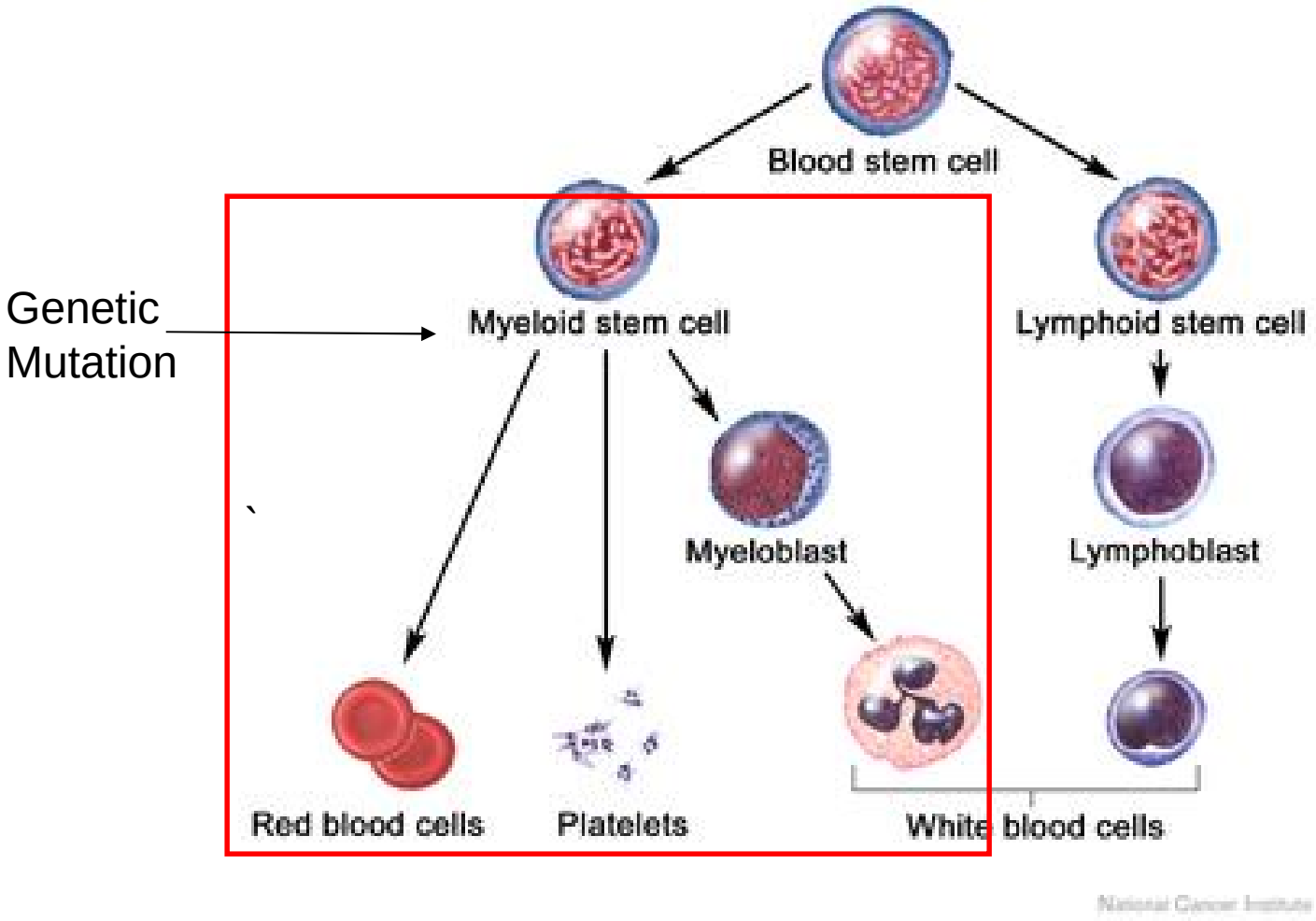
MYELOPROLIFERATIVE DISORDERS (MPD)

- The myeloproliferative disorders are a group of disorders characterized by *excess production of myeloid elements* (red blood cells, platelets, or certain white blood cells) in the bone marrow , which results in *marked splenomegaly and leukocytosis*.

§ The MPDs are predisposed to:

- ü Transformation to acute leukemia
- ü Myelofibrosis
- ü Thrombohemorrhagic complications

Hematopoietic Progenitors and MPNs



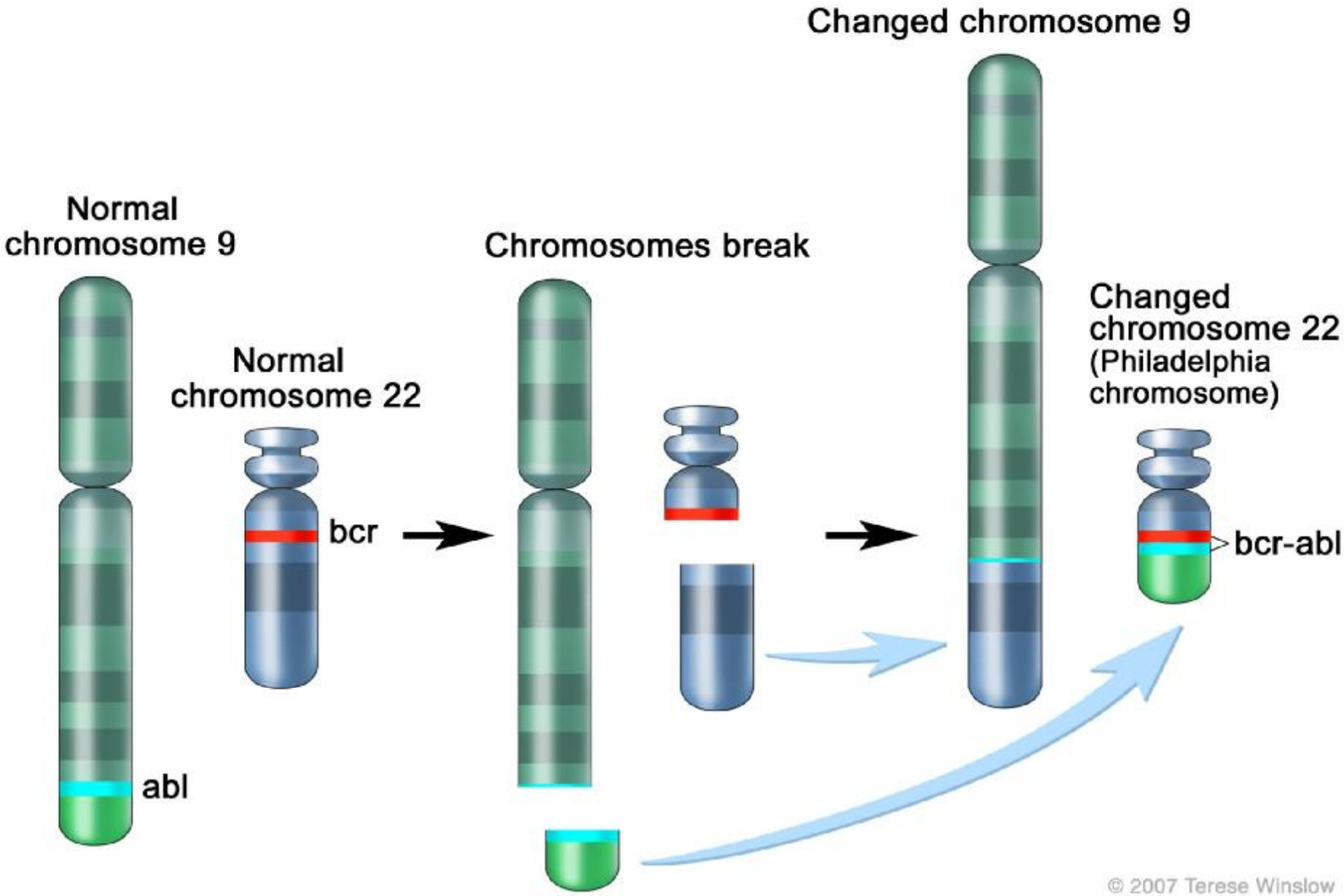
Classification

- Chronic myeloid leukemia (CML)
- Polycythemia vera (PV)
- Essential thrombocythemia (ET)
- Primary myelofibrosis (PMF)

CHRONIC MYELOID LEUKEMIA (CML)

Definition:

- CML is a MPD characterized by increased proliferation of the granulocytic cell line without the loss of their capacity to differentiate.
- A characteristic cytogenetic abnormality is *Philadelphia (Ph) chromosome positive in 100%.*



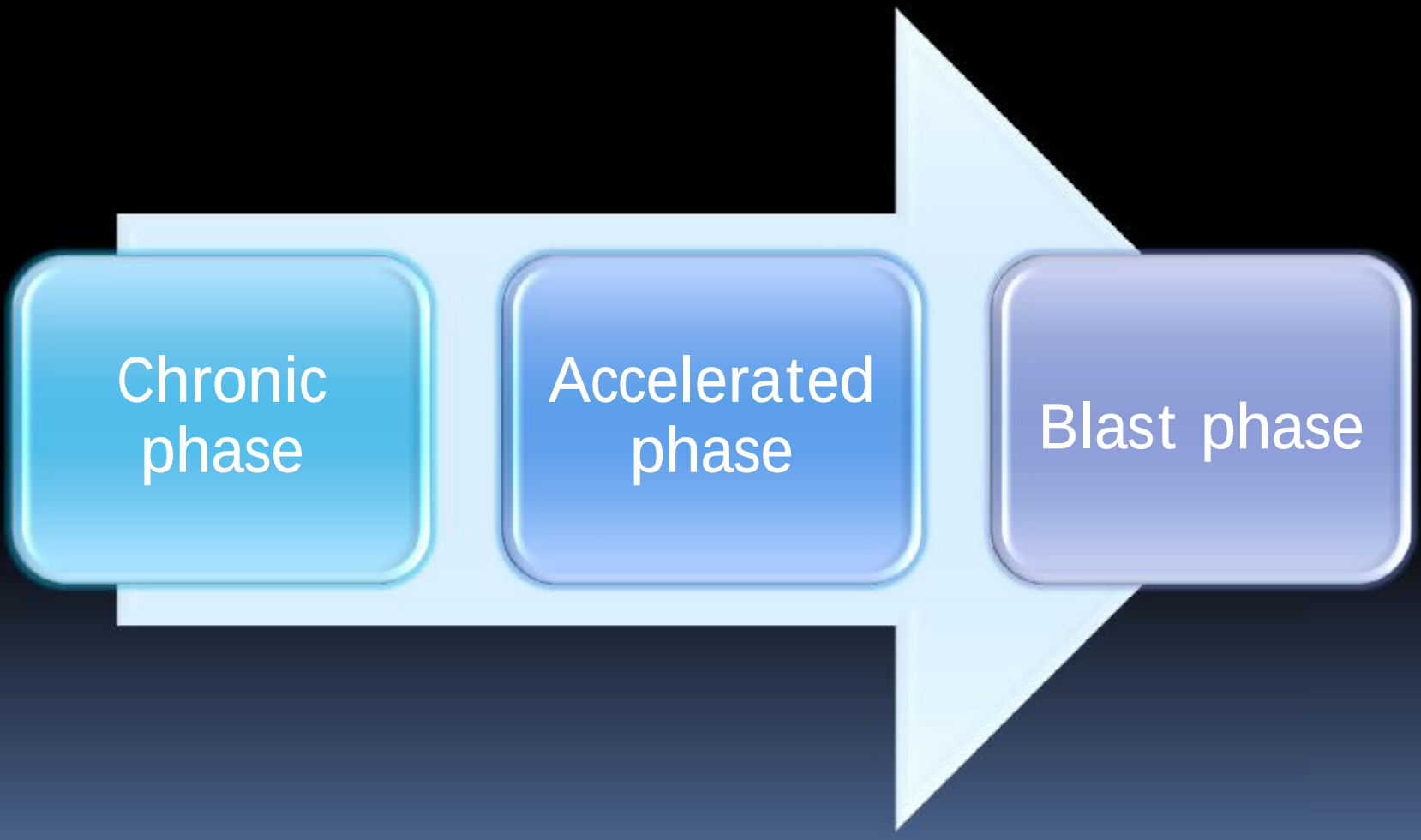
Philadelphia chromosome

- It is translocation between chromosomes 9 and 22 designated t(9:22).
- This translocation fuses the *abl* gene on chromosome 9 to the *bcr* gene on chromosome 22 and generates *bcr-abl oncogene*.
- The gene product found to *induce leukemia* in hematopoietic stem cells.

Epidemiology

- CML account 15-20% from all leukemia.
- The incidence of CML increases with age; the median age at diagnosis is 50-55 years.
- Males slightly affected higher than females.

Natural History



- Most (>90%) CML patients present in chronic phase (CP). *In chronic phase* the disease is responsive to treatment and is easily controlled.
- Without therapy, CML evolves from a chronic to an accelerated phase (AP) and eventually to blast crisis (BC).
- *Blast crisis*, in which the disease transforms into an acute leukemia, either myeloid (70%) or lymphoblastic (30%)

Clinical features

- About 40-50% of patients are *asymptomatic* until the disease is discovered accidentally.
- The *symptoms of CML*, are usually due to:
  - Anemia
  - Splenomegaly left upper quadrant fullness or pain
  - Fatigue, weight loss, malaise, and.

- Rarely, bleeding or thrombosis occurs.
- Other rare presentations include gouty arthritis, priapism, retinal hemorrhages, and upper gastrointestinal ulceration and bleeding.
- Symptoms of leukostasis

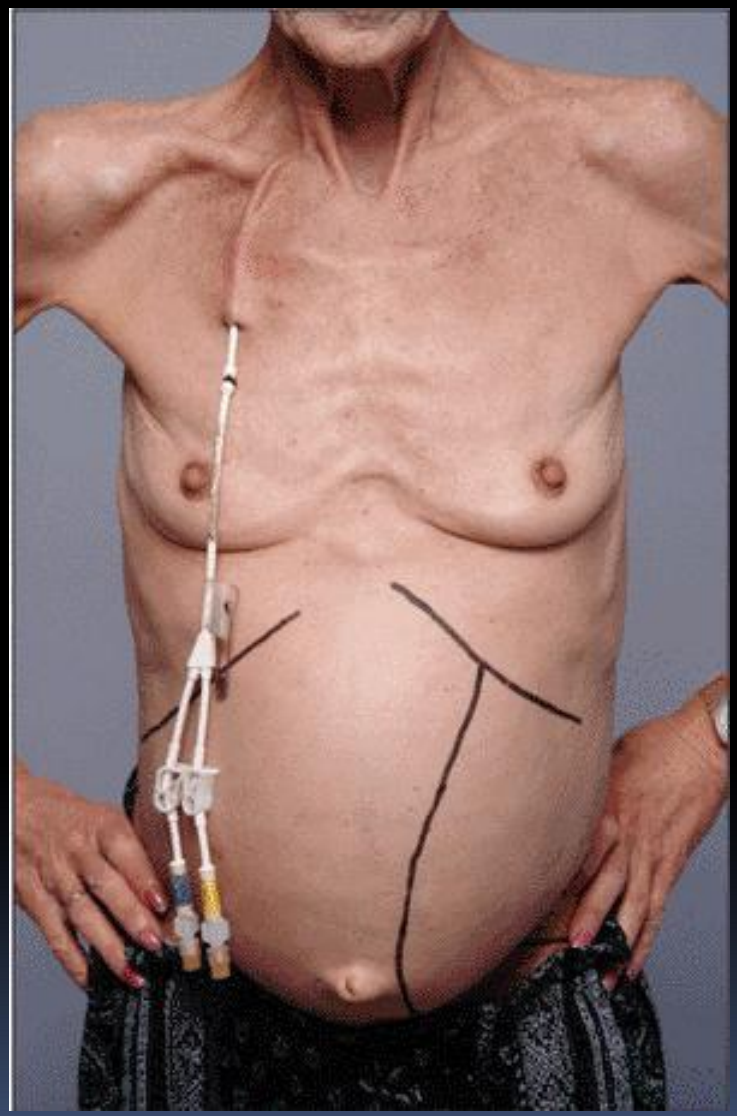
§ *The accelerated phase* is characterized by:

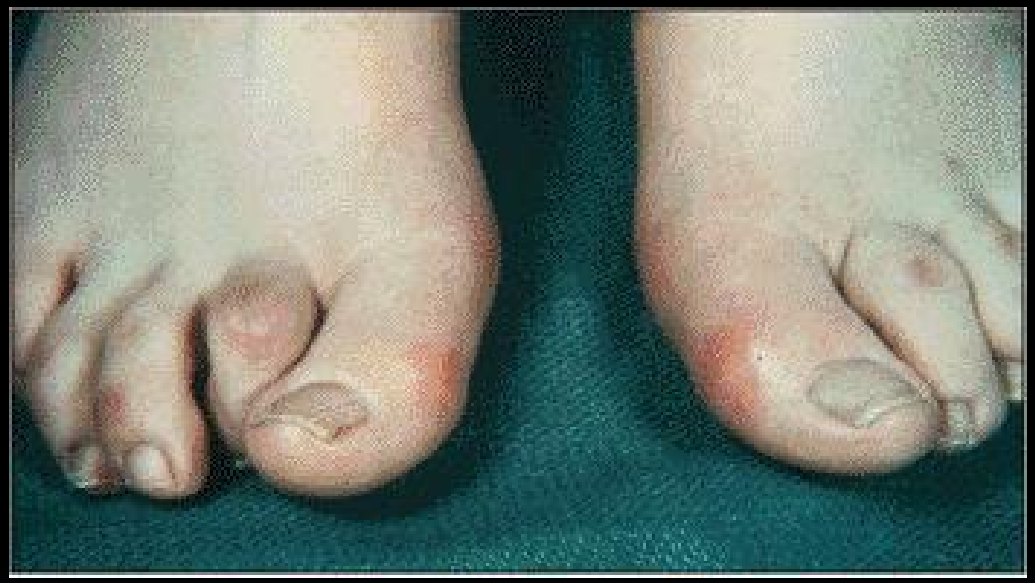
- ü Worsening anemia;
- ü Increasing splenomegaly or hepatomegaly;
- ü Infiltration of nodes, skin, bones, or other tissues; and
- ü Fever, malaise, and weight loss.

- *Blast crisis*, in which the disease transforms into an acute leukemia, and characterized by:
  - Fatigue
  - Bleeding
  - Infectious complication
  - Lymphadenopathy
  - CNS dysfunction

Signs

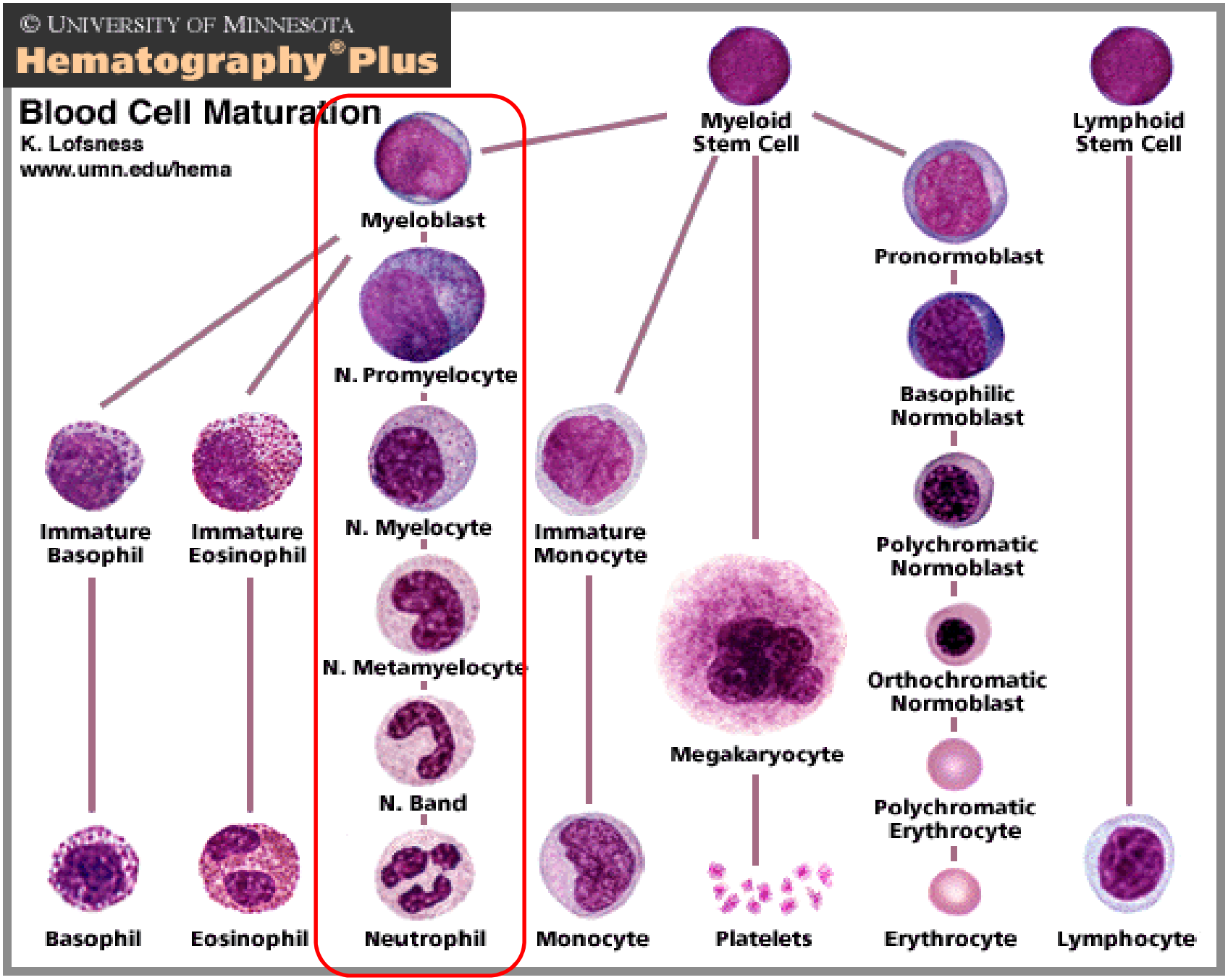
- Splenomegaly, the most consistent physical sign in CML, occurs in 90% of cases.
- Hepatomegaly is less common (10-20%) and usually minor.
- Lymphadenopathy is uncommon.

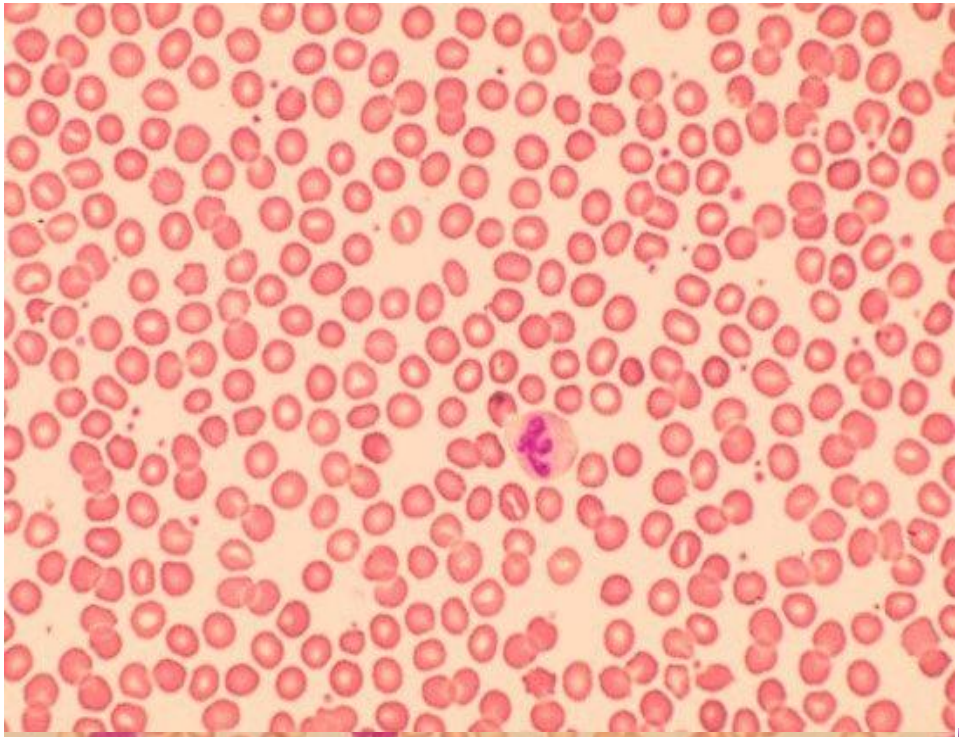


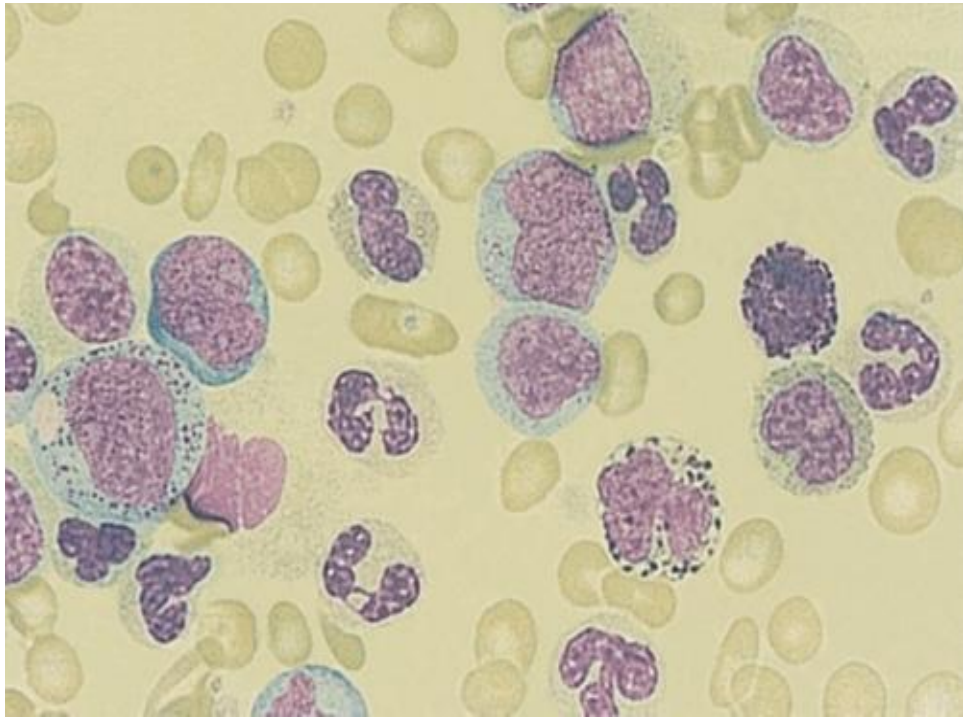


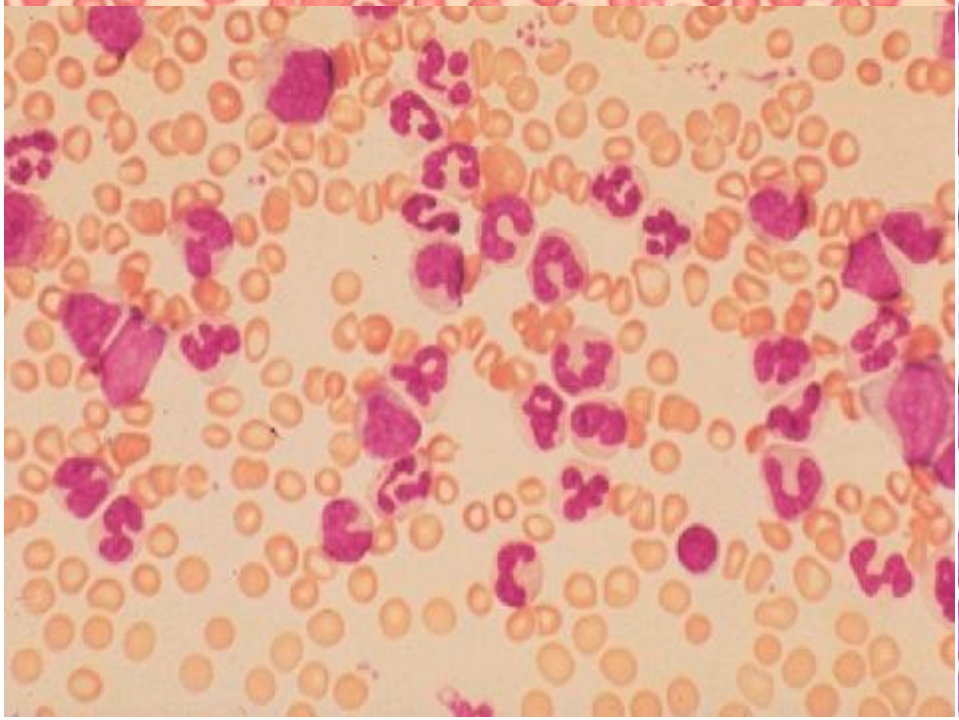
Diagnosis

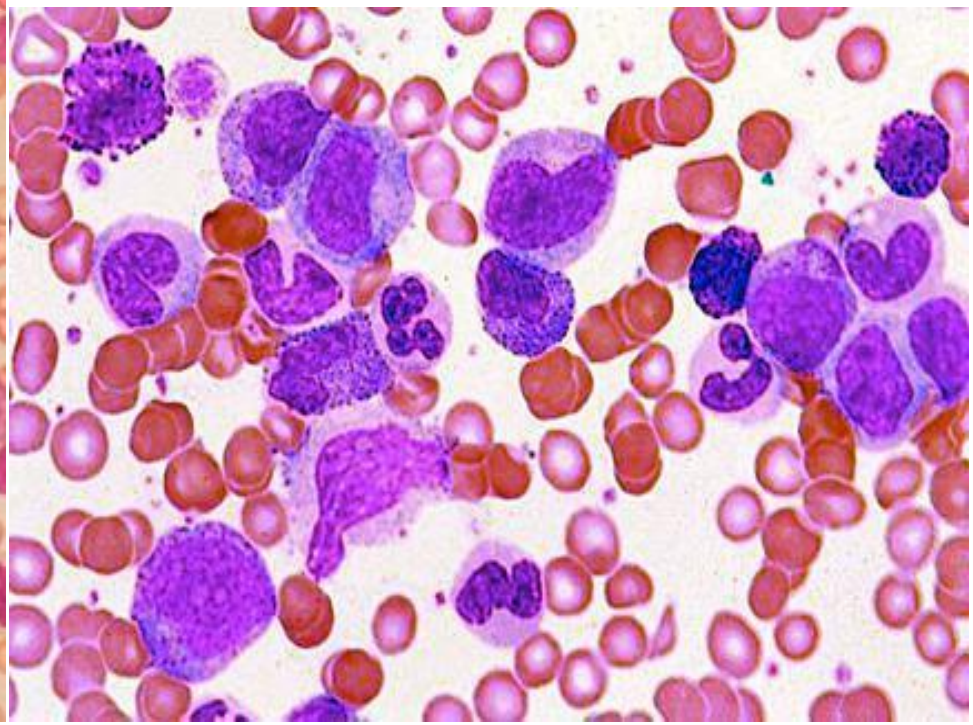
- Complete blood count:
  - Leukocytosis with a range 12-1000/microL.
  - The WBC differential typically shows all cells of the neutrophilic series, from myeloblasts to mature neutrophil.
  - Blasts typically account for < 10%
  - Absolute basophilia











Accelerated phase

- Blasts 10–19% in the peripheral blood and/or bone marrow
- Basophils ≥20% in the peripheral blood
- Persistent thrombocytopenia or thrombocytosis

Blast phase

- Blasts ≥20%.
- Extramedullary blast proliferation.

The following are features of chronic phase CML except:

- The WBC differential typically shows all cells of the neutrophilic series.
- Blasts count <10% of total WBC count
- Absolute basophilia (30%)
- 50% of patients are asymptomatic at time of diagnosis

Does BM examination is needed for diagnosis?

Bone marrow study

- The peripheral blood is useful diagnostically but BM material should be obtained for chromosome (Ph chromosome).
- At diagnosis, bone marrow cellularity is increased, with an increased myeloid-to-erythroid ratio.

Treatment

- For patients presenting in chronic phase CML, imatinib is first-line therapy.
- For those failing to respond or progress on imatinib:
  - Second-generation tyrosine kinase inhibitors such as dasatinib or nilotinib,
  - Allogeneic bone marrow transplantation (SCT)

- For patients presenting in accelerated phase, *imatinib* is indicated if the patient has not already received it.
- Patients progressing to advanced-phase disease on imatinib may respond to a *second-generation tyrosine kinase inhibitor*
- Patients with CML in the accelerated or blastic phase should consider *allogeneic SCT* as immediate, definitive therapy.

- *Interferon-alfa* was considered first-line treatment before imatinib was developed. Now a day it use in pregnant lady
- *Hydroxyurea* was previously used widely for initial control of disease, and is still useful in this context or in palliative situations.

Does we have to treat every patient with CML?