Polycythemia Vera[1]

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POLYCYTHEMIA VERA must be a very rare disease in Puerto Rico. In over 10,000 cases[2] examined in the University Hospital of the School of Tropical Medicine there has been encountered only one case (the one now reported) of this disease. In over 1,200 autopsies performed at the Department of Pathology of the School of Tropical Medicine[3] only one case of polycythemia vera has been found. As far as we know no reports have ever been made in the medical literature concerning polycythemia vera in this Island.

In view of this it seems to us that a brief description of the disease and the report of the one case is justified.

Polycythemia vera was first described in 1892 by Vaquez,[4] but it was not until 1903, when Osler[5] published his first paper on the condition, that the disease became recognized as a clinical entity. It is characterized by an increase in the number of circulating red blood cells, a peculiar cyanotic-plethoric facies, nervous symptoms such as insomnia, irritability, hallucinations, tremors, perspiration, numbness, tingling, etc., a palpable liver and spleen.

Polycythemia vera is more prevalent in males past the third decade and has been more frequently observed among Jews born in Eastern Europe.[6]

Many theories[7] have been proposed to explain the onset of the disease. Among them we can mention the following:

1. Familial
2. Endocrine
3. Thrombosis of splenic vein
4. Neoplastic
5. Increased secretion of gastric substance
6. Anoxic state of bone marrow

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1. Received for publication September 26, 1941.

2. From data to be published.

3. E. Koppisch, personal communication.

4. H. Vaquez, cited by P. Reznikoff, "Polycythemia," *A Symposium on the Blood.* Madison. University of Wisconsin Press. 1939.

5. W. Osler, "Chronic Cyanosis with Polycythemia and Enlarged Spleen: A New Clinical Entity." *A.J.M.Sc.* CXXVI:187-201. 1903.

6. P. Reznikoff, N. C. Foot, and J. M. Bethea, "Etiologic and Pathologic Factors in Polycythemia Vera," *Am.J.M.Sc.*, CLXXXIX:753-759. June, 1935.

7. P. Reznikoff, "Polycythemia," *A Symposium on the Blood.* Madison. University of Wisconsin Press. 1939.

The last one appears to be the most plausible.[8] Anoxemia is brought about by the thickening of the walls of capillaries in the bone marrow, stimulating thus the process of erythrogenesis. It is interesting to note that Osler suggested local anoxemia as the etiology of the disease.[9] In sixteen cases of polycythemia vera in which the bone marrow was carefully studied "markedly thickened capillaries were encountered, and in most cases adventitial and subintimal fibrosis of the arteries and arterioles."[10]

The liver and spleen are found at autopsy usually enlarged and engorged, and frequent thromboses of vessels are encountered. The bone marrow is found to be hyperplastic.

The most commonly encountered symptoms and signs are:

1. Headache, dizziness, fullness of head
2. Paraesthesias, pruritus
3. Hemorrhage from mouth and nose
4. Reddish blue cyanosis of skin and mucous membranes
5. Bloodshot eyes
6. Dilatation of superficial vessels
7. Hemorrhagic fundi; deeply colored retinae
8. Arteriosclerosis, thrombosis, varicosities, phlebitis
9. Hepatosplenomegaly

The blood pressure is usually normal or slightly elevated. In true polycythemia clubbing of the fingers is usually absent. The liver is enlarged in 50 percent of the cases; the spleen in 75 percent.[11] Rosenthal says, "Although the average polycythemia patient is depressed and has a rather sluggish mentality, some individuals demonstrate a combination of mental activity and instability which creates difficult social situations. Even when therapy has lowered the blood count to normal levels, many of the nervous symptoms persist and it is, therefore, probable that some of the disturbances are really due to vascular changes rather than to polycythemia."[12]

The most important laboratory findings are:

1. Polyglobulia with normocytosis
2. High hemoglobin
3. Leukocytosis

8. P. Reznikoff, *loc. cit.*
9. W. Osler, cited by P. Reznikoff, *loc. cit.*
10. P. Reznikoff, *loc. cit.*
11. B. Rosenthal, "Polycythemia," *Arch.Int.Med.*, LXII:903-917. December, 1938.
12. P. Reznikoff, *loc. cit.*

4. Decreased sedimentation rate
5. Increased blood viscosity
6. Increased total red cell mass

Rosenthal[13] divides the clinical phases into:

1. Asymptomatic
2. Polycythemic
3. Thrombocythemic
4. Leukoblastic and megakaryocytic
5. Erythroleukemic
6. Leukocytic and thrombocythemic
7. Leukemic and thrombocythemic
8. Chlorotic
9. Anemic

It is obvious from this classification that the diagnosis of polycythemia vera may at times be extremely difficult. Dameshek and Henstell[14] find that "The disease may masquerade for months to years under many different guises; among others may be listed neurasthenia, migraine, cardio-vascular and renal disease, gastrointestinal disorders and peripheral vascular disease." In 30 percent the platelets are increased, the white blood cells may vary from normal to a frank leukocytosis with polynucleosis.

Haden[15] believes that the only way to differentiate polycythemia vera from erythrocytosis secondary to other conditions, such as congenital heart and pulmonary diseases, is by determination of the red cell mass which has been found to be increased only in polycythemia vera.

The treatment of this disease has been based fundamentally in the destruction of the excess of red blood cells. For this purpose different drugs have been used, the most important among them being potassium arsenite (Fowler's Solution), phenylhydrazine, and acetylphenylhydrazine.

Several authors have claimed good results, using some of these drugs. Forkner *et al.*[16] prefers solution of potassium arsenite used in small amounts at the start and then gradually increasing the dosage

13. B. Rosenthal, *loc. cit.*
14. W. Dameshek and H. Henstell, "The Diagnosis of Polycythemia," *Ann.Int.Med.*, XIII:1360-1387. February, 1940.
15. R. L. Haden, "Treatment of Polycythemia Vera," *Cleveland Clin. Quart.*, VII:166-173. July 1940.
16. C. E. Forkner, T. F. M. Scott, and S. C. Wu, "Treatment of Polycythemia Vera with Solution of Potassium Arsenite," *Arch.Int.Med.*, LI:616-629. April, 1933.

until the point of tolerance is reached. Retznikoff,[17] on the other hand, prefers to use acetylphenylhydrazine. This drug, however, may produce toxic manifestations such as skin rash, fever, nausea, vomiting, and even liver disturbances. The most satisfactory method of treatment according to Haden[18] is venesection. He writes, "If sufficient blood is removed, an iron deficiency is produced, thus preventing the formation of cells. All patients respond to this treatment and all toxic reactions are avoided . . . . it is poor therapy to remove only small portions at a time, this may even stimulate blood formation rather than retard it." Radiation has proved ineffective.[19]

Polycythemia has been thought many times to be due to an excess of the antipernicious intrinsic factor. Based on this theory many workers have claimed improvement following gastric lavage.[20] Stephan in 1930[21] described a reduction in the red blood cells following the use of liver extract. This was corroborated by Ogawa[22] in 1932 and by Hitzenberger[23] in 1936. The logic for the use of liver extract was apparently based on the frequently encountered blood values indicative of primary anemia. Major,[24] however, could not obtain any improvement whatsoever with the use of liver extract. Based also on the theory that in polycythemia there is an excess production of Castle's intrinsic factor, several authors have utilized radiation therapy of the pylorus and Brunner's gland area in patients with polycythemia vera, but with discouraging results.[25] More recently a very unique method of treatment has been advocated by

17. P. Reznikoff, *loc. cit.*
18. R. L. Haden, *loc. cit.*
19. R. L. Haden, *loc. cit.*
20. R. S. Morris, L. Schiff, and M. Foulger, "Erythremia (Polycythemia vera). Theory Regarding Etiology," *J.Med.*, XIII:318-319. August, 1932. J. F. Briggs and H. Oerting, "Influence of Gastric Lavage on Familial and Non-familial Erythremia," *Minnesota Med.*, XVIII:499-504. August, 1935.
21. R. Stephan, "Symptomatische Polyglobulie und Lebersubstanztherapie, ein Beitrag zur Pathogenese der Pernizioesen Anaemie," *Klin.Wchnschr.*, IX:1068-1071. June 7, 1930.
22. J. Ogawa, "Über den Einfluss der Lebersubstanz auf Polycythemia Vera, zugleich ein Beitrag zur Milzdiattherapie," *Jap.J.M.Sc.* translated *Int.Med.Pediat. & Psychiat.*, II:267-273. August, 1932.
23. Karl Hitzenberger, "Zur Frage der Pathogenese der Polycythemia Vera," *Ztschr.f.klin. Med.*, CXXIX:778-782. 1936.
24. R. H. Major, "Effect of Liver Extract upon Polycythemia Vera," *J.Lab. & Clin.Med.*, XXIV:65-67. October, 1938.
25. J. W. Stenstrom, P. H. Hallock, and C. J. Watson, "Negative Results of Irradiation Therapy of Pylorus and Brunner's Gland Area in Patients with Polycythemia Vera," *Am.J.M. Sc.*, CMXCIX:646-650. May, 1940.

some French authors[26]—the production of hookworm disease, which will maintain a low red blood cell count.

PRESENTATION OF CASE

M.V. A 113. A white, married Puerto Rican male of 43 years of age, was admitted on September 26, 1939, to the Out-patient Department of the University Hospital of the School of Tropical Medicine, complaining of nervousness and tremors. Seven months previous to admission he had a "cerebral congestion" consisting of a sudden sensation of fullness in the occipital region. He was seen by a physician who prescribed liver extract, which gave him a severe reaction. He had only three injections. Subsequently he was seen by another physician because of "gasses" and pain in the right abdomen. This time he was prescribed some sedatives and injections of iron, arsenic, and vitamin B_1.

A few weeks after the onset of the illness he was seen by a psychiatrist because he had developed nervous symptoms, such as emotional instability, irritability, tremors, hallucinations, and insomnia. A diagnosis of an anxiety reaction engrafted in a somatic disturbance was made at that time.

Since the onset of the cerebral congestion he had had a cyanotic facies to which he referred as *renegrido.*

Past history. He had pneumonia at the age of 23, and was severely ill. For some time previous to the onset of present illness he had been neurasthenic, nervous, and often complained of spots before his eyes.

Physical examination revealed a well developed, fairly well nourished, white Puerto Rican of about the stated age, very irritable and quite restless, perspiring freely from the hands, with a peculiar, cyanotic plethoric appearance, and a cyanotic hue of nails and nail-beds. The blood pressure was 112/80 mm. of mercury; the heart slightly enlarged to the left on percussion, the spleen, although not palpable, was enlarged to percussion, and the liver was found to be enlarged and its edge was felt four finger breadths below the right coastal margin.

Laboratory Examinations: Hb. 160% or 23.2 grams (Hellige-

26. H. Bouquet, "La anquilostomiasis como medio de tratamiento," *Le Monde Médical.*, CMXLII:184-186. Julio-agosto, 1940.

Wintrobe); R.B.C. 6.53 million per c.m.; W.B.C. 6800 per c.mm.; P.N. 68%; L. 24%; M. 8%.

Reticulocyte Count: 0.3%
Sedimentation Rate: 0
Hanger Test: 0

Blood Chemistry:

N.P.N. 28.2 mg. percent; urea N. 13.8 mg. percent; cholesterol 130.7 mg. percent; total proteins 9.12 grams percent; serum albumin 2.96 gm. percent; serum globulin 6.16 gm. percent; calcium 10.6 percent; phosphorus 3.1 mg. percent.

X-ray of lungs: Negative.

On January 9, 1940, the patient was started on Fowler's Solution following the technique advocated by Folkner. He took as much as 60 drops per day before the point of tolerance was reached. In spite of very little improvement in the blood picture he claimed some symptomatic improvement. Tremors disappeared almost totally and he suffered less from insomnia and dizziness. However, this improvement did not last long. The drug was stopped on April 1, 1940.

Acetylphenylhydrazine was then tried very cautiously on May 27, 1940, but only two doses of .05 grams each could be administered, for he developed a marked toxic reaction characterized by weakness, dizziness, profuse perspiration and sensation of oncoming disaster.

On June 3 the patient was admitted to the University Hospital of the School of Tropical Medicine. Examination on admission revealed the same findings as before, and a blood pressure of 130/80 mm. of mercury. Determination of blood volume was performed according to the method of Rowntree[27] with the following results:

Total Blood Volume	10,587 c.c.
Total Blood Plasma	2,541 c.c.
Blood Cells	8,046
Blood Volume per Kg. body weight	189 c.c.

In view of these findings it was deemed reasonable to produce an iron deficiency state by removing enough blood and prescribing a low iron diet. Several blood lettings were accordingly performed. From June 5, 1940, to November 13, 1940, a total of 3650 c.c. of

27. Blood volume determination—Rowntree's Method, modified by Friedman—performed by Ramón Suárez, M.D.

blood was removed. Of these, 850 c.c. were removed up to July 31, and the rest, or 2800 c.c., from August 14 to November 13. With this treatment the hemoglobin came down to 83% and the red blood cells to 4.55 millions per cubic millimeter, while the cell volume dropped to 54. Notwithstanding this marked reduction in hemoglobin and red blood cells, the nervousness, emotional instability, insomnia, tremors, and perspiration have shown very little improvement.

The case presents all the typical findings of polycythemia vera. The patient had the nervous symptoms, the plethoric cyanotic facies, the polyglobulia and the increase of the total volume of circulating blood. In spite of some subjective improvement with the administration of Fowler's Solution, very little change was noted in the amount of hemoglobin and red blood cells. The removal of blood, although performed relatively slowly at the beginning, had, however, very marked effect on the lowering of the hemoglobin and red blood cells, but the patient has continued to complain of the same symptoms for which he sought medical care.

SUMMARY

The infrequency of polycythemia vera in Puerto Rico is pointed out. The literature on the condition is briefly reviewed. A typical case in a Puerto Rican is presented; the polyglobulia was partly controlled by venesection and iron-poor regime, but this had no beneficial effect on the more outstanding symptoms.