# Medical Education Systems, Inc.

# Lung Volume

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# LUNG VOLUMES AND CAPACITIES

**Learning Objectives**

- Define what is meant by lung volume
- Explain why lung volume is important and how it is measured
- Discuss the meaning and importance of Inspiratory Capacity (IC) and Expiratory Reserve Volume (ERV):
- Define and discuss Body Plethysmography
- Discuss the context in which one finds lung-volume-reduction surgery
- Describe what is meant by volume ventilators, and explain their function
- Explain what is meant by hypoxemia and discuss how it is treated

## Some Definitions

### I. Lung Volumes.

A. **Tidal volume ($V_T$)** = volume of air entering or leaving the lungs during a single breath.

B. **Inspiratory reserve volume (IRV)** = volume of air which can be inspired over and above the resting tidal volume

C. **Expiratory reserve volume (ERV)** = volume of air which can be expired after a normal expiration.

D. **Residual volume (RV)** = volume of air remaining in the lungs after a maximal expiration.
Can be estimated as 25% of the vital capacity.

### II. Lung Capacities.

A. **Inspiratory capacity (IC)** = maximum volume which can be inspired after a normal expiration = VT + IRV.

B. **Vital capacity (VC)** = maximum volume that can be expired after a maximal inspiration =
VT + IRV + ERV.

C. **Functional residual capacity (FRC)** = volume of air left in the lungs after a normal expiration = ERV + RV.

D. **Total lung capacity (TLC)** = volume of the lungs when fully inflated = VC + RV (or 1.25 x VC).

### III. Other.

A. **Respiratory rate (f)** = number of breaths per min.

B. **Minute ventilation ($V_E$)** = total volume of air expired per minute = $V_T$ x f.

C. **Dead space ($V_D$)** = volume of inspired air which is not available for gas exchange.

D. **Alveolar ventilation ($V_A$)** = volume of air which reaches the alveoli per min = ($V_T$ - $V_D$) x f.

# Lung Volume

Lung voumes can be divided into 4 components: Tidal volume, inspiratory reserve volume, expiratory reserve volume, and residual volume.

Tidal volume (TV) is the amt. of air that moves in and out of the lungs in a normal breath. For an adult, its around 500 ml.

The inspiratory reserve volume (IRV) is the max. amt. of air that can be inspired in excess of the normal TV. Conversely, the max. amt. that can be exhaled in excess of the normal TV is the expiratory reserve volume (ERV).

Some air will always stay in the lungs after expiration (about 1,200 ml) - this is the residual volume (RV).

LUNG CAPACITIES include the sum of two or more of these measures. The functional residual capacity (FRC) is the sum of RV and ERV. The inspiratory capacity (IC) is the sum of IRV and TV. The vital capacity (VC) is the max. amt. of air that can be exhaled from the point of max. inspiration. FINALLY, the TOTAL LUNG CAPACITY (TLC; about 5,800 ml or 5.8 liters for an adult male) is the total amt. of air that the lungs can hold. This value is about 20 to 25% less in females than in males. Dependant on the development of the 14-15 year old, and if the teenager was a he or she, the TLC would approximate an adult's (around 5 to 6 liters of air).

**LUNG VOLUMES AND CAPACITIES**

The volumes and capacities listed here are normally determined using a spirometer! A traditional "bell spirometer" is a canister of water with an inverted canister bell over it with air space inside the inverted canister bell. Pulleys attach the canister bell to a pen which records volumes on paper on the outside of the canister. A $CO_2$ absorber could be placed in the bell housing and used in experiments to determine $O_2$ consumption, working on the assumption that loss of volume of air in the bell housing correlated directly with the volume of $CO_2$ exhaled and absorbed. The bell housing with the paper recording revolved electrically or was driven by a windup mechanism. You could look at these old machines and quickly figure out how to use them! A modern spirometer looks a lot like a little adding machine with a mouthpiece, air tube and a small printout or a cable that feeds data into a computer! There are many brands available, each is a little different! One model is displayed below.


**Table 1 - Respiratory Volumes and Capacities (approximates which will vary somewhat between sources)**

| TV (rest) | IRV | ERV | RV | FRC | MV | VC | TLC |
|---|---|---|---|---|---|---|---|
| 500 mL | 3000 mL | 1300 mL | 1200 mL | 2500 mL | 500 mL | 5000 mL | 6000 mL |

**Resting Tidal Volume ($V_T$):** This is the volume of air taken into the lungs when you inhale. Tidal volume increases with exercise or activity.

**Inspiratory Reserve Volume (IRV):** Total lung capacity minus the volume of air in the lung at the end of a normal inspiration. This means that we have a reserve volume that we can tap into as tidal volume increases with exercise or activity.

**Inspiratory Capacity (IC):** Sum of the tidal volume plus the inspiratory reserve volume **(TV + IRV)**.

**Expiratory Reserve Volume (ERV):** This is the difference between the volume of air left in the lung at the conclusion of normal expiration versus at the conclusion of maximal expiration. That means that we have a "reserve" volume which we can tap into when our tidal volume increases with exercise or activity.

**Residual Volume (RV):** The residual volume is the volume of air left in the lungs at the end of maximal expiration (ie. the volume of air which you cannot voluntarily exhale from your lungs). As residual air cannot be exhaled, the volume can be estimated through gas dilution techniques and the use of helium in inspired air (we do not metabolize helium).

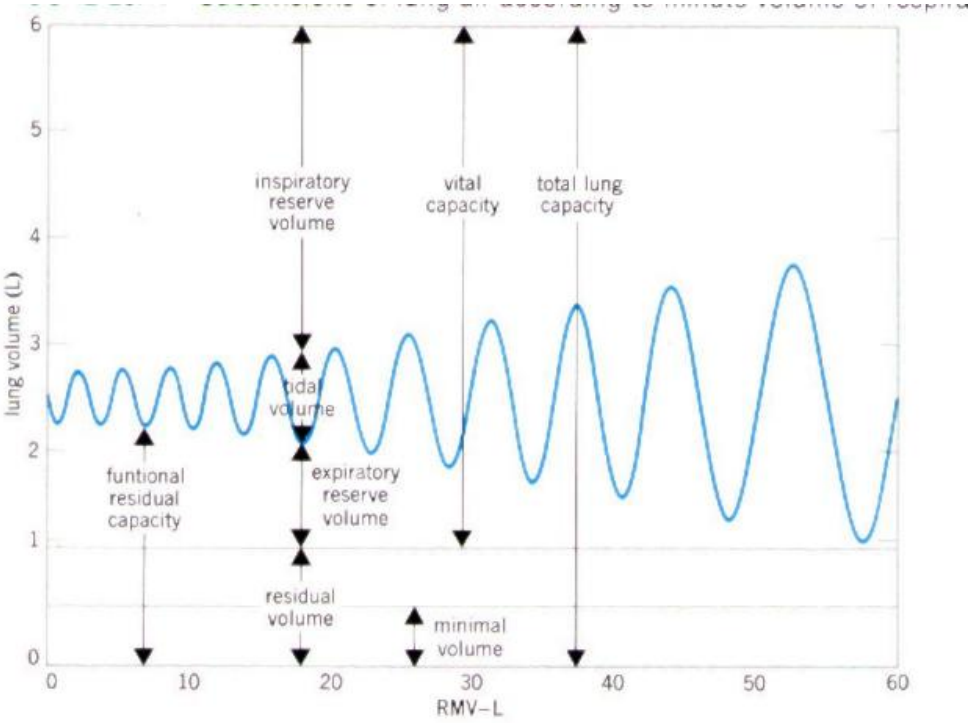
**Functional Residual Capacity:** This is the total volume of air left in the lungs at the conclusion of normal, resting expiration. This value includes the expiratory reserve volume plus the residual volume **(ERV + RV)**.

**Vital Capacity (VC):** Vital capacity is the total usable volume of the lungs which is under voluntary control. This value does not include the entire lung volume as it is not possible to breath all of the air out of the lungs.

**Total Lung Capacity (TLC):** The residual volume (air you cannot expire) + vital capacity (total volume available for use) = total lung capacity. In other words, TLC is the total volume of the lungs!

**Minimal Volume (MV):** Should the volume of the lungs fall below this value, the lungs will collapse.

**Figure: Respiratory Volumes and Capacities**




**Minute Respiratory Volume:** the volume of air exchanged in 1 min (respiratory frequency is approximately 12-15 breaths/min X tidal volume = 12 to 15 X 500 mL = 6000 to 7500 mL/min) (the average is closer to 6 L/min)

**Forced Expiratory Volume 1 (FEV1):** The volume of air that can be expired during the first second of expiration in a vital capacity determination.... generally about 80% of VC.

**Forced Expiratory Volume 1 (%) or FEV1(%):** FEV1/VC

**Anatomic Dead Space:** this is the volume of the air conducting pathways in which no gases are exchanged (approximately 150 mL in the average adult human being); this volume is optimized for the fastest delivery of air to the exchange zone with the least airflow resistance possible; when this volume gets messed up by something like an asthma attack, the volume is no longer optimized for low resistance and breathing quickly becomes a major problem! (see Poiseuille's Law).

**Physiologic Dead Space:** sum of the anatomic dead space plus the volume of any non-functional areas of the lungs. In young, health lungs, the volume of the anatomic dead space and physiologic dead space are equal.

**Alveolar Gas:** this is the volume of air in the alveoli following normal expiration at rest; this value would be just slightly less than functional residual capacity as this volume would not include anatomic dead space whereas functional residual capacity does! Alveolar gas, then, is close to 2.5L.

**Alveolar Ventilation** = (Tidal Volume - Anatomic Dead Space) X respiration rate = 5250 mL/min (at rest)

When we are resting quietly, our tidal volume drops so much that we only inhale enough air to fill our conducting zone as far as the distal ends of the terminal bronchioles (the border with the respiratory bronchioles)... and yet air still manages to reach our alveoli... can you guess by what mechanism gases are transferred between the ends of the terminal bronchioles and the alveoli?

**Ventilation rate** = total air flow/unit time

**Perfusion rate** = total blood flow through the lungs/unit time

Pressures are generally given in mmHg or $cmH_2O$ (1.3 mmHg = 1 $cmH_2O$)

**Pulmonary Capillary Blood Volume** at normal rest = 70 mL

**Pulmonary Blood Flow/min** at normal rest = 5000-6000 mL/min (ie. 100% of cardiac output)

**Systemic Blood Flow/min** at normal rest = 5000-6000 mL/min (ie. 100% of cardiac output)

## Lung Volume Tests

Factors which determine the size of normal lungs include: stature, age, sex, body mass, posture, habitus, ethnic group, reflex factors and daily activity pattern. Together with the forced ventilatory flows described in the next pages they are used in:

- Diagnosis of known or suspected lung disease
- Treatment of lung disease, monitoring the effect of preventive measures or diagnostic procedures
- Establishing a prognosis
- Pre-operative assessments
- Evaluation of pulmonary disablement
- Monitoring the respiratory health of populations
- Interpretation of other volume dependent lung function tests

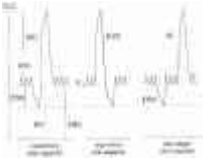


Fig. 1: Lung volumes and Capacities, schematic representation.

**Vital Capacity (VC):**

The Vital Capacity (VC) is the volume of gas measured on a slow, full inspiration after a maximal expiration (or a slow, complete expiration after a full inspiration), without forced or rapid effort. It is recorded in liters and reported at BTPS (Body Temperature, Pressure, Saturated with water vapor).

The measurement of the VC from a full inspiration after maximal expiration is called an IVC (Inspiratory Vital Capacity), the reversed (from a complete expiration after a full inspiration) is called an EVC (Expiratory Vital Capacity). The following ways are according to the European Respiratory Society (ERS) valid ways to obtain a VC:

- Inspiratory Vital Capacity (IVC): performed in a relaxed manner without haste or deliberately holding back.
- Expiratory Vital Capacity (EVC): performed in similar conditions.
- Two-stage vital capacity: determined in two steps as the sum of the Inspiratory Capacity (IC) and Expiratory Reserve Volume (ERV).
- Forced Vital Capacity (FVC): the volume of gas exhaled during a forced and complete expiration after a full inspiration.

**Notes**:
The variability of repeated measurements of the VC is between 90 and 200 ml. The EVC and FVC may be considerable less than the IVC in patients with airflow limitations. The two-stage vital capacity may occasionally be useful in very dyspnoic patients.

**Significance:**
Decreases in VC can be caused by a loss of lung tissue. In general this may be the result of tissue destruction or resections (lobectomy), space-occupying lesions (tumors), or changes in the composition of the parenchyma itself (fibrosis). The VC is often reduced in obstructive lung disease. Other causes of a decreased VC can also be: depression of the respiratory centers or neuromuscular diseases, reduction of available thoracic space (pneumothorax, cardiac enlargement) and limitations of thoracic (kyphoscoliosis) or diaphragmatic (pregnancy, ascites) movement.

**Inspiratory Capacity (IC) and Expiratory Reserve Volume (ERV):**

The Inspiratory Capacity (IC) and Expiratory Reserve Volume (ERV) are subdivisions of the VC, other subdivisions are Tidal Volume (Vt), Inspiratory Reserve Volume (IRV).

The IC is the maximal volume that can be inspired from the resting end-expiratory level (Functional Residual Capacity (FRC) level). The subdivisions of the IC are Vt and IRV (IC = Vt + IRV).

The ERV is the volume of gas that can be maximally expired from the level of the resting end-expiratory level (FRC level).

The Vt is the volume of gas which is inspired or expired during a respiratory cycle.

The IRV is the volume of gas which can be inspired from the resting end-expiratory level (FRC level).

All mentioned volumes are recorded in liters and corrected to BTPS.

**Notes**:
The accuracy of the measurement of IC and ERV depends on the determination of the passive end-expiratory level.
The Vt varies with the level of physical activity (rest, exercise) and measuring conditions (posture). The average value of at least six breaths should be used.

**Significance:**
The IC and ERV normally comprise about 75% and 25% of the VC, respectively. The ERV is decreased in obesity and is, in contrast to the IC, less in supine than in the sitting posture. Reduction of either the IC or ERV is consistent with restrictive defects.

**Functional Residual Capacity (FRC) and Residual Volume (RV):**

The Functional Residual Capacity (FRC) is the volume of gas remaining in the lungs at the average resting end-expiratory level.
The Residual Volume (RV) is the volume of gas present in the lung at the end of a full expiration.
RV = FRC - ERV or RV = TLC - IVC.
Both are recorded in liters and corrected to BTPS.

**Measurements**: The FRC can be assessed by 'gas dilution' method, by body plethysmography (see Thoracic Gas Volume (TGV)) or by radiography. The RV is calculated as FRC - ERV.

**Gas Dilution Method**:

- Open-Circuit Method: In this method the N2 in the lungs is gradually washed, out by breathing 100% O2, until the alveolar N2 concentration is less than 1%. The FRC volume can be calculated by the following formula:

$$FRC = \frac{FEN_{2,final} * ExpiredVolume - N_{2,tiss}}{FAN_{2,alveolar1} - FAN_{2,alveolar2}}$$

FEN2,final = Fraction of N2 in volume expired.
FAN2,alveolar1 = Fraction of N2 in alveolar gas initially (about 80%).
FAN2,alveolar2 = Fraction of N2 in alveolar gas at the end of test (alveolar sample).
N2,tiss = Volume of N2 washed out of blood and tissues.

A new method uses a rapid N2 analyzer to provide a 'breath-by-breath' analysis of expired N2, volume measurement by a pneumotachometer is integrated to derive the exhaled volume of N2 in each breath. The values from all breaths are added to calculate the total volume of washed out N2.

- Closed-circuit method: The FRC is calculated by rebreathing a known volume of gas to which helium (He) has been added. Rebreathing is normally continued until the He concentration changes by no more than 0.02% per 30 seconds. The FRC can be calculated by the following formula:

$$SystemVolume = \frac{He_{,added}}{F_{He,initial}}$$

and once the system volume is known, the FRC can be calculated by

$$FRC = \frac{\%He_{initial} - \%He_{final}}{\%He_{final}} * SystemVolume$$

**Notes**:
The variance of repeated FRC measurements is usually less than 10% in healthy subjects. The three methods of FRC measurement yield similar results in healthy subjects.

When measuring the FRC with the Open-Circuit Method corrections has to be made for the amount of N2 washed out of the blood and tissue and for the small

amount of N2 in 'pure' O2. In the newer method corrections must also be made for changes in the viscosity of the gas as O2 replaces N2 in the expirate.

In the Closed-Circuit method the FRC is corrected for the volume of He which dissolves in the blood (helium uptake has been estimated at 0,3 ml/min per %He in alveolar gas) and for the dead space volume of the breathing valve. A 'Switch-in' correction should also be made, but if the 'switch-in' correction is to large the test should be restarted after allowing the subject to breathe air for several minutes to clear any residual He from the lungs.

In both the open- and closed-circuit techniques, the ERV is measured as a subdivision of the FRC. This is the preferred method because the resting end-respiratory level is more reproducible than the point of maximal inspiration (Total Lung Capacity (TLC)) or maximal expiration (RV).

Both methods underestimate FRC and RV in subjects who have obstructive disease. A longer period to wash N2 out or mix He improves results somewhat but will not account for complete trapped gas, as in bullous emphysema. The ERS states that in subjects with severe flow limitations or emphysema the true lung volume is underestimated by the dilution method unless mixing time is prolonged to at least 20 min.

The FRC varies considerably with the level of physical activity, posture (lying down, sitting, standing) and the quantity of body fat (obesity).

**Significance:**
An increase in the FRC is considered pathological. An increase of more than 120% of the predicted represents hyperinflation, which may result from emphysematous changes, compensation for surgical removal of lung tissue, asthmatic or bronchiolar obstruction or thoracic deformity. Muscular and mechanical inefficiency can be the result of an increased FRC.

Increases in RV are characteristic in young asthmatics (usually reversible), emphysema and bronchial obstruction (chronic air trapping). An increased RV indicates that despite a maximal expiration, the lung still contain an abnormally large amount of gas. Gas exchange abnormalities (hypoxemia or CO2 retention) are often displayed with an increased RV.

In subjects with chest wall problems (skeletal deformity, fibrothorax) or

parenchymal disease (congestive heart failure, sarcoidosis, infections) the only physiological abnormality can be a lowered RV.

Decreases in FRC and RV are typically for restrictive diseases, and seen in diseases associated with extensive fibrosis (sarcoidosis, asbestosis, silicosis). A Restrictive disease pattern may also be seen in kyphoscoliosis, pectus excavatum, neuromuscular diseases and obesity. In diseases that occlude many alveoli, such as pneumonia, an decreased FRC and RV may also be seen.

**Thoracic Gas Volume (VTG):**

The thoracic gas volume is the volume of gas (whether communicating with open airways or trapped in any compartment of the thorax) contained in the thorax (at any level of thoracic compression) and is measured using the body plethysmograph. Measured at the end-expiratory level it is related to the FRC.

**Technique:** The technique is based on Boyle's law (the volume of gas varies in inverse proportion to the pressure to which it is subjected), if the temperature is held constant. The changes in pulmonary gas volume is measured by monitoring the change in pressure in a constant-volume plethysmograph.

**Significance:** The VTG measurement of FRC is often larger than the FRC derived from gas-dilution techniques, especially in diseases characterized by air trapping and in the presence of uneven distribution of ventilation (presence of very poorly or non ventilated airspace's). In severe obstructive patterns the FRC may be overestimated when the VTG technique is used. Normal lungs produce similar results when either method is used.

If a gas-dilution method and the VTG measurement are used to determine lung volumes the FRCbox/FRCgas ratio may be used as an index of gas trapping. The ratio is usually near unity in subjects having normal lungs or in subjects with have a mild restriction. Values greater than one indicate volumes of gas which are not detectable by gas-dilution techniques (non-ventilated gas volumes). The difference between VTG (plethysmograph) and FRC (dilution technique) provides information about non-ventilated air spaces in the thorax.

**Notes:**
The variation of repeated measurements of the TGV is about 5% in healthy subjects as well as in patients with obstructive lung disease.

The TGV is reported as the mean of three or more determinations which differ less than 5% from the mean; TLC as the mean TGV plus the largest of the inspiratory capacities. RV should be reported as TLC - IVC.

In patients with severe airflow limitations the measurement must be made at a frequency of less than 1/sec. (in higher frequency the pressure swings at the mouth during airway occlusion are not identical to the mean alveolar pressure; compliant extrathoracic airways change in volume permitting a small volume of air to flow between mouth and alveoli).

The plethysmographic determination of lung volumes is recommended in subjects with airflow limitation and air trapping. In infants overestimation of TGV may also be due to pressure swings due to the very compliant thorax.

**Radiological Estimation of Total Lung Capacity (TLC):**

TLC can be determined from posterior-anterior (P-A) an lateral radiographs of the chest (subjects must hold their breath at TLC when each film is exposed). It involves dividing the films into ellipsoidal segments and estimating the volumes of each segment. A planimeter can also be used to estimate the thoracic volume.

**Significance:** TLC values determined radiological correlate well with plethysmographic determinations in healthy subjects and subjects who have obstruction. In persons who have moderate to severe obstruction the radiological technique produce more accurate TLC values than gas dilution techniques. This technique offers a mean of double-checking the TLC determined by other methods and may provide lung volume information in subjects for whom other methods are impractical (e.g. those who have had a tracheotomy).
Pneumonia or pulmonary edema, and diseases that increase pulmonary tissue/blood volume may reduce the accuracy of the method.

**Notes:**
The chest radiographs should be taken at the level of TLC at a target-film distance of 185 cm. Corrections for non-gas containing structures in the thorax should be made. The within- and between-observer variability is about <1% and <5% respectively. The accuracy about 210 ml. The radiographic estimation of the TLC can not be used in subjects with an abnormal shape of the thorax (pectus excavatum, pectus carinatum) and spinal column (kyphoscoliosis).
The method is not recommended (due to evidence of accuracy) in subjects with disorders of the lung interstitium.

## Total Lung Capacity (TLC) and Residual Volume/Total Lung Capacity Ratio (RV/TLC * 100):

The TLC is the volume of gas in the lungs at the end of a maximal inspiration (measured in liters at BTPS). The RV/TLC ratio is the fraction of the TLC that can be defined as the RV (in percentage).

**Measurement:** The TLC can be calculated from TLC = RV + IVC, from TLC = FRC + IC (the latter is the preferred method in body plethysmography), or from the radiological method mentioned above. In addition the TLC can be calculated using several single-breath techniques (He or N2) which are commonly used in conjunction with other measurements (i.e. alveolar volume in DLCO measurements). The single-breath measurement of the TLC correlates (is about 17% smaller) well with multiple-breath techniques in healthy subjects but tend to be much lower than the true values in the presence of moderate to severe obstruction.

**Significance:** Decreases in TLC can be found in processes that occupy space in the lung such as edema, atelectasis, neoplasm's, fibrotic lesions and other diseases like pulmonary congestion, pleural effusion, pneumothorax and thoracic deformities. Restrictive diseases show proportional decreases in most lung compartments, although it is possible for one or more TLC subdivisions to be reduced more than others. When the TLC is less than 80% of the predicted a restrictive process should be suspected.

Normal or increased TLC can be found in subjects who have asthma, chronic bronchitis, bronchiectasis, cystic fibrosis or emphysema. An increased RV in conjunction with a normal or increased TLC (RV increased at the expense of the VC) is consistent with air trapping. When the TLC is greater than 120% of the predicted, as a result of an increased RV, hyperinflation is present.
Normal RV/TLC values may vary from 20% - 35%. A large RV/TLC in the presence of an increased TLC often indicates hyperinflation, while an increased RV/TLC with a normal TLC indicates that air trapping is present.

## Comparison of the methods to measure Lung Volumes:

**Gas dilution** underestimates the lung volume in the presence of very poorly or nonventilated airspace's. These are included in the **plethysmographic** and **radiographic** lung volumes.

The determination of **radiographic** and **plethysmographic** lung volumes include poorly or nonventilated airspace's, and in these cases it is considerably greater than lung volumes determined by **gas dilution** methods. The **radiographic** method gives values which do not differ significantly from **plethysmographic** determined values, even in subjects with airflow limitations.

**Body Plethysmography"**

**Definition:** When absolute air volumes in the lungs must be measured, spirometry is insufficient. Therefore, your doctor may order body plethsmography to get more precise measurements of lung volumes. Body plethsmography can measure residual volume, function residual capacity, and total lung capacity.

During a body plethsmography, the patient sits in an airtight box, inhales or exhales a particular volume, and then a shutter closes off the breathing tube. The patient is then directed to breathe against the shutter's resistance, causing the chest volume to expand and decompress the air in the lungs. This increase in chest volume reduces the box volume and slightly increases the pressure in the box.

## LUNG-VOLUME-REDUCTION SURGERY FOR EMPHYSEMA: THE NATIONAL EMPHYSEMA TREATMENT TRIAL (NETT)

**by W MacNee, Professor of Respiratory & Environmental Medicine and Honorary Consultant Physician, University of Edinburgh**

Lung-volume-reduction surgery (LVRS) has been proposed as a palliative treatment for patients with severe emphysema. The procedure leads to a decrease in lung volumes and an increase in elastic recoil of the lungs. Decreasing lung volumes improves respiratory muscle geometry and hence performance, while increasing elastic recoil increases expiratory airflow, leading to improved exercise performance and reduced dyspnoea. However uncertainty over the preoperative predictors of benefit and the effects on morbidity and mortality led to a National Institutes of Health-sponsored multicentre randomised control trial in the US, comparing LVRS with medical therapy for patients with severe emphysema. The outcome of this trial has recently been published in the *New England Journal of Medicine*.[1, 2]

Before randomisation, all of the patients in this trial underwent pulmonary rehabilitation. The primary outcome measurements were overall mortality and maximum exercise capacity two years after randomisation with secondary outcomes including results of six-minute walking test, lung-function tests and general health-related quality of life.

In the trial, 1,218 patients with severe emphysema as shown on CT scan assessment were randomised to either LVRS or medical therapy. An interim analysis of the study showed that patients with the most severe disease (FEV1 £20/% predicted and either homogeneous emphysema on HRCT or a carbon monoxide diffusing capacity of £20% predicted) had a higher risk of death following surgery than medical treatment.[3] In the subsequent analysis, 140 such patients were excluded leaving 538 patients randomly assigned to surgery and 540 assigned to medical therapy. Those assigned to surgery were more likely to have improvements in exercise capacity and quality of life but with no reduction in mortality during an average 29 months of follow-up.

However, secondary analyses showed that the effects of surgery on mortality varied widely depending on the presence of predominantly upper-lobe emphysema on high-resolution computed tomography of the chest and whether the patient had a high or low exercise capacity at baseline defined as a maximum work load at or below a cut-off value of 25 watts for women and 40 watts for men. In patients with predominantly upper-lobe emphysema and a low exercise capacity, the risk ratio for death in the surgery compared with the medical group was 0.47 ($p=0.005$), indicating a significant benefit of surgery. Those patients with predominantly upper lobe emphysema and high exercise capacity showed no benefit of surgery over medical treatment, and in those with non-upper-lobe emphysema and high exercise capacity the risk of death was higher among those who underwent surgery.

Mortality following LRVS varies greatly among centres. The NETT research group showed a 90-day surgical mortality of 7.9% in all randomised patients compared to 1.3% in a comparably medically treated arm.[1] The majority of this mortality was accounted for by high risk patients in whom the 90-day surgical mortality was 28.6% compared with 0% in the respective medical arm.[1] In non-high risk patients 90 day surgical mortality was 5.2% compared with 1.5% in medically treated patients.[1] During the first year of follow-up, the mean number of in-patient hospital days per person was significantly higher in the surgical group (24.9 days) compared with the medically treated group (4.9 days $p<0.001$). In contrast in the second year of the mean number of hospital days per person was significantly lower in the surgical group (3.2 days) than in the medically treated group (6.1 days, $p<0.005$) and in the third year there were no significant differences between the two groups in terms of the use of resources.

An economic evaluation revealed that the total medical costs were substantially higher in patients in the surgical group than for patients in the medical therapy group largely due to the costs of surgery during the course of the first six months, but from months 7-36 the mean medical cost was lower in the surgical group ($36,199) than in the medical group ($49,628, $p<0.001$), largely because patients in the surgical group had fewer hospital-admitted days during that period.

When the patients with high-riskconditions were excluded the cost effectiveness ratio for LVRS compared with medical therapy was $190,000 per quality-adjusted life-year gained. This compares, for example, with a $90,000 per quality-adjusted life-year gained for lung transplantation.[5]

The results of this trial have raised some questions about the interpretation of secondary analysis of the data collected in clinical trials. It was the purpose of the NETT trial to identify sub groups of patients who might benefit, or be at increased risk, from LVRS. Although there appears to be an interaction between upper-lobe disease and low exercise capacity in terms of reduced mortality, there is a risk when multiple characteristics of patients are considered that there is an increased probability that one or more tests will be statistically significant by chance.

Few studies have reported long-term results of LVRS, but they suggest widely varying long-term morbidity and mortality among centres, a return of spirometric function towards pre-operative baseline and worsening of dyspnoea over time.[5]

How then are we to interpret these results and translate them to clinical practice? It appears that the findings of the NETT study provide evidence that surgery has some benefit in terms of increased exercise tolerance and survival in patients with upper-lobe predominance of emphysema and low exercise capacity compared to medical treatment. The procedure is costly, but may be cost-effective if the benefits can be maintained over time.

**KEY POINTS**

- Emphysema is part of an important component of chronic obstructive pulmonary disease (COPD) which causes high disability associated with over inflated lungs, poor lung elasticity and impaired transfer of oxygen to the blood
- Reducing lung volume may allow respiratory muscles to work better and improve lung elasticity

**In highly selected patients:**

- Patients should have pulmonary rehabilitation before surgery is considered
- A North American study has shown that patients with heterogeneous emphysema in the upper lobes of the lungs, and poor access post rehabilitation can benefit from lung-volume reduction surgery
- The benefits of this option need to be shown

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## RESPIRATORY THERAPY: TREATMENTS, TECHNIQUES, EQUIPMENT

The result of weakening respiratory muscles is that the "vital capacity" of the lungs (the amount of air that a person can exhale after taking in a deep breath) decreases over time. The "forced vital capacity" — a measurement of how much air one can exhale with a maximum effort after taking in a deep breath — is based on your child's weight, height and age (see Pulmonary Function Testing). A normal capacity is 75 percent or greater of the "predicted," or normal, number for a person of a specific height, weight and age. The forced vital capacity is important because it indicates how much breathing reserve exists in the lungs.

Occasional deep breaths are vital in maintaining normal amounts of oxygen in the blood. Deep breaths prevent the smallest parts of the lungs from collapsing. Deep breaths are also necessary for effective coughing, which is the body's natural mechanism for removing mucus from the lungs. The cough reflex is an explosive expulsion of a volume of air from the lungs. The high pressure and speed of this air propel irritants, such as mucus, up and out of the lungs. Neuromuscular disorders can weaken the cough effort, which is vital in removing mucus during an acute respiratory infection.

### Exercises for Breathing Muscles: Incentive Spirometry

The primary focus of respiratory therapy applied to children with neuromuscular disorders is to assist in reducing the speed at which the vital capacity decreases. This is accomplished in stages over the progression of the disease with different methods of mechanical ventilatory assistance. Your doctor may or may not recommend one or more of the following treatments.

In our clinic, we've found that in the early stages of MD incentive breathing exercises are helpful. These exercises motivate the child to take "sigh breaths" — breaths two to four times larger than a regular breath. The amount of air in a regular breath is called a "tidal volume" breath. Tidal breathing without sighing doesn't allow total inflation of all the air sacs ("alveoli") in the lungs and can lead to the closing off of these sacs ("atelectasis").

An "incentive spirometer" is used to help open alveoli. The device provides a goal volume for a deep breath and the child is encouraged to hold that volume for 10 to 15 seconds. Fifteen to 20 deep breaths are suggested four to six times per day. Practicing this deep breathing exercise without the spirometer every hour or two would be ideal. Children are encouraged to begin this

form of respiratory therapy when their vital capacity measurement falls below 75 percent of the normal, or predicted, value.

The use of incentive breathing exercises is something that we individualize very carefully with each patient. The goal is simply to try to provide a substitute for the loss of "sigh breaths." We do not believe that we are making muscles "stronger." As we see muscles weaken by objective pulmonary function tests, incentive breathing exercises are discontinued in favor of other breathing assistance techniques.

**Aerosol Therapy: Nebulizers, Metered-Dose Inhalers**

Aerosol therapy is a method of delivering medications directly into the lungs. Specific medications that your doctor may prescribe include:

- mucolytics, which break down thick mucus
- decongestants, which decrease swollen tissues
- antibiotics, which combat infections
- bronchodilators, which relax smooth muscles in the airway and may assist with airway clearance

A nebulizer turns the liquid medication into a fine mist that can be inhaled. A small air compressor is attached to the nebulizer to generate a flow of air. Your child simply breathes slowly and deeply through the nebulizer for 15 to 20 minutes three to four times a day.

Another method of delivering medication directly into the lungs is the metered-dose inhaler (MDI). An MDI is a small, hand-held, plastic container of medication frequently attached to a "spacer" (a 6-inch cylindrical chamber and mouthpiece).

An aerosol treatment program is designed to meet the particular needs of your child during an acute respiratory illness. The pulmonary medicine team will assist parents in learning how to administer aerosol therapy and how to obtain the proper equipment.

**Cough Therapy: Intrapulmonary Percussionator, Emerson In-Exsufflator**

The "intrapulmonary percussionator" can be employed to assist in mucus clearance during an acute respiratory tract infection. This equipment is used when the vital capacity has declined, the child uses a wheelchair full time, and therapy must be performed in one body position.

The device is a small electrical machine that can simultaneously deliver aerosolized medication and loosen mucus from airway walls. Your child will breathe through the tubing and mouthpiece for 15 to 20 minutes three to four times a day until the mucus has cleared. The pulmonary medicine team will assist parents in learning how to use the intrapulmonary percussionator and how to obtain the equipment.

An in-exsufflator, also called the CoughAssist, is a small electrical machine that can assist a weak cough effort and make it effective in expelling mucus. The device can push a volume of air

into the lungs and quickly pull that same volume of air out of the lungs, imitating a strong cough effort. As with any respiratory therapy equipment, the pulmonary medicine team will assist parents in learning equipment operation.

We have found that the CoughAssist is a very valuable device and initiate its use at some point with all of our patients when the clinical picture and pulmonary function tests dictate.

**Mechanical Ventilatory Assistance: Volume Ventilators**

Modern "volume ventilators," which deliver a preset volume (amount) of air to the child with each breath, are valuable in the treatment of children with MD-related respiratory problems.

When the vital capacity has dropped below 40 percent of normal, a volume ventilator may be used during sleeping hours, a time when the child is most likely to be underventilating ("hypoventilating"). Hypoventilation during sleep is determined by a thorough history of sleep disorder with an oximetry study and a capillary blood gas (See Pulmonary Function Testing). The ventilator requires a nasal or face mask for connection to the airway. The masks are constructed of comfortable plastic with Velcro straps to hold them in place during sleep.

**PULMONARY FUNCTION TESTING**

Tests to evaluate the function of the lungs are generally noninvasive — that is, no needles or penetration of the body. These kinds of tests require a child to breathe into a computerized machine through a mouthpiece while a clip blocks the nose. The child must be mature enough to follow verbal instructions and cooperate with the respiratory therapist. Sometimes the therapist will use a computer, sometimes a simple hand-held measuring device. The function of the lungs is plotted over time, and when the numbers and physical exam show a decline, it's time to initiate some form of ventilatory assistance to move more air into and out of the lungs. If the rate of decline in breathing muscle function is well understood, decisions about the best form of assistance can be carefully considered before a breathing crisis develops.

**Pulmonary function tests include:**

*Computerized testing*

- lung flow rates, capacities and volumes
  A frequently used test is the "FVC," or "forced vital capacity," which measures how much air a person can expel as fast as possible after taking a deep breath. Information from a vital capacity maneuver can assist the physician in structuring a respiratory care plan for the specific needs of your child.
- breathing pattern analysis, which measures rib cage and abdomen coordination
- oximetry, which measures the amount of oxygen carried by the red blood cells
- capnography, which measures the amount of carbon dioxide in a breath
- (under some circumstances) capillary or arterial blood gases, which measure oxygen, carbon dioxide and bicarbonate levels in the blood

- A finger prick is needed to get a tiny amount of blood for capillary blood gas tests.

As the vital capacity declines to less than 30 percent of normal, a volume ventilator may also be needed during the day for more assistance. The child gradually will increase the amount of time using the ventilator during the day as needed. A mouthpiece can be used in the daytime and a nasal or face mask can be used during sleep. The machine can easily fit on a ventilator tray on the bottom of a power wheelchair.

There may be times — such as during a respiratory infection — when a child needs to rest his/her respiratory muscles during the day even when not yet using full-time ventilation. The versatility of the volume ventilator can meet this need, allowing tired breathing muscles to rest and also allowing aerosol medications to be delivered.

**Mechanical Ventilatory Assistance: Pressure Ventilators**

Some physicians and therapists recommend a different type of ventilation device — one that delivers air at a preset pressure instead of a preset volume. The type of device most often used is called a "BiPAP," which is short for "bilevel positive airway pressure." This machine delivers a set level of positive-pressure air during inspiration and can deliver a lower level of pressure during expiration. The volume delivered per breath is unknown, or variable. Furthermore, the volume changes dramatically with changes in lung stiffness and when airways are clogged with secretions from an infection. A nasal or face mask can be used for connection to the airway.

While mechanical ventilatory assistance must be individualized to the needs of each patient, we have found the vital capacity to be a useful guide, along with the clinical picture. Furthermore, we have found volume ventilators to be much more effective than pressure ventilators in neuromuscular disease.

**Alternative Airway Connection: Tracheostomy Tube**

When a volume ventilator is needed during the day as well as at night, alternate approaches to airway connection can be considered. However, many patients who require both day and nighttime ventilation continue to utilize nasal, oral and face mask attachments successfully.

Wearing the plastic nasal or face mask during the day may interfere with attending school and social contact with family and friends, and may cause skin irritation due to constant skin pressure. A mouthpiece may not be tolerated because of weakened facial muscles or air leakage. Sometimes an alternative must be considered.

*Tracheostomy ventilation*

The most commonly considered alternative approach to airway connection is a tracheostomy. A tracheostomy is a small, permanent incision in the neck just below the vocal cords which allows a small plastic tube (tracheostomy tube) to be placed directly into the airway. This keeps the face free of encumbrances and permits an easy connection to the ventilator.

A "trach" may interfere with speaking. Many children can vocalize using the air that can leak around the tracheostomy tube. A special valve (Passy-Muir valve) can be used to allow exhaled air to go around the tracheostomy tube and pass through the vocal cords to improve voicing as much as possible. Advantages of a trach include:

- small airway connection
- ability to remove secretions with a suction device, which reduces the chances for mucus plugging and infection
- ability to deliver aerosol medications directly into the lungs to keep secretions thin
- ability to deliver aerosol antibiotics directly into the lungs to combat infection

A tracheostomy tube requires careful attention to hygiene in order to prevent infection. Excessive secretions can be removed with a tiny tube ("catheter") attached to a suction machine. Caregivers must be instructed in sterile techniques for suctioning. Because the nose, through which air from the outside world is normally moisturized, has been bypassed, most people will need humidification, at least on a part-time basis. The sensation of taste may be diminished.

## Causes of Hypoxemia

Although low inspired oxygen is a potential cause of hypoxemia, it virtually never occurs clinically. Diffusion impairment occurs in several different forms. It is rare to see chronic fibrosis causing a diffusion block, but occasionally interstitial pneumonia’s do occur. Other less obvious causes of diffusion blocks include pulmonary edema, exudate in the alveoli, capillary dilatation resulting in a increased distance between alveoli and the red blood cell, changes in red blood cell shape or membrane and decreased area as with emphysema, or capillary hypoplasia which again is extremely rare in clinical medicine.

Inadequate alveolar ventilation (hypoventilation) will also cause hypoxemia. Of course this will always be accompanied by hypercapnia. This can be caused by obstructive or restrictive disease but more commonly is caused by central neurologic depression or septicemia resulting in weakness and inability to effectively ventilate.

Another common cause of hypoxemia is venous admixture (mismatching) or shunting. This may be caused by widespread atelectasis, consolidation, persistent fetal circulation, right to left

shunting, decreased blood flow (hypovolemia or right sided cardiac insufficiency), increased blood flow ( not enough time for full equilibration), pulmonary edema, exudate in the airway, or uneven blood flow.

## Mismatching

Mismatching can be thought of as the middle ground between shunting (blood that bypasses all gas exchange areas) and alveolar dead space ventilation (gas that never comes in contact with blood). The lungs are made of billions of alveoli which all have their own ventilation/perfusion (V/Q) ratios. The V/Q ratio at the top of the lungs is high (3.0). As you travel down the lung blood pressure increases faster than ventilation decreasing the ratio (0.6 near the bottom). The average V/Q ratio in normal individuals is about 0.8. However the average ratio in patients dying of respiratory disease because of extreme V/Q abnormalities is also usually 0.8. This is an instance where the physiology gets mixed up and does not follow common sense rules in the pathophysiology of lung disease. In essence the V/Q ratio does not change with severe disease because for any area of the lung which becomes over ventilated and under perfused, there is another part of lung which becomes over perfused and under ventilated. Thus respiratory patients die because more of their alveoli lie at the extremes of the V/Q ratio than near the ideal middle ground.

Mechanical ventilation may help correct mismatching since it can result in opening alveoli that have not been ventilated before, decreasing some intrapulmonary shunting. However mechanical ventilation may also over distend already opened alveoli resulting in compression of the capillary beds surrounding these alveoli and decreasing their blood supply, further disturbing the ventilation/perfusion matching. Obviously with billions of alveoli, some alveoli from both groups will be affected by ventilation. The success of ventilation in part depends on how many alveoli have an improved V/Q ratio and how many have a worse V/Q ratio as a result of ventilation. The art of mechanical ventilation is in adjusting ventilation to maximize the V/Q ratio.

**Clinical diagnosis of V/Q abnormalities:** Shunting can be differentiated from mismatching by a trial of 100% oxygen. Areas where mismatching is occurring will be corrected if the inhaled FIO2 is 1.0 (as long as the mismatching is not extreme). In the usual case the Pao2 will increase to 300-400 if mismatching is the only abnormality. If shunting is occurring then the Pao2 will not rise as much. A clinical rule of thumb is that if cardiac shunting (as apposed to intrapulmonary shunting) is occurring then the Pao2 will not rise above 100 mm Hg despite having an FIO2 of 1.0. In most cases with cardiac shunting (this is right to left shunting) the Pao2 will be between 40 and 60 mm Hg when the patient is on an FIO2 of 1.0.

The amount of alveolar dead space ventilation can be estimated by comparing ETCO2 with the Paco2. For adequate explanation of why, you should see the discussion on capnography. Using the formula (Paco2 - ETCO2)/ Paco2 the percentage of alveolar dead space ventilation can be estimated.

## Functional residual capacity in weak foals

In healthy individuals the functional residual capacity (FRC) is maintained so that almost all alveoli are open and ventilated. In foals who are weak or debilitated, the FRC can be significantly reduced resulting in poor ventilatory function. The FRC is maintained by the opposing forces of the rib spring which pulls the lungs outward and the elastic properties of the lungs which tends to make the lungs collapse. In newborn foals the chest wall is very compliant and does not have a good spring, resulting in less innate forces pulling the lungs open. Neonates can partially compensate for this by using their intercostal muscles to hold their chest wall out.

Neonates also have lower lung compliance resulting in a stronger force pulling the lungs close. If the foaled is weak or fatigued, he no longer can maintain his FRC and the lungs began to collapse to a volume, where alveoli collapse during expiration and must be opened on each breath to receive ventilation. Alveoli that repeatedly close in this manner will tend to squirt surfactant into the airway each time it closes, resulting in loss of surfactant. As the amount of surfactant decreases it becomes more difficult to open these alveoli on inspiration and eventually they can no longer be opened and atelectasis results.

This further decreases the compliance of the lungs and further tends to cause collapse of more alveoli. The sum affect of this is progressive atelectasis. Even in those alveoli which are being ventilated, the ventilation is less evenly distributed because alveoli not already open will not open until midway through inspiration. Other alveoli that are already opened will accept gas throughout inspiration. This results in maldistribution of ventilation and perfusion. Also alveoli that close during expiration only participate in gas exchange during inspiration.

The added work of opening alveoli during progressive atelectasis and the decreased compliance may result in fatigue of the respiratory muscles in the foal. Eventually the intercostal muscles will become so fatigued that they will no longer be able to hold the chest open during inspiration. As the diaphragm contracts producing a negative pressure in the thorax, the chest wall will tend to be pulled towards the lungs resulting in very inefficient ventilation. When these foals are observed, the chest wall will be seen to drop during inspiration as the abdomen expands secondary to the contraction of the diaphragm. This results in "wave chest" in which the thorax moves inward as the abdomen moves outward during inspiration. The abdomen moves inward as the chest moves outward during expiration. The development of " wave chest " heralds the onset of significant fatigue and respiratory failure which will lead to respiratory and cardiac arrest if not corrected.

Decreased FRC is most effectively treated through initiation of PEEP/CPAP. By increasing the airway pressure during expiration alveoli tend to stay open and on each new inspiration more alveoli may be recruited. Full recruitment using PEEP/CPAP requires 15-20 minutes. A full discussion of this ventilatory therapeutic modality is described elsewhere.

STATIC (EFFECTIVE) COMPLIANCE

= TIDAL VOL / PLATEAU PRESS-PEEP

This measure of compliance includes the compliance of the lung and the chest wall. It is a readily attainable, useful clinical parameter. It will decrease if there is an abnormality of the chest wall (a flail chest), decrease in functional alveolar numbers as with pulmonary edema, pneumonia or atelectasis and for other similar reasons. It may also be used to determine the best PEEP and best tidal volume if serial measurements are obtained at trial settings.

DYNAMIC COMPLIANCE

= TIDAL VOL / PEAK PRESS-PEEP

Dynamic compliance adds the effects of resistance to static compliance. Dynamic compliance will decrease with disorders of the airway, lung parenchyma, and chest wall. Dynamic compliance is less than static compliance when there is increased resistance such as with secretion in the airways or endotracheal tube, bronchospasm, or endotracheal tube kinking.

## TREATMENT

## Rx HYPERCAPNIA

## MECHANICAL VENT

Hypercapnia must be treated with increased ventilation. This may be achieved by mechanical ventilation or in selected cases with chemical stimulants. If the cause of hypoventilation is central depression of respiratory centers, methylxanthines maybe utilize as respiratory stimulants. Caffeine is the safest and most effective metylxanthine for use in foals. It can be given orally or if there is GI intolerance as in necrotizing enterocolitis, it is also effective when given rectally.

When mechanical ventilation is used to treat hypercapnia, the tidal volume and respiratory rate should be adjusted to result in an acceptable Paco2. A reasonable tidal volume to begin with is 8 to 10 mls /kg. An adequate tidal volume will open previously collapsed alveoli, but not over distend other areas of the lung. Extreme mismatching may result in hypercapnia. Ventilation can help correct this extreme mismatching at times. Another consideration in treating hypercapnia is in decreasing production of CO2. This means avoiding treatment with bicarbonate and preventing lipid metabolism by limiting intravenous lipid supplementation and excessive calories. The goal of treatment is to decrease the Paco2 to below 60 mm Hg long as the pH is normal. It should be recalled that frequently foals have a significant metabolic alkalosis with respiratory compensation resulting in hypercapnia. This hypercapnia is an important

compensatory mechanism which should not be undermined by ventilation. Hypercapnia secondary to metabolic alkalosis should be treated by correcting the cause of the metabolic component.

**Treatment of hypoxemia**

Hypoxemia should be treated when a Pao2 is consistently below 60 mm Hg or the Paco2 is > 60 mm Hg since on room air a Paco2 of 60 - 70 will result in hypoxemia. Oxygen saturation can also be used as a guideline. Considerations of therapy should be given to any patient with an oxygen saturation below 90-94%.

Hypoxemia due to ventilation perfusion mismatching can be corrected by intranasal insufflation of oxygen. If high intranasal flows of oxygen do not significantly increase the Pao2 than there may be significant shunting, atelectasis, consolidation, or persistent fetal circulation. Unless there is a large shunt, oxygen therapy will not only increase the Pao2 but will also decrease the work of breathing necessary to maintain oxygen delivery (work of respiratory muscles and also myocardial work).

In rare cases, respiratory efforts will stop when oxygen therapy is applied. This will occur when there is significant damage to the central receptor or significant central receptor depression so that they are not sensitive to Paco2 and the major drive for ventilation is hypoxemia. Most commonly this occurs with HIE but it can occur with phenobarbital overdose in seizing foals. Another potential problem of oxygen therapy is atelectasis secondary to complete absorption of high oxygen content gas in alveoli in poorly ventilated areas of the lung. Oxygen toxicity is also possible, however it is rare unless FIO2 > 0.5 for more than 24 hours. Usually oxygen toxicity does not appear clinically unless FIO2 > 0.8 for extended periods.

Unless there is a large shunt, oxygen therapy will not only increase the Pao2 but will also decrease the work of breathing necessary to maintain oxygen delivery (work of respiratory muscles and also myocardial work).

Mismatching and intrapulmonary shunting can been reduced by manipulation of ventilation and perfusion. Mechanical ventilation may open alveoli that are closed resulting in better distribution of ventilation. However if the tidal volume is too large, over distension may not only cause volutrauma but also result in compression of alveolar capillaries resulting in poor matching of perfusion. Addition of PEEP will result in better matching since the alveoli will remain open during the entire ventilatory cycle and gas exchange can occur throughout the cycle. Also the open alveoli more readily accept the breath resulting in much more even ventilation. Perfusion may also be increased in areas that have relative over ventilation. In alveoli that are being ventilated, decreasing a tidal volume or PEEP may encourage perfusion.

Likewise, increasing perfusion pressure may result in better perfusion. The cardiac output may be increased by insuring proper volume loading and through the use of inotropes. Placing the foal in a sternal position may also increase matching dramatically. Decreasing pulmonary edema through the use of furosemide and decreasing inflammatory disease by treatment of pneumonia

may also help improve matching. Surfactant therapy is also in theory a good idea, however in my hands it has not been very impressive.

CONTINUOUS POSITIVE ANYWAY PRESSURE

There are four methods of achieving CPAP:

1) endotracheal CPAP

2) nasopharyngeal CPAP (shortened endotracheal tube in posterior pharynx)

3) nasal prongs

4) negative end expiratory pressure (negative thoracic pressure)

Beneficial physiologic affects of CPAP are created by an increased transpulmonary pressure resulting in an increased FRC, stabilization of an unstable chest wall, and improvement in ventilation perfusion ratios. CPAP affects: pulmonary mechanics, cardiovascular stability, and pulmonary vascular resistance.

**PULMONARY MECHANICS:** CPAP is the major factor determining lung volume. At low CPAP (low volumes e.g. in diseased lungs), compliance is low; at higher volumes compliance increases; at high volumes (over distension ) compliance again decreases. Optimum FRC results an optimum compliance and the lowest work of breathing. Optimum CPAP = optimum FRC. Lung volume is also related to airway resistance. At low lung volumes (insufficient CPAP) airway resistance is high and since atelectasis is not resolved, the work of breathing is high. At optimum lung volumes airway resistance is low. Thus CPAP can improve distribution of ventilation to optimize FRC and therefore optimize both lung compliance and airway resistance.

**CARDIOVASCULAR STABILITY:** High CPAP can have a detrimental effect on the cardiovascular system, compressing right sided vessels, decreasing cardiac return which will result in decreased cardiac output. This may result in acidosis, tachycardia, decreased arterial blood pressure, etc. The amount of CPAP that is excessive and will produce this affect depends on the lung compliance. If the lung compliance is low, less intra-airway pressure will be transmitted to the plural space and cardiac compromise will be less. Hypovolemia will exacerbate the negative effect of high CPAP. Excessive CPAP may be detected by the development of acidosis, decreased dynamic lung compliance and increased CO2 retention. A trial of lower CPAP or increased IV fluids will resolved the problem, however it should be recalled that too low a CPAP will also cause acidosis.

**PULMONARY VASCULAR RESISTANCE:** Over distension of the lung may cause direct pressure on pulmonary arterials and capillaries, increasing pulmonary vascular resistance and pulmonary artery pressure. Low levels of CPAP do not resolve atelectasis. Atelectasis results in

shunting of blood away from collapsed alveoli and regional increase in pulmonary vascular resistance. Optimal CPAP will optimize the V/Q.

The affects of CPAP on renal perfusion have been controversial. However most are probably directly related to changes in cardiac output. CPAP's affects on cerebral pressure are directly related to the level of positive pressure applied to the airway and the lung compliance affecting blood flow. If the pressure is transmitted to the pleural space and the anterior vena cava, it may result in increased cerebral pressure.

Optimal CPAP can be found by producing a CPAP/PEEP grid: adjust CPAP to 1 cm above and 1 cm below current levels and after 10-15 minutes obtain Pao2 or lung compliance depending on the goal of the CPAP.

### NITRIC OXIDE THERAPY

The endothelium regulates vascular tone through its production of many vasoactive mediators, including endothelial-derived relaxing factor, prostaglandins, and endothelin which act on the underlying vascular smooth muscle. NO is constantly produced at a low level. It appears to be responsible for hypoxic vasoconstriction in the lungs. Patients with pulmonary hypertension appear to have low basal secretions of NO. In the endothelial cell L-arginine is converted by NOS to NO in a reaction that requires oxygen and calcium. NO results an activation of soluble guantanyl cyclase which results in smooth muscle relaxation. NO is metabolized as it diffuses into the vascular lumen. It is quickly bound to hemoglobin, producing nitrosyl hemoglobin and methemoglobin. This rapid binding and metabolism of NO inactivates it, providing local regulation of vascular tone in the microcirculatory beds of the body without generalized systemic effects. Therapeutically, this inactivation allows for the use of inhaled NO gas to treat pulmonary hypertension without danger of systemic hypotension. In patients with pulmonary hypertension, adding 20-40 ppm NO to the inhaled gases will help vasodilate pulmonary vessels often leading to significant improvement. In patients with uneven ventilation/perfusion, treating with NO will tend to improve matching since where ever the gas is delivered (ventilated areas) vasodilatation will occur resulting in improved perfusion.

Thanks to: Jon Palmer, Neonatal Intensive Care Unit, New Bolton Center, Kennett Square, PA.

## Can Patients With Emphysema Benefit From Lung Volume Reduction Surgery?

Medical Author: Zab Mohsenifar, MD

Emphysema is a crippling disease that affects almost 2 million people in the USA. Smoking is the principal cause of emphysema. Genetic (inherited through genes) forms of emphysema,

however, also exist. These genetic forms are caused by certain biochemical (enzyme) deficiencies in the lungs. The main symptom in patients with emphysema is shortness of breath at rest and even more so during exercise. The traditional medical treatment of emphysema includes drugs that widen or open the air passages (bronchodilator drugs), oxygen, exercise programs (regimens), and steroids when the disease worsens (exacerbates). I should point out, however, that oxygen therapy is the only treatment that has been associated with an actual improvement (increase) in the duration of life (survival) for certain patients with emphysema.

Emphysema is generally a diffuse disease of the lungs. Diffuse means that the disease is spread throughout and involves the entire lungs. Some parts of the lungs, however, may be involved more than other parts. For example, emphysema involves predominantly the upper parts (lobes) of the lungs in smokers and the lower lobes in people with the enzyme deficiencies. Conceivably, therefore, surgical removal (resection) of the diseased parts of lung can result in expansion of the healthy areas of lung. Expansion of the remaining lung would be expected to occur to make up (compensate) for the surgical loss of lung volume or just to fill the void. This expansion of lung tissue is the main principle and the rationale behind Lung Volume Reduction Surgery.

Numerous studies since the 1950s have suggested that surgical resection of the diseased portion of the lungs (lung volume reduction surgery) may benefit patients with emphysema. In the past, one of the biggest problems with this surgery has been that air can leak from the sutured (sewn closed) surface of the remaining lung. You see, the air can leak because the diseased (emphysematous) lung tissue may not heal well enough to hold the sutures properly. Moreover, continuous air leaks can create additional problems, such as infection in the lungs. With the development of new techniques for effectively closing off the remaining lung surface, however, this issue of air leakage has been somewhat resolved.

Nevertheless, important questions regarding lung volume reduction surgery still remain. These questions include:

- How effective is lung volume reduction surgery?
- Which patients might be expected to benefit from this operation?
- How long will the benefits of the operation last?

To answer these and other questions, the NIH (National Institutes of Health) and CMMS Center for Medicare and Medicaid Services) in 1996 organized a randomized clinical trial for the treatment of emphysema. In randomized trials, patients are assigned to one treatment or another simply by chance. This study is still ongoing. Patients at 17 participating major medical centers in the USA are randomly assigned to receive either maximal medical therapy or the lung volume reduction surgery. So far, close to 1100 patients with emphysema have entered the study.

Of course, we are anxiously awaiting the final results of this study. Recently, however, the investigators learned and revealed that the surgery indeed might harm certain patients, for example, those who had emphysema that was extremely severe and vastly diffuse (throughout the lungs). Thus, these particular patients did not benefit from the surgery and actually did not do well clinically after the surgery. (Emphysema was considered extremely severe if the result of a

lung function test called the forced vital capacity (FEV1) was less than 20% of the predicted normal value.)

The study will continue for an additional 2 years, at which time the final data will be analyzed in detail. Already, it is very clear that some patients with emphysema can benefit substantially from lung volume reduction surgery. The questions remain, however. Just which patients will benefit and how long will the benefit last?

## Bronchial Hygiene Therapy

Chest physiotherapy (CPT) is a time-honored mode of bronchial hygiene therapy. Nevertheless, CPT has been criticized by some patients who receive this type of therapy, as well as by those who provide it. Patients may complain that it is uncomfortable, time-consuming and requires the assistance of a second person. Patients generally demonstrate poor compliance with this traditional technique at home. Caregivers point out that CPT addresses the symptoms (stasis of secretions), rather than the underlying defect (collapsibility of airways). Also some caregivers are experiencing repetitive motion injuries, such as carpal tunnel syndrome and neck and shoulder injuries. Until recently, no clinical alternative to CPT was available. This situation has changed with the introduction of positive airway pressure PEP therapy.

PEP therapy was first described in Scandinavian literature in the late 1970's. PEP is now widely accepted in Europe and Canada and is gaining increasingly widespread clinical acceptance in the United States. PEP is particularly helpful for patients with pulmonary secretory problems. When originally studied, PEP mask therapy was applied to patients with cystic fibrosis, bronchiectasis and chronic bronchitis as an alternative and/or supplemental technique for mobilization of bronchial secretions. Additional literature has described the use of PEP to enhance the deposition of bronchodilator aerosol and in the treatment and prevention of pulmonary complications in patients who have undergone upper abdominal surgery.

Frischknecht-Christensen et al reported the successful use of PEP Mask Therapy in the long-term management of patients with chronic bronchitis. They found that treatment with a simple PEP device can reduce morbidity in patients with chronic bronchitis and may preserve lung function from a more rapid decline.

With the application of PEP, there is improved airway patency, promotion of airflow to/from previously obstructed airways and a resultant enhancement of mucus clearance from these areas. PEP has also been shown to enhance collateral ventilation. Two types of channels for collateral ventilation have been described in humans, the pores of Kohn, with a diameter of 3-13 micrometers, and the canals of Lambert with a diameter of 30 micrometers. The positive back pressure generated during PEP allows airflow to enter these channels behind areas of mucus obstruction, keeping the airways open during exhalation.

This mechanism is reminiscent of pursed-lip breathing, a pattern of ventilation that patients with unstable airways often teach themselves without any prompting whatsoever from their caregivers. During PEP therapy, the resistance imposed at the mouth is transmitted upstream. The resulting back pressure succeeds in splinting the airways open.

The so-called "choke point" has been defined as that point in the respiratory tract where extrinsic compression causes collapse of distensible airways. The addition of positive pressure at the lips tends to move the choke point away from the periphery and towards the central airways, which are anatomically more rigid and thus, less likely to collapse. In the absence of premature airway collapse, expiratory airflow is able to mobilize mucus towards the larger airways from which it can be coughed-up and expectorated. Predictably, PEP is particularly effective in clearing secretions from small airways.

Lieberman et al have evaluated the use of a fixed orifice (FO) resistor versus a threshold resistor (TR) for the delivery of PEP. Each device increased mean airway pressure (Paw) by comparable levels. The FO limited the peak expiratory flow rate (PEFR) and prolonged expiratory time (Texp), but did not significantly affect peak expiratory pressure. The FO caused no air trapping nor intrinsic PEEP. In contrast, exhalation through the TR caused increased peak expiratory pressure, Paw, FRC and PEEP in proportion to the level of expiratory pressure applied. As a result, the TR significantly increased the work of breathing. There were no significant changes in Texp or PEFR. The FO did not impose any change in the work of breathing. These investigators concluded that PEP provided by FO and TR had considerably different effects on pulmonary mechanics. When selecting equipment for administration of PEP therapy, the clinician must carefully consider the goals of the therapy and the patient's underlying pulmonary function to optimize their patient's response and to minimize complications. Patients generally find the fixed orifice device more comfortable and tolerate the therapy better.

One of the greatest benefits of PEP therapy resides in the fact that it is self-administered, leaving the adolescent or adult patient independent of daily assistance and therefore, enhancing compliance. Tyrell et al compared the use of the PEP mask with forced expiratory coughing to conventional chest physiotherapy over a one month period. The mask was well accepted, and allowed independent treatment by older patients. Currie et al surveyed fifty outpatients who were chronic sputum producers. Patients were asked to complete a questionnaire designed to assess their usual practice of postural drainage, their impression of its value and their problems and compliance with it. Seventeen patients had difficulty finding time for postural drainage, 15 found it distasteful and in 17 postural drainage caused discomfort or pain. Twenty-seven patients were judged to be performing inadequate postural drainage, despite individual initial instruction and regular follow-up in a respiratory out-patient clinic. Steen et al evaluated PEP as a method of chest physiotherapy, both alone and in conjunction with other physiotherapy techniques, in a randomized cross-over trial. Twenty-three of twenty-four patients chose to continue using PEP in conjunction with forced expiratory technique (FET) long-term as their chest physiotherapy/postural drainage program, as they felt it was an effective treatment allowing increased independence. PEP is easy to administer and is inexpensive.

PEP therapy improves lung function and the removal of pulmonary secretions. Groth et al investigated lung function during PEP physiotherapy in cystic fibrosis. They found that, during

PEP physiotherapy, functional residual capacity (FRC) increased significantly ($p<0.02$). There was a decrease of washout volume (WOV) ($p<0.05$), lung clearance index (WOV/FRC) ($p<0.001$) and volume of trapped gas ($p<0.05$). Total lung capacity, vital capacity, tidal volume and residual volume did not change significantly. They concluded that PEP physiotherapy enhances the uniformity of alveolar gas distribution and tends to open up lung regions that were preciously closed off. These results tend to explain the clinical observation that PEP physiotherapy increases the transcutaneous tension of oxygen and the expectoration of sputum. Tonnesen and Stovring compared PEP therapy with conventional lung physiotherapy in patients with cystic fibrosis. Residual volume ($p<0.02$) was reduced during 6-9 months of PEP therapy. Subjectively, sputum production was greater during the PEP period. Falk et al reported that the clinical effect of positive expiratory pressure therapy in cystic fibrosis was superior to other forms of lung physiotherapy, such as postural drainage, percussion/vibration, or forced expiration. The most pronounced effect of PEP was an increase in the ability to expectorate sputum.

PEP therapy can be implemented when the patient is admitted to the hospital and is usually well tolerated by patients of all ages. Hospitalized patients who learn to self-administer PEP can reduce health-care costs related to the administration of CPT by professional hospital staff. Patients upon admission, who are experiencing severe dyspnea and increased work of breathing often lack the concentration to learn PEP therapy. By day two or three, respiratory therapy orders may be written for the patient to be instructed in PEP. Initially, PEP is introduced alternating with CPT on a treatment-to treatment or daily basis. By day four or five of hospitalization, CPT can often be discontinued, with most patients able to assume full responsibility for the performance of their own PEP therapy.

**The equipment needed to perform PEP therapy includes:**

- A mouthpiece or mask
- A fixed orifice resistor kit
- An expiratory pressure indicator
- Noseclips (prn with mouthpiece)

**The procedure for PEP therapy involves the following:**

- Wash your hands and introduce yourself to the patient. Explain the procedure to the patient.
- Assemble the PEP equipment.
- Have the patient sit upright, with their elbows resting on a table in front of them.
- Select the largest fixed orifice.
- Encourage the patient to relax.
- While performing diaphragmatic breathing, the patient is instructed to inspire a volume larger than normal, but not all the way to inspiratory capacity, through the device.
- Have the patient perform an inspiratory hold for approximately three seconds.
- Instruct the patient to exhale through the expiratory resistor to functional residual capacity (FRC).

- Exhalation should be active by not forced. The therapist and the patient should observe the expiratory pressure indicator or manometer ensuring that 10-20 cm H2O is generated throughout the majority of exhalation.
- Adjust the fixed orifice as needed to result in an inspiratory to expiratory ratio of approximately one to three, while maintaining the desired PEP level. If the caregiver selects a port that is too large, exhalation will be too short, and the desired PEP level will not be attained. If the port selected is too small, the expiratory phase will be prolonged, work of breathing will be increased, leading to the risk of air trapping.
- A series of 10-20 breaths is performed.
- After removing the PEP device, the patient performs several forced expiratory maneuvers ("huff coughs") to raise secretions.

**Huff coughing** is a modified forced expiratory technique that is performed by forcefully exhaling through an open glottis from high to mid lung volumes. The patient takes in a slow, deep inhalation, followed by a 1-3 second breath hold. The patient then performs short, quick, forced exhalations with the glottis open. The patient may find it helpful to whisper the word "huff" during the exhalation. Younger children may be taught to flap their arms to their lateral chest as they perform the "huff" cough. This technique is sometimes referred to as the "chicken breath". This activity may help the child to focus on the forced exhalation and add enjoyment to the technique.

- This cycle of 10-20 PEP breaths, followed by huff coughing, is repeated 4-6 times per PEP therapy session.
- Sessions last approximately 10-20 minutes, and should be performed 1-4 times per day as needed.

**TheraPEP Positive Expiratory**

**Pressure Therapy System**

The expiratory pressure indicator serves a dual purpose. It is an instructional aid for selection of the appropriate size orifice and it provides ongoing visual feedback to the patient. The tendency for patients to become lax while performing PEP therapy is reduced by the visual confirmation provided by the indicator. During periods of exacerbation, patients should be instructed to increase the frequency of sessions rather than extending the length of individual sessions. Extending the length of PEP sessions may cause fatigue. The optimal times for performing PEP therapy are early morning and the late evening. The initial instruction takes approximately one hour, with a 30 minute follow-up session as needed.

**Care and cleaning of the PEP equipment is:**

- Once a day, wash the TheraPEP (resistor, pressure port connector and mouthpiece) in warm, soapy water.
- Rinse equipment well, making sure all remaining soap is removed.
- Soak the TheraPEP in a vinegar solution containing 2 parts white distilled vinegar with 3 parts distilled water for 20 minutes.
- Rinse equipment thoroughly, shake dry and place on a paper towel to dry. Allow to dry for one full day. It is very important that the equipment is completely dry to help prevent the growth of bacteria.

**Do not submerge the entire Pressure Indicator unit.** Submersion of the Pressure Indicator will affect the accuracy of the Indicator. Protect the clear Indicator section of the unit while cleaning. Inspect device on a routine basis to ensure proper use and function. If damaged, DO NOT USE. Discard and replace. The interior base of the Pressure Indicator should be inspected for cleanliness periodically. To inspect or rinse, remove the blue protective cap on the bottom. Ensure the interior is dry before replacing the blue cap.

All of this information regarding various aspects of lung volume needs to be understood in the larger context of lung structure and function. For your review, we present the following:

# STRUCTURE AND FUNCTION OF THE LUNG

## Structure and Function of the Normal Lung

### General Considerations

The main function of the lungs is (rapid) gas exchange. This is accomplished by a well-coordinated interaction of the lungs with the central nervous system, the diaphragm and chest wall musculature, and the circulatory system.

Gas exchange occurs in the alveolus where the thin laminar blood flow and inspired air are separated only by a thin tissue layer. Gas exchange takes 0.25 seconds or 1/3 of the total transit time of a red cell. The entire blood volume of the body passes through the

lungs each minute in the resting state, that is 5 liters per minute. The total surface area of the lung is about 80 meters square, equivalent to the size of a tennis court.

Only about 10% of the lung is occupied by solid tissue, whereas the remainder is filled with air and blood. Supporting structures of the lung must be delicate to allow gas exchange, yet strong enough to maintain architectural integrity, that is sustain alveolar structure. The functional structure of the lung can be divided into (1) the conducting airways (dead air space), and (2) the gas exchange portions. The two plumbing systems are: airways for ventilation, and the circulatory system for perfusion. Both are under low pressure.

Total lung weight is about 300-400 gms. Upper and middle lobes are anterior, while the lower lobes are posterior. Development of each lobe results in division into 19 bronchopulmonary segments which are relatively constant and which often have pathophysiologic correlates, i.e. secondary tuberculosis is seen in the apical segments.

### The Conducting Airways

From the trachea distally, the respiratory tree divides into paired branches of unequal length and diameter and is, therefore, described as having an arborizing branching pattern of irregular dichotomy.

The luminal diameter of a branch is related to the number of alveoli at the end of that branch (axial and lateral pathways). Since the longer airways with more branches and more alveoli usually have a wider lumen that allows greater airflow, newly inspired air reaches all of the alveoli throughout both lungs at the same time and in approximately the same amount, i.e. an even distribution of inspired air throughout all lobes in a given period of time. There are approximately 23 airway divisions to the level of the alveoli. The divisions include main bronchi, lobar bronchi, segmental bronchi (to designated bronchopulmonary segments), and so on to the smallest bronchioles which do not have alveoli and are lined completely by bronchial epithelium, the terminal bronchioles. Although the base airway diameter decreases with branching, the overall or total cross-sectional diameter increases tremendously so that peripheral airway resistance decreases.

## Structure of the Gas Exchange Portion

### Respiratory Bronchiole

This is the first bronchiole along which alveoli appear. There are 2-5 "generations" of respiratory bronchioles. Since these bronchioles are lined by cuboidal epithelium and have muscular walls, they function primarily as conducting tubes, and probably account for minimal gas exchange.

### Alveolar Duct

Alveolar ducts are completely lined by alveoli, have no muscle in their walls and are covered by attenuated squamous epithelium.

### Alveolar Sacs and Alveolus

Alveolar sacs represent the termini of alveolar ducts and are completely lined by alveoli. The alveolar sacs and alveoli are lined by attenuated squamous epithelium. The normal alveolus is angular.

### Acinus

The acinus is the functional or terminal respiratory unit of the lung and includes all structures from the respiratory bronchiole to the alveolus (alveolar ducts, alveolar sacs, and alveoli). An acinus averages 0.75 mm in diameter. Each person has about 20,000 acini and 300 million alveoli. The lobule is a less well-defined anatomic unit which includes 3-5 terminal bronchioles and their distal structures.

## Histology of the Airways

### General Considerations

The conducting airways are compliant tubes lined by respiratory mucosa and containing variable amounts of muscle and/or cartilage in their wall. Airways are for conducting air and are for clearance and filtering of foreign particles that are in the approximately 10,000 liters of inspired air per day. Bronchi are distinguished from bronchioles primarily by the presence of cartilage in their walls. Bronchioles also lack submucosal glands.

### Mucosa & Submucosa

### Epithelium

Pseudostratified ciliated columnar cells and mucous (goblet) cells are the two major components of the epithelium. Cilated cells predominate in number. Both derive from basal cells. Cilia beat at 1,000 to 1,500 cycles per minute resulting in cephalad movement of the mucus blanket at 0.5-1 mm/min in small airways and 5-20 mm/min in the trachea and main bronchi. All material which accumulates in the lungs is removed in about 24 hours. Goblet cells which release mucus granules into the bronchial lumen can increase in number dramatically following acute bronchial injury. The mucus blanket moistens inspired air, prevents drying of the walls, and traps particulate matter. Together the ciliated cells and the mucous blanket constitute the so-called mucociliary escalator.

Ciliated cells are liable to congenital structural defects and to acquired defects caused by agents such as cigarette smoke. Such abnormalities of ciliary structure and, subsequently, function lead to an increased propensity to pulmonary infection and chronic lung disease. There are a group of diseases classified as the immotile cilia syndrome in which the cilia have congenital ultrastructural defects and the mucociliary escalator does not operate.

One of these diseases is Kartagener's syndrome (chronic sinusitis, situs inversus and bronchiestasis) in which there is a defect of the dynein arms.

**Bronchial Submucosal Glands**

These mixed salivary-type glands are present in the submucosa of bronchi only and usually constitute less than 1/3 of the bronchial wall width. They secrete mucus into the respiratory lumen. These glands are neuronally controlled (myoepithelial cells & endocrine cells). Mucous cells (pale cytoplasm) and serous cells (basophilic cytoplasm) produce similar mucins which are secreted and mixed with a few other materials like lysozyme and IgA. This mucus accounts for 90% or more of the mucus in the blanket in the bronchus and is added to that produced by the surface goblet cells. It is the action of the cilia moving this mucus blanket which accounts for clearance of the distal airways. Bronchial gland volume is estimated by Reid's index.

**Myoepithelial cells**

Myoepithelial cells wrap around the outside of the glands. They are epithelial cells containing myofilaments, modified smooth muscle cells, and are capable of contraction. They are probably functionally associated with Kulchitsky cells (below) and are innervated.

**Kulchitsky cells**

These neuroendocrine (argyrophilic) cells are found next to bronchial glands and in the surface epithelium where they appear to have clear cytoplasm, histologically. They are metabolically active, have dense core neurosecretory granules which contain a variety of peptide hormones (serotonin, calcitonin, and bombesin), and have finger-like cytoplasmic extensions which reach the airway lumen. Kulchitsky cells may be related to certain lung neoplasms (i.e. small cell carcinoma and carcinoid tumors) that often secrete hormonally active substances. Although their precise function is as yet poorly understood, they seem to be involved in glandular secretion as well as vascular and bronchial tone. (see Neuroepithelial bodies; carcinoid tumor)

**Clara cells**

Clara cells are found in bronchiolar epithelium which normally lacks mucous cells. Clara cells produce a mucus-poor, watery proteinaceous secretion. The function of the secretion is thought to combine both that of surfactant, which is found distally in the alveoli, and

mucin which is found in the larger conducting airways; thereby helping with clearance and reduction of surface tension in small airways.

### Smooth Muscle

Circumferential layer: This layer is deep to the mucosa (except in the trachea, where it is only in the posterior, membranous wall) and becomes increasingly prominent as airway diameter and cartilage decreases. Circular smooth muscle is most prominent in the terminal bronchioles.

Smooth muscle tone: Controls the diameter of the conducting passages and controls resistance to the passage of air within the respiratory tree.

Tone regulation: Controlled by the autonomic nervous system, adrenal medullary hormones, and local factors.

**Cartilage** Cartilage lies outside the submucosa and decreases in amount as the caliber of the airway decreases. It is present distally in the bronchi, and is not in the bronchioles. The trachea has a C-shaped ring of cartilage in the wall, anteriorly. The lobar and segmental bronchi have haphazard and discontinuous plates of cartilage, circumferentially. Cartilage can be compressed by external pressure (e.g. a cough)

## Histology of the Alveolar Walls

### General Considerations

Anatomically, most of the alveolar wall is comprised of the capillary. At any given time the total lung capillary volume is about 75 ml., spread over an area of 80 m2 which results in a very thin layer of blood. Gases are exchanged between this channel of blood and the alveolar spaces. The entire surface of the alveolus is normally covered by epithelial cells. The alveolar wall has 2 basement membranes (BM), one associated with endothelial cells and one with epithelial cells. Where the wall becomes very thin these two (endothelial and epithelial) BM's fuse into a single BM. At this point, the capillary is closest to the alveolar space and the wall is composed only of a type I pneumocyte cell process, a single fused BM, and an endothelial cell process. This thin wall facilitates gas exchange.

The alveolar (pulmonary) interstitium contains other cells (fibroblasts and lymphoid cells) and represents a potential space.

### Type I (Membranous) pneumocyte

This cell type covers 95% of the surface area of the alveolar wall but accounts for only 40% of the number of epithelial cells. Type I pneumocytes are flat cells with broad cytoplasmic flaps which are too thin to have organelles. They have a perinuclear zone where the clustered organelles and nucleus synthesize products that diffuse into the flaps. These flaps increase the surface area of the cell while minimizing the distance across

which nutrients must diffuse. Unfortunately, the flaps also make the cell susceptible to injury. Type I cells cannot regenerate, i. e. have no mitotic potential. These cells also control fluid movement between the interstitium and the airspace so that when they are injured, fluid exudates and collects in airspaces.

**Type II (Granular) pneumocyte**

This rounded cell covers about 3% of the alveolar surface but accounts for 60% of the epithelial cells. Type II pneumocytes are plump or cuboidal and have a finely stippled cytoplasm and surface microvilli. By EM, this appearance is due to many osmiophilic lamellar bodies storing surfactant (phosphatidylcholine or lecithin) which is manufactured by the type II cells. Surfactant reduces the surface tension in the lung, equalizing pressures, stabilizing and maintaining all the alveoli in an open position despite the variation in alveolar size. Type II cells are capable of regeneration and replacement of type I cells after injury.

**Alveolar macrophages**

Alveolar macrophages constitute a small percentage of the cells in alveoli, but they represent the main cellular host defense mechanism in the alveolar space. They are part of the mononuclear phagocyte system and are derived primarily from blood monocytes, although there may also be a self-perpetuating population of macrophages in the lung itself. Macrophages wander through the lung and are the only alveolar clearance mechanism for particulate material that has escaped the tracheobronchial filters. To leave the lungs, these cells may either migrate to the nearest bronchiole and exit via the mucociliary escalator or they may pass into the interstitium and exit via the blood vessels or lymphatics, often accumulating in the regional lymph nodes. Macrophages release many factors including some that recruit neutrophils, and others which interact with T lymphocytes for cell-mediated immune response. Alveolar macrophages depend on oxidative metabolism.

**Neuroepithelial Bodies**

Neuroepithelial bodies represent clusters of neuroendocrine cells found in the epithelium of alveoli and distal bronchioles. They are thought to be related to Kulchitsky cells. They may act as oxygen sensors and direct the body to decrease perfusion where ventilation is poor.

**Pores of Kohn (Interalveolar Pores)**
Adjacent alveoli have numerous interalveolar connections or pores which function as a means of collateral ventilation; that is, if the lung is partially deflated, ventilation can occur to some extent through these pores. These pores also allow the passage of other materials such as fluid and bacteria as in the case of lobar pneumonia where there is a rapid influx of edema into alveoli. This fluid can spread rapidly to adjacent alveoli through these pores.

There is a similar system of cross ventilation between terminal bronchioles and alveoli called the canal of Lambert.

## Other Components of Lung Structure

### Blood Supply

The lung has a dual blood supply: pulmonary (venous blood) and systemic (arterial blood). The pulmonary circulation delivers deoxygenated blood from the right side of the heart and returns oxygenated blood to the left heart. The pulmonary circulation consists of larger elastic and smaller muscular arteries which accompany bronchi and bronchioles as bronchovascular bundles. The bronchial (systemic) system carries arterial blood to oxygenate lung tissue primarily along the larger conducting airways.

### Lymphatics

Lymphatics appear in the distal small bronchioles and steadily enlarge as they approach the draining lymph nodes in the hilum of the lung. Lymphatics are found in the pleura, interlobular septa, and bronchovascular bundles. Alveoli essentially lack lymphatics. Bronchial Associated Lymphoid Tissue"BALT" refers to lymphoid tissue which normally is in the submucosa of the bronchial tree as non-discrete aggregates. Lymph nodes appear along 2nd to 3rd order bronchi and into the hilum.

## Defense Mechanisms of the Lung

### General considerations

Refer to Robbins text on Pulmonary Defense Mechanisms, page 757.

### Physical (airway)

1. Upper airway filtering systems
2. Reflexes: sneezing and coughing
3. Mucociliary escalator

**Cellular (alveolar)**

1. Phagocytic: alveolar macrophage and neutrophil
2. Immunologic: IgA

**In the upper airways**

Filtering mechanisms in the nasal cavity trap and eliminate larger particles (>10μm). Two reflexes: sneezing and coughing.

### In conducting airways

Mucociliary escalator: there is some IgA in this layer, produced by the plasma cells in the submucosa.

**In alveoli**

1. Alveolar macrophages with some interplay with and by neutrophils.
2. Immunologic mechanisms: interplay between the alveolar macrophages and T and B lymphocytes; IgG.

**Particle size determinant**

>10 μm: Either filtered in the nose or impacted in the nasal and oral pharynx and then cleared by coughing or sneezing.

5-10 μm: Trapped in mucus blanket in the conducting airways and moved cephalad by ciliary action (cilia move only in the cephalad direction). At the level of the larynx they are either swallowed or expectorated.

<2 μm (aerodynamic diameter): Phagocytosed by alveolar macrophages.

Water-soluble gases: Tend to dissipate in the upper airways, while insoluble gases tend to diffuse into the lungs, where they can cause extensive damage.

# INFECTIONS OF THE LUNG

## General Considerations

Infections occur more frequently in the respiratory tract than in any other organ, yet this might be anticipated when one considers the heavy and constant environmental exposure to which the lung is subjected by breathing. Although most of these infections are in the upper airways, various types of microbial agents also injure the lung. In the upper airways, viral infections predominate.

Pneumonia is the commonest type of lung infection and accounts for 8.5-10% of hospitalizations in the US, as well as for 3% of deaths in the population . Pneumonia is the 5th or 6th leading cause of mortality, 4th in the population over 75 yrs. of age, and is a common autopsy finding, often representing the "immediate cause of death." 80% of AIDS patients die of respiratory failure and over 60% of these have a pulmonary infection . Pneumonia has a morphologic spectrum which traditionally includes bronchopneumonia, lobar pneumonia, and interstitial pneumonia. In addition, there is a category of infectious granulomas, due primarily to tuberculosis and a variety of fungi.

Bacterial infections typically cause lobar or bronchopneumonia both of which are characterized histologically by neutrophilic intra-alveolar exudates. Viral pneumonias generally manifest as interstitial inflammatory processes, while fungal and mycobacterial infections are granulomatous. Other infectious lesions are an abscess and empyema (infection of the pleura).

Atypical pneumonia is a clinical term applied to patients with an acute febrile respiratory presentation and patchy interstitial infiltrates without alveolar exudates. The most common

agents are mycoplasma and legionella. There is no specific morphologic counterpart for this type of disease.

The lung is normally a sterile environment. Infection results when there is alteration in normal host defense mechanisms or diminution in the general immune status of an individual, or when an immunocompetent individual is exposed to a virulent organism which overwhelms the host defenses.

## Entry of Microorganisms

### Inhalation

Most microbes can be inhaled but in most cases this exposure is without untoward effects on the host. Infection by inhalation depends in some instances on the virulence of the organism i.e. tuberculosis, and in other situations on the dosage of exposure i.e. histoplasma from bat droppings in caves. Bacteria & viruses are small enough to reside on aerosolized droplets that can be inhaled. Mechanisms which trap particles in the airways are more effective against dry materials than against liquid droplets.

### Aspiration

Aspiration, particularly at night, is a common event and may include small amounts of the bacterial and fungal flora which resides normally in our mouths. Nocturnal or similar aspiration is not usually a problem as our normal defense mechanisms can eliminate these small dosages. Sometimes, however, these microbes lodge in the upper airways and form larger colonies which when aspirated result in infection.

### Hematogenous dissemination from distant sites of infection

Although less frequent that the first two routes, hematogenous seeding of the lungs, as well as other viscera, can occur from such distant infections as osteomyelitis or endocarditis. Some of these may represent nosocomial infections.

### Direct extension from proximate sites

This route is uncommon. Examples of direct infection are from the liver (amebic abscess) through the diaphragm, across the pleura, and into the lung; and from the mediastinum. Actinomyces can also cross the diaphragm but usually starts in the lung. Trauma is another mode of infection by direct extension.

## Impaired Host Defense Mechanisms

**Immunocompetent hosts**

Immunocompetent hosts get pneumonia uncommonly, unless predisposing conditions such as the following exist:

a. bacterial pneumonia following an upper respiratory viral infection. Mechanism: Mucosal injury due to viral infection results in reparative metaplasia of the epithelium with loss of cilia and abnormal function of the mucociliary escalator.
b. Smoking or inhalation of hot/toxic fumes injures the epithelium causing metaplasia with loss of cilia.
c. Alcohol and sedatives cause diminished reflexes like coughing and sneezing. Alcohol also interferes with alveolar macrophage function. Diminished alveolar macrophage function can also be due to hypoxia, uremia, smoking, viral infection, and air pollutents.
d. Cold air, dry air, and medications may render the bronchial mucous too viscous.
e. Industrial smoke and fumes, and chronic bronchitis cause an increased goblet cell:ciliated cell ratio.
f. Genetic disorders such as mucoviscidosis (cystic fibrosis) and immotile cilia syndrome alter mucous and ciliary function, respectively, affecting the mucociliary escalator.
g. Obstructing lesions in the airways, e.g. foreign bodies, tumors or mucus plugs, prevent clearance from the lung.

All of the above abnormalities will interfere with the mucociliary escalator.

**Immunocompromised hosts**

Immunocompromise can be regarded as:

Primary (1¡ immunodeficiency) and
Secondary (2¡ [acquired] immunodeficiency)

Immunocompromise can be viewed simply as defects in T-lymphocyte or B-lymphocyte function, monocyte or granulocyte dysfunction, or a combination of these. In some patients immunocompromise may be iatrogenic, i.e. splenectomy or steroid therapy.

**Populations at Risk**

- Infants and children: who have more frequent exposure, an immature immune system, fewer specific antibodies than adults, and a narrower bronchial tree allowing for easier obstruction.
- Elderly: who have diminished defenses and reflexes.
- Post-operative patients: who have a diminished cough reflex or follow abdominal surgery.
- Unconscious patients: diminished cough reflex.

- Patients with pulmonary edema.
- Patients with immune deficiencies.
- Smokers.
- Children with genetic disorders.

**Microorganisms**

Bacteria; fungi; viruses; mycoplasma; protozoa; rickettsia.

One variable in the frequency of infection by particular organisms relates to the site of acquisition: community-acquired (viral infections--influenza, respiratory syncytial virus; bacterial--S. pneumoniae, H. influenza, etc.; fungal--histoplasmosis and coccidioidomycosis) versus hospital-acquired (resistant bacteria--Staphylococcus, Klebsiella, Pseudomonas; fungal--Aspergillus, Candida, Mucor; viral--cytomegalovirus and varicella; parasitic--pneumocystis). Other variables are virulence, dosage, and host immune status.

**Types of Infectious Pneumonia**

**General considerations**

Pneumonias can be classified by the etiologic agent, by the type of host reaction to injury or, most commonly in pathology, by the morphologic pattern of infection: bronchopneumonia (bacterial); lobar pneumonia (bacterial); interstitial pneumonia (viral); granulomatous pneumonia (mycobacterial and fungal).

The most important classification clinically is by etiologic agent since the traditional anatomic distinctions have little clinical relevance. Community-acquired infections are usually contrasted with nosocomial (hospital-acquired) infections of the lungs in terms of predicting etiologic agents and thus clinical course.

**Bronchopneumonia**

Bronchopneumonia corresponds to patchy consolidation of the lung since infection is centered around a bronchus or bronchiole and involves the immediately adjacent alveoli. Histologically, the response is suppurative inflammation. Bronchopneumonia can be so extensive and confluent as to overlap with lobar pneumonia. Spread of infection is through the airways. The pleura is usually not involved. Patients are usually younger or older, are febrile, and have a cough productive of sputum.

Gross characteristics: Patchy consolidation which is usually firm, raised and gray-white (pinkish in this image). This consolidation may involve one or more lobes. The color varies with the amount of necrosis and hemorrhage.

Histologic components: Neutrophils fill distal airways and alveoli and are admixed with proteinaceous (fibrinous) exudates and red cells (hemorrhage). Early in the evolution of bronchopneumonia are congestion and edema. Recruitment and accumulation of

neutrophils follow, leading to a neutrophilic exudate which fills alveoli and interfers with gas exchange in the involved portions of the lung. The process tends to clear through the airways, but may organize into fibrous tufts.

The most common bacteria involved are: gram positive (+) cocci, like staphylococcus: and streptococcus; and, gram negative (-) organisms, including H. influenza, Pseudomonas, E. coli, and Klebsiella.

A true sputum sample is necessary to aid in the diagnosis, since an inadequate sample may yield only normal mouth flora. Finding intracellular bacteria within macrophages or neutrophils from an adequate sputum sample is highly indicative of pneumonia. Culture is necessary for identification of the organism and determination of antibiotic sensitivities. In many cases, the microbiologic agent is never identified.

Certain organisms tend to be associated with distinctive histopathological changes as well as clinical courses. Some examples are:

a. Pseudomonas aeruginosa - tends to infect the lung hematogenously, causing infection and necrosis of vascular walls which results characteristically in a hemorrhagic pneumonia. Pseudomonas infection is common in burn and immunocompromised patients, and often has a fulminant course. Pseudomonas also occurs in patients with cystic fibrosis, where spread is airborne and the result again is usually fatal.
b. Legionella pneumonia has characteristic morphology described as an acute fibrino-purulent exudative pneumonia by which there is a mixture of neutrophils and macrophages, within a background fibrinous exudate. The inflammatory response tends to spare the alveolar walls, so necrosis and hemorrhage do not generally occur. Legionella is a short gram-negative coccobacillus which is difficult to visualize in tissue. Legionella was first recognized in 1976 after an outbreak of cases in Philadelphia. Since that time at least 23 species and 49 serogroups have been identifed and some have been attributed to other outbreaks such as "Pontiac fever." All environmental sources of legionella relate to water and include cooling towers, evaporative condensers, and potable water, especially hot water. Legionella often has an acute onset, but is usually responsive to appropriate antibiotics. Serology, culture, and immunofluorescence of sputum are now available for identification of the organism.

Histopathologic Variants of Bronchopneumonia are:

c. neutrophilic (exudative): which is the common appearance of pneumonia in which neutrophils fill alveoli. If the causative organism is recognized & treated with the appropriate antibiotic, resolution with preservation of the lung architecture generally occurs.
d. histiocytic: characteristic of legionella and mycoplasma; macrophages predominate.

e. With Hyaline Membranes: usually seen in interstitial viral pneumonias, with the exception of streptococcal and E. coli.
f. with coagulative necrosis:
g. with abscess formation:
h. with hemorrhage: particularly seen with Pseudomonas (septic vasculitis), and sometimes with Klebsiella.
i. with leukopenia: particularly in leukemic patients or other patients on chemotherapy in which there is profound iatrogenic neutropenia. These patients will get a pneumonia in which edema and many organisms are found in the absence of cellular infiltrates.
j. with granulomas: (will be discussed under infectious granulomas of the lung).

**Lobar pneumonia**

Lobar pneumonia is so named because the inflammatory process, also suppurative, tends to involve an entire lobe uniformly. In some cases however, the inflammation may extend to other lobes or be incomplete within a single lobe and be difficult to distinguish from bronchopneumonia. The causative organism in about 95% of the cases of lobar pneumonia is Streptococcus pneumoniae and hence the process is synonymous with pneumoccocal pneumonia, although pneumococcus can also result in a bronchopneumonia.

Classically, the inflammatory consolidation uniformly involves the entire lobe and is often accompanied by a reactive fibrinous pleuritis.

Pathogenetically, this infection spreads through the interalveolar pores; microorganisms enter the lung by inhalation and initially cause a profuse exudation of fluid which spreads rapidly and uniformly throughout the lobe, providing a good medium for bacterial growth. Pneumococcus, a gram-positive diplococcus has a thick polysaccharide coat which resists phagocytosis. This spread can involve the entire lobe within a matter of hours. Four stages of the disease are recognized and are based on the gross appearance of the lung.

k. Stage of congestion: at12-24 hours; edema.
l. Stage of red hepatization: 2-3 days; redness is due to intense congestion, and a bit of hemorrhage. Because of the fibrinous-neutophilic exudate, the lung solidifies and is firm, having the consistency of liver, whence the term, hepatization.
m. Stage of gray hepatization: 3-4 days: gray is due to increased numbers of white cells and fibrin and decreased intensity of blood in the lungs with compression of capillaries.
n. Stage of resolution: 2-5 days; follows macrophage phagocytosis and clearance, and usually restitution of the normal pulmonary architecture.
o. Organization: may be more prevalent since the advent of antibiotics, which are thought to alter normal inflammatory-repair mechanisms, resulting in organization and fibrosis rather than pure resolution`. Alternatively, organization may be due to superinfection by other organisms. With organization, tufts of

fibrous tissue fill distal airways and alveoli. Later this fibrous tissue is incorporated into the interstitium, resulting in interstitial fibrosis and remodeling of the normal architecture.

Complications of lobar pneumonia: 20-30% get bacteremias, which can lead to meningitis, endocarditis, arthritis, and a variety of infections elsewhere in the body. A significant proportion of those that get bacteremia die despite antibiotic therapy.

As an infectious process, lobar pneumonia often presents with fever, chills, and a productive cough. Sputum may vary from watery to rusty as the disease advances. With loss of functional parenchyma, patients become short of breath and may be cyanotic. Pleural involvement may cause pain or a friction rub. Antibiotics alter or interrupt the nature progression of the disease and may be responsible for scarring of the lung when its occurs. In most patients who survive without antibiotic intervention, the involved lung will return to normal.

**Complications common to lobar and bronchopneumonia**

Abcesses may be independent of pneumonia; two patterns:

Multiple abscesses usually occur with hematogenous infection or with bronchopneumonia by a virulent (often aerobic) organism that causes tissue necrosis.

Solitary abscess: usually due to an anaerobic organism, e.g. in alcoholics with depressed reflexes who aspirate.

Empyema is an infection of the pleura, in which there is a purulent exudative process. Since this occurs in a closed space, healing usually results in pleural fibrosis.

**Infectious granulomas**

**Mycobacterial-Tuberculosis**

Tuberculosis is a chronic communicable disease due to a bacteria which has a worldwide distribution and which most commonly infects the lungs but can involve any organ. In the U.S. in 1985, 22,201 new cases of tuberculosis were reported to the CDC, a slight decrease from the previous year. Of these, 2,481 were from New York. Males outnumbered females nearly 2:1. About 5 - 10 % died of their disease despite the fact that tuberculosis is considered preventable and curable. In 1986, a rise in the number of new cases of tuberculosis was reported in the US.

The accompanying schematic is a simplification of tuberculous infection in man taking into consideration mycobacterium in terms of infectivity, type of host response, and varied pathologic responses with respect to primary versus secondary infection.

Infectivity and disease depend on virulence, induced hypersensitivity, and immunity (or host resistance). Virulence and development of type IV immune hypersensitivity probably are related to the complex lipids and carbohydrates which form the mycobacterial wall. Induced hypersensitivity and immunity are probably both influenced by activated macrophages in the host. The typical cellular response 2-4 weeks after infection is formation of a granuloma.

Typically these undergo central necrosis (caseation ).

.

The causative agent is detected by culture and/or by tissue staining for acid-fast organisms. Mycobacteria are acid-fast bacilli which are slightly curved and beaded.

Primary infection refers to the initial exposure and this usually results in self-limited disease with formation of a solitary granuloma of the lung (Ghon focus), often with granulomas along the routes of lymphatic drainage from that segment of lung and in hilar lymph nodes (Ghon complex). The Ghon focus is usually in the upper portion of the lower lobe, or the lower portion of the upper lobe near the fissure.

Rarely there is progressive primary infection which may result in fulminant bronchopneumonia following airway spread of mycobacteria, or miliary spread either through the veins, arteries, or lymphatics. Essentially, the primary lesion during the process of caseation can erode into airways or vascular structures with dissemination to other areas appropriate for the distribution of that structure.

**Routes of Dissemination:**

Lymphatic spread:

multiple granulomas may result in a tuberculoma; obliterative bronchitis; obliterative pleuritis; bronchial compression by tuberculous lymphadenitis.

Airway spread:

acinar-nodose pneumonia may lead to tuberculoma; caseous pneumonia leads to cavitary abcess.

Arterial spread: pulmonary miliary tuberculosis.

Venous spread:

pulmonary or systemic miliary tuberculosis.

A small percentage of people will later develop secondary infection, 9201 probably due to reactivation of latent mycobacteria, although reinfection is another possible mechanism. Secondary infection usually occurs in the lung apices, possibly due to the higher oxygen tensions in these regions, keeping in mind that mycobacteria are strict aerobes. The apical infection usually resolves by fibrosis and calcification, but less commonly can develop into progressive secondary infection which again can result in pneumonia, miliary spread, empyema, or tracheobronchial infection. Isolated organ involvement also occurs (intestine; adrenal leading to acute Addison's disease; bone, such Pott's disease of the spine; and meninges). Chronic infection is occasionally associated with amyloidosis. Treatment is with antituberculous drugs.

## Fungal Pneumonias

### General Considerations

Fungi are the second most common cause of infectious granulomas in the lungs. They have a tendency to form necrotizing granulomas similar or identical to tuberculous granulomas, and often cavitate centrally. Sometimes they result in suppurative granulomas in which neutrophils dominate the center. The most common responsible fungi, 9213 are dimorphic molds, especially histoplasma, of which the tissue form is yeasts; other yeast include cryptococcus, coccidioidomycoses, and blastomycosis. The frequency of these infections varies with geographic location. The most common yeast infection around New York is histoplasma.

### Histoplasma

Histoplasma capsulatum is a small (2-5 micron) oval budding yeast which is common in the U.S., especially in Ohio and the Mississippi Valley. This dimorphic fungus is found in the soil and bird droppings such as bat droppings in caves, and infection is usually the result of inhalation.

The incidence of infection in the US is high although the most common manifestation is none, that is infection is latent and the patient is asymptomatic. Other expressions of disease are primary pulmonary which is self-limited; chronic pulmonary occasionally in the setting of COPD; and disseminated. The form that infection takes usually depends on host resistance and immunocompetence.

Pathologically lesions due to histoplasma vary, although the most common are incidental fibrocalcific nodules (old healed granulomas) which are densely hyalinized and contain only occasional histoplasma yeast. These lesions may calcify and erode into a bronchus causing broncholiths, or stones. An immunocompetent host can response with classical necrotizing or non-necrotizing granulomas. In fulminant disseminated infection, as seen in AIDS, yeast pack macrophages which fill alveoli and infiltrate the interstitium.

**Cryptococcus**

Cryptococcus neoformans is a somewhat pleomorphic round-to-oval 4-10 micron yeast which may have a characteristic thick mucinous capsule which stains bright red with mucicarmine stain; some cryptococci may be unencapsulated. This yeast has a worldwide distribution and is found in bird (pigeon) droppings. Infection again in by inhalation. The most common infection is meningitis (cerebral). The other basic form of infection is pulmonary,.

Encapsulated: more virulent and often results in fulminant infection

Non-encapsulated: frequently granulomatous inflammation

**Coccidioidomycosis**

Coccidioides immitis has large spherules filled with multiple endospores which excyst, enlarge and mature into a new spherule.ÊIn vitro, it also may have hyphae which form arthrospores, a particularly infectious agent which needs careful handling in the lab. Coccidioides is found in the Southwest US, Mexico, Central America and San Joaquin Valley in soil.

Clinical Expressions of infection are: (1) primary pulmonary coccidioidomycosis, which tends to be asymptomatic; (2) primary extrapulmonary occurring in skin, and uncommon; (3) residual pulmonary Infection occurs in 2-8% of patients with primary disease and is represented as a solitary nodule or cavitary lesion; and (4) disseminated form: <1% with a predilection for immunosuppressed, American Indians and Blacks.

**Blastomycosis**

Blastomycosis dermatitidis is practically limited to North America, especially the Mid-Atlantic states and the Mississippi River Valley. This dimorphic fungus has a yeast form which is 5-25 microns, has broad-based budding, and has a thick refractile wall. Clinical infection is usually either systemic, primarily with pulmonary involvement, and cutaneous where it is associated with pseudoepitheliomatous hyperplasia.

**Candida**

Candida is a fungus whose tissue forms include yeast and pseudohyphae. Candida is a normal component of the oral flora. Pulmonary infection is usually in immunodeficient hosts. Candida infects airways, spreads to lungs and causes focal lesions. More commonly see infection in the oral cavity (thrush) or esophagus, and tends to spread by hematogenous dissemination to the lung. See multiple lesions scattered in the lungs. Grossly, there may be multiple necrotic lesions or a bronchopneumonia or miliary pattern.

### Aspergillus

A saprophytic hyaline mold which causes bronchopneumonia with a propensity to vascular invasion and dissemination resulting in hemorrhage and necrosis. Several different pathologic forms exist in the lung which include intracavitary aspergilloma, invasive aspergillosis, allergic bronchopulmonary aspergillosis, and tracheobronchial aspergillosis. Aspergillus is most common in immunocompromised patients especially patients with acute leukemia.

Aspergillus has septate hyphae with dichotomous branching and even parallel walls. It tends to grow in a radial fashion. When confined to a dry cavity, aspergillus may develop fruiting bodies or, conidiophores, which, if seen, are diagnostic; otherwise it must be cultured or identified by immunofluorescence to be distinguished from similar fungi.

In the lung invasive aspergillosis, causes hemorrhagic infarctive pneumonia with multiple lesions; frequently involving airways and blood vessels. Aspergilloma, is a cavity containing a fungus ball.

Another uncommon expression is Allergic Bronchopulmonary Aspergillosis (ABPA) which may occur is asthmatics. In this condition, there is necrosis of bronchial walls, plugging of lumens by granular mucoid debris, proximal bronchiectasis, and infiltration of walls by lymphocytes, plasma cells, and eosinophils

### Mucormycosis (Zygomycosis)

Includes 3 fungi/ 2 of which are infectious: Rhizopus, Mucor. These fungi have large, non-septated hyphae with 90 degree angle-branching and non-parallel walls. These fungi have a tendency to invade blood vessels, and cause a hemorrhagic pneumonia with hemorrhagic infarcts like apsergillus. Mucormycosis, is seen in patients with Diabetis Mellitus and immunocompromised patients. Mucor can also develop into a mycetoma: cavity with big ball of fungus. On CXR the fungal ball will move in the cavity as the patient is rotated.

## Interstitial pneumonia

### Viral Pneumonias

### General Considerations

Viral infections of the lung are usually acquired through inhalation and typically result in interstitial inflammation. Most infections are due to influenza viruses, respiratory syncytial virus, and rhinovirus. The inflammatory changes are usually diffuse and confined to the interstitium with edema and lymphohistiocytic cellular infiltrates in the septae. More severe or advanced cases may have additional

changes resembling acute alveolar damage in which there is microvascular injury allowing leakage of proteinaceous fluid into the alveoli in association with pneumocyte necrosis, and resulting in "hyaline membrane formation." In general, the lungs tend to be heavy and diffusely firm without focal lesions.

Age factors into the type of virus, e.g. influenza infects elderly, while respiratory syncytial virus, adenovirus and parainfluenza infect infants.

**Viral isolation and identification.**

Diagnosis of some viruses is possible by light microscopy and identification of characteristic intracellular viral inclusions (Herpes, Measles and Adenovirus - see below.) Similarly cytologic may yield the diagnosis.

Serologic tests require acute and convalescent serum, looking for a fourfold rise in titre.

Viral Culture presents a time problem, e.g. CMV takes 1 week to 2 months to grow in cell culture.

DNA probes

**Cytomegalovirus**

Cytomegalovirus is a Herpes group DNA virus which causes cytomegaly or enlargement of infected cells. Infected cells also have a single large basophilic Cowdry Type A intranuclear inclusion like other herpes viruses, and may have multiple small cytoplasmic inclusions which are purple and PAS-positive. CMV usually causes subclinical infection in the lung of immunocompetent hosts, and clinical infection in immunocompromised patients. Infection of the lung can result in focal or diffuse interstitial pneumonia with or without hyaline membrane formation, intra-alveolar exudates, hemorrhage, and fibrosis. CMV primarily infects epithelial and endothelial cells.

**Herpes Simplex Viruses**

These DNA viruses include types I and II and pathologically in the lung resemble infections with (Varicella-Zoster), another herpes group DNA virus. The are two patterns of respiratory tract infection:

1. Necrotizing Tracheobronchitis Mechanism of spread is probably by contiguity, likely through aspiration of viral particles into the bronchial tree from infected lesions in the upper respiratory tract. The distribution in the lung is like that of bronchopneumonia with focal lesions often involving or surrounding small and

large airways. Microscopicaly, the submucosa and mucosa of the trachea are completely necrotic, and replaced by a fibropurulent exudate on top of the denuded mucosa undergoing coagulative necrosis. The virus is difficult to visualize without aids such as immunohistochemistry or electron microscopy because of the extensive necrosis. Similar mucosal-submucosal necrosis involves bronchi and bronchioles. In surrounding, adjacent airways there may be focal hemorrhagic, parenchymal necrosis in which viral inclusions are rarely found. Grossly, the lungs are diffusely firm due to interstitial inflammation and may have small yellow or red necrotic regions.

2. Hematogenous Dissemination A less common mode of infection is presumably hematogenous spread from another primary focus of infection. This type of infection leads to widespread lesions throughout both lungs which are histologically identical to those described above but are more randomly distributed throughout the parenchyma and the airways are less involved. Grossly there are small, yellow or red, soft necrotic foci. With herpes infection particularly of the tracheobronchial type, one often sees infection of the esophageal mucosa, which is usually an easier location to identify the viral inclusions and cytopathic changes in exfoliated cells. In the esophageal mucosa, the epithelium is ulcerated and at the edges of the ulcer, the remaining epithelium is disorganized, characteristically with atypical and multinucleate giant cells having enlarged nuclei which are glassy or contain a single large Cowdry Type A inclusion, similar for HSV I and II. By electron microscopy, the herpes viruses have round particles with a double membrane.

**Varicella-Zoster**

A member of the herpes group which has intranuclear inclusions which are indistuishable from those of herpes simplex. Lung involvement is similar to that of H. simplex. In children who have chickenpox with a pneumonic component, the infection in the lung may heal in such a pattern of focally fibrotic lesions as to resemble miliary tuberculosis on CXR.

**Measles**

Measles is due to an RNA virus. Infection leads to Warthin-Finkeldey cells (multinucleate giant cells) which have eosinophilic intranuclear Cowdry type A inclusions and smaller intracytoplasmic inclusions. Clinically there may be an acute interstitial pneumonia, like DAD, with hyaline membranes, intra-alveolar giant cells, and focal bronchiolar necrosis. Pulmonary infections are rarely seen in usual childhood measles infection, but can be seen in immunocompromised children.

**Adenovirus**

Adenovirus is a DNA virus which causes both upper and lower respiratory tract infections. Most commonly there is subclinical disease or an upper respiratory tract infection with mild symptoms. Clinical disease is seen in bone marrow and other transplant patients. Involvement in the lung is most evident in the bronchial tree where a necrotizing bronchitis and bronchiolitis are seen. Microscopically, "smudge cells," large cells with a large dense mass or inclusion filling the nucleus represent the virus.

**Influenza**

A RNA virus usually seen in adults, particularly older adults. Influenza has the highest morbidity and mortality of all viral lung infections. There is frequent spontaneous recovery and resolution.

**Respiratory Syncytial Virus**

A RNA virus, which is a significant cause of respiratory infection in infants and young children. The principle lesion is bronchiolitis, sometimes necrotizing, and less frequently, interstitial pneumonia.

**Mycoplasma Pneumonia**

A common cause of URI, with pneumonia in approximately 10%, but accounting for about 15-20% of all pneumonias in the general population. Mycoplasma is a benign, self-limited disease with few complications; so very few cases have been examined histologically. The peak incidence is 5-15 years of age. Cold agglutinins are frequently found in the blood (RBCs clump at 4 degrees). Infection causes a bronchiolar lesion with a nonspecific neutrophil-rich exudate in the lumina, bronchiolar metaplasia, and bronchiolar wall lymphoplasmacytic infiltrates.

Mycoplasma is the smallest free living organism (approx. 200 nanometers) and at one time was called Eaton's Agent.

**Pneumocystis (carinii) Pneumonia**

Pneumocystis was first descibed in 1905 (Brazil) in rats. During WW II pneumocystis pneumonia (PCP) was recognized in malnourished infants in Europe. In l957 was the first reported in case in the U.S.

Pneumocystis is an extracellular protozoan parasite (or possibly a fungus) which in humans almost exclusively infects the lung. Infection typically leads to an

interstitial infiltrate of lymphocytes and plasma cells, and to foamy, intra-alveolar exudates within which the organism are found. Pneumocystis attaches to pneumocytes without fusion, development of a glycocalyx, or invasion. The organisms occur as cysts, excysted forms, and trophozoites. The cysts are round and about 4 microns. The excysted forms are helmet-shaped and other irregular shapes. Pneumocystis organisms will stain with silver (GMS) and gram stains (gram posititve) while the trophozoites will stain with giemsa.

The cysts contain multiple sporozoites which excyst and develop as trophozoites. Pneumocystis organisms tend to cause injury by their selective attachment to type I pneumocytes. Diagnosis can be made by identifying the organism cytologically by looking for cysts or trophozoites in sputum, washings from the lung or bronchoalveolar lavage (BAL). Diagnosis can also be made by identifying the organisms on biopsy of the lung.

PCP is generally treated with either bactrim or pentamidine.

PCP is most frequently seen today in AIDS and less in other immunocompromised patients. PCP is rare in immunocompetent hosts, although there is an apparent increase in the incidence of PCP infections in patients who are minimally compromised. The route of spread is unknown. Pneumocystis cannot be cultured to date. AIDS patients tend to get recurrent infection and progressive scarring with diffuse interstitial fibrosis has been considered a complication of treatment.

## Lipid Pneumonia

### General Considerations

In essence, lipid pneumonia is an example of a foreign-body reaction which can occur following aspiration of gastric contents or mineral oil. Exogeneous and endogenous lipids can give rise to pneumonia, and exogenous lipids which are aspirated tend to develop a fibrotic granulomatous reaction.

### Exogenous

Exogenous lipid pneumonia often occurs in older patients who are taking mineral oil for constipation. Since their reflexes are diminished compared to younger people, they tend to aspirate this oil when it is taken orally. The apirated oil will usually find the most direct route into the lungs and depending on the posture frequently will enter the posterior segment of the right lower and upper lobe resulting in segmental opacification ("whiting-out") of the lung.

Organizing lipid pneumonia has large lipid droplets and vacuoles associated with a granulomatous fibrous reaction including chronic inflammatory cells.

**Endogenous**

Endogenous lipid pneumonia is usually associated with obstruction of an airways such as by a neoplasm or foreign object. Breakdown of cells will occur in lung segments distal to the obstruction with accumulation of small lipid droplets in alveolar macrophages. Alveoli then fill with these macrophages.

# INTERSTITIAL/RESTRICTIVE LUNG DISEASE

## General Considerations

Over 150 different disease processes cause infiltrative lung disease. In general, most of these processes affect the alveolar wall and as such can be contrasted with obstructive lung disease which primarily affects the conducting airways. Injury often involves not only the components of the interstitium, but also the alveolar epithelium and capillary endothelium. The functional changes reflect a restriction of airflow manifest by:

Reduced expansion of the lung parenchyma

Decreased total lung capacity

Decreased vital capacity

Decreased residual volume

Decreased lung compliance

There are two major subdivisions of restrictive lung disease:

1. Disorders involving the chest wall or pleural space, causing restriction of the chest bellows; includes polio and kyphoscoliosis (covered in the pathophys. ex.)

2. Interstitial or infiltrative diseases, which can be acute or chronic.

## Acute Infiltrative Lung Disease

Acute infiltrative lung disease is represented largely by interstitial pulmonary edema

**Definition of Pulmonary Edema**

An abnormal or excessive accumulation of fluid in intercellular tissue spaces or body cavities.

**Causes of Pulmonary Edema**

- Edema due to increased microvascular pressure

  Increased hydrostatic pressure (congestive heart failure and mitral stenosis)., Robbins Table 3-1

  Decreased colloid oncotic pressure of the blood (hypoalbuminemia)

  Increased interstitial colloid osmotic pressure (lymphatic obstruction)

  Decreased hydrostatic pressure of interstitial fluid.

- Edema due to damaged microvascular membrane (capillary injury)

  Results in increased endothelial permeability

  Leakage of plasma into the lung causes resultant damage.

**The prototype clinical syndrome**

The prototype clinical syndrome is ARDS - Adult Respiratory Distress Syndrome or "shock lung" (in clinical terminology)

**DAD - Diffuse Alveolar Damage**

**-- Etiologies of DAD (types of injury)**

- Aspiration: gastric contents or drowning
- Inhalation of fumes or toxic aerosols: Oxygen toxicity, smoke, chlorine
- Circulating toxins: Bacterial endotoxins
- Other: DIC, high altitude, trauma, radiation therapy, chemotherapy

**-- Mechanism of DAD (ARDS)**

- Prototypical injury is oxygen toxicity
- Hyaline membranes are composed of a combination of plasma proteins leaking out of the vascular space and necrotic cellular debris from Type I cells
- This is a diffuse process
- Patient with DAD is hypoxemic but refractory to oxygen therapy, since 75-100% O2 is one of the etiological factors.
- DAD has a low recovery and high mortality rate. Survivors may develop chronic disease (diffuse interstitial fibrosis) and even end-stage honeycombing of the lung.

**-- Pathogenic Mechanisms of DAD**

- In oxygen toxicity, hyperoxia damages alveolar macrophages (AM) which then release oxygen radicals that may directly injure lung tissue. More importantly, the AM's release factors that attract neutrophils, stimulate their intravascular adherence, and cause them to produce and release more oxygen radicals. This starts a vicious cycle with resultant damage to the lung.
- Other considerations as possible initiating mechanisms that might alone or in combinaton lead to microvascular injury

    Activation of the complement cascade

    Neutrophil aggregation, recruited by macrophages, as above

    Activation of the coagulation pathway, as in DIC

    Prostaglandins

**-- Pathology and Progression of the DAD**

- Gross

    Lungs are heavy due to fluid accumulation (interstitial and later alveolar)

- Histological
- Interstitial Edema

    There is widening of the interstitium, which separates the capillaries from their usual close association with Type I Pneumocytes, resulting in diffusional abnormalities (diffusion distance is increased).

    Cell infiltrates are few

- Acute Exudative Stage

    Interstitial widening increases

    Proteinaceous exudates begin to accumulate in the alveoli as the microvascular injury leads to breakdown of the basement membrane and leakage of plasma proteins

    Sloughing of the injured type I pneumocytes

Cell debris and plasma exudates accumulate to form hyaline membranes identical to those in infant hyaline membrane disease (both a result of surfactant deficiency).

A few inflammatory cells, including neutrophils, lymphocytes, macrophages, and monocytes are present and may be seen in the interstitium.

Interstitial fibroblasts are increased

- Proliferative Stage

Type II Pneumocytes proliferate to cover the alveolar surface from which necrotic Type I's have sloughed.

Fibroblasts enter alveolar spaces and begin to organize the exudates and membranes by laying down collagen, resulting in intra-alveolar fibrosis.

A little later, a separation can again be seen between vascular lumens and alveolar spaces, still with pneumocyte hyperplasia, and more organization of exudate.

The architecture is lost in some areas.

**-- Summary of Processes thus far**

- In the interstitium, inflammatory cells with fibroblasts are beginning to lay down collagen, resulting in interstitial fibrosis.
- In the alveoli, the exudates are beginning to organize with fibroblastic activity, collagen deposition and fibrosis in the alveolar space.

**-- Prognosis for the Surviving Patient**

- A surviving patient may develop diffuse Interstitial Pulmonary Fibrosis, the chronic form of the disease which will resemble morphologically "idiopathic pulmonary fibrosis" (IPF), or UIP (see below).
- It is interstitial not only because of the interstitial fibrosis itself, but also because the alveolar fibrosis is eventually incorporated into the interstitium.
- The alveolar fibrosis occurs because there is a stage when there is a tuft of fibrous tissue in the alveolus. It is covered by the Type II cells and then incorporated into the adjacent interstitial wall.
- Eventually, therefore, most of the fibrosis becomes part of the interstitium.
- The interstitial fibrosis can range from mild to extensive, in the same lung, with distorted, abnormal air spaces (see below).

**-- Time course of DAD**

- Many patients die within several days (10-90% mortality)
- Many survivors develop interstitial fibrosis within 14 days

**-- Experimental Model for DAD**

Description of progression from normal to abnormal air spaces, based on one group's experimental model of monkeys exposed to paraquat. DAD occurs in paraquat injury (Am J Pathol 118:452-475,1985).

- Within 2-3 days of paraquat injury, there is first interstitial edema, causing a separation of the basement membrane from the capillary endothelial cell and alveolar pneumocyte. Type I's slough, and the interstitium widens. The degree of injury varies from one alveolus to another.
- At one week, fragmentation of the basement membrane accompanies the edema and sloughing. Interstitial cells, fibroblasts, and perhaps myofibroblasts that become more fibroblast-like, go out into the alveolar space where there is proteinaceous fluid. Type II's begin to proliferate.
- At 3 to 4 weeks, myofibroblasts and fibroblasts in the interstitium are activated and begin laying down collagen. Fibroblasts in the alveolar space begin to lay down collagen and organize the exudates. There are fewer and fewer normal air spaces.
- The disease is diffuse in the lung, but involves each alveolus differently - many are damaged to some extent, but a few can recover.

**-- Summary of Mechanisms in DAD that lead to Fibrosis**

- Interstitial fibrosis actually within the alveolar septum.
- Organization of the intra-alveolar exudate, which becomes fibrotic and is incorporated into the septum.
- Alveolar collapse and folding: a recently proposed theory that some alveolar walls or whole alveoli collapse on themselves, so there is apposition of their walls. When an alveolus folds on itself, the Type II cells may proliferate over the folded surface and keep it folded. Thus the wall thickness doubles just by folding.

**Summary of Acute Infiltrative Lung Disease**

-- Pulmonary edema related to microvascular pressures, usually due to heart problems. It may resolve with improvement in cardiac function, however, with chronicity it can lead to deposition of hemosiderin and interstitial fibrosis, the so-called "brown induration" of chronic passive congestion. -- Alternatively, edema due to injury to the microvasculature, leading to cell death or permanent damage with remodeling of the lung parenchyma.

-- Resolution of the acute phase may overlap with chronic disease or IPF; however, as we will see below, chronic interstitial lung diseases of most etiologies are now thought to be secondary to "alveolitis".

## Chronic Infiltrative (Restrictive) Lung Disease

### General Comments Concerning Chronic Infiltrative Lung Disease

-- Chronic Infiltrative Lung Disease indicates a group of pulmonary diseases which have in common clinical and radiologic features, but are diverse in their etiologies and pathology.

-- Common Features of this Group of Diseases

- Decreased vital capacity
- Decreased total lung capacity
- Decreased residual volume
- Decreased lung compliance
- Cyanosis (sign of severe hypoxemia; attributed to ventilation-perfusion mismatching)
- Clubbing of digits
- Late in the disease, one may see pulmonary hypertension due to destruction of the alveolar capillary bed
- Pathologically, most of the disorders have both an interstitial infiltrate and some exudate in small airspaces

### Diseases Leading to Chronic Infiltrative Lung Disease (150, at least)

-- Environmental lung disease 25% (Example: hypersensitivity pneumonitis)

-- Sarcoidosis 20%

-- Idiopathic chronic interstitial pneumonias 13% (Example: IPF)

-- NOTE: Alveolitis seems to underly chronic infiltrative lung diseases of many etiologies. This premise has been supported by results of bronchoalveolar lavage.

- The change from normal to abnormal alveoli involves both recruitment and proliferation
- Experimental data and lavage studies have shown that there may be several different mechanisms of alveolitis involving different combinations of inflammatory and immune effector cells
- Two main types which have been distinguished by primary cell type are neutrophilic alveolitis and lymphocytic alveolitis

## Summary of Tables

-- Macrophages predominate in non-smokers, with small numbers of lymphocytes, and almost no neutrophils or eosinophils.

-- Smokers have twice the number of cells, but in the same proportions.

-- In both Sarcoidosis and IPF (Idiopathic Pulmonary Fibrosis, the prototype of the chronic disease), there are twice the number of cells, with a lower proportion of macrophages.

-- In IPF, there are proportionally more neutrophils, and it is referred to as neutrophilic alveolitis.

-- In Sarcoidosis, there is a higher percentage of lymphocytes, and it is called lymphocytic alveolitis. (Keep in mind that there are other etiologies of these two types of alveolitis, and possibly other types of alveolitis.)

**Idiopathic Pulmonary Fibrosis (IPF)**

**IPF is the Prototype of Neutrophilic Alveolitis**

-- Also Known as

- Cryptogenic Fibrosing Alveolitis
- Usual Interstitial Pneumonia (UIP)
- Hamman-Rich Disease

-- Subdivisions of IPF

- Usual Interstitial Pneumonia (UIP)
- Desquamative Interstitial Pneumonia (DIP)
- Lymphocytic Interstitial Pneumonia (LIP)
- Granulomatous Interstitial Pneumonia (GIP)
- Bronchiolitis Interstitial Pneumonia (BIP), now called Bronchiolitis Obliterans (BOOP)

**Proposed Mechanism of the Idiopathic Disease**

-- >Complement activation >C5a (chemotactic)

| | | | | | | |
|---|---|---|---|---|---|---|
| Unidentified Ag complexes with Ab | > | Immune complexes | > | Activation of macrophages | > | Release of Neutrophilic Chemotactic Factor |
| Injury to connective tissue and parenchymal cells | < | Oxygen radicals Collagenase | < | Recruitment of neutrophils | < | |

NOTE: a high percentage of patients with IPF have circulating immune complexes during active disease

**Progression of IPF**

-- Slowly progressive, chronic disease that involves the lung in a non-uniform fashion

-- Appears in middle age and is insiduous in onset

-- Most people with IPF eventually die of the lung disease after several years

-- No known effective treatment exists

**Pathology of IPF**

-- Gross Pathology

- In advanced disease, the lung is small and firm.
- White tissue seen on cut section represents the interstitial fibrosis (which results in decreased ventilation and diffusion in those portions of the lung).

-- Histologic Pathology

- Changes vary from histologic field to field, ranging from normal to fibrotic alveolar walls, with different degrees of fibrosis and collagen deposition.
- If extensive, it is like end-stage DAD, with abnormal air spaces having thickened, fibrotic walls, and with capillaries far from the air spaces. With this fibrotic process, the alveolar capillary bed is destroyed, eventually resulting in pulmonary hypertension, RV hypertrophy, and cor pulmonale.
- During active disease, there is frequently an inflammatory cellular infiltrate consisting mainly of lymphocytes and macrophages with many neutrophils; these cells are present in the interstitium and in the airspaces.
- There is also a metaplastic change in the epithelium, usually around the bronchioles; some of this is lambertosis, a metaplastic epithelial extension through the Canals of Lambert into the alveolar spaces adjacent to the bronchioles.

-- Summary of Slides

- Fibrotic alveolar walls with inflammatory cells but no visible capillaries; adjacent field showed minimal interstitial disease.
- Metaplasia around bronchioles, either columnar with mucin secretion or squamous metaplasia

-- Some Comments on Etiology

- As in the case of DAD, all of the histologic changes represent non-specific reaction to injury in the lung and one can not distinguish the etiology solely by the histology.
- Interstitial pneumonias with various etiologies - viral, radiation, drugs, chemotherapy, collagen vascular disease, pneumoconioses, or idiopathic: also give an identical gross and histologic picture.

**Final Note on Nomenclature**

-- DIP, as distinguished from UIP, is a more uniform process, with no alternating areas of scarring and normal lung. There is some widening of the interstitium (reaction of Type II's), and, most dramatically, there is filling of alveolar spaces by alveolar macrophages (not desquamated pneumocytes as originally thought).

-- Others now feel that DIP is an earlier stage of UIP, and so lump it all together as IPF. One reason for making the distinction is that the DIP patients may respond to steroids and have a better prognosis.

## Sarcoid

**Sarcoid is the Prototype for Lymphocytic Alveolitis**

-- Sarcoid is a multisystem disorder

-- Most common in the young, females, and Blacks

-- Etiology is unknown, but is probably due to an antigenic stimulus resulting in cell-mediated immune (type IV) injury

**A Characteristic of this Disease: non-caseating (non-necrotic) granulomas**

-- These are unlike the infectious ones in TB and histoplasmosis.

-- Can occur in all organs, but are most commonly found in the lungs.

-- Contain epithelioid histiocytes, multiple foreign-body type giant cells, and lymphocytes at the periphery.

-- The granulomas are often confluent (back-to-back).

-- The granulomas can involve all parts of the lung: the alveoli, interstitium, bronchial and vascular walls.

**Pathogenic Mechanism of Sarcoid**

-- This is an example of lymphocytic alveolitis, since lymphocytes predominate over macrophages and PMN's in lavage samples.

-- Most of the lymphocytes are T cells

**-- Many sarcoid patients have abnormal immune systems**

- Deficient cell-mediated immunity: patients are anergic to the TB skin test; it is proposed that all the helper T's are in the tissues, for example the lungs , leaving only the suppressor T's to circulate, thereby suppressing the skin test reaction.
- Often have a stimulated B-cell population with resultant hyperglobulinemia.

-- Actual mechanism involves an unknown antigen that stimulates macrophages leading to the recruitment of helper T cells. The T's release lymphokines and other substances which induce the B's, resulting in polyclonal B-cell activation and hyperglobulinemia. Monocytes are also recruited, and this recruitment plus the efffects of macrophage inhibitory factor result in granuloma formation.

**Clinical Picture of Sarcoid**

-- Most patients with sarcoid are asymptomatic or have some dyspnea or cough.

-- Chest X-ray Shows 1 of 3 Patterns:

- Bilateral hilar adenopathy: so characteristic of the disease that if a young, Black female has it, you should immediately think "sarcoid"
- Diffuse interstitial disease
- A combination of the two

-- Patients usually do well, with or without therapy, though a few develop fibrotic lungs.

**Other Chronic Infiltrative Lung Diseases**

**Hypersensitivity Pneumonias (HSP)**

-- Another example of lymphocytic alveolitis

-- Also known as extrinsic allergic alveolitis

-- With exposure to protein antigens in animals, plants, or microoranisms, these people develop immune resistance to the antigen, then with subsequent exposure may have acute or chronic attacks.

- In Farmer's Lung, the first described, the antigen is thermophilic actinomyces.
- There is a long list now, including air conditioner HSP and pigeon breeder HSP

**Eosinophilic Granuloma (Histiocytosis X)**

-- Considered by some to be a localized form of Histiocytosis X

-- Occurs bilaterally in the lung, centered on small airways, with stellate cellular infiltrates into both interstitial and alveolar spaces.

-- Resembles sarcoid clinically and in the evolution of the process - active then chronic or quiescent stage, with stellate scars around small airways.

-- Cells in the infiltrate are scattered eosinophils, alveolar macrophages, and Langerhans cells, identical to those in the skin - large cells with folded nuclei, from the monocyte-phagocyte system.

-- Langerhans cells contain characteristic "X" or Birbeck bodies in 2 shapes

- Tennis racquet
- Zipper

  (The presence of Langerhans cells with Birbeck bodies, seen in all forms of Histiocytosis X, distinguishes this type of alveolitis from both lymphocytic and neutrophilic alveolitis.)

-- Pathologic mechanism is unknown, and may be either reactive or neoplastic. The result is scarring when the lesion clears; injury involves both mesenchymal and epithelial cells.

**Alveolar Proteinosis**

-- Even though this is an alveolar process with normal interstitium, functionally it is a restrictive lung disease.

-- Has been related to both silica and viral injury, but etiology is still unknown.

-- Alveoli (often in the periphery of the lung) are filled with pink, granular acellular material.

-- this disease does not respond to drugs, so the patients should be left alone and it will clear in a few years.

-- since these patients tend to get opportunistic infections, steroids will worsen the condition by depressing the immune system.

-- bronchoscope and lavage: washing out the air spaces has sometimes been effective in an acute episode.

**Honeycomb Lung**

**This end-stage of chronic lung disease does not imply a particular etiology**

-- Comparable to end-stage renal disease and cirrhosis of the liver

-- Lungs are small with a nodular pleural surface, the effect of interstitial fibrosis causing retraction of the pleura

-- Abnormal air spaces, often large enough to be seen by the naked eye, cause the honeycomb effect.

-- Often accompanied by destruction of the capillary bed in the lung, which can result in pulmonary hypertension, RV hypertrophy , cor pulmonale, and can cause death.

**Clinical Aspects**

-- Main manifestation of both acute and chronic lung disease is hypoxemia; therefore the usual clinical presentation is one of difficulty breathing and especially tachypnea (rapid, shallow breathing)

-- Some patients develop clubbing of the fingertips and cyanosis. -- Pulmonary function tests are used to define the degree of interstitial involvement.

-- The chest X-Ray reveals the degree of alveolar involvement.

-- Both should be used in conjunction with one another.

## TUMORS OF THE LUNG

**Introduction**

The incidence of lung cancer has been increasing almost logarithmically and is now reaching epidemic levels but was not always a common disease. The incidence of most other cancers has remained constant except gastric cancer which is declining. The following table is from the Mortuary Registry of Paris and shows the distribution of 9118 deaths from cancer in 1844.

| | | | |
|---|---|---|---|
| Lungs | 7 | Colon | 7 |
| Ovary | 64 | Testicles | 21 |
| Rectum | 221 | Bladder | 72 |
| Breast | 1147 | Liver | 578 |
| Uterus | 2996 | Stomach | 2303 |

United States lung cancer incidence data for 1983 revealed about 135,000 new cases and 117,000 related deaths which underscores the fact that the cure rate is very low and the disease has a 90% death rate. The incidence among white males has tapered off but among the rest of the population it continues to rise. Cancer of the colon has also risen dramatically since 1844 while that of the uterus (mainly cervical cancer) is now under control due to screening with the pap smear.

Lung cancer now kills more adult men and women than any other neoplastic disease. Of the people who get this cancer, 85% are cigarette smokers but another15% have no relation to smoking. Because this ratio has remained constant over the last 3 decades with a rising total number of lung cancers, there seem to be other factors predisposing to lung cancer that increase in proportion to the increase in the number of cigarette smokers.

A study of the cause of death in a high risk popluation of men(> 45 yrs, heavy smokers) revealed 55% of the deaths were due to cardiovascular disease and another 29% were due to neoplasms. Half of the tumors (15% of the deaths) were lung cancers.

**Incidence of Lung Carcinoma Subtypes during the last 10 years**

| | | |
|---|---|---|
| Epidermoid | 31% | (used to be most common) |
| Adenocarcinoma | 49% | (now most common) |
| Oat cell carcinoma | 15% | |
| Large cell carcinoma | 5% | |

Epidermoid and adenocarcinoma have about the same 5-year survival probability. It is worse for large cell carcinoma, and oat cell carcinoma has almost no 5-year survival probability with a mean lifespan on the order of months from the time of diagnosis. Overall 8% of lung cancer cases live past 5 years.

**Major Subtypes of Lung Cancer**

**Epidermoid or Squamous Carcinoma**

Derived from reserve cells that differentiate into squamous cells. Reserve cells are small rounded cells which are found along the basement membrane of the bronchial epithelium and which proliferate and replace differentiated epithelium when it is injured or denuded.

**General characteristics**

These tumors are most commonly found centrally in the lung, usually in the major lobar or first segmental bronchus. The tumor begins as a localized area of thickening of the epithelium which has a granular surface. The first histologic change is metaplastic transformation which develops to squamous carcinoma in situ (not seen in the glandular or small cell types) and proceeds to invasion unless

it is detected early. Growth of the tumor occurs distally and proximally from site of origin, destroying normal tissue and structures which may be in the tumor's path.

Epidermoid carcinoma in situ, bronchus, lung, low power

Epidermoid carcinoma in situ, bronchus, lung, high power

Early diagnosis may occur following symptoms related to complicating infections and may be detected by pap smear of a sputum sample. Pneumonia is often the presenting illness and should raise suspicion when it occurs in a healthy adult, especially if it reoccurs in the same lobe.

Histologically, the tumor may be keratinizing or non-keratinizing. Keratinizing carcinomas tend to grow very large, metastasize late (usually only to regional lymph nodes) and may kill by local growth. These tumors grow more slowly and its cells are easily desquamated into the bronchial lumen since they lie on the surface of the bronchus. This desquamation allows for easy and early recognition of this tumor by cytology preparations.

Within the tumor, less differentiated areas of growth are peripheral where there is better vascular supply, while the central and surface areas are highly keratinizing and necrotic. These tumors often cavitate and resemble abscesses on radiographic studies grossly.

The tumor may be surgically resected but cure rate depends on the clinical stage at the time of diagnosis.

NOTE

**Cytology**

In general cancer cells have increased DNA content and abnormal chromatin structure which appears as increased nuclear size and hyperchromaticity . The nucleus has a coarse-grained texture and a jagged thickened nuclear membrane. More differentiated squamous type cells have abundant, densely eosinophilic cytoplasm. The malignant cells are often found in a background purulent exudate due to the secondary pneumonia.

Invasive lung carcinoma, sputum, pap smear

**Small Cell Carcinoma (Oat Cell Carcinoma)**

Probably derived from reserve cells though some say they are derived from the Kulchitsky (neuroendocrine) cells which are also found in the endothelium.

### General characteristics

Small cell carcinomas tend to arise in lobar or segmental bronchus . They may have some differentiation toward glandular or epidermoid patterns as it evolves, hence the notion they may arise from reserve cells rather than from more specialized neuroendocrine cells.

Small cell carcinoma is a very aggressive neoplasm which metastasizes very early by the blood and lymphatics. It commonly metastasizes to brain or bone but also to the liver and other sites throughout the body. Early symptoms are usually due to the metastases since the primary often remains while small metastases occur. Chest x-ray may reveal large hilar lymph nodes due to metastases.

The tumor tends to spread diffusely along and into the bronchial wall unlike the epidermoid carcinoma that protrude into the lumen and desquamate. Extensive necrosis within the tumor is common due to its rapid growth again outgrowing the blood supply.

Histologically small cell carcinoma can have different cell types including the so-called oat cell which resembles lymphocytes, and a slightly larger polygonal cell which may be mistaken for another type of tumor.

Primary small cell carcinomas are not generally considered resectable cancers since dissemination is likely to have occured by the time they are discovered. Radiation is useful therapy and they are very responsive to chemotherapy but are rarely curable.

### Cytology

In smears, the cells are small and often oval like oats (hence the name). They resemble lymphocytes but are two-to-three times larger and have a finely dispersed nuclear chromatin. Examination of the sputum often reveals characteristic smll clusters of exfoliated cells.

## Glandular Carcinoma (derived from bronchial epithelium)

Glandular carcinomas originate in the periphery of the lung from the small bronchioles and lung parenchyma, unlike the previously discussed two types of carcinoma where 2/3-3/4 of the tumors began in main lobar bronchi. Perhaps 1% arise from the alveolar epithelium. Due to location of primary lesion, sputum cytology is not very useful for detection of either of the two major subtypes of glandular carcinoma.

Adenocarcinoma of lung, gross

### Adenocarcinoma

Adenocarcinoma represent 2/3 of glandular lung cancers. Most are insidious and asymptomatic for a long time. They present initially as a small mass in the parenchyma. This mass is pale grey or white grossly and may have a glistening surface due to mucin production and secretion. Treatment is surgical and involves removal of entire lobe and with associated lymph nodes.

**Bronchioloalveolar Carcinoma**

Bronchioloalveolar carcinoma is actually a subtype of adenocarcinoma and represents about 1/3 of glandular lung cancers. In the classical form it appears as well differentiated mucin secreting columnar cells that form a single layer that lines the alveolar septae. In this form or pattern, the tumor grows on the underlying supportive structure of the lung parenchyma without causing much damage to that structure.

This type of carcinoma does not metastasize early but may have a rapid pneumonic spread to other areas of the lung which then makes it difficult to cure. Thus, on CXR it resembles a pneumonia-like infiltrate rather than a mass. This type of spread occurs throughout the airways from site to site within the lung as the cells exfoliate, but is not communicable. Advanced cases can spread into and infiltrate the entire lung and draining lymph nodes.

adenocarcinoma lung, g

bronchioaveolar carcinoma, lung, m

A counterpart to this tumor is found in South African sheep and is called JAAGSIEKTE, but it is communicable. (The jaagsiekte form is 1% or less of all lung cancer).

Cytology: In sputum smears the cells form clusters. The cells have large nucleoli, delicate nuclear staining, and pale cytoplasm which may contain mucin.

**Large Cell Carcinoma**

A "wastebasket" category of undifferentiated non-small cell carcinoma which probably includes both poorly differentiated epidermoid and glandular carcinomas which cannot be otherwise definitively identified and put into their respective categories.

In this category are carcinomas of the lung which are so poorly differentiated that by routine studies and light microscopy, they cannot be placed into either the epidermoid or glandular groups. It has been found by ultrastructural studies and other more investigative methods of cell identificatin, that these tumors will frequently have cytologic features fo either epidermoid cells or glandular cells or both.

## Other Neoplasms of the Lung

### Bronchial Carcinoid

Bronchial carcinoids arise from Kulchitsky cells and therefore is a neuroendocrine tumor. Grossly, they often occur as a small nodule .projecting into the bronchial lumen, i.e. endobronchial tumors. They are generally slow growing lesions and grow as a trabecular (or other) pattern similar to other neuroendocrine tumors. The individual cells have neuroendocrine granules (visualized by silver stain, immunoperoxidase, or electron microscopy) like Kulchitsky cells and may secrete serotonin as well as othe peptides. Through secretion of various polypeptides, these tumors then are associated with a variety of paraneoplastic syndromes. One secretory hormone in particular to remember is ACTH.

As you will learn about neuroendocrine tumors in general, their biologic behavior is difficult to predict and they all have the capacity to metastasize. In fact the only definitive indication that one of these tumors is malignant is the presence of metastases. Carinoids in the lung may also be peripheral. There is a histologic spectrum of carcinoid tumors which ranges from bland to atypical and probably eventually some of the small cell carcinomas.

## Lung Tumor Staging

For non-oat cell carcinomas, the next best prognostic indicator of survivability is the stage of the tumor.

Stage 1: single lesion < 3 cm. in diameter, within the lung parenchyma and +/- hilar nodemetastasis. Resection results in an 80% 5-year survival.

Any Other Stage: survivability decreases to < 10%.

Complete Resection: survival probability = 65%.

Incomplete Resection: < 5% survival. Of course oat cell carcinoma is excluded since it is not surgically treatable.

## Tumor Syndromes

### Pancoast Tumor

These are carcinomas which arise in the superior sulcus (apex of the lung) and can then invade neural structures around the trachea such as the brachial plexus and the cervical sympathetic plexus giving rise to Horner's syndrome (enopthalmusptosis, miosis, and anhidrosis) on the same side as the lesion and neurological problems including pain of the upper extremity. The important aspect is the anatomic location of the tumor and not the subtype. These may be difficult to visualize radiographically and are difficult to resect, but may respond to radiotherapy.

### Superior Vena Cava Syndrome

Some lung tumors may extend into the mediastinum and cause obstructin of the SVC. This type of involvement presents clinically as swelling of the face and fullness of the neck veins. Again this type of involvement by tumor is likely to be unresectable but may temporarily respond to radiotherapy.

## Metastatic Tumors of the Lung

adenocarcinoma, metastatic to lung, micro (primary in colon)

Brain metastases, adenocarcinoma (primary in lung)

Metastatic adenocarcinoma, lung (primary in adrenal)

Carcinoma of lung metastatic to pericardium with constrictive pericarditis

## Tumors of the Pleura

### Malignant Mesotheliomas

The incidence of pleural mesotheliomas is increasing. Most if not all of the diffuse epithelial and fibrosarcomatous mesotheliomas are believed to be related to asbestos exposure and are seen most frequently among people who have been employed in construction or insulation work.

Grossly, the diffuse or malignant form grows as multiple nodules studding the pleura and/or as a diffuse thickening of the pleura, and these nodules can form confluent aggregates visible and often accompanied by a painless effusion. The tumor will coat the surface of pleura and extend into lobar septae, thereby encasing the lung and obliterating the pleural space.

### Major subtypes

- Epithelial or (diffuse) Mesothelioma

  These tend to be multifocal and probably arise from the mesothelial cell layer.

  Mesothelioma, m, pleura

- Fibrosarcoma (or Sarcomatoid Type of Mesothelioma)

  These tumors also probably arise from the mesothelial lining cells and are malignant.

- Benign Mesothelioma

A third type of "mesothelioma" is the so-called localized fibrous type which is generally benign. This tumor however has no association with asbestos exposure and is thought to arise from the submesothelial mesenchymal cells and not from mesothelial cells. These tumors are rather uncommon.

Mesothelioma, fibrous, pleura, g

# ENVIRONMENTAL AND OCCUPATIONAL LUNG DISEASE

## Introduction

In studying the changes which occur in the lung, three things should be kept in mind: (1) the variety of potentially pathologic agents, (2) the diversity of possible pathologic responses in the lung, and (3) the numerous occupations in which exposure can occur.

Occupational lung diseases occur as a result of inhalation of noxious particles, fumes, and gases.

Remember that a person inhales about 10,000 liters of air per day and that this air is frequently polluted.

## General Comments about Occupational Lung Diseases

### Injury by Types of Particles, Fumes, or Gases

-- Organic dusts tend to produce allergic reactions.

-- Smoke and noxious fumes damage the conducting airways and/or cause acute diffuse alveolar damage (DAD).

-- Inorganic dusts, if small enough, penetrate into the periphery of the lungs and are associated with chronic disease resulting in fibrosis and occasionally neoplasia.

## Factors that Contribute to Lung Disease

### -- Size of Particle

Larger particles get trapped higher in the airways and are more easily eliminated

Smaller particles can get further out into the acini (see "pulmonary defense mechanisms" in Lecture 1).

### -- Solubility of Gases

Soluble gases tend to cause injury in the upper airways and tend to be more irritating,

Insoluble gases will get to the peripheral lung and cause edema.

**-- Duration of Exposure**

Usually the longer the exposure the more severe the disease.

An exception is asbestos in that there are certain diseases associated with both short and long term exposure.

-- Nature of the substance

-- Host susceptibility

-- Dosage

**Types of Reactions in both the Upper Airways and Lower Air Spaces**

**-- Acute**

In upper airways soluble gases (e.g. chloride and ammonia) will cause direct injury to the epithelium which will result in an acute inflammatory reaction followed by scarring with prolonged exposure.

Hypersensitivity reactions (asthma), immediate and dealayed, also occur in the upper airways, e.g. Farmer's Lung and Humidifiers Lung.

In the distal airspaces, acute reactions follow exposure to insoluble gases, some metals, and fumes. This manifests as acute edema or acute diffuse alveolar damage.

**-- Subacute**

Hypersensitivity pneumonia

Alveolar filling processes and accelerated fibrosis

**-- Chronic**

Includes the development of fibrosis, granuloma formation, carcinoma, and bronchitis.

Also leads to increased incidence of infections, such as tuberculosis.

These changes can occur anywhere in the respiratory tract.

**Types of Pathologic Responses or Changes in the Lung**

**-- Bronchial Asthma**

- Definition

  A state of hyperirritability of the conducting airways.

  Two Types

    Atopic/allergic asthma, which includes occupational asthma as a subset. People who develop allergic-type asthma have a hyperirritable conducting airway system and develop a combination of immediate type I-IgE and delayed type III-IgG immune reactions. These two factors make them susceptible to "asthmatic" attacks. Many environmental agents can cause "occupational" asthma.

    Non-atopic asthma usually related to viral infection.

- Pathology

  Involves the conducting airways and is a type of obstructive lung disease

  Morphologically, there is a hyperplasia of the submucosal mucus-secreting glands.

  Recurring bronchospasm leads to a muscular hyperplasia and thickening of the smooth muscle bundles in the wall.

  Immunological reaction that occurs leads to a cellular infiltrate composed of lymphocytes and some eosinophils.

  Frequently there is thickening of the basement membrane .

  Chronic and Recurring Process

    There is an increase in the secretion of mucus often with the formation of mucus plugs.

    In the mucus plugs there is some infiltration by eosinophils which eventually break down, and the cytoplasmic contents condense to form diamond-shaped Charcot-Leyden crystals.

    Mucus (Curschman) spirals representing formed casts of the smaller airways are found in the larger mucus plugs

**-- Allergic Alveolitis (Extrinsic Allergic Alveolitis or Hypersensitivity Pneumonitis)**

- Seen in the distal airways and alveoli.
- Invokes a combination of the type III and type IV immune reactions.
- Hypersensitivity Pneumonia

Is an example of lymphocytic alveolitis.

First hypersensitivity pneumonia to be described was Farmer's Lung, which is associated with exposure to microorganisms, thermophilic actinomycetes.

Tissue reaction combines interstitial lymphocytic and plasma cell infiltrates with an interstitial granulomatous reaction.

More common exposure today is to microbes residing in air conditioners.

**-- Diffuse Alveolar Damage**

An acute interstitial injury that can be caused by a variety of agents.

Due to injury to the microvasculature and the subsequent events which follow, as has already been discussed in a previous lecture.

**-- Bronchiolitis Obliterans**

Obliteration of the bronchioles that occurs as a result of a chronic scarring process which leads to a fibrous proliferation , eventually blocking the lumen of the bronchioles.

May occur after airway injury and is seen in firemen after inhalation of hot gases and smoke.

Keep in mind that there is no gas exchange in the airways and alveoli distal to the block, yet blood flow continues, leading to ventilation-perfusion mismatching

**-- Small Airways Disease**

Pathologically manifests as thickening of the walls of the respiratory and terminal bronchioles.

Fibrous and muscular thickening which causes constriction of the lumen.

Associated with smoking; also, some people feel that it may be associated with asbestos exposure.

**-- Alveolar Proteinosis**

An alveolar filling process by a granular, proteinaceous matrix.

A similar acute process has been seen in some patients who have been exposed to silica.

**Example of an Occupational Lung Disease: Coal**

**General Comments**

Coal is the prototype for inhalation of an industrial product which is relatively inert and does not usually cause parenchymal lung damage.

The disease is called coal worker's pneumoconiosis (pneumo=lung, conis=dust, osis=condition) in the setting of a known history of coal dust exposure. The separation of simple CWP and complicated CWP is generally based on CXR appearances.

There is a lot of controversy related to simple CWP as a clinical disease and over 1 billion dollars in workers compensation is being paid out each year because of this "disease". However, there is substantial doubt that coal by itself causes any clinically significant pathologic changes, and therefore no functional abnormalities for which coal workers should be compensated.

**Etiology/Pathology of CWP**

-- Important thing to remember is that coal itself does not cause much, if any, tissue reaction or damage in the lung.

**-- Exposure**

With exposure, inhaled coal dust is deposited and collects around the respiratory bronchioles partially due to alveolar macrophage ingestion and migration toward the lymphatics, with the formation of carbon aggregates or in the walls of these bronchioles.

No functional abnormality associated with this stage because there is no fibrous reaction and no injury to the wall; coal is located within the macrophages and in the interstitium.

**-- Further exposure**

Leads to additional deposition and aggregation and eventually larger lesions called coal macules.

- Emphysematous Changes of the Centriacinar Type

In time, one can observe these changes. Most of these patients smoke, however, and the emphysematous changes are thought to be secondary to the smoking.

- Growth of Macules

  Eventually the macules get larger.

  Often occurs when there is exposure to mixed dusts, especially other silicates.

**-- Simple Macular Disease**

Most people who get coal worker's pneumoconiosis get the simple macular disease while the smokers get the macules and emphysematous changes.

**-- "Complicated" Coal Worker's Pneumoconiosis**

Developed by a small percentage of cases.

Progressive massive fibrosis.

Large black nodules in the lung and diffusely black parenchyma.

Reason why this occurs in some people is unknown but it may be due to the addition of other silicates to the coal, or a postulated but unexplained relationship with tuberculosis.

**-- Diseases associated with CWP**

TB and Rheumatoid arthritis (Caplan's syndrome).

**Example of an Occupational Lung Disease: Silica**

**Pathology of Silicosis**

**-- Definition of Silicosis**

Fibrotic lung disease caused by the inhalation of crystalline silica dioxide.

Often a combination of interstitial and alveolar fibrosis.

Silicosis usually becomes clinically evident 20-40 years after exposure.

**-- Typical Lesion**

Nodule that has a densely hyalinized, whirled central core.

Around the core is a cellular proliferation made up of fibroblasts and macrophages.

Thought that silica is taken up by macrophages causing these cells to necrose and release the silica so it is phagocytosed by other macrophages.

**-- Probable Cause**

Silica probably causes fatal injury to macrophages by binding to cell membranes, such as lysosomal membranes, causing injury and an eventual release of their lysosomal contents.

**-- Fibrosis**

Is thought to be due to substances released by the macrophages as they break down which lead to a recruitment of fibroblasts and production of collagen.

**-- Reason for Disease Progression after Removal of Silica**

This sequence of events accounts for the morphology of the nodule having a central fibrous core and a periphery of activated macrophages; and explains why this disease continues to progress after silica dust exposure has been eliminated from the patient's environment.

**-- Placement of Nodules**

Usually one has scattered nodules mainly in the upper lobe.

Nodules fierst devellp around the respiratory bronchioles and in the pleura where lymphatics are found, but progress and may eventually coalesce.

**Additional Points**

-- Silicon comprises about 28% of the earth's crust and occurs either as free silica often bound to oxygen ($SiO_2$) or as silicates (bound to other elements).

-- Silica, like coal is associated with progressive massive fibrosis.

-- Increased exposure can lead to abnormal pulmonary functions.

-- People with silicosis have an increased incidence of TB; studies have shown that exposure to silica may cause the M. tuberculosis to replicate.

**-- Silica Usually Does Not Polarize Light**

Can not visualize silica under the light microscope.
If you do see polarization it is probably other silicates, like mica or talc.

**Example of an Occupational Lung Disease: Asbestos**

**General Points**

-- Asbestos is a ubiquitous, hydrated, fibrous silicate which is found in urban air.

-- 100% of normal urban dwellers are said to have been exposed and have detectable asbestos in their lungs.

**-- Two Main Types of Asbestos**

Curved (chrysotile).

Straight (amphiboles).

**-- Pathologic Expressions of Asbestos-Related Disease**

- Pleural effusions
- Pleural fibrosis
- Pleural plaques
- Interstitial fibrosis
- Bronchogenic carcinoma
- Mesothelioma

**-- "Asbestosis"**

"Asbestosis" refers to interstitial pulmonary fibrosis due to asbestos. (The other terms are merely indicators of exposure.)

On x-ray you see an interstitial process usually in the lower lung fields.

Interstitial lung disease is related to degree of exposure.

**-- Pleural Plaques**

Occur often on the domes of the diaphragm.

Are calcified, acellular, and hyalinized.

Plaques can occur with minimal exposure, hence, no dose-related response

**-- Pleural Fibrosis**

Can be very extensive, covering more than one lobe or both lungs.

**Pathology of Asbestosis**

-- Pathologically, "asbestosis" is identical to chronic interstitial pneumonia (usual interstitial pneumonia-UIP), the only difference being the presence of asbestos particles.

-- There is interstitial fibrosis and abnormal airspaces which alternate with other more normal areas of lung parenchyma.

-- Some of the asbestos fibers are coated with a protein-iron complex (see ferruginous bodies, below) but most of them are not.

Therefore, they can't be seen with light microscopy but can be seen with EM.

**-- Ferruginous Bodies**

- May be found under the light microscope or EM.
- Are generally "coated" straight asbestos fibers .
- May be found in macrophages or in the interstitium; usually found in the walls of the respiratory bronchioles.
- Ferruginous bodies are characteristic of but not pathognomonic for asbestos.
- Have Three Components

Central core of asbestos.

Coated by a protein-iron complex.

**Association of Asbestos with Certain Tumors**

**-- Bronchogenic Carcinoma**

- With asbestos exposure is usually located in the lower lobes
- In smokers it is usually in the upper lobes
- In asbestos-exposed people who don't smoke there is a 5-10x increase in bronchogenic CA
- In people who smoke and have been exposed there is a 50-100x increase incidence of bronchogenic CA, (therefore additive effects)

**-- Mesothelioma**

- A tumor that arises from the pleural lining
- Tends to spread over the pleural surface and can involve one or both lungs

(NOTE: This is the same mesothelium that is found in the peritoneum and some of these patients will develop a peritoneal mesothelioma.)

- Two Types of Cell Growth Involved with These Tumors

Epithelial

Fibrous / Fibrosarcomatous

- Some say that you can't diagnose mesothelioma until the patient has died because these cells have characteristics which overlap with other, more common adenocarcinomas and fibrosarcomas.
- Staining Mesotheliomas

    Stain with PAS but after digestion they will be negative (adenocarcinomas tend to stain positively after digestion)

    Immunoperoxidase stains

        Mesotheliomas tend to be positive with cytokeratin and,

        Negative with CEA (carcinoembryonic antigen).

- EM shows what looks like an epithelial cell with cell junctions and villi, but adenocarcinomas will look similar
- It is the combination of all information that allows you to determine if asbestos exposure has occurred and if the condition is a mesothelioma, and then to make an antemortem diagnosis and properly treat the patient.

**An Overview of Asbestos Exposure**

It is the interstitial lung disease that you refer to when you say pulmonary asbestosis. It usually relates to dose exposure while the pleural disease (for example the pleural plaques) and mesothelioma are not dose-related. The pleural plaques, pleural fibrosis, and the asbestos bodies are indicators for exposure.

## Examination

Select the ***best*** answer to each of the following items. Mark your responses on the Answer Form.

1. Lung voumes can be divided into components, including_____.

a. tidal volume
b. residual volume
c. inspiratory  reserve
d. All of the above

2. A traditional "bell spirometer" is a canister of water with an inverted canister bell over it with air space inside the inverted canister bell.

a. True
b. False

3. _____ is the total lung capacity minus the volume of air in the lung at the end of a normal inspiration.

a. Inspiratory Capacity (IC)
b. Residual Volume (RV)
c. Inspiratory Reserve Volume (IRV)
d. None of the above

4. _____ is the total usable volume of the lungs which is under voluntary control.

a. Total Lung Capacity (TLC)
b. Vital Capacity (VC)
c. Functional Residual Capacity
d. None of the above

5. _____ is the volume of the air conducting pathways in which no gases are exchanged (approximately 150 mL in the average adult human being)

a. Anatomic Dead Space
b. Physiologic Dead Space
c. Alveolar Dead Space
d. None of the above

6. Factors which determine the size of normal lungs include: stature, age, sex, body mass, posture, habitus, ethnic group, reflex factors and daily activity pattern.

a. True
b. False

7. The Vital Capacity (VC) is the volume of gas measured on a fast, full inspiration after a maximal expiration (or a slow, complete expiration after a full inspiration), with forced or rapid effort.

a. True
b. False

8. The variability of repeated measurements of the VC is between 90 and 200 ml. The EVC and FVC may be considerable less than the IVC in patients with airflow limitations.

a. True
b. False

9. The Functional Residual Capacity (FRC) is the volume of gas remaining in the lungs at the average resting end-expiratory level.

a. True
b. False

10. In the Closed-Circuit measurement method the FRC is corrected for the volume of He which dissolves in the blood (helium uptake has been estimated at 0,3 ml/min per %He in alveolar gas) and for the dead space volume of the breathing valve

a. True
b. False

11. An increase in the FRC is considered pathological. An increase of more than _____% of the predicted represents hyperinflation, which may result from emphysematous changes, compensation for surgical removal of lung tissue, asthmatic or bronchiolar obstruction or thoracic deformity.

a. 15
b. 25
c. 50
d. 120

12. Decreases in FRC and RV are typically for restrictive diseases, and seen in diseases associated with extensive fibrosis (sarcoidosis, asbestosis, silicosis). A Restrictive disease pattern may also be seen in kyphoscoliosis, pectus excavatum, neuromuscular diseases and obesity.

a. True
b. False

13. Total Lung Capacity (TLC) can be determined from posterior-anterior (P-A) an lateral radiographs of the chest (subjects must hold their breath at TLC when each film is exposed). It involves dividing the films into ellipsoidal segments and estimating the volumes of each segment.

a. True
b. False

14. The TLC can be calculated from TLC = RV + IVC, from TLC = FRC + IC (the latter is the preferred method in body plethysmography), or from the radiological method

a. True
b. False

15. When absolute air volumes in the lungs must be measured, spirometry is insufficient. Therefore, your doctor may order body plethsmography to get more precise measurements of lung volumes. Body plethsmography can measure _____.

a. residual volume
b. function residual capacity
c. total lung capacity
d. All of the above

16. Lung-volume-reduction surgery (LVRS) has been proposed as a palliative treatment for patients with severe emphysema. The procedure leads to _____.

a. a decrease in lung volumes
b. an increase in elastic recoil of the lungs
c. Both of the above
d. None of the above

17. Emphysema is part of an important component of chronic obstructive pulmonary disease (COPD) which causes high-disability associated with over inflated lungs, poor lung elasticity and impaired transfer of oxygen to the blood

a. True
b. False

18. The result of weakening respiratory muscles is that the "vital capacity" of the lungs (the amount of air that a person can exhale after taking in a deep breath) decreases over time.

a. True
b. False

19. When mechanical ventilation is used to treat hypercapnia, the tidal volume and respiratory rate should be adjusted to result in an acceptable Paco2. A reasonable tidal volume to begin with is 8 to 10 mls /kg.

a. True
b. False

20. CPAP is the major factor determining lung volume. At low CPAP (low volumes e.g. in diseased lungs), compliance is low; at higher volumes compliance increases; at high volumes (over distension ) compliance again decreases. Optimum FRC results an optimum compliance and the lowest work of breathing.

a. True
b. False

21. Optimal CPAP can be found by producing a CPAP/PEEP grid: adjust CPAP to 1 cm above and 1 cm below current levels and after 10-15 minutes obtain Pao2 or lung compliance depending on the goal of the CPAP.

a. True
b. False

22. **Huff coughing** is a modified forced expiratory technique that is performed by forcefully exhaling through an open glottis from high to mid lung volumes. The patient takes in a slow, deep inhalation, followed by a 1-3 second breath hold. The patient then performs short, quick, forced exhalations with the glottis open.

a. True
b. False

23. The main function of the lungs is (slow) gas exchange.

a. True
b. False

24. Total lung weight is about _____ gms. Upper and middle lobes are anterior, while the lower lobes are posterior.

a. 100-175
b. 200-320
c. 300-400
d. 425-600

25. Anatomically, most of the alveolar wall is comprised of the capillary. At any given time the total lung capillary volume is about _____ ml., spread over an area of 80 m2 which results in a very thin layer of blood.

a. 35
b. 75
c. 125
d. 200

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