Precursor Lesions of Bronchogenic Carcinoma

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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.

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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.]
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 predeterined 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

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, x 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, x 185. (Reproduced from Schreiber et al. (25) with permission.)
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