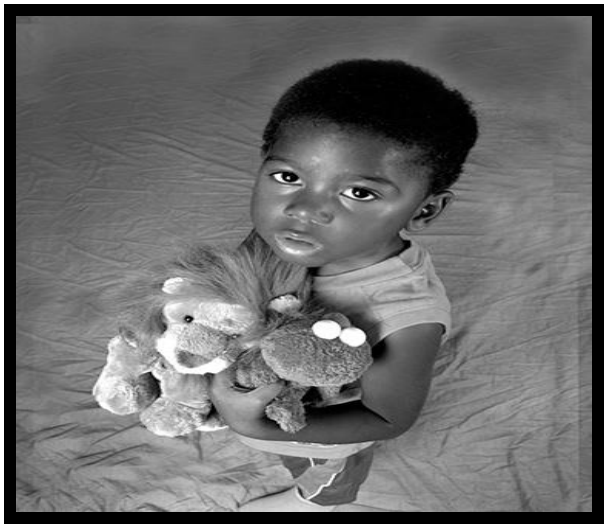
Pediatric Cancer

Roswell Park Cancer Institute
Department of Pediatrics

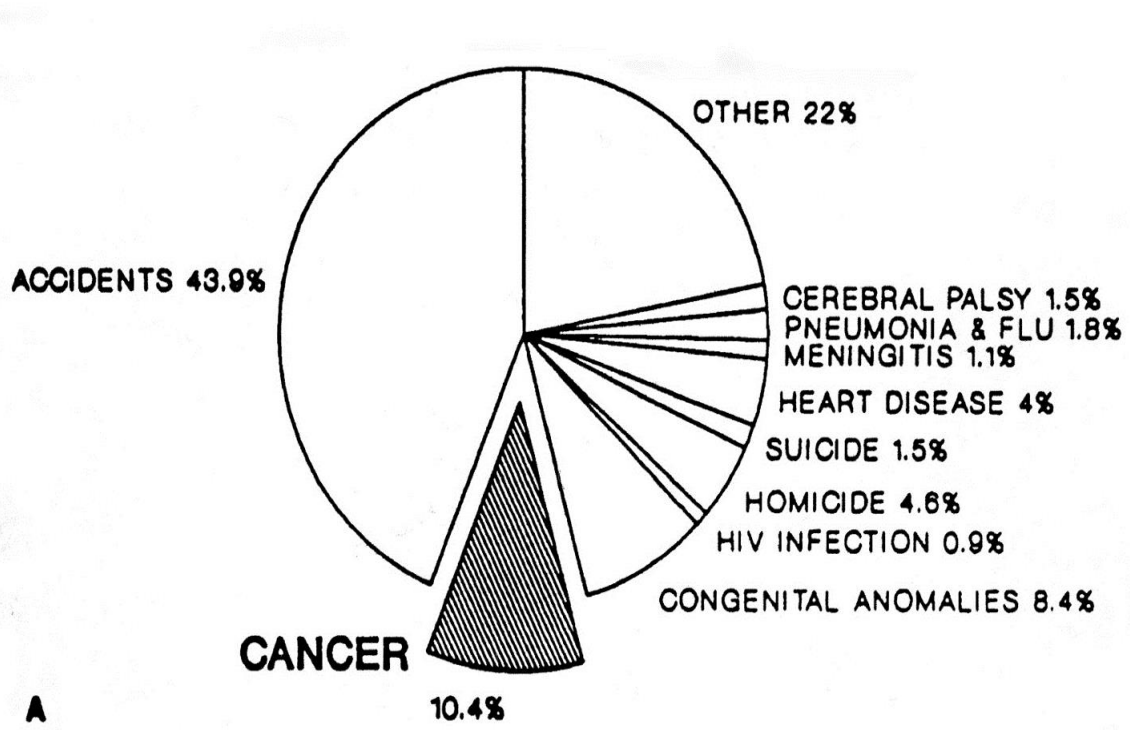
Fast Facts on Childhood Cancer



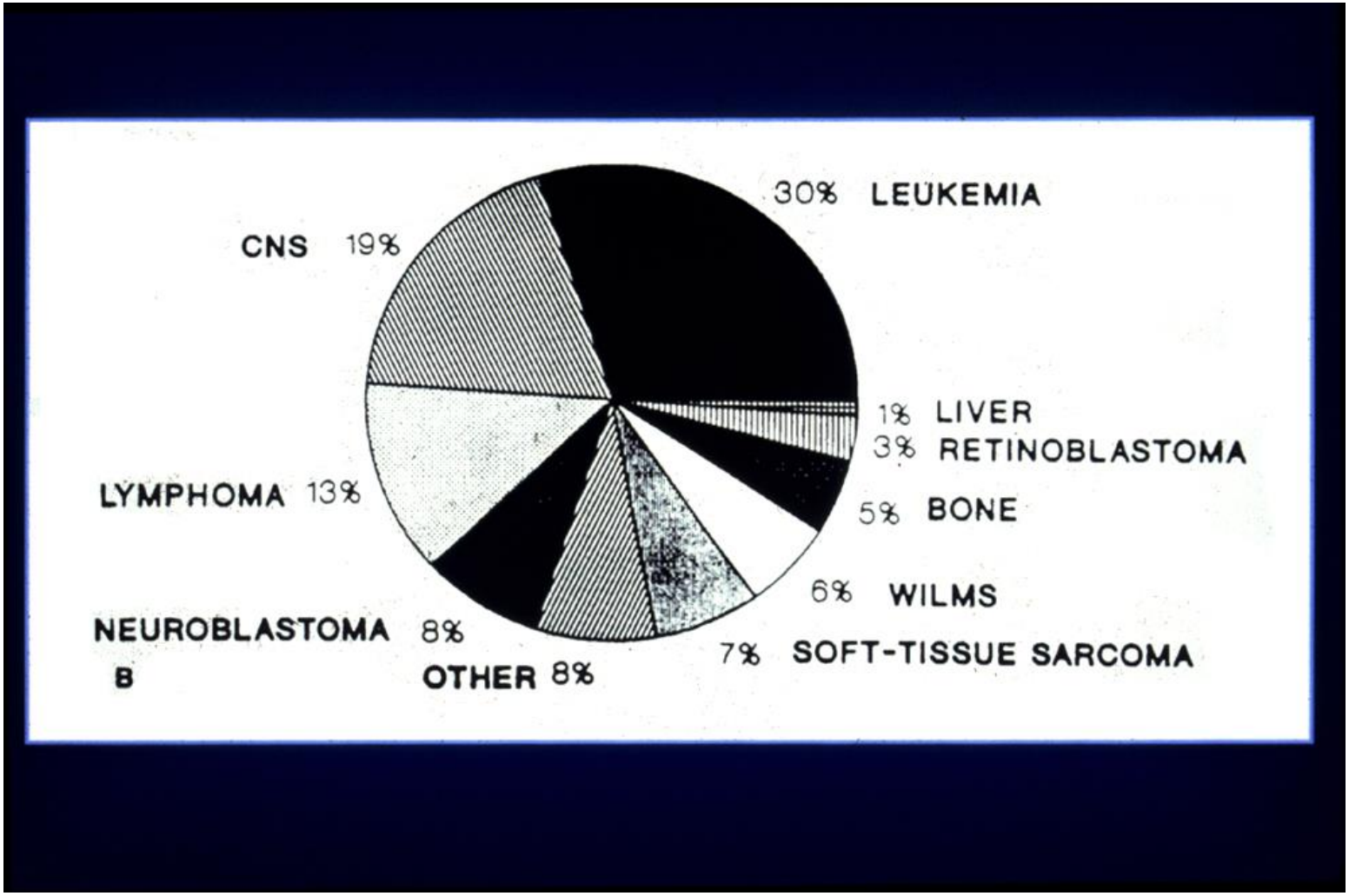
- **Every day 46 children are diagnosed with cancer.**
- **One in 330 children will develop cancer by age 20.**
- **Although the 5 year survival rate is steadily increasing, one quarter of children diagnosed will die.**
- **Cancer remains the leading cause of death by disease in America's children - more than Cystic Fibrosis, Muscular Dystrophy, Asthma and AIDS combined.**

-Candlelighter's Childhood Cancer Foundation

Leading Causes of Death in Children



Types of Cancer Distribution



Etiology

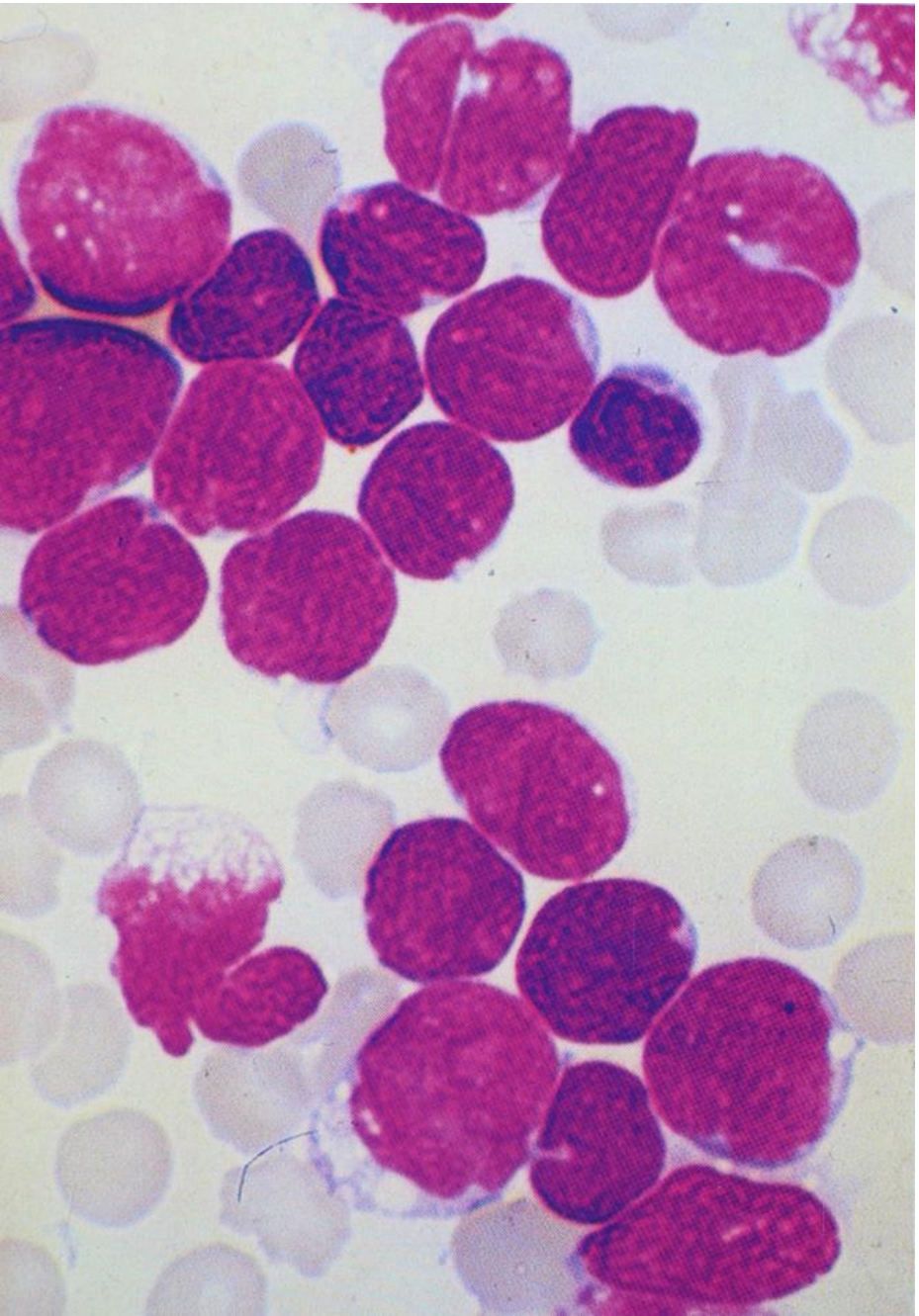
- **Unknown**
- **Genetics**
  - **some chromosomal abnormalities**
  - **identical twins - 20% concordance rate for leukemia if < 6 yrs**
- **Environmental - prenatal vs post natal**
  - **radiation**
  - **chemical carcinogens**
  - **diet - no evidence in children**

- **Viral Oncogenesis**
  - **EBV in Burkitt's, Hodgkin's**
- **Immune deficiency**
  - **increase in lymphoid malignancies with congenital immunodeficiency**
  - **cancer in AIDS patients**

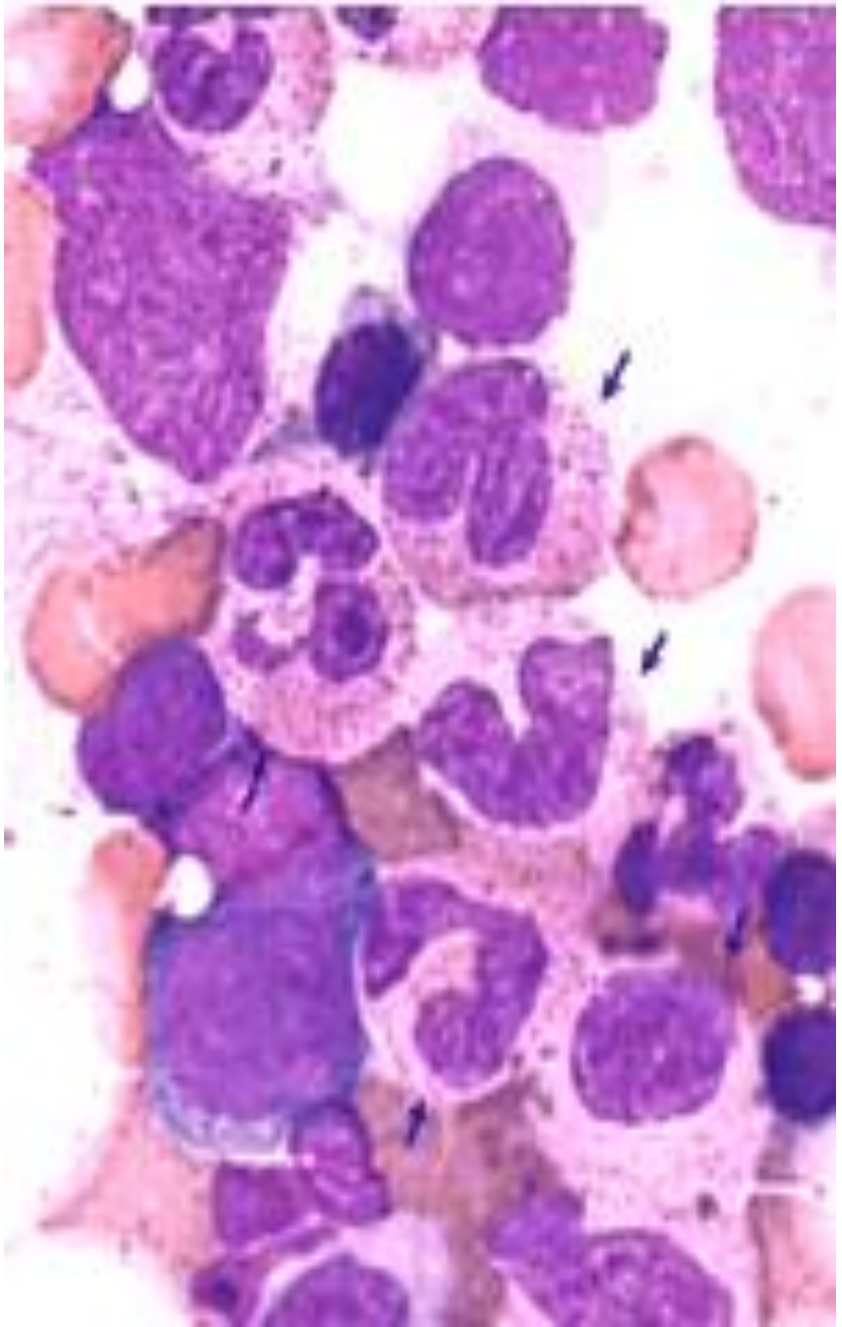
Acute Lymphoblastic Leukemia

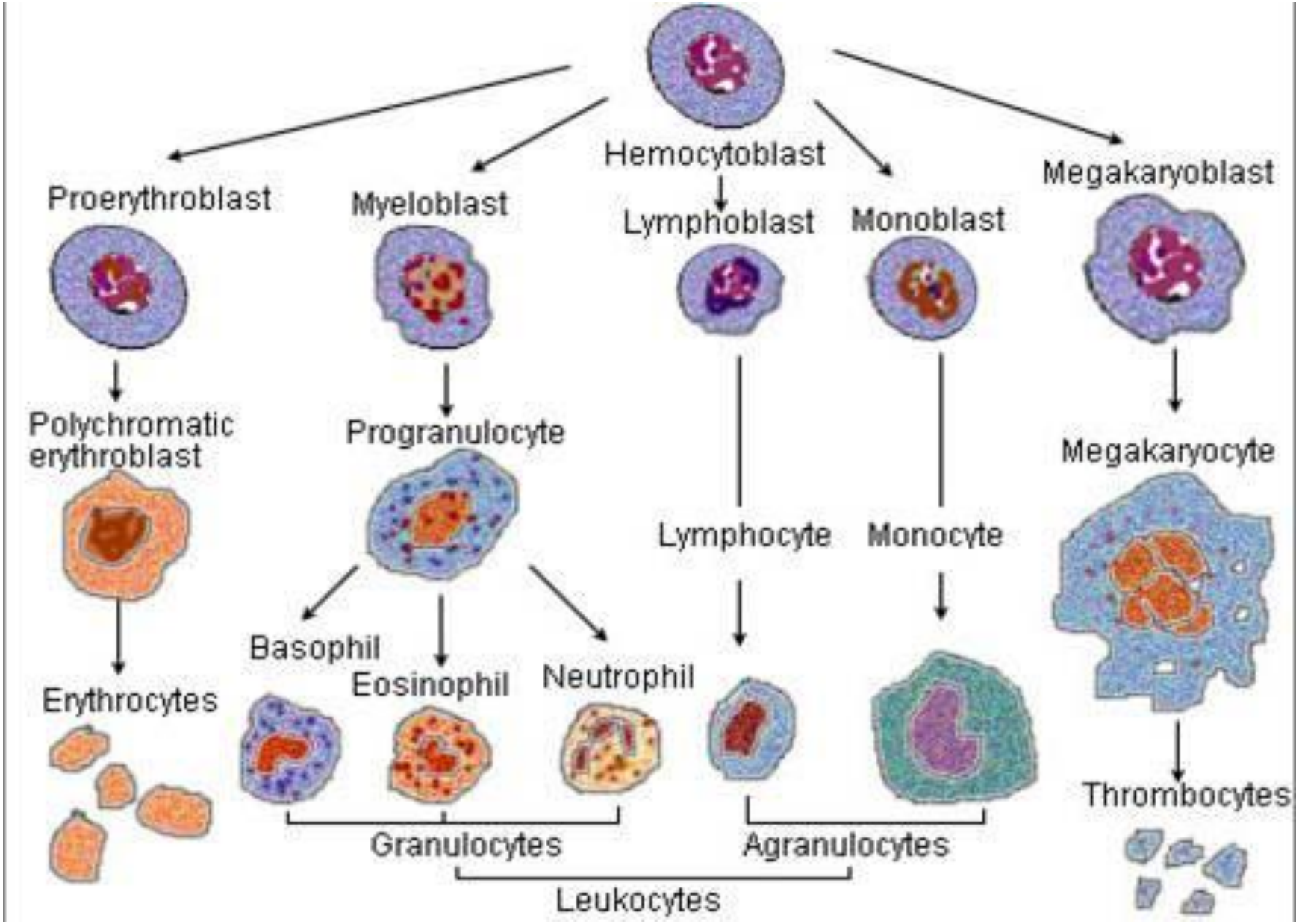
- Most common pediatric malignancy
- 80% of pediatric leukemias
- 1/25,000
- peaks at 3-5 years
- boys>girls

Lymphoblasts



Normal Bone Marrow



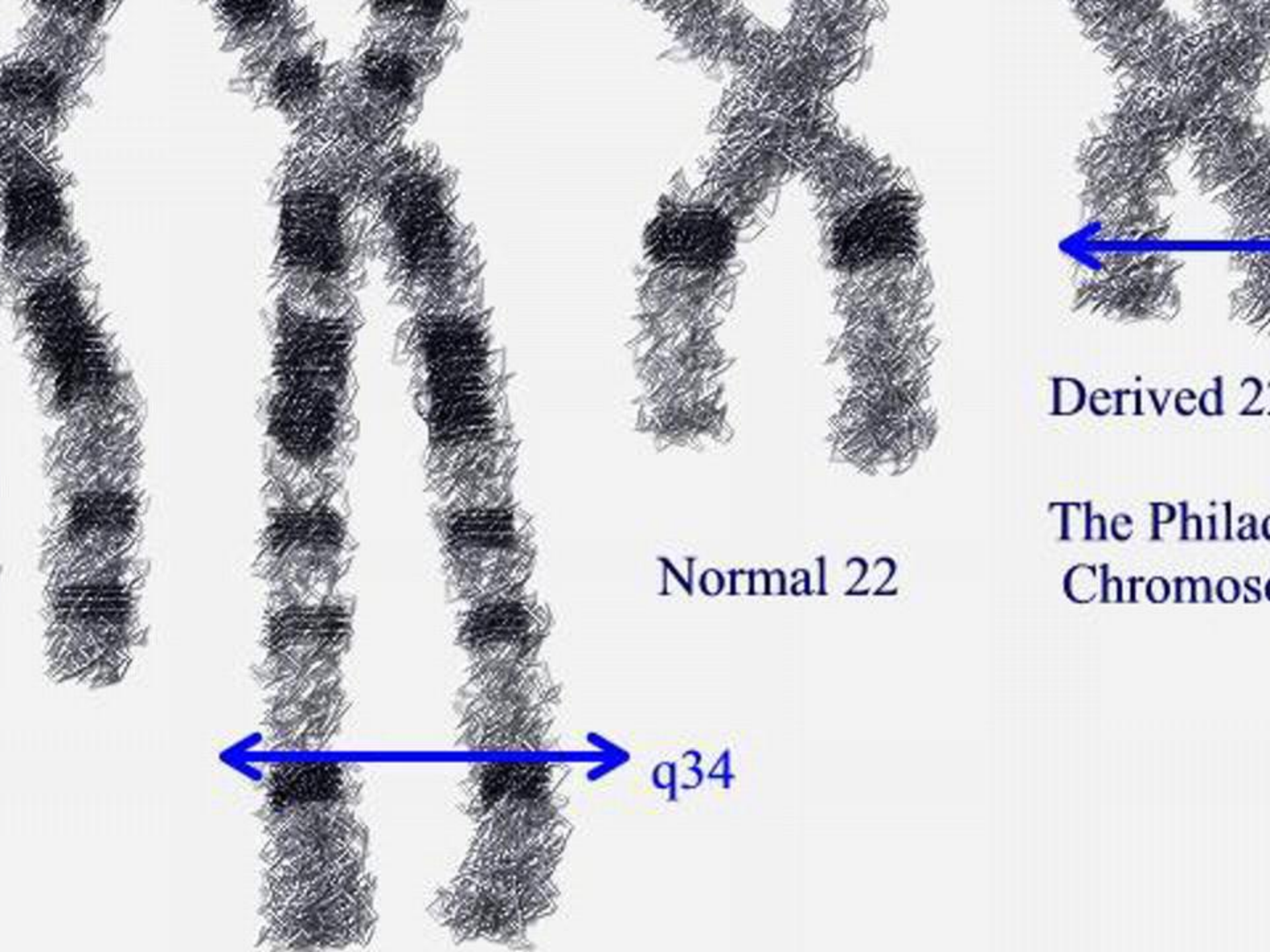

Hemocytoblast
Proerythroblast
Myeloblast
Lymphoblast
Monoblast
Megakaryoblast
Polychromatic erythroblast
Progranulocyte
Megakaryocyte
Lymphocyte
Monocyte
Basophil
Eosinophil
Neutrophil
Erythrocytes
Thrombocytes
Granulocytes
Agranulocytes
Leukocytes

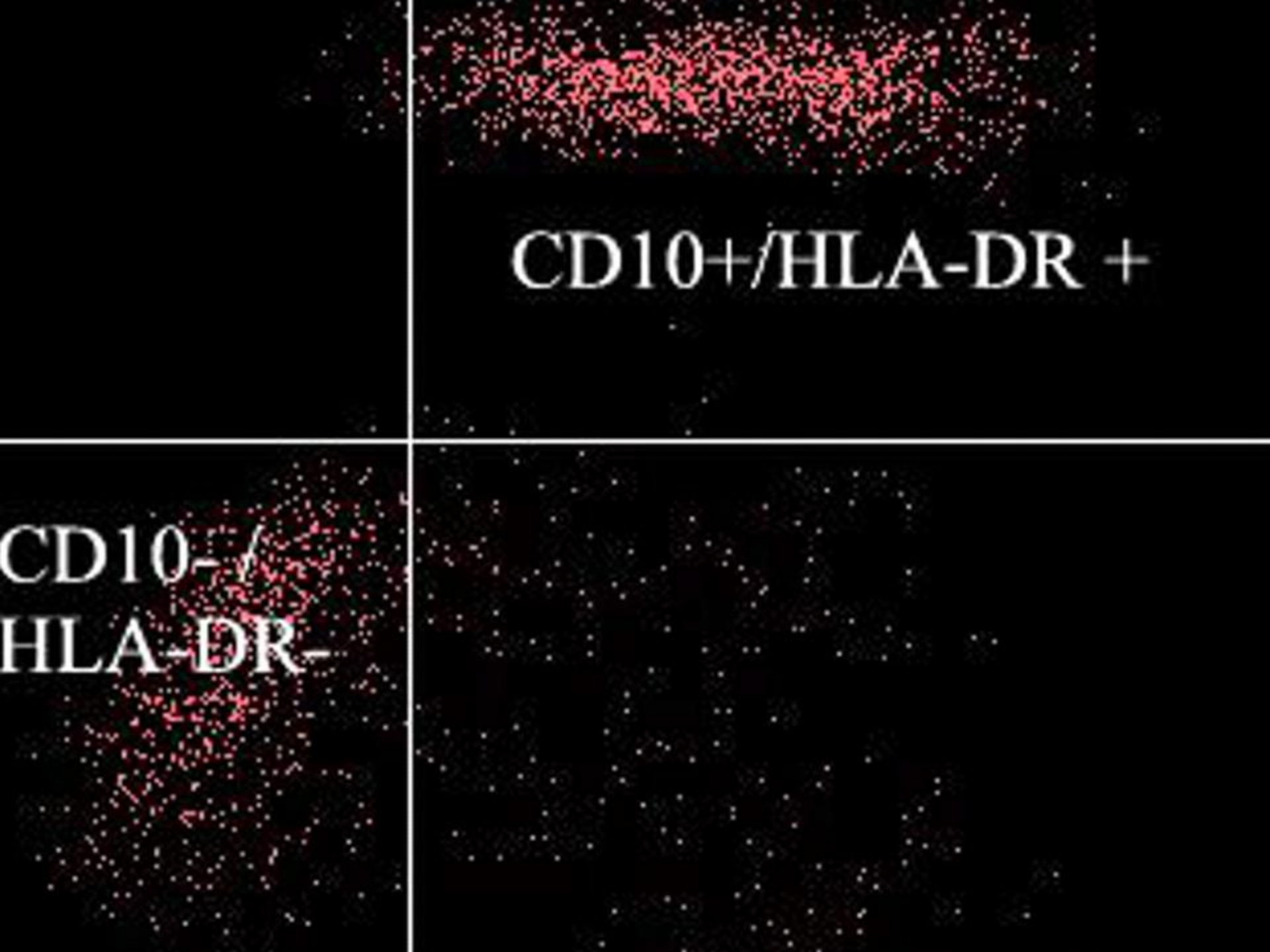
ALL

- Presentation
  - Related to bone marrow not functioning properly: High or low WBC (bone pain), anemia, thrombocytopenia (petechiae, epistaxis), elevated LDH, elevated uric acid
  - CNS disease Headaches, blurred vision
  - Testicular disease, swelling, mass
- Differential diagnosis
  - Mono, CMV, ITP, JRA, aplastic anemia, neuroblastoma,

ALL

- Diagnosis - bone marrow aspirate
  - morphology, histochemistry, flow cytometry, cytogenetics
- LP for CNS disease - prognosis poorer, prophylaxis for low/standard risk
- Prognosis
  - WBC > 50K, age <1 or >10 high risk
  - DI $\geq$ 1.16 favorable
  - Chromosones favorable vs. unfavorable


Normal 22
q34
Derived 2
The Philad
Chromose


CD10+/HLA-DR +
CD10-/
HLA-DR-

ALL

Markers - Tcell, B cell, B-lineage

Treatment based upon risk

standard vs. high risk vs. very high risk (ph+)

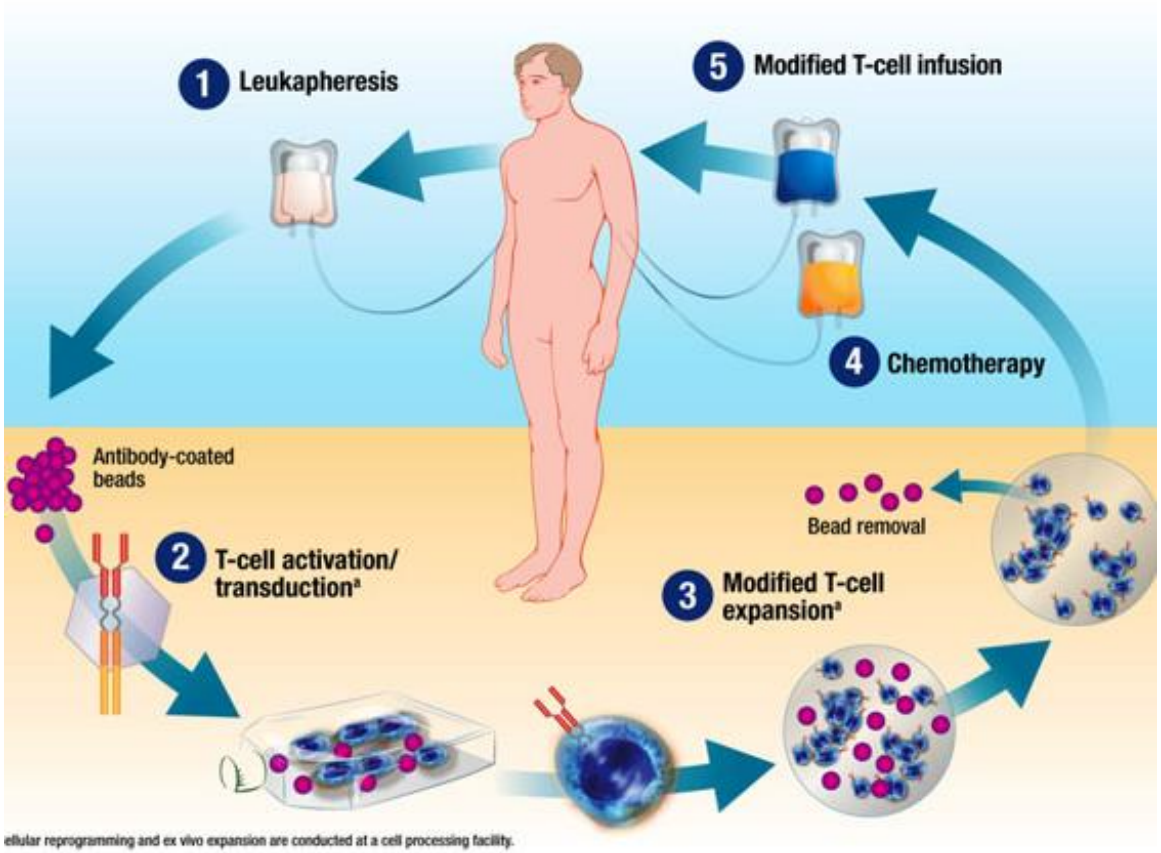
- Induction - clear marrow of evidence of leukemia (MRD)
  - 3 drug - VCR, pred, asp
  - 4 drug - add anthracycline for high risk

ALL

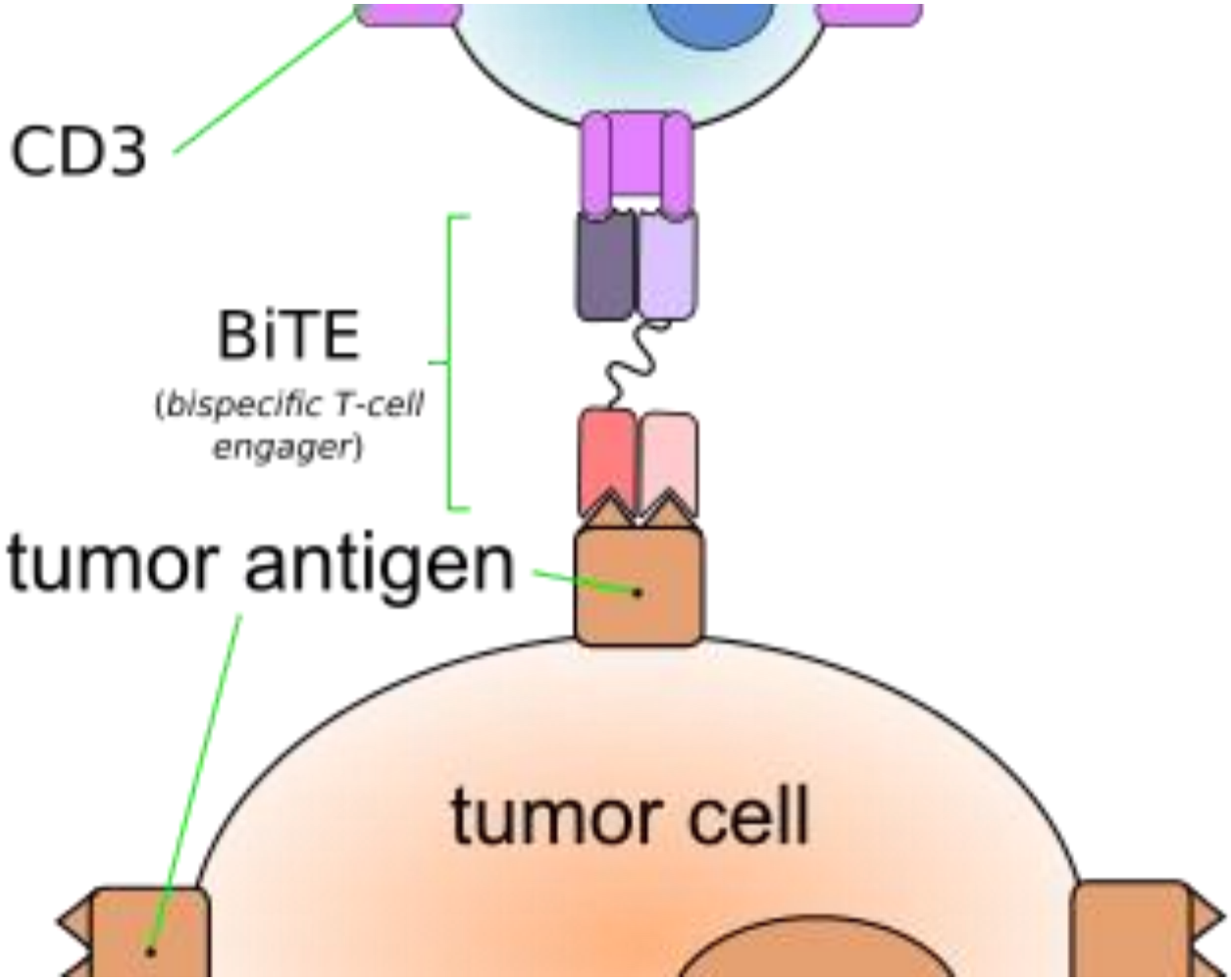
- Intensification/Consolidation
- Maintenance outpatient
- CNS prophylaxis - IT meds vs. Cranial RT
- Treatment 2 ½ yrs girls 3 yrs boys
- 80% cure overall

What to do when you refractory or relapse?

- Additional chemotherapy
- Transplant – depends on timing of relapse
- Where you come in – novel therapy
  - CarT cells
  - Blinatumomab – antibody with two binding sites: a CD3 site for T cells and a CD19 site for the target B cells
  - Targeted therapy based on mutations – Gleevac, dasatinib


1 Leukapheresis
5 Modified T-cell infusion
4 Chemotherapy
Antibody-coated beads
2 T-cell activation/ transduction[a]
Bead removal
3 Modified T-cell expansion[a]
ellular reprogramming and ex vivo expansion are conducted at a cell processing facility.

Car T Cells

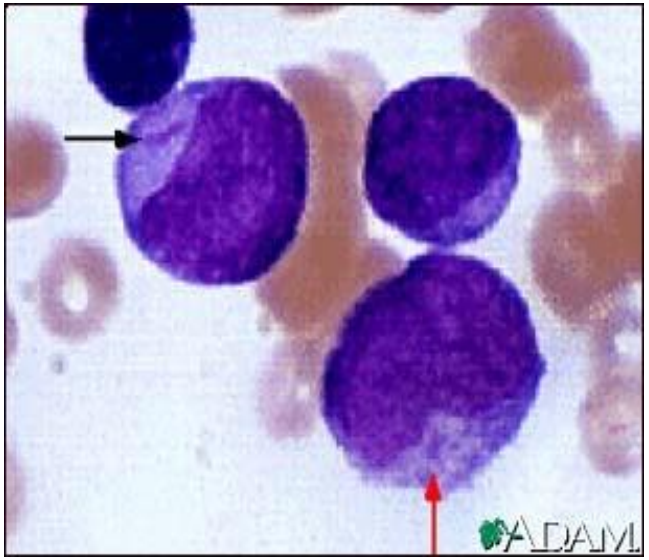


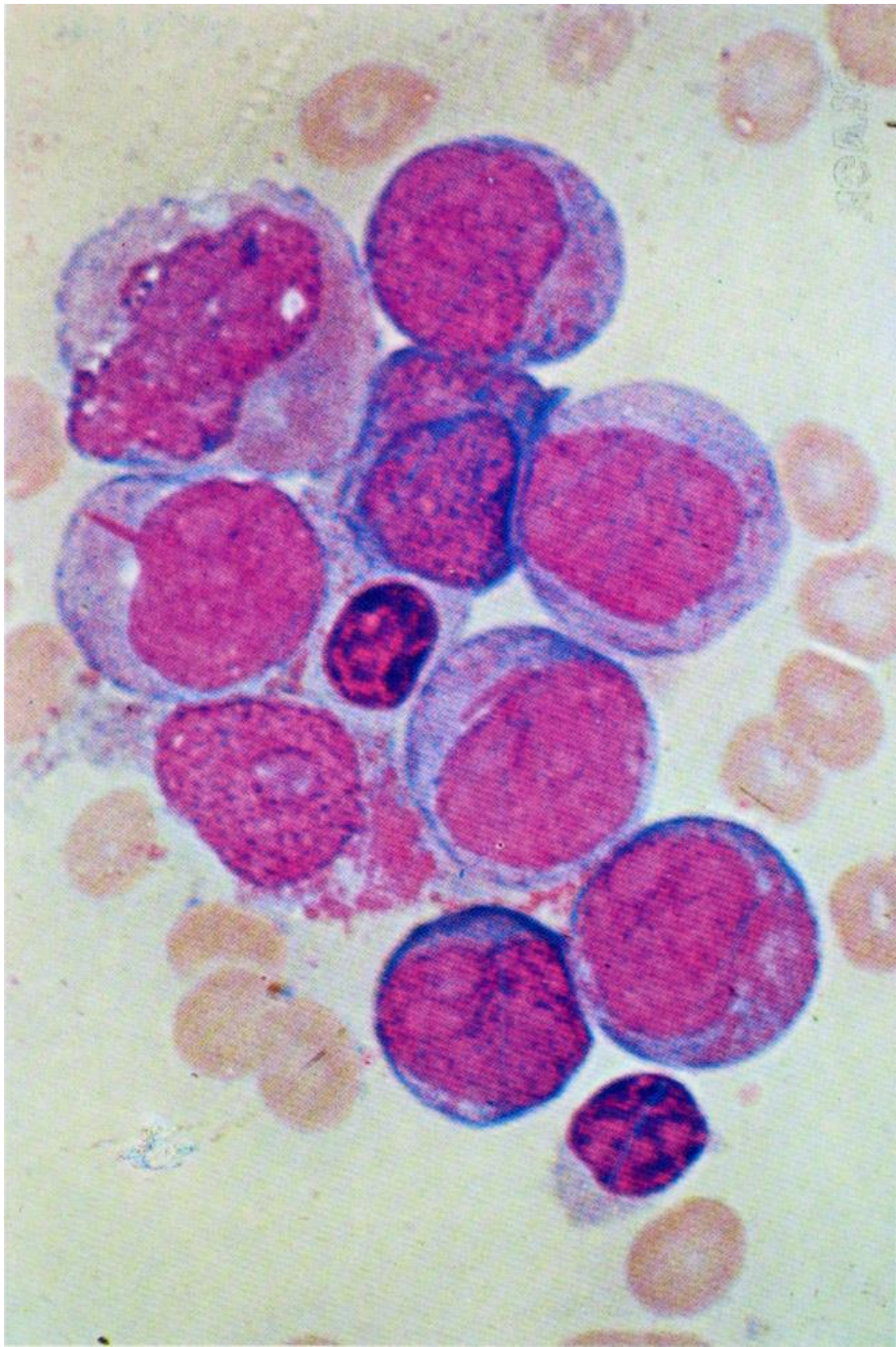
Blinatumomab

Acute Myelogenous Leukemia

- **500 new cases per year**
- **No age, sex preference**
- **presentation –anemia, thrombocytopenia (bruising, epistaxis), elevated/low WBC, DIC, gingivitis, hepatospleenomegaly**
- **20% with WBC > 100,000**
- **Bone marrow aspirate/biopsy**
- **LP CNS disease less common than ALL**

Myeloblasts





AML

- Treatment
  - **induction -Dauno, AraC, 6TG**
  - **intensification - HD AraC**
  - **Allogeneic BMT vs chemo**
- Cure rates - 60-70% sib allo BMT vs. 30-40% chemo only

So where do you come?

- Tyrosine Kinase inhibitors
  - Sorafanib and FLt3-ITD
- Histone deacteylase Inhibitors
  - Valproic acid, new agents, combination
- DNA-hypomethylating agent
  - 5-azacitadine, decitabine
- Targeted therapy
- Immune Modulation

Hodgkins Disease

- Peaks in adolescence, 20's in US, rare < 5 years
- More common in immunodeficiency
- Pathology - 4 types, NS most common
- Painless adenopathy -supraclavicular, cervical, axillary nodes
- firm, rubbery nodes
- 2/3 mediastinal involvement

Hodgkins Disease

- Spreads via contiguous nodal groups
- Lungs, pleura, pericardium
- Spleen/liver enlarged, marrow involvement
- “B” symptoms -fever, weight loss, night sweats
- Stage with CT neck/chest/abdomen, PET scan
- Stage I-IV determines treatment

Hodgkins Disease

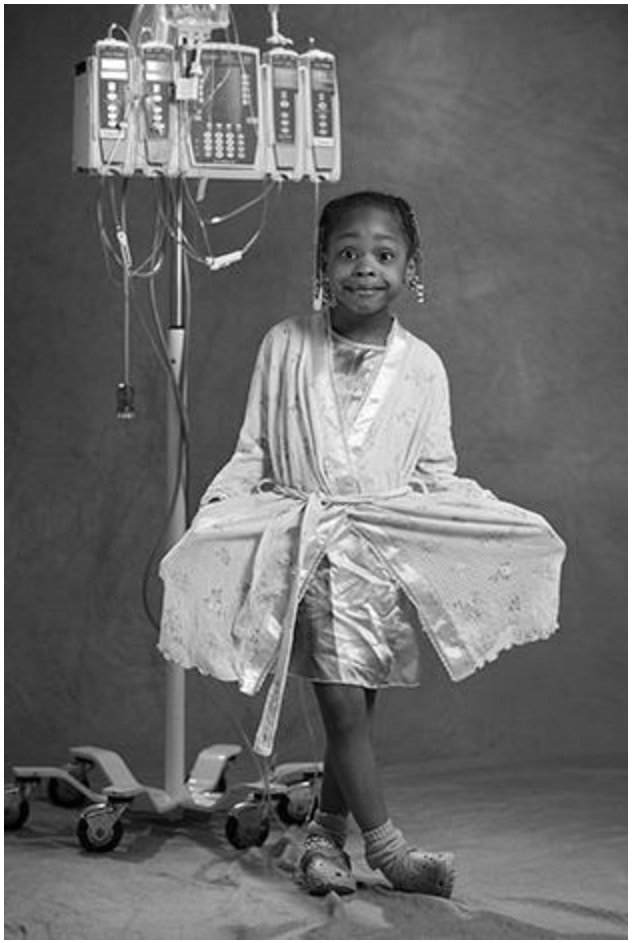
- Bone marrow aspirate/biopsy if advanced disease
- Therapy
  - Trend toward low dose chemo + low dose XRT in local disease
  - Advanced stage more aggressive chemo and involved field radiation
  - Recurrence Autologous BMT

Where do you come in?

- **Brentuximab Vedotin**
  - Anti CD 30 linked to antitubulin agent monomethyl auristatin E
- **Lintuzumab anti-CD33**
  - a humanized IgG1 anti-CD33 antibody
  - inhibit tumor assocaiated macrophage function (thought to promote tumor growth)

Non-Hodgkins Lymphoma

- Very different from adults - nearly all high grade
- Small noncleaved (undifferentiated) - Burkitt's
- Lymphoblastic
- Large cell



NHL

Small non-cleaved - “Burkitt’s”

- B cell, express surface immunoglobulin,
- abdominal mass +/- ascites, pain
- May have inguinal, iliac adenopathy
- Fast growing triplicates in 24 hours

Differential diagnosis: intussception, right iliac fossa mass, confused with appendicitis

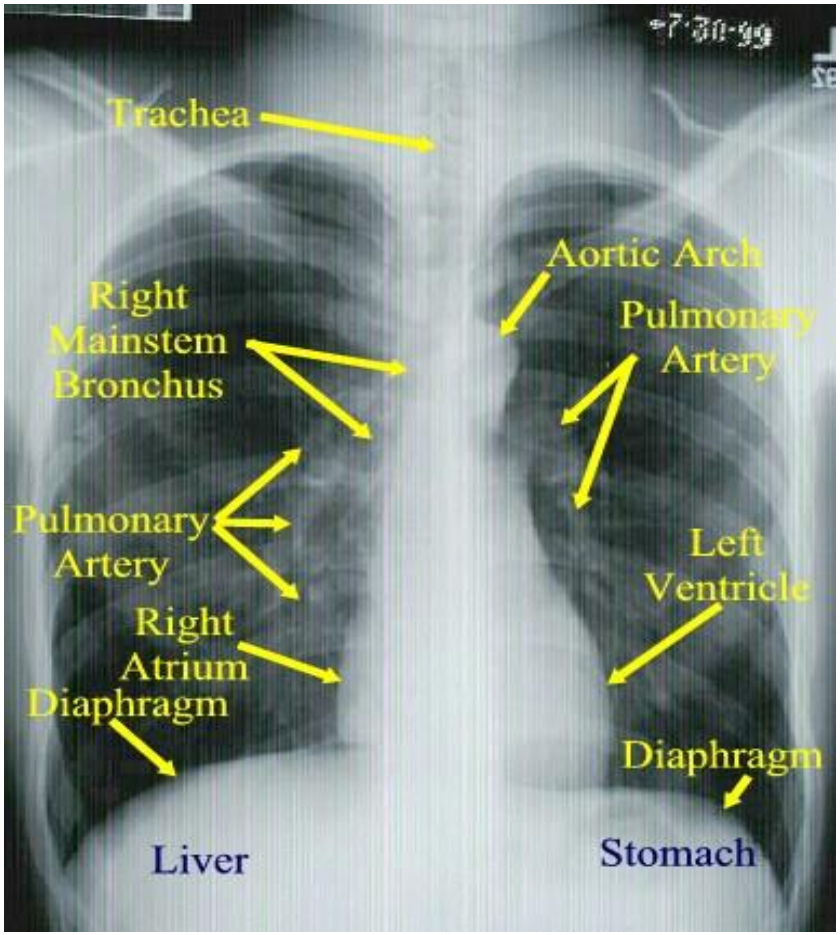
Large cell

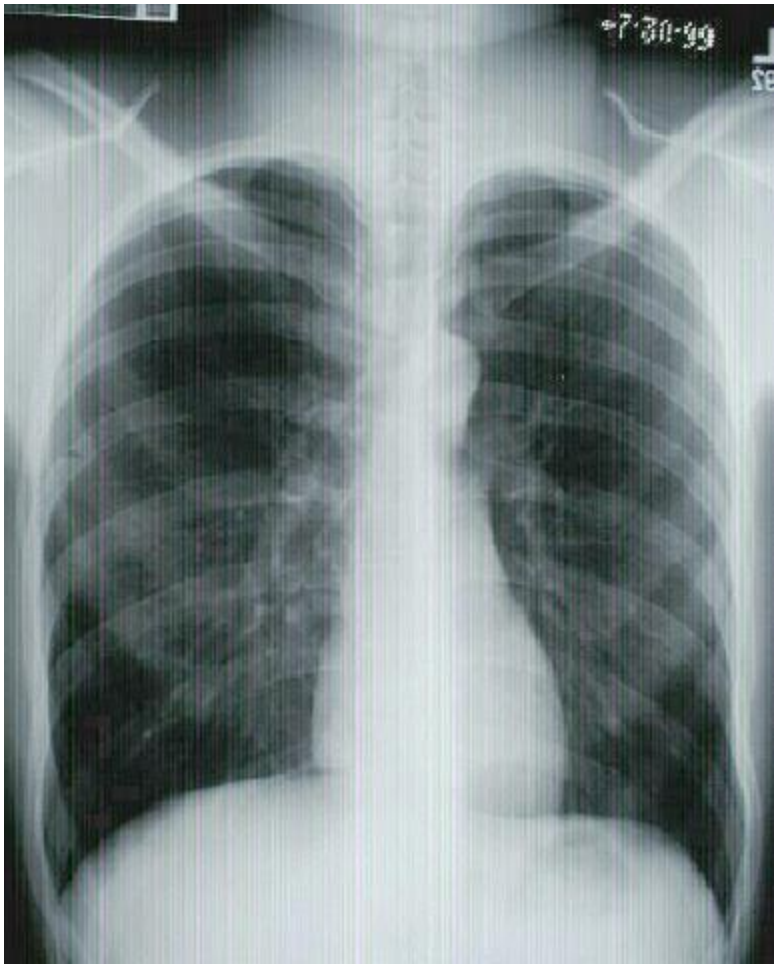
- usually B cell phenotype
- presentation similar to small noncleaved

NHL

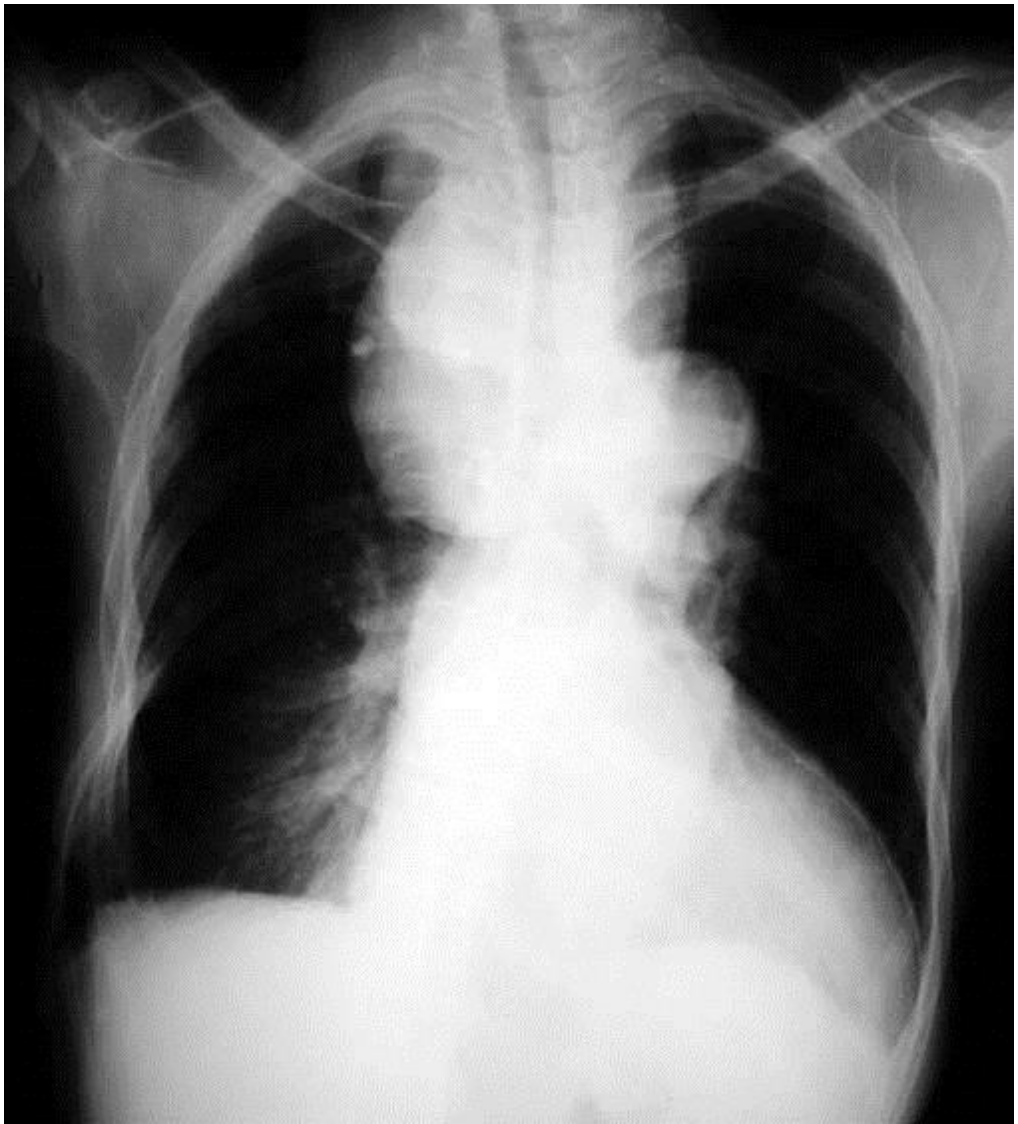
- Lymphoblastic
  - T cell phenotype
  - mediastinal mass, pleural effusion
  - SVC syndrome, dyspnea, often ICU admit
  - cervical adenopathy
  - abdominal involvement uncommon
- Staging - CT chest/abdomen/pelvis, bone marrow, LP
- Prognosis - tumor burden

Normal
Chest X-Ray





Mediastinal Mass



NHL

- Therapy – Chemotherapy
  - **Radiation no benefit except in emergencies**
  - **chemo differs, based on cell type**
  - **intensive, multiagent chemotherapy**
  - **CNS prophylaxis: intrathecal chemotherapy and cranial radiation.**

Brain Tumors

- **Most common solid tumor (1200 per year)**
- **Presentation dependent upon site of origin, not histology**
- **Obstructing, increased ICP - classic triad:**

  - morning headaches, -
  - nausea/vomiting,

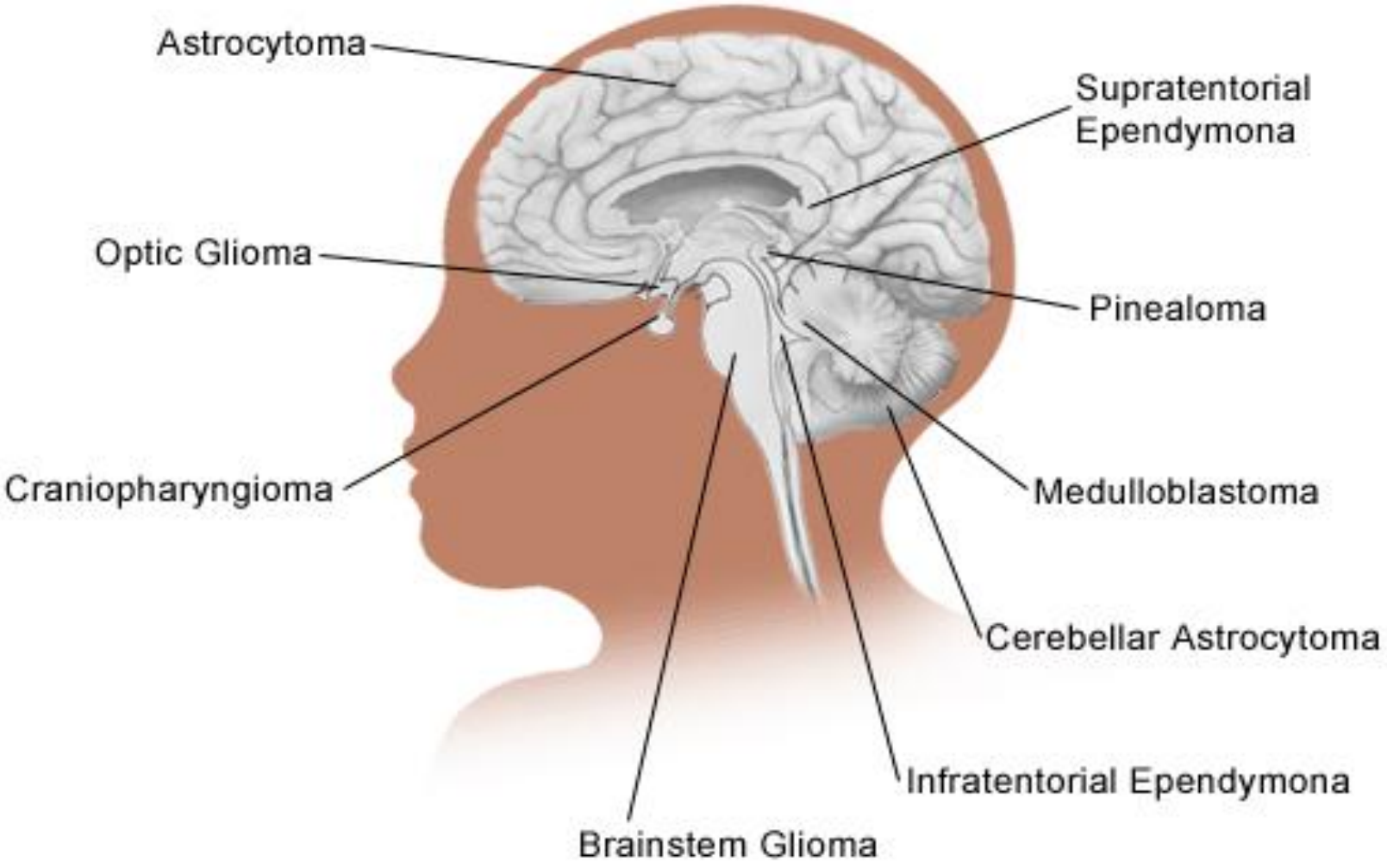
  - diplopia

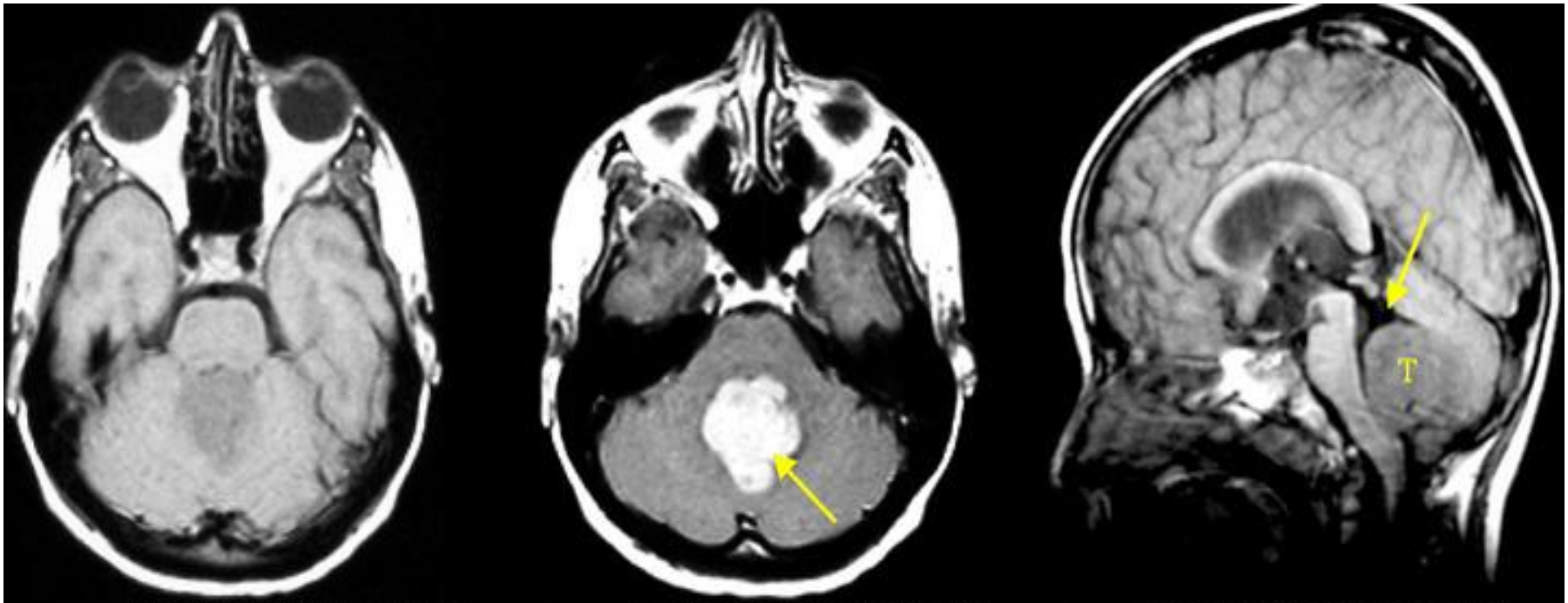
Brain Tumors

- Subacute ICP - poor school performance, fatigue, personality change, Headaches
- Infants, toddlers - irritable, anorexia, developmental delay, loss of milestones, optic pallor, macrocephaly
- Infratentorial -balance, truncal instability, difficulty with coordination, gait disturbance (ataxia)
- Supratentorial - seizure, hemiparesis, hemisensory loss, visual field defect

Brain Tumors

- Staging - MRI brain, spine for mets, LP for cytology, bone marrow aspirate/biopsy
- Treatment - SURGERY -prognosis better
- Craniospinal radiation
- Chemo - less of role for many types
  - advanced, metastatic
  - attempt to decrease XRT dose due to long term effects


Astrocytoma
Supratentorial Ependymona
Optic Glioma
Pinealoma
Craniopharyngioma
Medulloblastoma
Cerebellar Astrocytoma
Infratentorial Ependymona
Brainstem Glioma



Pre-contrast axial T1 Wtd MRI

Post-contrast axial T1 Wtd MRI

Pre-contrast sagittal T1 Wtd MRI

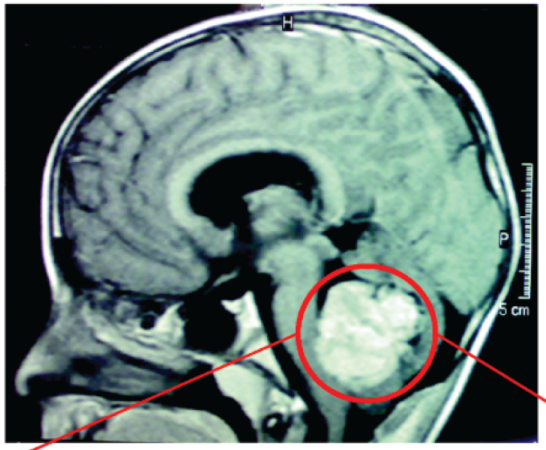
Findings:

An enhancing tumor (yellow arrow in B) seen posterior to the IV ventricle. Pre-contrast sagittal T1-weighted MR image (figure c) shows tumor (T) and its location posterior inferior to the IV ventricle (yellow arrow).

Diagnosis:

MEDULLOBLASTOMA

- Common pediatric brain tumor
- Common location is posterior to the IV ventricle, involving the vermis.
- Tumor enhances with contrast.



WNT (10%)	SHH (30%)	Group 3 (25%)	Group 4 (35%)
CTNNB1 mutation	*PTCH1/SMO/SUFU* mutation	*MYC* amplification	*CDK6* amplification
Monosomy 6	*MYCN* amplification	*PVT1-MYC* fusion	Isochromosome 17q
			SNCAIP duplication
WNT signaling	SHH signaling	Photoreceptor/GABAergic signaling	Neuronal/Glutamatergic signaling
	PI3K signaling	TGF-ß signaling	NF-kB signaling
MYC +	*MYCN* +	*MYC* +++	Minimal *MYC/MYCN*
5y OS 94%	5y OS 87%	5y OS 32%	5y OS 76%
Rare M+	Uncommon M+	Very frequent M+	Frequent M+

Wilm's Tumor

- Most common malignant renal tumor in children
- 460 cases per year
- Mean age 3-4 yrs
- WAGR Syndrome - del 11p13
- Beckwith-Wiedemann

Wilm's Tumor

- Abdominal swelling mass
- Abdominal pain, hematuria, fever
- Imaging
  - US, abdominal CT
  - MRI for caval patency
  - CXR for pulmonary mets

Wilm's Tumor

- Surgery upfront - nephrectomy
- Chemotherapy - VCR, actino +/- doxo
- XRT for advanced stages
- 65-90% RFS, overall 80%
- 5-7% bilateral

Neuroblastoma

- **Most common extracranial solid tumor (525 cases per year)**
- **Histology**
  - **Small round blue cell tumor**
  - **derived from post ganglionic sympathetic neuroblasts**
- **Arise in any site along sympathetic chain**

Neuroblastoma

- Most primaries - abdomen (adrenal)
- Infants - thoracic, cervical
- Most cases < 5yrs, rare > 10 yrs
- Metastasis - lymphatic, hematogenous
- Infants more localized vs older children more metastatic
- Cytogenetic chromosonal abnormalities

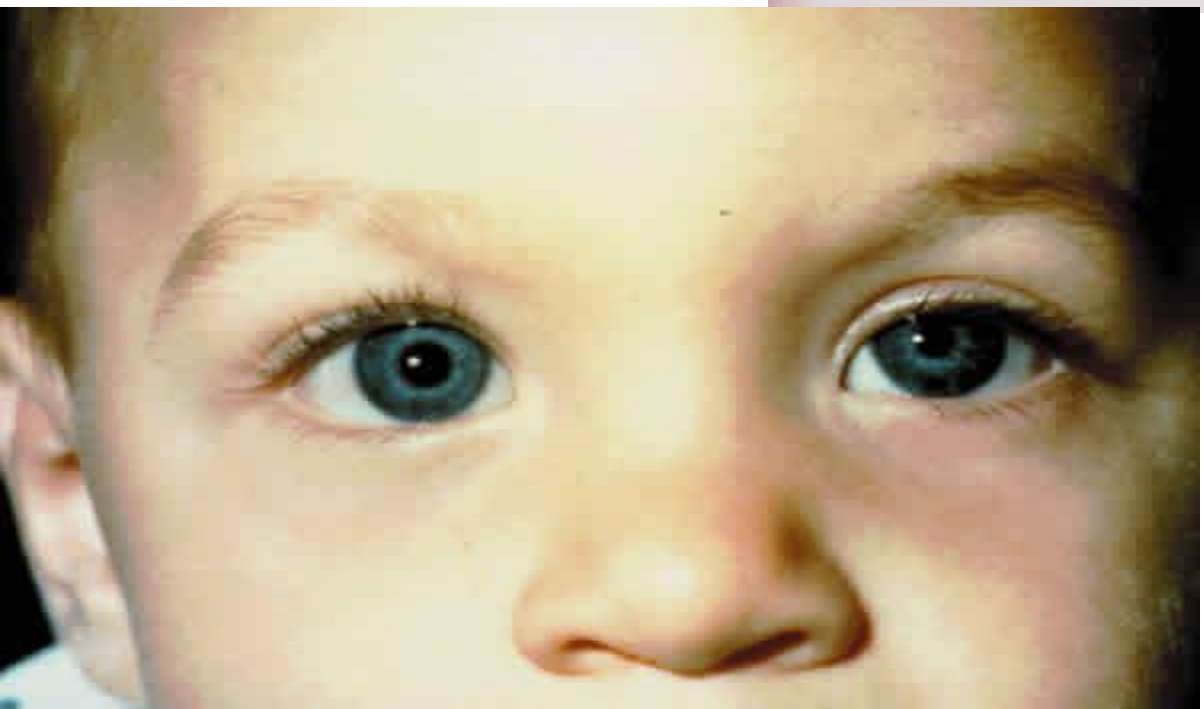
Neuroblastoma

- Surgery - pivotal role
- Chemotherapy - aggressive, multiagent
- radiation for advanced stages
- High-dose chemo with auto BMT? - delay recurrence?

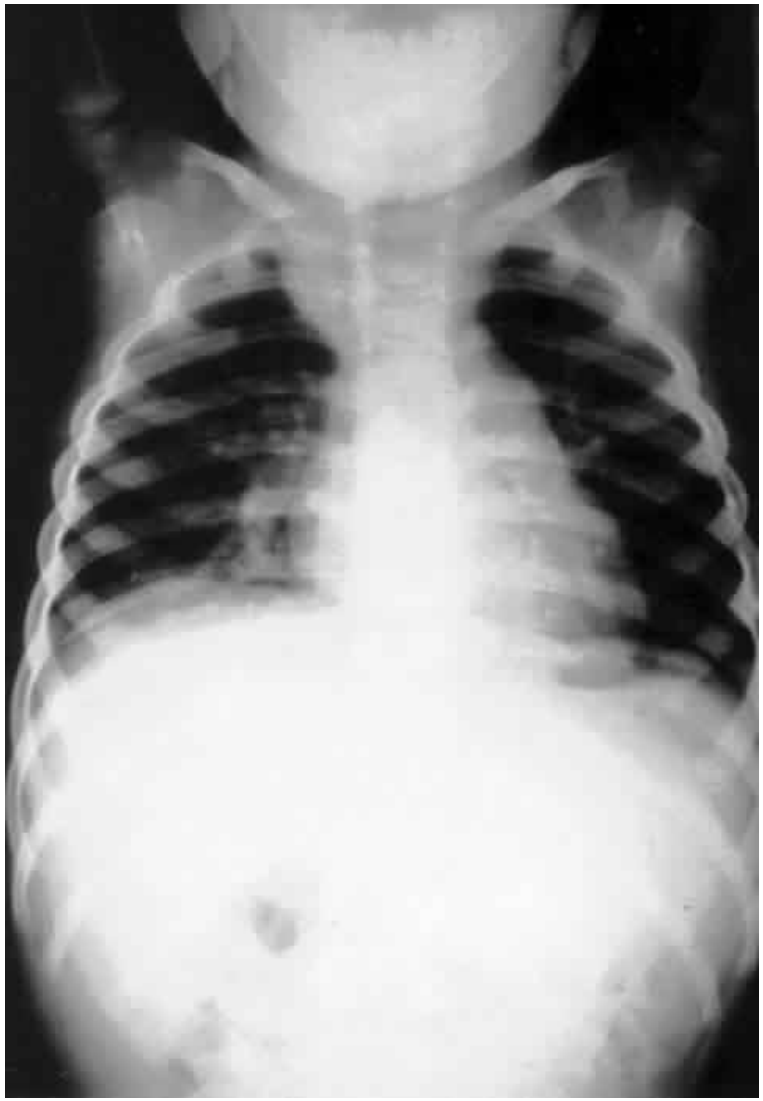
What science as done and what we still need to do

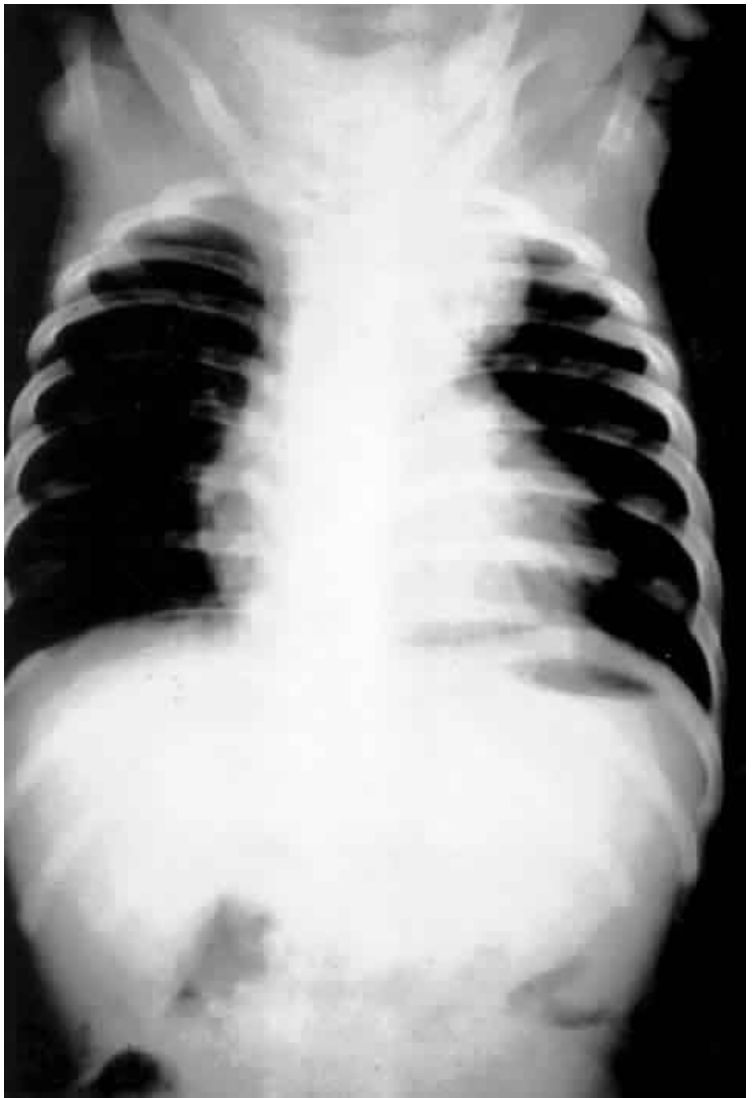
- Immune modulation and antibody therapy
- Teasing the disease apart to decrease toxicity and increase cure.

Horner's Syndrome



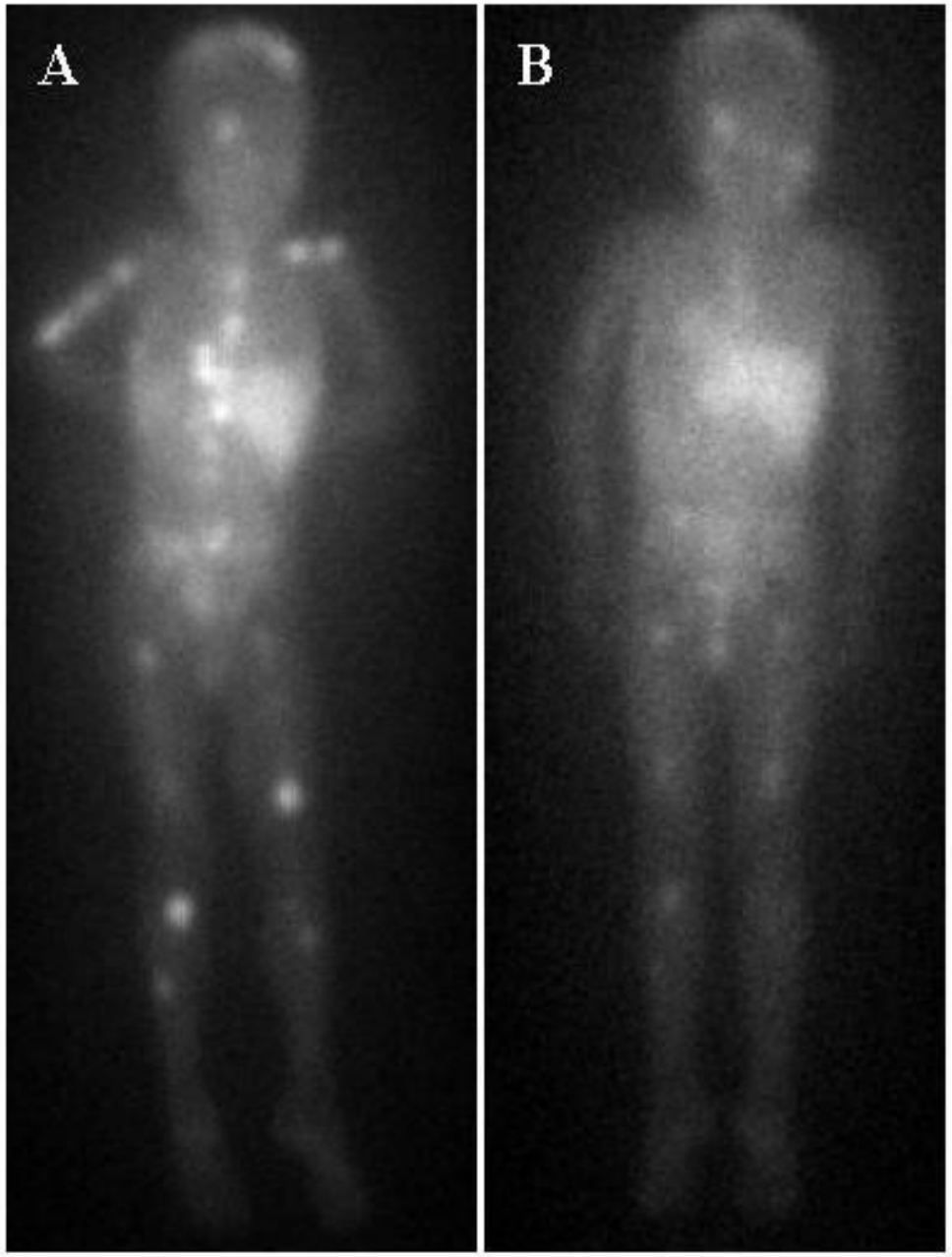
Mediastinal mass in neuroblastoma





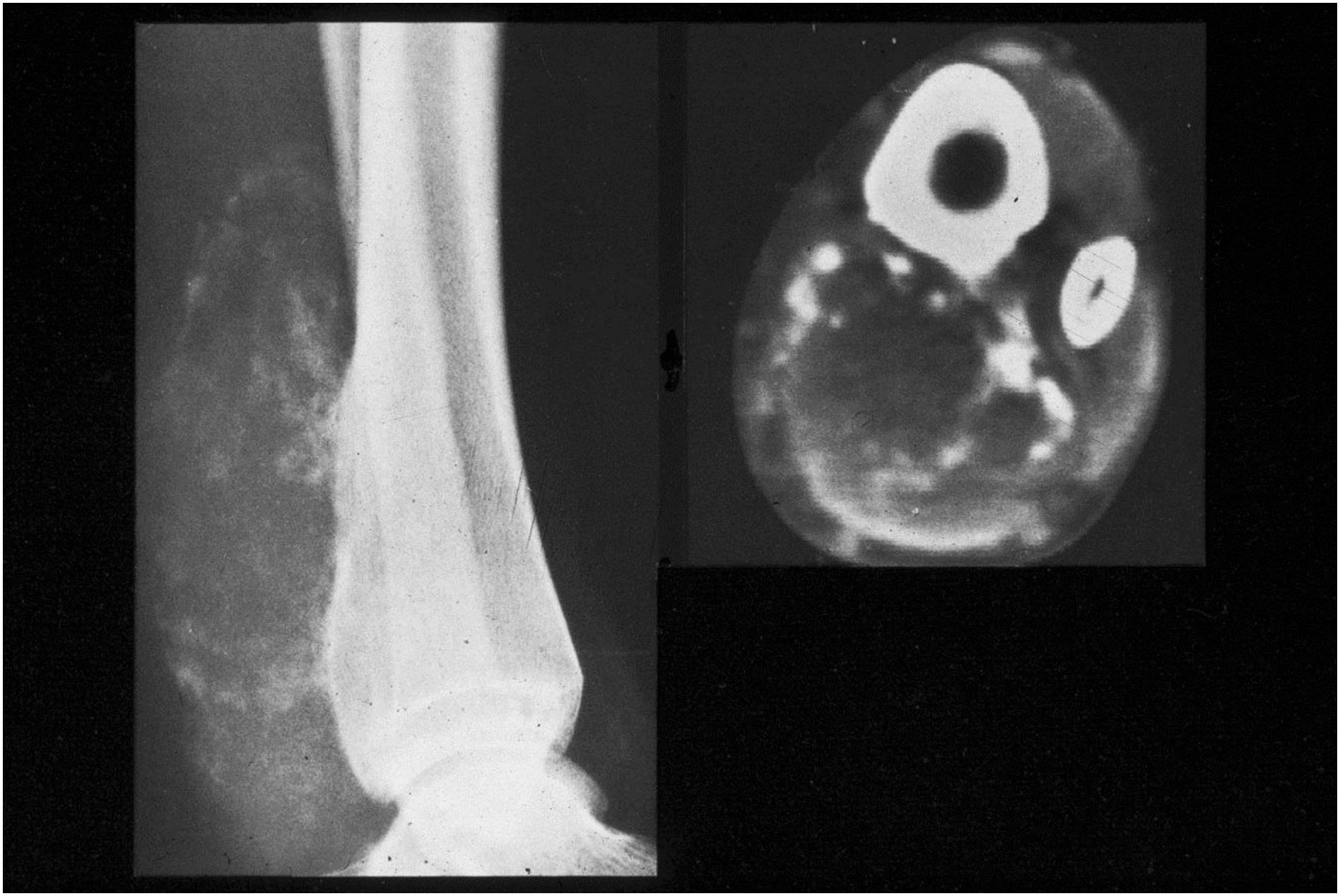
MIBG

Bone metastasis



Bone Tumors Osteogenic Sarcoma

- 7th largest, 3rd largest group in adolescents
- Osteosarcoma
  - **distal femur, proximal tibia, proximal humerus**
  - **Metaphysis of the bone**
  - **pain, soft tissue mass**
  - **20% metastatic at diagnosis- lung, bone**
  - **“Codman’s triangle”**
  - **stage - MRI primary, CT chest, bone scan**
  - **Neo-adjuvant chemo - limb-sparing surgery**
  - **80-90% RFS**
  - **Lung mets at diagnosis decrease survival rate**



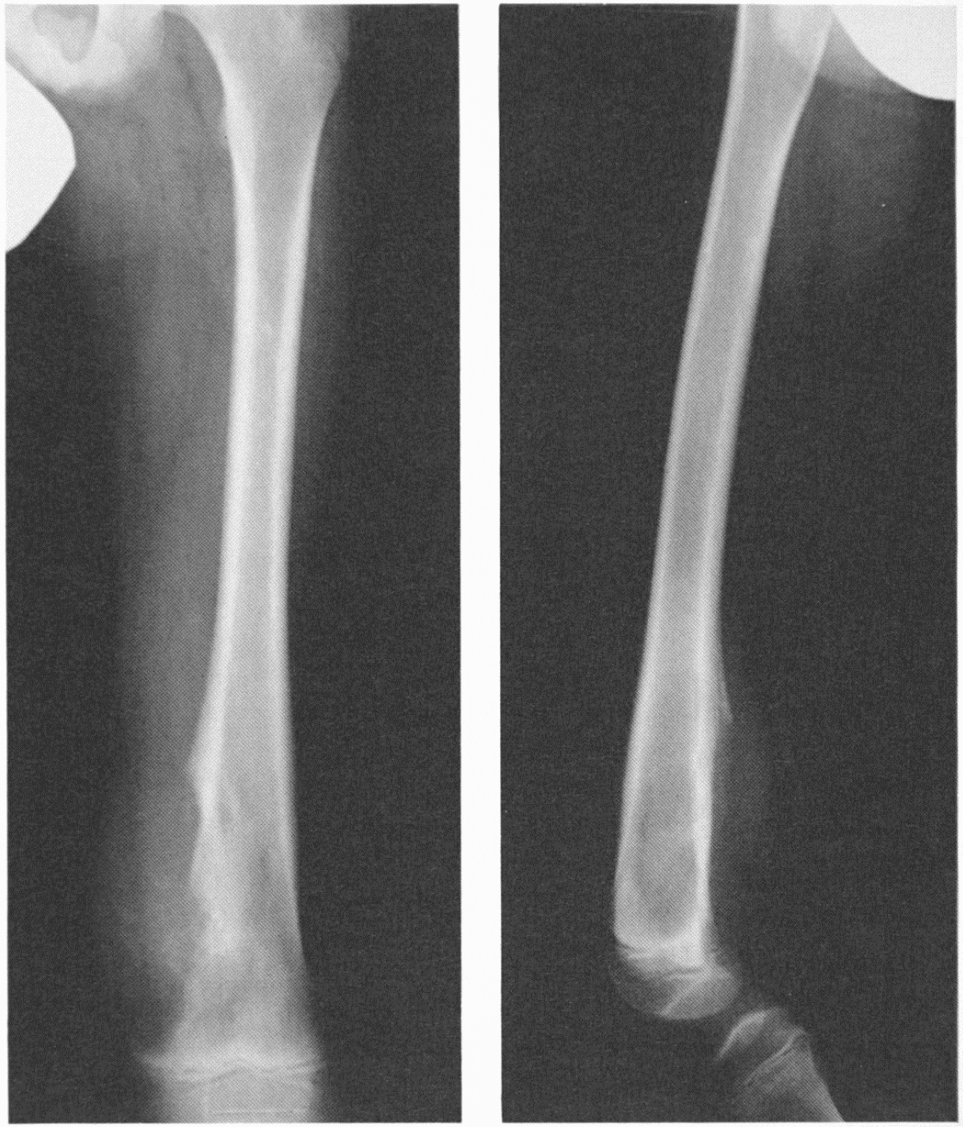
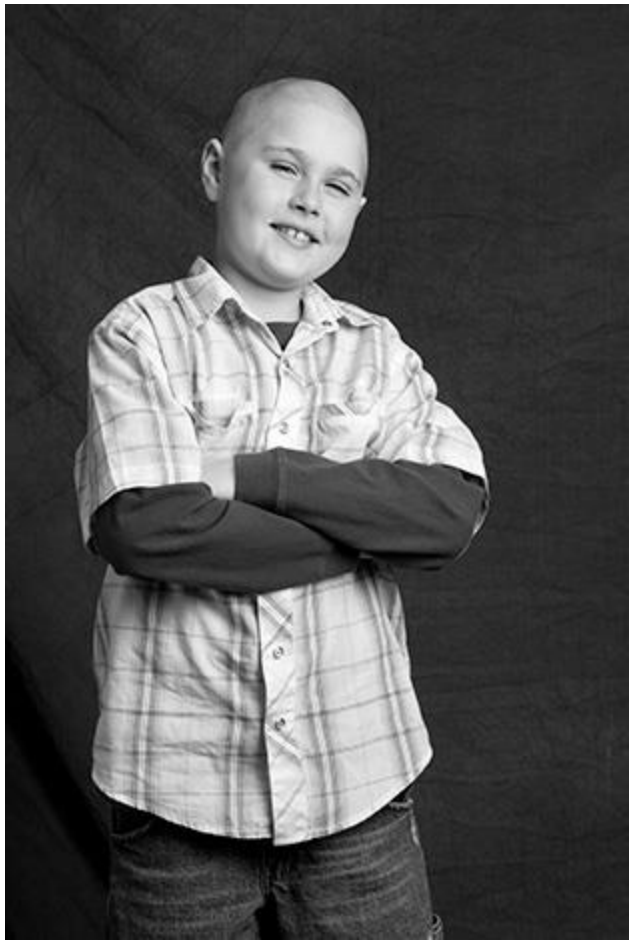


FIGURE 35–3. Radiographs (posteroanterior and lateral projections) of a conventional osteosacoma involving the distal femur and extending up the shaft. The tumor demonstrates a mixed lytic and sclerotic appearance, a soft tissue mass with ossification apparent in the soft tissue, and periosteal reaction and the formation of Codman's triangle proximally.

Bone Tumors Ewings Sarcoma



- Ewing's Sarcoma
  - **any bone - pelvis, femur, tibia, fibula, scapula, spine, ribs (axial)**
  - **pain, swelling, <u>fever</u>**
  - **metastasis - lungs, bone, marrow**
  - **Plain film "onion skin" appearance**
  - **Chemo, radiation**

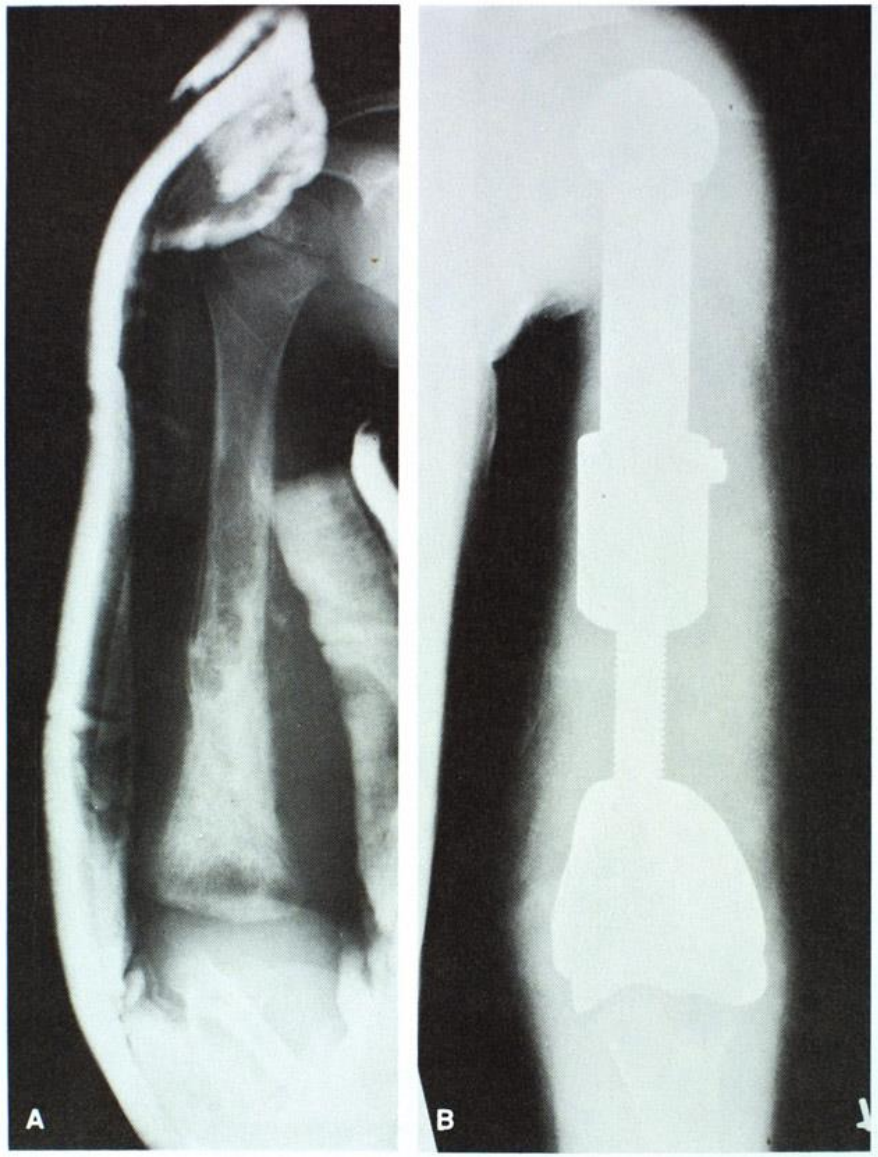


FIGURE 33–7. **A.** A plain radiograph of Ewing's sarcoma of the humerus in a 4-year-old patient. This was treated by induction chemotherapy followed by resection of the entire humerus. All margins were negative. Radiation was not used due to the child's age. **B.** Postoperative radiograph showing an expandable, total humeral prosthesis. (Courtesy of Dr. J. Eckardt of UCLA)