RELATIVE POLYCYTHEMIA — THE POLYCYTHEMIA OF STRESS*

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In a group of normal subjects going from sea level to approximately 16,000 feet we observed that very soon after arrival at high altitude there was hemoconcentration, as indicated by an increased red cell count and hematocrit, but a normal total red cell volume and a low plasma volume. This "apparent increase" in the number of red blood cells in the early days after arrival at high altitude is, of course, replaced by a real increase in red blood cells or an altitude polycythemia after the subject remains at altitude for longer periods of time, since altitude anoxia stimulates red cell production.[6]

At sea level we have observed patients referred to us with a probable diagnosis of polycythemia vera who have the same picture with reference to the red cell count and blood volume. These individuals have increased red cell counts and hematocrits, but normal total red cell volumes and decreased plasma volumes.[2] Although nearly all of these subjects have lived and are living at sea level or near sea level, it is our belief that they exhibit a relative polycythemia due to hemoconcentration possibly brought about by various forms of stress other than anoxic stress. In a series of 215 patients with elevated red cell counts, approximately 175 had polycythemia vera where there was a real increase in total red cell volume.[5] Twenty-two had polycythemia with increased total red cell volumes secondary to pulmonary or cardiac disease, and the remaining 18 (the subject of this paper) were patients exhibiting an increased red cell count and hematocrit but having a normal total red cell volume and a decreased plasma volume.

In the following discussion of these patients we refer chiefly to the 17 out of the total 18 who had no other associated organic pathology. In one female patient (#15) the finding of relative polycythemia was associated with multiple myeloma.

Age and sex. This condition is predominantly found in the male. Of the 17 patients with no apparent organic disease, 15 were males (#3 and #17 were female) varying in age from 16 to 68 and averaging 43 years. This is in sharp contrast to polycythemia vera where the average age of onset

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Received for publication March 31, 1952.

was 52 years. The sex incidence is also in marked contrast to polycythemia vera where 57% were males and 43% were females.[5]

History. There is no typical history. Six patients complained of dizziness. About one half of the patients were thought to have some significant anxiety state or to be mildly psychoneurotic. Two patients (#2 and #12) had been placed on thyroid extract because of a low BMR and one patient (#3) had a history of hyperthyroidism.

Physical examination. Eleven of the 18 patients had the ruddy cyanosis characteristic of polycythemia vera. The heart was not enlarged on physical or x-ray examination. The liver was not palpable (13 patients) or was questionably felt on deep inspiration (4 patients). None of the patients exhibited palpable enlargement of the spleen.

Eight of the 18 patients were thought to be overweight. Nine were hypertensive with a blood pressure greater than 150 systolic or 90 diastolic.

Laboratory Studies

Methods. In addition to the usual history and physical examination, the following studies were carried out:

(1) Complete blood count

(2) Blood volume with P^{32} labeled red blood cells[2]

(3) In most of the patients the following additional studies were done:
   (a) urinalysis
   (b) total protein, A/G ratio, blood uric acid and total bilirubin
   (c) blood oxygen saturation by the Scholander-Roughton method[8]
   (d) Fe^{59} turnover studies by the method of Huff *et al.*[4]

Laboratory Data

Red blood count. Thirteen of the 17 patients (excluding #15—multiple myeloma) had initial red cell counts in excess of 5.5 million and ranging up to 7.35. The remaining 5 patients had red cell counts between 4.9 and 5.5 million* (Table 1). Thus there was no tendency toward the extremely high red cell counts seen in polycythemia.

Hemoglobin. The hemoglobin varied from 13.1 gm./100 ml. in a patient who had been previously treated by phlebotomy to 18.5 gm./100 ml.—again showing a distribution closer to the normal than is seen in polycythemia vera.

Hematocrit. Six patients had a hematocrit below 50; in the remaining 12 it ranged from 50 to 58.

White cell count. Seven patients had white cell counts above 10,000 but of these only two were above 11,000. (This does not include the patient with multiple myeloma.)

* Higher counts were found by the referring physicians.

Reticulocyte count. The reticulocyte count varied from 0.2 to 1.4%.

Differential white cell count. No abnormal white blood cells were noted in the peripheral blood. This is unlike the situation observed in patients with polycythemia vera.

Bone marrow. Satisfactory bone marrow punctures were obtained in 13 patients, including the one patient with multiple myeloma. Excluding the latter patient, the differential counts showed an average of 27.9% nucleated red cells and an average total count of 182,000 red cells. In normal subjects the percentage of nucleated red cells equals 16%, and in polycythemia vera, 38%.[10] In only one case in the present series was this figure above 33%, and in that individual it was 52.5%. For the other 11 subjects the mean nucleated erythrocyte percentage was 24.7. Thus, there is no significant increase in the number of nucleated red cells in the bone marrow of this group. Although there is on the average a significant increase in the nucleated red cells in the marrow of patients with both primary and secondary polycythemia,[7, 10] study of the bone marrow puncture is not diagnostic.

Urinalysis. In three patients (#1, 2, 5) the urine contained occasional white cells, in one (#14) it contained in addition a slight trace of sugar and occasional granular and cylindrical casts.

Blood chemistry. In 13 patients the total proteins varied from 6.8 to 8.6 gm./100 ml. and averaged 8.0 gm./100 ml. The albumin varied from 3.8 to 6.9 gm./100 ml. and averaged 4.6. The globulin ranged from 1.5 to 4.8, averaging 3.5 gm./100 ml. The A/G ratio varied from 0.67 to 4.5 and averaged 1.5.

Bilirubin. In 7 patients the total serum bilirubin varied from 0.03 to 1.0 mgm.% and averaged 0.4 mgm.%.

Blood oxygen saturation. In 8 patients the blood oxygen saturation averaged 92.5%, which is in the range for normal subjects and for those with polycythemia vera.[9]

Blood volume. The characteristic finding in these patients was a low plasma volume. The average was 25.6 and the range 20.4 to 30.9 ml./kg. body weight (the lower limit of normal being 32 ml./kg.). The total red cell volume averaged 28.3 ml./kg. (normal for male is 29.9 and for female 27.0 ml./kg.).[1]

Fe^{59} turnover studies. These studies showed that the rate of disappearance of radioiron from the plasma and the amount of iron incorporated into red cells per day were normal and in good agreement with the patients' requirements. The characteristically rapid disappearance of radioiron from the plasma and the relatively high rate of utilization of iron for red blood cell formation seen in patients with polycythemia vera or secondary polycythemia[4] were not observed in this group.

TABLE 1

Pt.	Age	Height	Weight	Obesity	Ruddy cyanosis	B.P.	RBC†	Hgb.	WBC	Platelet	ml./kg. Body weight			Hmt.	Date
											Blood volume	T.R.C.V.	Plasma volume		
1.	44	6′ ½″	96 kg.	+	+	130/85	6.54	18.1	14,900	270,000	51.8	28.5	23.3	55	3–3–49
2.	43	6′ 0″	81.4		—	130/78	6.04	15.0	10,900	260,000	54.4 (4432 cc.)	26.1 (2127 cc.)	28.3 (2305 cc.)	48	3–9–51
			84.5			120/75	5.16	14.0	12,300	290,000	56.9 (4804 cc.)	27.6 (2330 cc.)	29.3 (2474 cc.)	48.5	9–28–51
3.	68	5′ 2½″	56.7		+	260/140	6.82	17.4	10,200	380,000	45.4 (2578 cc.)	25.0 (1418 cc.)	20.4 (1160 cc.)	55	2–9–51
			53.4			210/135	6.02	16.7	9,300	320,000	52.7 (2812 cc.)	29.0 (1547 cc.)	23.7 (1265 cc.)	55	11–16–51
4.	39	6′ 4″	135.4	+	+	125/75	6.04	17.1	10,100	360,000	52.1	23.4	27.6	45	1–16–50
5.	39	5′ 10″	93.2	+	+	155/115	7.35	17.5	8,000	240,000	52.4	26.7	25.1	51	10–21–49
			91.0			126/88	5.46	16.9	8,400	360,000	49.0	29.4	19.6	60	10–15–51
6.	59	5′ 9″	74.1		+	142/82	5.76	14.6	7,800	440,000	61.4 (4548 cc.)	30.7 (2274 cc.)	30.7 (2274 cc.)	50	1–23–51
			74.5				4.76	14.8	8,050	320,000	60.8 (4532 cc.)	30.4 (2266 cc.)	30.4 (2266 cc.)	50	10–31–51
7.	26	6′ 0″	76.8		—	140/80	5.78	16.6	6,600	320,000	54.4	28.4	25.6	52	1–30–51
8.	41	5′ 7″	83.2	+	+	130/98	5.37	15.6	7,200	310,000	54.7	26.8	27.3	49	2–28–50
9.	16	5′ 6½″	65.5		—	110/62	5.68	16.8	7,300	390,000	55.8	27.0	28.5	49	3–8–50
10.	57	5′ 10¼″	99.5	+	+	120/80	5.24	17.8	7,800	260,000	58.6 (5837 cc.)	32.8 (3268 cc.)	25.2 (2509 cc.)	56	2–27–50
			95.5			135/80	7.16	18.1	8,300	220,000	60.5 (5782 cc.)	36.3 (3469 cc.)	24.2 (2313 cc.)	60	2–27–51
11.*	46	5′ 7″	81.8	+	+	124/98	4.96	14.2	15,500	150,000	57.7 (4716 cc.)	28.0 (2287 cc.)	29.7 (2429 cc.)	48.5	2–17–50
							5.5	17.0	9,400		(5050 cc.)	(2190 cc.)	(2860 cc.)	47.5	10–10–51
12.	32	5′ 10″	89.5		—	148/105	6.15	18.5	7,100	180,000	56.6 (5056 cc.)	30.6 (3035 cc.)	26.0 (2030 cc.)	54	5–19–49
			86.4				5.10	17.2	8,300	242,000	58.8 (5077 cc.)	33.2 (2869 cc.)	25.6 (2208 cc.)	56.5	10–20–51
13.	47	6′ 0″	103.6	+	—	130/100	6.61	14.8	4,400	320,000	53.1	26.5	26.5	50.0	5–15–50
							5.18	13.8	4,500	210,000					
14.	33	5′ 6″	64.5		—	122/68	5.32	17.4	10,850	460,000	63.5 (4098 cc.)	31.8 (2049 cc.)	30.5 (1967 cc.)	50	1–4–51
			63.6				5.86	16.7	10,200	304,000	71.2 (4527 cc.)	36.3 (2309 cc.)	34.9 (2218 cc.)	51	9–22–51
15.	65	4′ 8″	47.9		+	182/98	4.95	17.5	15,000	380,000	52.6	27.0	25.6	51	1–18–49
16.	18	.....	79.1		+	118/72	5.90	16.7	6,900	420,000	65.4	36.0	29.4	55	12–19–51
17.	46	.....	60.1			160/100	5.95	13.1	11,000	360,000	59.4	28.5	30.9	48	9–7–51
18.	62	5′ 1″	76.8	+	+	185/85	5.79	15.8	7,130	260,000	57.7	33.5	24.2	58	3–12–52

T.R.C.V. = Total red cell volume.
Hmt. = Hematocrit.
* Second blood volume done by Dr. J. Stanton, Evans Memorial Hosp., Boston, Mass.
† Although some of these red cell counts are not elevated, they had been previously, since all of these patients were referred to us with a diagnosis of polycythemia vera.

Follow-Up

Follow-up studies of the history and physical findings and particularly of the blood volume were obtained in 8 patients at intervals varying from 6 to 24 months. During this interval the patients did not receive specific therapy and were not phlebotomized. The pertinent physical and hematological findings are presented in Table 1. In general there was no striking change in the symptomatology, physical, or hematological findings. In most of the patients the peripheral blood counts were in good agreement, particularly the hemoglobin concentration. (Patient ♯11 was seen here after previous phlebotomies and in the interval probably repleted his iron stores sufficiently to account for the increased hemoglobin.) In no instance was a significant change in the blood volume noted.*

Discussion

The typical patient with this type of polycythemia is a male in the fourth or fifth decade who is overweight, has a ruddy cyanosis, and may complain of vertigo. There is a moderate elevation of the red count, hemoglobin, or hematocrit with a normal white count and platelet count. Aside from the obesity, ruddy cyanosis, and moderate hypertension in half the cases, the physical examination is noncontributory. There is a normal total red cell volume but an abnormally low plasma volume leading to an apparent elevation of the red cell count, hemoglobin, or hematocrit. Fe^{59} turnover data are not characteristic of polycythemia vera or of secondary polycythemia and show a rate of incorporation of iron in the red blood cells that is within normal limits. In many respects these patients seem to fit into the group of patients described by Gaisbock in which there were polycythemia and hypertension but no splenomegaly.[3] It should be noted that the mean white blood cell count of the 17 patients (excluding patient ♯15) was 9,060. This was not significantly different from the mean white cell count (9,160) observed in 200 pre-employment examinations in this laboratory and is in marked contrast to that observed in polycythemia vera[2, 5] indicating that, at least from this standpoint, the bone marrow is not abnormal.

One is tempted to relate the blood volume changes in these patients to some form of emotional stress and to class this condition as a psychosomatic phenomenon. Our observations in normal subjects undergoing altitude anoxia show a similar change in blood volume, and in these cases there is a measurable physiological stress.

Therapy directed toward decreasing the total red cell volume is contraindicated in these patients since they have a normal total red cell volume.

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* In these patients the blood volume is tabulated in both absolute values and in terms of ml./kg. body weight to permit comparison when there has been a significant weight change.

It is important that the true condition of these patients be recognized and treated accordingly. Unlike patients with polycythemia vera they should not receive P^{32} therapy.

Summary

The findings have been presented in 18 cases of relative polycythemia. There was an increase in the red cell count, hemoglobin, or hematocrit, but a normal total red cell volume, the increase being due to a pathologically low plasma volume. In 17 of these cases no associated disease could be found. Sixteen of the 18 patients were males. Eight were obese and nine were hypertensive. The psychiatric background of some of these patients indicated that they had been subjected to undue nervous stress and strain. Although it is known that anoxic stress produces hemoconcentration, the possible effect of nervous stress and strain on blood volume is reported here for the first time.

Case Reports

Patient 1: A 44-year-old white physician was first seen in February 1949 with a chief complaint of fatigue of ten years' duration. In 1947 he had thromboses in the legs and several pulmonary infarcts for which he received continuous dicoumarol therapy. In May 1948 he had massive pulmonary bleeding which necessitated tracheotomy and transfusion of 3500 ml. of blood. In January 1949 he developed dizziness, occipital headache, and precordial pain which lasted several days. At that time an elevated red cell count and hemoglobin were observed. Physical examination revealed an obese white male with slight reddish cyanosis of the ear lobes and nail beds. The only other positive physical finding was a nonpitting, firm edema of legs, ankles, and feet. He had a history of numerous domestic, social, and economic problems of a very trying nature and later was incarcerated in a Federal Penitentiary.

Patient 2: A 43-year-old white salesman had attacks of faintness and weakness and some shortness of breath following pneumonia in 1938. These varied in frequency from one to four times per month. He had frequent frontal headaches lasting from one hour to one day not relieved by aspirin but alleviated by nosedrops. Because his basal metabolic rate was —35 he was given two grains of thyroid daily. On physical examination there was noted some obstruction of the nasal air passages; the thyroid was palpably enlarged; the liver was palpable at the costal margin. BMR was —3 and —5. Blood cholesterol was 155 mgm.%, total; 34 mgm.%, free cholesterol. Blood protein-bound iodine was 5.9 μg.%. At the time the patient was seen in this laboratory a diagnosis of hypothyroidism could not be established.

Patient 3: A 68-year-old white female presented herself with a one-year history of dizzy spells occurring every two months and lasting two to three days. She was a known hypertensive of seven years' duration. Three years ago she had a carcinoma of the bridge of her nose treated successfully with x-ray. She had had hypertension for the past seven years. Fifteen years ago a diagnosis of hyperthyroidism was made and she was treated for one year with iodine. Twenty-two years ago she had a radical mastectomy for carcinoma. There have been no recurrences of these past ailments. On physical examination a questionable slight exophthalmos and a definite lid lag were noted. The pulse was 102 and there was a Grade II systolic murmur at the aortic and mitral areas. The blood pressure was 260/140. She was very restless and fidgety.

Patient 4: A 39-year-old white male was struck on the head with a hammer 22 months before being seen in this laboratory. This was followed by a nearly continuous throbbing left parietal headache which has caused him to be irritable and "nervous." Six months ago he had a copious epistaxis with relief of the headache for one week. The only positive significant physical finding other than those detailed in the table was hyperesthesia of the scalp in the left parietal area.

Patient 5: A 39-year-old white male complained of low back pain of one week's duration, an erythematous rash of many years' duration, and a history of pyelitis 15 years ago. On physical examination an erythematous rash was noted on the face, chest, and back.

Patient 6: A 59-year-old white male had three attacks of severe dizziness during the past ten years. For several years his red blood count was high and his hematocrit slightly above normal. On physical examination the positive findings were a ruddy complexion, and a slight hyperemia of the mucous membranes of the nose, mouth, and pharynx.

Patient 7: A 26-year-old white male gave a history of fatigue and occasional attacks of tachycardia for the past two years, following infectious mononucleosis. On physical examination there was congestion of the mucous membranes of the nose, and a faint systolic murmur was heard at the base of the heart.

Patient 8: A 41-year-old male, who lived at an altitude of 5,000 feet complained of intermittent right lower quadrant pain, not associated with meals, for three to four years. For the past month he noted redness and burning of the tongue.

Patient 9: A 16-year-old white male complained of "heartburn" and belching after meals. On physical examination hyperemia of the pharynx was noted.

Patient 10: A 57-year-old white male, who lived at an altitude of 6,700 feet, complained of ascites and edema of two years' duration. In 1942 redness of the face and elevated red blood count were found and he was treated intermittently with phenylhydrazine and venesections. On physical examination an area of dullness with inspiratory rales was noted in the right chest posteriorly. X-ray showed no pulmonary disease. A systolic murmur was heard at the apex. X-ray of the abdomen showed enlargement of the spleen although it was not palpable.

Patient 11: A 46-year-old white male clergyman had a coronary thrombosis in 1945 from which he recovered after a prolonged period of rest. Since that time he has had typical anginal pain with exertion. In 1947 he had an elevated red blood count and hemoglobin and was treated by phlebotomy. He had malaria in 1932. On physical examination the optic fundi showed slight engorgement and there was slight enlargement of the isthmus of the thyroid. The liver and spleen were not palpable.

Patient 12: A 34-year-old white male gave a history of occipital headache, vertigo, and epigastric distress of ten to thirty minutes' duration. In October 1948, because he had a low BMR, he was given ½ grain thyroid three times a day; this was increased to 1 grain three times a day in January 1949.

The past history includes a possible attack of malaria in 1946. Physical examination was entirely noncontributory. From the neuropsychiatric standpoint the patient was described as being a nervous, hard-working person with inward repressions.

Patient 13: A 47-year-old Negro physician developed a headache nine days prior to his arrival at this laboratory. About one or two hours later he became dizzy and stumbled while walking. The dizziness was not a true vertigo. There was also an associated vomiting. There was no loss of consciousness. He was seen by his own physician who made a tentative diagnosis of labyrinthitis and prescribed dramamine and ammonium chloride. The past history included malaria. On physical examination, moderate injection of the pharynx was the only positive finding.

Patient 14: A 33-year-old white male first noticed attacks of vertigo while serving with the Navy during the Second World War and while under fire in the jungle. These started with a dizzy sensation after which he became nauseated but did not vomit. On some occasions he fell. The attacks, generally lasting five to ten minutes, recurred every two to three months, but have been less severe during the past year. In 1943 his red count was found to be high. In 1942 he had malaria and in 1944 he was thought to have a palpable spleen. On physical examination the positive findings included slight injection of the sclerae, moderate engorgement of the fundi oculi, and injection of the mucous membranes of the pharynx.

Patient 15: This 65-year-old white female had multiple myeloma.

Patient 16: An 18-year-old white male was referred by his physician with a history that in September 1949 the joints of his hands were swollen and thought to be involved

by arthritis. He was treated with salicylates up to 40 grains a day with definite improvement. However, the joints in his hands still remained larger than was felt normal for his size. He also complained of occasional fainting spells. A blood count by the referring physician showed a hemoglobin of 19.5 gms. and a red count of 6.25 million. The white blood and differential count were normal. In September 1949 and in November 1949 he had an upper respiratory infection at which time again a slight elevation of the hemoglobin and red count was seen. This elevation persisted throughout January 1950 and until November 1951 when he was seen in this laboratory. He then denied any joint swelling as described by his referring physician, and also denied the fainting episodes. On examination he had moist hands with considerable diaphoresis. He appeared to be quite disturbed, afraid, and very nervous. No other positive physical findings were noted.

Patient 17: A 46-year-old white female gave a history of progressive fatigue and nervousness of two years' duration. In 1949 and 1950 she was given tetanus antitoxin and in 1951 tetanus toxoid. Both antitoxin injections were followed by serum reactions, and the toxoid by a sensation of retro-orbital pressure. At the present time she complains of occasional headaches, urinary frequency, tachycardia, and substernal distress. The only significant finding on physical examination was a pulse of 100 with blood pressure of 160/100. From the neuropsychiatric standpoint the patient exhibited considerable apprehension and it was thought that most of her symptoms were on a neuropsychiatric basis. This patient consulted a large number of physicians about her problem, even a previous husband who was a physician.

Patient 18: A 62-year-old real estate man was referred to us with a history of elevation of the red blood count for the past six years. Two years ago diagnosis of polycythemia was made. The history included two years of easy fatiguability, dizziness, loss of mental alertness, and headaches. On physical examination the only remarkable finding was the obesity (44% of his body weight was fat as calculated from measurement from the body water and body specific gravity), and moderate hypertension (blood pressure 185/85).

References

1 Berlin, N. I., Hyde, G. M., Parsons, R. J., Lawrence, J. H., and Port, S.: Blood volume of the normal female as determined with P^{32} labeled red cells. Proc. Soc. Exp. Biol., N. Y., 1951, *76,* 831.

2 Berlin, N. I., Lawrence, J. H., and Gartland, J.: The blood volume in polycythemia as determined by P^{32} labeled red blood cells. Am. J. Med., 1950, *9,* 747.

3 Gaisbock, F.: Die Polyzythamie. Erg. inn. Med. Kinderh., 1922, *21,* 210.

4 Huff, R. L., Hennessy, T. G., Austin, R. E., Garcia, J. F., Roberts, B. M., and Lawrence, J. H.: Plasma and red cell turnover in normal subjects and in patients having various hematopoietic disorders. J. Clin. Invest., 1950, *29,* 1041.

5 Lawrence, J. H., Berlin, N. I., and Huff, R. L.: The physiology and treatment of polycythemia. Medicine (in press).

6 Lawrence, J. H., Huff, R. L., Siri, William, Wasserman, L., and Hennessy, T. G.: A physiological study in the Peruvian Andes. Acta med. scand., 1952, *142,* 117.

7 Merino, C. F. and Reynafarje, C.: Bone marrow studies in the polycythemia of high altitudes. J. Laborat. Clin. M., 1949, *34,* 637.

8 Roughton, F. J. W. and Scholander, P. F.: Microgasometric estimation of the blood gases. J. Biol. Chem., 1943, *148,* 541.

9 Wasserman, L. R., Dobson, R. L., and Lawrence, J. H.: Blood oxygen studies in patients with polycythemia and in normal subjects. J. Clin. Invest., 1949, *28,* 60.

10 Wasserman, L. R., Lawrence, J. H., Berlin, N. I., Dobson, R. L., and Estren, S.: The bone marrow picture in polycythemia vera before and after treatment with radioactive phosphorus. Acta med. scand., 1952 (in press).