accompanied by viral and bacterial infections. This seems to make sense to the clinician, who knows that the patient with severe airways obstruction is the most vulnerable person when faced by the winter respiratory epidemics.

**THE EMPHYSEMA RIDDLE**

It is unfortunately a fact that almost nothing is known about the relation of infection to the genesis and progression of emphysema. This is because, in life, it is extremely difficult to form any exact impression of the presence or absence of emphysema, primarily because of confusion with airways obstruction. Moreover, the consensus of current opinion certainly favours the view that a majority of cases found to have emphysema at autopsy have, in life, given a history of chronic bronchitis and may at autopsy exhibit increased depth of the sub-epithelial mucosal glands and increased number of goblet cells (Reid index—Reid, 1960). This is not to deny the existence of a small proportion of individuals with relatively pure emphysema, some of whom may possess the genetic abnormality of absence of \( \alpha \) trypsin inhibitor in the serum. One can take two divergent views of the emphysema problem—either denying the existence of any pathogenetic relationship with chronic bronchitis or affirming that the two so frequently co-exist that they must share some at least of the various causal factors proposed, for instance, cigarette smoking. Until good quantitative morphological methods have been evolved so that studies in
life can be compared with the true state of affairs in the lungs, it is difficult to believe that progress can be made.

CONCLUSION

One cannot undertake a review of this type without ending with a feeling of disappointment. So many of the present day conclusions are little better than beliefs, for they are founded upon inadequate knowledge. This must apply peculiarly to infection in relation to a prolonged chronic illness, for none of the criteria, such as the isolation of a specific organism from defined clinical states and reproduction of the clinical disease experimentally, can possibly apply. Moreover, there is universal agreement that multiple factors must be concerned in the aetiology of the chronic process. However, some of the pointers that have recently emerged are significant to the appraisal of chronic obstructive bronchitis. First and foremost is the astonishing fact that those who denied sputum production at entry to the prospective study of Fletcher et al. (1971) did not produce sputum during the seven year study. Those who had sputum at entry sometimes lost it, but there were no bronchitis 'recruits' such as had been expected from the rise in frequency of chronic bronchitis with age observed in prevalence studies in Britain but not in other countries such as the USA or Scandinavia. It seems that a cohort of British men exposed to some noxious influence in their youth may have been responsible for this curious age-prevalence and that this influence no longer exists. The severe atmospheric pollution experienced in past years in Britain may have been responsible for this phenomenon.

Secondly, a past history of pneumonia has often been observed in persons with established bronchitis, and the evidence of several British studies indicates the importance of air pollution in relation to pneumonia and other lower respiratory tract illnesses in childhood. Douglas and Waller (1966) studied a cohort of children born in 1946 and followed for the first fifteen years of life. They found that attacks of bronchitis and pneumonia in the first five years of life were more common in those living in areas with high coal consumption, and therefore high pollution levels, than in those with a lesser exposure. Holland et al. (1969), have recently studied 10,971 Kent school children by a questionnaire and study of peak expiratory flow rate. They found that in each of three age-groups, a history of attacks of bronchitis was significantly related to the peak flow. The relationship was graded so that the children with the lowest peak flows had had the most attacks of acute bronchitis. Residence in areas with high smoke concentrations also seemed to be related to low peak flow rates.

Both these studies emphasise the importance of environmental influences
at a tender age of life. Infection and air pollution both seem to be harmful to very young children, and by the time adult life is reached the stage may have been set for the symptoms of chronic bronchitis and the loss of ventilatory function from airways obstruction. On this prepared soil, the irritation induced by cigarette smoking may create further damage. Such an hypothesis is difficult to prove but the fact that interest is now focused in many parts of the world on both air pollution and infection of the respiratory tract is encouraging. Those who are interested in chest disease cannot but deplore the lack of progress in encouraging rejection of the cigarette habit. Perhaps this is symptomatic of the age in which we live in that dependence upon some form of drug usage seems to be socially acceptable.

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Book Review

*Year Book of Dermatology.* Ed. A. W. Kopf and R. Andrade. John Wiley & Sons Ltd., 1970. Price £6.30., 576 pages.

At a time when all medical literature has proliferated enormously it is remarkable that the *Year Book of Dermatology* has not greatly increased in size, although for the past few years the editors have, in addition to their 500 pages of abstracts, added 60 pages of other papers listed by title only. They may justly claim that no really important article escapes inclusion. Hence, for the dermatologist isolated from a library or with no spare time, this book is invaluable. It effectively mirrors all the areas of clinical and research progress during the year in the field of dermatology, such as: keratinisation and the biology of the stratum corneum; porphyria and light induced diseases; immunological aspects of lupus erythematosus, pemphigus and other bullous disorders, as well as of malignant melanoma; pathogenesis and treatment of psoriasis, acne and vasculitis.

The *Year Book* is introduced by an annual review article, and this year's is written by Dr J. E. Jelinek (New York) on the cutaneous manifestations, complications, and associations of diabetes mellitus. This will be of value equally to general physicians and dermatologists.

The articles are selected by an editorial team and show no personal bias. Many are accompanied by editorial comment from several members of the New York University Skin and Cancer Unit. This *Year Book* well maintains the previous high standard.

C. D. C.