PV and ET in 2015

Joyce Niblack Memorial Conference
on Myeloproliferative Disease
Mayo Clinic
Scottsdale, Arizona
February 21 - 22, 2015

Richard T. Silver, MD, FACP
Professor of Medicine
Weill Cornell Medical College

Outline of Talk

- Essential Thrombocythemia
  - ➢ Diagnosis
    - Bone Marrow
    - Molecular Profiling
  - Treatment
- Polycythemia Vera
  - Diagnosis
    - WHO Criteria (2008)
    - Important of Bone Marrow
  - Treatment
    - Phlebotomy
    - HU + Interferon
    - Ruxolitinib

WHO Criteria ET (2008)

Table 3. The 2008 World Health Organization (WHO) diagnostic criteria for essential thrombocythemia

Diagnosis requires meeting all four criteria.

1. Sustained* platelet count ≥ 450 × 10⁹/L.
2. Bone marrow biopsy specimen showing proliferation mainly of the megakaryocytic lineage with increased numbers of enlarged, mature megakaryocytes. No significant increase or left-shift of neutrophil granulopoiesis or erythropoiesis.
3. Not meeting WHO criteria for polycythemia vera,† primary myelofibrosis,‡ *BCR-ABL1*–positive chronic myelogenous leukemia,§ or myelodysplastic syndrome¶ or other myeloid neoplasms.
4. Demonstration of *JAK2*V617F or other clonal marker, or in the absence of *JAK2*V617F, no evidence for reactive thrombocytosis.**

Thiele J, Kvasnicka HM 2009

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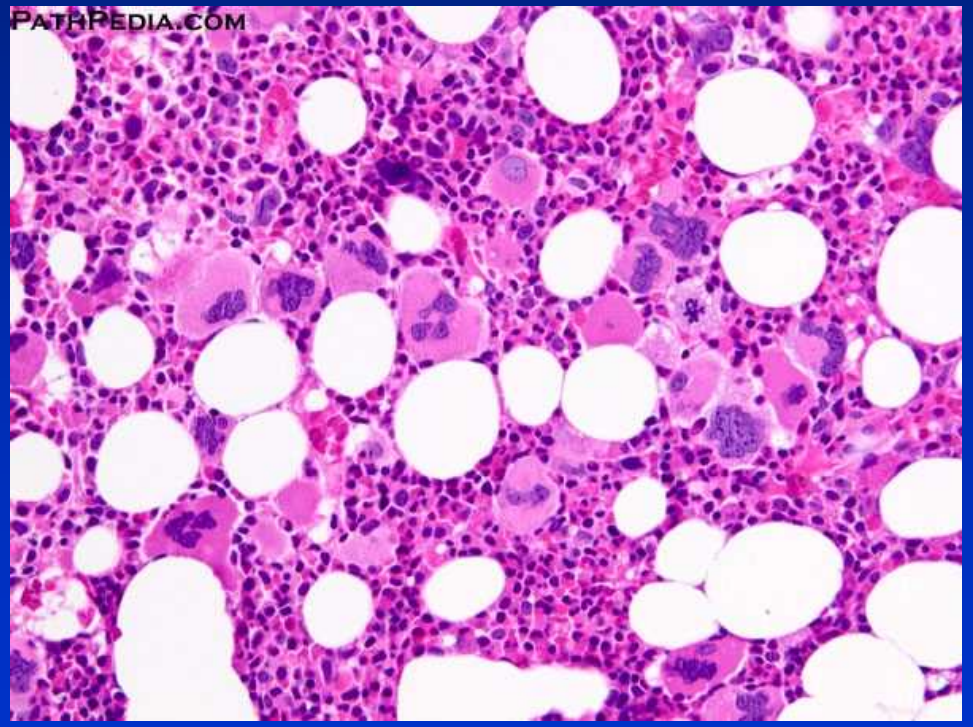
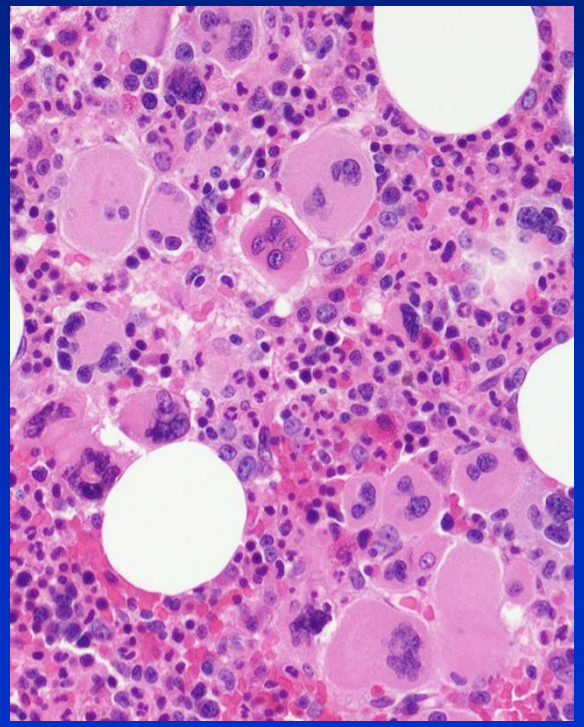
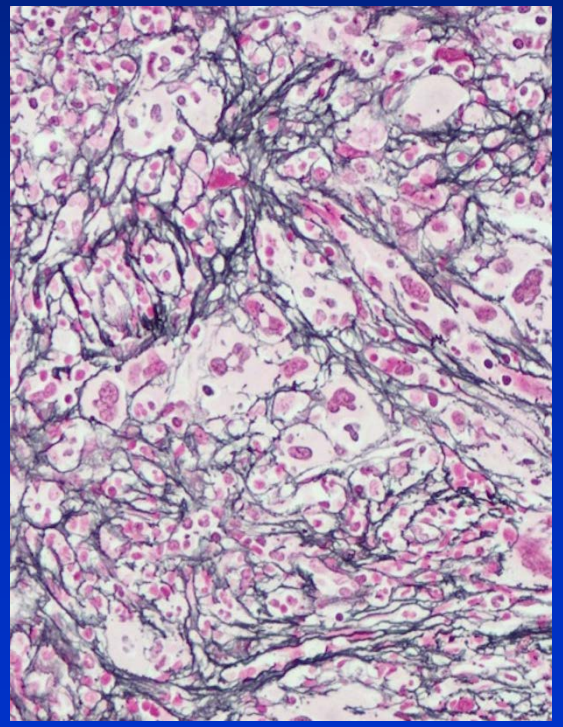
Bone Marrow Biopsy

Essential Thrombocythemia

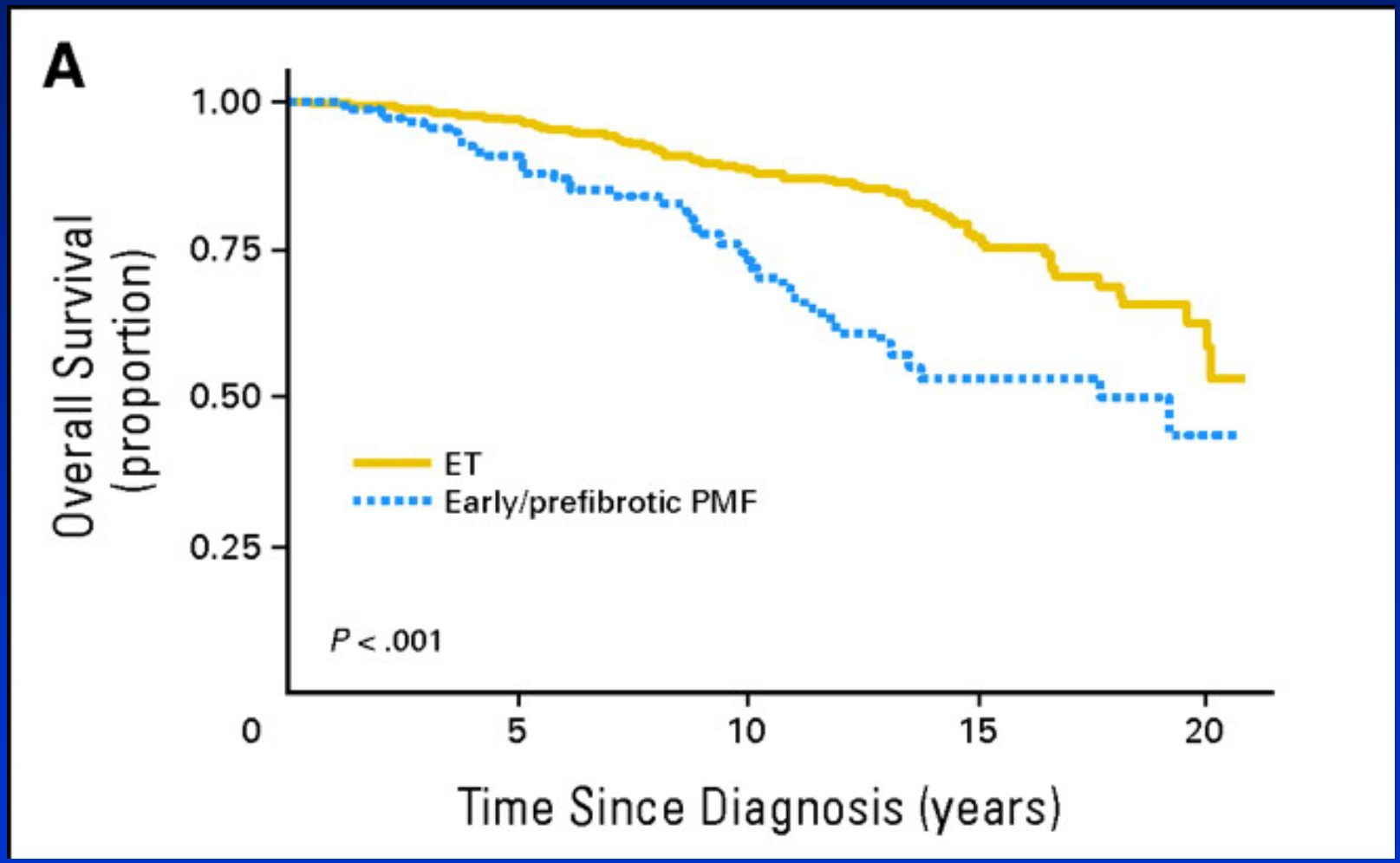


Early Primary Myelofibrosis





Overall Survival of ET vs EPMF



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Diagnosis of ET: Molecular Profiling

- Triple negative (JAK2, MPL, CALR) define GOOD risk patients, in contrast to PM

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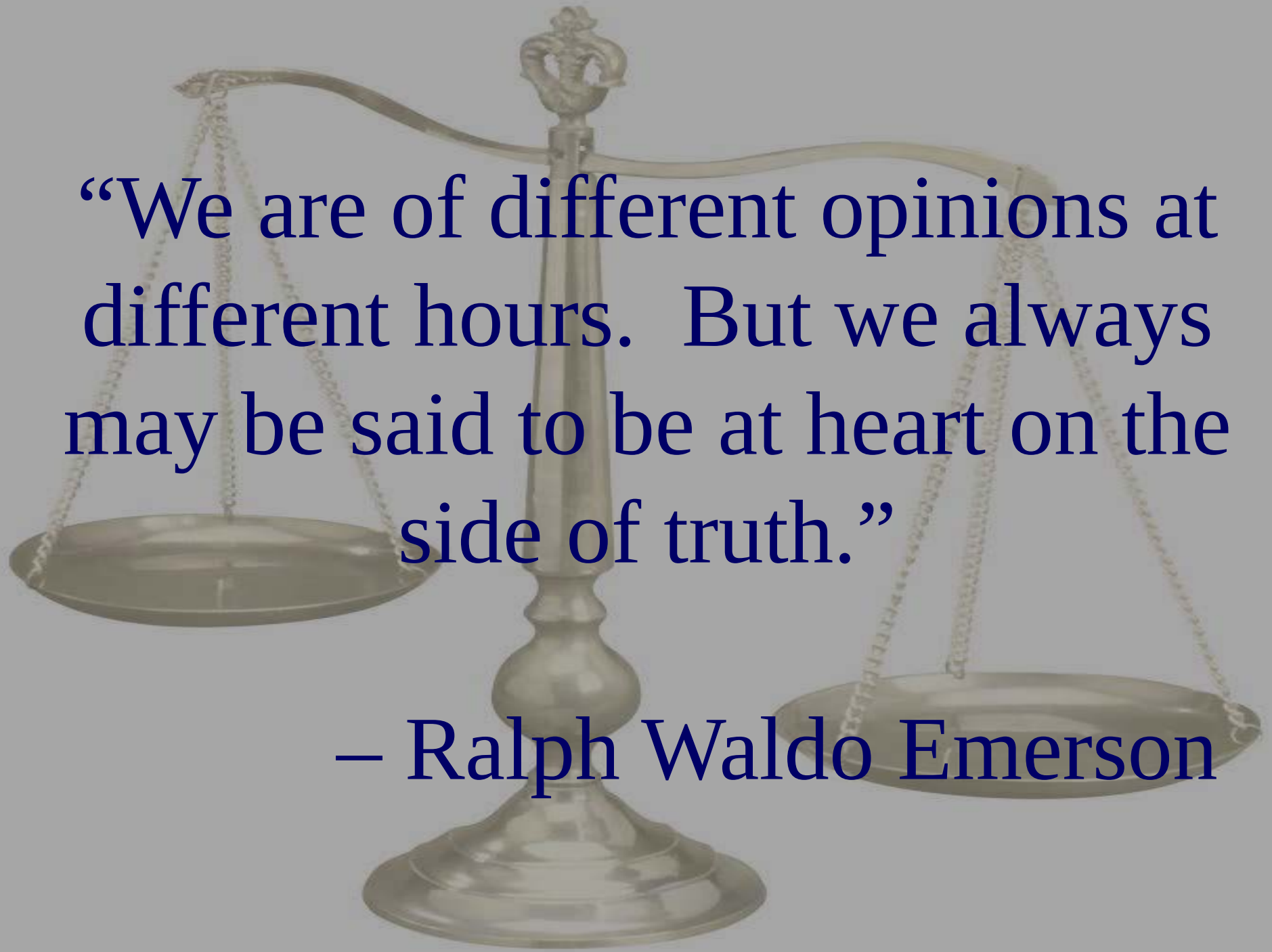
Treatment of ET

- Risk Categories
  - Low risk
    - Age < 60
    - No thrombotic history
  - High risk
    - Age > 60 and/or
    - Thrombotic history
- Earlier vs later treatment



"We are of different opinions at different hours. But we always may be said to be at heart on the side of truth."

– Ralph Waldo Emerson

Non Treaters vs Treaters

Conservative	Progressive
Old-fashioned	Modern
Passive	Active
Pre-Scottsdale 2015	At or post-Scottsdale 2015

Goals of Treatment of the MPNs

- Improve survival!
- Relief of symptoms (Quality of Life)

MPN Patients are highly symptomatic regardless of subset

Fatigue	87 %
Trouble Concentrating	62 %
Loss of appetite	61 %
Inactivity	61%
Weight loss	52 %
Itching	52 %

Geyer and Mesa, *Blood*, 2015

Low Risk Patient: Moderately to Highly Symptomatic

MF	PV	ET
44%	50%	41%

Major Thrombotic Risk

ET	PV
10 – 29%	34- 39%

Prototype Problem in ET

- 51 year-old Caucasian female NYC oncologist
- Platelets 700,000/dL
- No risk factors except husband who travels too much, two teenage daughters, one son in college with questionable roommates
- After hard day in the office became dizzy after telephone call with son
- Persisted, vague feeling of being unwell
- Saw neurologist, MRI brain: thrombosis
  - Right subinsular white matter consistent with microvascular ischemic change
- Anticoagulation, rIFN-alpha 45 mcg/week
- After 6 months, no dizziness, feels well, platelets 200,000/dL

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WHO Criteria PV (2008)

Table 1. The 2008 World Health Organization diagnostic criteria for polycythemia vera

Diagnosis requires meeting both major criteria and one minor criterion or the first major criterion and two minor criteria.

Major criteria

1. Hemoglobin > 18.5 g/dL in men, 16.5 g/dL in women or other evidence of increased red cell volume.*
2. Presence of *JAK2*V617F or other functionally similar mutation such as *JAK2* exon 12 mutation.

Minor criteria

1. Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid, granulocytic, and megakaryocytic proliferation.
2. Serum erythropoietin level below the reference range for normal.
3. Endogenous erythroid colony formation in vitro.

Thiele J, Kvasnicka HM 2009

Table 2. Diagnostic findings for the diagnosis of MPNs (n = 30)

Parameters						Number of patients	Final diagnosis
JAK2	RCM	HGB	HCT	BM biopsy result	EPO		
+	+	+	+	+	+	7	PV
+	+	−	+	+	+	7	PV
+	+	−	−	+	+	4	PV
+	+	−	+	+	−	2	PV
+	+	−	−	+	−	3	PV
+	+	+	+	+	*	3	PV
+	+	−	+	+	*	1	PV
+	+	−	−	+	*	1	PV
+	−	−	+	−†	+	1	ET
+	−	−	−	−‡	−	1	PMF

Silver et al, Blood 2013

Silver RT, Chow W, Orazi A, Arles SP, Goldsmith SJ. *Blood* 2013;122:1881-6

New Suggested Criteria (2014)

	Polycythemia vera (PV)[a]
Major criteria	
1	Hemoglobin >16.5g/dl (men) >16 g/dl (women) or hematocrit >49% (men) >48% (women)
2	BM trilineage myeloproliferation with pleomorphic megakaryocytes
3	Presence of *JAK2* mutation
4	
Minor criteria	
1	Subnormal serum erythropoietin level
2	
3	

Tefferi et. al., *Leukemia*, 2014

New Suggested Criteria Are Inadequate

- Using new criteria for PV, N=35 (unpublished data)
  - All JAK2 v617f +
  - 15 of 35 patients did not meet new criteria at time of diagnosis
    - All 15 had red cell masses > 125% of expected value
    - Hct < 49%: 9 male patients
    - Hct < 48%: 6 female patients
- EPO criterion incorrect in Cornell study
  - 14 of 40 patients (35%) with PV showed normal EPO levels

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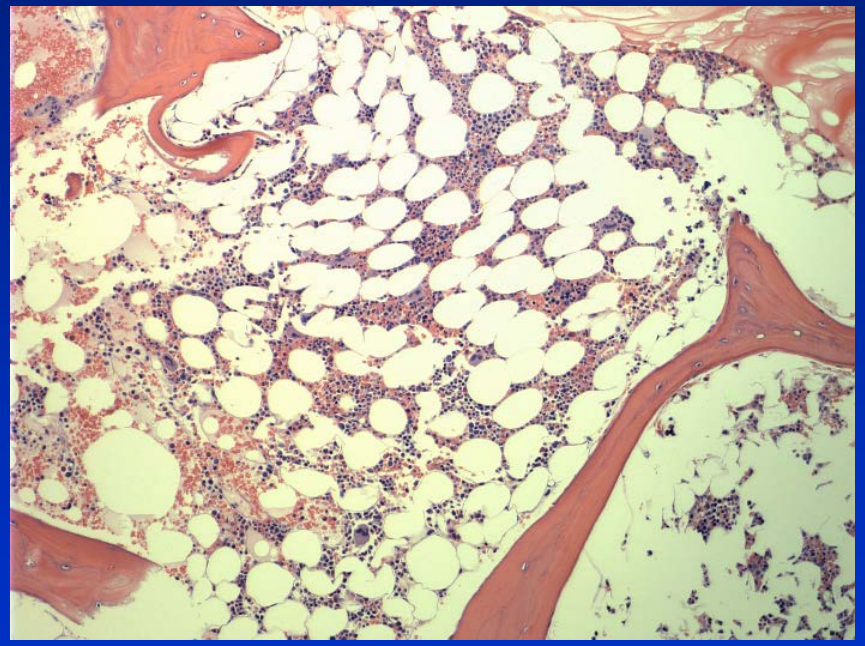
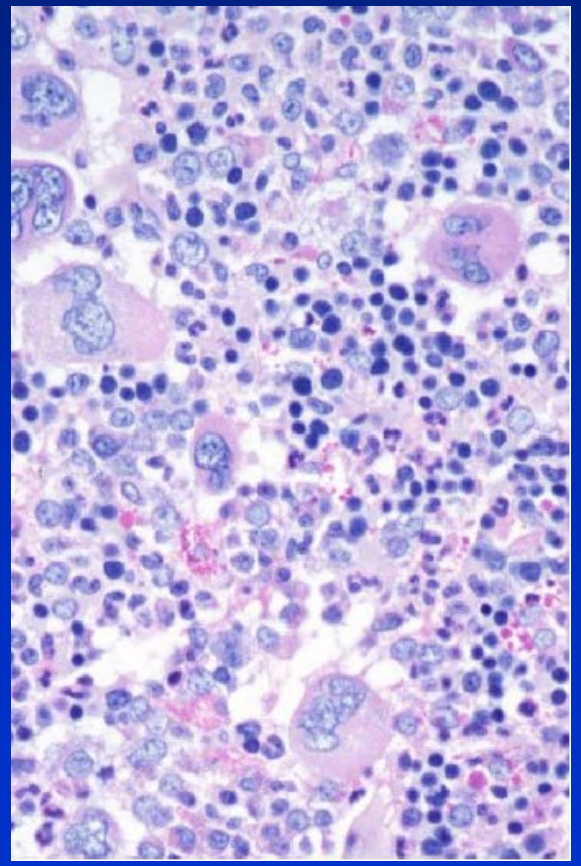
Diagnosis of PV: Bone Marrow Biopsy

Normal



PV



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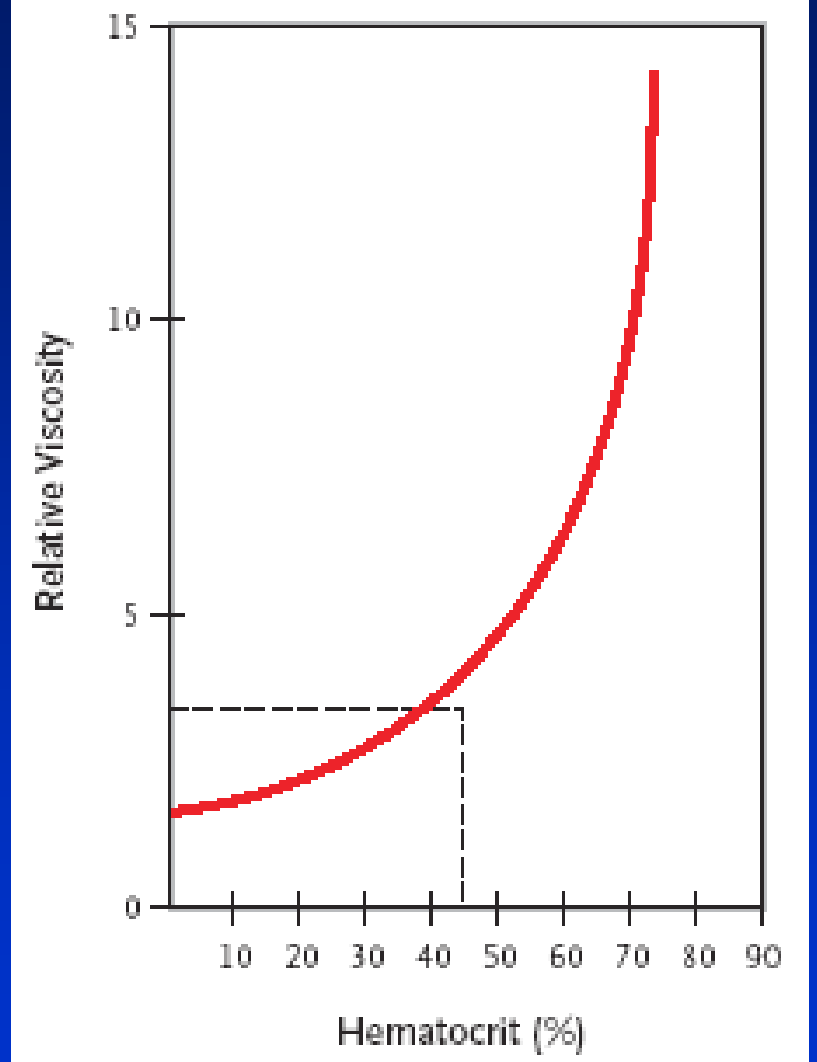
Effect of Hematocrit on Blood Viscosity



Spivak, J NEJM 350:2 January 8, 2004

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Phlebotomy requirements during the year prior to rIFNα, all patients (Cornell experience)

Quartile	# Patients	# PHL during the year prior to rIFNα	Median	Mean
1	9	1-4	3	2.8
2	9	5-7	5.5	5.7
3	8	8-12	9.5	9.6
4	8	12-25	15	16
Totals	34	Range: 1-25	7	8

Risk Categories in PV

- Low risk
  - Age < 60
  - No thrombotic history
- High risk
  - Age > 60 and/or
  - Thrombotic history
- Earlier vs later myelosuppression

Low Risk Patient: Treatment

- 47 year old dentist
  - Hgb: 23.3 g/dL
  - HCT: 69%
  - Platelets: 145,000 x10^9/L
  - Low ferritin
  - Phlebotomies
    - Initial 13
    - Maintenance: 6 per year
  - “Complaints of increasing asthenia that limits some activities ascribed to severe iron deficiency…”

How I Treat Polycythemia
Vannucchi, AM
Blood 2014, 124, 3212

“Those who cannot remember the past are condemned to repeat it.”

George Santayana, 1905

MYTH OF PHLEBOTOMY-ONLY
PHL-O UNACCEPTABLE
AS SOLE TREATMENT

1. Poor Clinical Tolerance
2. Frequency of Vascular Complications
3. Risk of Early Progression to Myelofibrosis (probably an association)

* Najean Y, Dresch C, Rain JD. Br J Haematol. 1994 Jan; 86(1):233-5.

PROBLEM WITH PHLEBOTOMY AS SOLE TREATMENT

Wasserman, 1955: “phlebotomy cripples”

PVSG, 1980: “phlebotomy - only” – protocol violations, many patients lost to follow up

Berlin: “What is almost entirely missing from the literature are 1997 data on the difficulty of maintaining patients on a phlebotomy regimen and in particular the effect of phlebotomy on “quality of life”

RESULTS OF 75 FRENCH PATIENTS

	No.	% (CUM)
No cases, PVSG protocols 01, 05	**75**	
Off study at 3 years	38	51%
Off study at 6 years	19	75%
Off study at 9 years	11	91%
On study at 9 years (remaining)	7	9%

No information regarding rate of PHL, progression of disease

Najean Y, Dresch C, Rain JD. Br J Haematol. 1994 Jan; 86(1):233-5.

Related to Anemia

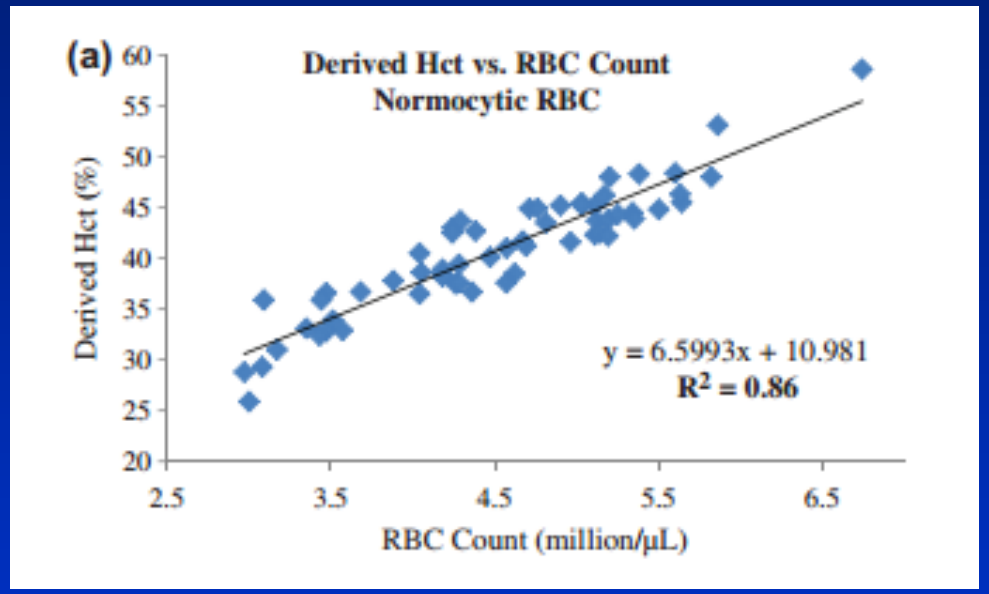
1) Cognitive impairment
2) Dementia
3) Poor Exercise Tolerance
4) Impaired Results after chemotherapy
5) Impaired Results after Myocardial Infarction
6) More Frequent Falls

Stanley Schrier, MD, Hem Onc, January 2015

DeLoughery, *New England Journal of Medicine*, 2014

The hematocrit value in polycythemia vera: caveat utilitor

Silver and Gjoni, *Leukemia* Lymphoma, 2014



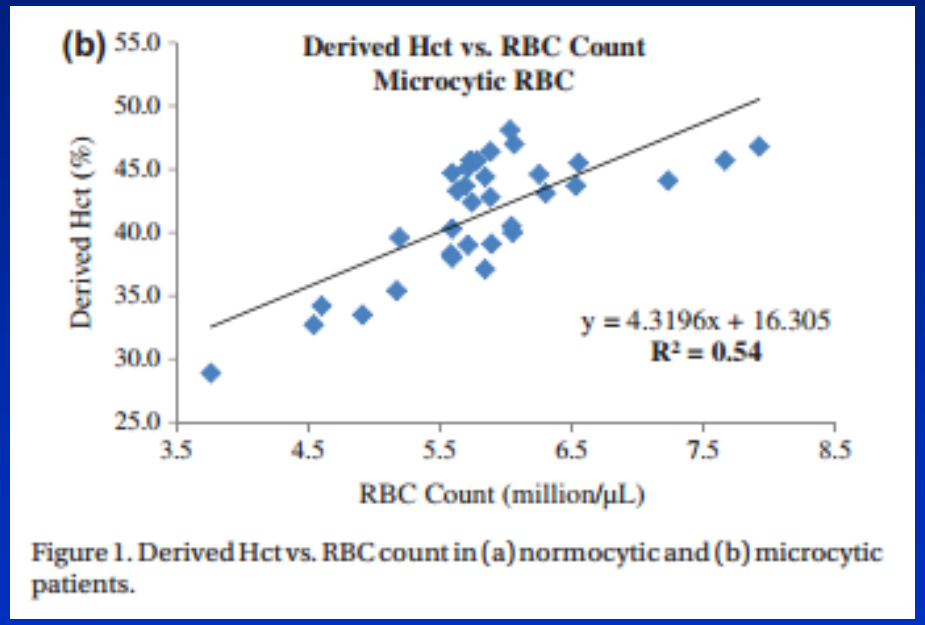


Figure 1. Derived Hct vs. RBC count in (a) normocytic and (b) microcytic patients.

RBC x MCV = Hct

As the MCV falls due to phlebotomy, the cells become smaller and hypochromic, thus making the hematocrit unreliable as a determination of RBC. It is the red cell that causes problems with viscosity, not hemoglobin.

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FAILURE, HU AT 1 YEAR, PVSG
(118 Patients)

Previously untreated: 27%

Previous myelosuppressives: 41%

PROBLEMS WITH HYDROXYUREA
(292 PATIENTS UNDER AGE 65)

1. **Unsatisfactory hematologic control: (high platelet count, low HGB)**
2. **Aphthous and leg ulcers in 20%**
3. **High risk of progression to myelofibrosis associated with high platelet counts**
4. **Risk of leukemia: 10% at 13th year**

Najean and Rain, Blood, 90:3370, 1997

Is HU Leukemogenic?

"No conclusive evidence for leukemogenic risk"

Kiladjian et al, JCO 211, 29. 3907

"HU not associated with increased risk"

ECLAP Study

Median F/U 2.8 Years

Study Design – Prevented Proper Assessment of total exposure to HU

European LeukemiaNet: "Proceed with caution in your new patients or in patients with cytogenetic abnormalities."

Final Report – French Intergroup JCO 2011, 29, 3907

Kiladjian, JJ et. al.

	HU	PiBr
Survival, Yes, Med	20.3	154
MDS/AML	Percentage	
10	6.6	13
15	16.5	34
20	24	52
MF	Percentage	
10	15	5
15	24	10
20	32	21

Obituary of Jean Lindenmann by Gina Kolata, January 22, 2015

- Basis for using Interferon

Jean Lindenmann, 90; Made Interferon His Life's Work

By GINA KOLATA

Dr. Jean Lindenmann, a Swiss scientist who, with a colleague, discovered interferon, the powerful antiviral substance used to treat some cancers as well as hepatitis C and multiple sclerosis, died on Jan. 15 in hospice care in Zurich. He was 90. The cause was complications of prostate cancer, his son Christian said.

Dr. Lindenmann made his discovery in 1957 when he was a postdoctoral student at the National Institute for Medical Research in London, working with Dr. Alick Isaacs.

The two began studying a puzzling phenomenon: If they killed viruses by heating them and then added those dead viruses to cells, the cells resisted subsequent infection with live viruses. Was it because the dead viruses tied up entry portals in the cells, preventing live viruses from getting in? Were the dead viruses secreting something that acted like a viral version of an antibiotic?

The answer, they discovered, was neither. It turned out that the dead viruses prompted the cells to resist infection by secreting a substance the scientists named interferon, because it interfered.

Researchers around the world leapt to investigate further and soon discovered an entire family of these substances, all produced by cells in response to viruses, either dead viruses or live ones. Interferons turned out to be too toxic to be used routinely, as antibiotics are used to treat bacterial infections. But they are used to treat specific cancers and other diseases.

Jean Lindenmann, circa 1957.

After his discovery, Dr. Lindenmann returned to his original institution, the University of Zurich, saying he wanted to leave further study of interferons to others. Instead, he turned to another puzzling phenomenon, asking why some strains of mice were resistant to influenza viruses that quickly killed other strains of mice.

A graduate student's discovery leads to a cancer weapon.

The answer turned out to be interferon again, but acting in an indirect way. Again, the viral infection made the cells produce interferon, but here, the interferon switched on a gene in the resistant mice. That gene then directed production of a protein that protected against the influenza virus.

Despite his efforts to study something other than interferon, Dr. Lindenmann ended up with another interferon discovery. He later wrote that "the sad truth" was that after two decades of work trying to figure out why one strain of mice was resistant to the virus, it turned out to be "interferon related."

Dr. Heinz Arnheiter, an emeritus scientist at the National Institutes of Health, said Dr. Lindenmann, a former teacher of his, was unusual. At a time when molecular biology was on the rise, he said, Dr. Lindenmann chose to focus on biology in its original form, meaning not molecules but studies using whole animals.

He got a sort of rude awakening, though, after he had gone to enormous efforts breeding and inbreeding mice to try to home in on the gene that was involved in resistance to viruses. Then one of his postdoctoral students went to work with Dr. Charles Weissman, a molecular biologist who was also at the University of Zurich, and found the gene's location with a single experiment.

Dr. Lindenmann was born on Sept. 18, 1924, to a Swiss father and Parisian mother living in Zagreb, Croatia. After a few years, the family moved to Zurich, where Dr. Lindenmann grew up.

He graduated from medical school in the 1950s and served in the Swiss Army. He married Ellen Buechler in 1957. She died in 2007.

In addition to his son Christian, Dr. Lindenmann is survived by another son, Jen-Michel, and four grandchildren.

More obituaries appear on the following page.

Specific Activities of Interferon-alpha (rIFN-a) of Interest in PV

- **Antagonizes action of PDGF by interfering with activation of G-0 cells for G-1 traverse and S-phase entry (Lin)**
- **Inhibits erythroid progenitors in vitro (Means, Krantz)**
- **Anti-angiogenic (Folkman)**
- **Directly represses megakaryopoiesis by inhibiting thrombopoietin-induced signaling (Wang)**
- **Involved in *JAK*-STAT signaling**
- **Affects PV stem cell (Mullaly)**

CRITERIA FOR RESPONSE (PVSG)

- **Freedom from phlebotomy**
- **Hematocrit < 45%**
- **Platelets < 600,000/dl**

RESULTS: TREATMENT OF PV WITH rIFN-a

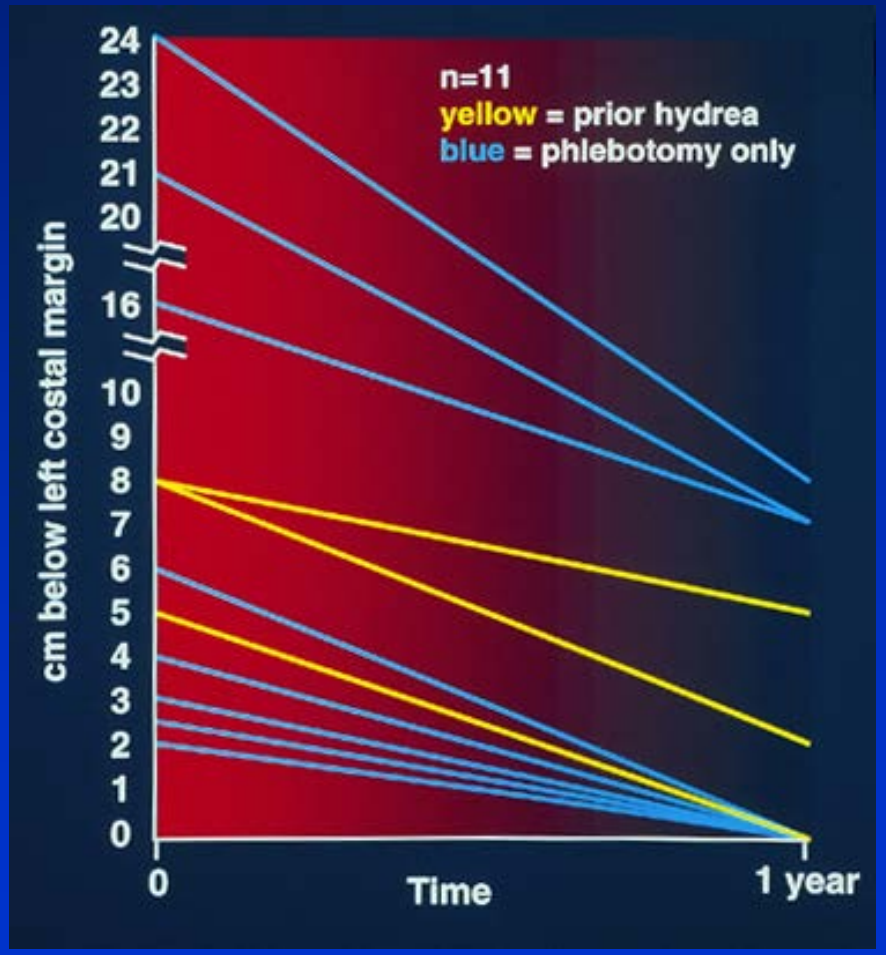
ACCORDING TO THE CRITERIA LISTED

All 55 patients have had clinical responses

No thrombohemorrhagic episodes

CHANGE IN SPLEEN SIZE

1 year after rIFN-a

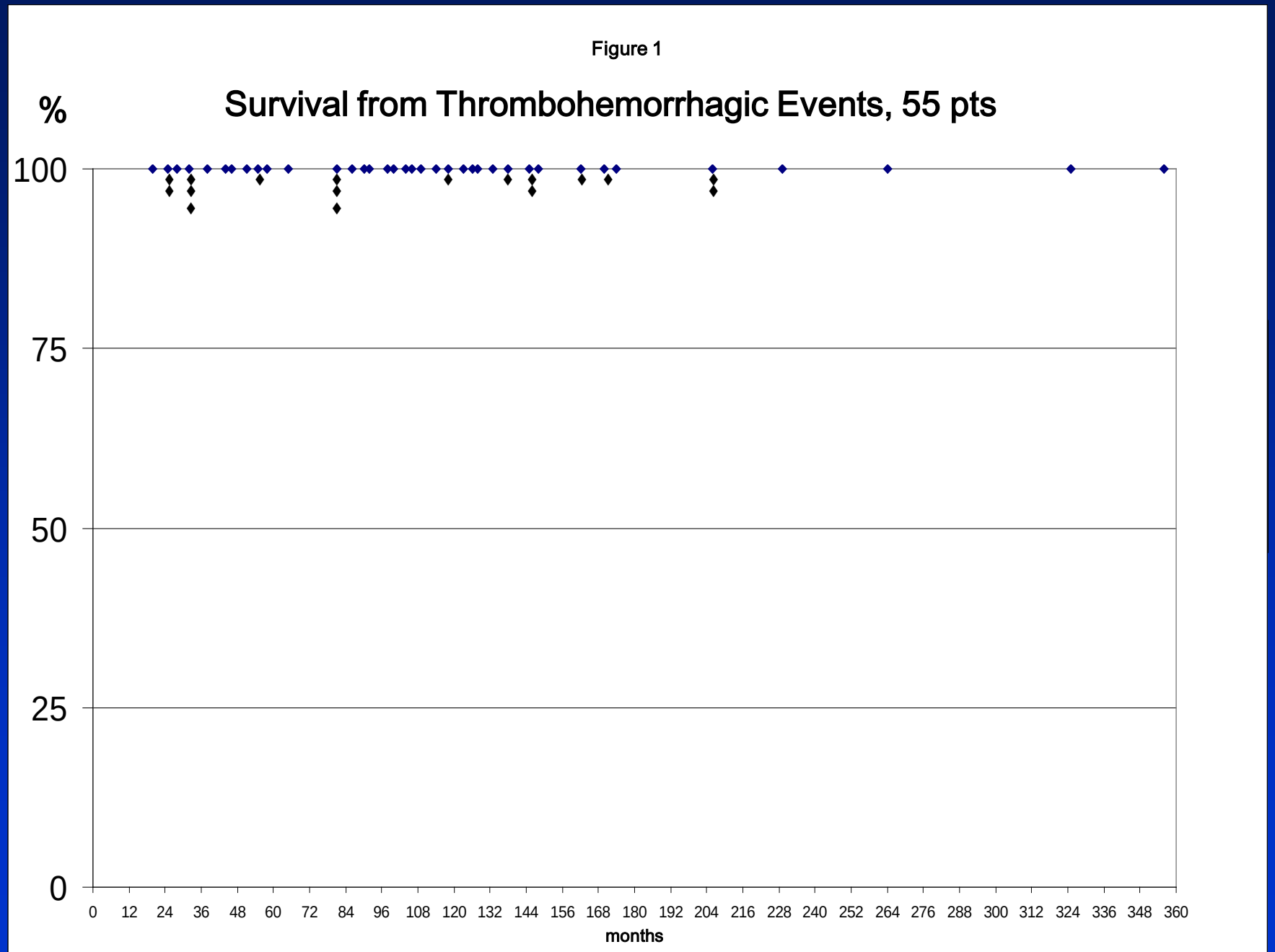


2 years after rIFN-a

- 27/30 (90%) patients with initial splenomegaly showed greater than 50 % reduction in spleen size
- In 23 (76.7%) patients, spleen became non-palpable

Silver, RT, *Cancer*, 2006

Figure 1


Survival from Thrombohemorrhagic Events, 55 pts
%
100
75
50
25
0
0 12 24 36 48 60 72 84 96 108 120 132 144 156 168 180 192 204 216 228 240 252 264 276 288 300 312 324 336 348 360
months

Molecular Changes with Peg-rIFNα

- Decrease in *JAK2*^{V617F} allele burden in 26 (90%) of patients (Kiladjian 2008)
- Undetectable in 24% - Kiladjian *et al* (2008)
- Undetectable in 14% - Quintas-Cardama (2009)
- Clinical response not correlated with molecular response. May be close. Kuriakose *et al* (2011)

Kiladjian J-J, *et al.* Blood 112:3065-3072, 2008

Quintas-Cardama A, *et al.* J Clin Oncol 27:5418-5424, 2009

Kuriakose E, *et al*. Haematol 97(4):538-542, 2011

TOXICITY OF rIFN-α (N=55)

Type of Toxicity	# Pts.	Treatment Continued	Treatment Discontinued
Initial Influenza-type Symptoms	55	X	
Liver Function Abnormalities	4	X	
Hypothyriodism	1	X	
Severe Asthenia	3		X
Skin Rash	1	X	
Complex Seizures	1		X
Depression	1		X
Peripheral Neuritis	1		X
Bone Pain	1	X	
Blurred Vision	2		X

Role of Other Mutations

1. TET2 mutations persist despite eradication of *JAK2* (TET2 may precede *JAK2*)
2. In patients with complete molecular response, *JAK2*(+) cells in some EPO-independent colonies
3. More mutations seen in poor responders to Interferon alfa

1, 2: Kiladjian, et al. Leukemia 24:1519-1523, 2010
3. Beer et al. Blood 115: 2891-2900, 2009
4. Quintas-Cardama et al. ASH Proceedings 2011 Abstract #281

ADVANTAGES OF rIFN-a TREATMENT FOR PV

- BIOLOGIC BASIS FOR ITS USE
- MAINTENANCE OF HEMATOCRIT AND PLATELET SUPPRESSION
- REGRESSION OF SPLENOMEGALY
- NOT MUTAGENIC
- ABATEMENT OF CONSTITUTIONAL SYSTEMS
- DELAYS ONSET OF PPMM (opinion)

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    - HU + Interferon
    - ➢Ruxolitinib

Ruxolitinib vs "Standard Therapy"

Vannucchi et. al. New England Journal of Medicine, 2015

- Eligibility: Inadequate response or unacceptable toxicity from hydroxyurea
- End points
  - Control of Hct for 8 weeks (<45%)
  - Reduction in spleen volume by 30%
- Results

	Ruxolitinib	Control
Hct Control	60%	20%
Spleen Reduction	5 %	1%

Important Safety Information, Jakafi

- Thrombocytopenia, anemia and neutropenia
- Serious bacterial, mycobacterial, fungal and viral infections
- Tuberculosis (TB) infection
- Herpes Zoster
- Non-melanoma skin cancers including basal cell, squamous cell, Merkel cell carcinoma

Indications and Usage

Jakafi (Ruxolitinib) is indicated for treatment of patients with polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea

Jakafi®
ruxolitinib (tablets)

NOW APPROVED

The first and only FDA-approved drug to treat Polycythemia vera (PV) patients who have had an inadequate response to or are intolerant of hydroxyurea

Drawing First Blood: When Should We Transplant in AML? ... p. 45

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VOLUME 01 | NUMBER 01 JANUARY 2015

New Indication for the *JAK* Inhibitor Ruxolitinib

Ruxolitinib, a *JAK1* and *JAK2* inhibitor approved for the treatment of intermediate or high-risk myelofibrosis, is now approved by the FDA for the treatment of polycythemia vera. This new indication is intended to treat the condition in patients who have an inadequate response to or are intolerant of hydroxyurea – another medicine often prescribed to reduce the number of red blood cells and platelets in the blood. The approval was based on results from a clinical study of 222 participants who had polycythemia vera for at least 24 weeks and had undergone a phlebotomy procedure and exhibited an enlarged spleen. Participants were randomly assigned to receive ruxolitinib or the best available therapy, as determined by the investigator on a participant-by-participant basis. At 32 weeks of follow-up, 21 percent of ruxolitinib-treated patients experienced a reduction in the need for phlebotomy and a reduction in spleen volume, compared to 1 percent of participants who received best available therapy. The most common side effects of ruxolitinib were anemia and thrombocytopenia: the most common non–blood-related side effects were dizziness, constipation, and shingles.

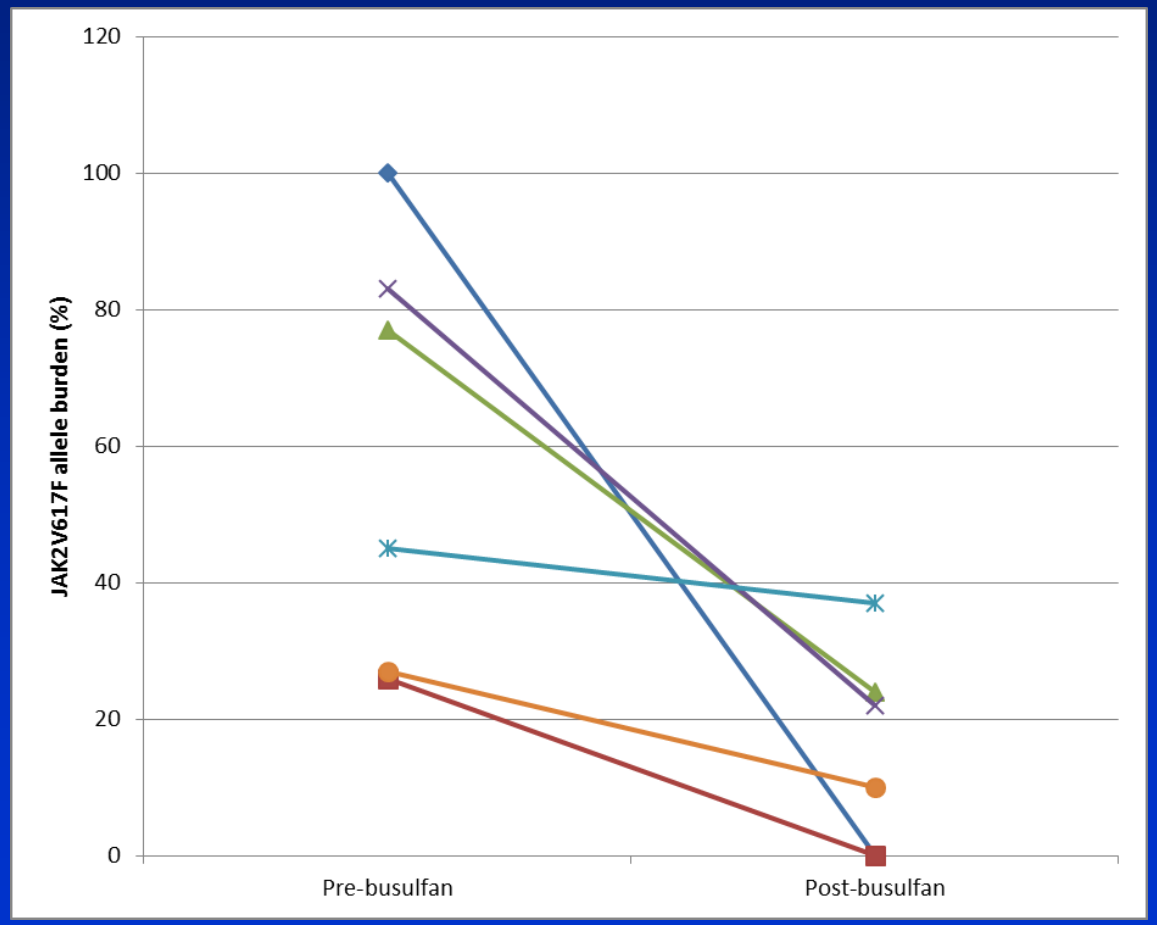
The FDA reviewed ruxolitinib's use for polycythemia vera under the agency's priority review program, because, at the time the application was submitted, the drug demonstrated the potential to be a significant improvement in safety or effectiveness over available therapy in the treatment of a serious condition. The drug also received orphan product designation because it is intended to treat a rare disease.

Source: FDA press release, December 4, 2014

"…the drug demonstrated the potential to be a significant improvement in safety or effectiveness over available therapy in the treatment of a serious condition."

Effectiveness of Busulfan in PV on JAK2 Allele Burden

(6 patients resistant to HU and/or Ifn)



Kuriakose et al.
Haemotologica, 2012

HERACLITUS of Ephesus

Heraclitus:

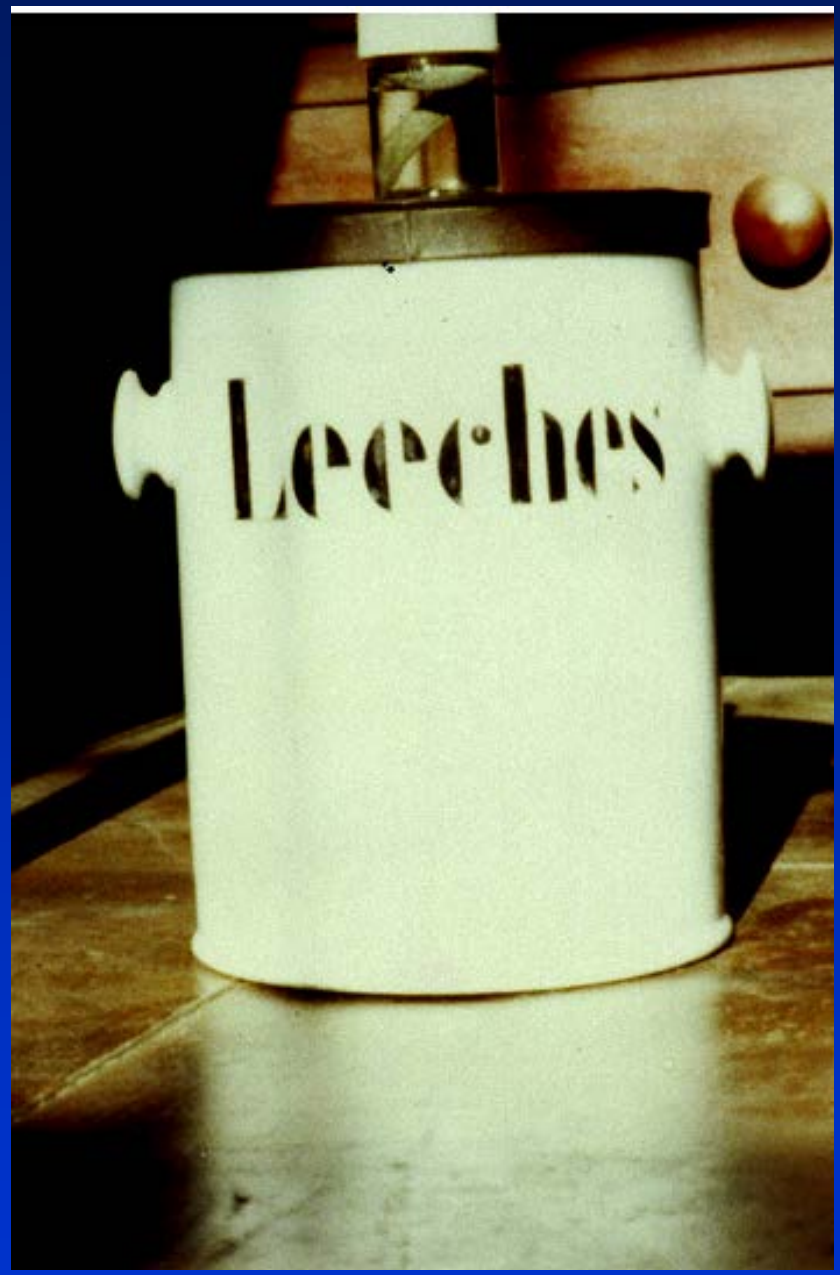
"We can never step into the same river twice"

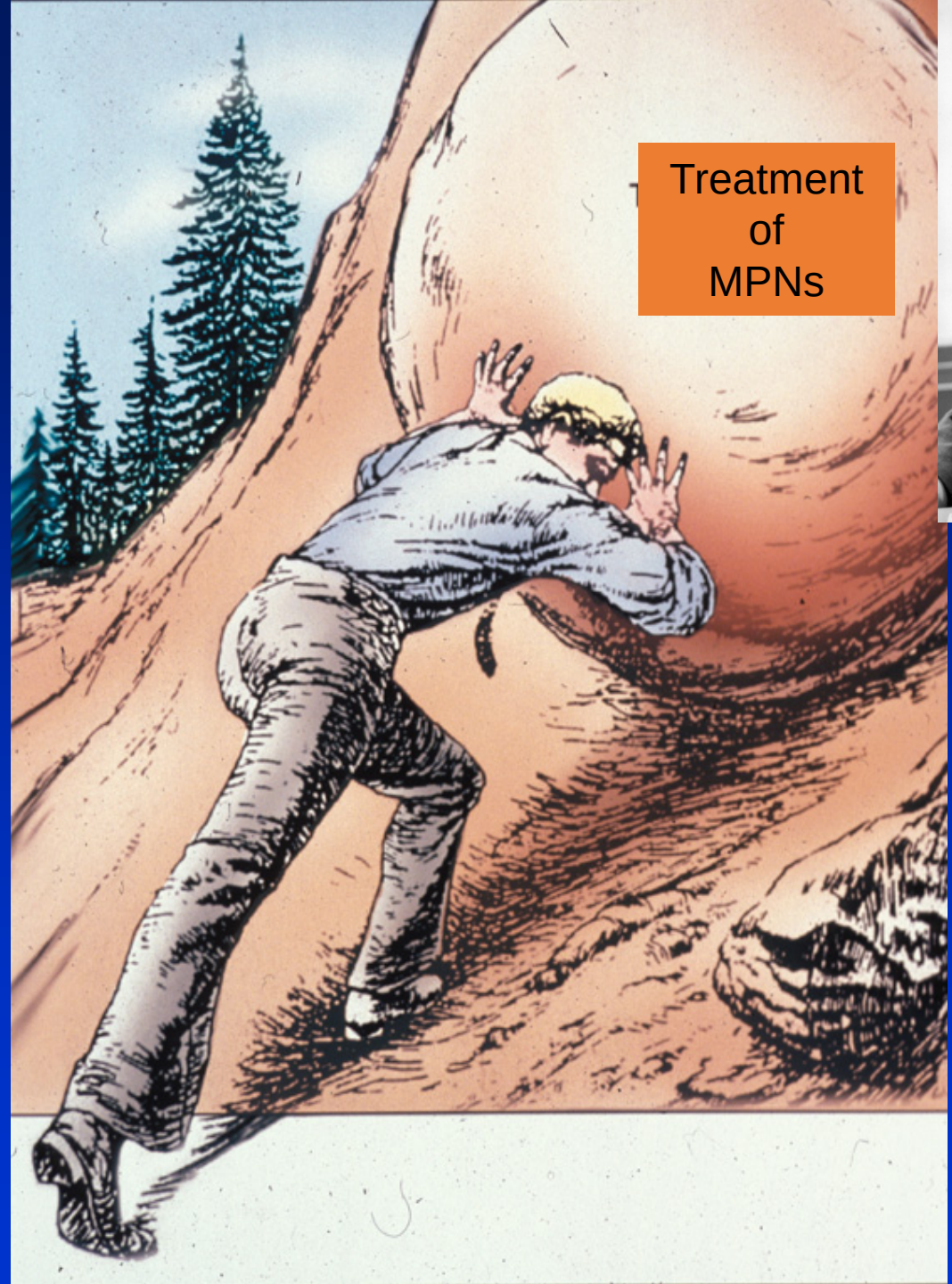
Heraclitus, the Obscure:

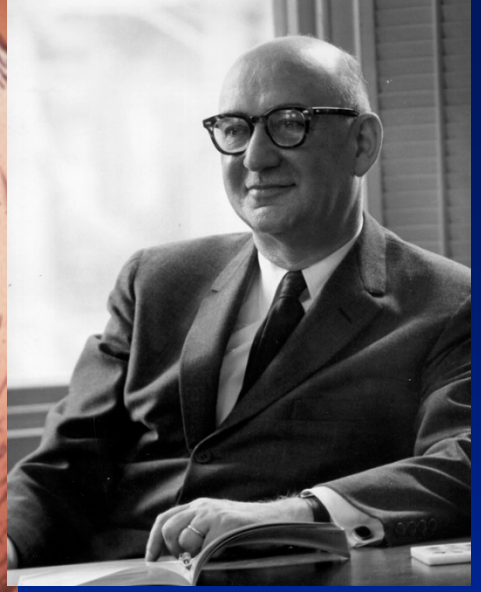
Sayings were full of contradictions

Heraclitus, the Weeping Philosopher:

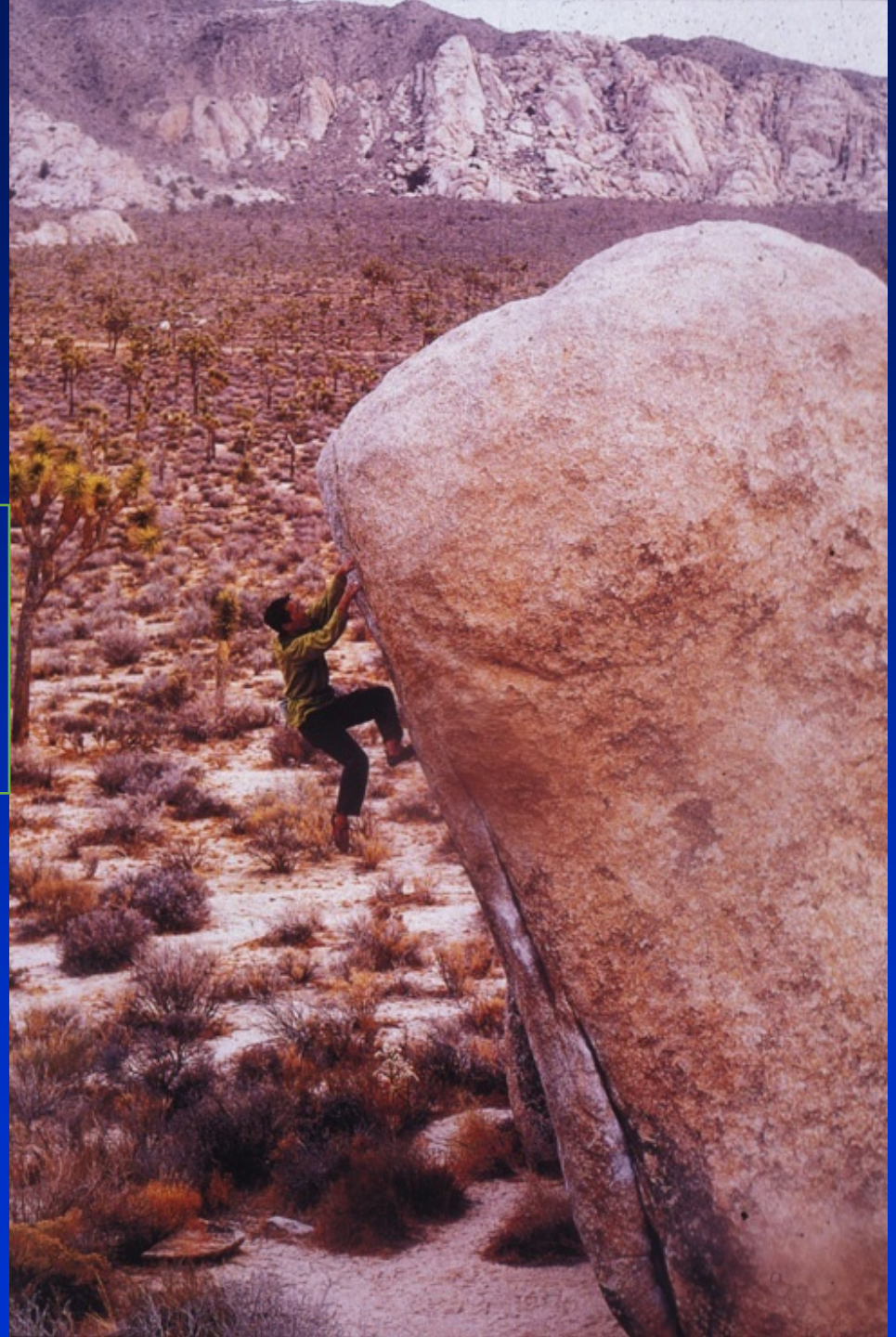
"….sobbed uncontrollably as he predicted on the state of the world…"

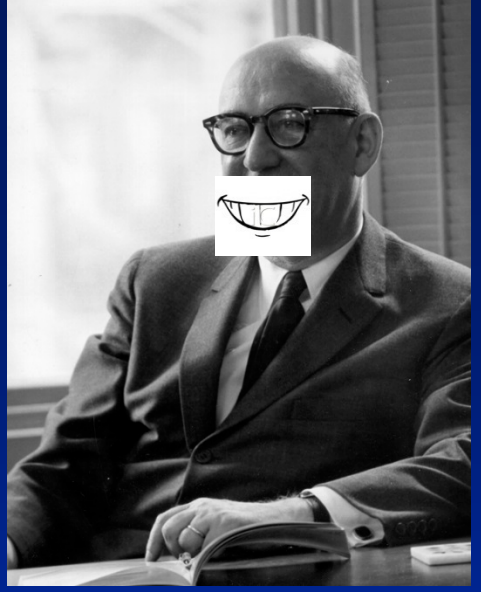

Leeches


Treatment
of
MPNs



Hydrea, Interferon, Ruxolitinib & others; transplantation, others





The woods are lovely, dark, and deep
But I have promises to keep
And miles to go before I sleep
And miles to go before I sleep

Stopping by Woods on a Snowy Evening
Robert Frost, 1923

THE END

VASCULAR EPISODES VS. HEMATOCRIT