Pathophysiological Conference

Participants

JOHN E. OLERUD, MD
H. THOMAS ROBERTSON, MD
KENNETH F. HOSSACK, MD
WIL B. NELP, MD
GEORGE F. ODLAND, MD
WARREN D. BOWMAN, Jr, MD
CLEMENT A. FINCH, MD

University of Washington School of Medicine

Refer to: Olerud JE, Robertson HT, Hossack KF, et al: A patient with polycythemia. University of Washington School of Medicine (Pathophysiological Conference). West J Med 135:375-382, Nov 1981

A Patient With Polycythemia

Case Presentation

THE PATIENT, a 56-year-old man of Finnish descent, had a ten-year history of polycythemia. In 1969, following an illness diagnosed as "Asiatic flu," he experienced fatigue and recurrent epistaxis, the latter finally stopped by cautery treatment. He had previously had occasional nosebleeds, perhaps three or four times a year, but at no time were they severe. In 1970 a routine blood study showed a hematocrit of 66. After initial phlebotomies in March 1971 he was referred to a diagnostic clinic, where it was noted that he also had pruritis. In a blood volume determination, the "red cell mass" of 47 ml of erythrocytes per kg of body weight was noted; bone marrow showed erythroid hyperplasia and blood uric acid levels were elevated. An excretory urogram showed no abnormalities. The only additional finding was an immune globulin spike of about 1 gram, which was considered to be a benign gammopathy. A diagnosis of polycythemia vera was made.

Because of the frequency with which phlebotomy was required, in December of the following year he was given pipobroman (Vercyte) at a dose of 100 mg a day to control erythrocyte production. After eight months of treatment, bone marrow suppression occurred and the drug was stopped. During the next four months some 14 units of packed erythrocytes were transfused to support his circulating hemoglobin. He was referred to the University Hospital in January of 1974, at which time hematocrit was 20, platelet count 60,000 and leukocyte count 3,100 per cu mm. On physical examination, in addition to pallor, numerous focal vascular lesions up to 1 or 2 cm in diameter were noted. These were distributed over the trunk; a hemangioma over the left scapula was noted as well. The patient was not certain but suggested the lesions had been present for only a year or two. There was no family history of similar vascular lesions, and examination of his two sons and mother showed no abnormalities. The patient's spleen and liver were not enlarged on physical examination. There was Bromsulphalein (BSP) retention of 19 percent. His marrow hypofunction was attributed to pipobroman therapy, and the question was raised as to whether this drug was also responsible for the liver dysfunction and vascular lesions.

Fluoxymesterone (Halotestin) therapy, 120 mg per day, was begun, and his marrow function improved during the following four months to the extent that his polycythemia returned, although his platelet count subsequently remained at about 100,000 and leukocyte count at about 4,000 per cu mm. Between 1974 and 1979 the patient's hematocrit was held in the low 50's by phlebotomy, but his exercise tolerance decreased to the point that in early 1979 he discontinued his daily three-mile run because of dyspnea and fatigue. On the suspicion that severe iron deficiency produced by phlebotomy was in part responsible for these

From the Divisions of Dermatology, Respiratory Disease, Cardiology, Nuclear Medicine and Hematology, Department of Medicine, University of Washington School of Medicine, Seattle.

Support was provided by the Clinical Research Center, University Hospital, University of Washington.

Reprint requests to: John E. Olerud, MD, Division of Dermatology, RM-14, University of Washington, Seattle, WA 98195.

ABBREVIATIONS USED IN TEXT

Pa_{O_2} = partial pressure of oxygen (arterial)
P_{O_2} = partial pressure of oxygen
P_{50} = partial pressure of oxygen at which hemoglobin is half saturated with oxygen

TABLE 1.—*Pulmonary Function Studies (August 1979)*

	Measured	*Predicted (percent of normal)*
Vital capacity (liters)	5.3	120
Total lung capacity (liters)	8.4	124
Forced expired volume in one second (FEV_1) (liters)	4.3	123
Diffusing capacity (ml/min-mm of mercury) (single breath, corrected to Hb of 15 grams per dl)	29.3	112
Alveolar gas uniformity (percent) (ΔN_2 per 500 ml)	0.5	(normal<1.0)

Hb = hemoglobin; ΔN_2 = changes in nitrogen distribution.

symptoms, therapeutic doses of iron were given, which resulted in a substantial increase in the amount of bleeding required to control his hematocrit; some 17 phlebotomies were done in the six months preceding admission.

He returned to the University Hospital in 1979 for evaluation of his persistent polycythemia and fatigue. On that admission the large number of spider-like vascular lesions over his upper thorax seemed increasingly prominent. A few lesions were also present on his lips and hands. Nasal and oral mucous membranes were minimally involved. Examination of the heart showed a basilar systolic murmur. There were no diastolic murmurs or gallops, and a jugular venous pressure was normal. Examination of the lungs showed no abnormalities. The spleen was not palpable, the liver dullness to percussion was 14 cm at the midclavicular line and no abnormal masses were palpable in the abdomen. The fingernails were slightly curved, with softened nail beds.

Laboratory studies showed the following: hematocrit 64, leukocyte count 4,600 and platelet count 109,000 per cu mm. Blood chemistry values were normal except for bicarbonate concentrations, which varied between 13 and 16 mEq per liter on several determinations. The anion gap, blood urea nitrogen and creatinine values and findings on analysis of urine were all within normal limits. Standard posteroanterior roentgenograms of the chest showed no abnormalities. An electrocardiogram showed sinus rhythm and left atrial and ventricular hypertrophy. Echocardiography suggested a moderate degree of aortic stenosis. Pulmonary function test findings (Table 1) were normal. Arterial blood gas values were as follows: partial pressure of oxygen (P_{O_2}) 62 mm of mercury, calculated arterial oxygen saturation 93 percent, partial pressure of carbon dioxide 26 mm of mercury and pH 7.41. Arterial saturation at night was monitored during sleep with an ear oximeter and found to be stable at between 87 percent and 89 percent saturation. Because of progressive exertional symptoms and documentation of aortic stenosis by catheterization, a prosthetic aortic valve was implanted at the patient's community hospital in November 1979. His exercise tolerance did not improve. In April 1980 further studies were carried out as indicated by the following consultations to evaluate the cause of the patient's polycythemia.

Hematology Consultation

CLEMENT A. FINCH, MD,* and
WARREN D. BOWMAN, Jr, MD†

THIS PATIENT was originally seen in 1974 when his marrow function was suppressed, presumably by the alkalating agent pipobroman. His polycythemia, however, returned and was investigated in 1979. At that time there were several findings that indicated a need to reevaluate the original diagnosis of polycythemia vera. There was no evidence of excessive granulopoiesis or thrombopoiesis, and there was no splenomegaly. The continued suppression of granulocytes and platelets from prior chemotherapy at a time when there was excessive proliferation of erythrocytes seemed atypical for polycythemia vera (where the affected cell clone is expected to have a greater than normal sensitivity to myelosuppressive agents). More important, the patient's vascular lesions and progressive hypoxia suggested another cause of the polycythemia.

In approaching the diagnosis of polycythemia systematically (Figure 1), the previous blood volume determination was helpful. The value of 47 ml of erythrocytes per kg of body weight excluded a hypovolemic type of polycythemia (stress

*From the Division of Hematology, Department of Medicine.
†From the Division of Hematology, Department of Medicine, Clinical Faculty; affiliated with Billings Clinic, Billings, Montana.

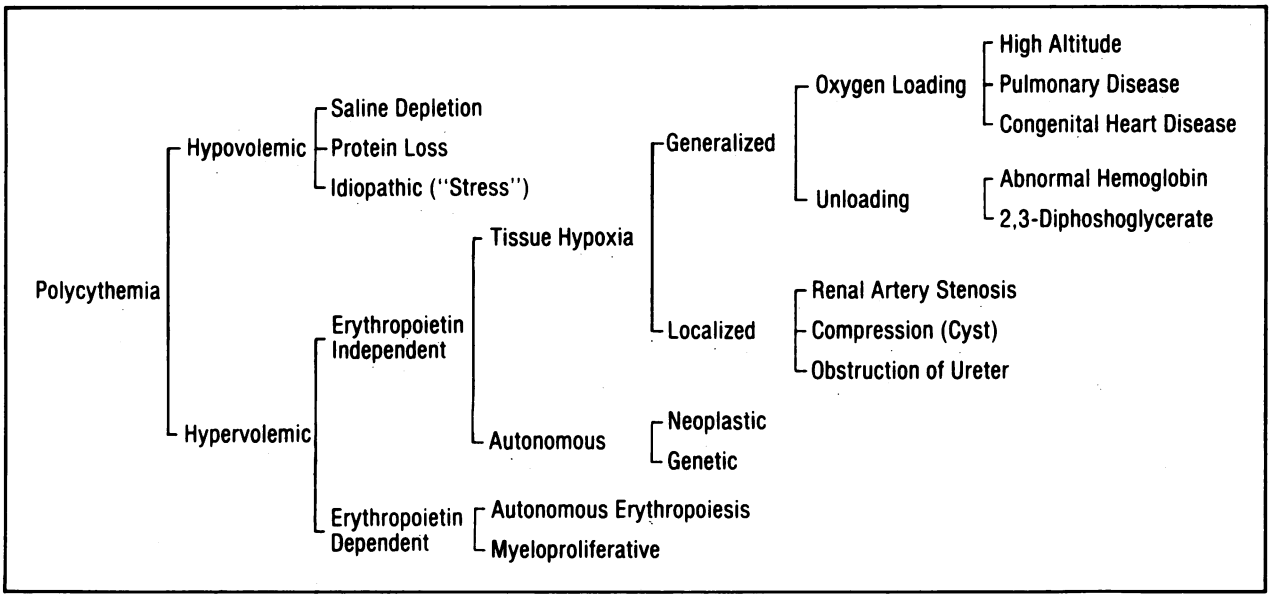

Figure 1.—Diagnostic approach to polycythemia.

polycythemia), although this would seem unlikely anyway in view of the severity and duration of the condition.[1] The next major question was whether the polycythemia was erythropoietin-induced or whether it was the result of autonomous activity of the erythroid marrow (polycythemia vera). Here the essential measurement was that of plasma or urinary erythropoietin at the patient's elevated hematocrit level.[2] A bioassay of the patient's plasma carried out by Dr. John Adamson (Chief of Hematology Section, Veterans Administration Medical Center, Seattle, Washington, Oct. 12, 1979) in polycythemic mice showed an incorporation of radioactive iron by erythrocytes of 17.8 ± 7.0 percent (controls 0.5 or 1.0 percent), indicating an erythropoietin level far above normal. This excluded polycythemia vera because erythropoietin output is suppressed in this condition.[3] The elevated erythropoietin could have been a result of hypoxia or an inappropriately high erythropoietin output. While distinction between these categories could probably have been made by following erythropoietin levels as the hematocrit was reduced by phlebotomy, a number of indicators of hypoxia had already been observed. There was mild clubbing of the fingers, an arterial oxygen saturation measured by ear oximeter of 89 percent and a decrease in carbon dioxide-combining power. To exclude an abnormality in erythrocyte metabolism (2,3-diphosphoglycerate) or an abnormal hemoglobin with a high affinity for oxygen,[4] the oxygen pressure required to half saturate the patient's hemoglobin in vitro (P_{50}) was determined and found to be 30.8 mm of mercury as compared with the normal value of 26.7 mm of mercury. Using the measured P_{50} to calculate a saturation for the original Po_2 determination of 62 mm of mercury, the calculated oxygen saturation was 89 percent. Further studies were undertaken to evaluate the progressive arterial deoxygenation.

Pulmonary Consultation

H. THOMAS ROBERTSON, MD*

AT THE TIME of admission in August 1979, the hypoxemia observed did not seem sufficient to have accounted for the long history of polycythemia. Generally, the arterial partial pressure of oxygen (Pao_2) must remain below 50 mm of mercury to induce polycythemia of the degree observed in this patient. However, a substantial abnormality in oxygenation was present, masked by compensatory hyperventilation. Using the alveolar gas equation, an alveolar-arterial oxygen difference of 48 mm of mercury was present, as contrasted to the normal value of less than 20 mm of mercury. This increase could be caused by pulmonary or cardiac shunts, ventilation-perfusion mismatching in the lungs or oxygen diffusion limitation, although from recent studies, the latter

*From the Division of Respiratory Disease, Department of Medicine.

mechanism has not been thought to be clinically significant.[5] After breathing 100 percent oxygen for 15 minutes, the patient's Pa_{O_2} value returned to normal range (Table 2). This finding suggested that hypoxemia was a result of a severe ventilation-perfusion mismatch rather than shunt, where desaturation would be only minimally improved by breathing 100 percent oxygen. Ventilation-perfusion abnormalities of this severity ordinarily are accompanied by severe airway obstruction and gas maldistribution. Because these findings were not observed (Table 1), a second study was undertaken to evaluate further the possibility of intrapulmonary shunting. Arteriovenous shunts within the lung are held open during full inspiration, whereas the normal alveolar microvasculature is compressed; the reverse occurs during full expiration.[6] When this simple test was done, the patient was found to have the lowest Pa_{O_2} while breathing 100 percent oxygen during inspiration, and the highest Pa_{O_2} during expiration (Table 3). We therefore reconsidered the possibility of an intrapulmonary shunt.

Exercise studies were done to evaluate the patient's complaint of dyspnea (Table 4). The limiting element in exercise performance can usually be identified by means of electrocardiographic findings, expired gas volumes and concentrations, and arterial blood gas determinations.[7] The patient showed a significant limitation in maximal exercise capacity—the oxygen volume uptake was 18 ml per kg of body weight per minute as compared to normal values of 30 to 35 ml—accompanied by a modest tachycardia but substantial hyperventilation. Within one minute at 100 kpm on the cycle ergometer, a level of exercise comparable to a slow walk on level ground, the arterial oxygen saturation dropped from 88 percent to 81 percent. This degree of exertional hypoxia provided an adequate explanation for the serious dyspnea and the polycythemia.

TABLE 2.—*Arterial Blood Gas Determinations*

	Date of Test		
	8/79	*4/80*	*4/80*
Oxygen concentration of inspired air (percent)	21	21	100
Pa_{O_2} (mm of mercury)	62	50	558
Pa_{CO_2} (mm of mercury)	26	28	28
pH	7.41	7.39	7.39
Bicarbonate (mEq/liter)	16	16	16
Oxygen saturation of hemoglobin (percent)*	88.8	78.9	99.9

Pa_{CO_2} = partial pressure of carbon dioxide (arterial); Pa_{O_2} = partial pressure of oxygen (arterial).

*Corrected for high P_{50}. (P_{50} = partial pressure of oxygen at which hemoglobin is half-saturated with oxygen.)

TABLE 3.—*Testing for Intrapulmonary Shunt*

Inspired Oxygen Concentration (percent) Breathing Maneuver	*21 Tidal Breathing*	*100 Tidal Breathing*	*100 Held Inspiration*	*100 Held Expiration*
Pa_{O_2} (mm of mercury)	48	467	438	497
Pa_{CO_2} (mm of mercury)	29	29	29	30
pH	7.45	7.44	7.46	7.44

Pa_{CO_2} = partial pressure of carbon dioxide (arterial); Pa_{O_2} = partial pressure of oxygen (arterial).

TABLE 4.—*Work Exercise Test*

	Load (kpm/minute)				
	Rest	*100*	*300*	*500*	*700*
Pa_{O_2} (mm of mercury)	60	48	47	46	44
Pa_{CO_2} (mm of mercury)	31	30	29	29	28
pH	7.40	7.40	7.40	7.39	7.37
$\dot{V}_{O_2}$ (liters/min)	0.338	0.513	0.751	1.01	1.25
$\dot{V}_E$ (liters/min)	27	37	53	72	101

Pa_{CO_2} = partial pressure of carbon dioxide (arterial); Pa_{O_2} = partial pressure of oxygen (arterial); $\dot{V}_E$ = minute ventilation; $\dot{V}_{O_2}$ = oxygen consumption.

Nuclear Medicine Consultation

WIL B. NELP, MD*

RADIONUCLIDE PERFUSION-DISTRIBUTION studies were done to verify the presence and the amount of pulmonary-to-systemic shunting. The patient received an antecubital intravenous injection of technetium 99m macroaggregated albumin. The injection contained 0.5 to 1.0×10^6 particles, with a mean particle size of 40μ—sufficiently large for trapping in the first capillary bed encountered. This study, carried out while the patient was resting (Figure 2A), showed the expected pulmonary perfusion pattern in the lungs, but also showed significant shunting of particles, with labeling of tissues of the systemic circulation. In the anterior view (Figure 2A), one can see most clearly the flow to the brain and abdominal organs. By total body imaging immediately following injection and computer analysis, it was estimated that approximately 80 percent of the injected activity was deposited in the lungs, while 20 percent of the activity bypassed the pulmonary circuit to enter the systemic circulation.

Two days later the study was repeated (Figure

*From the Division of Nuclear Medicine, Department of Medicine.

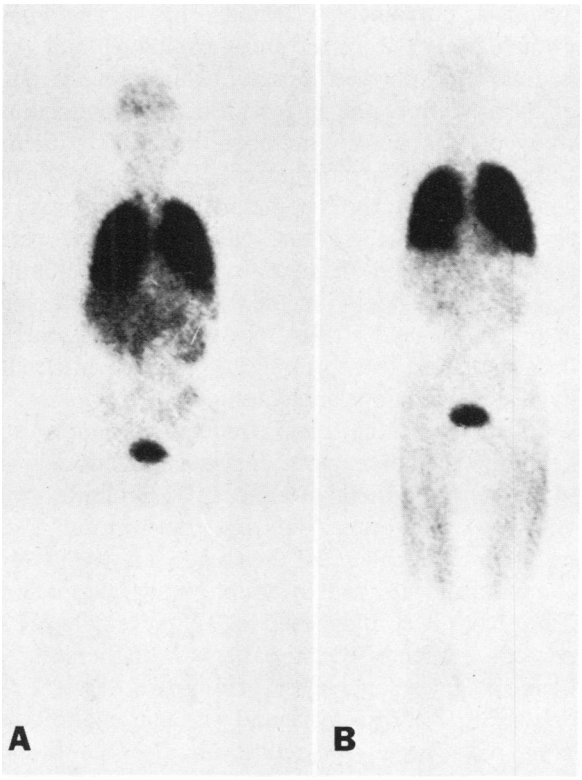

Figure 2.—Anterior gamma camera whole-body perfusion images following intravenous injection of technetium 99m macroaggregated albumin. **Figure 2A** shows shunting through legs to viscera and central nervous system following injection of medium with the patient in a resting position. **Figure 2B** shows the flow pattern following injection at peak exercise, with prominent shunting to muscles.

2B), this time when the patient had achieved maximum exercise on a bicycle ergometer (10.5 minutes at 400 kpm per minute). The estimated systemic shunt increased to 30 percent, and there was a major shift in the distribution of the systemic flow pattern because of the exercise. Note the substantial increase in relative flow to the leg muscles and a relative decrease in the cerebral and visceral components.

The macroaggregated, albumin-distribution studies confirmed the presence of a significant pulmonary-to-systemic shunt and suggested that the degree of shunting was increased during exercise. This latter finding was consistent with the patient's symptoms and pulmonary studies carried out during exercise. Detailed imaging of the lung perfusion pattern did not indicate exactly where the shunt was. In addition, a xenon 133 ventilation study gave normal results during inspiration, at equilibrium and in washout phases.

Cardiology Consultation

KENNETH F. HOSSACK, MD*

THE LONG HISTORY of increased erythrocyte production in this patient without overt arterial desaturation contributed to the difficulty in identifying the underlying pathological condition. In general, cardiovascular problems associated with secondary polycythemia in this age group suggest an intracardiac shunt with reversal of flow due to pulmonary hypertension. The latter is a reaction of the pulmonary vasculature to the initial increased pulmonary blood flow.[8] In the fifth and sixth decades of life, an atrial septal defect is the most common condition associated with this type of abnormal pathophysiology. Rarely patients with a patent ductus arteriosus or a ventricular septal defect may survive into their sixth decade. There are case reports of rare congenital abnormalities associated with intracardiac right-to-left shunting, and these include tetralogy of Fallot, ventricular septal defect associated with pulmonary stenosis and certain types of corrected transposition. In this patient there were no physical findings or electrocardiographic signs to support a diagnosis of pulmonary hypertension. Both the roentgenogram of the chest and the echocardiogram showed normal cardiac configuration, thus making intracardiac shunting extremely unlikely. This left an intrapulmonary abnormality as a more likely cause for the right-to-left shunt.

Catheterization was done to quantitate the right-to-left shunt and to locate an anatomic area of shunting. The likelihood of finding localized areas available for surgical resection seemed remote in view of the normal findings on the roentgenogram of the chest. Previously reported case histories of intrapulmonary right-to-left shunting usually have been associated with pronounced abnormalities shown on plane x-ray studies.[9-11] In Table 5 the hemodynamic and the oxygen content data obtained at the time of catheterization are presented. All the right-sided cardiac pressures were within normal limits. A peak systolic gradient of 34 mm of mercury across the aortic valve prosthesis was measured. The systemic blood flow was 7.4 liters per minute (cardiac index is 4.1 liters per minute per sq m). The effective pulmo-

*From the Division of Cardiology, Department of Medicine.

TABLE 5.—*Hemodynamic Studies*

	Pressure (mm of mercury)		Blood Oxygen Content (vol per dl)
	Phasic	*Mean*	
Site			
Superior vena cava	..	..	13.5
Inferior vena cava	..	..	13.0
Right atrium	..	8	13.1
Right ventricle	30/7	..	12.7
Pulmonary artery	30/15	18	12.8
Pulmonary capillary	..	12	..
Left ventricle	149/10	..	..
Aorta	110/68	84	16.6

Oxygen content data

Oxygen consumption = 281 ml/min

$$\text{Effective pulmonary flow} = \frac{281}{(18.7-12.8)\ 10} = 5.3 \text{ liters/min}$$

$$\text{Systemic flow} = \frac{281}{(16.6-12.8)\ 10} = 7.4 \text{ liters/min}$$

Right-to-left shunt: $7.4-5.3=2.1$ liters/min

nary blood flow was calculated assuming a 97 percent saturation of pulmonary capillary blood. This value was 5.3 liters per minute, with a right-to-left shunt of 2.1 liters per minute. Selective pulmonary angiography was done and this showed multiple small areas of increased blood flow consistent with arteriovenous malformations. No discrete large fistula was seen, consistent with normal findings on the roentgenogram of the chest. Similar negative x-ray findings have been reported to occur[11,12] but are rare.

Dermatology Consultation

JOHN E. OLERUD, MD, and
GEORGE F. ODLAND, MD*

THE PATIENT had a blood vessel dysplasia involving primarily the skin of the trunk (Figure 3A and B) and the lungs. The typical vascular lesion was a pulsating spider angioma (Figure 3C). In addition, a large vascular nevus seen on the back was thought to be a port-wine stain in which a nodular component had developed with advancing age. Although several aspects of the clinical presentation were atypical, it seemed possible that this patient's disorder represented a variant of hereditary hemorrhagic telangiectasia. Osler, in his classic description of that syndrome, characterized three types of cutaneous lesions.[13] They included pinpoint angiomas, spider angiomas (which he felt were the most common) and the nodular or split-pea variety, which he thought might arise from the spider form. In a meticulous study of skin lesions in more than 100 patients with hereditary hemorrhagic telangiectasia, Bean concluded that the characteristic lesion was a pinpoint angioma.[14] When spider-like lesions were present, Bean felt that they often could be clinically differentiated from the vascular spiders seen in pregnancy and cirrhosis by the relatively large body and short legs forming the "spider" in hereditary hemorrhagic telangiectasia.

Epistaxis is the most frequent symptom in hereditary hemorrhagic telangiectasia. It occurs in 90 percent of patients, frequently resulting in iron deficiency and often requiring transfusion.[15] Arteriovenous fistulae of the lungs are relatively common and are usually visible on x-ray studies. They have been diagnosed in 15 percent and 23 percent, respectively, of patients with hereditary hemorrhagic telangiectasia from two large kindreds.[10,16] Telangiectasia and vascular malformations have been reported to involve the brain, spinal cord,[17] retina,[18] heart, spleen, intestine, liver[19] and a variety of other tissues. The family history is positive in 70 percent to 85 percent of the cases,[20-22] and the disease characteristically becomes manifest in the third decade of life.

This patient had several features that were atypical for familial hemorrhagic telangiectasia, in addition to an apparently negative family history. Except for a single three-month episode of epistaxis, the patient had not had unusual bleeding and his iron deficiency was attributable to the many phlebotomies. The distribution of this patient's lesions was predominantly over the trunk as opposed to the usual distribution (in a decreasing frequency) of face, lips, nares, tongue and hands.[23] The vascular lesions themselves more closely resembled tiny arteriovenous fistulae rather than the defective venules usually seen. Many of the lesions had a central arteriole that was elevated and pulsated vigorously. Thus, the essential feature of this patient's vascular dysplasia appeared to represent primarily many minute arteriovenous fistulae present in both the skin and the pulmonary vasculature.

Skin biopsy and cutaneous blood flow studies were done in an attempt to clarify further the anatomy and physiology of these lesions. Blood flow studies were carried out by Dr. Allen Holloway (Research Assistant Professor, Center for

*From the Division of Dermatology, Department of Medicine.

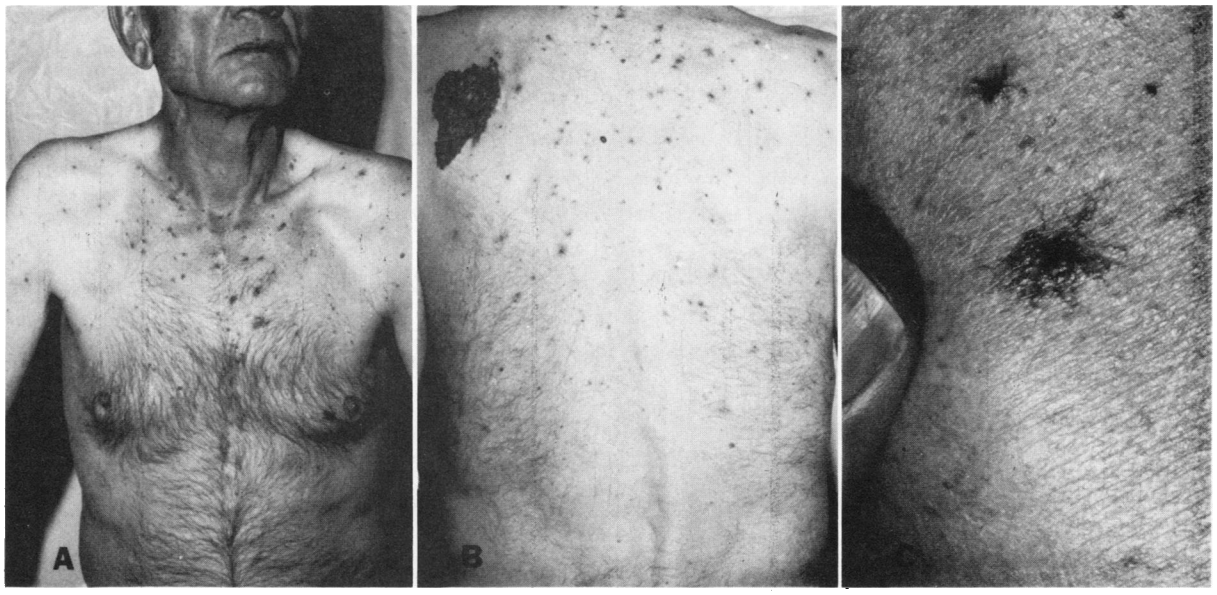

Figure 3.—Cutaneous involvement with vascular lesions is shown in **Figures 3A and B.** The large nevus on the left scapula is thought to represent a port-wine stain, in which nodular changes have developed with advancing age. **Figure 3C** shows a characteristic spider-like lesion with an elevated pulsatile center.

Bioengineering, University of Washington, Apr. 22, 1980), using a laser Doppler instrument.[24] A very high arterial blood flow was found in the center of the spider lesions, with a rapid decrease in flow in the legs. The flow in the center of the lesion was higher than could be measured by the laser Doppler instrument. Rough calculations using estimates of flow rates, vessel diameters and the number of spider-like lesions suggested that they could contribute to the high normal systemic flow.

Ultrastructure studies by Hashimoto and Pritzker[25] and by Menefee and co-workers[26] in familial hemorrhagic telangiectasia indicate that small tortuous vessels in the uppermost layer of the dermis have the morphology of a postcapillary venule and describe irregular fibrotic thickening of the wall of some vessels as well as replication of the basal laminae. Nödl's[27] description indicates that in the middermis there are vessels with thick hemilunar muscular coats, continuous with the dilated thin-walled vessels, suggesting arteriovenous anastomosis. A biopsy specimen of a vascular spider from this patient showed linear vessels extending for some distance through the dermis parallel to the surface, near the junction between the papillary and reticular dermis. These vessels had thin endothelial walls, large lumina, an irregular diameter and a uniform thickened and cellular wall suggesting perivascular fibrosis. A perforating "feeder" vessel was not identified. The changes seen were generally similar to those of familial hemorrhagic telangiectasia as previously described.

Summary

The differential diagnosis of polycythemia continues to present difficulties. An initial diagnosis of polycythemia vera based solely on an increase in erythrocytes without increases in leukocytes and platelets will frequently be wrong unless erythropoietin is also shown to be suppressed. Only with time and with increased exertional dyspnea was hypoxia considered in this patient, and the extent of hypoxia was not appreciated until studies were carried out during exercise. Vascular lesions on the thorax, later found to exist in the lungs as well, consisted of multiple arteriovenous aneurysms differing from the typical vascular lesions found in familial telangiectasia. The pulmonary lesions responsible for hypoxia were not apparent on ordinary radiographs and their physiological behavior was most unusual; tiny anatomic shunts could be partially oxygenated by high inspired oxygen concentrations. From a clinical standpoint, the polycythemia overshadowed the obscure hypoxia-producing pulmonary lesions. This case emphasizes the need for a physiological approach to the diagnosis of polycythemia.

REFERENCES

1. Brown SM, Gilbert HS, Krauss S, et al: Relative polycythemia—A nonexistent disease. Am J Med 50:200, 1971

2. Adamson JW: The erythropoietin/hematocrit relationship in normal and polycythemic man: Implications of marrow regulation. Blood 32:597-609, 1968

3. Koeffler HP, Goldwasser E: Erythropoietin radioimmunoassay in evaluating patients with polycythemia. Ann Intern Med 94: 44-47, 1981

4. Adamson JW, Finch CA: Hemoglobin function, oxygen affinity, and erythropoietin. Ann Rev Physiol 37:351-369, 1975

5. Wagner PD, West JB: Ventilation-perfusion relationships, *In* West JB (Ed): Pulmonary Gas Exchange, Vol 1. New York, Academic Press, 1980, pp 219-262

6. Huseby JS, Culver BH, Butler J: Pulmonary arteriovenous fistulas: Increase in shunt at high lung volumes. Am Rev Resp Dis 115:229-232, 1977

7. Wasserman K, Whipp BJ: Exercise physiology in health and disease. Am Rev Resp Dis 112:219-249, 1975

8. Wood P: The Eisenmenger syndrome. Br Med J 2:701-755, 1958

9. Cooley DA, McNamara DG: Pulmonary telangiectasia: Report of a case proved by pulmonary biopsy. J Thorac Surg 27: 614-622, 1954

10. Hodgson CH, Buchell HB, Good CA, et al: Hereditary hemorrhagic telangiectasia and pulmonary arteriovenous fistula. N Engl J Med 261:625-636, 1959

11. Mayer JH, Glantz G, Brest AN: Pulmonary arteriovenous fistula. Am Rev Resp Dis 100:177-188, 1969

12. Sagel SS, Greenspan RH: Minute pulmonary arteriovenous fistulas demonstrated by magnification pulmonary angiography. Radiology 97:529-530, 1970

13. Osler W: On multiple hereditary telangiectases with recurring haemorrhages. Quart J Med 1:53-59, 1907

14. Bean WB: Vascular spiders and related lesions of the skin, *In* Congenital and Hereditary Lesions and Birthmarks. Springfield, Charles C Thomas, 1958, pp 132-157

15. McCaffrey TV, Kern EB, Lake CF: Management of epistaxis in hereditary hemorrhagic telangiectasia—Review of 80 cases. Arch Otolaryngol 103:627-630, 1977

16. Bergqvist N, Hessen I, Hey M: Arteriovenous pulmonary aneurysms in Osler's disease (telangiectasia hereditaria haemorrhagica)—Report of four cases in the same family. Acta Med Scand 171:301-309, 1962

17. Roman G, Fisher M, Perl DP, et al: Neurological manifestations of hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber disease): Report of 2 cases and review of the literature. Ann Neurol 4:130-144, 1978

18. Davis DG, Simth JL: Retinal involvement in hereditary hemorrhagic telangiectasia. Arch Ophthalmol 85:618-623, 1971

19. Bird RM, Jacques WE: Vascular lesions of hereditary hemorrhagic telangiectasia. N Engl J Med 260:597-599, 1959

20. Stock MR: Hereditary hemorrhagic telangiectasia (Osler's disease)—A review of the literature and report of cases. Arch Otolaryngol 40:108-114, 1944

21. Figi FA, Watkins CH: Hereditary hemorrhagic telangiectasia. Ann Otol 52:330, 1943

22. Saunders WH: Hereditary hemorrhagic telangiectasia—Its familial pattern, clinical characteristics and surgical treatment. Arch Otolaryngol 76:245-259, 1962

23. Bird RM, Hammarsten JF, Marshall RA, et al: A family reunion—A study of hereditary hemorrhagic telangiectasia. N Engl J Med 257:105-109, 1957

24. Holloway GA Jr, Watkins DW: Laser Doppler measurement of cutaneous blood flow. J Invest Dermatol 69:306-309, 1977

25. Hashimoto K, Pritzker MS: Hereditary hemorrhagic telangiectasia: An electron microscopic study. Oral Surg 32:751-758, 1972

26. Menefee MG, Flessa HC, Glueck HI, et al: Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease)—An electron microscopic study of the vascular lesions before and after therapy with hormones. Arch Otolaryngol 101:246-251, 1975

27. Nödl F: Histopathogeneses der Telangiectasia Hereditaria Haemorrhagica Rendu-Osler. Arch Klin Exp Dermatol 204:213-235, 1957