CHAPTER 12

Tobacco smoke and respiratory disease

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Although tobacco has been used in Western culture for >400 yrs, inhalative cigarette smoking is a relatively new development. It was during the 20th century that cigarette smoking became a mass phenomenon. Interestingly, the evolution of the prevalence of tobacco smoking in a given population strikingly resembles the evolution of an infective epidemic [1]. Introduced by "trend-setters" into society, the "smoking epidemic" reached its maximum in the 1950s in the male population, with considerable geographic variation in time trends since then. However, the overall prevalence of smoking is determined by such factors as sex, social status, and age [1]. Currently, the prevalence of smoking around the world is estimated to be 47% amongst males and 12% amongst females, in Europe ~35% of males and 25% of females are active smokers [2, 3]. There are cross-sectional and longitudinal studies demonstrating the deleterious effect of smoking on respiratory health [4–6], but tobacco smoke is also a risk factor for cancer of the digestive and urinary tract, coronary and vascular disease, as well as a number of nonfatal conditions. Consequently, tobacco smoking is a major cause of premature death in Europe. Moreover, throughout the European Union, 32% of deaths in males aged 35–69 yrs and 10% of deaths in females in the same age range are attributable to smoking [7]. The proportion of deaths from respiratory diseases attributable to tobacco smoking are even higher: 54% for males and 42% for females [7]. The economic impact of smoking has been consistently estimated to be approximately 200–300 per capita in the USA and Europe [8]. Furthermore, since the 1970s there is increasing evidence that not only active smoking is a risk factor for respiratory diseases, but also environmental tobacco smoke exposure in nonsmokers, especially in children [9]. Taken together, the available data clearly demonstrate that active and passive smoking place a significant burden on public health, especially with regard to respiratory diseases. Extrapolations of the present data suggest that the proportion of tobacco-associated diseases will increase in the coming decades with chronic obstructive pulmonary disease (COPD) and lung cancer becoming the most prevalent causes of death in the year 2020 [10].

Trends in smoking prevalence

Time trends in cigarette consumption vary considerably between regions. During the last 30 yrs, cigarette consumption per adult was rather stable in Europe, decreased in America and increased in all other regions, particularly in the Western Pacific region. The apparent stability of global per capita cigarette consumption, thus, results from a decreasing consumption in developed countries counterbalanced by increasing consumption in developing countries. The analysis of temporal trends in 111 countries

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Table 1. – Number of countries and consumption of cigarettes per adult aged ≥15 yrs

WHO regions and countries	1970–1972 to 1990–1992		
	Increased	Decreased	Unchanged
WHO regions			
African region	15	6	5
Region of the Americas	9	17	0
Eastern Mediterranean region	9	0	3
European region	11	14	1
South-East Asia region	6	2	0
Western Pacific region	8	5	0
More developed countries	12	18	1
Less developed countries	46	26	8
World	58	44	9

Number of countries where consumption of cigarettes per adult aged ≥15 yrs increased, decreased, or remained unchanged in the period from 1970 – 1972 to 1990 – 1992 (according to the World Health Organisation (WHO) [11]).

[11] reveals that compared with the 1970s, cigarette consumption per adult increased in 58 countries and was stable or declining in the other 53 (table 1). The rise in cigarette consumption, however, includes the world's most populous countries, such as China.

Reasons for smoking

Smoking status is believed to be largely a function of genetic and sociodemographic factors, environmental determinants, behavioural factors and specific dimensions of personality [12, 13].

Genetic factors

Twin studies show a substantial genetic determination of smoking [14]. This is not surprising since genetic factors substantially contribute to major personality characteristics as well as to psychiatric dimensions.

Sociodemographic factors

Age is an important determinant for smoking status, since the earlier in life smoking is started the higher the likelihood of becoming a regular smoker. Moreover, the likelihood of stopping smoking decreases the earlier the habit is taken up [15, 16]. Gender differences show geographically and culturally different patterns. Higher smoking rates in females are frequently found in countries with a "Western lifestyle". Ethnic background is a major determinant of smoking status, with lower prevalences in Blacks than in Hispanics [17] and lower relative frequencies of smoking in Northern than in Southern Europe [11]. Across countries and rather consistently over time, growing up in intact, two parent families has been demonstrated to be associated with a decreased prevalence of smoking among children [18]. Parental socioeconomic status is generally considered to be inversely related to smoking in adolescents [19].

Environmental factors

Children of parents who smoke generally have a higher risk of taking up the habit themselves as compared to children of nonsmoker parents [20]. Likewise, an influence of

sibling smoking on adolescent smoking behaviour has been reported, and the influence of smoking by siblings may even be stronger than that of smoking by parents [21]. An authoritative, positive parenting style, positively associated with child competencies was inversely related to rates of smoking intention, initiation and experimentation in adolescents [22]. In addition to smoking behaviour in the family, peer smoking is sometimes even more of a consistent predictor of smoking [23]. Recently, SARGENT *et al.* [24] demonstrated a dose/response relationship between the number of cigarette promotional items owned by an adolescent and the likelihood of smoking. The authors interpreted their findings as support of a causal relationship between tobacco promotional campaigns and smoking behaviour among adolescents, but they did not adequately exclude the possibility that the tendency to start smoking may itself enhance the chance of collecting promotional items.

Behavioural factors

Good academic performance in school is a major predictor for nonsmoking among teenagers [25]. Risky behaviours such as carrying a weapon [26] and having a high number of sexual partners [27] are positively associated with smoking statistically, suggesting that smokers are generally more prone to potentially dangerous habits.

Personal factors

Perceived stress is associated with initiation and maintenance of smoking [28], and nonsmokers may have healthier coping strategies. Markers of high self-esteem are generally associated with lower smoking prevalence.

Of course, there are inconsistencies between some of the studies, and many markers used in these studies may only be proxies for underlying mechanisms, however, the majority of these findings can be translated into intervention programmes.

Composition of tobacco smoke

Cigarette smoke is a heterogenous aerosol produced by incomplete combustion of the tobacco leaf. More than 4,000 substances have been identified in cigarette smoke, including some that are pharmacologically active, antigenic, cytotoxic, mutagenic, and carcinogenic (table 2).

In cigarette smoke particulate matter is dispersed in the gas phase. During puffing, mainstream smoke emerges from the mouthpiece, whereas sidestream smoke is emitted between the puffs at the burning cone and from the mouthpiece. Of the mainstream smoke, 92–95% is in the gas phase and contains 0.3–3.3 billion particles·mL^{-1}. The mean particle size is 0.2–0.5 μm and therefore within the respirable range. Of special interest is the fact that cigarette smoke contains a high concentration of reactive organic radicals (RORs) and substances capable of producing RORs. Free radicals are formed in high amounts at the tip of the cigarette due to the high temperatures of up to 900°C. However, the lifetimes of these radicals are too short to allow inhalation by the smoker. Consequently, fresh mainstream smoke contains only low concentrations of radicals, whereas the concentration of RORs increases in the gas phase of cigarette smoke as it ages, with maximal concentrations reached after 1–2 min [29]. This implies that highly reactive free radicals are formed continuously within the smoke by chemical processes during inhalation [30]. An important source for radical production is the relatively stable nitric oxide (NO) radical that is found in cigarette smoke in high concentrations of

Table 2. – Selected constituents of cigarette smoke

Particulate phase	Main effects	Gas phase	Main effects
Tar	Mutagenic/carcinogenic	Carbon monoxide	Impairment of oxygen binding to haemoglobin
Nicotine	Dose-dependent stimulator or depressor of parasympathetic N-cholinergic receptors	Oxides of nitrogen	Irritant, pro-inflammatory, ciliotoxic
Aromatic hydrocarbons	Mutagenic/carcinogenic	Aldehydes	Irritant, pro-inflammatory, ciliotoxic
Phenol	Irritant, mutagenic/carcinogenic	Hydrocyanic acid	Irritant, pro-inflammatory, ciliotoxic
Cresol	Irritant, mutagenic/carcinogenic	Acrolein	Irritant, pro-inflammatory, ciliotoxic
β-Naphthylamine	Mutagenic/carcinogenic	Ammonia	Irritant, pro-inflammatory, ciliotoxic
Benzo(a)pyrene	Mutagenic/carcinogenic	Nitrosamines	Mutagenic/carcinogenic
Catechol	Mutagenic/carcinogenic	Hydrazine	Mutagenic/carcinogenic
Indole	Tumour acceleration	Vinyl chloride	Mutagenic/carcinogenic
Carbazole	Tumour acceleration		

up to 400 parts per million. NO is oxidised to the more reactive nitrogen dioxide radical by dioxygen. This radical reacts with isoprene that has been demonstrated in high concentrations in cigarette smoke to form various biologically active RORs [29]. Moreover, aqueous extracts of tar catalyse the formation of superoxide ($O_2\cdot^-$), hydrogen peroxide (H_2O_2), and the highly toxic hydroxyl radical ($\cdot OH$) in the presence of oxygen. These reactions are probably due to the presence of redox-cycling systems within cigarette tar [29, 31]. Today, many of the adverse effects of cigarette smoke on respiratory health are thought to be directly or indirectly associated with the high amount (1×10^{14}–10^{16}) of highly reactive free radicals inhaled by the smoker with each puff.

Mechanisms of tobacco smoke-induced lung disease

Among the effects that tobacco smoke exerts on the respiratory tract, two main mechanisms can be differentiated: 1) induction of inflammation; and 2) mutagenic/carcinogenic effects. The inflammatory reactions are composed of a variety of different effects that include ciliotoxicity, increased mucous secretion, and accumulation of activated inflammatory cells in the respiratory tract. Some of the constituents of tobacco smoke are irritants, others exert toxic effects on the airway epithelium by virtue of their chemical structure, *e.g.* acids, ammonia, aldehydes and, therefore, may cause cell damage or death as well as local inflammation. Moreover, the normal clearance function of the epithelium is impaired by ciliotoxic effects of these substances (table 2). Together with goblet cell hyperplasia and increased mucous production, reduced clearance induces mucous retention in the airways, a relevant predisposition for bacterial colonisation and infection, ultimately causing inflammatory exacerbations. In addition to these unspecific irritative and/or toxic effects caused by tobacco smoke constituents due to their physicochemical properties, another more specific lesion is linked to the inhalation of RORs. These RORs are either present in tobacco smoke or produced by tobacco smoke constituents within the lungs after solution of tar constituents in the epithelial lining fluid (ELF). Furthermore, oxidants in cigarette smoke have been shown to induce sequestration of neutrophils and monocytes in the lungs that also penetrate the endothelium and can be found in increased numbers in the bronchoalveolar lavage (BAL) fluid [32]. These cells, predominantly neutrophilic granulocytes, are able to produce large amounts of $O_2\cdot^-$ anions by the membrane bound reduced nicotinamide-adenine dinucleotide phosphate-oxidase. $O_2\cdot^-$ anions are transformed into more

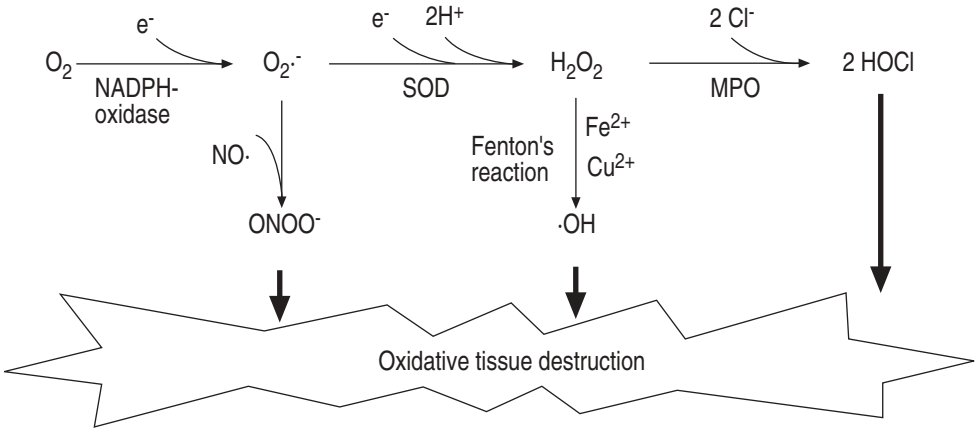

Fig. 1. – Overview of the metabolism of reactive organic radicals (ROR). NADPH: reduced nicotinamide-adenine dinucleotide phosphate; $O_2\cdot^-$: superoxide; SOD: superoxide dismutase; H_2O_2: hydrogen peroxide; MPO: myeloperoxidase; NO·: nitrosyl; ·OH: hydroxyl radical; $ONOO^-$: peroxynitrite.

aggressive oxidants like H_2O_2, ·OH and, in the presence of myeloperoxidase, hypohalides are formed (fig. 1). These oxidants may cause oxidative damage to a variety of different substrates (fig. 2) and will ultimately result in alterations or destruction of cells and constituents of the extracellular matrix of the lungs.

A special relationship exists between oxidants and the protease/antiprotease balance

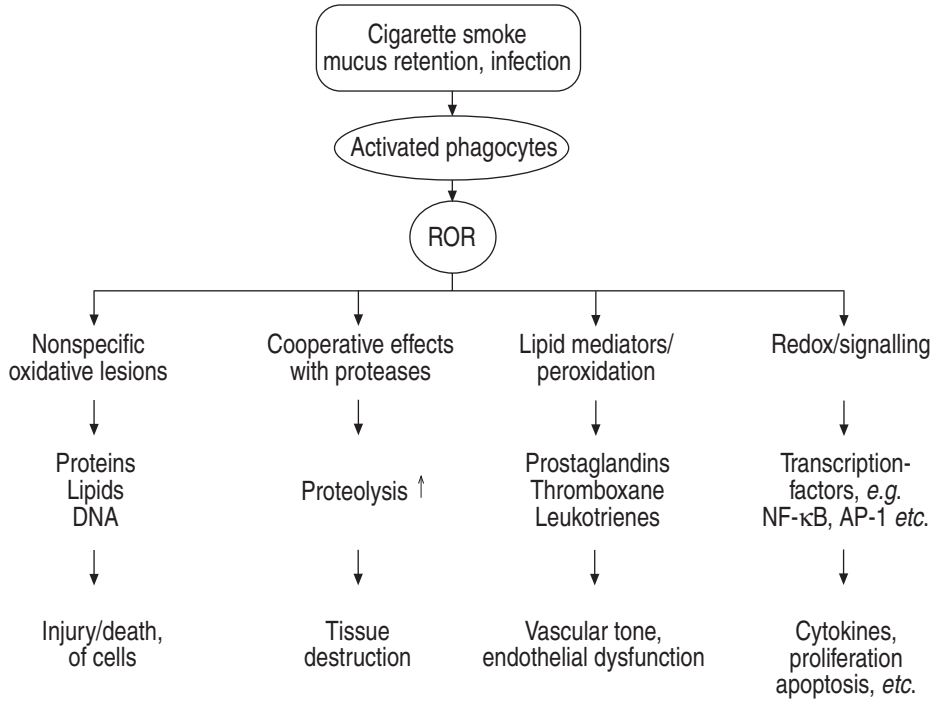

Fig. 2. – Mechanisms of cell injury and tissue destruction by reactive organic radicals (RORs). DNA: deoxyribonucleic acid; NF: nuclear factor; AP: activator protein.

Table 3. – Antioxidants of the lung

Scavengers	Enzymes	Enzyme systems
Serum proteins, albumin, transferrin, coeruloplasmin, *etc.*	Superoxide dismutase	γ-Glutamyl cycle
Lactoferrin, taurin	Catalase	Glutathione redox cycle
Vitamin C and E		
Glutathione		

within the lungs: oxidants may inactivate important antiproteases, such as α_1-proteinase inhibitor, and secretory leukoprotease inhibitor [33, 34]. Other proteases are activated by oxidation. Taken together, these effects of oxidants result in a protease/antiprotease imbalance in favour of proteolytic activity likewise inducing tissue damage and inflammation. This interaction between oxidants and the protease/antiprotease system is referred to as the "cooperative effect".

Another important aspect of oxidant injury induced by cigarette smoke is the damage of the antioxidant screen of the lung. Physiologically, oxidants are completely counterbalanced by antioxidants within the lungs. The highly active antioxidants in the lungs include scavengers, enzymes, and enzyme systems (table 3), which prevent oxidative damage.

Glutathione (GSH) is quantitatively the most important antioxidant of the lung in the extracellular and intracellular compartment [35]. Moreover, GSH is a scavenger for most biologically relevant oxidants and can be recycled intracellularly by the GSH redox cycle or the γ-glutamyl cycle, which allows for *de novo* biosynthesis of GSH using degraded extracellular GSH or glutathione disulphide as a substrate [35, 36]. It has been demonstrated that cigarette smoke leads to an acute intracellular drop of GSH but after several hours GSH production is increased and elevated levels of GSH have been measured in the ELF from smokers [37]. This may represent an effort of the lung to counterbalance the increased oxidant burden from smoking. Moreover, antioxidant enzymes such as catalase and $O_2\cdot^-$ dismutase, as well as the antioxidant vitamin C, have been reported to be elevated in the lungs of smokers. However, due to the increased amount of oxidation products and decreased plasma antioxidant capacity, a shift of the oxidant/antioxidant balance towards a more oxidated milieu has been indicated in smokers [38]. The causes and mechanisms of oxidant lung injury induced by tobacco smoke are summarised in figure 3. Taken together, smoking poses an increased oxidative burden on the lungs which is overall not adequately counterbalanced despite an elevated antioxidant screen.

Chronic obstructive pulmonary disease

In this context, the term COPD is confined to those obstructive respiratory conditions most closely associated with cigarette consumption, namely, chronic bronchitis and emphysema. MURRAY and LOPEZ [10] predicted that COPD, being the sixth most common cause of death in 1990, will advance to worldwide third place in 2020. The population attributable fraction of smoking for the development of COPD has been estimated to be 0.7–0.8 in males and 0.7 in females [39]. Despite a considerable healthy smoker effect which tends to mask effects of smoking on spirometric indices [40, 41], airflow obstruction is more common among smokers than nonsmokers. The increased longitudinal decline in forced expiratory volume in one second in smokers might be considerably lowered by smoking cessation even when mild-to-moderate COPD is already present [42]. Beside cigarette smoking, other less important risk factors for the development of COPD include those seen in table 4 [43].

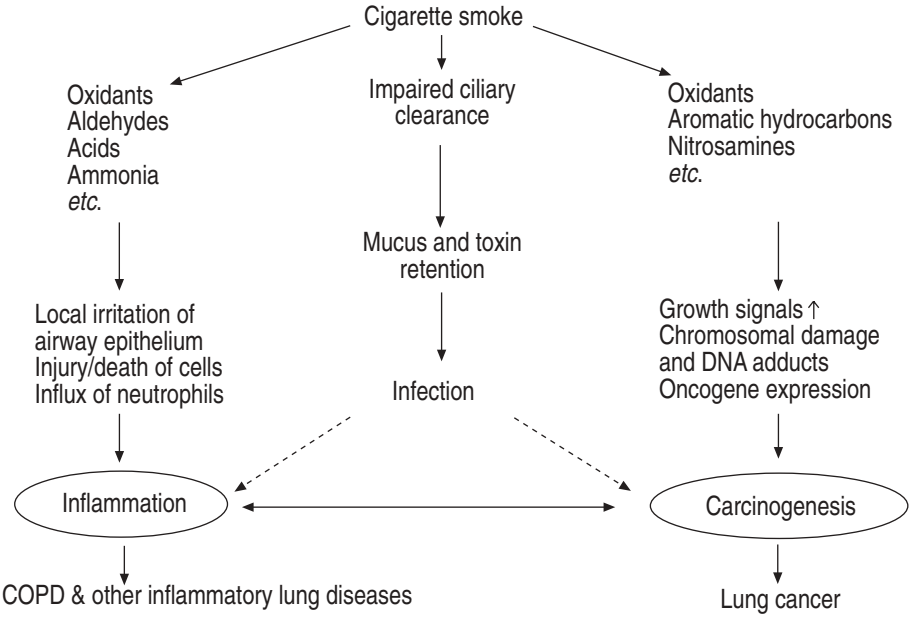

Fig. 3. – Mechanisms of cigarette smoke induced lung disease. DNA: deoxyribonucleic acid; COPD: chronic obstructive pulmonary disease.

The pathogenesis of smoking-related COPD includes the protease/antiprotease and oxidant/antioxidant hypotheses and abnormal repair processes. In short, proteolytic products from inflammatory cells, if not adequately counterbalanced by protective antiprotease systems, lead to bronchial injury and destruction of alveolar architecture. The protease/antiprotease hypothesis is based on the observation of premature emphysema in patients with severe α_1-proteinase inhibitor deficiency. Additionally, the pathogenetic role of neutrophil elastase is compatible with the involvement of neutrophils in the pathogenesis of COPD. Neutrophil elastase can damage the respiratory epithelium and enhances mucous production by goblet cells [44]. It increases interleukin-8 [45], which, in itself, is a potent chemoattractant for neutrophils. In addition to neutrophils, alveolar macrophages and enzyme macrophage elastase, a matrix metalloproteinase, play a role in the pathophysiology of emphysema [46]. However, the relative contribution of neutrophils and macrophages and their elastolytic products for the development of COPD is not fully understood. The oxidant/antioxidant hypothesis of COPD which has already been introduced in this article is based on a huge amount of data indicating that oxidative stress contributes to COPD [47, 48]. In smokers

Table 4. – Risk factors (other than smoking) for the devlopment of chronic obstructive pulmonary disease

Genetic predisposition	Host factors	Environmental factors
α_1-Proteinase inhibitor deficiency	Female sex	Childhood respiratory infections
Other familial predispositions	Atopy and BHR	Low socioeconomic status
	Eosinophilia	Alcohol consumption
		Industrial exposures
		Exposure to ETS
		Air pollution

BHR: bronchial hyperresponsiveness; ETS: environmental tobacco smoke.

and subjects with COPD, systemic increases in oxidants [49] and decreases in antioxidants [38] have been demonstrated. Incomplete repair processes may cause alterations in subepithelial structures leading to fibrosis of periobronchial tissue as well as to inhibition of extracellular matrix remodelling [50–52].

Despite cigarette smoking being the most important risk factor for the development of COPD, only a minority of smokers develop the disease. Therefore, research is increasingly focusing on the question of which endogenous factors predispose smokers to COPD [53–55].

Lung cancer

Since the beginning of the 20th century, from being a rare disease, lung cancer has become the most common type of lethal cancer throughout the world [7]. In a recent paper, MURRAY and LOPEZ [10] estimated lung cancer to be the 10th most common cause of death today, accounting for ~1 million deaths around the world annually. They also predicted that by the year 2020 lung cancer will advance to the fourth most common death cause in developed countries and to the fifth most common death cause worldwide [10].

The causal relationship between lung cancer and cigarette smoking was first reported in well conducted case-control studies in 1950 [56–59] and later confirmed in large population-based, prospective, cohort studies [60, 61]. For most developed countries it is currently estimated that 90% of lung cancer cases in males and 80% in females are attributable to smoking. The critical risk factors are the early start of smoking during teenage years and early adulthood, duration of smoking, number of cigarettes smoked daily, and inhalation practices [62–64]. Amongst the established occupational respiratory carcinogens, a multiplicative relationship with smoking has been shown for asbestos [65], radon [66], nickel [67], as well as silica [68], and an overadditive but not multiplicative relationship was demonstrated for arsenic [69].

As already stated, from a pathogenetic point of view, it is well established that cigarette smoke contains a mixture of highly toxic compounds like irritants, mutagenic and carcinogenic substances, including RORs that are fully capable of inducing alterations of cell proliferation, chromosomal damage, deoxyribonucleic acid (DNA)-adduct formation, and activation of oncogenes. Recently, DENISSENKO *et al.* [70] reported selective benzo(a)pyrene diol-epoxide adduct formation along exons of p53 in bronchial epithelial cells, thus, providing a direct mechanistic link between tobacco smoke and lung cancer. Therefore, toxin-induced injury or death of cells creates an environment of constant generation of inflammatory and growth signals, including oxidants that finally results in hyperplasia, metaplasia, mutagenic and carcinogenic transformation of resident cells of the respiratory tract. Despite increased epidemiological and pathophysiological knowledge about the links between smoking and lung cancer, it has to be kept in mind that <20% of smokers develop lung cancer during their lifetime suggesting that host-related factors are involved. Moreover, epidemiological studies revealed correlations between familial risk of lung cancer and lung function level of relatives suggestive of the existence of genetic susceptibility for the deleterious effects of cigarette smoke both as a carcinogen and as a substance inducing airway obstruction [71, 72]. Genetic influence may be mediated by various mechanisms like differences in carcinogen metabolism [73–75], mucociliary clearance [76], efficiency of DNA repair [77], and regulation of oncogene expression. A number of candidate genes for cancer suceptibility have already been identified [78]. The new tools of molecular biology like microarray chip systems may provide new insights into the genetic background of carcinogenesis in the near

Table 5. – Association between interstitial lung diseases (ILD) and cigarette smoking

ILD positively associated with smoking	ILD negatively associated with smoking
Usual interstitial pneumonia/idiopathic pulmonary fibrosis	Exogenous allergic alveolitis (hypersensitivity pneumonitis)
Desquamative interstitial pneumonia	Sarcoidosis
Respiratory bronchiolitis-associated ILD	
Connective tissue disease-associated ILD	
Pulmonary Langerhans' cell histiocytosis	

future. A better knowledge of individuals at risk might increase the efficacy of intervention programmes due to the possibility of focusing on better defined high-risk groups.

Interstitial lung diseases

Interstitial lung diseases (ILDs) represent a heterogenous group of lung disorders, generally characterised by dyspnoea, dry cough, diffuse interstitial infiltrates, restrictive lung function pattern, and impaired gas exchange. The most common forms of ILDs include sarcoidosis, idiopathic pulmonary fibrosis (IPF), pneumoconiosis, and those ILDs associated with connective tissue diseases. It has recently been suggested that a number of ILDs are positively linked to tobacco smoking whereas other forms are clearly inversely related to cigarette smoking (table 5).

Idiopathic pulmonary fibrosis/usual interstitial pneumonia

Reclassification of the interstitial pneumonias by KATZENSTEIN and MYERS [79] has defined usual interstitial pneumonia (UIP) as a clinical and pathological entity, and it is solely this entity which should be referred to as IPF. The prevalence of IPF/UIP ranges from 3–29 cases per 100,000 population, with this wide range being due to differences in definition, study design, and populations [80]. Most importantly for the patient, IPF/UIP has to be clearly differentiated from other interstitial pneumonias like respiratory bronchiolitis-associated (RB)-ILD or desquamative interstitial pneumonia (DIP) because of its significantly worse median survival time of ~3 yrs. The majority of cases are sporadic with only a few familial forms; there is a slight male preponderance (1–2:1; male:female), and most patients are >50 yrs of age [80–82]. The prevalence of current or former smoking varied widely from 41–83% in series of IPF/UIP [83] and was associated with an increased risk for developing the disease [84–86]. The role of smoking in the pathogenesis of IPF/UIP is not well understood and there is no evidence that smoking *per se* causes IPF/UIP. However, based on the pathogenetic mechanisms of tobacco smoke already outlined, the underlying inflammatory process in IPF/UIP might be enhanced by cigarette smoke.

Desquamative interstitial pneumonia

DIP is another form of the idiopathic interstitial pneumonias that is morphologically characterised by a uniform picture showing accumulation of pigmented macrophages within the alveolar spaces [79]. The clinical features of DIP are quite different from those of IPF/UIP; an average age of ~40 yrs, ~90% current or previous smokers, and ground-glass appearance of lung tissue in high-resolution computed tomography (CT) are characteristic [87, 88]. In contrast to IPF/UIP, most patients with DIP stabilise or

improve with corticosteroid therapy and complete remission is possible [89]. Overall, the long-term prognosis of the disease is somewhat better (average survival is 12 yrs). The role of smoking in the pathogenesis and for the treatment of DIP is unknown, although smoking cessation is clearly advocated.

Respiratory bronchiolitis-associated interstitial lung disease

RBILD was first described as an incidental autopsy finding in young male smokers [90]. Whereas respiratory bronchiolitis without accompanying ILD is a common finding in smokers, usually without any significant clinical implications, some smokers or exsmokers develop this symptomatic ILD [83, 90, 91]. Similarly to DIP, RBILD is characterised by intra-alveolar accumulation of pigmented macrophages. In contrast to DIP, these changes are less diffuse and clearly centred on respiratory bronchioles and peribronchiolar alveoli, sparing peripheral airspaces. There are only mild interstitial inflammatory changes in peribronchiolar parenchyma and frank fibrosis is absent. Clinical presentation is dominated by cough and exertional dyspnoea, there may be inspiratory cackles and occasionally clubbing is observed. Lung function tests reveal a mixed restrictive and obstructive impairment of mild-to-moderate degree. On chest radiographs reticular or reticulonodular changes are frequent, but normal chest radiographs have been reported in approximately one-third of affected patients [91]. On high-resolution CT areas of ground-glass attenuation are the most common finding whereas subpleural reticulations and honeycombing, typical findings in UIP, are distinctly absent. Overall prognosis is good, especially with smoking cessation. In some cases, corticosteroids have been employed with beneficial results. With respect to the similarities between DIP and RBILD regarding epidemiology, positive association with smoking and clinical as well as histopathological presentation, it has been suggested to use the term "smoking-related ILD" for both disorders.

Pulmonary Langerhans' cell histiocytosis

Pulmonary Langerhans' cell histiocytosis (PLCH; also known as histiocytosis X) is classified as a dendritic cell-related (Langerhans' cell) disease of variable, nonmalignant biological behaviour with a wide range of severity from spontaneous remission to lethality [92]. Rarely, PLCH is observed in the context of a multifocal Langerhans' cell histiocytosis affecting multiple organs; most of these diseases occur in children and are not related to smoking. By contrast, PLCH of the adult patient is observed almost exclusively in smokers (>90%) and smoking has been demonstrated to be a strong risk factor for PLCH in a case-control study [93]. Although the pathogenetic role of smoking has not yet been elucidated, an increase of Langerhans' cells on the surface of bronchial epithelium from smokers has been observed [94]. The peribronchial distribution of the lesions and the fact that Langerhans' cells are potent antigen-presenting cells suggest an inhaled antigen within cigarette smoke as the cause of PLCH.

Miscellaneous interstitial lung disease

Epidemiological associations between cigarette smoking and ILDs have been reported for some disorders with potential pulmonary manifestations. For rheumatoid arthritis (RA), most [95–100], but not all [101, 102], studies have reported a positive relationship between cigarette smoking and pulmonary function or radiological abnormalities.

Interestingly, in a study of 150 twin pairs discordant for RA, cigarette smoking was a risk factor for RA itself [103].

Antiglomerular basement membrane antibodies may cause nephritis and/or pulmonary haemorrhage by binding to glomerular and alveolar basement membranes. The term "Goodpasture's syndrome" refers to the subset of patients with both nephritis and pulmonary haemorrhage. Pulmonary haemorrhage, as observed in 60–80% of antibasal membrane antibody-associated disease, has been consistently found to be linked to cigarette smoking [104, 105]. However, in none of the reported diseases has the pathophysiological role of cigarette smoking within the disease process been clarified beyond the level of speculation.

Diseases with decreased incidence or severity in smokers

Hypersensitivity pneumonitis

Hypersensitivity pneumonitis (HP), or extrinsic allergic alveolitis, is a chronic inflammatory lung disease caused by inhalation of organic dust including antigens typically derived from animal proteins or microbes. Formation of precipitating antibodies against these antigens is characteristic for patients with HP. Consequently, a type-III immune response has been implicated in the pathogenesis of the disease but endotoxin may also be involved [106]. A number of studies report a decreased prevalence of precipitating antibodies among smokers within antigen-exposed populations [107–110]. Moreover, smokers are clearly underrepresented among patients with manifest HP [111–113]. In a prospective study by Arima *et al.* [114], HP was observed in 65.9% of the nonsmokers and in only 27.3% of the smokers. Based on these findings, several hypotheses have been proposed to explain the protective effect of smoking on the development of HP. Most of them focus on immunomodulatory effects of smoking, *e.g.* suppression of antibody production, reduction of T-helper cells in BAL, and impairment of macrophage function [115–117]. More recently, it has been reported that down-regulation of pulmonary GSH levels may be associated with disease manifestation in farmers [118]. Although the reason for these differences has not yet been elucidated, the observations are suggestive to assume that genetic predisposition may play a role in disease manifestation.

Sarcoidosis

Sarcoidosis is a systemic granulomatous disease of unknown cause with ~90% pulmonary involvement. It is generally believed that sarcoidosis might be an immunological disorder. Initiated by a putative inhaled antigen that leads to T-cell activation, sarcoidosis is characterised by a lymphocytic alveolitis with increased T-helper/T-suppressor cell ratio and by formation of noncaseating granulomas. As in hypersensitivity pneumonitis, smokers are underrepresented in patients with sarcoidosis suggesting that cigarette smoke provides some kind of protection against this disease [93, 119–121]. Although distinct differences in BAL differential cell counts and T-cell subsets have been observed between nonsmokers and smokers affected by sarcoidosis, there is no conclusive pathogenetic concept to explain the reduced incidence of sarcoidosis in smokers [121]. Smoking-induced alterations of antigen presentation, macrophage function, and lymphocyte proliferation may be involved.

Table 6. – A 5-day plan to quit smoking

The first step to quitting smoking is to decide to quit. Next, make an appointment with your healthcare provider, or contact a smoking cessation clinic to discuss your options for treatment. Set a quit date.
Quit day minus 5: List all of your reasons for quitting and tell your friends and family about your plan. Stop buying cartons of cigarettes.
Quit day minus 4: Pay attention to when and why you smoke. Think of new ways to relax or things to hold in your hand instead of a cigarette. Think of habits or routines you may want to change. Make a list to use when you quit.
Quit day minus 3: Make a list of the things you could do with the extra money you will save by not buying cigarettes. Think of who to reach out to when you need help, like a smoking support group.
Quit day minus 2: Buy the over-the-counter nicotine patch or nicotine gum, or get a prescription for the nicotine inhaler, nasal spray, or the nonnicotine pill, bupropion SR. Clean your clothes to get rid of the smell of cigarette smoke.
Quit day minus 1: Think of a reward you will get yourself after you quit. Make an appointment with your dentist to have your teeth cleaned. At the end of the day, throw away all cigarettes and matches. Put away lighters and ashtrays.
Quit day: Keep very busy. Change your routine when possible, and do things out of the ordinary that don't r emind you of smoking. Remind family, friends, and coworkers that this is your quit day, and ask them to help and support you. Avoid alcohol. Buy yourself a treat, or do something to celebrate.
Quit day plus 1: Congratulate yourself. When cravings hit, do something else that isn't connected with smoking, like taking a walk, drinking a glass of water, or taking some deep breaths. Call your support network. Find things to snack on, like carrots, sugarless gum, or air-popped popcorn.

Adapted from the Surgeon General [126].

Smoking cessation

There is scientific consensus that cigarette smoking is an addiction to the drug nicotine. As with any drug addiction, social, economic, personal and political influences play an important part in determining patterns of smoking prevalence and cessation [122]. Seventy per cent of smokers report that they would like to quit [123]. However, in a USA survey of exsmokers, respondents acknowledged little assistance in giving up smoking [124]. Therefore, within the last 10 yrs, particularly in the USA, tremendous public efforts have been undertaken to promote and spread plans for smoking cessation [125, 126] (table 6).

Given that the progression of COPD can be slowed down by smoking cessation [42] and that people who stop smoking even well into middle age avoid most of their subsequent risk for lung cancer [127], smoking cessation should be a crucial issue in

Table 7. – Some of the smoking cessation methods available

Massmedia and community programmes
Self-help
Educational (books and other material, *e.g.* from the Internet)
Brief clinical interventions (physician advice and counselling)
Clinics and groups
Voluntary agencies
Commercial programmes
Pharmacotherapy
Nicotine replacement
Chewing gum
Transdermal systems
Nasal spray
Inhaler
Bupropion
Behavioural
Hypnosis?
Acupuncture?

Modified from RENNARD and DAUGTON [128].

evidence-based health promotion driven by pulmonologists. Available methods are listed in table 7.

The "baseline rate" of successful quitting on a particular attempt ranges between 0.5–3.0% [128]. Brief clinical interventions can be provided by any clinician and reveal an increase in the odds of quitting (odds ratio (OR), 1.7; 95% confidence interval: 1.5–2.0), equal to an absolute difference in the cessation rate of ~2.5% [129]. Pharmacotherapeutic first-line drugs are nicotine (gum, inhaler, nasal spray, patch) and sustained-release bupropion hydrochloride [130]. A meta-analysis of 53 randomised controlled trials of nicotine replacement therapy in individuals motivated to quit smoking showed ORs for gum of 1.6, for transdermal patch of 2.1, for nasal spray of 2.9, and for inhaled nicotine of 3.1. These ORs were nonsignificantly higher in subjects with higher levels of nicotine dependence but were largely independent of the intensity of additional support provided or the setting in which nicotine replacement therapy was offered [131]. In a recent, randomised controlled study comparing the efficacy of sustained-release bupropion, a nicotine patch, or both for smoking cessation, the authors reported 12-month point (cumulative) prevalence abstinence rates of 15.6% (5.6%) in the placebo group compared with 16.4% (9.8%) in the nicotine patch group, 30.3 (18.4%) in the bupropion group, and 35.5 (22.5%) in the group given nicotine patches and bupropion [132]. Thus, although smoking cessation is obviously the best strategy for eliminating the health risks associated with smoking, the outlined strategies are effective only in a minority of patients. Since smoke-free environments, advertising bans and price increases have been demonstrated to be effective measures in many countries, primary prevention and cessation strategies should be combined on a large-scale sociomedico-political scale in order achieve better health.

Summary

During the 20th century, cigarette smoking has become a mass phenomenon. Within the last 30 yrs, cigarette consumption per adult has remained stable in Europe, decreased in America and increased in all other regions, particularly in the Western-Pacific region. Smoking status is believed to be largely a function of genetic and sociodemographic factors, environmental determinants, behavioural factors and specific dimensions of personality.

Cigarette smoke is a heterogenous aerosol produced by incomplete combustion of the tobacco leaf. More than 4,000 substances have been identified in cigarette smoke, including some that are pharmacologically active, antigenic, cytotoxic, mutagenic, and carcinogenic. Out of the different effects that tobacco smoke exerts on the respiratory tract, this chapter focused on two main mechanisms: firstly, induction of inflammation; and secondly, mutagenic/carcinogenic effects.

The most relevant tobacco-associated diseases of the respiratory system are chronic obstructive pulmonary disease (COPD) and lung cancer. COPD, being the sixth most common cause of death in 1990, will advance to third place worldwide in 2020. The pathogenesis of smoking-related COPD includes the protease-antiprotease and oxidant-antioxidant hypotheses and abnormal repair processes. Lung cancer has become the most common type of lethal cancer throughout the world. By 2020, it will advance to the fourth most common cause of death in developed countries and to the fifth most common worldwide. Additionally, it has recently been suggested that a number of interstitial lung diseases are positively associated with tobacco smoking (*i.e.* usual interstitial pneumonia, desquamative interstitial pneumonia, respiratory

bronchiolitis-associated interstitial lung disease, connective tissue disease-associated interstitial lung disease, and pulmonary Langerhans' cell histiocytosis).
There is scientific consensus that cigarette smoking is an addiction to the drug nicotine, with 70% of smokers reporting that they would like to quit. Thus, smoking prevention and smoking cessation should be crucial issues in evidence-based health promotion driven by pulmonologists. Brief clinical interventions can be provided by any clinician and reveal an increase in the odds of quitting, and the efficacy of pharmacotherapeutic intervention with nicotine and bupropion have been consistently demonstrated. Furthermore, smoke-free environments, advertising bans and price increases are effective measures in many countries.

Keywords: Chronic obstructive pulmonary disease, interstitial lung disease, lung cancer, oxidants, smoking cessation, tobacco smoke.

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