TREATMENT OF POLYCYTHEMIA VERA

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Polycythemia vera is characterized by an increase in the number of red blood cells. This disease is insidious in origin, chronic, and without pathognomonic symptoms or physical findings. Early in the disease and in mild cases there may be no detectable abnormality on physical examination. In well advanced cases the spleen usually is enlarged, the mucous membranes are injected, and the patient is cyanotic or rather a raspberry-red color. The enlargement of the spleen results from the excess storage of red cells; the injection and cyanosis depend on the slowed circulatory rate resulting from the high viscosity of the blood.

On physical examination or laboratory study, the one constant finding in polycythemia vera is the high red cell count. In erythrocytosis the erythrocyte count is high also. Here, however, the total blood volume is not increased. In polycythemia vera the total blood volume as well as the red cell count is constantly high. This increase occurs in symptomatic polycythemia vera as well as in the idiopathic type.

The determination of the blood volume thus becomes a valuable aid in differentiating erythrocytosis and polycythemia vera. The increase in blood volume is due entirely to the increase in the red cells so the most valuable indicator of the increase is the red cell mass per kilogram of body weight[1]. The mean mass of red cells in normal men is 30 cc. and in women 26.4 cc. per kilogram. While this figure is not increased in erythrocytosis, although the red cell count may be high, it is always increased in polycythemia vera and may be increased even to five times its normal volume.

A classification of polycythemia with the more important causes for the high red cell count is given in Table 1. In our laboratory the blood

TABLE 1

CLASSIFICATION OF POLYCYTHEMIA

I. Erythrocytosis (secondary or simple polycythemia)
   Increase in number of erythrocytes without increase in red cell mass per kilogram
II. Polycythemia vera or erythremia
   Increase in number of erythrocytes with increase in red cell mass per kilogram
   - A. Symptomatic polycythemia vera due to
     1. Low barometric pressure
     2. Impaired oxygenation in lungs from:
        - a. Bypassing of lungs in congenital heart disease
        - b. Decreased aerating surface by lung disease
     3. Impaired capacity of hemoglobin to carry oxygen as in methemoglobinemia
   - B. Idiopathic polycythemia vera from unknown cause

volume is determined by the method of Rowntree, Brown and Roth[2]. The total red cell mass is calculated from the hematocrit reading and the total blood volume.

Erythrocytosis is simply treated by an occasional venesection or may need no treatment at all. In polycythemia vera, however, treatment is always required since the symptoms of headache, dizziness, and weakness depend upon the high viscosity which can be lowered only by decreasing the number of red cells. The vascular symptoms can be helped only by removing the excess of cells.

Polycythemia vera has been treated both from the standpoint of destroying the excess cells and from preventing the formation of the excess. Acetylphenylhydrazine is the drug of choice in destroying the excess cells. It is less toxic than phenylhydrazine and less toxic than benzol which also has been used. Patients vary greatly in the sensitivity to the drug, both from the standpoint of toxic effect and hemolytic action. Some patients can take large amounts with little destruction of cells; others will develop a skin rash, fever, nausea, vomiting, and liver disturbances from small doses. With such a great variation in effect, the use of the drug is very unsatisfactory in most cases. If the drug is effective, the red cells may be destroyed at a very rapid rate so the amount of blood destruction cannot be controlled. The bone marrow usually responds rapidly to such a hemolytic anemia with a high reticulocyte count, which indicates rapid red cell regeneration. All the materials, especially iron, needed for red cell formation are still present so the new cells are formed rapidly. In an occasional patient the drug will have just the desired effect so the level of red cells is well controlled. Thus one patient treated himself satisfactorily for over ten years with small doses, using the color of his nose as the criterion for dosage.

With the hemolytic anemia produced by acetylphenylhydrazine, the cells are larger than normal so the red cell mass which is primarily treated is larger than normal for the number of cells instead of smaller as in an iron deficiency anemia.

If acetylphenylhydrazine is to be tried, 0.1 gram is given daily for ten days unless contraindications arise. The hemolysis may continue after the drug is withdrawn so if daily counts show evidence of rapid cell destruction, the drug should be discontinued at once. It is desirable to work out a regular dosage after the initial course. One dose of 0.1 gram weekly may be sufficient.

Irradiation of the spleen and long bones has been employed often. In the patients we have treated and in cases observed so treated elsewhere, there has been little beneficial effect from such treatment. Irradiation may have some place as an adjunct in treatment. It is valuable when the spleen is very large from coincidental myeloid hyperplasia.

The most satisfactory method of treatment is venesection. If sufficient

blood is removed, an iron deficiency is produced, thus preventing the formation of cells. With an iron deficiency, the cells decrease in volume so the red cell mass is small for the number of cells instead of large as with a hemolytic anemia due to acetylphenylhydrazine. All patients respond to this method of treatment and all toxic reactions are avoided.

In treatment by venesection, it is most important to remove a sufficient quantity of blood. The excess of red cells should be completely removed if no contraindications arise. In this way the regeneration of cells will be very slow. It is very poor therapy to remove only small portions at a time. This may even stimulate blood formation rather than retard it. The total red cell mass is calculated first from the total blood volume and the hematocrit reading. Knowing the normal red cell mass for the patient, it is easy to calculate the amount of blood to be removed. An illustrative calculation is as follows:

Male patient—weight 70 Kg.

The hematocrit reading shows 60 cc. of cells per 100 cc. of blood and the total blood volume is 8,000 cc.

Red cell mass $= 8{,}000 \times 60 =$	4,800 cc.
Normal for patient $= 70 \times 30 =$	2,100 cc.
Excess cells	2,700 cc.

As blood is withdrawn, the hematocrit reading will fall to the normal value of 45 cc. The mean will be about 52 cc. The amount of whole blood to be removed is $\frac{2{,}700}{52} \times 100 = 5{,}200$ cc. As the blood is withdrawn, a balance sheet is kept to determine the exact result of the treatment (Table 2). If the red cell mass is exceedingly high, it may not be possible to reduce the red cell mass to normal during the first course of treatment. This one patient recently had a red cell mass of 9,096 cc. when the normal for his weight was 2,100 cc. Nearly 7,000 cc. of blood was removed during a week and the red cell mass was still almost twice too high. This was reduced to normal by more venesections later.

After the red cell mass is reduced to normal by venesection, the regeneration of blood is very slow, seemingly due to the iron deficiency. Patients vary in the rate of regeneration but usually venesections are required only at intervals of six to twelve months. The mean cell volume remains low due to the iron deficiency (Table 3).

All patients in our series are now being treated by venesection. If the spleen is very large and the leukocyte count high, especially if myelocytes appear, irradiation of the spleen and marrow is utilized also. An occasional patient is taking some acetylphenylhydrazine where this treatment has been found satisfactory and no toxic effects have developed. The effect of the bleeding on the blood findings is shown in Table 3.

A detailed history of one patient observed for the past twelve years illustrates the many phases of idiopathic polycythemia vera, the chronic course, and the response to treatment.

TABLE 2

RED CELL MASS BALANCE SHEET

8/31/39	*Red cell mass (blood volume x hematocrit reading)*	*3,464 cc. (67 cc. per Kg.)*		
		Blood removed cc.	*Hematocrit reading cc.*	*Red cells removed*
	9/11/39 Venesection	600	67	402
	9/12/39 "	700	63	441
	9/13/39 "	750	54	405
	9/14/39 "	725	49	355
		2,775 cc.		1,603 cc.
9/5/39	Red cell mass — 1,675 cc. (32 cc. per Kg.) Calculated cells removed — 1,789 cc.			
11/10/39	Red cell mass — 1,926 cc. (34 cc. per Kg.)			
2/16/40	Red cell mass — 2,030 cc. (36 cc. per Kg.)			

Case Report

Case 1: This patient, a merchant thirty-seven years of age, was first seen in 1928, complaining of pain in the right foot which had been present for three months. The toes became red and painful but were not swollen. He had tried various measures such as arch supports without relief. The general examination was negative and no definite cause for the symptoms was found. At that time the red cell count was recorded as 4,780,000 and the hemoglobin as 85 per cent. The leukocyte count, however, was 16,300. No explanation for the leukocytosis was given. It is evident that this was due to polycythemia in view of the later developments.

The patient was not seen again until 1934, when he returned complaining of pain and swelling of the middle toe of both feet. Three weeks before admission blisters had appeared on the right middle toe. The foot became swollen and red. The toe was incised but no pus was obtained. He was now having similar symptoms on the same toe of the left foot. The toes were painful. He had large varicose veins. In an orthopedic examination it was noted that both feet were livid and that a fungus infection was present. The clinical diagnosis was vascular disease of both feet and epidermophytosis. The spleen was not palpable.

A blood count now, however, showed 6,290,000 red cells and 117 per cent hemoglobin. The leukocytosis observed six years previously was still present (white blood count 12,600). A blood volume study two weeks later showed 56 cc. of red cells per kilogram of body weight, (Normal, 30 cc.). The red cell count was now 7,100,000.

The administration of acetylphenylhydrazine was begun and a total of 2 gm. of the drug in 0.1 gm. doses was taken. The patient returned one week later complaining of retrosternal discomfort, burning in the epigastrium, and food distress. The icterus index was 10 units, the leukocyte count 16,800, and the red cell count was about the same. Three weeks later the congestion of the conjunctiva previously noted and the pain in the feet had decreased. The red cell count had fallen to 4,730,000 and the hemoglobin to 81 per cent. The leukocyte count was 18,600. The reticulocyte count was 3.5 per cent, indicating a rapid regeneration of cells. Two weeks later the blood count was much the same and the red cell mass was 28 cc. Two months later the red cell count and cell mass were again high so acetylphenylhydrazine was again given. This time the medication was not well tolerated and the patient developed fever, chills, and vomiting. The medicine was discontinued.

The patient was not observed again until ten months later when the red cell count was 6,950,000, the hemoglobin was 111 per cent, and the white count was 19,100. The total red cell mass was 50 cc. The use of acetylphenylhydrazine was advised but was not taken because of the previous experience with unpleasant reactions.

Fifteen months later the patient began to feel dull, listless, and dizzy. He had had a marked redness of one eye for the preceding week. The red cell count was now 7,010,000, the hemoglobin 111 per cent, and the total red cell mass 55 cc. per Kg.

The patient was next seen two months later at his home with his local physician. He stated that following a single dose (0.1 gm.) of acetylphenylhydrazine, fever, jaundice, and malaise developed. The leukocyte count was 18,000. There was tenderness over the gall bladder; the conjunctivae were icteric. An acute cholecystitis was suspected and operation was advised. On examination there was marked congestion of the conjunctivae and the lips were livid. The viscosity was 9.2 units. The findings suggested that the symptoms were secondary to the

TABLE 3

EFFECT OF BLEEDING ON NUMBER, SIZE AND SHAPE OF RED CELL

	Red cell count	*Red cell mass per Kg.*	*Volume index*	*Color index*	*Diameter*	*Thickness*
	millions	*cc.*			*microns*	*microns*
1. Before	7.75	67	0.96	0.77	7.6	1.90
After	7.72	36	0.77	0.65	7.6	1.55
2. Before	9.01	79	0.78	0.62	7.2	1.75
After	5.60	37	1.78	0.58	7.2	1.75
3. Before	8.33	88	0.97	0.74	7.5	2.00
After	8.38	44	0.77	0.62	7.0	1.85
4. Before	9.42	134	0.92	0.78	7.6	1.80
After	8.56	60	0.73	0.61	7.4	1.80
5. Before	9.55	99	0.91	0.82	7.2	2.00
After	8.04	38	0.69	0.54	7.2	1.60

high viscosity. The red cell count was 6,750,000. Following venesection and the use of physiologic sodium chloride solution intravenously all the symptoms cleared up quickly.

It was evident that this patient should be given no more acetylphenylhydrazine so bleeding was continued. Several venesections were done during the next six months.

During the past two years venesection has been done more frequently. One year ago four venesections were done to bring the blood to a normal level as follows:

Total red cell mass before treatment		3,838 cc.
Cells removed—first venesection	348 cc.	
Cells removed—second venesection	280 cc.	
Cells removed—third venesection	270 cc.	
Cells removed—fourth venesection	260 cc.	
Total removed	1,158 cc.	
Total red cell mass after treatment		2,733 cc.
Difference	1,105 cc.	

During the next eleven months, only 1,200 cc. of blood were removed. A blood study at this time showed a total red cell mass of only 52 cc. The conjunctivae were again injected. The spleen still was not palpable. The patient was having few symptoms. The red cell count was 7,920,000 and the white cell count was 17,650. The patient was again bled as follows:

Total cell volume before bleeding		4,062 cc.
Cells removed—first venesection	482 cc.	
Cells removed—second venesection	482 cc.	
Cells removed—third venesection	450 cc.	
Cells removed—fourth venesection	384 cc.	
Total removed	1,798 cc.	
Total cell volume after bleeding		2,204 cc.
Difference	1,858 cc.	

The actual number of cc. of cells removed (1,798 cc.) checks closely with the calculated amount (1,858 cc.). The red cell mass was now normal. Bleeding probably will not be necessary again for several months. The red cell mass in relation to treatment is shown in figure 1.

Comment: This patient is free of symptoms since the last treatment. He is very interesting and illustrates the chronic course of the disease and good control in bleeding. The leukocytosis and vascular disease were the first manifestations of any abnormality. The nature of the disease was not recognized early in its course. He was very sensitive to acetylphenylhydrazine as shown by the severe toxic symptoms with small doses and the exaggerated hemolytic response to the drug. The spleen

has never been palpable. The disease, when properly treated, has not interfered with normal activity. The vascular symptoms have not progressed.

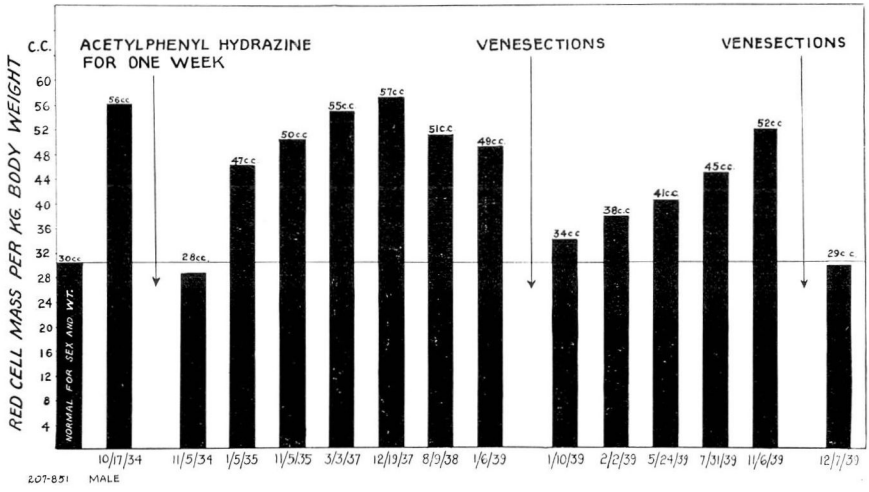

FIGURE 1: (Case 1): The red cell mass per Kg. of patient reported. Note the large mass before treatment. This fell to a point below normal with the administration of acetylphenylhydrazine but quickly rose again. The increase after venesection is very slow.

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