Precursor Lesions of Bronchogenic Carcinoma

Paul Nettesheim
Cancer and Toxicology Program, Biology Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee 37830

Summary

Clinical investigations and experimental studies concerned with preneoplastic and early neoplastic lesions in the respiratory tract are discussed. The occurrence of preinvasive states of carcinoma in the bronchus has been recognized for over 20 years. Histopathological and cytological studies suggest that it might become possible to identify even earlier preneoplastic precursor lesions provided the proper tissue or cell markers can be found. Experimental models that should be useful in establishing a better understanding of the evolution of the neoplastic diseases in the respiratory tract are now available.

The fact that so many eminent cancer researchers are congregated here for a meeting on "Early Lesions and the Development of Epithelial Cancer" suggests a consensus, namely, that cancer is preceded by something that is not yet cancer but that has the propensity to become cancer.

There seems to be a growing awareness on the part of clinical as well as experimental oncologists that the classical definition of cancer as an invasive, destructive, and metastasizing growth which kills the host may not adequately encompass and reflect our present-day knowledge of the natural history and evolutionary phases of a disorder of which only the final phase is characterized by autonomous, destructive growth. The narrow, classical definition, which undoubtedly has its great practical advantages, describes only the fatal end stage of a disease process rather than the totality of the disorder, which has multiple evolutionary phases characterized by varying degrees of disturbance of cell and tissue growth and differentiation.

The dilemma still prevailing today, created by the restricted use of the word "cancer," is reflected in the controversy surrounding the terms "carcinoma in situ" or "intraepithelial cancer" (9, 10, 17). This is more than just a matter of semantics. It points to the confusion created by the fact that, originally, "cancer" meant a rapidly growing, destructive tumor (a fatal diagnosis made when evidence could be provided for the tumor's invasive and metastatic properties), whereas today the use of the term cancer is more inclusive. We have learned that the invasive properties of cancer are only late manifestations of a disease process that develops over many years. The problem is of eminent practical importance and reflects both our knowledge, and the lack thereof, of the natural history of neoplasia.

The question that emerges is: What criteria are available that can be used to assign "early lesions" to a particular stage of the evolutionary process of "neoplastic disorders" rather than to that of inflammatory or degenerative diseases? And, equally important: What information is needed, and how can it be obtained, to develop new criteria for the identification of early manifestations of neoplastic disorders? The challenge confronts all oncologists concerned with diagnosis or treatment of cancer regardless of the field of specialization. However, those of us who are engaged either clinically or experimentally with neoplasias of the respiratory tract have special reason for concern. In his opening statement to the summary of a recent seminar on lung cancer diagnosis and treatment, Straus (27) stated: "The articles in this seminar indicate that long-term survival of lung-cancer patients has not increased over the past few decades."

As in other organ systems, histological and cytological abnormalities thought to be precursors of invasive neoplasia have also been described in various parts of the respiratory tract. It was suggested as early as 1926 by Brandt (4) that some proliferative and metaplastic lesions of the bronchial mucosa might be linked to bronchogenic carcinoma. In 1951, carcinoma in situ of the bronchus was diagnosed cytologically by Papanicolaou and Koprowska (19) and was confirmed histologically. Beginning in 1956, Auerbach published his classical histopathological studies (1-3) on bronchial lesions in smokers, and the incidence of hyperplasia, metaplasia, atypia, carcinoma in situ, and invasive carcinoma as it relates to cigarette consumption and age. Another important contribution was the cytological study of the uranium miners of the Colorado plateau by Sacco et al. (20, 21) which resulted in the description of sequential cytological changes in the sputum of individual miners (see Chart 1). Finally, with the advent and refinement of fiberoptic bronchoscopy (13), it has become possible to localize X-ray occult lesions and to correlate directly cytological and histopathological changes of the bronchial epi-
the lung (atypia) and ending with invasive carcinoma. In doing so we forget that we are not only observing the morphological manifestations of dose-dependent carcinogenicity, but also of dose-dependent (tobacco smoke) toxicity. What goes for tobacco smoke goes for most other pollutants with carcinogenic potential since humans rarely, if ever, inhale pure carcinogenic materials. The situation is even further complicated by the fact that most carcinogenic substances also have considerable cytotoxic effects. The question that then emerges is: Are there specific biological markers that can serve to identify cells or groups of cells that are on their way to become cancer cells—cells endowed with neoplastic growth potential—and how do we identify such markers should they exist?

Experimental models to study induction of lung cancer have been developed in various species (for review see Ref. 18), those most commonly used being hamsters, rats, and dogs. The most popular methods of introducing the carcinogen into the respiratory tract are inhalation exposure to carcinogenic vapors or aerosols and intratracheal injection of carcinogen suspensions. It is possible in such studies to expose the animals to pure carcinogens, which eliminates one of the complications encountered in interpretation of human respiratory tract lesions, namely, the effect of non-specific irritants (see above).

Epithelial lesions and tumors can be induced in this fashion in all segments of the respiratory tract. Dependent on

Chart 1. Carcinoma in situ among uranium miners. Cases are arranged to show the individual development of carcinoma of the lung, and the age at which each stage was initially observed. [Reproduced from Saccomanno et al. (20) with permission.]

DEVELOPMENT OF CARCINOMA IN SITU OF THE LUNG
(EPIDERMOID TYPE)
P. Nettesheim

Table 1
Histogenesis of squamous metaplasia

A. Increase in lysosomes, dilation of ER and abnormal nucleoli in ciliated and mucous cells
B. Abnormal basal cells
1. Pleomorphic nucleoli
2. Nuclear bodies
C. Basal cell hyperplasia
D. Sloughing of altered ciliated and mucous cells
E. Basal cells differentiate into abnormal squamous metaplastic cells
1. Regular squamous metaplasia
a. Cornification
b. Keratohyaline granules
c. Abnormal nucleoli
d. Defects in basement membrane
2. Atypical squamous metaplasia
a. Enlarged nuclei indented by cytoplasmic invaginations
b. Nucleolar plaques and microsegregation
c. Defects in basement membrane
d. Widened intercellular spaces and abnormal cellular junctions

* Modified from Harris et al. (11).

the species, the modalities of exposure, and (to a lesser extent) on the type of carcinogen, they in many instances resemble those seen in humans. The light and electron microscopic changes following multiple intratracheal carcinogen exposures of hamsters were reported by Harris et al. (11, 12) (Table 1). In similar studies conducted in our own laboratory, Schreiber et al. (24) investigated the sequential cytological changes in individual animals following repeated carcinogen exposure. The observations reported from these investigations support the notion that a sequence of morphological changes, closely resembling those commonly observed in humans exposed to carcinogenic contaminants of the breathing air, can be induced with known carcinogens in the tracheobronchial epithelium of laboratory animals.

These, and similar investigations from other laboratories, represent important advances in the field of experimental carcinogenesis. Up to this point, they have essentially confirmed what we already knew from the clinical studies. They have, however, added only little information to help us to establish unequivocally the morphogenetic sequence of respiratory tract neoplasias, nor have they provided us with the knowledge necessary to equate a given cytological or histological abnormality with the neoplastic potential acquired by the cells involved.

The experimental models discussed so far do not readily lend themselves to such studies because of the size and anatomical complexity of the tracheobronchial tree and the problem of dose distribution within this organ system; e.g., it is impossible to induce the same lesions twice with the same carcinogen dose per target area since one has little or no control over local distribution or persistence of carcinogen by use of either inhalation or intratracheal injection techniques. Thus, lesions developing simultaneously in the same segment of the conducting airways may have markedly different exposure histories.

Several systems have been developed in which the relationship of carcinogen dose to target site is more accurately defined. In 1957, Kuschner et al. (15) presented their studies on experimental carcinoma of the lung and described experiments with the intrabronchial pellet technique. A pellet containing either a radionuclide or a chemical carcinogen is inserted into the main bronchus of the rat. Using this technique, the same investigators reported several years later the morphogenesis of radiation-induced bronchogenic carcinoma (16). A similar approach using transplanted rat tracheas was later developed in our laboratory (7, 8, 14). This technique makes it possible to perform studies on a predetermined segment of the respiratory tract and to expose a target of known size to a known amount of carcinogen at a known dose rate. Upon cessation of carcinogen exposure, the fate of the lesions induced in this manner can be followed. A 3rd approach also developed in our laboratory by Schreiber et al. (25) is the tracheal-washing technique. The same apparatus developed for collection of exfoliative cells from the trachea (23) is used here to expose 6 to 8 tracheal rings in situ to a known concentration of a chemical carcinogen. Using this technique, it is possible to induce various early lesions and invasive cancers in a predetermined area of the respiratory tract of hamsters (Fig. 1) and to obtain and correlate cytological and histopathological material from the same carcinogen-exposed tracheal segment.

I think that these "localized tumor induction systems" provide us with some of the tools we need to approach the difficult problem of identification and characterization of early lesions in the evolutionary chain of respiratory tract neoplasia.

References

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Fig. 1. Tracheal carcinomas induced with N-nitroso-N-methylurea. a, carcinoma in the middle portion of hamster trachea 35 weeks after start of carcinogen application (21 weeks after last of 30 applications). Tumor is 10 to 15 mm from vocal cords and obstructs tracheal lumen. b, squamous cell carcinoma in the middle portion of hamster trachea 18 weeks after start of carcinogen application (4 weeks after last of 30 applications). Lumen of trachea is partially obstructed. Tracheal cartilage ring is embedded in tumor tissue. H & E, × 36. c, invasion of epidermoid carcinoma into cartilage ring of trachea. Tumor was found in the middle portion of hamster trachea 19 weeks after start of carcinogen application (5 weeks after last of 30 applications). H & E, × 185. (Reproduced from Schreiber et al. (25) with permission.)
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