CHRONIC BERYLLIUM POISONING

(Chronic Pulmonary Granulomatosis)

Preliminary Reports on Four Cases Treated with ACTH

H. S. VAN ORDSTRAND, M.D.
Department of Pulmonary Diseases

JOSEPH M. DE NARDI, M.D.*
and
ROBERT W. SCHNEIDER, M.D.
Department of Endocrinology and Metabolism

THE following case reports add confirmation to the recent article by Kennedy et al[1] (2 cases) which states that subjective and objective improvement have been demonstrated by the administration of ACTH in instances of chronic beryllium poisoning. Heretofore no therapy affording even temporary improvement has been found by us in progressive and severe cases of this disease. The factor of exposure to beryllium and/or its compounds has been present in each instance.

Case Reports

Case 1. A white man now 50 years of age was employed in a beryllium basic production plant on April 30, 1945. For the first 7 days he worked with the soluble fluoric salt compounds of beryllium but was transferred, because of evidence of dermal intolerance, to a department where melted and ground ore was treated with sulfuric acid. Three weeks later he developed a spasmodic productive cough, substernal discomfort and exertional dyspnea. A clinical diagnosis of acute chemical bronchitis was established. Roentgen examination of the chest was negative. Under ambulatory symptomatic therapy he made an uneventful recovery and returned to work on July 9, 1945; however, within 10 days the patient had a recurrence of subjective and objective symptoms. Following complete recovery he was ordered medically released from the industry on September 11, 1945.

His subsequent place of employment was approximately one and one-half miles from the beryllium plant and his permanent residence about nine miles away.

In October 1947 he first became aware of a refractive spasmodic productive cough, a progressive exertional dyspnea, and anorexia with associated weight loss.

The paroxysmal cough gradually increased in intensity and frequency and the expectorated mucus developed a greenish tinge. Exertional dyspnea and anorexia became pronounced. Eventually the severity of the symptoms forced him to forego all physical work in March 1948.

During the first 2 years of the disease the coughing paroxysms were associated with vertigo. Frequent attacks of "mild chills" and fever were experienced during the

*Lorain, Ohio

first few months following the onset and to a lesser degree up to the time of hospitalization in August 1950.

The patient was referred for consultation on April 26, 1948 following interpretation of a pulmonary roentgenogram. Temperature was normal, pulse 75, and respiratory rate 20. Blood pressure was 95/70. The vital capacity was read at 3.4 L. and computed as 82 per cent of the expected normal. The breath holding time was 20 seconds.

The patient did not appear acutely ill. Respiratory distress was not apparent at rest nor was acrocyanosis present.

Equal thoracic limitation of motion was noted on forced inspiratory effort at which time the patient complained of substernal pain. Percussion tone was unimpaired. No abnormalities were detected on auscultation.

The pulmonary roentgenogram taken on April 13, 1948 revealed a diffuse, granular involvement throughout the parenchyma of both lung fields. There was an associated prominence of hilar shadows without nodulation. X-rays of the hands showed no osseous changes. Clinical studies on blood and urine were essentially normal at this time. A diagnosis of "chronic pulmonary granulomatosis in a beryllium worker" was made.

The patient has been examined at regular and frequent intervals for the progress of the disease. Specialized studies were conducted at Rochester University School of Medicine in the fall of 1948.

Despite varied and intensive supportive therapy since the initial examination the patient became progressively worse and consequently was hospitalized on August 15, 1950.

Examination on hospital admission revealed a severely emaciated, mentally depressed patient exhibiting dyspnea at rest. Spasmodic coughing was pronounced during the entire examination.

Blood pressure was 110/74. The weight was 120, a 60 pound loss since the onset of symptoms in 1947. The vital capacity was read at 2.0 L. and computed as 48 per cent of the expected normal. Acrocyanosis and early clubbing of the finger tips were noticed. There was definite limitation of thoracic motion. The percussion tone was resonant throughout and sibilant rhonci were present at the bases.

A pulmonary roentgenogram taken on August 19, 1950 revealed the previouslv described pattern plus suggestive honeycombing of the upper part of each lung field.

Three days previously the patient had been placed on ACTH therapy. Up to September 7, 1950, the date of hospital discharge, he received a total of 1300 mg. of the drug. A maintenance dose of 20 mg. per diem is currently prescribed.

Roentgenograms taken on September 1 failed to reveal any appreciable change in the pattern. During the period of hospitalization several clinical blood studies and numerous urinalyses failed to disclose significant abnormalities. The temperature range was within normal limits, the pulse ranged between 80 and 100, and the respiratory rate between 20 and 30.

During the 3 weeks of hospitalization the patient developed an excellent appetite and gained 8 pounds. The mental outlook was definitely improved. A decrease in dyspnea and in the frequency of coughing paroxysms was noted.

The latest examination prior to this report was made on October 11. The patient has increased his weight to 132 pounds and his vital capacity to 2.4 L.

Case 2. A white woman, now 70 years of age, was referred in May 1950 for consultation on the basis of pulmonary roentgenogram interpretation.

The history of exposure to beryllium was rather meager. In 1941 she had resided two standard city blocks southwest of a beryllium basic production plant. From 1942

until the present time she has resided eight to nine blocks directly south of the same plant. No history of either direct or indirect contact with workers at the plant could be established. The patient did assert that, when living in the immediate area, she was conscious of fumes which caused coughing, especially at night.

Initial examination was made on May 17, 1949. The history of symptoms dated back to September 1948 with a coryza. The coryza improved but a definite "hoarseness" became apparent which was associated with a slight, "tickling" cough which gradually became productive in the course of several months.

The mucous was tenacious, of yellow color, and devoid of blood. The cough had progressed in severity and frequency and had been paralleled with a progressive dyspnea and a sense of substernal pressure and burning in the inspiratory phase. However the appetite had remained unimpaired and there had been no apparent weight loss.

The temperature was normal, pulse rate 96 and respiratory rate 32. Blood pressure was 150/70. The weight was 169 pounds; height 62½ inches. The vital capacity was read at 1.0 L. and computed at 32 per cent of the estimated normal. She exhibited severe dyspnea at rest. Pronounced acrocyanosis was noted. There was no pulmonary osteo-arthropathy.

Definite limitation of thoracic motion was evident. The patient complained of substernal pain on relatively mild inspiratory effort. Percussion tone was resonant throughout. Basal sibilant rhonci were present.

Pulmonary roentgenograms taken on May 18, 1949 revealed a diffuse granular involvement of the lung fields. The pattern indicated a diagnosis of chronic pulmonary granulomatosis. X-rays of the hands did not disclose osseous abnormalities as sometimes seen in Boeck's sarcoidosis.

The patient was examined at rather frequent intervals for progress of the disease. On November 29, 1949 clinical studies on a blood sample showed the following results: red blood count 5,300,000; hemoglobin 100 per cent; white cell count 12,150 with a normal differential; total protein of 7.2 mg. with an albumin globulin ratio of 1.7:1. Urinalysis was essentially negative.

As the patient's symptoms became progressively aggravated hospitalization for oxygen therapy became necessary on May 8, 1950. Until this time her mental outlook had been fairly optimistic and her cooperative spirit exceptional.

Examination on hospital admission revealed a rather well nourished but mentally depressed white woman, 62½ inches in height and weighing 160 pounds. Spasmodic coughing was almost constant throughout the examination. Constant high concentration of oxygen was necessary for the purpose of maintaining some degree of comfort. The respiratory rate was 48 per minute. Despite the oxygen therapy a pronounced acrocyanosis was apparent. The finger nails showed early evidence of "watch-glass" curving. Cardiac dullness was beyond normal limits bilaterally; cardiac rate was 120 and blood pressure 150/82. Thoracic motion was limited. The percussion tone was resonant throughout. Auscultation revealed sibilant inspiratory rhonci throughout. Moist rales were discerned at the bases posteriorly.

A pulmonary roentgenogram taken on May 10, 1950 revealed the same nodular and granular pattern of the parenchyma as previously described. Enlargement of the cardiac silhouette was evident.

Laboratory observations at admission were as follows: red blood count 4,140,000; hemoglobin 80 per cent; white blood count 10,250 with a normal differential; total protein of 10.4 mg. with an albumin globulin ratio of 1.3:1. Numerous urinalyses were essentially negative throughout her hospital stay. On September 27 the red blood count

was 4,520,000, hemoglobin 94 per cent, and white blood count 10,950 with a normal differential.

Approximately 4 Gm. of cortisone was administered between June 4 and 16, without any appreciable clinical response. Almost constant utilization of oxygen was necessary to relieve dyspnea and cyanosis. Due to an appreciable right sided cardiac failure with evidence of decompensation, mercuhydrin and digitalis were administered with some therapeutic response as shown by the disappearance of the peripheral edema.

On July 28 ACTH therapy was instituted. Until the date of hospital discharge 2 months later, she had received more than 3 Gm. of the drug. The patient has been on a daily maintenance dosage of 20 mg. of the drug to date.

In addition to cortisone and ACTH therapy, the patient received 12 million units of penicillin between May 14 and June 3 and also 10 Gm. of chloromycetin between July 24 and August 3. No apparent clinical improvement resulted from the use of the latter two drugs.

Pulmonary roentgenograms taken on August 7 disclosed some improvement. Further roentgen study on September 27 demonstrated additional improvement.

The temperature remained within normal limits throughout the period of hospitalization. The pulse rate ranged between 80 and 100; the respiratory rate between 20 and 40.

A gradual but appreciable clinical improvement was obvious within 2 days from the inception of ACTH therapy. Dyspnea and cyanosis receded. The need for oxygen became less frequent and has not been required since September 20. The mental attitude improved definitely and the patient acquired a rather optimistic attitude toward the future. There was a gradual weight loss despite a normal appetite. Some of this loss may be ascribed to the concomitant loss of cardiac decompensation edema. Weight at the beginning of ACTH therapy was 142 pounds as against a hospital discharge weight of 138 pounds.

Case 3. A 21-year-old housewife was admitted to the Cleveland Clinic Hospital on June 13, 1950, with the complaints of chronic cough, progressive shortness of breath and a 30 pound weight loss in the previous 3 years. She had been essentially bedfast during the last 7 months. The insidious onset, 3 years before, was postpartum and the symptoms were described as progressive and unrelenting. A diagnosis of sarcoidosis had been made elsewhere.

Past history was noncontributory except for the fact that, beginning in May, 1945, the patient had worked for 1 year as a baker on the ovens in a fluorescent tube manufacturing plant.

On initial examination obvious weight loss, cyanosis of the mucous membranes and nail beds, dyspnea at rest, moderate clubbing of the fingers and toes, and fine to medium inspiratory rales over the lower halves of both lung fields were evident, accompanied by a protodiastolic gallop rhythm. The temperature was normal, pulse rate 110, and weight 85 pounds with a height of 64 inches.

Stereoroentgenograms of the chest revealed a generalized fine nodulation with superimposed linear infiltration. The latter made the cardiovascular silhouette difficult to outline. X-ray examination of the hands showed changes in the terminal phalanges suggestive of hypertrophic osteo-arthropathy. The radiologist's interpretation of the chest was chronic berylliosis (chronic beryllium poisoning).

The clinical impression from the above studies was that of chronic beryllium poisoning (chronic pulmonary granulomatosis in a beryllium worker). The following studies were carried out: urinalyses negative in all respects; blood counts normal with the initial count showing 12.0 Gm. of hemoglobin with a white blood count of 6550 with a normal

differential; the blood sugar reading was normal with 93 mg. per cent fasting; Wassermann and Kahn reactions were negative; measurement of serum proteins by Kjeldahl's method showed an increase in the total proteins with a relative hyperglobulinemia, the total measuring 8.1 Gm. with 3.3 Gm. of albumin and 4.8 Gm. globulin; the erythrocyte sedimentation rate was elevated only slightly; multiple sputum examinations were negative on smear and cultural studies for tubercle bacilli, fusespirochetes, fungi and all other pathogenic organisms; neither of 2 electrocardiograms showed diagnostic changes; skin tests with coccidioidin and histoplasmin extracts were negative; the Kveim skin test for sarcoid, applied on June 13, 1950, was negative (with the site of the test being followed by periodic observations for 4 months); patch tests with 1 per cent buffered beryllium fluoride, beryllium sulfate and beryllium nitrate showed from 1 to 3 plus positive reactions. On admission the optimum vital capacity reading on 3 separate tests was 700 cc. (less than 25 per cent of the patient's computed normal). Arteriole oxygen saturation was 74 per cent.

On June 15 a right thoracotomy was performed by Dr. Donald B. Effler, head of the Department of Thoracic Surgery. Dr. John B. Hazard, Pathologist, interpreted the microscopic picture as representative of chronic pulmonary granulomatosis: "Sections reveal an intense inflammatory process, evidenced by pronounced thickening of alveolar walls due to an infiltration of lymphocytes and plasma cells and in addition forming the majority of the bulk in many areas; rather circumscribed collections of histiocytes, giant cells of foreign body type and in some places fibroblasts. Some of the giant cells show vacuolation of their cytoplasm. A connective tissue septum near one margin is of only slightly increased width and contains scattered lymphocytes. Alveolar lumina contain giant cells of foreign body type, occasional collections of histiocytes and pink granular coagulum in which are scattered lymphocytes. Bronchioles show a mucous membrane of usual character with common relationship to smooth muscle. Alveolar epithelium in some of the smaller alveoli which were found in regions of greatest involvement, is formed by cuboidal epithelium rather than usual flat type. There are no areas of caseous necrosis. A small amount of brownish-black granular pigment (carbon) is present in one area. The pleura shows engorged vessels and is infiltrated by moderate numbers of plasma cells, lymphocytes and a few eosinophiles."

Dr. Frank R. Dutra of the Kettering Laboratory of the University of Cincinnati studied a section of the above lung biopsy and agreed with Dr. Hazard that "microscopically the picture is that of beryllium granulomatosis."

Because of respiratory embarrassment and cyanosis, oxygen therapy had been instituted on the patient's first day of hospitalization. On June 21 a course of ACTH was instituted and continued until July 16, having been maintained under appropriate laboratory control and at maximum limits of tolerance. Within 24 hours the patient showed both subjective and objective improvement. Within 48 hours the cyanosis had disappeared and oxygen was discontinued. On June 28 the oxygen arteriole saturation was found to have risen to 85 per cent and within a week to 96 per cent. The vital capacity showed slow but steady improvement, measuring 1.5 L. (1500 cc.) by the time of discharge on July 25.

A second thoracotomy lung biopsy (this time on the left) was obtained by Dr. Effler on July 17. This Dr. Hazard reported as showing no apparent histologic change as compared with the previous biopsy.*

**It is to be emphasized that the quotation of no essential histologic change in the second biopsy after ACTH administration was qualitative. Dr. Hazard is carrying out further study of histologic detail from a quantitative standpoint as the amount of exudate may be quantitatively less in the second biopsy. This further study will be reported subsequently.*

The patient was returned to the hospital on August 3 because of recurrence of initial symptoms in the 72 hours previous to readmission. Her vital capacity was found to have dropped to 1 L. (1000 cc.). Mild cyanosis and the original gallop rhythm had reappeared. ACTH therapy was again instituted with satisfactory subjective and objective clinical response. On August 15 cortisone was substituted for ACTH. However as a mild relapse was observed, this medication was discontinued and ACTH resumed.

The patient was discharged on August 28, on an established 12 hour maintenance level of 8.0 mg. of ACTH. Subsequent ambulatory check-ups have been made and the patient appears relatively symptom-free on moderately restricted activity. Subsequent serial x-rays have shown questionable improvement. Her weight, on dismissal, was 91 ½ pounds.

Case 4. A 32-year-old housewife was observed at the Clinic on September 14, 1950. For the previous 3 years she had experienced progressive shortness of breath, and for 2 of these a progressive cough and anorexia; during this latter period a 34 pound weight loss occurred. The cough was nonproductive and related to exertion.

Physical examination revealed a patient with normal temperature, regular pulse, and blood pressure of 120/76. The weight was 101 pounds and height 64 inches. Numerous inspiratory fine to medium rales along with sibilant rhonchi were elicited over two-thirds of both lung fields, most evident in the bases.

The referring physician kindly loaned x-ray films and a cervical lymph node biopsy slide which had been made of the patient in March 1950. Dr. John B. Hazard interpreted the lymph node histology as chronic granulomatous lymphadenitis. It was his opinion that chronic beryllium poisoning should be considered in the differential diagnosis.

Roentgenograms taken at this time showed no essential change from those of the previous March; both disclosed generalized fine nodulation characteristic of the pattern observed in chronic beryllium poisoning (chronic pulmonary granulomatosis in a beryllium worker).

Past history revealed that the patient had been employed in a fluorescent lamp plant from March 1942 until March 1944, during which time she had done considerable salvage work.

The maximum vital capacity determination on the original visit was 1.52 L. (with the patient's computed normal estimated at 2.8 L.). The hemoglobin was 15.2 Gm. with a white count of 6950; the cell volume was 48 cc. The urinalysis was negative in all respects. The blood sugar reading was 104 mg. per cent fasting, and Wassermann and Kahn reactions were negative.

She entered the hospital on October 12 for further diagnostic studies. In the interval the patient had experienced a further progression of symptoms, including shortness of breath and paroxysms of nonproductive coughing on limited exertion. Her weight had decreased to 98 pounds.

Additional diagnostic studies were essentially negative, including multiple sputum examinations, Kveim skin test for sarcoid, skin tests with histoplasmin and coccidioidin extracts, and bromsulfalein test of liver function. The serum proteins measured 7.3 Gm., with the albumin 3.9 Gm. and the globulin 3.4 Gm. Patch tests with 0.1 to 1.0 per cent beryllium compounds showed positive reactions varying from 1 to 2 plus which persisted and even increased in reactions to 2 and 3 plus respectively during the remainder of hospitalization.

On October 15 the conclusion was reached that chronic beryllium poisoning existed and ACTH therapy was instituted. The initial dosage was 40 mg. every 6 hours, con-

trolled by appropriate laboratory study; the maximum tolerated dosage was 60 mg. every 6 hours, attained on October 19 and maintained until 3 days prior to discharge when the dosage was reduced. ACTH was discontinued on November 4, and the patient returned home the following day.

During this therapy the patient showed both subjective and objective improvement and a weight of 110 pounds was attained; this, however, was attributed in part to concomitant edema, and at the time of discharge she weighed 105½ pounds. The vital capacity demonstrated a steady increase, having reached 2.1 L.

It was decided to await development in the patient's condition before placing her on a maintenance dosage of the drug. However a recent letter reveals a symptomatic relapse and she has been scheduled for further progress studies. It is anticipated that additional ACTH therapy will be indicated as a maintenance measure.

Summary

1. Four patients treated with ACTH are reported. Each had progressive and disabling chronic beryllium poisoning.

2. At least a moderate degree of temporary improvement has occurred in each case with this therapy. We have obtained no such benefit from any other form of treatment.

3. This report covers only a period of up to 6 months observation with ACTH medication. Prolonged observation is necessary before a final evaluation can be made.

4. ACTH therapy, as demonstrated in these patients, may serve as at least a regressive measure.

ADDENDUM: Since the preparation of the foregoing case reports, 2 additional patients with chronic beryllium poisoning have been treated with ACTH with satisfactory initial response. These further cases will be incorporated in a later report.

Reference

1. Kennedy, B. J., Pare, J. A. P., Pump, K. K. and Stanford, R. L.: Effect of adrenocorticotropic hormone (ACTH) on beryllium granulomatosis. Canad. M.A.J. **62**:426 (May) 1950.