

Myeloproliferative disorders

Chris hatton

Proliferate or accumulative

- Bone marrow produces 10^{11} cells – mainly erythrocytes
- Production must be balanced by cell death – apoptosis
- Myeloproliferative disorders are failures of apoptotic mechanisms

The disorders

- Chronic myeloid leukaemia
- Polycythaemia rubra vera
- Myelofibrosis
- Essential thrombocythaemia

The Talk

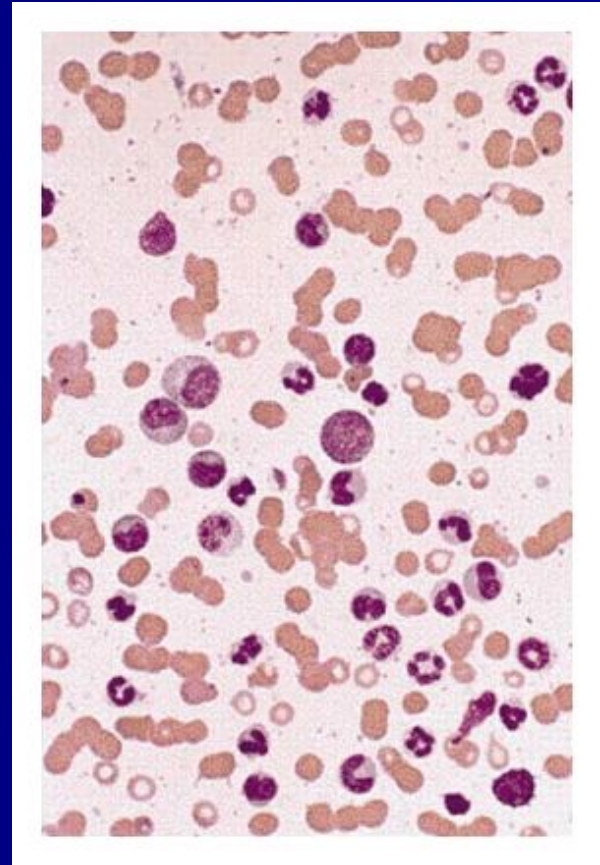
- Background on CML following the introduction of Gleevec
- Essential thrombocythaemia and oral chemotherapy
- Polycythaemia rubra vera

Chronic myeloid leukaemia

- Chronic myeloid leukaemia (CML) is a rare disorder 4-6 new cases per year in Oxford
- Presents
 - Sweats, fever, wt loss
 - Hepatosplenomegaly
 - Bleeding/thrombosis
 - hyperleucocytosis

Laboratory findings

- Leucocytosis – occ very high 300-500 x 10⁹/l
- Basophilia
- Thrombocytosis
- Anaemia which corrects on treatment



CML: a Progressive and Fatal Disease

Chronic phase

Median duration

5–6 years

Accelerated phase

Median duration

6–9 months

Blast crisis

Median survival

3–6 months

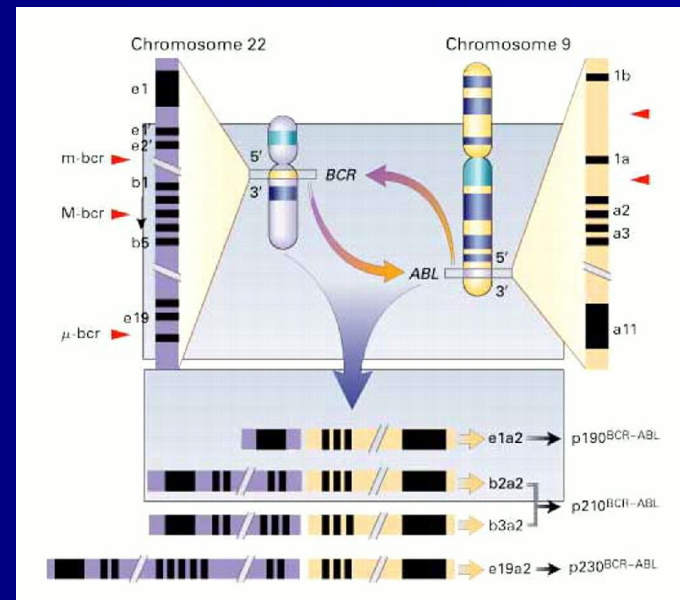
Treatment Options for CML

- Hydroxyurea
- Interferon
- Busulphan
- Allogeneic Bone Marrow Transplant

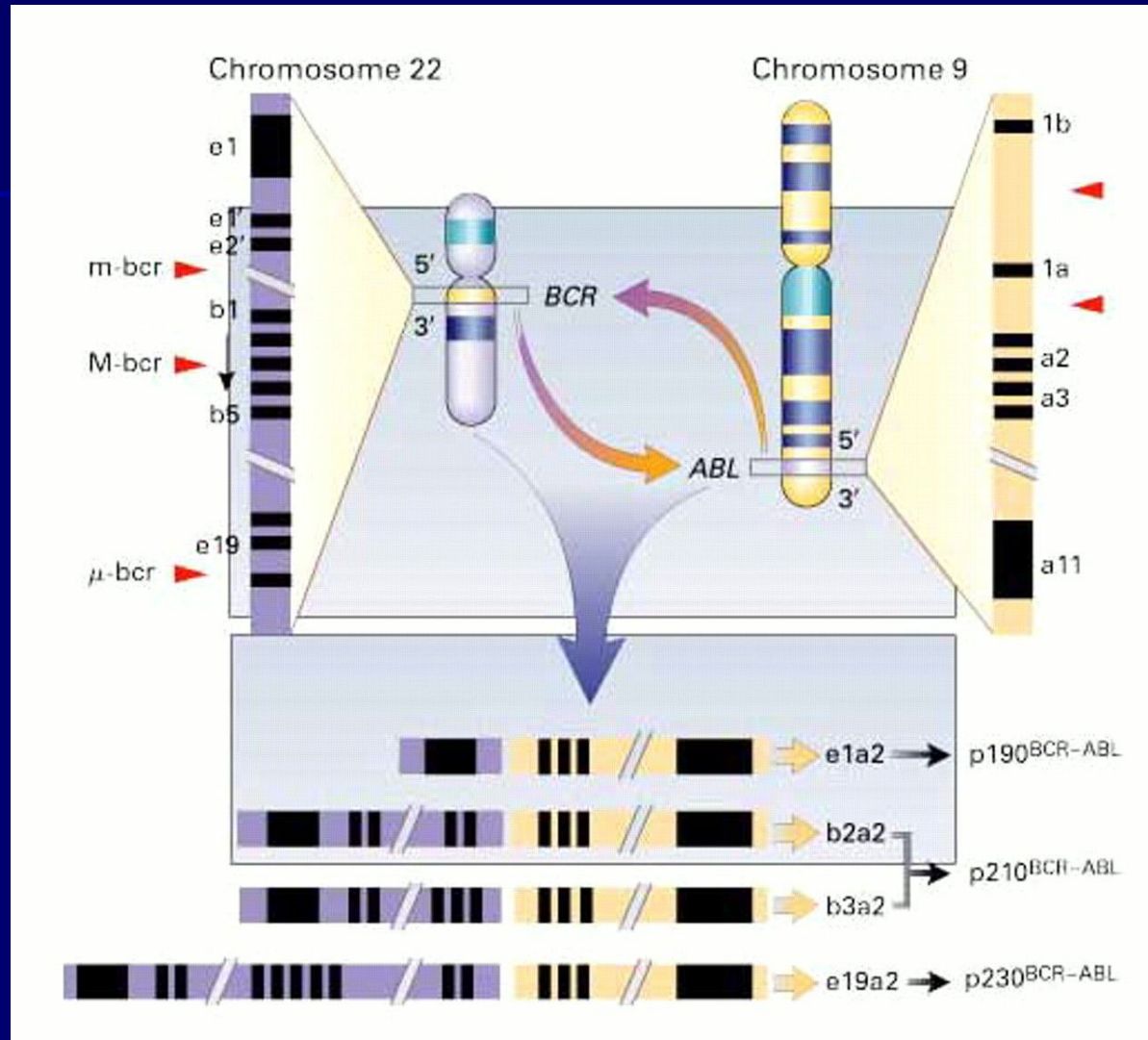
Cytogenetics and molecular biology

- Philadelphia chromosome
 - t(9 : 22)
- Novel gene
 - BCR-ABL
- Novel protein
 - tyrosine kinase

Translocation leads to novel protein



The Translocation of t(9;22)(q34;q11) in CML

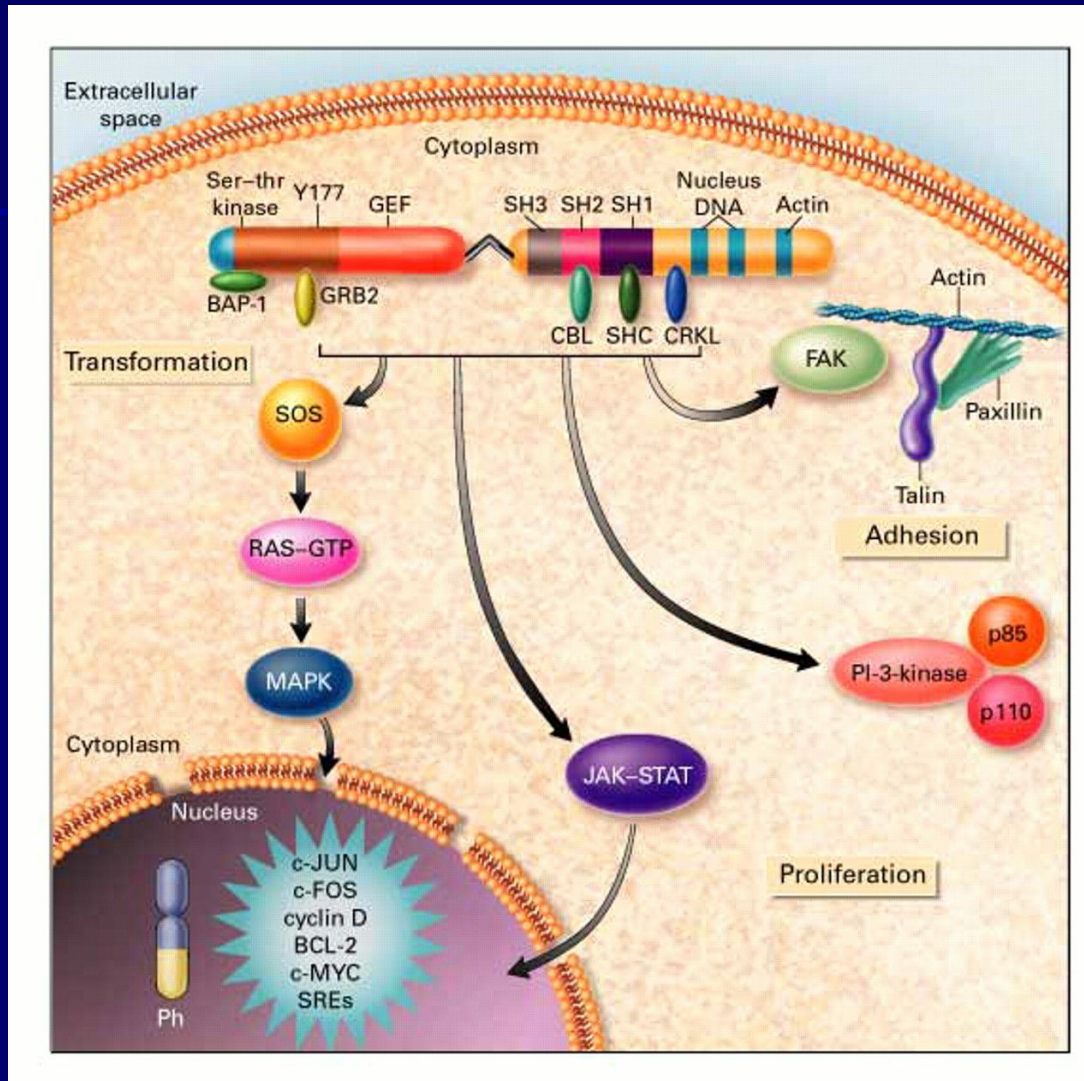


Faderl, S. et. al. N Engl J Med 1999;341:164-172



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Signaling Pathways of p210BCR-ABL

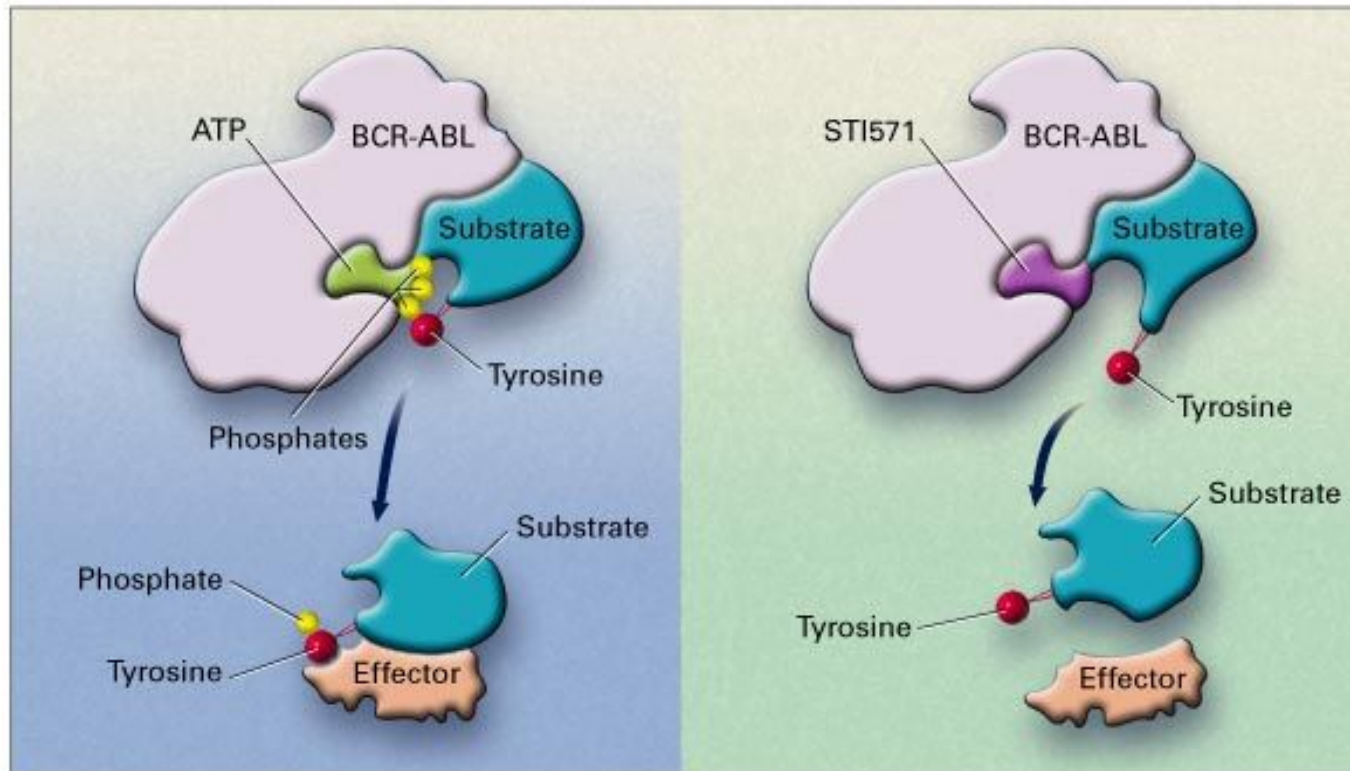


Faderl, S. et. al. N Engl J Med 1999;341:164-172



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Likely Mode of Action of STI571



Goldman, J. M. et. al. N Engl J Med 2001;344:1084-1086



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- Gleevec-tyrosine kinase inhibitor

Magic Cancer Bullet



How a Tiny Orange Pill Is
Rewriting Medical History

DANIEL VASELLA, M.D.

Chairman and CEO, Novartis

with ROBERT SLATER

Phase I Study: Gleevec® Achieves Hematologic and Cytogenetic Responses

Typically 4 weeks to achieve CHR, 2 to 10 months to achieve MCR

A maximal tolerated dose (MTD) was not reached (up to 1000mg/day)

Chronic Phase IFN- α Failure 300–1000mg/day(n=54)

100%

98%

31%

13%

Blast Crisis, Myeloid 300–1000mg/day(n=38)

55%

11%

Blast Crisis, Lymphoid 300–1000mg/day

(n=20)

70%

20%

11%

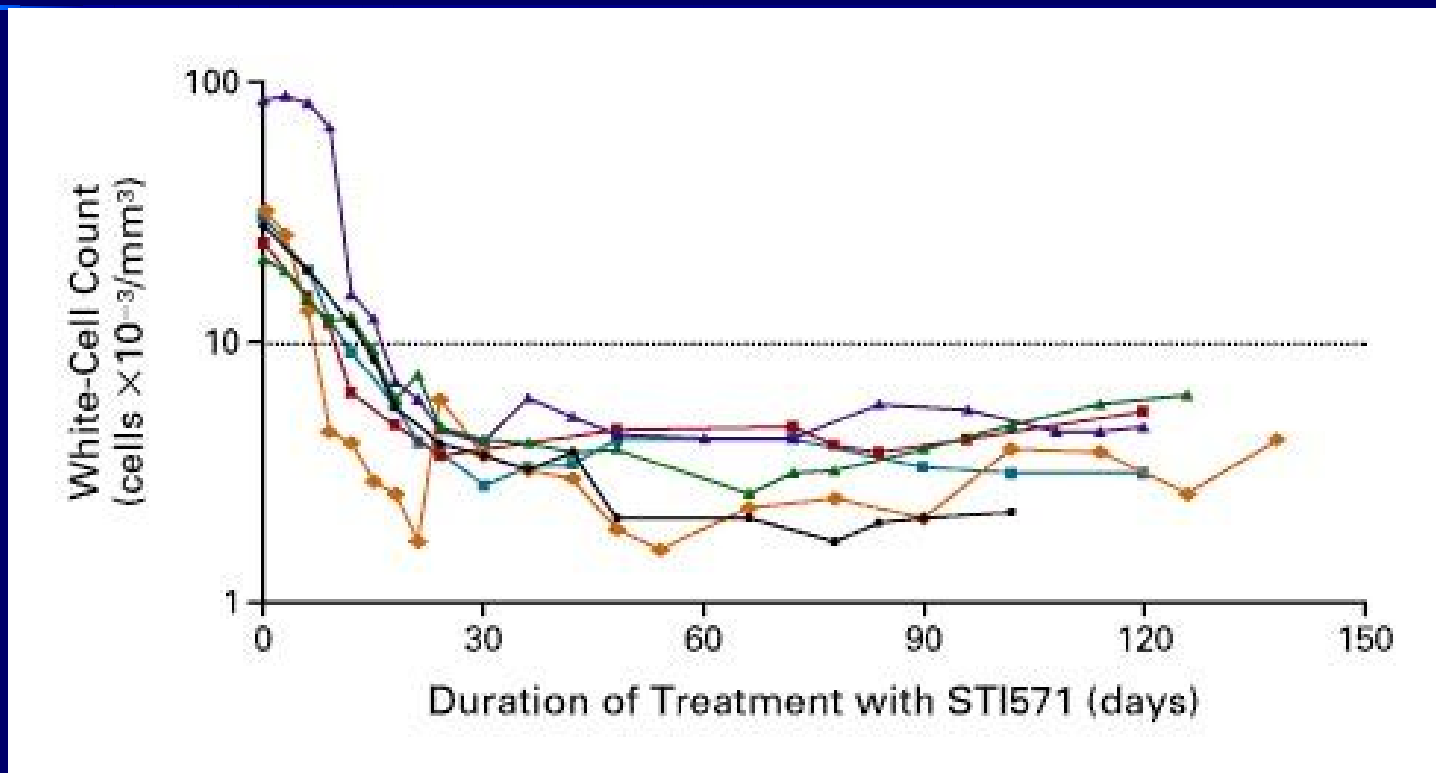
8%

TABLE 2. DRUG-RELATED ADVERSE EVENTS ACCORDING TO THE DAILY DOSE OF STI571.*

ADVERSE EVENT	25-140 mg (N=14)		200-300 mg (N=23)		350-500 mg (N=18)		600-1000 mg (N=28)		TOTAL (N=83)
	GRADE 1 OR 2	GRADE 3 OR 4	GRADE 1 OR 2	GRADE 3 OR 4	GRADE 1 OR 2	GRADE 3 OR 4	GRADE 1 OR 2	GRADE 3 OR 4	GRADES 1-4
	% of patients								no. (%)
Nausea	21	0	30	0	50	0	50	0	36 (43)
Myalgias	21	0	52	0	33	6	28	14	34 (41)
Edema	21	0	22	0	33	0	55	7	32 (39)
Diarrhea	14	0	4	0	33	0	38	3	21 (25)
Fatigue	14	0	22	0	11	0	24	3	17 (20)
Rash	7	0	17	0	11	0	28	3	16 (19)
Dyspepsia	14	0	13	0	28	0	17	0	15 (18)
Vomiting	0	0	13	0	11	0	34	0	15 (18)
Thrombocytopenia	0	0	4	0	11	6	7	24	13 (16)
Neutropenia	0	0	9	4	6	6	0	24	12 (14)
Arthralgias	0	0	4	0	6	0	28	3	11 (13)

*The adverse events listed here were considered to be related to STI571 and were reported in more than 10 percent of patients. A grade of 1 indicates a mild adverse effect, a grade of 2 a moderate effect, a grade of 3 a severe effect, and a grade of 4 a life-threatening effect.

Hematologic Responses in Six Patients Receiving 500 mg of STI571 per day



Druker, B. J. et. al. N Engl J Med 2001;344:1031-1037



Gleevec

- Cost - £64 PER DAY
- £15,000 PER ANNUM PER PATIENT
- NICE APPROVED

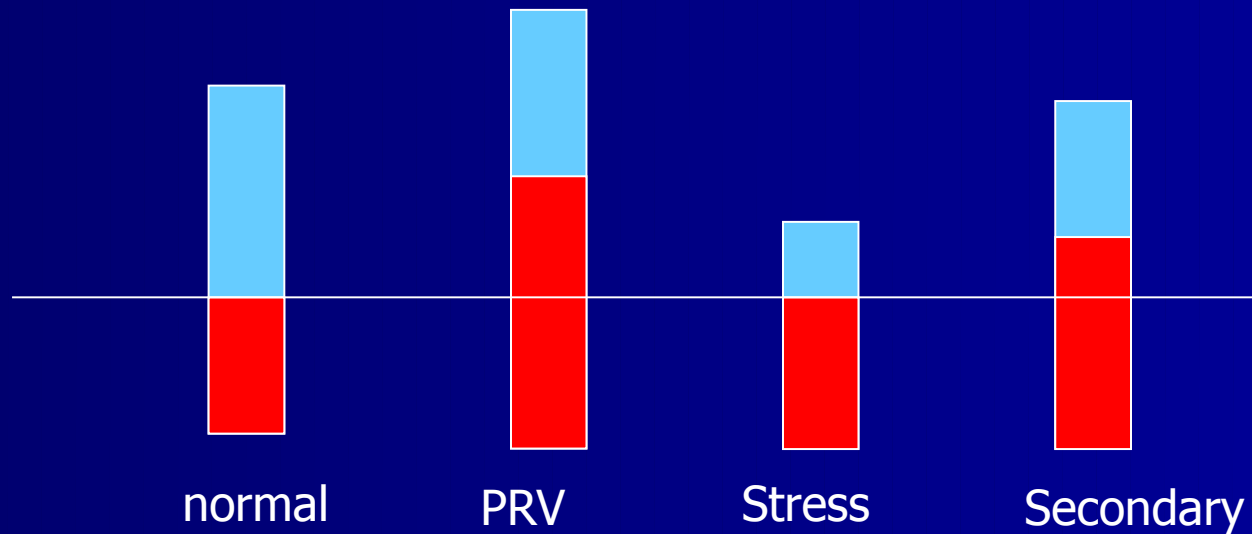
Gleevec

**Leukemia drug Gleevec slows
accumulation of major
component of senile plaques in
cell studies and in guinea pigs !**

September 2003

Polycythaemia

- Elevated haemoglobin



Polycythaemia rubra vera

- Red cell life span is not prolonged in PRV
- Multipotent stem cell
- Renal failure does not suppress
- Hypoxia does not drive it further
- Phlebotomy does not accelerate it
- Low serum erythropoietin

Polycythaemia rubra vera

- Reduction of the red cell mass and maintaining it at a safe level by phlebotomy (hematocrit level of < 45% in men and < 42% in women and < 36% during pregnancy) is the first principle of therapy in polycythemia vera.
- Venesection is a safe and immediately effective therapy and its desired side effect, iron deficiency, is not a liability, claims that cannot be made for any of the surrogate therapies for polycythemia vera that have been proposed to date.
- Reduction of the red cell mass and maintaining it at a physiologic level removes a major source of complications and may also alleviate systemic hypertension and pruritus and reduce splenomegaly.

Polycythaemia rubra vera

- For many patients, no other therapy may be necessary for many years. Aspirin or anticoagulants such as warfarin are not substitutes for adequate phlebotomy.
- Occasionally, with blood loss or overzealous phlebotomy, symptomatic anemia can ensue. Judicious iron replacement can accelerate the recovery process but too much iron will result in an explosive increase in red cell mass.

Polycythaemia rubra vera

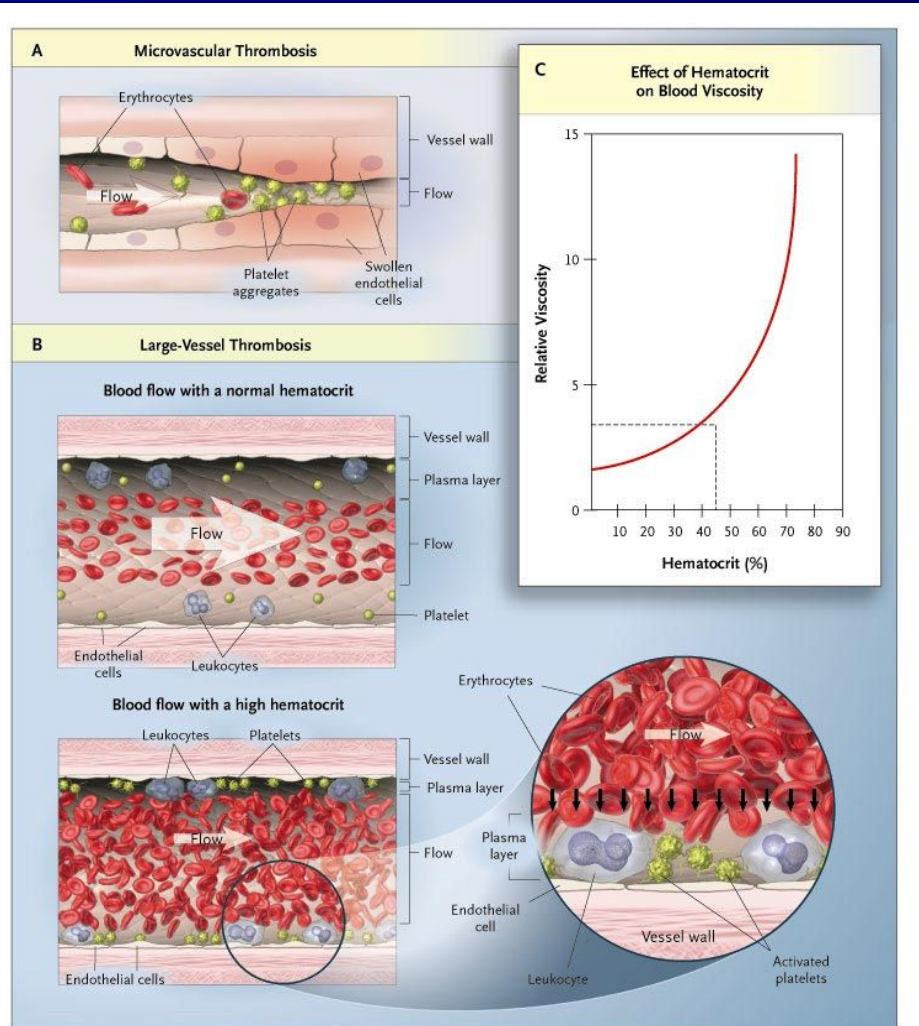
- Microvascular occlusive or hemorrhagic phenomenon
- Hyperuricemia,
- Pruritus and acid-peptic disease,
- Aspirin alone or anagrelide may be sufficient to combat the microvascular occlusive syndrome associated with thrombocytosis.
- A modest leukocytosis requires no correction; however, if progressive, leukocytosis is a harbinger of extramedullary hematopoiesis or disease acceleration. In which case, the leukocytosis can serve as a guide to disease control following the institution of therapy.

Thrombosis and PRV

Spivak, J. N Engl J Med 2004;350:99-101



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Essential thrombocythaemia

- Disorder of the elderly
- Diagnosis of exclusion
 - reactive causes
 - Bleeding
 - Inflammation
 - malignancy
- High incidence of thrombotic complications
 - cerebral
 - myocardial
 - peripheral arterial thromboses
 - pulmonary embolism and deep-vein thrombosis are less frequent.

Essential thrombocythaemia

- Thrombocytosis and abnormal platelet function may contribute to the complications, but there is no clear evidence that they do.
- Two thirds of patients with essential thrombocythemia are asymptomatic
- High vascular-complication rate among patients **older than 60** years and patients who had already had a **thrombotic event**. Such patients could be candidates for treatment to reduce their platelet counts.

Treatment of ET

- Physicians often use hydroxyurea for the initial treatment of essential thrombocythemia.
- This drug has a broad dose–response range, mild side effects, and theoretically little mutagenic risk.
- Discontinuation of the drug quickly reverses any unwanted myelosuppression.
- Although hydroxyurea reduces the platelet count, there is no convincing evidence that it also decreases thrombotic episodes in patients with essential thrombocythemia.
- Indeed, no clear relation has been established in this disease between the absolute platelet count and the frequency of thrombosis. Moreover, hydroxyurea, which does not permanently control the thrombocytosis, must be given indefinitely.
- This arouses concern because of the leukemogenic potential of hydroxyurea and clouds estimates of the drug's risk–benefit ratio.

ET

- Young patients with very high platelet counts
- Pregnant women