MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

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PLEURAL EFFUSIONS

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REFERENCES

REVIEWS

1. Ungerleider, J. Thomas: The diagnostic significance of pleural effusion. Dis. of Chest. 32:83-92, 1957.

2. Lowell, James R.: Pleural effusion: a study of the literature. J. of Okla. State Med. Assoc. 52:510-521, 1959.

3. Carr, David T., Edward H. Soule and F. Henry Ellis, Jr.: Management of pleural effusions. Med. Cl. of North America. 48:961-975, 1964.

4. Stead, William W. and John M. Sproul: Disease-a-Month. 3-48, July, 1964.

5. Therapy of Pleural Effusion - A Statement by the Committee on Therapy. Am. Rev. Resp. Dis. 97:479-483, 1968.

The statement by the Committee on Therapy of the American Thoracic Society (5) is only four pages long, but it contains a large amount of factual information. Of the general reviews, the one by Stead and Sproul (4) is probably the best.

ETIOLOGIES OF EFFUSIONS

6. Tinney, W. S. and A. M. Olsen: The significance of fluid in the pleural space: a study of 274 cases. Proc. Staff Meetings of the Mayo Clinic. 20:81-89, 1945.

7. Engelhardt, H. T. and J. L. Wilson: Some observations on the etiological significance of fluid in the pleural spaces. South. Med. J. 40:1023-1025, 1947.

8. Sahn, S. H., M. Leichtling, and H. E. Bass: The significance of pleural effusion in patients past the age of 50. New Engl. J. Med. 246:927-928, 1952.

9. Leuallen, Edmund C. and David T. Carr: Pleural effusion - A statistical study of 436 patients. New Engl. J. of Med. 252:79-83, 1955.

10. Myerson, R. M.: Pleural effusion. A statistical analysis of 100 cases in which thoracentesis was performed. Del. Med. J. 28:87-90, 1956.

11. Schless, James M., Harold N. Harrison and James A. Wier: The role of thoracotomy in the differential diagnosis of pleural effusion. U. S. Armed Forces Med. J. 10:1055-1078, 1959.

These articles give only a rough index of the frequency of causes of pleural effusions, since considerable selection bias enters each series. Of the 1294 patients included, 880 are from the Mayo Clinic in the articles by Tinney and Olsen (6) and Leuallen and Carr (9). It is likely that these series are heavily weighted against acute diseases. Engelhardt and Wilson's (7) study was from Charity Hospital in New Orleans; congestive heart failure and acute pneumonia made up somewhat more of their cases and neoplasms somewhat less than the cases from Mayo's. However, their cases were selected to be "non surgical". Sahn's (8) series came from institutions not admitting known cases of tuberculosis, and all of the patients were over 50 years old. Myerson's (10) cases were all men from a V. A. Hospital. Schless's (11) cases were all young army troops. In addition, the most recently published of the series was 1959; there may well have been a change in relative frequency of etiologies since that time. Nevertheless, these data are the most representative that are available.

TABLE I

Etiology of Pleural Effusions

Malignancy	496	38%
Congestive heart failure	163	13%
Tuberculosis	118	9%
Miscellaneous	118	9%
Pneumonia	90	7%
Undiagnosed	309	24%
TOTAL	1294	100%

According to these data, malignancies cause about one third of all pulmonary effusions. It should also be noted that 24% of the pleural effusions remained undiagnosed.

FLUID FORMATION AND REMOVAL

12. Allen, Lane, and Elkin Vogt: A mechanism of lymphatic absorption from serous cavities. Am. J. of Physiol. 119: 776-782, 1937.

13. Courtice, F. C. and W. J. Simmonds: Absorption of fluids from the pleural cavities of rabbits and cats. J. Physiol. 109:117-130, 1949.

14. Prentice, Theodore C., William Siri and Ethel E. Joiner: Quantitative studies of ascitic fluid circulation with tritium-labeled water. Am. J. Med. 13:668-673, 1952.

15. Courtice, F. C. and W. J. Simmonds: Physiological significance of lymph drainage of the serous cavities and lungs. Physiol. Rev. 34:419-448, 1954.

16. Clauss, Roy H., Hagop Yacoubian and Harold G. Barker: Dynamics of pleural effusions. Surg. Forum. 6:201-204, 1956.

17. Burgen, A. S. V. and P. B. Stewart: A method for measuring the turnover of fluid in the pleural and other serous cavities. J. Lab. Clin. Med. 52:118-124, 1958.

18. Agostoni, E., A. Taglietti and I. Setnikar: Absorption force of the capillaries of the visceral pleura in determination of the intrapleural pressure. Am. J. Physiol. 191:277-282, 1957.

19. Stewart, P. B. and A. S. V. Burgen: The turnover of fluid in the dog's pleural cavity. J. Lab. Clin. Med. 52:212-230, 1958.

20. Burke, Hugh E.: The lymphatics which drain the potential space between the visceral and the parietal pleura. Am. Rev. Tuberc. 79:52-65, 1959.

21. Wilson, John L., Chester M. Herrod, Gilbert L. Searle, Thomas V. Feichtmeir and William A. Reilly: The absorption of blood from the pleural space. Surg. 48:766-774, 1960.

22. Dumont, Allan E., Roy H. Clauss, George E. Reed, and David A. Tice: Lymph drainage in patients with congestive heart failure. New Engl. J. Med. 269:949-952, 1963.

23. Stewart, P. B.: The rate of formation and lymphatic removal of fluid in pleural effusions. J. Clin. Invest. 42:258-262, 1963.

24. Agostoni, E. and J. Mead: Statics of the respiratory system. Handbook of Physiology. Section 3. Respiration. Vol. 1, ed. by W. D. Fenn and H. Rahn. Washington, D. C., American Physiological Society, 387-409, 1964.

25. Rodbard, S. and S. Kira: Filtration into the pleural and airway spaces. Jap. Heart J. 8:728-733, 1967.

26. Agostoni, E., E. D'Angelo and G. Roncoroni: The thickness of the pleural liquid. Resp. Physiol. 5:1-13, 1968.

27. Agostoni, E., G. Miserocchi and M. V. Bonanni: Thickness and pressure of the pleural liquid in some mammals. Resp. Physiol. 6:245-256, 1969.

28. Agostoni, Emilio and Edgardo D'Angelo: Thickness and pressure of the pleural liquid at various heights and with various hydrothoraces. Resp. Physiol. 6:330-342, 1969.

The formation of pleural fluid is determined by the hydraulic and colloid-osmotic pressures across the pleural membranes. The visceral pleura is supplied mainly by capillaries from the pulmonary artery which have a pressure of approximately 11 cm H_2O. Since the pressure on the surface of the visceral pleura is approximately minus 5 cm H_2O, the hydraulic pressure across the visceral pleura is approximately 16 cm H_2O tending to filter liquid into the pleural space. Since there is some leak of large molecules, the pleural liquid contains approximately 1.5 gms per cent protein causing the colloid-osmotic pressure of the pleural liquid to be about 8 cm H_2O. Since the plasma colloid-osmotic pressure is about 34 cm H_2O the colloid-osmotic pressure across the visceral pleura is 26 cm H_2O. Therefore, the visceral pleura absorbs protein free liquid under a pressure of 26 - 16 = 10 cm H_2O. Experimental evidence from dogs by Agostoni, et al (18) indicates that the pleural surface of the lung absorbs saline with a pressure related to these forces. The parietal pleura is supplied by capillaries from the systemic circulation which have a pressure of about 30 cm H_2O. Since the other factors are the same, a pressure of approximately 9 cm H2O drives liquid from the parietal pleura into the pleural space. The balance between absorption and filtration is determined by the relative resistances of the two membranes, and hence by the relatively greater vascularity of the visceral pleura. This would lead to a complete removal of the pleural liquid if it were not for local stretching of the pleural membrane when the amount of liquid is reduced to a minimum. Such stretching of the membrane opposes a further reduction of the amount of liquid in the pleural space by lowering the pressure of the pleural liquid. This total mechanism causes a turnover of fluid in the pleural space of 30 to 75% per hour (17) a value

similar to that found in the peritoneal cavity (14).

The protein that escapes from the pleural capillaries is re-absorbed by the pleural lymphatics. The absorptive surface is primarily the lower mediastinum and the parietal pleura. Evidently there is little lymphatic absorption on the visceral pleura. Lymphatic flow averages 0.37 mg/kilogram of body weight/hour for each hemithorax. Since fluid movement in lymphatics is dependent on the pumping force of the respiratory movements, lymphatic flow is accelerated by hyperventilation and retarded by hypoventilation.

An excess of pleural fluid, a pleural effusion, may be produced by alterations in any of the factors controlling inflow or outflow of normal fluid. Diseases that increase the hydraulic pressure, heart failure, or decrease the colloid-osmotic pressure, hypoalbuminemia, cause an excess of fluid by Starling mechanisms. Factors that increase capillary permeability, malignancy or tuberculosis, may cause such an increase of protein containing fluid that the lymphatics are unable to keep up with the burden; the increase osmotic pressure of the pleural fluid results in the filtration of more liquid into the pleural space. Factors that decrease the efficiency of the lymphatics, lymphomas, may prevent re-absorption of the normal amount of protein, and hence lead to pleural effusion.

CONSTITUENTS OF FLUID

29. Carr, David T. and Marschelle H. Power: Clinical value of measurements of concentration of protein in pleural fluid. New Engl. J. Med. 259:926-927, 1958.

30. Feldstein, Arthur M., Joseph Samachson and Herta Spencer: Levels of calcium, phosphorus, alkaline phosphatase and protein in effusion fluid and serum in man. Amer. J. Med. 35:530-535, 1963.

31. Pillay, V. K. G.: Total proteins in serous fluids in cardiac failure. South African Med. J. 39:142-143, 1965.

32. Chandrasekhar, Arcot J., Angus Palatao, Alvin Dubin and Harold Levine: Pleural fluid lactic acid dehydrogenase activity and protein content. Arch. Intern Med. 123:48-50, 1969.

25% malig effusions have protein < 3.0 gm%

Freely diffusible ions such as sodium are found in the same concentration in pleural fluid as in plasma. Considerable attention has been paid to non diffusible substances to aid in the diagnosis of pleural effusions. The most widely used measurement is undoubtedly the protein content of the pleural fluid. Although it is recognized that the protein concentration will not differentiate between malignancy and tuberculosis, it is widely used to separate transudates (pleural fluid related to hydraulic or colloid-osmotic problems) from exudates (pleural fluid due to increased capillary permeability or poor lymphatic re-absorption). The dividing line between transudates and exudates is generally said to be 3.0 grams per cent after the original work of Carr and Power (29). However, it is apparent that the protein concentration is not as reliable as was originally thought, and there is a great deal of overlap of values above and below 3.0 grams per cent. It should be particularly noted that diuretic therapy causes the protein content of effusions to rise in patients with congestive heart failure, and the protein content is also higher in patients with long standing heart failure.

33. Wroblewski, Felix: The clinical significance of alterations in lactic dehydrogenase activity of body fluids. Amer. J. Med. Sci. 234:301-312, 1957.

34. Wroblewski, Felix and Rita Wroblewski: The clinical significance of lactic dehydrogenase activity of serous effusions. Ann. Intern. Med. 48:813-822, 1958.

35. Kirkeby, K. and H. Prydz: Lactic dehydrogenase activity in pleural and peritoneal effusions. Scan. J. Clin. and Lab. Invest. 11:185-189, 1959.

36. Vincente de Torregrosa, Mercedes : Results of lactic dehydrogenase determinations in benign and malignant effusions. Amer. J. Med. Sci. 238:552-556, 1959.

37. Wroblewski, Felix: The significance of alterations in lactic dehydrogenase activity of body fluids in the diagnosis of malignant tumors. Cancer 12:27-39, 1959.

38. Erickson, Russell J.: Lactic dehydrogenase activity of effusion fluids as an aid to differential diagnosis. J. A. M. A. 176:794-796, 1961.

39. Horrocks, J. E., J. King, A. P. B. Waind and J. Ward: Lactate dehydrogenase activity in the diagnosis of malignant effusions. J. Clin. Path. 15:57-61, 1962.

40. Brauer, Mark J., Michael West and Hyman J. Zimmerman: Serum enzymes in disease. Cancer. 2:533-541, 1962.

Initial reports by Wroblewski indicated that the lactic dehydrogenase activity of pleural effusion caused by cancer were almost always higher than LDH activity in the serum of the same patient. However, subsequent studies have failed to support this thesis, and neither the absolute pleural fluid concentration of LDH or the pleural fluid-blood ratio of LDH can be relied on to differentiate pleural effusions due to cancer from other effusions due to increased capillary permeability.

41. Calnan, W. L., J. O. Winfield and Mary F. Crowley: Diagnostic value of the glucose content of serous pleural effusions. Brit. Med. J. 1:1239-1240, 1951.

42. Carr, David T. and Marschelle H. Power: Pleural fluid glucose with special reference to its concentration in rheumatoid pleurisy with effusion. Dis. Chest. 37:321-324, 1960.

43. Russakoff, A. H., Charles A. LeMaistre and Hal J. Dewlett: An evaluation of the pleural fluid glucose determination. Amer. Rev. of Resp. Dis. 85:222-223, 1962.

44. Carr, David T. and Warren F. McGuckin: Pleural fluid glucose. Amer. Rev. Resp. Dis. 97:302-305, 1968.

The pleural fluid glucose is approximately the same as the blood glucose in most situations, but it lags behind changes in blood glucose by one to three hours. Statistically, the pleural fluid sugar in cases of tuberculous effusion is lower than in other types of effusion. However, it is usually not so low as to be helpful in diagnosis. In pleural effusions due to rheumatoid arthritis, the pleural fluid glucose is usually extremely low (less than 10 mg per cent). The cause for the low glucose in this disease is not known, although it has been demonstrated that there is no glycolytic substance in the pleural fluid (44). Although extremely low glucose values are considered to be diagnostic of rheumatoid pleural effusion, Carr, Soule and Ellis (3) mention that they have seen three cases of malignant effusion with extremely low glucose values. amylase ↑↑ in pancreatitis & remains longer.

45. Yam, Lung T.: Diagnostic significance of lymphocytes in pleural effusions. Ann. Intern. Med. 66:972-982, 1967.

Bloody pleural effusion most likely malig. esp. > 100,000.

Fluids caused by hydraulic or osmotic abnormalities tend to have few cells, while those due to altered capillary permeability or decreased lymphatic absorption tend to be rich in cells. In this excellent study an effusion was called lymphocytic when it contained lymphocytes in percentages of 50 or more. Effusions characterized by lymphocytosis were found in 47 of the 49 caused by tuberculosis; 14 of the 15 by lymphoma, 28 of the 51 by carcinoma; 18 of the 43 by cardiopulmonary diseases; 3 of the 30 effusions by pulmonary infections; 10 of the 23 from patients with unknown or uncertain diagnosis; and 3 of the 9 from the miscellaneous group consisting of one systemic lupus erythematosus, one cirrhosis of the liver, and one infectious mononucleosis.

EFFECT ON RESPIRATION

46. Jones, Dean B.: Basal pleural fluid accumulations resembling elevated diaphragm. Radiology 50:227-233, 1948.

47. Rothstein, Emil and Francis B. Landis: Infrapulmonary pleural effusion simulating elevation of the diaphragm. Amer. J. Med. 8:46-52, 1950.

48. Richter, Curt P.: The physiology and cytology of pulmonary edema and pleural effusion produced in rats by alpha-naphthyl thiourea (antu). J. of Thoracic Surg. 23:66-91, 1952.

49. Wade, O. L.: Movements of the thoracic cage and diaphragm in respiration. J. Physiology 124:193-212, 1954.

50. Wilson, John W.: Diagnosis of infrapulmonary pleural effusion. J. A. M. A. 158:1423-1427, 1955.

51. Barry, William F., Jr.: Infrapulmonary pleural effusion. Radiology 66:740-743, 1956.

52. Felson, B.: Fundamentals of Chest Roentgenology, Philadelphia, W. B. Saunders Co., 1960, p 221.

53. Yoo, Ok Hi and Er Yi Ting: The effects of pleural effusion on pulmonary function. Amer. Rev. of Resp. Dis. 89:55-63, 1964.

mechanics

54. Mulvey, R. B.: The effect of pleural fluid on the diaphragm. Radiology 84:1080-1086, 1965.

55. Swingle, J. D., R. Logan and J. H. Juhl: Inversion of the left hemidiaphragm. J. A. M. A. 208:863-864, 1969.

56. Campbell, E. J. Moran: The Respiratory Muscles and The Mechanics of Breathing. Year Book Publishers, Chicago, 1958.

Many effusions do not take the characteristic radiographic picture of a concave density in the costophrenic sulcus, but instead they layer over the surface of the diaphragm below the inferior margin of the lung. These subpulmonic effusions micmic the contour of the diaphragm closely and they frequently are not diagnosed unless the patient is placed in a lateral decubitus position which causes the effusion to flow up the lateral chest wall. It is possible that all effusions start in this manner, but this has not been proven.

In some patients the weight of the effusion causes the diaphragm tq become flattened. Indeed, on the left side the diaphragm may occasionally become inverted. This may be diagnosed radiographically by flattening or displacement of the gas bubble in the stomach.

Approximately 70% of normal gas movement into the lungs is caused by the downward movement of the diaphragm. In addition, the vector of force as the diaphragm contracts is such that it causes a significant part of the thoracic cage expansion during inspiration. Both of these functions are lost when the diaphragm becomes flattened. If the diaphragm becomes inverted, not only are these functions destroyed, but the diaphragm moves paradoxically upward during inspiration causing the volume of that hemithorax to decrease. These factors lead to marked impairment of ventilatory function out of proportion to the amount of lung volume compressed by the pleural effusion. In such patients, the removal of enough fluid to allow the diaphragm to assume its domed position will cause marked improvement of pulmonary function even if there is a large volume of fluid remaining in the thorax.

PLEURAL BIOPSY

57. Sutliff, W. D., Felix Hughes and Marion L. Rice: Pleural Biopsy. Dis of Chest. 26:551-557, 1954.

58. DeFrancis, Nicholas, Emanuel Klosk and Edwin Albano: Needle biopsy of the parietal pleura. New Engl. J. Med. 52:948-949, 1955.

59. Heller, Paul, William F. Kellow and Bernhard Chomet: Needle biopsy of the parietal pleura. New Engl. J. Med. 255:684-690, 1956.

60. Donohoe, Robert F., Sol Katz and Mary J. Matthews: Pleural biopsy as an aid in the etiologic diagnosis of pleural effusion: review of the literature and report of 132 biopsies. Ann. Int. Med. 48:344-362, 1958.

61. Abrams, Leon D.: A pleural-biopsy punch. Lancet 1:30-31, 1958.

62. Weiss, William: Needle biopsy of the parietal pleura in tuberculosis. Amer. Rev. Tuberc. 78:17-20, 1958.

63. Samuels, Melvin L, Jacob W. Old and Clifton D. Howe: Needle biopsy of pleura. Cancer 2:980-983, 1958.

64. Misra, S. S.: Pleural biopsy with the Vim-Silverman needle. Tubercle 40:54-57, 1958.

65. Cope, Constantin: New pleural biopsy needle. J. A. M. A. 167:1107-1108, 1958

66. Mestitz, Paul, M. J. Purves and A. C. Pollard: Pleural biopsy in the diagnosis of pleural effusion. Lancet 2:1349-1353, 1958.

67. Leggat, P. O.: Needle biopsy of the parietal pleura in malignant disease. Brit. Med. J. 2:478-479, 1959.

68. Richert, Joel H., James A. Wier, John M. Salyer and James C. Beyer. The reliability of tissue diagnosis of pleurisy: a preliminary report. Ann. Int. Med. 52:320-325, 1960.

69. Shaw, Richard K.: Biopsy of the parietal pleura. Amer. J. Med. Sci. 241:593-601, 1961.

70. Niden, Albert H., Benjamin Burrows, John E. Kasik, and William R. Barclay. Percutaneous pleural biopsy with a curetting needle. Amer. Rev. Resp. Dis. 84:37-41, 1961.

71. Carpenter, R. L. and James R. Lowell: Pleural biopsy and thoracentesis by a new instrument. Dis. of Chest. 40:182-186, 1961.

72. Hampson, F. and A. J. Karlish: Needle biopsy of the pleura in the diagnosis of pleural effusion. Quar. J. Med. 30:249-255, 1961.

73. Reese, Owen, Ross L. McLean and Tom D. Raaen: Acid-fast bacilli in pleural biopsy specimens. Arch. of Intern. Med. 108:438-441, 1961.

74. Thiruvengadam, K. V., V. C. Anguli, N. Madanagopalan and Solomon Victor: Etiologic diagnosis of pleural effusion by punch biopsy of the parietal pleura. Dis. of Chest 42:529-533, 1962.

75. Sison, Benjamin S.: Needle biopsy of the parietal pleura in patients with pleural effusion. Brit. Med. J. 2:298-300, 1962.

76. Hanson, Gillian and Trevor Phillips: Pleural biopsy in diagnosis of thoracic disease. Brit. Med. J. 2:300-303, 1962.

77. Levine, Harold and David W. Cugell: Blunt-end needle biopsy of pleura and rib. Arch. Int. Med. 109:516-525, 1962.

78. Schools, George S.: Needle biopsy of parietal pleura. Texas State J. Med. 59:1056-1061, 1963.

79. Conklin, E. F., C. B. Yeoh, J. M. Jones, J. A. Malcolm and J. M. Ford: Internal-Mammary-lymph-node biopsy as a diagnostic aid in pleural effusion. New Engl. J. Med 271:1346-1348, 1964.

80. Rao, Nakhate V., Peron O. Jones, Donald Greenberg, David Bahar, Alberto O. Daysog, Jr., H. Irving Schweppe, Jr. and Daniel E. Jenkins: Needle biopsy of parietal pleura in 124 cases. Arch. of Int. Med. 115:34-41, 1965.

81. Scharer, Lawrence and John H. McClement: Isolation of tubercle bacilli from needle biopsy specimens of parietal pleura. Amer. Rev. of Resp. Dis. 97:466-468, 1968.

Needle biopsies of the pleura were first performed by DeFrancis, Klosk and Albano in 1955. The Vim-Silverman biopsy needle was the first to be used, but most physicians now use the Harefield needle described by Abrams, or the needles described by Cope or Carpenter. With any of these latter needles the procedure is simple, and adequate tissue can be obtained by even an inexperienced operator. In the 1,409 reported biopsies in which information is available, there have been 57 complications (4%) despite the fact that many of these biopsies were performed by persons in training. Only 3 of the reported complications were serious enough to require treatment. Thus, the procedure is as safe as a thoracentesis without biopsy. These results refer to pleural biopsies when pleural effusion is present. Biopsy in the absence of fluid is more likely to cause complications, and is less likely to produce a diagnosis.

Since various authors use different indications for biopsy the percentage of biopsies leading to diagnosis would be misleading.

One does not expect a biopsy to be helpful in a patient with effusion due to a hydraulic or colloid-osmotic problems. A more reasonable means of looking at the data is to note the number of biopsies that were diagnostic in patients with exudative pleural effusion in whom the diagnosis was ultimately made by some means.

TABLE 2

Results of Needle Biopsy of the Pleura

	Number of cases	Biopsy diagnostic	% diagnosis
Tuberculosis	526	341	64.8
Malignancy	461	270	58.5

The yield in patients with tuberculous effusions may be increased by culturing part of the biopsy specimen for Mycobacterium tuberculosis. In malignancy, the pleural fluid cytology is positive in about 50% of the cases, and the biopsy is positive in about 50% of the cases in which the cytology is negative. Thus, in combination, the diagnosis can be made approximately 75% of the time. It must be stressed that a positive biopsy is diagnostic in these and other conditions, but that a negative biopsy does not exclude these possibilities.

SPECIFIC CAUSES

82. Paterson, Robert C.: The pleural reaction to inoculation with tubercle bacilli in vaccinated and normal guinea pigs. Amer. Rev. Tuber. 1:353-371, 1917.

83. Pinner, Max: A note on exudative and productive processes in pleural tuberculous infection. Amer. Rev. Tuberc. 17:627-633, 1928.

84. Sherwood, Marion B.: Some cellular reactions and immunity in tuberculosis. J. of Immunol. 17:481-500, 1929.

85. Gaarde, Fred W.: The prognosis of pleurisy with effusion. J. A. M. A. 95:249-250, 1930.

86. Kallner, Sixten Karlson: On the prognosis of Exudative Pleurisy I. Acta Medica Scandinavica 92:549-568, 1937.

87. Bonilla, J. L, Jr.: Pleurisy with effusion. Amer. Rev. Tuberc. 46:59-66, 1942.

88. Farber, Jason E.: Prognosis in cases of serofibrinous pleurisy. New Engl. J. Med. 228:784-787, 1943.

89. Jones, Edward G. and Myrtle Dooley: Tuberculous pleurisy with effusion. Amer. Rev. Tuberc. 54:133-139, 1946.

90. Thompson, Brian C.: Pathogenesis of pleurisy with effusion. Amer. Rev. Tuberc. 54:349-363, 1946.

91. Kraft, Joseph R.: The diagnostic problem of primary pleural effusions. Amer. Rev. Tuberc. 59:259-269, 1949.

92. Falk, Abraham: The prognostic significance of idiopathic pleural effusion. Dis. of Chest. 18:542-561, 1950.

93. Stead, William W., Alfred Eichenholz and Hans-Karl Stauss: Operative and pathologic findings in 24 patients.with syndrome of idiopathic pleurisy with effusion, presumably tuberculous. Amer. Rev. Tuberc. 71:473-502, 1955.

94. Roper, William H. and James J. Waring: Primary serofibrinous pleural effusion in military personnel. Amer. Rev. Tuberc. 71:616-634, 1955.

95. Filler, Juan: Comparison of pulmonary function following tuberculous pleural effusion treated with or without adrenal corticosteroids. Amer. J. of Dis. Child. 102:735-736, 1961.

96. Sohn, Esuk, Bin Hwang and Taik Koo Yun: The effect of chemotherapy on tuberculous pleurisy. Amer. Rev. Resp. Dis. 86: 197-210, 1962.

97. Arrington, Clifton W., Joseph A. Hawkins, Joel H. Richert and Alan R. Hopeman: Management of undiagnosed pleural effusions in positive tuberculin reactors. Amer. Rev. Resp. Dis. 93:587-593, 1966.

98. Allen, J. C. and M. A. Apicella: Quantitative study of extravascular proteins in a hypersensitivity reaction. Clin. Res. 14:291, 1967.

99. Damany, S. J., K. T. Shah: Treatment of pleural effusion with and without triamcinolone in addition to usual antituberculosis chemotherapy. J. Ind. Med. Assoc. 51:591-593, 1968.

100. Allen, James C. and Michael A. Apicella: Experimental pleural effusion as a manifestation of delayed hypersensitivity to Tuberculin PPD. J. of Immunol. 101:481-487, 1968.

101. Levine, Harold, Paul B. Scanto, and David W. Cugell: Tuberculous pleurisy. Arch. Int. Med. 122:329-332, 1968.

Tuberculous pleural effusions are caused by spillage of tubercle bacilli into the pleural space from pulmonary parenchymal lesions located adjacent to the visceral pleura. Lesions have been demonstrated to be present at time of thoracotomy even though they are not apparent on the chest x-ray. The effusion is a manifestation of delayed hypersensitivity and experimentally may be produced in sensitized animals even with dead tubercle bacilli. Since the effusion is a manifestation of delayed hypersensitivity, the tuberculin skin test is almost invariably positive. Patients are usually reactive to intermediate strength PPD, although a few are reactive only to second strength PPD. Evidently only a few tubercle bacilli are necessary to produce the effusion, and direct smear of the effusion fluid rarely reveals acid fast organisms. Reported series vary in the number of effusions that are positive for tubercle bacilli on culture, but at most this amounts to 25%. Since the effusion is caused by bacilli fortuitously falling into the pleural space, bilateral effusions are virtually never seen simultaneously. On rare occasions, an effusion occurs on one side and is followed by an effusion on the opposite side at a later date. When a patient develops clinical pulmonary tuberculosis after an effusion, the tuberculosis does not necessarily occur on the same side as the effusion.

In 10 series of patients with "idiopathic" pleural effusions reported before 1950, 780 of 2,155 (36%) patients developed overt pulmonary tuberculosis following the effusion; 80% occurred within 5 years of the pleural effusion. The work up of the patients in these series frequently did not include reports of skin testing. In two series comprising 241 patients with idiopathic pleural effusions who were skin test positive for PPD, 113 (46.8%) developed pulmonary tuberculosis following the episode of effusion. One-hundred of these patients were followed for only 1 year, and hence the incidence of subsequent pulmonary tuberculosis is minimal. Thus, a patient with an undiagnosed pleural effusion who is skin test positive has a very high likelihood of subsequently developing clinical pulmonary tuberculosis. Such patients should be considered to have tuberculosis unless a specific etiology can be made. Our custom has been to treat such patients with 300 mgm of INH daily for at least 18 months. This treatment is not agreed to by everyone, and many suggest that the patients receive

double drug therapy as if they had overt pulmonary parenchymal disease.

102. Bethune, Norman: Pleural poudrage. J. Thoracic Surg. 4: 251-261, 1935.

103. Paul, John S., E. J. Beattie, Jr. and Brian Blades: Lung function studies in poudrage treatment of recurrent spontaneous pneumothrorax. J. Thoracic Surg. 22:52-61, 1957.

104. Ultmann, John E., George A. Hyman, Charles Crandall, Horst Naujoks and Alfred Gellhorn: Triethylene-thiophosphoramide (Thio-Tepa) in the treatment of neoplastic disease. Cancer. 10:902-911, 1957.

105. Knowles, John H., Richard Gorlin and Clifford F. Storey: Effects of pleural talc poudrage on pulmonary function. J. Thoracic Surg. 34:250-256, 1957.

106. Weeth, John B. and Albert Segaloff: Diuretic therapy for malignant effusion. J. A. M. A. 181:258-260, 1962.

107. Weisberger, Austin S.: Direct instillation of nitrogen mustard in the management of malignant effusions. Ann. New York Acad. Sci. 68:1091-1096, 1958.

108. Dybicki, Jerzy, Oscar J. Balchum and George R. Meneely: Treatment of pleural and peritoneal effusion with intra-cavitary colloidal radiogold (Au^{198}). Arch. Int. Med. 104:802-815, 1959.

109. Haupt, George J., Rudolph C. Camishion and John Y. Templeton III: Treatment of malignant pleural effusions by talc poudrage. J. A. M. A. 172:918-921, 1960.

110. Gellhorn, Alfred, Jack Zaidenweber, John Ultmann and Erich Hirschberg: The use of atabrine (Quinacrine) in the control of recurrent neoplastic effusions. Dis of the Chest 39:165-175, 1961.

111. Jensik, R., J. E. Cagle, Jr., F. Milloy, C. Perlia, S. Taylor, S. Kofman, and E. J. Beattie, Jr.: Pleurectomy in the treatment of pleural effusion due to metastatic malignancy. J. Thoracic and Cardiovas. Surg. 46:322-330, 1963.

112. Starkey, George W. B.: Recurrent malignant pleural effusions, New Engl. J. of Med. 270:436-438, 1964.

Malignant pleural effusions are most commonly caused by carcinoma of the lung, carcinoma of the breast or lymphoma. They are characterized by their tendency to recur rapidly. Since the effusion frequently causes dyspnea, the physician is forced into performing repeated thoracentesis. However, this is not only inconvenient for the patient but also causes marked loss of protein. As the references indicate, various approaches have been made to decreasing the rate of formation of the pleural effusion, but none of these are entirely satisfactory. The proponents of each technique claim about 50% success in preventing reformation of the fluid. Recently we have been using the technique of thoracostomy tubes with complete drainage of all fluid for a period of a few days in the hope that the parietal and visceral pleura will grow together and obliterate the space in which fluid forms. If this fails, we have usually gone on to nitrogen mustard ▲ 0.4 mg/kg "5-FU" better

113. Meigs, Joe V., S. H. Armstrong, and H. H. Hamilton: A further contribution to the syndrome of fibroma of the ovary with fluid in the abdomen and chest, Meigs' syndrome. Amer. J. of Ob-Gyn 46:19-37, 1943.

114. McKay, D. G., H. J. Sparling, Jr. and S. L. Robbins: Cirrhosis of the liver with massive hydrothorax. Arch. Int. Med. 79:501-509, 1947.

115. Morrow, C. S., Milton Kantor and Robert N. Armen: Hepatic hydrothorax. Ann. of Int. Med. 49:193-203, 1958.

116. Clinicopathologic Correlation. New Engl. J. Med. 268: 320-325, 1963.

117. Johnston, Robert F. and Rodolfo V. Loo: Hepatic hydrothorax. Ann. of Int. Med. 61:385-401, 1964.

Patients with ascites frequently develop pleural effusions which may be unilateral or bilateral. The pleural fluid originates in the abdomen and traverses the diaphragm either through the lymphatics or through small microscopic communications. It is likely that all patients with ascites have movement of fluid from abdomen to chest, but only those whose re-absorptive mechanisms in the chest are impaired develop clinical effusion. The case reported as a CPC in the New England Medical Journal is of particular interest, since the patient had massive pleural effusions, presumably due to cirrhosis, but had no demonstrable ascites. In the discussion of the case three additional such cases are mentioned but not documented.

118. Emerson, Peter A.: Pleural effusion complicating rheumatoid arthritis. Brit. Med. J. 1:428-429, 1956.

119. Horler, A. R. and Malcolm Thompson: The pleural and pulmonary complications of rheumatoid arthritis. Ann. of Int. Med. 51:1179-1203, 1959.

120. Lee, Philip R., Harold C. Sox, Francis S. North and George A. Wood: Pleurisy with effusion in rheumatoid arthritis. Arch of Int. Med. 104:634-639, 1959.

121. Carr, David T. and John G. Mayne: Pleurisy with effusion in rheumatoid arthritis, with reference to the low concentration of glucose in pleural fluid. Amer. Rev. Resp. Dis. 85:345-349, 1962.

122. Ward, Richard: Pleural effusion and rheumatoid disease. Lancet 2:1336-1338, 1961.

123. Berger, Herbert W. and Stanley G. Seckler: Pleural and pericardial effusions in rheumatoid disease. Ann. of Int. Med. 64:1291-1297, 1966.

124. Champion, G. D., M. R. Robertson and R. G. Robinson: Rheumatoid pleurisy and pericarditis. Ann. of Rheumat. 27: 521-530, 1968.

125. Nosanchuk, Jerome S. and Bernard Naylor: A unique cytologic picture in pleural fluid from pa tients with rheumatoid arthritis. Amer. J. of Clin. Path. 50:330-335, 1968.

126. Levine, Harold, Martin Scanto, Hans G. Grieble, Gerhard L. Bach and Truman O. Anderson: Rheumatoid factor in non-rheumatoid pleural effusions. Ann. Int. Med. 69:487-492, 1968.

Pleural effusions in the course of rheumatoid arthritis are evidently fairly common, and may occur even before the arthritis is manifest. An extremely low pleural fluid glucose (less than 10 mg per cent) is almost diagnostic, but may not occur in all cases. Pleural biopsy is frequently helpful.

127. Rabin, Coleman B.: Bilateral pleural effusion. J. of Mt. Sinai Hosp. 24:45-53, 1957.

Pleural effusions due to congestive heart failure virtually never occur in the presence of a normal size heart.