OCCUPATIONAL CANCER

Cytology in Industrial Applications

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The main objective of cytology in the industrial setting is the detection of cancer and pre-cancer, chiefly of the lung. The ideal cancer-detection program should discover the cases of invasive or late cancer in the early phase. Assuming that all exposed individuals continue to be screened on a regular basis, the remainder of the program should detect cancers in their developmental or in situ stages for confident cure.

The Philadelphia and London projects which screened for early lung cancer by x-ray in the 1950s and '60s failed to significantly reduce the mortality from lung cancer, although early cases were detected (1-3). The investigators of these projects and other investigators have concluded that most patients with a roentgenographically invisible lung neoplasm will develop a visible lesion within 6 to 12 months, at which time the tumor is at least 1 cm in diameter and is comprised of one billion cells (4-6). At this stage it is too late to improve prognosis significantly. Our most compelling task then is to detect the invisible lesions with the microscope.
Detection rates depend on:

the nature and number of specimens,
the method of specimen preparation and its quality, and
the proficiency of the cytology laboratory.

The **nature and the quality of the specimen** is basically the responsibility of the physician. He should explain to the patient the proper technique for acquiring sputum. It is important to do this without frightening the individual, since undue anxiety at the prospect of having cancer may result in a nervous, uncooperative patient and unsatisfactory specimens. Early-morning, "deep-cough" sputum is the only practical specimen for the out-patient. On arising, the screenee should first clean and rinse the teeth and mouth to eliminate food fragments and loose squamous cells from the upper tract. After about five deep breaths and at the height of inspiration of the last breath, he produces an explosive cough by tightening the abdominal muscles and expectorating into a shallow, wide-mouth jar. A fresh, unfixed, specimen thus procured is a very desirable specimen since cellular outlines and detail are well preserved. Unfortunately, it must be delivered immediately to the cytology laboratory. (Cells in unfixed sputum may remain in good condition for several hours, but it is best not to give the patient the option of holding it that long.) Another disadvantage is that the mucus will cause some areas of the smear to be too thick for adequate assessment of cells caught within the mucus. For the patient who cannot cough and produce satisfactory sputum, aerosol induction is advised; several methods for this are described in the literature (7-13). Chest wall percussion (14) and postural drainage (15) techniques are usually unnecessary in the industrial patient, although they may be of value in one with symptomatic disease.

For the out-patient, it is preferable that he expectorate into a jar half-filled with Saccomanno fixative (16), a mixture of 50% ethanol and 2% Carbowax. The fixative allows the patient to collect specimens at home on three to five consecutive mornings; the method has the disadvantage, however, of making the preparation of the smear somewhat cumbersome and it introduces microscopic artifacts. These artifacts are not serious but they might not be familiar to many cytodiagnosticians. A satisfactory specimen is one that contains adequate cellular material from the lung. At the very least, pulmonary macrophages should be present—though they are not siginificant to the evaluation—and ideally, there should be bronchial epithelium.

Several studies have shown the value of multiple specimens for cancer detection (17-19). The detection rate is about 40% with one specimen; the rate increases to about 80% for three specimens and 90% for five. It is recommended, therefore, that the high-risk industrial employee collect five consecutive sputum samples in a half-filled container of Saccomanno fixative. The container may be retained until it is convenient for delivery to the laboratory.

Specimen preparation and laboratory proficiency depend on effective quality control, which is the responsibility of the cytology personnel. Fresh, unfixed sputum is selected for smearing between two glass slides by picking out whitish, opaque or bloody areas or tissue pieces. The smears are fixed immediately without air-drying by rapid immersion in 95% ethanol. Saccomanno specimens are placed in a blender for several seconds to break up the mucus. The blend is then centrifuged and smears are made from the sediment.

Proficiency varies from laboratory to laboratory, depending on how each acquires and utilizes follow-up information. Overall, the more proficient laboratories should detect about 80% of lung cancers (20). Regardless of the laboratory's record of proficiency, a single diagnosis of malignancy should always be confirmed by a second diagnosis to rule out laboratory error.

Data from screening programs of high-risk persons indicate what we may expect in screening for lung cancer in industry.

Uranium - In the 1950s and '60s, a sputum screening program for 3,557 uranium miners (smokers and non-smokers) detected 1% in situ and 4% invasive carcinomas. A similiar detection rate occurred in the control group of smoking non-miners. The two groups differed in that smoking miners developed cancer 10 years earlier than the smoking non-miners (21).

Asbestos - A screening project is currently underway at the asbestos plant in Tyler, Texas. The preliminary report indicates that 2 out of 554 former asbestos workers (ie, 0.4%) had occult, invasive lung cancer and 18 (3.2%) had severe atypia (22).

Cigarettes - A third screening program is for volunteers who are heavy cigarette smokers; it is a major project called the National Lung Cancer Cooperative Study and is sponsored by the National Cancer Institute. It is currently being conducted at Mayo Clinic, Memorial Sloan-Kettering Institute for Cancer Research and Johns Hopkins University Medical School. The prevalence and incidence rates for all carcinomas, in situ and invasive, are summarized in Table 1.

TABLE 1 - Results of the National Lung Cancer Cooperative Study, as of 1977 (23,25,36)

	Mayo	Kettering	Hopkins
Prevalence rates, all carcinomas	8/1000 (0.80%)	4.6/1000 (0.46%)	6.5/1000 (0.65%)
Subsequent incidence rates, new carcinomas	(from all 3 institutions) (0.4-0.5%)		

The cited incidence rate of 0.4-0.5% corresponds to the current lung cancer mortality rate of 38 per 100,000* (assuming that approximately 10% of the population are heavy smokers and that lung cancer mortality rate can be roughly equated with incidence rate). The survival rates are encouraging for those patients who were discovered with early asymptomatic carcinoma (in situ or with focal invasion)—85% survive 3 years. The remaining asymptomatic patients with later disease have a worse prognosis—15% survive 3 years (23).

Similar screening in the future apparently will depend on a balance between the tremendous expense of funding such projects and the undeniable medical and ethical contention that the only effective control of lung cancer—short of removing carcinogens from the environment—is early detection and therapy.

In industry, cytologic surveillance could be done in a manner similar to the National Lung Cancer Study. For those known and suspected industrial carcinogens, see Table 2. We believe that uranium and asbestos workers and those exposed to benzo(a)pyrene certainly should be screened. Whether it is feasible and practical to do so in other industries depends on fiscal factors and health and safety mandates for the employees.

*North Carolina Division of Health Services, Public Health Statistics Branch, 1978.

TABLE 2 - Industrial Agents Associated with Lung Cancer*

	Typical exposures
acrylonitrile	acrylic fiber/textile & resin production; fumigation
arsenic	very numerous
asbestos	numerous
benzo(a)pyrene	cigarette smoke, coke oven emissions
beryllium	numerous
bis-chloromethyl ether (BCME)	organic chemical production, ion-exchange plants
chloromethyl methyl ether (CMME)	organic chemical production
chromium and chromates	numerous
hematite	hematite mining
nickel and its compounds	numerous
soot, tars and oils	numerous
uranium and radon	underground mining
vinyl chloride	polyvinyl chloride (PVC) resin & rubber plants, organic chemical production

*Modified from Schottenfeld, D et al. 1979. Cancer 29:144

There is a reasonable certainty that lung cancer and other cancers undergo a developmental sequence. Auerbach et al (24) did a systematic autopsy study in which they mapped epithelial changes in the bronchi of cigarette smokers, including those with lung cancer. Three changes were observed in bronchial epithelium: hyperplasia, loss of cilia and the presence of atypical cells. Any or all of these changes were more pronounced in smokers than in non-smokers. It was concluded, therefore, that a pathogenetic, developmental sequence precedes invasive lung cancer.

Saccomanno and his co-workers (21), while engaged in the uranium project, proposed a sequence that begins with squamous metaplasia and proceeds through atypical metaplasia to carcinoma in situ, and ultimately invasive carcinoma. The development from squamous metaplasia to invasive carcinoma in their work took 5-15 years. However, the Sloan-Kettering group has advanced another theory based on their study of nine occult cancers detected cytologically in the National Cancer Cooperative Study. The tumors were localized then resected, and multiple tissue sections of bronchi were examined. These researchers proposed that carcinoma begins as basal cell atypia without regard for either preexisting squamous metaplasia or basal cell hyperplasia (25). Therefore, the exact nature of sequential development of human bronchogenic carcinoma remains somewhat unsettled.

In hamsters, tumor induction by benzo(a)pyrene has been demonstrated to proceed through squamous metaplasia of mucous cells to anaplasia and invasion by the metaplastic cells (26,27,32,34). There is strong ultrastructural evidence that this may also be the situation in man. Thus, another developmental theory has been proposed:

The early stage is the proliferation of mucous cells from basal cells, with late conversion of mucous cells to squamous cells with atypia and eventually malignant invasion (31,33).

Whatever the histogenetic sequence of bronchogenic carcinoma is, there is general agreement on the diagnostic criteria for exfoliated atypical cells in sputum. Squamous metaplasia is represented by groups of generally angular cells which are somewhat larger than bronchial basal cells and with acidophilic, frequently glassy, cytoplasm. With increasing degrees of atypical metaplasia, there are increased nuclear hyperchromasia, irregular nuclear shapes, irregular chromatin distribution and occasionally very dense nuclei. Nucleoli tend to occur in the more severe atypias. The cytoplasm is usually eosinophilic or orangeophilic (keratinized), more so than in non-atypical squamous metaplasia, but it may be basophilic. In the most advanced in situ atypia (carcinoma in situ), cells are more likely to occur singly. Again, the nuclei possess marked atypicalities and are markedly enlarged in proportion to the cytoplasm; however, the cells themselves may be quite small.

Cells of invasive squamous cell carcinoma occur singly for the most part and usually reveal considerable variation and irregularity in size and shape, even to the point of being bizarre. Abundant keratination is very common. Many cells will be degenerative or necrotic; in such an instance, the only clue in sputum to an invasive carcinoma is a streak of necrotic material containing outlines of degenerated anucleate cells with abnormal shapes.

Squamous cell carcinoma has generally been regarded as the most common type of lung cancer; however, there is an increasing awareness of the frequency of adenosquamous carcinoma—up to as much as 50% of the lung tumors (28-34). The ultrastructural study, which proposed the above sequence of events in the development of lung cancer, also demonstrated a combined adenosquamous carcinoma wherein the mucous cells retain some of their mucinous properties as they progress down the line (31-34). Then too, the mucinous cells may skip the squamous metaplasia stage and progress to pure adenocarcinoma, which appears to be increasing in incidence (33). This proposed sequence bears resemblance to Auerbach's finding in smoker's bronchi (24), although he did not develop a specific sequence pattern. Developmental sequences for adenosquamous carcinoma and pure adenocarcinoma as reflected in exfoliated cells in the human has not been demonstrated and will be an interesting challenge.

The other two major types of bronchogenic carcinoma are the large cell and small cell, undifferentiated carcinomas. Large cell undifferentiated carcinoma is the designation for a heterogeneous group of poorly differentiated tumors in the squamous, adeno and adenosquamous family. Ultrastructure frequently detects differentiating features, which allows us to re-classify such a tumor as a poorly differentiated squamous cell carcinoma. Therefore, the developmental scheme for large cell undifferentiated carcinoma is probably not significantly different from the one just discussed.

Small cell undifferentiated carcinoma—frequently referred to as oatcell carcinoma—has suffered through years of confusing terminology and subtyping; the situation now appears to be clearing up. The etiology of this tumor is unknown; although, a few such tumors were recognized in the smoking uranium miners and one has also developed in a hamster exposed to benzo(a)pyrene. There is strong evidence that many of these highly lethal tumors are actually more malignant variants of the less aggressive bronchial carcinoid, which has its early growth phase in the deep mucosa and submucosa. If such is the case, there may be little hope for the early detection of small cell tumors by exfoliative cytology.

When and how does one take clinical action on the finding of early or developing lung cancer? Several diagnostic problems must be recognized and seriously considered at this point. First, the difference in what is "severe atypia" and "carcinoma in situ" is usually a personal preference of the pathologist; the two may even be considered equal. Each condition represents serious bronchial epithelial disease and indicates the need for a definite management protocol. Less has been learned about the developmental sequence of lung cancer in contrast to cervical cancer, mainly because of the relative inaccessibility of the bronchi; systematic and comprehensive studies of the bronchi are inconvenient. However, the progression of developing carcinoma in both organs appears remarkably similar. Most uncertain is the time required for severe atypia in the lung to progress to invasive cancer. A few, long-term clinical observations of patients with untreated, severe, bronchial atypia have been made (23); these suggest that the progression may be a few years longer in the lung than in the cervix. Thus, once severe atypia or carcinoma in situ is diagnosed, the when and how of clinical management should be tempered by extenuating circumstances of the individual patient.

A second point to consider before beginning therapy is that the diagnosis of severe atypia in sputum is only preliminary. Fiber-optic bronchoscopy, bronchial brushing and biopsy are essential to localize the lesion. Furthermore, there may be more than one bronchial lesion, emphasizing the need for multiple and systematic bronchial study. One should also realize that a radiographic mass in a patient with severe atypia may be a benign, unrelated lesion.

And thirdly, severe atypia or malignant cells in sputum does not necessarily indicate a lesion in the lung unless lesions in the upper respiratory tract, mouth and pharnyx have been excluded.

In conclusion, cytodiagnosis of sputum, when properly carried out, is readily applicable to industrial screening. In the hands of skillful staff, it is the most reliable and only feasible method for the detection of early curable lung cancer.

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