COPD and environmental risk factors other than smoking

12. Infection in adults

Author : P N Lee
Date : 2nd January 2008

1. Papers identified

The procedures described in "COPD and risk factors other than smoking. 1. Identifying Relevant Papers" were carried out to identify papers (and reviews) that were relevant to infection in adults.. In the MEDLINE searches papers relating "COPD" (or "chronic bronchitis" or "emphysema") to "infection" with restriction to studies in humans.

2. Reviews

A few of the general review papers referred to in the first report refer to the relationship between COPD and infections in adults. The 1984 US Surgeon General Report[1] referred to four reports[2-5] noting negative results and stating that "It is now apparent that mucus hypersecretion and airflow obstruction are separate pathophysiological entities that have a common cause – cigarette smoking". However, Higgins (1991)[6] lists "Infections of the respiratory tract" under "Risk Factors for COLD" and, more vaguely, Becklake (1989)[7] lists "Past health" as a "putative" risk factor implicated in the development of COPD.

Whereas, for other COPD risk factors, the MEDLINE searches revealed a relatively large number of relevant papers presenting results from epidemiological studies and only a handful of reviews, here the situation was different, with far more reviews than epidemiological evidence! For convenience I summarize these reviews in chronological order.

The earliest review, by Stuart-Harris in 1968[8] is of "the role of bacterial and viral infection in chronic bronchitis." No firm conclusions are reached, the author noting that "much more work requires to be done on the early and possibly the reversible stages of chronic bronchitis before the aetiological

role of either virus or bacterial infection will be understood" and that "the question whether infection precedes the state of chronic hypersecretion of mucus or follows it is still unsolved."

The same author published a further review 3 years later[9]. Again, no clear conclusions are reached, the author noting that "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." He notes an early report from Fletcher's longitudinal study of transport workers[10] showing that "the frequency of chest illnesses, the frequency of production of purulent specimens and the presence of antibodies to *H. influenza*e 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."

A review by Tager and Speizer in 1975[11] concerned "the role of infection in chronic bronchitis". Much of the paper concerned evidence relating infections to exacerbations of the condition in patients with chronic bronchitis (CB). They note that though "respiratory infections appear to contribute to the episodic worsening of cough and phlegm", "clinical data … find no support for a role of respiratory infections experienced in adult life in the progressive obstructive airway disease found in some patients."

In 1976, Langman and Cooke[12] published a review paper entitled "Gastric and duodenal ulcer and their associated diseases". Since such ulcers are now known to be strongly associated with *H. pylori* infection, it is of some interest

to note the evidence linking these ulcers with respiratory disease. Most of the studies reviewed did report such an association although it is clear from the text that most, if not all, of these did not control for smoking and that some did not even control for gender.

A review by Pride in 1982[13] addresses two basic questions: "(1) do broncho-pulmonary infections affect the course of development of airflow obstruction in subjects with chronic bronchitis?, (2) are infections the cause of chronic bronchitis, damaging the normal defence mechanisms and leading to chronic mucus hypersecretion?" In considering the first question he notes that "Some features of bronchial infection in chronic bronchitis appear well established and uncontroversial:

1. clinically-apparent infective episodes are the commonest cause of acute deterioration in patients with advanced chronic airflow obstruction and so are often finally responsible for the death of many of these patients,
2. the frequency of infective episodes increases with increase in severity of airflow obstruction,
3. the colonization of the lower respiratory tract with bacteria and persistence of polymorphonuclear cells in the sputum are common in subjects with chronic cough and phlegm even in the absence of evidence of acute infection and obviously purulent sputum,
4. morphological examination of the lung either at post-mortem (when the findings are complicated by acute changes) or in lobectomy specimens shows abundant evidence of inflammatory changes in association with obstructive changes."

Leaning heavily on the results from Fletcher's study[4] (though pointing out some limitations of it) he concludes that "In Western Europe and North America repeated bronchial infection in smokers appears to be predominantly a consequence of the accompanying mucus hypersecretion, causing a temporary but not permanent decline in lung function." Though he

considered that "Infection may have a more important causative role in communities with poor socio-economic conditions where infections are particularly common and severe and are less likely to be treated with antibiotics", he notes that "The studies in smokers have shown that it is wrong to simply assume that repeated infection is the cause of hypersecretion and obstruction. We now require equally rigorous studies of the role of infection in particular groups of high-risk non-smokers with a high incidence of chronic hypersecretion and airflow obstruction."

A review by Niewoehner in 1988[14] notes that "Traditionally, inflammation and hypertrophy of the mucus-secreting elements within the central airways (chronic bronchitis), manifest clinically by chronic cough and recurrent bouts of purulent sputum expectoration due to infection, were held to be important in the development of COPD. While chronic cough and purulent bronchitis contribute to the morbidity associated with established COPD, epidemiologic studies suggest that neither is an independent factor in its causation."

Murphy and Sethi (1992)[15] published an extensive review of the evidence on bacterial infection in COPD. Much of the paper concerns issues not central to this document. In the section on the effect of acute infectious exacerbations on the natural history of COPD they cite results from four prospective studies, three of which[2,4,16] found no correlation between infection and loss of pulmonary function, and one of which[17] found that more frequent illness was correlated with a more rapid decline. No clear verdict is reached, the need for further studies being emphasised.

In 1998, von Hertzen *et al*[18] reviewed the evidence on *Chlamydia pneumoniae* (Cpn) and its role in COPD. The author notes that "the role of infection in COPD, although investigated over the past 40 years has remained unsolved." In the conclusions it is noted that risk factors including advanced age, current smoking and chronic disease "can modulate immune responses to favour a Th2-type response … fundamental in the case of infections .. such as *C.*

pneumoniae which evidently require a strong Th1-type response in order to be cleared", and also that "it is possible that chronic *C. pneumoniae* in the lungs of these patients amplifies the inflammation caused by smoking."

In 1998 and 1999, Wilson published two short papers[19,20] on the role of infection in COPD. The first paper notes that "The available evidence shows that bacterial infection has a significant role in acute exacerbation, but its role in disease progression is less certain." Both reviews are really concerned with the role of infection in patients with COPD rather than its role in causing COPD.

Markewitz *et al* (1999)[21] review the role of various factors, including infections, on the development of COPD. They note that "As several prospective studies failed to show a relationship between mucus hypersecretion or acute chest infections and the rate of decline of FEV_1, this theory has been discounted by many. It should be noted, however, that a role for childhood infection as a risk factor for the development of COPD remains credible." They also point out that "Proponents of a role for bacterial infection in COPD have recently advanced the 'vicious circle' hypothesis. In this view, bacterial products and the host's response to them propagate, but do not initiate, lung disease. Specifically, bacterial infection/colonization stimulates an inflammatory response that causes local proteolytic injury and progression of obstructive lung disease. Concomitantly, bacterial injury of the airway epithelium impairs host defenses, laying the foundation for further bacterial infection/colonization, establishing the 'vicious circle'. "

A series of papers in 1999-2001 by Hogg[22-25] concern the role of viruses in COPD. Although he considers that "Lower respiratory tract infection is one of the factors that contribute to the risk of developing COPD, and our studies of latent adenoviral infection suggest mechanisms by which latent adenoviral infection results in amplification of cigarette smoke-induced lung

inflammation"[24] and that "Latent adeno-viral infections may have a role in the pathogenesis of obstructive airway disease by amplifying the response to cigarette smoke and inducing steroid resistance"[25], the epidemiological evidence (e.g.[4]) is not discussed at all.

A long "state-of the art" review by Sethi and Murphy in 2001[26] concerns bacterial infection in COPD. It concerns a wide range of issues, but little or nothing on the epidemiological evidence relating to onset of COPD.

Clementsen *et al* (2002)[27] reviewed the role of CP infection in asthma and COPD. They note that "it has been suggested that infection may be responsible for the initiation of the diseases in previously healthy individuals" but say that such a theory needs final proof, though "it is today broadly accepted that infections can cause exacerbation in obstructive lung disease."

Scannapieco *et al* (2003)[28] review the evidence relating periodontal disease to hospital-acquired bacterial pneumonia and to COPD. They note that several studies demonstrate a "potential association" with COPD, but "the results are preliminary and large-scale longitudinal and epidemiologic and RCTs are needed."

Proud and Chow (2006)[29] review the role of viral infections in asthma and COPD. The summary states that "Substantial evidence implicates common respiratory viral infections in the pathogenesis of asthma and chronic obstructive pulmonary disease (COPD). Children who experience recurrent virally induced wheezing episodes during infancy are at greater risk for developing asthma. In addition, respiratory viral infections are a major trigger for acute exacerbations of both asthma and COPD. Despite the importance of viral infections in asthma and COPD, the mechanisms by which viruses predispose to, or cause exacerbations of, these diseases remain poorly understood. It is clear that viral infections lead to enhanced airway inflammation and can cause airways hyperresponsiveness." The evidence

relating infection in adults to lung function decline in healthy adults is not discussed.

Roussos *et al* (2006)[30] ask whether there is a link between *Helicobacter pylori* (HP) infection and respiratory diseases. They note that HP is the main cause of peptic ulcer disease, and that COPD had been associated with peptic ulcer diseases many years ago, citing three epidemiological studies which showed that the prevalence of COPD in peptic ulcer disease was increased two- to three-fold compared with that in ulcer-free controls, and a prospective study showing that CB was a major cause of death among patients with peptic ulcer disease. They note some limitations of this evidence including failure to adjust for cigarette smoking.

HP infection is also considered by Kanbay *et al* (2007)[31]. They note that "the primary evidence for an association between HP infection and chronic bronchitis has come from serology-based case-control studies. Research on the relative risk of developing chronic bronchitis in the setting of HP infection is required. As well, there is a need to investigate how HP eradication affects the natural history of chronic bronchitis, and the pathogenetic mechanisms that underlie the association between HP infection and this disease."

3. Studies

The relevant studies are considered in this section, starting with prospective studies which are most relevant to interpretation. Within both prospective studies and other studies, the publications are considered in chronological order.

3.1 Prospective studies

In 1966 the Medical Research Council[32] carried out a double-blind trial of antibacterial drugs in therapy and prophylaxis in men aged 40-59 with early CB. Oxytetracycline or dummy tables were given for 8 months as prophylaxis in combination with either chloramphenicol or sulphamethoxypyridazine as treatment of exacerbations. Over a 5 year follow-up period prophylaxis by

oxytetracycline had no effect on the number of illnesses or on the rate of decline of FEV or the volume and purulence of sputum specimens.

In 1967 Howard[33] carried out a 7 year follow-up study of 125 patients with COPD. The authors noted that "there was some relation between the size of the regression coefficient and the number of acute exacerbations of the disease requiring antibiotic therapy, but, in individual plots, acute chest illnesses in the majority had no more than a minor effect on the F.E.V. curve".

In 1970 Howard[2] reported on an 11 year follow-up of 159 engineering workers in Sheffield. Men who claimed to have sputum throughout the study had a significantly higher rate of loss of FEV than the group as a whole, and this difference was not entirely explained by the lower mean FEV of those with sputum, though the authors noted that "this does not necessarily indicate that the disease process responsible for sputum causes the loss of FEV". Similar results were obtained for chest illnesses, with men claiming such illnesses kept them off work for two or more consecutive years having a lower FEV and a higher rate of decline.

In 1971 Fletcher *et al*[34] reported preliminary results of a follow-up study of engineering and clerical workers in London (The "Fletcher study"). These results were analysed in much more detail in 1976 (see below). Here the authors noted that "The frequency of chest infections is much greater in those with sputum than in those without and tends to increase with increasing sputum volume" but "this association seems to be due to mucus hypersecretion increasing liability to chest infection rather than the reverse".

In 1973 Bates[16] reported results of 10 year follow-up from a study of CB in four centres in Canada. Men in the study had to have MRC clinical criteria of CB, but still be working, so not disabled. In one analysis 31 men with large lung function changes over the period were compared with 29 men with minimal changes. The proportion with chest infections was very similar in the two groups.

In 1973 May *et al*[35] reported results from the Fletcher study based on 623 men for whom tests for *H. influenzae* precipitin (H_1 antibody) had been carried out on a single occasion. The presence of H_1 precipitin was most strongly associated with smoking habits, but after adjusting for this there was no correlation with FEV_1, FEV_1/FVC or the rate of decline of these parameters. The authors concluded that "infection by *H. influenzae* plays no significant role in the development of airway obstruction and that reported correlations between airway obstruction and H_1 precipitin are due to cigarette smoking, which promotes the development of both abnormalities independently".

The main results of the Fletcher study were published in a 150 page document entitled "The natural history of chronic bronchitis and emphysema: an eight-year study of early chronic obstructive lung disease in working men in London"[4]. Data on lung function, recent bronchial infections and mucus hypersecretion were collected in six-monthly surveys conducted between 1961 and 1969. Their detailed analyses divided factors into those that caused irreversible airflow obstruction (smoking) and those that did not (bronchial infection and allergy). For bronchial infection, the authors noted that:

"We have concluded that symptomatic bronchial infection was not a cause of persistent airflow obstruction in our sample of men. We have great confidence in this conclusion because of the strength and consistency of our negative evidence. None of our indices of infection correlated with FEV slope after adjustment for FEV level and there was no evidence that the chest episodes we observed had any permanent effect on FEV level (Table 5.11, p. 91). We also consider that this conclusion is of general validity because we have found no published observation to support the widely held belief (*British Medical Journal* leading articles 1973, 1976; Hallett 1973; Crosby 1974) that acute infective exacerbations of chronic obstructive lung disease may cause a permanent loss either of FEV or of any other index of ventilatory capacity. In patients with severe airflow obstruction, a slight reduction of FEV is often seen when an exacerbation of infection occurs (Howard 1967), but such losses are usually only temporary (Felix-Davies and Westlake 1956).

Although Howard (1967) reported a few sudden losses of FEV in bronchitis patients attending hospital, a later repetition of his study (Howard 1974) on a similar series showed no such effects.

"Apart from the above cases, the view that clinical infections cause permanent obstructive damage appears to be based on three inadequate pieces of evidence:

1. There is a correlation between low FEV and frequent chest infections, but this correlation exists chiefly because both are associated with mucus hypersecretion (Table 6.1, p. 107).
2. Some patients give a misleading history (see, for example, Chart F.I, in the Appendixes), suggesting that their respiratory disability dates back only to an acute respiratory infection.
3. At autopsy, there is an association between obstructive lesions and inflammatory processes; however, the inflammatory processes are not necessarily related to clinical (or even to subclinical) infections, and, even if they were, association need not imply causation.

"We cannot, of course, say that no clinical infection ever causes an appreciable degree of irreversible airflow obstruction, but we can assert that this must be a rare event in adult life".

Interested readers may also wish to read a letter to the British Medical Journal in 1976[36] in which Fletcher rails against a leading article starting "with the hypothesis that mucopurulent bronchitis is a stage on the road to obstructive disease".

Johnston *et al* 1976[3] report the results of a study in Scotland in which 111 patients with CB were followed for up to 11 years. The authors note that the duration of antibiotic treatment has not significantly affected the decline of FEV_1 with advancing age.

Fletcher and Peto (1977)[37] give a brief presentation of the main results from the Fletcher study. They note that "there are two largely unrelated disease

processes, chronic airflow obstruction and the hypersecretory disorder (including infection processes)".

Monto and Ross (1978)[38] followed up a random sample of residents of Tecumseh, USA for a year, during which occurrences of acute respiratory illnesses, chronic symptoms and lung function were recorded on a regular basis, and blood samples were tested for type A and B influenza, respiratory syncytial virus and *Mycoplasma pneumoniae*. Within smoking groups infection rates were noted to be higher in those with definite than in those with suspect bronchitis, although this difference, even for the combined data, is not significant according to my calculations. An association between FEV_1 and infection rates is marginally significant (again on my calculations) but is not controlled for smoking. The authors consider that their results "suggest that acute infection may play an independent role in the pathogenesis of chronic respiratory disease".

In a study in Utah, Kanner *et al* (1979)[17] followed 84 subjects with COPD for a period of two or more years. In a multivariate analysis including age, smoking, SES, $alpha_1$-antitrypsin level and airway reactivity, the number of lower respiratory tract illnesses per year was significantly associated with the rate of loss of FEV_1 and FVC.

Peto *et al* (1983)[5] reported results from a 20-25 year mortality follow-up of 2718 British men in which lung function tests had been carried out and mucus hypersecretion and smoking habits assessed. 104 of the men died of COPD in the follow-up period. Given the initial degree of air-flow obstruction, "age-specific COPD death rates were not significantly related to initial mucus hypersecretion, supporting the concept that air-flow obstruction and mucus hypersecretion are largely independent disease processes". As for mucus hypersecretion, a history of chest illnesses was on its own strongly predictive of COPD mortality, but this relationship essentially disappeared after adjustment for initial FEV_1.

3.2 Other studies

Oswald *et al* (1953),[39] in a study in London, compared 1000 patients with CB and 300 hospital controls of similar age, sex and social status, without pulmonary disease. The CB patients had a higher mean annual number of colds (2.6 vs 1.6) and were much more likely to have colds that went down to the chest (90% vs 27%).

Rather similar results were reported by Higgins (1957)[40] in a study based on a random sample of agricultural workers in Wales. Subjects with CB reported an above average frequency of past attacks of pneumonia, CB, head colds and colds going to the chest.

Huhti (1965)[41] described a study of the prevalence of respiratory symptoms, CB and pulmonary emphysema in a Finnish rural population aged 40-64. Subjects with and without chronic nonspecific lung disease (CNSLD) were compared with healthy subjects in regard to their history of past chest illnesses. A history of pneumonia was higher in the CNSLD group, significantly for men but not women. No notable differences were seen in regard to a history of pulmonary TB or pleurisy.

In 1969, Gregg[42] carried out a study in which 213 male and 113 female patients in London were divided into 6 groups – normal subjects, symptomless smokers, mucus hypersecretors, history of chest infections but never consulted, known to have had acute bronchitis (a) not more than 2 episodes, (b) more than 2 episodes, and asthmatics. Peak expiratory flow (PEF) was measured and serum samples taken for measurement of precipitins to *H. influenzae*. "In both sexes a history of previous acute bronchitis was found to be associated with significant reduction of peak expiratory flow. In men, but not in women, serological evidence of previous infection by H. influenzae was found to correlate both with the number of episodes of acute bronchitis and also with severity of airways obstruction".

Yamaguchi *et al* (1988)[43] report the results of a cross-sectional study in Beijing of risk factors associated with CB symptoms and obstruction, involving over 3000 subjects. There was a clear positive association of past chest illness with both disease categories in a multiple regression analysis adjusting for age, sex, area, SES, smoking and parental history of respiratory disease.

Matsuse *et al* (1992)[44] carried out lung tissue resection from 20 patients with airways obstruction and 20 patients without airways obstruction, matched for age, sex and smoking habits. Polymerase chain reaction (PCR) analysis showed the EIA region of the viral genome was present in greater amounts in patients with COPD.

Von Hertzen *et al* (1996)[45] compared three groups of elderly male subjects in Finland, 36 with acute exacerbations of COPD, 54 diagnosed as having COPD (mainly mild to moderate) according to the ATS criteria, and 321 without COPD, asthma or symptoms of COPD. Compared to the controls, IgA seropositivity to *Chlamydia pneumoniae*, was much higher in the group with acute exacerbations (OR 7.37, 95% CI 2.11-25.7 after adjustment for age and smoking) but was not significantly elevated in the non-hospitalized patients (1.45, 0.74-2.86). IgG seropositivity to chlamydial infection did not vary by group. The authors noted that "the findings may indicate a chronic *C. pneumoniae* infection in these patients".

In a study in Turkey, Gencay *et al* (1998)[46] compared serological markers for *Chlamydia pneumoniae* in various groups of subjects, including 74 healthy adult females and 13 adult females with COPD. IgG positivity was found in respectively 59.4% and 100.0% of cases (calculated unadjusted $p < 0.005$).

In a case-control study in Italy, Caselli *et al* (1999)[47] compared 60 patients with CB without acute exacerbations or URT infections in the previous month and 69 subjects without a history of upper GI infection or evidence of CB, well matched for age and social class. Seropositivity for *H. pylori* was seen in

81.6% of cases and 57.9% of controls (p=0.0079), a difference confirmed by multiple regression analysis.

In cross-sectional analyses based on 3736 subjects attending for the third examination in the Copenhagen City Heart Study, Lange *et al* (2003)[48] carried out a multiple logistic regression with CB as the dependent variable. This "showed that smoking, chest infections in childhood, recent chest infections, exposure to dusts and fumes, and alcohol consumption of more than 3 drinks a day were all significant and independent predictors of chronic bronchitis". For those with 6 or more respiratory infections in the past 10 years, the OR was 6.2 (95% CI 4.1-9.2).

Ehrlich *et al* (2004)[49] carried out a cross-sectional study of predictors of chronic bronchitis based on a national household survey of South African adults. In multivariate analyses, the strongest predictor, in both men and women, was a history of tuberculosis (men OR 4.9, 95% CI 2.6-9.2; women 6.6, 3.7-11.9).

Zhao *et al* (2004)[50] carried out two studies to determine a possible association between *Chlamydiae pneumoniae* infection and COPD. One study, in Wistar rats, involved groups treated with cigarette smoking and Cpn infection, cigarette smoking only, Cpn infection only, or neither. The other study used PCR to detect Cpn DNA in lung tissue from COPD patients and controls, with Cpn IgG and IgA antibodies also measured. The authors concluded that "There were no direct relationship between COPD and Cpn infection. Infection with Cpn cannot induce COPD simply. But it can exacerbated the air obstruction of COPD on the bases of pulmonary impairment by cigarette smoking". [Based on English abstract from paper in Chinese, not translated.]

Brandén *et al* (2005)[51] studied 199 consecutive patients in a hospital in Sweden who underwent bronchoscopy due to longstanding airway symptoms and for whom spirometry and serum samples for serology were available. 30 patients had COPD without any features of asthma and 85 had chronic Cpn

infection. "A statistically significant association, remaining after correction for smoking, was observed between chronic Cpn infection and COPD, and there was a trend for decreasing lung function with increasing antibody titres. The results suggest that chronic Cpn infection may be an independent risk factor for the development of COPD".

Crothers *et al* (2006)[52] carried out analyses based on a study of 1014 HIV-positive and 713 HIV-negative male US Veterans matched for age, race and site. "After adjusting for age, race/ethnicity, pack-years of smoking, IDU [injection drug use], and alcohol abuse, HIV infection was an independent risk factor for COPD. HIV-infected subjects were approximately 50 to 60% more likely to have COPD tan HIV-negative subjects (by ICD-9 codes: odds ratio [OR], 1.47; 95% confidence interval [CI], 1.01 to 2.13; p = 0.04; by patient self-report: OR, 1.58; 95% CI, 1.14 to 2.18; p = 0.005)".

4. Summary

While it is clear from various reviews that infections are a major cause of exacerbations of existing COPD, the evidence that infections in adulthood can lead to onset of COPD is much less convincing. In determining whether such infections have a causal role, one has to be able to exclude reverse causation, with the presence of COPD rendering patients more subject to infections (and also perhaps more likely to recall past infections). It is clear from the reviews considered in section 2 that the general opinion is that though exposure to infections in adult life may lead to onset of COPD, this is certainly far from proven.

The most relevant evidence establishing causation comes from prospective studies, considered in section 3.1. Although 13 papers are referred to, it is of interest to note that the most recent was in 1983. With the exception of a single small study[17] the evidence seems consistent that infective episodes do not cause long-term loss of lung function. By far the most impressive study is that by Fletcher, Peto and colleagues, with the 1976 paper[4] an extremely good and well-presented analysis, which suggested that infections

had little or no relevance to long-term loss of lung function. The evidence also indicates that antibiotic treatment does not affect the decline of FEV_1 with advancing age.[3,32]

The data from other studies, mainly of case-control or cross-sectional design, and considered in section 3.2, are much more indicative of an association. Though many of these studies are more recent than is the case for the prospective studies, they generally do not allow one to exclude with confidence the possibility that the COPD facilitates the infection, rather than the reverse. Nevertheless it remains possible that some infections may help to cause COPD.

5. References

1. US Surgeon General. *The health consequences of smoking. Chronic obstructive lung disease. A report of the Surgeon General*. Rockville, Maryland: US Department of Health and Human Services; Public Health Service; 1984. DHHS (PHS) 84-50205. http://www.cdc.gov/tobacco/sgr/index.htm

2. Howard P. A long-term follow-up of respiratory symptoms and ventilatory function in a group of working men. *Br J Ind Med* 1970;**27**:326-33.

3. Johnston RN, McNeill RS, Smith DH, Legge JS, Fletcher F. Chronic bronchitis: measurements and observations over 10 years. *Thorax* 1976;**31**:25-9.

4. Fletcher C, Peto R, Tinker C, Speizer FE. *The natural history of chronic bronchitis and emphysema. An eight-year study of early chronic obstructive lung disease in working men in London*. New York, Toronto: Oxford University Press; 1976.

5. Peto R, Speizer FE, Cochrane AL, Moore F, Fletcher CM, Tinker CM, *et al*. The relevance in adults of air-flow obstruction, but not of mucus hypersecretion, to mortality from chronic lung disease. Results from 20 years of prospective observation. *Am Rev Respir Dis* 1983;**128**:491-500.

6. Higgins M. Risk factors associated with chronic obstructive lung disease. *Ann N Y Acad Sci* 1991;**624**:7-17.

7. Becklake MR. Occupational exposures: evidence for causal association with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1989;**140**:S85-S91.

8. Stuart-Harris CH. The role of bacterial and viral infection in chronic bronchitis. *Arch Environ Health* 1968;**16**:586-95.

9. Stuart-Harris C. Infection, the environment and chronic bronchitis. *J R Coll Physicians Lond* 1971;**5**:351-61.

10. Fletcher CM, Peto R, Speizer FS, Tinker CM. Unknown. In: Orie NGM, van der Lende R, editors. *Bronchitis III. Third International Symposium, Groningen*. Assen, Netherlands: Royal Van Gorcum, 1971;103

11. Tager I, Speizer FE. Role of infection in chronic bronchitis. *N Engl J Med* 1975;**292**:563-71.

12. Langman MJS, Cooke AR. Gastric and duodenal ulcer and their associated diseases. *Lancet* 1976;**i**:680-3.

13. Pride NB. Role of infections. *Eur J Respir Dis* 1982;**118(Suppl)**:43-50.

14. Niewoehner DE. The role of chronic bronchitis in the pathogenesis of chronic obstructive pulmonary disease. *Semin Respir Infect* 1988;**3**:14-26.

15. Murphy TF, Sethi S. Bacterial infection in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1992;**146**:1067-83.

16. Bates DV. The fate of the chronic bronchitic: a report of the ten-year follow-up in the Canadian Department of Veterans Affairs coordinated study of chronic bronchitis. The J Burns Amberson lecture of the American Thoracic Society. *Am Rev Respir Dis* 1973;**108**:1043-65.

17. Kanner RE, Renzetti ADJr, Klauber MR, Smith CB, Golden CA. Variables associated with changes in spirometry in patients with obstructive lung diseases. *Am J Med* 1979;**67**:44-50.

18. von Hertzen LC. *Chlamydia pneumoniae* and its role in chronic obstructive pulmonary disease. *Ann Med* 1998;**30**:27-37.

19. Wilson R. The role of infection in COPD. *Chest* 1998;**113**:242S-8S.

20. Wilson R. Bacterial infection and chronic obstructive pulmonary disease. *Eur Respir J* 1999;**13**:233-5.

21. Markewitz BA, Owens MW, Payne DK. The pathogenesis of chronic obstructive pulmonary disease. *Am J Med Sci* 1999;**318**:74-8.

22. Hogg JC. Childhood viral infection and the pathogenesis of asthma and chronic obstructive lung disease. *Am J Respir Crit Care Med* 1999;**160**:S26-S28.

23. Hogg JC. Chronic bronchitis: the role of viruses. *Semin Respir Infect* 2000;**15**:32-40.

24. Hogg JC. Latent adenoviral infection in the pathogenesis of emphysema: the Parker B. Francis Lectureship. *Chest* 2000;**117**:282S-5S.

25. Hogg JC. Role of latent viral infections in chronic obstructive pulmonary disease and asthma. *Am J Respir Crit Care Med* 2001;**164**:S71-S75.

26. Sethi S, Murphy TF. Bacterial infection in chronic obstructive pulmonary disease in 2000: a state-of-the-art review. *Clin Microbiol Rev* 2001;**14**:336-63.

27. Clementsen P, Permin H, Norn S. Chlamydia pneumoniae infection and its role in asthma and chronic obstructive pulmonary disease. *J Investig Allergol Clin Immunol* 2002;**12**:73-9.

28. Scannapieco FA, Bush RB, Paju S. Associations between periodontal disease and risk for nosocomial bacterial pneumonia and chronic obstructive pulmonary disease. A systematic review. *Ann Periodontol* 2003;**8**:54-69.

29. Proud D, Chow C-W. Role of viral infections in asthma and chronic obstructive pulmonary disease. *Am J Respir Cell Mol Biol* 2006;**35**:513-8.

30. Roussos A, Philippou N, Mantzaris GJ, Gourgoulianis KI. Respiratory diseases and *Helicobacter pylori* infection: is there a link? *Respiration* 2006;**73**:708-14.

31. Kanbay M, Kanbay A, Boyacioglu S. Helicobacter pylori infection as a possible risk factor for respiratory system disease: a review of the literature. *Respir Med* 2007;**101**:203-9.

32. Medical Research Council. Value of chemoprophylaxis and chemotherapy in chronic bronchitis. A report to the Medical Research Council by their Working Party on Trials of Chemotherapy in early chronic bronchitis. *Br Med J* 1966;**1**:1317-22.

33. Howard P. Evolution of the ventilatory capacity in chronic bronchitis. *Br Med J* 1967;**3**:392-5.

34. Fletcher CM, Peto R, Speizer FS, Tinker CM. A follow-up study of the natural history of obstructive bronchitis. In: Orie NGM, van der Lende R, editors. *Bronchitis III. Third International Symposium, Groningen*. Assen, Netherlands: Royal Van Gorcum, 1971;103-19.

35. May JR, Peto R, Tinker CM, Fletcher CM. A study of hemophilus influenzae precipitins in the serum of working men in relation to smoking habits, bronchial infection, and airway obstruction. *Am Rev Respir Dis* 1973;**108**:460-8.

36. Fletcher CM. Natural history of chronic bronchitis [Letter]. *Br Med J* 1976;**1**:1592-3.

37. Fletcher C, Peto R. The natural history of chronic airflow obstruction. *Br Med J* 1977;**1**:1645-8.

38. Monto AS, Ross HW. The Tecumseh study of respiratory illness. X. Relation of acute infections to smoking, lung function and chronic symptoms. *Am J Epidemiol* 1978;**107**:57-64.

39. Oswald NC, Harold JT, Martin WJ. Clinical pattern of chronic bronchitis. *Lancet* 1953;**265**:639-43.

40. Higgins ITT. Respiratory symptoms, bronchitis, and ventilatory capacity in random sample of an agricultural population. *Br Med J* 1957;**2**:1198-203.

41. Huhti E. Prevalence of respiratory symptoms, chronic bronchitis and pulmonary emphysema in a Finnish rural population. Field survey of age group 40-64 in the Harjavalta area. *Acta Tuberc Pneumonol Scand* 1965;**LXI(Suppl 61)**:1-111.

42. Gregg I. Infection and chronic bronchitis. A study carried out in general practice. *Respiration* 1969;**26(Suppl)**:16-30.

43. Yamaguchi S, Kano K, Shimojo N, Sano K, Xu XP, Watanabe H, *et al*. Risk factors in chronic obstructive pulmonary malfunction and "chronic bronchitis" symptoms in Beijing district: a joint study between Japan and China. *J Epidemiol Community Health* 1988;**43**:1-6.

44. Matsuse T, Hayashi S, Kuwano K, Keunecke H, Jefferies WA, Hogg JC. Latent adenoviral infection in the pathogenesis of chronic airways obstruction. *Am Rev Respir Dis* 1992;**146**:177-84.

45. von Hertzen L, Isoaho R, Leinonen M, Koskinen R, Laippala P, Tõyrylā M, *et al*. *Chlamydia pneumoniae* antibodies in chronic obstructive pulmonary disease. *Int J Epidemiol* 1996;**25**:658-64.

46. Gencay M, Dereli D, Ertem E, Serter D, Puolakkainen M, Saikku P, *et al*. Prevalence of *Chlamydia pneumoniae* specific antibodies in different clinical situations and healthy subjects in Izmir, Turkey. *Eur J Epidemiol* 1998;**14**:505-9.

47. Caselli M, Zaffoni E, Ruina M, Sartori S, Trevisani L, Ciaccia A, *et al*. *Helicobacter pylori* and chronic bronchitis. *Scand J Gastroenterol* 1999;**34**:828-30.

48. Lange P, Parner J, Prescott E, Vestbo J. Chronic bronchitis in an elderly population. *Age Ageing* 2003;**32**:636-42.

49. Ehrlich RI, White N, Norman R, Laubscher R, Steyn K, Lombard C, *et al*. Predictors of chronic bronchitis in South African adults. *Int J Tuberc Lung Dis* 2004;**8**:369-76.

50. Zhao Y-N, Zhao M-W, Pei F, Li X-Y, Yao W-Z. (The relationship between chronic obstructive pulmonary disease and *Chlamydiae pneumoniae* infection). *Chin J Intern Med* 2004;**43**:333-7.

51. Brandén E, Koyi H, Gnarpe J, Gnarpe H, Tornling G. Chronic *Chlamydia pneumoniae* infection is a risk factor for the development of COPD. *Respir Med* 2005;**99**:20-6.

52. Crothers K, Butt AA, Gibert CL, Rodriguez-Barradas MC, Crystal S, Justice AC. Increased COPD among HIV-positive compared to HIV-negative veterans. *Chest* 2006;**130**:1326-33.