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BERYLLIUM POISONING: REPORT OF A CASE TREATED WITH ADRENOCORTICOTROPIC HORMONE

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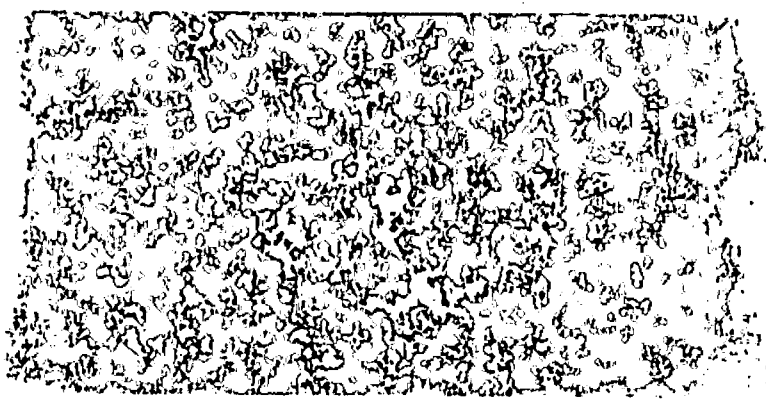
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TREATED WITH ADRENOCORTICOTROPIC HORMONE

R. Lowry Dobson and John C. Weayer

October 27, 1950

Berkeley, California

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BERYLLIUM POISONING: REPORT OF A CASE
TREATED WITH ADRENOCORTICOTROPIC HORMONE

R. Lowry Dobson and John C. Weaver

October 27, 1950

The chronic and progressive pulmonary disease of a 37 year old man has been studied since illness was first detected in October, 1945. A number of interesting features have presented themselves: the problem of differential diagnosis early in the course of his disease was difficult; however, the typical course and the progressive incompatibility of this course with other diseases being considered together with a history of inhalation exposure to beryllium oxide dust in the Spring of 1942, three years before the onset of symptoms, have led to the probable diagnosis of delayed chemical pneumonitis caused by beryllium; the response of the patient to therapy with adrenocorticotrophic hormone (ACTH) at a time when he was gravely ill and the limited response he has shown since that time are of aid in the evaluation of this type of treatment in berylliosis.

PAST HISTORY: The patient was born in Utah in 1913, where he lived until the age of 24. He moved to Berkeley, California when he was 24 years old. His general health in the past has always been good. During childhood he had measles, mumps and chickenpox. There is no history of scarlet fever, rheumatic disease or any other serious illness. He has suffered no serious accidents. An appendectomy was done when he was 14 and a tonsillectomy when he was 18.

Family History: The family history is non-contributory. There is no history of tuberculosis, malignancy, heart-disease, kidney disease, blood

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dyscrasias, nervous disorders or allergy.

System Review: Apart from the present illness, the system review was non-contributory.

OCCUPATIONAL HISTORY: The patient went to work for the Radiation Laboratory shortly after the entry of this country into the war in December, 1941. He continued at the Laboratory in Berkeley until January, 1944. During this period he did not receive significant radiation exposure. He worked with an electromagnetic separator and used a number of different elements, e.g., Tl, Hg, Pb, and U. From April, 1942, through the Spring of 1943, the group with which he was working had occasion to use beryllium ceramics which they fabricated themselves. The patient does not recall having made any of these himself, but remembers specifically having used a power drill on several occasions to make holes in a beryllium oxide crucible. He recalls that during this process much dust was formed by the drill, which he inhaled while doing close work.

Between January, 1944, and June, 1945, the patient worked at Oak Ridge, Tennessee. Again there was no significant exposure to radiation. He worked chiefly with the electromagnetic separation of uranium isotopes and recalls having had inhalation exposures to uranium oxide, uranium tetrachloride, uranium hexafluoride, uranium metal, finely divided steel and stainless steel dust, by-products from welding torches, finely divided carbon, hydrochloric acid, fluorine, and possibly small amounts of phosgene gas.

Between June and October, 1945, he worked in and out of the Laboratory at Los Alamos, New Mexico. There was no known exposure to radiation, beryllium,

or other toxic materials during this time. After his stay at Los Alamos, he returned to the Radiation Laboratory in Berkeley where he remained until his most recent hospitalization.

PRESENT ILLNESS: The patient was apparently perfectly well until the summer of 1945, at which time he noticed a gradual onset of shortness of breath, easy fatigability and the development of a dry, paroxysmal, non-productive cough. There was an associated weight loss of 20 lbs. in the course of a few months. Chest x-rays taken in October and November of that year showed a diffuse, fine mottling throughout both lung fields (Fig. 2) contrasting with a normal x-ray picture in 1943 (Fig. 1).

He was seen by a physician* at that time because of these complaints. Examination showed the temperature to be 99° F, pulse 74 per minute, blood pressure 122/80. The vital capacity was 4.5 liters. Another chest film showed again diffuse widespread infiltration. X-ray studies of the hands and feet were normal. Plasma proteins totaled 6.09 mg percent; albumin, 4.43 mg percent; globulin, 1.66 mg percent. The red blood cell count was 5.38 M, with a hemoglobin of 106 percent; the white blood cells numbers 3,700, with 53 percent Polys, 2 percent Basophiles, 32 percent Lymphocytes, and 13 percent Monocytes. The Wintrobe sedimentation rate was 16 mm corrected. His urine was negative. A slit lamp examination was made and no uveitis or other evidence of Boeck's sarcoid was found. The diagnosis made at the time was Boeck's sarcoid with pronounced pulmonary infiltration.

The persistence of his symptoms and of the pulmonary infiltration as shown by x-ray led to his admission to the University of California Hospital.

* Dr. Morris Dailey, then medical consultant to the Radiation Laboratory.

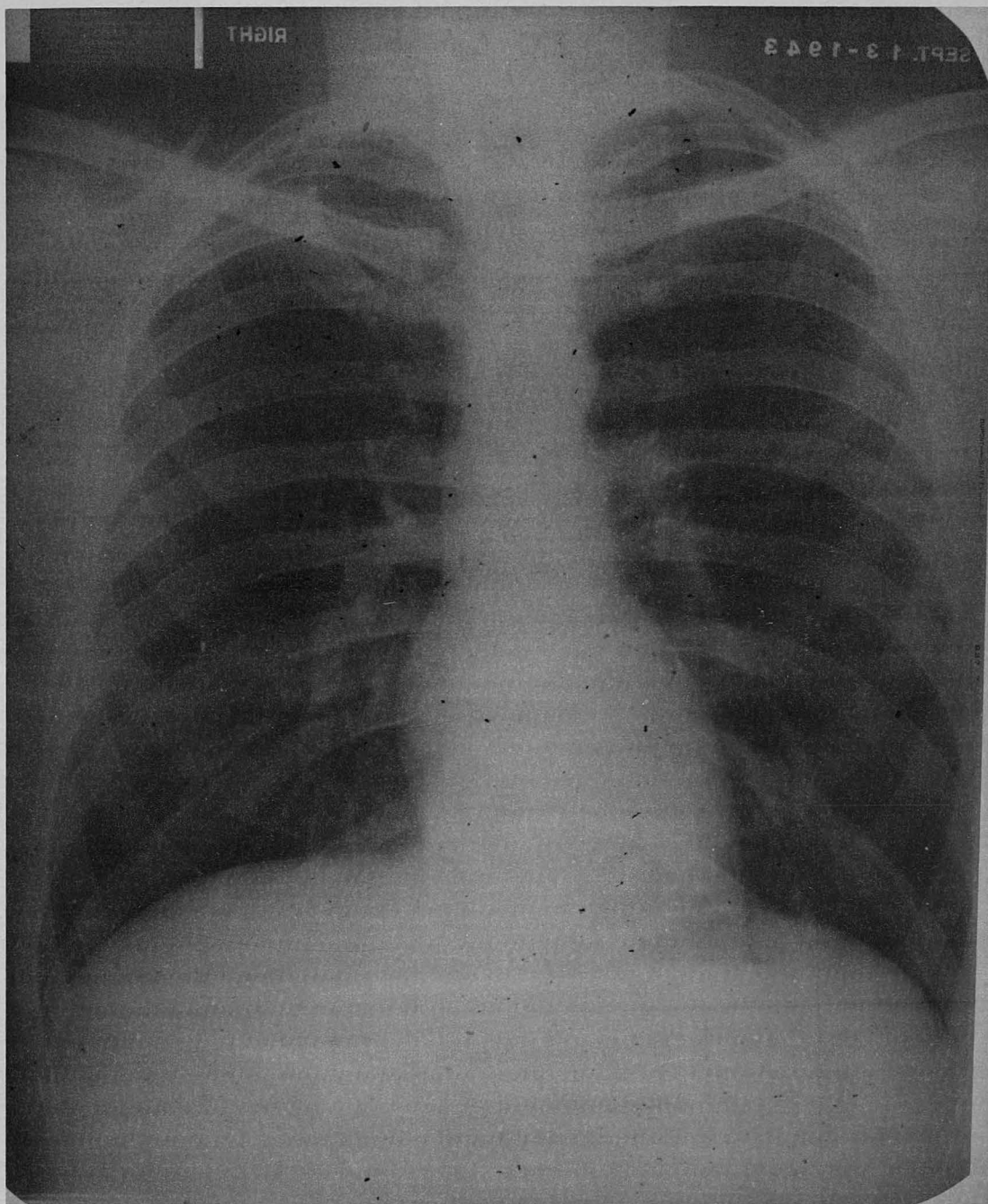


FIG. 1

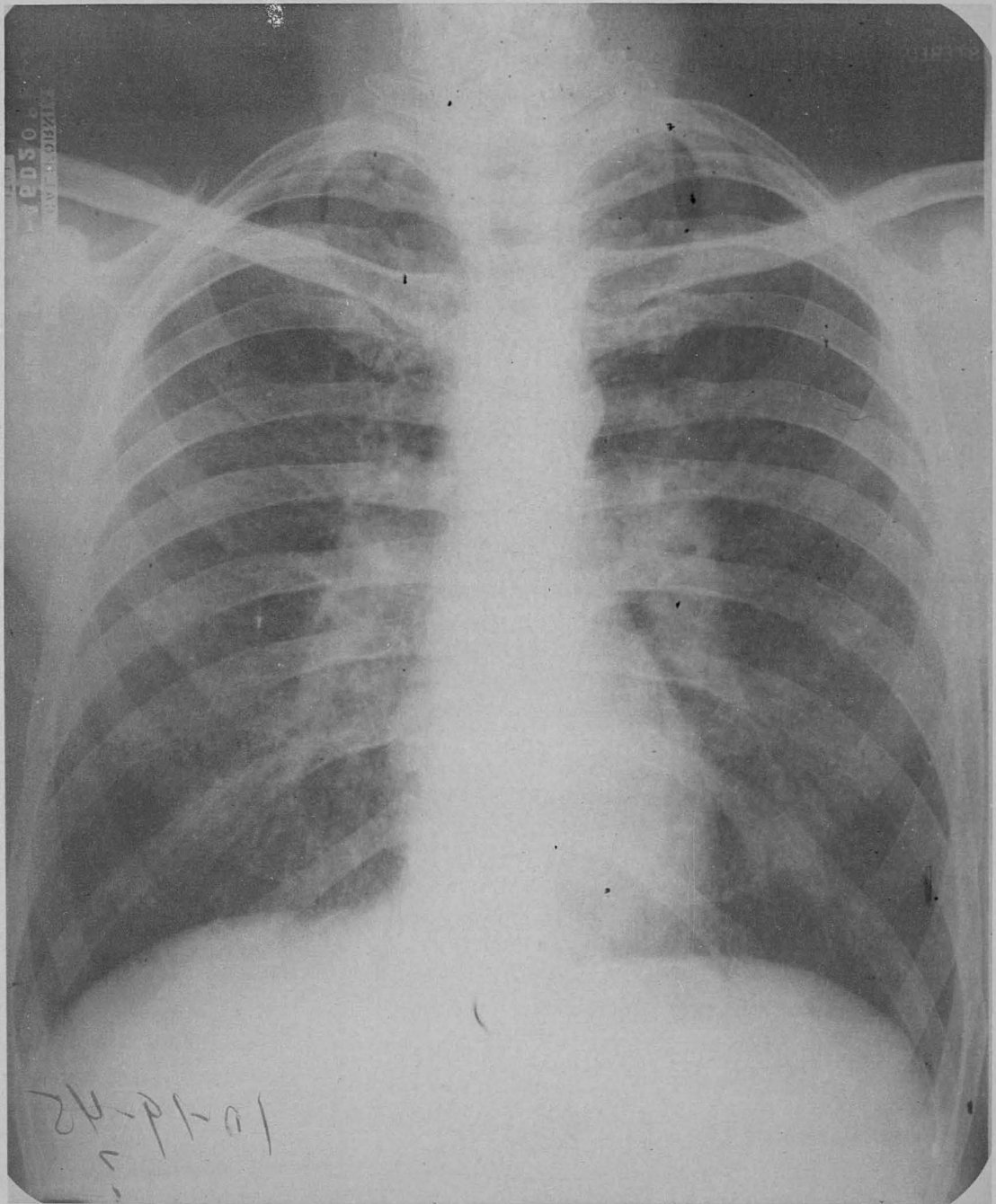


FIG. 2

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FIRST HOSPITALIZATION: The patient entered the hospital on January 4, 1946.* At the time of his admission he showed marked dyspnea on climbing one flight of stairs. There was no dyspnea at rest and no orthopnea. During periods of dyspnea he complained of distress during inspiration rather than during expiration. Deep inspiration elicited involuntary coughing. There was no hemoptysis, fever, or night sweats. Some cyanosis had developed with the present illness.

Physical Examination: The patient was a slender, 31 year old, underweight male showing some evidence of recent weight loss, but otherwise well developed and nourished. Height, 187.5 cm; weight, 75.8 kg; temperature, 37° C; pulse, 90; respirations, 20; blood pressure, 130/100. There was cyanosis of the nail beds and lips, slight pallor of the skin, no clubbing of the fingers. There was a small lymph node felt in the left supraclavicular fossa and one at the anterior edge of the trapezius muscle on the right. There was no generalized adenopathy. The thorax was long with a narrow A-P diameter, and expanded symmetrically with an expansion of 4 inches. The clavicles were held in an elevated position. The supra and infraclavicular fossae were retracted. There was no abnormal fremitus; resonance was slightly impaired bilaterally. Breath sounds were roughened, and the expiratory phases were prolonged. Crepitant rales were heard with inspiration on both sides posteriorly and over the right upper chest anteriorly. There were inconstant, fine, rales at both apices and at the right base. These rales persisted after coughing. There were no abnormal cardiac findings. The liver was palpable at the right costal margin and in the midline three cm below the xiphoid. The upper border was thought to be at the level of the seventh intercostal space. It was non-tender and firm. The

* The patient during this hospitalization and until sometime after his second hospitalization, was under the care of Dr. S. P. Lucia, to whom we are indebted for the results of the hospital studies.

spleen was not palpable. Genitals were normal. The rectal examination was negative. Extremities were normal, except for cyanosis of the nail beds. Reflexes were normal throughout.

Laboratory Findings:

Blood: Hgb., 15.9 gms; RBC, 5.34 M; WBC, 3,500; PMN, 60 percent (F, 44 percent; N-F, 16 percent); Lymph., 29 percent; Mono., 11 percent; hematocrit, 52; corrected Wintrobe sedimentation rate, 25 mm. Heterophile antibody determination was negative.

Urine: slightly cloudy, yellow; specific gravity, 1.015; reaction, neutral; reduction, green; acetone, negative; albumin, negative; microscopic: slight amount of mucus, occasional epithelial cells, amorphous debris.

A Mosenthal urine concentration test showed a maximum specific gravity of 1.033.

A urea clearance test showed 87 percent A.N.F.

I. V. pyelograms were done on January 9, 1946, and no intrinsic pathology of the urinary tract was found.

Vital Capacity was 3.8 liters.

Tuberculin, 1 to 1,000, intradermally was negative after 48 hours; tuberculin, 1 to 100, intradermally was negative after 48 hours.

Coccidioidin, 1 to 1,000 was negative after 48 hours.

Agglutination tests were done for Undulant Fever, Tularemia, Typhoid, Paratyphoid A and Paratyphoid B. All were negative.

Davidsohn's presumptive test for Infectious Mononucleosis was negative.

Cold agglutination titer was negative.

Complement fixation for Psittacosis was negative.

A sternal marrow aspiration was done. No definite abnormality was found.

A lymph node biopsy from the right inguinal region on January 9, 1946, showed the following upon microscopic examination: the capsule of the lymph node shows an increase in its thickness secondary to collagenous proliferation. The sinusoids beneath the capsule show a moderate dilatation. Germinal centers are prominent and show a loose structure throughout of lymphocytes. The medullary sinusoids are dilated and show some sinusoidal reticulo-endothelial hyperplasia. Usually the central portion of the medullary aspect of the nodes is considerably fibrosed. There is nothing present to suggest Boeck's sarcoid. Diagnosis: lymph node.

A cervical lymph node was removed for biopsy and microscopic examination on January 17, 1946, which revealed: sections show lymph node tissue having germinal follicles. Throughout the gland scattered at random there are round and oval cellular structures completely replacing the normal tissue. These nodules are mainly made up of large cells with abundant palely staining, eosinophilic cytoplasm and large vesicular nuclei. The cell boundaries are indistinct with thin cytoplasmic projections extending across the clear intercellular spaces. Infiltrating this reticular mesh are seen a fair number of lymphocytes and plasma cells. No caseation is noted, no giant cells are found, and only a very thin minimal fibrous reaction is occasionally present, which is confined strictly to the immediate peri-nodular region. No acid fast organisms are found. Diagnosis: lymph node - compatible with Boeck's sarcoid. Tuberculosis cannot be ruled out.

X-ray films of the chest were taken on January 7 and January 17, 1946. Widespread infiltration throughout the lungs and apparent enlargement of the hilar nodes and/or pulmonary arteries were found.

He was discharged from the hospital on January 12, 1946. The diagnosis

of his disease was not clear. Sarcoidosis, toxicity from radioactive materials, pulmonary tuberculosis and pneumoconiosis were being considered.

INTERVAL NOTE: After discharge from the hospital, the patient spent the period from February to April, 1946, at Yuma, Arizona, in a dry warm climate at low elevation. In May, 1946, he was put on potassium iodide.

In general, after May he felt better with some improvement in his recovery time following exercise. Exertional dyspnea persisted however: after walking two blocks on the level or up one flight of stairs he needed two to four minutes to catch his breath. He had an irritative cough upon lying down at bedtime. In the mornings he produced two to three cc of yellow mucoid sputum with no blood streaking. Coughing often caused sore throat and anterior chest pain. Exertion occasionally caused some dull, precordial pain which rapidly subsided with rest. Repeated chest films showed no change in either the quality or quantity of the lesions throughout the chest and no change in the evidence of lymph node enlargement in the hilum (Fig. 3).

A cold agglutination test on May 6, 1946, was negative. A complement fixation test for Psittacosis was negative on June 13, 1946. On October 14, a blood sample was sent to Dr. C. E. Smith of Stanford University for Coccidioides studies. He reported "the complement fixation tests, serial dilutions of serum (0.25 cc) - entirely negative. Precipitin tests, serial dilutions of antigen - entirely negative. Conclusion: no evidence of active infection due to Coccidioides immitis. Confirms belief that his illness is not coccidioidal and checks with negative coccidioidin."

There were no urinary symptoms. However, on December 27, 1946, the urine was found to be slightly cloudy, yellow, with a specific gravity of 1.025 and reaction of 5.5. Microscopically there were many red and white cells per H.P.F.

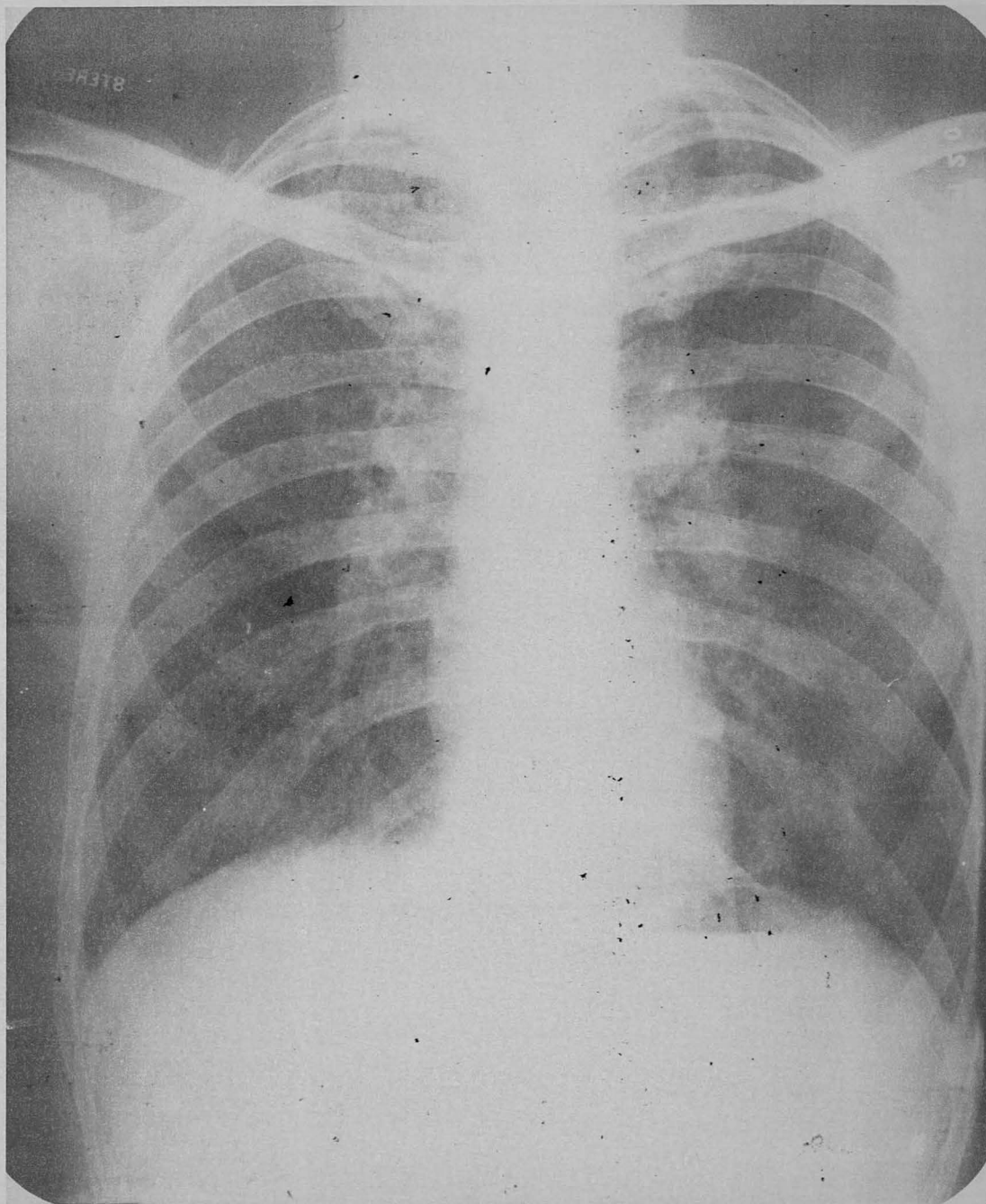


FIG. 3

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and some bacteria. The urinalysis was repeated on January 7, 1947, at which time it was slightly cloudy and yellow with three to five red cells and seven to ten white cells per H.P.F. Three granular casts were seen on the slide.

SECOND HOSPITALIZATION: He re-entered the University of California Hospital on February 17, 1947, because of microscopic hematuria and because of persistent dyspnea and palpitation on exertion since the onset of his illness one and one-half years previously.

Physical Examination: The patient was a fairly healthy appearing, pleasant young man showing evidence of weight loss, but in no acute distress. His temperature was 36.5° C, pulse 84, respirations 23 and blood pressure 135/95. The skin was pale; no cyanosis was noted. There were scars in the right cervical and inguinal regions from his recent biopsies. There was a suggestion of deep post-cervical nodes, but no discreet nodules were felt. Findings in the head and neck were normal. The expansion of the thorax was equal on both sides, amounting to 3-1/2 to 4 inches. There was dullness in the right base posteriorly, fine rales through both upper-posterior lung fields, which partially cleared on coughing, and generalized emphysema. The area of cardiac dullness was not enlarged; the PMI was in the fifth interspace in the mid-clavicular line. P-2 was greater than A-2. There was a questionable soft pulmonic systolic murmur. The liver was not enlarged to palpation. There was no clubbing of the fingers and no edema or tremor of the extremities.

Laboratory Findings:

Blood: Hgb., 19.5 gms; RBC, 5.97 M; WBC, 4,900; PMN, 68 percent (F, 60 percent; N-F, 8 percent); PME, 1 percent; PMB, 1 percent; Lymph., 26 percent; Mono., 4 percent. The K. and K. was negative. Corrected Wintrobe sedimentation rate was 8 mm; PCV, 50.5 percent.

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Urine: yellow, cloudy; specific gravity, 1.020; reaction, alkaline; reduction, none; albumin, none; microscopic: amorphous phosphates, occasional WBC per H.P.F. A Mosenthal test showed a maximum specific gravity of 1.027, two to three WBC and five to six RBC per H.P.F., and one to two granular casts per slide. A PSP test showed 30 percent excretion of the dye in the first 15 minutes. After several days in the hospital an Addis count showed no abnormal hematuria; casts and WBC were above normal.

An intravenous pyelogram was reported to show no evidence of disease in the kidneys or ureters. The left kidney was rather broad but not otherwise unusual in appearance. The demonstration of the calices on the left was not sufficiently good to exclude disease.

Four stool examinations were reported: Endamoeba coli and E. coli were the only organisms recorded.

Blood serum proteins totaled 7.11 gms percent, albumin, 4.22 gm percent; globulin, 2.69 gm percent.

The NPN was 39 mg percent.

Cold agglutinins were negative at serum dilutions of 1:10 to 1:160.

Agglutination tests for Typhoid, Paratyphoid A, Paratyphoid B, Tularemia and Brucellosis were negative.

Trichinella skin test, 1:10, was negative.

The vital capacity was 1,800 cc.

Twenty-four and thirty-six hour sputum specimens were examined microscopically and were negative for acid fast organisms and for fungi.

A Feldman culture on a 24 hour sputum specimen was negative for acid fast rods after 2-1/2 months.

A Sabouraud culture of the sputum was negative for fungi.

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Repeated Sabouraud and Feldman cultures were negative after 2-1/2 months. A guinea pig was inoculated and was negative for tuberculosis on autopsy April 23, 1947.

A marrow tap was done, and was within limits of normal.

X-ray studies were done on February 18, 1947 (see Fig. 4). They were reported as showing "no evidence of change in the appearance of the widespread fibrotic process in both lungs and the small heart and the peripheral emphysema. Hands appear normal."

At the time the patient was discharged from the hospital, on February 25, 1947, the etiological diagnosis could not be established, but the patient was thought to have chronic diffuse interstitial fibrosis of the lungs with emphysema - etiology undetermined; secondary polycythemia and early cor pulmonale; and possible renal embolus from pulmonary vein thrombus.

The diagnostic possibilities were discussed at some length during this hospital stay and it was agreed that the main question revolved about the determination of a specific agent to which his symptoms and lung findings could be attributed.

The thoughts at the time were that the chronic afebrile course with negative sputum and skin tests made tuberculosis unlikely. Coccidiosis, psittacosis and virus infections seemed to be ruled out by serological tests. There remained the possibility of other parasitic or fungus diseases including Ascaris infestation, blastomycosis, torulosis and geotrichosis. The possibility that aspergillosis and histoplasmosis could result in the fibrosis was also considered. A strong possibility of an industrial disease in this patient, which is suggested by his work with radioactive and other chemical agents, was mentioned. Beryllium was mentioned as a possible etiological agent because it is known to

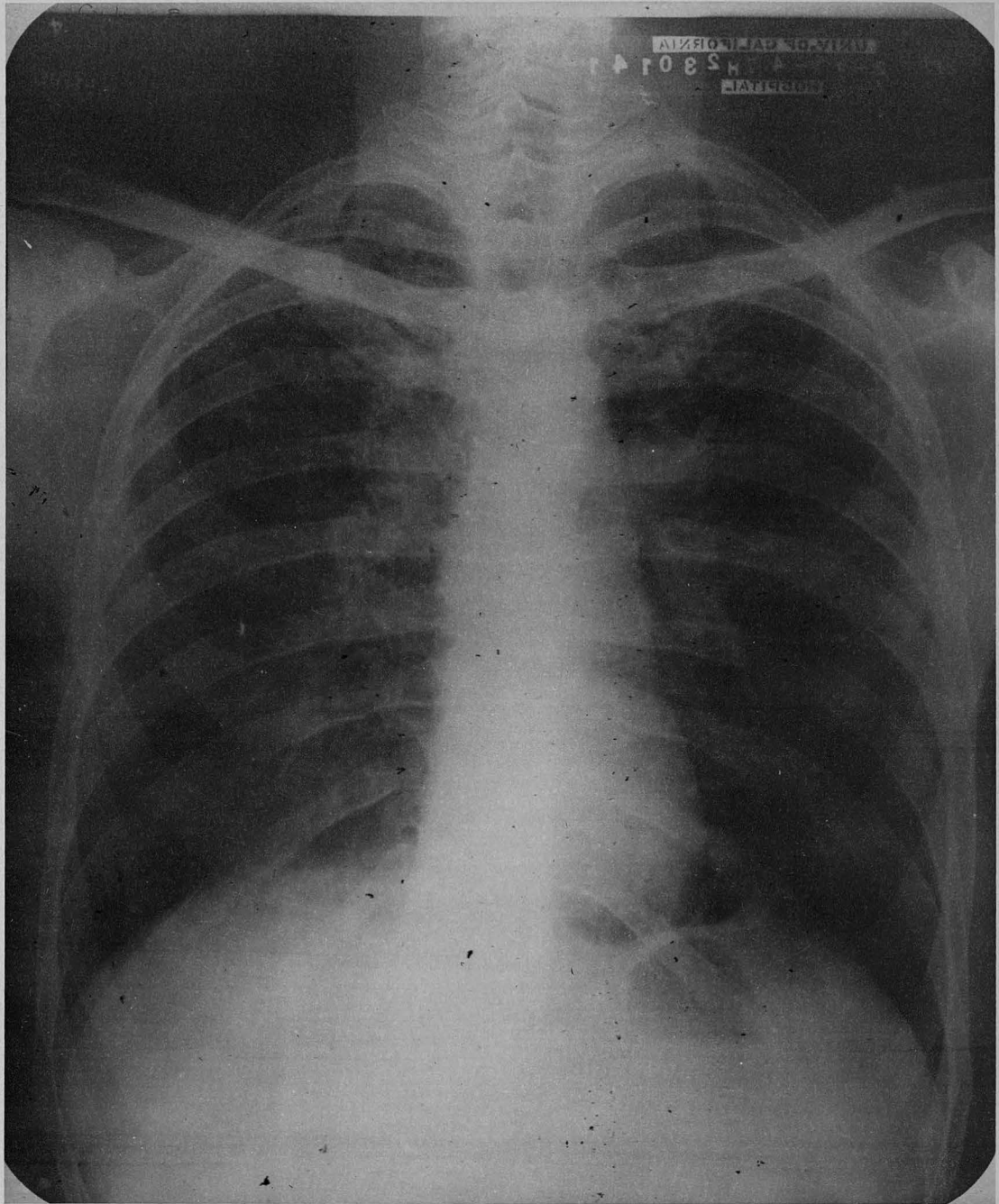


FIG. 4

-13-

cause chronic fibrosing pneumonitis (1); uranium was also considered because it is known to cause kidney damage. It was thought that Boeck's sarcoid would be a diagnosis of exclusion in this case since there was no real indication of a positive nature. Mention also was made of cases of acute diffuse interstitial fibrosis of the lung, reported by Hamman and Rich in 1944 (2), and by Eder et al. in 1945 (3), which presented similar pictures of exertional dyspnea, cough, cyanosis, cor pulmonale and diffuse pulmonary infiltration, but with pain, pleural friction rub and a fatal course with terminal bronchopneumonia and peripheral and renal emboli from small pulmonary vein thrombi. Pancreatic fibrosis was also present. The etiology of the underlying pulmonary disease in these cases remained obscure. It was suggested that perhaps this patient might represent a static chronic phase at this time of the same type of process.

The primary discharge diagnosis was, however, chronic diffuse interstitial fibrosis of the lungs with emphysema - etiology undetermined.

INTERVAL NOTE: During the two year period following his discharge from the hospital, February, 1947, until December, 1948, the patient changed very little clinically. He carried on his work at the Radiation Laboratory, but continued to have exertional dyspnea. There was no weight change. He coughed two or three times during the night and two or three times during the day with the production of a small amount of yellow sputum; there was no blood streaking. A blood count in August, 1948, showed the Hgb., 18 gms; RBC, 6.28 M; and WBC, 14,000.

Although the patient reported no change in his symptoms, it was apparent to those who observed him that his dyspnea had increased and was very noticeable at rest. Chest films taken late in 1947 revealed small bilateral apical pneumothoraces, and there was an increase in the density of the hilar shadows (Fig. 5).

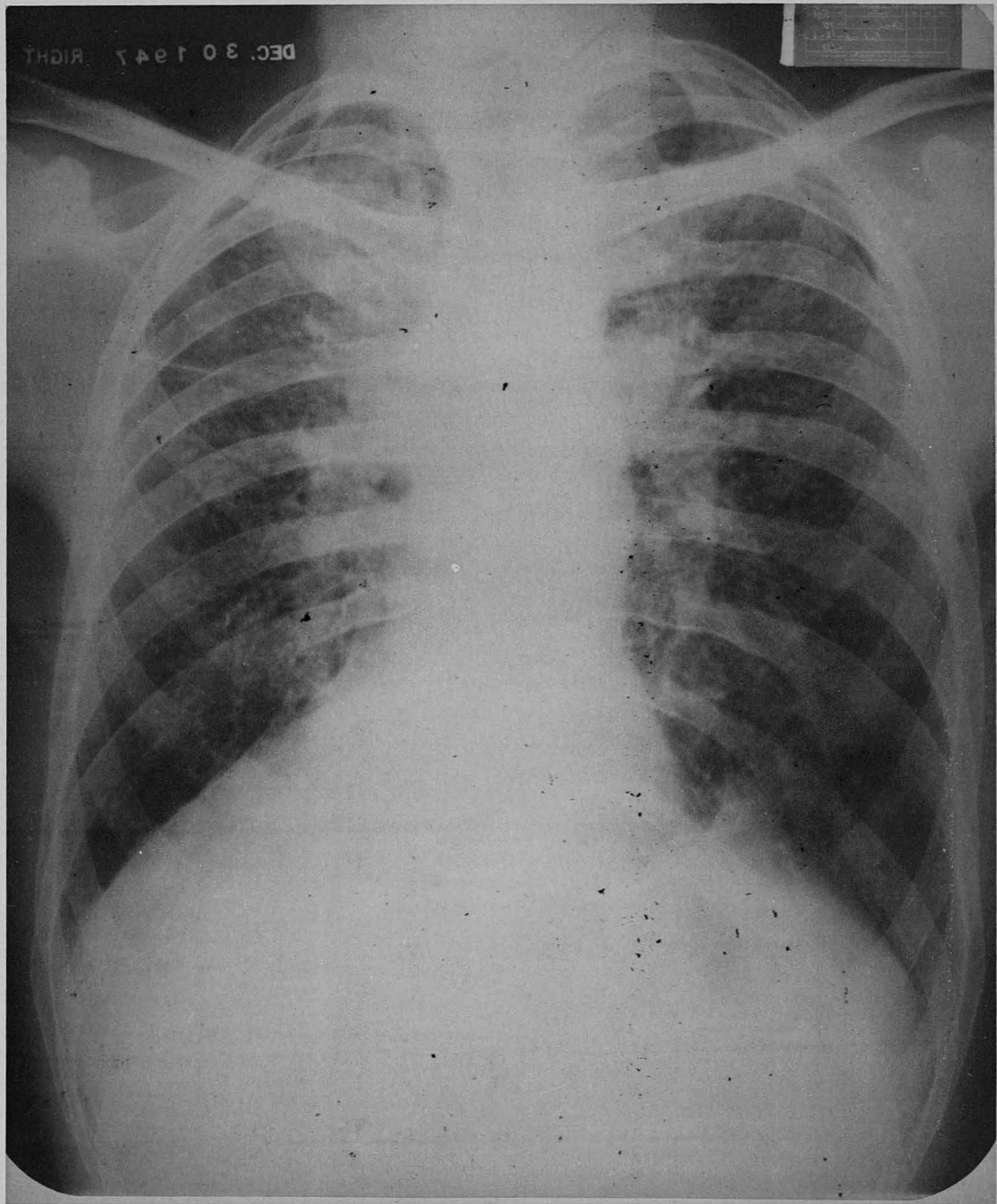


FIG. 5

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Films taken during 1948 showed changes in the pneumothoraces, but the parenchymal shadows remained for the most part the same (Figs. 6 and 7). Early in December, 1948, the vital capacity was 1,750 cc. Because of the typical slowly progressive downhill course and the characteristic symptoms and signs the diagnosis considered at this time to be most likely was chronic pulmonary disease caused by beryllium.

On December 12, 1948, while the patient was at home resting, he developed fairly suddenly a severe pain in the left chest and marked dyspnea. He was thought to have a spontaneous pneumothorax. Twelve hours after the onset of his pain, the patient was hospitalized.

THIRD HOSPITALIZATION: The patient entered the Alta Bates Hospital in Berkeley on December 12, 1948.*

Physical Examination: His temperature on admission was 103.2° F, pulse rate 160, respirations 28. The patient was acutely dyspneic and cyanotic. The trachea and mediastinum were shifted to the right. The left chest was tympanitic with diminished to absent breath sounds. Many fine to crackling rales were heard in the right lower chest. The point of maximal impulse was at the right sternal border. Other physical findings were a single tiny right epitrochlear lymph node and two small left axillary nodes. Abdominal findings were negative. There was a faint suggestion of clubbing of the fingers. No edema was present.

Laboratory Findings:

Blood: Hgb., 14.9 gms; RBC, 5.18 M; WBC, 16,500, with 97 percent neutrophils. The hematocrit was 50 percent.

Urine: specific gravity, 1.028; there was a trace of albumin; no sugar; three WBC per H.P.F.

An EKG showed slight right axis deviation.

* During this hospitalization the patient was under the care of Dr. A. F. Goggio, to whom we are indebted for the hospital record.

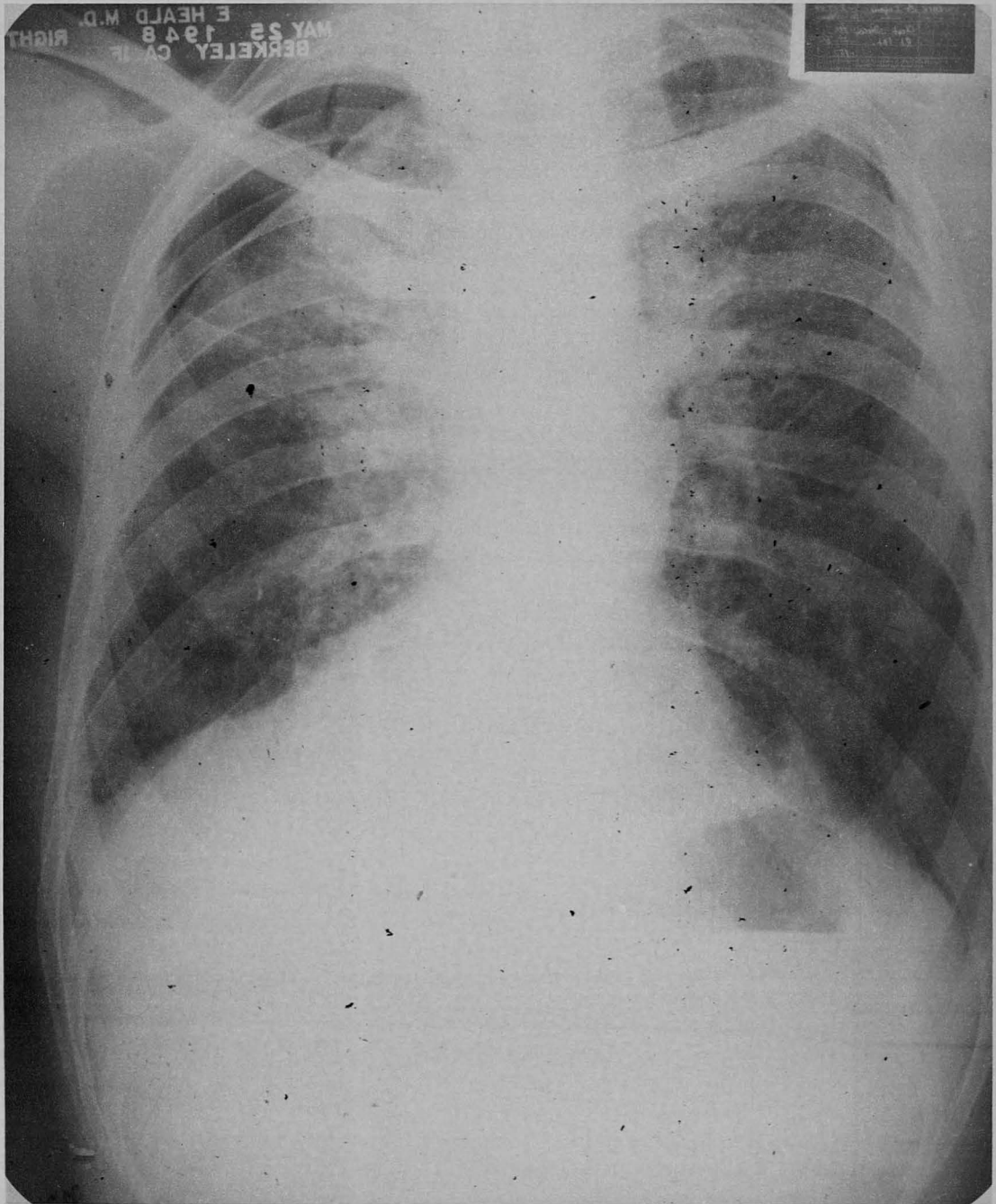


FIG. 6

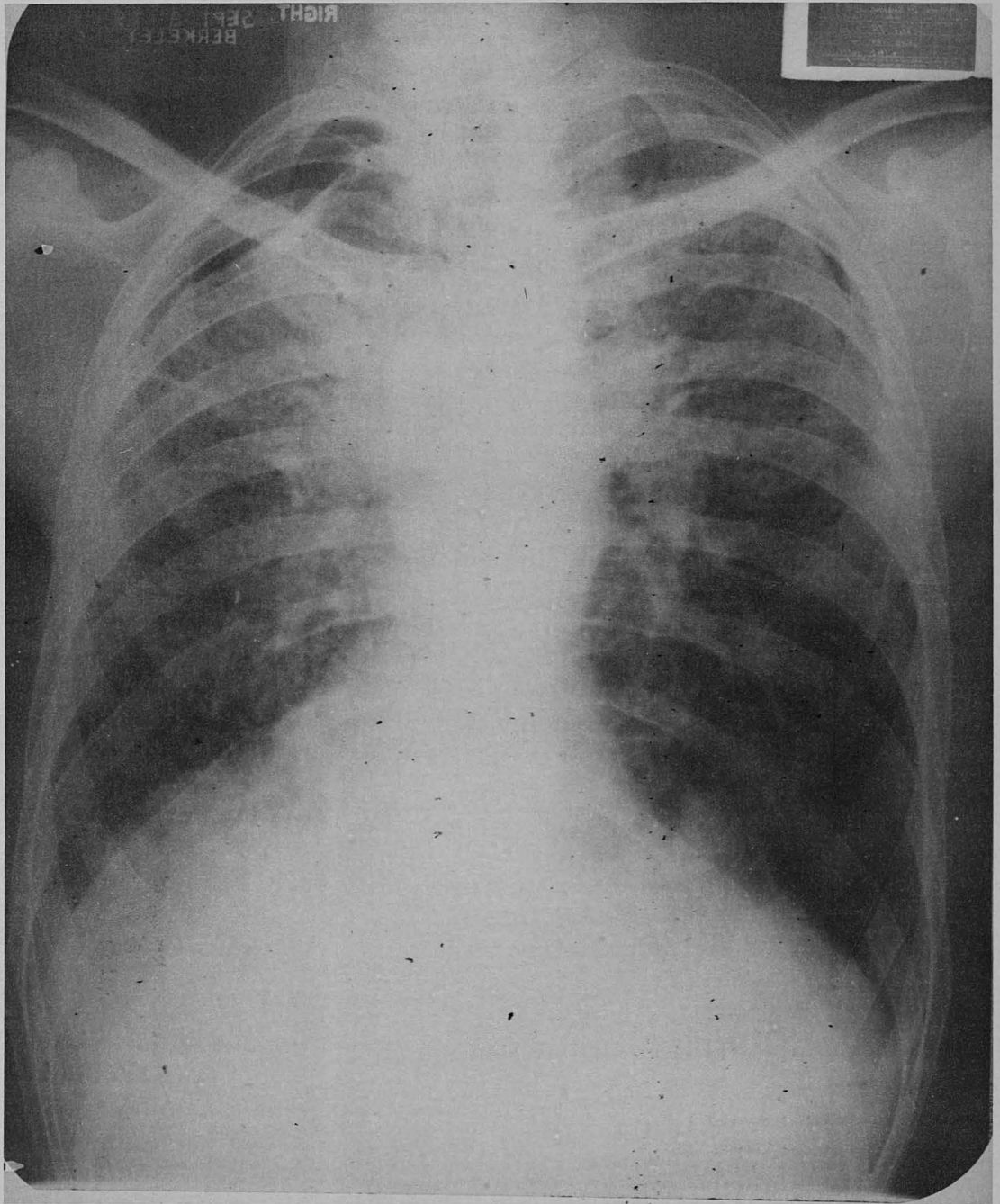


FIG. 7

A chest x-ray showed diffuse bilateral pulmonary disease, bilateral pneumothorax with mediastinal shift to the right (Fig. 8).

The diagnosis was acute left pneumothorax secondary to chronic pulmonary fibrosis. His course in the hospital was one of gradual improvement in an oxygen tent. His temperature after 24 hours in the hospital ran between normal and 100° F and his pulse gradually came down to the normal range. A chest x-ray repeated five days after the admission film showed some decrease in the left pneumothorax and a small amount of fluid in the left base (Fig. 9). In five more days the lung was re-expanded (Fig. 10). Since he continued to be dyspneic at bed rest and slightly cyanotic, it was felt that further hospitalization and observation were required. So he was discharged on December 23, 1948, and transferred by ambulance for sanatorium care.

FOURTH HOSPITALIZATION: He entered the Permanente Foundation Hospital at Vallejo on December 23, 1948.* During his stay in the hospital he improved considerably in strength and morale and learned to conduct his activities within the scope of his diminished pulmonary capacity. Continuous oxygen therapy, which was at first required at all times, was tapered off and discontinued. He was discharged from the hospital on May 14, 1949.

INTERVAL NOTE: He was well enough so that, after a short period of complete rest at home, he went to work three mornings a week at the Laboratory. Though he was very dyspneic with mild exertion, he was able to live fairly comfortably within the limits of his disease. There was no significant change in his condition until March 8, 1950, when while sitting at rest at home, he suddenly coughed up about 50 cc of bright red blood. A few hours later he coughed up a

* During this and his next hospitalization and the intervening period, the patient was under the continuous care of Dr. Seymour M. Farber, to whom we are indebted for the results of hospital studies.

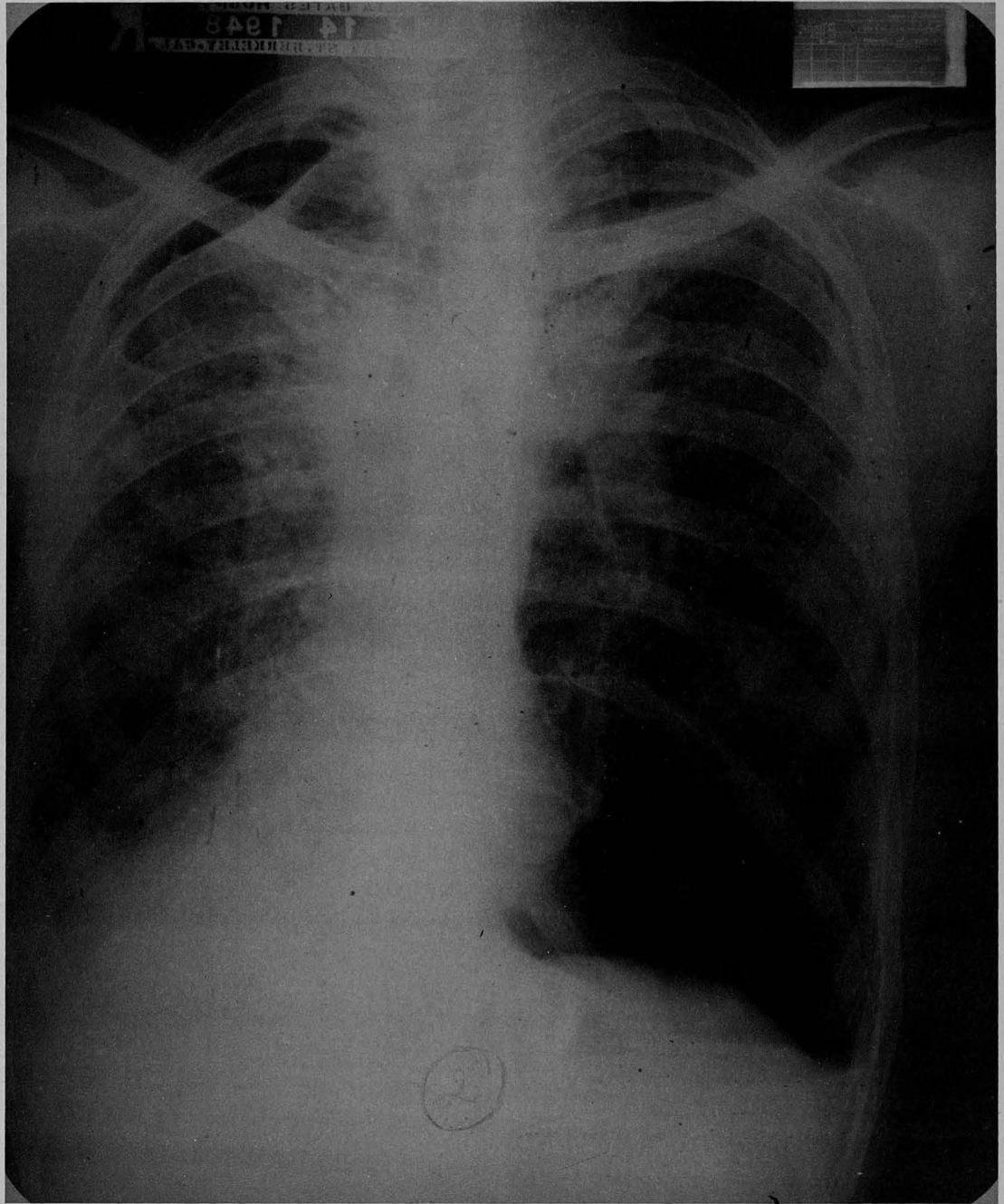


FIG. 8

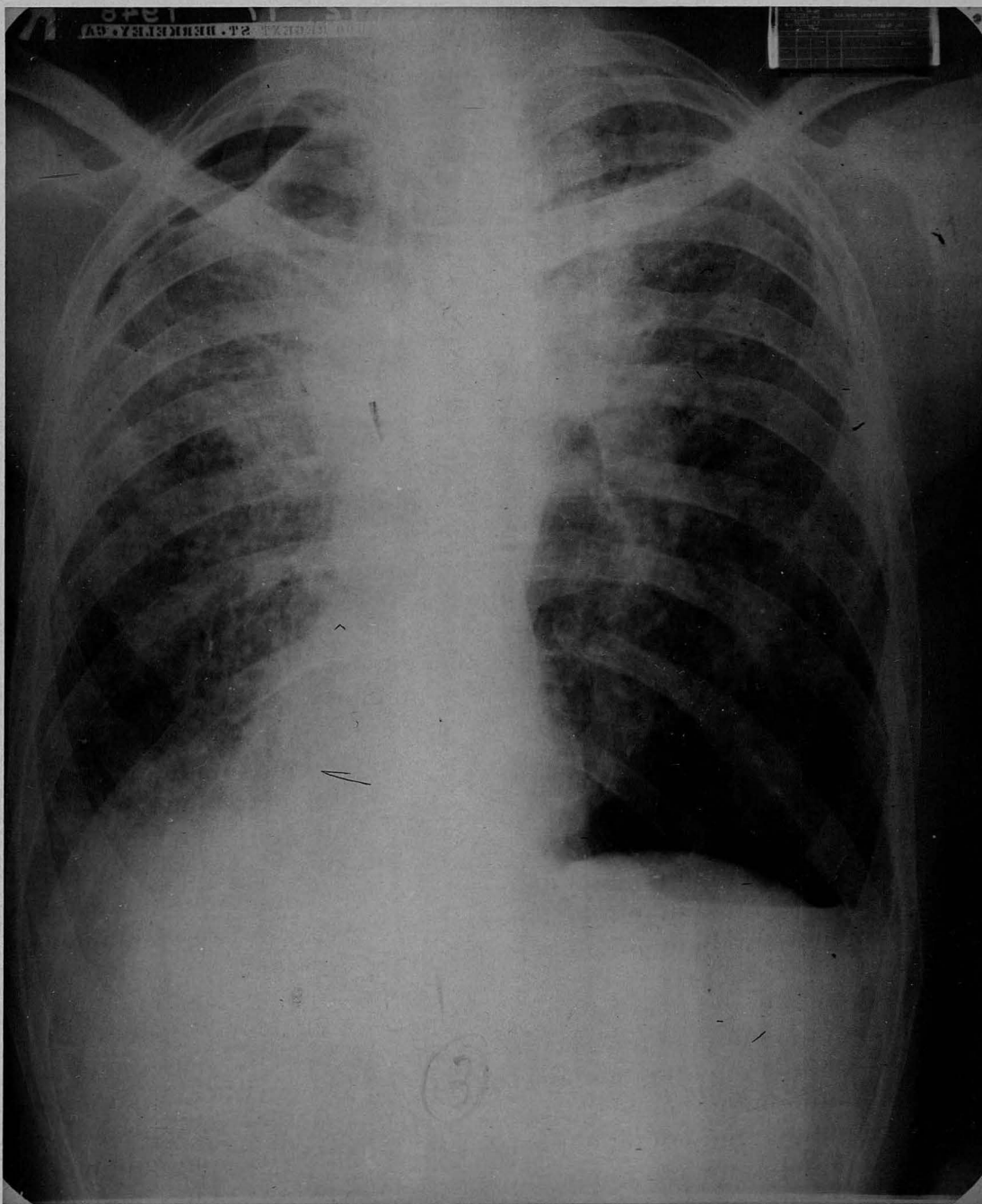


FIG. 9

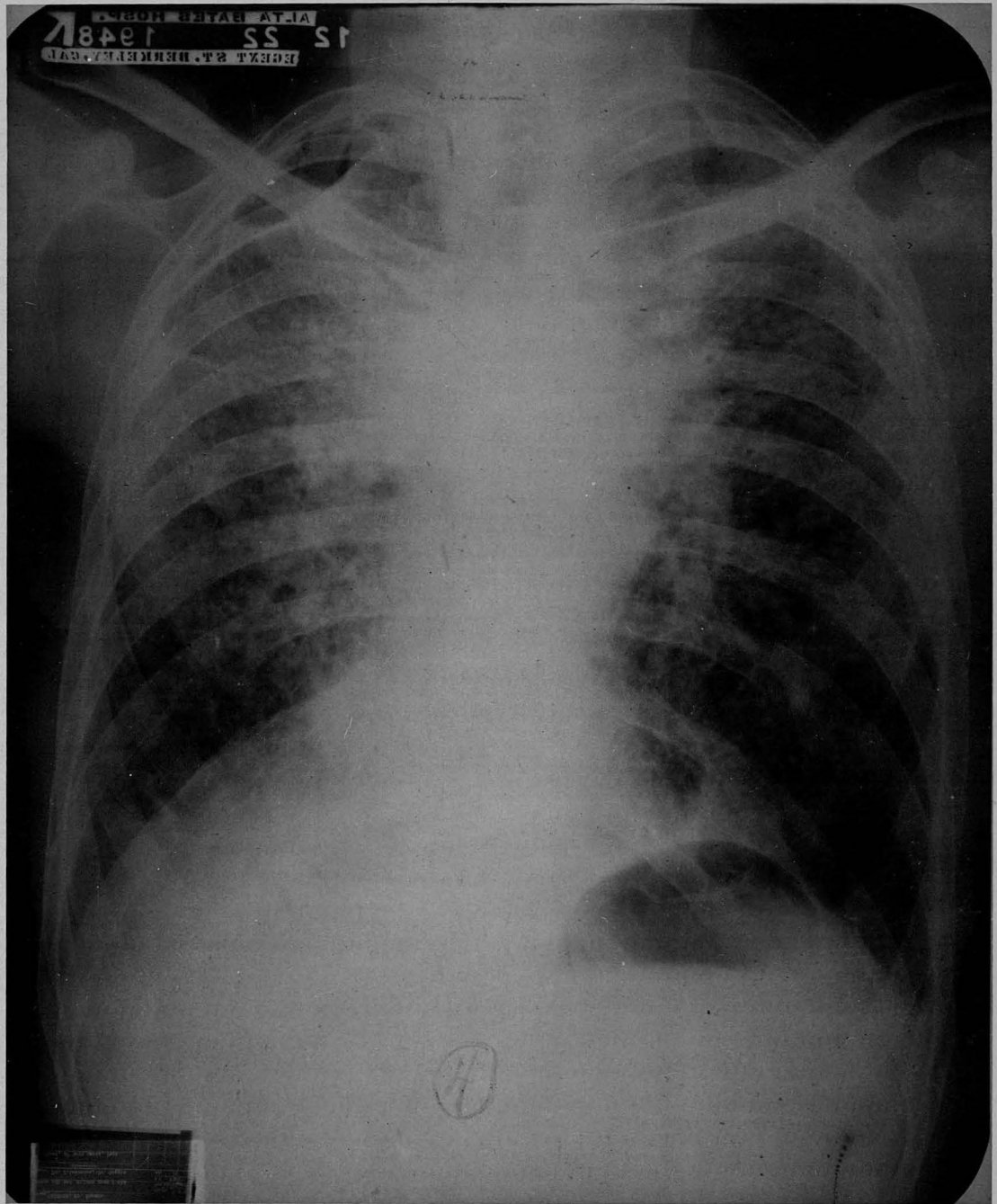


FIG. 10

-16-

small amount of frothy blood. No signs or other symptoms accompanied this episode, and he was kept at bed rest at home. A chest film on March 13, 1950, suggested some increase in the abnormal shadows in the lung fields (Fig. 11).

FIFTH HOSPITALIZATION: He was readmitted to the Permanente Hospital at Vallejo March 23, 1950, because his condition in general seemed to be deteriorating. He was dyspneic at rest and appeared gravely ill.

Physical Examination: On admission his temperature was 102.2° F, pulse 100, respirations 32, blood pressure 110/70. He was acutely ill and slightly dyspneic while in a semi-sitting position in an oxygen tent. When not in the tent there was cyanosis of the lips and fingernails and increased dyspnea. He appeared wasted and asthenic. There were no palpable lymph nodes. Respiratory movements of the thorax were limited. Throughout the lung fields were many inspiratory and expiratory coarse to crepitant rales and expiratory rhonchi. The percussion note was hyperresonant at both bases. The breath sounds were broncho-vesicular over both bases, but obscured elsewhere by the rales. The PMI was in the 4th left interspace. Cardiac rhythm was regular. The heart sounds were good; P-2 was greater than A-2. There were no murmurs. No masses or tenderness were noted in the abdomen. The fingernails were long and curved anteriorly with slight cyanosis. True clubbing was questionable.

While in the hospital he had daily spiking temperature ranging between 98° and 100° F in the morning and 102° and 103.8° F in the afternoon. The pulse ranged from 90 in the morning to 130 in the afternoon and while continuously in the oxygen tent the respirations were roughly 30 per minute.

Laboratory Findings:

Blood: Hgb., 14.1 gms; RBC, 4.75 M; WBC, 14,700; PMN, 54 percent (N-F, 12 percent); Lymph., 30 percent; Mono., 3 percent; PME, none; FMB, 1 percent.

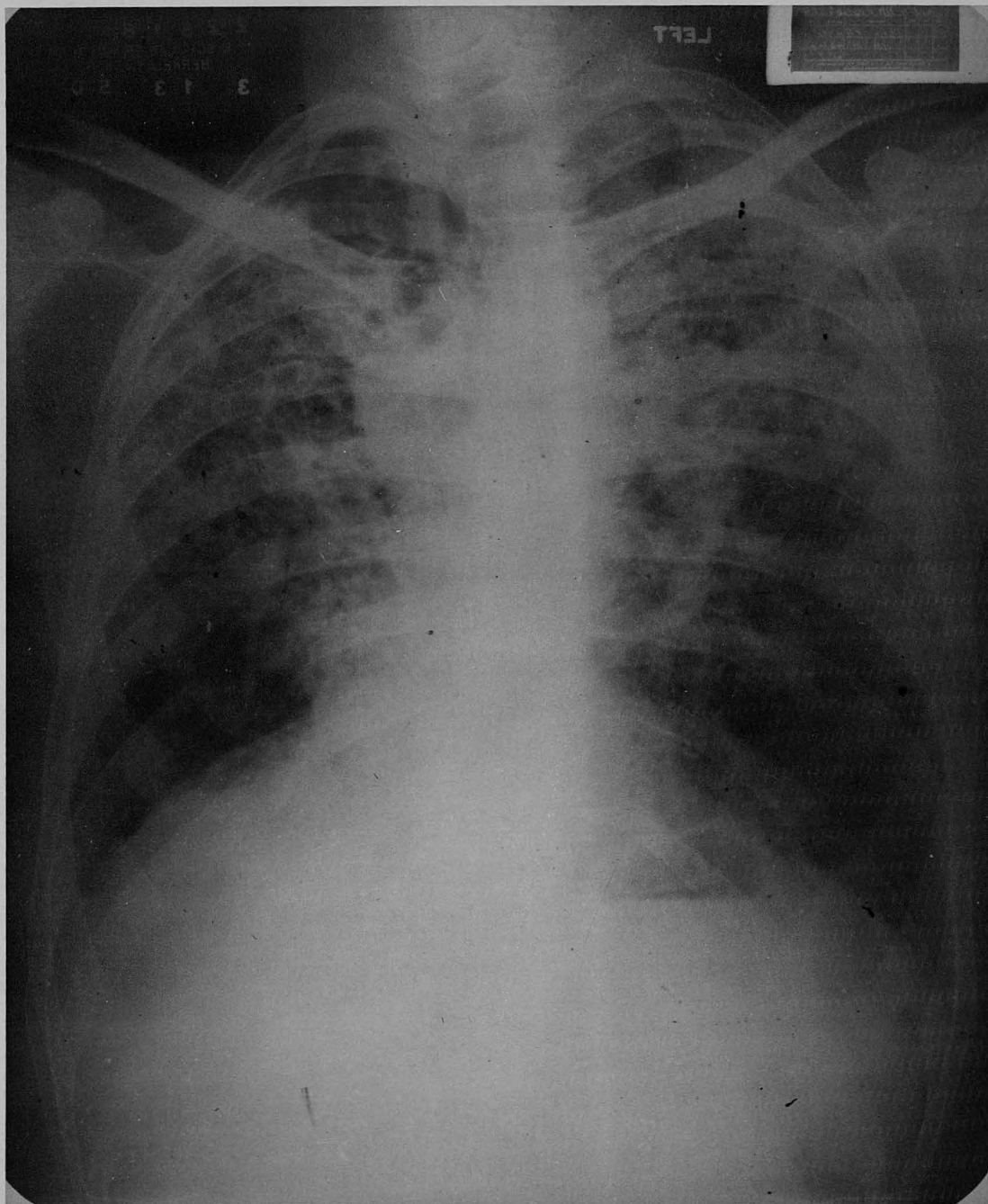


FIG. II

-17-

Urine: cloudy, yellow; p. H., 5; specific gravity, 1.020; negative for albumin and sugar; large amount amorphous urates seen microscopically.

Because of the fever, it was thought that the patient probably had an infection in the chest in addition to the diffuse pulmonary fibrosis.

The diagnosis was diffuse pulmonary fibrosis - etiology unknown, but probably beryllium; emphysema, cor pulmonale, hemoptysis and probable superimposed tuberculosis.

He was treated with penicillin, aureomycin, streptomycin and paraaminosalicylic acid.

On March 25, 1950, at three o'clock in the afternoon while lying quietly in bed, there was a massive spontaneous hemoptysis of about 700 cc of bright red frothy blood. The patient became very weak and appeared moribund. The fever was not noticeably affected by combined antibiotic therapy. He received oxygen continuously. A chest x-ray taken with a portable machine on April 19, 1950, showed a definite increase in the pulmonary shadow especially in the left upper field (Fig. 12).

On April 25, 1950, acid fast bacilli were found by microscopic examination of a sputum specimen. Sputum specimens were sent to the State Laboratory for culture and guinea pig inoculation. Both were subsequently found positive for tubercle bacilli.

The spiking febrile course continued and the patient seemed to be going down hill. A consultant in Industrial Medicine was asked to see the patient and review the case.*

After a thorough review of the record, of the progress and status of the

* Dr. Leon Lewis, then Associate Professor of Industrial Medicine, University of California, Berkeley.



FIG. 12

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patient, and in light of the history of exposure to beryllium oxide, which was obtained at that time, it was again emphasized that the most likely diagnosis was delayed chemical pneumonitis caused by beryllium or its compounds, and pulmonary tuberculosis. Treatment with adrenocorticotrophic hormone or cortisone was suggested.

Cortisone therapy was started on April 13, 1950, with a dosage of 100 mg three times a day. The streptomycin was continued. Three days after the beginning of cortisone therapy, the temperature, which had been swinging daily from 100° to almost 104°, fell to 98.8° F. During the next three days, however, it rose to 100, 101, and 102.5° F. At this time ACTH was substituted for cortisone, 100 mg per day being given in divided doses. The temperature promptly fell within 24 hours to 100.2° F. During the next week it did not rise above 99.6° F, and subsequently the temperature was normal. The pulse response was equally dramatic. Daily swings from 90 to 120 changed to 60 to 80. Streptomycin was continued throughout this time. During the next few weeks the patient's clinical condition was markedly improved. His appetite increased and he was able to be out of the oxygen tent for two to three hours without becoming cyanotic. His lung sounds improved markedly and his vital capacity increased to 2,200 cc.

Following the initial response to ACTH therapy the patient's condition has failed to improve noticeably during the past six months with the exception of some clearing of the x-ray shadows ascribed to his tuberculosis in the upper lung fields, especially on the left (Fig. 13). Three weeks after ACTH was started the dose was reduced to 25 mg for one day. By night there was considerable increase in moisture in the lungs, and by the next morning the temperature was up to 101.2° F. The patient became much worse clinically. The dose was then increased to 75 mg daily in divided doses, and the patient promptly returned to his improved status.

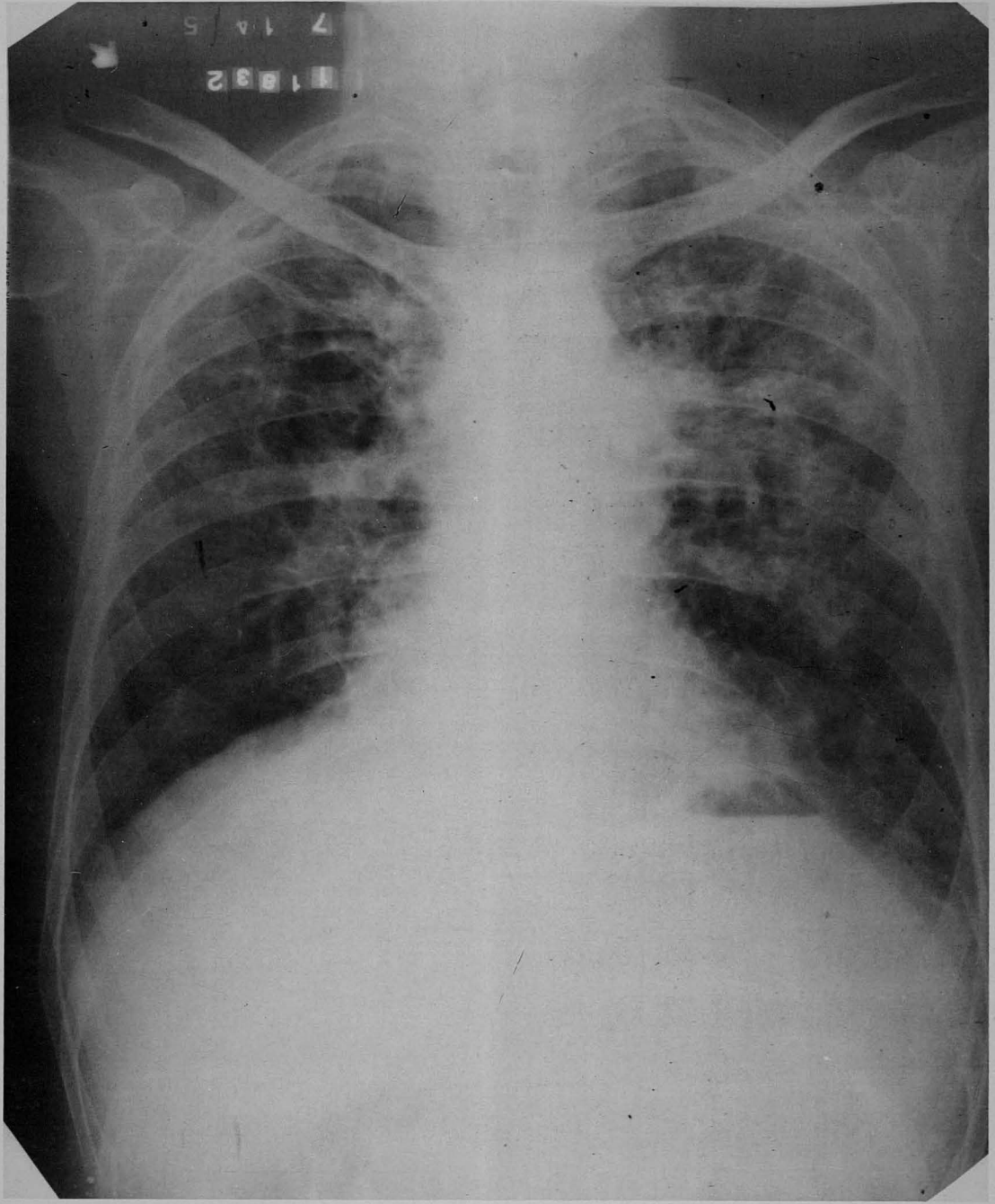


FIG. 13

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Ancillary treatment has consisted of low sodium, high potassium diet, calcium lactate 1 gm five times daily, potassium chloride 3 gms five times daily, and ascorbic acid 500 mg five times daily.

The patient has slowly developed a moon face and has deposited a considerable amount of adipose tissue in the abdominal wall. Hypertension and abdominal striae have not appeared. He has not developed edema.

A few acid fast rods were still present three months after the start of ACTH, but the sputum culture at that time was negative. Since then the sputum has been negative.

DISCUSSION: The diagnostic possibilities which were considered early in this case were those entering into the differential diagnosis of a disease characterized by a diffuse nodular pattern of density seen by x-ray throughout the lung fields, associated with symptoms of weight loss, easy fatigability, cough, and exertional dyspnea. The early findings seemed compatible with tuberculosis, sarcoidosis, pneumoconiosis, pulmonary neoplasm, Hodgkin's disease, and a number of other bacterial, virus and fungus diseases such as tularemia, psittacosis and coccidiosis. As was pointed out in the discussion of his second hospitalization (see page 12), the chronic afebrile course with negative sputum and skin tests, and negative guinea pig, seemed to rule out tuberculosis, as did negative serological tests the various infectious diseases being considered. Repeated stool and sputum examinations were likewise negative for parasites.

As the patient went into the third and then the fourth year of his disease, neoplasm of the lung could no longer be entertained as a diagnosis since such a malignancy could not be expected to run so long a course after metastases were as widespread as the nodules in the patient's lungs at the outset. It became apparent however, that the course of the disease was slowly progressing downhill.

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Of the remaining diagnostic possibilities, Hodgkin's disease was ruled out by the clinical course, absence of splenomegaly or lymphadenopathy, and the lymph node biopsies done during the first hospitalization. The skin lesions which are present in some 50 percent of patient's with Boeck's sarcoid (4) did not appear, nor did uveoparotid fever or involvement of the hands or feet. The course of sarcoidosis, which is characteristically benign and free from serious constitutional symptoms, stands in contrast to that of the patient. The disease then most certainly belongs in the group of pneumoconioses. There was no evidence of the patient's having been exposed to silica or other materials known to produce pneumoconiosis with the exception of the history of exposure, in 1942, to beryllium oxide in the form of a fine powder suspended in the air. This further substantiated the diagnosis of delayed chemical pneumonitis caused by beryllium. The onset of symptoms some time after exposure (in this case three years) is characteristic (1, 5). Additional evidence for implicating beryllium in the etiology of this disease would perhaps be provided by the recovery of beryllium from the patient. Since his exposure was apparently small, the probability is that significant amounts of the element will be found only in the lungs and hilar nodes. The patient has not been well enough to undergo a biopsy of a deep cervical node. Such a procedure is planned if the patient improves sufficiently. It is of interest to note here that the lymph node biopsy done in 1946, which was interpreted at the time to be compatible with Boeck's sarcoid or tuberculosis is by the same token compatible with berylliosis as well since the histological picture of the granulomatous lesions in these diseases may be very similar (1, 5, 6, 7, 8, 9, 10).

The response to ACTH was dramatic. The patient had been losing ground rapidly and appeared to be in extremis. Very soon after ACTH was begun he

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became exhilarated, his appetite, formerly very poor, became voracious, his temperature and pulse became normal, rales cleared from his lungs, his vital capacity improved from 1,750 cc to 2,300 cc. The patient became able to do without the oxygen tent for several hours at a time, and finally altogether. Having improved to a certain point, however, he appears to have remained stationary for several months. The patient is still bedridden, and can exert himself very little without marked dyspnea and fatigue. The disease is apparently not improving noticeably at this time. It is hoped that with continued therapy and observation it can be determined whether ACTH is exerting a beneficial effect on the primary pulmonary lesions.

SUMMARY: The case is presented of a young man with progressive pulmonary fibrosis or granulomatosis of five years duration presumably caused by the inhalation of beryllium oxide. His illness was complicated by the development of pulmonary tuberculosis. Treatment with ACTH caused remarkable improvement at a time when he appeared to be terminal. Following this he failed to improve further and his condition has remained stationary for six months on continued ACTH therapy.

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