# Welcome

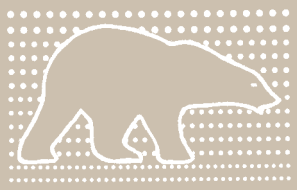
Welcome to the Snowdrift Frontline Treatment Monographs. The authors welcome you to this series of monographs that aim to disseminate worldwide new knowledge about common pulmonary disorders. We offer our messages to anyone who will find them useful in the diagnosis and treatment of the many pulmonary 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 Common Pulmonary Presentations

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## Preface

Most patients go to see their doctors because they have specific complaints. When people are suffering, whatever the cause, they want relief, either by treatment or by reassurance, and the sooner the better. The reasons why patients seek medical help have been catalogued, and complaints originating in the chest are always among the most common. Certain aches, pains, and functional upsets are often ignored for long periods, but the onset of cough, chest pain, or shortness of breath is frightening, signifying—as it may and as most people realize—grave internal mischief that warrants prompt attention. Equally worrying corollaries of this classic triad of chest-based symptoms are hemoptysis, wheezing, and stridor. The origin, differential diagnosis, and management of these six everyday symptoms, which impel patients to visit their frontline physicians, are described in this monograph.

In addition, this mongraph includes four other types of pulmonary presentations that frontline physicians are likely to have to cope with. The first is what to do about a positive tuberculin skin test reaction, which may have been detected as part of a routine office check up or in a survey carried out in school or the work place. Next, we discuss how to manage two common pulmonary disorders, pleural effusion and solitary pulmonary nodule, either of which may be an accidental chest x-ray finding or picked up in a film taken to evaluate a patient who presented with pulmonary symptoms. Finally, we review the perplexing problem of unresolved pneumonia, which nearly always turns up in someone initially thought to have ordinary community-acquired bacterial pneumonia, in whom a follow-up chest x-ray after antibiotic treatment reveals a persistent pulmonary infiltration.

As in our other monographs in this series, *Frontline Treatment of Common Pulmonary Presentations* aims to provide concise information of practical value that will assist frontline physicians in their daily struggles to deal with the multitude of patients who arrive in the office with many different kinds of problems. We do not intend this book as a compendium of "must-follow" guidelines. The contents can best be viewed as recommendations that were formulated by a group comprised of both academic and practicing specialists, all of whom have had considerable experience in the care of patients with pulmonary disease. We hope that readers will profit from the lessons that we have learned in our practices, and that, in turn, your patients will be the final beneficiaries. ■

*The Authors*

**Pearls**

- A thorough medical history is the best way to make a diagnosis and to guide the selection of diagnostic studies.
- All patients with presumed infectious pneumonia must have follow-up chest x-rays to verify that the infiltration has resolved. If not, further work-up is required.
- In nonsmokers with normal chest x-rays the most common cause of cough is post-nasal drip. Remember, too, that chronic cough occurs in 10% to 20% of all patients taking angiotensin converting enzyme inhibitor drugs.
- Cough, not wheezing, may be the predominant symptom in patients with asthma. In those who present with wheezing, beware of asthma mimics.
- One half of patients with chronic cough due to gastroesophageal reflux disease have none of the classical symptoms of reflux.
- Chest pain of cardiac origin, with the exception of pericarditis, is seldom worsened by breathing; in contrast, chest pain of respiratory origin, especially pleurisy, characteristically is worsened.
- The major diagnostic goal in massive hemoptysis is localization of the bleeding site so that surgical removal or embolization can be performed.

- Tuberculin skin testing should be regarded as a diagnostic aid but is not to be relied on for ruling in or out active tuberculosis.
- Immediately following thoracentesis, patients may experience relief of dyspnea and chest pressure, but hypoxemia may persist for several hours.
- Pleural effusions of moderate size or larger in a symptomatic patient with presumed pneumonia require a thoracentesis.
- Solitary pulmonary nodules due to tuberculosis and histoplasmosis commonly calcify, whereas those due to coccidioidomycosis do not.
- Review of old x-rays is extremely useful in establishing chronology of disease, thereby avoiding expensive invasive procedures. ■

**Communication skills lie at the heart of the physician-patient relationship.**

## A. Approach to the Patient

### Introduction

Patients go to see their doctors for a variety of reasons, only one of which is to seek relief from disturbing signs and symptoms of medical disease. As every primary care physician knows, a large number of patients who visit doctors do not have detectable, much less serious, underlying disease. Indeed, the most common single diagnosis in general medical practice is "no disease." One explanation for the lack of correlation between the presence of complaints and visits to physicians lies in the important distinction between **disease** (the biologic abnormality) and **illness** (the person's unique experience of whatever disease he or she has and the behavior resulting from it). Thus, some patients have little or no disease but manifest severe illness, and conversely, some patients have severe disease but display little or no illness. When patients are first seen, however, their physicians do not know the cause of their complaints and are obliged to look for whatever sickness that may be responsible. This Section, then, provides some guidelines on how to approach the patient, especially during the all-important first encounter. Although the emphasis is placed on patients who have pulmonary disease, the general approach applies to other disorders as well.

### Communication

Communication skills lie at the heart of the physician-patient relationship. Doctors must know how to communicate effectively with patients and their families, including how to deal with the psychosocial, preventive, and rehabilitative aspects of illnesses. Most physicians, though, are better at obtaining a medical history and assessing compliance than in learning about patients' understanding of their illnesses, and in ascertaining the patients' emotional response to their disease. Doctors find it easier and are more comfortable with communications related to the medical aspects of a particular disease than with the psychosocial complications associated with the same condition. Communication is more than words; it is an interaction of intellectual and medical give and take

that creates an atmosphere whose quality has enormous impact on the subsequent behavior of the patient. Effective communication requires calm surroundings, a relaxed environment, and plenty of time, prerequisites that are not always easy to provide in a busy practitioner's office.

## Medical History

There is much more to the medical history than asking questions and recording answers, especially by questionnaire; the expanded concept is reflected in the alternative term, the face-to-face medical interview, with its verbal and nonverbal nuances. From this interaction, especially the first one, physicians and patients learn a lot about each other, and this knowledge has considerable influence on subsequent trust, understanding, concern, and compliance. Even in the contemporary era of high technology and reliance on laboratory studies, more diagnoses are made on the basis of a medical history than by any other method. Of equal importance is the fact that the differential diagnosis derived from the initial medical history determines which laboratory tests will be ordered.

**Present Illness:** The three cardinal symptoms of lung disease are dyspnea, cough, and chest pain; other common manifestations are hemoptysis and wheezing. All are discussed in subsequent Sections. Regardless of which complaint the patient comes in with, each must be explored in detail. **When** did the symptom begin and under what circumstances; when does the symptom occur now, at night, on awakening, or during exercise? **What** brought the symptom on to begin with; moreover, what makes it worse or relieves it now? The time-course after onset provides important clues to etiology; is the complaint intermittent, progressive, or evanescent? Also crucial is **how** the symptom is affecting the patient's life style; are daily activities unrestricted, or are there limitations to going to work, attending school, or shopping and other household tasks? The intensity of pain needs to be documented; is it bearable or does it force the sufferer to stop what he

or she is doing? Similarly, the **severity** of breathlessness should be quantified; how many stairs are manageable or how much exercise is tolerable? Finally, the consequences of cough should be ascertained; is it productive, and if so, what is produced; does it wake the patient up at night?

It is equally important to ask questions about associated systemic features, such as fever, sweats, weight loss, weakness, and fatigue, which are important corollaries of chronic disease, especially infection and malignancy. No evaluation of pulmonary symptoms is complete without a detailed history of smoking habits. If the patient says "no" when asked "do you smoke?" the next question must be "did you ever smoke?" Exposure to cigarettes is customarily quantified as the number of "pack-years," which is calculated by multiplying the average number of packages of cigarettes smoked daily by the number of years they were consumed.

**Family and Social Histories:** Household contact with a family member known to have tuberculosis or some other respiratory infection may account for similar disease in another family member. A positive family history provides important clues to the presence of both common (e.g., asthma) and rare (e.g., hereditary hemorrhagic telangiectasia) pulmonary diseases. Knowledge of the site(s) of residence helps to diagnose endemic fungal diseases, and a history of travel suggests possible diseases that may have been encountered in other countries. It is important to determine if there are risk factors for infection with human immunodeficiency virus; questions concerning homosexual activity among men and use of drugs by injection should be asked.

**Occupational History:** Though often included as part of the social history, the occupational history is such a key part of the medical history of patients with lung disease that it should be considered separately. The

relationship between the patient's complaints and work should be queried. Has there been exposure to dusts, chemicals, or fumes? Are other workers similarly afflicted? For completeness, the physician should be concerned about the patient's entire environmental exposure, not just at work. Careful sleuthing about hobbies, recreational activities, and contact with pets and other animals may furnish solutions to mysterious medical diseases.

**Past History:** Many pulmonary diseases tend to recur, especially infections like tuberculosis and many malignancies. Thus, questions should be asked about previous illnesses, operations, and trauma involving the chest and/or lungs. One of the most useful aids in evaluating patients who present with pulmonary symptoms and an abnormal chest x-ray is a previous chest x-ray. Thus, all patients should be asked about past x-ray examinations, and every effort should be made to obtain the actual films, not just the reports. Finally, a history of current and past medications should be obtained with specific identification of any allergies.

## Physical Examination

A key element in the initial evaluation of every patient is a complete physical examination. Subsequent examinations may be more abbreviated as the situation warrants. This Section emphasizes the detection of signs indicative of pulmonary disease, but finding abnormalities of other organs is equally important in evaluating patients with different complaints.

**Pulmonary Findings:** Examination of the lungs still incorporates the basic techniques of inspection, palpation, percussion, and auscultation. The results of these modalities are complementary and, as shown in Table 1, allow the examiner to infer the presence and type of many common pulmonary disorders. "Crackles" is the new generic term for the discontinuous sounds that used to be called "rales." Moreover, all former descriptors of rales, such as

## Table 1 Classic Physical Findings in Some Common Pulmonary Disorders

| Disorder | Inspection | Palpation | Percussion | Auscultation |
|---|---|---|---|---|
| Bronchial asthma | Hyperinflation; use of accessory muscles | Impaired expansion; decreased fremitus | Hyperresonant; low diaphragm | Prolonged expiration; inspiratory and expiratory wheezes |
| Pneumothorax (complete) | Lag on affected side | Absent fremitus | Hyperresonant or tympanitic | Absent breath sounds |
| Pleural effusion (large) | Lag on affected side | Decreased fremitus; trachea and heart shifted away from affected side | Dullness or flatness | Absent breath sounds |
| Atelectasis (lobar obstruction) | Lag on affected side | Decreased fremitus; trachea and heart shifted toward affected side | Dullness or flatness | Absent breath sounds |
| Consolidation (pneumonia) | Possible lag or splinting on affected side | Increased fremitus | Dullness | Bronchial breath sounds; bronchophony; pectoriloquy; crackles |

"fine," "dry," and "wet," have been discarded. The continuous sounds, wheezes and rhonchi, have also been lumped together in current terminology, but retain some pathogenic utility: a wheeze is an uninterrupted musical sound that generally originates from narrowing of medium or small airways, whereas, a rhonchus has a gurgling quality that usually indicates secretions rattling around within large airways. Other useful signs are a pleural friction rub, a leathery creaky sound, which is often localized and intensified by pressure with the stethoscope, and a mediastinal crunch, which sounds like pulmonary crackles (rales), but which are synchronous with the heart beat and can be heard during breath-holding. A variety of other sounds may occasionally be heard that originate within the chest wall, such as the rubbing of hairs underneath the stethoscope, the crackling of subcutaneous emphysema, and the popping of fractured ribs. It should be emphasized that the absence of physical signs does not exclude the presence of significant lung disease. A complete evaluation requires a chest x-ray, and sometimes specialized examinations (e.g., pulmonary function tests or computed tomography) are needed.

**Extrapulmonary Findings:** Clubbing of the digits occurs in many different disorders, including chronic pulmonary infiltrative and suppurative diseases, and most importantly in bronchogenic carcinoma. Cutaneous lesions are less specific, but may also indicate certain underlying lung diseases. The examiner should listen to the heart carefully, palpate the abdomen for enlarged organs or masses, and search the extremities for edema or other findings. Any abnormality on physical examination may be of great help in deciphering the cause of the patient's complaints.

**Diagnosis**

The diagnosis of "no disease" can often be confidently made from the medical history alone. Moreover, when significant disease of the lungs or neighboring structures is present, the medical history provides important clues as to its origin and what types of studies should be obtained to confirm its presence or absence. The results of the physical examination supplement those from the history in deciding which diagnostic tests to order. For suspected respiratory disease, the first diagnostic test is usually a chest x-ray. For suspected cardiac disease, the first test is usually an electrocardiogram. From then on, the workup proceeds or referral is indicated as discussed later in this monograph and in other medical textbooks.

**Treatment**

Making a diagnosis alone seldom satisfies a sick person. Patients want relief of the complaint they went to see the physician for in the first place, and that means treatment. Here again, the distinction between disease and illness must be remembered. The doctor must treat the underlying disease, for example antibiotics for community-acquired bacterial pneumonia, but must also attend to the accompanying illness, which might manifest intolerable pleurisy, nausea and vomiting, or intractable cough. Treatment options should be discussed thoroughly, and in certain instances, such as before carrying out invasive procedures or administering toxic drugs, signed consent must be obtained. Because successful treatment, particularly as an outpatient, requires the patient's active cooperation, education and explanation concerning exactly what must be done is vital; enlisting the support and collaboration of a family member or friend is helpful.

**Medicolegal Concerns**

As emphasized in all our previous monographs for primary care physicians, efforts should constantly be directed toward **preventing** medical litigation. Patients must be kept informed about what tests are being

ordered and why, what treatment is being recommended, what the alternatives are, and what plans are being made for follow-up. Perhaps the most frequent cause of medicolegal awards, ones that concern all patients, not just those with respiratory disorders, is failure to document adequately in the medical record all contact with, the advice given to, and the rationale for the approach to a patient and his/her particular problem. Another common mistake is neglecting to inform the patient, **in writing,** how to contact the doctor should the need arise.

**Summary**

The onset of symptoms, especially those arising in the chest, is one of the chief reasons patients seek help from their physicians. Evaluation of presenting complaints begins with a medical interview and is followed by a thorough physical examination. From these fundamental maneuvers, physicians formulate a clinical impression about what and where the abnormality is, and if necessary, test this hypothesis by ordering laboratory tests, radiographic examinations, or other diagnostic procedures. Subsequent evolution of the condition can also be assessed simply and inexpensively through the medical history and physical examination, and, when needed, by selected confirmatory tests. ■

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**Spirometry is useful in assessing pulmonary mechanics which become abnormal in both obstructive and restrictive ventilatory disorders.**

## B. Dyspnea

### Introduction

Dyspnea, the sensation of breathlessness or inadequate breathing, is the most common complaint of patients with cardiopulmonary diseases. Evaluation of the complaint is complicated by the fact that in many circumstances, shortness of breath is a normal consequence of exertion. Furthermore, perception of shortness of breath varies considerably among individuals at the same level of fitness and work and even in the same individual performing comparable work at different times. In disease states, perception of dyspnea can vary greatly among individuals. Consequently, assessment of the subjective sensation of dyspnea must balance the concepts of physiologic work and ventilatory demand with the individual's perception of breathlessness. This Section provides an overview of basic concepts on the mechanisms of dyspnea, lists those disease states in which the complaint is encountered, gives a diagnostic pathway for the evaluation of the complaint, and concludes with treatment options.

### Basic Mechanisms

The physiologic system that regulates ventilation is extraordinarily complex. The headquarters for the spontaneous initiation of breathing and its control resides in the medulla and to a lesser extent the pons in the form of discrete aggregations of interconnected "respiratory" neurons. The medullary centers receive afferent neural input that originates in sensors that monitor the rate and depth of breathing and the levels of oxygen and carbon dioxide in the bloodstream; chief among these are receptors in the muscles and tendons that participate in breathing; chemosensitive cells in the carotid and aortic bodies; and receptors situated in the upper and lower airways and elsewhere in the lungs themselves. Afferent input also comes directly from chemosensitive cells close to the surface of the medulla that respond to changes in pH, which in turn is regulated largely by the level of $PCO_2$, in the nearby cerebrospinal fluid. Efferent and presumably coordinated instructions to the muscles engaged in

breathing come through two pathways in the spinal cord: the medullary control centers send messages through axons in the ventral portion, whereas the cortex communicates through axons in the more dorsal corticospinal tract.

Neural information about breathing that is received and integrated in the medulla and pons clearly is relayed to the cortex, where the sensation of dyspnea is perceived, but the anatomic pathways are poorly described. Increased afferent activity from one or more of the sensors that monitor the various acts of breathing (e.g., muscle contraction, airflow, and lung expansion) and their consequences (e.g., levels of $PO_2$ and $PCO_2$ in the bloodstream) are almost certainly involved. The exact mechanisms underlying dyspnea is also largely unknown and probably varies with different medical conditions and may differ depending on which one or more receptors are involved.

The major physiologic components that are thought to contribute to dyspnea are shown in Table 2. The sense of effort is mediated primarily through cortical function and is basically a subjective assessment of afferent input or ventilatory need. Both peripheral mechanoreceptors and chemoreceptors influence the medullary center directly and can increase its efferent activity. Of the mechanoreceptors, muscle receptors in the intercostals seem to play a major role in enhanced afferent signals to the medullary and cortical centers. Airflow in the larger airways, particularly when there is airflow obstruction, results in enhanced afferent activity from lung and airway receptors. Dyspnea seems to occur most commonly when afferent input from peripheral receptors is enhanced or when cortical perception of respiratory work is excessive.

*(continued)*

## Table 2 Main Physiologic Components of Dyspnea

| |
|---|
| Mechanoreceptors (respiratory muscles) |
| Hypoxia (carotid and aortic bodies) |
| Airflow (airway and parenchymal receptors) |
| Changes in $PCO_2$/pH (medullary center) |
| Irritants (airway and parenchymal receptors) |
| Medullary center (afferent input and efferent output) |
| Cortical function (sense of effort) |

## Table 3 Severity Scale of Dyspnea

| Grade | Degree | Characteristics |
|---|---|---|
| 0 | None | Only with strenuous activity |
| 1 | Slight | When hurrying on level ground or climbing a slight incline |
| 2 | Moderate | Needs to walk more slowly than others of the same age or has to stop for breath when walking at own pace on level ground |
| 3 | Severe | Stops for breath after 100 yards or after a few minutes |
| 4 | Very severe | Housebound or dyspnea when dressing or undressing |

**Disease States**

Abnormalities of cardiopulmonary function are most commonly associated with dyspnea. All diseases of lung parenchyma and airways can cause dyspnea. These include COPD, asthma, fibrotic and infiltrative diseases, and pulmonary vascular disease. With the exception of asthma, most of these conditions first cause dyspnea with extreme exertion. As the disease progresses, dyspnea appears with less exertion, and finally is manifested at rest. Asthma constitutes the most important exception and is characterized by episodic onset of dyspnea not necessarily related to exertion.

Cardiovascular disease is a prominent cause of breathlessness. Many times the underlying problem is evident, such as in pulmonary edema or acute myocardial infarction. At other times, the cause is less clear, as in atrial septal defect or early mitral stenosis. Particularly in patients with diabetes mellitus, myocardial ischemia from coronary artery disease can present as intermittent dyspnea without chest pain. Chronic heart failure is a troublesome cause of breathlessness, since the complaint will sometimes linger after apparently adequate treatment. In these cases the clinician must reevaluate the efficacy of treatment and look for other causes such as anemia or pulmonary embolism.

Neuromuscular disease is a well-known cause of dyspnea. Patients with Guillain-Barré disease, myasthenia gravis, amyotrophic lateral sclerosis, or late-occurring muscular dystrophies can present with this complaint. Severe weight loss from malnutrition, malignancy, or chronic disease may also cause respiratory muscle weakness with associated dyspnea.

Anemia is a prominent cause of dyspnea when the hemoglobin concentration falls below eight to ten g/dl. As the hemoglobin declines further, dyspnea becomes more pronounced. This relationship is most prominent in acute anemia. Various compensatory mechanisms help to blunt the sensation of dyspnea in chronic anemia.

Renal disease leads to dyspnea from acidosis, anemia, and volume overload. The complaint is much less common now than before owing to more effective dialysis and the availability of recombinant erythropoietin to increase red blood cell production.

Patients with chronic liver disease often complain of dyspnea but the mechanism is frequently obscure. One particular cause can be small arteriovenous shunts at the lung bases. This condition is classically associated with breathlessness and oxyhemoglobin desaturation on assuming the upright position as when arising from bed in the morning. This symptom is known as platypnea.

Endocrine abnormalities, particularly hyperthyroidism, can be associated with dyspnea. In this setting, the sensation is probably related to the hypermetabolic state associated with thyroid over-activity. In the late stage, dyspnea can be associated with high-output heart failure.

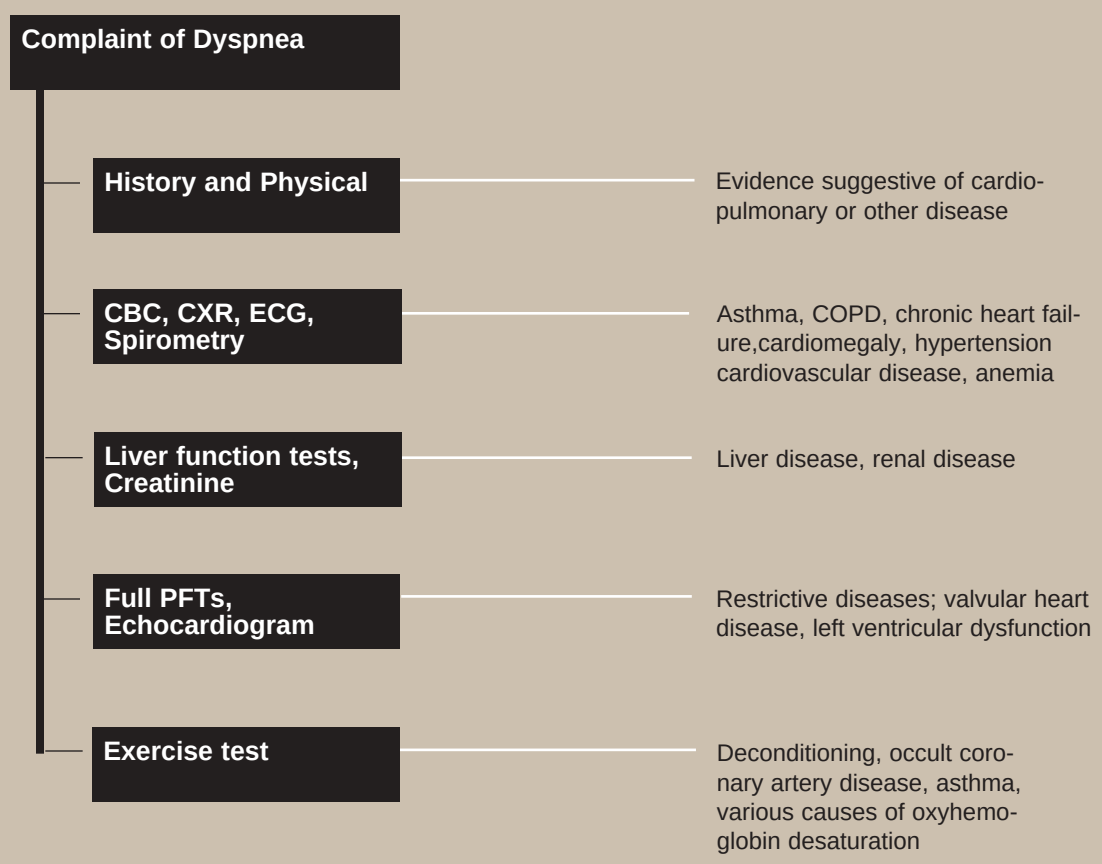
Early sepsis with bacteremia is associated with hyperventilation and sometimes with dyspnea. In some cases, hyperventilation and dyspnea may be the first manifestation of sepsis. The cause is likely multifactorial and includes acidosis, tissue ischemia, and perhaps a direct effect on the brainstem respiratory center and carotid bodies by various mediators.

*(continued)*

## Table 4 Key Questions in Evaluation of Dyspnea

| Question | Probable Pathophysiology |
|---|---|
| Associated only with exertion? | Heart failure, restrictive or obstructive lung disease |
| Associated with exertion and occurs at night? Cough and wheeze? | Asthma or heart failure |
| Associated with exertion, chest, arm or neck discomfort and concurrent nausea or diaphoresis? | Angina pectoris |
| Worse when assuming upright position? | Liver disease with arteriovenous shunts at the lung bases (platypnea) |
| Present in the lateral decubitus position? | Unilateral lung or pleural disease (trepopnea) |
| Fast onset when supine, relieved by lateral or upright positioning? | Bilateral phrenic nerve dysfunction |
| Occurring within minutes or hours of becoming recumbent? | Heart failure (orthopnea) |

## Figure 1 Evaluation of Dyspnea



## Clinical Evaluation

Evaluation of this complaint always begins with a careful history and physical examination. Careful attention should be paid to the duration and severity of dyspnea and to those activities that make it worse. Table 3 gives a severity scale for dyspnea developed by the American Thoracic Society. Activities and body positions that provoke dyspnea can often help to focus the diagnostic work-up. Key questions are listed in Table 4. Although the history alone rarely gives the diagnosis, these historical points are useful to point toward more specific testing. The physical examination should focus on the organ systems mentioned above, with meticulous attention to the respiratory and cardiovascular systems. Figure 1 shows a diagnostic pathway with the points where a particular diagnosis is frequently made.

Routine laboratory tests include spirometry, chest x-ray, (CXR), echocardiogram, (ECG), and complete blood count, (CBC). If a diagnosis has still not emerged, liver and kidney function tests may be helpful. If these tests are unrevealing, more specialized pulmonary function testing (PFT, lung volumes and single breath diffusing capacity) and echocardiography are useful. Consultation with a specialist is often helpful—particularly if the results of specialized tests are equivocal or therapy proves ineffective. When dyspnea is associated with exertion, a formal exercise test is sometimes necessary to differentiate myocardial ischemia from asthma, pulmonary vascular disease, and physical deconditioning. When exercise testing is being considered, referral to a specialist is recommended.

Psychogenic dyspnea is a particularly interesting type of breathlessness because it is usually a diagnosis of exclusion. The malady occurs more commonly in women than men and tends to appear in the third or fourth decades of life. The condition should be considered when the physical examination, chest x-ray, ECG, and spirometry are all normal. Patients with

psychogenic dyspnea often exhibit extreme anxiety with concurrent symptoms of hyperventilation including visual complaints, dizziness, near-syncope, and perioral and finger tingling and numbness. Arterial blood gases show a chronic respiratory alkalosis. Psychogenic dyspnea is better treated with counseling and biofeedback, although the temptation to employ anxiolytics is great.

Sighing dyspnea appears in middle-aged individuals with mild heart or lung disease. The patient complains of inability to take a deep breath at rest and so periodically makes a conscious effort to sigh, which is invariably unsatisfactory since physiologic sighing is an involuntary action. This presentation is usually not associated with anxiety or symptoms of hyperventilation. Arterial blood gases are normal in most cases of sighing dyspnea. Sighing dyspnea usually responds to reassurance, nonspecific support, and treatment of the underlying condition.

It must be stressed again that in the great majority of cases, strong hints as to the cause of dyspnea emerge during the performance of a thorough medical history and physical examination. Use of the pathway outlined in Figure 1 allows a cost-effective approach to sequential diagnostic testing to help confirm the tentative diagnosis.

Treatment of dyspnea is best aimed at the underlying cause. When heart or lung disease can be improved, the sensation of dyspnea is often greatly ameliorated. Severe restrictive lung disease as manifested by pulmonary fibrosis or neuromuscular abnormality poses a particularly difficult problem. In these cases, the complaint is often permanent and debilitating. The most effective treatment of dyspnea in cases of far-advanced pulmonary fibrosis, is single lung transplantation.

Until recently, the same was said of advanced emphysema. Now it appears that lung volume reduction surgery can significantly relieve dyspnea by reducing functional residual capacity, which reduces the work of breathing by improving the mechanical function of the lungs and diaphragm. Studies are now in progress to evaluate how best to select candidates for this type of surgery.

A number of studies have examined opiates and benzodiazepines in the treatment of intractable dyspnea. While anecdotal reports have indicated some short-term value, controlled clinical trials have failed to confirm long-term benefit; moreover, these studies have demonstrated deleterious events in a substantial number of patients.

## When to Refer

Many patients with dyspnea can be evaluated and treated without referral to a specialist. However, unexplained dyspnea after routine evaluation usually justifies referral. Specifically, equivocal results after full pulmonary function testing or echocardiography or unsatisfactory response to preliminary treatment warrants referral. Referral is also warranted when cardiopulmonary exercise testing is being considered.

## Medicolegal Concerns

Acute dyspnea can be associated with life-threatening diseases such as pulmonary embolism and myocardial infarction. Failure to pursue these diagnoses in patients with unexplained dyspnea promptly and accurately can lead to untimely deaths and subsequent lawsuits. Chronic dyspnea is often the only symptom of primary pulmonary hypertension or thromboembolic pulmonary hypertension. Failure to pursue these diagnoses, including failure to refer the patient for further evaluation, can lead to malpractice litigation, as well.

*(continued)*

**Summary**

Dyspnea is the most common symptom the frontline physician encounters in managing the spectrum of cardiopulmonary diseases. The complaint is entirely subjective and highly variable, but a thoughtful, stepwise approach, beginning with a careful medical history and physical examination, leads to a satisfactory diagnosis in most patients. Patients with dyspnea that remains unexplained after routine evaluation should be referred to a specialist. This Section offers a sequential approach to dyspnea, beginning with simple inexpensive evaluations and proceeding to more sophisticated testing. ■

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**Cough is an important defense mechanism that plays a major role in maintaining the integrity of the airways and can be voluntary or involuntary.**

## C. Chronic Cough

### Introduction

Cough is one of the most common symptoms prompting a visit to the primary care physician's office. Apart from smoking, most coughs are caused by acute viral upper respiratory tract infections and are self-limiting. Some coughs persist for weeks to years, and cause patients to go from one physician to another seeking relief from incessant coughing which may rob them of sleep, cause urinary incontinence, chest pain, or syncope, and interfere with work and life style. Cough can be a vexing problem for the patient and the physician alike. Successful treatment depends on making an accurate diagnosis and giving specific therapy. This presentation will focus on establishing the causes of chronic cough, which has been defined as a cough that persists for more than three weeks.

Cough is an important defense mechanism that plays a major role in maintaining the integrity of the airways and can be voluntary or involuntary. The pathophysiology of cough is incompletely understood. Cough is commonly triggered by mechanical or chemical stimulation of receptors in the pharynx, larynx, trachea, and bronchi. Cough receptors also exist in the nose, paranasal sinuses, external auditory ear canals, tympanic membranes, parietal pleura, esophagus, stomach, pericardium, and diaphragm.

### Causes of Chronic Cough

Causes of chronic cough range from the common (Table 5) to the obscure (Table 6). Chronic bronchitis secondary to smoking is probably the most common cause of chronic cough, but most smokers do not acknowledge "cigarette cough" and do not seek medical advice until the onset of other serious complaints, such as dyspnea. A change in the pattern of a smoker's cough may herald associated complications such as bronchogenic neoplasm.

In nonsmokers with normal chest x-rays the most likely causes of chronic cough are: post-viral respiratory tract infections, post-nasal drip, asthma,

## Table 5 Common Causes of Chronic Cough

| |
|---|
| Chronic bronchitis due to smoking |
| Post-nasal drip |
| Post-infectious |
| Viral |
| Bacterial—*Bordetella pertussis, Mycoplasma, Chlamydia* |
| Gastroesophageal reflux disease |
| Asthma |
| Angiotensin converting enzyme inhibitors |

## Table 6 Less Common Causes of Chronic Cough

| |
|---|
| Infectious causes |
| Tuberculosis—typical or atypical |
| Fungal |
| Endobronchial lesions |
| Benign — bronchial adenoma, carcinoid tumor |
| Malignant — bronchogenic carcinoma, metastatic cancer |
| Foreign body |
| Interstitial lung diseases |
| Hypersensitivity pneumonitis |
| Bronchiolitis obliterans with organizing pneumonia, ( BOOP) |
| Sarcoidosis |
| Chronic interstitial pneumonia |
| Chronic aspiration |
| Masses in the neck/thyroid disorders |
| Hair impinging on the tympanic membrane |
| Bronchiectasis |
| Occult congestive heart failure |
| Disorders of the pleura, pericardium, diaphragm |
| Psychogenic/habitual cough |
| Occupational bronchitis |
| Enlarged tonsils or uvula |

## Table 7 Frequency of Causes of Chronic Cough*

| Cause of Cough | Percent of Cases |
|---|---|
| Post-nasal drip | 41 |
| Asthma | 24 |
| Gastroesophageal reflux disease | 21 |
| Chronic bronchitis | 3 |
| Bronchiectasis | 4 |
| Miscellaneous | 3 |

*102 Patients studied by Irwin RS, et al. Am Rev Respir Dis 1990;141:640-647.

gastroesophageal reflux disease and drug-related (angiotensin converting enzyme inhibitors) (Table 5). Multiple causes are frequently encountered in the same patient. For example, in a study of the frequency of chronic cough in 102 outpatients (Table 7), Irwin and colleagues found a single cause in only 38%, whereas two or more causes were felt to be responsible in 59%. Assessment of the patient with chronic cough begins with a comprehensive history and physical examination, chest x-ray, and spirometry.

**History**

The cause(s) of chronic cough may become apparent after taking a careful history. Is the symptom a cough, "hawking," or clearing the throat? It helps to have the patient act out the cough to distinguish true cough from throat clearing. Is the cough dry or productive? If so, what is produced? Are systemic symptoms such as fever, night sweats, or weight loss present? A detailed history of the work and home environment should be taken with emphasis on possible exposure to noxious inhalants or allergens. The history should include the time and circumstances of onset, frequency, and aggravating and relieving factors. Patients with asthma may note worsening of cough on exposure to cold air, irritants, or allergens. Is there an allergic history? Does the patient wheeze with cough? Is the cough accompanied by dyspnea? If so, congestive heart failure or interstitial lung disease may be suspected. Is the cough related to time of day, eating, or position? A nocturnal cough may be associated with asthma, post-nasal drip, congestive heart failure, or gastro-esophageal reflux disease, (GERD). Half of the patients with GERD have none of the classic symptoms. Does the patient cough while eating? Chronic aspiration is common in the elderly patient, especially following stroke. Is the patient on angiotensin converting enzyme inhibitors or other drugs that may predispose to cough or asthma? Do not overlook ophthalmic preparations. Beta blocker drops used for glaucoma may precipitate asthma.

**Physical Examination**

The physical examination may provide clues to the causes of cough. Examination of the upper airways may show nasal mucous membrane swelling, post-nasal drip, or nasal polyps. Hairs impinging on the tympanic membrane is a rare cause of cough, but is easily treated. The finding of wheezes, rhonchi, or crackles may indicate asthma, bronchitis, chronic obstructive pulmonary disease, (COPD), interstitial lung disease, or congestive heart failure. The finding of unilateral wheezing may be due to an endobronchial lesion or foreign body. Masses in the neck, including thyroid enlargement, can compress the trachea and cause cough.

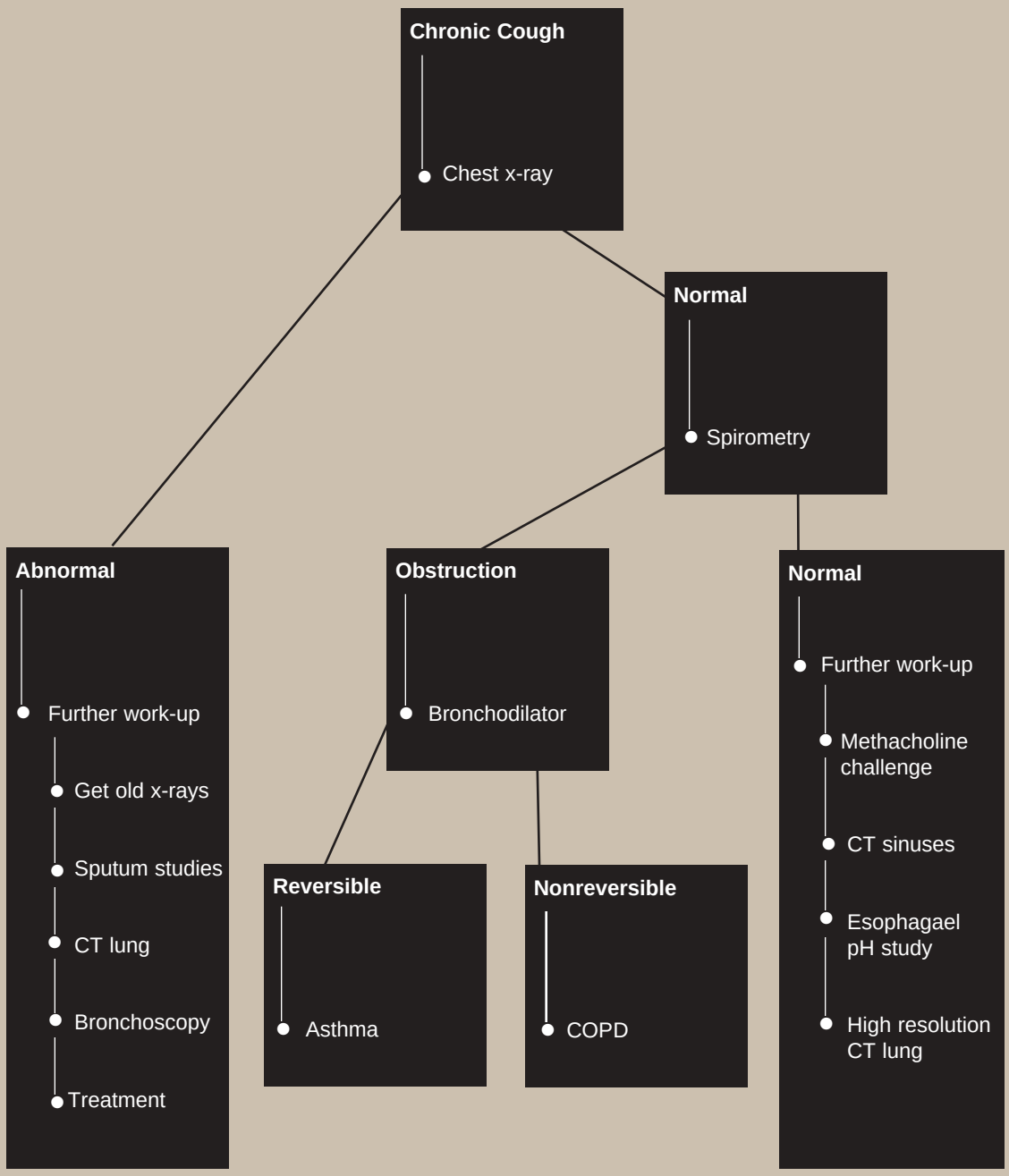
**Diagnostic Studies**

The work-up for chronic cough should begin with standard posteroanterior, (PA), and lateral chest x-rays; these often reveal the presence of underlying infectious or neoplastic causes of chronic cough. Spirometric studies before and after bronchodilator administration may reveal reversible airways obstruction (asthma). In patients with normal baseline spirometry, methacholine inhalation challenge, (MIC), is indicated to rule out asthma that presents primarily with cough. Computerized tomograms, (CT), of the sinuses are superior to plain x-rays in identifying sinusitis. High-resolution or spiral CT scans of the thorax may reveal subtle changes consistent with cough due to chronic interstitial pneumonia or bronchiectasis. The finding of a reduced single breath diffusing capacity may suggest interstitial lung disease. Barium esophagograms and upper gastrointestinal endoscopy have a low sensitivity (48%) and specificity (76%) for identifying GERD as the culprit in chronic cough; monitoring the esophageal pH for 24 hours is the gold standard. In patients suspected of having chronic aspiration, a video swallowing study with a speech therapist in attendance should be performed. A systematic approach to the work-up of a patient with nondrug-related chronic cough is presented in Figure 2.

*(continued)*

## Figure 2 Systemic Work-up of a Patient With Chronic Cough

**Algorithm showing a systemic approach to the work-up of a patient with chronic cough.**



**Post-nasal Drip Syndrome**

Post-nasal drip syndrome is said to be one of the most common causes of chronic cough and is caused by a variety of conditions including vasomotor rhinitis, allergic rhinitis, nasal polyps, and chronic sinusitis. The diagnosis is made on clinical grounds. Patients may complain of a tickle or drainage of liquid in the back of the throat. On examination, cobblestoning of the nasal or oropharygeal mucosa may be observed. In many patients, cough may be the only symptom of post-nasal drip syndrome. Confirmation of the diagnosis may depend on the resolution of symptoms after treatment with antihistamines and intranasal or systemic corticosteroids.

**Asthma**

Typically, asthma patients complain of episodic wheezing, cough, chest tightness, and dyspnea and demonstrate reversible obstructive airflow. In so called cough-variant asthma, a dry cough, particularly at night, is the only symptom and routine spirometry is normal. The diagnosis is often made on the basis of a favorable clinical response to empirically administered beta$_2$-agonist bronchodilators and inhaled corticosteroids, and a positive bronchoprovocation test using methacholine inhalation challenge, (MIC). A positive MIC test, defined as a 20% or greater decrease in the FEV$_1$ after MIC, indicates bronchial hyperreactivity but not necessarily asthma. For example, bronchial hyperreactivity may follow viral respiratory tract infections and persist for as long as six weeks. Because MIC has a positive predictive value of from 60% to 80%, Irwin and colleagues advise that a positive test must be correlated with favorable response to therapy before concluding that a patient has cough-variant asthma.

*(continued)*

## Gastroesophageal Reflux-related Chronic Cough

GERD is a very common problem. Surveys of the general population have led to estimates that 10% of the adult population of the United States have daily heartburn and a third have intermittent symptoms; moreover, GERD has been shown to cause 10% to 40% of cases of chronic cough. Cough in GERD is triggered by reflux of acid into the distal esophagus and stimulation of an esophageal-tracheobronchial reflex. Cough is not dependent on aspiration into the larynx or tracheobronchial tree.

Proving the relationship of chronic cough to GERD can be difficult. The lack of typical symptoms of reflux and negative endoscopic and radiographic studies do not rule it out. The 24-hour esophageal pH monitoring test has become the gold standard for diagnosis and has both a sensitivity and specificity approaching 90%. Correlation of the results of pH monitoring with response to therapy adds to the reliability of the test. If GERD is the sole cause of chronic cough, aggressive anti-reflux therapy should eliminate the cough in nearly all cases. One study reported 100% success. Treatment involves the use of dietary, mechanical, and drug therapy. Drug therapy should be initiated with proton pump inhibitors and prokinetic agents. After three months, an $H_2$-antagonist can be substituted for the proton pump inhibitor.

**Post-infectious Cough**

Patients who have had recent viral respiratory tract infections may have prolonged cough that is refractory to treatment. Airway hyperresponsiveness can be demonstrated by MIC testing in some cases. Treatment with bronchodilators and inhaled or systemic corticosteroids in moderate to high doses may help relieve symptoms. The cough can be self-perpetuating and cause continuing trauma to the airways, and in these cases, prolonged suppression with narcotics may eventually allow resolution.

*Bordetella pertussis* (the cause of whooping cough) infection in adults should be included in the differential diagnosis of chronic cough. In one series of 75 patients with chronic cough lasting longer than two weeks, 21% had pertussis.

**Angiotensin Converting Enzyme Inhibitor Cough**

Angiotensin converting enzyme inhibitor, (ACEI), drugs are frequently used in the treatment of hypertension, congestive heart failure, and myocardial infarction. The generic and brand names of most commonly used drugs are listed in Table 8. Ten to 20% of patents taking ACEI drugs develop cough. There is no evidence at this time that any one ACEI drug is less likely to cause cough than another. In spite of this well-documented side effect, referrals to a specialist for evaluation of chronic cough still occur frequently. Many of these patients have had extensive and costly work-ups and treatment with a variety of medications, including antihistamines, antibiotics, cough suppressants, and corticosteroids, without relief.

The pathophysiology of ACEI-induced cough remains an enigma. Clinically, the cough may begin from as early as three weeks to as long as a year after starting treatment. The severity of the cough can vary from a mild tickle in the throat to a severe hacking, debilitating cough that interferes with sleep, work, and social

## Table 8 Angiotensin and Angiotensin II–Related Medications

**Angiotensin Converting Enzyme Inhibitors**

| Generic | Brand Name |
|---|---|
| Quinapril | *Accupril* |
| Perindopril | *Aceon* |
| Ramipril | *Altace* |
| Captopril | *Capoten* |
| Benazepril | *Lotensin* |
| Trandolapril | *Mavik* |
| Fosinopril | *Monopril* |
| Lisinopril | *Prinivil, Zestril* |
| Moexipril | *Univasc* |
| Enalapril | *Vasotec* |

**Angiotensin II Receptor Antagonists**

| Generic | Brand Name |
|---|---|
| Losartin | *Cozaar* |
| Valsartan | *Diovan* |
| Telomisartan | *Micardis* |

function. It is frequently worse at night and in the supine position. When the ACEI drug is discontinued, the cough usually abates in two weeks but may persist for months. Angiotensin II receptor antagonists, a new class of antihypertensive agents, have not been associated with an increased incidence of cough.

**Less Common Causes of Cough**

Chronic cough may be the presenting complaint in patients who ultimately prove to have tumors, both benign and malignant, sarcoidosis, or other infiltrating lung diseases; all these conditions require special investigations to make the diagnosis. Psychogenic or habitual cough does exist but patients should not be put in this category without an exhaustive work-up, failure of empirical therapy, and prolonged follow-up.

**Symptomatic Treatment**

The treatment of cough is effective only if directed at the cause, but patients should be offered symptomatic relief while awaiting the results of specific therapy. Expectorants such as iodides and guaifenesin, hydration, inhaled steam, cough lozenges, and hard candies are helpful. Dextromethorphan and codeine are effective cough suppressants. In the future, a better understanding of the cough reflex may allow the development of more effective cough remedies.

**When to Refer**

When the patient with chronic cough remains symptomatic despite evaluation and treatment for six to eight weeks, the primary care physician should consider referral to a specialist. In difficult cases, referral to a pulmonologist for evaluation and treatment, and for specific testing such as fiberoptic bronchoscopy and MIC is recommended. Referral for upper gastrointestinal endoscopy and 24-hour pH monitoring may be indicated to rule out cough due to GERD. Referral to an allergist may be indicated for allergy testing and subsequently for immunotherapy if the patient is sensitive to an unavoidable antigen.

*(continued)*

**Medicolegal Concerns**

One of the most common reasons patients file suit is for failure to diagnose cancer. Even though bronchogenic carcinoma is an uncommon cause of chronic cough in the context of a normal chest x-ray, it must not be overlooked. Failure to diagnose tuberculosis is another cause of litigation, but again, would be an unlikely cause of chronic cough with normal chest roentgenograms.

**Summary**

Cough is a common presenting complaint in the frontline physician's office, but in most patients the symptom is self-limiting. In others, symptoms may persist from weeks to years and are associated with significant morbidity. Successful treatment depends on finding the cause and initiating specific therapy. The most common causes are smoking, post-nasal drip, asthma, GERD, or post-viral respiratory tract infection. Multiple causes in the same patient are common. When the cough persists in spite of specific or empiric therapy and either the physician or the patient is dissatisfied with the diagnosis or treatment, referral to a specialist should be considered. ■

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**Pain has been defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage and mediated by specific nerve fibers to the brain where its conscious appreciation may be modified by various factors.”**

## D. Chest Pain

### Introduction

Pain has been defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage and mediated by specific nerve fibers to the brain where its conscious appreciation may be modified by various factors." Pain follows the bumps and bruises encountered in daily life, and all persons have experienced unpleasant but innocent headaches, sore throats, and muscle aches. In contrast, pain that seems to originate in the chest generates far greater concern because it may announce the presence of severe, occasionally life-threatening disease. The new onset of chest pain and what it may connote provokes anxiety and fright; consequently, it is one of the symptoms most likely to cause the victim to seek prompt medical attention.

Because it is a subjective experience and difficult to quantify, epidemiological surveys of the prevalence of chest pain and physiological studies of its mechanisms are limited. The different thoracic and neighboring organs that give rise to chest pain, however, are well described as are the identifying hallmarks of the sensations that are typically produced when certain structures are involved. These characteristic features serve as the basis for the classification of the many different causes of chest pain that are listed in Table 9. The most common of these will be discussed in this Section.

### Myocardial Ischemia

The pain of myocardial ischemia is described first because of its clinical importance, both in terms of its frequency and in terms of its diagnostic and therapeutic implications. Even though the receptors, chemical transmitters, and sensory pathways that mediate cardiac pain are not well understood, the message being sent by the oxygen-deprived heart is clear and needs to be listened to.

**Coronary Artery Disease:** The pain of myocardial ischemia is believed to be provoked by an imbalance between the oxygen needs of the myocardium and the

## Table 9 Sources, Types, and Most Common Causes of Chest Pain

| | |
|---|---|
| **Cardiovascular disorders** | |
| *Myocardial ischemia* | |
| | Angina pectoris |
| | Variant angina |
| | Acute myocardial infarction |
| | Cocaine |
| | Aortic valve disease |
| | Mitral valve prolapse |
| | Hypertrophic cardiomyopathy |
| *Pericardial pain* | |
| | Infection |
| | Dressler's syndrome |
| | Postcardiotomy syndrome |
| | Idiopathic |
| *Substernal and back pain* | |
| | Aortic dissection |
| **Musculoskeletal disorders** | |
| *Costochondral pain* | |
| *Neuritis-radiculitis* | |
| | Herpes zoster infection |
| | Disorders of the spine |
| *Shoulder-upper extremity pain* | |
| | Pancoast carcinoma |
| | Thoracic outlet obstruction |
| | Shoulder-hand syndrome |
| *Chest wall pain* | |
| | Rib fracture |
| | Muscle injury (myalgia) |
| | Infection |
| | Malignancy |
| **Pleuropulmonary disorders** | |
| *Pleuritic pain* | |
| | Infection |
| | Pulmonary embolism |
| | Spontaneous pneumothorax |
| | Collagen vascular disease |
| *Pain of pulmonary hypertension* | |
| | Pulmonary embolism |
| | Primary pulmonary hypertension |
| | Eisenmenger's syndrome |
| *Tracheobronchial pain* | |
| | Infection |
| | Inhalation of irritants |
| | Malignancy |
| **Gastrointestinal disorders** | |
| *Esophageal pain* | |
| | Reflux esophagitis |
| | Motility disorders |
| *Epigastric-substernal pain* | |
| | Cholecystitis |
| | Peptic ulcer disease |
| | Acute pancreatitis |
| | Disorders of intestinal motility |
| **Psychiatric disorders** | |
| *Atypical anginal pain* | |
| | Neurocirculatory asthenia |
| | Hyperventilation syndrome |
| | Panic disorder |
| **Other** | |
| *Substernal pain* | |
| | Mediastinal emphysema |

supply available through the coronary circulation. This explains why the resulting pain has similar features in all circumstances, but is associated with a continuum of myocardial injury that varies from angina pectoris (reversible ischemia) at one end to myocardial infarction (death of heart muscle cells) at the other. The pain of angina pectoris is usually described as an intense "pressure," "squeezing," or "constriction," originating underneath or to the left of the sternum. Radiation to the neck or down the inner aspect of one or both arms is common. The pain is usually provoked by exercise, but may accompany heavy meals, excitement, or emotional distress. When angina occurs, the victim is generally forced to stop whatever he or she is doing, and the pain will subside within two to ten minutes. Relief can be accelerated by sublingual nitroglycerin. In variant (Prinzmetal's) angina, the pain occurs at rest rather than during exercise. The pain of acute myocardial infarction is similar in location and radiation to that of angina pectoris, but in contrast, tends to be much more severe, is not relieved by nitroglycerin, and typically requires opiates for control. Important distinguishing features of acute myocardial infarction are the accompanying profuse sweating, nausea and vomiting, and profound weakness; massive myocardial infarction may cause intractable hypotension or pulmonary edema.

The coronary artery vasoconstricting and cardiac stimulating effects of cocaine frequently cause anginal chest pain from myocardial ischemia and occasionally, frank myocardial infarction. Cocaine is a common and frequently overlooked cause of visits to the emergency department for chest pain.

**Related Syndromes:** The pain of myocardial ischemia has many mimics, some of which arise within the heart and others within nearby organs. The pain of pericarditis occasionally resembles angina pectoris, but more typically is pleuritic in nature (see next Section)

from involvement of the contiguous pleura. Sharp steady pain along the upper ridge of the trapezius muscles is said to be quite specific for pericarditis. The pain of myocardial ischemia may accompany diseases that affect the coronary artery ostia, especially aortic stenosis. Surprisingly, cardiac diseases that spare the coronary arteries also cause pain that mirrors that of myocardial ischemia. Nearly 50% of patients with severe mitral valve prolapse, 20% of those with myocarditis, and 10% of those with hypertrophic cardiomyopathy complain of such pain. Dissection of the aorta is always in the differential diagnosis, but can usually be differentiated by its unbearable severity from the moment of onset, and its "tearing" or "ripping" quality that extends up into the neck, through to the back, or down into the abdomen.

As will be described, certain gastrointestinal disorders and psychiatric disorders can also cause pain resembling that of myocardial ischemia. The only pulmonary condition that does so, and rarely at that, is pulmonary hypertension, usually of the primary type.

**Pleurisy**

One of the most characteristic and easy to diagnose types of chest pain is pleurisy from inflammation or irritation of the parietal pleura, which is innervated by branches of nearby intercostal nerves and, over the center of each hemidiaphragm, by the phrenic nerves. In contrast, the visceral pleura is not innervated by nociceptive (pain) receptors, but owing to the contiguity of the visceral and parietal pleural surfaces, inflammatory processes in the periphery of the lungs often cause the pain of pleurisy by extension across the membranes.

Because most intrapulmonary disorders are apt to be localized within a single lung, pleuritic pain is usually sharply restricted to the ipsilateral chest wall or shoulder, cutaneous areas supplied by the involved intercostal or phrenic nerves, respectively. But perhaps

the most singular feature of pleurisy is its unmistakable relationship to breathing movements. The pain may be variously described as "sharp," "dull," "achey," sometimes "burning," or simply a "catch." Whatever its designation, it is worsened by taking a deep breath, and either coughing or sneezing causes intense distress. The aggravation by breathing causes patients to seek, find, and remain in the body position that most restricts movement of the affected region.

**Infection:** The classic cause of pleurisy, which is frequently sudden in onset, is community-acquired pneumonia. Other infectious processes of the lung parenchyma that abut the visceral pleura, such as lung absess, can also cause pleurisy. Infections within the pleural space itself, such as empyema or tuberculous pleuritis with effusion, are obvious causes of pleurisy that are apt to be gradual in onset and lingering.

**Noninfectious Causes:** A wide variety of noninfectious disorders can cause acute pleurisy by sudden involvement of the pleural surfaces or adjacent lung parenchyma. The most important of these include pulmonary embolism, with or without pulmonary infarction, and spontaneous pneumothorax. Both primary bronchogenic cancer and secondary metastases can involve the pleural surfaces and present with chronic pleurisy. Most of the collagen vascular diseases, but particularly rheumatoid arthritis and lupus erythematosus, can cause pleurisy.

*(continued)*

## Disorders of the Chest Walls

Inflammation of or trauma to the various components of the chest wall is a common cause of chest pain. Because these structures move during breathing, there may be a "pleuritic" element to the resulting pain. In contrast to classic pleurisy, chest wall pain is more limited in its distribution and is nearly always associated with localized tenderness.

**Trauma:** Probably the most common cause of chest wall pain is trauma. Usually, pain is the aftermath of a remembered injury during a fall, fight, or accident. Occasionally, chest wall pain seems to be spontaneous, but in these instances is probably related to an unrecognized strain or tear of an intercostal muscle or rib fracture during exercise, a bout of coughing, or a forgotten injury.

**Other Causes:** A peculiar type of chest wall pain occurs from costochondritis, inflammation at one of the costochondral junctions, which is also known as Tietze's syndrome, or of the costosternal bridges that form the cartilaginous shield of the anterior rib cage. The discomfort is often described as dull with a gnawing aching quality to it. Respiratory movements have surprisingly little effect, and the diagnostic key is the presence of swelling and tenderness at the affected site. Superficial, knifelike pain of intercostal neuritis-radiculitis may cause diagnostic confusion. Finding hyperalgesia or analgesia over the involved nerve root helps to define the problem. A day or two later, the diagnosis usually becomes evident with the appearance of the vesicular rash of herpes zoster. A variety of so-called shoulder-arm syndromes have been described. Of these, an unrelenting deep pain that begins in the shoulder and then progresses to the arm characterizes the Pancoast syndrome, an uncommon but important presenting manifestation of bronchogenic carcinoma.

**Tracheobronchial Disorders**

Tracheal pain, usually described as "raw" or "burning," is felt in the midline anteriorly, from the larynx to the xyphoid. Pain from either main bronchus is felt to the left or right of the sternum or in the anterior neck near the midline. Tracheobronchial pain may be exaggerated by deep breaths that seem to "cut off" inspiration. Such pain is found in viral and bacterial tracheobronchitis, less often with a tracheal cancer. In addition, healthy people may experience tracheal pain when exercising in heavily air-polluted environments or in extremely cold air.

**Abdominal Disorders**

Several gastrointestinal tract disorders, particularly those arising in the esophagus, are established causes of chest pain that may resemble angina pectoris in all respects, including location and radiation, quality, and relief with nitroglycerin. This type of pain may arise from either gastroesophageal reflux or from disorders of esophageal motility. It is said to account for symptoms in 10% to 30% of patients suspected of having angina pectoris but whose coronary arteries are normal by angiography. In a reversal of the phenomenon of certain lung diseases, particularly acute bacterial pneumonia in children, presenting with upper abdominal pain, certain abdominal disorders may present with pain in the lower chest. This confusing situation is most apt to occur with cholecystitis, peptic ulcer disease, and acute pancreatitis.

**Psychiatric Disorders**

No diagnosis is ever made in many patients who complain of chest pain. In some of these persons psychosocial factors are believed to be important, but an exact causal role is difficult to establish. Certain psychiatric disorders are recognized as causing chest pain that simulates angina pectoris. The most important of these are neurocirculatory asthenia, the hyperventilation syndrome, and panic disorders. The problem is complicated by the fact that patients with documented heart disease may also have panic

attacks or other psychiatric disorders. This is particularly true in patients who have coronary artery disease or mitral valve prolapse.

**Differential Diagnosis**

This brief review highlights not only the many different causes of chest pain, but also that they vary in seriousness from innocent to life-threatening. Thus considerable clinical judgment is required to decide which patients should be further studied and which tests should be used in the evaluation. As stressed in Section A, *Approach to the Patient,* the work-up begins with a thorough medical history. Emphasis should be placed on nuances in the behavior of the pain itself, its quality, location, duration, inciting factors, and relieving measures. Questions should be asked concerning other cardinal symptoms of cardio-respiratory diseases such as dyspnea (Section B), cough (Section C), and hemoptysis (Section E). In this regard, it is worth noting that cardiac causes of chest pain are often accompanied by shortness of breath. In contrast to many respiratory causes of chest pain and dyspnea, and with the exception of pericarditis, the pain of heart disease does not vary with breathing. Associated systemic features, especially fever, night sweats, weight loss, weakness, and edema, provide important clues that help direct the work-up. Similarly, a thorough physical examination may reveal signs of chest wall, pleural, pulmonary, cardiac, or abdominal involvement. Next, depending on the need for additional studies and the examiner's initial suspicion, either a chest x-ray or electrocardiogram is warranted. At this point, three options are generally available: (1) whether or not the patient can be watched and followed by the primary care physician; (2) whether the work-up for pleural effusion, pulmonary mass, or parenchymal infiltrate, if shown radiographically, should proceed as outlined in the last three Sections of this monograph; (3) whether the patient should be referred for special diagnosis and treatment, perhaps in a hospital, as discussed in the next Section.

## When to Refer

Patients with chest pain of cardiac origin may need emergency hospitalization and are likely to require further diagnostic evaluation by a cardiologist for coronary artery disease or valvular dysfunction. This may entail echocardiography, cardiac catheterization, treadmill testing, or coronary angiography with possible angioplasty or stent placement. Consultation with a pulmonologist is needed for patients who might require fiberoptic bronchoscopy, pleural biopsy, or specialized pulmonary function testing, including during exercise. Similarly, if invasive procedures are contemplated to evaluate chest pain of possible esophageal origin or somewhere in the abdomen, referral to a gastroenterologist is warranted. In selected cases of intractable chest pain of presumed psychological origin, referral to a psychiatrist can be helpful.

## Medicolegal Concerns

Perhaps the most frequent cause of medicolegal conflict, one that concerns all patients, not just those with chest pain, is failure to document adequately all contact with and advice given to patients. For patients who are seen for new-onset chest pain, particularly if conceivably caused by life-threatening myocardial ischemia or pulmonary embolism, failure to hospitalize and to seek appropriate consultation are grounds for legal action.

## Summary

Chest pain is one of the most common medical symptoms. Although most of the time innocuous and often difficult to pinpoint, chest pain must always be thoughtfully considered because it may be the first signal of serious, potentially lethal disease. A careful medical history is the first step in unraveling the mysteries of chest pain. Then, a thorough physical examination and, when indicated, one or two tests, an electrocardiogram and chest x-ray, completes the baseline information necessary to decide what to do next: watch and wait, proceed with management, or refer for specialized evaluation. ■

*(continued)*

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## E. Hemoptysis

### Introduction

Hemoptysis, the act of coughing up blood, is an important symptom since it frequently reflects serious underlying lung disease. Because many of the lung conditions that are heralded by hemoptysis are treatable, the symptom requires systematic and thorough evaluation to discover its etiology. A possible exception is mild hemoptysis occurring in a patient with chronic bronchitis during an acute exacerbation. Hemoptysis in this situation is common, usually mild, and self-limited. Therefore, it may be observed without further work-up. However, if the hemoptysis is substantial, persistent, or recurrent then further evaluation is indicated, particularly since patients with chronic bronchitis related to smoking are at high risk for lung cancer.

### Sources

The first step in the evaluation of hemoptysis is to decide if it is really hemoptysis—that is, is the blood coming from the bronchial tree, lungs, or from some other site? In most cases, history will suggest that blood is actually being coughed up from the airways or lungs, but it may be difficult at times to distinguish blood being coughed up from the respiratory system from blood coming from two other sites: bleeding in the upper respiratory tract, in the nasopharynx or sinuses, or blood originating in the gastrointestinal tract that was regurgitated or vomited. A history of frequent nosebleeds, hoarseness, or some other change in the voice or history of mouth lesions might suggest bleeding from the upper respiratory tract. If bleeding is not clearly from the lungs, then a thorough examination of the upper respiratory system is indicated. If the source remains equivocal, i.e., no abnormality in the upper respiratory tract is found on initial examination and no source is found after further pulmonary work-up as described below, then an examination by an otolaryngology specialist may be warranted. Hematemesis occasionally may be difficult to distinguish from hemoptysis; moreover, blood from a respiratory source may be swallowed and may

## Table 10 Differential Diagnosis of Hemoptysis

| | | |
|---|---|---|
| **Pulmonary** | | |
| | Airways diseases | |
| | | bronchitis |
| | | bronchiectasis |
| | | cystic fibrosis |
| | Neoplasms | |
| | | bronchogenic carcinoma |
| | | bronchial carcinoid |
| | Inflammatory disorders | |
| | | tuberculosis |
| | | pneumonia |
| | | lung abscess |
| | | aspergilloma |
| | Pulmonary vascular diseases | |
| | | pulmonary thromboembolism |
| | | pulmonary vasculitis |
| | | arteriovenous malformations |
| **Cardiovascular** | | |
| | Mitral stenosis | |
| | Congestive heart failure | |
| **Miscellaneous** | | |
| | Use of anticoagulants or fibrinolytics | |

present as coffee-ground emesis. Gastrointestinal, (GI), symptoms suggest an upper GI work-up when the bleeding source is unclear.

The second question to be asked is whether the bleeding is massive (or life-threatening), which if present, changes the approach to management as well as affecting the differential diagnosis. Massive or life-threatening hemoptysis has usually been defined by the rate of bleeding, defined as greater than 200 ml per day by various authors. The bleeding rate is critical since the problem with massive hemoptysis is not exsanguination but asphyxiation from blood that floods alveoli or clots that functionally obstruct airways. Thus, any amount of bleeding at a high rate, even over a short period of time, should be managed as being potentially life-threatening. The approach to massive hemoptysis is described in more detail below.

## Differential Diagnosis

The differential diagnosis of hemoptysis is shown in Table 10. The most common causes are bronchitis, lung cancer, pneumonia, lung abscess, tuberculosis, bronchiectasis, and pulmonary thromboembolism. The prevalence of these disorders in causing hemoptysis appears to be changing and varies considerably in different series. In North America, tuberculosis (both active and inactive) and bronchiectasis appear to be decreasing as a cause of hemoptysis whereas they are still extremely frequent causes of hemoptysis in many other parts of the world. In many (but not all) series, a significant proportion of cases remain undiagnosed despite extensive work-up.

Conditions that cause massive hemoptysis are generally inflammatory disorders which erode into the bronchial circulation. Because the bronchial circulation is under systemic vascular pressure, the bleeding is likely to be more severe than if the source of bleeding were the pulmonary circulation. Thus, causes of massive hemoptysis consist mainly of suppurative or chronic infections or conditions complicated by infection (lung

abscess, tuberculosis, bronchiectasis, or cystic fibrosis), but also include lung cancer.

**Evaluation of Hemoptysis**

The initial evaluation in all patients consists of a careful history and physical examination, and upright PA and lateral chest x-rays. The history should elicit and detail any acute or chronic pulmonary symptoms, including cough, sputum production, shortness of breath, or wheezing, and any previous history of lung disease. Systemic symptoms such as fever, sweats, weight loss, and malaise may reflect ongoing inflammation or reflect a catabolic process related to cancer or chronic infection. The history should uncover symptoms associated with the specific causes in the differential diagnosis including symptoms of heart disease (especially mitral stenosis), vasculitis, and with particular attention given to pulmonary thromboembolism. In considering pulmonary thromboembolism, in addition to the acute onset of pulmonary symptoms and any leg symptoms reflecting possible deep venous thrombosis, the most important part of the history focuses on asking about possible risk factors for deep venous thrombosis.

Physical examination includes auscultation, listening for generalized wheezing (COPD/asthma), localized wheezing (local bronchial obstruction), or diffuse or localized crackles or rhonchi which may reflect infectious or inflammatory processes including lung abscess, pneumonia, and bronchiectasis. A careful cardiovascular examination should be done, particularly looking for congestive heart failure, evidence of mitral stenosis, and signs of deep venous thrombosis. It is important to recognize that signs of deep venous thrombosis are lacking in at least half of the cases in which deep venous thrombosis is eventually proven. A negative result of the examination, therefore, clearly does not rule out deep venous thrombosis or the possibility of pulmonary thromboembolism.

A complete blood count and coagulation studies should be ordered. A PA and lateral chest x-ray should be routinely obtained. The chest x-ray may be very helpful in suggesting a source of the hemoptysis, such as pulmonary inflammatory disease or cancer. If the chest x-ray is abnormal, it will often suggest subsequent steps in the work-up. Sputum cytology on expectorated sputum should be obtained in any patient at significant risk for lung cancer based on epidemiologic considerations, whether or not the chest x-ray is suspicious for cancer. This includes all patients with COPD.

If the chest x-ray is negative or unrevealing, it does not rule out important disease as a cause of hemoptysis. Therefore, one must make a clinical decision about how much further to go in the evaluation. This decision should be individualized according to each clinical situation and the availability of diagnostic facilities and subspecialty consultation. Generally, CT of the chest is the preferred next study since it is noninvasive, can detect small cancers in the bronchial tree and lung parenchyma, and can diagnose bronchiectasis. Chest CT might also provide information useful to the bronchcoscopist if bronchoscopy becomes a consideration. Three forms of chest CT are available that might be helpful in diagnosing the cause of hemoptysis: chest CT with contrast; high resolution chest CT; and spiral CT of the chest. Each has its advantages for diagnosing some of the conditions in the differential diagnosis. Consultation may be indicated to determine which form of chest CT should be ordered for evaluation of a given patient.

**Specialized Work-Up**

Fiberoptic bronchoscopy is generally the next study to be considered. The decision to perform bronchoscopy should be made in consultation with a pulmonologist. Fiberoptic bronchoscopy may identify an endo-bronchial lesion, most often lung cancer, as the cause for hemoptysis and can help localize the lobe or

segment from which the blood originates. The combination of fiberoptic bronchoscopy and chest CT has been shown to give a higher yield of specific diagnoses than either test alone.

Fiberoptic bronchoscopy is indicated in certain categories of patients: those in whom the diagnosis is not evident from history, physical examination, chest x-ray, or chest CT; those with significant bleeding (greater than 30 ml per day) or in whom hemoptysis persists for longer than one week; and those who have systemic symptoms suggesting cancer or who are at particularly high risk for lung cancer, especially smokers over the age of 40. If none of these conditions is present, then the chance of finding lung cancer on bronchoscopy is very low and a decision to observe the patient should be considered.

If suspicion of a pulmonary embolus is moderate, particularly if risk factors exist for deep venous thrombosis and pulmonary thromboembolism, then a ventilation/perfusion lung scan should be obtained.

**Therapy**

The therapy of hemoptysis consists of that treatment appropriate for the underlying disease process, for example, antibiotic therapy for infectious etiologies. Otherwise, the treatment is nonspecific. The exception to this is when massive hemoptysis is present.

**Management of Massive Hemoptysis**

When the rate of bleeding qualifies as massive hemoptysis (a rate of greater than 200 ml per day) the situation should be considered to be a medical emergency requiring referral for immediate diagnostic and therapeutic steps. The treatment of massive hemoptysis includes consideration of either surgical removal of the bleeding site or bronchial angiography with embolization of the bleeding site, when feasible. Although there is some debate regarding the role of bronchial embolization, with some authors suggesting it be performed in all cases, the standard management for life-threatening bleeding due to localized disease in

a patient with good pulmonary reserve is usually surgical resection. If emergent surgery is being considered, the diagnostic goal consists of localizing the bleeding site. First, determine which lung is bleeding and then, if possible, identify which lobe or segment contains the bleeding source. Bronchial arterial embolization is usually indicated in patients with nonlocalized disease and/or limited breathing reserve to preserve pulmonary parenchyma and function. Localization can also be helpful when bronchial embolization is being considered, because it permits selective bronchial angiography to be undertaken, which markedly shortens the angiographic procedure. Bronchoscopy, either fiberoptic or rigid bronchoscopy, should be performed as soon as possible in an attempt to localize the site of bleeding within the lung. Localization of the bleeding source is much more successful if some degree of active bleeding is still occurring.

If the lung from which the bleeding is occurring is suspected (e.g., based on the chest x-ray or the patient's subjective impression), the patient should be positioned with the affected lung placed in a dependent position to prevent drainage of blood into the contralateral lung. The patient may be lightly sedated or tranquilized to diminish cough, but the state of consciousness should not be impaired such that the patient is unable to cough and maintain a clear airway. Once it is decided that surgery is indicated, then control of the airways should be obtained. Ideally, a double lumen tube should be inserted. However, if the required experience is not available, a standard endotracheal tube should be placed. If the bleeding is suspected to be from the left lung, then the tube can be placed in the right mainstem bronchus and the right lung ventilated while the patient is prepared for emergent surgery.

*(continued)*

**When to Refer**

Indications for referral to subspecialists for evaluation of hemoptysis include the following:

- Consideration of CT scan (to help determine type).
- Consideration of bronchoscopy (see indications above).
- Presence of massive or life-threatening hemoptysis.
- Persistent or recurrent undiagnosed hemoptysis.

**Medicolegal Concerns**

The biggest concern for liability on the part of the physician in evaluation of hemoptysis is failure to diagnose lung cancer. A less frequently occurring situation is the failure to diagnose pulmonary thromboembolism. Because these clinical situations have differing concerns they will be treated separately.

Eventual diagnosis of lung cancer when the patient presented earlier with hemoptysis is a cause for malpractice litigation. Two considerations allow appropriate evaluation while protecting the physician from risk. The first is to recognize the patient at risk for lung cancer from demographic data and smoking history, and include a sputum cytology (and, if warranted clinically, fiberoptic bronchoscopy) in the initial work-up. The second is to clearly record the advice given to the patient with suspected bronchitis and mild hemoptysis that stops spontaneously to return for further evaluation should hemoptysis recur.

Hemoptysis is an infrequent but important symptom in pulmonary thromboembolism. The liability here is failure to consider pulmonary thromboembolism and to order appropriate tests when hemoptysis is associated with other acute symptoms (including shortness of breath and/or pleuritic chest pain) in a patient at risk for deep venous thrombosis.

**Summary**

There are several important steps in evaluation of the patient with hemoptysis. First, it should be determined whether the bleeding represents true hemoptysis or whether the source of bleeding is in the upper airway or in the gastrointestinal tract. Second, the significance of the bleeding should be evaluated, specifically ascertaining whether life-threatening bleeding is present. Third, a differential diagnosis based on the initial history should be developed. This will help focus subsequent questioning, physical examination, and laboratory studies on likely sources of bleeding for the specific clinical situation. A chest x-ray should be obtained. If history and physical examination, and a chest x-ray do not reveal the source of bleeding, then a chest CT should be considered. Patients who are candidates for bronchoscopy include those with bleeding of more than 30 ml per day, hemoptysis which has been persistent for one week, and patients at high risk for lung cancer, particularly smokers older than 40 years of age. Massive or life-threatening hemoptysis (bleeding at a rate of greater than 200 ml per day) constitutes an emergency with the major diagnostic objective being localizing the source of the bleeding so that emergent surgery to remove the bleeding site can be carried out. Bronchial arteriography and embolization should be considered in patients with poor pulmonary reserve due to pre-existing lung disease. ■

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## F. Wheezing–Stridor

### Introduction

Wheezing is manifested as high-pitched, musical, variable sounds with breathing, most prominently during expiration. The sound is generated by gas flowing through narrowed or irregular airways. In some instances it is immediately audible, but in most cases, it is heard only by auscultation of the chest. Generally, wheezing is due to asthma, although a variety of other conditions may be associated with this finding.

Stridor, by contrast, is the typically shorter, crowing sound, which is often evident during inspiration and expiration, but which is louder and longer during inspiration. It is heard readily without the aid of a stethoscope. Stridor is almost universally associated with mechanical or functional narrowing of the larynx or subglottic airways. Clinically, stridor is most commonly heard with either viral/bacterial infections, usually of infants and children, which result in epiglottitis or laryngitis. Sometimes, aspirated food or foreign bodies may cause acute stridor. Chronic stridor is most often the result of conditions that cause fixed narrowing of the extrathoracic airways. Laryngeal carcinoma, paralyzed vocal cords, or subglottic granulation tissue are among the more common causes of chronic inspiratory stridor. Because the causes of stridor are acutely and readily identified by clinical pattern and/or laryngeal examination, this symptom will not be discussed further in this Section.

Various components of the history and physical examination, or laboratory assessment can aid in diagnosing asthma or the recognition of other conditions that result in wheezing. Some relatively common disorders might be mistaken for asthma (See Table 11). The table is organized by anatomical sites in order to aid with a systematic consideration of options. Table 12 includes selected elements that are useful in this process. In addition, a general principle for practitioners is to re-evaluate the diagnosis of asthma or to refer to specialists when patients do not respond

## Table 11 Various Disorders Associated with Wheezing–Stridor*

| |
|---|
| **Laryngeal:** |
| *Vocal cord dysfunction syndrome, (VCDS)* |
| Factitious asthma (malingering) |
| Vocal cord paralysis |
| Vocal cord dystonia |
| Vocal cord nodules or polyps |
| Laryngeal carcinoma |
| Viral or bacterial infection of epiglottis or larynx |
| Angioedema of epiglottis or larynx |
| **Subglottic:** |
| Post-tracheostomy scarring/narrowing |
| Post-intubation scarring/narrowing |
| Thyroid compression, goitrous or cancerous |
| **Tracheal and Large Airway:** |
| *Foreign bodies, aspirated* |
| *Bronchial adenomas* |
| Endobronchial sarcoidosis |
| Bronchogenic carcinoma and endobronchial metastases |
| Peribronchial lymph node compression, infectious or cancerous |
| Webs |
| Vascular rings |
| **Small Airways:** |
| *Bronchiolitis, infectious or idiopathic* |
| Lymphangioleiomyomatosis |
| Eosinophilic granuloma/histiocytosis-x (Langerhans' cell disorders) |
| **Alveolar and Vascular:** |
| *Cardiogenic pulmonary edema* |
| Fibrosing alveolitis |
| Pulmonary emboli |

* Conditions more commonly confused with asthma are indicated by italics.

## Table 12 Criteria to Distinguish Asthma from Other Wheezing Disorders*

| | Asthma | VCDS | Tracheo-bronchial Obstruction | COPD | Bronchio-litis Obliterans | Cardiogenic Pulmonary Edema |
|---|---|---|---|---|---|---|
| **I History** | | | | | | |
| Seasonal | + | - | - | - | - | - |
| Labile/abrupt | +++ | ++ or +++ | - | - | - | + |
| A.M. dipping | + | - | - | Rare | - | + |
| Sinusitis | ++ | - | - | - | - | - |
| Exercise induced | ++ or +++ | + | + | -/Rare | - | ± |
| Responds to therapy | ++ or +++ | ± | - | + | ± | - |
| Post URI | ++ | - | - | + | + | - |
| Heavy tobacco use | Rare | Rare | +,with cancer | +++ | Unrelated | +, with ASHD |
| **II. Physical** | | | | | | |
| Expiratory wheezes | ++ or +++ | ± | + | ++ | ± | ± |
| Volume lung | ↑or ↑↑ | Normal | Normal, + | ↑↑ or ↑↑↑ | ↑ | Normal |
| Breath sounds | Normal, ↓ | Normal | ↓ | ↓↓ | ↓ | Normal or ↓ (Effusions) |
| Pulsus paradoxus | +, when severe | - | - | - | - | - |
| Inspiratory wheezes | + | +++ | + | - | ± (Crackles) | Crackles & wheezes |
| **III. Pulmonary Function Tests, (PFT's)** | | | | | | |
| Expiratory flow | ↓ | ± | ↓ | ↓ | ↓ | ↓ |
| Inspiratory flow | Normal or ↓ | ↓↓ | ↓ | ↓ | Normal | Normal |
| Volumes | ↑ | Normal | Normal or ↓ | ↑↑ | ↑ or ↑↑ | ↓ |
| Reversible | ++ or +++ | - | - | ± | - | ± |
| $D_LCO$ | Normal or ↑ | Normal | Normal or ↓ | ↓ or ↓↓ | ↓ | Normal or ↑ |

| | Asthma | VCDS | Tracheo-bronchial Obstruction | COPD | Bronchio-litis Obliterans | Cardiogenic Pulmonary Edema |
|---|---|---|---|---|---|---|
| **IV. Chest X-ray** | | | | | | |
| Volumes | ↑↑ | Normal | Normal, ↑or ↓ | ↑↑↑ | ↑ | Normal |
| Infiltrates | Occasionally | - | Occasionally | - | Occasionally (BOOP) | Usual |
| Symmetry | Usually (mucus plugs may cause atelectasis) | Normal | ↑Asymmetry (get inspiratory/ expiratory views) | Normal | Usual | Usual |
| **V. Arterial Blood Gases, (ABGs)** | | | | | | |
| $O_2$ | ↓ | Normal | Normal or ↓ | ↓ | ↓ | ↓ |
| $CO_2$ | ↓ | ↓ | ↓ | Normal or ↑ | ↓ | Variable |
| **VI. Others** | | | | | | |
| EOS | ±↑ | Normal | Normal | Normal | Normal | Normal |
| IgE | ±↑ | Normal | Normal | Normal | Normal | Normal |
| Hgb/Hct | Normal | Normal | Normal | Normal or ↑ | Normal | Normal |
| ECG | NST | NST | Normal | RVE/RVH | Normal or RVE/RVH | LVE/RVH |

*Abbreviations ASHD=arteriosclerotic heart disease; BOOP=bronchiolitis obliterans with organizing pneumonia; COPD= chronic obstructive pulmonary disease; $D_LCO$=diffusion test; ECG=echocardiogram; EOS=eosinophils; Hct=hematocrit Hgb=hemoglobin; lgE=immunoglobin E; LVE= left ventricular enlargement; NST= non-significant T-wave; RVE=right ventricular enlargement; RVH=right ventricular hypertrophy; URI=upper respiratory tract infection; VCDS=vocal cord dysfunction syndrome.

satisfactorily to standard management (see above). Asthma and some of the conditions more frequently mistaken for this disorder are described briefly below.

**Asthma**

Patients who present with episodic wheezing and dyspnea very likely suffer from asthma. However, the diagnosis should be confirmed, including steps to both document and characterize the asthma, as well as to rule out other disorders that might complicate or simulate the asthma.

Baseline diagnostic steps in the initial evaluation include elements of the history and physical examination, and laboratory studies. Historical features to suggest asthma include a familial pattern, associated conjunctivitis and rhinosinusitis, seasonality, episodic appearance, worsening with coughing in late night and early morning, and/or provocation by exercise, exposure to pets, cold air, aspirin, or nonsteroidal anti-inflammatory drugs, (NSAID's). Physical examination characteristically demonstrates prolonged expiratory high-pitched musical sounds heard prominently in the mid and lower lung fields. Tachypnea, tachycardia, and diaphoresis are prominent with acute illness. In severe and chronic cases, overinflation of the thorax with increased anterior-posterior diameter and limited chest wall excursion are seen. Coughing is variably prominent, typically with production of sparse but tenacious secretions. Rhinitis with boggy membranes is common. Nasal polyps may indicate "triad" asthma (asthma, sinusitis, and polyps due to aspirin sensitivity). The key laboratory study to confirm the diagnosis of asthma is spirometry, which typically demonstrates reduced forced expiratory volume in one second, ($FEV_1$), that is reversible with inhalation of ß-adrenergic aerosols. Between episodes, however, pulmonary function tests, (PFT's), may be normal. In patients suspected of having asthma but whose initial spirometric studies are normal, bronchial challenge

tests with histamine or methacholine will reveal bronchial hyperresponsiveness; in its absence, alternative diagnoses are likely.

Seasonal, allergically-mediated asthma may be accompanied by peripheral blood eosinophilia and elevated levels of immunoglobulin E, (IgE). Other investigations to identify disorders that may complicate asthma include CT scans of the paranasal sinuses and assessment for gastroesophageal reflux by barium contrast studies or 24-hour pH monitoring. Among children and young adults with asthmatic symptoms and abnormal spirometry with partially reversible obstructive deficits, consideration should be given to the co-existence of mild forms of cystic fibrosis. Chest x-rays need not be done with typical asthma that is readily responsive to therapy. But among patients with complicated or poorly responsive wheezing syndromes, radiographic studies may help suggest alternative diagnoses as delineated in Table 12. Specific features of the more common disorders that are potentially confused with asthma are described below.

**Vocal Cord Dysfunction Syndrome, (VCDS)**

Several articles have described patients with episodic dyspnea, wheezing and stridor from episotic airflow obstruction originating in the larynx. Vocal cord dysfunction syndrome, (VCDS), merits particular emphasis due to its recent recognition and the general lack of familiarity on the part of clinicians. Also of importance is the potential for immense iatrogenic morbidity if misdiagnosed as refractory asthma.

Typically, VCDS is associated with *inspiratory* wheezing due to paradoxical closure of the cords. Features which help to distinguish it are: failure to respond to standard therapy, inspiratory stridor (the anomaly of inspiratory wheezes may be overlooked due to the patient's dramatic distress), the patient's indication that the obstruction is most pronounced in the neck, coarseness of voice around the attacks, the absence of hypoxemia

despite severe respiratory distress, and the failure of patients to report nocturnal awakening or early morning symptoms.

VCDS is thought to be a conversion reaction, not deliberate malingering. Two groups have been noted to be at greater risk: women, ages 20 to 50 years, many of whom work in helping or para-medical roles, and young adolescents who are high-achieving athletes or students and whose attacks come at times of stress.

Diagnosis of VCDS is based upon the clinical presentation, evidence of upper airway obstruction and laryngoscopic demonstration of anomalous vocal cord motion. Treatment entails speech therapy, psychological intervention, and weaning from asthma medication (provided that there is documentation of the absence of bronchial hyperresponsiveness). Most critically, patients should be withdrawn from the high doses of corticosteroids that they are typically receiving for "refractory asthma."

**Other Disorders Commonly Mistaken for Asthma**

In addition to VCDS, the following are notable for the frequency with which they are mistaken for asthma.

**Central Airway Masses:** Granulation or scar tissue may form within the subglottic area or trachea following tracheostomy or prolonged intubation. This may produce substantial impairment of airflow, stridor, and dyspnea. Similarly, thyroid masses may compress this region of the trachea. If the obstructing lesion lies outside the thorax, inspiratory stridor may be the most prominent manifestation. Lower lesions may cause both inspiratory and expiratory wheezing.

**Bronchial Masses:** Various obstructive lesions, benign or malignant, may narrow the lumina of major bronchi, causing dyspnea, wheezing, and cough. Aspirated foreign bodies and bronchial adenomas are

especially prone to confusion with asthma due to their occurrence in younger persons and the absence of systemic findings to suggest the diagnosis.

**Small Airway Lesions:** Bronchiolitis obliterans, (BO), a disorder characterized by obstructive proliferation within the very small peripheral airways, also confounds the diagnosis of asthma. Associated with a variety of predisposing diseases or idiopathic, BO typically presents with cough and shortness of breath. Wheezes may or may not be present. In contrast to BO with organizing pneumonias, (BOOP), the chest x-ray is usually within normal limits or mainly shows overinflation. High resolution CT may reveal patchy or mosaic variation of lung tissue density thought to reflect heterogeneous zones of air-trapping caused by BO. Spirometry reveals reduced expiratory airflow with minimal or no improvement with bronchodilators. Many patients, however, respond to systemic corticosteroids, sometimes leading to a diagnosis of variant asthma. Diagnosis is made by lung biopsy.

**Cardiogenic Disorders:** Cardiogenic pulmonary edema has considerable clinical overlap with asthma. Episodic dyspnea, nocturnal worsening, aggravation with exercise, and, on occasion, wheezing that responds to bronchodilators, are all potential components of cardiogenic pulmonary edema. Therefore, careful review of risk factors plus physical examination and laboratory studies to identify cardiac dysfunction are essential.

## When to Refer

Most individuals who complain of episodic dyspnea, chest tightness, and anxiety that is associated with expiratory wheezes have asthma. Spirometry should be done to confirm the diagnosis and to quantify the degree of airway obstruction. These patients should be managed in accordance with recently published guidelines and their treatment stratified by disease severity. However, among individuals with

uncharacteristic symptoms, physical findings, or laboratory studies, alternative diagnoses should be considered. Failure to respond to conventional treatment, including the requirement for chronic oral steroids, should be regarded as an important indication for referral.

**Medicolegal Concerns**

Perhaps the most compelling considerations are the morbidity that derives from extended, inappropriate use of corticosteroids for conditions other than asthma or from delayed/missed diagnosis of central airway narrowing from tumors or foreign bodies. Also, failing to provide to the patient and/or family a plan of care for escalating or refractory symptoms is deemed substandard practice.

**Summary**

It is still true that "not all that wheezes is asthma." However, most is! Historical, radiological, and physical findings as well as pulmonary function testing generally allow clinicians to distinguish asthma from other conditions. But, among selected patients, alternative diagnoses may prove diagnostically elusive. By considering Tables 11 and 12 and the narrative sections above, practicing physicians should be assisted in recognizing asthma and the diverse conditions that can mimic this disorder. ■

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## G. Positive Tuberculin Skin Test

### Introduction

The human defensive response against tuberculosis, (TB), largely entails cell-mediated immunity, (CMI). This is in contradistinction to the humoral or antibody-mediated response to most bacterial infections. Delayed-type hypersensitivity, (DTH), a closely related but not identical phenomenon to CMI, is manifested clinically as a type IV immune response mediated by lymphocytes and is characterized by indurated response to the intradermal injection of protein from the cell wall of the tubercle bacillus. The most commonly used test employs the Mantoux technique wherein a small amount of tuberculoprotein (purified protein derivative, or PPD), is introduced into the intradermal tissues with a small-gauge needle. The amount of induration is measured between two and five days later.

Historically, the reaction was originally regarded as either "positive" or "negative." However, recently, in an effort to maximize the utility of this diagnostic test, reactions have been categorized by different criteria depending on the circumstances of the patient. This is the so-called "5-10-15 millimeter system." The clinical applications of this stratified interpretation system, as applied to preventive chemotherapy, are displayed in Table 13. This stratification is an effort to make the tests both relatively more sensitive and more specific. Problems with interpretation will be discussed more fully below.

### Who Should Have the Tuberculin Skin Test, (TST)?

**Diagnosis of Disease:** Historically, the tuberculin skin test, (TST), has been regarded as a major element in the diagnosis of tuberculosis. This, however, may not be a wholly appropriate use of this test. There are three potential pitfalls to the TST in clinical care: false negatives, false positives, and true but irrelevant positives. The major problem with the TST in the diagnosis of active disease is that substantial numbers of patients with active TB do not have significant reactions to the test. In various studies among HIV-

## Table 13 Isoniazid Preventive Therapy, (IPT)*

**1994 American Thoracic Society/Centers for Disease Control Guidelines**

| Condition | Duration of IPT | PPD | Comments |
|---|---|---|---|
| HIV + **or** suspect | 12 months | ≥ 5 mm induration or regardless of PPD | May give IPT to those at high risk of tuberculosis infection by epidemiology alone. |
| Close contact to newly diagnosed, infectious case | 6 months | ≥ 5 mm induration or regardless of PPD | IPT for infants/young children exposed; may stop if PPD remains negative at 3 months. |
| Recent tuberculin conversion (in past two years) | 6 months | ≥ 10 mm if < 35 years<br>≥ 15 mm if ≥ 35 years | IPT for all PPD reactors < 4 years. Induration increases of 10mm or > are significant. |
| Fibronodular scarring in lung apex | 12 months | ≥ 5 mm induration | • Any age group<br>• Rule out active disease |
| Medical conditions with increased tuberculosis risk | 6 months | ≥ 10 mm induration | IDDM, prolonged steroids, immunosuppressive Rx, cancers, IDU, ESRD, rapid loss of weight or malnutrition. |
| PPD reactor < 35 years old with racial, socioeconomic or other non-medical risk factors | 6 months | ≥ 10 mm induration | • Foreign born, high risk area<br>• Disadvantaged poor/minority<br>• Residents of at risk facilities (NHs, correctional or psych) |
| PPD reactor < 35 years old without special risk factors | 6 months | ≥ 15 mm induration | Consider risk-benefit on ad hoc basis |

*Abbreviations: ESRD=end-stage renal disease; HIV=human immunodeficiency virus; IDDM=insulin-dependent diabetis mellitis; IDU=injection drug user; IPT=isoniazid preventive therapy; NHs=nursing homes; PPD=purified protien derivative

negative adult patients with active pulmonary disease, 15% to 25% of individuals at the time of diagnosis did not have a positive response. As might be expected, patients with HIV infection/AIDS have progressively higher rates of anergy or false negative reactions to the tuberculin test as their CD4+ T-lymphocyte count diminishes. Among persons with HIV infections but no other AIDS-defining illnesses and high numbers of CD4 lymphocytes, the likelihood of a positive skin test is approximately 70%. However, among patients with advanced AIDS and CD4+ T-lymphocyte depletion, as few as 10% to 20% of the patients with tuberculosis may react to the TST. These false negatives are of potentially major consequence if clinicians allow this test to be a major element in their diagnostic thinking, with the erroneous notion that "a negative TST excludes TB." Furthermore, the TST may yield "false positive" reactions (see below). In addition, patients may have a true-positive TST, but not have active TB, i.e., a true but irrelevant positive reaction. Hence, it is recommended that the tuberculin skin test be regarded only as a diagnostic aid without major significance in terms of ruling in or ruling out active tuberculosis.

In summary, a significant tuberculin reaction increases the likelihood of any given condition being tuberculous in etiology. But the test must be used with full recognition of its limitations. Clinicians should ask themselves, how will a positive or negative result affect their thoughts and actions?

**Diagnosis of Infection:** Probably the most appropriate utilization of the TST is to identify people who have latent infection with TB. Among HIV-negative individuals infected with *Mycobacterium tuberculosis,* authorities estimate that 10% to 15% will eventually develop active tuberculosis. The TST is used to identify individuals with latent infections so that they may be offered chemotherapy to prevent progression from clinically inapparent infection to active disease. In this setting, the TST is the only diagnostic tool. Because the

test defines the condition, we are not able to tell whether false negative reactions occur. However, it is reasonable to presume that some portion of individuals harboring latent tuberculosis do not react to the TST. This is particularly the case with infants or HIV-infected persons who have been recently exposed to a case of communicable tuberculosis. Another variety of "false negative" TSTs merits attention: tests which truly yield a significant amount of induration, but are erroneously read by health professionals as negative. Repeated studies demonstrate that unpracticed physicians and nurses "read" TSTs erratically with a tendency toward underestimation.

Given the relative paucity of tuberculosis in the general population of the United States, not all persons are candidates for screening with the TST. Current epidemiology indicates that the groups shown on Table 13 are at relatively high risk of tuberculosis. These persons might be routinely screened with the TST attempting to identify latent infection and to offer preventive chemotherapy. But given the propensity of the tuberculin skin tests to generate false positive results, it may be argued that tuberculin skin tests should not be used on individuals at low risk of tuberculosis infection. This is due to the likelihood of generating significantly more false positive reactions than true positives. If the tuberculin skin test is used in individuals with a high likelihood of having underlying tuberculosis infection, it performs quite well. However, when used in a population with a tuberculosis infection prevalence of less than 5% (an accurate representation of the white indigenous population of the United States), it will predictably result in substantially more false positive reactions than true positive reactions, a situation that is not helpful in terms of individual or public health.

False positive reactions to the TST have been clearly identified in relationship to prior infections with nontuberculous mycobacteria, (NTM), or to vaccination

with bacille Calmette-Guérin, (BCG), a vaccine prepared from an attenuated but living strain of *M. bovis*—an organism closely related to the tubercle bacillus. NTM infections are widely distributed across the United States, but are most common in the warm, moist environment of the Southeast. Hence, for individuals who have resided in this region, particular caution should be exercised in interpreting TST results. Also, TST results in persons who have received BCG vaccination are problematic. Most individuals who receive a BCG vaccination become only transiently (six months to five years) reactive to tuberculin. If no other BCG vaccinations are given and if infection with TB or NTM does not occur, after ten to 20 years, the great majority of these persons will not react to TST. Thus, authorities have indicated that most individuals from parts of the world that are endemic for tuberculosis who have positive TSTs, should be presumed to be infected with TB. Although there will be some false positive reactions when using this model, the implications of missing latent tuberculosis infection—and the opportunity to administer preventive chemotherapy—among this high risk group are regarded as unacceptable.

**Surveillance**

Again, the TST is the only useful tool for surveillance of populations at risk for TB infection. In this setting, there is interest both in finding the infection in individuals, so that they may be offered preventive chemotherapy, and for the detection of recently-transmitted infection, in order to monitor the risk of transmission in an institution or community. In this setting, care must be taken to avoid false positive skin test conversions. These false positives may result in inappropriate administration of isoniazid, (INH), preventive therapy, an intervention which has modest but real risk of drug toxicity and which predictably produces great anxiety.

False negative initial test results may also pose a problem. To avoid this sort of confusion, authorities

have recommended that individuals to be surveyed should have two-step testing to take advantage of the phenomenon of "boosting". Boosting overcomes the fact that with the passage of time, TST reactivity may wane. However, the placement of the first TST, to which the reaction is negative, stimulates waned immunity and causes the next TST to become positive. If the individual is given TST #1 at the time of enrollment, and no other testing is done for several months, when TST #2 becomes positive the inference must be that the individual has been newly infected during the interval period. Instead, the newly positive test merely reflects boosted DTH. To avoid this, TST #1 and #2 should be given within one to four weeks of each other. If the first test is negative, test #2 is applied at seven days to 21 days after the initial test. If the second test is reactive, the conclusion is that the result reflects boosting, not new infection. While the likelihood of boosting is greater with advanced years (the period of time for waning is greater in older persons), virtually any population to undergo surveillance should have two-step testing to avoid erroneous interpretations that the second positive TST represents a conversion. It should be noted that boosting may occur due to prior infection with *M. tuberculosis,* a prior BCG vaccination, or prior infection with NTM.

Current public health practices and Occupational Safety and Health Administration, (OSHA), guidelines indicate that healthcare workers including laboratory personnel, autopsy suite personnel, and medical and nursing students should all have routine tuberculin surveillance to detect new tuberculosis infection. This umbrella has been extended to staffs and clients of correctional facilities and nursing homes where epidemic tuberculosis has been noted to occur. Current OSHA guidelines indicate that institutions should establish a regular policy for tuberculin skin testing for all employees regardless of exposure to patients or clients. This may not be appropriate given the

performance characteristics of the test. Nevertheless, these guidelines are presently in effect. In these settings, annual skin testing is indicated. However, testing up to twice yearly has been advocated for persons at high risk of exposure, such as those working in inner city emergency rooms, intensive care units, and TB or AIDS wards.

**What to Do for Persons Found to React to the TST**

If a child or adult is found to have a significantly positive TST, several issues arise:

- Where did they become infected? Particularly, among younger persons or adults with recently converted TSTs, it is critical to attempt to locate the person(s) responsible for transmitting the infection. This is important both to identify the source case, so that they may be treated, and to determine whether others may also have been infected. The investigation should be directed to clarify whether transmission occurred at home, at work, at school, or in social settings. This function is generally undertaken by the community Public Health Department.

- What additional work-up is indicated? The critical immediate question is whether the individual with the positive TST has active TB. To investigate this possibility, clinicians should conduct a careful history and physical examination, as well as perform screening laboratory studies.

  Elements of this history which merit particular attention include any systemic symptoms mindful of TB, such as feverishness, sweats, weight loss, malaise, failure to thrive, or to achieve regular growth landmarks for infants or children. Also, organ-specific symptoms such as cough, phlegm, hemoptysis, chest pain, dyspnea, swollen glands, masses, difficulty with urination, hematuria, and/or back/hip/joint pain should be explored.

Physical examination should include focused attention upon lymphadenopathy (particularly in the supraclavicular, anterior cervical, and posterior triangle chains), paraspinal/hip/inguinal masses, adnexal masses, or adhesions in women, and, among persons with AIDS, cutaneous nodules.

Laboratory studies should include a PA and lateral chest x-ray, a complete blood count with an erythrocyte sedimentation rate, and a urinalysis. Other studies should be obtained in accordance with findings in the history and physical examination. Sputum smears and cultures for acid-fast bacilli, (AFB), are mandatory for patients with chest x-ray abnormalities or suggestive respiratory symptoms. Gastric aspirates may be obtained for infants who are unable to cooperate with sputum collection.

- What therapeutic intervention(s) is(are) indicated? If the initial data suggest that the patient does have or may have active TB, treatment should be initiated and the "suspected" case reported to local public health authorities for contact tracing. In some communities or special situations, public health systems may supervise treatment of the patient, particularly if directly-observed therapy is to be administered. If the final results of the initial evaluation indicate that the patient does not have active TB, the initial multi-drug treatment may be regarded as intensive preventive chemotherapy. In these cases, treatment can be terminated at three to four months and the patient is considered to have received a full-course of preventive therapy (See American Thoracic Society/Centers for Disease Control Guidelines).

  On the other hand, if there is no evidence in the initial evaluation to suggest active TB, consideration should be given to INH preventive therapy. Current indications for INH chemoprophylaxis are presented in Table 13. Notable aspects of this document

include the variable criteria for "significant" tuberculin reactivity, differing recommendations for the duration of INH therapy (twelve months for HIV-infected persons or persons with inactive apical fibrotic lesions, nine months for infants or children, and six months for all others) and practices to monitor for potential drug toxicity.

**When to Refer**

As noted above, all cases of proven or suspected TB should be reported to local public health authorities. This does not mean that management of the patient will necessarily be relinquished, although the option of directly-observed therapy should be explored.

Patients who require bronchoscopy, biopsies, or aspirations of organs, nodes or masses should be sent to appropriate specialists.

**Medicolegal Concerns**

Probably the greatest areas for concern are failure to recommend isoniazid preventive therapy for persons with a positive TST who are at high risk for TB, e.g., an HIV-infected individual, and, once chemoprophylaxis is begun, failure to monitor adequately for INH-associated hepatitis. ■

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## H. Pleural Effusion

### Introduction

Normally, very small amounts of pleural fluid are present in the pleural spaces, and fluid is not detectable by routine methods. When certain disorders occur, excessive pleural fluid may accumulate and cause pulmonary signs and symptoms. Simply put, pleural effusions occur when the rate of fluid formation exceeds that of fluid absorption. Once a symptomatic, unexplained pleural effusion occurs, a diagnosis needs to be established.

### Signs and Symptoms

Pleuritic chest pain, chest pressure, dyspnea, and cough are the most common symptoms of pleural effusion. Pain may occur with little fluid formation as the symptom is related to the intense inflammation of the pleural surfaces. Chest pressure usually does not occur until the effusion is in the moderate (500 to 1,500 ml) to large (> 1,500 ml) category. Dyspnea rarely occurs with small effusions unless significant pleurisy is present. Often the patient will not complain of dyspnea until the effusion is massive with contralateral mediastinal shift on the chest x-ray. Cough is usually related to the associated atelectasis, which to some degree accompanies all pleural effusions. Classic physical findings associated with pleural effusions may occur when the volume begins to exceed 500 ml and include diminished breath sounds, dullness to percussion, reduced tactile and vocal fremitus, and occasionally a pleural friction rub. In contrast to pneumonia and atelectasis, crackles are not heard with an isolated pleural effusion.

### Noninvasive Diagnostic Techniques

When the presence of a pleural effusion is suspected by physical examination, confirmation with a chest x-ray is necessary. With some pleural effusions, especially when subpulmonic in location (layering below the lung but above the hemidiaphragm), a lateral decubitus film usually confirms the presence of fluid. Pleural space ultrasound is extremely helpful to locate small amounts or isolated loculated pockets of fluid.

*(continued)*

## Table 14 Common Pleural Fluid Tests*

| Test | Significant Value | Frequently Associated Condition |
|---|---|---|
| Red blood cells | > 100,000 µl | Malignancy, trauma, pulmonary embolism |
| White blood cells | > 10,000 µl<br>Neutrophils > 50%<br>Lymphocytes > 90%<br>Eosinophils > 10%<br><br>Mesothelial cells | Pyogenic infection<br>Acute pleuritis<br>Tuberculosis, malignancy<br>Asbestos effusion, pneumothorax, resolving hemothorax<br>Absent tuberculosis |
| Protein | PF/S ratio > 0.5 | Exudate |
| Lactate dehydrogenase | PF/S ratio > 0.6; absolute level >.45 upper limit of serum | Exudate |
| Specific gravity<br>Glucose<br>Amylase | > 1.018<br>< 60 mg/dL<br>PF/S ratio > 1 | Exudate<br>Empyema, tuberculosis, malignancy<br>Pancreatitis, malignancy, esophageal rupture |
| Antinuclear antibodies | PF/S ratio > 1 | Lupus pleuritis |
| Rheumatoid factor | > 640 titer | Rheumatoid pleuritis |
| Hyaluronic acid | > 1 mg/ml | Mesothelioma |
| Adenosine deaminase | > 70 IU/L | Tuberculosis |
| Bacteriologic | Positive | Etiology of infection |
| Cytology | Positive | Diagnostic of malignancy |

PF/S ratio = ratio of value in pleural fluid to serum level.

*Modified from Kinasewitz GT. Pleuritis and Pleural Effusion. Pulmonary and Critical Care Medicine on CD-ROM 1997; Chapter One.

Thoracentesis can be performed simultaneously using ultrasound guidance. Chest CT is most helpful to distinguish between parenchymal and pleural disease and may demonstrate pleural thickening, pleural calcification, a pleural based mass, or loculated collections of fluid.

**Thoracentesis and Pleural Fluid Analysis**

To establish the etiology, a thoracentesis usually needs to be performed. Fifty to 100 ml of fluid are usually removed and sent for analysis (See Table 14). Not every effusion needs to be tapped, but when the patient has no obvious clinical cause for the effusion, is febrile, or has pulmonary compromise, fluid should be removed. The first step is to determine if the fluid is a transudate or an exudate. Transudative effusions occur when **systemic** factors that influence the formation and absorption of pleural fluid are altered (e.g., low serum proteins or increased pulmonary venous pressure). Exudative effusions occur when **local** factors that influence the formation and absorption of fluid are altered (e.g., infection or malignancy). The lactate dehydrogenase, (LDH), protein levels or specific gravity of the fluid can distinguish these two. Most agree that exudates must meet one or more of the following criteria, whereas transudates meet none:

- Pleural fluid/serum protein > 0.5 or absolute value > 3 g/dl.
- Pleural fluid/serum LDH > 0.6 or absolute value > 0.45 upper normal serum limit.
- Pleural fluid specific gravity > 1.018.

Once an effusion is categorized as transudative or exudative, etiologic considerations narrow. Additional pleural fluid studies that help to establish a diagnosis include glucose, amylase, white blood cell counts with differential, and cytologic and microbiologic examination.

*(continued)*

## Table 15 Etiology of Transudative Effusions

| |
|---|
| Congestive heart failure |
| Cirrhosis |
| Nephrotic syndrome |
| Peritoneal dialysis |
| Superior vena cava syndrome |
| Myxedema |
| Atelectasis (early) |

## Table 16 Etiology of Exudative Effusions*

| | |
|---|---|
| Parapneumonic | Atelectasis |
| Simple | Acute respiratory distress syndrome, (ARDS) |
| Complicated | Asbestos exposure |
| Empyema | Hemothorax |
| Tuberculosis | Chylothorax |
| Other infections | Cholesterol effusions |
| Fungal | Drug reactions |
| Parasitic | Dressler's syndrome |
| Malignant | Meigs' syndrome |
| Metastatic disease | Uremia |
| Mesothelioma | Sarcoidosis |
| Pulmonary embolism | Yellow nail syndrome |
| Collagen vascular disease | Radiation therapy |
| Rheumatoid arthritis | Ovarian hyperstimulation syndrome |
| Systemic lupus erythematosus | |
| Wegener's granulomatosis | |
| Churg-Strauss syndrome | |
| Familial Mediterranean fever | |
| Abdominal disease | |
| Pancreatitis | |
| Subphrenic abscess | |
| Esophageal rupture | |
| Postoperative | |

*Modified from Kinasewitz GT. Pleuritis and Pleural Effusion. Pulmonary and Critical Care Medicine on CD-ROM 1997; Chapter One.

## Etiology of Pleural Effusions

**Transudates:** The causes of transudative pleural effusions are listed in Table 15.

*Congestive Heart Failure:*
This is the most common cause of pleural effusion. Frequently the effusions are bilateral (approximately 75% of the time) but may occur alone on either side with the right side being more common. Fluid is usually straw-colored, with a low white blood cell count (< 500 cells/μl) and a mononuclear cell predominance. With severe congestive heart failure, fluid may persist in spite of vigorous diuresis.

*Cirrhosis, Nephrotic Syndrome, and Hepatic Hydrothorax:*
In disorders associated with low serum proteins and ascites, bilateral effusions are common. Cell counts are low and lymphocytes predominate. Glucose remains normal (> 60 mg/dl). Hepatic hydrothorax occurs in about 5% of patients with ascites and cirrhosis. The effusion occurs (usually on the right side) because of direct movement of peritoneal fluid through communications in the hemidiaphragm.

**Exudates:** The causes of exudative pleural effusions are listed in Table 16. The most common causes of exudative pleural effusions are parapneumonic (associated with pneumonia), malignancy, pulmonary embolism, trauma (including hemothorax and esophageal perforation), collagen vascular disease (especially rheumatoid arthritis), post-cardiac injury (including surgery), tuberculosis, trapped lung, and atelectasis. The characteristics of pleural fluids are listed in Table 17.

*Parapneumonic Effusion:*
Bacterial pneumonias are frequently associated with pleural effusions (as often as 50% of the time) and when they become complicated, require drainage. Complicated parapneumonic effusions include empyema (the finding of gross pus in the pleural

## Table 17 Pleural Fluid Characteristics in Common Diseases

| Etiology | Appearance & predominant WBC | Total WBC (per µl) | | RBC (per µl) | Glucose | Comment |
|---|---|---|---|---|---|---|
| **Transudates** | | | | | | |
| Congestive heart failure | Clear, straw-colored | < 1,000 | M | 0-1,000 | PF = S | Usually bilateral |
| Cirrhosis | Clear, straw-colored | < 500 | M | < 1,000 | PF = S | Incidence of 5% with ascites |
| **Exudates** | | | | | | |
| Parapneumonic (uncomplicated) | Turbid | 5,000-25,000 | P | < 5,000 | PF = S | Resolves with antibiotics only |
| Empyema | Turbid to purulent | 25,000–100,000 | P | < 5,000 | 0-60 mg/dl | Requires drainage plus antibiotics |
| Pulmonary embolism | Straw-colored to bloody | 5,000-15,000 | P | 1,000-100,000 | PF = S | Small to moderate effusion with alveolar infiltrate & volume loss |
| Malignancy | Turbid to bloody | < 10,000 | M | 1,000 to > 100,000 | PF = S or < 60 mg/dl | Cytology & pleural biopsy enable diagnosis in 80% |
| Tuberculosis | Straw-colored to serosanguinous | 1,000-5,000 | L | < 5,000 | PF = S or < 60 mg/dl | Positive TST, AFB smear and culture on pleural fluid or biopsy |
| Rheumatoid | Turbid, green to yellow | 1,000-5,000 | M | < 1,000 | Very low (10-20 mg/dl) | High rheumatoid titer (> 640) Cholesterol crystals |
| Chylothorax | Milky | 1,000–7,500 | L | < 1,000 | PF = S | Triglycerides > 110/dl, chylomicrons present, usually large |
| Pancreatitis | Turbid | 5,000-20,000 | P | 1,000 – 10,000 | PF = S | Elevated amylase (PF/S > 2) If glucose < 30 mg/dl consider esophageal rupture |

AFB=acid fast bacilli, L=lymphocyte, M=mononuclear, P=polymorphonuclear, PF=pleural fluid, S=serum, TST=tuberculin skin test.
RBC = red blood count; WBC = white blood count. Exudative fluid must have one of the following (transudates have none): PF/S protein >.5 or absolute value >3 grams; PF/S LDH >.6 or absolute value >.45 upper normal serum limit; specific gravity >1.018.

space), those with positive pleural fluid cultures or gram stains, and those in which the microbiology is negative but the patient continues to show signs of infection with fever, severe pleuritic pain and leukocytosis. In this last category the pleural fluid usually shows a high white blood cell count with polymorphonuclear predominance, glucose < 30 mg/dl, and high LDH (> 500 units/dl). Complicated parapneumonic effusions require drainage by tube thoracostomy. The patient who has pneumonia with a small amount of pleural fluid present and is clinically responding to antibiotic therapy (now afebrile, no pleuritic pain, normal white blood cell count) does not require thoracentesis. By contrast, rapid accumulation of pleural fluid in a patient with pneumonia is an indication for immediate thoracentesis.

*Malignant Effusions:*
Malignancy is the second most common cause of exudative pleural effusions with lung (36%), breast (25%), and lymphoma (10%), being the most frequent causes. Typical pleural fluid characteristics include a mononuclear predominant exudate (average 2,500 cells/µl), with an average red blood cell count of 40,000 cells/µl, normal glucose (> 60mg/dl), and positive cytology. At the time of diagnosis one-third of patients have a low pleural fluid glucose (< 60mg/dl), which is associated with more extensive disease and a poorer prognosis.

*Effusion Secondary to Pulmonary Embolism:*
These exudative effusions are usually bloody, and associated with pleurisy and dyspnea. The effusion may increase in size the first 24 to 48 hours after initial anticoagulation. Unless there is significant pulmonary compromise, or the effusion continues to increase, these effusions can be observed. There are reports of transudative effusions associated with pulmonary embolism, but atelectasis secondary to splinting from pleurisy is a more likely cause.

*Tuberculous Effusion:*
Typically, this predominantly lymphocytic exudate is devoid of mesothelial cells and may occur without any obvious parenchymal involvement. The glucose may be low (< 60 mg/dl) and adenosine deaminase levels are usually elevated (> 70 IU/L). Historically, in the non-immunocompromised host, pleural fluid smears are rarely positive but pleural fluid cultures are positive in 25%. In contrast, thoracoscopic pleural biopsy and culture is positive more than 80% of the time. Initially, the TST may be negative but after a six to eight week observation time usually converts to positive. Although tuberculous pleurisy that develops in the course of primary infection is a self-limited disease that clears without treatment, in as many as 65% of these patients pulmonary tuberculosis or disease elsewhere will develop within five years. If all tests, including the TST, are negative but tuberculous pleurisy is suspected, a repeat TST should be done and if positive, the patient requires six months of multidrug therapy.

*Effusions Secondary to Collagen Vascular Disease:*
Effusions secondary to rheumatoid arthritis are predominantly mononuclear cell exudates, typically with very low glucose levels (< 10 mg/dl), high titers of rheumatoid factor (> 640) and a cloudy appearance (pseudochylous or cholesterol effusions). They are usually moderate in size and unilateral. In systemic lupus erythematosus, effusions are usually small, bilateral, and are polymorphonuclear exudates. The finding of an antinuclear antibody titer that exceeds that of serum is diagnostic. Severe pleurisy is frequent.

*Miscellaneous:*
Atelectasis is a common cause of small to moderate effusions. Frequently, they are seen postoperatively or with prolonged bed rest and inactivity. There are no unique diagnostic features, and these effusions usually fit exudative criteria, have normal glucose levels, and

WBC counts of 1,000 to 2,000 cells/μl with mononuclear cell predominance. Transudates may occur with atelectasis. Since this is a diagnosis of exclusion, other causes of pleural effusions must be eliminated. Esophageal rupture and pancreatitis produce polymorphonuclear-predominant exudative effusions, with high amylase and normal or low glucose (< 30 mg/dl) values. Chylothorax occurs when the thoracic duct is disrupted and is characterized by the presence of chylomicrons and triglyceride values of > 110 mg/dl in the pleural fluid. Lymphoma, trauma, and thoracic surgery are the most common causes of chylothorax. Dressler's syndrome may occur as a complication of myocardial infarction or open-heart surgery. The resulting pleural fluid demonstrates a polymorphonuclear-predominant exudate without specific findings. With a trapped lung (one that cannot fully expand secondary to a visceral pleural peel), exudative pleural fluid fills the pleural space and the characteristics of the fluid depend on the etiology (e.g., malignancy, post-parapneumonic, trauma).

**Diagnostic Thoracoscopy and Pleural Biopsy**

Thoracoscopy is an excellent technique to determine the etiology of an undiagnosed exudative pleural effusion. The procedure is superior to the old closed pleural biopsy techniques because of its higher diagnostic yield. A rigid thoracoscope with a cold light source is used and second point of entry is necessary to provide biopsy forceps access to the pleural space. This technique continues to be most helpful in diagnosing malignant effusions (including mesothelioma), tuberculosis, and trapped lung.

**When to Refer**

Depending on local medical practice, referral to determine if thoracentesis is necessary and to perform the thoracentesis may be most appropriate. Because some imaging techniques including ultrasound and chest CT may be necessary to coordinate thoracentesis and chest tube placement, referral to combine these

efforts is indicated. In patients with persistent and undiagnosed pleural effusions, or effusions in severely ill patients with pneumonia, referral to facilitate prompt diagnostic and therapeutic measures is recommended. This includes evaluation for thoracoscopy, chest tube placement, and pleurodesis.

**Medicolegal Concerns**

Most medicolegal issues involving pleural disease are usually related to complications that occur in the following situations: 1) lack of appropriate follow-up (e.g., complicated parapneumonic effusion resulting in fibrothorax), 2) system failure where physicians do not receive critical data (e.g., a positive TB culture at eight weeks), and 3) missed diagnosis of a potentially life-threatening event such as a pulmonary embolism. **ALWAYS,** always follow-up on pleural fluid cultures and cytologies.

**Summary**

Pleural effusions are associated with many systemic disorders. Thoracentesis to determine if the pleural fluid is a transudate or an exudate coupled with other appropriate diagnostic studies provides a diagnosis most of the time. Because pleural fluid findings are often nonspecific (except for positive cytology and bacteriology), clinical correlation and response to therapy are critical. Not every pleural fluid study needs to be ordered on every pleural effusion. Clinical judgement remains the key. ■

*(continued)*

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## I. Solitary Pulmonary Nodule

### Introduction

The term "solitary pulmonary nodule," (SPN), describes a well-circumscribed, rounded, smooth edged, dense pulmonary lesion, 3 cm or less in diameter. The older term "coin lesion" has been replaced by SPN since these lesions are spherical, not flat. Many solitary pulmonary nodules are malignant. Because lung cancer is the leading cause of cancer death for both men and women in the United States, with an overall five year survival rate of only 12% to 15%, the thorough evaluation and careful selection for operative removal of those SPNs that are malignant is especially important. If a malignant solitary pulmonary nodule is resected early, the prognosis is excellent, with five year survival rates as high as 70% TO 80%.

### Etiology

Solitary pulmonary nodules are a frequent diagnostic challenge. Features associated with non-malignant etiologies include age younger than 30 years, no smoking history, no evidence of obstructive lung disease, calcification within the lesion, and no radiographic change over two years. By contrast, the incidence of lung cancer is as high as 80% in patients with SPNs, who are older than 50 years, have COPD, a smoking history, and a non-calcified lesion which is new or has grown within a two year interval. The overall chance of an SPN being malignant is about 40%.

### Benign Lesions

A benign pulmonary nodule is usually the result of an inflammatory response to a previous granulomatous infection, tuberculosis, coccidioidomycosis, histoplasmosis, or atypical mycobacteria. Those due to histoplasmosis and tuberculosis commonly calcify, but nodules due to coccidioidomycosis usually do not. Fungal granulomas are typically caused by *Coccidioides immitis* in the southwestern United States, *Histoplasma capsulatum* in the upper Mississippi region, and less commonly by cryptococcus or blastomycosis.

*(continued)*

The most common presentation of an SPN as a benign neoplasm is a hamartoma, which can be recognized by its classic pattern of diffuse or "popcorn" calcification, when present. Other causes of benign SPNs include: anthracosilicosis, rheumatoid arthritis with fibrosing alveolitis, bronchogenic cysts, or sequestration, hemangiomas, lymph node hyperplasia (Castleman's disease), and rarely pulmonary embolism with infarction or Wegener's granulomatosis.

A solitary pulmonary nodule in a tropical region may be a parasitic infection, most commonly a helminthic infection caused by the animal filarial parasite *Dirofilaria,* the intestinal ascarid, *Toxocara,* or the human filarial parasite, *Wuchereria* or *Brugia*. These infections are prevalent in certain temperate, tropical and subtropical regions of the world. Most cases are diagnosed after a lung resection for an SPN presumed to be malignant. Although patients with pulmonary dirofilariasis are typically asymptomatic, patients with toxocariasis or visceral larva migrans are more likely to complain of symptoms of cough, asthma, pneumonia, and have persistent eosinophilia.

**Malignant Lesions**

The likelihood that an SPN is malignant increases with the patient's age and smoking history. Unfortunately, only a small proportion of lung cancer patients, about 16% to 18%, present with "early stage" disease. An SPN in a patient under the age of 35 has less than a 1% chance of being malignant, contrasted with up to a 60% incidence in patients age 50 years or older. In specialty referral settings, up to 90% of patients evaluated for SPNs, will have malignancy. Although all lung cancer cell types can present as an SPN, most malignant nodules are adenocarcinoma or squamous cell carcinoma. About 5% of small cell lung cancer present as an SPN. An SPN may also present as metastatic cancer from a known or unknown primary lesion.

*(continued)*

## Table 18 Characteristics of Solitary Pulmonary Nodules

| Variable | Benign | Malignant |
|---|---|---|
| Age | < 30 years | > 50 years |
| Calcification | Popcorn, dense, concentric | None or minimal |
| Nodule edge | Smooth, round | Irregular, spiculated |
| Smoking history | Never smoked | > 20 pack-years |
| Size of diameter | < 1.5 cm | > 1.5 cm |

**X-ray Characteristics**

The characteristics on chest x-rays that help to differentiate between benign and malignant nodules are outlined in Table 18. The most important characteristic of a benign nodule is the presence of calcification, which can be a diffuse speckled, or "popcorn," pattern, typical of a hamartoma, or a large central nidus or concentric calcification typical of a granuloma. Occasionally, however, a malignant nodule has a small "fleck" of calcification present or it engulfs a nearby small granuloma during its growth and a metastatic osteogenic sarcoma may calcify, so the presence of a very small amount of calcification does not ensure benignity.

The second important factor distinguishing a malignant from a benign nodule is the growth rate. Since the "doubling time" of a lung cancer ranges from 15 to 450 days, the nodule that does not increase in diameter over a two year period can be considered benign. Any lesion that increases in size over a two year period of observation, or less, must be considered malignant until proven otherwise. One exception is a nodule doubling in less than 20 days, which usually suggests an acute inflammatory process.

The third important characteristic is the appearance of the nodule's edge. Benign lesions have smooth rounded edges, whereas the incidence of neoplasm increases dramatically in lesions with irregular, spiculated borders. An increasing incidence of malignancy occurs, ranging from 20% to 93%, depending on the degree of border irregularity (Table 18).

Clinical circumstances may suggest a benign explanation for a "new" nodule, such as the development of a nodule during resolution of a pneumonia, pulmonary contusion, or pulmonary embolism with infarction. Other radiologic findings,

such as small size, increased density, smooth borders, or vessels entering the lesion suggesting an arteriovenous fistula, increase the likelihood of a benign condition.

**Diagnosis**

The first step in evaluating an SPN is to try to obtain old chest x-rays for comparison. If this is not possible, and the nodule does not have a classic, calcified appearance typical of a granuloma or hamartoma, then further testing or a period of careful observation must be undertaken. A CT scan can help distinguish the pattern of calcification, and classify lesions as "indeterminate" based on the presence of stippled or eccentric calcification and medium density, or "benign" based on the presence of fat density typical of a hamartoma. The most common CT finding in early stage adenocarcinoma and squamous cell carcinoma of the lung is that of a solitary pulmonary nodule that enhances after administration of intravenous contrast. In small cell carcinoma, however, hilar and mediastinal adenopathy secondary to metastases is the most common CT presentation. The presence of irregular margins, associated air bronchogram, convergence of the surrounding structure, or the involvement of three or more blood vessels is more likely in malignant lesions. Because of the difficulty with noninvasive diagnosis of the SPN, new radiologic techniques are being studied, including positron emission tomography imaging, (PET), which is able to distinguish benign from malignant pulmonary nodules by measuring 18-fluorodeoxyglucose, (FDG), and by showing increased FDG uptake and retention in malignant cells. PET scanning is a valuable, noninvasive tool with a 95% sensitivity for identifying malignancy and a specificity of 85% or greater. However, false positive results may be obtained in lesions containing an active inflammatory process, and this diagnostic modality is not generally available.

*(continued)*

If a period of observation is chosen, chest x-rays, and possibly serial CT scans, should be done at three-month intervals over at least a two year period to determine if any change in the size of the nodule has occurred. An increase in the diameter of the nodule by 25% indicates a doubling of the mass volume.

**When to Refer**

Once the decision has been made that the patient's SPN may represent a malignancy, a histologic diagnosis is needed. If the patient's SPN has characteristics strongly suggesting malignancy, and there are no contraindications to surgery, refer to a thoracic surgeon. In most other circumstances, refer to a pulmonologist for further work-up. Diagnostic procedures may include: fiberoptic bronchoscopy aided by fluoroscopy, or CT-guided transthoracic fine needle aspiration. The yield of these procedures in the diagnosis of the small solitary pulmonary nodule (< 1.5 cm in diameter) is about 40% for fiberoptic bronchoscopy, and 50% for fine needle aspiration. The incidence of pneumothorax requiring chest tube insertion from bronchoscopic transbronchial biopsy is about 5% and from needle aspiration about 25%, depending on patient characteristics and variation, of local physician experience. Thoracoscopic resection or thoracotomy is needed for diagnosis in about 20% of patients, in whom the less invasive techniques were not successful.

**Medicolegal Concerns**

Physicians should discuss the possibility of lung cancer presenting as an SPN in those patients who have lesions that cannot be confirmed to be benign based on their presence on old films with over two years of stability, or classic calcification typical of a benign lesion. Patients should play an active role in the decision to remove, evaluate with invasive procedures, or observe their SPN. The pros and cons of pulmonary resection should be discussed and a recommendation made. This should be carefully documented in the patient record, and if observation is chosen, advice for follow-up given. Then, it is important for the physician to insure that follow-up actually occurs.

**Summary**

The overall probability that a solitary pulmonary nodule is malignant is approximately 40%. Aggressive efforts are needed to establish whether the lesion is benign or malignant. This Section gives an approach for estimating malignancy versus benignity. The evaluation of a solitary pulmonary nodule should be systematic and appropriate for the individual patient. There is an increasing frequency of malignancy occurring in lesions with irregular edges, without calcification, occurring in patients over the age of 50 years, whose lesions double within a two year period. The decision for operative removal versus electing a period of observation of the nodule can be made based on nodule characteristics, patient age, and rate of growth of the lesion. ■

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## J. Unresolved Pneumonia

### Introduction

Unresolved pneumonia, especially in older patients, presents a problem to the primary care physician that doesn't go away. Pneumonia strikes over 2,000,000 Americans annually, resulting in over 800,000 hospitalizations and 50,000 deaths. X-ray manifestations of many pneumonias fail to resolve in 30 days, requiring a decision as to the need for additional costly and potentially harmful evaluations. The work-up can be straightforward or frustrating. The following approach is presented for practical resolution of unresolved pneumonias.

Infiltrates thought to be due to pneumonia must be followed to their radiologic resolution. Because most pneumonias are treated without identifying the etiology, the practitioner frequently does not know the extent of "normal" duration of resolution and therefore, must depend on indirect information to infer the cause and natural history for a specific patient. Factors that influence the rate of resolution are listed in Table 19. The most important of these are age, host defenses, and comorbidities.

When one or more of these factors is present, it may be necessary to wait six to eight weeks for resolution to occur, unless there are early clinical clues that raise the suspicion of an unusual infection or noninfectious process such as malignancy. If the causative organism is known, Table 20 may be useful for estimating the duration of resolution.

When radiologic resolution is not satisfactory, additional evaluations are needed and the various causes of unresolved infiltrates need to be considered (see Table 21).

*(continued)*

## Table 19 Factors Associated with Prolonged Resolution

| |
|---|
| Age > 60 years |
| Alcoholism |
| Virulent or resistant organisms |
| Chronic obstructive pulmonary disease, (COPD) |
| Congestive heart failure |
| Asthma |
| Diabetes mellitus |
| Malnutrition |
| Chronic liver disease |
| Patient noncompliance |
| Immunodeficiency |
| Delay in initiation of therapy |

## Table 20 Evolution of Common Pneumonias*

| Infecting Organism | Initial Radiographic Worsening | Maximum Time to Resolution | Residual Radiographic Abnormalities |
|---|---|---|---|
| *Streptococcus pneumoniae* | | | |
| Bacteremic | Majority | 3-5 months | 25-35% |
| Nonbacteremic | Occasional | 1-3 months | Rare |
| Group B Streptococci | Common | 1-3 months | Common |
| *Staphylococcus aureus* | Majority | 3-5 months | Common |
| *Haemophilus influenzae* | Occasional | 1-5 months | Occasional |
| *Legionella* | Majority | 3-5 months | 25% |
| *Chlamydia pneumoniae* | Rare | 1-3 months | Occasional |
| *Moraxella catarrhalis* | Rare | 1-3 months | Uncommon |
| Enteric gram-negative organisms | Occasional | 3-5 months | 10-20% |
| Viruses | Variable | Variable | Occasional fibrosis, bronchiolitis obliterans organizing pneumonia |
| *Mycoplasma pneumoniae* | Variable | Variable | Uncommon |

*Modified from Niederman MS, Sarosi GA. Respiratory Infections. Philadelphia, W.B. Saunders Co., 1994, 278.

## Table 21 Causes of Unresolved Infiltrates

| |
|---|
| **Infectious Causes** |
| *Common infectious causes* |
| Pneumococci |
| *Haemophilus influenzae* |
| Viral agents |
| *Staphylococcus aureus* |
| *Legionella organisms* |
| Gram-negative organisms |
| *Uncommon infectious causes* |
| Mycobacteria |
| Fungi |
| Protozoa |
| Metazoa |
| Undetected resistant organisms |
| Mixed organisms, including anaerobes |
| **Noninfectious Causes** |
| Neoplasm, including lymphoma |
| Pulmonary emboli |
| Foreign body |
| Drugs |
| Antiarrhythmics |
| Amiodarone |
| Antimicrobials |
| Nitrofurantoins |
| Penicillins |
| Anticonvusants |
| Diphenylhydantoin |
| Antirheumatics |
| Methotrexate |
| Diuretics |
| Hydrochlorothiazide |
| Opiates |
| Cocaine |
| Heroin |
| Methadone |
| Occupational lung disease |
| Congestive heart failure |
| Radiation pneumonitis |
| Fibroproliferative phase of acute respiratory distress syndrome, (ARDS) |
| Idiopathic |
| Hypersensitivity pneumonitis |
| Bronchiolitis obliterans organizing pneumonia, (BOOP) |
| Wegener's granulomatosis |
| Interstitial pulmonary fibrosis |

## Common Unresolved Pneumonias

A review of the most distinctive features of these pneumonias can be useful in eliciting clues to the identity and, therefore, the natural history of the infectious causes of unresolved infiltrates.

**Pneumococcal Pneumonia:** The pneumococcus causes the greatest number of unresolved pneumonias. Aspiration, often associated with sedation, is a very common cause. Delayed resolution is seen most often in the elderly and in cases associated with bacteremia. Eight to eleven weeks resolution time is often encountered. Residual atelectasis and pleural abnormalities are present at two months in about one-third of the elderly patients and in 10% of younger patients.

**Staphylococcal Pneumonia:** Staphylococcal pneumonia frequently follows influenza or other viral respiratory infections, is seen more frequently in the elderly, and is often the cause of hospital-acquired pneumonia, especially in patients with COPD. Bilateral lower lobe involvement and pleural effusions, often empyema, are common. Resolution of staphylococcal pneumonia may be expected to follow a prolonged course.

***Haemophilus influenzae* Pneumonia:** Older patients with COPD and alcoholism are especially susceptible to this organism. The hospital course and eventual resolution are frequently prolonged.

***Legionella* Pneumonia:** This pneumonia results from inhalation of airborne water contaminants or pharyngeal contents and occurs more often than originally believed. It is seen more frequently in smokers and in patients with chronic pulmonary, cardiac, renal, and neoplastic disease. Twenty-five to 50% progress to multi-lobar involvement, and resolution of this pneumonia is one of the slowest of any community-acquired pneumonia. Residual fibrosis may occur in as many as one-quarter of the cases. Complete resolution occurs in only 55% of the cases in

twelve weeks. Unless other clinical information is of concern, follow up chest radiography at six to eight weeks intervals is sufficient without significant risk of misdiagnosis.

**Gram-Negative Pneumonias:** Nursing home, elderly, and hospitalized patients are more commonly affected. Comorbidities such as COPD, neoplasm, diabetes mellitus, and bronchiectasis increase the risk for this type of pneumonia. Abscesses and residual fibrosis are common.

**Viral Pneumonias:** The elderly and the immunosuppressed are more susceptible to viral pneumonias. Superinfection with other organisms such as *Staphylococcus aureus* and *Haemophilus influenzae* is common. Even typical viral pneumonia may be associated with other diagnoses such as bronchiolitis obliterans with organizing pneumonia, bronchiectasis, and pulmonary fibrosis.

***Mycobacterium Tuberculosis* Pneumonia**: Immigrants from Africa, Latin America, and many countries of Asia have a higher incidence of tuberculosis than the general population of the United States. The presence of alcoholism, cavities and/or apical infiltrates are additional reasons to raise the suspicion of tuberculosis. As in other pneumonias, AIDS may alter the typical radiographic presentation of tuberculosis.

## Noninfectious Causes of Unresolved Infiltrates

**Neoplasm:** Neoplasms are one of the most common and important causes of unresolved pneumonia. Patients with neoplasms presenting with pneumonia may also have stridor, wheezing, or sudden onset of marked shortness of breath. Hemoptysis occurs in 25% to 50% of cases. Smokers older than 45 years of age, especially with weight loss or recurrent pneumonia, should undergo additional work-up. Obstructive endobronchial lesions may be primary

malignant lesions, metastatic from breast, kidneys, or GI tract, or on occasion may be bronchial carcinoid tumors or papillomas. Cavitary lesions may signify a necrotizing neoplastic process. Bronchoalveolar cell carcinoma may present as lobar consolidation with air bronchograms resembling pneumonia.

**Pulmonary Emboli:** Pulmonary embolism with infarction can masquerade as pneumonia, occurring more commonly in older, immobilized, or obese patients, and in those with heart failure. These infiltrates are usually peripheral and resolve by shrinking slowly over several weeks.

**Other Causes:** A variety of unusual conditions may declare themselves as unresolved pneumonia. These include amyloid infiltrations, asbestos-induced round atelectasis, and various noninfectious granulomas (e.g., rheumatoid, Wegener's, and bronchocentric).

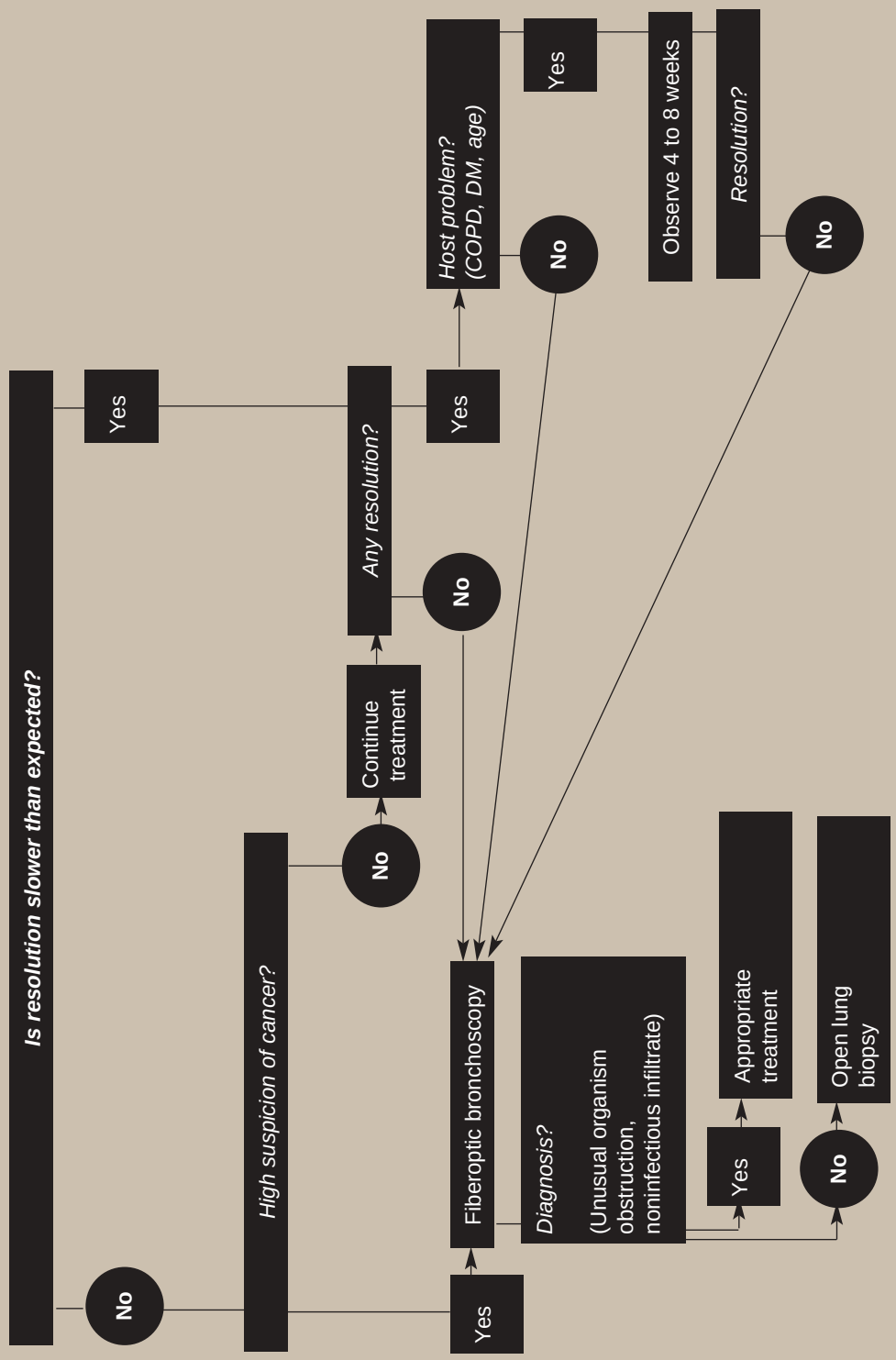
## Clinical Approach to Diagnosis

Figure 3 suggests an overall diagnostic approach to unresolved infiltrates. Chest x-rays that show persistent infiltrates need to be periodically evaluated to their satisfactory resolution. Once the estimated time for resolution of what was thought to be an infectious process has passed, one should proceed to a more detailed evaluation. This repeat assessment, as emphasized in Section A, should include a search for previously unelicited symptoms, including complete travel, occupational, drug, and hobby history. Signs and symptoms of systemic diseases such as collagen vascular disease, rheumatoid arthritis, etc. may present clues to more obscure etiologies.

Fever, shortness of breath (Section B), a persistent cough (see Section C), weight loss, or chest pain (Section D) or hemoptysis (Section E), necessitates a repeat chest film. Evaluation of the chest x-ray, however, is seldom helpful in identifying the cause of the non-resolution. Once the plain film identifies a

## Figure 3 Diagnostic Approach to Unresolved Pulmonary Infiltrates

**Algorithm showing an overall diagnostic approach to unresolved pulmonary infiltrates.**




COPD=chronic obstructive pulmonary disease DM=diabetes mellitus
From Niederman MS, Sarosi GA. Respiratory Infections. Philadelphia, W.B. Saunders Co., 1994, 285.

problem, but not a cause, computed tomography is indicated to find possible cavities, masses, endobronchial lesions, adenopathy, effusions, or other abnormalities. At this point, referral to a specialist is recommended for consideration of further diagnostic procedures such as bronchoscopy, transbronchial biopsy, transthoracic needle aspiration, thoracoscopic lung biopsy, or open lung biopsy. Bronchoscopy can be diagnostic in up to 80% of the cases.

Other useful tests in selected patients are cultures and/or cytologic examination of sputum (expectorated or induced) and bronchoalveolar lavage fluid for mycobacteria and fungi. Thoracentesis is indicated in patients with accessible pleural effusions. Other useful procedures include pleural biopsy or thoracoscopy.

The ultimate diagnostic procedure is thoracotomy with lung biopsy. When the suspicious lesion is peripherally located and where expertise and facilities are available, biopsy or even resection may be carried out by thoracoscopy.

**When to Refer**

Each practitioner has his or her own level of expertise, but when there is any doubt, a consultation is indicated. Examples are: (1) when neoplasm is suspected and cannot be ruled out by noninvasive methods, (2) when unresolved densities require invasive procedures, and (3) when help is needed in treatment of obscure causes.

*(continued)*

**Medicolegal Concerns**

- Failure to diagnose lung cancer is high on the list of causes for malpractice lawsuits. Maintain a high level of suspicion and a low threshold of referral for consultation.
- Unfortunately, tuberculosis is frequently overlooked. As in potentially neoplastic cases, having a high index of suspicion is very important, and when there is the slightest doubt, culture the sputum for mycobacteria or seek consultation.
- What appears to be pneumonia should be followed to resolution on the anticipated schedule. A histologic diagnosis of residual masses and dense infiltrates that suggest malignancy is commonly necessary. Make sure your patient knows that follow-up is mandatory and that diagnostic procedures may be needed.
- One should be very cautious with patients who fail to follow instructions and/or do not follow-up with their appropriate evaluations. Explain thoroughly to the patient as well as the family the importance of following instructions exactly and returning for appropriate follow-up. Document completely all these conversations.

**Summary**

Unresolved radiographic densities can be approached in a systematic way that avoids unnecessary expense and risks to the patients. Knowledge of the natural history of the common pneumonias and the exercise of judgement as to when to refer are important aspects of the approach to these problems. Fortunately, most cases can be resolved without undue complications and expense. Refer when in doubt and be sure that appropriate follow-up is accomplished. ■

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## K. Postscript and Biographical Sketches of Authors

The authors of this and the first four Frontline monographs of this series are long-time friends. This friendship is a bond of affection which exists amongst our group with different backgrounds and interests both in and out of medicine. Each year we convene at the Frontier Fishing Lodge at Great Slave Lake in the Northwest Territories of Canada. After a day of angling for lake trout, grayling, and northern pike, we write the monographs.

We planned this series for the purpose of advancing knowledge in pulmonary medicine to our friends and colleagues throughout the profession, but mostly for those who practice on the frontlines. Thus, it is appropriate to end this monograph with some quotations about the meaning of friendship and comments about our favorite pasttime of fishing.

Like many friends, we don't always agree, but we have learned to disagree, without being disagreeable. (Borrowed from John Wooden–UCLA basketball coach)

**On Friendship:**

*Friendship is seldom lasting but between equals, or where the superiority on one side is reduced by some equivalent on the other.*

Dr. Samuel Johnson, 1750

*A man cannot be said to succeed in this life, who does not satisfy one friend.*

Henry David Thoreau, 1857

*The holy passion of friendship is so sweet and steady and loyal and enduring in nature that it will last through the whole of lifetime, if not asked to lend money.*

Mark Twain, 1894

**On Fishing:**

*If there are no fish in this place, then drop your hook in another.*

Chinese

*The fish will soon be caught that nibbles at every bait.*

English

*If you're afraid to get wet, you'll never make a good fisherman.*

American

**Co-Editor**

**John F. Murray, M.D.**
After receiving his B.A. (1949) and M.D. (1953) degrees, both from Stanford University, Dr. Murray had two years of medical residency training at San Francisco General Hospital and two more years at Kings County Hospital (New York). Afterward, he had a year of research training at the Royal Postgraduate Medical School in London.

He started his faculty career at the University of California, Los Angeles in 1957, rising to the rank of Associate Professor of Medicine and Physiology. In 1966 he moved to the University of California, San Francisco, where he became Professor of Medicine in 1969. He was also a member of the Senior Staff of the Cardiovascular Research Institute and Chief of the Chest Service at San Francisco General Hospital (1966 to 1989).

He became Professor Emeritus in 1994, and now works mainly in Paris, France as President (1992 to 1996) of the International Union Against Tuberculosis and Lung Disease. Dr. Murray received the College Medal of the American College of Chest Physicians (1985), the Trudeau Medal of the American Thoracic Society (1989) and the President's Award of the European Respiratory Society (1996).

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Dr. Hudson received his B.S. from Washington State University in Pullman, Washington and his M.D. from the University of Washington, Seattle. He did his internship at Bellevue Hospital Center (New York) and his residency at New York Hospital, Cornell Medical Center (New York) and at the University of Washington (Seattle). From 1971 to 1973, Dr. Hudson was an attending physician at Colorado General Hospital in Denver. In 1973, he moved to the Harborview Medical Center in Seattle, where he rose to Associate Physician-in-Chief in the Department of Medicine.

In 1985, Dr. Hudson became Head of Pulmonary and Critical Care Medicine at the University of Washington. Since 1982, he has been a Professor of Medicine at the University of Washington, Seattle.

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*(continued)*

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Thomas L. Petty, M.D. received his M.D. at the University of Colorado in 1958. He interned at Philadelphia General Hospital and received his residency training at the University of Michigan and the University of Colorado. His pulmonary training was at the University of Colorado. He is a pulmonologist and Professor of Medicine at the University of Colorado Health Sciences Center in Denver and at Rush University in Chicago. He was previously head of the Division of Pulmonary Sciences at the University and Director of the Fellowship Training Program.

Dr. Petty was founding President of the Association of Pulmonary Program Directors, (APPD), and has served as President of the American College of Chest Physicians. He is a former member of the Board of Governors of the American Board of Internal Medicine.

Dr. Petty has received the Distinguished Service Award of the American Thoracic Society (1995), elected to the Colorado Pulmonary Physicians' "Hall of Fame" (1995) and received the annual award for excellence by the American Association for Respiratory and Cardiovascular Rehabilitation (1995). He was elected to Master Fellow of the American College of Chest Physicians (1995). He also received the Master Award of the American College of Physicians in 1996.
Dr. Petty has been named Chairman of the National Lung Health Education Program, (NLHEP). Its goal is the early diagnosis of COPD and lung cancer.

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.

**J. Roy Duke, Jr., M.D.**
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.

Dr. Duke joined the Palm Beach Medical Group in West Palm Beach, Florida in 1967 and has practiced pulmonary medicine and internal medicine there to the present. He has served as Chief of Medicine and Chief of Staff of Good Samaritan Hospital in West Palm Beach and is currently the Director of Pulmonary Services.

He has an interest in Hyperbaric Medicine, which is an extension of his hobbies of scuba diving and underwater photography. He is also an avid fly fisherman and fly tier.

Dr. Duke is married to Bobbye Craig Duke and has two children, Denise and Christopher.
*(continued)*

**James T. Good, Jr., M.D.**
Dr. Good received his M.D. degree from the University of Kansas and then also completed a medical internship, residency and chief medical residency also at the University of Kansas. He then completed a three-year pulmonary and critical care 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, 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.

**Thomas M. Hyers, M.D.**

Dr. Hyers received his M.D. 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.

Dr. Hyers has held the rank of Professor of Internal Medicine at St. Louis University since 1985. He has a long-standing interest in thrombosis and antithrombotic therapy and has conducted clinical research in the diagnosis, treatment and prevention of venous thromboembolism. Dr. Hyers continues to write and lecture frequently on this topic.

Since 1997, Dr. Hyers has maintained a private practice in pulmonology and pulmonary occupational medicine at St. Joseph's Hospital in Kirkwood, Missouri, a suburb of St. Louis. Recently, he developed an interest in internet education and, with a great deal of help, designed a website (careinternet.com) to help caregivers deliver antithrombotic therapy more effectively. He is married with two grown sons.

In his spare time, Dr. Hyers enjoys creative writing, gardening and fishing.

*(continued)*

**Michael D. Iseman, M.D.**
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's College of Physicians and Surgeons, receiving his M.D. in 1965. He took 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 diseases 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*.

**Dean D. Mergenthaler, M.D.**
Dr. Mergenthaler has an undergraduate degree in chemistry and biology from Cornell University, a master's degree in human anatomy from the University of Miami School of Medicine, a medical doctor degree from Jefferson Medical College, with internship at Robert Packer Guthrie Hospital and Clinic and internal medicine residency and pulmonary fellowship at Jackson Memorial Hospital.

Dr. Mergenthaler has been in private practice of pulmonary and internal medicine for the past 30 years in Palm Beach County, Florida. He has been active in the development and medical directorship of several hospital Respiratory Therapy Departments, as well as in the development of a local community medical center.

His hobbies include fishing, traveling, reading and gardening. He and his wife Mary Beth have two grown children.

*(continued)*

**Donald R. Rollins, M.D.**
Dr. Rollins is a pulmonologist engaged in clinical practice in Loveland, Colorado, where he is Medical Director of the Cardiopulmonary Department at McKee Medical Center. He is a Fellow of the American College of Chest Physicians and he is an Associate Clinical Professor in the Pulmonary Division at the University of Colorado Health Sciences Center in Denver and continues to be actively involved with clinical research. Dr. Rollins received his B.A. at St. Olaf College and his M.D. from the University of North Carolina. He did his internship, residency and pulmonary fellowship at the University of Texas.

He enjoys fishing with friends and playing string bass and guitar with his daughter Elizabeth and wife Susan, both accomplished musicians.

**Acknowledgements:**
The authors wish to express their appreciation to Aja Lipavsky and Linda Berteau for their editorial and secretarial assistance in the preparation of this monograph.

**IDENTIFICATION DATA** Fill in the following information as it relates to you. PLEASE PRINT.

Name_____ Date_____ #_____

Address_____ Date of Birth_____

_____ (zip code) ___Married ___Separated ___Divorced ___Widowed ___Single

Home Telephone_____ (area code) Education: ____years Elementary ____years High School

Employer_____ ____years College, Technical, Business, etc.

Business Telephone_____ (area code) Occupation_____

## SPECIAL PROBLEMS OR SYMPTOMS

1. In the blank lines below, please describe any special problems or symptoms you would like to discuss with the doctor today:

_____

_____

_____

_____

2. How long have you had this problem? ..... ____for 1 week ____for 1 month ____for 1 year ____over 1 year
3. Have you ever seen a doctor for this problem in the past? ..... ____Yes ____No

   IF YES: a. How did the doctor diagnose your problem?_____

   _____

   b. How did the doctor treat your problem?_____

   _____

   c. Did the treatment help you? ..... ____Yes ____No

## GENERAL SCREEN

1. Please place an (X) next to any of the following problems that you have right now:

_____frequent headaches
_____trouble with eyes or vision
_____trouble with ears or hearing
_____trouble with nose
_____congested nose or nose bleeds
_____trouble smelling
_____coughing spells
_____coughing up a lot of phlegm
_____trouble breathing (shortness of breath)
_____dizzy spells

_____trouble with stomach or digestion
_____vomiting
_____trouble with bowels
_____constipation
_____loose bowels
_____blood in stools
_____trouble with urination
_____difficulty starting urine
_____trouble with genitals
_____trouble with periods

_____trouble with bruises
_____aching muscles or joints
_____numbness in fingers
_____crying spells
_____work or family problems
_____sexual difficulties
_____fever
_____weight changes
_____fatigue

2. Have you ever considered committing suicide? ..... ____Yes ____No
3. Have you ever used marijuana or heroin, LSD, or similar drugs? ..... ____Yes ____No
4. Are you allergic to any medications, foods or other substances? ..... ____Yes ____No
   IF YES, what? _____
5. List all medications you are currently taking: _____
   _____
6. When is the last time you had a physical examination? ..... _____Year
7. Have you ever been told you had any chronic or serious illness? ..... ____Yes ____No
   IF YES, please list the illnesses you have now or have had: _____
   _____
8. Give the following information for the last three times you have been hospitalized starting with the most recent. (Do not list normal pregnancies.)

| | HOSPITALIZATION (1) | HOSPITALIZATION (2) | HOSPITALIZATION (3) |
|---|---|---|---|
| Type of operation or illness: ..... | | | |
| Month and year hospitalized: ..... | | | |
| Name of hospital: ..... | | | |
| City and State: ..... | | | |

9. Please list the following information for your blood relatives:

| | *Year of Birth* | *Major Illnesses* | | If dead, age at death and cause. *Age* | *Cause* |
|---|---|---|---|---|---|
| Father | | | | | |
| Mother | | | | | |
| Brothers or Sisters | | | | | |
| | | | | | |
| | | | | | |

CONTINUE TO NEXT PAGE

(Do not write below this line. For doctor's notes.)

_____
_____
_____
_____
_____
_____

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(continued)

Please answer each of the following questions by placing an (X) in the blank at the right that most applies to you. If you are unable to answer a question for any reason, place a solid circle (●) in the first blank.

| | |
|---|---|
| 1. ..... Has anyone in your family had lung disease? | 1. ___Yes ___No |
| 2. ..... Has anyone in your family ever had asthma, hayfever or chronic bronchitis? | 2. ___Yes ___No |
| 3. ..... Has anyone in your family had allergies? | 3. ___Yes ___No |
| 4. ..... Are you allergic to any drugs? | 4. ___Yes ___No |
| IF YES: ..... Please list the drugs you are allergic to in the blank space at the right: | _____ |
| | _____ |
| 5. ..... Were you ever allergic to milk? | 5. ___Yes ___No |
| 6. ..... Are you now allergic to any foods? | 6. ___Yes ___No |
| IF YES: ..... Please list the foods you are allergic to in the blank spaces to the right: | _____ |
| | _____ |
| 7. ..... Have you ever been treated for asthma? | 7. ___Yes ___No |
| 8. ..... Have you ever been treated for hayfever? | 8. ___Yes ___No |
| 9. ..... Have you ever been treated for intestinal parasites? | 9. ___Yes ___No |
| 10. ..... Do you have any other allergies? | 10. ___Yes ___No |
| IF YES: ..... Please list them in the blank spaces at the right: | _____ |
| | _____ |
| 11. Have you ever had any of the following illnesses: | 11. |
| a. ..... a chest operation | a. ___Yes ___No |
| b. ..... a chest injury | b. ___Yes ___No |
| c. ..... broken ribs | c. ___Yes ___No |
| d. ..... sinus trouble | d. ___Yes ___No |
| e. ..... pneumonia | e. ___Yes ___No |
| f. ..... pleurisy | f. ___Yes ___No |
| g. ..... emphysema | g. ___Yes ___No |
| h. ..... fungus disease of the lung | h. ___Yes ___No |
| i. ..... lung cancer | i. ___Yes ___No |
| j. ..... collapsed lung | j. ___Yes ___No |
| 12. ..... Have you ever had tuberculosis (T.B.)? | 12. ___Yes ___No |
| 13. ..... Have you been exposed to someone with active tuberculosis? | 13. ___Yes ___No |
| 14. ..... Have you ever had a positive T.B. skin test? | 14. ___Yes ___No |
| 15. ..... Have you had a chest x-ray in the past year? | 15. ___Yes ___No |
| 16. ..... Have you ever had an abnormal chest x-ray? | 16. ___Yes ___No |
| 17. ..... Have you ever had a breathing (blowing) test? | 17. ___Yes ___No |
| 18. ..... Have you ever had an abnormal breathing test? | 18. ___Yes ___No |

| | |
|---|---|
| 19. ..... Have you ever had air put into your chest or abdomen as a treatment? | 19. ___Yes ___No |
| 20. Have you ever lived in any of the following places: | 20. |
| a. ..... Arizona | a. ___Yes ___No |
| b. ..... Ohio Valley | b. ___Yes ___No |
| c. ..... the South | c. ___Yes ___No |
| 21. ..... Have you ever traveled through or lived in Southern California? | 21. ___Yes ___No |
| IF YES: ..... Did you get sick with a sudden flu-like illness while there? | ___Yes ___No |
| 22. ..... Have you been abroad in the last 5 years? | 22. ___Yes ___No |
| IF YES: ..... List the countries you visited in the blank spaces at the right: | _____ |
| | _____ |
| 23. ..... Have you ever been a metal worker? | 23. ___Yes ___No |
| 24. ..... Have you ever worked in a foundry? | 24. ___Yes ___No |
| 25. ..... Have you ever been a welder? | 25. ___Yes ___No |
| 26. ..... Have you ever worked in any mines? | 26. ___Yes ___No |
| 27. ..... Have you ever been a stone quarry worker? | 27. ___Yes ___No |
| 28. ..... Have you ever worked as a farmer? | 28. ___Yes ___No |
| 29. ..... Have you ever worked as a plumber? | 29. ___Yes ___No |
| 30. ..... Have you ever worked with or been exposed to asbestos? | 30. ___Yes ___No |
| 31. ..... Have you ever been exposed to moldy wheat or wheat dust? | 31. ___Yes ___No |
| 32. ..... Have you ever worked with or been exposed to beryllium? | 32. ___Yes ___No |
| 33. ..... Have you ever been in contact with anyone who had beryllium poisoning? | 33. ___Yes ___No |
| 34. ..... Do you have any pets? | 34. ___Yes ___No |
| IF YES: a. ..... Do you have any cats? | a. ___Yes ___No |
| b. ..... Do you have any dogs? | b. ___Yes ___No |
| c. ..... Do you have any birds? | c. ___Yes ___No |
| d. ..... Do you own any pigeons? | d. ___Yes ___No |

*(continued)*

| | |
|---|---|
| 35. ..... Do you have a cough? | 35. ___Yes ___No |
| IF YES: a. ..... How long have you had a cough? | a. ___for 1 month ___for 1 year ___over 1 year |
| b. ..... How often do you have a cough? | b. ___almost always ___often ___sometimes |
| c. ..... How severe has your cough been? | c. ___severe ___moderately severe ___mild |
| d. ..... When do you cough most often? | d. ___when lying down<br>___when arising in the morning<br>___at night<br>___during the day |
| e. ..... Do you bring up phlegm or mucus each day? | e. ___Yes ___No |
| IF YES: (1) ..... What color is the phlegm you bring up? | (1) ___greenish<br>___white and foamy<br>___gray and foamy<br>___bloody |
| (2) .... Do you have to cough more than 5 times to clear your throat of phlegm? | (2) ___Yes ___No |
| (3) ..... Do you bring up phlegm when arising from bed? | (3) ___Yes ___No |
| 36. During the past 3 years have you coughed up phlegm for 3 or more weeks at a time? | 36. ___Yes ___No |
| 37. ..... Have you ever coughed up blood? | 37. ___Yes ___No |
| 38. ..... Do you have a cold now? | 38. ___Yes ___No |
| 39. ..... How many colds a year do you get? | 39. ___ colds per year |
| 40. ..... Do you get more colds during the winter than in the summer? | 40. ___Yes ___No |
| 41. ..... Do your colds always seem to settle in your chest? | 41. ___Yes ___No |
| 42. ..... Do you have difficulty shaking off a cold? | 42. ___Yes ___No |
| 43. ..... Are you troubled with hoarseness? | 43. ___Yes ___No |
| IF YES: a. ..... How long has this been happening? | a. ___for 1 month ___for 1 year ___over 1 year |
| b. .... Have you had hoarseness that began after a thyroid (goiter) operation? | b. ___Yes ___No |
| 44. ..... Do you have shortness of breath? | 44. ___Yes ___No |
| IF YES: a. ..... How long has this been happening? | a. ___for 1 month ___for 1 year ___over 1 year |
| b. ..... How often has this been happening? | b. ___daily ___weekly ___monthly |
| c. ..... How severe has your shortness of breath been? | c. ___severe ___moderately severe ___mild |
| d. ..... When do you get short of breath? | d. ___when climbing stairs<br>___when just walking on level ground<br>___walking up a slight hill<br>___walking with people your own age<br>___sleeping in bed |

45. ..... Do you have wheezing or whistling sounds when you breathe?
IF YES: a. ..... How long has this been happening?
b. ..... How often has this been happening?
c. ..... How severe has your wheezing been?
d. ..... Do you wheeze when you exert yourself?
e. ..... Do you cough when you exert yourself?
46. Have you ever had stabbing chest pains that worsened when you took a deep breath?
47. ..... Do you awaken at night in a sweat?
IF YES: a. ..... How long has this been happening?
b. ..... How often has this been happening?
c. ..... How severe has this sweating been?
48. ..... Do you have a tendency to sneeze in the morning?
49. ..... Have you had a problem with diarrhea or frothy stools?
50. Do you smoke any of the following:
a. ..... cigarettes?
b. ..... a pipe?
c. ..... cigars?
51. If you smoke cigarettes, how much do you smoke:
a. ..... less than 10 a day?
b. ..... between 10 and 20 a day?
c. ..... between 20 and 40 a day?
d. ..... over 2 packs a day?
52. If you smoke cigarettes, how long have you been smoking at your present rate:
a. ..... for about a month?
b. ..... for about a year?
c. ..... for several years?
53. ..... If you do not smoke now, did you ever smoke?
IF YES, write in the year when you stopped:

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45. ___Yes ___No
a. ___for 1 month ___for 1 year ___over 1 year
b. ___daily ___weekly ___monthly
c. ___severe ___moderately severe ___mild
d. ___Yes ___No
e. ___Yes ___No
46. ___Yes ___No
47. ___Yes ___No
a. ___for 1 month ___for 1 year ___over 1 year
b. ___daily ___weekly ___monthly
c. ___severe ___moderately severe ___mild
48. ___Yes ___No
49. ___Yes ___No
50.
a. ___Yes ___No
b. ___Yes ___No
c. ___Yes ___No
51.
a. ___Yes ___No
b. ___Yes ___No
c. ___Yes ___No
d. ___Yes ___No
52. ___Yes ___No
a. ___Yes ___No
b. ___Yes ___No
c. ___Yes ___No
53. ___Yes ___No
_____year stopped

*(end of form)*

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