Polycythemia: A Manifestation of Heart Disease, Lung Disease or a Primary Blood Dyscrasia

By George N. Bedell, M.D., Raymond F. Sheets, M.D., Harry W. Fischer, M.D., and Ernest O. Theilen, M.D.

DR. GEORGE N. BEDELL: The purpose of this conference is to discuss some of the problems encountered in the differential diagnosis of polycythemia. Polycythemia may be a manifestation of heart disease, lung disease, or a primary blood dyscrasia. Polycythemia vera is a disease of unknown cause. In our hospital we make a diagnosis of polycythemia vera on the basis of finding leukocytosis, high platelet count, and splenomegaly in addition to polycythemia. We require exclusion of conditions capable of producing secondary polycythemia, such as cyanotic heart disease, lung disease, chronic exposure to high altitude, and respiratory center depression. Secondary polycythemia is diagnosed when the patient has polycythemia associated with cyanotic heart disease or lung disease in the absence of leukocytosis, high platelet count, and splenic enlargement. The differentiation of polycythemia vera from secondary polycythemia is sometimes a difficult task. Ratto, Briscoe, Morton, and Comroe have discussed the theoretical reasons that make this distinction possible by measuring arterial oxygen saturation. Also they point out the practical obstacles. The hypothesis is that uncomplicated polycythemia vera should not lead to arterial hypoxemia. No disturbance in pulmonary ventilation, pulmonary circulation, or in the ability of oxygen to diffuse from the alveolus into the red blood cell has been demonstrated in patients with polycythemia vera. If the oxygen saturation of arterial blood is reduced in patients with polycythemia, this suggests that polycythemia is secondary to hypoxemia. This conclusion is questionable because arterial oxygen desaturation may exist from other causes: 1. Patients with polycythemia vera are usually more than 50 years of age. Healthy persons of this age may have slight reduction of arterial oxygen saturation. 2. Patients with polycythemia vera may have concomitant lung disease to account for arterial hypoxemia. 3. Most patients with polycythemia vera whose arterial blood has been studied have no hypoxemia, however, arterial hypoxemia has been reported in polycythemia vera. We believe that arterial desaturation in the polycythemic patient is evidence that polycythemia vera exists with another disease or that polycythemia is secondary to another disease. The following cases have been chosen to illustrate how the patient with polycythemia can be studied to evaluate his basic disease.

Case 1

Mr. C. K., a 49-year-old farmer, was admitted to the University Hospitals on January 6, 1956. He was active and able to do his work until December 1955. At that time, coughing, dyspnea on exertion, and hemoptysis began. His nails had been clubbed since childhood.

The physical examination revealed a white man with clubbing of the fingers and cyanosis of the lips. The blood pressure was 110/78 mm. Hg. The anteroposterior diameter of the chest was increased. The chest was hyperresonant to percussion but the breath sounds were normal. The cardiac rate was 78 per minute and the rhythm was regular. The right heart felt moderately overactive. The pulmonic second sound was extremely loud. There was a grade III systolic murmur in the second and third interspaces to the left of the
spleen. No diastolic murmurs were heard. The
spleen was felt just below the costal margin.

The hemoglobin was 22.5 Gm. per 100 ml., the
red blood count was 8,76 million per mm.\(^3\) and
the hematocrit reading was 70 per cent. The white
blood cell count was 7,600 per mm.\(^3\) and the plate-
let count was 134,000 per mm.\(^3\) The electrocardio-
gram showed right ventricular hypertrophy.

**Dr. Bedell:** Dr. Fischer, will tell us
about the x-rays and cardiac fluoroscopy.

**Dr. Harry W. Fischer:** I will comment
first of all on the heart itself and then con-
sider the lungs. In this posterior-anterior
view of the chest (fig. 1) the heart is just
barely enlarged by measurement. It has a
Danzer ratio of .51. The striking thing
about the appearance of the heart is the very
pronounced bulging of the pulmonary artery
segment. On the oblique view (fig. 2) the
pulmonary artery segment is very prominent.
In figure 1 the lung fields show very promi-
nent hilar vessels with an irregular and
abrupt attenuation of the vasculature so that
the peripheral lung fields are essentially clear
and the vascular markings are difficult to see.
This attenuation is thought to indicate pul-
monary hypertension. The fluoroscopist
thought that the findings were suggestive of
primary pulmonary hypertension, and that
there was no evidence of left-to-right shunt.
A search for arteriovenous fistulas was made
but were not found at cardiac fluoroscopy.

**Dr. Bedell:** Pulmonary function studies
are recorded in table 1. The lung volumes
were normal. The minute volume of venti-
lation was normal. The per cent nitrogen
at the end of 7 minutes of oxygen breathing
is a test of the evenness of distribution of
inspired air and was normal in this patient.
The mechanics of breathing were essentially
normal. When the patient’s arterial blood
was studied it was 78 per cent saturated with
oxygen while the patient breathed room air.
After he breathed 100 per cent oxygen for
10 minutes his arterial saturation rose to 95
per cent. The normal value for this test is
100 per cent plus 2.00 volumes per cent of
oxygen dissolved in the plasma and in the
watery parts of the red blood cells. The
P\(_{\text{CO}_2}\) was normal. Failure of the blood to
attain full values of oxygenation after
breathing 100 per cent oxygen means that
some of the arterial blood is flowing from
the right to the left side of the heart without
passing through pulmonary capillaries which
are in contact with ventilated alveoli. When
arterial oxygen saturation is as low as 95
per cent after breathing oxygen for a long
enough time to wash out nitrogen from the
lungs, it nearly always means that right-to-
left shunt is present. On the basis of these
findings we could not localize the shunt. Our
interpretation of the pulmonary function
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Table 1.—Results of Pulmonary Function Tests

<table>
<thead>
<tr>
<th></th>
<th>Normal values</th>
<th>Patient C.K.</th>
<th>Patient J.S.</th>
<th>Patient H.H.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lung volumes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital capacity (ml.)</td>
<td>—</td>
<td>2875</td>
<td>2850</td>
<td>2550</td>
</tr>
<tr>
<td>(% of normal)</td>
<td>100</td>
<td>70</td>
<td>52</td>
<td>57</td>
</tr>
<tr>
<td>Residual volume (ml.)</td>
<td>—</td>
<td>2900</td>
<td>3790</td>
<td>2200</td>
</tr>
<tr>
<td>(% of normal)</td>
<td>100</td>
<td>119</td>
<td>156</td>
<td>196</td>
</tr>
<tr>
<td><strong>Ventilation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minute volume (L.)</td>
<td>4.5</td>
<td>7.5</td>
<td>9.6</td>
<td>—</td>
</tr>
<tr>
<td>Distribution</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% N₂ end 7 min. O₂ (% N₂)</td>
<td>2.5</td>
<td>1.0</td>
<td>9.4</td>
<td>—</td>
</tr>
<tr>
<td>Single-breath O₂ test (% N₂)</td>
<td>1.5</td>
<td>—</td>
<td>—</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Mechanics of breathing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximal breathing capacity (L./min.)</td>
<td>—</td>
<td>85</td>
<td>83</td>
<td>99</td>
</tr>
<tr>
<td>(% of normal)</td>
<td>100</td>
<td>88</td>
<td>62</td>
<td>84</td>
</tr>
<tr>
<td>Maximal expiratory flow rate (L./min.)</td>
<td>400-600</td>
<td>490</td>
<td>100</td>
<td>215</td>
</tr>
<tr>
<td>Maximal inspiratory flow rate (L./min.)</td>
<td>400-600</td>
<td>282</td>
<td>147</td>
<td>171</td>
</tr>
<tr>
<td><strong>Arterial blood studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Breathing air</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O₂ saturation (%)</td>
<td>96-99</td>
<td>78</td>
<td>90</td>
<td>95</td>
</tr>
<tr>
<td>Pcco₂ (mm. Hg)</td>
<td>38-42</td>
<td>41</td>
<td>45</td>
<td>39</td>
</tr>
<tr>
<td>Breathing 100% O₂</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O₂ saturation (%)</td>
<td>100±2.00*</td>
<td>95</td>
<td>100+0.94</td>
<td>100+1.34</td>
</tr>
<tr>
<td>Pcco₂ (mm. Hg)</td>
<td>38-42</td>
<td>40</td>
<td>49</td>
<td>40</td>
</tr>
</tbody>
</table>

* Values following + sign refer to ml. O₂ per 100 ml. of blood in excess of that required to saturate hemoglobin (i.e., dissolved O₂).

tests was that they showed normal lung function in the presence of arterial hypoxemia, and evidence of a right-to-left shunt. Therefore an angiocardiogram was done and Dr. Fischer will comment on it.

**Dr. Fischer:** The angiocardiograms did not show a right-to-left shunt. However, they did confirm the impression of a distorted irregular vascular pattern with abrupt attenuation of the vessels as they left the hilar region. For these reasons the radiologist thought this was primary pulmonary vascular disease with pulmonary hypertension.

**Dr. Bedell:** The next thing we did to try to localize the shunt was cardiac catheterization. Dr. Theilen, will you describe the findings?

**Dr. Ernest O. Theilen:** The cardiac catheter was passed without difficulty into the right branch of the pulmonary artery. The patient had pulmonary hypertension (table 2) with pressures in the pulmonary artery of 116/76 mm. Hg. The mean pulmonary artery pressure was slightly higher than the arterial mean pressure of 90 mm. Hg. This is not a significant difference. The oxygen content in the pulmonary artery was 3 volumes per cent higher than in the right ventricle. The samples from the right ventricle, the right atrium, and the superior cava were all in the range of 16 to 16.5 volumes per cent, indicating that a left-to-right shunt was not present either at the ventricular or atrial level. He had an abnormal arterial

Table 2.—Cardiac Catheterization Findings on Patient C. K., Age 49

<table>
<thead>
<tr>
<th>Catheter position</th>
<th>Pressure, mm. Hg</th>
<th>Blood O₂ content vol. %</th>
<th>Satur. %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior vena cava</td>
<td>—</td>
<td>—</td>
<td>16.4</td>
</tr>
<tr>
<td>Right atrium</td>
<td>—</td>
<td>7</td>
<td>15.9</td>
</tr>
<tr>
<td>Right ventricle</td>
<td>121/9</td>
<td>—</td>
<td>16.4</td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>116/76</td>
<td>96</td>
<td>19.4</td>
</tr>
<tr>
<td>Femoral artery (breathing air)</td>
<td>125/75</td>
<td>90</td>
<td>20.5</td>
</tr>
<tr>
<td>Femoral artery (breathing oxygen)</td>
<td>—</td>
<td>—</td>
<td>24.9</td>
</tr>
<tr>
<td>Arterial oxygen capacity</td>
<td>—</td>
<td>—</td>
<td>25.2</td>
</tr>
</tbody>
</table>
oxygen saturation—81 per cent while breathing room air. Breathing 100 per cent oxygen increased the arterial saturation to 99 per cent. I think the data are indicative of a shunt into the pulmonary artery from the aorta, such as a patent ductus arteriosus. The shunt is bidirectional. There is severe pulmonary hypertension. Ordinarily the treatment of a patient with patent ductus arteriosus is surgical ligation of the ductus. In this patient ligation is contraindicated because of pulmonary hypertension.

Dr. Bedell: This patient has secondary polycythemia. He has none of the diagnostic characteristics of primary polycythemia. His white blood cell count and platelet count are normal. The significance of his palpable spleen is unknown. He had arterial hypoxemia but this has been discussed. At this point I would like to ask Dr. Sheets to discuss the therapy of the polycythemia in this patient.

Dr. Raymond F. Sheets: This patient did not seem to be in cardiac failure, so I do not think we have to discuss the ordinary treatment of congestive failure. Polycythemia in this instance is a compensatory mechanism that produces more hemoglobin and red cells so that more oxygen can be carried to the tissues in a given time. I think I can illustrate this briefly. With 14.0 Gm. per 100 ml. of hemoglobin 70 per cent saturated with oxygen the patient has the equivalent of 9.8 Gm. of saturated hemoglobin. When the hemoglobin increases to 22 Gm. per 100 ml. and is only 70 per cent saturated, there is the equivalent of 15.4 Gm. per 100 ml. of hemoglobin that is saturated with oxygen. This actually is not an entirely valid comparison because other factors, such as oxygen dissociation, are involved here, in addition to how much hemoglobin is available to carry oxygen; but I think this gives you the idea of how the compensatory mechanism operates and the reason for it. Difficulty arises after optimal compensation has been made and the regulatory thermostat, which may be erythropoietin stimulated by hypoxemia, fails to stop. Too many erythrocytes are produced. The high viscosity of the blood may overburden the heart and congestive failure may be precipitated. The circulation time may be increased because of the viscosity of the blood so that fewer cells are exposed per unit of time to the respiratory membrane. Consequently the amount of oxygen carried per unit of time will be less than could be carried had not the compensatory mechanism overextended itself. This is illustrated in a recent book by Nadas. The specific viscosity of the blood was measured and plotted against the hematocrit (fig. 3). Note that the viscosity increases abruptly between hematocrit values of 60 and 70 per cent. Dr. Hamilton and I have observed that some patients are worse if the hematocrit is reduced too drastically and they are better when the hematocrit is above normal. Look at the curve. When the hematocrit is greater than 70 per cent the viscosity of the blood increases rapidly and the blood becomes so sticky that it is difficult to propel through the cardiovascular system. The implication of this study is that patients with secondary polycythemia should be bled gradually and slowly to the point where their hematocrit values are between 60 and 70 per cent. The exact point depends on the individual patient. These patients know when they feel...
best and that is the place to stop and to hold the hematocrit level. To hold a patient’s hematocrit steady is rather difficult. I think it is unwise to use irradiation, either P32 or x-rays, to do this because it is difficult to control the dose exactly. If a patient eventually develops iron deficiency from phlebotomies, as is probable, it is necessary to give iron. These patients may develop severe iron deficiency and have little hemoglobin in their cells. When this happens the patient will be pushing around a considerable volume of stroma with little oxygen-carrying capacity. This is illustrated quite well in the case of children as was shown by Rudolph, Nadas, and Borges.9 Children with congenital cyanotic heart disease are stimulated immediately at birth to produce more red cells. Soon the iron stores are used up and dietary content of iron is inadequate. During this period of rapid growth, production of red cells far outstrips the iron stores and secondary iron deficiency develops. When this occurs, these young children can be benefited by the administration of iron; but then they produce too many red cells, so that phlebotomies are necessary to control the polycythemia.

DR. PAUL M. SEEBOHM: Dr. Sheets, I should like to ask whether or not increased physical activity in the patient who is developing secondary polycythemia in any way influences the degree of the polycythemia. Some patients who live a sedentary life develop this, and others are working vigorously when they develop the polycythemia. Is there any correlation with exercise?

DR. SHEETS: I would guess that there is, but it would be difficult to measure. The reason I believe this is that exercise enhances the degree of hypoxemia. Consequently the erythropoietic stimulus would be great. On the other hand it would be difficult to measure because of the slowness of such a response. The important thing may be the duration of the hypoxemic stimulus throughout the day. In other words, some patients with emphysema may not have secondary polycythemia because they are saturated at rest, which is most of the time, and it is only at certain times when they exercise that they become desaturated.

DR. SEEBOHM: We had better not let that dangle, however, because there are patients with pulmonary emphysema who have hypoxemia at rest and no polycythemia. As a matter of fact this seems to be the rule.

DR. SHEETS: Dr. Seebohm, the time has come when we should do some work on this problem. You and I have batted this question around for a good many years and are fast reaching the point where we are believing our guesses. Several mechanisms have been advanced to explain this, such as blood loss from duodenal ulcer, increased rate of red cell destruction, or failure of the erythropoietic stimulus. Maybe none of these is the explanation.

DR. HENRY HAMILTON: Dr. Bedell, I believe you stated that the lung volumes were normal in this man. Is that correct? What is your range of normal for the vital capacity?

DR. BEDELL: In this patient the vital capacity was 70 per cent of predicted normal. I do not know what the range of normal is; this is probably down some, but I think there is a fairly wide range of normal. I consider 80 to 100 per cent of predicted normal as normal.

CASE 2

Mr. J. S., a 50-year-old coal hauler, was admitted to University Hospitals in August 1952 because of shortness of breath for 2 years, severe occipital headaches for 3 months, and obesity. He had gained weight from 225 to 290 pounds during the 2 years prior to admission. Physical examination revealed a very obese white man in no discomfort. The blood pressure was 164/114 mm. Hg; the pulse rate was 84 and the respiratory rate was 18 per minute. The lips were cyanotic. The chest was symmetrical with equal expansion bilaterally. Moist rales were present over the left base. The left border of cardiac dullness was percussiond at the anterior axillary line. No murmurs were heard. The liver was 2 to 3 fingerbreadths below the costal margin. The hemoglobin was 17.8 Gm. per 100 ml., the red blood cell count was 6.03 million per mm.3, the white blood cell count was 9,750 per mm.3, and the platelet count was 180,000 per mm.3. The electrocardiogram was normal.

DR. BEDELL: Dr. Fischer will tell us about the chest x-rays.

DR. FISCHER: These films were taken in
August 1952 (figs. 4 and 5). The ratio of the transverse diameter of the heart to that of the chest is .65, which is quite a bit above normal limits. The lungs show some increased markings but their significance is questionable because the patient is extremely obese. Lung markings like these are sometimes seen when the exposure is made through a heavy layer of fatty tissue. It is possible that they could be the result of pulmonary congestion. There is no pleural effusion. There is no increase in the anteroposterior diameter of the chest and no depression of the diaphragm. We were looking for signs of pulmonary emphysema. However, we cannot make this diagnosis radiographically.

Dr. Bedell: The clinical diagnoses were hypertensive cardiovascular disease, obesity, and polycythemia. He was treated with a low-salt, low-calorie diet, digitalis, and mercurial diuretics. Between August 1952 and February 1956 the patient was seen at University Hospitals 7 times. He continued to be overweight. His chief complaint remained shortness of breath on exertion. He continued to work as a coal hauler. During these admissions his red blood cell count ranged between 5.48 and 6.19 million per mm.\textsuperscript{3}, hemoglobin varied from 16.4 to 18.1 Gm. per 100 ml., and the hematocrit ranged from 52 to 65 per cent. The white blood cell count ranged from 7,200 to 12,250 per mm.\textsuperscript{3}, and the platelet count from 138,000 to 180,000 per mm.\textsuperscript{3} X-ray films of the chest were taken on numerous occasions and were interpreted as showing cardiac enlargement but an otherwise healthy chest. Dr. Fischer, would you comment on his chest x-ray taken in 1955?

Dr. Fischer: We have 4 other examinations over a period of about 3 years. All showed cardiac enlargement of varying degrees. The markings of the lungs did not change particularly. The last film, taken in August 1955 (fig. 6), shows essentially the same findings. The heart is smaller than it was on that original film but the lungs look the same. The impression was that this was a healthy-appearing chest for this individual.

Dr. Bedell: At one point this man was seen in the Allergy Clinic because he stated that on exposure to dust from oats and wheat he became very short of breath. Skin tests for the usual inhalants were negative with the exception of house dust, which was slightly positive. The presence of lung disease was always in doubt until 1954, when pulmonary function studies were done (table...
1). These show that his vital capacity was reduced to 50 per cent of normal, and his residual volume was increased to 156 per cent of normal. The minute volume of ventilation was normal. The test for distribution of inspired air was very abnormal, 9.4 per cent when it should be 2.5 per cent. The mechanical tests were also abnormal. The maximal breathing capacity and maximal flow rates were reduced, especially the expiratory flow rate, which was reduced out of proportion to the inspiratory rate.

Arterial blood studies showed that while he was breathing room air, his arterial blood was 90 per cent saturated. When he breathed 100 per cent oxygen for 10 minutes, arterial saturation came up to 100 per cent + 0.9 volumes per cent dissolved. He could have had some venous admixture with arterial blood in the lungs, but a right-to-left shunt is effectively excluded as the cause of his hypoxemia. The arterial Pco2 while he was breathing room air was 45 mm. Hg. This is slightly elevated.

The results of these tests are consistent with pulmonary emphysema. During much of the time of observation the clinical diagnosis was polycythemia vera in spite of many normal white blood cell counts and normal platelet counts. After the pulmonary function studies were done, secondary polycythemia was diagnosed. When last seen, in February 1956, his weight was 247 pounds. He was working and clinically he was unchanged. Therapy consisted of bleeding, weight reduction diet (which was not very successful), and occasional mercurial diuretics.

This patient demonstrates some of the problems in diagnosis of polycythemia. Many observers were willing initially to accept the diagnosis of polycythemia vera in spite of the fact that the white blood cell counts and platelet counts were not elevated, the spleen was not palpable, and heart and lung disease had not been excluded completely. At this point I would like to state that it is not unusual for a patient with emphysema to have an essentially normal-appearing chest x-ray. The chest x-ray may be read as "healthy chest" but that is a semantic error. It should be read as "normal-appearing chest x-ray." This does not convey the impression that all types of pulmonary disease were eliminated by the simple procedure of taking a chest x-ray. In the clinical diagnosis of emphysema few signs are present invariably. Increased anteroposterior diameter of the chest or the so-called barrel chest is much talked about, but emphysema can exist without this deformity. A simple useful test is to have
the patient blow his air out as rapidly as possible. If expiration is slow, one may suspect airway obstruction, possibly caused by emphysema. In addition the normal vesicular breath sounds are usually absent, especially over the bases of the lungs. Confirmation of the clinical diagnosis is not difficult. The single-breath oxygen test reveals uneven distribution of inspired air, a hallmark of the disease. The maximal inspiratory and expiratory flow rates give objective evidence regarding the patency of the airways in inspiration and expiration. In typical emphysema the inspiratory flow rate is relatively well maintained, but the expiratory flow rate is severely reduced. Polycythemia is not universally associated with emphysema as Dr. Seebohm has mentioned already. Although polycythemia may be a response to hypoxemia and certainly is in persons with cyanotic congenital heart disease and in persons at high altitudes, the mechanism of this response is unknown and factors that may modify the response are unknown. Ratto et al.\(^1\) pointed out that some patients with severe emphysema may have polycythemia, but this is unusual. They postulate that the polycythemic response is inhibited by chronic infection or perhaps carbon dioxide retention. Dr. Sheets has suggested other mechanisms to explain the absence of polycythemia in the hypoxic patient with emphysema, namely the possibility of a hemolytic mechanism or bleeding from a duodenal ulcer. As regards therapy of this patient, I think that it is the same as that of the first patient; is that right, Dr. Sheets?

Dr. Sheets: I would like to ask you a question first. What sort of congestive failure do these people with emphysema have? Is it high output failure or low output failure?

Dr. Bedell: Some think it is high-output failure; other people think that it is normal output or low-output failure. I do not believe that this is definitely known.

Dr. Sheets: I suppose that is a good answer. As far as the treatment of the polycythemia itself is concerned, the remarks we made about the previous patient hold in this situation. As far as the treatment of congestive failure in these patients is concerned, one must question the idea that digitalis is not helpful because this is high-output failure. Sometimes digitalis will aid these patients and sometimes it will not. The only way to find out is to try it.

Dr. Bedell: The third case presents a different problem.

Case 3

Mr. H. H., a 25-year-old station agent, had hemoptysis in 1941. Because of this he was admitted to a tuberculosis sanatorium and diagnosed as having minimal pulmonary tuberculosis. Pneumothorax treatment was complicated by hemopneumothorax. His left lung re-expanded, however, and he was discharged from the sanatorium in November 1945. He returned to work as a station agent and got along well until October 1956, when he developed malaise and increasing nervousness. In November 1956 he suffered a painful blow to the abdomen in a fall from a truck. He was hospitalized because of the possibility that he had ruptured his spleen. Routine blood counts at that time demonstrated polycythemia. His family physician treated the polycythemia with phlebotomies. He suspected that the patient had polycythemia vera and in February 1957 referred him to University Hospitals for treatment with radioactive phosphorus.

Physical examination revealed a thin white man who was alert and cooperative. His blood pressure was 130/80 mm. Hg; the pulse was 90 per minute, and the respirations 20 per minute. The chest was symmetrical. There was a right thoracic, left lumbar scoliosis. The anteroposterior diameter of the left chest was narrow; the right side expanded well and the left side less well. The breath sounds were normal. There were no rales or wheezes. The heart was normal in size. The pulmonic second sound was louder than the aortic second sound. The rhythm was regular. There was a systolic thrill in the third left intercostal space and a grade IV systolic murmur in this area. The hemoglobin was 17.5 Gm. per 100 ml., the red blood cell count was 7.69 million per mm.\(^3\), and the hematocrit was 50 per cent. The platelet count was 489,000 per mm.\(^3\).

Dr. Bedell: Dr. Fischer, will you tell us about his chest x-ray?

Dr. Fischer: I think you can see that this man has considerable chest deformity secondary to the suspected tuberculosis, the
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therapeutic pneumothorax and the complicating hemothorax (fig. 7). You didn't say whether or not that was infected, but I suspect that it may have been. This man has a very greatly thickened pleura with deformity of his thorax. The thickened pleura is encroaching upon the left lung. From this we would suspect that perhaps the left lung is not functioning normally. Possibly there is inadequate oxygenation of the blood passing through this lung. The right lung is normal except for the distorted position of the heart. That there is sufficient pulmonary abnormality to interfere with oxygenation is only a suspicion, for even with these pronounced radiographic abnormalities, the patient may have normal pulmonary function.

Dr. Bedell: The results of pulmonary function studies are shown in table 1. The vital capacity was 57 per cent of normal. The residual volume was 159 per cent of normal. The single-breath oxygen test was normal. The maximal breathing capacity was essentially normal; his maximal flow rates were about half of normal. Arterial blood studies were normal. The clinical diagnoses were polycythemia vera, old pleuritis of the left lung with secondary scoliosis, and ventricular septal defect. The patient was treated with radioactive phosphorus.

This man is particularly interesting because he has polycythemia vera, lung disease, and heart disease. In this patient the diagnosis of polycythemia vera rests on solid ground. He has a high red blood cell count, hemoglobin, hematocrit, white blood cell count, and platelet count. He has a palpable spleen and normal arterial oxygen saturation. His lung disease has not produced arterial hypoxemia. Dr. Sheets will discuss the decision regarding therapy in this patient.

Dr. Sheets: This man is asymptomatic at the present time—his polycythemia was discovered when he fell off a wagon and hit his belly on the sideboard. At that time he had a big spleen and the diagnosis of polycythemia vera was made. Either horn of the dilemma that occurs in polycythemia vera may cause difficulty. On the one hand, these patients develop vascular thromboses, which are troublesome, and on the other hand they bleed excessively, which gets them into difficulty. Much of the therapy is directed at alleviating these 2 conditions in addition to the trouble caused by too many red cells. In this hospital Dr. Fowler and Dr. Hamilton have obtained good control of many of these patients with phlebotomy only. Some patients can be bled once every 6 months or so and maintain a relatively normal hematocrit. Eventually if they become deficient in iron, so that their hemoglobin concentration is grossly below their red cell count, their diet should be supplemented with iron so that the red cells which they circulate are normal in hemoglobin content. Finch, Haskins, and Finch, who studied the treatment of polycythemia vera with phlebotomy thought that one of the mechanisms of control of this disease with phlebotomy was to make the patient deficient in iron. It takes about 6 months of frequent, repeated bleedings to make many of these patients deficient in iron and it will not control the red cell production in all patients. When it does not, those who are deficient and continue to make cells will have a high volume of red cells as measured by hematocrit, although they may have a very low hemoglobin. This patient at one stage in his treatment was in such a situation. The other important factor in the patient with polycythemia vera is the platelet count. This man's was fairly high—489,000 per mm. In this hospital the normal is 100,000 to 150,000 per mm. Some patients have platelet counts of 2 to 3 million per mm. Phlebotomy will not control the platelet count and one must use radiation to do this. It seems to make very little difference whether one uses x-ray or P³² as far as the final result is concerned. At the present time P³² is used in most hospitals. The total dose is around 9 millicuries. This dose was established in a study by Lawrence et al. If one were seeing a patient for the first time, the initial dose of P³² would be
given immediately, followed in 3 or 4 days by phlebotomies to reduce the red blood cell volume. Three months later evaluation would be made to determine the rate at which red blood cells and platelets had reformed. Another dose of P32 might be given at that time.

Dr. I. McLean Smith: Do patients with polycythemia vera get leukemia more often than patients with secondary polycythemia?

Dr. Sheets: The incidence of leukemia in secondary polycythemia is the same as in the ordinary population, but it is somewhat higher in polycythemia vera.

Dr. Hamilton: Dr. Bedell, did this patient have proved pulmonary tuberculosis?

Dr. Bedell: No, it was not bacteriologically proved but apparently the x-rays were compatible with it.

Dr. Hamilton: Is it possible that the patient had a thrombosis of the pulmonary vessels from polycythemia to give that picture?

Dr. Bedell: It seems a long time—it was almost 15 years. He was in the tuberculosis hospital in the early 1940's and then his polycythemia was discovered in 1955.

Dr. Hamilton: I would like to call to your attention the fact that the platelet count may rise long before the hematocrit does, heralding polycythemia vera even when asymptomatic.

Dr. Bedell: We have discussed 3 patients with polycythemia. I can summarize the conference with the following statements.

Patients with polycythemia vera usually have high white blood cell counts, high platelet counts, and palpable spleens but this is not always so. Arterial oxygen saturation during the breathing of room air is normal in every patient with uncomplicated polycythemia vera. Patients with secondary polycythemia have an elevated red blood cell count, hemoglobin, and hematocrit in the absence of leukocytosis, increased platelets, or splenomegaly. All have arterial hypoxemia. Although the presence of heart or lung disease is not always apparent immediately, careful physiologic evaluation usually will disclose the mechanism producing hypoxemia.

Treatment in patients with this disease must be individualized. We believe that some patients with polycythemia vera can be treated with phlebotomy alone. When patients with polycythemia vera have high platelet counts this is considered an indication for irradiation, with either x-ray therapy or radioactive phosphorus. We recommend that patients with secondary polycythemia be bled to the point where their hematocrit is around 65 per cent.

REFERENCES
Polycythemia: A Manifestation of Heart Disease, Lung Disease or a Primary Blood Dyscrasia
GEORGE N. BEDELL, RAYMOND F. SHEETS, HARRY W. FISCHER and ERNEST O. THEILEN

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