permanently eradicated in up to 80% of cases by resection. It is factual that some patients with NSCLC in stages II and III achieve long-term survival, but the extent to which long-term survival is the result of treatment, as compared with the natural history of the cancer, is arguable. The evidence that long-term survival requires resection always is essentially solid. Occasional patients with SCLC appear to have long-term control of their neoplasms from chemotherapy or resection, but the curability of this type of cancer is still argued.12,18 It is reasonable to be optimistic and to accept the hypothesis that all types of lung cancer in all stages are potentially curable. However, whenever proposed therapy is likely to affect a patient's quality of life adversely, it is equally sensible to acknowledge the arguable efficacy of treatment for stage II and III cancers. For example, it is justified to do a right pneumonectomy for stage IIIIA NSCLC in a patient with moderately impaired preoperative pulmonary function? I cannot definitively answer this and similar questions, but I can stress the need always to keep the risk-benefit balance uppermost in mind when treating lung cancer.

For progress to be made, there must be a common language with which to describe lung cancers precisely, and there must be scientifically rigorous attention to systemic and locally adjuvant treatment methods. We must be willing to abandon tradition in favor of current evidence and approaches. Traditional language is illustrated by Meek (see next issue), who discusses "resectable but inoperable lung cancer." I know of no way to resect a lung cancer without operating. A cancer that is found to be nonresectable after an hour of dissecting the pulmonary hilum is hardly "inoperable." I suggest that the word "inoperable" be abandoned. "Inoperability" connotes inability to operate, either because the patient declines the recommendation or because the surgeon refuses to operate. If the surgeon declines to operate, he or she should define the reason for refusal in precise terms, using TNM nomenclature as an explanation for whether the lesion is considered curable or incurable and anatomic terms to explain why a lesion is considered resectable or nonresectable.

Patterson (see pages 520 to 523) gives an in-depth discussion of neoadjuvant therapy. This is an attractive, thoroughly logical approach with historic roots in the 1950s.19 The problem is the lack of truly effective chemotherapy, failure of adjuvant irradiation to prolong life,14 and refusal of many clinical investigators to do concurrently controlled studies. For the time being, neoadjuvant therapy belongs in carefully controlled cooperative clinical trials; it is not proven treatment, and therefore it is not ready for general therapeutic use.

Nowhere in medicine is there greater frustration and greater opportunity than in the lung cancer dilemma. The frustration is the result of delayed diagnosis of a disease that is frequently aggressive and often systemic when it is discovered. Lung cancers have poorly predictable biologic behavior, and therapeutic decisions are therefore difficult. The opportunity lies in the fact that we have mastered the surgical and radiotherapeutic methods necessary for local control, and there is emerging evidence that we will soon have a better understanding of the family of diseases that constitute lung cancer. Molecular biologic, endocrinologic, and cytogenetic methods promise eventually to provide insights as to who is a susceptible host, what tumor markers may signal early disease, and which neoadjuvant therapies are likely to work.

References

Lung Cancer*
Making the Diagnosis
Sergey Lyubsky, M.D., Ph.D.; and Myron J. Jacobson, M.D., F.C.C.P. (CHEST 1991; 100:511-20)

In current clinical practice, in the asymptomatic patient, lung cancer most commonly presents as a nodule or mass found on a chest x-ray film. Over the years, large series4-8 have shown consistently that up to half of all such circumscribed nodules will be found to be carcinoma and the remainder benign.

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CHEST / 100 / 2 / AUGUST, 1991 511
Until the 1960s, in the era of rigid bronchoscopy, most patients with a preoperative diagnosis of lung carcinoma underwent thoracotomy without prior cytologic or histologic proof of the diagnosis. Thoracotomy, however, is not without its risks. Mortality rates for a simple wedge or segmental resection of the lung vary from 0.5% to 1.9%. For lobectomy, they are close to 3%; for pneumonectomy, between 6% and 11%. Therefore, direct or indirect methods that establish malignancy or benignity would seem to directly decrease patient mortality, as well as avoiding unnecessary thoracotomy.

Keagy and colleagues recently analyzed the data on 303 patients who underwent thoracotomy between 1970 and 1980 for suspected but unconfirmed malignancy. Because of the location of the lesion, 102 underwent a major resection for presumed carcinoma (93 lobectomies and 9 pneumonectomies). Carcinoma was found histologically in 69 patients and benign disease in 33. Of the 303 patients, 122 underwent a minor resection only. Of these, 79 were found to have benign disease. Thus, more than one third (112/303) underwent thoracotomies for benign disease.

**ROLE OF COMPUTED TOMOGRAPHY**

Various radiologic criteria have been developed over the years that might suggest malignancy in the solitary pulmonary nodule. These include size over 3 cm, irregular and or spiculated borders, and absence of calcification. Smaller size, smooth or lobulated borders, and the presence of calcification are more suggestive of benignity. However, none of these has been of sufficient reliability to be the basis for a therapeutic decision.

There is a well-established clinical dictum that if there has been no change in the size of a pulmonary nodule over a 2-year period, using previous chest x-ray films for comparison, the physician is justified in assuming that the lesion is benign. This criterion should not be used for following up a patient prospectively.

In the early 1980s, Khouri et al. were able to identify 20 of 33 nodules as benign in a group of 91 nodules without calcification in conventional tomograms. A computed tomography (CT) number greater than 164 was used to differentiate benign from possibly malignant nodules. Others, however, had difficulty in reproducing the findings. Further investigation revealed that CT numbers vary from scanner to scanner, vary in time within the same scanner, and are affected by the size of the nodule and the position of the patient.

In a multi-institutional study, Zerhouni et al. studied 384 pulmonary nodules. Twenty-two were recognized as benign without CT densitometry. In the total group, a correct diagnosis of benign was made 65 out of 66 times with use of CT densitometry. On the basis of CT criteria, it is now possible to distinguish benign nodules. However, a radiology department must be thoroughly conversant with this technique to make such a determination. It certainly would be prudent to follow at regular intervals those nodules considered to be benign on the basis of CT criteria. Conventional chest radiographs may be used to follow lesion size.

**SPUTUM DIAGNOSIS**

Examination of sputum provides a technically easy and efficient method for the early diagnosis of lung cancer. The percentage of positive rate for sputum cytologic studies depends on the histologic features, size, and site of the tumor and the degree of admixture with blood and tumor surface necrosis. The Joint Lung Project conducted simultaneously by Johns Hopkins University, Mayo Clinic, and Sloan Kettering Memorial Hospital showed that in a high-risk group of patients (men over 45 years old with a smoking history), screening by sputum cytology improved the early detection of squamous cell carcinoma. In another large series of 449 consecutive cases of primary lung cancer, the overall detection sensitivity was 82.8% (85% for small cell carcinoma, squamous cell carcinoma, and large cell carcinoma; 75% for adenocarcinoma, bronchioloalveolar carcinoma, and adenosquamous carcinoma). In a series from Tokyo Medical College, a positive sputum diagnosis was established on the basis of sputum cytologic findings in 77.7% of central tumors and 47.3% of peripheral tumors. A higher proportion of positive results also occurred in large tumors, lower lobe tumors, and those associated with collapse and consolidation.

Identification of cancer cells in sputum specimens may indicate a more favorable prognosis than when carcinoma is diagnosed with the use of more invasive tests. The best survival figures after surgical resection have been reported in symptom-free patients with radiologically occult disease detected by positive sputum cytology.

Many authors have studied the optimal number of sputum specimens from 1 patient. In the series of Ng and Horak, diagnostic accuracy was optimal in the cases with 3 or more sputum samples: 83% for those with 3 samples and 90% for those with 5 or more samples. A similar effect was observed by Pilotti et al. They noted a significant increase in sensitivity from 0.37 to 0.57 when 3 samples, rather than 1, were examined. Beyond 3 samples, the increase in sensitivity was insignificant: only another 0.01 positive case was uncovered when 4 to 6 samples were studied. Similar results were obtained by Liang.

Evans and Shelley conducted a study of consistency of diagnosis on sputum cytology and found an average false-positive rate of 1.3%, an average false-negative rate of 5%, and an overall disagreement on the degree of cellular atypia of 9.3%. The major causes of false-positive diagnoses are chronic bronchitis, asthma, and tuberculosis. Other causes are irradiation of the chest, exposure to air pollutants, bronchiectasis, acute lung infection, interstitial lung disease, and pulmonary infarcts.

Sputum cytologic examination also can suggest the presence of the premalignant process (dysplasia) in respiratory epithelium. Risse et al. studied 46 patients with dysplastic cells in the sputum. On follow-up, carcinoma had developed in 21 (46%) patients. The immunostaining of sputum slides for tumor-related antigens significantly improved the sensitivity, with recognition of neoplastic antigen expression 2 years prior to the clinical appearance of lung cancer. So far, the antibodies to neoplastic antigens are not commercially available. Patients with severely dysplastic cells and/or the presence of tumor-related antigens on the cells in the sputum should undergo bronchoscopy with multiple bronchoscopic brushings of all areas showing suspicious mucosal changes together with segmental bronchial washings. In the
event that a malignant process cannot be located, Risse et al. recommend that sputum examinations be repeated at 3-month intervals.

In general, except as a screening tool, cytologic study alone as a means of diagnosis has fallen into disuse since bronchoscopy is usually needed anyway and has a higher overall yield.

**Bronchoscopy**

Flexible fiberoptic bronchoscopy has become the single most useful diagnostic procedure in the diagnosis of endobronchial lung carcinoma. More recently, even thinner bronchoscopes have become available, which allow access to previously inaccessible areas. Prakash used a 3.5-mm pediatric bronchoscope with a 1.2-mm channel to detect endobronchial occult tumors in 3 cases; those tumors were inaccessible with larger instruments. Tanaka and colleagues developed a new thin bronchoscope, which fits into the channel of a conventional flexible bronchoscope. They were able to observe and photograph lesions as small as 2 mm. However, conventional flexible transbronchial biopsy or open lung biopsy would be needed to confirm the diagnosis. The usefulness of that bronchoscope in locating otherwise undetectable lung carcinomas remains to be seen.

As with all biopsy procedures, attention must be paid to the fact that frequently the surface of a tumor is soft and necrotic and does not contain histologically identifiable material. To obtain high yield, 3 or 4 biopsy specimens should be taken. For the occasional lesions that are of unusually hard consistency or in a location difficult to reach, use of a spear forceps and/or a curette has proved useful.

We are particularly indebted to Shure and Fedullo for emphasizing the role of bronchoscopy in detecting submucosal and peribronchial spread. Bronchoscopic findings in these cases are subtle and include indentation of the bronchus, concentric narrowing, and either absent mucosal markings or a hypervascular-appearing mucosa. In one series, Shure found that forceps biopsy was positive in 55% of 31 lesions, transbronchial needle biopsy was positive in 71%, and the two combined were positive in 87%. Similar results were observed by Schenk and colleagues.

Very few complications have been reported with flexible bronchoscopes; the most common are pneumothorax, bronchospasm, and bleeding. Deaths have occurred in patients with severe underlying disease (myocardial infarction, severe pneumonia, severe chronic obstructive pulmonary disease, and advanced cancer).

In the large modern series, the diagnostic yield of fiberoptic bronchoscopy and biopsy for endobronchial lesions is above 90%. Bronchial biopsy is more sensitive than bronchial washing and brushing, especially in cases of small cell carcinoma, probably due to its predominantly submucosal location.

In a very large series of 1,156 patients, single or multiple specimens yielded a positive diagnosis of malignancy in 289 patients. The total positive yield of cytology was 88%, and the overall cytologic accuracy in correlation with the histologic findings was 73%. When the tumor was bronchoscopically visible, the yield for washings was 76%; for brushings, 74%; and for biopsy, 82%, giving a total yield of 94%. Peripheral bronchoscopically nonvisible tumors had corresponding yields of 52%, 52%, and 61%, respectively, giving a total yield of 86%. Both washings and brushings have relatively high diagnostic yields in endobronchial masses (about 80%), but neither appears to add significantly to the diagnostic yield of forceps biopsy. Piloti et al. studied 370 consecutive patients with histologically confirmed pulmonary carcinoma and found that the overall sensitivity of examination of bronchoscopically obtained cytologic specimens was 67%. However, the values were 78% and 28%, respectively, in cases with and without visible lesions of the bronchi. Sputum examination enhanced the sensitivity to 79% overall and to 84% and 62%, respectively, for the two groups, with a greater benefit for the group with negative bronchoscopic findings.

The typing accuracy of bronchoscopic biopsy and cytology is not high. Chuang et al. found that the examination of tissue obtained by surgical resection yielded a different cell type from that identified in specimens obtained at fiberoptic bronchoscopy in 38% (41/107) of cases. Rudd et al. found the rates of agreement with the final diagnosis to be 95% for bronchial biopsy through the fiberoptic bronchoscope and 86.5% for bronchial biopsy through the rigid bronchoscope. The diagnosis of small cell carcinoma by any technique was very reliable. The most common error was the incorrect diagnosis of squamous cell carcinoma or adenocarcinoma as large cell undifferentiated carcinoma. The application of immunoperoxidase staining to sputum and bronchial washings did not increase the accuracy of typing compared with the cytologic diagnosis.

The overall cytologic typing accuracy for 252 cases of histologically confirmed pulmonary carcinoma was 66% (range, 19% to 86%), depending on the histologic type. Typing failures were essentially confined to adenocarcinoma and large cell carcinomas.

**Transbronchial Needle Aspiration**

Some experience has accumulated on the application of transbronchial needle aspiration (TBNA) through a flexible bronchoscope. The technical problem of having a needle flexible enough for use in the fiberoptic bronchoscope but rigid enough to allow penetration of the tracheal wall has been overcome with the development of the intraluminal stylet. Wang and Terry were able to diagnose 73% of cases of malignancy in the mediastinum. Very significantly, this technique was also found to be valid for the detection of micrometastasis.

Use of TBNA also appears promising for the diagnosis of peripheral nodules. Schenk et al. performed TBNA in 20 patients, 15 with nodules and 5 with masses and no endobronchial abnormalities. The TBNA cytopathologic findings were positive for malignancy in 11 patients, and TBNA provided the only diagnostic specimen in 7. The TBNA yield was significantly higher than that of forceps biopsy or bronchial brushings either alone or in combination (p<0.05).

In a series of 91 consecutive patients with lung cancer, Schenk et al. found that addition of TBNA increased the diagnostic yield to 71%, compared with an overall diagnostic yield for brushings, washings, and biopsy of 64%.

As might be expected, TBNA fails to contribute significantly to the diagnosis of patients with lesions readily accessible by conventional bronchoscopic techniques.
Shure and Fedullo\textsuperscript{39} reported an application of transcarinal needle aspiration for staging subcarinal nodes in 134 consecutive patients with suspected bronchogenic carcinoma. They used a prototype 20-gauge 1-cm needle and obtained positive results in 15% of 110 patients with cancer. There were no false-positive results, and the transcarinal needle aspirate provided the only evidence of unresectability in 69% (11/16) of the patients in whom the findings were positive. The experience of the Mayo Clinic also proved transcarinal needle aspiration to be beneficial, especially in patients with small-cell lung cancer with extrinsic compression of bronchi.\textsuperscript{40}

One cautionary note was sounded by Cropp et al.,\textsuperscript{8} who reported that during TBNA of subcarinal and peritracheal lymph nodes, the aspirate can be contaminated with tumor cells located on the epithelium of the airway surface.

Bronchoscopic needle aspiration may be useful in endobronchial friable tumors, with which there is a risk of bleeding during forceps biopsy. Buirski et al.\textsuperscript{41} found its yield to be higher than that of forceps biopsy (80% vs 67% in 80 patients), and Lundgren et al.\textsuperscript{42} found it less effective (65% vs 85%).

**TRANSTHORACIC NEEDLE ASPIRATION**

During the past 2 decades, needle aspiration has gained tremendous popularity in the diagnosis of lung cancer, especially peripheral tumors that are inaccessible by fiber-optic bronchoscopy. There is a general feeling among practicing physicians that this technique will be used more extensively in the future. Gobien et al.\textsuperscript{43} found that needle aspiration reduced the need for diagnostic thoracotomy, shortened the time from admission to diagnosis, reduced the total number of thoracotomies, shortened the length of the hospital stay, and resulted in significantly reduced average and total hospitalization charges.

Tao et al.\textsuperscript{44} concluded that in about 35% of the cases in which transthoracic aspiration was performed, surgery became unnecessary. The indications for use of fine needle aspiration were failure of lesser procedures to allow diagnosis of malignancy (53%), distant metastases or bilateral pulmonary lesions (30.3%), coexistent significant cardiopulmonary disease (13.6%), and patient refusal to undergo thoracotomy (3.0%). Stittik et al.\textsuperscript{45} added to this list the presence of a Pancoast tumor. The procedure is ideally performed in patients with presumed lung carcinoma who have negative sputum and bronchial cytologic findings and who are candidates for chemotheraphy and/or irradiation.\textsuperscript{46}

General contraindications for the procedure include pulmonary hypertension, pulmonary arteriovenous fistula, pulmonary cyst, pulmonary abscess, coagulopathy, and advanced pulmonary emphysema. Lesions located in the hilar region were once considered a contraindication for the procedure, due to the proximity of large vessels. Further experience shows that biopsy of these lesions can be performed safely with use of the fine needle aspiration technique. The only absolute contraindication is the inability of a patient with a small lesion to hold his breath for a brief period of time due to uncontrolled cough or anxiety.

The aspiration is usually performed under fluoroscopic or CT guidance. Sedation and other premedications are not routinely required. To avoid the possibility of air embolism, some authors recommend that the biopsy be performed with the patient recumbent.

During preliminary fluoroscopy, the approach should be thoroughly planned. A metal marker on the skin should be aligned with the intercostal space and the exact portion of the mass to be sampled in one straight line. The intercostal space should be penetrated in its lower half to avoid the intercostal neurovascular bundle; the point of penetration should not be directly over the rib. For all apical lesions located above the first rib anteriorly, the biopsy approach is from the back, so as to avoid the anteriorly located subclavian artery and vein. Some authors recommend first making a small incision (0.2 to 0.3 cm) into the skin and subcutaneous tissue with a scalpel blade, which permits free passage of the needle through the skin and allows better sensitivity of increased resistance when the needle touches the pulmonary mass;\textsuperscript{47} we do this routinely. It is better to obtain the biopsy specimen from the margins of the tumor, because the center is often necrotic. We send our cytotechnologists to the room where the aspiration is taking place (usually the CT room). During the procedure the fresh specimen is smeared, immediately fixed in 95% alcohol, and stained. After study of this initial smear, a cytopathologist immediately conveys to the physician whether the quality of material is sufficient for diagnosis.

The major complication of the procedure is pneumothorax. Its rate depends on operative skills and the type of needle used. Needles designed to obtain fragments of tissue produce a high rate of pneumothorax. Westcott\textsuperscript{48} used a slotted 20-gauge needle on 400 patients. The slotted opening measuring 2.2 mm in length was located approximately 3 mm from the tip of the needle. The slot created a second cutting edge in addition to the needle tip. It seemed to enable aspiration of small fragments of tissue in 50% of biopsies. Unfortunately, the pneumothorax rate was as high as 27%, with 10% of pneumothoraces necessitating placement of a chest tube. With a larger (18-gauge) needle, pneumothorax necessitating tube drainage occurred in 5.8%\textsuperscript{49} to 12% of cases.\textsuperscript{50} Vine et al.\textsuperscript{51} used a large 17-gauge core-cutting Lee needle and a track-obliterating technique that utilized an autologus clot. This approach resulted in a 9% pneumothorax rate, which compared well with the rate obtained when smaller needles were used.

The advantage of having tissue fragments for diagnosis led some clinicians to use specially designed thin needles. Greene et al.\textsuperscript{52} obtained biopsy specimens from 150 consecutive suspected lung cancer's using fine needles with circumferentially beveled tips. With these needles they were able to obtain not only aspirate for cyto logic examination but also small fragments of tissue. The rates of simple and complicated pneumothorax in their series were 10% and 4%, respectively.

There have been a very small number of published cases of dissemination of cancer cells along the needle track.\textsuperscript{53,54} Recently Moloo et al.\textsuperscript{55} reported a case in which lung cancer recurred after aspiration with a 22-gauge Chiba needle. Of 23 reported deaths related to needle biopsy, 15 were due to bleeding, 10 involved the use of cutting needles, and only 5 were related to aspiration with thin needles.\textsuperscript{56} Yazdi et al.\textsuperscript{57} compared the results obtained with a 22-gauge needle and 21-gauge needles (E-Z-EM, Westbury, NY) through a 19-
gauge needle guide. They found that the cutting biopsy specimen consisted mostly of clotted blood, lung tissue, and/or fibrous tissue and did not facilitate or improve the diagnosis. In general, there is a consensus that thin (21- to 23-gauge) needles should be used. Pathologists are now feeling more confident in making a cellular diagnosis of lung malignancy on the basis of the findings in aspiration material.

It is often not possible to achieve the precise typing of adenocarcinoma versus squamous cell carcinoma on aspiration smears. However, Young et al. in an analysis of the data on 250 patients, concluded that if a case is difficult to type on an aspiration smear, it will also be difficult to type on histologic section. Nevertheless, we routinely centrifuge the aspirated material and process for cell block. By the combination of smears and cell block sections, we increase the diagnostic yield. Simpson et al. using an 18-gauge needle to obtain material from 233 patients, found that aspirate smear alone yielded 37% of true-positive results. Tissue fragments alone were positive in 12% of cases. In 51% of the cases, both the aspirate smear and the tissue fragments were positive.

Aspiration smears may present a very difficult diagnostic problem for pathologists without specific training in their analysis. Zaman et al. reported 0.2% false-positive results due to reactive changes in alveolar cells associated with granulomatous disease. They suggested that (1) malignancy should not be diagnosed in scanty smears; (2) a malignant diagnosis should not be rendered on the basis of findings in poor preparations; and (3) most malignant epithelial neoplasms present as a single type of cell, while most inflammatory lesions and connective tissue neoplasms are polymorphic.

**DIFFERENTIAL DIAGNOSIS OF LUNG CANCER**

Besides primary non-small cell carcinomas, the lung also is a site of other primary and metastatic tumors. The small (oat) cell carcinoma of intermediate variety occasionally can be confused with undifferentiated large cell carcinoma, especially in cytologic preparations. It was shown that there is a continuum of cell sizes from small to large cell undifferentiated carcinomas, and that for small (oat) cell carcinomas cell size is partly dependent on the size of the biopsy specimen. It appears that electron microscopic (EM) examination and immunohistochemistry could be of value for this differentiation. For example, Mooi et al. used EM to study 14 cases that were considered borderline at light microscopy and found that the presence of neuroendocrine granules on an EM study correlated with poorer clinical course. Johnston et al. observed positive staining with monoclonal antibody 72.3 in needle aspirates of the great majority of “non-small cell carcinomas” of the lung. In contrast, small cell carcinomas of the lung, malignant melanomas, and lymphomas stained negatively with the antibody.

The diagnostic problems come mostly from adenocarcinomas and large cell carcinomas. In cases of large cell carcinoma, especially the clear cell variant, renal cell carcinoma, large cell lymphoma, and amelanotic melanoma should be considered. Renal cell carcinoma cells are filled with glycogen particles, but occasionally kidney examination is warranted. Melanoma can be readily recognized with EM. Even tissue retrieved from paraffin blocks has identifiable promelanosomes. An EM study can also be used to differentiate large cell carcinoma from lymphoma on the basis of the occasional presence of desmosomes and secretory organelles in carcinoma. Immunohistochemistry with antibodies to leukocyte common antigen and epithelial membrane antigen can also be helpful. Immunostaining with antibody to S100 protein is no longer considered useful because, in addition to melanomas, it stains poorly differentiated carcinomas and lymphomas.

Adenocarcinoma of the lung often has to be differentiated from metastatic adenocarcinoma, especially from the gastrointestinal tract. Here, too, EM can be helpful. In a mixed population of 96 adenocarcinomas, it was found that microvilli with rootlets constitute the best morphologic marker for intestinal adenocarcinoma. Hanna and Kahn reported that the presence of short microvilli with rootlets on malignant cells in effusions was specific for gastrointestinal malignancies. On the other hand, other authors conclude that the presence of cell surfaces with microvilli having core rootlets and glycocalyxal bodies does not permit the distinction between primary and metastatic adenocarcinoma in lung. The lamellar inclusions of type II pneumocytes are diagnostic of bronchiolalveolar carcinoma.

The utilization of certain organ-specific antibodies like those to prostatic-specific antigen and prostatic acid phosphatase provides additional help in making the distinction between primary and metastatic adenocarcinoma. For example, in cases of clinically suspected primary lung cancer, their application helped to arrive at the correct diagnosis of metastatic prostatic cancer.

Adenocarcinoma of the lung is easily confused with malignant mesothelioma. Every pathologist is aware how difficult this distinction can be on the level of light microscopy. Electron microscopy can be very helpful if one finds long, slender, branching microvilli and perinuclear condensation of microfilaments, which are characteristics of mesothelial cells.

Recently, immunomorphologic methods for this differentiation were tested. Otis et al. used a panel of antibodies (keratin, carcinoembryonic antigen [CEA], anti-human milk fat globule-related antigen, MC-1, B72.3, and Leu M-1). They found that adenocarcinomas and mesotheliomas are distinguishable by titrating the antibody concentration, but the lack of a detectable specific antigen in mesothelioma continues to make some cases difficult to evaluate with immunohistochemistry alone. Szpak et al. showed that monoclonal antibody B72.3 reacted with at least 10% of tumor cells in 19 of 22 adenocarcinomas of the lungs, whereas none of the 20 cases of malignant mesothelioma demonstrated comparable reactivity. Other antibodies raised against lung adenocarcinoma cell lines have been successfully utilized.

Kahn et al. and Cibas et al. noted that a panel of mucin histochemistry, reactivity for CEA, and peripheral staining for keratin are highly characteristic markers for adenocarcinomas, and the panel was of assistance in recognizing the majority (38/39) of these tumors. Said et al. showed that CEA was strongly positive in adenocarcinomas, whereas positive staining for keratin with negative or focal weak staining for CEA was characteristic of mesothelioma. Walts
Table 1 — WHO Histologic Classification of Epithelial Bronchogenic Carcinomas

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
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<tbody>
<tr>
<td>I.</td>
<td>Benign</td>
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<tr>
<td>II.</td>
<td>Dysplasia and carcinoma in situ</td>
</tr>
<tr>
<td>III.</td>
<td>Malignant</td>
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<tr>
<td>A.</td>
<td>Squamous cell carcinoma (keratin)</td>
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<tr>
<td>B.</td>
<td>Small cell carcinoma</td>
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<tr>
<td>C.</td>
<td>Adenocarcinoma</td>
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<td>D.</td>
<td>Large cell carcinoma</td>
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et al. examined exfoliated cells in effusions and found that the presence of epithelial membrane antigen useful in distinguishing adenocarcinoma cells (strongly positive) from reactive mesothelial cells (negative or weakly positive). Unfortunately, exfoliated cells from two mesotheliomas were also strongly positive for epithelial membrane antigen. Carcinembryonic antigen is always negative in mesotheliomas and mostly positive in adenocarcinomas. A negative reaction for keratin is strong evidence against a diagnosis of carcinoma or mesothelioma.

Heterogeneity of Lung Cancer

Currently the World Health Organization (WHO) classification of lung cancer is the most widely used classification (Table 1). Since its publication in 1981, there have been no major criticisms or competing classifications. The general gross and microscopic pathologic features of the major types of lung cancer have been extensively described in the literature.

Despite extensive coverage of the pathology of lung cancer in the literature, several additional remarks are warranted. Non-small cell lung carcinomas are notoriously heterogeneous, with many different combinations of cancer cell differentiation observed in individual tumors. Even in a single cancer cell viewed under the electron microscope, one can occasionally see various combinations of differentiating features, such as bundles of keratin tonofilaments (squamous differentiation), developed secretory apparatus with mucin vacuoles (glandular differentiation), and dense core granules (neuroendocrine differentiation).

The heterogeneous nature of lung cancer is seldom recognized in biopsy specimens and usually requires extensive sampling of resected specimens to be appreciated. Roggli et al. studied 100 cases of lung cancer, examining at least 10 blocks from each tumor. They found heterogeneity with the presence of histologic types other than the predominant type on one or more slides in 45% of cases. In our view, these data do not represent real heterogeneity because in most instances there is an admixture of large cells with other differentiated cells. Roggli et al. considered large cell carcinoma a separate histologic type, while we classify this as a poorly differentiated variant of the main histologic type.

With extensive sampling in this series, the tumors composed of a mixture of squamous cell carcinoma and adenocarcinoma represented only 10%.

Some Uncommon Non-Small Cell Lung Cancers

The WHO system considers one type of mixed-differentiation tumor as a separate entity — adenosquamous carcinoma. This tumor is diagnosed when both components are clearly present in the same tumor. Fitzgibbons and Kern examined 1,125 primary lung cancers and found the frequency of adenosquamous carcinoma to be 0.6%. In the series of Nauheim et al. its frequency was 2.3%. Both series confirmed its highly aggressive behavior (median survival for patients with stage III was 5.0 months). For comparison, for stage III small cell cancer showed a median survival of 9.6 months; adenocarcinoma, 9.0 months; and squamous cancer, 7.8 months. Therefore, it seems reasonable to recognize adenosquamous carcinoma as a separate entity.

Spindle cell carcinoma is considered a variant of squamous cell carcinoma. It has been suggested that spindle cell mesenchymal tumors with potential bone, cartilage, or muscle differentiation without keratin immunoreactivity and absence of desmosomes by EM should be called carcinosarcomas. Spindle cell carcinoma should be diagnosed only if the tumor is keratin-immunoreactive or it has tonofilaments or true desmosomes by EM analysis.

Adenocarcinoma

As for adenocarcinoma of the lungs, there is a growing awareness that this group represents tumors that originated from different cell types. Kawai et al. studied 105 cases of lung adenocarcinoma with antibodies to keratin, vimentin, CEA, and secretory component. They found that keratin was positive in a higher number of adenocarcinomas that originated from the bronchial surface epithelium, goblet cells, and bronchial glands than in adenocarcinomas from Clara cell or type II alveolar cell origin. Kitinya et al. utilized monospecific IgG against pulmonary surfactant apoprotein in 57 adenocarcinomas and 43 large cell carcinomas. They found 6 peripheral adenocarcinomas and 1 peripheral large cell carcinoma to be histogenetically related to type II pneumocytes, although these tumors demonstrated different histologic patterns (acinar, papillary, or solid growth). It appears from data concerning papillary adenocarcinomas and scar adenocarcinomas that subtyping based on cell type might have prognostic implications. One should expect further progress in cell subtyping of this group with wider application of immunoperoxidase and EM methods.

There are rather good correlations between the pattern of adenocarcinoma and its biologic behavior. Sorensen et al. evaluated patients with inoperable stage III disease and found that bronchioloalveolar carcinoma had the longest median duration of response to chemotherapy (47 weeks), time to progression (33 weeks), and median survival (40 weeks). Solid carcinomas with mucus formation had corresponding values of 8, 12, and 22 weeks. Aciar and papillary adenocarcinomas were intermediate. Every one of those groups is histogenetically heterogeneous, however, as shown by immunohistochemistry and EM. For example, bronchio-
loalveolar carcinoma may be derived from either type II cells, Clara cells, or bronchial mucus cells. Therefore, the subdivisions within the adenocarcinoma group most likely might represent the common cellular origin as well as a degree of differentiation (grading) of a heterogeneous group of tumors. It is well known that grading based on degree of differentiation correlates very well with biologic behavior of lung cancer. Chung et al. analyzed 96 cases of lung cancer and found that, compared with patients with grade 1 and grade 2 tumors, patients with grade 3 adenocarcinoma had more local recurrences and those with grade 3 squamous cell carcinoma had more distant metastases.

**LARGE CELL CARCINOMA**

Large cell carcinomas constitute about 16% of all lung cancers. This diagnostic category is considered a general wastebasket for tumors that cannot be further classified by the available methods. Yesner et al. used histochemical staining to identify squamous and glandular components of large cell carcinoma and decreased the frequency of the diagnosis to 10% by subclassifying some of the cases into either the squamous or the adenocarcinoma group.

Use of EM and immunomorphology can further diminish the proportion of large cell carcinoma. Kodama et al. studied 27 cases of surgically resected large cell carcinoma of the lung by EM and immunocytochemistry. Ultrastructurally, of 18 large cell carcinomas, 8 showed differentiation toward adenocarcinoma, 4 toward adenosquamous carcinoma, and 1 each toward squamous cell carcinoma and neuroendocrine cell carcinoma. However, the remaining 4 were undifferentiated. Similar results were obtained by Saba et al. and Herrera et al. In the series of Horie and Ohta, it was shown that large cell carcinomas with the ultrastructural feature of squamous differentiation showed a better prognosis than those with adenosquamous or adenocarcinomatous differentiation. However, in a study of 48 patients with large cell carcinoma, Albain et al. did not find any difference between 15 cases with squamous differentiation, 17 cases with adenocarcinomatous differentiation, and 14 cases of anaplastic large cell carcinoma.

The WHO classification of large cell carcinoma includes 2 variants: clear cell carcinoma and giant cell carcinoma. Edwards and Carlile studied 6 tumors of the lung initially classified as clear cell carcinoma. On EM study, glandular (adenocarcinomatous) differentiation was seen in 3 cases and squamous differentiation in 2. One case did not show any ultrastructural features of differentiation. The clear appearance of the cytoplasm is due to the fact that glycogen is partially removed during processing. The other variant of large cell carcinoma, giant cell carcinoma, apparently is justly separated due to its more aggressive behavior and the dedifferentiation that is reflected in the lack of keratin and epithelial membrane antigen immunohistochemically.

Besides the histologic type of tumor, other microscopic features are also prognostically important. Chung et al. analyzed 96 patients who underwent lobectomy or pneumonectomy for lung cancer. They found that poor differentiation, vascular invasion, and lymph node metastases represent poor prognostic indices in patients undergoing surgery. Lipford et al. on analysis of 173 stage I and stage II primary non-small cell carcinomas, found the following features to have a negative influence on the prognosis: large cell undifferentiated histologic features, lymph node metastases, tumor size, presence of tumor giant cells, and absent or minimal plasma cell infiltration.

Takise et al. specifically addressed the histopathologic prognostic factors in peripheral lung adenocarcinomas less than 2 cm in diameter. They found pathologic stage, lymph node involvement, and pleural involvement to be major determinants of prognosis (p<0.01). In addition, other single factors, such as tumor differentiation (p<0.01), vascular invasion (p<0.01), the degree of collagenization in the fibrotic focus (p<0.01), the standard deviation of nuclear areas (p<0.05), and mitotic index (p<0.05), correlated significantly with prognosis.

James and Davey noted the importance of mitotic activity. Vascular invasion appears to be independent of histologic type, grade of the tumor, and lymph node involvement. The application of flow cytometry to the specimens of non-small cell lung cancer has added aneuploidy and proliferative activity of tumor cells as additional reliable correlates with survival.

**CHANGING PATTERNS OF LUNG CANCER**

Recently, many authors have noted a shift in the relative incidence of histologic types of lung cancer. Valaitis et al. reviewed histologic types of lung cancer initially diagnosed at Lutheran General Hospital, Park Ridge, Illinois, from 1963 through 1967 and from 1974 through 1976. They found a relative increase in the frequency of adenocarcinoma in men and an overall increase in lung cancer in women. The increased frequency of adenocarcinoma in men was accompanied by a corresponding decrease in the frequency of squamous cell carcinoma, probably due to environmental measures such as a drop in smoking and pollution control.

Similar data were reported by Wu et al., who studied the histologic patterns of lung cancer in Los Angeles County. They found that the total lung cancer incidence in men was fairly constant, but that there was a shift in the histologic pattern with an increase in adenocarcinoma and decrease of other cell types.

In a study of 2,580 cases of lung cancer diagnosed at Duke University Medical Center over a 15-year period, Johnston found that the absolute and relative incidences of lung adenocarcinomas within other types of cancer in women showed a striking increase from 21.8% to 29.9%. In the series of 4,928 cases at Baptist Memorial Hospital in Memphis between 1964 and 1985, adenocarcinoma was demonstrated to be the most common lung tumor in women at the level of about 40%. During the same period, squamous cell carcinoma remained the predominant histologic type in men; however, its incidence decreased from 50% to 37%, while the incidence of adenocarcinoma increased from 13% to 27%.

Adenocarcinoma also predominates over squamous cell carcinoma in Japan, but a recent autopsy series of 282 cases in 1950 through 1983 showed a trend toward a reduction in the proportion of adenocarcinomas and an increase in the proportion of squamous cell carcinomas, a trend apparently opposite to that in the United States.

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Lung Cancer Staging*

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Accurate identification and description of the extent of disease is crucial to making proper management deci-

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sions and reporting of results in bronchogenic carcinoma. The American Joint Committee on Cancer and the Union Internationale Contre le Cancer have recently adopted a revision of the lung cancer staging system based on the TNM descriptors (Table 1). This system has recently been reported by Mountain.1

The major changes in this new system move T1N1 tumors into stage II. Another major change divides stage III into A and B categories, with stage IIB, except in unusual circumstances, being inoperable disease. In addition, a new stage IV is created, in which all but unusual cases of carinal involvement are inoperable. In an excellent review of a very large number of surgically staged patients, Naruke et al have clearly shown that survival is related to stage of disease. In that 25-year review, many patients were not staged preoperatively with computed tomography (CT) or mediastinoscopy. Nonetheless, their review clearly shows the inaccuracy of clinical staging of bronchogenic cancer. Five-year survival rates were as follows: stage I, 65.0%; stage II, 42.9%; stage IIIA, 22.5%; stage IIIB, 5.5%; stage IV, 1.7%. There is a statistically significant difference in survival between all groups, with the exception of stage IIIB and stage IV.

Assessment of the Primary Tumor

Obviously, plain chest roentgenograms and tomograms are of great value in the assessment of most primary tumors. Accurate assignment of an appropriate T descriptor is

<table>
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<tr>
<th>Stage</th>
<th>Types</th>
<th>Characteristics</th>
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<tbody>
<tr>
<td>I</td>
<td>T1N0M0, T2N0M0</td>
<td>A tumor that can be classified T1 and T2 without any metastasis to nodes or distant metastasis</td>
</tr>
<tr>
<td>II</td>
<td>T1N1M0, T2N1M0</td>
<td>Any tumor classified as T1 or T2 with metastasis to the lymph nodes in the peribronchial or ipsilateral hilar region only</td>
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<tr>
<td>IIIA</td>
<td>T3N0M0, T3N1M0, T1N2M0, T2N2M0, T3N2M0</td>
<td>A tumor that can be classified as T3 without nodal metastasis or with metastasis limited to the peribronchial, ipsilateral hilar, and ipsilateral mediastinal lymph nodes; T1 and T2 tumors that have metastasized to the level of the ipsilateral mediastinal lymph nodes only are also included</td>
</tr>
<tr>
<td>IIB</td>
<td>T(any)N3M0, T4N(any)M0</td>
<td>Any tumor more extensive than T3, any tumor with supracavicular or contralateral mediastinal lymph node involvement, or any tumor with a malignant pleural effusion but without evidence of distant metastasis</td>
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