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Early Detection and Localization of Lung Tumors in High Risk Groups

Edited by P R Band

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With 79 Figures and 66 Tables

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Pierre R. Band, M.D.

Institut du Cancer de Montréal
Centre Hospitalier Notre-Dame
1560 Est, Sherbrooke
Montréal, H2L 4M1, Canada

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Preface and Acknowledgements

Lung tumors are the leading cause of death from cancer in men, and projections indicate that within this decade the same will hold true in women. Sputum cytology provides a means to diagnose centrally located preneoplastic lung lesions and in situ carcinoma. With fluorescence bronchoscopy the possibility of localizing in situ tumors is becoming an increasing reality, whereas the chemopreventive potential of retinoids raises the hope of reversing premalignant changes.

This symposium, held on the occasion of the centennial of Notre-Dame Hospital in Montréal, addresses itself to the current status of early detection and localization procedures in groups at high risk of developing lung cancer. The conference and its publication was made possible through the generous contributions of the Exécutif du Conseil des Médecins et Dentistes de l'Hôpital Notre-Dame and La Fondation Notre-Dame; the Faculty of Medicine, the Vice-Rectorate in Research, and the Department of Continuing Medical Education of the University of Montréal; the Institut du Cancer de Montréal; the Royal College of Physicians and Surgeons of Canada; and Echanges Scientifiques Canada-France.

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Pierre R. Band

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Inhalation Carcinogenesis: An Overview

J. Chrétien*

Hôpital Laennec, 42 rue de Sèvres, F-75007 Paris, France

The marked rise in the incidence of respiratory carcinomas, particularly bronchogenic ones [7, 43], and the disappointing results of their treatment have led to emphasis on the importance of prevention as well as early detection. Accordingly, it is interesting to consider the pathogenesis of respiratory carcinomas and especially its relationship to inhaled substances. This contribution, from the point of view of pulmonary medicine, will first consider the environmental factors and second the specificity of the respiratory system with respect to environmental carcinogens in comparison with the other sites of tumors.

Environmental Inhaled Carcinogens

The respiratory epithelium, which consists of 60–90 m^2 [45] of alveolar surface, conducting airway, and nasopharynx is largely and directly exposed to environmental carcinogens. A variety of environmental carcinogens (urban, domestic, and/or occupational) carried by the 12 m^3 of air normally inhaled every day can reach the respiratory epithelium. Some of these agents have been identified or suspected [7, 10, 15, 31, 34], others have not been yet recognized as oncogenic in man. These substances may act as elementary components, or they may cause complex reactions because of interactions between numerous carcinogens. The relationships may produce simple additive effects of more often synergistic effects. A complex inhaled aerosol such as tobacco smoke is especially oncogenic for the following reasons [8, 12, 13, 16]:
First, tobacco smoke aerosol contains numerous carcinogenic components with synergistic effects: Table 1 summarizes the main carcinogens that have been identified.
Second, the physical conditions of tobacco aerosol also play an important role: it is a monodispersed aerosol with a low standard deviation in the diameter of particles in suspension, and the mean size of particles is small, under 1 μm. These physical conditions favor a slow sedimentation and a prolonged stability in ambient air. This results in repetitive inhalation by smokers (and unfortunately by nonsmokers too) and after inhalation, penetration deep into the lung followed by a long retention due to the

* The author is indebted to Dr. R. Masse for his contributions and redaction of this paper

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Table 1. Identified carcinogens in tobacco smoke (C. C. Harris, 1974)

Gas phase:
Dimethylnitrosamine, diethylnitrosamine
Methylethylnitrosamine, *N*-nitrosopyrrolidine
Nitrosopiperidine
Particulate phase:
Benzo(a)pyrene, methylbenzo(a)pyrenes
Dibenz(a,h)acridine, dibenz(a,j)acridine
Dibenz(c)carbazole, β-naphthylamine
Benzo(b)fluoranthene, benzo(j)fluoranthene
Methylfluoranthene, benzo(a)anthracene
Chrysene, methchrysenes
Benzo(c)phenanthrene

slow clearance from this compartment. This penetration deep into the lung is favored by the consumer himself when he voluntarily inhales the smoke deeply with each puff. If the smoker stops breathing during inspiration for one or several seconds the risk of deposition and retention of particles and gases increases even further. If we use the model drawn from the equation of Landhall (Fig. 1), we can see, for instance, that all the particles may be removed and retained in alveoli, depending on the duration of the breathhold. The slow clearance for this compartment will lead to a long contact time, in particular between the carcinogenic components and the respiratory structures.

Finally, the smoker's behavior also contributes to the pathogenicity of this carcinogen:

Inhalation is voluntary and repeated. Measures designed to protect against this will not be easily accepted. The smoker's microenvironment constantly modifies the other toxic components of his environment, for instance in occupational exposure [24]. In plastic industry workers, for example, the cloud of inhaled plastic particles, the mean size of which is usually large, only reaches the upper airway. In contrast if this same cloud passes through a burning cigarette, pyrolysis changes the size of the particles, thereby allowing them to penetrate to and be deposited in the deep regions of the lungs, and to be retained for a long time.

Although tobacco smoke is obviously the inhaled carcinogen most strongly correlated with respiratory cancers, other physical and chemical agents that act by inhalation have been detected by epidemiological and experimental studies.

Table 2 gives details of type of exposure, ways of penetration, and histological type of tumors produced. Radioactive minerals, asbestos [33, 41, 42], arsenic [23, 27], nickel [2, 18, 44], chromium [35], cadmium [5], and beryllium [30] are among the occupational factors most often incriminated.

Several other points need to be emphasized. The list of chemical environmental inhaled carcinogens is not closed. Not all the hazards have yet been recognized or clearly demonstrated, because of lack of experimental data or longitudinal epidemiological studies. Risk factors may be suddenly unmasked and become obvious, although previously unsuspected. This may happen with any material, whether introduced as a replacement (e.g., glass fiber instead of asbestos) or as a new material either in industry or in domestic environments. Hence the need to develop reliable

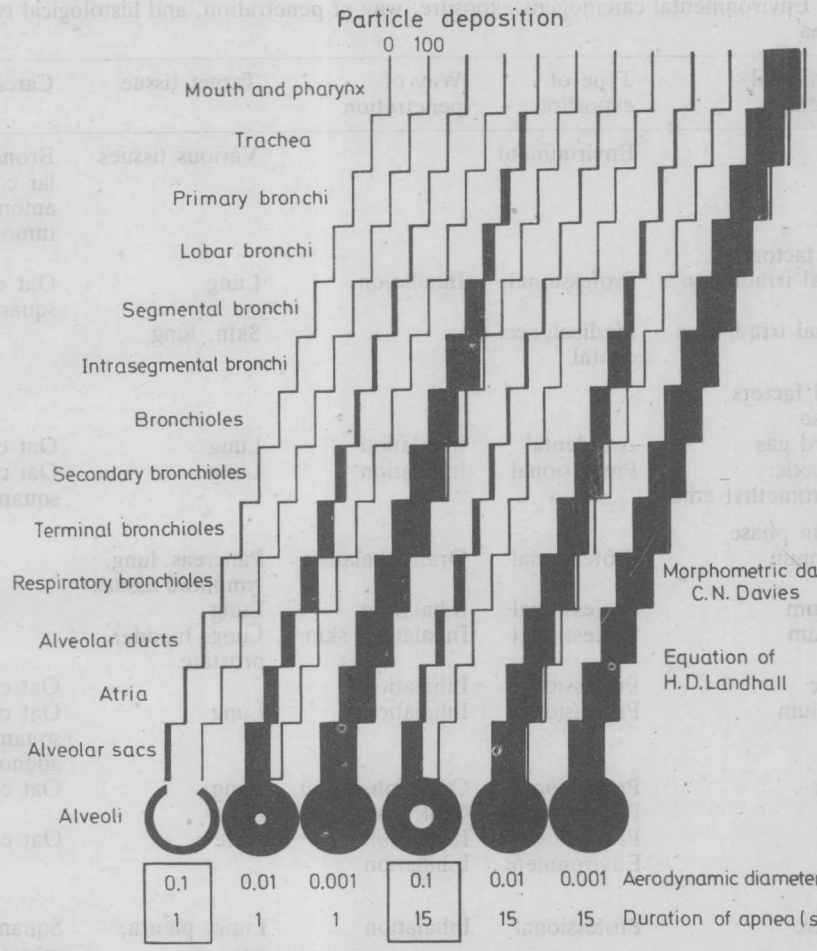

Fig. 1. Particle deposition according to aerodynamic diameter and duration of apnea

screening tests in vitro or in experimental animal models [37], such as the mutagenicity tests [1, 29] or the radon and cofactor exposure model in rats [39], to identify environmental agents that may be carcinogenic in man. Nevertheless, even by act of broad national or international agencies or laboratories, it will be difficult to solve the constantly renewed problems due to environmental agents with carcinogenic effects. Precise identification of carcinogens remains one of the major problems not yet solved in environmental pathology.

A carcinogenic effect can become suddenly obvious under the influence and by way of a cofactor, which really acts as a "revealer" (e.g., tobacco consumption in the case of asbestos or other workers). This cofactor can be a promoter or accelerator but not have its own carcinogenic effect in the sense of not being an initiating component. All the effects of environmental inhaled toxic products should be reexamined in conditions of their usual association with other components, defined as exactly as possible. Another major difficulty in assessing environmental factors concerns the risk of carcinogenicity at low doses and finally the dose-response relationship and the toxicity

Table 2. Environmental carcinogens exposure, way of penetration, and histological type of induced carcinoma

Environmental carcinogens	Type of exposure	Way of penetration	Target tissue	Carcinoma type
Virus	Environment		Various tissues	Bronchioloalveolar carcinoma among lung tumors
Physical factors				
Internal irradiation	Professional	Inhalation	Lung	Oat cell, squamous cell
External irradiation	Medical, accidental		Skin, lung	
Chemical factors				
Gas phase				
Mustard gas	Accidental	Inhalation	Lung	Oat cell
Anesthetic: Bichloromethyl ether	Professional	Inhalation	Lung	Oat cell, squamous cell
Particulate phase				
Aluminium	Professional	Oral, inhalation	Pancreas, lung, lymphoid tissues	
Beryllium	Professional	Inhalation	Lung	
Cadmium	Professional	Inhalation, skin	Lung, bladder, prostate	
Arsenic	Professional	Inhalation		Oat cell
Chromium	Professional	Inhalation	Lung	Oat cell, squamous cell adenocarcinoma
Copper	Professional	Oral, inhalation	Lung	Oat cell
Iron	Professional	Oral, inhalation	Lung	
Nickel	Professional	Inhalation	Nose	Oat cell
Lead	Environment	Inhalation		
Fibrous				
Asbestos	Professional	Inhalation	Lung, pleura, gut	Squamous cell, mesothelioma
Glass fibers	Professional environment	Inhalation	Pleura (?)	Mesothelioma (?)
Other components				
Aromatic amines	Professional, environment	Inhalation	Bladder	
Auramine	Professional	Oral, inhalation	Bladder	
Woods (dusts)	Professional	Inhalation	Pancreas, lung, lymphoid tissues	
Benzene	Professional	Oral, inhalation, skin	Bladder	
Aromatic hydrocarbons	Professional, environment	Oral, inhalation	Lung, bladder	Epidermoid
Polyvinyl chloride	Professional	Oral, inhalation	Liver, lung	Adenocarcinoma
Coal tar	Professional	Skin, inhalation	Skin, lung	
Complex aerosols				
Tobacco smoke	Environment	Oral, inhalation	Bronchial, alimentary tract, bladder	

threshold. One of the main reasons for failure of assessment by experimentation is that only one or few variables are tested and generally under conditions far from those of real human exposure.

Carcinogenic inhaled agents, regardless of their composition, lead to respiratory cancer according to local conditions and specific behavior. This explains the modalities of appearance and growth of tumors, as well as differences in individual susceptibility. On the other hand respiratory surfaces can be vulnerable not only to inhaled carcinogens, but to carcinogens entering the body by other routes. For instance, the lung can be involved in the biological chain resulting from metabolism of carcinogens brought by ingested foods and ingested or injected drugs [17]. Conversely, inhaled carcinogens can exert their effect on targets other than the lung and airways, such as tumors of the pleura in asbestos exposure or bladder or other tumors in tobacco smoke exposure.

Mechanisms Implicated in Carcinogenesis at Respiratory Surfaces: Specific and Individual Factors

For each oncogenetic process, the inhaled agents mentioned above may induce a transformation of cellular structures by interaction with macromolecules [10, 15, 22, 31, 34] according to the schema shown in Fig. 2. Many chemical oncogens form, by either spontaneous or enzymatic activation, electrophil reactants binding to cellular macromolecules. Thus, they introduce new characters in DNA or modify preexisting characters and act as derepressors of genes. This last modality is suggested for bronchoalveolar carcinoma in which viral antigens and complete virions are found in animal models and cell cultures [6, 20, 28].

If, of the inhaled oncogens, viruses, chemical carcinogens, and radioactivity have DNA as target, the target for asbestos and metals remains less definite [13, 15, 31]. There may be a relationship between the mutagenic effects of nickel and its great affinity for nucleic acids, and similarly for chromium and cobalt. For asbestos, cytogenic alterations induced by hydrocarbons absorbed on fibers have also been suggested as playing a major role, but the carcinogenicity due to asbestos fibers is obviously complex and depends partly on fiber size and type. Asbestos also acts as a cofactor, and its oncogenicity is strongly increased when associated with tobacco consumption, as shown by epidemiological studies [4, 42], and when associated with benzopyrenes, as evidenced by experimental procedures [22].

Further work is nevertheless necessary to define the mechanisms of oncogenicity of the usual chemical inhaled carcinogens and there is still a great deal of uncertainty about the precise mechanism implicated in the initiation of bronchial tumor cells. This uncertainty belongs to the "unresolved problems in carcinogenesis" discussed by Berenblum [3]. Also among the unresolved problems is that of latency time, which is correlated with the life span of each species [10] and not clearly explained by the multistage model proposed for carcinogenesis.

Besides these general concepts, which apply to all forms of carcinogenesis, cancers due to inhalation require a consideration of two other points: the specific defense mechanisms of the respiratory tract, and the reasons why the bronchial cells are usually the target for inhaled carcinogens, rather than the other cells in the lung.

The oncogenicity of inhaled carcinogens depends in large part on conditions of deposition and clearance of inhaled aerosols and is closely linked to individual factors.

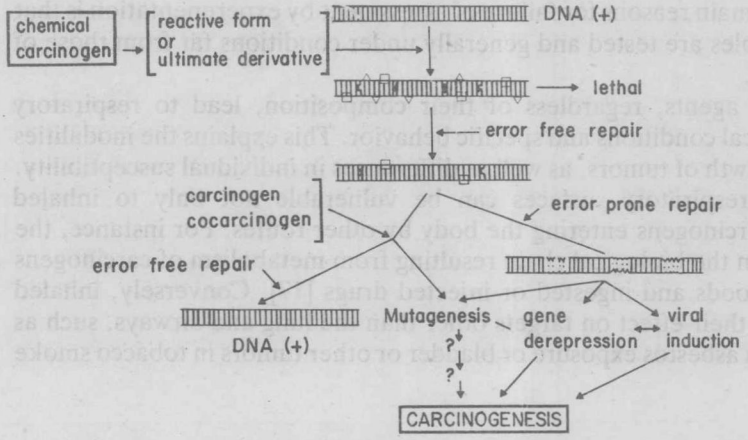

Fig. 2. Hypothetical mechanisms for chemical carcinogenesis. DNA synthesized by error prone process is indicated by the zigzag line segment. We suppose that carcinogen or cocarcinogen could also act to inhibit the error free repair process and give rise to mutagenesis [Sarasin A, Meunier-Rotival M (1976) How chemicals may induce cancer. Biomedicine 24: 304–336]

The risk of cancer after inhalation of an oncogenic substance varies with the duration of contact (e.g., benzopyrene is of little oncogenicity alone, but it is highly oncogenic if given with a substance which prolongs its retention time). Thus it is of great importance to consider the specific conditions of lung clearance. This complex system includes mechanical, immunological, and biochemical factors [9, 16, 21], the study of which requires close collaboration between pneumonologists and oncologists, particularly to establish the role of specific factors and to determine individual susceptibility and risk.

In this regard various factors may be of importance, in particular genetic factors in enzymatic defenses. The Pi system could play a role in inhibiting the growth of tumor cells [19, 36], but the most important is probably the role of metabolic enzymes responsible for detoxification or activation of environmental inhaled carcinogens, such as aryl hydrocarbon hydroxylase (AHH) [11]. This substance induces less toxic molecules but also ultimately more toxic carcinogens such as 7,8-diolepoxybenzo(a)pyrene capable of linking with nucleic acid. The possibility of testing these enzymes on lymphocytes, the discovery of human groups with low, middle, or high AHH inducibility, and correlations with the presence or absence of bronchial cancers provide hope of determining individuals with a high or low risk for lung cancer [26]. Recent reports have diminished this hope [38] and additional studies are needed to assess potential susceptibility by specific analysis in the appropriate tissue, namely the respiratory epithelium.

In immunological protection, the role of alveolar macrophages in antitumor cytotoxicity, notably by the intermediary of the C3B fraction of complement, appears to be important [8, 14]. However, in a personal series [31], experimental stimulation of immunity by preventive treatment with BCG did not inhibit but rather facilitated the growth of experimental radiation-induced tumors.

Among other factors influencing susceptibility to inhaled carcinogens, hormonal, metabolic (in particular vitamin A deficiency as shown in experimental models), infectious, or toxic factors may act in a synergistic fashion [7, 10, 15, 22]. They may

modify mechanical defenses such as mucociliary clearance, immunological defenses such as secretory immunoglobulins A, or respiratory epithelial components, for instance by transforming them into metaplastic cells with higher affinity for oncogenic polycyclic hydrocarbons.

Among the more than 30 types of cells that constitute the airway and alveolar structures, bronchial cells are the most vulnerable to inhaled carcinogens. The differences in renewal rate of different cells (e.g., type I pneumocytes in comparison to type II pneumocytes) and the conditions of exposure of other cells (e.g., fibroblasts in comparison to epithelial cells) could explain the difference in vulnerability. But stable aerosols including carcinogens reach and become deposited on the whole epithelium from the upper to the lower respiratory tract.

The retention of particles is prolonged deep in the lung but is much shorter in the upper respiratory tract because of mucociliary transport. However, cancers are more frequently found in main bronchi than in the lower respiratory tract and alveoli. Several hypotheses could explain this paradox of localization of cancer induced by inhaled substances [10, 15, 31]:

1) The surface area for deposition of particles in bronchi is much less than the alveolar surface. Thus, concentration of potential carcinogens is much higher. Moreover augmented deposition and stasis in different parts of the bronchial tree could occur because of local disorders of mechanical clearance: differences in regional conditions of ventilation could provoke even greater concentrations in some areas (such as the spurs or their vicinity).
2) The lung parenchyma could be quickly cleared of its particles by alveolar macrophages, whereas macrophages remain for a long time in the bronchial tree, where particles may be released. Moreover particles can directly enter and stay in bronchial cells [32].
3) Enzymes responsible for transformation of chemical inhaled carcinogens into ultimate carcinogens reside in bronchial cells.
4) Factors due to species differences about which we know little may also play a role in localization of target cells: for instance oat cell tumors arising from Kulchitsky cells are not observed in radiation-induced tumors in the rat although foci of hyperplastic cells are observed in the early stages of adenomatosis. Squamous cell carcinomas and adenocarcinomas are the usual cell types seen in these experiments.

In fact the above hypotheses do not satisfactorily explain the elective vulnerability of certain respiratory sites or cells. Why is tracheal cancer rare, compared with cancer of the proximal or distal bronchial tree? Why are the oat cell tumors of Kulchitsky cells frequent in uranium miners, even nonsmokers [40]? Why does the maximal dose to the bronchial cells not correlate with the site of radon-induced cancer [10, 15, 25, 31]? Why does asbestos exposure induce tumors from mesothelial cells in nonsmokers rather than from bronchial cells? And why does inhalation of asymmetric dimethylhydrazine induce a high rate of pulmonary angiosarcoma rather than epithelial tumors [31]?

The answers to these questions probably lie in a better knowledge of the pulmonary clearance mechanisms of each inhaled substance and their effects on cell metabolism, as well as in a better understanding of the synergistic action of carcinogens, and of the various endogenous and exogenous factors.

Specific research is needed in three fundamental areas:

1) The deposition and clearance of aerosols, especially those containing carcinogenic components, with theoretical approaches and clinical determinations in humans.
2) Specific enzymatic induction activity in the lung.
3) Specificity of the lung in immunological defense mechanisms against tumors compared to those regulating systemic defenses, and their interrelationships.

Should this ambitious program be realized, pulmonary medicine by using epidemiological and clinical data together with its specific experience in morphology, immunology, and physiology of the lung, could make a major contribution to a better approach in respiratory carcinogenesis.

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