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SELECTED CURRENT ISSUES IN POLYCYTHEMIA

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INTRODUCTION

The issues expressed by an increase in red cell numbers, commonly termed polycythemia, have recently expanded to a broad clinical expression involving aspects of cellular production and replication, mechanisms of cellular differentiation and a re-examination of the physiologic sequelae of hyperviscosity. I plan to approach a series of questions that project some of these issues in polycythemia. This presentation represents an expansion of a part of a series of chapters on myeloproliferative lesions in the new William Kelley Textbook of medicine (1,2).

1. EP Frenkel: Polycythemia Vera. In: Textbook of Medicine. Editor William Kelley. JB Lippincott Company, Philadelphia, PA. In press, 1987.

2. EP Frenkel: The approach to the Polycythemic Patient. In: Textbook of Medicine: Editor William Kelley. JB Lippincott Company, Philadelphia, PA. In press, 1987.

I. PROBLEMS IN NOMENCLATURE:

An absolute increase in the mass of the circulating red blood cells is termed Polycythemia. The term polycythemia has been restricted by some to clinical circumstances in which an autonomous mechanism results in a generalized marrow hyperplasia with the increase in red cell mass (ie polycythemia vera). Using that concept, the term erythrocytosis is used for clinical states in which the increase in red blood cells is secondary to an identifiable stimulus (ie "secondary' polycythemia_. Finally, a reduction in the plasma volume (with a normal red cell mass) can result in an elevated hematocrit; this has been termed "relative" polycythemia, but since the red cell mass is normal it should more appropriately be called Spurious Polycythemia (or erythrocytosis).

II. ESTABLISHED DIAGNOSTIC CRITERIA FOR POLYCYTHEMIA VERA

Polycythemia Vera (PV) is an autonomous clonal proliferation of a multipotential stem cell that results in an absolute increase in the numbers of circulating red blood cells for the age and sex of the individual. By definition the term polycythemia vera implies that this expansion of the erythron occurs in the absence of any physiologic or other identifiable pathophysiologic mechanism, thereby separating it from non-autonomous drives to hematopoiesis. During the course of the disease, the clinical manifestations undergo slow progression, similar to the other myeloproliferative

lesions, and an enhanced propensity to leukemic transformation is characteristic of the disease.

The current criteria for the diagnosis of PV are shown in Table 1. These were established by the Polycythemia Study Group in 1967 an have served to provide consistent parameters for the evaluation of the disease course and the response to therapeutic trials.

Table I - POLYCYTHEMIA VERA DIAGNOSTIC CRITERIA*

Category A	Category B
1. Measured increase in Red Blood Cell Mass men $\geq$ 36 ml/kg female $\geq$ 32 ml/kg	1. Thrombocytosis: platelet count > 400,000/ml
2. Normal Arterial Oxygen Saturation: $\geq$ 92%	2. Leukocytosis: White Blood Cell Count > 12,000/ml (in absence of fever or infection)
3. Splenomegaly.	3. Elevated Leukocyte Alkaline Phosphatase Score: >100 (in absence of fever or infection)
	4. Elevated Serum Vitamin B_{12} Content: >900 pg/ml and unbound B_{12} Binding Capacity: >2200 pg/ml

The diagnosis of Polycythemia Vera is acceptable:

1. If all three in Category A are present

or

2. If only one or two in Category A are present, at least two added criteria from Category B as needed.

*Adapted from Reference 4.

3] Berlin, NI. Diagnosis and classification of the Polycythemias. Semin Heme 12:339, 1975.

4] Wasserman, LR. The treatment of Polycythemia. Semin Heme. 13:57, 1976.

5] Wasserman, LR. The management of Polycythemia Vera. Br J Heme. 21:371, 1971.

6] Loeb, V Jr. Treatment of Polycythemia Vera. Clin Haemat. 4:441, 1975.

III. CURRENT CONTROVERSY IN THE EPIDEMIOLOGY OF POLYCYTHEMIA VERA:

Traditional epidemiologic data for polycythemia vera has been considered unreliable because it was compiled prior to the use of accurate red cell mass determinations (7) and specific diagnostic reference criteria. (4). Incidence analysis and demographic data (8,9) estimate an annual incidence of approximately 5 cases per million with a slight male predominance (eg ratio of men to women of 1.2 to 1)

Recent interest in epidemiologic characterization of polycythemia vera by the Center for Environmental Health of the Centers for Disease Control has generated new controversy (10). Prior to their report the only substantive epidemiologic data was the recognition of polycythemia vera in Japanese survivors of the atomic bomb blasts at Hiroshima (11). Inexplicably, similar findings were not seen in the Nagasaki survivors. This inconsistency and the relatively small number of cases identified made any relationships between radiation and polycythemia vera doubtful. The CDC analysis focused on military personnel involved in an atmospheric nuclear test ("Smoky") detonated 31 August 1957 (10). Follow-up studies on 3,217 participants traced through 1981 had previously shown an increased incidence of leukemia (12). Parenthetically an increase in other types of neoplasms was not seen (13). In the current study (10) 4 cases of polycythemia (2 of which were certain and 2 were suspected) were identified in the smoky test group. Their estimated case incidence for this population base was 0.2 cases. The standard mortality rate (SMR) was calculated on the Baltimore data of Modan (8) and was 10 for the 2 definite cases and 20 if all four cases were included.

Table 1.—Polycythemia Vera (PV) Occurring in Nuclear Test Participants

Diagnostic Test	Criteria: Modan	Criteria: Polycythemia Vera Study Group	Case No.*: 1	2	3†	4
RBC mass, mL/kg	. . .	>36	+NOS	101.7	30.8	52.8
Hematocrit value, %	>55	. . .	60	74	55	60
Hemoglobin level, g/dL	>18	. . .	20.2	24	17.9	20
RBC count/cu mm	$>7\times10^6$	. . .	?	?	5.4	?
Splenomegaly	Present	Present	Absent	Present	Absent	Present
WBC count/cu mm	>10,000	>12,000	11.8	11.8	12.9	12.0
Platelet count/cu mm	>400,000	>400,000	?	522	600	+NOS
Arterial O_2 saturation, %	Normal	92	No chronic anoxia	96	?	ND
Overt lung disease	Absent	. . .	COPD, 1978‡	Absent	?	Absent
Renal tumor	Absent	. . .	Absent	Absent	Absent	Absent
Renal cyst	Absent	. . .	Absent	Absent	Absent	Absent
Fever	. . .	Absent	?	Absent	?	Absent
Infection	. . .	Absent	Absent	Absent	?	Absent
Leukocyte alkaline phosphatase score	. . .	>100	Pending	176	ND	ND
Serum B_{12} level, pg/mL	. . .	>900	Pending	ND	ND	ND
Unsaturated B_{12} binding capacity, pg/mL	. . .	>2,200	Pending	ND	ND	ND
Bone marrow, consistent with or diagnostic of PV	. . .	. . .	Yes	Yes	ND	Yes
Age, yr						
At exposure: mean, 32.8; median, 31	. . .	. . .	48	25	37	21
At diagnosis: mean, 48.0; median, 48	. . .	. . .	65	38	58	31
At death	. . .	. . .	70	49	Alive	Alive
Latent period, yr Mean, 14.5; median, 14	. . .	. . .	16	12	20	10
Cumulative gamma radiation exposure for 1957, mrem	. . .	. . .	40	430	1,834	112

*+NOS indicates test results were positive but not otherwise specified; question mark, not reported but not stated as negative or absent; and ND, not determined.

†Many records missing, only complete blood cell counts available are after phlebotomy; timing of RBC mass determination not specified with regard to date of diagnosis.

‡COPD, 1978 indicates a case of chronic obstructive pulmonary disease occurring in 1978.

Table 2.—Observed and Expected Frequency of Polycythemia Vera in Nuclear Test Participants*

Age Group, yr	Person-Years	Incidence per Million	Expected No.	Observed No.	Poisson Probability	Observed/Expected	Observed/Expected, 95% Two-Sided Confidence Limits
≤19	550.3	. . .	. . .	0	. . .	. . .	. . .
20-29	16,818.2	. . .	. . .	0	. . .	. . .	. . .
30-39	26,009.7	0.8	0.02	2	0.0002	96.1	11.6-347.2
40-49	19,270.7	3.5	0.07	0	. . .	0.0	0.0-54.7
50-59	6,636.1	10.7	0.07	1	0.0685	14.1	0.4-78.5
60-69	1,942.5	17.2	0.03	1	0.033	29.9	0.8-166.6
≥70+	255.3	20.6	0.01	0	. . .	0.0	0.0-701.4
Total All Groups	71,482.8	. . .	0.20	4	.0001	20.2	5.5-51.7

*Probability of finding the observed number or more cases given the expected number and the assumption that the observed values follow a Poisson distribution.

The latent period in these cases (ie the time interval from exposure to diagnosis) ranged from 10 to 20 years (mean of 14.5 years). The gamma radiation exposure ranged from 40 to 1834 m rems. This modest exposure was considered a "minimal" value

since no data exists concerning inhaled or ingested radionuclides absorbed during the nuclear test experience.

This report has generated two (post-Chernobyl) subsequent reviews. The first (14) re-calculated the case incidence using the CDC age-specific person-years of follow-up and compared this data to the population of Rochester, MN. The expected number of definite cases (only) with this Rochester data base is 0.82. The SMR for the exposed group then is 2.44. If all 4 cases are used in the analysis the SMR is 4.88. These authors suggested that the apparent increase in frequency was within chance expectation (14).

The importance of a potential etiologic mechanism and the paucity of data is emphasized by a second analysis of the Smoky nuclear test exposure data. Webster (15) used the radiation exposure data reported from the Smoky tests and noted that the radiation dose averaged 271 m rem (2.71 m Sv) for the two certain cases and 604 m rem (6.04 m Sv) for all cases.

Using the concept of the "Doubling Dose", that is the dose that doubles the normal incidence of a given disease (or lesion), data can be projected concerning risk. For such calculations a linear dose-effect relationship must be assumed.

$$\text{Doubling Dose} = \frac{\text{Dose received}}{(\text{SMR}-1)}$$

Using the available data:

Doubling dose ranges:

For the 2 certain cases:	30 m rem (o.32 m Sv) to 188 m rem (1.88 m Sv).
For all 4 cases:	32 m rem (0.32 m Sv) to 156 m rem (1.56 m Sv)

Webster has argued (15) that doubling doses in this range are too low to be implicated as causative because:

1. The average background radiation level in the U.S. is approximately 80 m rem (0.8 m Sv) per year (16) or 2400 m rem (24 m Sv) over a 30 year period. If such a dose is then responsible for the normal incidence of polycythemia vera, then presumably a

additional 2400 m rem (24 m Sv) would be required to double the incidence. The exposure data is well below that number.

2. This doubling dose number would actually be a minimal value for the true doubling dose. Conceptually this can be projected as follows: If background radiation were responsible for 10% of the true incidence of cases of polycythemia vera, then the extra dose required to double the normal incidence would be 24000 m rem (240 m Sv) which is more than 100 times greater than the doubling doses calculated from the Smoky data.

3. Focusing on the doubling dose of 188 m rem (1.88 m Sv) projects the consideration that the normal background radiation over a two year period should produce the expected incidence of polycythemia vera. Therefore the background dose accrual over a 20 year period should yield a ten fold increment.

4. Since our Mountain States have a further 50 m rem /year (0.5 m Sv/yr) increment in background exposure, the incidence in these areas should be five fold greater than the rest of the US; This is not the case.

Although some have argued that the biologic effect per rem of background exposure is less than that for pulse exposures, the National Academy of Science review panel have not provided a basis for reduction of the biologic effect (16). From these studies Webster has argued that the excess cases of polycythemia vera identified were not likely to be due to the radiation exposure during the Smoky weapons test (15).

A residual rebuttal is that the radiation exposure data base utilized film badges which did not record all of the external exposure (eg neutrons) nor did it account for internal (eg inhaled, ingested) exposure. Although this latter argument has validity, the lack of data provides only a speculative relationship between radiation and polycythemia vera.

7] Frenkel EP, McCall MS, Reisch JS, Minton, PD. An Analysis of Methods For The Prediction of Normal Erythrocyte Mass. Amer J Clin Path. 58:260, 1972.

8] Modan B. An Epidemiological Study of Polycythemia Vera. Blood 26:657, 1965.

9] Modan B, Kallner H, Zemer D, Yoran C. A Note On The Increased Risk of Polycythemia In Jews. Blood 37:172, 1971.

10] Caldwell GG, Kelley DB, Heath CW, Zack M. Polycythemia Vera Among Participants of A Nuclear Weapons Test. JAMA 252:662, 1984.

11] Committee For The Compilation of Materials On Damage Caused By The Atomic Bombs At Hiroshima and Nagasaki: Hiroshima and Nagasaki. The Physical, Medical and Social Effects. Edit Ishikawa. Basic Books, NY, pp200, 1984.

12] Caldwell GG, Kelley DB, Heath CW, Jr. Leukemia Among Participants in Military Maneuvers at A Nuclear Bomb Test. JAMA 244:1575, 1980.

13] Caldwell GG, Kelley DB, Zack M, Heath CW. Mortality and Cancer Frequency Among Military Nuclear Test (Smoky) Participants 1957 Through 1979. JAMA 250:620, 1983.

14] Sobell JL, Codd MB, Silerstein MN, Kurland LT. Polycythemia Vera Among Participants of A Nuclear Weapons Test. JAMA 257:1178, 1987.

15] Webster EW. Polycythemia Vera Among Participants of A Nuclear Weapons Test. JAMA 257:1179, 1987.

16] Committee on the Biological Effects of Ionizing Radiation: The Effects on Populations of Exposure to Low Levels of Ionizing Radiation. Nat Acad Press pp66, 1980.

17] Mossman KL, Thomas DS, Dritschilo A. Environmental Radiation and Cancer . Envir Carcino Revs 4:119, 1986.

IV. WHAT PATHOGENETIC MECHANISMS COULD EXPLAIN THE CLONAL AUTONOMY IN POLYCYTHEMIA VERA?

Neither the pathogenetic mechanisms nor the molecular biologic events in PV are known. Considerable evidence implicates the multipotent stem cell as the site of the defect that results in hyperplasia of the entire marrow mass. Moreover, recent data suggest that at least some patients with PV have B lymphocytes, as well as red blood cells, granulocytes, and megakaryocytes, that are derived from the neoplastic clone (18). However, this panmyelosis

is characteristic not only of PV but the other myeloproliferative disorders as well. How perturbation of the multipotent stem cell results in a selective increase in the production and release of red cells in PV, as opposed to granulocytes in chronic granulocytic leukemia (CGL) or platelets in essential thrombocythemia, is not clear.
One explanation for the specificity of lineage involvement in the myeloproliferative disorders would invoke a multi-step model of transformation.

An early event, presumably common to all the myeloproliferative disorders, would confer a proliferative advantage to a multipotent stem cell, eventually resulting in predominantly clonal hematopoiesis. A second, possibly later, event would account for the lineage specificity of the disease. Although no consistent chromosome abnormality has been described in PV, the model of another myeloproliferative disorder CGL supports this hypothesis. Indeed, there is evidence that the Philadelphia chromosome, observed in nearly all cases of CGL, is not the initial event in the pathogenesis of this leukemia (19). Thus, in PV an analogous second mutation or other molecular event, although not cytogenetically recognizable, could account for the selective involvement of the erythron in PV.
An alternative model is that a single etiologic event, analogous to the Philadelphia chromosome in CGL, accounts for the pathogenesis of PV. Thus, altered expression of a normal regulator of stem cell proliferation would result in the panmyelosis of the hematopoietic mass so characteristic of PV but not separable from other myeloproliferative states. This growth regulator presumably would have only modest specificity for cell lineage at the level of the multipotent stem cell. However, at a later level of differentiation the etiologic mutation would act to produce the amplification of a specific cell population, i.e. the red blood cell in PV.

Using X-linked enzyme markers(eg G6PD), studies of cellular mosaicism and erythroid colony growth in vitro have shown the existence of both normal and neoplastic multipotent stem cells in the marrow early in the disease. The unregulated amplification of the neoplastic clone, however, results in decreased production from the normal clones, with the most marked suppression apparently occurring just beyond the erythroid burst forming (BFU-E) stage. Normal clones are

dependent on erythropoietin and other growth factors for amplification at the later stages of differentiation; by contrast the growth of neoplastic erythroid precursors is relatively independent of these factors. At the primitive stem cell level, however, these factors appear to have essentially no role in the self-renewal or commitment of either normal or neoplastic clones.

Spivak and coworkers (20) recently examined the abnormal clone of cells in polycythemia vera for their ability to produce growth factors. They were able to demonstrate that circulating mononuclear cells obtained from patients with polycythemia vera contained intracellular mitogenic and transforming growth factors that were not found as a common product in all myeloproliferative disorders. In addition, these growth factors were distinct from platelet derived growth factor (PDGF) and epidermal growth factor (EGF). Three separate proteins were identified and separated with molecular masses of 13-, 17, and 65- kDa. Of interest, is that the 13-kDa protein was only mitoagenic, and the 17- kDa protein was only transforming. The 65-kDa protein had both properties. What role such growth factors may play in the autonomous hematopoiesis that characterized polycythemia vera is now the exciting focal issue.

18] Raskind WH, Jacobson R, Murphy S, Adamson JW, Fialkow PJ. Evidence for the Involvement of Lymphoid Cells in Polycythemia Vera and Essential Thrombocythemia. JCI 75:1388, 1985.

19] Martin PJ, Najfeld V, Fialkow PJ. B-lymphoid Cell Involvement in Chronic Myelogenous Leukemia: Implications For The Pathogenesis of the Disease. Can Genet Cytogenet 6:359, 1982.

20] Eid J, Ebert RF, Gesell MS, Spivak JL. Intracellular Growth Factors in Polycythemia Vera and Other Myeloproliferative Disorders. Proc Natl Acd Sci 84:532, 1987.

21] Barosi G, Baraldi A, Cazzola M, Fortunato A, Plaestra P, Polino G, Ramella S, Spriano P. Polycythemia Following Splenectomy in Myelofibrosis With Myeloid Metaplasia. Scand J Heme 32:12, 1984.

RELATIONSHIP OF CLINICAL SYMPTOMS TO PATHOPHYSIOLOGY AND THE RATIONAL FOR STAGING OF POLYCYTHEMIA VERA.

PV is most commonly identified in the 50-70 year age group, although patients as young as age 15 have been seen. The primary clinical findings in PV are usually related to the effects of the greatly expanded red cell mass. However, several clinical stages occur during the natural history of PV and the clinical findings are best related to these phases (4).

The pre-erythrocytic (sometimes called development) phase of PV is often unrecognized and the signs and symptoms commonly are insidious in development. During this phase the circulating red cell mass has not yet increased. A complaint of post-bathing pruritus or the finding of splenomegaly may be the only clinical feature. Occasionally mild thrombohemorrhagic symptoms or erythromelalgia (painful or "burning" erythematous palms and soles) results from the increased number of circulating platelets that may be present.

An important presenting clinical feature of the erythrocytic phase is occlusive vascular lesions that result in transient ischemic episodes or actual cerebrovascular accidents, myocardial ischemia, portal venous obstruction, or superficial venous thrombosis. The expanded red cell mass produces symptoms of hyperviscosity and the reduced cerebral blood flow can result in headaches, dizziness, and visual disturbances. Plethora and conjunctival or oral mucosal suffusion are the evident physical hallmarks of this lesion. A second presenting feature is that of hemorrhagic phenomena, often mucosal (epistaxis, ecchymosis, gastrointestinal or genitourinary bleeding). Gastrointestinal symptoms and peptic ulcer disease also occur with increased incidence in PV.

Indeed, the diagnostic elevated red cell values may be obscured by significant gastrointestinal bleeding on presentation.

Splenomegaly is the prominent physical finding during this stage, being identified in nearly 90% of cases.

Hepatomegaly occurs in approximately 50% of patients. Episodes of acute gout associated with over production of urate may occur and occasionally are the presenting complaint.

During this phase significant symptomatic (thrombohemorrhagic signs and symptoms) thrombocythemia may occur and this has been termed the proliferative phase. A progressive leukocytosis is also seen, but this does not produce clinical findings. Progressive splenomegaly is common during this phase.

Evolution into the spent or postpolycythemic myeloid metaplasia phase is very gradual and many patients complain only of asthenia. Symptoms related to progressive splenomegaly and an increasingly severe anemia commonly occur, as does an increase in the severity of hemorrhagic (particularly cutaneous) findings. Other common features during this phase are weight loss, generalized wasting, and progressive asthenia. Many of the clinical features of myelofibrosis may develop during this phase, and extra-medullary hematopoiesis in lymphoid sites may produce symptoms due to mass effect in the gastrointestinal, respiratory or even in the central nervous system.

Finally, the patient may transition to a leukemic phase marked by the typical clinical findings of acute non-lymphocytic leukemia.

TABLE 4: CLINICAL STAGES OF POLYCYTHEMIA VERA

STAGE	Signs/Symptoms	Cardinal Laboratory Features
Pre-Erythrocytic	Post-Bathing Pruritus Splenomegaly Thrombohemorrhagic Symptoms Erythromelalgia	Increased Mast Cells Increased Platelets
Erythrocytic	Plethora Occlusive Vascular Lesions Hyperviscosity symptoms Thrombohemorrhagic Symptoms Gout Splenomegaly	Absolute increase in red cell mass Marrow panmyelosis Elevated: WBC Platelets B_{12} B_{12} binding protein
Proliferative	Thrombohemorrhagic findings Progressive splenomegaly	Progressive increase in platelets and WBC's
Post-Polycythemia Myeloid Metaplasia	Asthenia Anemia Increasing Splenomegaly Weight loss Wasting Extra-medullary hematopoietic masses	Leukoerythroblastosis Marrow Fibrosis
Leukemia	Clinical findings of acute leukemia	Leukemia

22] Frenkel EP. Polycythemia Vera and Myelofibrosis. In Medical Oncology: Basic Principles and Clinical Management of Cancer. Edit. P. Calabressi, P. Schein, S. Rosenberg. Publisher Macmillian Publish Comp. pp576 , 1986.

23] Ellis JT, Silver RT, coleman M, Geller SA. The Bone Marrow in POlycythemia Vera. Semin Heme 12:433 , 1975.

24] Silverstein MN. The Evolution Into and The treatment of Late Stage Polycythemia Vera. Semin Heme 13:79 ,1976.

25] Glen RH, Haese WH, McIntryre. Myeloid Metaplasia With Myelofibrosis: The Clinical Spectrum of Extramedullary Hematopoiesis and Tumor Formation. Johns Hopkins Med J 132:253 , 1973

26] Ellis JT, Peterson P, Geller SA, Rappaport H. Studies of the Bone Marrow In Polycythemia Vera and the Evolution of Myelofibrosis and Second Hematologic Malignancies. Semin Heme 23:144 , 1986.

27] Landaw SA. Acute Leukemia In Polycythemia. Semin Heme 23:156, 1986.

VI. COURSE OF POLYCYTHEMIA VERA

Prior to the formation of the Polycythemia Vera Study Group, criteria for the diagnosis of PV were far from specific and case compilations contained many forms of erythrocytosis other than PV. Nevertheless, it is clear that therapy has significantly altered the course of the disease. An oft quoted statistic is that the median survival in untreated patients is approximately 18 months. By contrast, with appropriate therapy survival approaches that expected for age matched controls. The duration of the pre-erythrocytic phase is least well defined and appears to last from months to a few years. The duration of the erythrocytic and proliferative phase is 5-20 years when treated. There are sequelae of specific therapies that affect the clinical course, quality of life, and survival.

Thus, therapy of the erythrocytic phase with frequent phlebotomy is associated with a significant increase in the incidence of thrombotic events, particularly during the first 2 to 3 years after initiation of the treatment program. The likihood of these

complications has not correlated with the platelet count and has not been reduced by the addition of antiplatelet therapy with aspirin and dipyridamole. Iron deficiency may also occur during this secondary to the bleeding and to phlebotomy therapy. Although iron-deficient erythrocytes have reduced deformability, with resultant increased whole blood viscosity, this has not been shown to be clinically significant and does not warrant therapy with iron. The use of cytoreductive agents in these patients also increases the urate load on the kidney and thus may exacerbate the previously noted risk of gout and even urate nephropathy.

Approximately 20% of patients with PV eventually develop post-polycythemic myeloid metaplasia (PPMM). The time to conversion is approximately 10 years. This transition results not only in the development of new and severe symptoms, but also a shortened survival, as most patients die from clinical complications or conversion to acute leukemia within 3 years of progression to this stage. Patient's in the PPMM phase have a 25-50% likihood of further progression to leukemia. Unlike PPMM, conversion rate to leukemia is affected by therapy, being significantly greater in those treated with systemic alkylating agents or radiophosphorus. Like most secondary leukemias, survival is approximately 4 to 12 weeks, with few patients achieving durable remissions with cytotoxic therapy (8).

Surgery represents a special problem in patients with PV. Since the well-managed patient has a long survival, elective surgery in patients in this age group is not infrequent. In addition, surgery is occasionally performed to remove a symptomatic painful spleen in the PPMM phase of the disease. Although patients with PV have a greater operative morbidity and mortality than a matched population group, these risks decline when the elevated peripheral red cell values are reduced to normal prior to surgery (28,29). Indeed, the better the hematologic control achieved, the more closely the surgical risk approaches that of control groups.

28] Wasserman LR, Gilbert HS. Surgery in Polycythemia Vera. NEJM 269:1226, 1963

29] Wasserman LR, Gilbert HS. Surgical Bleeding in Polycythemia Vera. Ann NY Acad Sci 115:122, 1964.

VII. DIFFERENTIAL DIAGNOSIS OF POLYCYTHEMIA.

The common causes of polycythemia (see Table 5) have limited pathophysiologic mechanisms. In spurious relative polycythemia some basis for constriction of the plasma volume is present, since the measured red cell mass is normal (or high normal) and the plasma volume reduced. The underlying pathogenesis of spurious polycythemia is not known. In true (absolute) polycythemia there is either an autonomous drive to hematopoiesis (ie polycythemia vera) or a stimulus to increased red cell production due to a physiologic or a pathophysiologic alteration in erythropoietin (Ep) production. Erythropoietin (Ep) is a polypeptide hormone capable of stimulating red cell production. Cellular hypoxia is the primary initiating stimulus to Ep production and release. The exact site of the oxygen sensor is not certain but the major site of production is the kidneys with about 10% from extra renal (primarily hepatic) tissue. The true physiologic half-life of Ep is not certain, but disappearance is affected by erythropoietic activity. A pulse Ep secretion results in a reticulocyte response by 4-5 days suggesting its effect is on the stem cell. Ep acts by transforming undifferentiated erythroid committed precursors (CFU-E) to proerythroblasts and by accelerating the cells in the maturation sequence.

Any alteration in ambient oxygen content (ie high altitude), disorders (or diseases) associated with decreased arterial oxygen tension (ie cardiac or arteriovenous shunts), reduced oxygen carrying capacity of the blood (ie presence of elevated carboxyhemoglobin levels with smoking), or altered oxygen delivery to tissues (ie as with a high oxygen affinity hemoglobin) will produce increased erythropoietin and will result in polycythemia (often termed "secondary" polycythemia). In the absence of measurable hypoxia "secondary" polycythemia may be caused by aberrant or inappropriate erythropoietin production (table 1), and this may be either familial or acquired.

CAUSES OF POLYCYTHEMIA

CLINICAL PATHOPHYSIOLOGIC MECHANISMS:	SALIENT LABORATORY FEATURES(s):
I. Normal Red Blood Cell Mass: (Spurious Polycythemia)	Normal Measured (^{51}Cr) Red Blood Cell Mass Decreased Plasma Volume
1. Acute: Hemoconcentration (eg dehydration)	
2. Chronic: Spurious (Relative; Stress; Gaisbock's syndrome)	
II. Increased Red Blood Cell Mass: (Absolute Polycythemia)	Increased Measured (^{51}Cr) Red Blood Cell Mass
1. Neonatal: Physiologic	
2. Familial:	
a] Altered Hemoglobin Structure or Function	Decreased P_{50} of Whole Blood Left Shift in Oxygen Dissociation Curve
b] Decreased 2.3 Diphosphoglycerate DPG) -DPG Mutase Deficiency	Decreased P_{50} of Whole Blood
-Hereditary High ATP	Decreased P_{50} of Whole Blood
c] Autonomous Erythropoietin Production	Increased Erythropoietin
3. Polycythemia Vera	Splenomegaly Increased Platelets and White Blood Cells Increased $Vitamin_{12}$ and B_{12} Binding Proteins
4. Acquired:	
a] Secondary to Decreased Arterial Oxygen Tension -High Altitude -Pulmonary Diseases with Hypoventilation -Cardiovascular Shunts	Arterial Oxygen Saturation Below 92% P_{aO_2} below 65 mm Hg.
b] Secondary to Decreased Oxygen Carrying Capacity -Elevated Carboxyhemoglobin "smokers" Polycythemia	Direct Measurement: of Carboxyhemoglobin
-Methemoglobinemia	of Methemoglobin
c] Secondary to Decreased Oxygen Delivery -Hemoglobin with Altered Structure of Function: ie High Oxygen Affinity Hemoglobin (see familial above)	Decreased P_{50} of Whole Blood Left Shift in Oxygen Dissociation Curve
d] Secondary to Aberrant (Inappropriate) Erythropoietin Production -Renal: Renal Artery Stenosis, Cystic Disease, Renal Cell Carcinoma, Transplant Rejection -Liver: Hepatoma -Uterus: Leiomyoma -Adrenal: Pheochromocytoma	Increased Erythropoietin
e] Secondary to Other Hormones: -Cushings Syndrome	Hormone Assays

A simplified sequential approach to the patient with evidence of increased circulating red cell values is shown in Table 6. The clinical history is a critical component in the evaluation of (acute) mechanisms that produce spurious polycythemia. Since most cases of familial polycythemia are initially recognized during adult years, family data may be particularly helpful when, for instance, family members have become dedicated blood donors. In addition, a smoking history also focuses the subsequent evaluation, since a meaningful characterization of any other pathophysiologic mechanisms necessitates cessation of smoking prior to evaluation.

The measurement of the red cell mass (done with ^{51} chromium labeled red cells) is the next step in the evaluation. When the hematocrit is consistently greater than 60 vol%, it is unlikely that the red cell mass will be normal, making it possible in circumstances of very high hematocrits to bypass this measurement.

The most common cause of absolute polycythemia is decreased oxygen delivery. The next step therefore is arterial blood gas measurements and carboxyhemoglobin levels. If abnormal, the diagnosis is easily defined (Table 5). If normal, three diagnostic categories exist. The first is that of an autonomous drive to hematopoiesis, i.e. polycythemia vera, and splenomegaly and an elevated platelet and white blood cell count would provide strong support for this diagnosis. The second is the inappropriate secretion of erythropoietin, currently measurable by a variety of methods. Finally, a defective oxygen delivery system to tissues (ie high affinity hemoglobin or an alteration in DPG biology) would require the measurement of P_{50} and the pattern the oxygen dissociation curve. Since most such abnormal hemoglobins do not produce an abnormal hemoglobin electrophoretic pattern, special structure studies are required for these cases.

As noted in Table 5, a variety of organs have been implicated in cases of aberrant or inappropriate secretion of erythropoietin. Most cases result from lesions of the kidney or liver. Thus, when no other localizing signs or symptoms are present the appropriate approach is to proceed with abdominal sonography followed by computed tomographic study where indicated.

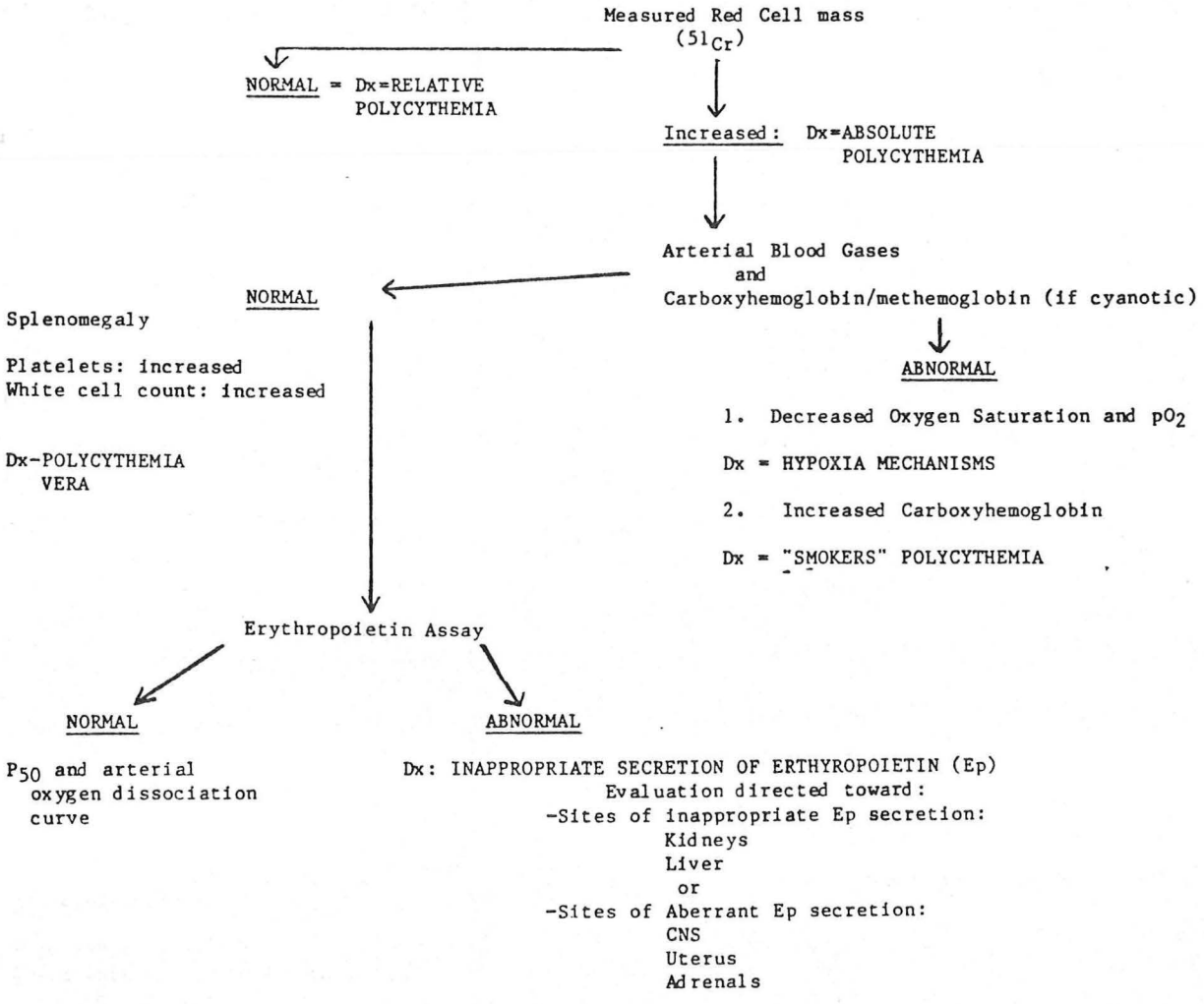
TABLE 6

SEQUENTAL APPROACH IN THE EVALUATION OF PATIENT WITH ELEVATED PERIPHERAL VENOUS HEMATOCRIT

1. Clinical history to evaluate acute mechanisms of hemoconcentration, drugs (eg diuretics, androgens, etc), smoking; or, family history and phelebotomy data.

2. Physical examination for cyanosis, spleen and liver size, endocrine abnormalities, cardiopulmonary disese.

3. Laboratory Studies:



ABNORMAL:

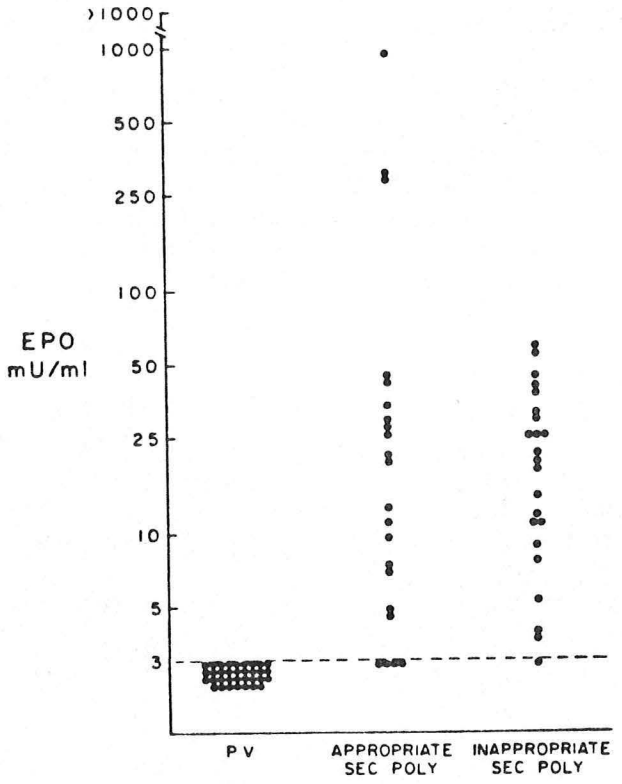
Dx= ABNORMAL OXYGEN DELIVERY:
High Affinity Hemoglobin
DPG Defect

30] Weinreb NJ, Shih C. Spurious Polycythemia. Semin Heme 12:397, 1975.

31] Adamson JW. Familial Polycythemia. Semin Heme 12:383 , 1975.

VIII: CURRENT OBSERVATIONS ON ERYTHROPOIETIN: UNDERSTANDING ITS MECHANISM OF ACTION AND ROLE IN POLYCYTHEMIA:

Classical teaching is that erythropoietin is the primary mediator of normal erythropoiesis by its direct effect on the erythroid compartment. Tissue oxygen availability is the generally accepted mode of regulation of erythropoietin "secretion". A "normal" level of erythropoietin resulting in "normal" red cell production can be perturbed by tissue hypoxia to increase erythropoietin availability with increased (or compensatory) red cell production as a response to that hypoxia. Measurements of erythropoietin (Ep) in serum and/or urine have been seriously hampered by technical problems. As a result of the difficulties most measurements have been done in conditions of significantly perturbed erythropoiesis. In general, absent or reduced levels of Ep have been found in patients with polycythemia vera and increased levels in secondary types of polycythemia (32).



[redacted] Plasma erythropoietin in the polycythemias. Erythropoietin titers as measured by bioassay of concentrates prepared from plasma of patients with hematocrits greater than 53 percent [redacted]. In uncontrolled polycythemia vera, plasma erythropoietin is below the limits of detection (3 mU/ml). Elevated levels are characteristic of most cases of secondary polycythemia. Similar findings have been reported for radioimmunoassay [redacted] (33)

Recent application of a radioimmunoassay (33) have appeared to confirm this classical pattern.

Erslev (34) has recently summarized the evidence that the kidney is the site of the oxygen sensor as well as the major site (approximately 90%) of Ep production, thereby laying to rest two decades of controversy. Although Ep is produced by the liver, its secretion requires a greater degree of hypoxia. In brief this evidence is:

(1) Isolated kidneys obtained from anemic rats and rabbits and then perfused with plasma free culture media continue to synthesize Ep (35).

(2) Isolated kidneys obtained from normal rats can be induced to synthesize Ep when the perfusion media is at low oxygen tension (34).

(3) Ep can be directly extracted from kidneys of hypoxic rats (36).

(4) Messinger RNA coding for Ep has been extracted from kidneys and used for the synthesis of biologically active Epin frog eggs (37).

(5) The exact site in the kidney is not yet established. Our data (38) from anemic sheep placed it at the outer rim of the glomerulus. Erslev (39) has shown a 3 fold greater concentration in the tubules than in the glomerulus. Finally Jelkman et at (40) have shown mesangial cell synthesis of Ep.

Similarly, the exact location of the erythropoietin-linked oxygen sensor is not known. We find Erslev's view that it is reasonable to conclude that this sensor is located in the same cell that produces Ep.

A. Mechanism of Action:

Although the human Ep gene was cloned in 1985 and site-specific antibodies have provided interesting structural information, very little is known concerning the mechanism of action. At a "macroscopic level" one can provide the following schema for erythropoiesis:

STEM CELL ⟶ BFU-E ⟶ CFU-E ⟶ Erythroid Precursors

Ep is known to act on BFU-E, CFU-E, and on erythroid precursors effecting:

-initiation of division of the committed stem cell
-initiation of hemoglobin synthesis
-increase of <u>per cell</u> hemoglobin synthesis
-shortening of the cell cycle
-release of reticulocytes from the marrow

A.J. Erslev and J. Caro

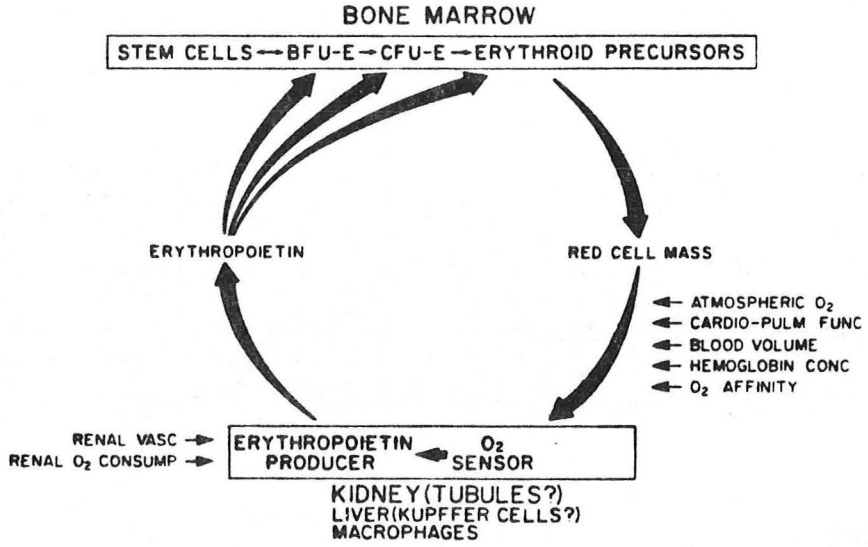


Fig. 1. Feedback circuit linking an oxygen sensor in the kidney with erythroid progenitor cells in the marrow and mediated in one direction by red cell containing oxygen and in the opposite direction by erythropoietin. In addition to the kidney, oxygen sensing and erythropoietin production may take place in the liver and in some macrophages. The target for erythropoietin is primarily the erythropoietin dependent progenitor cells, CFU-E, with lesser action on the burst forming progenitor cells, BFU-E, and the precursor cells

The first important clues to a mechanism of action of Ep have just been reported (41). Choi et al have shown that Ep remarkably <u>reduced</u> the phosphorylation of a prominent 43-kDa phosphoprotein (pp43) in the membranes of erythroid cells (41).

The effect was time dependent (occurring within 30 minutes of Ep exposure) and concentration dependent. A similar effect was achieved when erythropoietin-responsive Rauscher murine leukemia cell membranes were exposed to Ep.

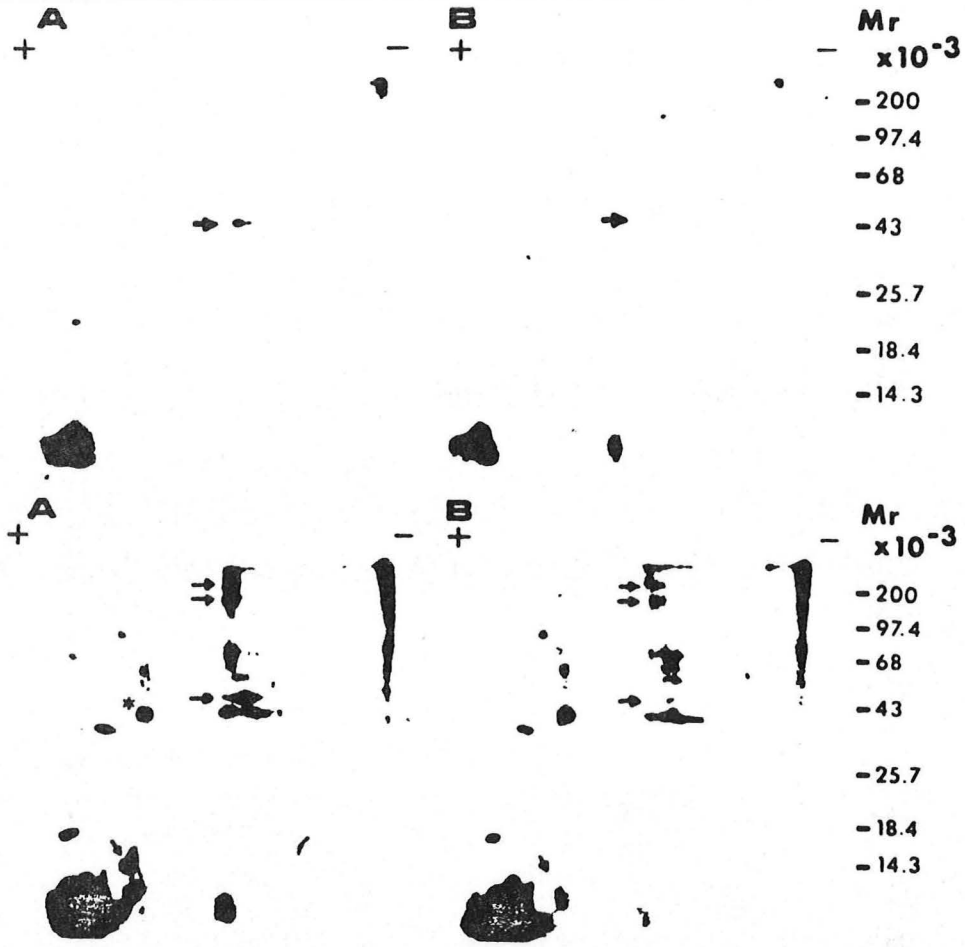


FIG. 1. **Effect of erythropoietin on phosphorylation of pp43 in phenylhydrazine-treated mouse splenic erythroid cell membranes.** Membranes were labeled with [γ-^{32}P]ATP after incubation in the absence (*panel A*) or presence (*panel B*) of erythropoietin.

FIG. 2. **Effect of erythropoietin on phosphorylation of phosphoproteins in Rauscher murine erythroleukemia cell membranes.** Membranes were labeled with [γ-^{32}P]ATP after incubation for 60 min in the absence (*panel A*) or presence (*panel B*) of erythropoietin. Results are quantified in Table I.

Although the function of pp43 and other phosphoproteins in the cell membrane is not known and the precise mechanism whereby Ep alters phosphorylation has not been elucidated, these findings do suggest that Ep may produce its effect on the erythroid membrane thereby resulting in the activation of a signal transduction mechanism affecting several phosphoproteins.

B. Current Clinical Application of the Radioimmunoassay in Polycythemia.

The recent application of radioimmunoassay technology (33) has been evaluated in a large group of patients with polycythemia by our English colleagues (42). Their findings are important for anyone using Ep assays in differential diagnosis of patients with an elevated hematocrit:

Table 1. Subjects of the Study.*

Characteristics of Group	No. of Subjects (M/F)	Age	Hemoglobin	Packed Red-Cell Volume	Serum Erythropoietin†
		yr	*g/dl*		*mIU/ml*
Normal controls					
Men	14	44±16	14.8±0.7	0.43±0.02	26 (19–35)
Women	11	32±13	13.2±1.0	0.39±0.03	24 (18–35)
Polycythemia rubra vera	12/12	62±11	18.1±1.9	0.57±0.06	16 (8–22)
Secondary erythrocytosis	8/4	56±14	18.2±1.9	0.56±0.06	30 (14–123)
Erythrocytosis of unknown cause	15/4	54±15	18.1±1.1	0.54±0.04	27 (13–>400)‡
Raised packed red-cell volume, without erythrocytosis, with a low plasma volume	12/1	53±14	18.3±1.2	0.55±0.03	23 (17–39)
Raised packed red-cell volume, without erythrocytosis, with a normal plasma volume	22/0	49±13	17.6±0.7	0.52±0.03	24 (15–37)

*Plus–minus values are means ±SD

†Values are geometric mean (range)

‡An erythropoietin estimate of 400 mIU per milliliter was used in place of an observed value above 400 in the calculation of the geometric mean

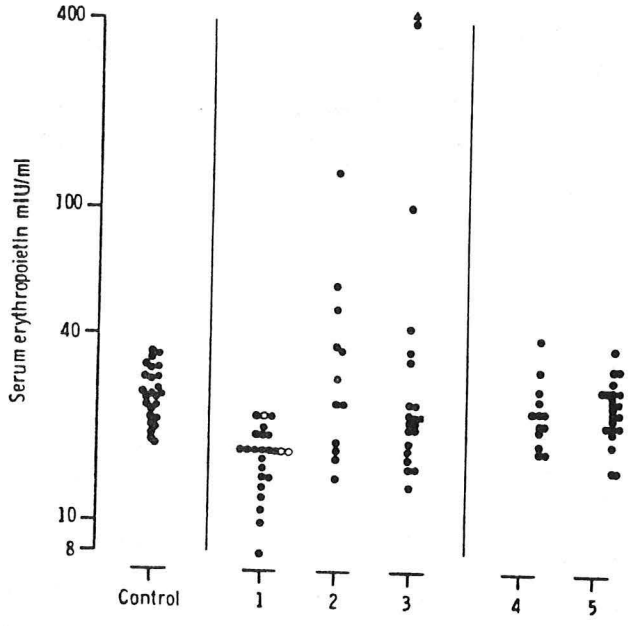


Figure 1. Estimated Levels of Serum Immunoreactive Erythropoietin in Normal Controls and in Other Subjects.

Column 1 shows values for patients with polycythemia rubra vera, column 2 for patients with secondary erythrocytosis, and column 3 for patients with erythrocytosis of unknown cause. Values for patients without erythrocytosis but with a raised packed red-cell volume are shown in columns 4 (patients with a low plasma volume) and 5 (patients with a normal plasma volume). Open circles denote subjects previously treated with radioactive phosphorus.

From their data: (MIU/ml)

	mean	range
"Normal" controls:	25	17-38
Polycythemia Vera	16	8-22

-61% of the patients with polycythemia vera were within the normal range.

Secondary Polycythemia	30	14-123

-Ep levels were above normal in 25% and were above the level observed in polycythemia vera in 67%.

Erythrocytosis of unknown origin	27	13-400

-This group was separated because they had neither hypoxia nor the diagnostic criteria of polycythemia vera; and a cause was not found.

Thus:

1. The measurement of Ep (at least in a single specimen) may not have a high discriminatory value in separating polycythemia vera from secondary polycythemia.

2. The maintenance of secondary erythrocytosis is serum immunoreactive Ep (at least above the level of normal).

3. In patients with an increased hematocrit with a normal red cell mass, ie spurious polycythemia, the Ep levels were normal regardless of the plasma volume.

32] Erslev AJ, Caro J, Kansu E, Miller O, Cobbs E. Plasma Erythropoietin in Polycythemia. Amer J Med 66:243, 1979.

33] Koeffler HP, Goldwasser E. Erthropoietin Radioimmunoassay in Evaluating Patients with Polycythemia. Ann Int Med 94:44, 1981.

34] Erslev AJ, Caro J. Secondary Polycythemia: A Boon or A Burden? Blood Cells 10:177, 1984.

35] Erslev Aj. In Vitro Production of Erythropoietin by Kidneys Perfused With a Serum Free Solution. Blood 44:77, 1974.

36] Fryed W, Barone-Varelas J, Berman M. Detection of High Erythropoietin Titres in Renal Extracts of Hypoxic Rats. J Lab Clin Med 87:82, 1981.

37] Mach B, Ucla C, Fisher JW, Zanjani ED. Translation of mRNA From Kidneys of Hypoxic Rats Into Biologically Active Erythropoietin Following Microinjection Into Frog Oocytes. Clin Res 31:484, 1983.

38] Frenkel EP, Suki W, Baum J. Some Observations On The Localization Of Erythropoietin. Ann NY Acad Sci 149:292, 1968.

39] Caro J, Erslev AJ. Biologic and Immunologic Erthropoietin Activity in Tissue Extracts From Separated Glomerular and Tubular Fractions of Hypoxic Rat Kidney. J Lab Clin Med 103:922, 1984.

40] Jelkman W, Kurtz A, Bauer C. Extraction of Erythropoietin From Isolated Renal Glomeruli Of Hypoxic Rats. Exp Heme 11:581, 1983.

41] Choi HS, Wojchowski DM, Sytkowski AJ. Erthropoietin Rapidly Alters Phosphorylation of pp43, An Erythroid Membrane Protein. J Biol Chem 262:2933, 1987.

42] Cotes PM, Dore CJ, Yin JA, Lewis SM, Messinezy M, Pearson TC, Reied C. Determination of Serum Immunoreactive Erythropoietin In The Investigation of Erythropoiesis. NEJM 315:283, 1986.

IX. ISSUES IN THE INTERPRETATION OF VISCOSITY IN POLYCYTHEMIA

Although the clinical sequelae of hyperviscosity and an expanded blood volume are well known to all, the accurate measurement of these factors in vivo has made pathophysiologic characterization and interpretation difficult. Our problem is to define the specific role viscosity exerts in the modification of blood flow and oxygen delivery to tissue in any (each) given clinical circumstance.

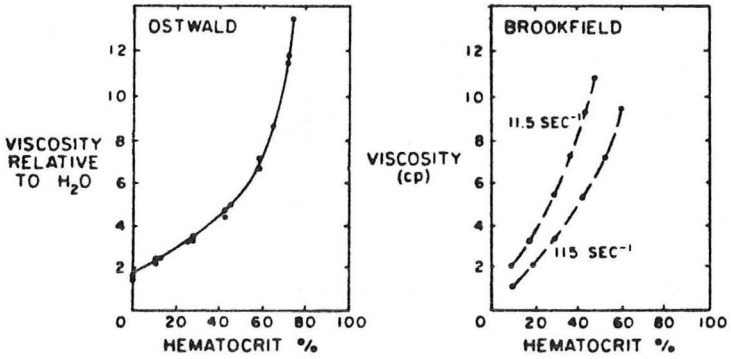


Fig. 2. Viscosity of normal human heparinized blood adjusted to different hematocrits by adding or removing plasma. The viscosities are measured with an Ostwald glass viscosimeter at a fixed sheer rate or with a Brookfield cone-plate viscosimeter at two sheer rate, 115 sec^{-1} corresponding to blood flow in small vessels and 11.5 sec^{-1} corresponding to flow in large vessels

From Ref. 34

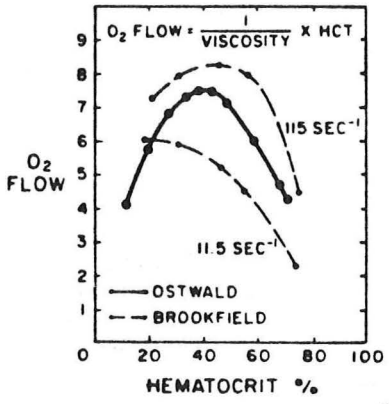
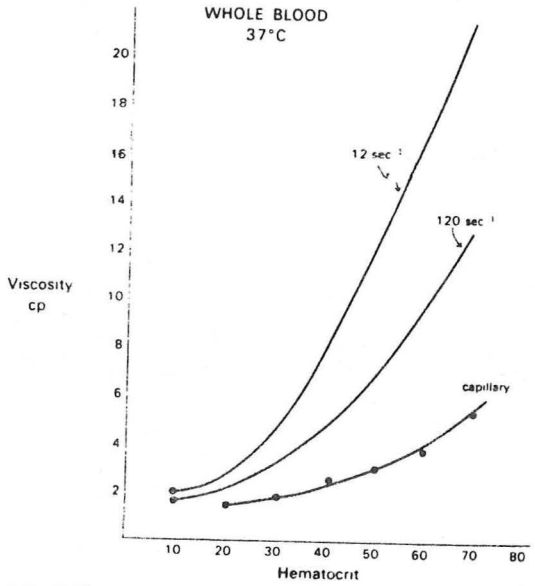


Fig. 3. Oxygen flow at various hematocrits as in Figure 2 and calculated from the hematocrit and the blood flow which is inversely proportional to viscosity

From Rep 34

The measurements of viscosity in vitro have been difficult to translate to the in vivo or physiologic circumstance (43,44). Viscosity, commonly defined as $\frac{\text{stress}}{\text{velocity gradient}}$

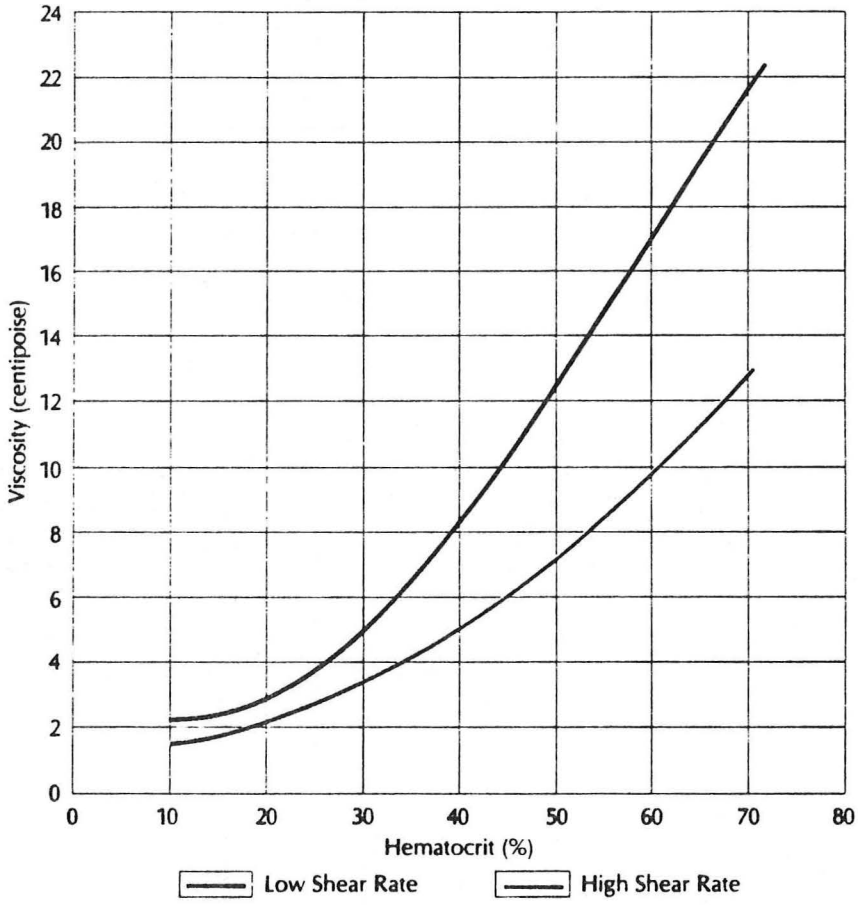
(where the velocity gradient is shear rate), is usually expressed on the basis of Poiseuille's law. That is, the rapidity of flow is proportional to the radius. Unfortunately this "abbreviated physics" does not apply to non-Newtonian fluids as blood where the viscosity changes with the rate of flow. In blood the shear rate is not directly proportional to the shear stress, so that blood is more viscous at slow flow rates. Thus at the low shear rates that characterize venous flow, viscosity is high. The relationship of flow rates to viscosity has been best defined by Wells (44):



. Relation of VPRC (hematocrit) to blood viscosity in centipoise (cp) as measured in a capillary viscosimeter compared with that calculated for shear rates of 120 sec^{-1} (ascending aorta) and 12 sec^{-1} (medium arteriole). (From Wells RE Jr, Merrill EW: The variability of blood viscosity. Am J Med 31:505, 1961.)

Thus, at higher flow rates (higher rates of shear) the curve shifts downward and to the right, a pattern of decreased viscosity.

The non-linear relationship between hematocrit and viscosity expresses the classical observation that the viscosity expresses the classical observation that the viscosity rises more sharply than the hematocrit number (45):



The viscosity of blood is a nonlinear function of the hematocrit. At each hematocrit value, viscosity is higher at the lower rate of shear, a difference that is exaggerated at high hematocrits. In polycythemia vera, the high hematocrit and enlarged blood volume lead to increased blood viscosity, reduced rate of blood flow, and predisposition to thrombosis. (From Wells RE Jr, Merrill FW: J Clin Invest 41:1591, 1962)

Obviously the primary issue is how such changes affect oxygen delivery to tissues. In polycythemia the high hematocrit and the expanded blood volume result in increased viscosity with decreased blood flow. An added factor in polycythemia vera is the commonly event of thrombocythemia farther predisposing to thrombosis and/or hemorrhage.

43] Castle WB, Jandle JH. Blood Viscosity and Blood Volume. Opposing Influences Upon Oxygen Transport in Polycythemia. Semin Heme 3:193, 1966.

44] Wells R. Syndromes of Hyperviscosity. NEJM 283:183, 170.

45] Conley CL. Polycythemia Vera. Diagnoses and Treatment. Hospital Prac p107, 1987.

X. THERAPY OF POLYCYTHEMIA VERA

The survival of patients with PV has remarkably changed with the advent of treatment. Median survival in the pre-therapy era (1930's-1960's) was 18 months. The two decades of the Polycythemia Vera Study Group experience shows a median survival of 8.9 years in the chlorambucil (alkylating agent) treated group, 11.8 years for the radiophosphorus (^{32}P) group and 13.9 years for the phlebotomy treated group (46).

The evolving clinical features during the phases of PV require different therapeutic approaches at different stages of disease. Thus, in the pre-erthrocytic phase when pruritus is a common symptom, histamine (H_2 antagonists such as cimetedine (300 mg, three times/day) particularly in combination with an H_1 blocker (eg Cyproheptadine 4mg three times/day or Astemizole 10 mg/day) are effective. During the erthrocytic and proliferative phase the patients treated with phlebotomy alone have a higher incidence of thrombotic events than those groups treated with myelosuppressive agents particulary during the early treatment period (ie first 5 to 7 years). A trial of platelet anti-aggregation therapy with aspirin (300mg, three times/day) and Diprimadole (75mg three times/day) failed to alter the thrombotic events and was associated with significant gastrointestinal hemorrhage; lower aspirin doses have not been examined.

During the erthrocytic phase the excellent median survival with phlebotomy therapy alone established this as the treatment of choice except for the elderly (over 70) and in patients with increased risk factors for thromboses (eg. obesity, diabetes). Thrombotic episodes are more common in that age group with the blood volume changes attendant to phlebotomy. Therefore, phlebotomy should be limited to 100-200 ml with volume replacement. Myelosuppressive therapy affects the survival curve beyond year seven when the increased incidence of leukemic transformation begins; thus,

radiophosphorus (^{32}P) is an excellent modality for those over age 70.

For younger patients with a phlebotomy requirement in excess of 6 units per year, where the risk of thrombosis is increased, or where there are proliferative features (significant thrombocytosis and splenomegaly) the myelosuppressive agents are indicated. Hydroxyurea, an inhibitor of riboside reductase activity in pyrimidine biosyntheses, is the drug of choice since, to date it has not demonstrated mutagenic potential. The usual dosage for hydroxyurea is 15mg/kg/day with the goal of maintaining the hematocrit below 50 vol% and the platelets below 1 million/ul. Dosage adjustments may be required; downward for the development of cytopenias or upward if control is not adequate. Patients with decreased renal function require closer follow-up. Most patients achieve excellent control within 12 weeks of institution of therapy.

Therapy during the post-polycythemic myeloid metaplasia period is largely supportive. In some the developing anemia is improved by androgen therapy. Symptomatic extramedullary tumors (even those sometimes found in the central nervous system) have been effectively managed by local radiation. Recurrent painful splenic infarctions or symptomatic congestive splenomegaly may require splenectomy; coagulation defects in such patients are associated with increased operative risk. Finally, as with other secondary leukemias this transformation responds less well to therapy than de novo forms of leukemia.

An abbreviated summary of the Polycythemia Study Group guidelines for therapy of PV is as follows (46):

1. No form of treatment in PV is free of risk.

2. For those under 50 (and probably to age 70) phlebotomy only unless thrombosis-associated risk factors are present.

3. Hydroxyurea is the myelosuppressive agent of choice.

4. Absolute proof that elevated platelet counts contribute to thrombotic events is (still not proven.

46] Berk PD, Goldberg JD, Donovan PB, Fruchtman SM, Berlin NI, Wasserman LR. Therapeutic Recommendations in Polycythemia Vera Based on Polycythemia Vera Study Group Protocols. Semin Heme 23:132, 1986.

47] Wasserman LR, Goldberg JD, Balcerzak SP. Influence of Therapy on Causes Of Death in Polycythemia Vera. Clin Res 29:573, 1981.

48] Tartaglia AP, Goldberg JD, Berk PD, Wasserman LR. Adverse Effects of Antiaggregating Platelet Therapy In The Treatment of Polycythemia Vera. Semin Heme 23:172, 1986.

49] Kaplan ME, Mack K, Goldberg JD, Donovan PB, Berk PD, Wasserman LR. Long Term Management of Polycythemia Vera With Hydroxyurea: A Progress Report. Semin Heme 23:167, 1986.

XI. IS THERE A ROLE FOR PHLEBOTOMY IN SECONDARY POLYCYTHEMIA?

Since secondary polycythemia is interpreted as a physiologic compensation, the proper clinical approach is to identify and treat the primary cause. This is particularly true for aberrant or inappropriate secretion of erythropoietin, where correction of the lesion is often curative.

When repair of the primary lesion is not possible the nature of the physiologic burden of the increased red cell mass must be considered. Classical clinical wisdom is that the increase in red cells provide a needed compensation for the underlying disease (usually hypoxia) and that therapy should not perturb that compensatory effect. The adaptation to altitude has been used to confirm that view (50). As example, the natives in San Cristabol are known to lead active hard working lives with hemoglobins that are 25 g/dl. It is of interest that the high altitude acclimatization process is associated with a shift to the right of the oxygen dissociation curve thereby enhancing the unloading of

oxygen to the tissue.

However, as we've reviewed on our comments on viscosity, polycythemia is not a particularly efficient way to enhance oxygen transport. Indeed, Erslev (51) has made a case for the increased blood volume as the primary benefit resultant from the polycythemia rather than any effect on increased carrying capacity of oxygen. This view proposes that the opening of new capillaries with a shortening of the mean distance between capillary and tissue cell, thereby permitting a low mean capillary oxygen pressure provides the "compensatory" or "enhanced" oxygen to the tissues. Recurring serious concern has been expressed that in many circumstances of hypoxia (eg secondary polycythemia) red cell production overcompensates for physiologic needs and that the resultant polycythemia is counterproductive.

Since oxygen delivery to the tissue is the absolute goal, many have tried to use models of oxygen delivery to examine this question and one expression of such data is depicted:

Theoretical Oxygen Delivery At Varying Hemoglobin Levels when Saturation changes.

Hemoglobin gm/dl	O_2 carrying capacity* ml/dl	$Sa_{\%}O_2$	Amount of oxygen content	Oxygen delivered ml/min.
15	20	95%	19	1140**
20	26.7	95%	25.3	1518
20	26.7	60%	25.3	960
15	20	60%	12	720

** Capacity estimated as 1 1/3 ml of O_2 per g. hemoglobin

* Calculated O_2 delivered:
Amount of O_2 content: 19 ml/dl or 190 ml/l in normal

Estimated cardiac output: 6 l/min.

O_2 delivered = (cardiac output) x (amount content)
6 x 190 = 1140 ml/min.

The critical problem is to try and identify an altered (presumably improved) response from any "therapeutic" maneuver. The criteria of such a measured response are difficult to define but should include:

1. Improved organ function (eg increased maximal treadmill performance, improved renal function, improved cognitine skill testing)

   To date such observations have been limited either because of the achieved changes are too modest or non-existent.

2. Improved mixed venous O_2 saturation.
In sense this attempts to balance in viscosity due to the increased red cell mass from the hemoglobin content by using the mixed venous oxygen saturation as the parameter. This presumes that the arterial oxygen content changes only slightly while a greater potential exists for the extended extraction of oxygen in the venous circuit. This is graphically displayed by the Fick equation:

$$\text{cardiac output} = \frac{\text{oxygen consumption}}{\text{A-V oxygen difference}}$$

Since the oxygen consumption is reasonably constant, the major shifts are either changes in cardiac output or better venous oxygen extraction. (One can project an arterial O_2 of 19 and a venous O_2 of 15; so that a significant extraction reserve does exist.

3. "Improvement" as expressed by the patient.
commonly subjective symptoms and/or performance (function) change as reported by the patient are the "measured" parameters of effect of a therapeutic program.

Some experimental studies have tried to define these relationships:

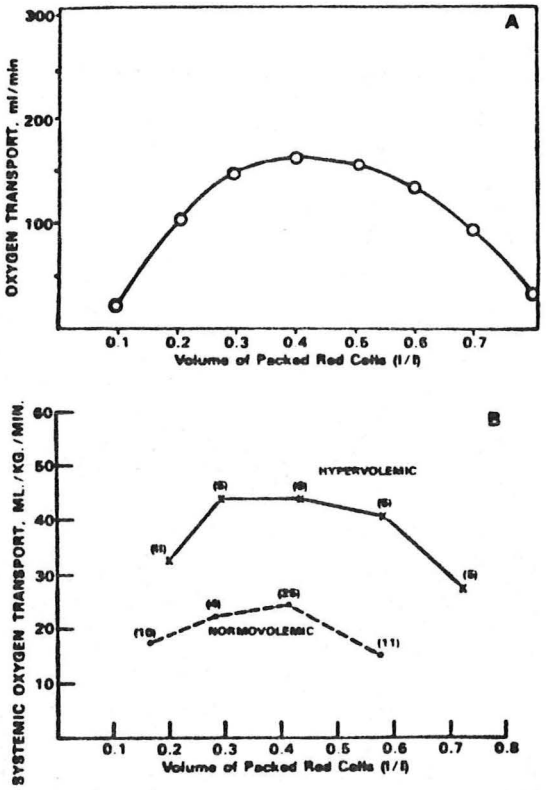


FIG. 42-4. Arterial oxygen transport at different VPRCs and thus different viscosity values. A, Values in this curve were calculated from blood viscosity values as measured by Pirofsky[24] and flow values calculated in the lower portion of Figure 42-3. B, Systemic oxygen transport as calculated from cardiac output measured in normovolemic and hypervolemic dogs. (From Murray JF et al: The circulatory effects of hematocrit variations in normovolemic and hypervolemic dogs. J Clin Invest 42:1150, 1963.)

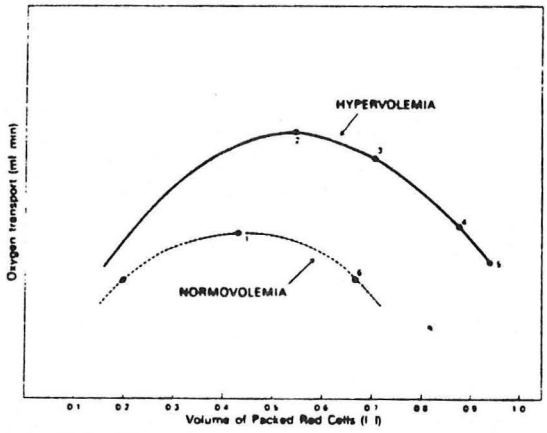


FIG. 42-5. Hypothesis depicting the relationship between oxygen transport and VPRC in normovolemic and hypervolemic situations. Cardiac output is assumed to remain constant. Point 1 refers to a normal subject at rest, with normal VPRC and normal oxygen transport. Point 2 describes the patient with erythrocytosis (elevated VPRC, blood volume *and* oxygen transport) at rest. Points 3, 4, and 5 refer to the effects of increasing VPRC; oxygen transport presumably decreases from optimal values as the VPRC increases, but may exceed values for oxygen transport in normovolemic patients until very high VPRC values are reached. Point 6 indicates the situation in normovolemic polycythemia produced by exchange transfusion, i.e., increased VPRC, decreased oxygen transport. (Modified from Thorling EB, Erslev AJ: The "tissue" tension of oxygen and its relation to hematocrit and erythropoiesis. Blood 31:332, 1968.)

Several clinical studies have attempted to sort out these multiple variables and identify a change in status of patients with secondary polycythemia during or after a phlebotomy program. Some of these have shown:

1. Harrison et al (52) measured improved work capacity in patients whose hematocrits were reduced from 63 to 48 (their blood was replaced by equal volumes of Dextran 40). Interestingly measurable improvement in pulmonary function was not seen. Mean pulmonary artery pressure during exercise decreased and calculated pulmonary vascular resistance decreased without change in arterial blood gases. Their data has been considerably consistent with improved tissue capillary perfusion past phlebotomy (53).

2. Weisse, et al (54) studied a group of patients with stable cor pulmonale and secondary erythrocytosis before and following phlebotomy. Decreasing the hematocrit to 50% resulted in significant decrease in both mean pulmonary artery pressure and total pulmonary resistance. Oxygen transport decreased but oxygen consumption did not change. Right ventricular end-diastolic pressure and cardiac output did not change. Right ventricular work either fell or was maintained by increased output. Supine exercise improved. A second stage phlebotomy program to 44 vol.% resulted in no further changes. Again, these studies do support the concept of overcompensating erythrocytosis in secondary polycythemia.

3. Thomas et al (55) demonstrated that lowering the hematocrit from 54% to 45% resulted in a 73% increase in cerebral blood flow whereas the measured viscosity only decreased 30%.

4. Wade et al (56) also showed a 21% increase in cerebral blood flow with phlebotomy with a significant improvement in mental status (primarily alertness) in this group.

5. York et al (57) also demonstrated that phlebotomy resulted in a significant increase (doubling) of supratentorial blood flow; the subjective clinical correlate was a major resolution of CNS symptoms.

6. Chetty et al (58) studied the effects of phlebotomy in patients with COPD and secondary polycythemia. After

phlebotomy there were no significant changes in pulmonary function, blood gases, oxygen consumption or carbon dioxide production at rest. However, following phlebotomy there was -
- a significant increase in exercise tolerance
- a significant increase in:
  - -mean workload
  - -duration of exercise
  - -maximal oxygen consumption
  - -maximal carbon dioxide production
  - -ventilation at maximal exercise

They concluded that the improved exercise tolerance was due to an increased cardiac output resultant from an increased stroke volume.

Thus a variety of studies provide support for the view that red cell production frequently overcompensates for physiologic needs. Because of the difficulties is achieving critical quantitative data documenting improvement, the use of the patients subjective symptoms (eg improvement) appears to be an appropriate clinical parameter during a phlebotomy program to reduce the red cell mass. Current evidence suggests that most adult patients with secondary polycythemia will have maximal performance with hematocrits maintained in the range of 47-52 vol.%.

50] Hurtado A. Some Clinical Aspects of Life At High Altitudes. Ann Int Med 53:247, 1960.

51] Thorling EB, Erslev AJ. The "Tissue" Tension of Oxygen and Its Relation To Hematocrit and Erythropoiesis. Blood 31:332, 1968.

52] Harrison BDW, Davis J, Madwick RG. The Effects of Therapeutic Decrease In Packed Cell Volume On The Responses To Exercise of Patients With Polycythemia Secondary To Lung Disease. Clin Sci Mol Med 45:833, 1973.

53] Balcerzak SP, Bromberg PA. Secondary Polycythemia. Semin Heme 12:353, 1975.

54] Weisse AB, Moschos CB, Frank MJ, Levinson GE, Cannilla JE, Regan TJ. Hemodynamic Effects of Staged Hematocrit Reduction In Patients With Stable Cor Pulmonale and Severely Elevated Hematocrit Levels. Amer J Med 58:92, 1975.

55] Thomas DJ, Marshall J. Cerebral Blood Flow In Polycythemia. Lancet 2:161, 1977.

56] Wade JPF, Pearson TC. Cerebral Blood Flow and Blood Viscosity in Patients With Polycythemia Secondary To Hypoxic Lung Disease. BMJ 283:689, 1981.

57] York EL, Jones RL. Effects of Secondary Polycythemia On Cerebral Blood Flow In Chronic Obstructive Pulmonary Disease. Amer Rev Resp Dis 121:813, 1980.

58] Chetty KG, Brown SE, Light RW. Improved Exercise Tolerance Of The Polycythemic Lung Patient Following Phlebotomy. Amer J Med 74:415, 1983.

COMMENT

The present review was intended to focus on a series of selected problems and issues of current interest in polycythemia. These biologic and pathophysiologic aspects have had recent re-evaluation and renewed clinical interest.

59] Bunge PS, Johnson WS, Prankerd TAJ. Morbidity and Mortality in Pseudopolycythemia. Lancet 1:1266, 1975.

60] Person TC, Wetherly-Mein G. Vascular Occlusive Episodes and Venous Hematocrit In Primary Proliferative Polycythemia. Lancet 2:1219, 1978.

61] Adamson JW. Analysis Of Hemopoiesis: The Use of Cell Markers and In Vitro Culture Techniques in Studies of Clonal Hemopathies in Man. Clin Heme 13:489, 1984.

62] Smith JR, Landaw SA. Smokers Polycythemia. NEJM 298:6, 1978.

63] Silverstein MN, ReMine WH. Splenectomy in Myeloid Metaplasia. Blood 53:515, 1979.

64] Van de Pette JEW, Guthrie DL, Pearson TC. Whole Blood Viscosity In Polycythemia: The Effect of Iron Deficiency At A Range Of HEmoglobin and Packed Cell Volumes. Brit J Heme 63:369, 1986.