Myeloproliferative Neoplasms (MPN)
Part 01

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Objectives

- Definition
- Classification
- Clinical features
- Diagnosis
- Treatment

Introduction

- Group of conditions arising from marrow stem cells
- Characterised by clonal proliferation of one or more haemopoietic components in the BM
- Can progress to acute leukaemia
- Can progress to severe BM fibrosis

MPN

- Granulopoiesis –CML (Chronic Myeloid leukaemia)
- Erythropoiesis- PV (Polycythaemia Vera)
- Thrombopoiesis- ET (Essential Thrombocythaemia)
- Primary Myelofibrosis - MF

MPN-Classification

Philadelphia (+)

- Granulopoiesis
  CML

Philadelphia(-)

Erythropoiesis- PV

Thrombopoiesis- ET

Primary Myelofibrosis - MF

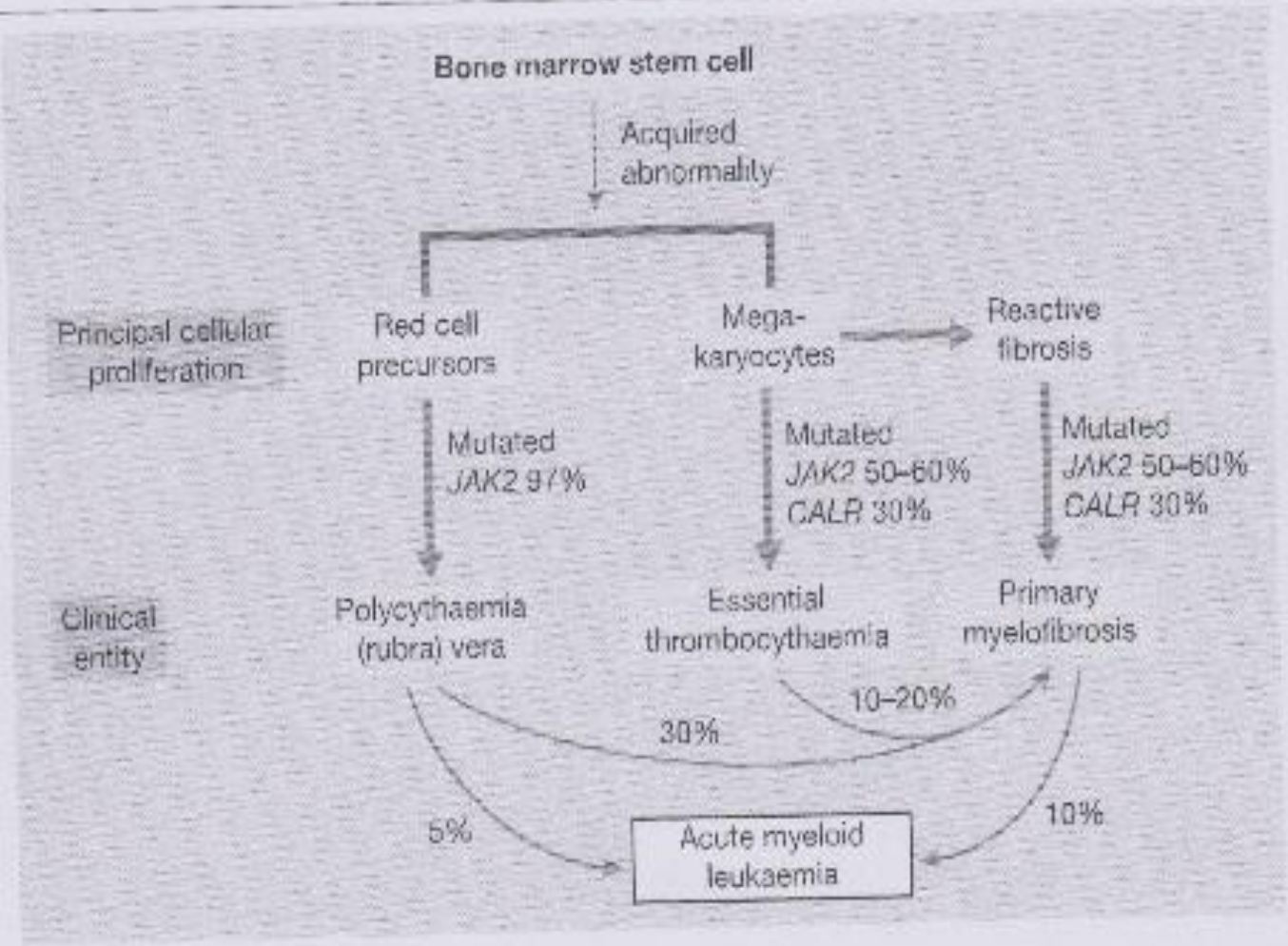
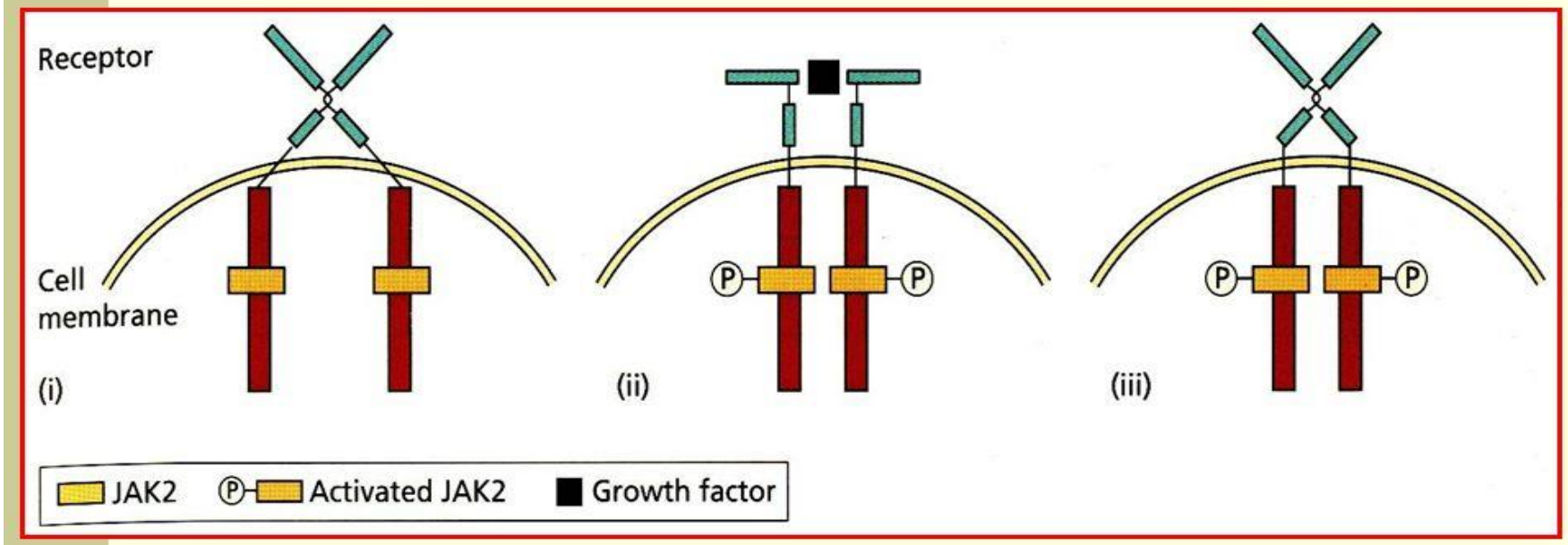


Figure 15.1 Relationship between the three myeloproliferative diseases. They may all arise by somatic mutation in the pluripotential stem and progenitor cells. Many transitional cases occur showing features of two conditions and, in other cases, the disease transforms during its course from one of these diseases to another or to acute myeloid leukaemia. The three diseases, polycythaemia rubra vera, essential thrombocythaemia and primary myelofibrosis, are characterized by *JAK2* or *CALR* mutation in a varying proportion of cases.

JAK 2 and haemopoiesis

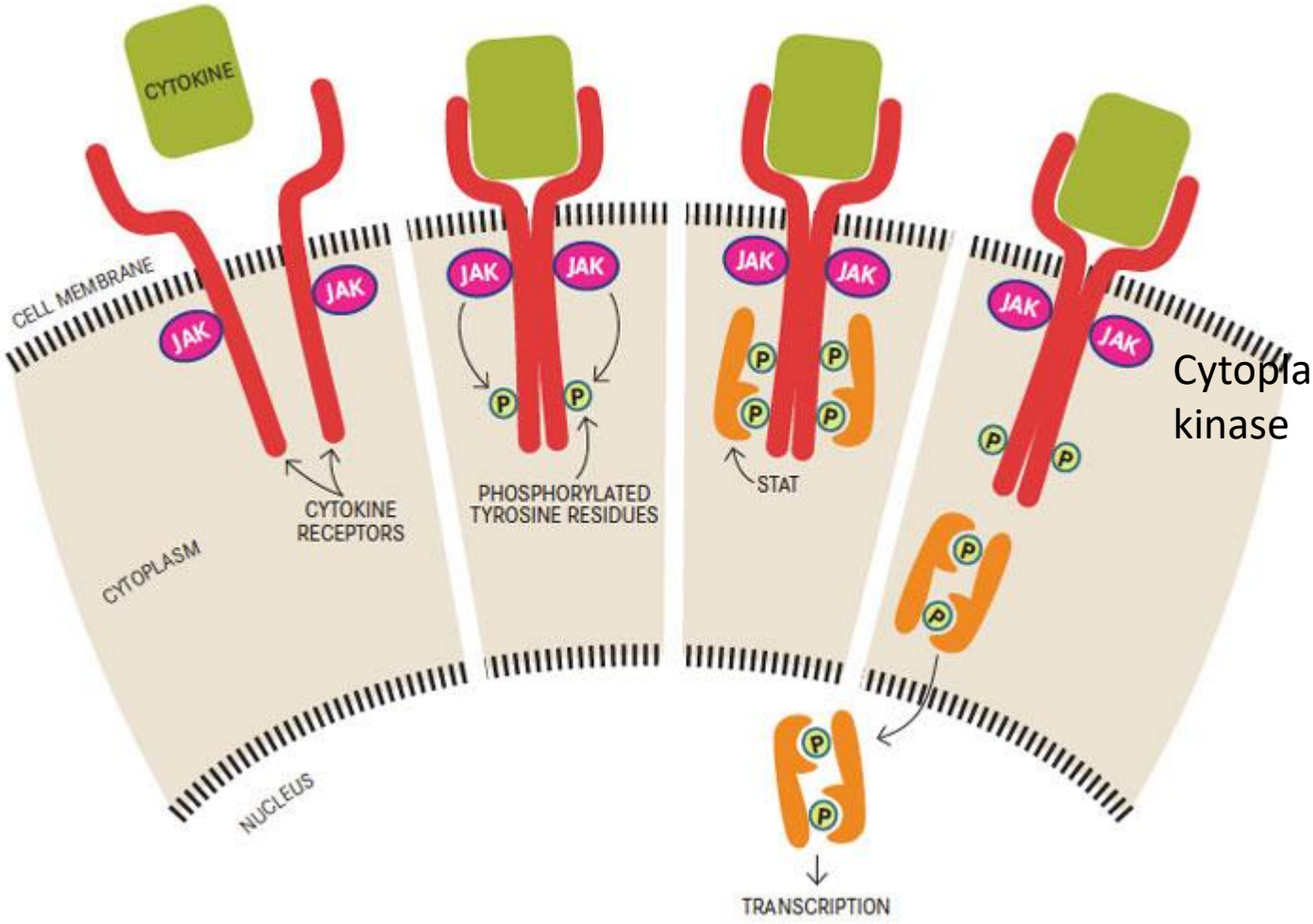


The role of JAK2 mutation in the generation of myeloproliferative diseases. (a) (i) Most haemopoietic growth factor receptors do not have intrinsic kinase activity but associate with a protein kinase such as JAK2 in the cytoplasm. (ii) When the receptor binds a growth factor the cytoplasmic domains move closer together and the JAK2 molecules can activate each other by phosphorylation. (iii) The V617F JAK2 mutation allows the JAK protein to become activated even when no growth factor is bound.

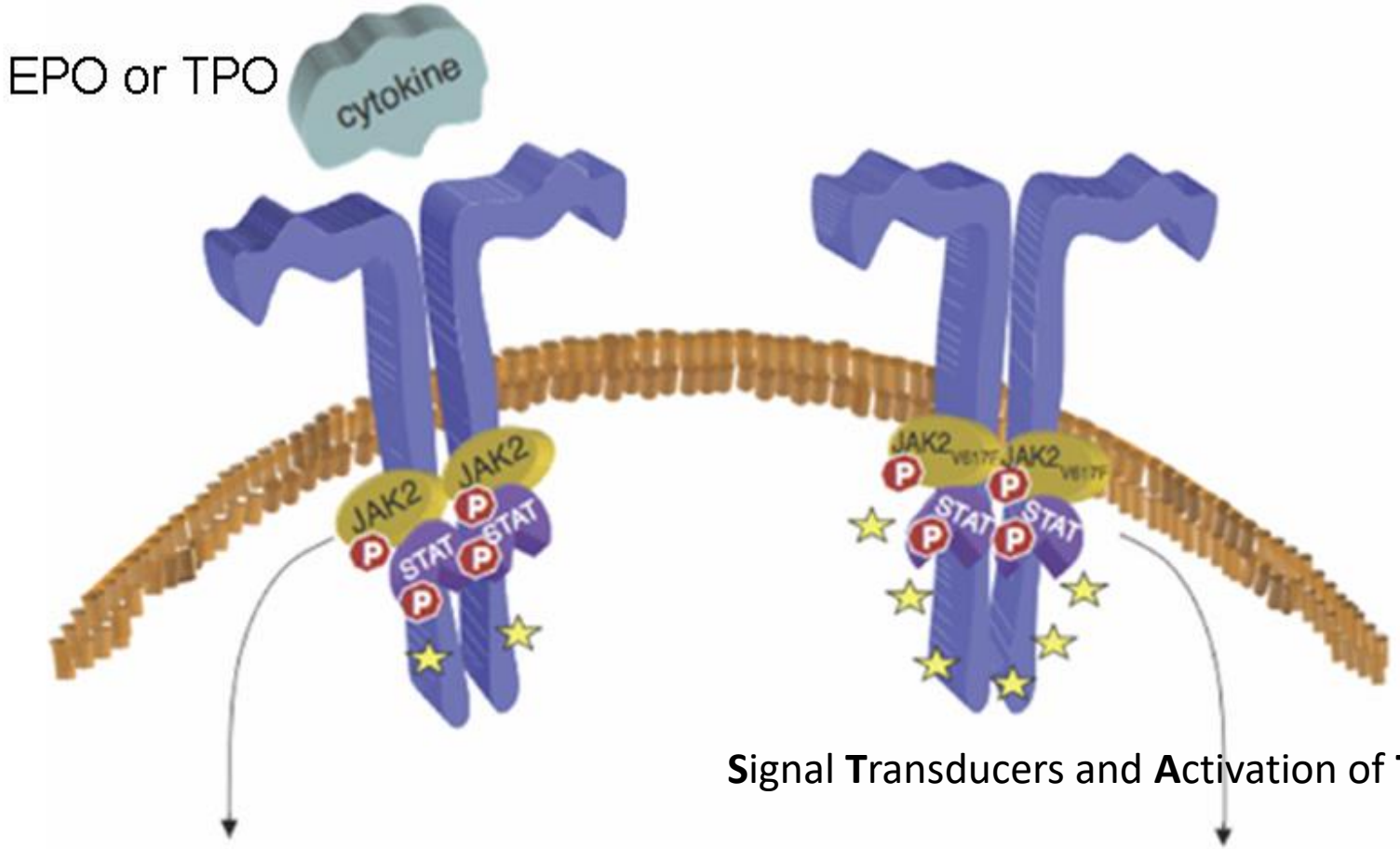
Hoffbrand AV, Moss PAH, Pettit JE. Essential haematology .5th ed. Oxford : Blackwell Publishing; 2006.p.231.

JAK 2 and haemopoiesis

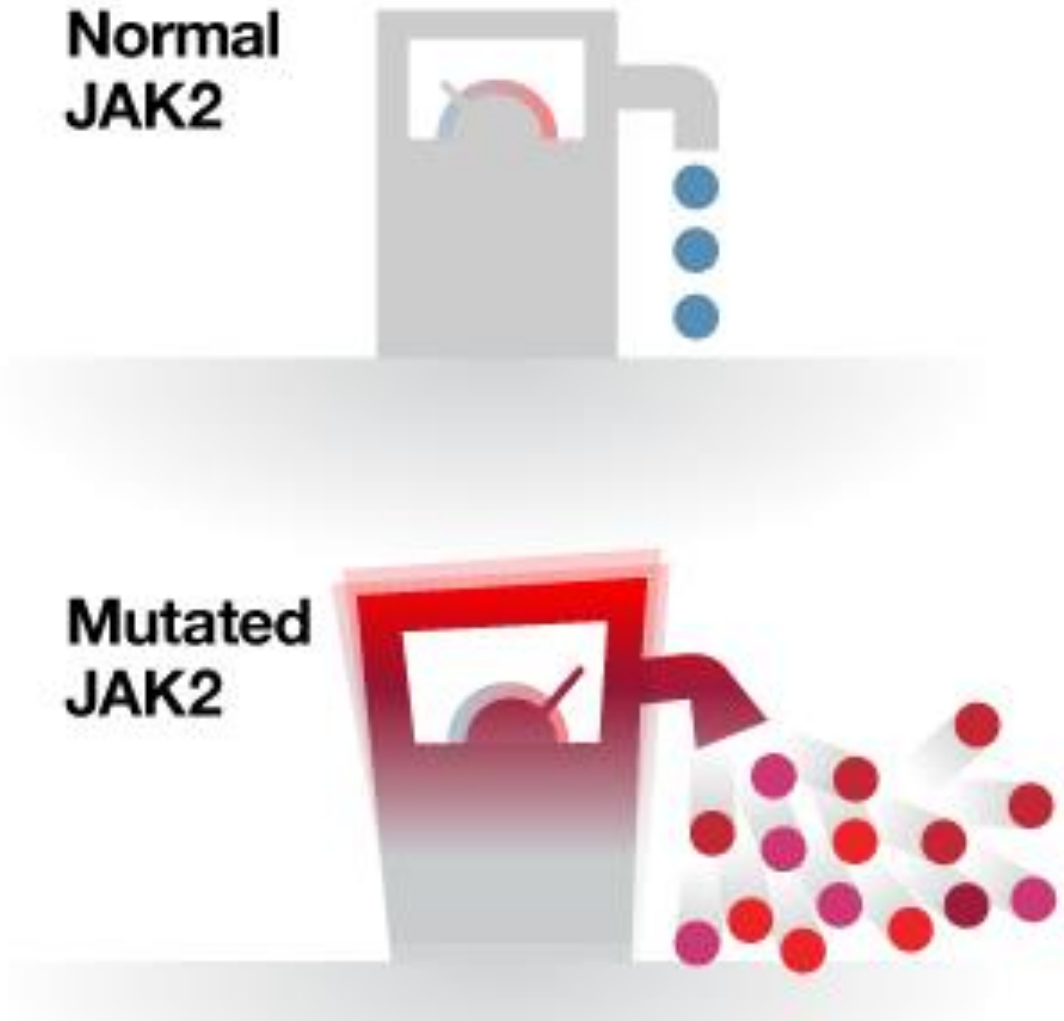
Cytokine-Erythropoietin, GCSF, GMCSF, Thrombopoietin,IL



Cytoplasmic thyrosine kinase



Signal **T**ransducers and **A**ctivation of **T**ranscription


Normal
JAK2
Mutated
JAK2

JAK 2 and MPN

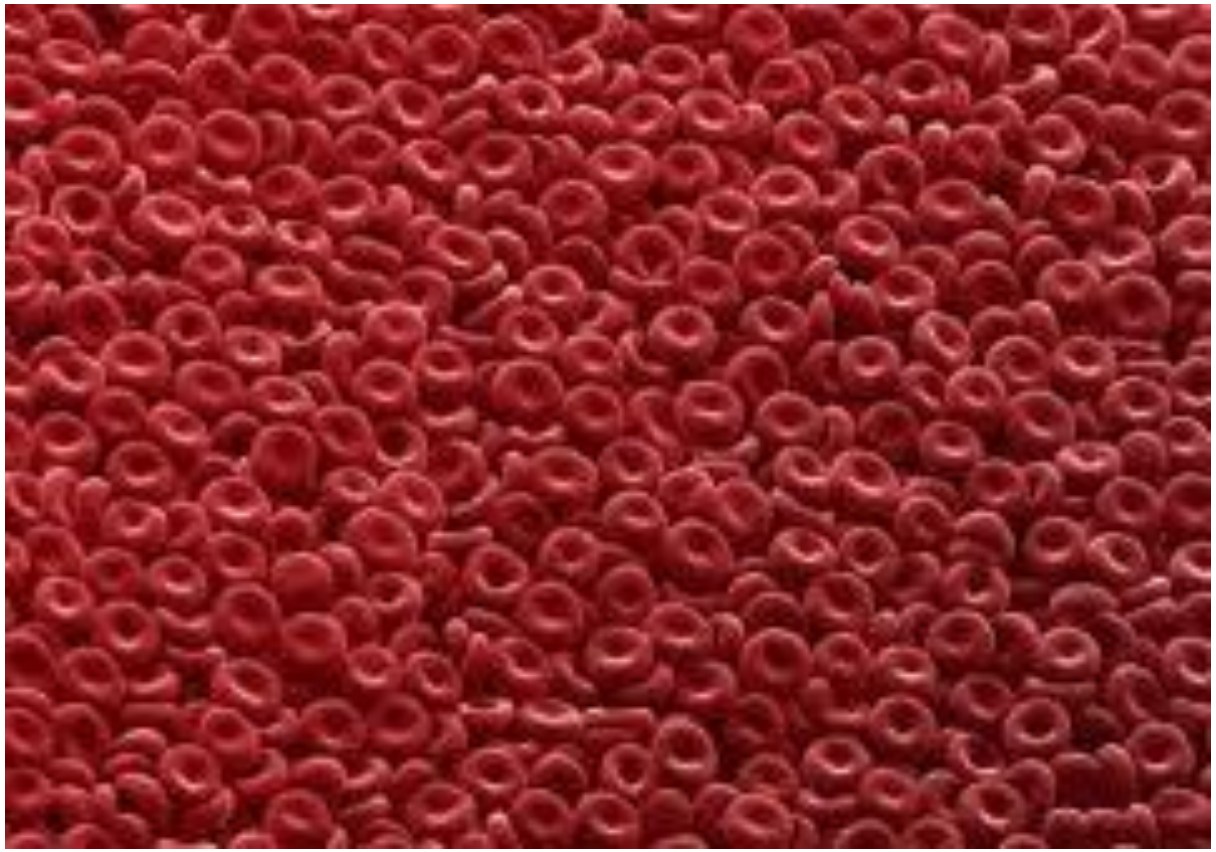
	Frequency
PV	95%
ET	50%
MF	50%

Other Genetic abnormalities

Table 15.1 Genetic mutations in myeloproliferative diseases and other myeloid neoplasms.

Disease	Gene mutations
Chronic myeloid leukaemia	*ABL1*
Polycythaemia vera	*JAK2*
Primary myelofibrosis	*JAK2, CALR, MPL*
Essential thrombocythaemia	*JAK2, CALR, MPL*
Mastocytosis	*KIT*
Myeloid neoplasm with eosinophilia	*PDGFRA, PDGFRB, FGFR1*

Polycythaemia



- Raised Hb
- What is next?
- ?True/spurious
- Repeat on a non tourniquet sample after good hydration
- Still elevated

	Male	Female
Hct	.49	.48
Hb	16.5g/dl	16.0g/dl

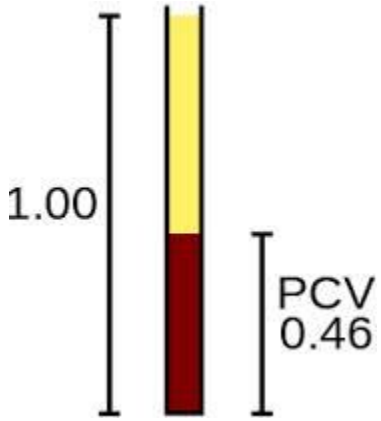
Polycythaemia

Absolute

- Raised RCM >125%

Relative

- RCM-nl
- Plasma volume-reduced



Absolute erythrocytosis

Primary

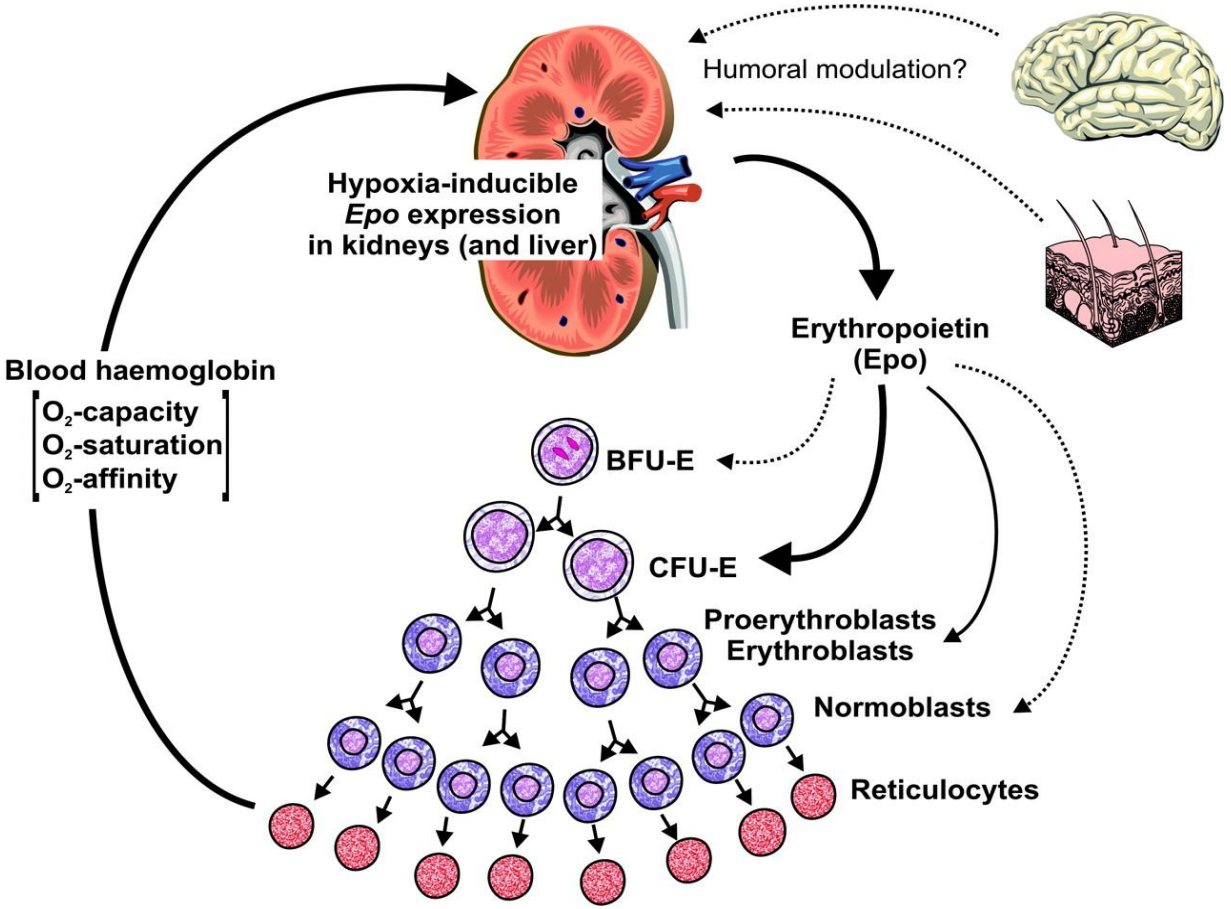
Congenital

Acquired(PV)

Secondary

Congenital

Acquired



Acquired absolute erythrocytosis- secondary causes

Erythropoietin mediated

- Central hypoxia
- Chronic Lung diseases
- R/L cardiac shunts
- CO poisoning
- Smoking
- Sleep apnoea
- High altitude

Acquired absolute erythrocytosis-secondary causes cont.

Local Hypoxia

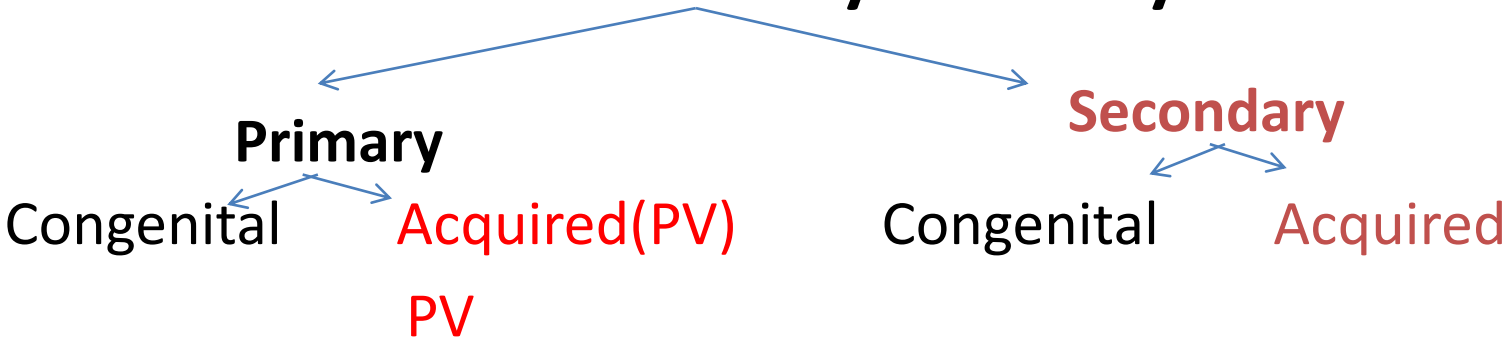
- Renal artery stenosis
- End stage renal diseases
- Hydronephrosis
- Renal cysts(PCKD)

Pathological erythropoietin secretion

- Tumors- Cerebellar haemangioblastoma,
  meningioma
  parathyroid tumors
  hepatocellular ca
  renal cell ca
  phaeochromocytoma
  uterine leiomyoma
- Drugs

Erythropoietin, Androgen

Absolute erythrocytosis



Polycythaemia vera

- Clonal stem cell disorder
- (Val 617 Phe)/V617F- JAK 2 mutation-95%
- Exon 12 mutation-some
- excessive production of all myeloid cell lines
- predominantly red cells - ↑ RCV

Clinical features

- Old age- 6 th decade
- CF → Hyperviscosity
  → Hypermetabolism

Clinical features

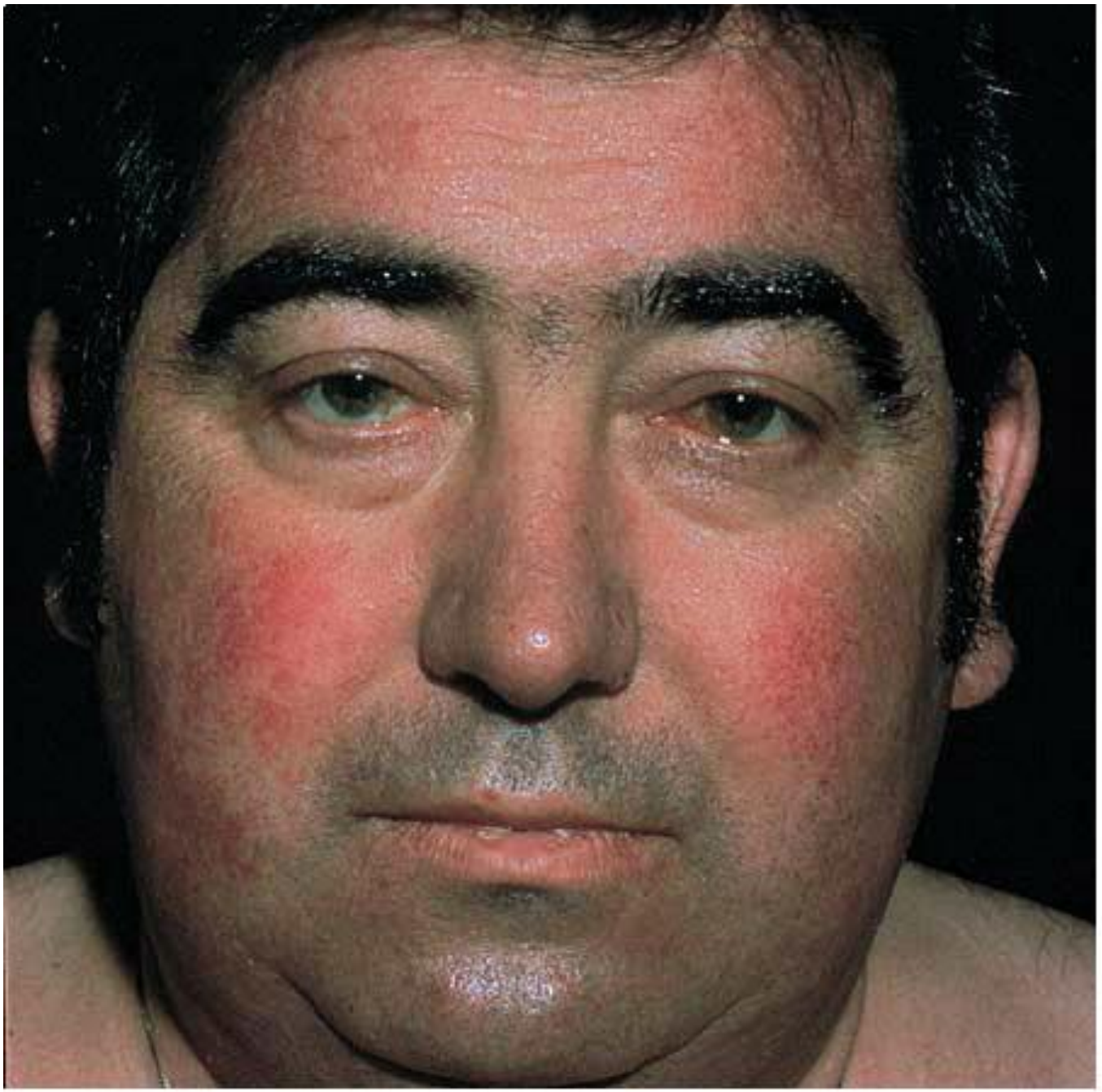
1. Headache, dyspnoea, blurred vision
2. Plethoric appearance, conjunctival suffusion
3. Night sweats
4. Pruritus
5. Splenomegaly in 75%
6. Haemorrhages
7. Thrombosis-arterial/venous
8. Hypertension
9. Gout

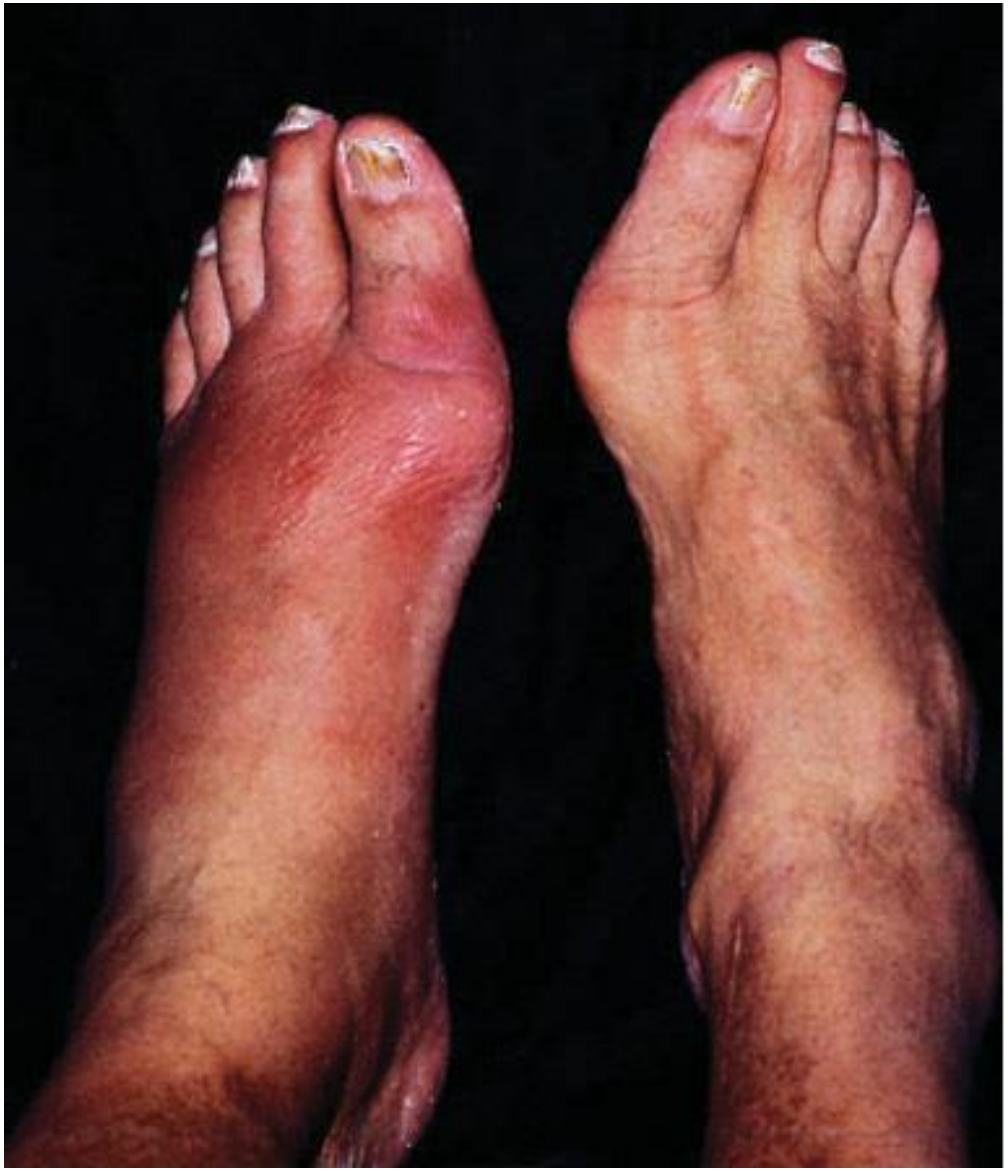
H/W

Explain the factors contributing to

a)Thrombosis

b) Bleeding in Polycythaemia Vera.



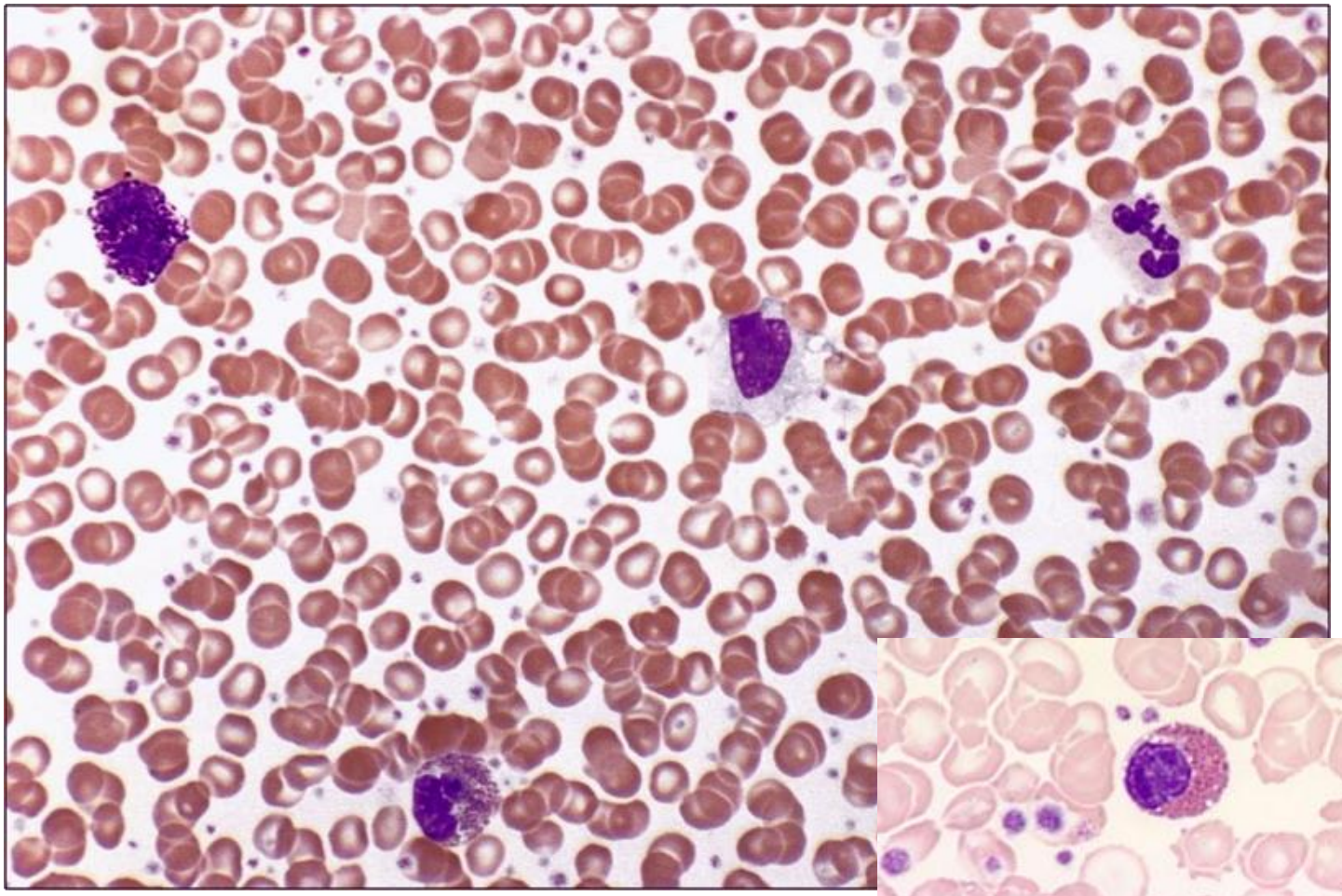


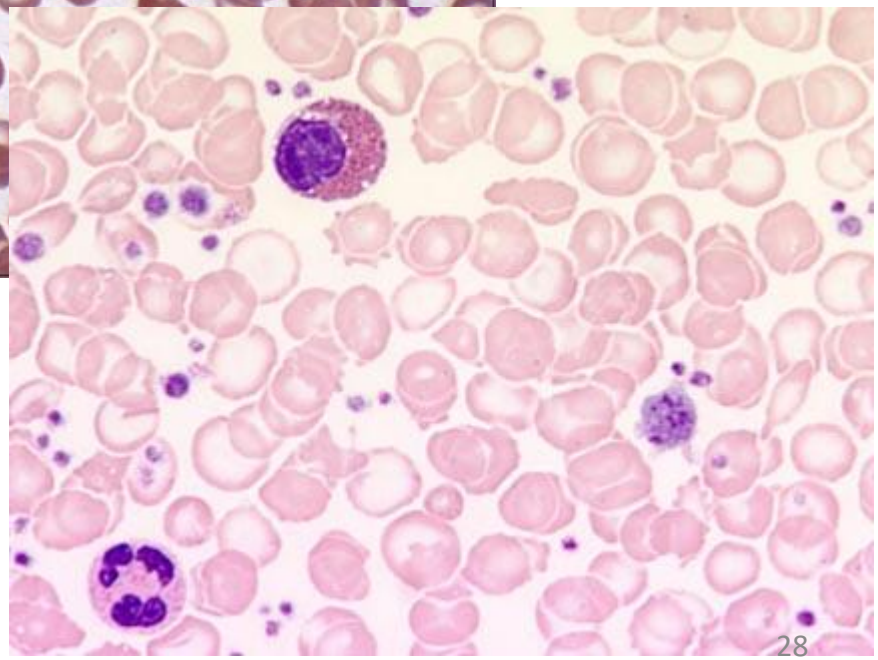
Lab findings

- FBC-Hb/Hct/RCC increased
- Neutrophil leucocytosis & thrombocytosis-50%
- Eosinophilia/ Basophilia
- BP-Crowded RBC
- BM-Hypercellular,panmyelosis
- Erythropoietin-Low
- Uric acid-Increased
- LDH-NL/Slightly raised

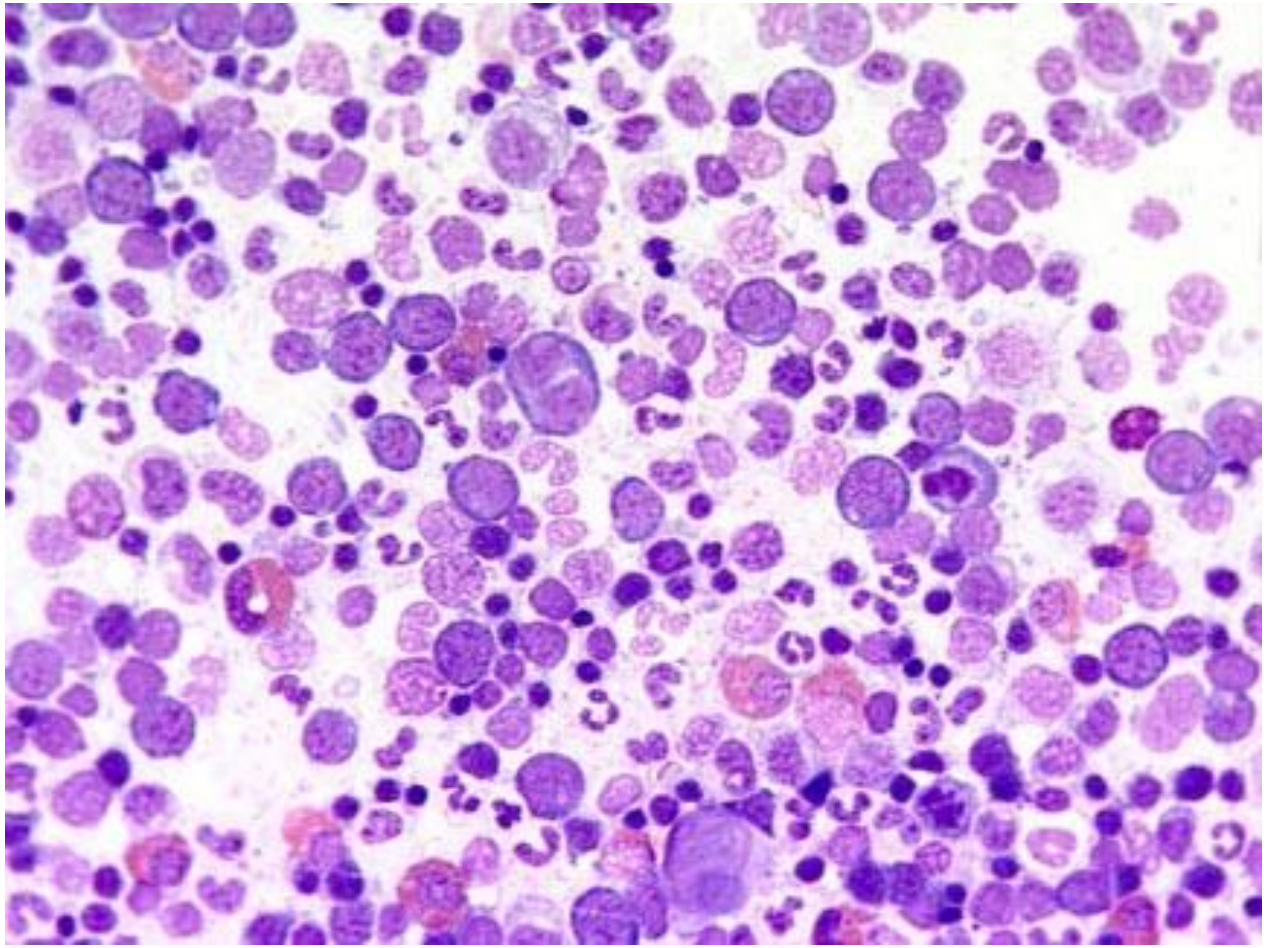
PRV - typical blood count

WBC x 10^9/L	**18.0**	**[4-11]**
Hb g/dl	20	[13-18]
HCt	0.62	[.42-.51]
MCV fl	**75**	[80-100]
Platelets x 10^9/L	**850**	**[150-450]**
Neuts x 10^9/L	14.6	[2-7.5]
Lymphs x 10^9/L	2.0	[1.5-4]
Monos x 10^9/L	0.8	[0.2-0.8]
Eos x 10^9/L	0.1	[0-0.7]
Basos x 10^9/L	**0.5**	**[0-0.1]**

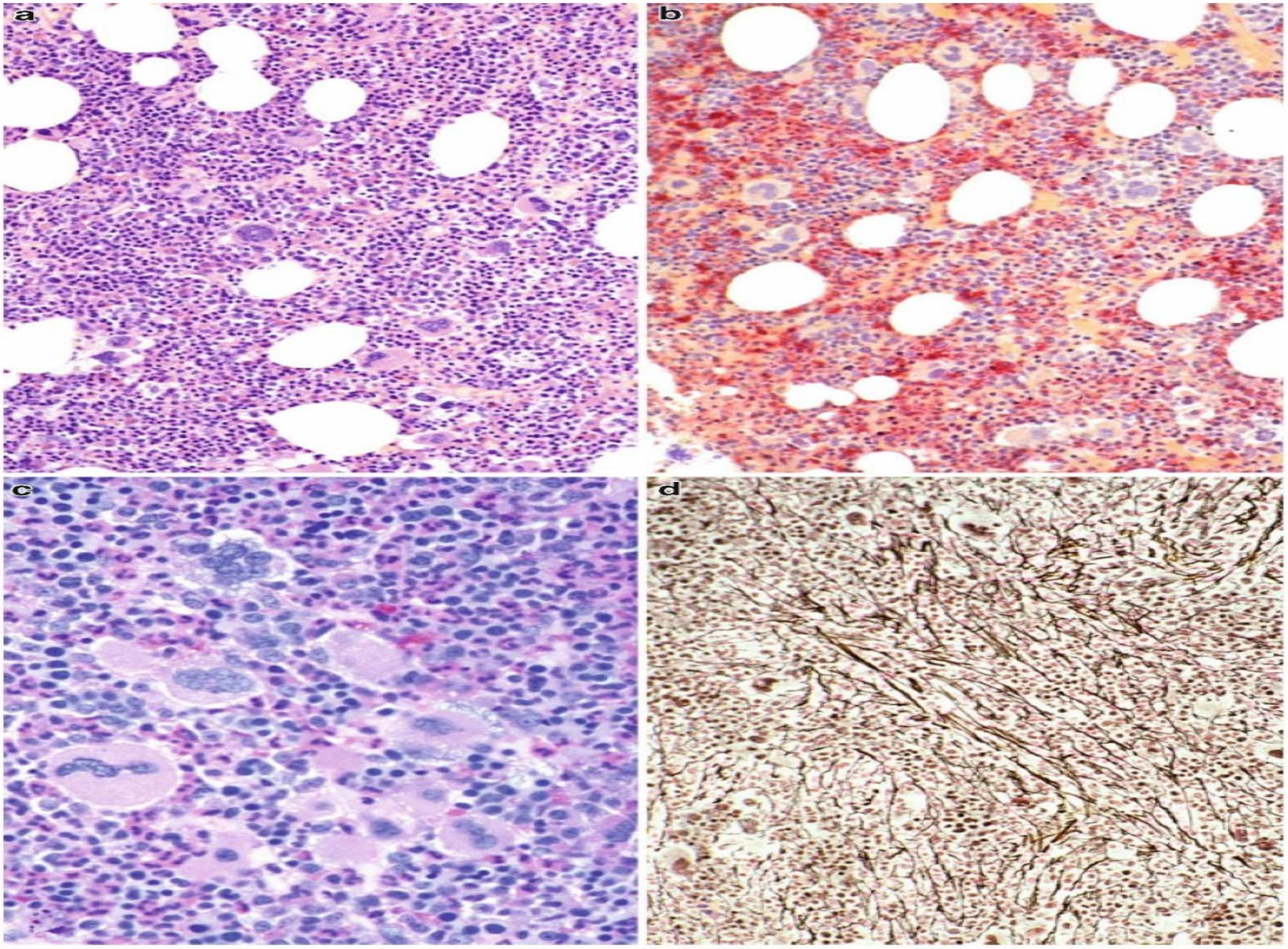




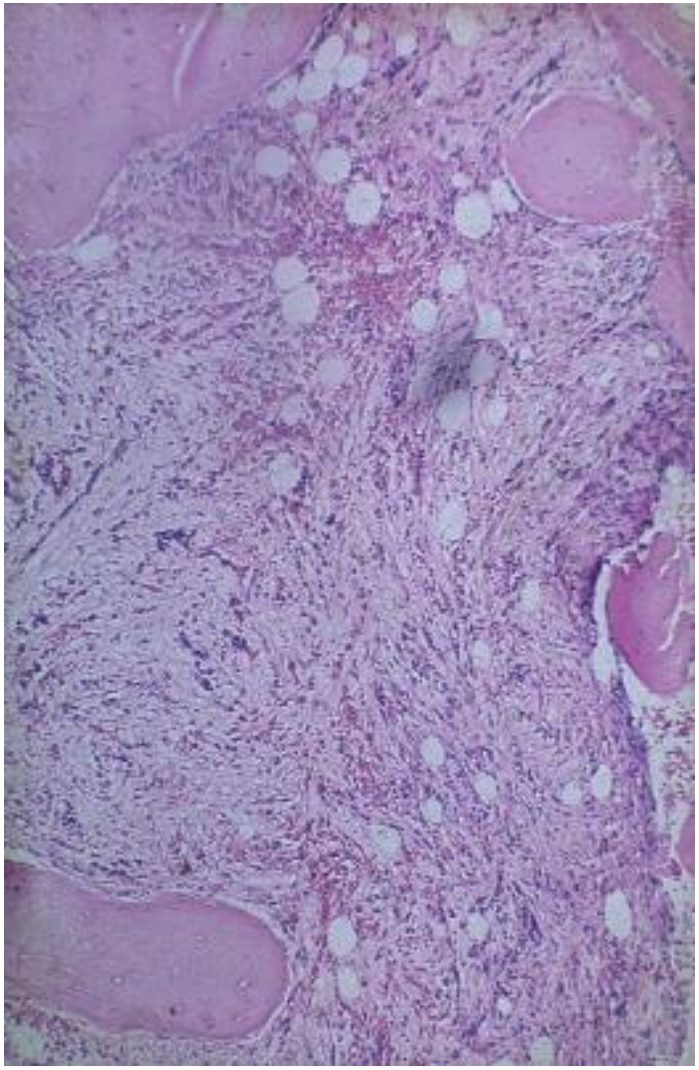
PV-BM

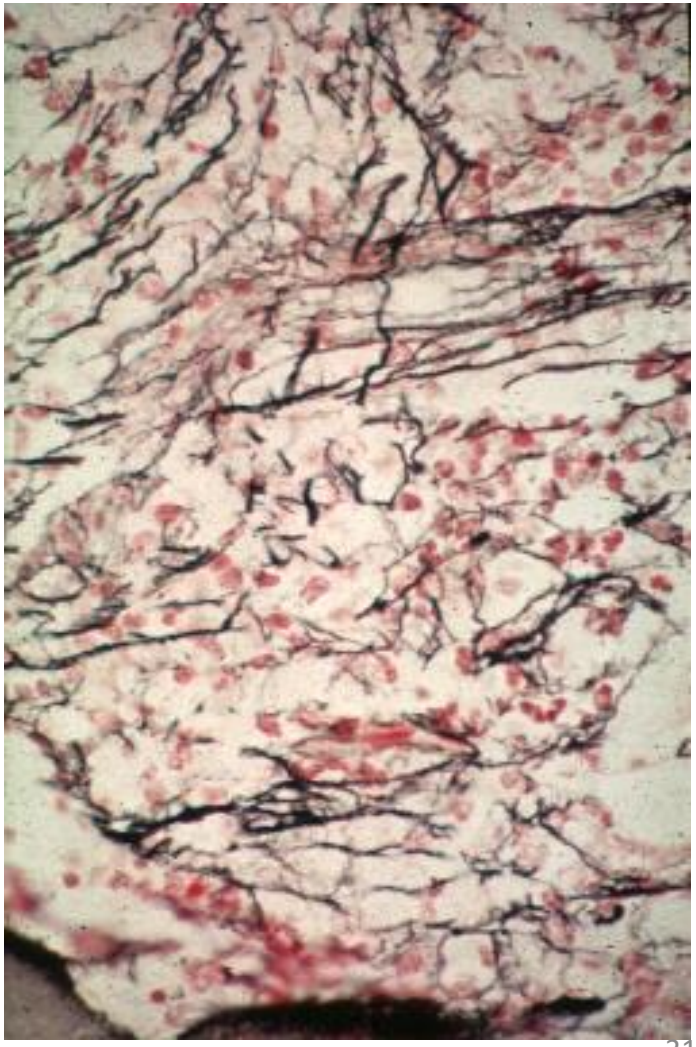


PV-BM



Post PV Myelofibrosis





Reticulin stain

- Based on BCSH guidelines/WHO criteria
- Take a very good history –
  - identify the secondary causes
  - assess the complications

WHO PV criteria

- **Major criteria**

1. Hemoglobin .16.5 g/dL in men
- Hemoglobin .16.0 g/dL in women

  or,
- Hematocrit .49% in men
- Hematocrit .48% in women

  or
- increased red cell mass (RCM)*

2. BM biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)

3. Presence of JAK2V617F or JAK2 exon 12mutation

- **Minor criterion**
- Subnormal serum erythropoietin level

Diagnosis of PV requires meeting either all 3 major criteria, or the first 2 major criteria and the minor criterion†

*More than 25% above mean normal predicted value.

Treatment

- Aim –maintain normal blood counts
- HCT<45%
- Platelets<400x10^9/l

Identify modifiable risk factors for thrombosis and treat

Ex : HPT/DM/Hypercholesterolaemia/Obesity

Treatment cont.

All patients:

- Venesection to maintain the Hct to <0·45
- Aspirin 75 mg/d unless contraindicated.

Treatment cont.

Cytoreduction should be considered if:

- poor tolerance of venesection
- symptomatic or progressive splenomegaly
- other evidence of disease progression,

e.g. weight loss, night sweats;

- thrombocytosis

Cytoreductive drugs

- Hydroxyurea
- Busulphan
- P 32
- Interferon

H/W-Read side effects

Jak 2 inhibitors

Choice of cytoreductive therapy,

- <40 years old:
  - 1 st line interferon
  - 2nd line hydroxycarbamide or anagrelide
- 40–75 years old:
  - 1 st line hydroxycarbamide
  - 2nd line interferon or anagrelide;
- >75 years old:
  - 1 st line hydroxycarbamide
  - 2nd line ^{32}P or intermittent low dose busulphan.

Course and prognosis

- Good prognosis when treated-10-16 y survival
- Complications –Thrombosis/bleeding
- Transformation to MF-30%
- Progression to acute leukaemmia-5%

Summary

- MPN –Clonal stem cell disorders with proliferation of 1 or more cell lines
- PV,ET,MF
- JAK 2 mutation
- Polycythaemia could be due to various reasons
- Secondary causes should be excluded
- Primary PV-Thrombosis & haemorrhage
- Treatment-maintain normal Hct by venesection or cytoreduction