B. Pathogenesis

The true pathophysiology of asbestos pleural effusions is unknown. As discussed above, animal and human studies have shown that asbestos fibers can migrate to the peripheral lung parenchyma and can be demonstrated in the pleural effusions of asbestos exposed workers (101–104). These data suggest transpleural seeding of fibers in the parietal pleura (105). Alternatively, in light of the role of lymphatic drainage of asbestos fibers (106), the asbestos fibers might also gain access to the pleura by retrograde lymphatic drainage (55,107). Once in the pleural space, the fibers themselves induce an inflammatory response that results in fluid exudation and clinically obvious effusions. For example, instillation of crocidolite into the pleural space promotes neutrophil chemotaxis (98). Influx of neutrophils and macrophages in the pleural space may help promote resolution of the inflammatory response to asbestos fibers, but also may contribute to pleural fibrosis (108). This low-grade pleural fibrotic reaction is hypothesized to result in altered lymphatic clearance or increased permeability of the parietal pleural. As has been described in the lung parenchyma itself, the pleural inflammatory reaction involves a cascade of inflammatory events involving both neutrophils and macrophages and the release of neutrophil chemotactic factors, oxygen free radicals, leukotrienes, cytokines, and growth factors (7,52,109). Inflammatory changes in both the parietal and visceral pleura are observed. It is noteworthy that pleural fluid eosinophilia has also been described in approximately one fourth of patients with asbestos pleural effusions, although the role these cells may play in pathogenesis remains open to speculation. The pleural pathology seen in individuals with these effusions is typical of other acute exudative pleural responses, with biopsies demonstrating nonspecific inflammation and fibrosis in those with effusions.

C. Clinical Presentation

Benign asbestos pleural effusion is a diagnosis of exclusion. Benign asbestos effusions are defined as effusions occurring in individuals who have pleural effusion with no other known causes and who have been directly or indirectly exposed to asbestos (73). The effusion is typically exudative and may be hemorrhagic. It is important to exclude other important causes, including infection, malignancy, and pulmonary embolism. One half to two thirds are asymptomatic (73,110), detected as an incidental finding on chest radiograph or thoracic computed tomography. Notably, however, such effusions can be associated with significant pleuritic pain, with or without fever. Of those who present clinically with these effusions, approximately 17–50% report pleurisy. Other symptoms include cough and dyspnea. The effusions may be detected in the presence or absence of other findings of asbestos-related disorders such as asbestosis or diffuse pleural thickening. Pleural plaques, especially with calcification, are infrequently seen in concert with asbestos pleural effusions, probably because the effusions occur so much earlier in the course of disease. In approximately 20% of cases, severe diffuse pleural thickening will ensue. While

this condition can spontaneously resolve in some cases, it should be considered a chronic condition, prone to recurrences and subsequent diffuse pleural thickening. The typical case will last for approximately one year, spontaneously clear, but then recur in approximately one third of individuals. The extent of pleural thickening often increases with each episode of effusion (75). Approximately 5% of patients with benign asbestos effusions will later develop malignant mesothelioma, necessitating careful clinical follow-up (98).

Cases are usually first suspected when a unilateral or, less commonly, bilateral pleural effusion is detected on chest radiograph. In one major series, 11% were large (>500 mL) effusions. Confirmation of this diagnosis is customarily made by thoracentesis, which reveals a typical exudative effusion profile, with elevated total protein, elevated total protein pleural:serum ratio, elevated total lactate dehydrogenase (LDH), pleural LDH:serum LDH ratio, normal glucose level, with elevated while cell count consisting principally of neutrophils, macrophages, and sometimes eosinophils (in one fourth of cases). Two thirds will contain mesothelial cells. As discussed above, the effusion is commonly hemorrhagic, even in the absence of malignancy. Nonetheless, when hemorrhagic effusions are detected, additional testing and careful clinical monitoring to rule out malignant mesothelioma or lung cancer should be considered. It is important to recognize that hemorrhagic effusions in asbestos workers do not necessarily implicate mesothelioma.

D. Treatment

There is no known treatment for asbestos pleural effusion that will alter the clinical course of this disorder. When effusions are large and associated with dyspnea, thoracentesis may help relieve shortness of breath. Anti-inflammatory medications may be prescribed for acute pleurisy symptoms. Diligent follow-up of these cases is important because of the small but significant risk of subsequent mesothelioma. Thoracoscopic pleural biopsy may be warranted in some cases to help clarify whether areas of pleural thickening are due to diffuse pleural fibrosis or malignancy. However, most cases may be followed clinically for signs of improvement, without invasive studies beyond the initial thoracentesis.

VII. Rounded Atelectasis

A. Epidemiology

Rounded atelectasis is one of the more unusual but distinctive pleural sequelae of asbestos exposure. While uncommon, it is important to recognize because it can mimic lung tumors (111) and provoke unnecessary medical and surgical interventions. The invagination of pleura with associated peripheral lobar collapse was first described in the French literature (112) in relation to infection and complications of therapeutic pneumothorax. Later, Blesovsky (113) made the link between "folded lung" and asbestos exposure when he observed this condition in a pipe fitter, a ship's engineer, and a laborer in a sugar refinery—

all of whom had exposures to asbestos and pleural plaques. While rounded atelectasis has been reported as a consequence of pulmonary infarction, Dressler's syndrome, and tuberculous effusion, asbestos is now recognized as the leading cause. Multiple published case series describe the condition and support its association with asbestos exposure, but do not provide good estimates of prevalence and incidence (111,113–122). By inference, rounded atelectasis must be a relatively late and rare event following asbestos exposure, given that Epler and colleagues reported no case in their review of 1135 asbestos workers' chest x-rays (73). Hillerdal estimated a yearly incidence of 5–15 cases per 100,000 in men older than age 40 in Sweden, although this denominator was not adjusted for history of asbestos exposure (121).

B. Pathogenesis

The pathogenesis of rounded atelectasis remains speculative. Hanke and Kretzschmar (123) suggested that the condition starts with a pleural effusion that allows infolding of a portion of the lung and the formation of a cleft around an atelectatic segment of lung. Schneider and others (116,117) have questioned this hypothesis because of the rarity with which pleural effusions are seen in cases of rounded atelectasis. However the process is initiated, the consequence is an infolding of the visceral pleura and of lung tissue subjacent to an area of pleural plaque or pleural thickening. The asbestos-induced pleural plaque itself probably contributes to the invagination of the visceral pleura. At time of thoracotomy, Blesovsky described a thick membrane covering the involved lung segment. Some cases had evidence of adhesions from the lung to the diaphragm with hyalinized plaques on the diaphragm. In another surgical series, predominantly visceral pleural thickening was observed in association with a pleuroparenchymal mass, as well as hyaline plaques on the parietal pleura (115). Histologically, the visceral and parietal pleura show fibrosis with clusters of reactive mesothelial cells and nonspecific inflammatory changes as well as laminated areas of collapsed pulmonary tissue. Some cases show evidence of interstitial pulmonary fibrosis with lymphocytic infiltration consistent with asbestosis, although in most cases the lung tissue itself appears collapsed but histologically normal (113,115).

C. Clinical Presentation

Patients with rounded atelectasis are often asymptomatic. Occasionally they may present with cough and either pleuritic or nonpleuritic chest pain. Most commonly, this condition is detected incidentally when a chest radiograph is obtained for purposes of screening for asbestos-related lung disease. The symptoms have been reported to resolve following decortication (115), although such surgical intervention is rarely warranted. Rounded atelectasis is a benign condition that can occur unilaterally or bilaterally, usually in the lower lobes.

On chest radiograph, rounded atelectasis is not necessarily round, but is a pleural-based curvilinear shadow most commonly seen along the posterior surface of the lower lobe, less frequently in the middle lobe or lingula

(111,113–117,119–121). It may have sharp or irregular borders, blurring most where the pleura intercalates with blood vessels and bronchi. Entrapment of adjacent lung may create a sweeping, "comet-tail" pattern as the segment of lung becomes compressed into the lung. These findings may be evident on chest radiograph, but usually a CT scan will be needed to provide greater confidence. Signs of lung collapse, such as diaphragmatic elevation, retraction of the fissure, or displaced hilum, are uncommon because rounded atelectasis rarely involves more than a few segments of a single lobe. Other disorders that may be confused with rounded atelectasis on chest radiograph include arteriovenous malformation, loculated effusion or empyema, mesothelioma, metastatic disease, and fibrinous pleurisy.

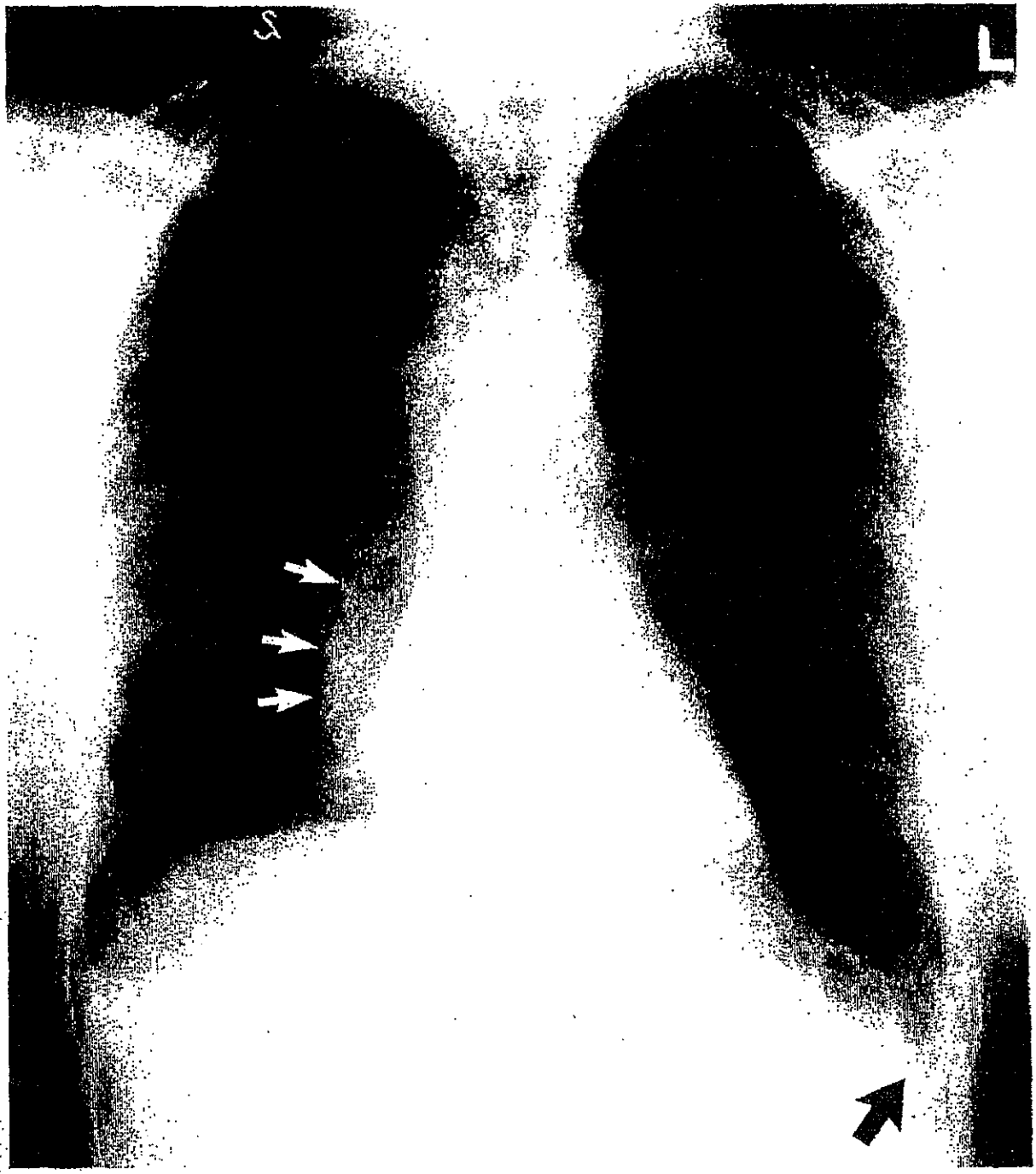
Rounded atelectasis is best defined by thoracic CT scan (Fig. 4) (116,119). Chronic pleural thickening will be seen adjacent to the curvilinear or oval mass. It can be shown to connect to the pleura. The degree of pleural thickening is greatest adjacent to the curvilinear mass, even in individuals who show diffuse pleural thickening or pleural plaques elsewhere in the chest.

The findings on CT scan are so characteristic that patients rarely require any form of invasive procedure to make the diagnosis. As discussed above, when the typical "comet sign" is observed, the only major consideration is to have ruled out other known causes of rounded atelectasis (116,119,124).

When followed longitudinally, the CT scan and chest radiograph will show no or very slow change over time (116,117,121). Hillerdal performed follow-up assessments in 61 of 64 patients (121), with an average observation period of 6 years. In this group, 55% had a known history of asbestos exposure. In the observation period, 24 remained stable with no other changes except slight worsening of pleural plaques. In 12 individuals, progressive diffuse pleural thickening and parenchymal changes consistent with asbestosis were observed over the next 2–15 years. Two of these individuals developed contralateral benign pleural effusions. An additional 23 patients developed bilateral progressive pleural fibrosis. The patients with rounded atelectasis who did not have asbestos exposure in Hillerdal's cohort remained stable over time, except for one case of spontaneous resolution. Notably, nine of the individuals—all of whom had asbestos exposure—died during the observation period: three from asbestosis and two due to pneumonia. Postobstructive pneumonia and pulmonary thrombosis in entrapped vessels have been reported and can result in death due to rounded atelectasis (125). On rare occasions malignancies have been masked by rounded atelectasis (126).

D. Treatment

There is no specific treatment for rounded atelectasis. In surgical series reported by Blesovsky (113) and later by Payne and colleagues (115), the surgeons were able to release the entrapped lung, resulting in reexpansion of the folded lung segment. In some individuals who had experienced chest pain, the pain resolved with this surgical intervention. In some instances the rounded atelectasis



(a)

Figure 4 In a patient with past tremolite exposure, diffuse pleural thickening with rounded atelectasis has developed over time. (a) On the chest radiograph, unilateral obliteration of the left costophrenic angle (black arrow) can be seen, which is typical for diffuse pleural thickening. In addition, this radiograph depicts a right-sided mass (white arrows) located medially and at the level of the heart. (b) Computed tomography demonstrates bilateral pleural-based masses associated with pleural thickening. The right-sided mass has a "comet tail" that is pathognomonic for rounded atelectasis.

(b)

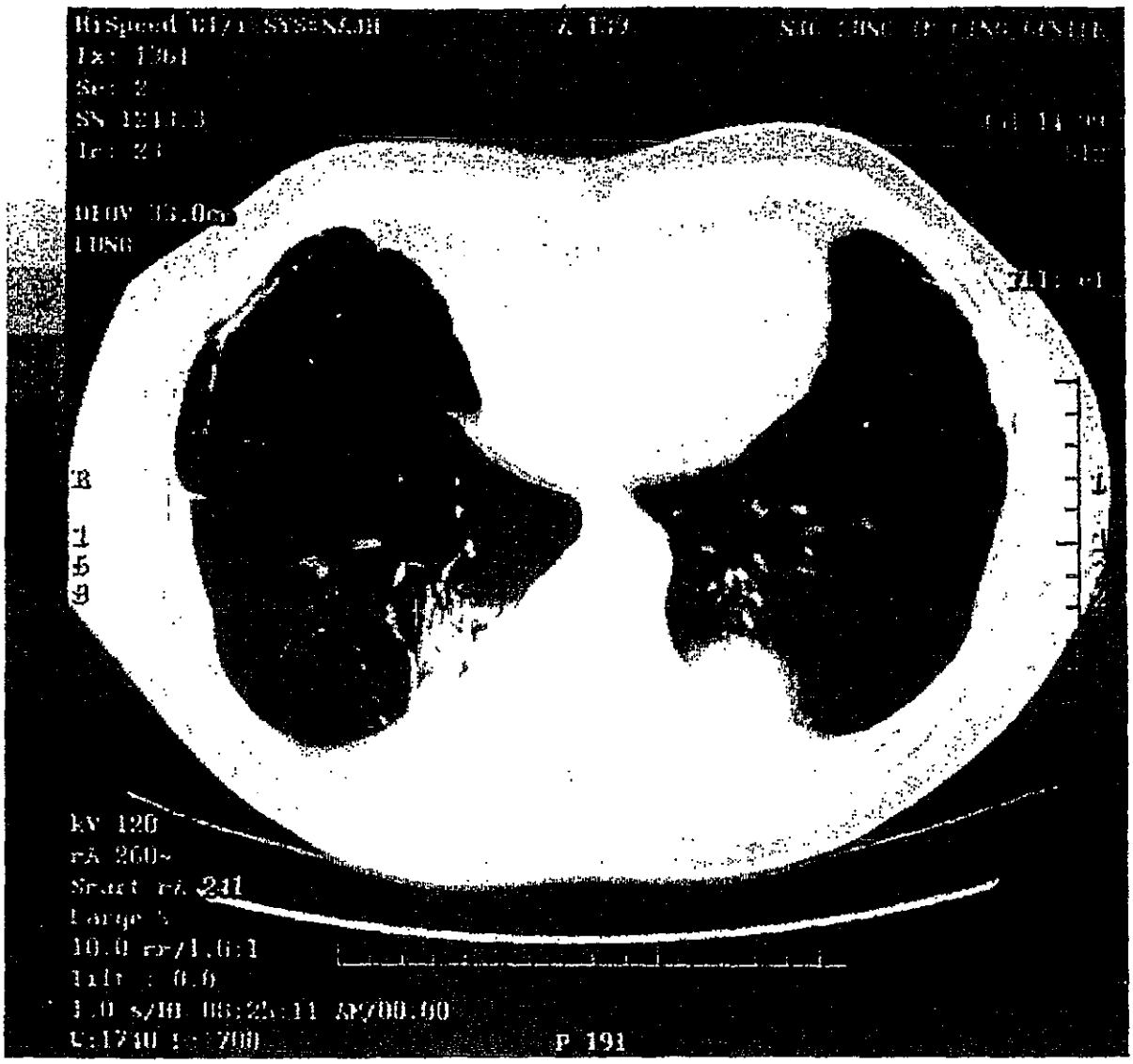


Figure 4 Continued.

reoccurred despite stripping of the lung from the pleura. Based on their experience, Payne et al. recommended thoracotomy with removal of the visceral pleura as a treatment for patients with intractable chest pain. However, when the typical CT findings are observed, unnecessary surgical intervention can be avoided in most cases. Patients should be monitored periodically for the stability of the lesion on chest radiograph or CT scan. Clinicians must remain alert for evidence of postobstructive pneumonia, intercurrent lung malignancy, mesothelioma, pulmonary thromboses, or hematoma due to rounded atelectasis, although these are all rare events.

References

1. Stanton MF, Layard M, Tegeris A, Miller E, May M, Morgan E, Smith A. Relation of particle dimension to carcinogenicity in amphibole asbestoses and other fibrous minerals. J Natl Cancer Inst 1981; 67:965–975.

2. Pott F. Some aspects on the doseometry of the carcinogenic potency of asbestos and other fibrous dusts. Staub Reinhold Luft 1978; 38:486.
3. King EJ. Effect of asbestos and asbestos and aluminium on the lungs of rabbits. Thorax 1946; 1:118.
4. Klosterkotter W. Experimentelle Untersuchungen über die Bedeutung der Faserlange für die Asbest-fibrose sowie Untersuchungen über die Beeinflussung der Fibrose durch Polyvinylpyridin-n-oxid. In: Biologische Wirkungen des Asbestos. Vol. 47. Berlin, 1968.
5. Scymczykiewicz K, Wiecek E. The effect of fibrous and amorphous asbestos on the collagen content in the lungs of guinea pigs. Proc. 13th International Conference of Occupational Hygiene, New York, 1960.
6. Hillerdal G. Nonmalignant pleural disease related to asbestos exposure. Clin Chest Med 1985; 6:141–152.
7. Robledo R, Mossman B. Cellular and molecular mechanisms of asbestos-induced fibrosis. J Cell Physiol 1999; 180:158–166.
8. Yegles M, Saint-Etienne L, Renier A, Janson X, Jaurand MC. Induction of metaphase and anaphase/telophase abnormalities by asbestos fibers in rat pleural mesothelial cells in vitro. Am J Respir Cell Mol Biol 1993; 9:186–191.
9. Jensen CG, Jensen LC, Rieder CL, Cole RW, Ault JG. Long crocidolite asbestos fibers cause polyploidy by sterically blocking cytokinesis. Carcinogenesis 1996; 17:2013–2021.
10. Desai R, Richards RJ. The absorption of biological macromolecules by mineral dusts. Environ Res 1978; 16:449–464.
11. Yazicioglu S, Ilcayto R, Balci K, Sayli BS, Yorulmaz B. Pleural calcification, pleural mesotheliomas, and bronchial cancers caused by tremolite dust. Thorax 1980; 35:564–569.
12. Kiviluoto R. Pleural calcification as a roentgenologic sign of non-occupational endemic enthophyllite-asbestosis. Acta Radiol 1960; 194:1–67.
13. Irwig LM, du Toit RS, Sluis-Cremer GK, Solomon A, Thomas RG, Hamel PP, Webster I, Hastie T. Risk of asbestosis in crocidolite and amosite mines in South Africa. Ann NY Acad Sci 1979; 330:35–52.
14. Bourbeau J, Ernst P, Chrome J, Armstrong B, Becklake MR. The relationship between respiratory impairment and asbestos-related pleural abnormality in an active work force. Am Rev Respir Dis 1990; 142:837–842.
15. Becklake MR. Asbestos and other fiber-related diseases of the lungs and pleura. Distribution and determinants in exposed populations. Chest 1991; 100: 248–254.
16. Rogan WJ, Ragan NB, Dinse GE. X-ray evidence of increased asbestos exposure in the US population from NHANES I and NHANES II, 1973-1978. National Health Examination Survey. Cancer Causes Control 2000; 11:441–449.
17. Rogan WJ, Gladen BC, Ragan NB, Anderson HA. US prevalence of occupational pleural thickening. A look at chest x-rays from the first National Health and Nutrition Examination Survey. Am J Epidemiol 1987; 126:893–900.
18. Hillerdal G. Pleural plaques in the general population. Ann NY Acad Sci 1991; 643:430–437.
19. Lee YC, Runnion CK, Pang SC, de Klerk NH, Musk AW. Increased body mass index is related to apparent circumscribed pleural thickening on plain chest radiographs. Am J Ind Med 2001; 39:112–116.
20. Fletcher DE. A mortality study of shipyard workers with pleural plaques. Br J Ind Med 1972; 29:142–145.