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Smoking and Respiratory Disease

Overview

British American Tobacco believes that smoking is an important risk factor for chronic obstructive pulmonary disease (COPD), which includes chronic bronchitis and emphysema.

COPD is a complex chronic disease of the airways of the lungs, thought to develop over decades of life. Overt symptoms of the disease may not be evident until fifty or more years of age. COPD is characterised by a progressive and largely irreversible obstruction to air flow, as if the airways were partially blocked. This causes shortness of breath and can lead to disability and eventually death. Other symptoms of COPD include chronic cough, increased mucus production, frequent clearing of the throat and a limited tolerance to exercise. While lung function declines normally in the population as a whole after about twenty five years of age, this decline is accelerated in patients with COPD and as a result can become clinically limiting.

Studies performed on people over the last few decades have demonstrated that as a group, people who smoke are more likely to develop COPD than people who have never smoked [1]. Studies of this nature also report that the relative risk of developing COPD tends to decrease if people smoked fewer cigarettes or smoked for

shorter periods of time [1, 2]. Moreover, the acceleration as a result of COPD of the normal age-related decline in lung function decreases to some extent in people who quit smoking compared with people who smoke throughout their lifetime [1,3,4]. THIS STATISTIC IS EVIDENCE SUGGESTS THAT SMOKING IS A CAUSE OF COPD

In contrast to COPD, when taken as a whole, statistical studies suggest that in general, smoking is not a risk factor for an increased incidence of asthma.

Research continues to try to establish exactly how and why COPD occurs. Science has yet to clearly identify a mechanism by which tobacco smoke might cause this disease.

Despite the lack of scientific knowledge about the causal mechanisms of COPD, many public health agencies believe that smoking is a cause of this disease. ~~British American Tobacco fully accepts that smoking is an important risk factor for COPD and that it may be a cause of this disease~~. Therefore it is reasonable for public health agencies to assume that smoking contributes to an increased incidence of COPD in smokers and for such agencies to promote this proposition. Indeed, we believe that this proposition has been well publicised, and that in general the public is well aware of it.

COPD – definition

COPD has recently been defined as *"a disease state characterized by*

the presence of airflow obstruction due to chronic bronchitis or emphysema; the airflow obstruction is generally progressive, may be accompanied by airway hyperreactivity, and may be partially reversible" [5].

Although emphysema and chronic bronchitis have historically been categorised as components of COPD, experts have disagreed at times about how these two individual conditions should be defined [1, 5, 6].

For example, the term "chronic bronchitis" has had different meanings at different times and in different countries. In the United States, chronic bronchitis has usually been defined by the presence of chronic productive cough for three months in each of two successive years in a patient in whom other causes of chronic cough have been excluded [1]. In Great Britain, however, "chronic bronchitis" has been used synonymously with the term COPD.

Emphysema has been defined as a condition of the lung characterised by abnormal permanent enlargement of the airspaces distal to the terminal bronchiole, accompanied by the destruction of their walls and without obvious fibrosis [7]. These changes can be seen only at autopsy and may be evident at various sites within the lung, indeed at least four different types of emphysema are recognised [8]. Nonetheless, a broad diagnosis of emphysema is usually applied to living patients who have shortness of breath ('dyspnea') and obstructive lung function. Like "chronic bronchitis" in Britain, the term "emphysema" has been used in the United States as synonymous with COPD [6]. Some patients with COPD have features of both chronic bronchitis and emphysema, although one

condition is usually more prominent than the other.

The association between smoking and COPD

Our conclusion that smoking is a risk factor for COPD is based upon epidemiological studies. Epidemiology is a statistically-based science. Epidemiologists investigate, for example, whether the incidence of diseases such as emphysema and bronchitis differ between groups of people and, if so, whether the differences in incidence are statistically associated with differences in the lifestyles (including smoking or not smoking) or experiences of these groups of people.

The historical differences regarding the definitions and diagnosis of COPD, as well as the potential for misreporting of COPD on death certificates [9], means that in many instances it has not been possible to measure accurately either the incidence of COPD or mortality rates from COPD. This, in turn, has complicated the analyses of epidemiological studies relating to smoking and COPD. However, such studies have consistently reported that there is a significantly greater mortality from COPD in groups of smokers compared to non-smokers. The results of these studies are expressed in terms of 'relative risk ratios' or 'odds ratios', which indicate the incidence of, or mortality from, COPD in groups of smokers compared to non-smokers. Based on data from the large 'CPS II' epidemiological study in the US, Thun and co-workers calculated a relative risk for mortality from COPD of 11.7 in male current cigarette smokers [10]. However, as noted by the US Surgeon General, the size of the reported relative risk tends to vary between studies and populations,

examples being 24.7 in British physicians and 2.20 in Swedish women [1].

Of relevance to the variations in the reported relative risks of COPD in different groups of smokers, a recent review reported the failure of cigarette smoking to explain international differences in mortality from COPD in 31 different countries world-wide [11]. While the authors of this review concluded that this failure might be explained by inadequate or unreliable data, an alternative interpretation is that it may illustrate to some extent the influence of factors other than smoking to the incidence of COPD. Indeed, apart from smoking, a large number of other risk factors have been statistically associated with the disease, including air pollution, occupational exposures, socio-economic factors, childhood respiratory infections, and genetic factors [12].

For a time asthma was included under the heading of COPD in the United States. It is now generally recognised to be distinct from COPD and indeed could be regarded as more of a syndrome than a separate disease entity [13]. In most asthmatics the obstruction to airflow is intermittent and largely reversible, either spontaneously or with medicaments. There are some overlaps between the symptoms of asthma and COPD, particularly in the elderly. These can make differential diagnosis between asthma and COPD difficult.

Epidemiological studies have failed to show a consistent relationship between smoking and the incidence of asthma. Some studies report a small (relative to that for COPD) increase in risk in groups of smokers [14], others either no significant increase [15], or even a

decrease in relative risk [16].

Research to understand the link between smoking and COPD

COPD is thought to result from varying pertubations in both airway and interstitial lung tissue [12]. These pertubations include increased airway wall thickening, accumulation of mucus within the airway lumen, hypertrophy (excessive growth) of airway smooth and, in emphysema, permanent destructive enlargement of airspaces distal to the terminal bronchioles [17].

A number of hypotheses have been proposed concerning the mechanisms involved in the development of COPD. These include non-specific irritation [8], inflammation [18] and, increased oxidative stress [19]. Individuals with a congenital deficiency of the anti-protease $alpha_1$ anti-trypsin develop emphysema prematurely, especially if they smoke cigarettes [20]. This observation led to the hypothesis that certain proteins normally present in the lung are thrown out of balance with each other, leading to the destruction of lung tissue. However, despite many years of research, none of these mechanisms have been verified, nor has a role for how smoking may influence these mechanisms been clearly identified.

Animal Studies

Over the last few decades there have been many attempts to establish animal models of COPD in which to investigate the effects of tobacco

smoke. These attempts have been hindered by considerable variations in the pulmonary response of different laboratory animal species to inhalation of either tobacco smoke or some of its constituents [21]. Furthermore, in such studies it is extremely difficult, if not impossible, to reproduce all the intrinsic and extrinsic factors that may contribute (either alone or in combination) to the development of COPD in humans.

These difficulties are particularly pertinent to animal studies of emphysema. A 1989 review article stated: "It has yet to be conclusively shown that there is a laboratory animal model for emphysema produced solely as a result of exposure to cigarette smoke" [22]. The relevance and utility of recently described animal models of emphysema [23] remains to be established. Similarly, in animal models of chronic bronchitis, although prolonged cigarette smoke exposure reportedly causes an increase in the number of secretory cells and an oversecretion of mucus [24], essentially similar changes are seen following exposure to chemical irritants such as ozone and sulphur dioxide and also bacterial products [25].

The failure to dissociate any effect of tobacco smoke inhalation from a general non-specific effect of, for example, atmospheric pollutants, has broader implications in that it is difficult to explain the apparent epidemiologic link between COPD and cigarette smoke in humans in mechanistic terms.

Conclusions

British American Tobacco respects the fact that public health

authorities around the world have to base their opinion and advice on the data they have to hand, and that, despite the lack of understanding of biological mechanisms involved in COPD, most believe that smoking causes COPD and in particular emphysema and chronic bronchitis.

British American Tobacco will continue to respect the work of public health authorities to educate people about smoking and COPD.

We also continue where possible to support academic research into obtaining a better understanding of the biological basis of COPD, in pursuit of an explanation of the relationship between smoking and COPD, and in the expectation that such an explanation could lead to changes in our product.

We believe that, since smoking is an important risk factor for COPD, and may be a cause, it is appropriate that smoking should be a choice made by adult consumers in recognition of the risks associated with smoking.

On the basis of current knowledge, we do not believe that smokers in general are at an increased risk of developing asthma. However we will continue to monitor and where possible support the evolving science in this respect and, if appropriate, will modify our view accordingly.

These are the views of British American Tobacco (Holdings) Limited. References in this paper to British American Tobacco when denoting opinion refer to the company - British American Tobacco (Holdings) Limited - and

when denoting business activity refer collectively to its group of operating companies.

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