# Hematopathology

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OPTH 727



# Hematological Diseases that we will cover

- Lymphoid hyperplasia
- Bleeding disorders
  - Hemophilia
  - Von Willebrand's disease
  - Thrombocytopenia
- Anemia
  - Acquired
  - Inherited
    - Sickle cell anemia
    - Thalassemia

We covered these last year in IB class. We will not repeat this year.

- Blood dyscrasias
  - Neutropenia
  - Agranulocytosis
  - Cyclic neutropenia
  - Aplastic anemia
- Malignancies/myeloproliferative diseases
  - Leukemia
    - Myelodysplastic disorders
  - Hodgkin Lymphoma
  - Non-Hodgkin Lymphoma
    - Burkitt Lymphoma
  - Multiple myeloma
    - Plasmacytoma
  - Polycythemia Vera
  - Langerhans Cell Histiocytosis

# Hematologic disorders

- Who treats?
  - Hematologists/Oncologists

| | | |
|---|---|---|
| White Blood Cell Count | **15.2** K/UL | *4.0 - 10.0 K/UL* |
| Red Blood Cell Count | **3.58** MIL/UL | *4.50 - 5.90 MIL/UL* |
| Hemoglobin | **10.3** GM/DL | *13.6 - 17.0 GM/DL* |
| Hematocrit | **31.5** % | *42.0 - 50.0 %* |
| Mean Corpuscular Volume | **88.0** FL | *80.0 - 96.0 FL* |
| Mean Corpuscular Hemoglobin | **28.8** PG | *27.0 - 34.0 PG* |
| Mean Corpuscular Hgb Concen | **32.7** GM/DL | *31.0 - 36.0 GM/DL* |
| Red Cell Distribution List | **19.1** % | *11.5 - 14.5 %* |
| Platelet Count | **229** K/UL | *150 - 400 K/UL* |
| Mean Platelet Volume | **9.4** FL | *9.6 - 12.8 FL* |
| Neutrophils (Auto Diff %) | **68.5** % | *40.0 - 75.0 %* |
| Lymphocytes (Auto Diff%) | **15.3** % | *20.0 - 48.0 %* |
| Monocytes (Auto Diff%) | **9.7** % | *4.0 - 12.0 %* |
| Eosinophils (Auto Diff %) | **4.9** % | *0 - 6.0 %* |
| Basophils (Auto Diff%) | **1.6** % | *0 - 1.0 %* |
| Neutrophils (Auto Diff#) | **10.41** K/UL | *1.5 - 6.6 K/UL* |

- Tools of the trade
  - Blood testing
    - Blood cell counts (CBC)
    - Many, many more advanced tests
  - Bone marrow biopsies
  - Clinical/Radiographic examination
    - Splenomegaly
    - History

# Head and Neck Exam: What is going on here?

Question? Why palpate head and neck during your examinations?

- Reason #1:  Look for enlarged lymph nodes
  - Regular sized lymph nodes not palpable
  - Lymphadenopathy = enlarged nodes
    - Sometimes enlarged nodes = very bad things (i.e. metastatic disease or primary cancers)

- Reason #2:  Look for other swellings/asymmetries:  any number of pathologic entities may present in the head and neck area: epidermoid cysts, lipomas, developmental cysts etc.

# Enlarged lymph nodes usually a response to infection (lymphoid hyperplasia).

**Acutely inflamed nodes**

- Soft
- Movable
- Tender (pain on palpation)
- Usually resolve

**Chronically inflamed nodes**

- Rubbery/firm
- Non-movable
- Non-tender
- Mimic malignancy!
  - Lymphomas
  - Metastatic disease

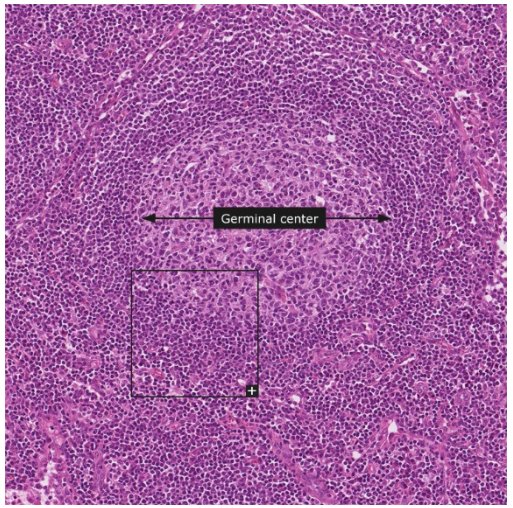
Not on exam

Q: What is done about a persistently enlarged lymph node?
A: Evaluate for malignancy.

- Clinical examination
  - Follow up (does the lymph node stay enlarged or does it resolve?)
  - Symptomatic (lymphomas often present with fever/malaise)
- Imaging-
  - From imaging, may be able to discern cancerous behavior (radiographic borders)
  - Imaging modalities
    - Ultrasound
    - CT
    - PET
- Biopsy
  - Techniques?
    - Fine needle aspiration, core biopsy or excisional biopsy
  - Lymphoid hyperplasia
    - Histopathology will show “normal looking” lymphoid tissue, germinal centers, etc.

# Lymphoid hyperplasia -

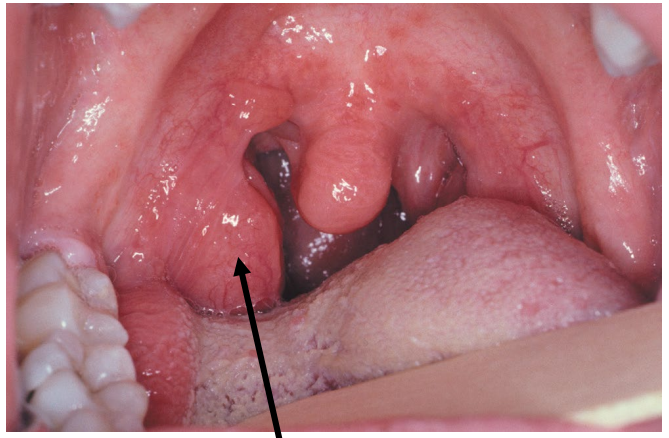
- Q:  What is it?
  - A:  Proliferation of lymphoid tissue in response to insult (usually infection)
  - Remember… Hyperplasia IS NOT CANCER.  IT IS NOT A NEOPLASM.
- Q. Where do we see lymphoid hyperplasia?
  - Anywhere there is a collection of lymphoid tissue…  tonsils, spleen, lymph nodes, MALT (mucosa associated lymphoid tissue)



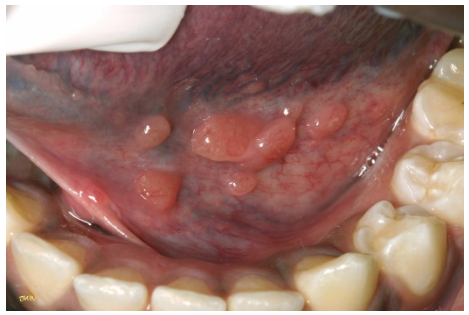

Histopathology will show “normal looking” lymphoid tissue, germinal centers, etc.

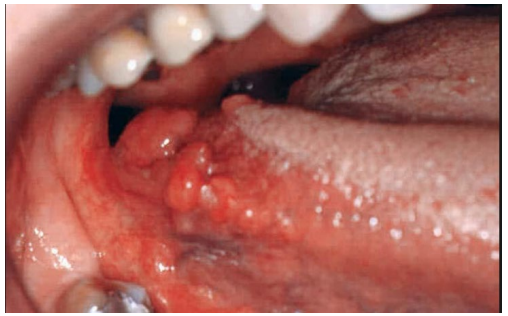
# Where do we see lymphoid hyperplasia intraorally?

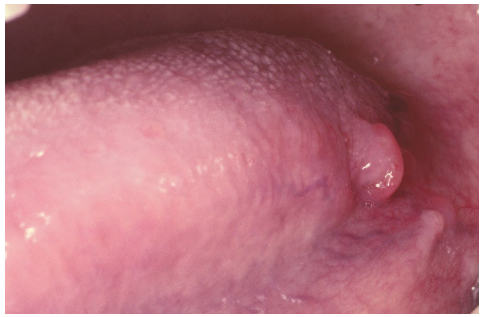
- Waldeyer's ring- lymphoid tissue in oropharynx
  - Tonsils- filled with lymphoid tissue
    - Pharyngeal, palatine, lingual,
  - Soft palate
- Where else?
  - Floor of mouth
  - Posteriolateral tongue

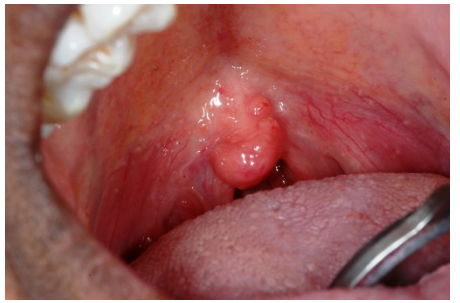


Enlarged tonsil









# Examples of hematopoetic neoplasia (we have established that lymphoid hyperplasia is not neoplastic, right?!?!)

- Leukemia
- Lymphoma
  - Hodgkins
  - Non-Hodgkins
- Multiple myeloma
- Myelodysplasia
- Langerhans cell histiocytosis
- Polycythemia vera

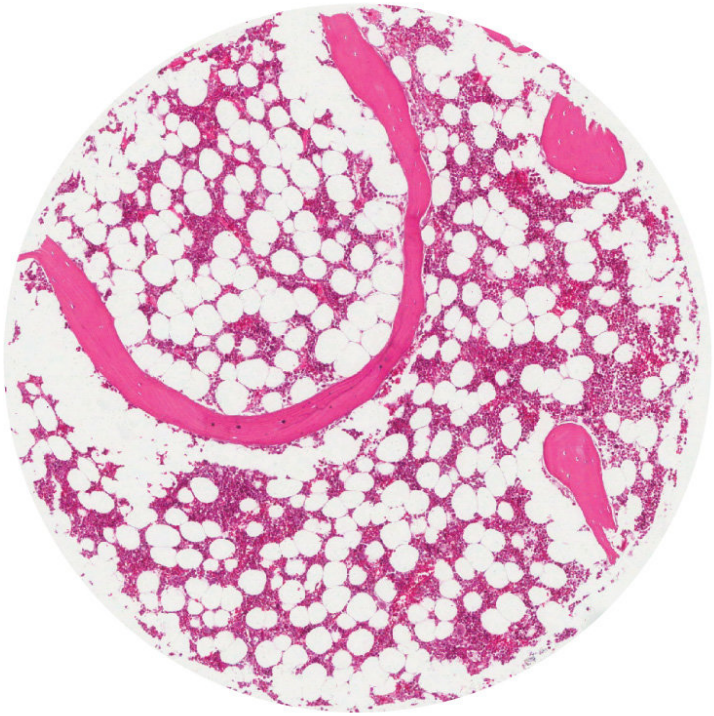
These **may** be highly aggressive

# Leukemia – malignancy of bone marrow stem cells

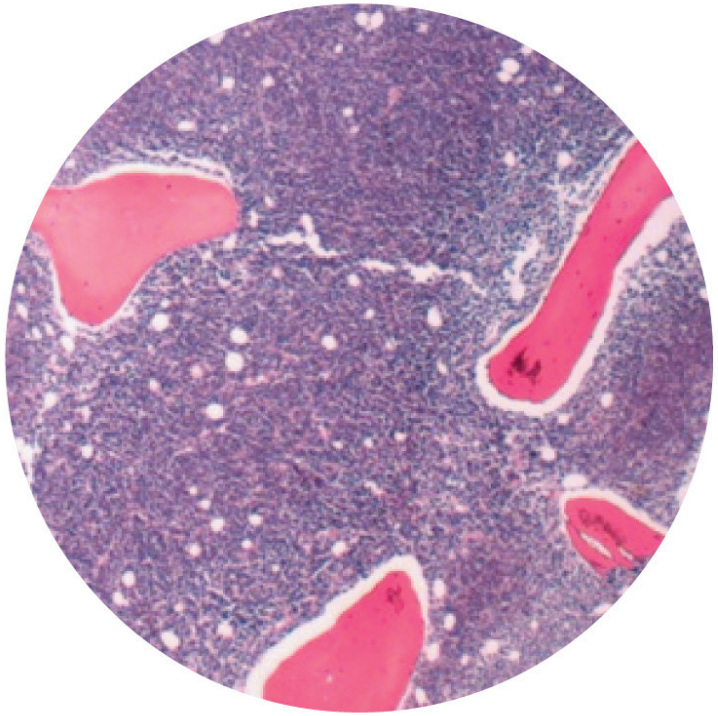
- Uncontrollable cell division inside bone marrow
  - Non-functional immune cells created
  - Normal blood cells are displaced by malignant cells
    - This may lead to:
      - Anemia due to fewer red blood cells
      - Increased infections due to fewer white blood cells
      - Reduced clotting ability due to fewer platelets (thrombocytopenia)
- Treated with chemotherapy
  - Chemotherapy may further diminish blood counts
  - Bone marrow transplant can replenish bone marrow stem cells destroyed by chemotherapy.
- Cells may spill out in circulation – and produce tumor like masses –
  - In oral cavity, gingival enlargement can be seen (see next slides)

# Leukemia- proliferating cells crowd out normal marrow.

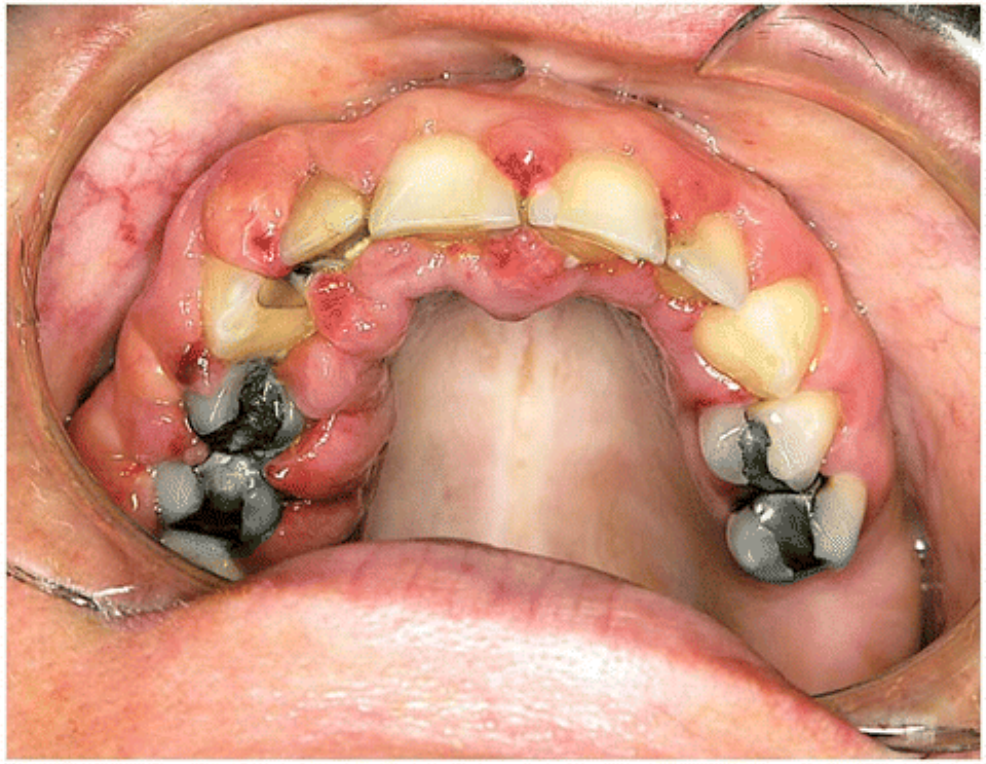
Healthy
bone marrow

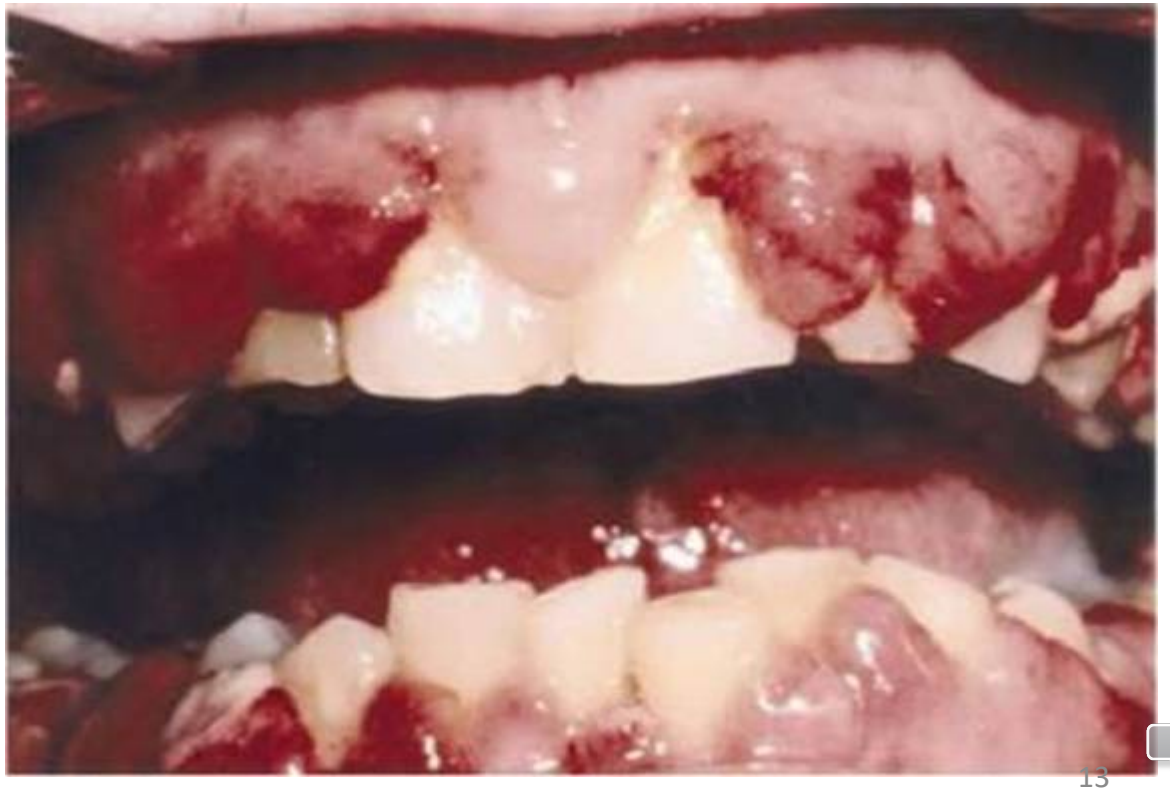


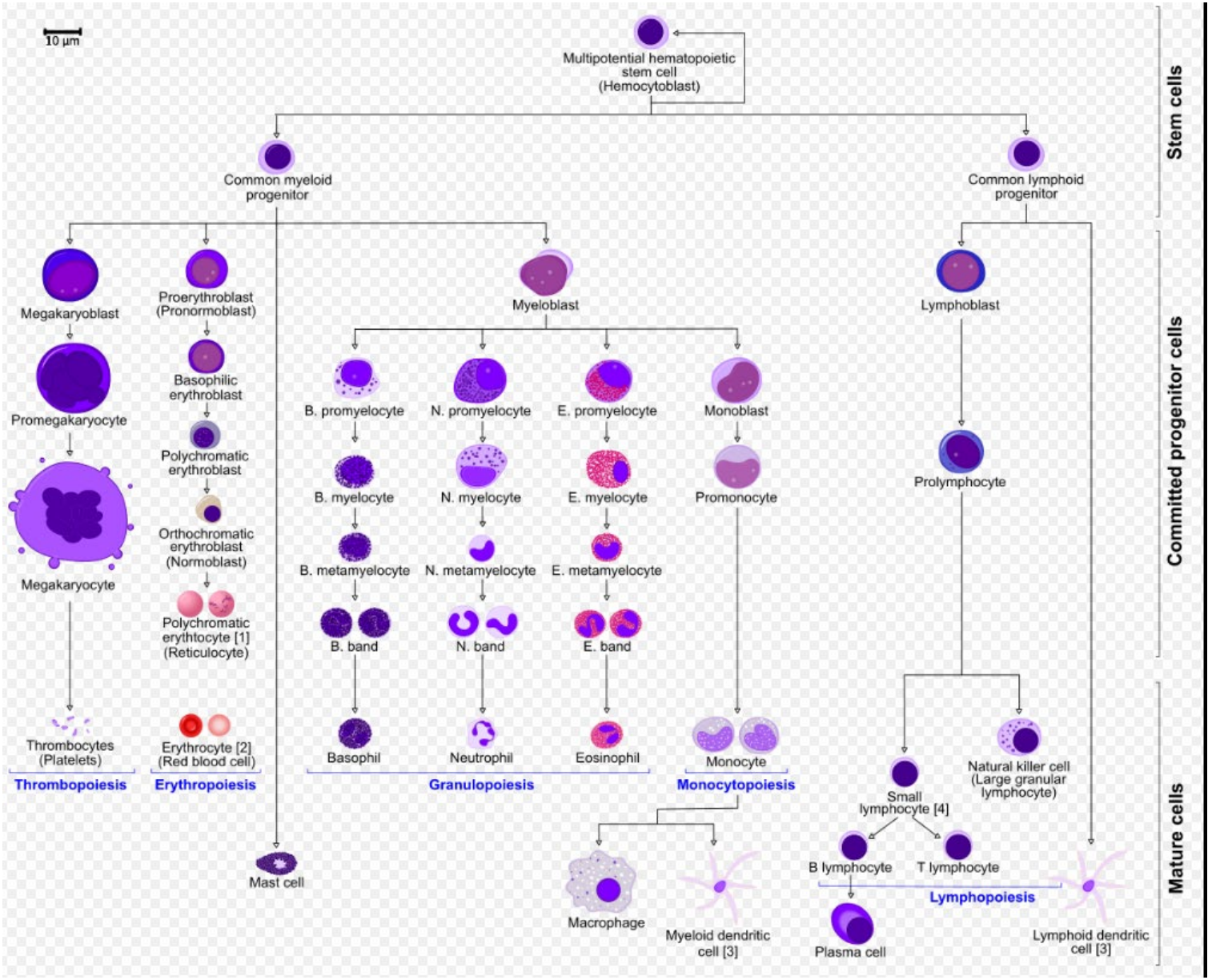
Leukemia



Oral manifestations of leukemia- Cells may spill out in circulation – and produce tumor like masses – In oral cavity, gingival enlargement is seen.





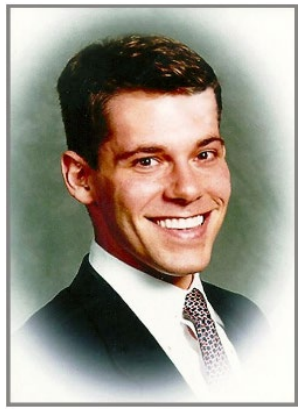

10 µm
Multipotential hematopoietic stem cell (Hemocytoblast)
Common myeloid progenitor
Common lymphoid progenitor
Megakaryoblast
Promegakaryocyte
Megakaryocyte
Thrombocytes (Platelets)
Thrombopoiesis
Proerythroblast (Pronormoblast)
Basophilic erythroblast
Polychromatic erythroblast
Orthochromatic erythroblast (Normoblast)
Polychromatic erythtocyte [1] (Reticulocyte)
Erythrocyte [2] (Red blood cell)
Erythropoiesis
Mast cell
Myeloblast
B. promyelocyte
N. promyelocyte
E. promyelocyte
Monoblast
B. myelocyte
N. myelocyte
E. myelocyte
Promonocyte
B. metamyelocyte
N. metamyelocyte
E. metamyelocyte
B. band
N. band
E. band
Basophil
Neutrophil
Eosinophil
Granulopoiesis
Monocyte
Monocytopoiesis
Macrophage
Myeloid dendritic cell [3]
Lymphoblast
Prolymphocyte
Small lymphocyte [4]
Natural killer cell (Large granular lymphocyte)
B lymphocyte
T lymphocyte
Lymphopoiesis
Plasma cell
Lymphoid dendritic cell [3]
Stem cells
Committed progenitor cells
Mature cells

# Four main types of leukemia

- Classified based on clinical behavior and histiogenesis
  - Acute vs chronic
    - Acute leukemias are usually aggressive while chronic forms are more indolent
  - Lymphocytic vs. myelogenous (myelocytic, myeloid)

- The four types are:
  - Acute lymphocytic leukemia
    - Mostly kids… one of the most common childhood malignancies
  - Acute myelogenous leukemia
  - Chronic lymphocytic leukemia
    - Most common type of leukemia overall – affects mostly adults
  - Chronic myelogenous leukemia
    - Associated with Philadelphia chromosome (see next slide) – translocation of genetic material between chromosome 9 and 22 that produces oncogene

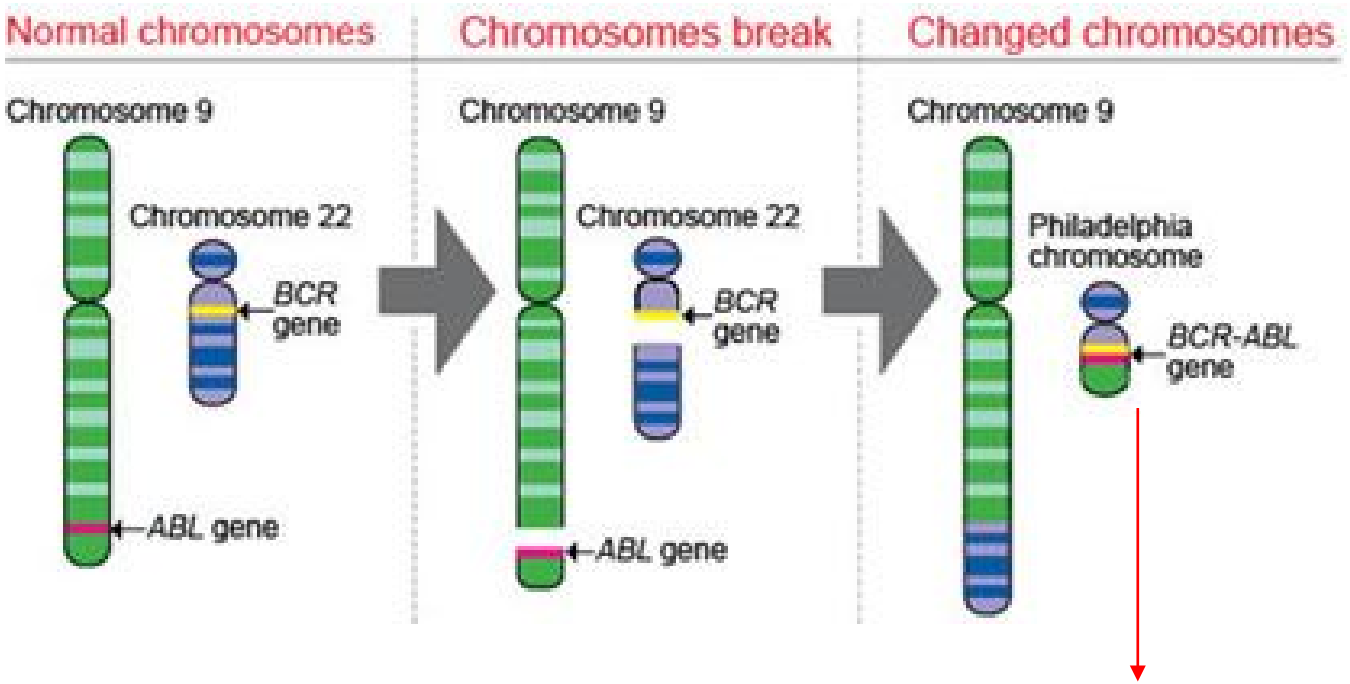
- Myelodysplasia – not leukemia perse, but considered to be a low-grade malignancy
  - abnormal growth/maturation in bone marrow



Richard Lehman, DMD

1973 - 2004

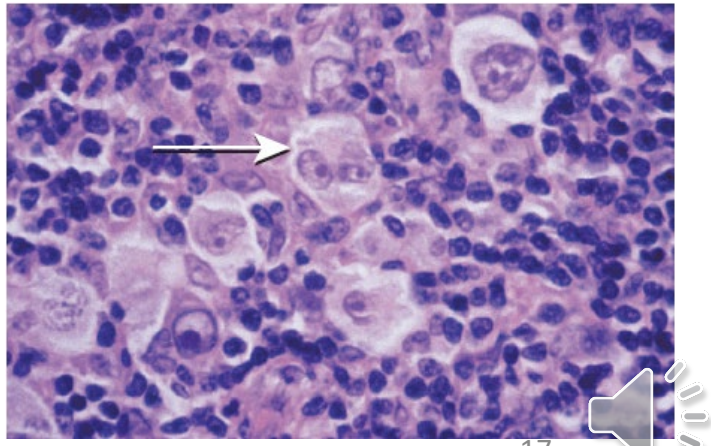
Philadelphia Chromosome- translocation of genetic material  from chromosome 9 to 22.



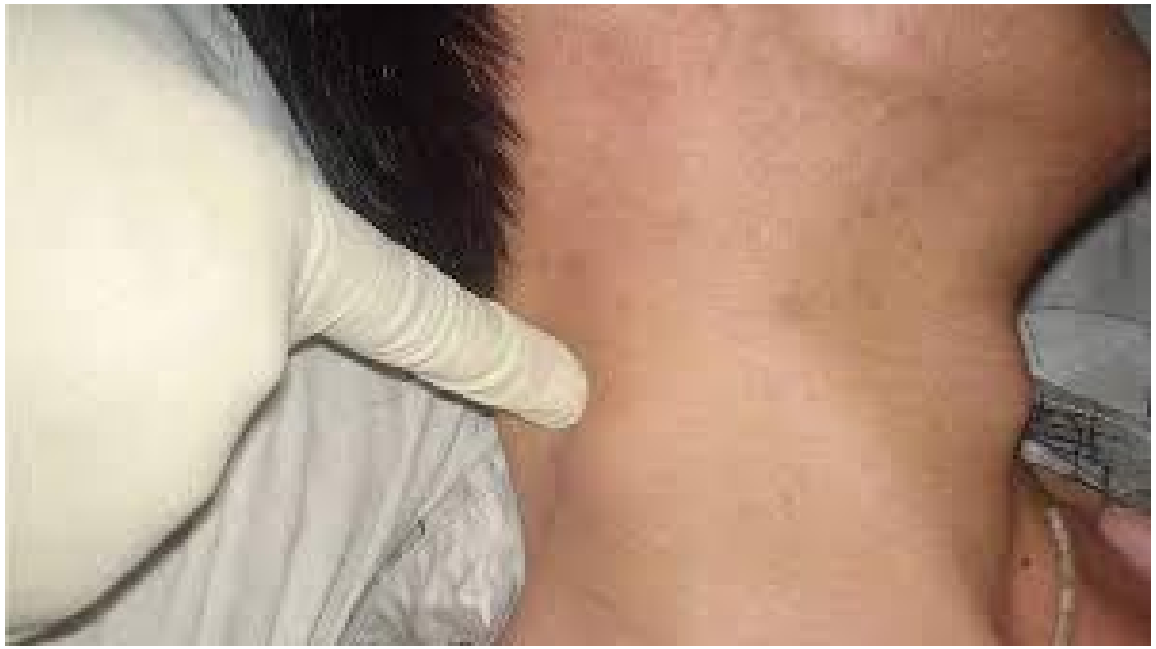

Chromosomal translocation leads
To fusion of two genes – uncontrolled expression of a cell-cycle gene which leads to non-stop cell division – tumor formation

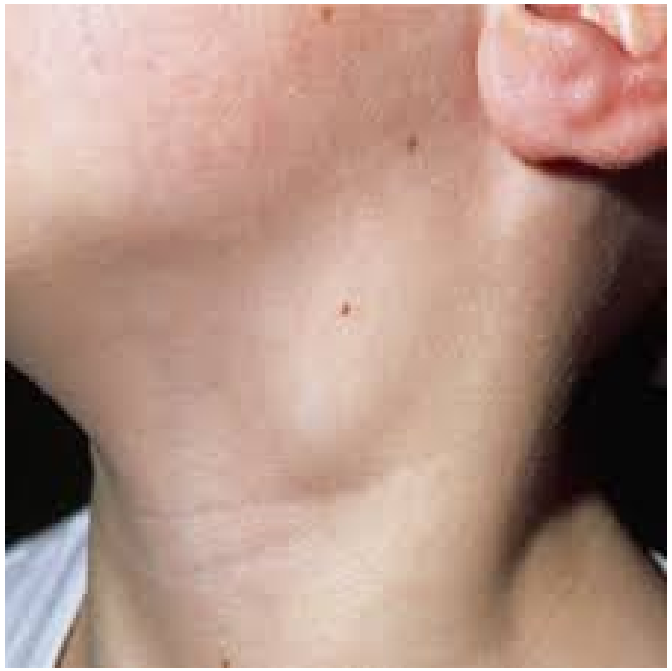
# Hodgkins Disease (Hodgkins Lymphoma)

- Malignancy of lymph nodes (and spleen)
- Malignant cells are Reed-Sternberg Cells
- Cervical and supraclavicular nodes are most common sites
- Bimodal age peak.  Peak #1 between 15 – 35,  Peak #2, older than 50
- Many subtypes
  - All carry different prognosis, treatment regimen



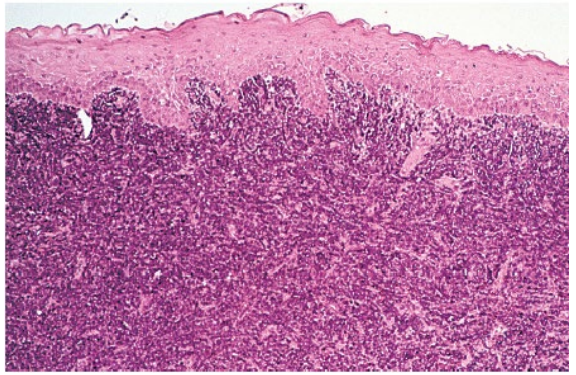
# Hodgkin’s Disease

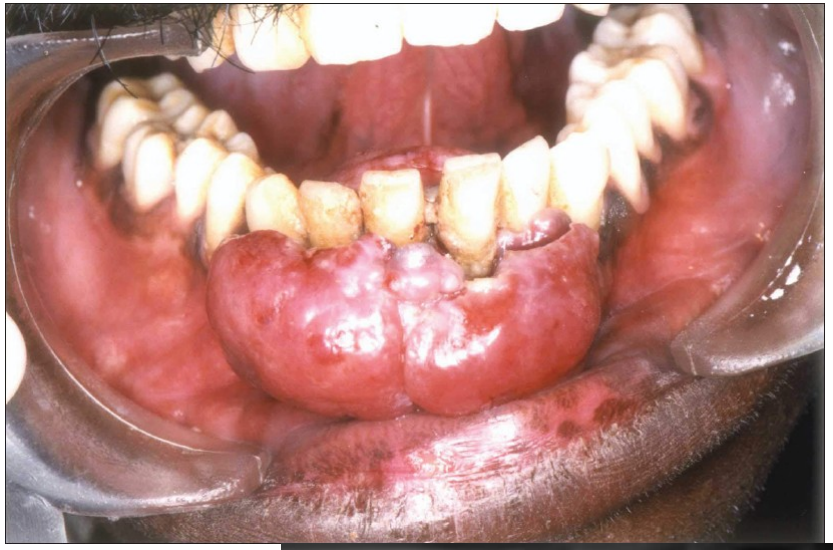


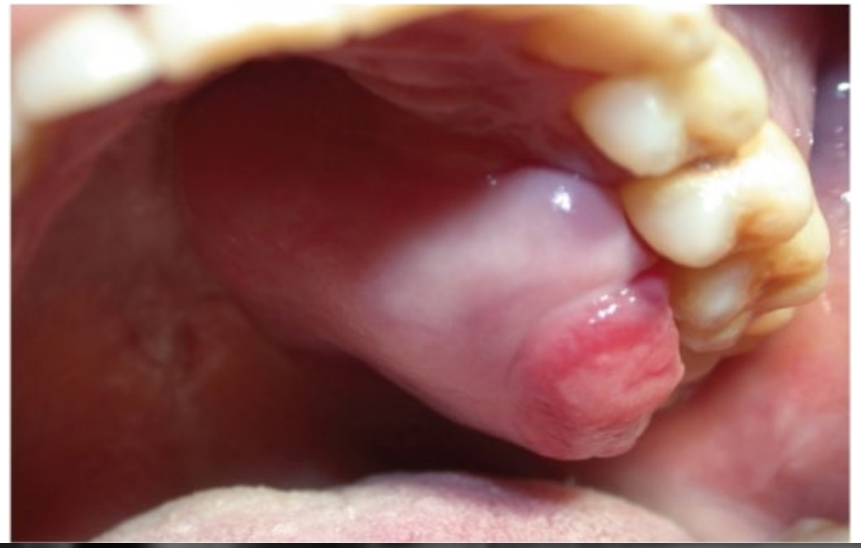


# Non-Hodgkin's Lymphoma

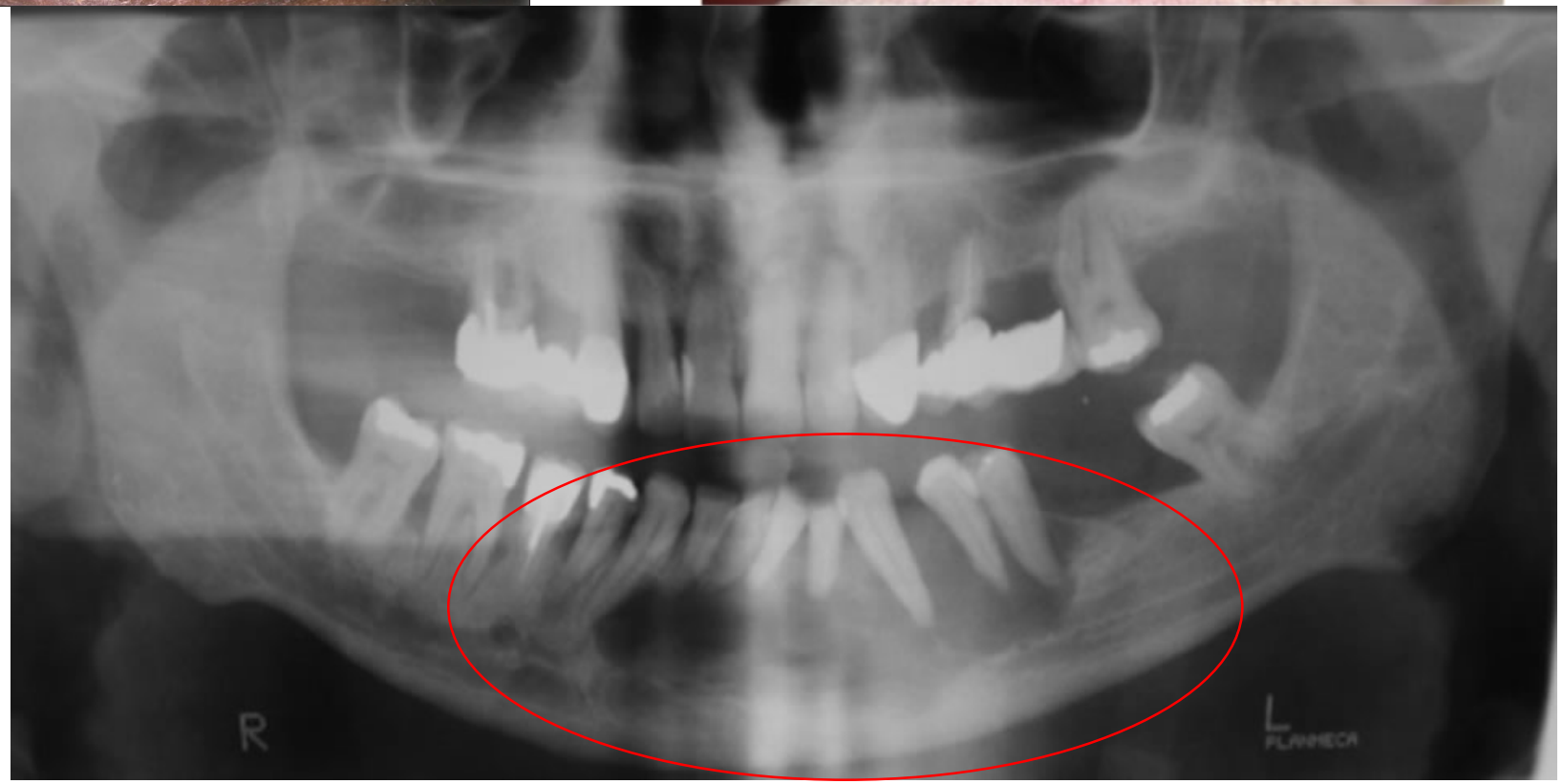
- Diverse group of lymphocytic malignancies (nearly 100 subtypes)
  - Highly variable clinical behavior
    - Some indolent and some extremely aggressive
  - May be B-cell or T-cell origin
  - Characterized based on
    - Histomorphology of lymphocytes
    - Cell surface antigen profile
    - Genetic modifications
- Usually arise in lymph nodes
  - Grow as solid masses
- Can have "extra-nodal" presentation, i.e. found outside lymphoid tissue (bone or soft tissues)
  - Oral lymphoma
    - 2nd most common malignancy in oral cavity (#1 is squamous cell carcinoma)





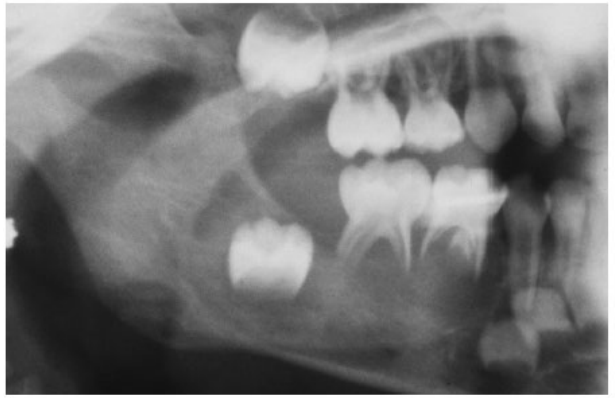


Oral lymphoma

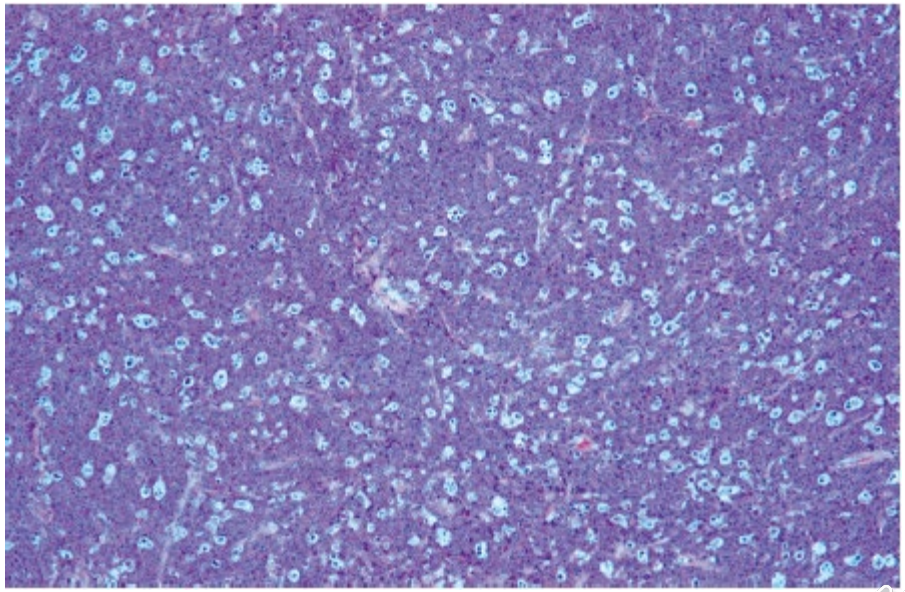


# Burkitt lymphoma

- Very aggressive lymphoma (initially described in Africa)
  - Associated with EBV
- Tends to involve jaws
- Often multifocal
- Usually seen in young children



• **Fig. 13-37 Burkitt Lymphoma.** This 4-year-old child had evidence of bone destruction with tooth mobility in all four quadrants of his jaws. Note the patchy, ill-defined loss of bone. (Courtesy of Dr. Gregory Anderson.)



"Starry night sky" appearance histologically

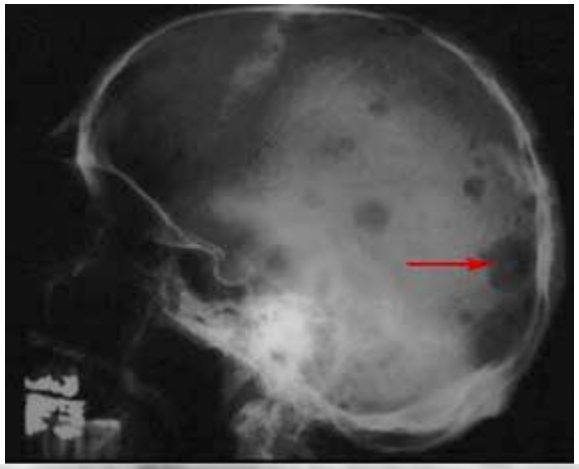
# Multiple Myeloma

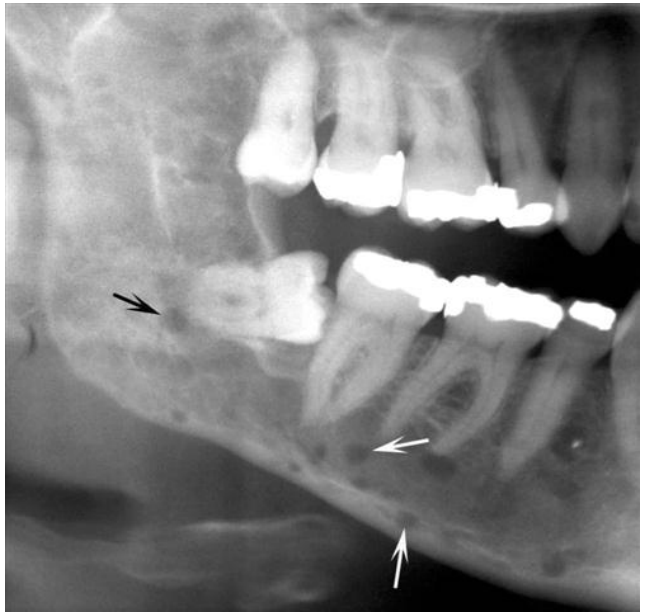
- Malignancy of **plasma cell** origin
- Presents in bone
- Multifocal
- Almost always in Adults!

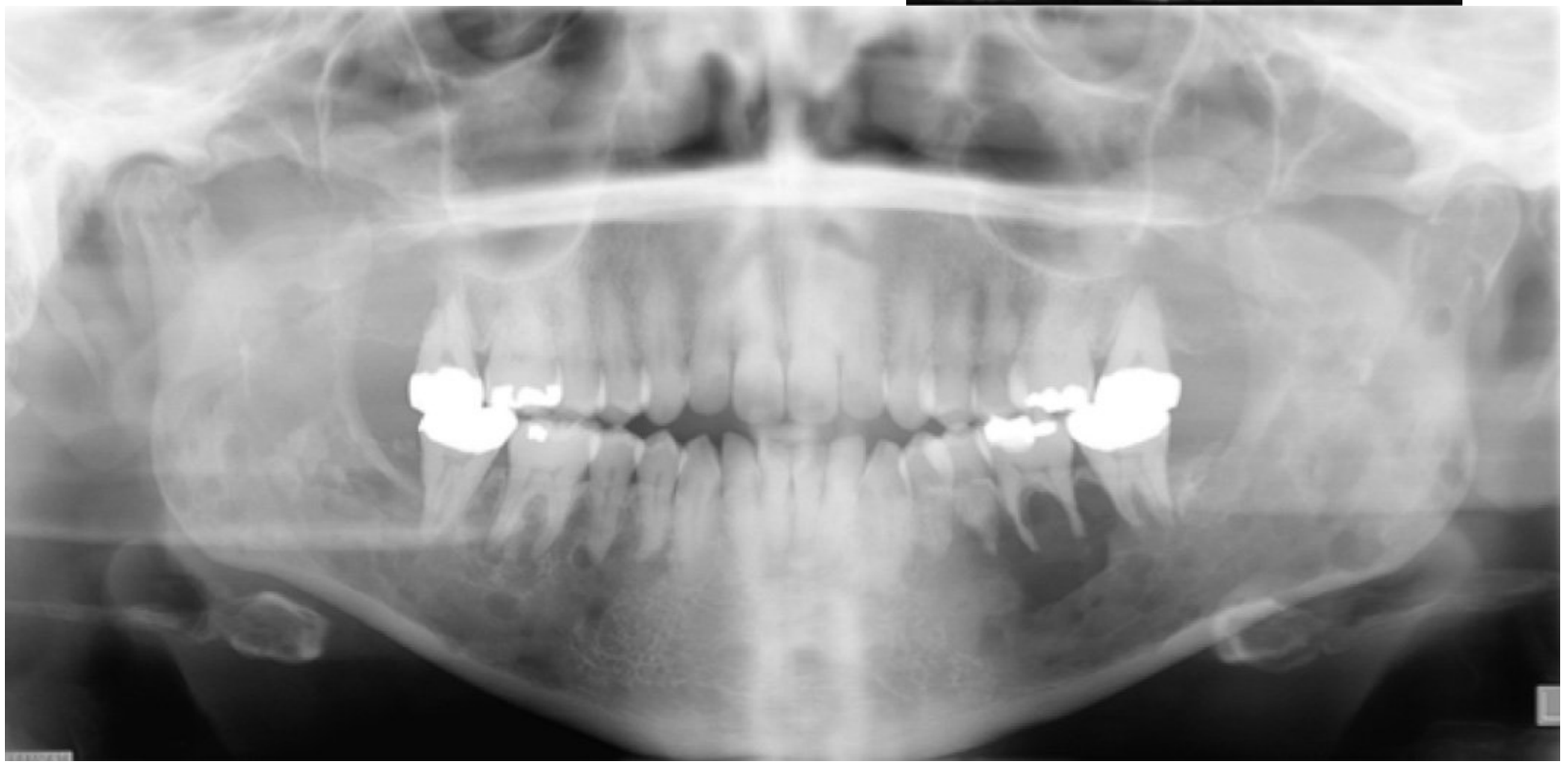
- Radiographically, multiple, well-defined, "punched out" radiolucencies.
- MM is characterized by the presence of Bence-Jones proteins in urine or serum
  - What are Bence-Jones proteins? Immunoglobulin light chains
    - Remember… plasma cells produce antibodies… so, a neoplasm of plasma cells will produce A LOT of circulating antibodies.



# Multiple myeloma

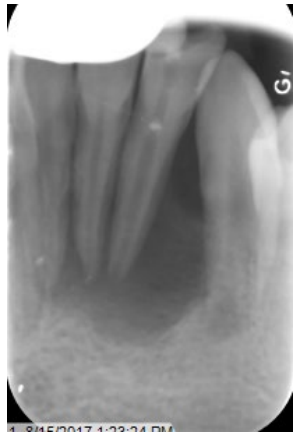






# Langerhans Cell Histiocytosis

- Tumor of histiocytic cells
  - Histologically – a proliferation of histiocytes and eosinophils is seen
- Single or multi-organ involvement
- Wide age range – high percentage of cases found in kids under 15 y/o
- Jaws often affected
  - Scooped out appearance when alveolar bone is destroyed
  - May look like severe perio disease
  - "Teeth floating in air" appearance
  - Could be in periapical position – may look like periapical pathology
    i.e. cyst or granulation tissue associated with dental infection
  - Disease can break out of bone and into gingiva and create a soft tissue mass



# Polycythemia vera

- Uncontrolled proliferation of red blood cells
  - Often has concurrent proliferation of platelets also

- Almost always in adults
- Problems?
  - Greater propensity for thrombus formation
    - Excess cells thicken the blood – slows down flow – leads to increased propensity for thrombus formation

# Bleeding disturbances (too much bleeding because of insufficient clotting)

- Most often clotting “issues” are drug related
  - Use of anti-clotting medications.  Why may someone be on clotting medications?
  - When blood becomes too “thin”, hemorrhage more easily
- Acquired conditions
  - Thrombocytopenia- not enough platelets generated
  - Vitamin K deficiency
  - Liver disease – many clotting factors produced in the liver

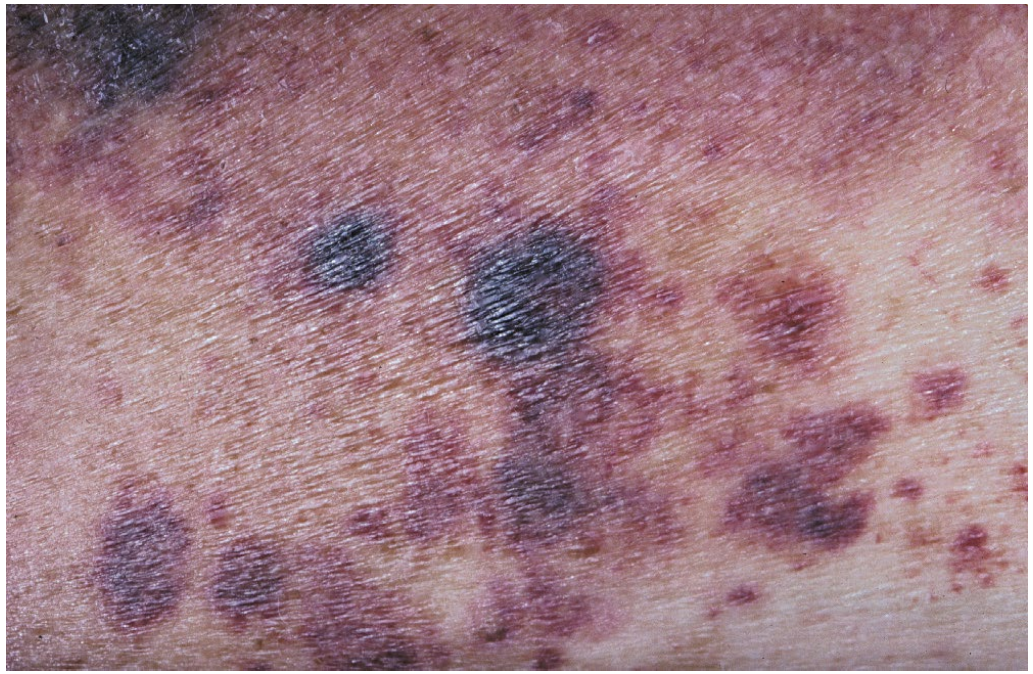
- Inherited
  - Von Willebrand’s disease
    - Affects both males and females
  - Hemophilia A
    - Males only
  - Hemophilia B
    - Males only

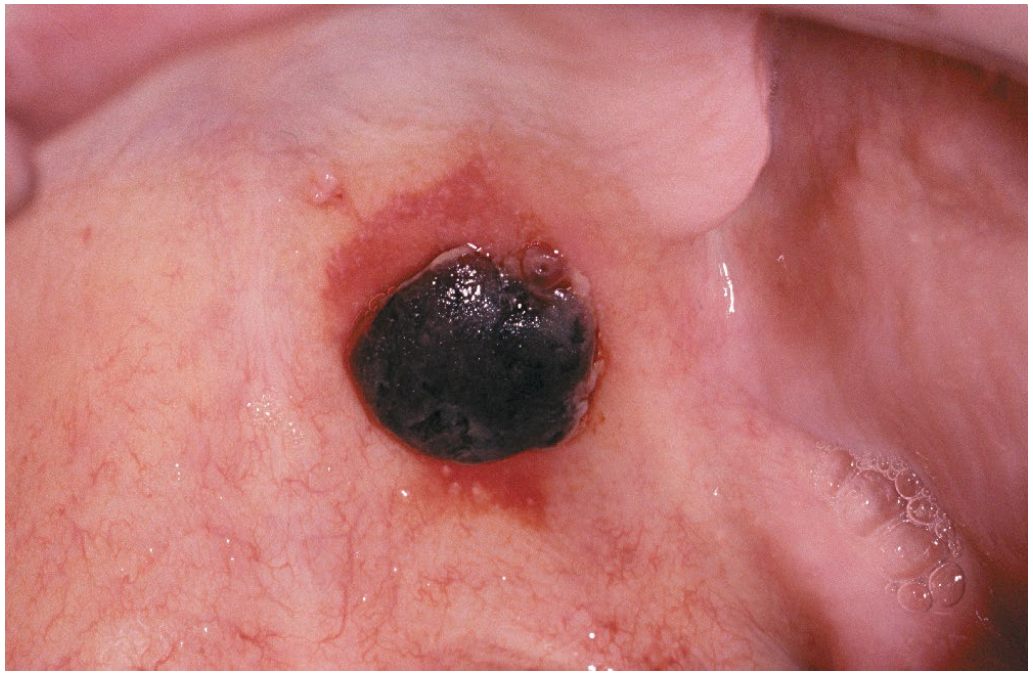
# Thrombocytopenia

- Marked decrease in circulating platelets (normal is 150-400K/ul)
- Platelet count < 100, may see symptoms
- Causes –
  - Leukemia
    - Reduces number of platelets produced
  - Chemotherapy
    - Reduces number of platelets produced
  - Drug reaction (heparin is one such drug)
    - Causes immune mediated destruction of platelets
  - Diseases that cause splenomegaly
    - Portal hypertension secondary to liver disease
    - Leukemia
    - Enlarged spleen = dysfunctional spleen. Spleen stores platelets… when spleen enlarges, blood supply/drainage is compromised and platelets not available for body to use for clotting

# Thrombocytopenia

- Remember the terminology that describes these?





# Von Willebrands Disease

- Inherited (genetic)
  - Far more common than hemophilia
  - Usually mild bleeding disease
  - VW disease is autosomal dominant – therefore, both males and females affected.
    - Hemophilia is X-linked recessive, therefore only males are affected.
- Abnormal von Willebrand's factor
  - VW Factor aids platelet adhesion at bleeding site



# Hemophilia- is caused by mutations in clotting factor genes

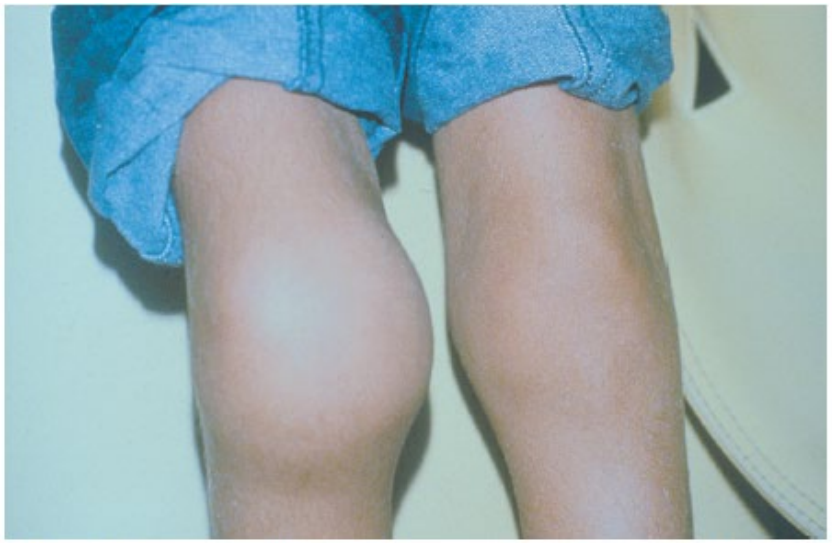
- Hemophilia A – Clotting factor 8 deficiency
  - Far more common than Hemophilia B
- Hemophilia B – Clotting factor 9 deficiency
- Both are X-linked recessive.  Only males have disease! Females are carriers.
- Highly variable clinical presentation- not all hemophiliacs “bleed out”
  - Some have very mild disease (clinically insignificant)
    - 25% of clotting factor is enough for normal function
  - 1% have very severe disease
    - Why might there be such a wide range of clinical presentation?



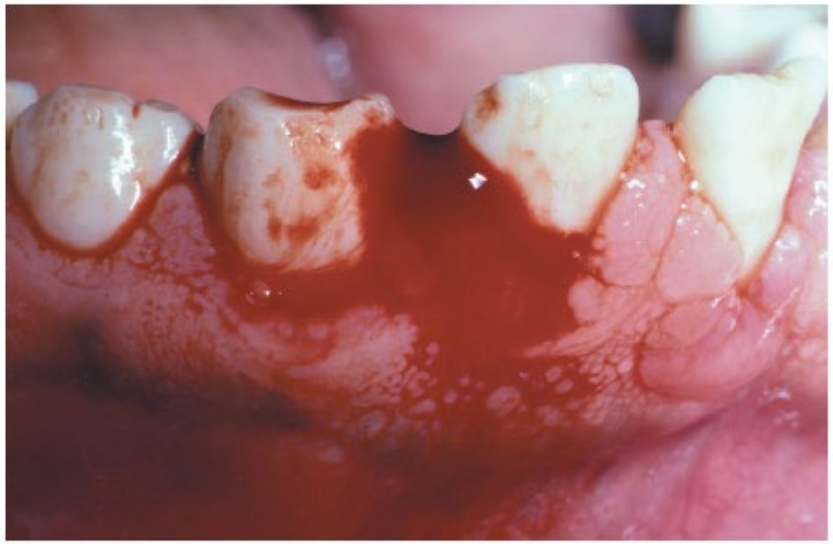
# Hemophilia

- Clinically – similar to thrombocytopenia – hematoma, ecchymoses, purpura. Uncontrolled bleeding in severe cases

- Treatment?
  - Clotting factor replacement therapy (as needed)
  - Mild hemophiliacs – may need clotting factor supplementation when undergoing surgery
  - Severe hemophiliacs – take clotting factor replacement regularly
    - May have bleeding into joints - hemarthrosis
- Dental implications – be very careful – get medical consult for patients with clotting diseases (thrombocytopenia, von Willebrands disease, hemophilia, liver disease, patients on anti-clotting medications).

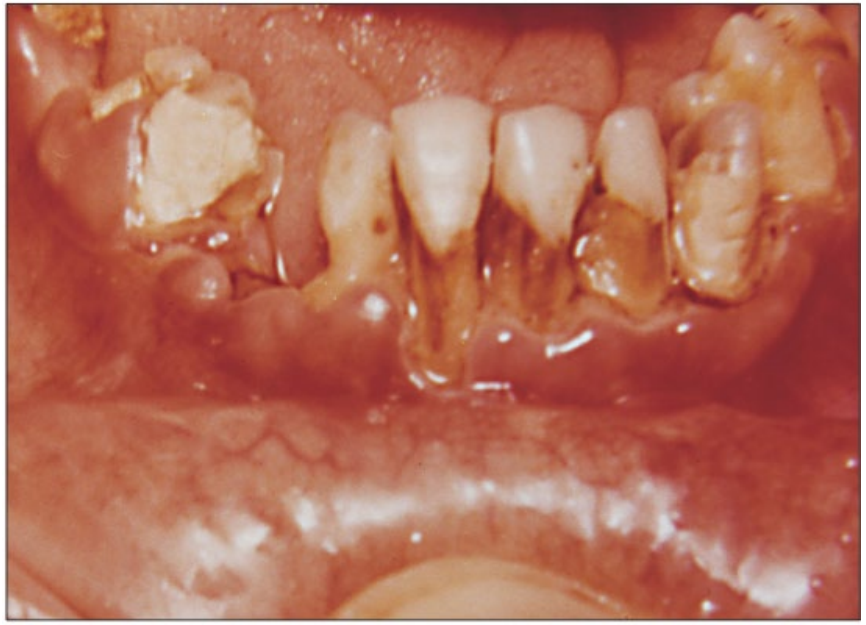


• **Fig. 13-4 Hemophilia.** The enlargement of the knees of this patient with factor VIII deficiency is due to repeated episodes of bleeding into the joints (hemarthrosis). Inflammation and scarring have resulted.



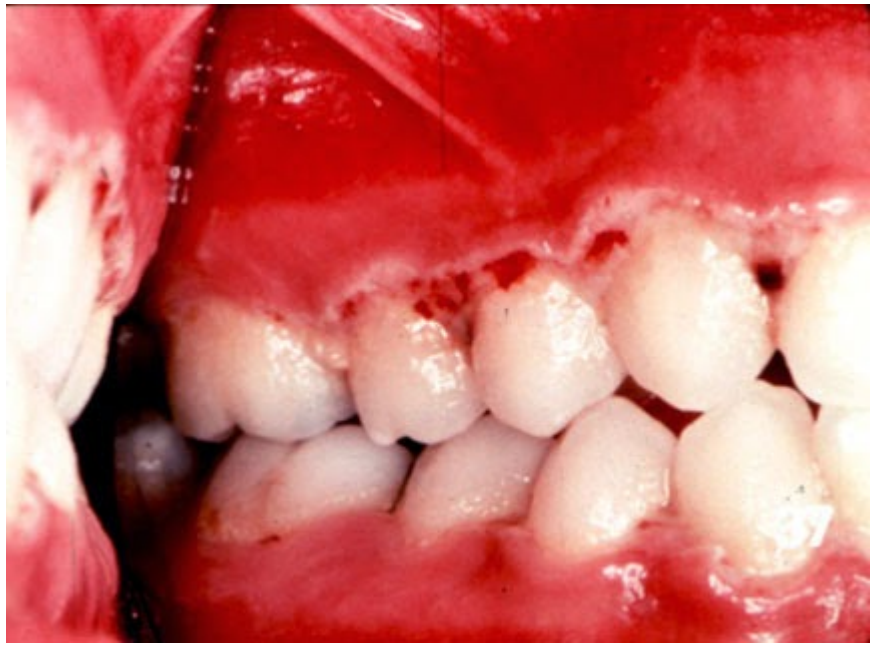
• **Fig. 13-5 Hemophilia.** Hemorrhage in a patient with factor IX deficiency occurred after routine periodontal curettage.

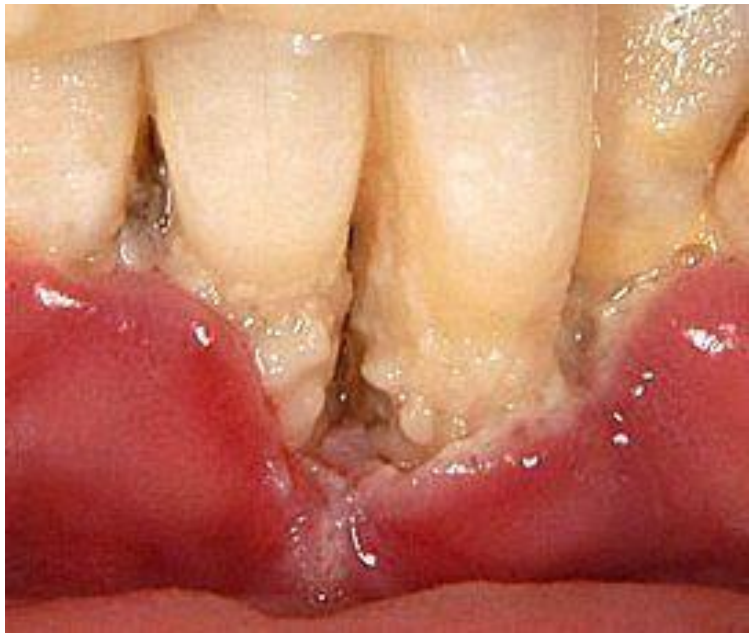
# Neutropenia



- General
  - Decrease in number of circulating neutrophils.
  - Many causes
    - Leukemia
    - Chemotherapy
    - Infections exacerbated by immune compromise
  - Results in infections
    - Fever, malaise
    - Especially bacterial
    - Often times, no abcess (remember: need neutrophils for acute inflammation)
  - Oral?
    - Frequently ulcerated gingiva  (Necrotizing Ulcerative Gingivostomatitis)
    - Can see ulcers on tongue, buccal mucosa
    - Early periodontal disease

# Necrotizing ulcerative gingivitis – common sequalae of immune compromise





Necrotic lesions in other oral soft tissues may also be present… but why is gingiva so commonly affected?

- Cyclic neutropenia
  - Cyclic reduction of neutrophils
  - Children
  - 21 day cycle, very low neutrophils for a few days then back to normal
  - Leads to constant illness
  - Oral manifestations are same as generalized neutropenia- (NUG)

- Agranulocytosis
  - Granulocytes severely lowered
    - What are granulocytes?  Neutrophils, basophils, eosinophils
  - Clinical manifestiations very similar to neutropenia
    - Increased infections including oral infections
  - Causes?
    - Often drug induced.  Chemotherapy



# Aplastic anemia

- Rare and life threatening
- Causes
  - Environmental toxins
  - Antibiotic - chloramphenicol
- Pancytopenia
  - Failure of bone marrow to produce all of the blood cells
    - RBCs, WBCs, platelets
- Oral manifestations?
  - Take a guess?

# What is Anemia?

- WHO definition – low blood concentration of hemoglobin (<13.0 g/dL)
  - Most often a sign/symptom of another underlying disease
  - Often seen in elderly – but not due to "old age" – usually another reason
  - Main symptoms are WEAKNESS and FATIGUE
    - Due to less oxygen
- MOST anemias are ACQUIRED (not inherited)
  - Nutritional deficiencies most common cause worldwide (iron, B12, folate)
  - Inflammatory diseases, chronic infections, liver or kidney disease
  - Diseases of spleen (splenomegaly)
  - Blood cancers (leukemia), cancer treatment (chemotherapeutic drugs)
  - Internal bleeding
- Thalassemia and Sickle cell disease are inherited anemias
  - Defects (or polymorphisms) in genes that produce hemoglobin
  - Hence, called "hemoglobinopathies"

Please know this slide for exam

# Hemoglobin levels; normal vs anemic

- 13.0 – 17.0 Normal range (men, women slightly lower)
- 11.0 – 13.0 Mild anemia, mostly unnoticeable (asymptomatic)
- 7.0 – 11.0 Noticeable weakness – symptoms are worse with lower levels.
- Under 7.0 –Transfusions necessary to stay alive (heart does not receive enough oxygen to function)

Do not need to know these for exam