Physiologic Studies of Pulmonary Edema at High Altitude

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ACUTE pulmonary edema at high altitude may occur as a result of rapid exposure to an altitude of over 9,000 feet without adequate prior acclimatization. Initial symptoms usually appear 12 to 36 hours after arrival from sea level. Acclimatized individuals living at high altitudes who spend a short period of time at sea level and then return to a high altitude seem more susceptible than individuals exposed for the first time to high altitude. Repeated attacks in the same individual are common. Several recent reports have described the essential clinical features of this syndrome.1-5

Autopsy studies including histologic examination of the lungs have been made in four cases. In one case diffuse pulmonary edema was associated with an interstitial pneumonitis of possible viral origin, whereas in the other three cases diffuse pulmonary edema without evidence of pneumonitis was found.3,6

The mechanism of production of acute high-altitude pulmonary edema remains unknown. While a pneumonitis may be accompanied by acute pulmonary edema, in most cases evidence of infection is absent and oxygen administration without antibiotics results in prompt recovery. Pre-existing cardiac disease does not appear to be present.

Although the clinical features of the syndrome are well known, hemodynamic studies have been carried out during the acute stage in only one reported instance. This was in a physician who developed severe pulmonary edema while skiing at Alta, Utah (altitude 8,600 to 11,500 feet). Cardiac catheterization studies revealed pulmonary hypertension, arterial unsaturation, and a normal left atrial pressure. Pulmonary artery wedge pressures could not be determined. It was suggested that a possible causative factor was constriction of the pulmonary vein due to hypoxia.4 In the summer of 1961 and 1962, hemodynamic studies were carried out in four patients in the Peruvian Andes with typical high-altitude pulmonary edema. Three asymptomatic individuals who had previously experienced attacks of acute pulmonary edema were studied in a similar manner. Because of the paucity of physiologic data regarding the mechanism of high-altitude pulmonary edema, these observations are reported.

Materials and Methods

Studies were carried out at the Chulec General Hospital, which is at an altitude of 12,300 feet near the city of La Oroya in the central Andes of Peru. This area can be reached from Lima by train or auto in 4 to 6 hours. Approximately 12 patients with severe, acute high-altitude pulmonary edema are hospitalized annually at the Chulec Hospital.

After preliminary clinical and laboratory examination, the patients were placed on a fluoroscopic table in the x-ray department. Cardiac catheters of appropriate size were inserted into the antecubital vein through a small skin incision with use of 2 per cent procaine anesthesia. Brachial or femoral arterial puncture under local anesthesia was performed with Courand or Riley needles. After insertion of the arterial needle and placement of the catheter in the pulmonary artery, the patient rested for 15 minutes to allay apprehension and to achieve a suitable resting state. No oxygen was administered to the patients for at least 2 hours prior to the study. During the study 100 per cent oxygen was delivered by a tightly fitting face mask at sufficient flows to keep
the equalizer bag full at all times. Gas mixtures of oxygen and nitrogen were delivered from a cylinder to fill several 35-liter meteorologic gas balloons. These were fitted with appropriate wide-bore tubing, and the mixture was inspired by means of a mouthpiece, flutter valve, and nose-clip. Gas mixtures were analyzed for oxygen content by a Broughton-Scholander gas analyzer.

Pressures were recorded by means of a P23D Statham strain-gage and a Sanborn Twin-Beam oscillograph and a Sanborn Twin-Beam strain-gage amplifier. Paper speeds of 25 mm. per second were employed, and a simultaneous electrocardiogram was recorded as a reference tracing. The system was calibrated with a mercury manometer before and after each study. The midpoint of the posteroanterior chest diameter was used as a zero reference point. Mean pressures were determined by planimetry throughout at least two respiratory cycles. Blood gas analyses were carried out according to the technic of MeNeill and Van Slyke, or by the spectrophotometric method of Nahas with a Beckman Model B spectrophotometer (patient 2). Vital capacities were determined with a McKesson Vitalograph.

The evaluation of any physiologic studies at high altitude is difficult because of the paucity of information regarding normal values. Studies reported in this paper have been compared with data obtained by the following three groups of workers in normal acclimatized residents of high-altitude areas: 1. Vogel—studies on 28 acclimatized residents of Leadville, Colorado, living at 10,150 feet in the Colorado Rockies, age range 15 to 17 years.2 2. Hultgren—studies on 30 acclimatized native subjects living at 12,300 feet in the Peruvian Andes, age range 18 to 45 years.3 3. Penaloza—studies on 60 acclimatized native subjects living at 14,900 feet in the Peruvian Andes, age range 1 to 34 years.4 For purposes of comparison, calculated pulmonary arteriolar resistances are expressed as dynes sec. cm.5. Penaloza and his workers5 have determined the following values in Peruvians, which are used for comparison: 1. Sea level adults—69 dynes sec. cm.5; S.E. 5.7; 17 to 23 years. 2. High-altitude residents—332 dynes sec. cm.5; S.E. 35.9; 17 to 34 years; 14,900 ft. 3. High-altitude residents—459 dynes sec. cm.5/M.2; S.E. 57.0; 6 to 14 years; 14,900 ft.

Case Reports

Case 1

M.S., a white American boy, entered the Chuluc General Hospital at 10:00 a.m. on July 19, 1961, complaining of dyspnea and a persistent, nonproductive cough.

Past History

He was born in La Oroya, Peru (altitude 12,300 feet), on April 21, 1953. His growth and development had been normal. At 4 years of age a faint middiastolic murmur just medial to the apex was noted. An electrocardiogram at that time was compatible with right ventricular hypertrophy. A chest film was normal. Prior to 1958 he visited Lima approximately 10 times, usually for 2-week periods, without experiencing any difficulty upon returning to La Oroya.

Figure 1

Electrocardiogram of patient 1, M.S., recorded on entry to the hospital, July 19, 1961.

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Present Illness

Prior to his present hospital entry he had spent 15 days in Lima. After he had been there 4 days, he developed a head cold that lasted for 5 days. He had been otherwise perfectly well. He arrived at La Oroya at 3:00 p.m. on July 18, 1961, and, as a precautionary measure, went promptly to bed. During the night he became pale, dyspneic, vomited several times, and noted some precordial pressure. Early in the morning he developed a persistent dry cough with rapid respirations and entered the hospital.

Physical Examination

The temperature was 99°, the pulse 110, the respiratory rate 34, and the blood pressure 110/70. There was moderate cyanosis, tach-
ypnea, and a dry cough but no distress. Fine crepitant rales were present at both lung bases posteriorly. There was a slight systolic heave along the left sternal margin. The second sound at the pulmonic area was accentuated and palpable. No abnormal splitting was noted. A grade-III/VI midsystolic murmur was present at the fourth interspace, 3 cm. to the left of the sternum. The remainder of the physical examination was not remarkable.

Laboratory studies revealed the following: hemoglobin 13.0 Gm.; hematocrit level 40 per cent; white blood cells 8,200, polymorphonuclear cells 60 per cent, lymphocytes 32 per cent, monocytes 6 per cent. Urinalysis: clear, albumin negative, specific gravity 1.010, sediment negative.

The total vital capacity was 1.2 L. in 2 seconds, and 1.1 L. in 1 second (predicted normal 1.3 to 2.9 L.).

The electrocardiogram revealed a pattern compatible with right ventricular hypertrophy that was essentially unchanged from previous records (fig. 1). In addition, there was a sinus tachycardia with prominent peaking of the P waves, especially in lead II.

Roentgenograms of the chest revealed bilateral pulmonary densities, more marked on the right, and prominence of the central pulmonary vessels but no cardiac enlargement (fig. 2).

Physiologic Studies

At noon on July 19, after being out of the oxygen tent for 4 hours, he was given preliminary sedation with 50 mg. of phenobarbital. Under local anesthesia, a no.-7 Courand cardiac catheter was inserted into a prominent vein at the right elbow and guided without difficulty into the main pulmonary artery. It was possible to advance the catheter during deep inspiration into several wedge positions in both the right and left lung. After the wedge and pulmonary artery pressures were recorded several times, 100 per cent oxygen was administered by mask for 20 minutes. Pressures were again recorded. After the administration of oxygen was begun, coughing ceased. An arterial blood sample was obtained from the femoral artery before and after 10 minutes of oxygen breathing. At the conclusion of the procedure, the patient was returned to his room and placed in an oxygen tent. The results of the study are summarized in table 1A.

Hospital Course

After being given oxygen, the patient remained asymptomatic. On July 21 when he was discharged from the hospital, his chest was clear to auscultation and the roentgenogram was normal. A phonocardiogram revealed an apical third sound that had not previously been present. The second sound at the pulmonic area was less intense. On July 20 the electrocardiogram was essentially similar to that recorded prior to his episode of pulmonary edema. The total vital capacity was 1.4 L. in 2 seconds and 1.3 L. in 1 second.

Follow-up Physiologic Studies

On the afternoon of August 6 this patient was studied by cardiac catheterization for the second time. He was at this time asymptomatic, with a perfectly normal physical

Table 1A

<table>
<thead>
<tr>
<th>Pulmonary artery pressure (mm. Hg)</th>
<th>Room air</th>
<th>100% Oxygen breathing</th>
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<tr>
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<td>96/41</td>
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<td>Mean wedge pressure</td>
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<td>71</td>
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<tr>
<td>Heart rate/min.</td>
<td>129</td>
<td>78</td>
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<tr>
<td>Respiratory rate/min.</td>
<td>34</td>
<td>15</td>
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<tr>
<td>Right atrial pressure</td>
<td>2.9</td>
<td>—</td>
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<tr>
<td>Arterial oxygen saturation (%)</td>
<td>76</td>
<td>—</td>
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<tr>
<td>Hematocrit (%)</td>
<td>44.5</td>
<td>—</td>
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<tr>
<td>Hemoglobin (Gm.)</td>
<td>14.2</td>
<td>—</td>
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<tr>
<td>Mixed venous oxygen content (ml./100 ml.)</td>
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<td>—</td>
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<td>A-V oxygen difference (ml./100 ml.)</td>
<td>5.8</td>
<td>—</td>
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<tr>
<td>Cardiac index (L./min./M.²)</td>
<td>2.6</td>
<td>—</td>
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<tr>
<td>Pulmonary vascular resistance</td>
<td>2900</td>
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PULMONARY EDEMA AT HIGH ALTITUDE

Table 1B
Physiologic Studies Following Recovery from Acute Pulmonary Edema at High Altitude. Patient 1, M.S., August 6, 1961

<table>
<thead>
<tr>
<th>Pulmonary artery pressure (mm. Hg)</th>
<th>Rest</th>
<th>100% O₂ 5 min</th>
<th>11% O₂ 5 min</th>
<th>100% O₂ 5 min</th>
<th>Room air 5 min</th>
<th>10% O₂ 4 min</th>
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</thead>
<tbody>
<tr>
<td>S/D</td>
<td>56/33</td>
<td>50/20</td>
<td>94/64</td>
<td>—</td>
<td>—</td>
<td>68/23</td>
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<td>Mean</td>
<td>47</td>
<td>35</td>
<td>82</td>
<td>—</td>
<td>—</td>
<td>47</td>
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</tbody>
</table>

Pulmonary artery wedge pressure
Mean (mm. Hg) 4 — — 7 7 6
Heart rate/min. 88 72 138 63 87 130
Respiratory rate/min. 36 24 — 24 — —
Right atrial pressure
Mean (mm. Hg) 7 — — — — 4
Arterial oxygen saturation (%) 89 100 65 — — —

examination. A chest roentgenogram was normal. The electrocardiogram was similar to that of July 20 with a slower heart rate.

A no. 6 cardiac catheter was inserted into a vein at the left elbow and easily guided into the right pulmonary artery. After resting pressures had been recorded, 100 per cent oxygen was given by mask for 5 minutes. During this time further pressure measurements were made. A period of breathing room air was then followed by a 5-minute period of breathing 11 per cent oxygen by mask (equivalent to a 6.9 per cent oxygen concentration at sea level). One hundred per cent oxygen was then given for 5 minutes, followed by room air breathing for 5 minutes, and then a final 4-minute period of 11 per cent oxygen breathing was carried out. Appropriate pressure measurements were made during each of these periods and are summarized in table 1B. During the period of low oxygen breathing, the patient became restless, cyanotic, and his respirations became irregular. He experienced a headache and moderate nausea. These phenomena were quickly reversed upon resumption of oxygen breathing.

In May 1962 the patient left the mountains for a vacation. On August 2, 1962, after 3 months at sea level, a third heart catheterization study was performed. After the completion of resting studies, 10 per cent oxygen was administered for 9 minutes and immediately following, 100 per cent oxygen was given for 10 minutes. The pertinent data are summarized in table 1C. Resting pressures were slightly lower than the lowest resting pressures obtained on breathing room air a year previously at high altitude. A lesser degree of hypoxia produced a slight rise in

Table 1C
Physiologic Studies Following Recovery from Acute Pulmonary Edema at High Altitude and after 3 Months' Residence at Sea Level. Patient 1, M.S., August 2, 1962

<table>
<thead>
<tr>
<th>Right ventricle pressure (mm. Hg)</th>
<th>Room air rest</th>
<th>10% O₂ 9 min</th>
<th>100% O₂ 10 min</th>
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<tr>
<td>S/D</td>
<td>58/5</td>
<td>71/5</td>
<td>60/5</td>
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</table>

Pulmonary artery pressure (mm. Hg)
S/D 47/9 55/10 40/8
Mean 22 25 18

Pulmonary artery wedge pressure
Mean (mm. Hg) 9 10 —
Heart rate/min. 68 95 70
Respiratory rate/min. 17 22 —
Right atrial pressure
Mean (mm. Hg) 6 — 6
Arterial oxygen saturation (%) 97 78 100

Mixed venous oxygen content (ml./100 ml.) 14.6 14.8 17.0
Cardiac index (L./min. /M²) 3.7 — —
Pulmonary vascular resistance (dynes sec. cm⁻⁵ /M²) 310 — —

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pulmonary artery pressure, and 100 per cent oxygen resulted in a fall in pulmonary artery pressure below the initial resting level. Of interest was the demonstration of a mild pulmonic stenosis probably of the infundibular variety. No pressure gradient was demonstrated in the two previous studies despite adequate pressure tracings from the right ventricle and pulmonary artery. An electrocardiogram recorded at the same time revealed a right ventricular hypertrophy pattern essentially similar to the tracing of August 6, 1961.

In September the patient returned to La Oroya from Lima by auto. As a preventive measure, oxygen was given intermittently from a portable tank en route and on arrival he was admitted to the hospital overnight, where he received oxygen by tent. He was released the next morning clinically well. He slept well that night but the following night, the third night after arrival at La Oroya, he developed typical pulmonary edema confirmed by x-ray examination. He was hospitalized again, given oxygen, and recovered in 24 hours.

Case 2

G.D., a 27-year-old American engineer, entered the Chuluc General Hospital at 10:00 a.m. August 9, 1962, because of acute dyspnea and cough of 24 hours’ duration.

Past History

There was no history of previous cardiopulmonary disease. He had worked for many years in mines at altitudes of over 9,000 feet in the Colorado Rockies without ill effects. For the preceding 2 years he had worked at Climax, Colorado (altitude 11,500 ft.).

Present Illness

He left Colorado for Peru on July 21 and went from Lima to La Oroya (12,300 ft.) on August 4. On August 4 and 5 he was very active, riding horses, dancing, and going to late parties. On August 6 he had a pre-employment physical examination that revealed no cardiopulmonary abnormalities, a hemoglobin of 18 Gm., and a normal chest x-ray. He went to Yauricocha (14,000 ft.) that night and worked hard all the following day in the mine. During the afternoon he noted increasing dyspnea and during the night he became very dyspneic, noted “gurgling sounds” in his chest, and coughed up clear liquid sputum but no blood. He received oxygen by nasal catheter in the morning and immediately felt better. His dyspnea returned when the oxygen was stopped. Around noon he became mentally confused and on the following day he was transferred to the Chuluc General Hospital. He had noted a mild sore throat on August 7 but this had subsided the following day.

Physical Examination

The temperature was 99F., the pulse 110, the respiratory rate 30, and the blood pressure 112/75. The patient was dyspneic, cyanotic, and drowsy. The extremities were cold and the peripheral pulses were small. The throat was slightly reddened. There were no cervical nodes. The neck veins were flat. No precordial heaves were noted. No murmurs were present. The first sound was accentuated at the lower left sternal edge and the second sound at the pulmonic area was moderately loud. Rales were present at both lung bases.

Laboratory studies revealed the following: hemoglobin 21.1 Gm.; hematocrit level 62 per cent; white blood cells 19,500, polymorphonuclear cells 90 per cent, lymphocytes 8 per cent, eosinophils 1 per cent, monocytes 1 per cent; serum bilirubin, total 2.0 mg., direct 1.0 mg., indirect 1.4 mg.; total serum proteins 8.0 Gm., albumin 5.0 Gm., globulin 3.0 Gm.

An electrocardiogram revealed a vertical frontal plane axis with a low-voltage QRS complex in lead I. The T waves were low in V6. There was no evidence of right ventricular hypertrophy, and the P waves were normal.

Roentgenograms of the chest revealed numerous bilateral pulmonary densities compatible with patchy pulmonary edema. The apical areas were clear. The heart was not enlarged (fig. 2C).

Physiologic Studies

At 6:35 p.m. on August 9 after removal of the oxygen tent for the preceding 4 hours, cardiac catheterization studies were per-
formed under local anesthesia without pre-
liminary sedation. A no.-9 wedge-tip catheter
was easily guided into the pulmonary artery,
and several wedged pressure tracings were
recorded. A Courmand needle was inserted into
the exposed brachial artery. After measure-
ments of cardiac output, a Valsalva maneuver
(blowing a 40-mm. pressure resistance for
12 seconds) was performed (fig. 3). Supine
exercise was then carried out with a bicycle
ergometer. Following a 15-minute recovery
period, a mixture of 10.5 per cent oxygen in
89.5 per cent nitrogen (equivalent to a 6.6
per cent oxygen concentration at sea level),
was given by means of a mouthpiece and
noseclip for 5 minutes. Following this pro-
cedure, 100 per cent oxygen was given for 15
minutes. On August 15, after complete re-
covery, additional studies were performed.
The data are summarized in table 2.

Case 3

R.F., a white schoolgirl of German descent,
entered the Chulec General Hospital at 2:30
a.m. on August 4, 1961, because of possible
pneumonia and coma of 48 hours’ duration.

Past History

She was born in Lima and was brought at
a few weeks of age to Casapalca (altitude
13,745 ft.) where she lived until she was six.
She then moved to Lima to go to school. Dur-
ing this time she made one visit to Casapalca
(June 1961) but felt so bad that she returned
to Lima at once.

Present Illness

On August 1, 1961, she traveled from Lima
to Concepcion (altitude 9,100 ft.). The fol-
lowing morning she went shopping and spent
2 to 3 hours walking around the town. That
evening she felt tired and noticed a severe
headache. During the night she developed
dyspnea and cyanosis, and appeared comatose.
She had no cough. A physician treated her for
possible pneumonia with antibiotics but she
did not respond and her coma persisted. She
was transferred to the Chulec General Hos-
pital on August 3.

Physical Examination

The temperature was 97.4F., the pulse 120,
the respiratory rate 36, and the blood pressure
124/70. She was pale and unconscious, and
appeared moribund. Cyanosis of the lips and
nailbeds was marked, and audible respiratory
gurgles were present. There was no cough.
Crepitant rales were present over both lung
fields. No murmurs were noted. The neck was
rigid. Kernig and Brudzinski tests were posi-
tive. The patellar reflex was absent on the
right but weakly present on the left. Abdomi-
nal reflexes were absent. The remainder of
the neurologic examination was normal. The
fundus were normal.

Laboratory studies revealed the following:
hematocrit 46 per cent, white blood cells 14,000,
lymphocytes 16 per cent, monocytes 4 per cent.
The corrected sedimentation rate was 12 mm.
Urinalysis: acid, negative for albumin, sediment
normal. A throat culture was negative. A
serologic test for syphilis was negative. Total
serum proteins were 6.9 mg. per cent with
an albumin of 3.5 mg. per cent and a globulin
of 3.4 mg. per cent. The venous pressure was
6 cm. of water above the mid-chest. An elec-
trocardiogram revealed right axis deviation
with normal precordial leads. Roentgenograms
of the chest (fig. 2D) revealed diffuse, almost
confluent, pulmonary densities involving both
lungs. The cardiac size was normal.

Physiologic Studies

At 2:00 p.m. on August 5, 1961, cardiac
catheterization studies were performed under
local anesthesia but no sedation. For 4 hours
preceding the procedure the patient had not
Table 2


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<td>Pulmonary artery wedge pressure</td>
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<td>(dynes sec. cm.-²/M.²)</td>
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</table>

* Right ventricular pressure.

reached oxygen. During this time she became slightly delirious and complained bitterly of headache. Respirations were labored. Coarse bubbling rales were present at both lung bases. Cyanosis was marked. The heart was not remarkable. A no.-8 cardiac catheter was inserted into a prominent vein at the right elbow and easily guided into the right pulmonary artery. A Courmand needle was inserted into the right brachial artery. Intravascular pressures were recorded and blood samples were obtained preceding and following the administration of 100 per cent oxygen given by mask. Resting arterial samples were very dark, indicating severe unsaturation. After oxygen breathing, arterial samples were bright red and appeared fully saturated. These samples could not be differentiated by inspection from samples equilibrated with room air in a tonometer for 20 minutes. The results are summarized in table 3. After 10 minutes of oxygen breathing, the patient felt greatly improved, no longer noted headache, and appeared alert. The cyanosis had disappeared. Roentgenograms of the chest revealed moderate basal pulmonary edema prior to the study. No change was detectable following the procedure.

Hospital Course

Oxygen was immediately given by tent and penicillin was continued. The highest recorded temperature was 100.6F. The blood pressure varied between 122/80 and 96/70. Two days after entry the total white blood-cell count was 24,000 with 80 per cent polymorphonuclear cells, 7 per cent lymphocytes, and 4 per cent monocytes. After 18 hours of oxygen adminis-
tration, the heart rate decreased to 90 per minute, the respiratory rate slowed to 25 per minute, the headache and dyspnea disappeared, the neurologic signs became normal, and the patient became alert and oriented. She improved slowly and was discharged on August 8. At that time she was asymptomatic, her chest film was normal, and her physical findings were normal.

Case 4

P.S., an 8-year-old white schoolboy, entered the Chulee General Hospital at 10:30 a.m. on August 2, 1961, because of cough and dyspnea of 14 hours’ duration.

Past History

He was born in Argentina but had lived in La Oroya for the past 7 years. During this time he had made several trips to the seacoast without developing pulmonary edema. He had always been well and healthy and periodic examination had been normal.

Present Illness

On July 31 he arrived in La Oroya from Lima, where he had spent a 2-week vacation. During the first week in Lima he had a mild head cold and a dry cough had persisted to the time of departure for La Oroya. He appeared well on the afternoon of arrival but slept poorly that night. The following night he developed more severe cough, palpitation and dyspnea, and on the following morning, August 2, he was brought to the hospital.

Physical Examination

The temperature was 100.6°F., the pulse 144, the respiratory rate 48, and the blood pressure 100/70. He was pale but not cyanotic. A frequent dry cough was present and occasional audible rhonchi were noted. Crepitant rales were present over both lung fields. The second sound at the pulmonic area was accentuated. No cardiac murmurs were noted.

Laboratory studies revealed the following: hemoglobin 16.8 Gm., hematocrit level 50 per cent, white blood cells 20,800, polymorphonuclear cells 91 per cent, lymphocytes 5 per cent, monocytes 3 per cent. Corrected sedimentation rate was 4 mm. Urinalysis: acid, specific gravity 1.030, negative for albumin, normal sediment. Chest roentgenograms revealed moderate bilateral pulmonary edema.

Table 3

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Physiologic Studies during Acute Pulmonary Edema at High Altitude. Patient 3, R.F., August 5, 1961</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse:</td>
<td></td>
</tr>
<tr>
<td>Pulmonary artery pressure (mm. Hg)</td>
<td>Rest</td>
</tr>
<tr>
<td>S/D</td>
<td>47/25</td>
</tr>
<tr>
<td>Mean</td>
<td>37</td>
</tr>
<tr>
<td>Mean (mm. Hg)</td>
<td>5</td>
</tr>
<tr>
<td>Mean (mm. Hg)</td>
<td>115</td>
</tr>
<tr>
<td>Mean (mm. Hg)</td>
<td>28</td>
</tr>
<tr>
<td>Mean (mm. Hg)</td>
<td>2</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>119</td>
</tr>
<tr>
<td>Mean (mm. Hg)</td>
<td>49</td>
</tr>
<tr>
<td>Appearance of arterial blood</td>
<td>bright red</td>
</tr>
</tbody>
</table>
Table 4

Physiologic Studies during Acute Pulmonary Edema at High Altitude. Patient 4, P.S., August 2, 1961

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>2 min.</th>
<th>100% Oxygen breathing 8 min.</th>
<th>10 min.</th>
<th>12 min.</th>
<th>Room air 10 min.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary artery pressure (mm. Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S/D</td>
<td>41/24</td>
<td>35/14</td>
<td>35/18</td>
<td>-</td>
<td>-</td>
<td>37/18</td>
</tr>
<tr>
<td>Mean</td>
<td>33</td>
<td>25</td>
<td>27</td>
<td>-</td>
<td>-</td>
<td>28</td>
</tr>
<tr>
<td>Pulmonary artery wedge pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (mm. Hg)</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>12</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Heart rate/min.</td>
<td>110</td>
<td>94</td>
<td>90</td>
<td>88</td>
<td>84</td>
<td>98</td>
</tr>
<tr>
<td>Respiratory rate/min.</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Right atrial pressure</td>
<td>-3</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3</td>
</tr>
</tbody>
</table>

Physiologic Studies

At 6:30 p.m. on August 2 cardiac catheterization studies were carried out under mild barbital sedation and local anesthesia. A no.-6 cardiac catheter was introduced into a prominent vein at the right elbow and easily guided into the right pulmonary artery. Pressures were recorded at rest and during the administration of 100 per cent oxygen by mask for 12 minutes. The data are summarized in table 4.

Hospital Course

Bed rest and oxygen by tent resulted in rapid improvement, so that he was discharged on August 4 free from symptoms and with a normal chest roentgenogram.

Case 5

A.S., a white schoolgirl, was born in Lima on August 31, 1948. She had lived in La Oroya since infancy. In February 1961 she returned to La Oroya after spending 5 weeks in Lima and developed a typical episode of pulmonary edema of moderate severity. There was no prior evidence of heart disease. Physical examination in August 1961 was entirely normal. An electrocardiogram was normal and x-ray films of the chest were entirely normal.

Physiologic Studies

No premedication was used. Under procaine anesthesia, a no.-7 cardiac catheter was inserted into a prominent vein at the right elbow. The catheter tip was guided into the

Table 5

Physiologic Studies 6 Months Following Acute Pulmonary Edema at High Altitude. Patient 5, A.S., August 8, 1961

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>10.6% O2 breathing 2½ min.</th>
<th>10.6% O2 breathing 5 min.</th>
<th>Room air 3 min.</th>
<th>100% O2 5 min.</th>
<th>Room air 10 min.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary artery pressure (mm. Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S/D</td>
<td>22/7</td>
<td>53/32</td>
<td>57/36</td>
<td>23/0</td>
<td>22/8</td>
<td>25/4*</td>
</tr>
<tr>
<td>Mean</td>
<td>14</td>
<td>42</td>
<td>43</td>
<td>17</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Pulmonary artery wedge pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (mm. Hg)</td>
<td>8</td>
<td>6</td>
<td>7</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Heart rate/min.</td>
<td>75</td>
<td>118</td>
<td>110</td>
<td>84</td>
<td>72</td>
<td>85</td>
</tr>
<tr>
<td>Respiratory rate/min.</td>
<td>16</td>
<td>19</td>
<td>21</td>
<td>-</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>Right atrial pressure</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6</td>
</tr>
<tr>
<td>Mean (mm. Hg)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6</td>
</tr>
</tbody>
</table>

* Probably right ventricle.
right pulmonary artery. Pressure measurements were made during room air breathing and during 10.6 per cent oxygen breathing of 5 minutes' duration (equivalent to 6.7 per cent oxygen concentration at sea level). Following a 5-minute period of room air breathing, 100 per cent oxygen was administered by mask for 10 minutes. The data are summarized in Table 5.

Case 6

H.L., a 21-year-old Peruvian laborer, was born in Yauli (13,430 ft.). He lived and worked at La Oroya (12,300 ft.). On July 26 he arrived in La Oroya after a 40-day stay in Lima. On July 27 he noted malaise, headache, cough, dyspnea, hemoptysis, chest pain, and fever, and he was admitted to the hospital.

Physical Examination

The temperature was 96°F, the pulse 12, the respiratory rate 52, and the blood pressure 95/80. He was pale and dyspneic. Crepitant rales were present over both lungs. The hematocrit level was 46 per cent. A blood count revealed 40,100 white cells with 91 per cent polymorphonuclear cells. Chest x-rays revealed numerous bilateral densities. A diagnosis of acute bronchopneumonia and pulmonary edema was made. He was treated with antibiotics, oxygen, and bed rest and improved gradually. His highest oral temperature was 102°F. On July 30 he was asymptomatic but a few bilateral pulmonary densities were still demonstrable by x-ray. On August 7 his chest film was clear and there was no cardiac enlargement. Physical examination at that time was normal.

Physiologic Studies

On August 7 at 7:00 p.m., cardiac catheterization studies were performed. No premedication was used. After procaine infiltration, a no. 8 cardiac catheter was inserted into a prominent vein at the right elbow and advanced into the right pulmonary artery. Pressure measurements were made during room air breathing and during the administration of a 10 per cent oxygen mixture in nitrogen (equivalent to a 6.3 per cent oxygen concentration at sea level). Following a period of breathing room air again, 100 per cent oxygen was given by mask for 6 minutes. The data are summarized in Table 6.

Case 7

R.L.V., an 8-year-old Peruvian boy, had experienced acute pulmonary edema in February 1961 and again in March 1962. On August 20, 1962, he was active and asymptomatic. Physical examination was normal. His electrocardiogram was normal. A chest roentgenogram revealed no abnormalities of the heart or lungs. Cardiac catheterization studies revealed a right ventricular pressure of 35/6 mm. Hg. The mean right atrial pressure was 6 mm. Hg and the contour was normal. The pulmonary artery could not be entered.

Table 6

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>10% O₂ 5 min.</th>
<th>Room air 5 min.</th>
<th>100% O₂ 6 min.</th>
<th>Room air 5 min.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary artery pressure (mm. Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S/D</td>
<td>38/8</td>
<td>79/43</td>
<td>49/13</td>
<td>34/5</td>
<td>43/7</td>
</tr>
<tr>
<td>Mean</td>
<td>25</td>
<td>60</td>
<td>30</td>
<td>19</td>
<td>22</td>
</tr>
<tr>
<td>Pulmonary artery wedge pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (mm. Hg)</td>
<td>–</td>
<td>1</td>
<td>6</td>
<td>5</td>
<td>–</td>
</tr>
<tr>
<td>Heart rate/min.</td>
<td>81</td>
<td>100</td>
<td>72</td>
<td>68</td>
<td>68</td>
</tr>
<tr>
<td>Respiratory rate/min.</td>
<td>19</td>
<td>30</td>
<td>20</td>
<td>18</td>
<td>–</td>
</tr>
<tr>
<td>Right atrial pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (mm. Hg)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>2</td>
</tr>
</tbody>
</table>

Circulation, Volume XXIX, March 1964
indicates isk pulmonary acute Mean pulmonary left mean in normal Fred et al. 14,900 ft. MM HG.

demonstrated four analysis: (1) anoxic pulmonary arteriolar ure; and study presented edema pulmonary or low normal pressures; (3) no evidence of pulmonary artery and exercise. Studies on 28 normal

**Figure 4**
Mean pulmonary artery and wedge pressures during acute pulmonary edema and after recovery. The asterisk indicates mean pulmonary artery pressure and mean left atrial pressure in the patient reported by Fred et al. The range and mean of values obtained in normal acclimatized high-altitude residents at 14,900 ft. are indicated for comparison.9

**Discussion**

The data obtained in the present study have demonstrated four important features of pulmonary edema at high altitude that merit analysis: (1) pulmonary hypertension due to anoxic pulmonary arteriolar constriction; (2) normal or low pulmonary artery wedge pressures; (3) no evidence of left ventricular failure; and (4) no evidence of underlying cardiac disease.

Pulmonary artery pressures obtained in the present study during pulmonary edema are clearly higher than normal sea level values and exceed values commonly seen in acclimatized normal subjects living at the same altitude (fig. 4). The normal or low pulmonary artery wedge pressures with a low cardiac output indicate that the pulmonary arteriolar res- istance is increased. Calculated values in patients 1 and 2 are higher than values observed in normal subjects at high altitude.9 The prompt and striking fall in pulmonary artery pressure induced by oxygen breathing suggests that the arteriolar constriction is due to hypoxia. The pressure fall is far greater than that seen in normal residents at high altitude (fig. 5). The decrease in pulmonary artery pressure following recovery when peripheral arterial saturation has returned to normal also supports this view.

Although the principal stimulus to pulmonary arteriolar constriction leading to pulmonary hypertension in high-altitude pulmonary edema is the low oxygen tension of high altitude, three additional factors contribute to further elevation of pulmonary artery pressure in patients who develop pulmonary edema: (1) physical activity, (2) impairment of diffusion, and (3) excessive anoxic pulmonary vasoconstriction.

Normal residents at high altitude will increase their pulmonary artery pressures markedly during exercise. Studies on 28 normal

**Figure 5**
Effect of 100 per cent oxygen breathing upon mean pulmonary artery pressure during acute pulmonary edema. The asterisk refers to the patient reported by Fred et al. The range and mean of values obtained in normal acclimatized high altitude residents at 12,300 ft. are indicated for comparison.8

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residents at high altitude of the Peruvian Andes (altitude 12,300 ft.) have demonstrated a rise in mean pulmonary artery pressure from 22 mm. at rest to 35 mm. during light supine exercise sufficient to increase oxygen consumption by 260 per cent. Vogel et al. have demonstrated a mean pulmonary artery pressure of 130 mm. Hg during heavy exercise in a healthy resident of Leadville, Colorado (altitude 10,150 ft.). The rise in pulmonary artery pressure in patient 2 in this series is similar to that observed in healthy residents at high altitude during similar amounts of exercise. It is probable that similar marked rises in pressure would have occurred in the other patients with pulmonary edema had they been exercised. There is suggestive evidence that heavy physical activity predisposes to pulmonary edema at high altitude. This may account for the higher incidence of pulmonary edema in boys than in girls in the La Oroya area, and its frequent occurrence among mountaineers. Even extreme physical activity in an acclimatized person may produce pulmonary edema as suggested by its occurrence in a physician mountaineer on Mt. Makalu at an altitude of 27,400 ft.

Once pulmonary exudate appears, further arterial unsaturation is produced by impairment of diffusion. The low arterial oxygen saturation persisting in patients 1 and 2 after 100 per cent oxygen breathing supports this viewpoint. Fred and his co-workers obtained similar data in their study. Administration of 100 per cent oxygen results in a rise in arterial oxygen saturation and a prompt and striking fall in pulmonary artery pressure. Normal high-altitude residents respond to similar oxygen mixtures by only a slight fall in pulmonary artery pressure, as illustrated in figure 5.

After recovery the impairment of diffusion is no longer present as evidenced by the normal response of patient 2 to the administration of 100 per cent oxygen. Thus pulmonary edema at high altitude tends to produce arterial anoxia which, by causing further pulmonary hypertension, appears to perpetuate the process. A right-to-left shunt at the foramen ovale cannot be excluded as a possible cause of additional arterial unsaturation but this seems unlikely, since right atrial pressures have not exceeded pulmonary artery wedge pressures or left atrial pressures in the patients studied to date.

The history of recurrent attacks in the same person (as in patient 1) and the absence of pulmonary edema in a larger number of subjects exposed to high altitude under identical conditions suggest a difference in response to hypoxia in susceptible persons. Hypoxia in patients 1 and 6 resulted in a more marked rise in pulmonary artery pressure than was
found in acclimatized subjects studied in a similar manner at the same altitude. These responses are illustrated and compared in figure 6. The response of patient 5 was probably not abnormal. Although patient 1 exhibited an abnormal hypoxic rise in pulmonary artery pressure at high altitude following recovery, his response to hypoxia at sea level was normal. Clearly, more data are needed to determine if an exaggerated hypoxic response of the pulmonary circulation is an important factor in susceptibility to pulmonary edema at high altitude.

The sequential studies in patient 1 illustrate the effect of various arterial oxygen tensions at high altitude and sea level upon the pulmonary circulation (fig. 7). During acute pulmonary edema, a very low oxygen tension was present due to the diffusion defect of this condition. Hypoxic pulmonary hypertension was marked. This was partially reversed by 100 per cent oxygen breathing. Upon recovery when acute hypoxia was no longer present, resting pulmonary artery pressure had decreased further but was still elevated above sea-level values. The pressure was only slightly affected by 100 per cent oxygen but rose sharply during acute hypoxia. After 3 months at sea level a further decrease in resting pulmonary artery pressure occurred and responses to 100 per cent oxygen and hypoxia were similar to those of subjects who had always lived at sea level. Since the pulmonary artery wedge pressure was normal in all these studies and cardiac output was only slightly affected, the pressure changes are largely related to changes in pulmonary arteriolar resistance. The data also indicate the possible difficulty of assessing sensitivity to hypoxia at sea level in patients who have had pulmonary edema at high altitude.

Of particular interest is the finding of normal pulmonary artery wedge pressures in all patients. No technical difficulties were encountered in obtaining wedge-pressure tracings from several positions in the lung during quiet breathing in each patient. Pullout tracings demonstrated the usual abrupt transition from the characteristic wedge-pressure contour to a pulmonary artery pressure curve. A total of 20 wedge-pressure tracings were analyzed in four patients at rest and during 100 per cent oxygen breathing (fig. 8). Minimum and maximum values were 1.0 mm. and 6.0 mm. (mean 2.8 mm.). These are comparable to minimum and maximum values of 2.0 mm. and 11.0 mm. (mean 6.4 mm.) found in healthy acclimatized high-altitude residents.

Oxygen breathing actually was accompanied by a slight rise in pulmonary artery wedge pressure in patients with pulmonary edema from a mean value of 2.8 mm. to 6.2 mm. This change is statistically significant. The pressure is still within normal limits. Oxygen breathing in normal high-altitude residents did not significantly affect the pulmonary artery wedge pressure (fig. 5). In patients with pulmonary edema, the pulmonary artery wedge pressure was not elevated above 10 mm. Hg by either added hypoxia or supine exercise. The rise in pulmonary artery wedge pressure to normal levels during 100 per cent oxygen breathing could be due to an increase in cardiac output.
secondary to pulmonary arteriolar dilatation.

The above data exclude acute left ventricular failure as a causative mechanism. Other observations are also incompatible with the presence of left heart failure. The brachial arterial pressure response to a Valsalva maneuver was normal in patient 2 (fig. 3). There was no roentgenographic evidence of increased heart size and no consistent decrease in heart size after recovery. Venous pressures in six patients were normal. Circulation time (arm-to-tongue Decholin) was normal in one patient. Intravenous ouabain given to one patient with severe pulmonary edema produced no change in the clinical picture but subsequent oxygen administration was accompanied by rapid improvement. Previous studies have demonstrated no clinical improvement after the administration of digitalis preparations. Autopsy studies have not demonstrated enlargement or dilatation of the left ventricle or left atrium.

None of the patients in this series had any evidence of underlying cardiac disease. Patient 1, M.S., had a higher pulmonary artery pressure than normal for healthy residents at 12,300 ft. and this pressure was moderately elevated at sea level. The mild degree of pulmonic stenosis encountered at sea level would not appear to be important in producing pulmonary edema at high altitude. The four patients in this series who were studied after recovery had resting pulmonary artery pressures that were normal for residents of that area (fig. 4). Other studies have clearly demonstrated the absence of underlying cardiac disease in patients with pulmonary edema at high altitude.

The data presented in this paper compare closely with results of studies performed by Fred et al. in a physician skier with pulmonary edema at high altitude in Utah. They observed a pulmonary artery pressure of 68/39 mm. Hg, a left atrial pressure of 9/3 mm. and a cardiac index of 2.9 L./min./M.². Calculated pulmonary vascular resistance was high (13.8 mm. Hg L./M.²). Arterial unsaturation (76 per cent) not fully corrected by oxygen breathing was also noted. Pulmonary artery wedge pressures were not recorded, apparent-ly owing to coughing. Although the authors speculate that pulmonary venous constriction might be present, the normal pulmonary artery wedge pressures obtained on similar cases in the present study make it quite likely that the pulmonary artery wedge pressure in the Salt Lake case was also not unduly elevated.

Studies so far, therefore, indicate that the most important single feature of pulmonary edema at high altitude is severe pulmonary hypertension due primarily to hypoxic pulmonary arteriolar constriction, probably made more severe by exercise. Left ventricular failure or pulmonary venous constriction does not appear to be present. How pulmonary edema is produced by pulmonary hypertension cannot be answered at the present time.

Summary

Cardiac catheterization studies have been performed in four patients during acute pulmonary edema at an elevation of 12,300 feet in the central Peruvian Andes.

Pulmonary hypertension, low cardiac output, arterial unsaturation, and low normal pulmonary artery wedge pressures were observed. Oxygen breathing was accompanied by a prompt, marked fall in pulmonary artery pressure and a slight rise in wedge pressure, indicating the presence of anoxic pulmonary arteriolar constriction.

In one patient, pulmonary artery wedge pressures were not elevated during added hypoxia nor during exercise. The blood pressure response to the Valsalva maneuver was normal.

Similar studies were carried out in four subjects after recovery from pulmonary edema. One 9-year-old boy had persisting pulmonary hypertension. None had evidence of underlying cardiac disease. An abnormal rise in pulmonary artery pressure during induced hypoxia was observed in three of four patients.

It is concluded that pulmonary edema at high altitude is a unique form of pulmonary edema produced by hypoxia under certain conditions of exposure at high altitude. Severe pulmonary hypertension due to anoxic pulmonary arteriolar constriction is present. There is no evidence that pulmonary venous con-
striction and cardiac failure are causative mechanisms.

Acknowledgment

The authors are grateful to Dr. Kurt Hellriegel and Dr. Emilio Martinez of the Cerro de Pasco Corporation for their assistance. Dr. Richard Turner of the Western Regional Hospital, Edinburgh, kindly provided the sea-level studies on patient 1, M.S. Elizabeth Stone provided valuable technical assistance.

References


Medical Science and the Humanities

The physician must not only be a man of science. He is not today and even less should he be so tomorrow. The other facet of his personality is called culture . . .

I shall only say that I still believe, just as before, that a cardiologist, as a scientist, must be a man of culture if he is to be anything and I only repeat myself to insist upon the imperious necessity of fomenting in him a modern humanism, “so much the more profound and passionate, the greater the limitations imposed by a demanding and exclusive scientific education.”—Dr. Ignacio Chavez. Speech delivered at the Inaugural Ceremony of the IV World Congress of Cardiology. Universidad Nacional Autónoma de México, México, D.F., 1962, p. 9.
Physiologic Studies of Pulmonary Edema at High Altitude
HERBERT N. HULTGREN, CESAR E. LOPEZ, EINAR LUNDBERG and HARRY MILLER

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