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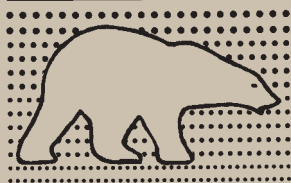
Welcome to the Snowdrift Frontline Treatment Monographs. The authors welcome you to this series of monographs that aim to disseminate worldwide new knowledge about common pulmonary disorders. We offer our messages to anyone who will find them useful in the diagnosis and treatment of the many pulmonary disorders that continue to plague mankind around the world. We invite you to download these monographs and use them in your teaching and practice of medicine. We feel a fraternal connection to all practitioners who serve the suffering. We hope that we can move toward the prevention of disease as an alternative to premature morbidity and mortality.

The Authors.

Mission Statement

The Snowdrift Pulmonary Conference is a not-for-profit corporation that is dedicated to the dissemination of knowledge about the lungs and lung diseases. Composed of both private practice pulmonologists and academicians, the conferees have launched a consumer-oriented program for primary care practitioners and the patients they serve. As a result, the following concise and authoritative monographs have been written.

Snowdrift Pulmonary Conference



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Frontline Assessment of Lung Cancer & Occupational Pulmonary Diseases

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Diagnostic Approach to Lung Cancer

Preface

Lung cancer is the most common fatal malignancy in both men and women in the United States today, and also the most common cause of cancer death worldwide. Tobacco smoking is responsible for approximately 90% of all lung cancers, but we are not making great progress in reducing the prevalence of smoking in this country. The worldwide prevalence of smoking continues to skyrocket. Thus, the epidemic of lung cancer will continue to increase.

Unfortunately, lung cancer is usually diagnosed late in its course, and mostly on the basis of symptoms of advanced stage or metastatic disease. Although screening programs for all other major cancers are advised, such is not the case in lung cancer. This policy must change. Today we have the knowledge and technology to change the outcome of lung cancer.

Occupational lung disease represents a wide spectrum of hypersensitivity, fibrotic and neoplastic diseases. Some of these occupational diseases relate to lung cancer, such as fibrotic lung diseases where lung cancer is a complication. Prevention of disease initiation or progression is the goal of medicine, and could reduce or eliminate these disorders.

The frontline practitioner encounters the great majority of smokers who are at risk of lung cancer. A pragmatic approach to the early diagnosis of lung cancer is critical to improving survival. Frontline practitioners also see the majority of patients who have occupational-related lung diseases. Thus, this monograph is directed to the frontline practitioners who encounter these patients first.

As in the previous five monographs of this series, the authors are all specialists in pulmonary medicine from both academia and the private practice sector. We have prepared a practical approach to assessment of lung cancer and occupational lung diseases for the frontline practitioner. As with our other monographs, we do not present our advice as a cookbook approach or as guidelines that are set in stone. Rather, we aim to offer you and your patients a pragmatic approach to the initial assessment of lung cancer and occupational lung diseases in hopes of early treatment and resolution of these problems. ■

The Authors

Frontline Assessment of Lung Cancer

Pearls

- Lung cancer is the most common cause of cancer deaths in men and women.
- Smoking cessation is the only proven method to reduce the risk of lung cancer.
- Lung cancer is four to six times more common in smokers with airflow obstruction than with normal airflow, as measured by spirometry.
- Surgical resection cures greater than 80% of patients with stage I lung cancer.
- A second primary lung cancer will occur in 5% to 20% of previously cured lung cancer patients.
- Adenocarcinoma has replaced squamous cell carcinoma as the most common histologic type of lung cancer.
- Lung cancer occurs more commonly in non-smoking women than in non-smoking men.
- Small-cell lung cancer is primarily treated with chemotherapy. ■

A. Epidemiology and Etiology

Epidemiology

Lung cancer worldwide constitutes 16% of all malignant tumors and accounts for 28% of cancer deaths (35% in males and 19% in females) and about 6% of all deaths. By the year 2000, there will be 1,331,000 deaths annually from lung cancer worldwide. The American Cancer Society (ACS), projects that 169,500 new cases of lung cancer will be diagnosed in the United States (90,700 in males and 78,800 in females) in 2001, and 157,400 affected patients will die from the disease (90,100 males and 67,300 females). Although the mortality rate from most solid tumors has been declining in the United States, the mortality rate from lung cancer has continued to rise over the past several decades (See Figures 1 and 2). The slight drop in mortality in men is overwhelmed by the mortality increase in women.

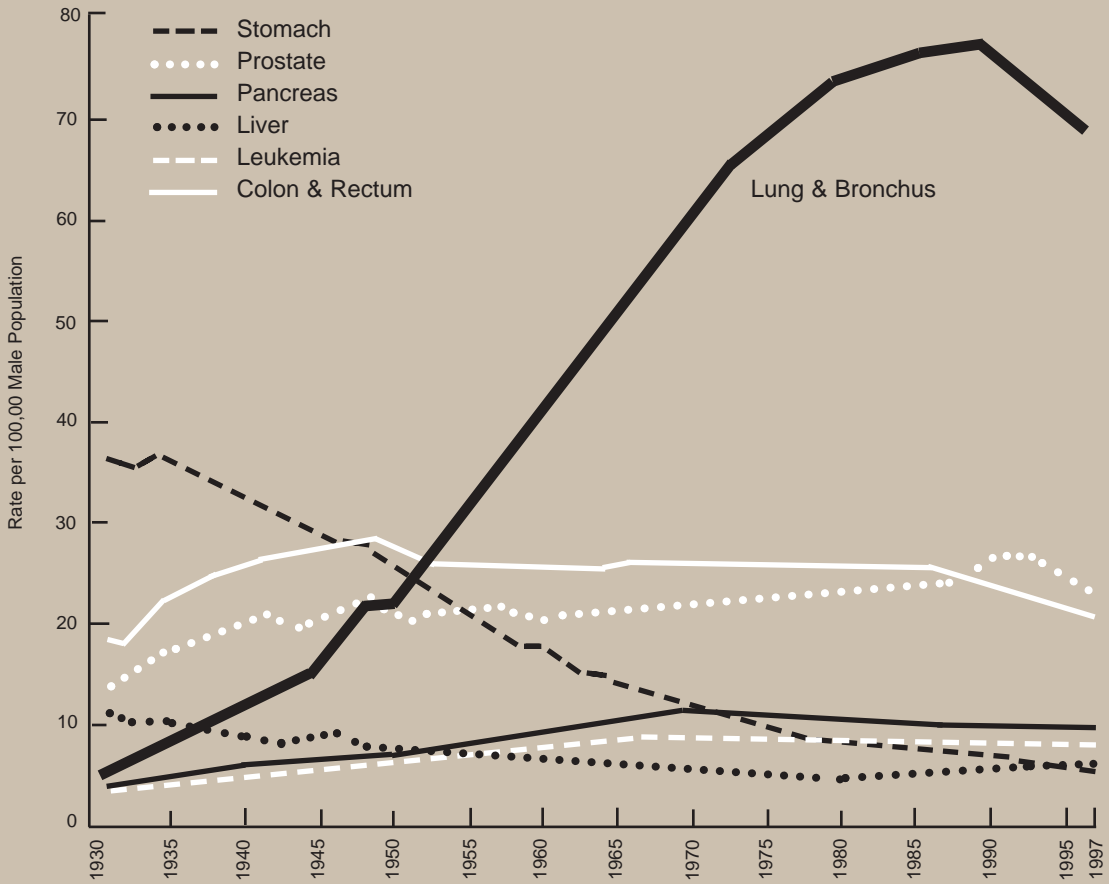
Patients with lung cancer are typically heavy tobacco smokers in their sixth or seventh decade of life. Less than 5% of affected patients are under 40 years of age. Lung cancer used to be primarily a male disease. However, recently the prevalence has increased more rapidly in women (See Figures 1 and 2). The increase of lung cancer in females parallels the well-documented increase in the number of women smokers. In the past four decades, there has also been a marked increase in adenocarcinoma of the lung, which is now the most commonly diagnosed histologic type, followed by squamous cell, small-cell and large-cell carcinomas.

The economic cost of lung cancer is enormous. In the United States alone, lung cancer-associated medical costs are estimated to exceed \$10 billion, representing 1.5% of the total cost of illness. Twenty percent of the cost is from direct health care, whereas lost wages and productivity account for 80%.

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Figure 1

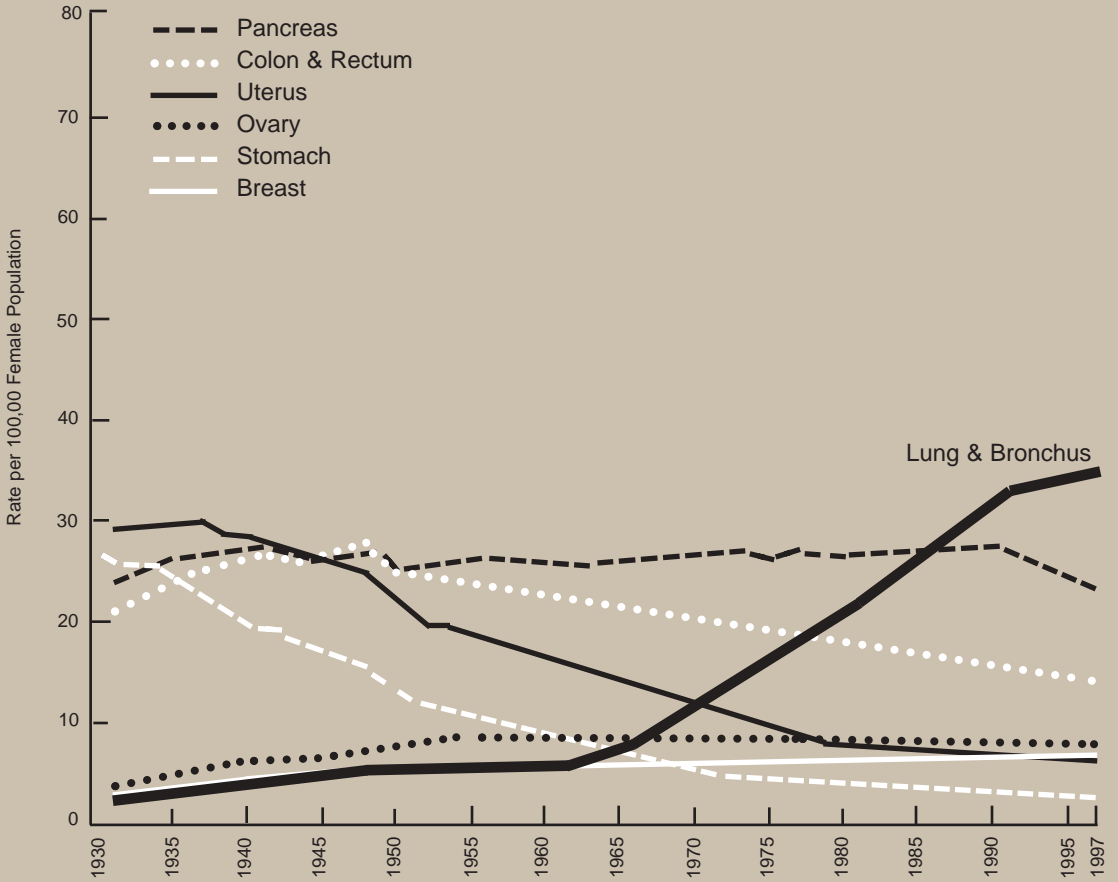
Age-Adjusted Cancer Death Rates, for Males by Site, US, 1930–1997



Source: Greenlee RT, Hill-Harmon MB, Murray T, Thun M. Cancer statistics, 2001. *CA Cancer J Clin* 2001; 51:28.

Figure 2

Age-Adjusted Cancer Death Rates, for Females by Site, US, 1930–1997



Source: Greenlee RT, Hill-Harmon MB, Murray T, Thun M. Cancer statistics, 2001. *CA Cancer J Clin* 2001; 51:27.

Etiology and Risk Factors

Tobacco Smoking

A vast amount of statistical evidence has incriminated tobacco smoking, especially in the form of cigarettes, as the main cause of the progressive rise in mortality rates from lung cancer. The risk in smokers is related directly to the number of cigarettes smoked, the duration of smoking in years, the age of initiation of smoking, the depth of inhalation and the tar and nicotine levels in the cigarettes smoked. Smokers who consume one pack per day have approximately a nine- to ten-fold increased risk over non-smokers for developing lung cancer, while those who smoke two or more packs per day have at least a ten- to 25-fold increased risk.

Cigarette smoke, a complex aerosol composed of both gaseous and particulate compounds, reaches the lungs as either mainstream smoke, which is produced by inhalation of air through the cigarette, or sidestream smoke which is produced from smoldering of the cigarette between puffs. Sidestream smoke is the major source of environmental tobacco smoke.

Tar is the total particulate matter of cigarette smoke after nicotine and water have been removed. Tar exposure appears to be the major link to lung cancer risk. Mainstream smoke contains a large number of potential carcinogens.¹ Radioactive materials² are also present in tobacco smoke. The tobacco-specific N-nitrosamines (TSNA's) are formed from the nitrosation of nicotine both during tobacco processing and smoking. Of the TSNA, NNK³, appears to be the most important cause of lung cancer. When tobacco smoke is inhaled, TSNA's are delivered directly to the lungs, and because they are absorbed systemically, they also reach the lung via the pulmonary circulation.

1 Polynuclear aromatic hydrocarbons, aromatic amines, N-nitrosamines and miscellaneous organic and inorganic compounds such as benzene, vinyl chloride, arsenic and chromium.

2 Radon and its decay products, bismuth and polonium (radium).

3 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, a tobacco-specific nitrosamine.

The intensity of tobacco use is a function of a smoker's nicotine dependence. Although cigarettes now contain less nicotine and tar than previously, to satisfy nicotine need, smokers tend to take more puffs per minute and to inhale more deeply. With deeper inhalation, small airways in the periphery of the lung, which lack protective epithelium, are selectively exposed to carcinogens, as opposed to the major bronchi. The marked increase in adenocarcinoma of the lung, largely a peripheral tumor, has been attributed to the increased delivery of carcinogens such as NNK to the outer portions of the lung. Use of filters to produce smaller particles is also a factor in the peripheral deposition of carcinogens and associated adenocarcinoma.

Environmental Tobacco Smoke (Secondhand Smoke)

The United States Environmental Protection Agency now classifies environmental tobacco smoke (also called secondhand smoke) as a lung carcinogen. In one large study, the relative risk of lung cancer in women with husbands who smoke was 1.2, an increase in lung cancer incidence of 20%. The relative risk in non-smoking men with smoking wives was somewhat less, but still was elevated at 1.1.

Genetic Alterations

Smoking has been shown to be associated with mutations in the *p53* tumor suppressor genes, the most common genetic alterations detected in human cancers. Such mutations have been associated with a history of heavy tobacco use, but they have also been detected in non-smokers with lung cancer.

Airway Obstruction

The presence of airway obstruction is also a risk factor for lung cancer after adjustment for smoking history. Moreover, there is a statistically significant association between the presence of airflow obstruction and the development of lung cancer in women who have never smoked.

(continued)

Gender

The lung cancer mortality rate has risen more than 500% in women since 1950. Although most of this increase could be attributed to the increase in the prevalence of cigarette smoking among women since the 1940's, two disturbing facts have emerged. First, women appear to be more susceptible to carcinogens in cigarettes than men. Zang and Wynder showed that odds for the development of lung cancer were 1.2- to 1.7-fold higher in women than in men. Second, it also appears that lung cancer occurs more commonly in non-smoking women than in non-smoking men. In a case-controlled study, Zang and Wynder found that women are twice as common as men in the small group of lung cancer patients who never smoked.

Diet

Various studies in several countries have shown that low dietary intake of fruits and vegetables is associated with increased lung cancer risk and that a lower serum level of beta-carotene (a provitamin A occurring in fruits and vegetables) is associated with risk for later development of lung cancer. Persons in the lowest quartile of beta carotene intake have approximately a 50% to 100% increase of lung cancer risk as compared with persons in the highest quartile. Unfortunately, large-scale epidemiological studies assessing whether beta carotene and vitamin E might be useful as cancer chemopreventive agents did not demonstrate a reduction in the incidence of lung cancer mortality or overall mortality.

Occupational Carcinogens

Substances encountered in the workplace that are considered causative of lung cancer are listed in Table 1.

Asbestos may be the most frequent occupational cause of human lung cancer. Among asbestos workers, one death in five is due to lung cancer. The latency period (the interval between the beginning of exposure and the onset of lung cancer) is usually 20 years or more. Most cases of lung cancer in occupationally exposed workers occur in smokers with asbestosis (interstitial lung

Table 1

**Substances Encountered in Workplace Exposures
Categorized as Causative for Bronchogenic Carcinoma****Substance**

Arsenic

Asbestos

Bis(chloromethyl) ether and chloromethyl methyl ether

Chromium and certain chromium compounds (hexavalent chromium)

Ionizing radiation, gamma radiation (x-rays)

Man-made mineral fibers (certain kinds only)

Mustard gas

Nickel in nickel refining

Radon progeny (decay products)

Soots, tars, mineral oils (polycyclic aromatic hydrocarbons)

Vinyl chloride

Adapted with permission from Beckett WS. Epidemiology and etiology of lung cancer. Clin Chest Med 1993;14:8.

disease due to asbestos), and the distribution of cell types is about the same as that of smokers without asbestos exposure.

All types of radiation may be carcinogenic. There is a strong association between exposure to uranium among miners and development of bronchogenic carcinoma, particularly small-cell lung cancer. Combining smoking and uranium exposure markedly increases the risk of developing lung cancer.

Radon is a radioactive gas which occurs naturally in the earth's crust as part of the decay chain of uranium-238, and although concentrations of radon remain low in outdoor air, the gas can build up inside homes. The incidence of lung cancer increases with increasing radon concentrations in homes. It has been recently estimated that occurrence of radon in people's homes may account for one in 20 cases of lung cancer. ■

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Zang EA, Wynder EL. Differences in lung cancer risk between men and women: Examination of the evidence. *J Natl Cancer Inst* 1996;88:183-192. Reviews the apparent increased susceptibility of women to develop lung cancer.

B. A Practical Approach to Early Diagnosis and Staging

In 2001, approximately 169,500 new lung cancers will be diagnosed in the United States. Only about 25% of these patients will be candidates for resectional surgery because most lung cancer is diagnosed in late or metastatic stages. The frontline practitioner can help with the diagnosis of early lung cancer by the following approach.

Early Diagnosis

Ninety percent of lung cancer occurs in smokers. Unfortunately, due to the lingering effects of the carcinogen-induced mutations from tobacco smoke, today more lung cancer is diagnosed in former smokers than in current smokers. Occupational risks for lung cancer include asbestos and uranium mining, and exposure to volatile toxins such as benzene and certain forms of industrial ether, which are rare. Although x-ray screening and the use of sputum cytology as case finding tools for lung cancer are not recommended today by the American Cancer Society (ACS), the National Cancer Institute (NCI) or any medical society, it is likely that this dogma will be replaced by a new pragmatic approach to screening in patients at highest risk.

Late diagnosis results in high costs for cancer care in the range of \$43,758 to \$52,124 per patient, and results in a five-year survival rate of approximately 13%. Prospective studies have shown that subjects who have smoked 30 to 40 or more pack-years, and who have any degree of airflow obstruction, have a high prevalence of malignant or premalignant cells in their sputum. In one study, 1.8% of such subjects were found to have carcinoma *in situ* or invasive carcinoma; another 25% had moderate dysplasia which yielded additional carcinomas over the subsequent follow-up period. The combination of smoking with the presence of airflow obstruction results in four to six times more lung cancer than if airflow is normal, with all other risk factors being equal.

Figure 3 is a simple algorithm which stratifies the risk of patients having lung cancer. Currently, we recommend that all smokers with airflow obstruction have at least a chest x-ray and sputum cytology (if a reliable cytopathology laboratory is available) for risk assessment and case finding. Patients with abnormalities should be appropriately staged. According to the steps in Figure 4, patients with moderate or greater degrees of risk should receive at least an annual chest x-ray, or better, a yearly helical CT scan and sputum cytology. The low-radiation dose CT scan is emerging as more sensitive than the PA and lateral chest x-ray. Very likely a combination of CT and sputum cytology will become the preferred approach to early diagnosis. Currently, a prospective study is underway at the Mayo Clinic which will determine the cost and effectiveness of such an approach to the early diagnosis of lung cancer.

Staging

When lung cancer is diagnosed by sputum cytology, biopsy or resection, staging is the next step. Small-cell carcinoma is staged as central (90% of cases), or peripheral (10% of cases), and localized or disseminated. For non-small-cell carcinoma, staging is necessary to plan treatment and for prognostic purposes. Recently, a new, more detailed staging system has been offered by Mountain. It is presented in Table 2. The descriptors used in the staging system are presented in Table 3. The diagnostic tools used in staging are discussed in the next Section. Positron emission tomography (PET) scans and surgical exploration (mediastinoscopy or thoracotomy) are also used in staging. (See Section C for a discussion of the application of the new tools in the diagnosis and staging of lung cancer.)

A new healthcare initiative, known as the National Lung Health Education Program (NLHEP), proposes that simple, handheld, accurate office spirometers be used by all primary care physicians. Patients who

B. A Practical Approach to Early Diagnosis and Staging *(continued)*

should have spirometry are all smokers over the age of 45, patients with a family history of lung cancer or chronic obstructive pulmonary disease (COPD), and any patient with cough, inappropriate dyspnea, wheeze or excess mucus production. All smokers, particularly those with symptoms of airflow obstruction, should be assisted in smoking cessation. When heavy smoking and airflow obstruction are both present, the patient should be evaluated for lung cancer annually by CT scanning and sputum cytology. If moderate or severe dysplasia is found, chemoprevention should be considered. The details of chemoprevention go beyond the scope of this discussion. Today, clinical trials are underway to further evaluate the reduction in lung cancer risk from smoking cessation. Stopping smoking may result in a regression of dysplastic changes in the bronchial epithelium. ■

Figure 3

Algorithm for Determination of Risk of Lung Cancer in Smokers Versus Non-smokers

Assumes no additional risk; for example, asbestos exposure, uranium mining, or family history of lung cancer.

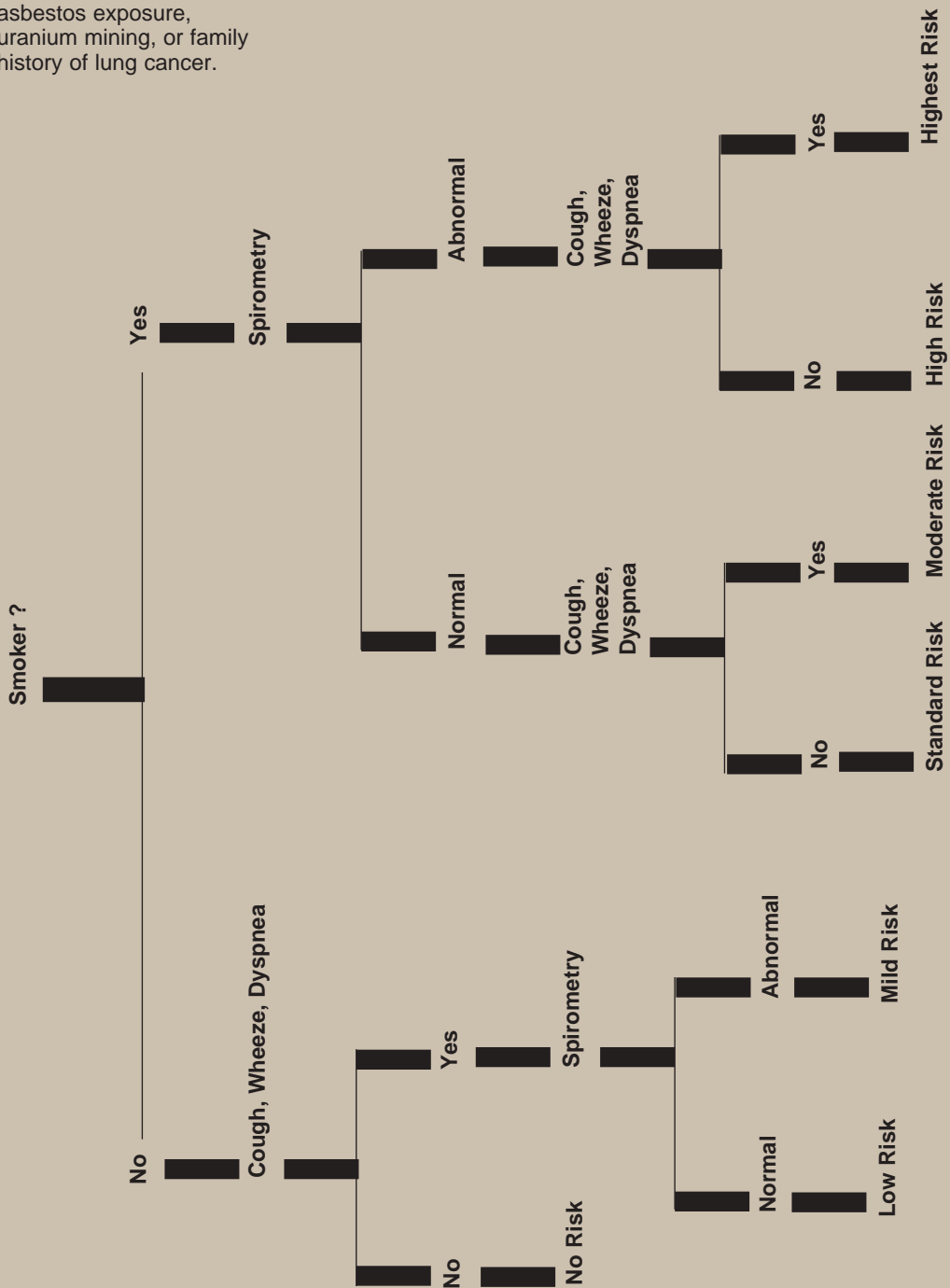


Figure 4

Diagnostic Approach to Lung Cancer

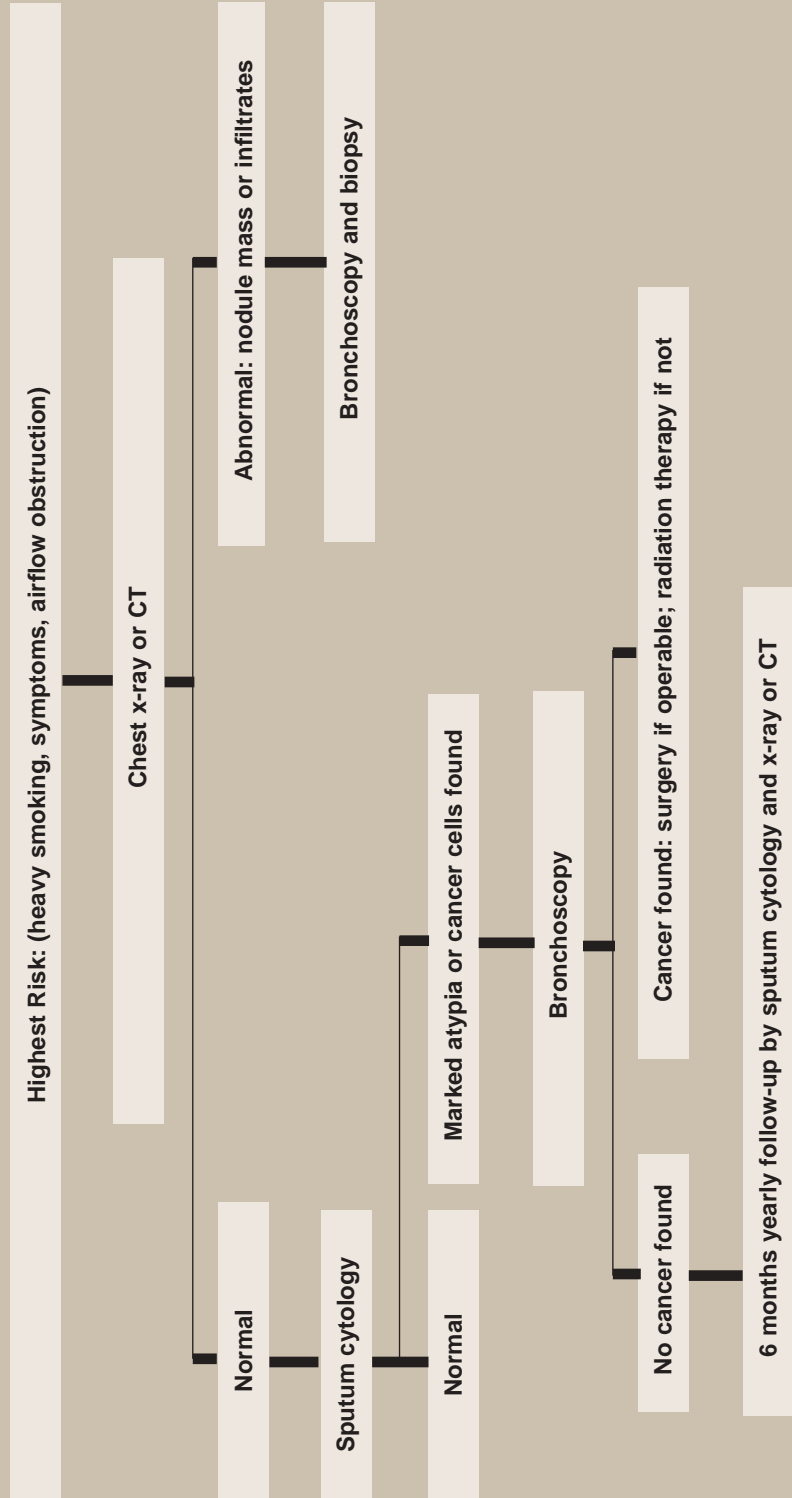


Table 2

Stage Grouping B TNM Subsets¹

| Stage | TNM Subset |
|-------|--------------------------|
| 0 | Carcinoma <i>in situ</i> |
| IA | T1N0M0 |
| IB | T2N0M0 |
| IIA | T1N1M0 |
| IIB | T2N1M0 |
| | T3N0M0 |
| IIIA | T3N1M0 |
| | T1N2M0 |
| | T2N2M0 |
| | T3N2M0 |
| IIIB | T4N0M0 |
| | T4N1M0 |
| | T4N2M0 |
| | T1N3M0 |
| | T2N3M0 |
| | T3N3M0 |
| | T4N3M0 |
| IV | Any T Any N M1 |

¹ Staging is not relevant for occult carcinoma, designated TXN0M0.

Source: Mountain CF. Revisions in the International System for Staging Lung Cancer. *Chest* 1997;111:1712, Table 3.

B. A Practical Approach to Early Diagnosis and Staging *(continued)*

Table 3

TNM Descriptors

| | | |
|---------------------------------|--|---|
| Primary Tumor (T) | TX | Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy |
| | T0 | No evidence of primary tumor |
| | Tis | Carcinoma <i>in situ</i> |
| | T1 | Tumor ≤ 3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus ¹ (i.e., not the main bronchus) |
| | T2 | Tumor with any of the following features in size or extent: > 3 cm in greatest dimension Involves main bronchus, ≥ 2 cm distal to the carina Invades the visceral pleura Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung |
| | T3 | Tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium; or tumor in the main bronchus < 2 cm distal to the carina, but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung |
| T4 | Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; or tumor with a malignant pleural or pericardial effusion, ² or with satellite tumor nodules(s) within the ipsilateral primary-tumor lobe of the lung | |
| Regional Lymph Nodes (N) | NX | Regional lymph nodes cannot be assessed |
| | N0 | No regional lymph node metastasis |
| | N1 | Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes involved by direct extension of the primary tumor |
| | N2 | Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s) |
| | N3 | Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s) |

(continued)

| | | |
|-------------------------------|----|---|
| Distant Metastasis (M) | MX | Presence of distant metastasis cannot be assessed |
| | M0 | No distant metastasis |
| | M1 | Distant metastasis present ³ |

1 The uncommon superficial tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified T1.

2 Most pleural effusions associated with lung cancer are due to tumor. However, there are a few patients in whom multiple cytopathologic examinations of pleural fluid show no tumor. In these cases, the fluid is non-bloody and is not an exudate. When these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient's disease should be staged T1, T2 or T3. Pericardial effusion is classified according to the same rules.

3 Separate metastatic tumor nodule(s) in the ipsilateral nonprimary-tumor lobe(s) of the lung also are classified M1.

Source: Mountain CF. Revisions in the International System for Staging Lung Cancer. Chest 1997;111:1711, Table 2.

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C. New Technologies in Diagnosis

The early diagnosis of lung cancer remains a difficult challenge. While newer technologies are helping to accomplish this, the majority of lung cancers diagnosed today are not curable at the time of diagnosis. Symptoms of cough and hemoptysis may occur with a small (curable) tumor if it is strategically located in an area to produce early bronchial irritation or obstruction, but these symptoms usually only appear with advanced disease.

Patients with symptoms of cough, dyspnea and wheeze, strong smoking histories and documented airflow obstruction are more likely to develop lung cancer than patients without these symptoms. This subset of patients is at high risk for lung cancer. Annual sputum cytologies can identify those with sputum atypia who are at even higher risk of developing lung cancer.

The standard diagnostic techniques over the past 15 years for identifying lung cancer include the chest x-ray, thoracic computed tomography (CT) and fiberoptic bronchoscopy. While the chest x-ray can identify nodules greater than 1 cm in diameter, smaller lesions, and those hidden by bony, mediastinal and cardiac structures are often missed. Once a lesion is identified, previous CT and x-ray studies should be reviewed, and appropriate consultation obtained. If the lesion is new, a three-month period of observation may be followed and the appropriate study repeated at this time. If observation seems inappropriate, then a biopsy to confirm a tissue diagnosis should be done.

When establishing a tissue diagnosis, the approach that is least invasive and has the highest yield should be employed. At times, a direct surgical approach is best to provide better staging and to eliminate sampling error. For newly diagnosed lung nodules and masses bronchoscopy, or transthoracic needle biopsy or video assisted thoracic surgery (VATS) are commonly used.

(continued)

Standard diagnostic techniques over the past 15 years to identify lung cancer include the chest x-ray, CT and fiberoptic bronchoscopy. A newer technique is low-radiation-dose CT to screen patients at high risk. The technique is much more sensitive in identifying non-calcified pulmonary nodules than the standard chest x-ray. Because of rapid imaging capabilities it is cost-effective.



C. New Technologies in Diagnosis

(continued)

With smaller peripheral lesions (<2 cm) transthoracic biopsy or VATS is the procedure of choice. When patients present with atelectasis or if pulmonary infiltrates suspicious for endobronchial obstruction are suspected, fiberoptic bronchoscopy is indicated.

New Technologies

Three newer techniques merit separate discussions. First, is the use of low-radiation-dose CT to screen patients at high risk for lung cancer. The technique is much more sensitive in identifying non-calcified pulmonary nodules than the standard chest x-ray. Because of the rapid imaging capabilities (20 seconds for an entire study), it is cost-effective.

Second, is the use of a special bronchoscope to detect dysplasia and carcinoma *in-situ* by tissue autofluorescence. The Lung Imaging Fluorescence Endoscope (LIFE), device takes advantage of the difference in the autofluorescence between normal and dysplastic tissue when blue light (instead of white light) is utilized. The abnormal areas are then biopsied under direct vision and sent for histopathologic evaluation. Currently, this technology is only being used in high-risk patients who have airflow obstruction, a heavy smoking history and sputum atypia.

Because of the high incidence of unsuspected advanced (stage II, III and IV) disease when lung cancer is initially diagnosed, a technique that could identify metastatic disease would be extremely helpful. CT scans may show enlarged nodes but many times pathological correlation is not good. The PET technique is more accurate than CT for the staging of lung cancer. Fluorodeoxyglucose (FDG) is administered to the patient and has increased accumulation in malignant cells. The FDG PET scan identifies malignant nodes and metastatic disease that is unsuspected by conventional imaging. Solitary pulmonary nodules that have increased uptake of FDG are more likely to be malignant and require tissue diagnosis, while those that do not enhance may be

observed for three months and then reimaged with a chest x-ray or low-radiation-dose CT. The FDG PET scan looks promising for accurate non-surgical staging of lung cancer, as well as early response to chemotherapy. ■

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D. Chemotherapy, Radiation Therapy and Other Therapies

Newer diagnostic procedures are emerging that can change the outcome of lung cancer with high expectations of cure of early-stage disease. These developments are the major message of this portion of the monograph. Improvements in lung cancer chemotherapy for advanced stages of disease also offer important new options in our goal to reduce the suffering of this country's most common fatal malignancy. This Section informs the frontline practitioner about new strategies of chemotherapy of advanced stages of disease that are available to the oncologist and pulmonologist who are involved in lung cancer chemotherapy. Radiation therapy and other treatments are briefly cited. This Section also considers measures to control pain and suffering in late-stage and metastatic lung cancer.

Chemotherapy

An excellent review of chemotherapy for lung cancer, which cites new agents with significant benefit has appeared in a special supplement. Expectations in current chemotherapy regimens for metastatic non-small-cell carcinoma are cited in Table 4. Table 5 cites the newer regimens for chemotherapy for metastatic non-small-cell carcinoma.

Differing strategies of combination chemotherapy for the various stages of disease go beyond the scope of this Section. Suffice it to say that the nihilism of the past needs to be replaced with a hopeful outlook. At least palliation is possible with chemotherapy. Today, there is a strong impetus to popularize the concept of the “thoracic oncologist” or pneumo-oncologist. This person could be a pulmonologist, thoracic surgeon, radiation oncologist or medical oncologist who has particular interest and expertise in lung cancer. Very likely, many of the complexities of managing lung cancer can be handled by such an individual, or perhaps more realistically by a team of individuals with special expertise in lung cancer diagnosis and treatment in specialized centers.

(continued)

Table 4

Expectations from Current Chemotherapy Regimens for Metastatic Non-Small-Cell Lung Cancer

| Setting | Meaningful Response Rate (>50%) | Average Survival | 1-Year Survival | 2-Year Survival | Relief of Symptoms |
|---|---------------------------------|------------------|-----------------|-----------------|--------------------|
| No therapy or failure to respond | 0% | 6 months | 10% | 0% | No |
| Older chemotherapy: etoposide-cisplatin, vinblastine-cisplatin | 20%–30% | 7–9 months | 25% | <5% | Yes |
| Newer chemotherapy: paclitaxel, docetaxel, vinorelbine or gemcitabine with a platinum | 40%–60% | 1 year | 40%–50% | 10%–15% | Yes |

Source: Ruckdeschel JC. Chemotherapy for lung cancer: New agents with significant benefit. *Prim Care & Cancer* 1998;18:27S, Table 1.

D. Chemotherapy, Radiation Therapy and Other Therapies *(continued)*

Drugs that appear to have the best activity against non-small-cell lung cancer include carboplatin, VP-16, taxines, paclitaxel and docetaxel (See Table 5). Most current regimens include carboplatin and one or more additional agents, such as vindesine or VP-16 (etoposide or gemritabine). Complete and partial response rates are in the range of 30% to 50%. Toxicity can be significant. Factors that appear to correlate best with response to chemotherapy are, extent of disease and performance status. Whether any subtype of non-small-cell lung cancer (NSLC) tumor may respond better to chemotherapy has not been demonstrated consistently. Currently, the most realistic recommendation is to use chemotherapy as part of a protocol in patients with a reasonably modest tumor burden and good clinical performance.

Chemotherapy is the treatment of choice for small-cell lung cancer. Survival has been increased from between two and three months in untreated patients to between eight and 14 months and sometimes longer in patients treated with combination chemotherapy. A variety of drug regimens are effective, but the most effective include cisplatin plus etoposide alternating with cyclophosphamide, doxorubicin and vincristine. Several studies have documented overall response rates in the range of 80% to 95%. However, only 10% of patients with small-cell lung cancer will survive for five years.

Radiation Therapy

In patients whose co-morbidity (e.g., COPD, heart disease, advanced age), precludes surgical resection, radiation therapy may be palliative and occasionally curative. Co-modality therapy using chemotherapy with radiation is sometimes advocated for small-cell lung cancer. The additional effect of radiation therapy added to chemotherapy is small.

Photodynamic Therapy

Photodynamic therapy (PDT) using new generation protoporphyrins may be curative for *in situ* carcinoma. PDT may also be used in early-stage small endobronchial cancers which have not invaded the

Table 5

Newer Regimens of Chemotherapy for Metastatic Non-Small-Cell Lung Cancer

Paclitaxel (Taxol)
Taxol-Cisplatin (Platinol)
Taxol-Carboplatin (Paraplatin)
Taxol

Vinorelbine (Navelbine)
Navelbine-Cisplatin
Navelbine-Carboplatin

Docetaxel (Taxotere)
Taxotere-Cisplatin
Taxotere-Carboplatin

Gemcitabine (Gemzar)
Gemzar-Cisplatin
Gemzar

Source: Ruckdeschel JC. Chemotherapy for lung cancer: New agents with significant benefit. *Prim Care & Cancer* 1998;18:30S, Table 4. Gemzar, Navelbine, Paraplatin, Platinol, Taxol and Taxotere are registered trade names.

D. Chemotherapy, Radiation Therapy and Other Therapies *(continued)*

bronchial cartilage and in patients who are poor candidates for surgical resection due to advanced age, tumor location or co-morbidity.

Laser Therapy, Brachytherapy and Endobronchial Prostheses

Local approaches to the treatment of malignant endobronchial lesions have included laser therapy with or without hematoporphyrin derivative and brachytherapy with endobronchial radioisotopic implantation. Endobronchial stents may be used to palliate obstruction. These treatments have been used for both *in situ* lesions as well as palliative therapy for advanced endobronchial disease.

Chemo-prevention

Another emerging approach under intense interest is chemoprevention of lung cancer in patients with high degrees of dysplasia judged by sputum cytology. The effect of vitamin E and beta carotene and the incidence of lung cancer and other cancers in male smokers appears to be unfavorable.

Palliative and Supportive Care

The emotional and physical trauma produced by lung cancer usually overwhelms the newly diagnosed patient. As physicians, our first duty is to provide patient comfort. Emotional support though honest and informative discussion is paramount. Therapeutic options must be openly presented and, while physicians must be careful not to eliminate hope, statements about “curing the disease” when it is already metastatic must be avoided. In some situations, supportive and palliative care is all that is desired and all that is appropriate.

The most troubling symptoms associated with metastatic lung cancer include pain, dyspnea, cough and hemoptysis. Opiates remain the most effective agents available to control symptoms of pain and dyspnea. The use of anti-anxiety medications and non-steroidal anti-inflammatories may have a secondary role. In the long-term management of pain, the use of oral agents is preferable to intravenous administration of medications. Commonly used opiates for control of pain and dyspnea are listed in Table 6. ■

Table 6

Commonly Used Opiates for Control of Pain and Dyspnea

| Medication | Dose |
|--|---|
| Hydromorphone hydrochloride (Dilaudid) | 2, 4, 8 mg tablets every 4 hours |
| Long-acting oral morphine sulfate (MS Contin) | 15, 30, 60, 100 mg tablets (dose based on pain control needs) |
| Immediate release oral suspension of morphine sulfate (Roxanol) | 10, 20, 30 mg/cc Start at 10 mg every 4 hours and increase as needed |
| Fentanyl transdermal system (Duragesic patches) | 25, 50, 75, 100 mcg released per hour Change patch every 72 hours |
| Oxycodone (Percocet and Roxicet also have 325 mg of acetaminophen) | 5 mg of oxycodone 1 or 2 tablets every 4 hours |

Dilaudid, Duragesic patches, Percocet and MS Contin are registered trade names. Roxanol and Roxicet are registered trademarks.

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E. When to Refer to a Specialist

The frontline physician should partner with a local or regional pulmonologist or oncologist to provide improved care for patients with lung cancer. Since patients with lung cancers that present as asymptomatic chest lesions have a much better prognosis than those diagnosed with accompanying symptoms, the frontline practitioner has an important role in screening patients with COPD and a smoking history for possible neoplasm.

Additionally, the frontline practitioner plays an important role in referring patients to a pulmonary specialist for several specific indications to help in their screening, preoperative evaluation and care of post-operative complications. Assistance in the post-operative period can be helpful in shortening the length of hospitalization and dealing with complications of surgery. After discharge, the pulmonologist can help direct the patient's rehabilitation to optimize pulmonary function.

For patients who have resection of their cancer, a long-term surveillance program is appropriate to watch for either recurrence of their initial lung cancer or the development of a second primary lung cancer. A new lung cancer will occur in 5% to 20% of previously treated patients.

Patients who undergo non-surgical treatment with either chemotherapy or radiation therapy have specific complications, such as infection related to bone marrow suppression or pulmonary fibrosis secondary to radiation therapy, which a pulmonologist can help diagnose and treat.

Finally, patients with malignant pleural effusions, persistent atelectasis, recurrent pneumonia or rapidly declining pulmonary function secondary to progression of their underlying pulmonary disease or cancer treatment program, need the assistance of a pulmonary

The frontline physician should partner with a local or regional pulmonologist or oncologist to provide improved care for patients with lung cancer. When a chest x-ray is deemed suspicious for lung cancer, the patient should be referred immediately to a specialist. CT is rapidly replacing chest x-ray in the diagnosis of early stage lung cancer.



specialist to optimize pulmonary function and to improve quality of life.

Reasons to Refer

Abnormal Chest X-ray or CT

The chest x-ray is the means by which the frontline practitioner usually detects lung cancer. As such, it is an extremely valuable diagnostic tool for the detection of lung cancer. When a chest x-ray is deemed suspicious for lung cancer, the patient should be referred immediately to a specialist. CT is rapidly replacing chest x-ray in the diagnosis of early stage lung cancer.

Hemoptysis

Hemoptysis is a special indication for referral since it may be the initial sign of lung cancer or other serious pulmonary disease, such as pulmonary embolus. Patients younger than 40 years with normal findings on a chest x-ray are at very low risk of bronchogenic carcinoma and probably can be observed closely with serial chest x-rays unless other significant risk factors, such as heavy smoking history, COPD or a positive family history for lung cancer are present.

Preoperative Evaluation

Since pulmonary complications are the most common form of postoperative morbidity experienced in patients who undergo abdominal or thoracic surgery, a careful preoperative risk assessment by a pulmonologist is important in patients who are referred for surgical treatment of lung cancer. In addition to pneumonia and ileus, patients undergoing chest surgery are at risk for lobar collapse due to central airway mucous plugging with secondary atelectasis, and hypoxia, which may result in respiratory failure. Currently, the incidence of postoperative pulmonary complications after thoracotomy and lung resection is about 30%, which is related to both the removal of lung tissue as well as alterations in chest wall mechanics. Pulmonary function measurements (spirometry) often fall dramatically in the postoperative period and do not return to preoperative levels for six to eight weeks. Careful preoperative evaluation and postoperative care by a pulmonologist is an important indication for referral, especially if a previous diagnosis of COPD is present.

Pulmonary function studies and lung scans can help to predict postoperative residual lung function after anticipated lung cancer resection. This is especially important in patients whose preoperative spirometry makes them borderline candidates for surgical resection because of the postoperative impairment to lung function that will ensue after surgery. Table 7 outlines preoperative tests which help to predict if the patient is at high risk for complications after major lung resection.

Follow-up of Patients After Surgery

After lung cancer surgery there is a significant risk of lung cancer recurrence. Accordingly, close follow-up by a pulmonologist is appropriate. One-fourth of lung cancer diagnosed in the United States each year will undergo an attempt at cure with surgical resection. A pulmonologist can help with the evaluation and management of the complications of lung cancer recurrences when they occur. During the five years after lung cancer surgery, recurrences will develop in approximately 5% to 20% of patients with stage I disease, 50% with stage II, and in 70% to 80% of patients with stage III disease. Early detection of either recurrence or a second primary lung cancer may benefit a patient by allowing an opportunity for re-resection of local or regional disease, or instituting non-curative medical therapies as soon as possible to prolong life or to help manage complications at this stage of the patient's illness to improve quality of life.

Several leading cancer treatment centers have similar follow-up programs to detect cancer recurrence. A systematic follow-up of this group of patients includes frequent chest x-rays and office visits at three to four month intervals for the first two years, at six month intervals the third and fourth postoperative years and annually thereafter. Further diagnostic testing is based on patient symptoms, physical examination findings and any new abnormalities on the chest x-ray or CT scan.

(continued)

Table 7

Preoperative Tests For Assessing Pulmonary Risk Prior to Major Lung Resection

| Test | Percent of Predicted or Actual Value ¹ |
|--|---|
| FEV ₁ % | > 60% |
| DLCO% | > 60% |
| Predicted postoperative FEV ₁ | > 800 mL |
| Predicted postoperative FEV ₁ % | > 40% |
| Predicted postoperative DLCO% | > 40% |
| VO ₂ max during exercise | >15 mL/kg/minute |

¹ These parameters are not absolute and neither guarantee a successful outcome nor rule out major resectional surgery in individual patients.

Adapted from: Ferguson MK. Preoperative assessment of pulmonary risk. *Chest* 1999;115:59S.

Pleural Effusion

In patients with documented lung cancer, a pleural effusion may be due to numerous etiologies, including malignancy of the pleura, pulmonary embolus, pneumonia, congestive heart failure and lung cancer recurrence. Prompt referral to a pulmonologist for either diagnostic thoracentesis or management of a recurrent malignant pleural effusion is appropriate. Some patients will require chemical pleurodysis to manage their recurrent effusion. Others only require periodic therapeutic thoracentesis for relief of dyspnea, depending on the clinical circumstances, health and functional status of the patient. ■

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F. Medicolegal Issues

Failure to diagnosis lung cancer is an increasingly common cause of litigation when lung cancer is missed on chest x-rays. When abnormalities such as a new solitary nodule, atelectasis, mass or infiltrate are overlooked on a chest x-ray taken for any purpose, litigation may follow. All chest x-rays should have an official interpretation by a radiologist. Be sure to view the films yourself when a nodule or infiltrate is reported by a radiologist or another specialist. When a suspicious shadow is reported by a radiologist, you would be wise to view all chest x-rays that you order. Review old films for comparison, if they are available.

Failure to evaluate and to explain the cause of hemoptysis is a common error. At a minimum, a chest x-ray, or better, a CT scan, sputum cytology and fiberoptic bronchoscopy are required unless there is a plausible explanation for the hemoptysis. A follow-up film taken at four to eight weeks should show complete clearing of any abnormality seen in the first film.

Be alert to pneumonia that fails to resolve on a chest x-ray. This is another common cause of malpractice litigation, because the underlying abnormality may be carcinoma of the lung. ■

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Frontline Assessment of Occupational Pulmonary Diseases

Pearls

Asbestosis and the Other Pneumoconioses:

- Asbestosis typically involves the lower lung zones whereas silicosis and coal workers' pneumoconiosis typically involves the mid and upper lung zones.
- Continued cigarette smoking increases the progression rate of asbestosis.
- Question the diagnosis of malignant mesothelioma of the pleura if the patient is not experiencing significant chest pain.
- Mesothelioma is linked to asbestos exposure but not to tobacco use.
- When a patient presents with interstitial pulmonary infiltrates and a biopsy showing non-caseating granuloma, take an occupational history for beryllium exposure. ■

Pearls

Occupational Asthma and Hypersensitivity Pneumonitis:

- Suspect occupational asthma when symptoms begin shortly after a patient enters a new work environment.
- Occupational agents are estimated to account for 5% to 10% of cases of adult asthma.
- After the diagnosis of occupational asthma or hypersensitivity pneumonitis, prompt and complete removal of the worker from the offending agent is essential to therapy.
- Since workers with occupational asthma may be symptom-free during office visits, referral to a specialist is often helpful for bronchoprovocation and other testing.
- Failure to recognize hypersensitivity pneumonitis may lead to irreversible pulmonary fibrosis.
- Asthma is characterized by cough and wheezing, whereas hypersensitivity pneumonitis is more likely to present with fever, dry cough and pulmonary infiltrates. Acute hypersensitivity pneumonitis is characterized by fever, cough and dyspnea within three to 12 hours of exposure. ■

G. Asbestosis, Lung Cancer and Mesothelioma

The heat and noise abatement properties of certain mineral silicates known collectively as asbestos have been recognized for several millennia, but the health hazards associated with chronic exposure have only been widely appreciated for about 50 years. Asbestos exposure results in a fibrotic lung disease termed asbestosis, in pleural scarring known as plaque or thickening, and in two prominent malignancies, lung cancer and malignant mesothelioma. All of these diseases are dependent on the amount of asbestos fibers that are inhaled (dose-dependency) and at this time only begin to appear after a latency period of at least ten to 15 years following first exposure.

Dose-dependency and latency are important characteristics of asbestos-induced lung diseases. However, it should be noted that clinicians are currently seeing the less severely affected remnant of a large spectrum of disease that began with the widespread industrial use of asbestos at the end of the nineteenth century. Patients with more severe asbestosis and pleural disease are long since dead. In the early part of the last century, latency periods for disease were considerably shorter because of a generally larger dose of inhaled fibers.

Non-malignant Lung Diseases

Inhalation of asbestos fibers can lead to pleural and parenchymal lung diseases. Pleural changes generally appear after a 10- to 15-year latency. The abnormality is manifest on chest x-rays either by circumscribed, flat pleural plaque on the parietal pleura and diaphragm or by diffuse pleural thickening, which probably represents coalescence of multiple pleural plaques. Occasionally, linear calcification will be seen within a plaque. This finding is best seen radiologically along the diaphragm on a lateral view. Rarely, pleural disease leads to pleural effusions that wax and wane. The effusions are usually exudative and may or may not contain eosinophils. Recurrent pleural effusions seem to predispose to diffuse pleural thickening. Pleural plaque, the most common pleural manifestation, is usually asymptomatic and

Table 8

**Lung Diseases and Findings Associated with
Asbestos Exposure**

| Benign | Malignant |
|---------------------|------------------------|
| Pleural plaque | Lung cancer |
| Pleural thickening | Malignant mesothelioma |
| Pleural effusions | |
| Rounded atelectasis | |
| Asbestosis | |

G. Asbestosis, Lung Cancer and Mesothelioma *(continued)*

rarely progresses. Occasionally, diffuse pleural thickening can lead to significant restrictive lung disease. None of these pleural changes are thought to presage malignancy (See Table 8).

Pleural thickening, especially along a distal intralobar fissure, can contract and form a nodule-like lesion that resembles a mass. This is referred to as “rounded atelectasis” and, while rare, is probably most often seen in association with asbestos-induced pleural disease. Open biopsy is sometimes necessary to rule out malignancy, although careful examination of the CT scan will often save the patient an unneeded surgical procedure.

Asbestosis is characterized by a chest x-ray pattern of small, non-calcified, irregular, parenchymal opacities in the lower and mid lung fields. Today, the disease has a typical latency period of at least 20 to 25 years. Concurrent pleural disease is usually present. The development of asbestosis generally requires inhalation of more asbestos fibers than does pleural disease. Asbestosis is more likely than pleural disease to progress. Once exposure has ceased, continuation of tobacco smoking appears to be the major risk factor for progression of fibrosis. Whether asbestosis itself increases the risk for lung cancer, remains controversial. Some authorities will not implicate asbestos exposure in the pathogenesis of lung cancer unless asbestosis is present, whereas other authorities see both asbestosis and lung cancer as separate dose-dependent diseases that are caused by inhalation of asbestos fibers.

Lung Cancer

Lung cancer has become the most lethal malignancy in both men and women in developed countries. As a cause of lung cancer, asbestos ranks well below tobacco use, and probably below radon gas exposure, as well. However, lung cancer induced by asbestos exposure is nearly always an occupational disease, and its causation is often complicated by heavy tobacco use in the affected individual. The two carcinogens, asbestos and

tobacco smoke, act synergistically to increase the risk for lung cancer. In this regard, smokers with significant asbestos exposure can greatly lower their risk of lung cancer with permanent smoking cessation.

Today, the combination of lung cancer and asbestos is seen most often in older construction workers who have previously worked in close proximity to asbestos for many years. Many of these workers have also been heavy smokers. A latency period of at least 25 to 30 years from the first exposure to asbestos to the appearance of lung cancer is usually present. The incidence of lung cancer is crudely dependent on intensity and duration of asbestos exposure, but clinical asbestosis need not be present to implicate asbestos in causation. Causation can also be demonstrated with a suitable exposure history and the presence of pleural plaque or with microscopic evidence of asbestosis in resected lung tissue. Some authorities have required that clinical asbestosis be present before asbestos can be implicated in causation of lung cancer. This position has some merit, primarily because other inflammatory lung diseases such as idiopathic pulmonary fibrosis also seem to be linked to an increased risk of lung cancer. However, most authorities consider the mineral, asbestos, not the process, asbestosis, to be the proper carcinogen, and attribute the increased incidence of lung cancer seen with clinical asbestosis to the dose-response effect between asbestos exposure and both lung cancer and clinical asbestosis.

In a person with significant asbestos exposure, the relative increase in risk for lung cancer is approximately five-fold. The relative risk increase for lung cancer in a non-asbestos exposed smoker with 20 pack-years is approximately ten-fold. The synergistic effect of the two carcinogens is demonstrated by multiplying the two relative risks to obtain a 50-fold increase in risk in a smoker with significant asbestos exposure.

G. Asbestosis, Lung Cancer and Mesothelioma *(continued)*

The classic description of the causal link was an increase in adenocarcinoma in the lower lobes in association with asbestosis in shipyard workers and insulators. Now, it is widely recognized that all cell types of lung cancer are increased with asbestos exposure and that the disease can appear anywhere in the lung. Many cases are overlooked for lack of an occupational history or a proper examination of the chest x-ray. Asbestos-containing products have not been manufactured in the United States for almost 25 years. Occupations most at risk today in the U.S. are end-product handlers of asbestos such as insulators, pipefitters, boilermakers, millwrights, bricklayers and general laborers, all as a result of exposure that occurred over the previous 20 to 50 years in the workplace.

Diagnosis and therapy are no different than with any other lung cancer. However, in surgical cases where asbestos is a suspected carcinogen, resected lung tissue should be processed for asbestos bodies and uncoated fibers.

Diffuse Malignant Mesothelioma

This rare tumor (15 cases per million men and two per million women) is linked to asbestos exposure in at least 75% of patients. The disease typically appears after a long latency period (>30 years) and seems to be less dependent on asbestos dose than the other diseases. Diffuse malignant mesothelioma should not be confused with benign localized mesothelioma, an even more rare condition, which is not linked to asbestos exposure.

Exposure to ionizing radiation has been implicated in sporadic cases of mesothelioma. Perhaps the clearest link to a non-asbestos cause is the association of mesothelioma with exposure to the non-asbestiform minerals, zeolite and erionite. These fibrous minerals are mostly concentrated in and around the nation of Turkey, with a few deposits in New Zealand and in the state of Oregon. The primary site for malignant

mesothelioma can be either pleural or peritoneal. The pericardium and tunica vaginalis are extremely rare sites of origin. In contrast to lung cancer, tobacco use has not been implicated in the causation of malignant mesothelioma, and should not be considered a co-carcinogen in such cases.

Chest pain, which is often pleuritic, is a prominent symptom of malignant mesothelioma. Some authorities are skeptical of the diagnosis if pain is not present. On the chest x-ray, pleural mesothelioma is manifested as a unilateral pleural effusion associated with lumpy thickening of the parietal pleura. Depending on cell type, mesothelioma can be confused with adenocarcinoma or sarcoma. When a diagnostic procedure is performed, sufficient tissue should be obtained for immunohistochemical and ultrastructural analyses. Such an approach usually requires at least a thoracoscopic biopsy. Open procedures may sometimes be necessary.

Treatment results have been dismal. The tumor responds poorly to traditional chemotherapy, and is usually so advanced at diagnosis that curative resection is impossible. Most patients die within one year of detection. A few surgeons have recently advocated radical extrapleural pneumonectomy for cure of malignant mesothelioma, but long-term survival benefit has not been demonstrated. A new potential therapeutic agent, the ribonuclease known as Onconase®, is currently under investigation for treatment of malignant mesothelioma. In general, we do not recommend surgery or chemotherapy unless the patient is entering a formal research protocol.

Other Causes of Lung Cancer

Ionizing radiation has long been known to cause lung cancer. This link was first observed almost 500 years ago in underground miners working in close proximity to uranium. In the last century, the link was further confirmed in atomic bomb survivors. Today, chronic

G. Asbestosis, Lung Cancer and Mesothelioma *(continued)*

exposure to radon gas is the predominant way ionizing radiation results in lung cancer.

Certain metals have been implicated in lung cancer. Arsenic exposure, particularly in copper smelting, was one of the first substances to be identified. Nickel, chrome and coke oven workers are said to be at higher risk of lung cancer (See Table 9). The alkylating agent, bis(chloromethyl) ether (BCME), is an intermediate in the synthesis of organic solvents, bactericides and fungicides. BCME is linked to small-cell lung cancer and has been declared a human carcinogen by the Occupational Safety and Health Administration (OSHA).

Whether other inorganic particles can cause lung cancer continues to be debated. The presence of silicosis has been linked to lung cancer in some epidemiologic studies, whereas other studies have shown no association. In all the industrial and environmental exposures tobacco smoking is often a major co-risk. Complete and permanent smoking cessation will greatly decrease the risk of lung cancer for patients with any occupational exposure, and this therapeutic intervention should always be pursued. ■

Table 9

Other Causes of Lung Cancer

| Carcinogen | Where Encountered |
|-------------------------|--------------------------------------|
| Radon gas | Home basements and underground mines |
| Arsenic | Copper smelting |
| Nickel, chrome and coke | Smelters, kilns and foundries |
| Bis(chloromethyl) ether | Organic chemical synthesis |

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H. Other Pneumoconioses

Pneumoconiosis has been defined as lung disease resulting from the chronic inhalation of inorganic dust. This Section will focus on the most common of the pneumoconioses, excluding asbestosis. Over the last half of the twentieth century, regulatory efforts in North America and Western Europe have reduced exposure to coal dust, silica and other inorganic substances, and have greatly improved morbidity and mortality among workers. Dust-related diseases, however, are becoming more of a problem in the rapidly developing industrial areas of the world.

The reaction of the lung to inhaled dust depends on multiple factors, including the chemical nature of the dust, the size and concentration of the dust particles and the duration of exposure. Individual susceptibility to the effects of an inhaled substance is an important, but difficult to quantify factor. Some workers may have severe pulmonary impairment, while others with similar exposure are not affected. Tobacco smoking is an important multiplying factor.

Silicosis

Silicosis is a parenchymal lung disease caused by inhalation of silica dust in the form of free silica dioxide. Silica is the second most common element in the earth's crust. As many as one million Americans have industrial exposure in mines, quarries, sandblasting, stone finishing, foundries, ceramics manufacturing and a variety of other occupations (See Table 10). The pathogenesis of silicosis is incompletely understood. Silica particles from 5 μ to 10 μ deposit in the proximal airways and are cleared by the mucociliary defense system. They are usually not pathogenic. Smaller particles ranging in size from .5 μ to 5 μ reach the alveoli and are ingested by macrophages. This causes the release of inflammatory mediators and an influx of lymphocytes, polymorphonuclear leukocytes and plasma cells, which eventually leads to the classic hyaline nodule, an acellular core of hyalinized collagen surrounded by macrophages, plasma cells and fibroblasts. Silica crystals may be seen at the center. The

Table 10

Occupations Associated with Silica Exposure

Abrasive manufacture

Ceramics manufacture

Foundry workers

Quarrying

Sandblasting

Tunneling

Use of silica flour (cosmetics, abrasives and paint extenders)

Adapted from: Fraser RS, Muller NL, Colman N, Paré PD. Diagnosis of Diseases of the Chest. W. B. Saunders Company, Philadelphia, PA 1999 pp 1077, 2387.

smaller nodules may coalesce forming larger masses that may go on to cavitate.

Clinical Features

The diagnosis of silicosis is based on the finding of diffuse nodular or interstitial infiltrates on the chest x-ray of exposed workers. Workers are usually asymptomatic, but may complain of dyspnea or chronic cough. Four clinical presentations may be seen in patients with silica exposure: (a) chronic simple silicosis, (b) complicated silicosis, (c) acute silicosis and (d) silicotuberculosis.

Chronic Simple Silicosis

Chronic simple silicosis is diagnosed by x-rays. Chest x-rays show small rounded densities with sharp margins, primarily in the upper lobes, measuring from 2 mm to 10 mm in diameter. Hilar adenopathy occurs frequently and lymph nodes may show “egg shell” calcifications. Patients are asymptomatic and have normal to near normal pulmonary function. If further exposure is eliminated, the disease does not progress.

Complicated Silicosis

Complicated silicosis (also called conglomerate or progressive massive fibrosis) is characterized radiographically by nodules greater than 10 mm in diameter that may coalesce and produce mass-like densities. Radiographic changes slowly progress over time and retraction of the upper lobes leads to compensatory over-expansion. Clinically, patients complain of cough, sputum production and progressive dyspnea. Pulmonary function tests show a restrictive or mixed restrictive and obstructive dysfunction. There is no specific treatment. Progression leads to hypoxemia, cor pulmonale and death. In the laboratory, positive antinuclear antibody and rheumatoid factor tests are frequently present, suggesting the presence of an autoimmune mechanism.

Acute Silicosis

Acute silicosis is caused by intense exposure to silica over a relatively short period of time. It has been encountered in sandblasting, ceramic workers and miners who drill holes in rock for inserting explosives.



Patients present with symptoms of dry cough, fever, dyspnea and weight loss. Chest x-rays show ground glass or fibrotic opacities in the upper lung fields. The pathological findings on biopsy resemble those of alveolar proteinosis. An association with tuberculosis and histoplasmosis is known to occur. Patients do not respond to corticosteroids, and progressive respiratory failure often leads to death in months to years.

Silicotuberculosis

There is a four- to six-fold increase in the incidence of tuberculosis among patients with silicosis. Silica is toxic to macrophages, preventing ingestion and killing of mycobacteria. Infection with *M. tuberculosis*, *M. avium* and *M. kansasii* may be encountered. Antimycobacterial chemotherapy is less effective in patients with silicosis.

Treatment and Prevention

There is no specific treatment for silicosis. The primary goal is prevention by reducing exposure to silica dust and screening workers regularly with pulmonary function studies and chest x-rays. The incidence of lung cancer is probably not increased in non-smoking workers exposed to silica dust. Patients with silicosis should have annual tuberculin skin tests, and workers with positive reactions should have a comprehensive evaluation to rule out active tuberculosis. If studies are negative for active disease, workers should be treated for four months with isoniazid and rifampin, or for 12 months with isoniazid alone. Lung transplantation has rarely been used in patients with acute silicosis.

Coal Worker's Pneumoconiosis

Exposure to coal dust causes chronic bronchitis, coal worker's pneumoconiosis (CWP), and progressive massive fibrosis (PMF). Respiratory illness in coal miners is now seen less frequently in North America and Western Europe due to an increase in mechanization in the mines and measures to reduce exposure to coal dust. It is still a significant health problem in Russia, South Africa and China.

Coal dust is composed primarily of carbon, with varying amounts of minerals, metals and organic compounds. Although a small amount of silica is present in coal dust, the development of CWP depends on the deposition of carbon in the lungs. Deposition of coal dust in the lungs stimulates the migration of macrophages, neutrophils, epithelial cells and fibroblasts into alveoli and respiratory bronchioles, causing an inflammatory reaction. This leads to the development of nodules (coal macules) ranging in size from 1 mm to 5 mm. With continued exposure, the nodules enlarge and coalesce, leading to the development of macroscopic black, rubbery masses that occasionally cavitate.

Radiographic Findings

Chest x-rays in CWP show small nodular infiltrates predominately in the upper lobes measuring from 1 mm to 10 mm in diameter. The margins are typically less well defined than in silicosis. The nodules rarely calcify. In PMF, the nodules are 1 cm or larger in size, and may raise the suspicion of bronchogenic carcinoma. Cavitation due to tissue necrosis may occur with or without mycobacterial infection.

Clinical Features, Treatment and Prevention

Chronic cough with sputum production may occur in non-smoking coal workers. A significant decrease in pulmonary function may occur in patients with progression to PMF or who smoke tobacco. There is no specific treatment for CWP other than eliminating exposure to coal dust and tobacco smoke.

A number of immunological abnormalities have been associated with CWP, including elevated serum IgA and IgG levels, antinuclear antibodies and rheumatoid factor, suggesting an immunological mechanism involved in the pathogenesis. Miners with rheumatoid arthritis may have Caplan's Syndrome, characterized by the presence of multiple large rounded nodules in the lungs. These nodules may cavitate. Rarely do they spontaneously disappear. Caplan's Syndrome may also

be seen in rheumatoid arthritis patients exposed to silica, asbestos, iron and aluminum powder.

Siderosis

Siderosis is caused by the deposition of iron (primarily iron oxide) in the lungs. It is seen most commonly in electric arc welders. It may also be seen in silver polishers, iron ore miners, other miners, steelworkers and foundry workers. Siderosis is primarily a radiologic diagnosis and chest x-rays show multiple small reticular-nodular opacities scattered diffusely throughout the lungs. Under light microscopy, deposits of iron oxide are seen within macrophages in the peribronchial and perivascular lymphatics. There is no convincing evidence that iron oxide alone leads to fibrosis.

Siderosis is generally considered to be a benign condition, and is not associated with respiratory symptoms or significant physiological impairment unless there is concomitant exposure to other minerals such as silica or asbestos. This has been called into question by investigators who recently observed mild obstructive and restrictive pulmonary dysfunction independent of the effect of tobacco smoking.

Berylliosis

Beryllium is a rare metal, used as an alloy to increase the tensile strength of other materials. Exposure may occur in ceramic workers, beryllium processors, aerospace workers and in dental laboratory technicians (See Table 11). Exposure to beryllium can cause dermatitis, acute pneumonitis and chronic beryllium disease (berylliosis).

Berylliosis is a chronic, multisystem, granulomatous disease caused by exposure to beryllium dust or fumes. Berylliosis is clinically, histologically and radiographically indistinguishable from sarcoidosis. It is the result of a delayed-type hypersensitivity reaction and is characterized pathologically by noncaseating granulomas. Not all workers exposed to beryllium become sensitized, and not all sensitized workers go on to develop berylliosis. There may be a latent period of from two to 15 years before respiratory symptoms

Table 11

Occupations Associated with Berylliosis

Aerospace industry

Beryllium miners and processors

Ceramic workers

Dental laboratory technicians

Manufacture of x-ray tubes

Adapted from: Kotloff RM, Richman PS, Greenacre JK, Rossman MD. Chronic beryllium disease in a dental laboratory technician. *Am Rev Respir Dis* 1993;147:205-207, and Balkissoon RC, Newman LS. Beryllium copper alloy (2%) causes chronic beryllium disease. *J Occup Med* 1999;41:304-308.

appear. Dyspnea on exertion and a dry, non-productive cough are usually the presenting symptoms. Physical examination may be normal, or crackles may be heard at the lung bases.

Radiographic Findings

Radiographic abnormalities are non-specific. The most common x-ray presentation is that of diffuse fine granular mottling. Poorly defined nodules of moderate size may also be seen and may coalesce. Hilar adenopathy is seen less commonly than in sarcoidosis. Thin-sectioned computed tomograms (CT's) have been shown to be more sensitive than chest x-rays in detecting chronic beryllium disease.

Diagnosis

The clinician should consider the diagnosis of berylliosis when confronted with a patient with chronic cough, progressive dyspnea, a restrictive defect on pulmonary function testing and x-ray and pathological findings suggesting sarcoidosis. The employment history should be reviewed in detail as to beryllium exposure. The beryllium lymphocyte proliferation test provides a reliable method of distinguishing sarcoidosis from berylliosis. This test has been positive in over 90% of the cases of berylliosis.

Treatment and Prevention

Patients with berylliosis respond to treatment with corticosteroids, but there is no convincing evidence that they are curative. Dust control is the most important element of prevention. Periodic chest x-rays and pulmonary function studies are recommended. Using the beryllium lymphocyte proliferation test will identify workers at risk. Approximately 50% of workers with a positive test will go on to develop chronic beryllium disease. It is unknown whether or not removal of the worker from exposure will prevent the later development of berylliosis. ■

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I. Occupational Asthma

Occupational asthma has become the most prevalent occupational lung disease in developed countries. The incidence of asthma worldwide is 5% to 10%. Recent studies suggest that 10% to 15% of new cases of adult asthma are due to occupational exposure. This common disorder poses important health and vocational problems for workers. Individuals may develop disabling respiratory symptoms due to agents in the workplace, and optimal therapy requires removal of affected workers from exposure to the causative agent. Occupational hygiene, medicolegal and disability issues also make occupational asthma a major concern for industry and for society.

Occupational asthma is defined as variable airflow limitation or bronchial hyperresponsiveness associated with conditions in a particular work environment, and not with stimuli outside the workplace. Asthma may develop for the first time due to occupational exposure, or pre-existing asthma may be aggravated in the workplace setting. Individuals with established asthma may develop increased symptoms due to immune responses to new workplace allergens, or increased symptoms may occur due to non-specific reactions to irritants in the work environment.

Occupational asthma due to sensitization to allergens develops following a latency period after exposure. A similar syndrome may develop without latency following exposure to high concentrations of irritant gases or chemicals. This type of reaction has been named the reactive airways dysfunction syndrome (RADS) or non-immune occupational asthma.

Etiology

Over 250 agents have been reported to cause immunologic occupational asthma. Major categories of allergens include animals and animal products, plant and wood dusts, biologic enzymes, isocyanates, anhydrides, metals, fluxes, latex, drugs and other

Table 12

**Occupational Asthma:
Examples of Workers at Risk and Causal Agents**

| Occupational Work | Causal Agents |
|--------------------------|--|
| Animal handlers | Urine protein, dander |
| Bakers | Wheat, rye, buckwheat; mites, a-amylase, hemicellulas, glucoamylase, papain, soybean |
| Chemical workers | Sulfonechloramides, azo dyes, ethylenediamine, anthraquinone |
| Coffee or tea workers | Green coffee, tea dust |
| Detergent workers | Bacillus subtilis, esperase |
| Entomologists | Locusts, blowfly |
| Fishery workers | Sea squirts, prawns, crab |
| Insect handlers | Bee, moth, cockroach, river flies, locust, meal worm, screw worm |
| Insulators | Urea foam |
| Metal processors | Platinum salts, cobalt, nickel |
| Oil extractors, crushers | Castor beans |
| Pharmaceutical workers | Pepsin, flaviastase, penicillin, cephalosporins, phenylglycine acid chloride, spiramycin |
| Plastic workers | Phthalic anhydride, trimellitic anhydrides, diisocyanates |
| Printers | Arabic gum, gum acacia |
| Processors | Prawns, hoyo, egg powder, tobacco leaf |
| Spice and enzyme workers | Garlic powder, papain, pectinase, trypsin, karaya gum, maiko |
| Woodworkers | Quillaja bark, red cedar, Douglas fir, African zebra wood, iroko |

Adapted from: Alberts WM, Brooks SM. Advances in occupational asthma. Clin Chest Med 1992;13:281-302.

chemicals. Table 12 lists some occupations at risk and examples of common agents that may lead to sensitization.

A number of specific factors have been identified that increase the risk of development of occupational asthma. Both the sensitizing potential of the allergen and the degree of workplace exposure are independent risk factors. Smokers and individuals with known atopy are known to be at increased risk in many settings. Sensitization often occurs rapidly, but may develop over months to years.

Non-immune asthma (RADS) may develop without latency following exposure to high concentrations of toxic gases such as chlorine or ammonia, usually in accidental circumstances. Whatever etiologies or mechanisms lead to the new onset of asthma symptoms, similar changes in pathologic findings and non-specific bronchial hyperreactivity are present.

Workplace dusts and pollutants acting as irritants may also increase symptoms in patients with pre-existing asthma. This complication is potentially preventable with appropriate industrial hygiene measures.

Diagnosis

Occupational asthma is so common that possible workplace origin must be considered in any adult with new onset asthma or sudden worsening of pre-existing asthma. The diagnostic work-up must first confirm a clinical diagnosis of asthma with appropriate findings on history, physical examination and pulmonary function testing. Then a careful search for potential environmental allergens in both home and work is essential. The patient may work in an industry in which asthma is known to be a common hazard and exposure is obvious (e.g., wood dust exposure in carpentry). In other individuals, the exposure may be subtle, or the offending agent uncommon. In these patients, a possible workplace etiology for symptoms may be suspected

because of the onset of symptoms that correlate with a new work environment. Improvement of asthma symptoms during weekend and holidays with worsening on return to work also strongly suggests an occupational cause. Work-related allergic nasal or eye symptoms may be further clues that wheezing is occupational in origin. If occupational asthma seems likely, reference to published lists of industrial allergens and potential workplaces may then help to identify the responsible agent.

If occupational asthma seems likely, Material Safety Data Sheets can be obtained from employers to learn what potential allergens exist in a specific work environment. The responsible agent may also be identified through reference to comprehensive published lists of industrial allergens and potential workplaces where they may occur.

If asthma is strongly suggested by history, but the patient is free of wheezing on examination with normal spirometry, pulmonary consultation may be of value to establish the diagnosis of asthma and its cause. The spirometric response to inhaled methacholine can be measured to demonstrate the presence of bronchial hyperreactivity, a characteristic feature of asthma. Peak flow measurements may be of value to establish an occupational cause for asthma if patients are optimally motivated and cooperate fully for reliable results. Peak flows measured at the beginning and end of the workday may show significant falls after workplace exposure. These tests may be misleading, however, as asthma symptoms may begin hours after the worker has returned home and may persist until the following day. An excellent means to evaluate a suspected occupational cause is to perform morning and evening peak flow testing during a week at the workplace, followed by a week at home.

Allergy specialists can identify potential workplace antigens by skin testing or serum IgE antibody studies. However, these tests do not prove a cause-and-effect relationship to asthma symptoms. For definitive diagnosis, specific bronchial hyperreactivity can be tested by spirometric studies before and after inhalation challenge to the suspected occupational allergen. Any testing of inhaled allergens must be done in carefully controlled conditions, with facilities for emergency treatment readily available.

Treatment and Prevention

The pharmacologic therapy of patients with occupational asthma is no different than that of any other asthmatic patient. The unique measure in dealing with this disorder is control of the workplace exposure. Environmental improvements may allow employees with pre-existing asthma to remain in a work area without increased asthmatic symptoms. However, for those individuals with allergic sensitization to workplace antigens, any level of exposure cannot be tolerated. Asthma treatment may minimize symptoms, but patients who remain in the same job and continue to be exposed to the same causal agent, generally worsen with time. Since minimal concentrations of allergens lead to immunologic responses, optimal therapy for the patient with occupational asthma is complete removal from any antigen exposure. Unfortunately, despite removal from exposure, many patients do not recover fully from occupational asthma and continue with symptoms and the need for medication. Since the duration of symptoms prior to leaving the workplace is a prognostic factor in the degree of recovery patients may achieve after withdrawal from exposure, early removal of patients from the workplace is essential.

It is necessary for physicians, employers and governmental agencies to recognize occupational asthma as a common industrial problem. Workplace

risk for all employees must be minimized to decrease the number of individuals sensitized to industrial allergens. Employers must be sensitive to employee needs by shifting them, if possible, to areas free of the offending allergens and minimizing workplace irritants to protect those with pre-existing asthma. For physicians, the challenge is to be alert for the possibility of unsuspected occupational asthma in individuals with new onset of respiratory symptoms, and to identify links between patient symptoms and work exposures. Public health officials must make information available to both physicians and industry relative to known possible causes of industrial asthma. Finally, those involved in evaluation and adjudication of disability must understand the individual and sometimes unique problems of patients with occupational asthma, such as multiple triggering factors in asthma. ■

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J. Hypersensitivity Pneumonitis (HSP)

Hypersensitivity pneumonitis (HSP) is a clinical/pathological syndrome caused by inhalation of agents to which the host has developed cell-mediated sensitivity. In the United Kingdom, this disorder is generally referred to as extrinsic allergic alveolitis, but since the process clearly involves more than “alveolitis,” HSP seems a preferable label.

The prototype of HSP is “farmer’s lung,” which was described in the 1930’s and found to be caused by inhalation of moldy hay contaminated with the spores of thermophilic actinomycetes. Since that time, numerous other causal agents have been found to produce HSP, including antigens derived from various microbes, plants and animals as well as several inorganic chemicals and elements which presumably act as haptenes.

For the clinician, awareness of HSP is critical since many cases are related to exposure at work or at home. Failure to recognize this disorder may result in disabling symptoms, and if undiagnosed, can lead to irreversible, fibrotic lung injury.

Pathogenesis, Etiology and Risk Factors

Because precipitating antibodies to offending agents were found in farmer’s lung, it was originally thought that the pathogenetic process of HSP involved a type III antigen-antibody complex deposition in the injured tissue. However, subsequent studies have indicated that the primary pathological process entails cell-mediated hypersensitivity to the offending antigen, a type IV reaction. The immunopathogenesis is believed due to repeated exposure to an antigen with the eventual evolution of “hypersensitivity.” Then, upon re-exposure, an immune-mediated reaction occurs with characteristic clinical x-ray and physiological findings. Yet, the rapid onset of acute HSP suggests there may be mechanisms other than pure type IV delayed hypersensitivity.

The list of causes of HSP expands continuously. Rather than simply note all of the recognized agents, the known causal elements are delineated according to the usual sites or modes of exposure in Table 13.

In the case of most of the microbial antigens, the microorganism is **not** believed to be an "infectious pathogen" in the classical sense. Rather, it merely provides an antigen which evokes the damaging "immune" process. However, in the case of some of the water-borne mycobacterial exposures including *Mycobacterium avium complex* (MAC), or the rapid-growing mycobacteria (RGM), the potential virulence of these bacilli raises the possibility of simultaneous HSP and infection.

In most cases of plant-derived HSP, the etiologic agent is not present when the crop is harvested. Rather, the microbes proliferate when the crop is stored in a warm damp environment.

Environmental Risk Factors

In nearly all cases of HSP, exposure to the offending agent occurs in an enclosed, indoor environment, which presumably means that a critical concentration of antigen is necessary.

Comprehensive data on the incidence of HSP are not available. However, for certain industrial or other situational exposures, rough attack-rates have been derived. Estimates of the cumulative incidence of farmer's lung disease among agrarian populations has ranged from 2% to 9%. By strict criteria, the annual incidence of farmer's lung in one series was 44 per 100,000. By contrast, the cumulative incidence of HSP among pigeon fanciers is higher, 6% to 15%. Among those who keep parakeets, 1% to 7% report findings consistent with HSP.

(*continued*)

Table 13

Agents Associated with Hypersensitivity Pneumonitis (HSP)

Worksite-related Agents**Organic Antigens****Conditions Caused by Microbes**

| | |
|---------------------------------------|--|
| Farmer's lung | <i>Micropolyspora faeni</i> <i>Aspergillus</i> species <i>Streptomyces albus</i> |
| Malt worker's lung | <i>Aspergillus</i> species |
| Wood worker's lung | <i>Penicillium chrysogenum</i> <i>Alternaria</i> species <i>Merulius lacrymans</i> <i>Saccharomonospora viridis</i> <i>Cryptostroma corticale</i> <i>Aureobasidium pullulans</i> Wood dust |
| Cheese worker's lung | <i>Penicillium casei</i> |
| Sugar cane worker's lung (Bagassosis) | <i>Thermoactinomyces vulgaris</i> |
| Detergent worker's lung | <i>Bacillus subtilis</i> |
| Cork worker's lung | <i>Penicillium frequentens</i> |
| Coffee worker's lung | Coffee bean dust |
| Cotton worker's lung (Bysinnosis) | Bract of cotton flower |
| Wheat worker's lung | Wheat weevil |
| Metal worker's lung | Rapid growing mycobacteria |

Inorganic Antigens Associated with HSP**Non-microbial**

| | |
|-------------------------------------|-----------------------|
| Paints, resins, plastics | Diisocyanates |
| Insulation, polyurethane | Trimellitic anhydride |
| Vineyard sprayer's lung (fungicide) | Copper sulfate |
| Pesticide/insecticide | Pyrethrum |

Home or Work-related Agents**Organic Antigens****Microbial**

| | |
|--|--|
| Humidifier lung | <i>Acanthamoebae castellani</i> <i>Acanthamoebae polyphaga</i> <i>Naegleria gruberi</i> <i>Thermoactinomyces candidus</i> |
| Bird breeder's lung (budgies, pigeons) | Bird droppings |
| Rodent handler's lung | Urinary antigens, serum, pelts |
| Hot tub/spa lung | <i>Mycobacterium avium</i> complex |

Inorganic Antigens Associated with HSP**Non-microbial**

| | |
|------------------------------|---------------|
| Polyurethane foam insulation | Diisocyanates |
|------------------------------|---------------|

Host Risk Factors

A potentially confusing aspect of HSP is that some, but not all, persons exposed to the offending agents become ill. While this may to some extent reflect the extent of exposure, it is clearly more complex. Indeed, with nearly all of the well-described HSP syndromes, there is an obvious component of individual susceptibility. Although the data are variable, there is a broad pattern suggesting genetically controlled immunological variables as an important element of risk. Other seeming components of HSP vulnerability include the general observation that non-smokers are at relatively **greater** risk and pregnancy/parturition seems to heighten the hazard for those exposed to pigeons.

Diagnosis

Due to obvious similarities to “infectious” pneumonia, the most important element in diagnosis of HSP is awareness. Once a clinician gives consideration to HSP, there usually are readily ascertainable clues that point to the diagnosis. Some of the more useful elements are briefly noted in Table 14. Various components of the diagnostic process are discussed below.

Clinical Features

Clinical features vary according to acuity and exposure. The “acute” syndrome is thought to be associated with intense exposure following sensitization. An influenza-like illness with dry cough, dyspnea, wheezing or congestion, fever, malaise, anorexia and/or myalgias may appear between three and 12 hours following exposure. Physical findings include fever, tachypnea, tachycardia and lower zone crackles. Evidence of consolidation or pleural friction rubs have not been reported.

In cases of “chronic” HSP, symptoms of respiratory inadequacy dominate over the influenza-like acute syndrome. Chronic cough, exertional dyspnea, and wheezing or congestion may be present, even away from exposure. In cases with extensive fibrosis, cyanosis and right heart failure (cor pulmonale) may develop. Digital

Table 14

Clinical Clues Pointing to Hypersensitivity Pneumonitis

Historical

Repeated episodes of an influenza-like illness

Episodes of an influenza-like illness in temporal relation to specific occasions or locations

Illness among workers without evidence of transmission to home contacts

Influenza-like illness without a typical prodromal pharyngitis

“Atypical pneumonia” unresponsive to antibiotics

Laboratory/Radiographical

“Atypical pneumonia” with no microbiological or serological evidence of usual pathogens

Miliary shadows on chest x-rays or CT scans in individuals not at risk for tuberculosis

Diffuse ground glass shadowing without air-bronchograms on CT scan

clubbing may be seen in some cases, particularly in pigeon breeder's lung disease.

Routine Laboratory Studies

Routine laboratory studies are of limited utility. Early, the chest x-ray may be interpreted as normal. Occasionally there may be a diffuse, finely nodular pattern which is similar to "miliary" tuberculosis. A neutrophilic leukocytosis, not eosinophilia, is common. Arterial blood gas studies typically reveal hypoxemia or widened alveolar-arterial oxygen gradients with reduced carbon dioxide levels consistent with hyperventilation. Spirometry characteristically demonstrates a restrictive pattern with proportional reductions in both the forced expiratory volume in one second (FEV₁) and the forced vital capacity (FVC).

Obviously, the constellation of findings described above is quite non-specific. To confirm a diagnosis of HSP, the studies noted below may be required.

Special Studies

Bronchoalveolar lavage (BAL) obtained via fiberoptic bronchoscopy characteristically (but not diagnostically) yields highly elevated numbers and percentages of T-lymphocytes. In acute HSP, there may also be a significant BAL neutrophilia. Increased mast cells have also been reported. Notable as well, is the absence of pathogenic bacteria or fungi on special stains and/or culture. Therefore, there is an inability to recover microbes on BAL points to HSP or other diffuse lung disorders.

Although precipitating antibodies to potential offending agents are no longer believed to play a central role in the pathogenesis of HSP (See Table 13), their presence may be helpful in diagnosis. Serum panels are available to confirm exposure to various microbes or antigens that may be involved with HSP. However, it must be stressed that simply having precipitating antibodies to the putative etiologic agents does **not** confirm their role in HSP. Broadly, such tests may be seen to be quite sensitive for HSP due to a particular microorganism,

(patients with HSP due to the agent always have antibodies) but not very specific (a large number of individuals may have developed antibodies to the agent without now or previously having HSP).

Computed Tomography (CT), Lung Scans

Computed tomography (CT) lung scans are substantially more helpful than routine x-rays in identifying HSP. Particular findings that suggest HSP include mixed reticular and finely nodular shadows, “ground glass” opacification without prominent air bronchograms and, with repeated episodes, the appearance of interstitial fibrosis. In some cases in which bronchiolitis is present with HSP there may be focal areas of air trapping with hyperlucent zones. A normal high-resolution CT scan in the presence of clinical findings makes HSP highly unlikely. While these radiographic findings may be typical of HSP, no particular abnormality or constellation of findings is diagnostic of HSP. However, in patients with classical histories of exposure and other findings as noted above, a characteristic CT scan may provide a presumptive diagnosis of HSP without open lung biopsy.

Pulmonary Physiology Testing

Pulmonary physiology testing may provide supportive, but not diagnostic evidence. In acute HSP, a restrictive pattern with reduced diffusion capacity (DLCO), is seen. The resting arterial oxygen level is low, and considerable desaturation is seen with exercise. Air trapping is seen in association with bronchiolitis. Airflow obstruction may be seen in some cases, usually with minimal or modest response to bronchodilators.

Lung Biopsy

Lung biopsy may be required in cases in which the above studies are equivocal or nondiagnostic. Due to sampling error and the relative non-specificity of findings, transbronchial biopsy is inadequate. Open lung biopsy is required, usually by video assisted thoracoscopy (VAT) to confirm or exclude HSP.

(continued)

The histopathology of HSP is somewhat non-specific, although the findings may be of utility either by demonstrating another disorder or by revealing features characteristic of HSP. Acute HSP is typified by a mononuclear (lymphocyte/plasma cell) alveolitis in a bronchocentric pattern with associated noncaseating, epithelioid granulomas. In this form it is difficult to distinguish HSP from berylliosis (a variant of HSP), or sarcoidosis. Neutrophils, eosinophils or features of vasculitis are not typical. Birefringent foreign bodies may be seen in cases with various types of inorganic dust inhalation.

In chronic HSP the pathology shifts toward an interstitial infiltrative process featuring lymphocytes, plasma cells and macrophages. There may be bronchiolar inflammation including intraluminal granulation tissue or bronchiolitis obliterans. Granulomas tend to subside with chronicity, and interstitial fibrosis with honeycombing develops in longstanding cases.

The differential diagnosis for patients with suspected HSP is extensive. A list of those conditions likely to be confused with HSP is displayed in Table 15.

Treatment and Prevention

If HSP is proven or suspected, avoidance of the presumed site or source of the offending agent is the most important element of care. However, if the exposure occurs at the workplace, e.g., farming, complete avoidance may have unacceptable financial implications. For persons with strong attachments to their pets/hobbies this option may be emotionally problematic. Clearly, the critical issue here is whether continued exposure will inevitably lead to progressive constitutional symptoms and/or respiratory insufficiency. In some series, farmers or pigeon fanciers who remained in or returned to these exposures have not experienced inevitable progression in disease. In some instances this may reflect “tolerance” associated with continued exposure, while in others, improved

Table 15

Common Disorders Which Can Mimic Hypersensitivity Pneumonitis

| Condition | Comments |
|--|--|
| Lifeguard's lung | Probably contamination of aerosols by lipopolysaccharide (LPS) derived from gram-negative rods in water |
| Silo-filler's disease | Exposure to nitrogen dioxide from fermented corn or alfalfa |
| Sarcoidosis | An idiopathic disorder, more similar to chronic hypersensitivity pneumonitis |
| Berylliosis | Beryllium workers may develop hypersensitivity to the metal with an illness that actually is a form of hypersensitivity pneumonitis |
| Eosinophilic pneumonia | An acute or sub-acute process with x-ray and clinical features similar to acute hypersensitivity pneumonitis; eosinophils in peripheral blood or bronchoalveolar lavage should distinguish |
| Allergic bronchopulmonary Aspergillosis (ABPA) | Typically associated with refractory asthma, ABPA may have features of acute pneumonia with fever, cough and dyspnea |
| Infectious pneumonias | "Atypical pneumonias" including psittacosis, legionellosis, mycoplasma and nontuberculous mycobacterioses |

ventilation or the use of respiratory protective devices may have ameliorated the problem.

In cases with an identified source of contamination (e.g., a humidifier, swamp cooler, air conditioner or hot tub) attempts may be made to “sterilize” the system. However, this may be difficult to achieve or sustain. Such measures should be undertaken only in concert with environment hygienists. In general, avoidance is preferable.

In acute HSP, the clinical x-ray physiologic abnormalities tend to subside within five to ten days following termination of exposure. With a simple acute episode, a return to normal may be expected. However, with repeated or protracted episodes, there is an increasing probability of prolonged or even chronic functional and physiological derangements. Thus, a vital issue is which patients should receive corticosteroid therapy. Currently agreed upon indications include:

1. Acute respiratory insufficiency with hypoxemia refractory to supplemental oxygen,
2. Patients with sub-acute disease that is not improving despite cessation of exposure, and/or
3. Persons with chronic disordered physiology consistent with bronchiolitis.

Typical dosage of prednisone would be 1 mg/kg body weight daily for two to four weeks, with a rapid taper when physiological and symptomatic improvement is seen. ■

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K. When to Refer to a Specialist

Occupationally-related lung disorders are frequently unrecognized because of the difficulty in linking the patient's physical findings with the workplace exposure. Furthermore, many illnesses may be due to unrecognized occupational factors. Therefore, there are few reliable estimates of the proportion of work-related conditions encountered in the primary care setting. A 1995 survey of family practice physicians reported that 9% of their time was spent dealing with occupationally-related health problems. Because of the extremely complicated nature of occupational lung disease, including complex patient history, physiologic impairment, work-related injury, legal issues and requirements for long-term follow-up, referral to a pulmonologist is frequently necessary (See Table 16).

A careful history is necessary to diagnose occupational lung disease. Referral to a pulmonologist or allergist may assist in making this diagnosis. Specifically, occupational asthma develops after a variable period of asymptomatic exposure to a sensitizing agent at work. Exposure in the workplace to airborne dusts, gases, vapors or fumes can result in "irritant-induced asthma." To make this diagnosis, it is important first to confirm that a patient does indeed have asthma. Then these questions must be answered: Is there a history of childhood allergies or asthma? Did the patient have asthma that went into remission and now resurfaced after workplace exposure, or was the reoccurrence of asthma secondary to exposure to a respiratory infection in the community? Is there a family history of asthma? Does the patient's employment history correlate with the onset of respiratory illness?

Pneumoconiosis (See Sections G and H) usually presents in a subtle manner with chronic symptoms, such as cough or dyspnea and may be confused with COPD. Patients with such conditions may have experienced exposure to inorganic dusts 20 to 40 years prior to their presentation, making the distinction between smoking-

Table 16

When to Refer a Patient to a Specialist

Occupational asthma

Hypersensitivity pneumonitis

Persistent cough, wheeze or dyspnea associated with occupational lung disease

Pneumoconioses

Superimposed mycobacterial infection

Asbestosis

Other work-related interstitial lung diseases, i.e., siderosis

Need for supplemental oxygen therapy

Cor pulmonale and pulmonary hypertension related to occupational lung disease

related COPD and occupationally-related lung disease difficult. By contrast, symptoms of hypersensitivity pneumonitis are more readily correlated with exposure to the work environment. This association can be delineated with a careful history and job description, (See Section J).

Etiology

After it is established that a patient has asthma and an occupational cause is suspected, it is important to identify the specific workplace exposure which may be the setting initiating this illness. A careful history and evaluation of workplace Material Safety Data Sheets may give clues to agents to which the patient has been exposed.

Diagnosis

Although the diagnosis of occupational lung disease may be inferred from the history, it must be confirmed objectively. The diagnosis of occupational asthma, for example, should be documented by serial measurements of spirometry or peak flow at the workplace. Referral for skin testing may be useful in determining the atopic status of the patient. Assessment of workplace symptoms, mainly cough and dyspnea, and complications such as pulmonary fibrosis or cor pulmonale should be evaluated by a specialist.

Interstitial lung disease and more complex pleural-parenchymal lung disease will require more thorough evaluation, sometimes including lung or pleural biopsy for diagnosis. Referral of these patients to a pulmonary specialist can expedite the evaluation when the etiology of the patient's illness is unclear and distinction is needed between pre-existing COPD, asthma or idiopathic pulmonary fibrosis and a new occupationally-related lung disease.

Treatment and Prevention

After diagnosis of occupational lung disease is confirmed, the patient should be advised to stop exposure to the offending agent. Medical therapy is often required for asymptomatic patients with

occupational asthma, but the strategy for management of the disease is no different from that for other patients with asthma, i.e., removal of environmental sensitizing agents, management of airway inflammation and symptomatic treatment with oral and inhaled bronchodilator medication. Patients with active interstitial lung disease may require lengthy anti-inflammatory treatment necessitating referral to a specialist to both initiate a therapy plan and to periodically monitor the patient's medication use and response to therapy. In all cases, medical therapy of the patient's disease should not be considered an alternative to environmental control and avoidance of the inciting agent.

The natural history of occupational asthma and hypersensitivity pneumonitis may be one of complete resolution after exposure is terminated. However, the disease may persist as chronic asthma or interstitial lung disease. This leads to long-term treatment and serious long-term consequences for the patient and the workplace. The worker is faced with either losing his/her job or risking disability with continued exposure. Therefore, referral to a pulmonologist can help to clarify the diagnosis, the degree of impairment and to outline a treatment plan. ■

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L. Medicolegal Issues

In each of the five previous monographs of this series, this Section carried advice for the frontline physician about avoiding litigation concerning poor clinical outcomes due to alleged physician negligence. Such advice is presented in the lung cancer portion of this monograph.

In occupational lung disease, medical and legal issues often go beyond allegations of negligence by the managing physicians and focus on industrial and occupational liability. Thus, this Section includes a broader scope of medical and legal issues.

Asbestos-induced Lung Diseases

The diseases caused by inhalation of asbestos fibers are generally acknowledged to be acquired in the workplace. This link between disease and occupation often results in litigation over compensation for injuries sustained. In this Section, we offer important aspects of this issue that will help the frontline physician in evaluating patients with possible occupationally-induced lung disease. In all cases, obtaining a careful occupational history is paramount. In many cases, referral to a specialist in pulmonary or occupational diseases will be helpful.

Asbestosis

Compensation for asbestosis comes through product liability suits or workers' compensation and is usually obtained once agreement has been reached on the diagnosis. However, diagnosis of asbestosis may be disputed because there are many other causes of pulmonary fibrosis. For this reason, a diagnosis based on chest x-ray findings alone is usually not enough. The patient must be carefully interviewed and examined to rule out other causes of pulmonary fibrosis before a confident diagnosis of asbestosis can be made. In some cases, laboratory testing to rule out other conditions, e.g., connective tissue disease, may be necessary. The minimal requirements for the diagnosis of asbestosis include a suitable exposure history with a latency period of at least 15 to 20 years and the

presence of typical parenchymal opacities on chest x-ray with no other explanation for the x-ray findings. Pleural plaque or thickening, which will be present in most cases of asbestosis, strengthens the diagnosis. Other authorities require the presence of crackles on lung examination, restrictive ventilatory defect, a low diffusing capacity (DLCO) on pulmonary function tests and digital clubbing. In our opinion, the more stringent definition that includes all of the above criteria is rarely met, and only by patients with advanced disease. As such, requiring all of the above criteria is not a useful case finding tool.

Lung Cancer

In cases of lung cancer with previous asbestos exposure, the issue of causation is nearly always complicated by a history of tobacco smoking, which is a more potent carcinogen than asbestos. Consequently, most authorities require more than a history of occupational exposure before they will implicate asbestos in the causation of lung cancer. The causation link is usually conceded for patients with evident asbestosis who develop lung cancer. Assignment of causation to asbestos for patients with only pleural plaque is more difficult and many medical authorities will not testify to a link in these cases. However, if asbestos and not asbestosis is the carcinogen, a suitable exposure history with pleural plaque should be sufficient to assign causation in cases of lung cancer even when tobacco smoking has been present as a co-carcinogen. Finally, asbestos can be implicated if histopathology of resected lung tissue shows typical fibrosis with ferruginous bodies or uncoated asbestos fibers. The latter can best be demonstrated with electron microscopy.

Malignant Mesothelioma

Tobacco smoking is not thought to cause diffuse malignant mesothelioma. Causation is generally easy to establish for patients who develop this disease following sufficient exposure to asbestos, but a contentious debate often arises in establishing the diagnosis of malignant mesothelioma. Depending on cell type, diffuse malignant mesothelioma can be confused with

adenocarcinoma or sarcoma. Special immunohistochemistry and ultrastructural analyses of resected tissue are usually necessary and even then the diagnosis may remain in doubt. When this happens, the clinical presentation and course are helpful. Malignant mesothelioma usually presents with prominent chest pain. It rarely metastasizes until late in its course, and progresses rapidly and inexorably to death from respiratory failure and inanition, usually within one year of diagnosis.

In summary, establishing a causal link between asbestos exposure and lung cancer requires a careful occupational history, a suitable latency period and some objective evidence, either on chest x-ray or in histopathology, to corroborate the exposure history. In many cases tobacco use will be present as a co-carcinogen. In cases of diffuse malignant mesothelioma, the diagnosis should be firmly established and the exposure history documented. Objective evidence of asbestos exposure on either chest x-ray or by histopathology is helpful, but not always necessary, to implicate asbestos in causation of malignant mesothelioma.

Pneumoconiosis

Historically, workers with CWP (coal worker's pneumoconiosis or black lung disease), silicosis and asbestosis have been involved with litigation to receive compensation for disability. The frontline physician should be alert to the possibility that a patient with chronic lung disease manifested by nodular and/or interstitial chest x-ray may have a work-related illness and be entitled to compensation. The clinician must have a high index of suspicion, take a careful occupational history and consider referral to a pulmonologist to confirm or rule out pneumoconiosis.

Chronic beryllium disease is rare, but can masquerade as sarcoidosis. The signs, symptoms, chest x-ray, pathology and response to corticosteroid therapy are identical, and the potential for litigation for failure to

diagnose and to refer to the appropriate specialist is considerable.

Occupational Asthma

Medicolegal issues in occupational asthma concern primarily the liability of employers for inadequate protection of workers from potential respiratory hazards or for insufficient employee education relative to those hazards. Litigation may also relate to the degree to which an industrial exposure is causative in a worker developing new or worsening asthma symptoms. Issues of respiratory disability and appropriate compensation are also common medicolegal questions. Careful pulmonary specialist evaluations and appropriate lung function testing are often central to these complex disputes.

Hypersensitivity Pneumonitis

The most common issues surrounding HSP relate to occupation-associated situations. In these cases, aspects of workers' compensation, liability litigation, responsibility for remediation and return to the work site may be of major importance. Hence, careful documentation and consultation with occupational/environmental or pulmonary medicine specialists may be indicated. ■

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M.
Postscript and
Biographical
Sketches of
Authors

But for smoking, there would be little interest in a disease as rare as lung cancer. Lung cancer was so unusual in the early part of this century that it was considered a curiosity. The keen observations of Alton Ochsner began to draw attention to smoking as the major cause of lung cancer. In 1959, a landmark article written by Doll and Hill appeared in the *British Medical Journal*, and Wynder and Graham authored a classic article in the *JAMA*. We now recognize that tobacco smoke is responsible for apparently 90% of all lung cancers. Unfortunately, the link between smoking and lung cancer has been denied by the tobacco industry until recently. The continued promotion of tobacco to our youth is a sad commentary about how we ignore the health of our future citizens.

Even occupational lung diseases may have a smoking component. Some have viewed “black lung” as “a disease invented by Congress to compensate smokers who work in mines!” Certainly, there are real workplace health hazards. But the greatest hazard of the workplace is active and passive smoking.

Let us consider the following selected quotations about smoking:

*More would I, but my lungs are wasted so
That strength of speech is utterly devoid me.*
Shakespeare in *King Henry IV*

*To cease smoking is the easiest thing I ever did; I ought
to know because I've done it a thousand times.*
Mark Twain

The best way to stop smoking is to carry wet matches.
Anonymous

*Usually we trust that nature has a master plan. But
what was it she expected us to do with tobacco?*
Bill Vaughan

*Tobacco is a dirty weed. I like it,
It satisfies no normal need. I like it,
It makes you thin, it makes you lean,
It takes the hair right off your bean
It's the worst darn stuff I've ever seen.
I like it.*

Graham Lee Hemminger

*Smoking is very bad for you and should only be done
because it looks so good.
People who don't smoke have a terrible time finding
something polite to do with their lips.*

P. J. O'Rourke

As ye smoke, so shall ye reek.

Anonymous

*I read in the Reader's Digest that cigarettes are bad for
you. So I had to give up reading the Reader's Digest.*

Anonymous ■



(continued)

Co-Editor

**Thomas M. Hyers, MD**

Dr. Hyers received his MD degree from Duke University in 1968. He completed his medical internship at Cleveland Metropolitan General Hospital in 1969 and then served three years in the U.S. Public Health Service at the National Institutes of Health, where he helped coordinate early studies of urokinase and streptokinase in the treatment of pulmonary embolism. He did his medical residency and chief residency at the University of Washington in Seattle, and then completed a pulmonary fellowship at the University of Colorado in Denver. He served for five years as a faculty member at the University of Colorado, Denver Veterans Administration Medical Center, and then moved to St. Louis University where he was Director of the Division of Pulmonology and Pulmonary Occupational Medicine from 1982 to 1997.

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Today, Dr. Petty also remains active in teaching, patient care and research. He enjoys fishing, small game hunting and playing with his three "kids" and eight grandchildren.

(continued)

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Dr. Duke was born in Ocala, Florida and attended Tulane University School of Medicine in New Orleans, Louisiana, obtaining his medical degree in 1960. After a two-year stint in the U.S. Air Force, he completed his postgraduate training in pulmonary medicine at Tulane in 1967.

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Dr. Good received his MD degree from the University of Kansas and completed a medical internship, residency and chief medical residency at the University of Kansas. He then completed a three-year pulmonary and critical care medicine fellowship at the University of Colorado. The next four years he remained on the faculty at the University of Colorado as an Assistant Professor of Medicine and was Medical Director of both the Respiratory Therapy Department and the Critical Care Unit at Denver General Hospital. His scientific interests include management of critical patients with acute respiratory failure, pleural diseases and asthma. He is a fellow of the American College of Physicians and the American College of Chest Physicians (ACCP), and served as the Governor for the states of Colorado and Wyoming for the ACCP from 1988 to 1994.

He currently is in the private practice of pulmonary and critical care medicine in south Denver and is Medical Director of the Swedish/Columbia Critical Care Unit. He remains actively involved in clinical research, teaching medical students and residents and in continuing medical education programs.

(continued)

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Mike Iseman grew up in Fremont, Nebraska, receiving his undergraduate degree from Princeton University, where he majored in history and played football. He attended Columbia University's College of Physicians and Surgeons, receiving his MD in 1965. He received his training in internal medicine and pulmonary medicine in New York City between 1965 and 1972.

Joining the faculty of the University of Colorado in 1972, he spent ten years at Denver General Hospital. Then he moved to National Jewish Hospital in 1982 as Head of the clinical mycobacterial disease program. His primary research interests relate to drug-resistant tuberculosis and disease due to the "atypical mycobacteria." He currently is Professor of Medicine in the Division of Pulmonary Medicine and Infectious Diseases. He is also Editor-in-chief of the *International Journal of Tuberculosis and Lung Diseases*.

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Dr. Levine and his wife, Shirley, have five children and currently five grandchildren. His hobbies are hiking, biking and visiting grandchildren.

(continued)

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Richard Matthay received his AB degree from Stanford University in 1963. He served as an officer in the Army Medical Service Corps in Texas, Louisiana and Korea from 1963 to 1965. In 1970, he received his MD from Tufts University School of Medicine. He completed internship, residency, and pulmonary and critical care medicine fellowship at the University of Colorado Medical Center between 1970 and 1975. He has been Associate Director and Training Director of the Pulmonary and Critical Care Section at Yale University School of Medicine since 1975. In 1994, Dr. Matthay was awarded the Boehringer Ingelheim Chair of Medicine at Yale.

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