Lung tumors

- Primary lung cancer is a common disease accounting for 95% of primary lung tumors
- Carcinoma: Is the single most important cause of cancer-related deaths in industrialized countries accounts for about one third of cancer deaths in men, and has become the leading cause of cancer deaths in women

- The peak incidence of lung cancer is in persons in their 50s and 60s.
- The prognosis with lung cancer is dismal:

1. The 5- year survival rate for all stages of lung cancer combined is about 16%,
2. Disease localized to the lung, the 5-year survival rate is 45%

- The four major histologic types of carcinomas of the lung

a. Adenocarcinoma

b. Squamouscell carcinoma,

c. Small cell carcinoma,

d. Large cell carcinoma

- Because of changes in smoking patterns in the U.S., adenocarcinoma has replaced squamous cell carcinoma as the most common primary lung tumor in recent years
- Carcinomas of the lung were classified into two groups:

a. Small cell lung cancer (SCLC) and

b. Non-small cell lung cancer (NSCLC), including adenocarcinomas and squamous cell carcinomas.

- The reason for this historical distinction was that virtually all SCLCs have metastasized by the time of diagnosis and are not curable by surgery and are treated by chemotherapy, with or without radiation therapy
- By contrast, NSCLCs were more likely to be resectable and usually responded poorly to chemotherapy

; however, now therapies are available that target specific mutated gene products present in the various subtypes of NSCLC, mainly in adenocarcinomas.

- NSCLC must be classified into histologic and molecular subtypes

ETIOLOGY

- There is strong evidence that cigarette smoking and, to a much lesser extent, other environmental insults are responsible for the genetic changes in lung cancers.
- About 90% of lung cancers occur in active smokers or those who stopped recently.
- The increased risk becomes 60 times greater among habitual heavy smokers (two packs a day for 20 years) than among nonsmokers

- Since only 11% of heavy smokers develop lung cancer, however, other predisposing factors must play a role.
- The mutagenic effect of carcinogens is conditioned by (genetic) factors.
- Many chemicals (procarcinogens) require metabolic activation via the P- 450 monooxygenase enzyme system for conversion into ultimate carcinogens

- Persons with specific genetic polymorphisms involving the P-450 genes have an increased capacity to metabolize procarcinogens derived from cigarette smoke, and thus have the greatest risk for development of lung cancer
- For reasons not clear, women have a higher susceptibility to carcinogens in tobacco than men.

- Although cessation of smoking decreases the risk of developing lung cancer over time, it may never return to baseline levels
- Passive smoking increases the risk of developing lung cancer to approximately twice that of nonsmoker
- The smoking of pipes and cigars also increases the risk, but only modestly

- There is increased incidence of lung carcinoma in asbestos workers; and workers exposed to dusts containing arsenic, chromium, uranium

Note

- Exposure to asbestos increases the risk of lung cancer fivefold in nonsmokers.

- Heavy smokers exposed to asbestos have an approximately 55 times greater risk for development of lung cancer than that for nonsmokers not exposed to asbestos

PATHOGENESIS

- Smoking-related carcinomas of the lung arise by a stepwise accumulation of a multitude of genetic abnormalities that result in transformation of benign progenitor cells in the lung into neoplastic cells.
- The sequence of molecular changes is not random but follows a predictable sequence that parallels the histologic progression toward cancer.

1. Inactivation of tumor suppressor genes located on the short arm of chromosome 3 (3p) is a very early event, whereas TP53 mutations or activation of the KRAS
2. In Adenocarcinomas

a. Activating mutations of the epidermal growth factor receptor (EGFR) and these tumors are

sensitive to agents that inhibit EGFR signaling, but the response often is short-lived.

b. MET tyrosine kinase gene amplifications

c. In 4% of adenocarcinomas are EML4-ALK tyrosine kinase fusion genes and

4. ALK tyrosine kinase fusion genes and c-

- These abnormalities, while rare, are important because of their therapeutic implications, as they can be targeted with tyrosine kinase inhibitors.

- The identification of genetic alterations producing overactive EGFR, ALK, and MET has opened up a new era of "personalized" lung cancer therapy

- Among the major histologic subtypes of lung cancer, squamous and small-cell carcinomas show the strongest association with tobacco exposure.

- MORPHOLOGY

1. Squamous cell carcinomas :

a. Are more common in men than in women

b. Are closely correlated with a smoking history;

c. They tend to arise centrally in major bronchi and eventually spread to local hilar nodes,

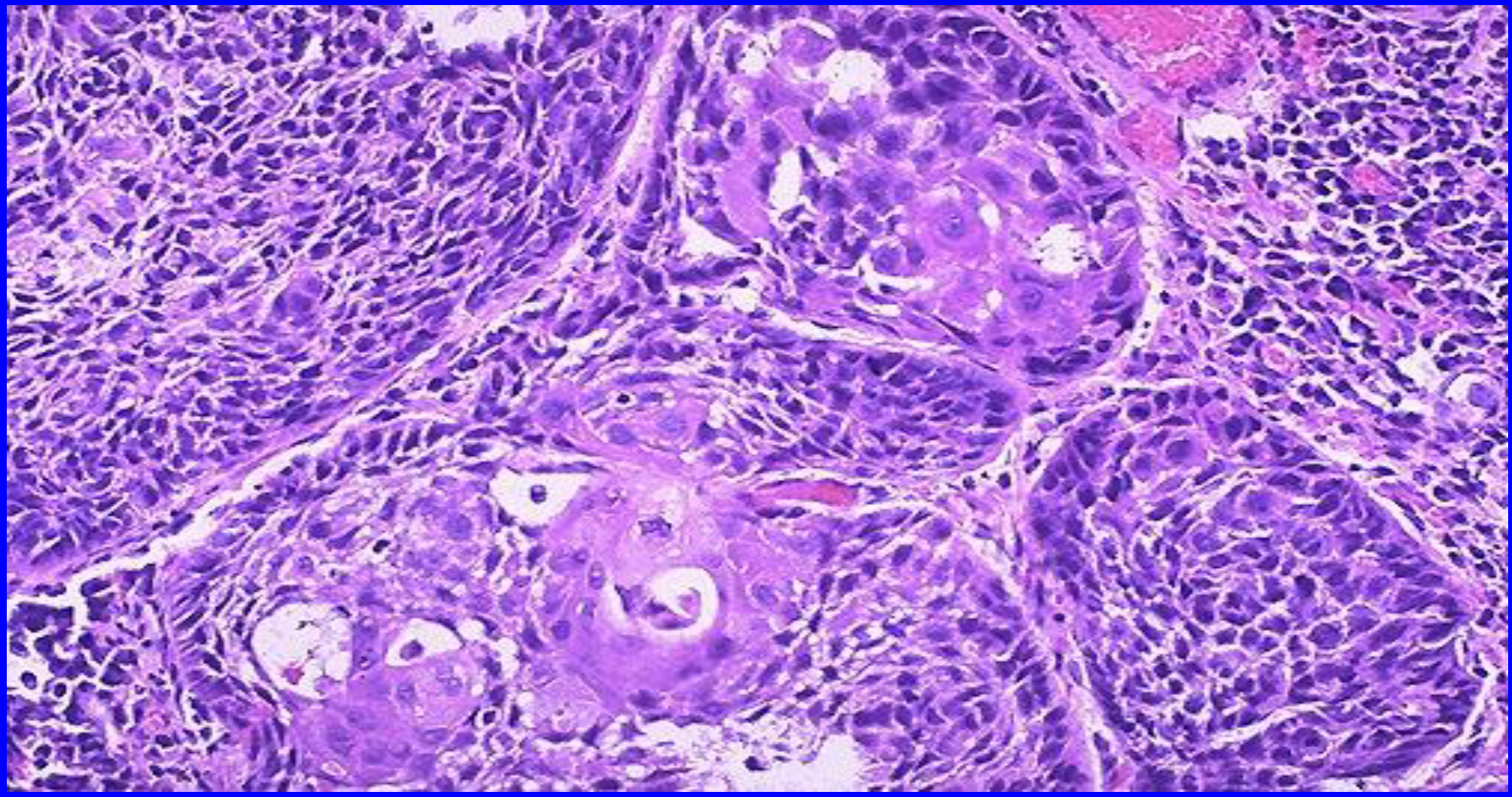
d. Disseminate outside the thorax later than do other histologic types

e. Large lesions may undergo central necrosis, giving rise to cavitation.

f. Are preceded by the development, over years, of squamous metaplasia or dysplasia in the bronchial epithelium,

h. Eventually, the small neoplasm reaches a symptomatic stage, when mass begins to obstruct the lumen of a major bronchus, often producing distal atelectasis and infection.

Squamous cell carcinoma of lung



2. Adenocarcinomas:

a. May occur as central lesions but usually are more peripherally located, many with a central scar.

b. Are the most common type of lung cancer in women and nonsmokers

c. In general, adenocarcinomas grow slowly and form smaller masses than do the other subtypes

d. They tend to metastasize widely at an early stage

- On histologic examination, they may assume a variety of forms, including :

A. Acinar(gland-forming) ,

B. Papillary,

C. Mucinous which often is multifocal and may manifest as pneumonia

D. Solid types. :Requires demonstration of intracellular mucin production by special stains

Note: Although foci of squamous dysplasia may be present in the epithelium proximal to resected adenocarcinomas, these are not the precursor lesions for this tumor.

- The precursor of peripheral adenocarcinomas is atypical adenomatous hyperplasia which progresses to

a. Adenocarcinoma in situ

b. Minimally invasive adenocarcinoma (tumor less than 3 cm and invasive component measuring 5 mm or less),

c. Invasive adenocarcinoma (tumor of any size that has invaded to depths greater than 5 mm).

Adenocarcinomain situ (AIS), formerly called bronchioloalveolarcarcinoma, often involves peripheral parts of the lung, as a single nodule.

- The key features of AIS are:

a. Diameter of 3 cm or less,

b. Growth along preexisting structures,

c. and preservation of alveolar architecture

D. By definition, AIS does not demonstrate destruction of alveolar architecture or stromal invasion with desmoplasia, features that would merit the diagnosis of frank adenocarcinoma

3. Small cell lung carcinomas (SCLCs) are:

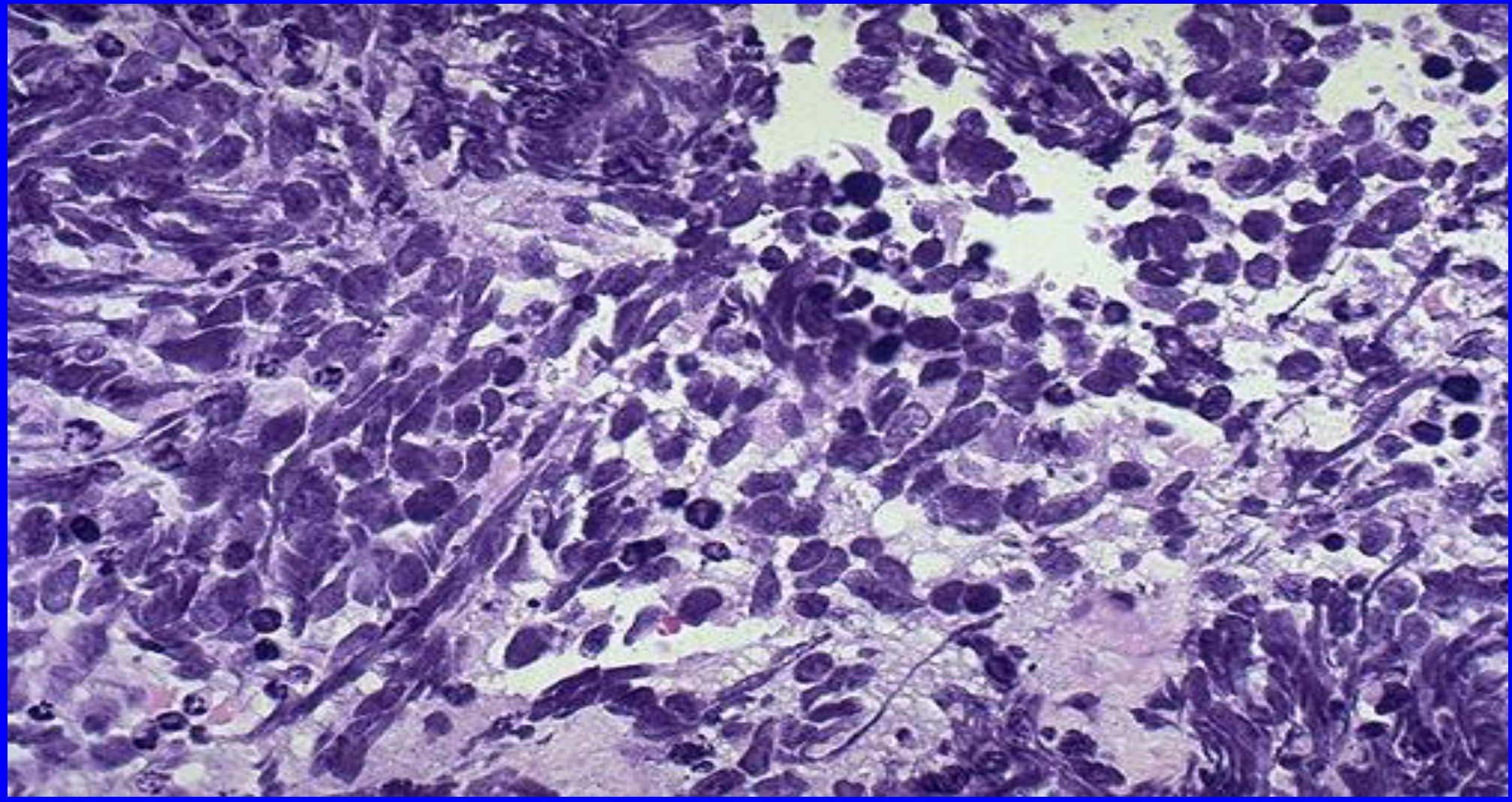
a. Centrally located with extension into the lung parenchyma

b. Early involvement of the hilar and mediastinal nodes.

c. Are composed of tumor cells with a round shape, scant cytoplasm, and finely granular chromatin with many mitotic figures .

- Necrosis is invariably present and may be extensive
- Fragile cells that show fragmentation and "crush artifact".
- Nuclear molding resulting from close apposition of tumor cells that have scant cytoplasm.

Small cell carcinoma of the lung



1. For all of these neoplasms, it is possible to trace involvement of successive chains of nodes in carina, in the mediastinum, and in the neck (scalene nodes) and clavicular regions and then distant metastases.

- Involvement of the left supraclavicular node (Virchow node) is particularly characteristic and sometimes calls attention to an occult primary tumor

3. They may infiltrate the superior vena cava to cause either venous congestion or the vena caval syndrome

- .Apical neoplasms (Pancoast tumors) causes Pancoast syndrome characterized by:

a. Invasion of the brachial or cervical sympathetic plexus to cause severe pain in the distribution of

the ulnar nerve r to produce Horner syndrome (ipsilateral enophthalmos, ptosis, miosis, and anhidrosis).

b. Is accompanied by destruction of the first and second ribs and sometimes thoracic vertebrae

Clinical Course

- Are silent, cancers that in many cases have spread so as to be unresectable before they produce symptoms.
- In some instances, chronic cough call attention to still localized, resectable disease.
- By the time hoarseness, chest pain, superior vena cava syndrome, pleural effusion, makes its appearance, the prognosis is grim

- Too often, the tumor presents with symptoms resulting from metastatic spread to the brain (mental or neurologic changes), liver (hepatomegaly), or bones (pain).
- Although the adrenals may be nearly obliterated by metastatic disease, adrenal insufficiency (Addison disease) is uncommon,

- About 3% to 10% of all patients with lung cancer develop clinically overt paraneoplasticsyndromes.

1. Hypercalcemia: caused by secretion of a parathyroid hormone-related peptide by squamous cell carcinoma
2. Cushing syndrome (production of Adrenocorticotropic hormone);by small cell carcinoma

3. Syndrome of inappropriate secretion of antidiuretic hormone; by small cell carcinoma
4. neuromuscular syndromes, including a myasthenic syndrome, peripheral neuropathy, and polymyositis
5) clubbing of the fingers and hypertrophic pulmonary osteoarthropathy by any type of carcinoma

3.Pulmonary Hypertension

Pulmonary blood pressures are only about one eighth of systemic pressures.

- Pulmonary hypertension is when pulmonary pressure is one fourth of systemic levels
- Is most often secondary to:

a. a decrease in the cross sectional area of the pulmonary vascular bed,

b. or to increased pulmonary vascular blood flow.

I. Secondary type and II. Primary type

I. The causes of secondary pulmonary hypertension include:

a. Chronic obstructive or interstitial lung disease, which is accompanied by destruction of lung parenchyma and may consequent reduction in alveolar capillaries.

- This causes increased pulmonary arterial resistance and secondarily, elevated arterial pressure

b. Recurrent pulmonary emboli:- Lead to a reduction in the functional cross-sectional area of the pulmonary vascular bed

c. Heart disease, for example, mitral stenosis, which increases left atrial pressure

d . Congenital left-to-right shunts

II. Primary, or idiopathic, pulmonary arterial hypertension

1. The vast majority of cases are sporadic
2. 6% are familial with an autosomal dominant mode of inheritance

PATHOGENESIS

- Pulmonary endothelial cell and/or vascular smooth muscle dysfunction is the probable underlying basis for most forms of pulmonary hypertension

1. .In states of secondary pulmonary hypertension

- endothelial cell dysfunction arises as a consequence of the underlying disorder due:

a. To increased blood flow in left-to-right shunts,

b. or biochemical injury produced by fibrin in recurrent thromboembolism

- **Endothelial cell dysfunction**

1.Reduces production of vasodilatory agents :nitric oxide, prostacyclin and while increasing synthesis of endothelin.

2- There is production of growth factors and cytokines that induce the migration and replication of vascular smooth muscle and elaboration of extracellular matrix.

2. In primary pulmonary hypertension

a. In the uncommon familial form, the TGF-

β signaling pathway has emerged as a key mediator of endothelial and smooth muscle dysfunction., Specifically, germline mutations of bone morphogenetic protein receptor type 2 (BMPR-2), have been demonstrated in 50% of familial cases.

- It is a cell surface molecule that binds to a variety of TGF-β pathway ligands: The BMPR2gene product is inhibitory in its effects on proliferation; hence, loss of-function mutations of this gene result in abnormal vascular endothelial and pulmonary smooth muscle proliferation

b. Sporadic forms of primary pulmonary hypertension

- There is a possible role for the serotonin transporter gene (5 HTT)
- Specifically, pulmonary smooth muscle cells from some patients with primary pulmonary hypertension demonstrate increased proliferation on exposure to serotonin

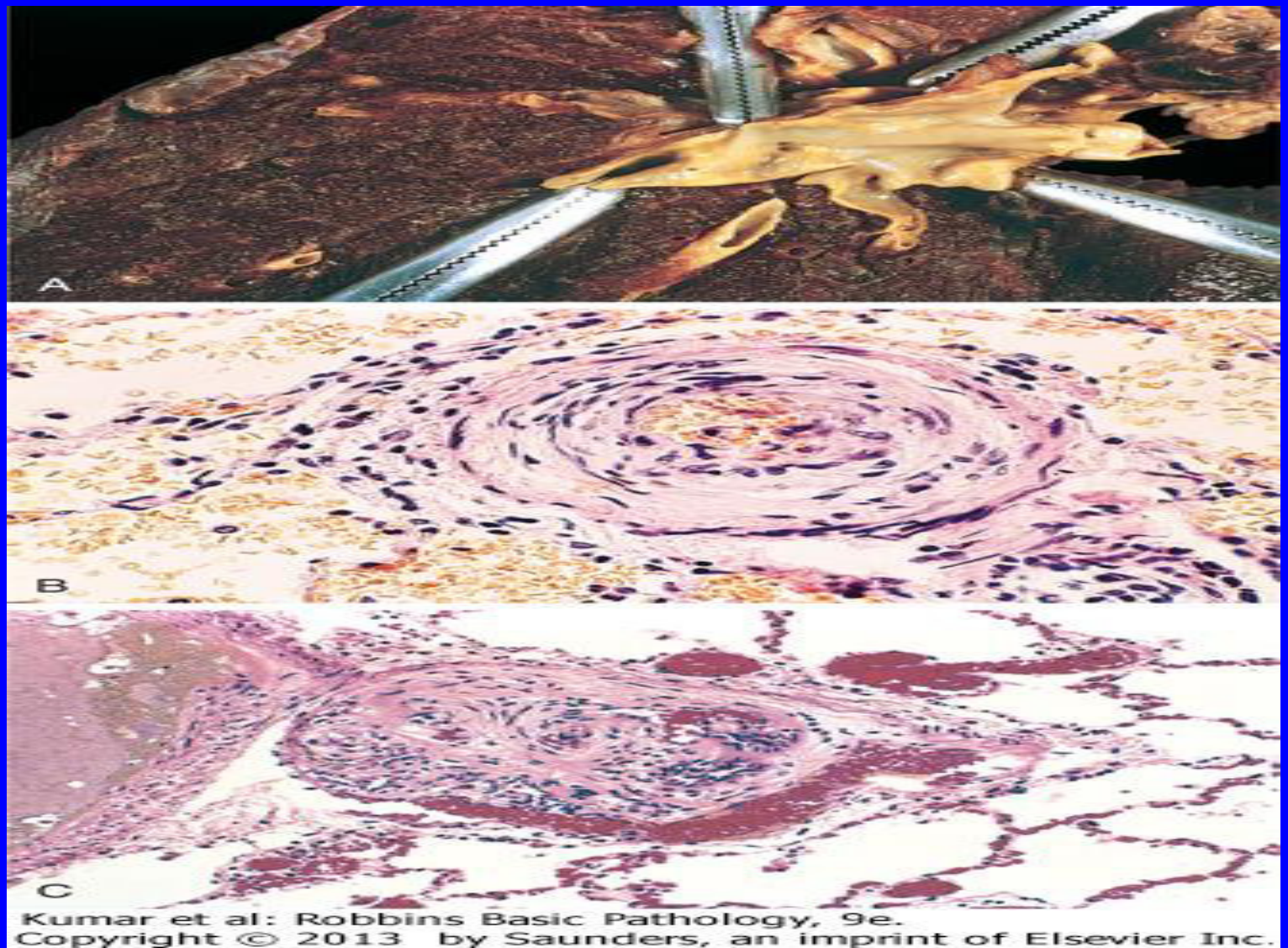
- Genetic polymorphisms of 5HTT that lead to enhanced expression of the transporter protein on vascular smooth muscle are postulated to cause their proliferation

Morphology

1. In medium sized muscular arteries :Thickening of the intima and media with narrowing of the lumina; and
2. in smaller arteries and arterioles : medial hypertrophy, and reduplication of the internal and external elastic membranes and the wall thickness may exceed the diameter of the lumen, which is sometimes narrowed to the point of near obliteration.

- Persons with idiopathic pulmonary arterial hypertension have characteristic **plexiform lesions,** in which endothelial proliferation forms multiple lumina within small arteries where they branch from a medium-sized artery

Pulmonary hypertension



Kumar et al: Robbins Basic Pathology, 9e.

- Clinical Features

1. Secondary pulmonary hypertension develop at any age.

- The clinical features reflect the underlying disease, usually pulmonary or cardiac, with accentuation of respiratory insufficiency and right sided heart strain

2. Primary pulmonary hypertension,

- Is almost always encountered in young adults,
- more commonly affect women, marked by fatigue, syncope (on exercise), dyspnea on exertion.
- Eventually severe respiratory insufficiency and cyanosis develop

- Death usually results from right sided heart failure (decompensated cor pulmonale) within 2 to 5 years of diagnosis.

- Some amelioration of the respiratory distress can be achieved by vasodilators , and continuous prostacyclin infusions may prolong life (months to years),
- but without lung transplantation the prognosis is still grim