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Original Articles

Medical Progress

Medical Intelligence

Editorials

... to decide on the treatment for certain ... those at any age having recurrent disease ... previous operation often insist on radioactive ... Some at any age from fear of radiation insist ... operative treatment. Few patients seem anxious ... prolonged or repeated courses of drug therapy, ... patients in this group are often restive and ... operative in a successful therapeutic program. ... though the fetal uptake of radioactive iodine does ... begin until the fourth month of pregnancy, I ... advise this treatment during pregnancy and ... advised against its use in those below a pre... age because of possible genetic damage. ... age limits have varied since some age ... were introduced in 1944. At first, it was up ... fifty years; more recently, it has been reduced ... forty to twenty-five years. However, the num... of children treated by individual physicians is ... a significant group for observation on the ... effects of radiation. The late effects of this ... on will be revealed in time, but so far, the oc... occurrence of nodules of regenerative hyper... or adenomas has been most significant.

... thyroid drugs have the most important role in ... the management ... hyperthyroidism ... children ... during pregnancy, but certain factors must be ... accepted as an indication for subtotal thyroidectomy. Toxic reactions to drug therapy, relapse after re... prolonged drug therapy, progressive enlargement of the goiter under medical treatment and psychic factors in the patient or family that render medical therapy impractical are each indications for operation. The ease and safety of operative treatment after proper preparation with antithyroid measures has decreased the incidence of complications to a very low level and lowered the time required in the hospital to an average of one week. The skill of the individual surgeon remains the decisive factor in reduction of complications, and so it is that thyroidectomy is no longer the province of the "general" surgeon but should be performed by one especially trained in thyroid surgery.

(To be continued)

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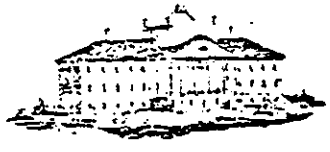
CASE RECORDS
OF THE
SACHUSETTS GENERAL HOSPITAL



Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

BETTY U. KIBBEE, *Assistant Editor*

CASE 73-1961

PRESENTATION OF CASE

Admission. A fifty-one-year-old man entered ... hospital because of left-sided pleuritic chest pain ... twelve hours' duration.

... previously he was admitted to the hos... because of pneumonia of the upper lobe of the ... lung. At the time of discharge the x-ray films ... chest were normal except for a small residual ... of pleural effusion on the right side (Fig. 1). ... He was well until the onset of the present ... illness. He had had many occupations, including work ... as upholsterer and in a slaughterhouse. Beginning nineteen years before entry he worked for five years in confined spaces in the holds of ships, where he was exposed to dust and asbestos.

On admission the patient was acutely ill, with a temperature of 104°F. and signs of pneumonia in the upper lobe of the left lung. X-ray films of the chest (Fig. 2) demonstrated complete opacification of the left-upper-lung field; the trachea was deviated to the left. Penicillin, streptomycin and chloramphenicol were given, and he began to respond by the fourth hospital day. Sputum cultures grew out coliform and proteus organisms, and a subsequent culture demonstrated Friedländer's organisms. A tuberculin skin test was negative. On the eighth hospital day the fever recurred, and *Staphylococcus aureus* was recovered from a sputum culture. With sodium methicillin (Staphcillin) therapy the patient improved. Serial x-ray films of the chest revealed a progressive but incomplete reduction in volume of the density in the left-upper-lung field. A film taken on the twenty-first hospital day (Fig. 3) demonstrated a central, rarefied area within the left apical density that had a sharply defined inferior margin and peripheral air pockets. He was discharged improved on the thirtieth hospital day.

Second admission (two weeks later). In the interim the patient experienced persistent weakness, unsteadiness and anorexia, although he gained 5 pounds in weight. No productive cough, chills or fever occurred. X-ray films of the chest five days before admission again demonstrated a large density occurring the lateral portion of the left ...

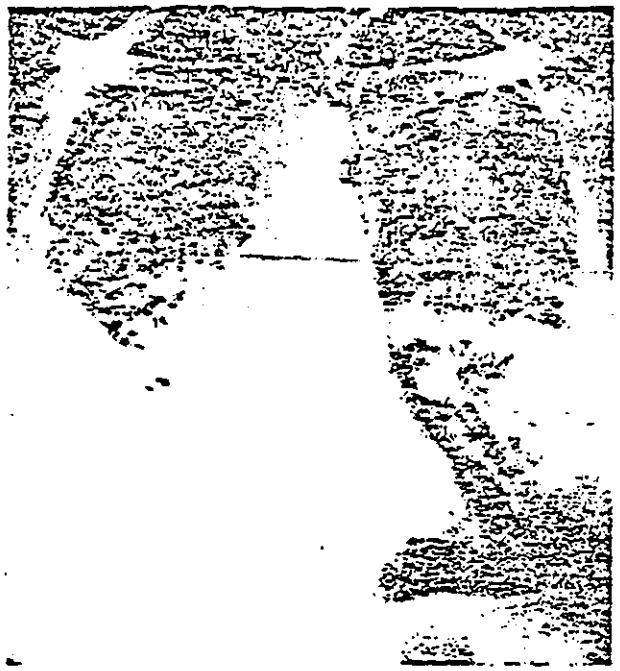


FIGURE 1. *Film of the Chest Taken Six Years before Admission, Showing a Loculated Pleural Effusion at the Right-Lung Base, with an Area of Pneumonitis in the Upper Lobe.*

FIGURE 2. *Film of the Chest Taken on the First Admission, Showing Opacification of the Left Upper Lobe.*

thorax, with marked deviation of the trachea to the left; considerable loss of volume of the left upper lobe, elevation of the left hilus, dilatation of bronchi and patchy fibrotic changes were observed.

Physical examination revealed a well-nourished man with bronchial breath sounds throughout the left upper lobe. A Grade 2 systolic murmur was audible at the apex of the he...

FIGURE 3. *Detail from a Later Film of the Chest, Showing an Area of Central Rarefaction in the Lesion Suggestive of Loculated Effusion or Pleural Thickening along the Lateral Chest Wall.*

The temperature, pulse and respirations were normal. The blood pressure was 135 systolic, 65 d...

The urine was normal. Examination of the blood revealed a hemoglobin of 13.6 gm. per 100 ml., hematocrit of 37 per cent and a white-cell count of 7400. The prothrombin content was 11[illegible] per cent. The fasting glucose was 82 mg., the bilirubin 0.4 mg. and the urea nitrogen 12 mg. per 100 ml. The alkaline phosphatase was 3.2 Bodansky units, the cephalin flocculation was negative in forty-eight hours. The amylase was 9 Russell units. A stool specimen gave a negative guaiac test. A bronchoscopic examination revealed marked inflammation and edema at the orifice of the left-upper-lobe bronchus. A bronchogram demonstrated filling of the ordinary branches of the left upper lobe, with no evidence of obstruction; the peripheral branches did not fill [illegible].

An operation was performed on the eighth day.

DIFFERENTIAL DIAGNOSIS

DR. HELEN S. PITTS[illegible]: We have the problem of a man who entered the hospital after having a [illegible]

[illegible] Board [illegible] Hospital

...rs. Three important points are brought ... past history. Six years previously after an ... pneumonia he still had a residual ... on the right side which discharged. There ... on of the condition of the left lung at that know that he was then well for six years. ... notation of interest is the occupational ... which included five years of work in the ...ips, as well as employment as an upholsterer ...laughterhouse at unknown times.

...looking at the x-ray films I should like to ... about the first admission. The physical ...ated pneumonia with an open bronchus, and ...worthy that the trachea was described as ...oward the lesion instead of away from it, ...that the pneumonia was superimposed on ...th a reduced volume from a pre-existing ...he same area. The acute process responded ...to the three antibiotics that were given ...dy pending the reports of the cultures. ...llinder organisms were probably the in... ..., and I suspect that they were present ...sent, although not cultured until the second ... that the consolidation was apparently ...ment with Friedländer's pneumonia, ... superimposed upon an underlying proc... ...next significant finding was the culture ...*aph. aureus*, perhaps secondary to the anti... ...py. Either the Friedländer or the staphy... ...nisms could have produced the rarefied ...he air pockets that were visible on the ...day. Now, may we see the x-ray films?

...ED L. WEBER: The films of the chest ...ars before admission (Fig. 1) demonstrate ...a in the upper and middle fields of the ...consistent wi... pneumonia and a pleural ...ich cleared with the exception of a small ...right costophrenic angle. On an examina... ...ears later there is no evidence of pneu... ...the obliteration of the right costophrenic ...present.

...AN: Are the lungs entirely clear near the

... Yes. On the first examination during ...illness (Fig. 2) one can see a homo... ...sity filling the upper chest cavity on the ...iterating the mediastinal border and ex... ...e lateral chest wall. The inferior border ...d sharply defined. The left hilus is not ... there is no evidence of a mass in that ... r-lung field and the right-lung field ...y opinion, the trachea is only slightly ...e left. The visualized rib structures are ...films taken eight days later show mul... ...ar translucent areas within the previ... ...trated homogeneous density, which has ...red. A fairly homogeneous density is ...along the left lateral chest wall.

...N: Is that ... consistent with ...?

DR. WEBER: I... compati... ...loculated fluid in the upper chest cavity. Th... ...amination performed a few days la... shows an increase in the translucent areas in the upper-lung field and again the presumed fluid along the left upper chest wall, with streaky densities in the lower-lung field that might be atelectatic areas.

DR. PITTMAN: There definitely is not a pronounced deviation of the trachea toward the lesion, as I assumed from the description.

DR. WEBER: The patient had a slight scoliosis of the upper dorsal spine, with a convexity to the left contributing to deviation of the trachea. Also, if one examines the films in sequence one notices a slight deviation that developed during the course of the illness.

DR. PITTMAN: However, it doesn't imply the pre-existing reduction in volume of the upper-lung field pulling the trachea over that I had anticipated.

DR. WEBER: The final examination (Fig. 3) demonstrates more clearing or more translucency in the homogeneous density in the upper lung, with persistence of the homogeneous density along the left upper chest wall, which is compatible with pleural fluid or perhaps pleural thickening.

In addition to the conventional examinations laminagraphic and bronchographic studies were performed. Although the bronchogram is inadequate, the trachea, the left-main-stem bronchus and the primary bronchi are well shown, and an intrinsic lesion is not evident. There is slight elevation of the left-main-stem bronchus, consistent with reduction in the volume of the left upper lobe.

DR. PITTMAN: Therefore, on the first of the two recent admissions I assume that this man had pneumonia, probably due to Friedländer's organisms with a superimposed staphylococcal infection. When he left the hospital he was not well, but improved, and nine days after discharge x-ray films showed a large density peripherally, with loss of volume and elevation of the hilus, that was probably a pleural rather than an intrapulmonary process. We now have to consider the symptoms and signs in addition to the changes demonstrated radiologically that led to the second admission. They were predominantly weakness, unsteadiness, anorexia and a heart murmur. The absence of a productive cough suggests that the process that was present at that time did not communicate with the bronchus, and now that I have seen the x-ray films I am convinced that it was in the pleural cavity, anyway. There were no signs of obstruction on bronchoscopic examination, which showed merely inflammatory changes. The only abnormal laboratory finding was a minimally elevated bilirubin of 1.[illegible] mg. per 100 ml. The choice of tests performed suggests that the attending physicians had in mind a lesion in the [illegible]

What processes must I consider in this case? Since the available data are sparse, I am trying not to neglect even the smallest hint in the information given to us. I shall run quickly through the possibilities that I considered before seeing the x-ray films because they no longer seem relevant. I thought of an alveolar-cell carcinoma, which can produce fibrosis, but I was overemphasizing the tracheal deviation. Profuse sputum is usually a manifestation of that type of cancer, and the involvement frequently is bilateral. This man had a process six years before admission and a recent process that was comparable in many respects, but the first one cleared completely, and it seems unnecessary to look for an underlying, long standing neoplasm. The lesion was not suggestive of adenocarcinoma, which is a peripheral process, and it bore no resemblance to a metastatic carcinoma, the suspicion of which was apparently the motive for the tests of liver function and the amylase determination. Certainly, tuberculosis could produce this picture, and the negative tuberculin test doesn't exclude it, but it does make it less likely. There was nothing to suggest sarcoidosis.

Having discarded those entities, I shall turn to a consideration of the patient's varied occupational history, beginning with the hazards that he may have encountered from industrial dusts. He was exposed to asbestos a number of years before entry. Asbestosis is a form of silicosis, and whether or not asbestos gets into the alveoli depends upon the particle size. It is my understanding that the particles that are encountered during handling of the manufactured product are too large to reach the alveoli. It is when one works in the asbestos industry itself that the dust exposure is dangerous and I'm going to rule out the holds of ships as regards a diagnosis of asbestosis. Another pertinent pneumoconiosis is byssinosis, which is produced by cotton dust. That seems the most likely harmful agent that he might have been exposed to during his career as an upholsterer, but again the particle size would have been too large, and that condition isn't suggested by this picture. The question of an infection related to his occupation arises next. Admittedly, his occupation may have had nothing to do with this illness, but I have to use the few facts given in search of a clue. Fungous infections may be associated with many types of dust, and one that I think of particularly is histoplasmosis. I don't believe that poultry is killed in slaughterhouses, and I'll merely touch on that diagnosis and discard it. Histoplasmosis can be responsible for fibrotic peripheral masses and can induce cavitation, but otherwise the findings in this case bear no resemblance to it. There are other fungi, but I'm not going to take the time even to name them. As for slaughterhouse disease that I shall mention in passing is tularemia. You can kill rabbits a [illegible] produce abscess cavities that persist for months and can cau pleural effusion.[1,2]

I have come down the list to one other, more mon and to my mind much more logical disease a slaughterhouse worker might have. He may h infected large animals, including swine, and thinking now of brucellosis, which can cause ch pulmonary lesions and effusions. It is manifeste many systemic symptoms, and in working with meager history I cannot neglect the weakness unsteadiness that this man experienced and the diac murmur because brucellosis can produce carditis and can cause murmurs without recog endocarditis.[3] I find this the least unlikely explan of the patient's illness, both past and present. T fore, I shall say that he had on the first recent a sion an acute left-upper-lobe pneumonia, pro due to Friedländer's organisms with a superim *Staph. aureus* infection, and that that condition cured. In addition, I am going to accuse hi having chronic brucellosis, probably acquired infected swine while working in a slaughterhouse haps first manifested six years ago by the proc the right lung and currently producing eff fibrosis and possibly some granulomas in the left with a systemic reaction.

DR. LEWIS W. KANE: Was this man an alcoh

DR. JOHN H. KNOWLES: No, he was not.

DR. BENJAMIN CASTLEMAN: Why do you as

DR. KANE: This story is perfectly consistent multiple aspirations of saliva producing infecti the right lung originally and subsequently infe and a lung abscess on the left side. The mi types of organism in the cultures support that nosis. I think that the patient ended up wi empyema as well as a lung abscess on the ba aspiration of contaminated material.

DR. SAMUEL THIER: I might add that becau epigastric pain and vomiting an upper gastrointe series was done during the first recent admissio was normal. The question of aspiration pneu was considered. Also observed at that time w treme leukopenia, which was the reason for trea with so many antibiotics while we were tryi decipher the cultures. The white-cell count w the range of 2000, and this was one of several pneumonic processes accompanied by leukopeni we had seen within the last few months.

DR. WARREN POINT: Dr. Pittman, do I unde you to imply that the pneumonia was basica duced by brucellosis, or do you think that the b losis was simply another infection concurrent wi clear-cut classic pneumonia?

DR. PITTMAN: I am suggesting in my fantasi he [illegible] brucellosis.

DR. POINT: Why do you have to bring tha explain anything except that he was a slaughte worker?

PITTMAN: I don't — I must did.

...AN: If this was Friedländer's pneumonia, ... expect the left upper lobe to be larger ... with the septum bulging downward ... than the marked reduction in volume?

R. PITTMAN: I would, and that is why, as I read the record, I thought that the lung was the site ...vious change because of the repeated mention ...viation of the trachea. A chronically scarred lobe ... reduced volume seemed the only way to account ... superimposed pneumonia and deviation of the ... toward the involved area. I explained the ... contour that was shown on the x-ray film ... basis of an increase in size of a portion of lung ... could still expand.

R. KANE: What operation do you think was performed?

R. PITTMAN: Previously, I believed that it was a ...ectomy because from the description of the x-ray ... I didn't expect an effusion and had in mind ...ion of an area of residual pneumonitis or possibly ...nulomatous lesion. I now suspect that the surgeon opened the chest to drain an empyema.

...ARLE M. CHAPMAN: One occupational dis... you didn't mention is so-called metal-fume ... which is believed to be allied to zinc and other ... products. Such fumes are characteristically ... in confined spaces in the holds of ships, and the ... probably results from fine metal fragments that ...ge the lung diffusely. That condition might ...formed a background in this case for the subse... bacterial infection, whatever it was.

R. PITTMAN: This patient last worked in the ... of ships fourteen years before these admissions.

R. CHAPMAN: I am speculating that the background was scarring of the lung from fine metal particles he inhaled in those confined areas.

R. CASTLEMAN: What was the thinking on the ...?

DR. THIER: Our initial impression was that the ... might be ... pneumonia, with the formation of a ...bscess, perhaps secondary to obstruction behind ...plasm, and he was treated on that premise. ...urpose of the operation was to find out whether ... a tumor and, if not, perhaps to resect the ...ved lung tissue.

CLINICAL DIAGNOSIS

...pneumonia, ? carcinoma, left upper lobe.

DR. HELEN S. PITTMAN'S DIAGNOSES

...onic ...ccellosis with fibrosis, left lung.

...ural effusion, left.

...monia, acute, left upper lobe, probably due to Friedländer's organisms, with superimposed ...Staph. aureus infection, mixed ...

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: When the surgeon opened this patient's chest he found no fluid. The left upper lobe was bound down to the chest wall, and it was necessary to employ sharp dissection to dissect the adherent visceral from the parietal pleura, which was extraordinarily thick. The left upper lobe had shrunk into an ovoid mass, about 12 by 8 by 5 cm., reminding the surgeon of the size and shape of a tangerine. The disease did not involve the lingula of the upper lobe, but merely the upper segment, and he was able to dissect it free from the lingula, which was expanded at the time of operation. Since the resected segment was hard and fibrotic, he believed that he was dealing with a chronic pneumonitis rather than a tumor.

On section the pleura was extremely thick, hyalinized and acellular, and it was obvious why the surgeon had difficulty in dissecting it. This is not the usual finding in chronic pneumonitis, even with extensive pleuritis. I think the area on the x-ray films that suggested loculized empyema or fluid was the thickened pleura, which in places measured almost 1 cm. Microscopically, there was marked fibrosis obliterating portions of the lung parenchyma. Section of another area showed very severe, chronic pneumonitis, with exudate in some of the air spaces and marked chronic inflammation, including the phagocytes filled with lipid that one expects with any long standing, chronic pneumonitis (Fig. 4).

FIGURE 4. *Chronic Pneumonitis*

The alveolar walls are thickened; the air spaces are filled

DR. PITTMAN: Can these changes occur during a six-week course of illness?

DR. CASTLEMAN: I think they could, but in this case the background was probably much older than six weeks. Of course, we don't have a film taken during the three years before admission, but I am sure that something had been going on for a matter of months, perhaps even a year.

Careful examination of the air spaces under the microscope showed a number of brown, irregular bodies with a knob at each end, characteristic of the clubbing and the irregularity of asbestos bodies (Fig. 5). The fiber is in the center and is covered with protein, which then degenerates slightly to cause the irregularity. Asbestos bodies stain brown because of the impregnation with iron that occurs in their formation. Therefore, the underlying disease in this case was almost certainly asbestosis. Some authorities believe that symptoms and signs and a pneumonitis arise only when a secondary infection is superimposed on the pre-existing asbestos fibers — that the asbestos fibers are fairly inert, but when a secondary infection intervenes pneumonitis may develop. Thickening of the pleura (Fig. 6) is typical of asbestosis, and, in fact, a pathologist with some experience with the disease immediately thinks of asbestosis when he sees that change. There were no metaplastic changes of the bronchi suggesting that a tumor was being formed in this case, and we made a careful search because asbestosis is one of the predisposing factors for carcinoma of the lung.

DR. PITTMAN: The findings interest me very m because from my reading and from what I have h Dr. Harriet L. Hardy say repeatedly, asbestosis d ops only after exposure to minute particles of asb less than 3 and no more than 10 microns in siz didn't think that it was possible to contract the di merely from applying asbestos in preparation and dealing with the dust of the mining of asbestos.

DR. CASTLEMAN: Of course, the disease devel several years ago, when the hazards even in the of a ship were probably far greater than they are when more precautions are taken.

DR. KANE: The patient did have a lung abs didn't he?

DR. CASTLEMAN: There was no evidence of a abscess at the time of operation. He must have an infection in the lung that shrank, but all our f ings can be explained by secondary infection o underlying asbestosis.

DR. KNOWLES: Dr. Castleman, I don't r understand how you can relate the exposure asbestos to this man's recent illness. How can associate a localized disease in one little part of lung with the coincidental finding of asbestos fi

DR. CASTLEMAN: He had the asbestos fibers undoubtedly.

DR. KNOWLES: But he had had those for nine years.

DR. CASTLEMAN: That's right, and then a seco ary infection developed in the left upper lobe.

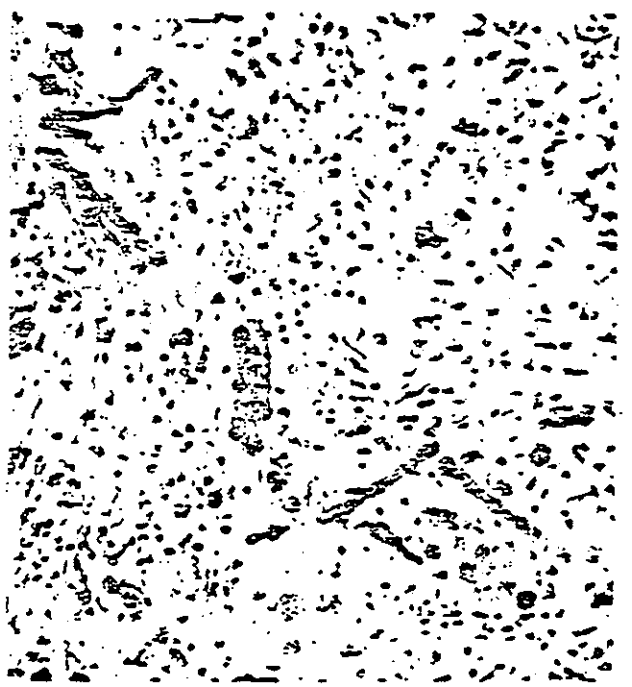


FIGURE 5. ... Asbestos ... Inflammatory Area.

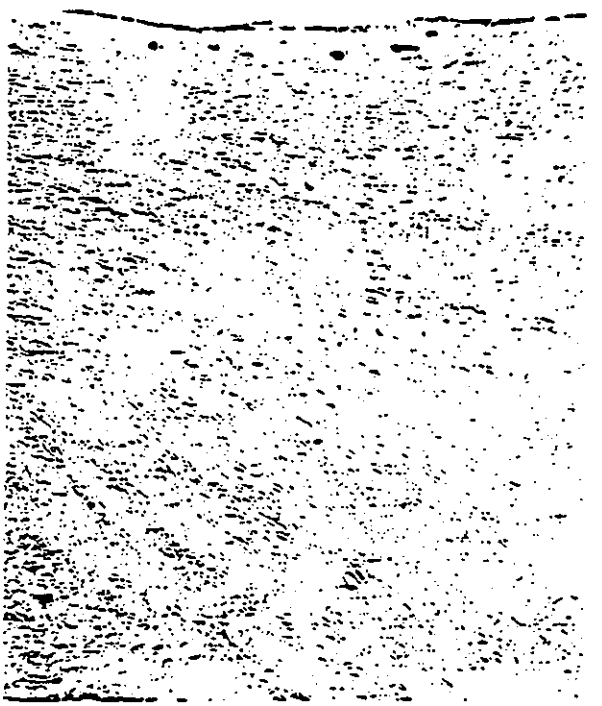


FIGURE 6. ... and Thickening of the Pl ... (X18)

...WLES: So the ... ...ovis is not necessarily ... out a chronic organizing pneumonia of the ... lobe.

CASTLEMAN: Superimposed on the asbestosis. ...estion is whether the infection would have ...ed without the asbestosis.

KNOWLES: The x-ray films show only one ...ea of pleural thickening, and I find it difficult ...ain, even though it was marked, the localized ... thickening, particularly in an upper lobe, on ...is of asbestosis, which ordinarily produces ...l lower-lobe changes and lower-lobe pleural ...ing.

CASTLEMAN: It isn't necessarily bilateral.

PITTMAN: How do you explain the complete ... of the comparable process on the right side ...s before admission? This man must also have ...estosis in the right lung at that time, and yet it ... without the development of thick pleuritis.

CASTLEMAN: It probably was a less severe ...

ANATOMICAL DIAGNOSES

... pneumonitis and marked pleuritis, left ... lobe.

(...

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CASE 74-1961

PRESENTATION OF CASE

...-week-old male infant was admitted to the ... because of rapid deterioration.

...hild was the product of a normal third pregnancy and delivery, except that the mother was said ... had endometritis with a temperature of ... a few days after delivery. The birth weight ... pounds, 14 ounces. The neonatal examination ... a husky, blond infant, with a vigorous cry ... evident abnormalities. He fed well and ... pounds, 10 ounces, when discharged on the ... tum day. He progressed normally until ... before entry, when his nurse noted that he ... 10 p.m. and 2 a.m. feedings poorly. Although ... by his condition at 6 a.m. on the fifteenth ...fe, she delayed calling the mother until 7 a.m. ...ther summoned a pediatrician, who found the ...orly responsive, with sunken eyes, poor color and slow, shallow respiration. The infant was rushed to the hospital. No vomiting or diarrhea had occurred.

Physical examination on arrival revealed a well developed, well nourished infant who appeared hypothermic and was cyanotic and without respiration. The eyes and fontanels were sunken. The nose and throat were normal. No heart sounds were audible. The edge of the liver was palpable 2 cm. below the right costal margin.

The heart rate was 50 after artificial respiration was instituted. While oxygen was administered under positive pressure through an endotracheal tube, intracardiac epinephrine was given, and a cutdown for intravenous-fluid therapy was performed. After a few minutes the baby became pink, and the pulse stabilized at a rate of 100 to 120 per minute. Spontaneous respiration began, he cried loudly, and good movements of all extremities were seen. The lungs were clear. A truncal maculae erythematous skin eruption was observed. The intravenous-fluid therapy initially consisted of 15 ml. of saline solution followed by 1 gm. of albumin. Subsequently, a multiple electrolyte, potassium-containing solution was infused, to which chloramphenicol, erythromycin and later digoxin and 20 mg. of cortisol hemisuccinate were added. During the next four hours breathing stopped twice. The first time, resuscitative measures were successful in restoring spontaneous respiration. The second time, during an hour and a half of assisted breathing, the heart rate gradually decreased. The child died four and a half hours after admission.

DIFFERENTIAL DIAGNOSIS

DR. NATHAN B. TALBOT*: In this case one can only guess the pathological diagnosis. Rather than try to catalogue all the conditions that might have caused this child's exitus, I prefer to focus attention on the most common causes of this type of problem. In reviewing what little information we have I notice that the mother had endometritis, and it would be interesting to know whether the placenta of this pregnancy was examined since the microscopical examination of the placenta may reveal infection that can be shared by the baby.

DR. JOHN S. ROBEY: A frozen-section examination wasn't done, but the placenta was grossly normal.

DR. TALBOT: This baby was fairly large at birth. Was the mother diabetic by any chance?

DR. ROBEY: No.

DR. TALBOT: If the child had a blood incompatibility we would have been informed of it. I must proceed on the assumption that he was apparently all right until fourteen days of age. This is the age when congenital malformations and inborn errors are often detected, and one also thinks of trauma and of infec-

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CASE RECORDS
OF THE
SSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

BETTY U. KIBBEE, *Assistant Editor*

CASE 62-1963

PRESENTATION OF CASE

ifty-six-year-old plumber was admitted to the al because of pain in the chest.

tient had been in good health until twenty- previously, when he began to experience ideu chest pain. Six months later he was told n x-ray film of the chest was abnormal. Twelve before admission he entered another hos- because of persistent chest pain accompanied ipnea and a cough productive of white spu- There had been no chills, fever, weight loss igue. A tuberculin skin test (second-strength was reported as strongly positive, but studies of utum and gastric washings for tuberculosis were e. X-ray films of the chest demonstrated a l density on the right side, which was thought resent partially organized hydrothorax; bron- pic and bronchographic studies were negative. sided exploratory thoracotomy was performed, ecortication of the pleura; the pathological di- was "dense fibrotic pleuritis." He was dis- d home on isoniazid, 100 mg. three times daily. months after discharge the patient re-entered ne hospital because of continuing chest pain, had not been improved by nerve block per- in a surgeon's office. An x-ray film of the evealed thickening of the apical pleura on the nd a linear density overlying the diaphragm the left cardiac border; on the right side , nogeneous shadow compressed the lung ard and medially and extended from the the level of the second rib; another density d from the third costal interspace to the dia- The fourth, fifth and sixth intercostal nerves vided in an attempt to relieve the pain, and e examination of a specimen of the pleura re- relieved by the operation, and he was referred to a psychiatrist for further evaluation and treatment. Two weeks before admission he entered a mental hospital for management of depression. Anisocoria was observed on admission. An x-ray film of the chest showed a decrease in volume of the right hemithorax, with partial collapse of the right lung, pleural effusion, shift of the mediastinum to the right and an extensive density in the right-middle-lung field. Transfer to this hospital was arranged.

Bilateral nerve deafness had been present for seventeen years. The patient had worked as a plumber for forty years, having spent about half of that period installing insulation on boilers and pipes. He had smoked 1½ packages of cigarettes daily for many years. Five years previously x-ray films were interpreted as showing a peptic ulcer. There had been a loss of 30 pounds in weight during the three months before entry.

Physical examination disclosed a pleasant man who did not appear depressed. A right-sided Horner syndrome and drooping of the right shoulder were observed. Dullness and diminished breath sounds were heard over the lower third of the right lung; the heart was normal, and there were no murmurs. The liver edge was felt 2 fingerbreadths below the right costal margin.

The temperature was 98.6°F., the pulse 116, and the respirations 22. The blood pressure was 120 systolic, 70 diastolic.

The urine was normal except for a rare red cell and 1 or 2 white cells per high-power field in the sediment. The hematocrit was 38 per cent, and the white-cell count was 11,850. The fasting glucose was 100 mg., the urea nitrogen 15 mg., the calcium 9.0 mg., the phosphorus 3.0 mg., the bilirubin 0.5 mg., and the protein 6.8 gm. (the albumin 4.4 gm.,

rovide several interesting findings. First of all, a fairly extensive reaction along the periphery t right lung (Fig. 1). Its outline is irregular, d it seems to be a soft-tissue reaction extending ound the entire lung. This change means a dease in volume of the lung, which is further indied by elevation of the right leaf of the diaphragm d by retraction of the heart and mediastinum tord the right side. Within the lung field there is a ttern of fine fibrosis and perhaps a nodular infilte. I am less certain about the findings on the left e, but there appears to be pleural thickening along left lateral chest wall, as well as a similar but ch less marked pattern of fibrosis and nodular iltrate. The abnormality is confined almost enely to the perihilar and basal regions of the lungs. e lateral film of the chest taken at the same time ain demonstrates the elevation of the diaphragm d the extensive alteration that is apparently a ural reaction. A fluoroscopic spot film (Fig. 3) en shortly thereafter reveals a fine, linear, reticular ttern that is probably indicative of fibrosis, and xed in with that change or superimposed upon it see a pattern composed of very small nodules, ich in some areas, particularly in the lower zones, ce into conglomerate shadows. Finally, a high- tion film (Fig. 2), which was taken primarily show the extent of the apparent pleural reaction, so demonstrates very nicely that in at least two bs, the right fourth and the right fifth, the anrior part of the cortex is missing. This picture is rtainly consistent with erosion or destruction, and ere is probably also slight erosion of the sixth and venth ribs.

DR. KNOWLES: The films demonstrate that this an had bilateral pleural involvement, but preominantly of the right side. Furthermore, he had lateral parenchymal changes that were largely conned to the lower lobes. He also had erosive dissolun of at least two ribs on the right side. I'd like to k a few questions pertaining to the radiologic udies because the crux of the problem, as I see it, whether the patient had either bronchogenic carnoma or a pleural mesothelioma as a complication what I believe was diffuse pulmonary asbestosis. r. Dreyfuss, will you tell me about the character the carina, in view of the fact that there might ave been metastatic malignant disease in the conguous lymph nodes, which would distort it?

DR. DREYFUSS: The outline of the carina is sharp, hat fact is against significant subcarinal ade-

DR. KNOWLES: Secondly, would you say that the ural fibrosis on the right side definitely extends to the mediastinal structures and even into the oracic inlet on that side?

DR. DREYFUSS: The change that appears to be ural fibrosis or thickening definitely, and probably nificantly, extends along the medial surface of the the right lung along the cardiac and mediastinal border.

DR. KNOWLES: Do you see any evidence of a Pancoast tumor, or so-called superior-sulcus tumor, invading the soft tissues of the right thoracic inlet and thereby giving rise to the Horner syndrome?

DR. DREYFUSS: Of course, a soft-tissue lesion above the apex of the lung always raises the suspicion of a superior-sulcus tumor, but I interpret the alteration in this case as a continuous process actually encasing the lung. Another clue that I should like to see before making a diagnosis of a Pancoast tumor is evidence of erosion or destruction of the first, second or third rib, which is not indicated on these films.

DR. KNOWLES: Can you state fairly definitely that fluid was absent and that the major portion of the change was due to fibrotic disease?

DR. DREYFUSS: I am quite certain of the absence of a significant amount of fluid. The left leaf of the diaphragm is very sharp, and the usual tapered sign of fluid extending up the posterior gutter is lacking on the right side.

DR. KNOWLES: One other point is that, even though the right hemidiaphragm was elevated the liver extended 2 fingerbreadths below the right costal margin. So I assume that there was significant hepatomegaly.

DR. DREYFUSS: It is certainly suggested.

DR. KNOWLES: As I see it, the argument in this case rests on four key findings: the disease was bilateral and both pleural and parenchymal; the patient had persistent chest pain; erosive dissolution of the ribs had occurred; and a right-sided Horner syndrome had developed. The last three features suggest a malignant process and remove the disease from the simple class of just a fibrotic reaction to asbestosis. The only conclusion that I can reach is that he had chronic pulmonary asbestosis, and that a complication of some type had developed.

At this point perhaps a brief historical review of asbestosis is in order.[1] Asbestos is a Greek word meaning unquenchable or unconsumable in the sense of being indestructible. In 450 B. C. the Romans discovered that clothing made of this flexible fiber facilitated the collection of the ashes after cremation. Its contemporary use is as insulating material for pipes, linings for chemical containers and brakes on automobiles, insulating slabs and shingles, firefighter suits, theater curtains and undercoating for ships and automobiles.[2] Two years ago pulmonary asbestosis was reported in Massachusetts in a man whose occupation included spraying undercoating on cars[3]; the material used had an asphalt base with about 50 per cent asbestos, and he had true pulmonary asbestosis. Asbestos is the name given to a series of minerals composed of certain fibrous silicates, magnesium and iron. It is mined as crushed rock and is then carded, woven and spun

DR. CASTLEMAN: The sputum was examined both tumor cells and asbestos fibers, and neither found.

R. KNOWLES: My argument is becoming less tenable by the moment. Were the so-called asbestos corns observed on physical examination? These are small, nodular fibrous areas that may develop on the hands, arms and legs of people who work with asbestos fibers.

DR. CASTLEMAN: None were found.

DR. KNOWLES: I should like to say a word about the pathologic physiology of this disease, although it requires extraordinary courage to stick with my original premise after all these questions have been answered in the negative. Pulmonary asbestosis is commonly associated with the alveolar-capillary-block syndrome.[3] The full-blown syndrome is characterized by reduction in lung volume, unobstructed air flow, increased respiratory rate and ordinarily cyanosis on exercise, but with a normal carbon dioxide level or even mild respiratory alkalosis since there is no obstruction to the diffusion of carbon dioxide.

What else should be considered in the differential diagnosis? Tuberculosis and fungous disease such as actinomycosis are possibilities, since both cause pleural fibrosis and bilateral chronic disease, but there is no evidence of chronic infection in this patient. [illegible] disease, with the exception of actinomycosis, does not erode ribs but causes a periosteal proliferative reaction. So I can dismiss those two diagnoses.

The presence of the Horner syndrome bothered me considerably, but there is no question that a neoplastic mesothelioma, by invading the lower cervical ganglions and sympathetic fibers or the upper thoracic fibers, could be responsible for this condition. The fact that it was noticed soon after the operation made me worry about metastatic disease or even a little infarct in the medulla, but with no other associated neurologic findings of the so-called lateral medullary or Wallenberg syndrome one has to place the cause of the Horner syndrome peripheral to the spinal cord and to the medulla. A superior-sulcus tumor with invasion of the sympathetic stellate ganglion or compression of the stellate ganglion by a cervical rib, perhaps due to manipulation during the operation, seems unlikely on both clinical and radiologic grounds. A final point to be explained is the elevated alkaline phosphatase level. It is possible that the high value reflected metastases to the bone or the liver from a bronchogenic carcinoma, but I interpret the elevation of the right leaf of the diaphragm as a sign of significant hepatic enlargement and choose to say that a pleural mesothelioma invaded the diaphragm and also the liver.

My conclusion is that this man suffered from pulmonary asbestosis, with diffuse parenchymal interstitial and nodular fibrosis as well as extensive pleural fibrosis. In addition, I believe that he had a pleural [illegible] choice on the negative evidence — that is, the negative bronchoscopic study, the nonspecific radiologic findings with no suggestion of a localized mass and the negative sputum examinations. I think that the operation was another right-sided thoracotomy, with, I hope, pleural and pulmonary biopsies and perhaps even biopsy of a diseased rib. I doubt whether curative surgery could be done.

DR. LAMAR SOUTTER: Why do you think the patient lost so much weight?

DR. KNOWLES: I attribute the weight loss to the debilitating effects of chronic pain and ultimate invasion of the liver, either by metastatic disease or by direct extension. Loss of appetite may be the key symptom of hepatic involvement.

DR. KENNETH T. BIRD: Diffuse lung disease, whether or not of occupational origin, may result in weight loss. This effect is probably a manifestation of persistent hypoxia. For example, the presenting complaint of the patient with pulmonary emphysema is often progressive weight loss.

It is important to note that the crystalline form and size of inhaled particles may determine the response of the host in pulmonary disease associated with occupational exposure. Crocidolite, one of the several varieties of asbestos fibers, may give rise not only to parenchymal and pleural disease but also to peritoneal manifestations.[4] Chrysotile, $3MgO \cdot 2SiO_2 \cdot 2H_2O$, is the main asbestos of commercial use.

DR. CASTLEMAN: Dr. Isselbacher, do you have a comment?

DR. KURT J. ISSELBACHER: As Dr. Knowles mentioned, in 1953 we became interested in a possible relation between asbestosis and the development of bronchogenic carcinoma. It seemed important to document such a relation, if it existed, because of the magnitude of the asbestos industry in this country. We were impressed by the preponderance of involvement of the lower lung when the carcinoma occurred in association with asbestosis. Another factor pointing toward an association of the two entities was the high incidence of bronchogenic carcinoma — namely, 13.8 per cent. A third feature, which Dr. Knowles has emphasized in this case, was the bilateral nature of the disease. In view of the occupational history in the present case, I find Dr. Knowles's diagnosis most attractive.

CLINICAL DIAGNOSES

? Asbestosis.
? Carcinoma of lung.

DR. JOHN H. KNOWLES'S DIAGNOSES

Pulmonary asbestosis.
Pleural mesothelioma, with invasion of mediastinum, chest wall, right hemidiaphragm and liver.

PATHOLOGICAL DISCUSSION

The patient died ten days after this operation. At autopsy the entire right side of the chest was obliterated by dense fibrous tissue that in many places was obviously neoplastic. In the region of the right lower lobe the pleura had a thickness of as much as 5 cm. As Dr. Knowles surmised, the pleural tumor had extended through the diaphragm and overlay the surface of the liver (Fig. 6). However, the parenchyma of the liver was spared except for a few small metastatic nodules. The neoplastic tissue extended into the lower lobe of the right lung, producing the serrated or cobblestone margin, as it projected from the pleura into the lung, that is characteristic of the mesothelioma. The left lung was also involved by this dense pleural tumor, and there were a few small metastatic nodules within its parenchyma.

The tremendous mass of the mesothelioma involved the entire mediastinum, and compression of the subclavian veins on the right side accounted for the Horner syndrome. The tumor extended down to involve the pericardium as well, and there were two small nodules on the epicardium. From the pleura it extended into the ribs, as was seen on the x-ray films, and two of the ribs were completely destroyed. The vertebras were also involved, not by direct extension but by actual metastasis. As I mentioned, the huge tumor extended down from the chest and overlay the right lobe of the liver, and when it was peeled off nodules were seen on the surface of the liver. The omentum was completely covered with mesothelioma implants, which were present throughout the abdomen, especially in the region of the right lower quadrant over the cecum, the ascending colon and the terminal ileum.

Microscopical examination of one of the metastases within the left lung (Fig. 7) revealed mesothelial cells with a tremendous fibrous-tissue counterpart, which is characteristic of the mesothelioma, as I indicated (Fig. 8). In fact, an occasional mesothelioma is almost entirely fibrous, and at times it is very difficult for the pathologist to differentiate it from merely dense collagen or a fibrosarcoma. We know from experimental evidence that the mesothelioma cell, when grown on tissue culture, may produce collagen, and that is what it was doing in this metastasis. On the other hand, other mesotheliomas are predominantly made up of large mesothelial cells,

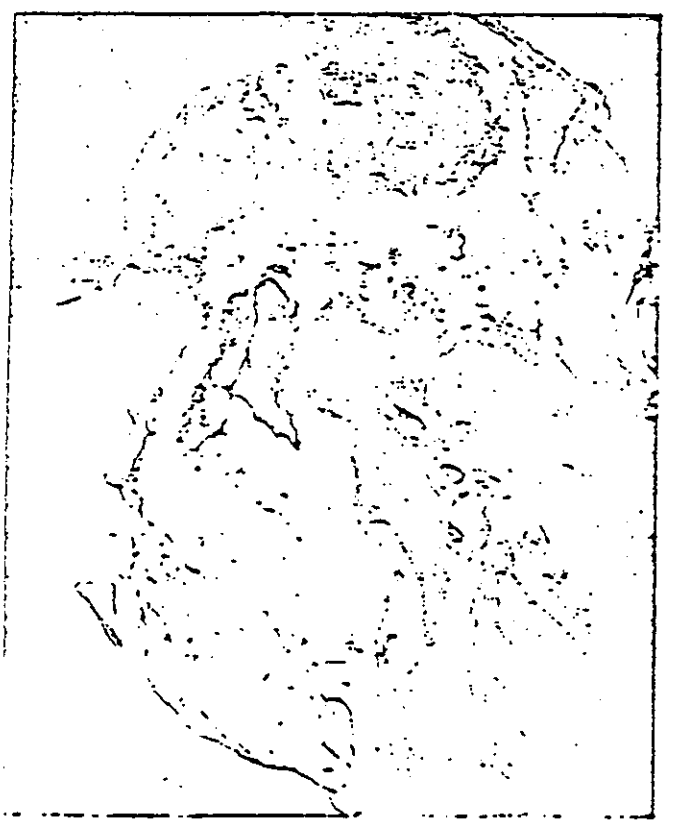

FIGURE 6. *Sagittal Section through the Lower Lobe of the Right Lung, Diaphragm and Liver.*

The mesothelioma encircles the lung (above) and overlies the anterior surface of the liver (below). Note the pleural

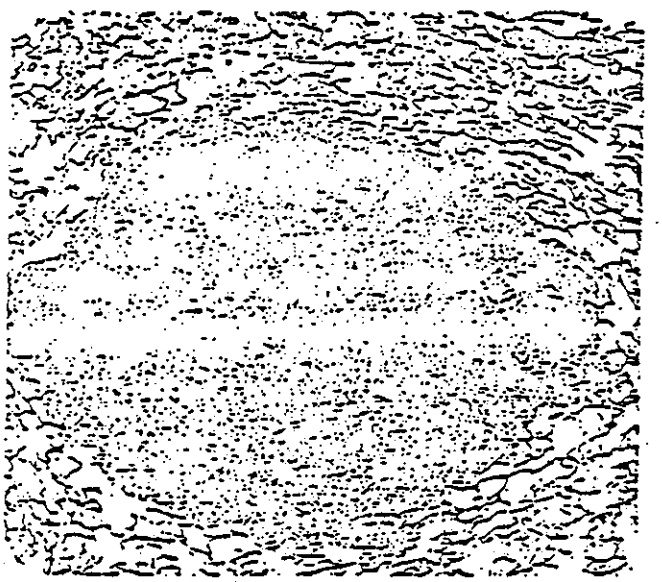

FIGURE 7. *Metastatic Nodule in the Left Lung. (X15)*

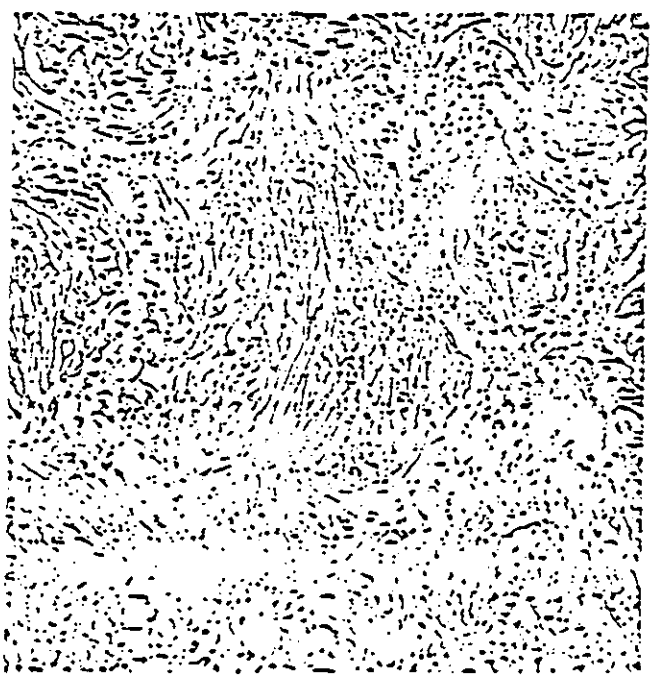

FIGURE 8. *Mesothelioma with Predominance of Fibrous-*