QUESTION 43
Which one of the following asbestos-related diseases requires the greatest exposure to asbestos fibres for its development?
A. Bronchogenic carcinoma. – dose related exposure
B. Pleural plaques. – low intermittent exposure in pleura
C. Mesothelioma. – rare does not appear to be dose related
D. Pulmonary fibrosis. – related to intensity and duration
E. Diffuse pleural thickening. – less specific to asbestos sensitive pleura low intermittent

So the answer is either A or D – given A also has an additive dose response curve in the context of cigarette smoking the most correct answer is D

Answer: D

From Harrisons
Asbestosis is a diffuse interstitial fibrosing disease of the lung that is directly related to the intensity and duration of exposure. Except for its association with a history of exposure to asbestos (generally in a work setting), asbestosis resembles the other forms of diffuse interstitial fibrosis (Chap. 243). Usually, moderate to severe exposure has taken place for at least 10 years before the disease becomes manifest.

Physiologic studies reveal a restrictive pattern with a decrease in lung volumes. Flow rates are commonly reduced less than would be predicted on the basis of the volume reduction. An early sign of severe disease may be a reduction in diffusing capacity.

Pulmonary fibrosis may occur following sufficient exposure to any of the asbestiform fiber types. The fibrotic lesions result from proinflammatory effects of reactive oxygen species released from phagocytes reacting with transition metals on the surface of the fibers. The clinical manifestations are typical of those physical findings in any patient with pulmonary fibrosis.

Lung cancer (Chap. 75), either squamous cell carcinoma or adenocarcinoma, is the most frequent cancer associated with asbestos exposure. The excess frequency of lung cancer in asbestos workers is associated with a minimum lapse of 15 to 19 years between first exposure and development of the disease. Persons with more exposure are at greater risk of disease. In addition, there appears to be a significant multiplicative effect that leads to a far greater risk of lung cancer in persons who are cigarette smokers and have asbestos exposure than would be expected from the additive risk of each factor. To date, efforts to consider these high-risk individuals for special surveillance studies, including sputum cytologic examinations and repeated chest x-rays as frequently as every 4 to 6 months, have resulted in neither significant early detection nor prolonged survival once the lung cancer is found. The use of HRCT in such at-risk subjects is currently under investigation.

Mesotheliomas (Chap. 245), both pleural and peritoneal, are also associated with asbestos exposure. In contrast to lung cancers, these tumors do not appear to be associated with smoking. Relatively short-term asbestos exposures of 1 to 2 years or less occurring some 20 to 25 years in the past have been associated with the development of mesotheliomas (an observation that emphasizes the importance of obtaining a complete environmental exposure history). The risk for this type of tumor peaks 30 to 35 years after initial exposure. Since maximum exposure took place in the United States between 1930 and 1960, peak incidence of disease in men occurred in 1997, with a total of 2300 cases. Incidence is expected to decline over the next 30+ years to about 500 cases per year.

From E medicine
Pathogenesis
The pleura are more sensitive than pulmonary parenchyma to the effects of the fibers. Thus, pleural plaques develop after low, intermittent exposure, whereas asbestosis is associated with cumulative, high-level, long-term, continuous exposure in association with a definite dose-effect relationship. Nonmanual workers in industries involving asbestos, inhabitants of areas immediately surrounding asbestos mills, and families of asbestos workers have an increased incidence of mesothelioma. However, even with significant industrial exposure, asbestosis is unusual.
Pleural plaques are the most common manifestation of asbestos exposure, occurring after a latent period of approximately 20-40 years. A history of exposure can be elicited in more than 80% of patients. Histologically, pleural plaques consist of acellular collagen bundles that form a basket-weave pattern, which almost exclusively involves the parietal pleura. The plaques may contain chrysotile asbestos fibers.

The precise pathogenesis of pleural plaques remains undetermined. That they were caused by the mechanical effect of asbestos fibers piercing the visceral pleura (the scratching theory) was assumed. Currently, however, the fibers are believed to be transported to the parietal pleura via lymphatic channels, where they incite an inflammatory response. Plaques slowly grow over time, even after cessation of exposure, but they are not considered premalignant.

Calcification occurs later, often 30-40 years following exposure. Pleural plaques tend to occur in isolation without any other manifestations of asbestos-related disease; however, the converse is not true. Asbestosis is rarely seen in the absence of plaques.

Diffuse pleural thickening is less specific for asbestos exposure than the presence of pleural plaques, since thickening also may be seen following TB pleuritis, hemothorax and empyema. Usually, the latent period is approximately 15 years. The pathogenesis is unclear, but it is believed to be due to inflammation and fibrosis of the visceral pleural lymphatics, and it has been considered to be an extension of parenchymal fibrosis. Histologically, the appearances are similar, although in diffuse pleural thickening, fusion of the visceral and parietal layers and asbestos bodies (which are absent in pleural plaques) is profuse. Development of diffuse pleural thickening has a similar time line as plaque formation.

Benign asbestos-related pleural effusions are often the earliest manifestation of asbestos-related disease, typically occurring within 10 years of exposure. The effusions are exudative. Occasionally, they are hemorrhagic, but otherwise, their features are nonspecific. Effusions tend to be self-limiting, with a duration of a few months, but they can be chronic or recurrent. Diffuse pleural thickening not uncommonly develops following resolution of the effusion.

Fibers not cleared by mucociliary action are believed to be transported into the interstitium, where they form aggregates, usually at the level of the respiratory bronchiole. Research results suggest that the fibers stimulate the release of a collagenase inhibitor–like protein that locally disturbs the balance of collagen turnover, resulting in fibrogenic changes within the interstitium.

Asbestosis is usually seen when levels reach 10 million asbestos fibers per gram of pulmonary tissue. Asbestosis characteristically occurs following a latent period of 15-20 years, with a progression of disease even after exposure has ceased. Fibrosis first arises in and around the respiratory bronchioles, predominating in the subpleural portions of the lung in the lower lobes. This progresses to involve the alveolar walls, eventually causing honeycombing in a minority of patients.

Folded lung (also termed round atelectasis, pulmonary pseudotumor, or Blesovsky syndrome) specifically refers to an area of atelectatic lung adjacent to pleural thickening, with characteristic in-drawing of bronchi and vessels. Blesovsky first reported folded lung in 1966. Although folded lung is strongly associated with asbestos exposure, it may also be seen as a consequence of any inflammatory or infective organizing pleural exudate.

The presence of the effusion has been postulated to cause passive atelectasis, with infolding of the lung resulting in invagination of the adjacent pleura. This process causes tethering, which prevents reexpansion of the lung upon resolution of the effusion and which causes round atelectasis. A more accepted alternative explanation is that an insult to the pleura leads to localized inflammation and fibrosis, which results in volume loss and buckling of the underlying lung. Interestingly, the changes have been shown to resolve after decortication. The lingula is the most common site, followed by the middle and then the lower lobes, although lesions may be multiple and bilateral.

Malignant pleural mesothelioma is a rare neoplasm, accounting for less than 5% of pleural malignancies. Malignant pleural mesothelioma is strongly associated with asbestos exposure, particularly crocidolite exposure, although the association does not appear to be dose-related because significant numbers of cases occur after
trivial environmental or household exposure. No relevant history of any asbestos exposure is found in 20% of patients. The disease is frequently seen in the absence of any other manifestations of asbestos exposure and usually develops after a long latent period of 35-40 years.

Mesothelioma is 80% pleural and 20% peritoneal in origin. Pleural effusions are not a precursor of mesothelioma, but they often antedate development of malignancy. A confident diagnosis is often difficult to make and usually requires ultrastructural analysis and histochemical and immunohistochemical tests. Histologically, 3 forms of malignant mesothelioma are recognized: epithelial, mixed, and sarcomatous or mesenchymal. These must be differentiated from mesothelial hyperplasia and metastatic adenocarcinoma. The most common histologic subtype is epithelial, accounting for 50% of cases.

Bronchogenic carcinoma is estimated to develop in 20-25% of heavily exposed asbestos workers. Smoking has a cumulative effect, further increasing the risk of lung cancer to a factor of 90 versus a factor of 5 in exposed nonsmokers. Often, asbestos-related interstitial disease is associated; however, no correlation exists between the severity of asbestosis and the development of lung cancer. Furthermore, lung cancer has been reported in individuals without interstitial lung disease who are exposed to asbestos. A latency period of 25-35 years is usual. Histologically, the predominant subtype is bronchoalveolar cell carcinoma, but adenocarcinoma and squamous cell carcinoma also occur.

Associations between asbestos exposure and other cancers have been reported anecdotally. Carcinomas of the larynx, esophagus, stomach, colon, and a variety of lymphoid malignancies have been described.