Disease 5

APPROVED

Each disease is covered in the following manner:
1. characteristic history/physical/lab findings
2. pathophysiology
3. pathology
4. staging
5. treatment

Epidemiology is also thrown in.
I made a summary on slides 159-160.

Chronic Myelogenous Leukemia

There were 4 lectures scheduled for hematologic malignancies, but the lecturers crammed the material into 3. This is part 3 of 3. This notesgroup is also 160 slides long.

Case 5

Important findings have been highlighted in orange.

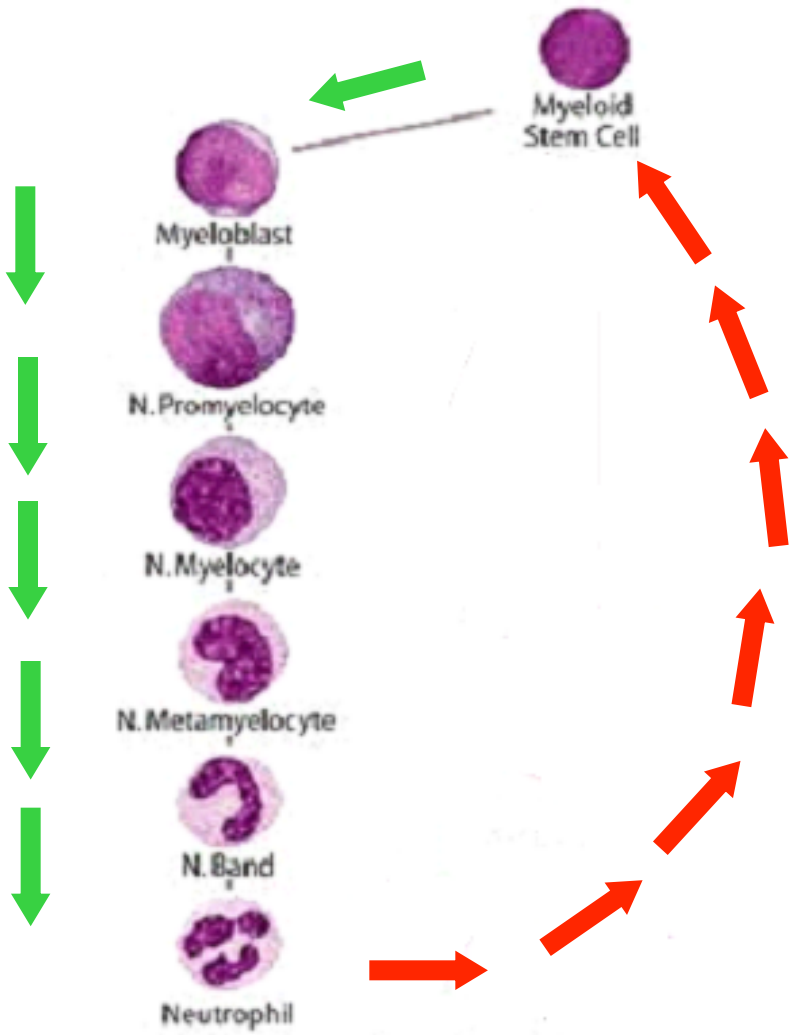
Old age is an important clue.

- 63 year old man who noted progressive fatigue (symptom of anemia). He did have left upper quadrant pain and his belly was enlarging but he thought he was just getting old. He was seen, a markedly elevated WBC was noted.

- Physical examination:
  - ABD: marked enlargement of the spleen, 10 cm below the left costal margin

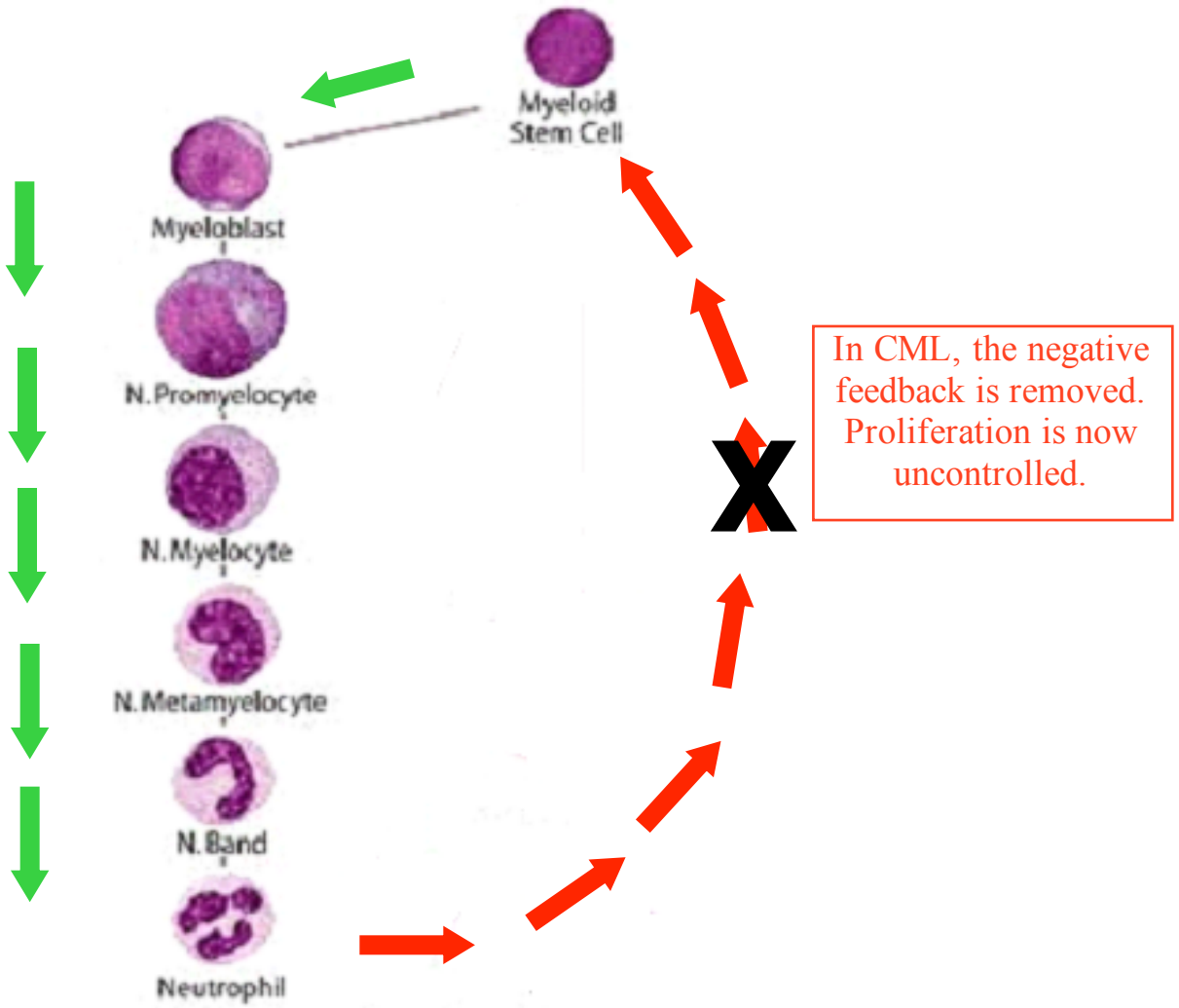
- LAB:
  - Hct: 31% Anemia
  - WBC: 110,000/mm^3 Leukocytosis
  - Platelet: 487,000/mm^3 Thrombocytosis

Feedback Control

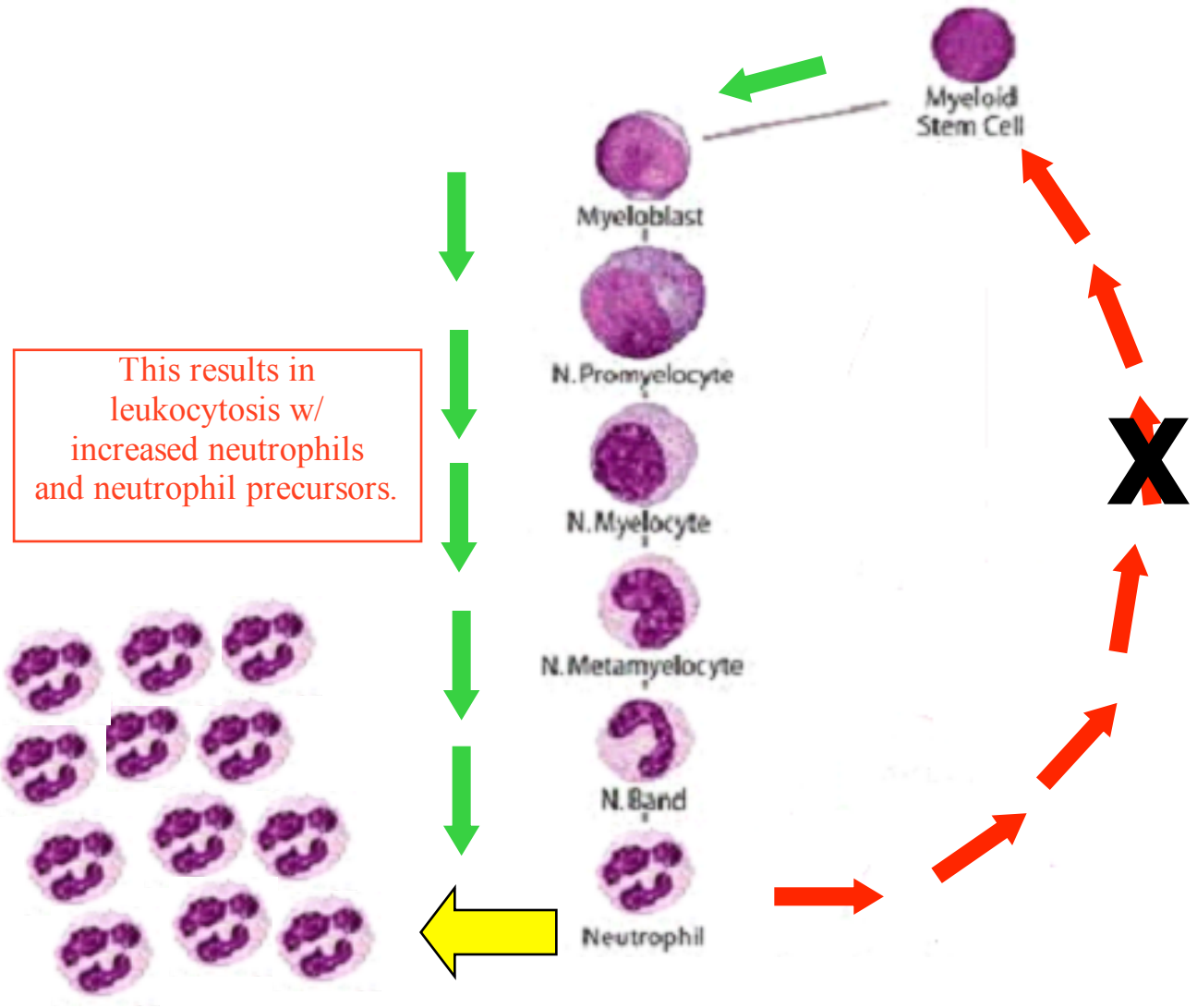


This is what normally happens. There is negative feedback to regulate myeloid stem cell proliferation and differentiation.

Chronic Myelogenous Leukemia: Pathophysiology Maturation and Uncontrolled Growth



Chronic Myelogenous Leukemia: Pathophysiology Maturation and Uncontrolled Growth



This results in leukocytosis w/ increased neutrophils and neutrophil precursors.

Chronic Myelogenous Leukemia Definition

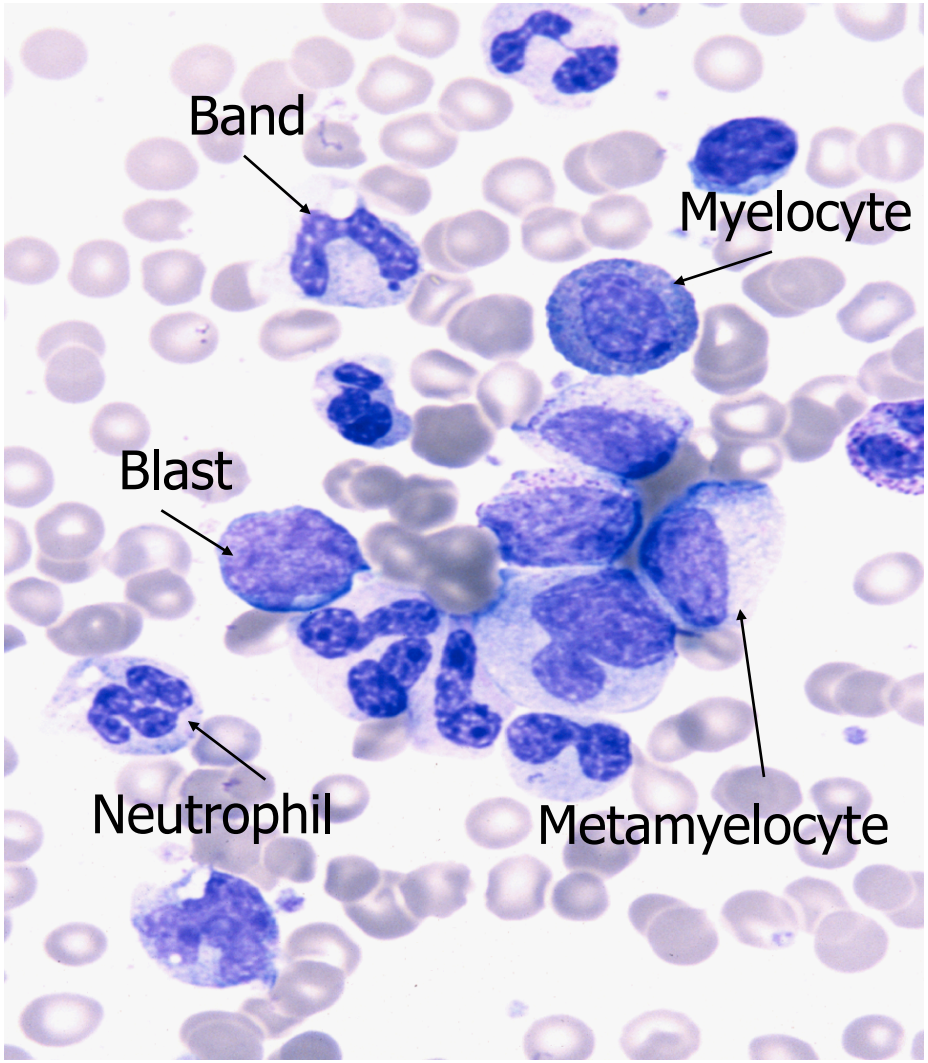
- CML is a clonal disorder of the pleuripotent stem cell characterized by excess of proliferation of the late progenitor, or relatively mature myeloid compartments

Chronic Myelogenous Leukemia Diagnosis

- **Morphology**
- **Cytogenetics**

Here cytogenetics is more important.

Chronic Myelogenous Leukemia: Morphology



You will see a mixture of myeloid lineage cells in the peripheral blood smear.

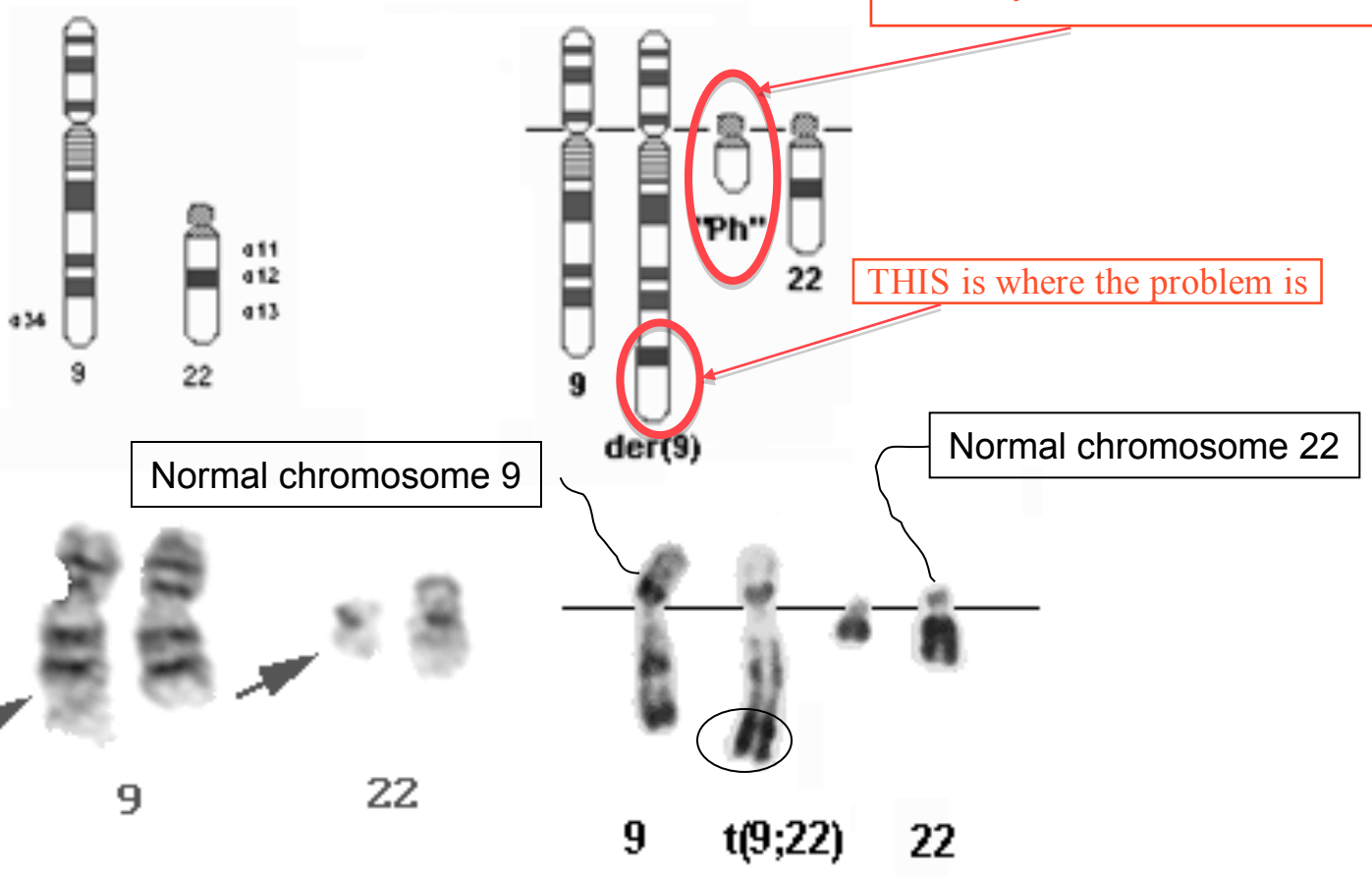
Usually there is thrombocytosis as well.

Chronic Myelogenous Leukemia: Diagnosis

t(9;22)(q34;q11)

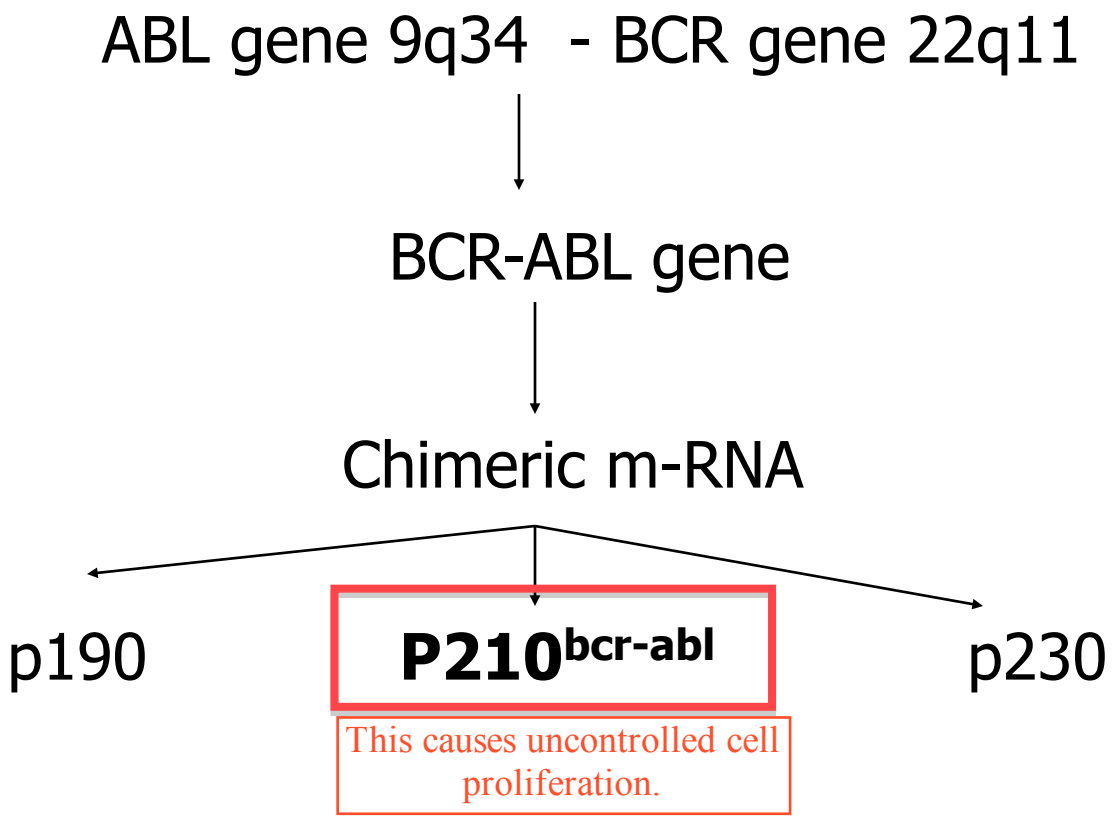
The classic translocation that causes CML.

While the stubby chromosome 22 is known as the "Philadephia chromosome," the problem is really on chromosome 9.

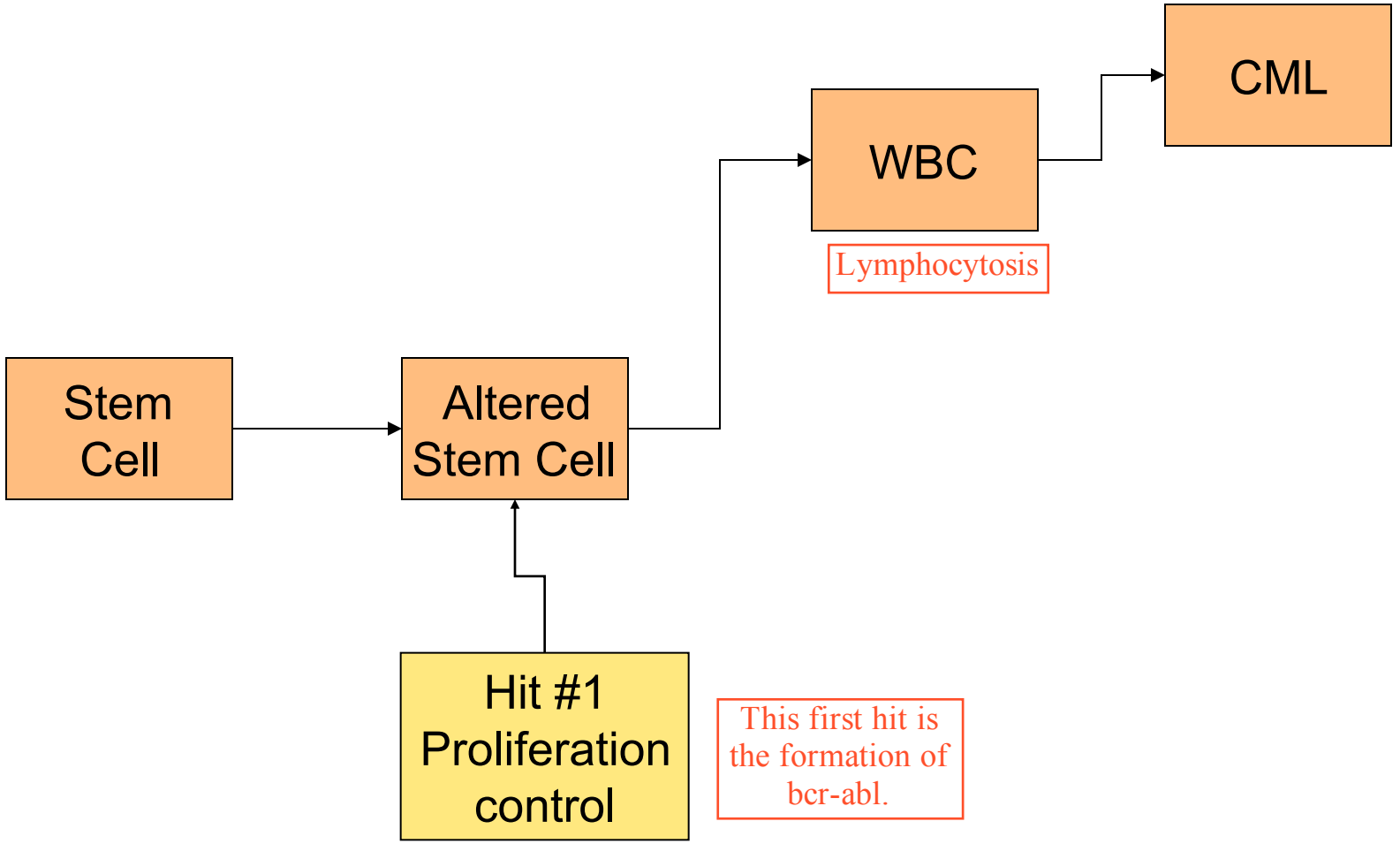


http://www.infobiogen.fr/services/chromcancer/Anomalies/t0922CML.html

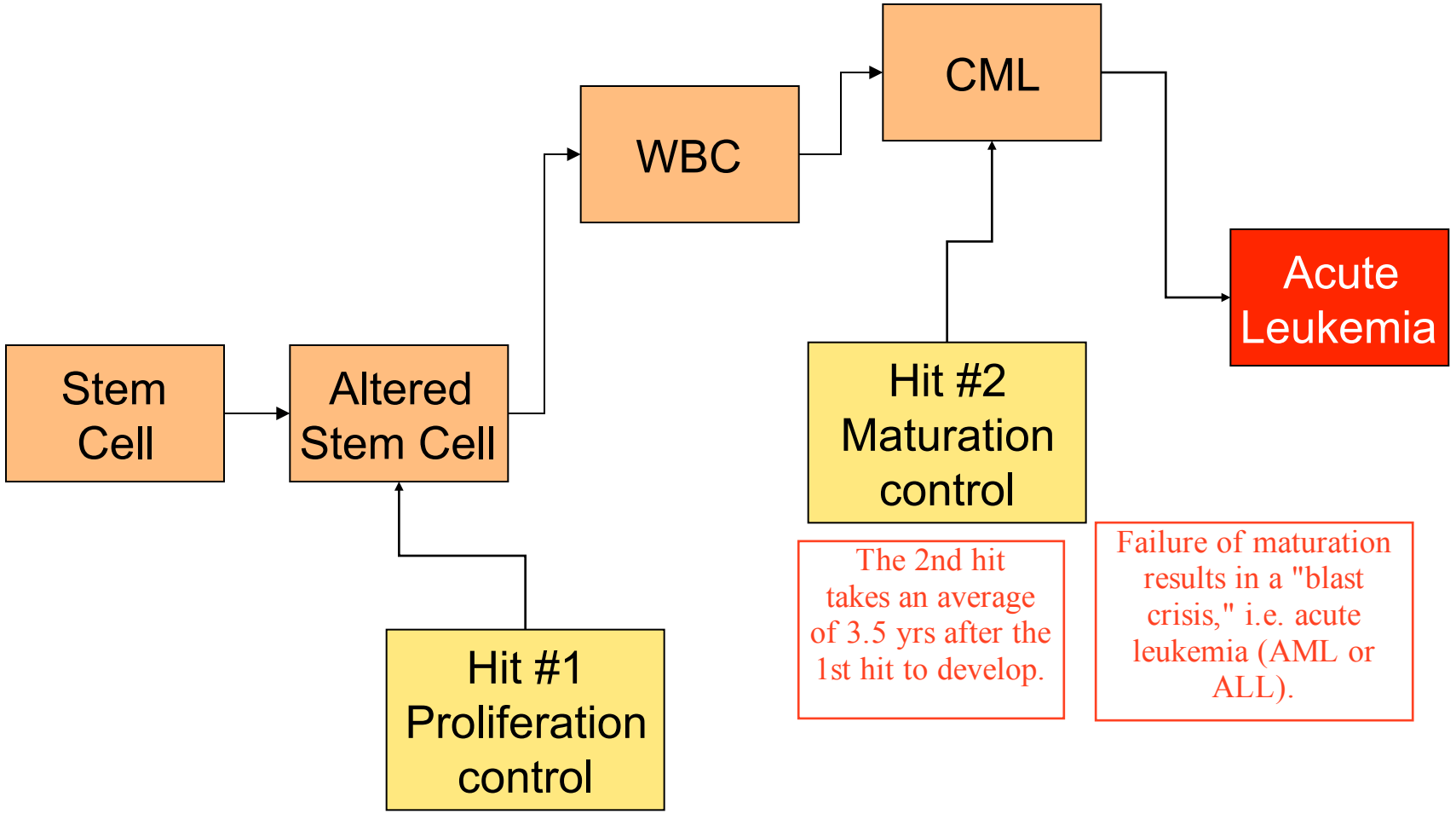
Chronic Myelogenous Leukemia: Diagnosis t(9;22)(q34;q11)



Chronic Myelogenous Leukemia Pathophysiology



Chronic Myelogenous Leukemia Pathophysiology



Definition of Phases
Staging

- Chronic phase.
  - < 15% blast in bone marrow or peripheral blood.
- Accelerated phase.
  - Cytogenetic clonal evolution.
  - Peripheral blood with ≥ 15% blasts, or ≥ 30% blasts plus promyelocytes, or ≥ 20% basophils.
  - Thrombocytopenia < 100,000 not related to therapy.
- Blast phase
  - ≥ 30% lasting bone marrow or peripheral blood.
  - Extra medullary involvement

This phase lasts ~3.5 yrs (as mentioned previously, this is the time it takes to develop the 2nd hit that inhibits maturation, which then causes progression to the blast phase)

It is this last stage, which lasts 3-6 months, that is life-threatening to the patient.

BCR-ABL Fusion Genes in Leukocytes of Normal Individuals

- 16 healthy subjects
- 7 hematopoietic cells lines
- 1 murine fibroblast line (4 batches)
- peripheral blood
- analysis
  - conventional cytogenetics
  - FISH with BCR and ABL probes
  - RT-PCR
    - amplifications of p210 and p190 BCR-ABL transcripts
      - detects 1 leukemia cell in 10^5 to 10^6 nonhematopoietic cells

Here's a scary thing:
in 16 healthy people, quite a few had the BCR-ABL protein!!!

Bose (Hammersmith Hospital) Blood 92:3362-3367,1998

BCR-ABL Fusion Genes in Leukocytes of Normal Individuals

Here's the data showing what was said on the previous slide.

Type Fusion mRNA	Cells	Result
p210	Healthy individuals	4/15
	Hematopoietic cell lines	3/7
	Fibroblast cell line	0
p190	Healthy individuals	11/16
	Cell lines	7/7
	Fibroblast cell lines	0/4

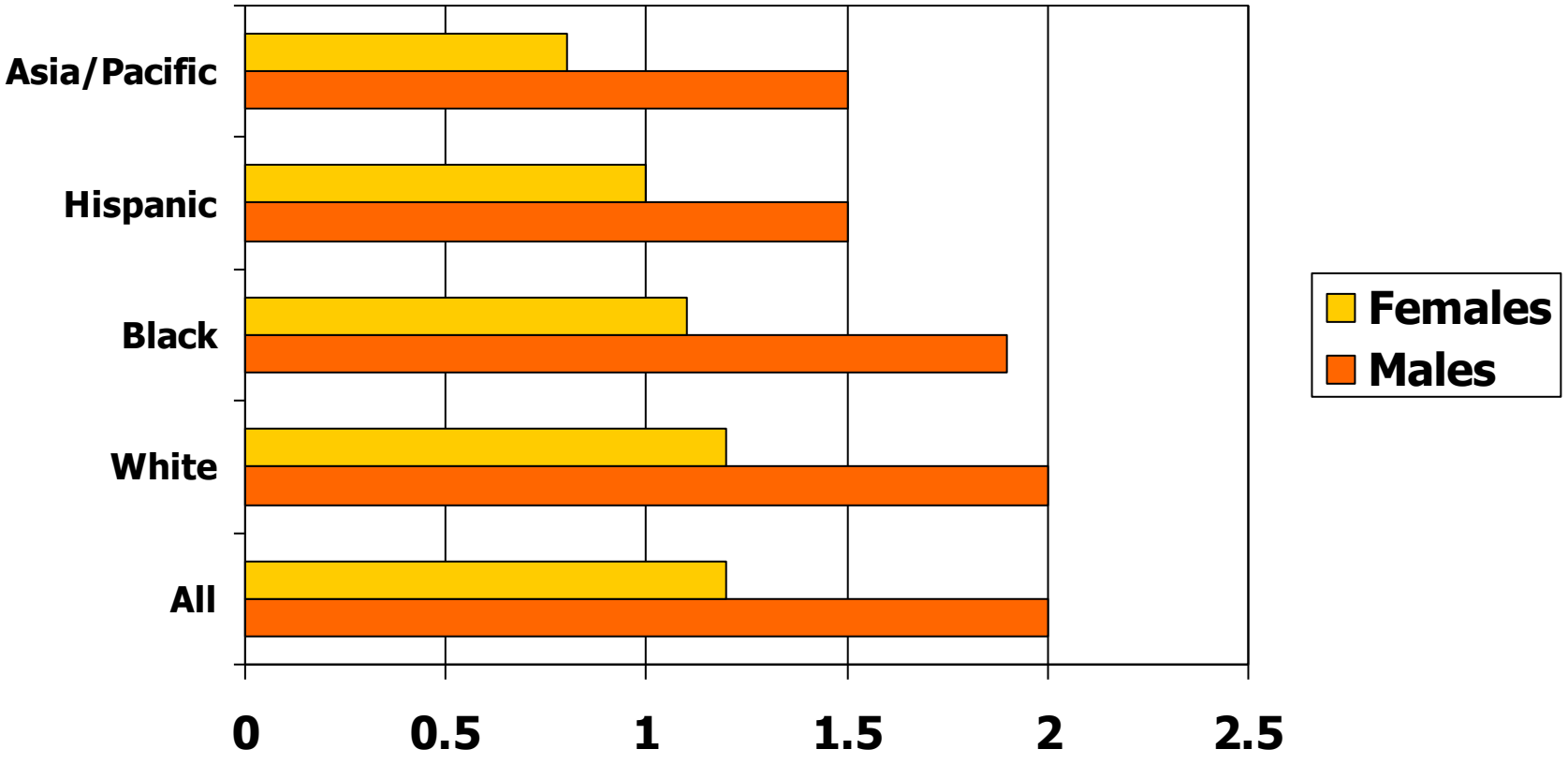
Bose (Hammersmith Hospital) Blood 92:3362-3367,1998

Poor Prognostic Factors

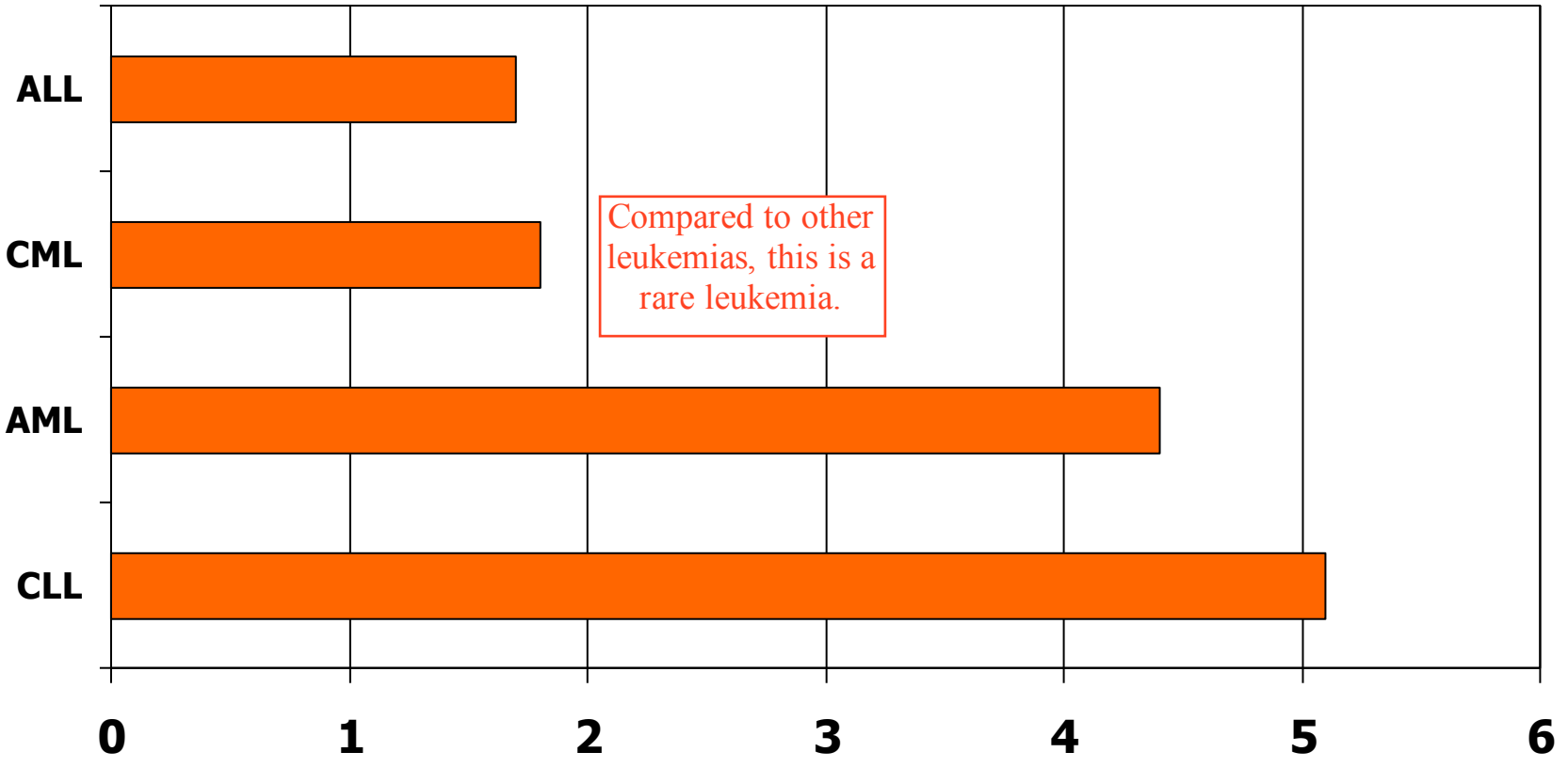
- Age (higher)
- Spleen size (larger)
- Liver size (larger)
- Hematocrit (lower)
- WBC count (higher)
- Platelet count (higher)
- Percent blasts in blood (higher)

Chronic Myelogenous Leukemia Incidence Rates by Race per 100,000 Population per Year

There is a higher incidence in males among all races.
Between races, Asians have the lowest incidence.



Chronic Myelogenous Leukemia Incidence Rates by Race per 100,000 Population per Year

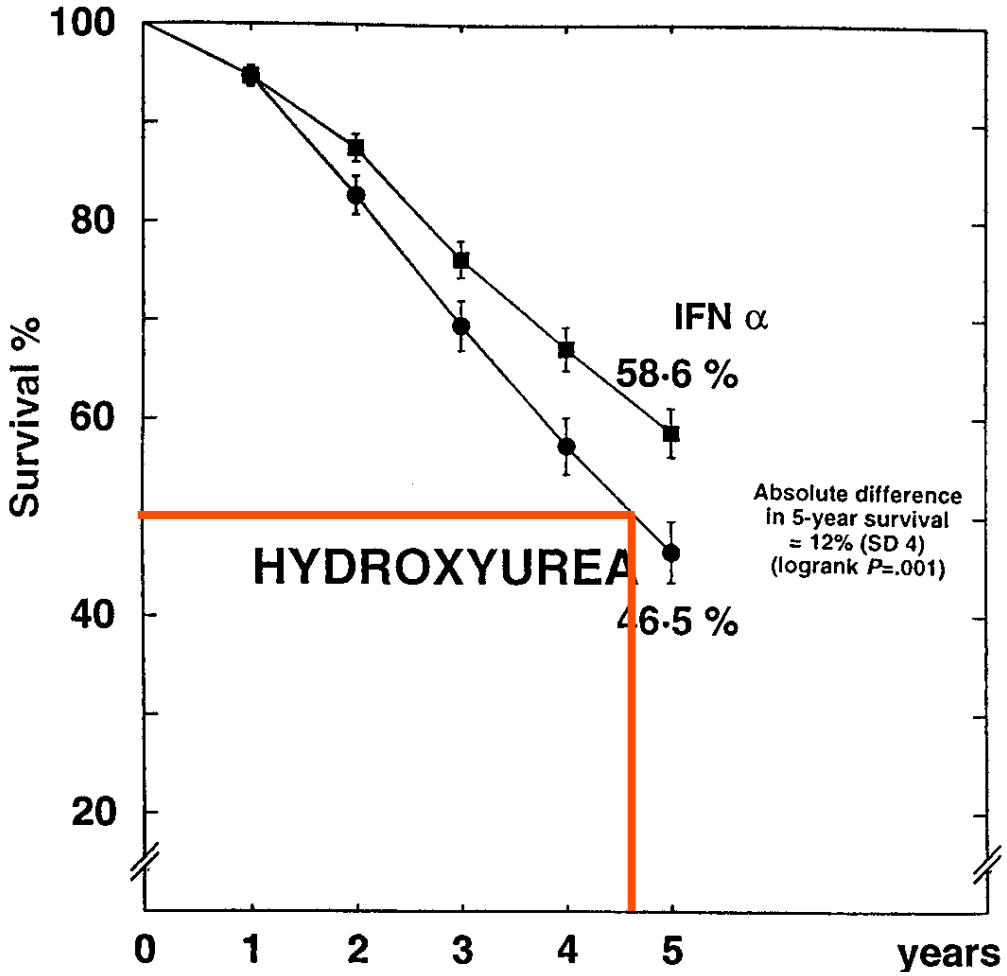


Chronic Myelogenous Leukemia Epidemology

- Ionizing radiation

This was discovered upon observation of Hiroshima survivors. It remains the only known cause of CML.

CML IFN vs Chemotherapy
CML Trialists' Group

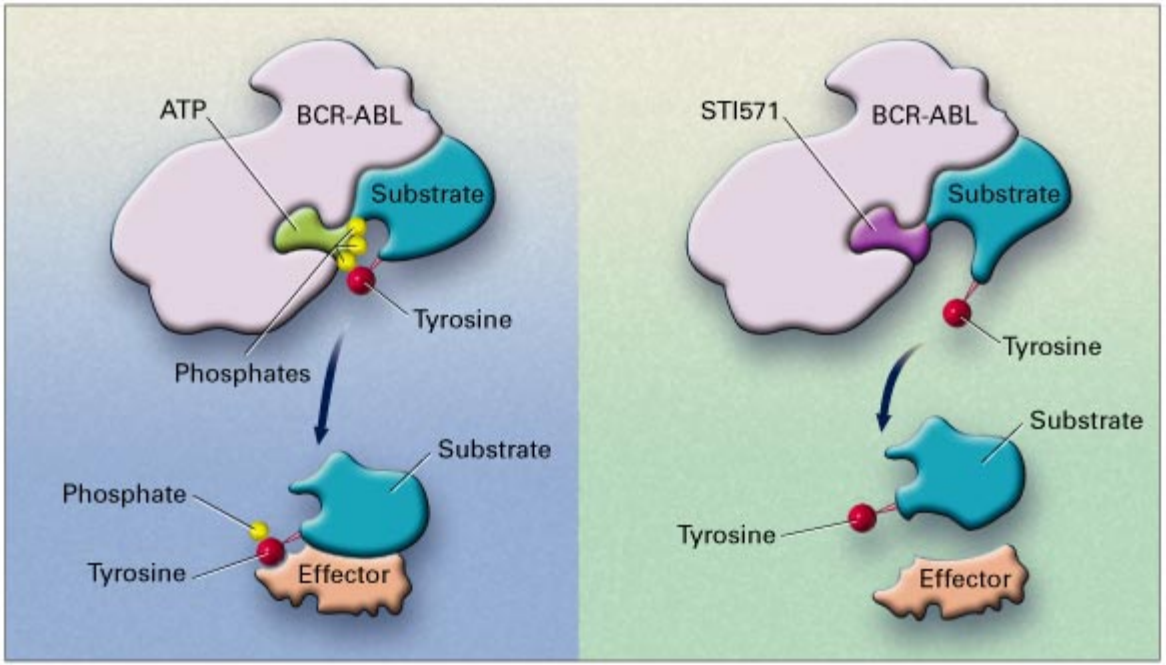


This is survival data for CML treatments from the pre-imatinib era.

CML Trialists' Collaborative Group, J Nat Cancer Inst 89:1616, 1997

Trade name: Gleevec

Imatinib Mechanism



Goldman and Melo, N Engl J Med 344 (14): 1084, 2001

STI 571 (Imatinib) Study Characteristics

During the initial trials, imatinib produced dramatic improvements in 2 weeks in patients who failed with other treatments!

- Chronic phase CML
  - Blasts and basophils < 15%
  - Ph+
  - IFN failed
    - no Hematologic CR at 3 months
    - no cytogenetic response at 12 months
  - IFN intolerance
- 83 patients
  - Hematologic resistance: 37
  - Cytogenetic resistance: 33
  - IFN intolerance: 13

Druker et al. N Engl J Med 2001;344:1031-7.

STI 571 (Imatinib) Study Results

Hematologic Complete Response	98%
Cytogenetic responses	54%
Cytogenetic responses MAJOR (≤35% of cells Ph+)	31%
Cytogenetic responses COMPLETE	13%
Time to cytogenetic response Median Range	 148 days 2-10 months

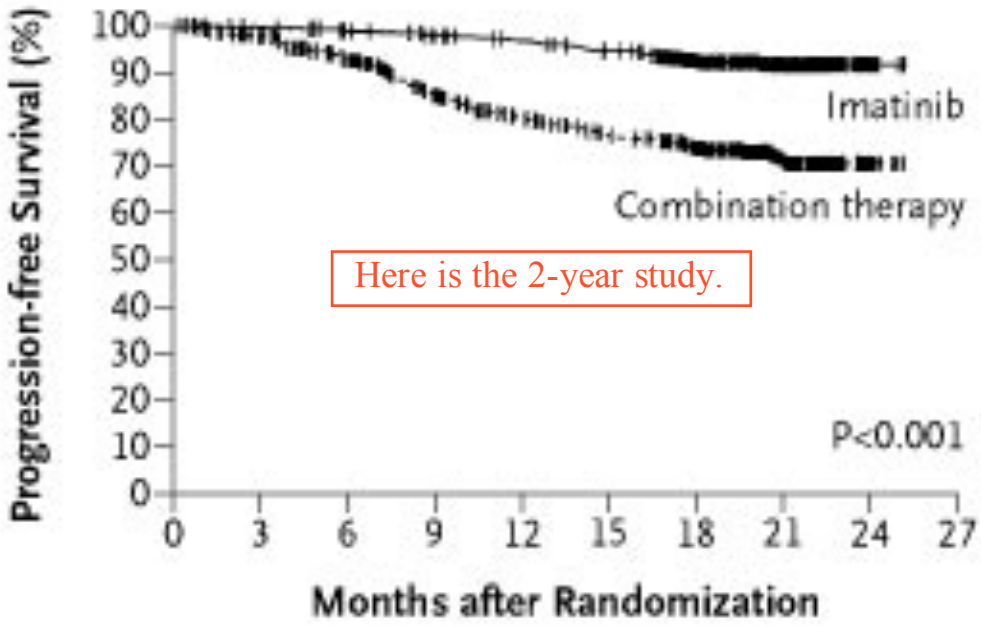
This is good

Druker et al. N Engl J Med 2001;344:1031-7.

Imatinib Compared with Interferon and Cytarabine

Progression Free Survival

More good results from imatinib.

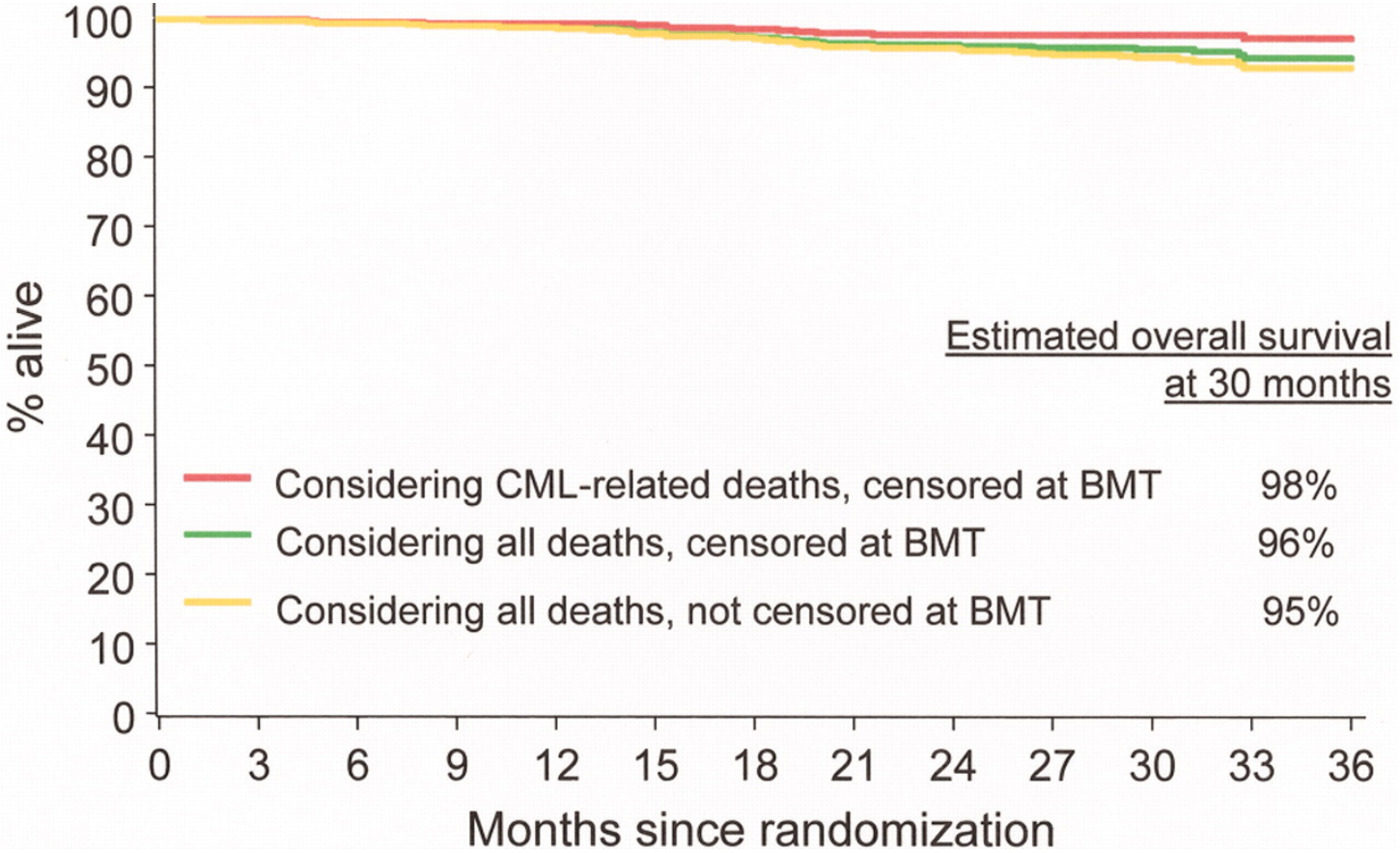


No. of Events								
Imatinib	2	7	12	18	29	41	42	42
Combination therapy	12	38	73	94	108	119	125	125
No. at Risk								
Imatinib	543	530	518	505	487	392	162	7
Combination therapy	498	442	376	334	302	255	99	7

IRIS Investigators, N Engl J Med 348:974-1004, 2003

Imatinib in Chronic Phase CML

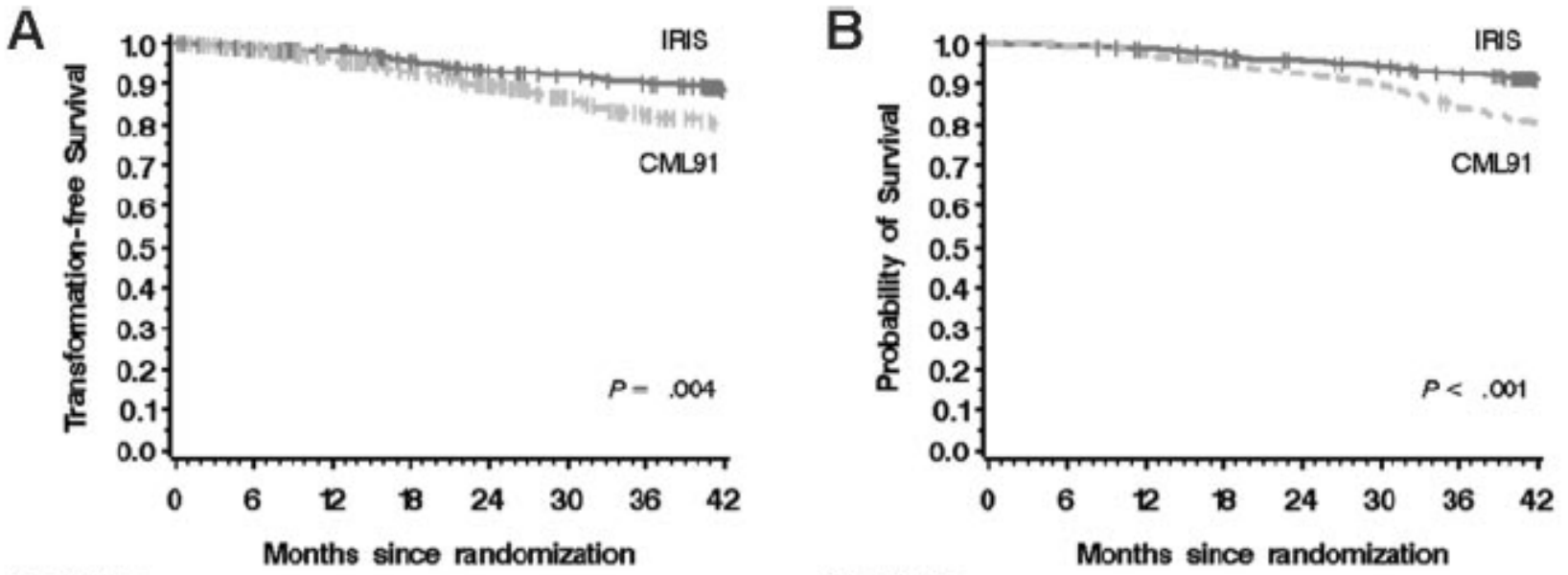
Here is the 3-year study



ASH Education Book, 2004

Imatinib vs IFN/Ara-C
Historical Comparison of Randomized Patients

Here is the 4 yr study



Roy, et al. Blood 108:1478-1484, 2006

Chronic Myelogenous Leukemia Summary

- Uncontrolled accumulation of mature cells
- Increase in all cell lines
- Splenomegaly
- Possible transformation to acute leukemia

- Inhibit tyrosine kinase

Case 6

Chronic Lymphocytic Leukemia

History

- 68 year old man seen for annual exam. He has not had an exam in 5 years. He is well.

  Asymptomatic

- FH: Brother had some sort of blood problem but he is well.

- PE: small, soft, 1 cm lymph nodes in cervical region; spleen tip is palpable

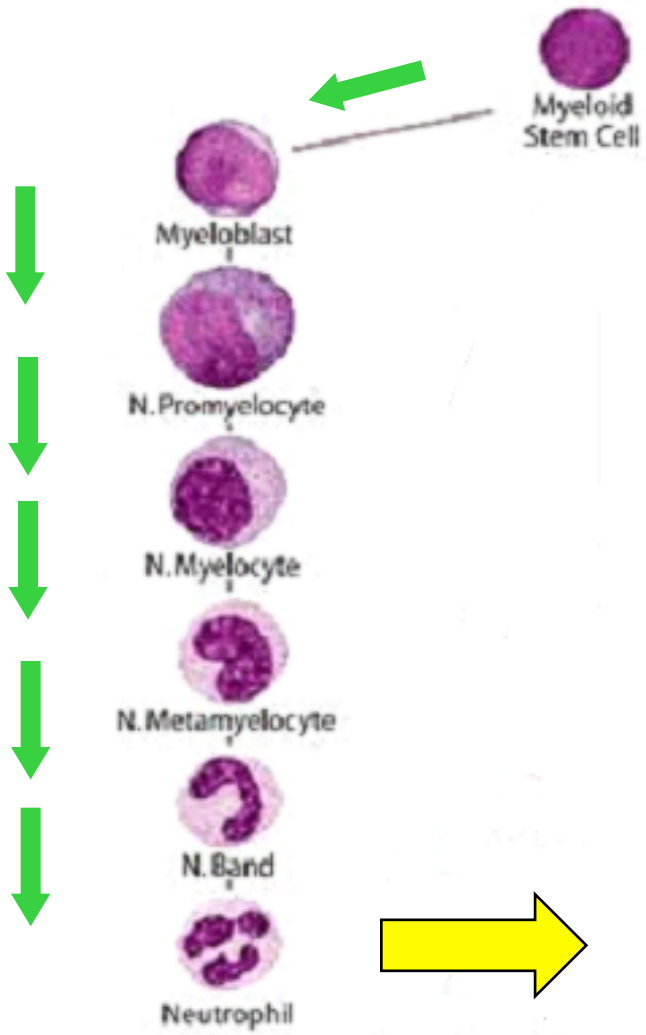
  But some suspicious physical findings…

Laboratory

WBC	32,300
Hct	39%
Platelets	187,000
Lymphocytes	22,868

Chronic Lymphocytic Leukemia: Pathophysiology
Apoptosis Defective

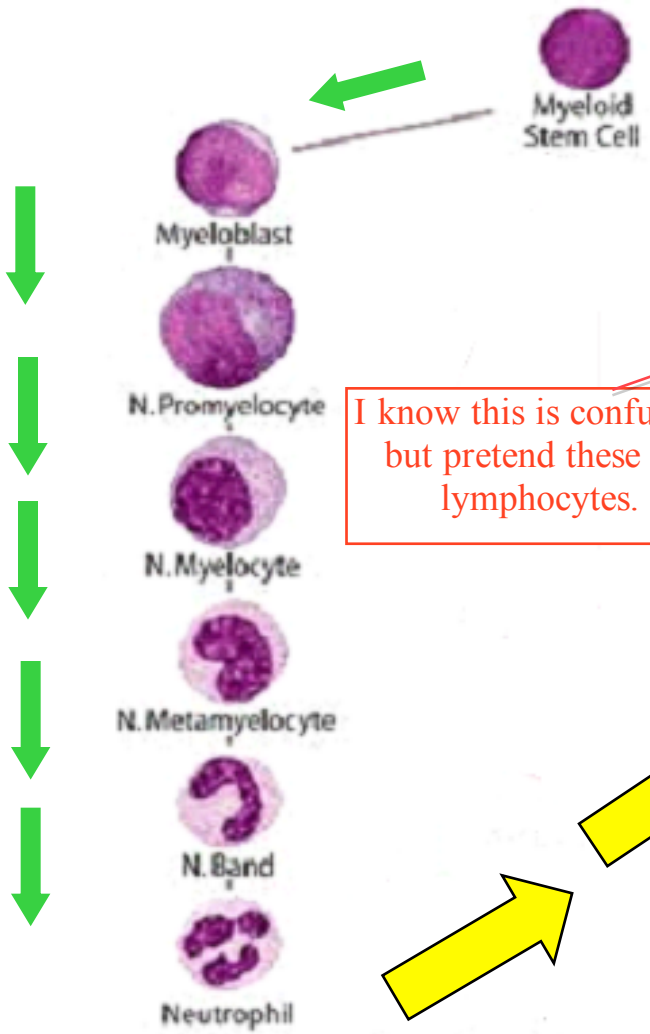
This shows a myeloid lineage, but for our discussion let's pretend that it's a lymphoid lineage. The same concepts apply.



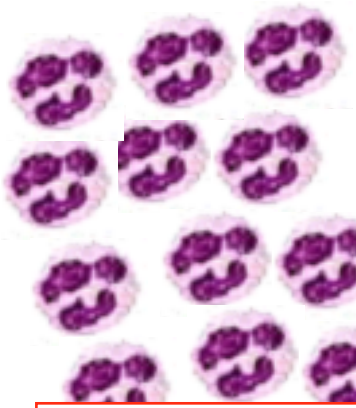
Apoptosis
Programmed cell death

Low Grade NHL: Pathophysiology
Apoptosis Defective – Cells Accumulate

Again, pretend this diagram depicts a lymphoid lineage.



I know this is confusing, but pretend these are lymphocytes.



Apoptosis is defective in CLL

In CLL, a defect in LYMPHOCYTE apoptosis causes LYMPHOCYTOSIS (see slide 34).

Apoptosis
Programmed Cell Death
X X X X

Chronic Lymphocytic Leukemia: Diagnosis

- Morphology
- Immunophenotype

Chronic Lymphocytic Leukemia: Diagnosis Criteria

- Diagnosis
  - Lymphocytes > 5 x 10^9/L
  - Bone marrow lymphocytes > 30%

However, people can have 3 or 4 e9/L lymphocyte counts, which is still high. This is currently a gray zone that perhaps needs clarification.

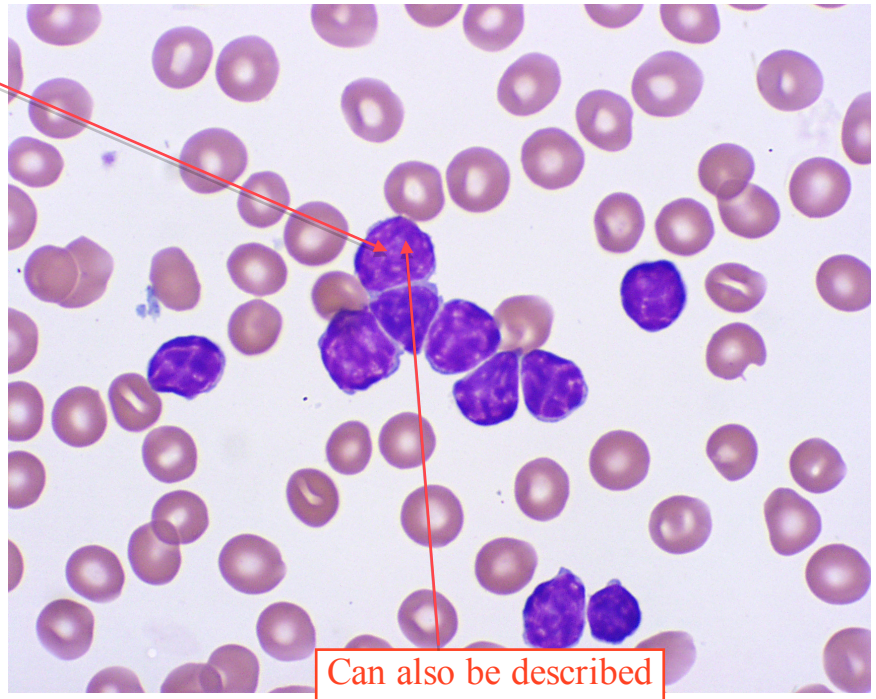
Chronic Lymphocytic Leukemia (CLL)

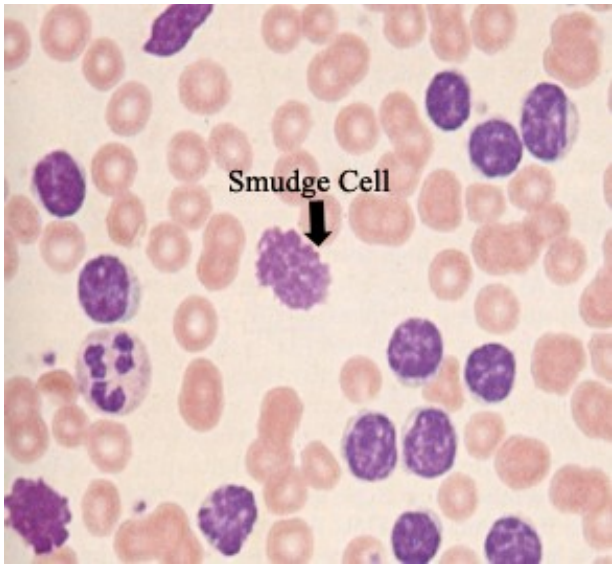
Pathology

Diagnose CLL with good old morphology and cytometry.

Morphology: CLL in Blood

Coarsely clumped chromatin.

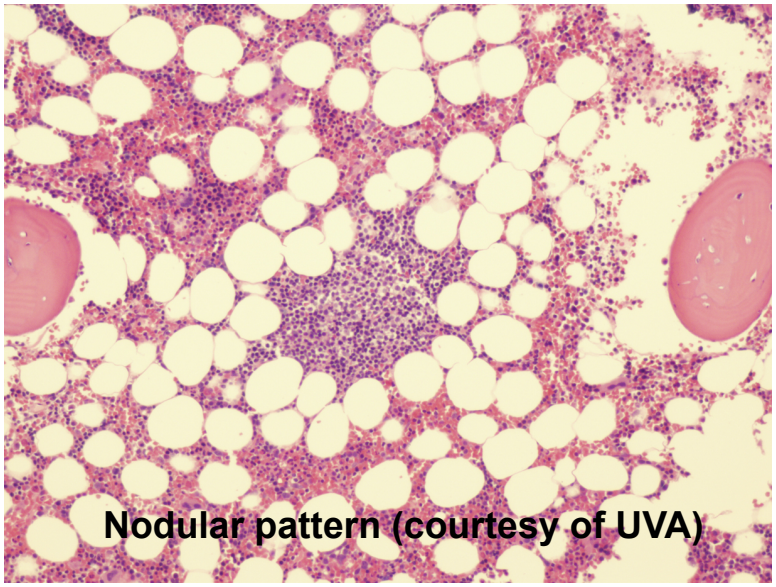




Smudge cells are artifacts, but are characteristic of CLL peripheral blood smears, so know them.

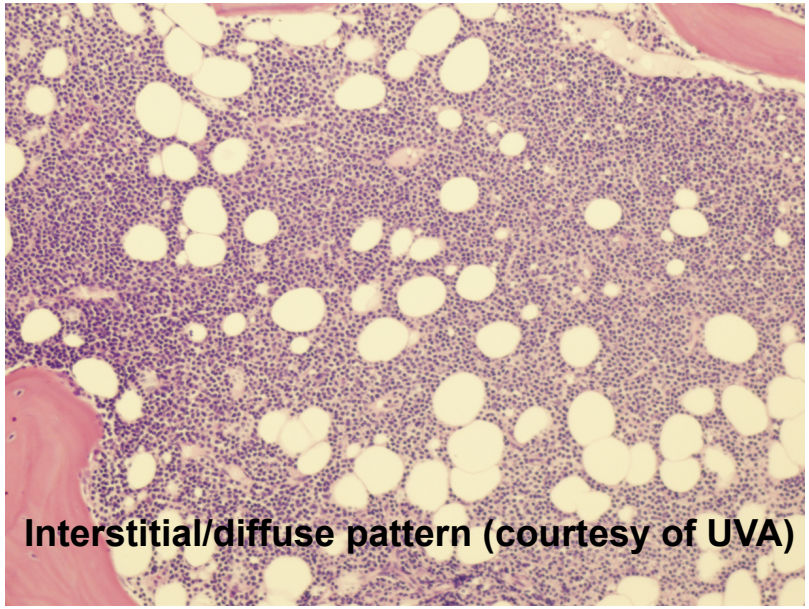
Can also be described as a"dried streambed" or "soccer ball" chromatin appearance.

Morphology: CLL in Bone Marrow



Nodular pattern (courtesy of UVA)

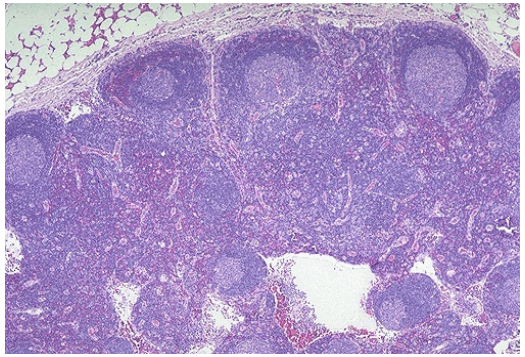
As the disease progresses, the appearance of the bone marrow shifts from top left (nodular) to lower right (diffuse)



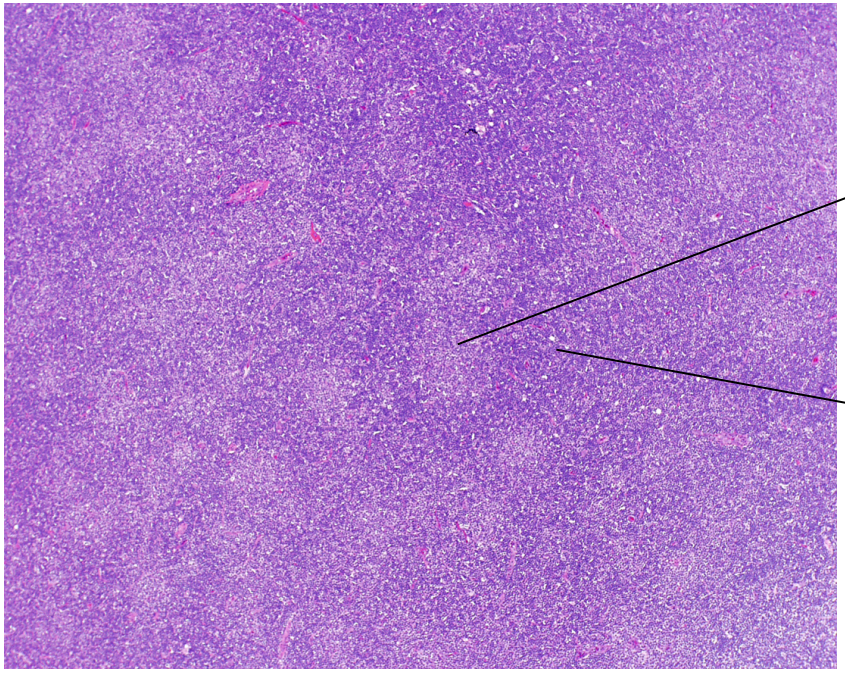
Interstitial/diffuse pattern (courtesy of UVA)

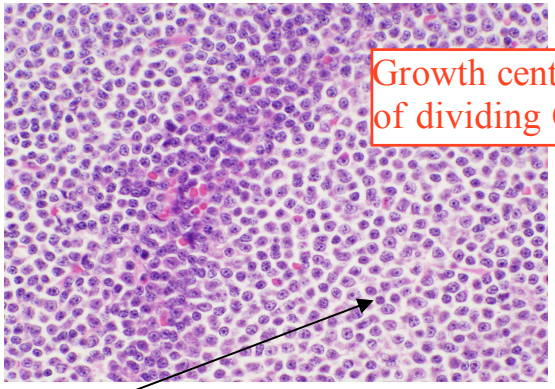
SLL is small lymphocytic lymphoma. It is the same disease as CLL, but has a different presentation (more lymph node than peripheral blood involvement in SLL).

CLL (SLL) in Lymph Nodes



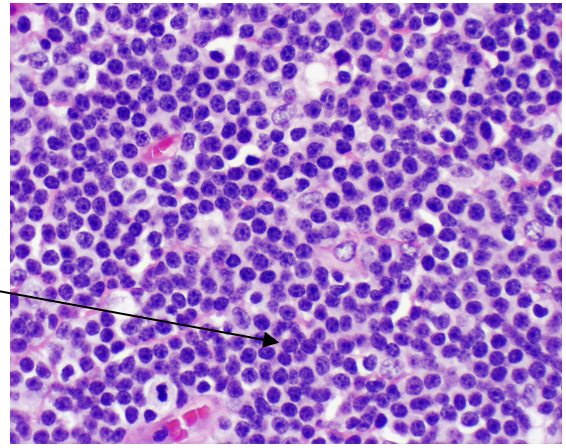
Normal Lymph Node





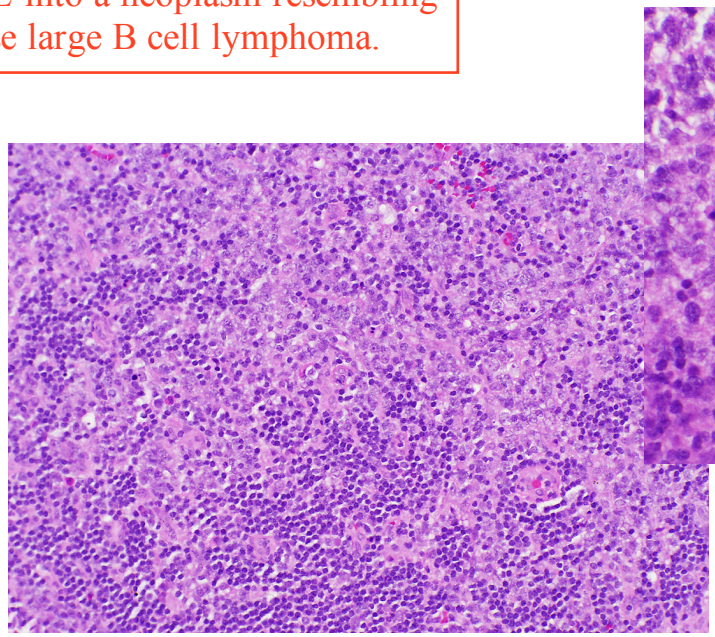
Growth centers consist of dividing CLL cells.

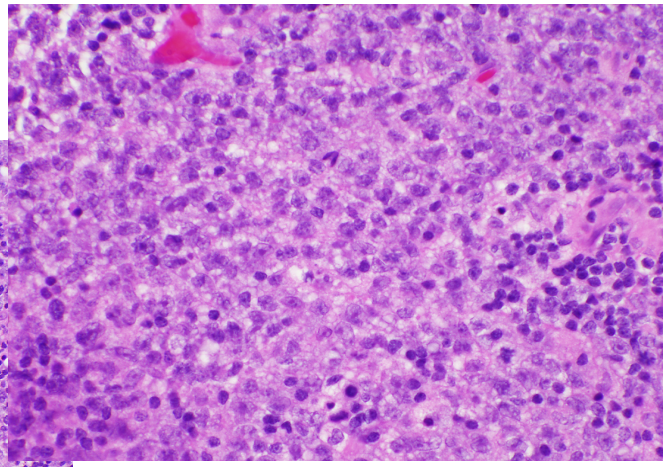
"Growth Center"



Transformed CLL/SLL: "Richter's Transformation" (2-8%)

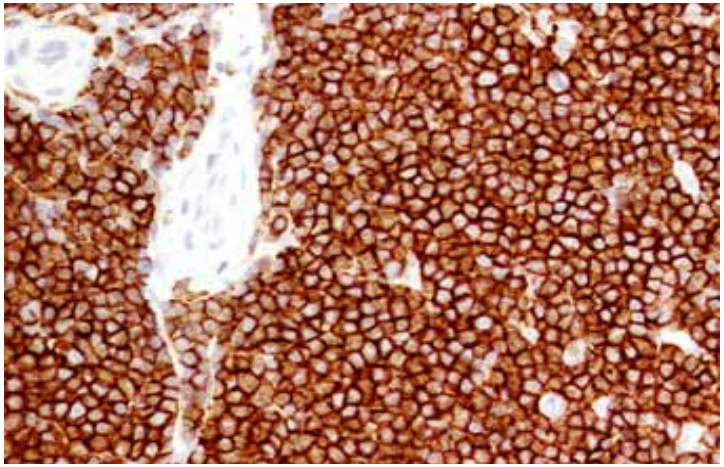
Sometimes CLL cells sustain a second hit. "Richter's transformation" turns CLL into a neoplasm resembling diffuse large B cell lymphoma.





CLL Diagnosis: Immunophenotype

Cytometry is important, because CD5+/CD23+ is characteristic of CLL. This is elaborated in the next few slides.

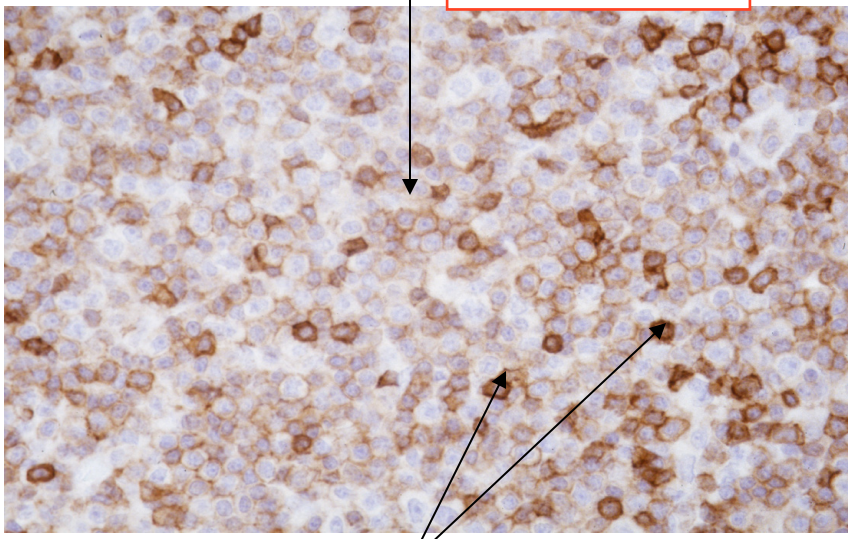


CD20 (B cell antigen)

CD5 is normally expressed by T cells and weakly by a small proportion of normal B cells. CLL cells express CD5, so it is possible, but by no means certain, that they may be derived from B cells that weakly express CD5. Regardless, CD5 is useful for diagnosing CLL.

CD5+ B cells (weak)

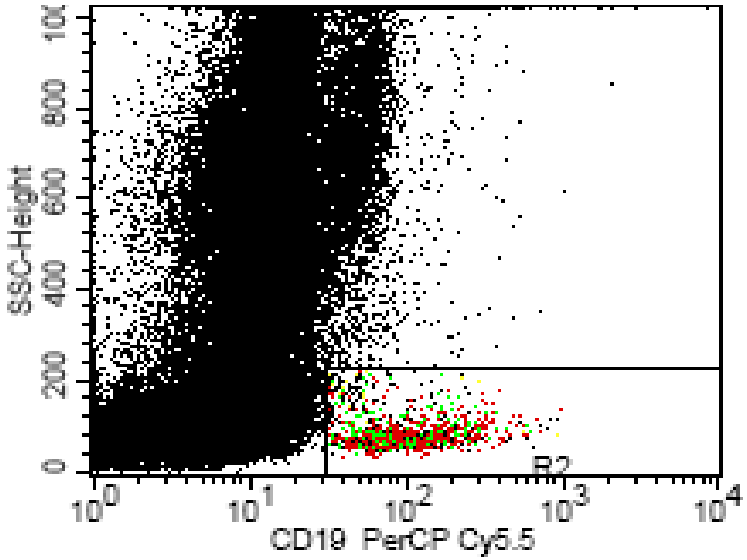
These are CLL



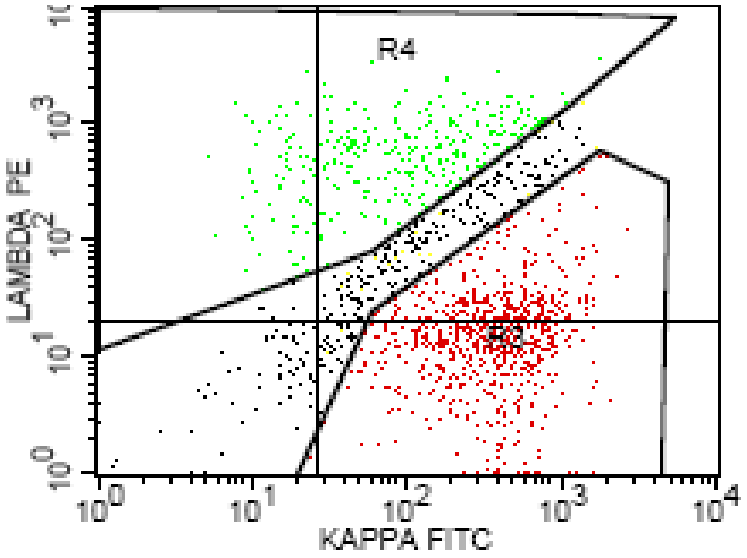
CD5+ T cells (strong)

These are reactive T cells.

Flow Cytometry: Normal (Polyclonal) B Cells

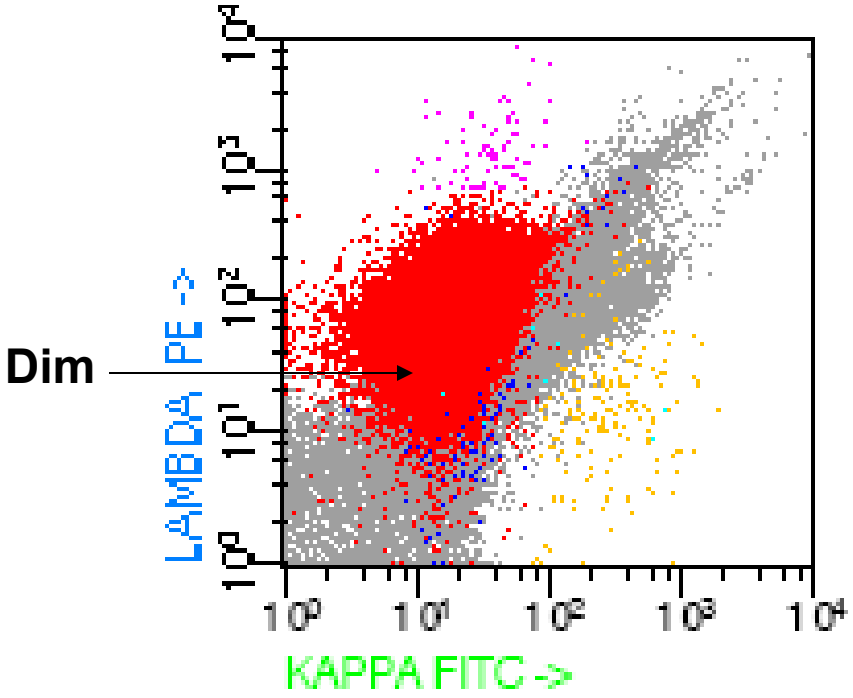


This demonstrates polyclonality. Compare it with the cytometry on the next slide.



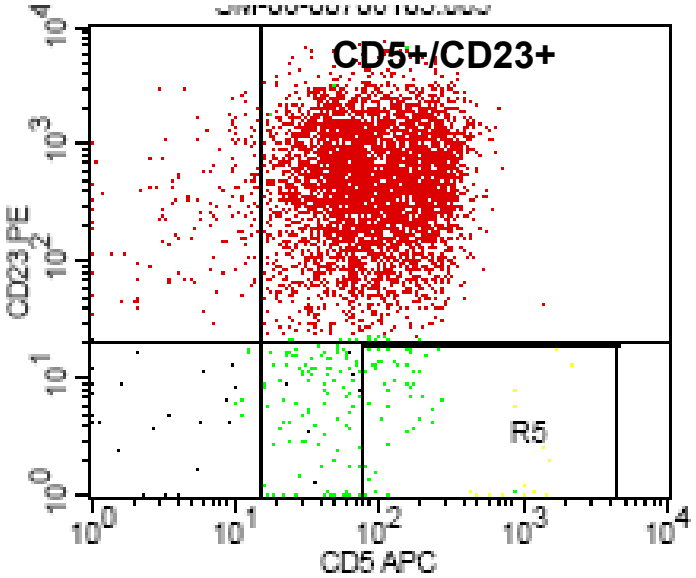
There is a normal distribution of kappa and lamba light

CLL Diagnosis: Flow Cytometry



This demonstrates monoclonicity. Almost all these neoplastic B cells express lambda light chains.

CLL cells are also CD23+, which helps pathologists distinguish CLL from mantle cell lymphoma, which is also CD5+, small B cell.



Chronic Lymphocytic Leukemia: Diagnosis Immunophenotype

- Immunophenotype
  - CD19+ CD20+(Dim) CD5+ CD23+
  - FMC7 -
  - Surface Ig (IgD or IgM) sparse

Chronic Lymphocytic Leukemia: Diagnosis Immunophenotype

These 2 markers diagnose CLL.

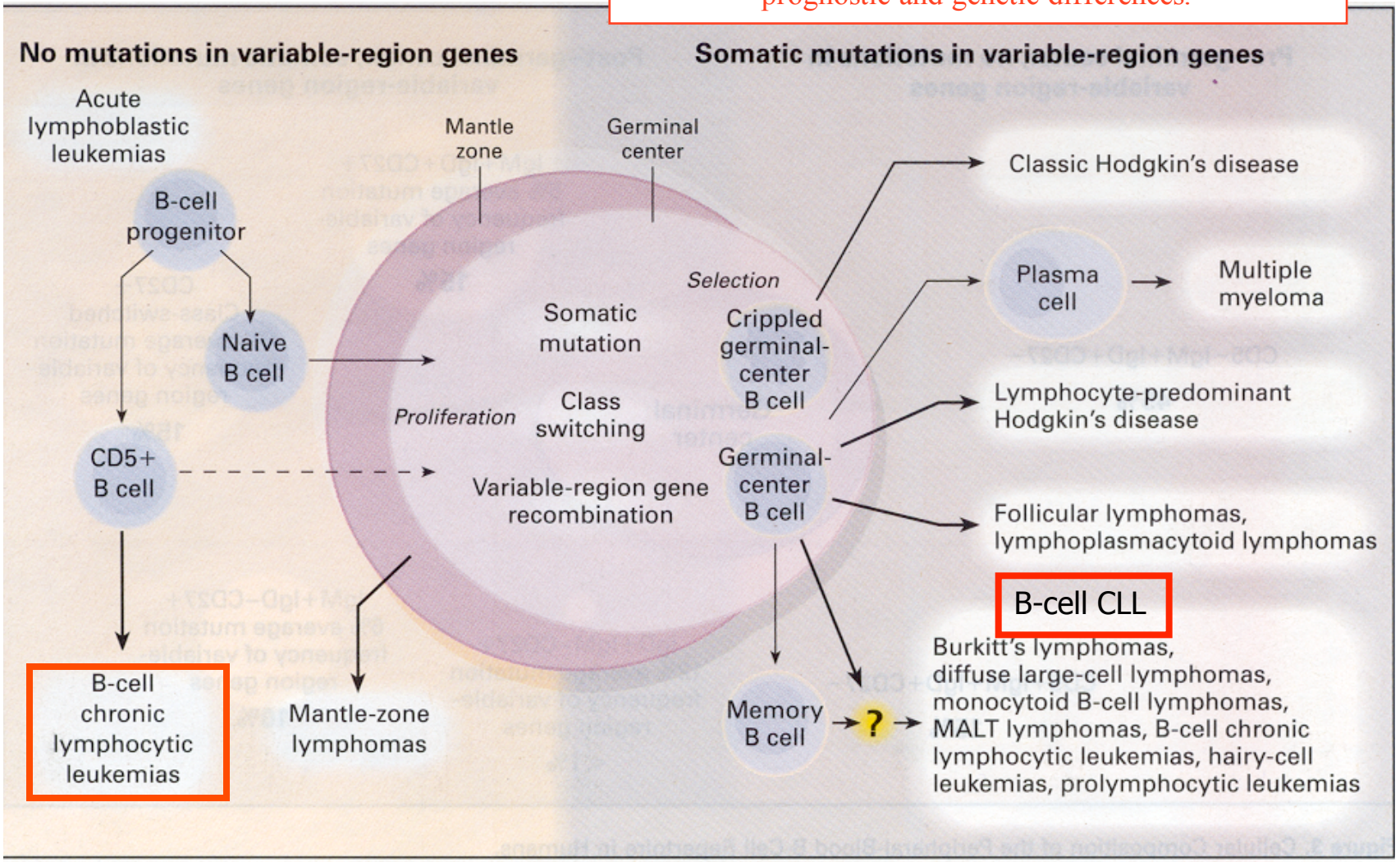
	CD5	CD2	CD3	CD19	CD20	SIg	CD11c	CD25	CD22	CD10	HLA-Dr	CD23	FMC7
CLL	++	-	-	++	++	++ (Dim)	-	-	+/-	-	++	Br	-
MCL	++	-	-	++	++	++ (Br)	-	+	++	+/-	++	-	-
PLL	-	-	-	++	++	++ (Br)	-	-	++	+/-	++	-	+
FSC	-	-	-	++	++	++ (Br)	-	-	+	+	++		-
HCL	-	-	-	++	++	++ (Br)	++	++	++	-	++		-
SLVL	-	-	-	++	++	++ (Br)	-	+/-	++	-	++		-
MBCL	-	-	-	+/-	++	++	++	-		-	++		-

++ = marker present in 80+%
+ = marker present in 40-80%
+/- = marker present in 10-40%
- = marker present in < 10%
Br = bright

CLL = chronc lymphocytic leukemia
MCL = mantle cell lymphoma
PLL = prolymphocytic leukemia
PSC = follicular small cleaved NHL
HCL = hairy cell leukemia
SLVL = splenic lymphoma with villous lymphocytes
MBCL = monocytoid B-cell lymphoma

Chronic Lymphocytic Leukemia: Classification Mature vs Immature

However, to complicate things, there are different subtypes of CLL. As more research is being done, CLL may soon be split into different diseases due to prognostic and genetic differences.



Chronic Lymphocytic Leukemia: Staging Rai System

This is 1 of 2 systems used commonly today to stage CLL.

The basis for CLL staging is:
1. how far the leukemia has spread
2. how much damage the leukemia has done

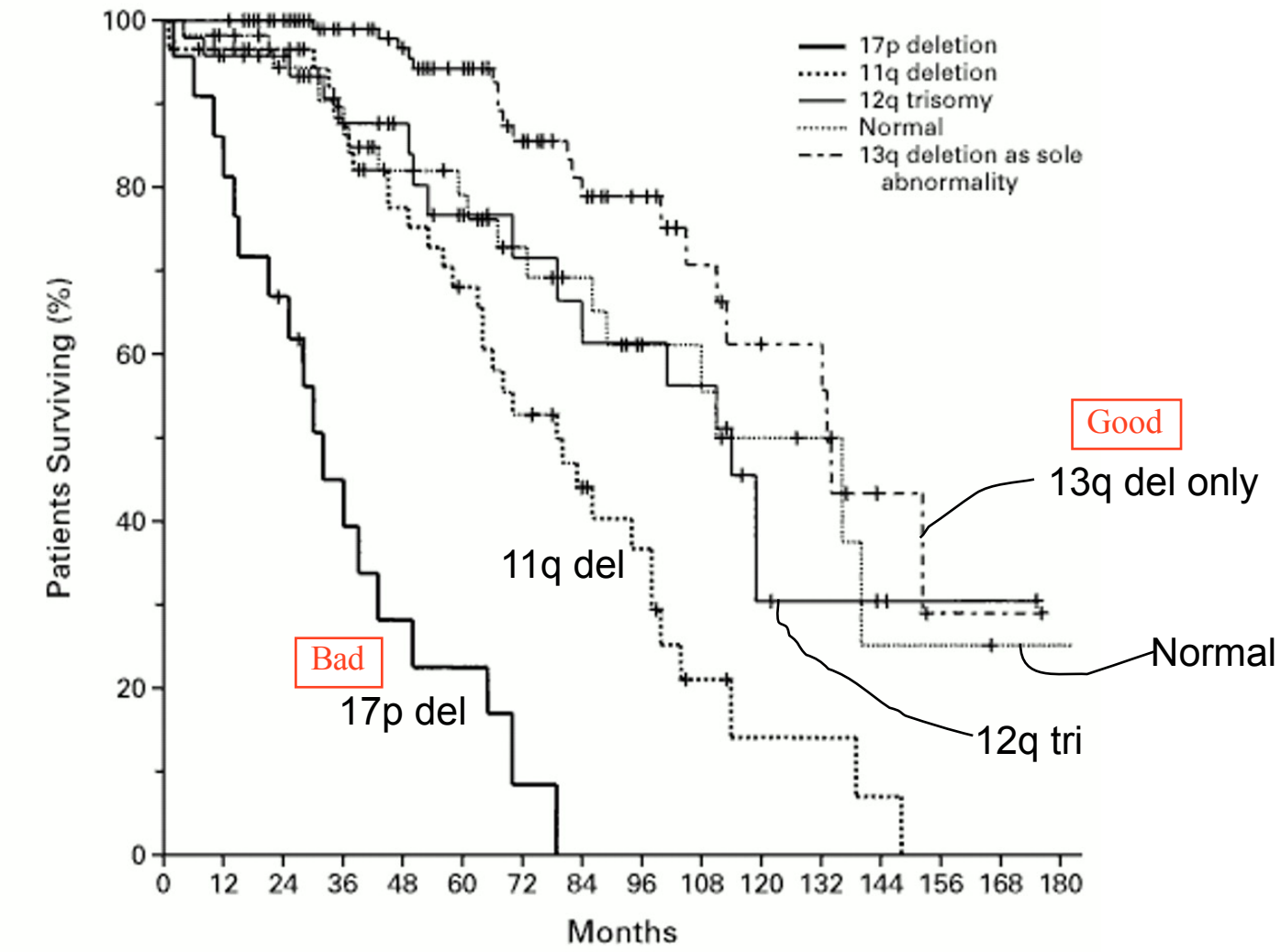
Stage	Criteria	Survival (months)
0	Lymphocytosis	> 150
1	Enlarged lymph nodes	101
2	Enlarged liver and/or spleen	71
3	Anemia (Hb < 11 g/dl)	19
4	Thrombocytopenia (plat < 100,000/ul)	19

This is where damage starts occurring.

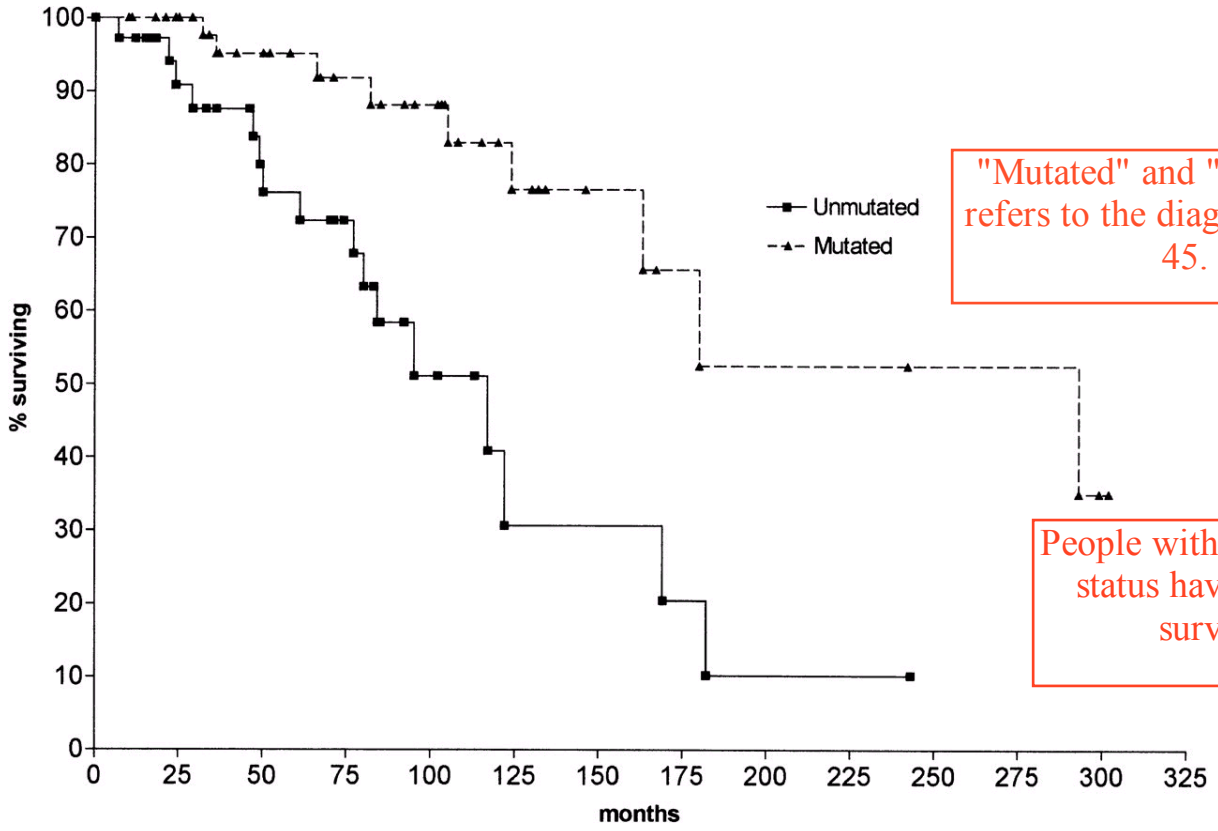
Rai et al. Blood 1975;46:219

Chronic Lymphocytic Leukemia: Prognosis Cytogenetics

Here's a more sophisticated genetic method to predict prognosis.



Chronic Lymphocytic Leukemia: Prognosis Mutational Status



"Mutated" and "unmutated" refers to the diagram on slide 45.

People with a "mutated" status have a longer survival.

Hamblin et al. Blood 1999; 94:1848-54

Chronic Lymphocytic Leukemia: Statistics

- 30% of new leukemias
- 10,000 new patients/year

- M/F 2:1
- Median age 68
- 90% age > 40

Very rare in young people.

Chronic Lymphocytic Leukemia: Epidemiology

The ONLY leukemia (at least until recently) where there is no known association.

- Unknown

New development: There may be an association of CLL with agent orange.

- Not
  - Alkylating agents
  - Radiation
  - Chemotherapy

This lack of associations is unusual for leukemia.

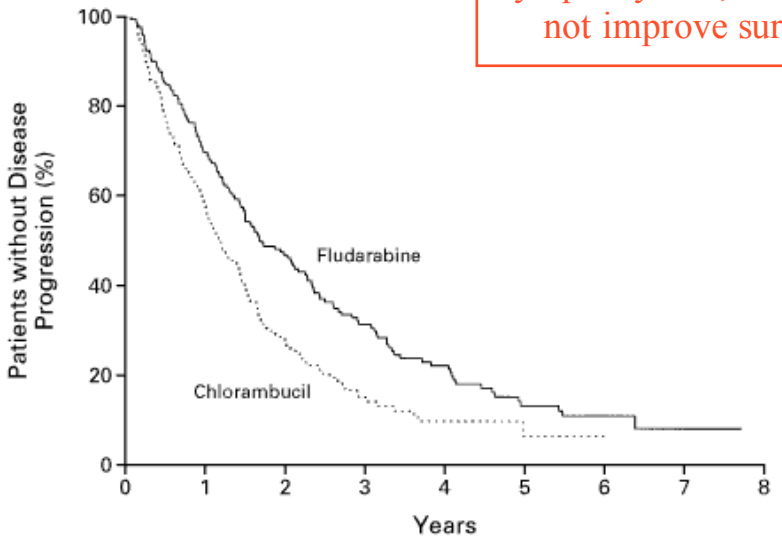
  - Chemicals
  - Immunosuppression (AIDS)

Chronic Lymphocytic Leukemia: Clinical

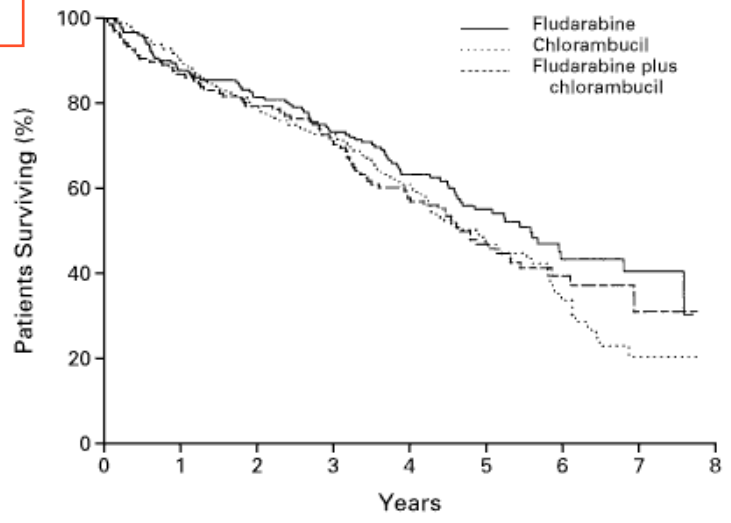
- Mean age: 69.6
- Male: 59.1%
- Lymph nodes:
- Splenomegaly

Chronic Lymphocytic Leukemia: Treatment Fludarabine vs Chlorambucil

While fludarabine helped w/ disease progression (i.e. lymphadenopathy, lymphocytosis, etc.), it did not improve survival.



No. at Risk									
Fludarabine	172	116	74	43	27	13	6	3	0
Chlorambucil	183	99	44	17	7	2	1	0	0

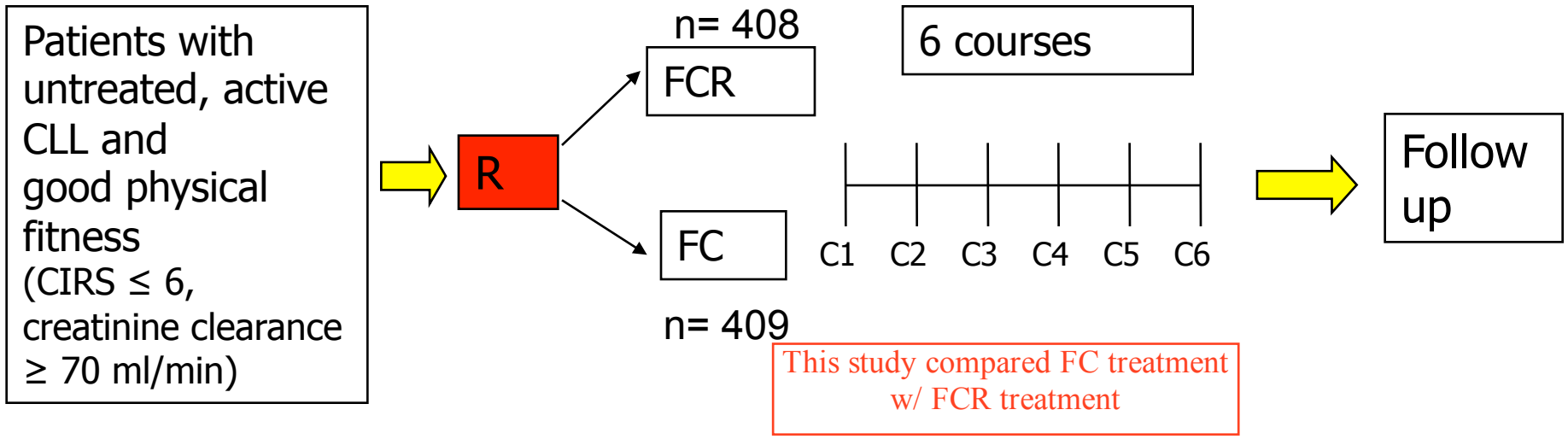


No. at Risk									
Fludarabine	178	155	140	124	95	60	24	9	0
Chlorambucil	193	172	147	132	101	52	21	6	0
Fludarabine plus chlorambucil	136	117	106	94	70	44	19	5	0

Rai et al. N Engl J Med 2000;343:1750-7

What did help was rituximab (Rituxan), as we will see.

GCLLSG CLL8 Study Design



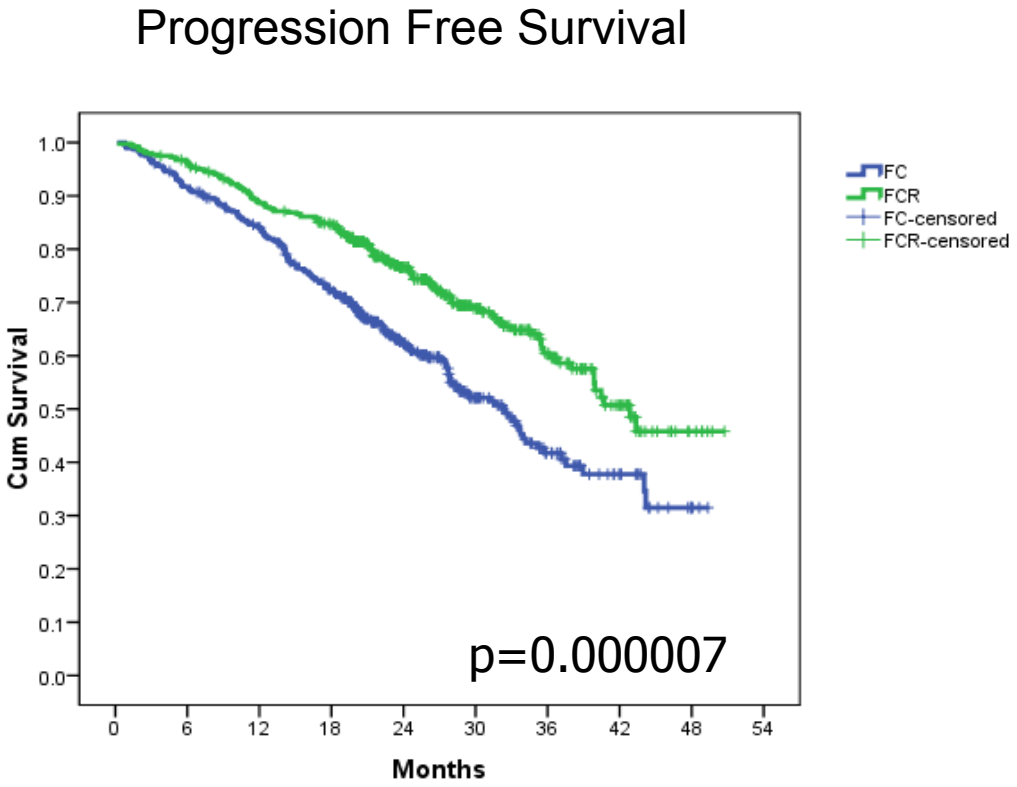
F = fludarabine
C = cyclophosphamide
R = rituximab

Courtesy of M. Hallek

Progression Free Survival FCR vs FC

Conclusion: FCR has improved survival compared to FC.

F = fludarabine
C = cyclophosphamide
R = rituximab



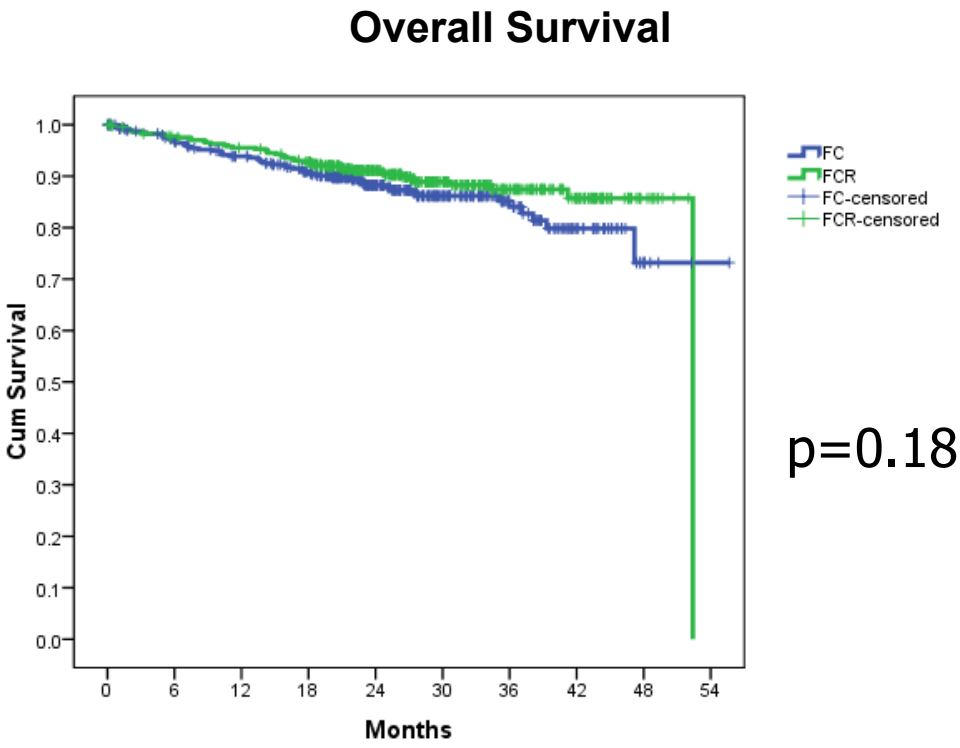
Median PFS: 32.3 months for FC vs 42.8 months for FCR

Median observation time 25.5 months

Courtesy of M. Hallek

Overall Survival

F = fludarabine
C = cyclophosphamide
R = rituximab



p=0.18

Median observation time 25.5 months

Courtesy of M. Hallek

Chronic Lymphocytic Leukemia: Summary

- Older, men
- Incidental finding
- Lack of apoptosis/slowly accumulating lymphoid cells

Plasma Cell (Multiple) Myeloma

Case

- 67 year old, African-American, man is seen for pain localized to the back. He notes some fatigue but is otherwise well.

Common chief complaint for patients w/ undiagnosed multiple myeloma. We will see soon that multiple myeloma wreaks havoc on bones.

- PE: normal except for tenderness over the T12 area

Laboratory

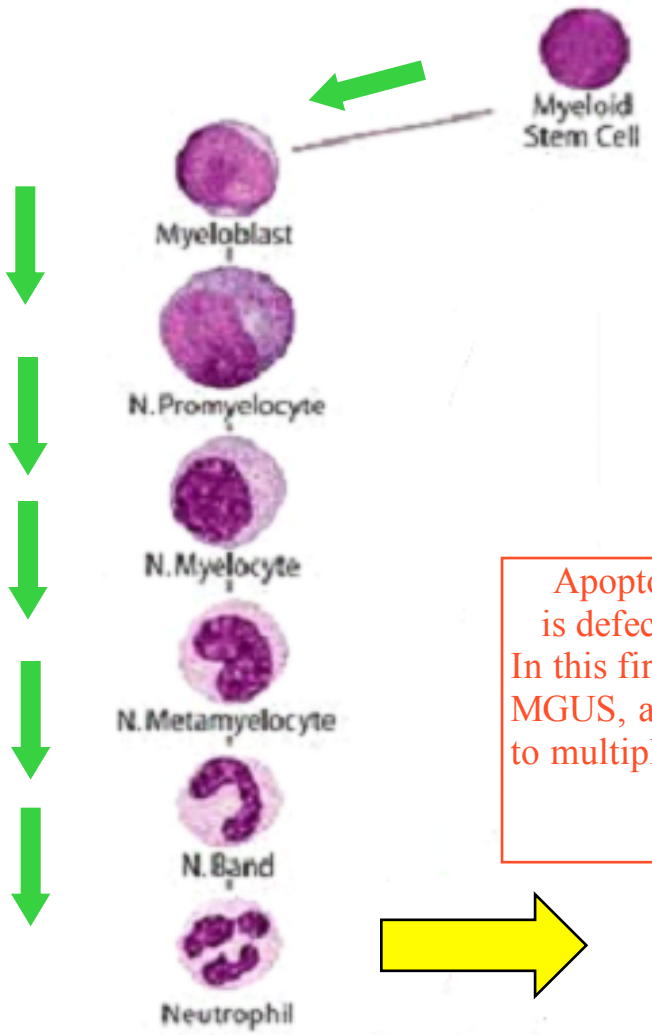
WBC	4,200 a little low
Hct	31% anemic
Platelets	98,000 a little low
Plasma cells	0.5%

BUN	29
Creatinine	1.6 A little high
Calcium	10.9 hypercalcemia
Albumen	2.5 Low

As a side note, multiple myeloma produces Bence-Jones (light chain) proteinuria, which leads to a nephropathy known as "myeloma kidney" that then produces these renal findings

Multiple Myeloma: Pathophysiology Apoptosis Defective

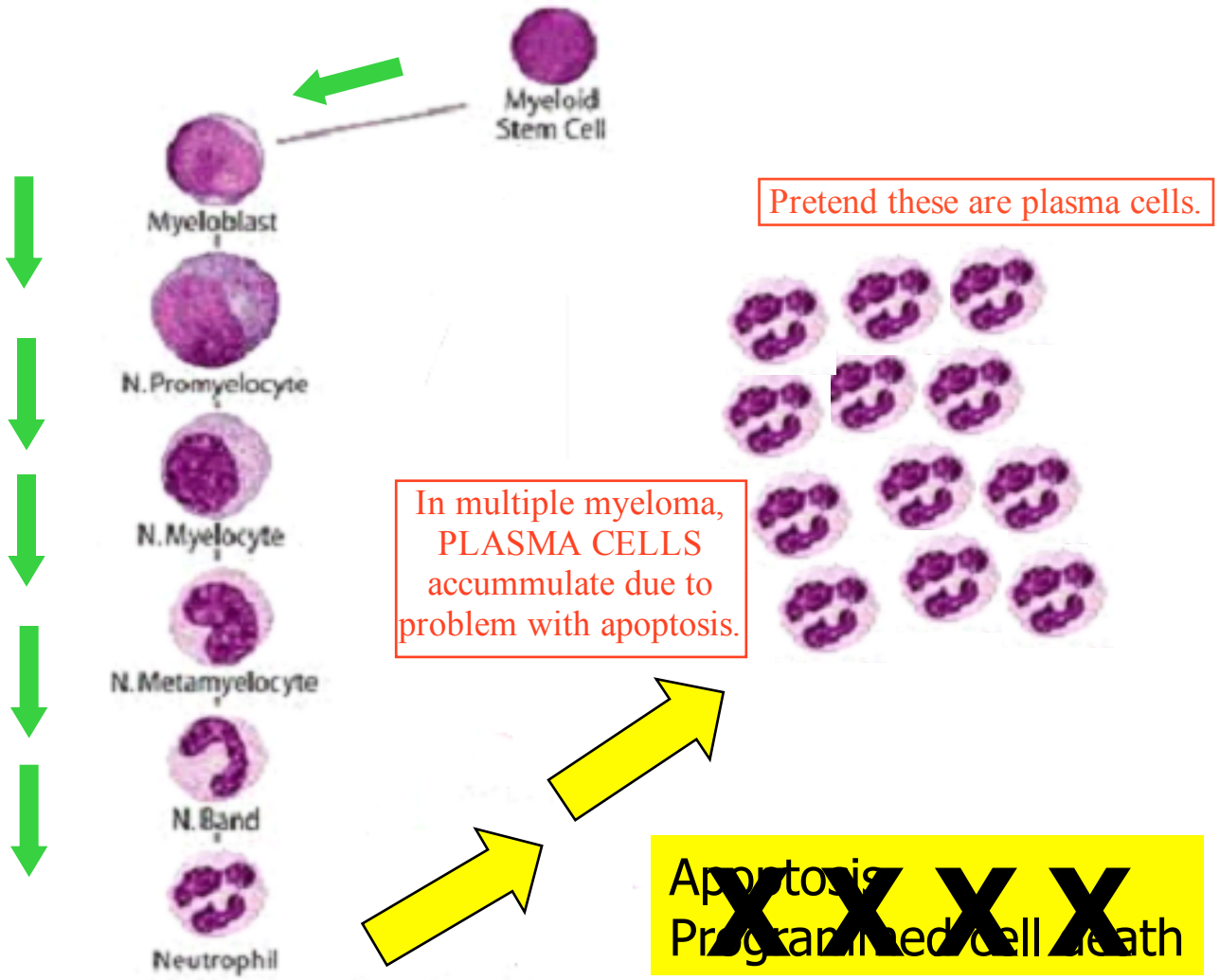
Again, pretend that this is a lymphoid line in our discussion of multiple myeloma.



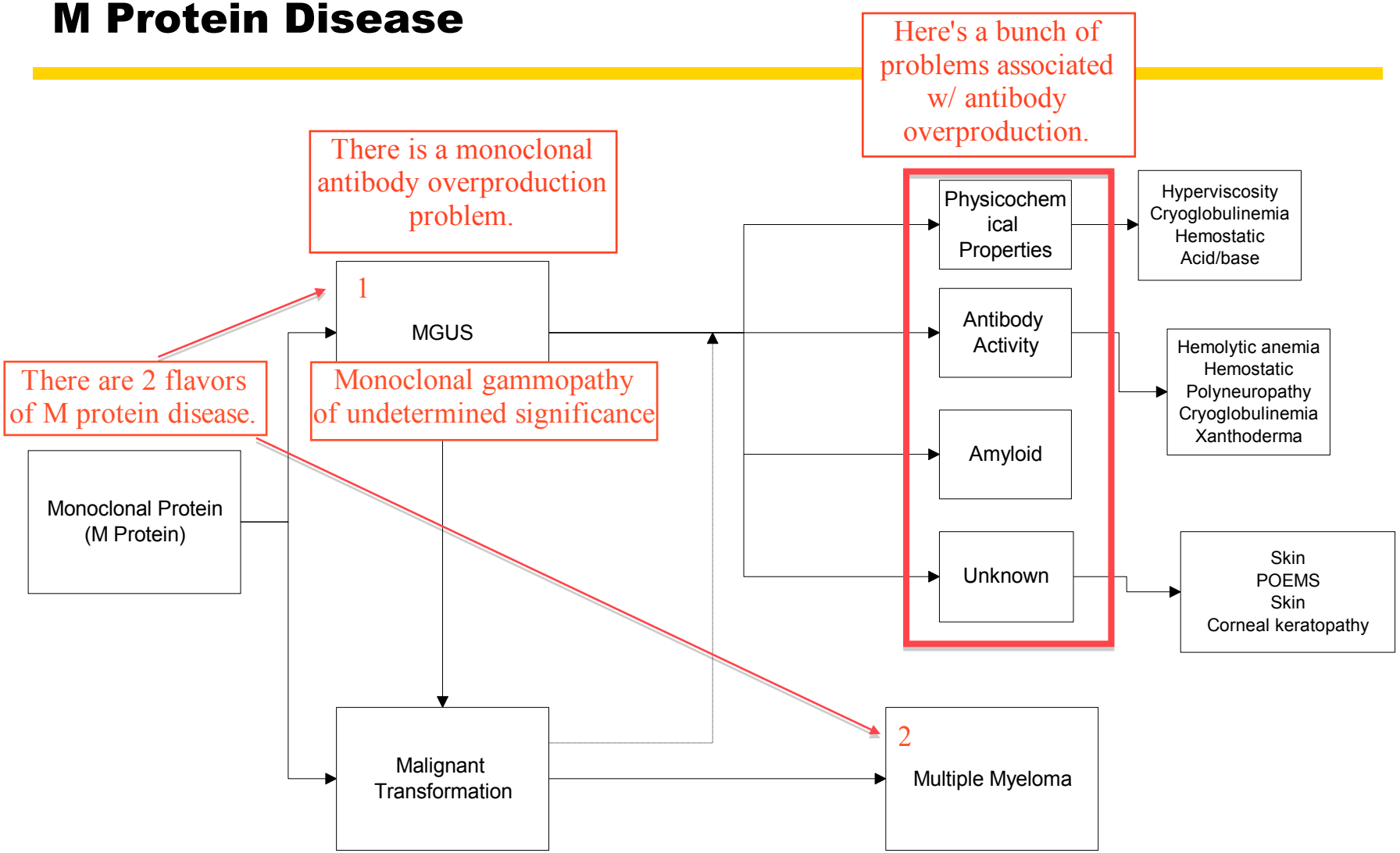
Apoptosis of PLASMA CELLS is defective in multiple myeloma. In this first stage, the disease is called MGUS, and may or may not progress to multiple myeloma (more on this in a bit).

Apoptosis
Programmed cell death

Multiple Myeloma: Pathophysiology
Apoptosis Defective – Cells Accumulate

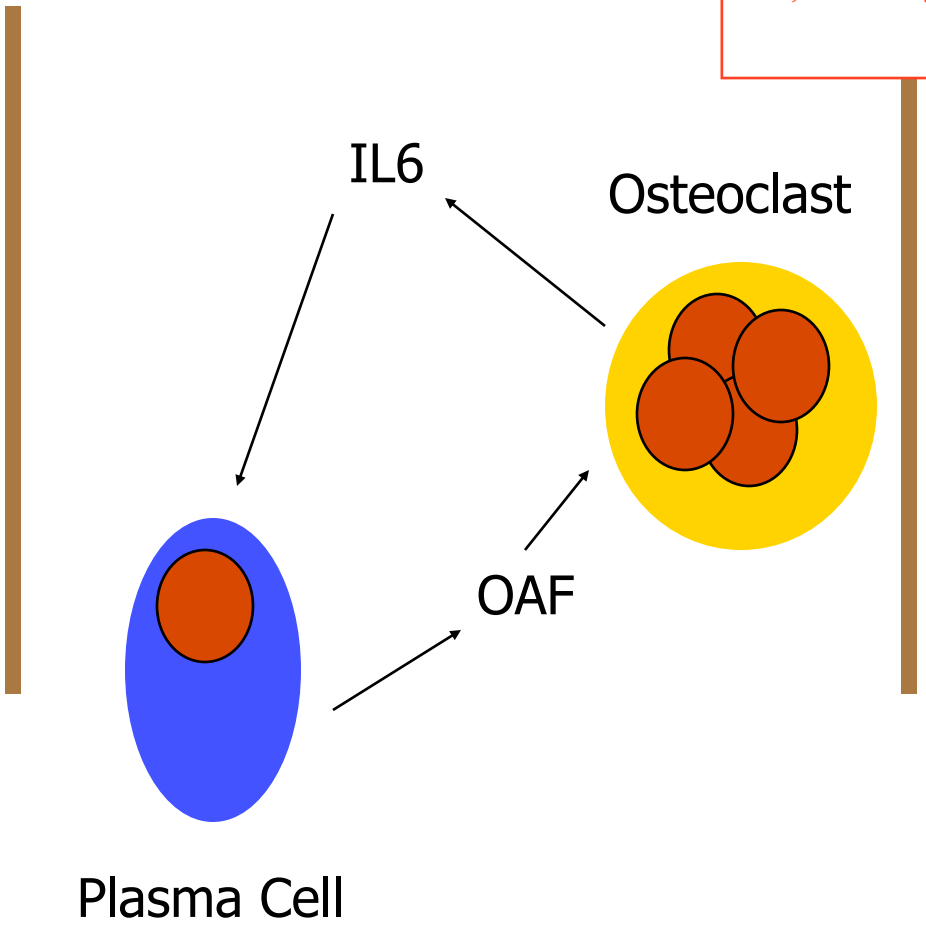


Concept
M Protein Disease



Concept Pathophysiology

This is an old diagram, but makes a critical point: if you have a plasma cell that is resistant to apoptosis, sooner or later it can accumulate a 2nd mutation, which then causes it to acquire the ability to secrete OAF* (osteoclast activating factor), which stimulates osteoclasts and causes bone destruction. Osteoclasts then release IL-6, which is a growth factor for plasma cells, resulting in a positive feedback cycle to produce even more damage.



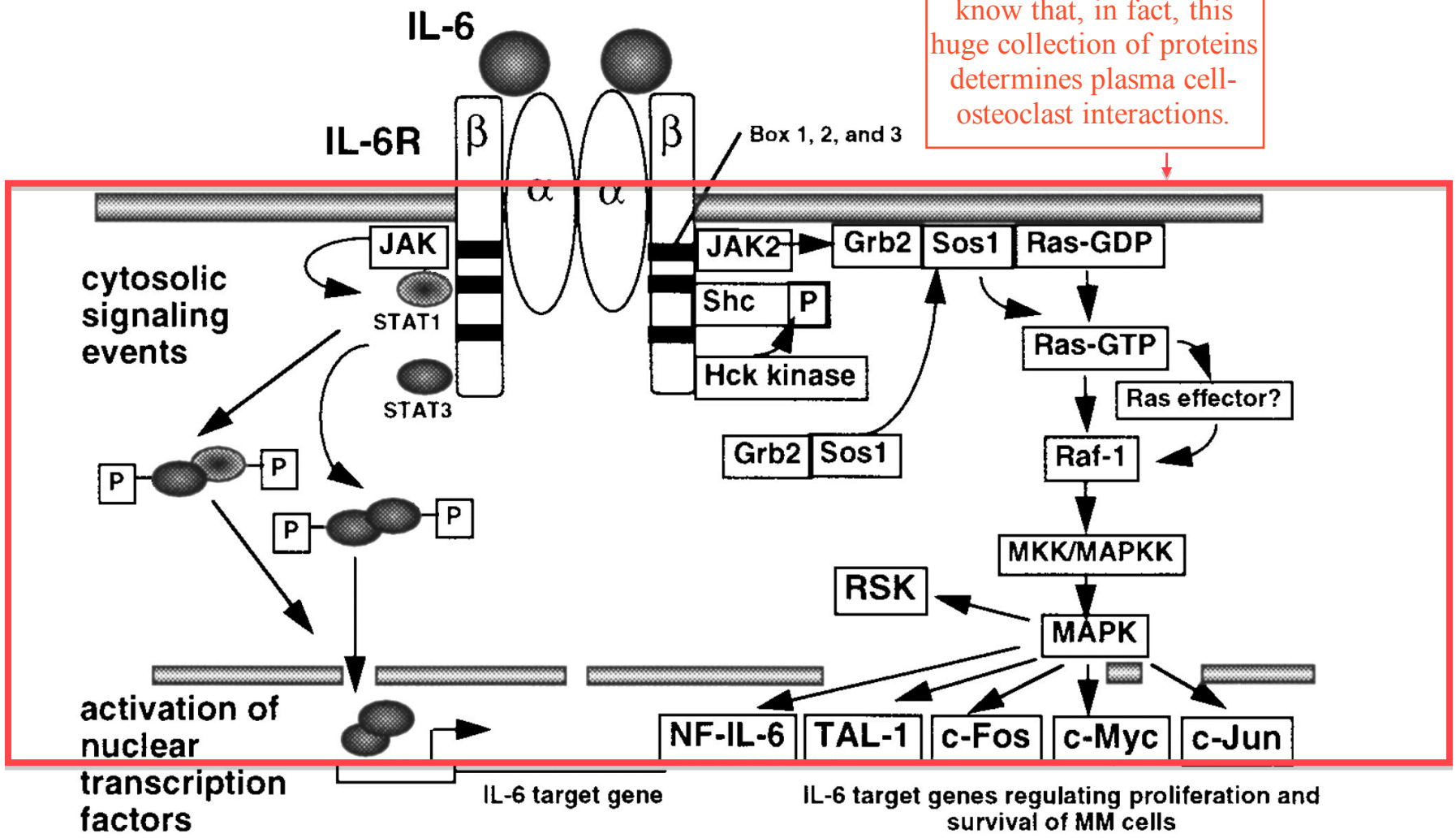
*We now know that OAF is not a single protein. In fact, a very complex set of factors plays a role in the plasma cell-osteoclast interaction (see the next slide)

Pathophysiology: Elaborate Model

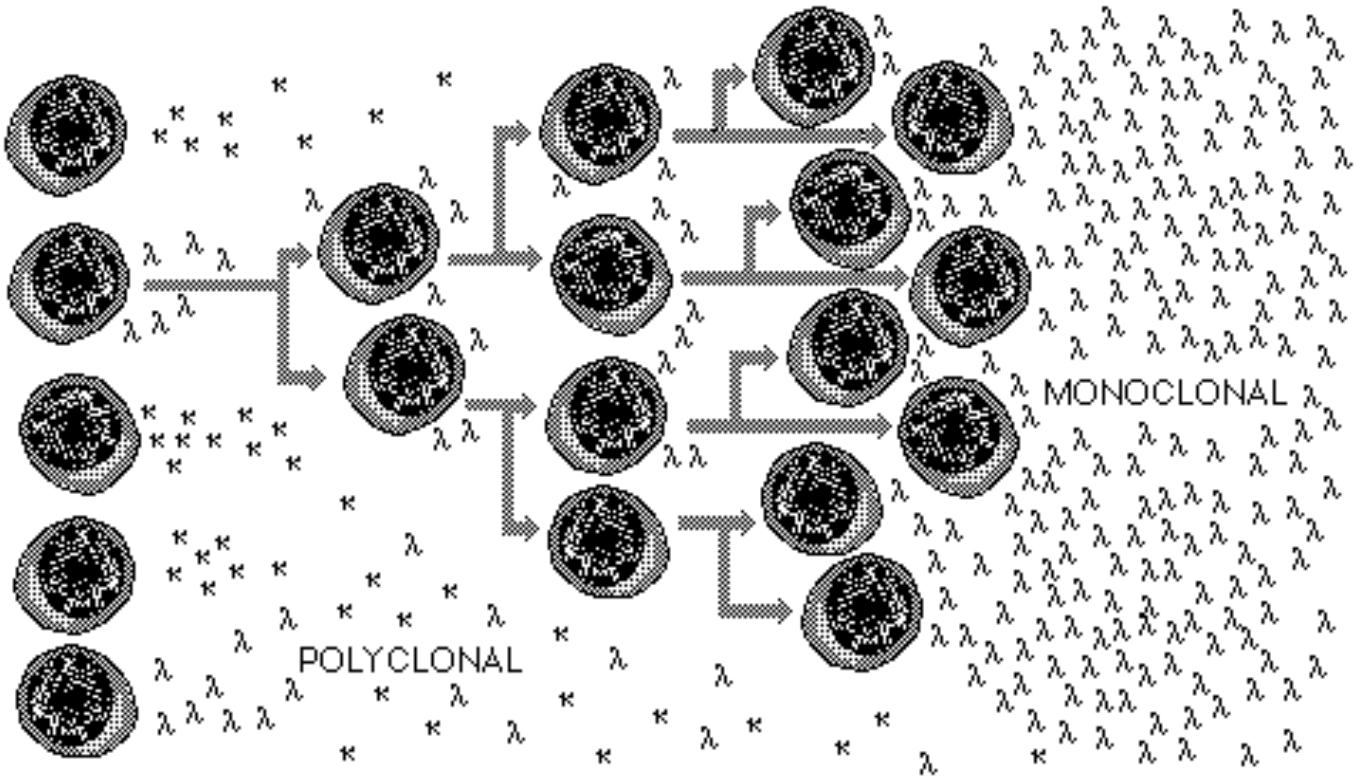
Michael Hallek, P. Leif Bergsagel, and Kenneth C. Anderson

Blood, Vol. 91 No. 1 (January 1), 1998: pp. 3-21

Here's a more recent, more complex diagram. We now know that, in fact, this huge collection of proteins determines plasma cell-osteoclast interactions.

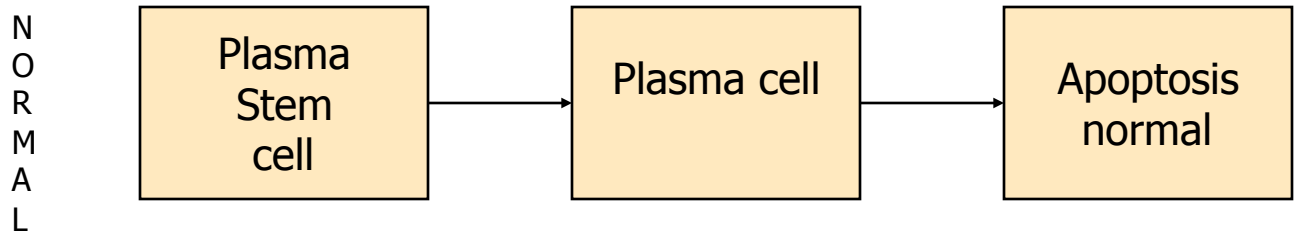


Concept
Monoclonality

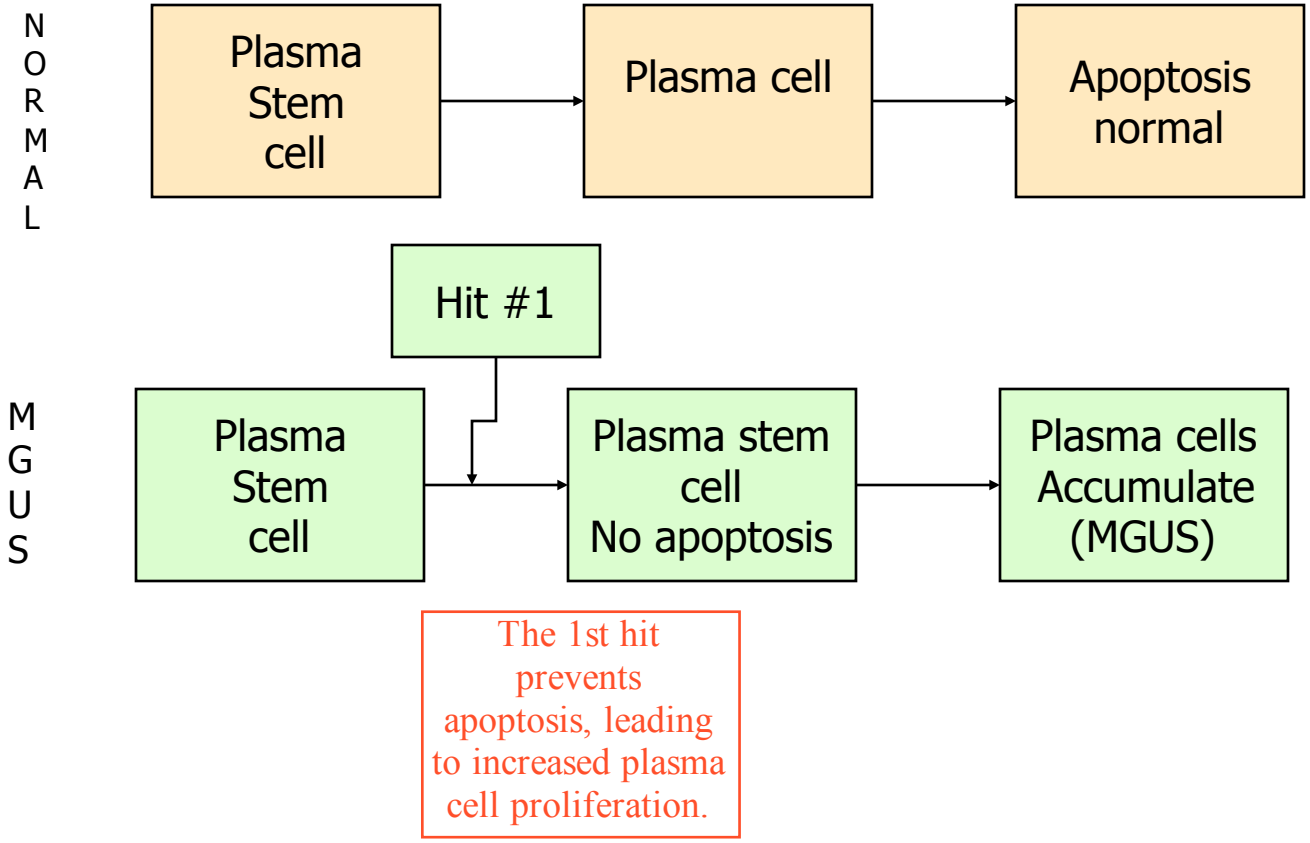


http://images.google.com/imgres?imgurl=http://www.meded.virginia.edu/courses/path/innes/images/wcdjpeg/wcd%2520spep%2520monoclonal%2520iga.jpeg&imgrefurl=http://www.meded.virginia.edu/courses/path/innes/wcd/immunointro.cfm&h=141&w=214&sz=17&hl=en&start=13&tbnid=z5zPKEmJmczT8M:&tbnh=70&tbnw=106&prev=/images%3Fq%3Dserum%2Bprotein%2Belectrophoresis%26svnum%3D10%26hl%3Den%26lr%3D%26sa%3DN

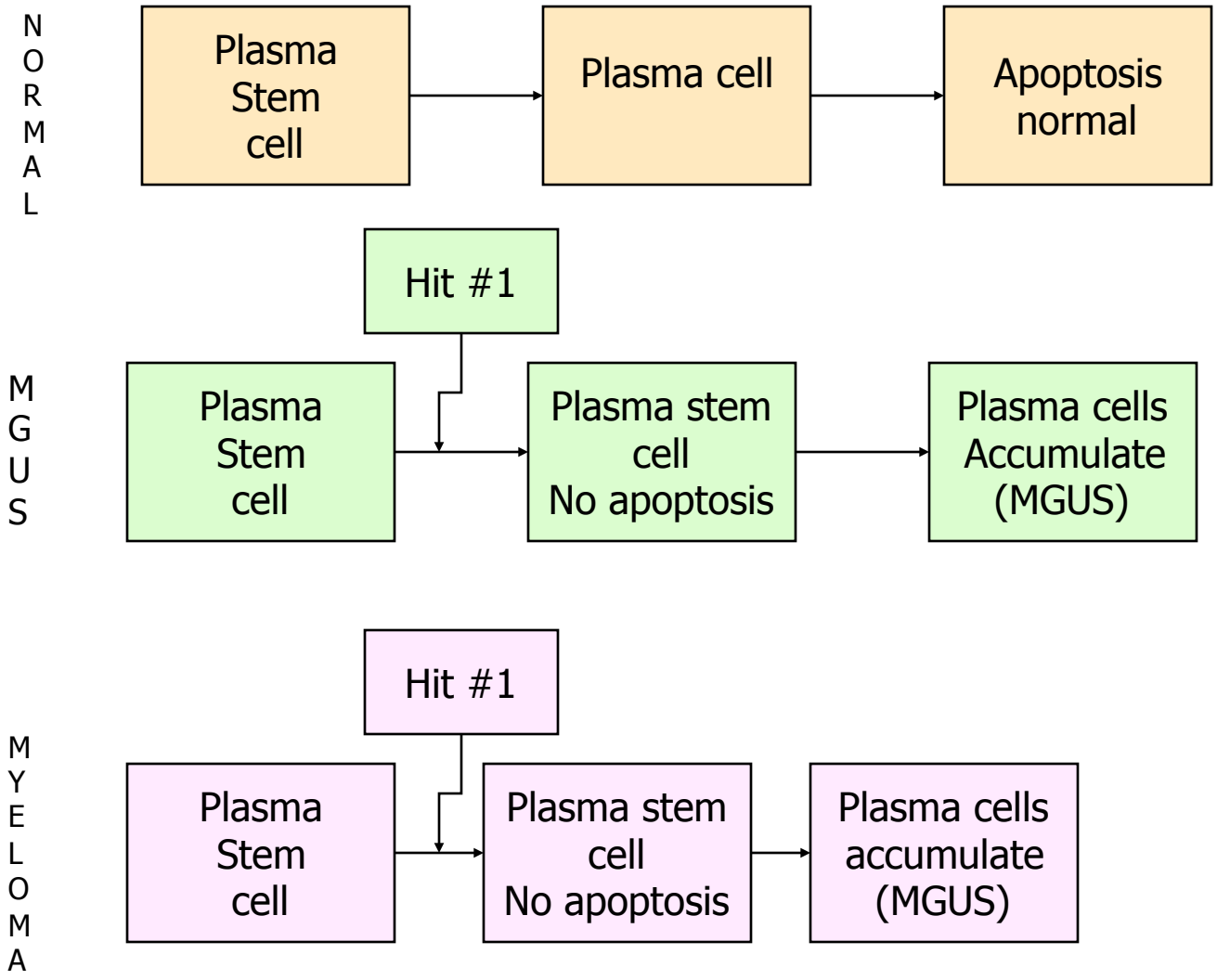
Multi-hit hypothesis of multiple myeloma



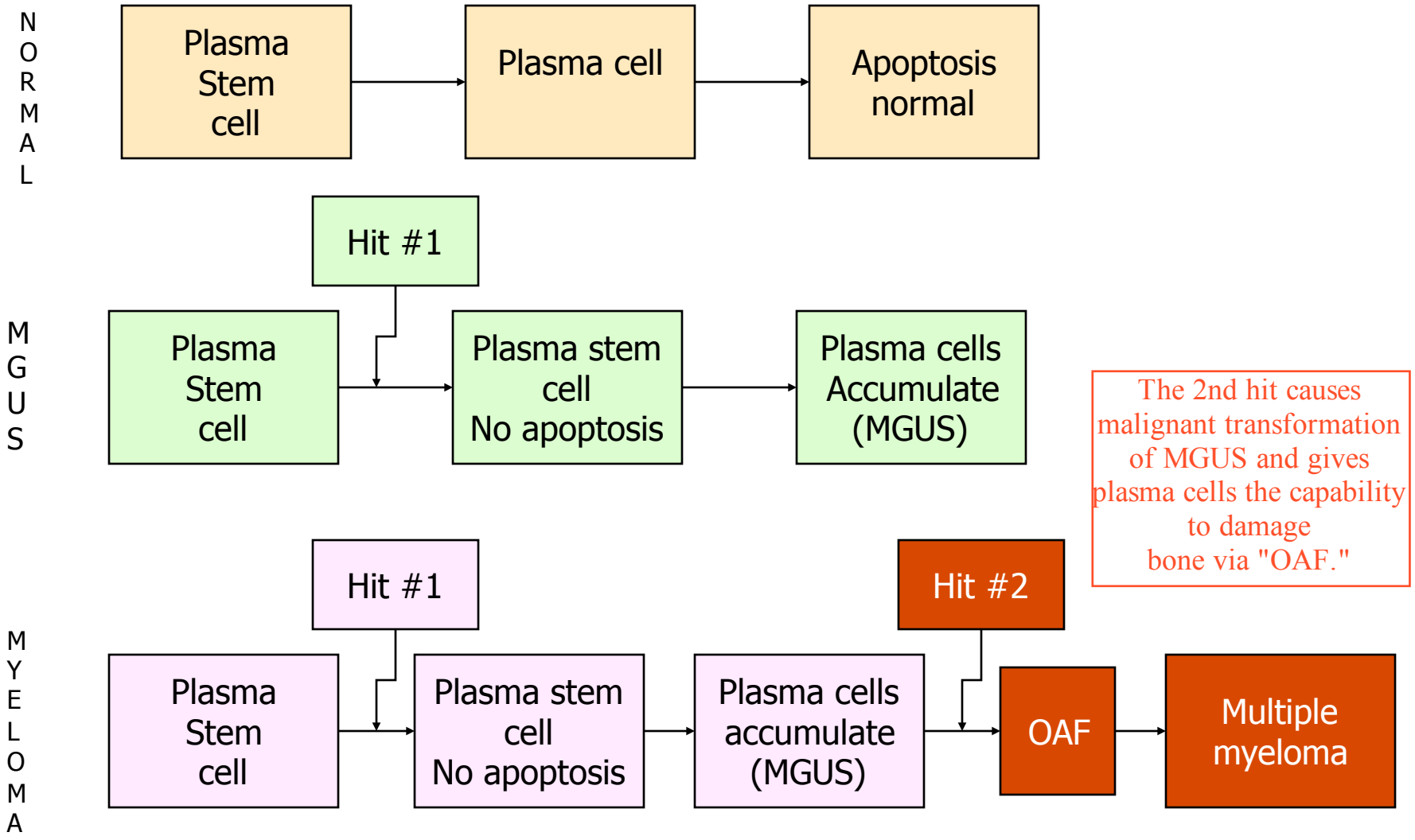
Multi-hit hypothesis of multiple myeloma



Multi-hit hypothesis of multiple myeloma

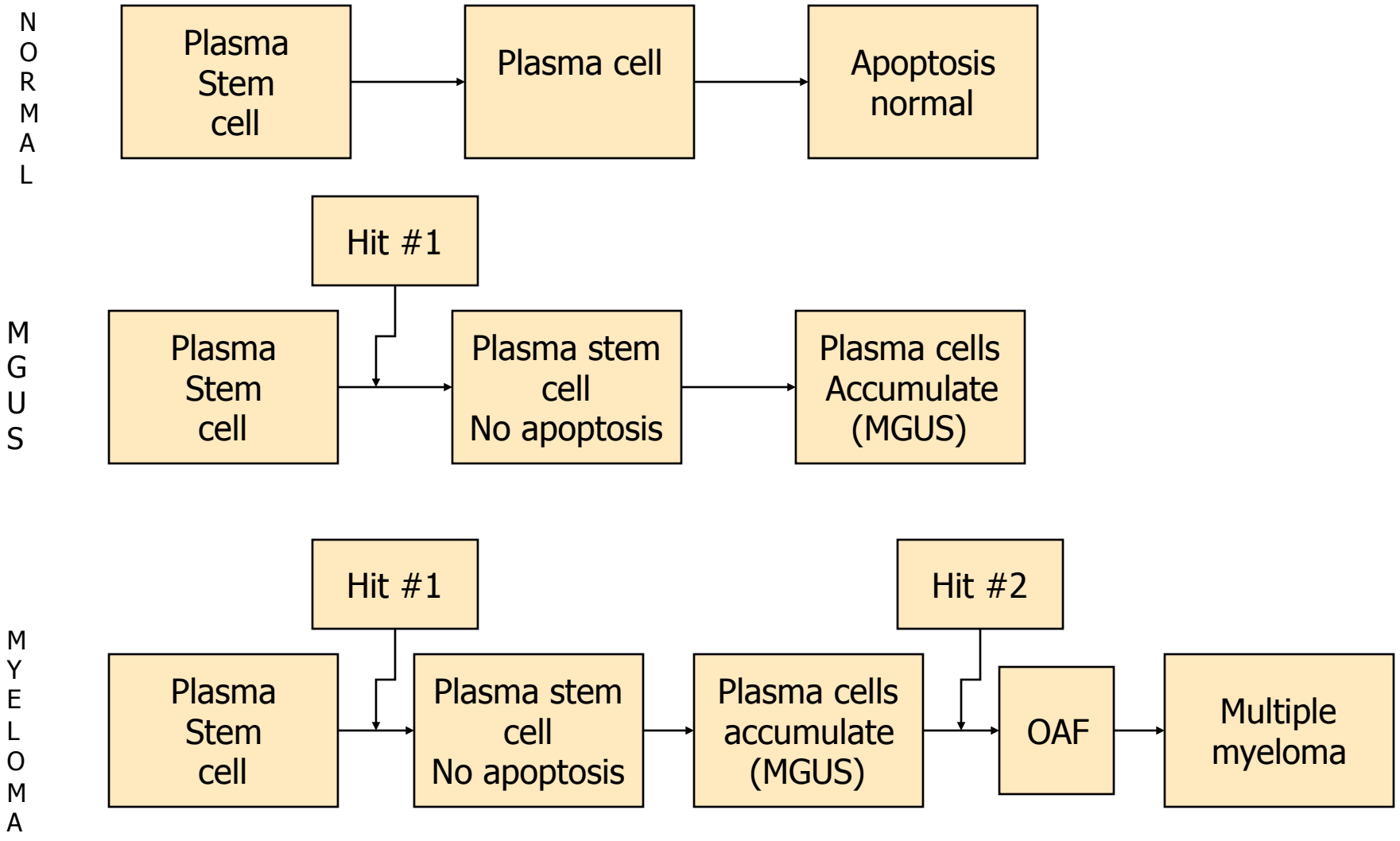


Multi-hit hypothesis of multiple myeloma



The 2nd hit causes malignant transformation of MGUS and gives plasma cells the capability to damage bone via "OAF."

Multi-hit hypothesis of multiple myeloma



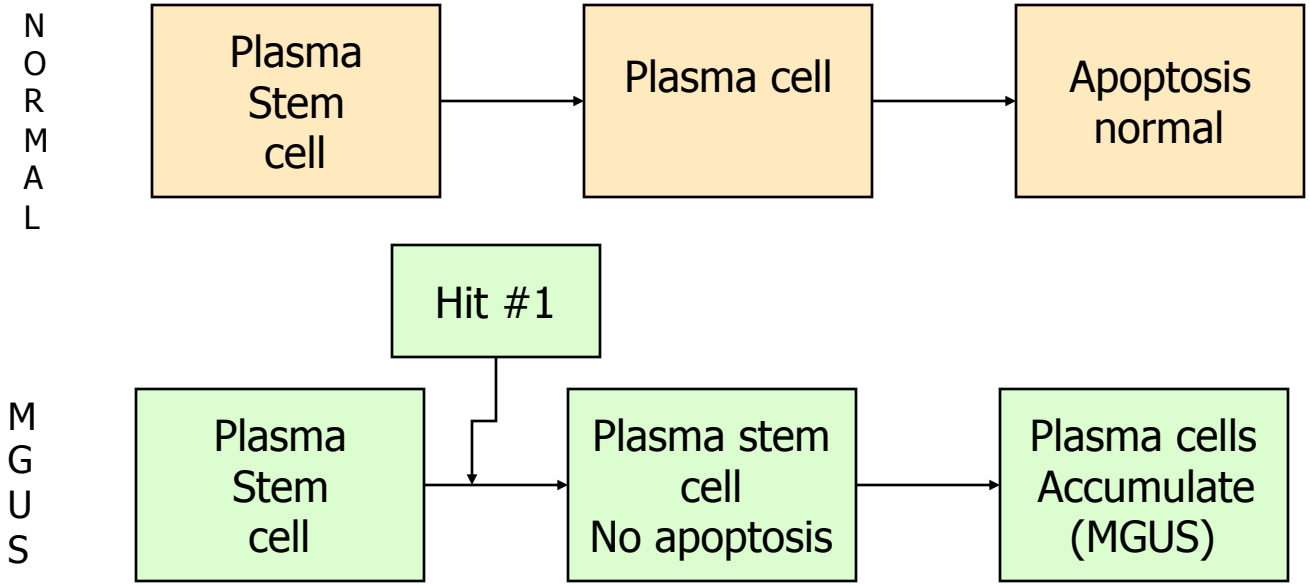
Definitions

- MGUS
  - Monoclonal Protein only
- Smoldering Myeloma
  - M-protein > 3 g/dL
  - BM plasma cells $\geq$ 10%
  - no other abnormalities
- Multiple Myeloma
  - M-protein > 3 g/dL
  - BM plasma cells $\geq$ 10%
  - Damage

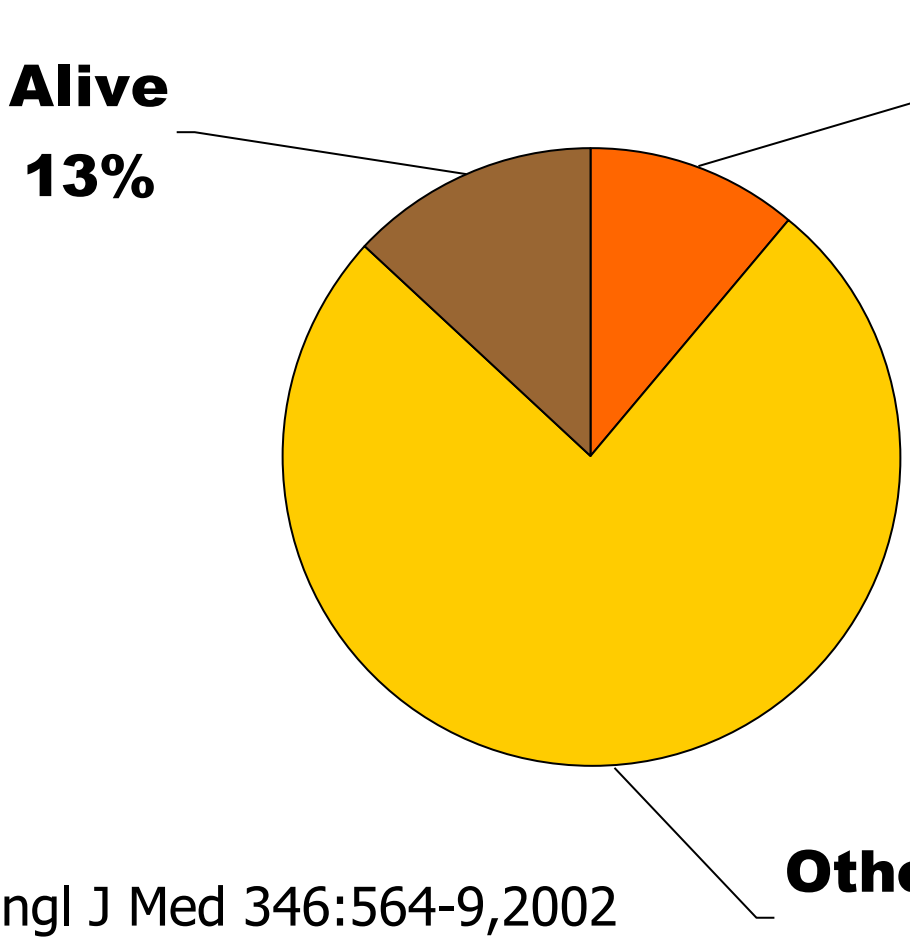
Protein only -> MGUS
Protein + bone destruction -> Multiple myeloma
Something in between -> Smoldering myeloma

Kyle, NEJM 302:1347-1349, 1980

Multi-hit hypothesis of multiple myeloma



Deaths Related to Myeloma 25 Years

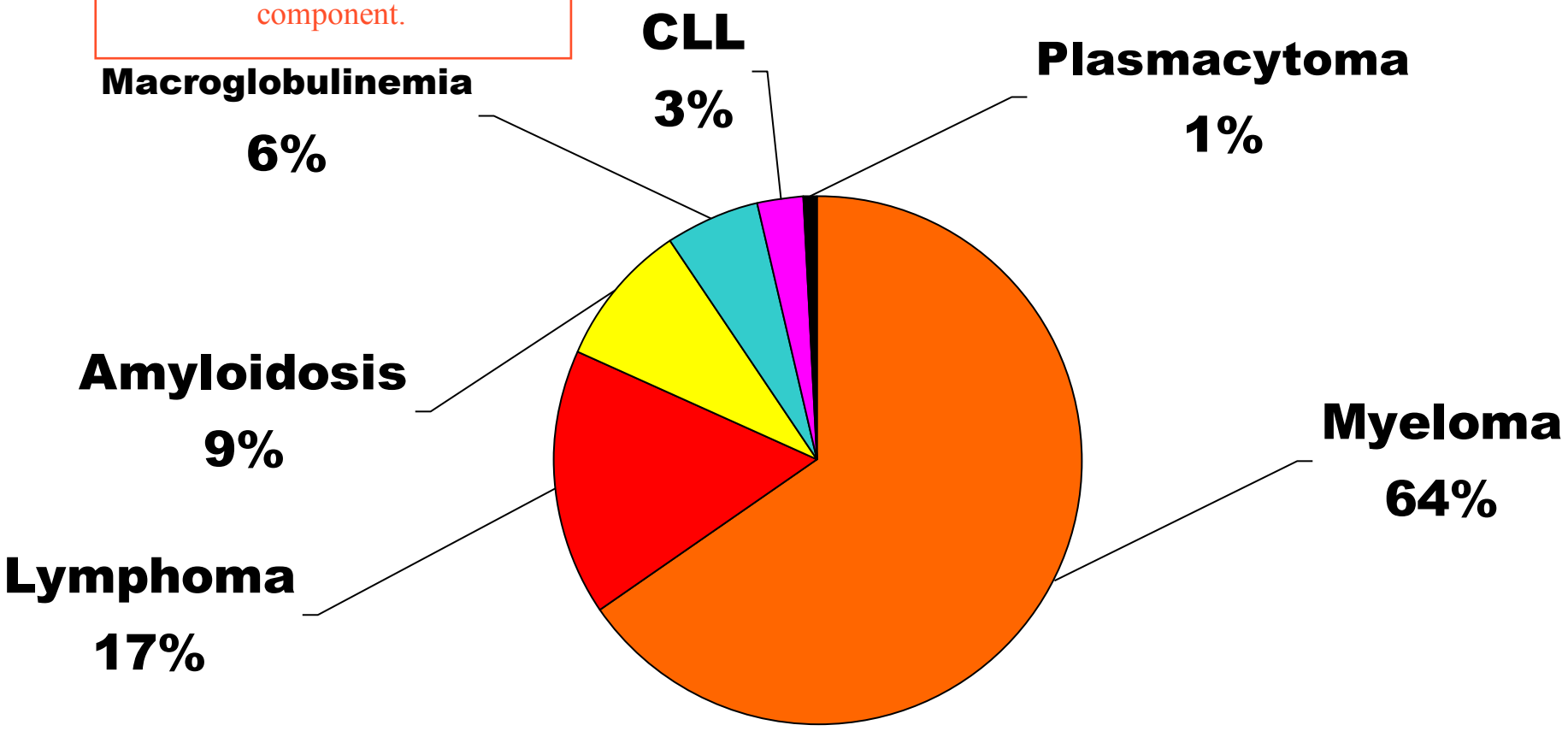


Some dude at the Mayo decided to draw blood on everyone from Olmstead County who came to Mayo for any medical reason. This gave him a large sample population (40 yrs of blood samples, 75% of population!) to study myeloma incidence. There's more on this in 3 slides.

Kyle, N Engl J Med 346:564-9,2002

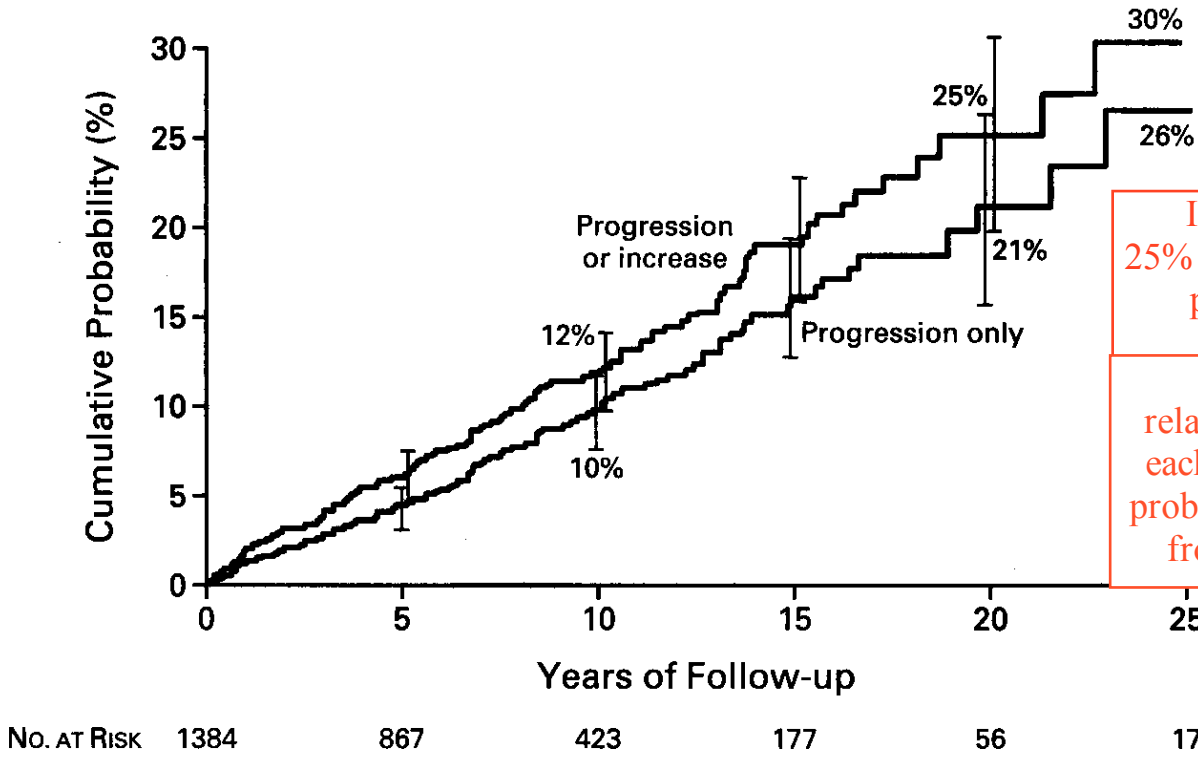
Deaths Related to Plasma Cell Disease 25 Years

While myeloma causes the majority of plasma cell disease, these other diseases also have a plasma cell component.



Kyle, N Engl J Med 346:564-9,2002

Probability of Progression From Diagnosis of MGUS



In 25 years, 25% of people have progressed.

The linear relationship implies that each year, there is a 1% probability of progression from MGUS to MM.

Kyle, N Engl J Med 346:564-9,2002

Prevalence of MGUS

- All living residents in Olmstead County, Minnesota
- Serum in Mayo Clinic labs or asked resident for serum sample
- Age > 50 years old
- SPEP

- 21,463 residents donated serum out of 28,038 enumerated residents

- Prevalence of MGUS
  - Age > 50, 3.2%
  - Age > 70, 5.3%
  - Age > 85, 7.5%

Kyle, N Engl J Med 2006; 354:1362-9

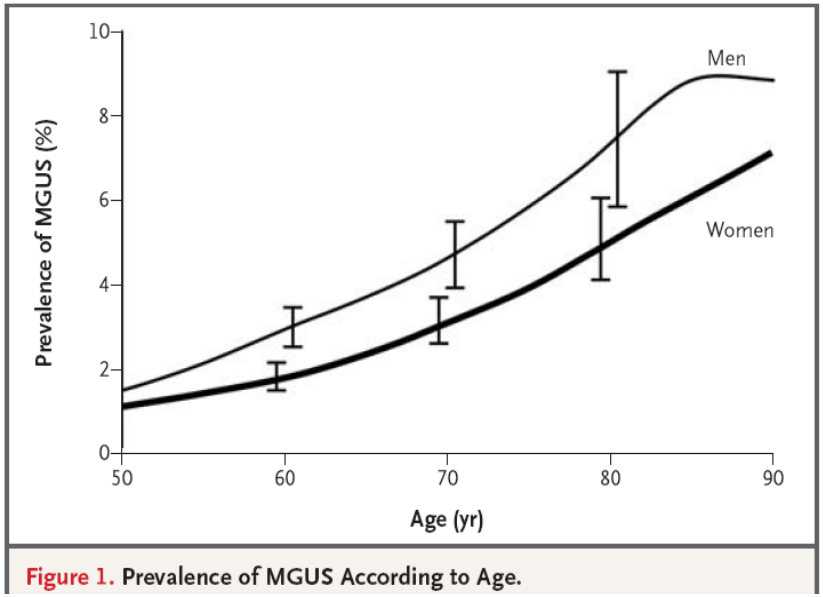


Figure 1. Prevalence of MGUS According to Age.

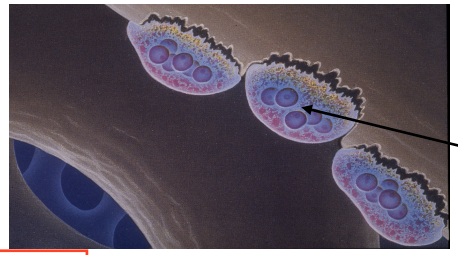
As you age, the chance you get MGUS increases.
If you are African American, your risk is equivalent to that of a Caucasian who is 10 yrs older.

Multiple Myeloma (PCM)

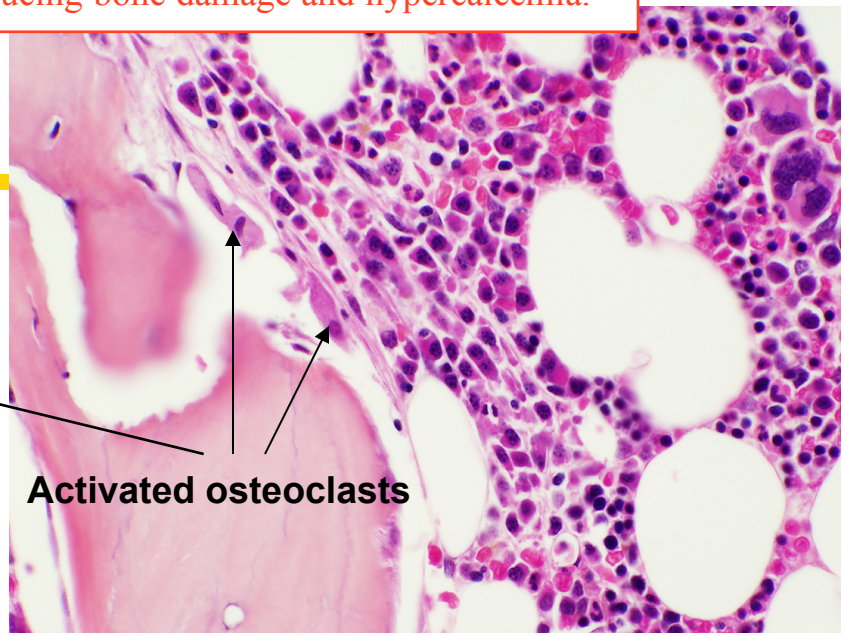
Pathology

PCM in Bone Marrow

One finds too many plasma cells in the bone marrow.

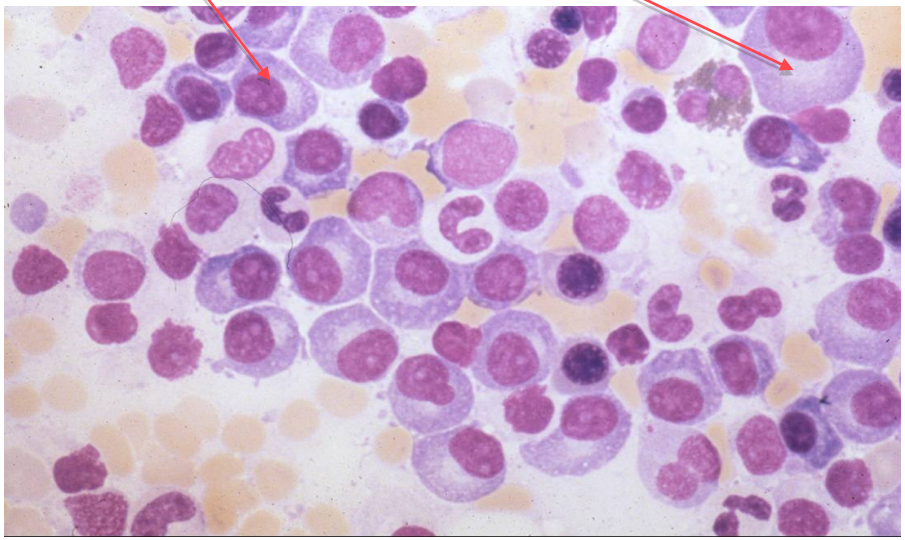


Here osteoclasts are eating away at the bone, producing bone damage and hypercalcemia.



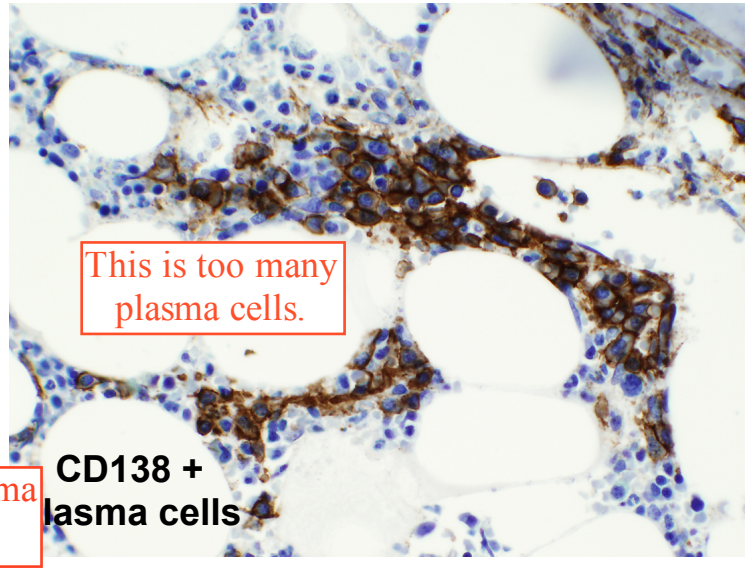
Normal plasma

Abnormal plasma



Bone marrow aspirate

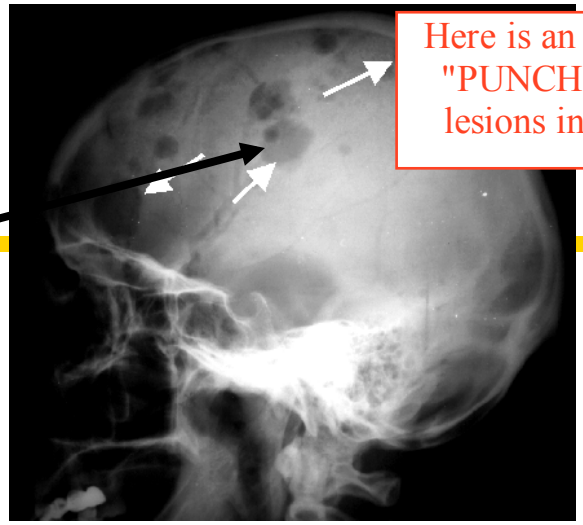
Bone marrow biopsy



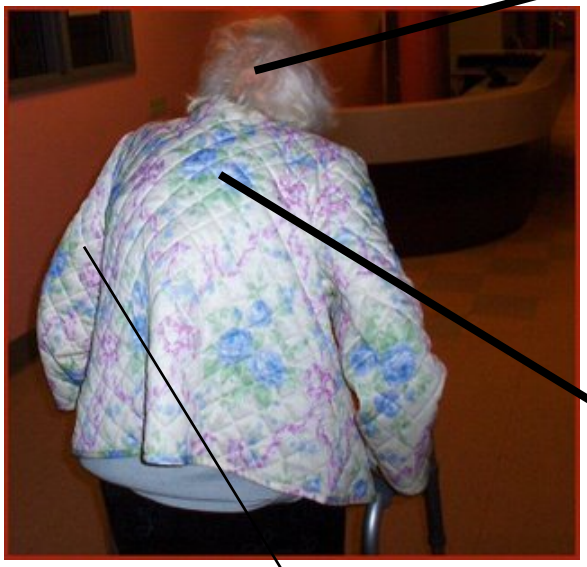
CD138 is a good plasma cell marker.

Multiple myeloma is characterized by multiple lesions due to collections of plasma cells causing osteoclastic activation and bone damage.

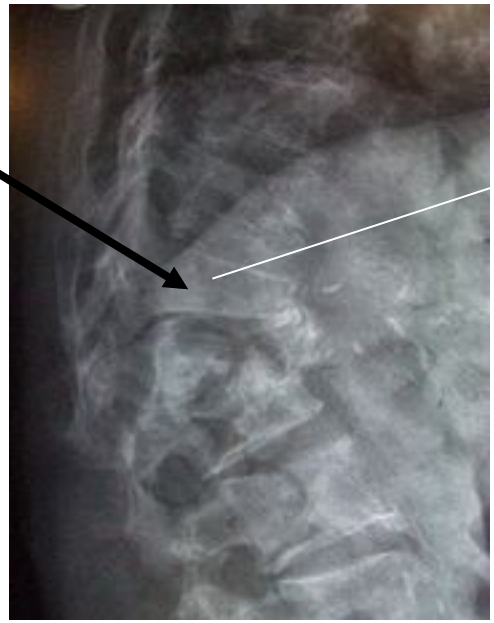
PCM: Bone Lesions

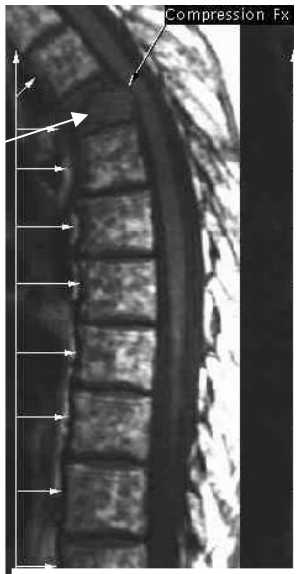


Here is an example of "PUNCHED OUT" lesions in the skull.



Vertebral compression

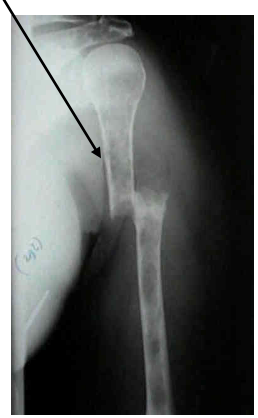




The vertebral body is compressed.

Pathologic fracture

Bone damage predisposes one to fractures.



Tools: How is PCM Monitored?

Serum Protein Electrophoresis and Immunofixation Electrophoresis (SPEP/IF

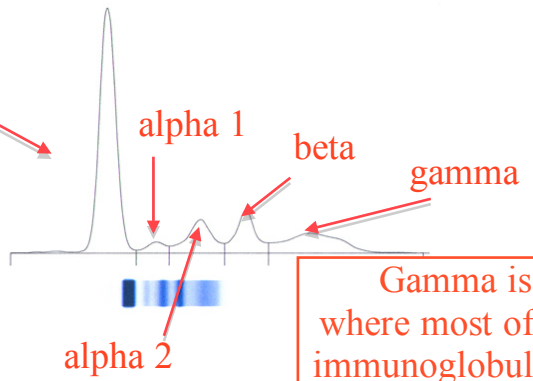
This is a common way to follow patients undergoing treatment for multiple myeloma.

Normal

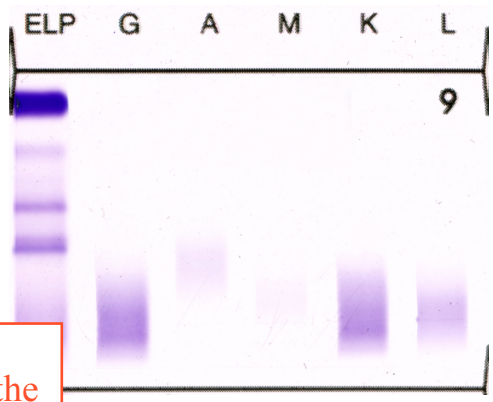
Serum Protein Electrophoresis

Fraction	%	Ref %	g/dl	Ref g/dl
Albumin	65.3	58.8 - 69.6	4.83	4.00 - 5.30
Alpha 1	2.5	1.8 - 3.8	0.19	0.10 - 0.30
Alpha 2	9.6	3.7 - 13.1	0.71	0.40 - 0.90
Beta	9.6	8.9 - 13.6	0.71	0.60 - 1.00
Gamma	13.0	8.4 - 18.3	0.96	0.50 - 1.40

A/G 1.88 T.P.: 7.4



Gamma is where most of the immunoglobulin is



Serum protein electrophoresis (SPEP) (also UPEP)

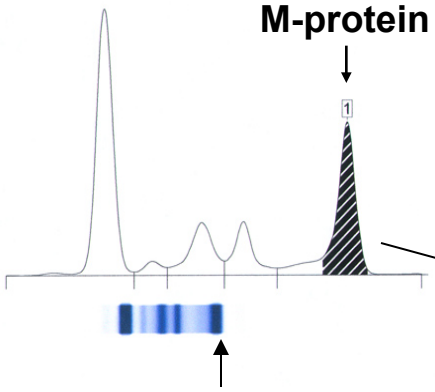
Immunofixation electrophoresis (IFE)

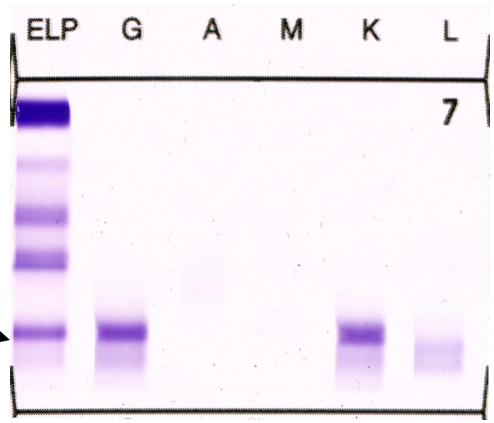
This is a monoclonal spike that you see in multiple myeloma.

Serum Protein Electrophoresis

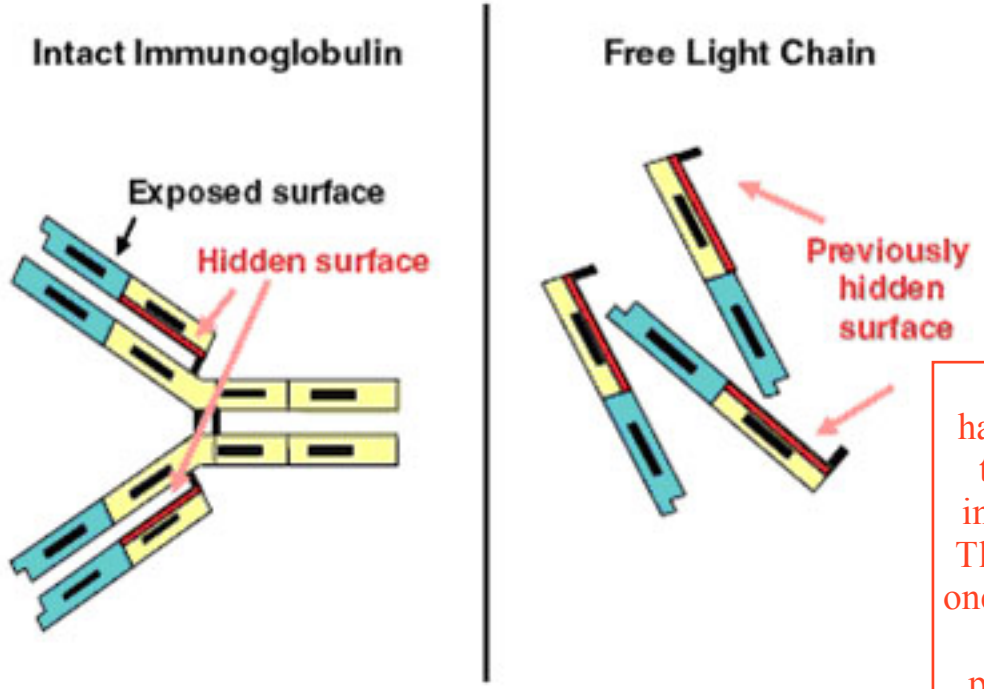
Fraction	%	Ref %		g/dl	Ref g/dl
Albumin	48.6	58.8 - 69.6		4.03	4.00 - 5.30
Alpha 1	2.4	1.8 - 3.8		0.20	0.10 - 0.30
Alpha 2	11.6	3.7 - 13.1	+	0.96	0.40 - 0.90
Beta	9.3	8.9 - 13.6		0.77	0.60 - 1.00
Gamma	28.1	8.4 - 18.3	+	2.33	0.50 - 1.40
1	24.0			1.99	

A/G 0.95 T.P.: 8.3





Serum-free Light Chains Assay



Free light chains have an exposed surface that is not exposed in intact immunoglobulin. This creates a target that one can use to follow free light chain levels in patients with myeloma

The important measure is the ratio of kappa to lambda Ig light chains

Here's one way to stage

Staging

Once again, the big picture:
protein: low stage
protein + destruction: high stage

This is multiple myeloma

This is MGUS Stage I	Stage II	Stage III
Hb > 10 g/dL Ca ≤ 12 mg/dL Bone normal or single lesion Low M protein IgG < 5 g/dL IgA < 3 g/dL Urine light chain < 4 g/24 h	Neither Stage I or II	Hb < 8.5 g/dL Ca ≥ 12 g/dL Advanced lytic bone lesions High M Protein IgG > 7 g/dL IgA > 5 g/dL Urine light chain > 12 g/24 h

Durie and Salmon, Cancer 36:842-854, 1975

Staging

Stage	Median OS (months)
IA	191
IB	-
IIA	54
IIB	11
IIIA	34
IIIB	5

Durie and Salmon, Cancer 36:842-854, 1975

CRP and B2M Prognosis

CRP= C reactive protein
B2M= beta 2 microglobulin

Here's another way to stage!

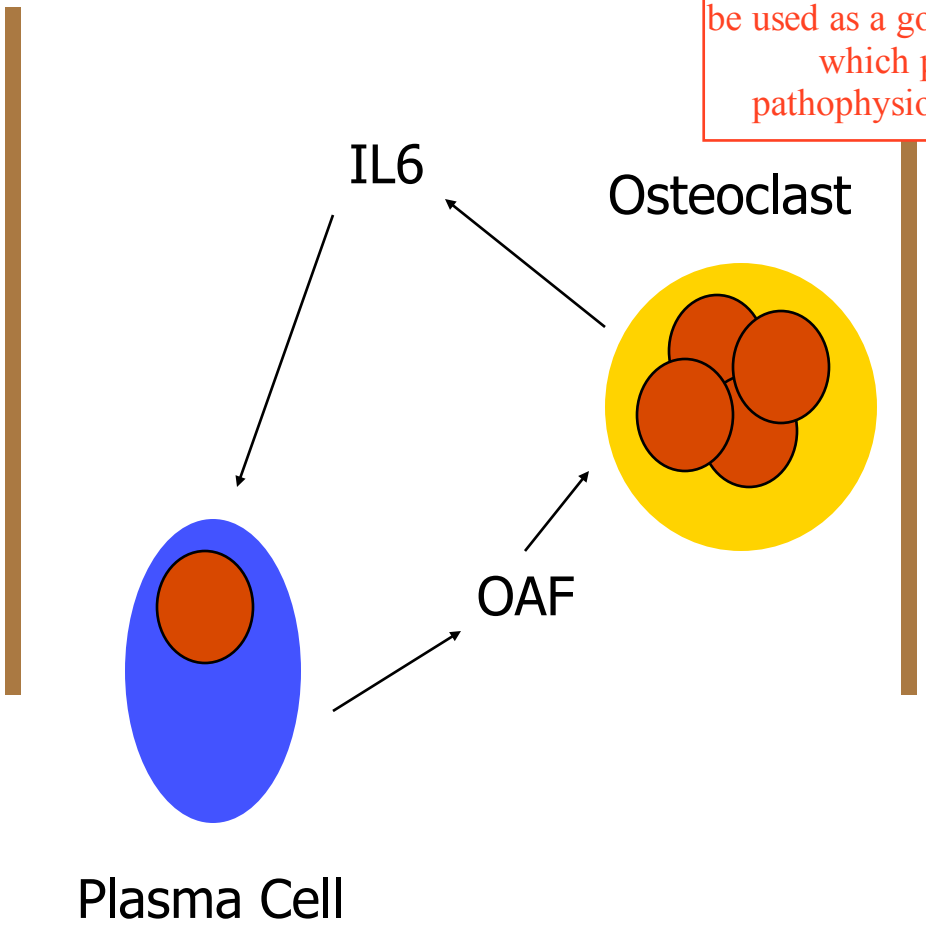
These 2 markers are great predictors of survival. The reason CRP is a good predictor is explained on the next slide.

Criteria	Survival (months)
CRP < 6 mg/L B2M < 6 mg/L	54
CRP > 6 mg/L or B2M > 6 mg/L	27
CRP > 6 mg/L and B2M > 6 mg/L	6

Bataille. Blood 1992 Aug 1;80:733-7

Concept
Pathophysiology

IL-6 is very difficult to measure. However, IL-6 induces CRP production, so CRP can be used as a good surrogate marker for IL-6, which plays a huge role in the pathophysiology of multiple myeloma.



CRP and B2M Prognosis

Criteria	Survival (months)
CRP < 6 mg/L B2M < 6 mg/L	54
CRP > 6 mg/L or B2M > 6 mg/L	27
CRP > 6 mg/L and B2M > 6 mg/L	6

Bataille. Blood 1992 Aug 1;80:733-7

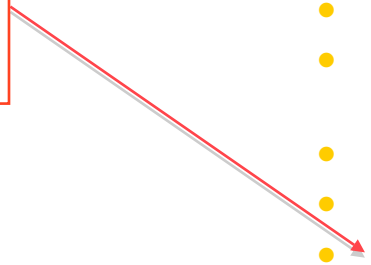
International Staging System Multiple Myeloma

- 10,750 patients
- Multiple myeloma
- Untreated
- Symptomatic
- 17 institutions
  - North America
  - Europe
  - Asia

This was a massive international study that was done in an effort to establish YET ANOTHER staging system for multiple myeloma.

- Collected data
  - Initial treatment
  - Age
  - Sex
  - Ethnicity
  - Hemoglobin level
  - Platelet cunt
  - Level and type of M-protein
  - Calcium level
  - Creatinine
  - Albumin
  - Durie-Salmon stage
  - Number of bone lesions
  - Compression fracture
  - Bone marrow plasma cell percentage
  - LDH
  - Serum beta-2-microglobulin
  - C-reactive protein
  - Standard cytogenetics

The problem with this study was that only the French got this data on patients, so there was not enough data for CRP.



Greipp, J Clin Oncol 23:3412,2005

International Staging System: Multiple Myeloma
Ten most important prognostic factors in univariate analyses

Table 1. Comparison of Univariate and Multivariate Correlates of Survival Duration*

Univariate				Multivariate†		
No. of Patients/ Total No.	%	Hazard Ratio	Variables	Hazard Ratio		Sequence of Entry
2,428/4,313	56	1.81	$S\beta_2M \geq 3.5$ mg/L	1.81	•	$S\beta_2M$ 1
570/4,878	12	1.73	Platelet count (Platelets) < 130,000/μL	1.63	•	Platelets 2
1,842/5,358	34	1.67	Age ≥ 65 years			ALB 3
868/5,181	17	1.66	Serum CREAT ≥ 2 mg/dL	1.28	•	CALC 4
533/2,050	26	1.5	Serum LDH value > normal			CREAT 5
2,077/5,175	40	1.49	Hemoglobin < 10 g/dL			
938/3,100	19	1.44	Performance status > 3			
1,940/4,770	40	1.4	Serum ALB < 3.5 g/dL	1.28	•	
1,588/4,754	33	1.32	Serum CALC > 10 mg/dL	1.28	•	
2,897/4,996	58	1.29	Bone marrow plasma cells ≥ 33%			

Abbreviations: $S\beta_2M$, serum $beta_2$-microglobulin; ALB, albumin; CREAT, creatinine; LDH, lactate dehydrogenase; CALC, calcium.
*See text for details.
†These are results of stepwise multivariate regression analysis. Each sequential hazard ratio reflects adjustment for prior variables.

Greipp, J Clin Oncol 23:3412,2005

International Staging System Multiple Myeloma

In practical terms, this staging system is actually not used very often. People usually just stick to one of the first 2 staging systems described earlier.

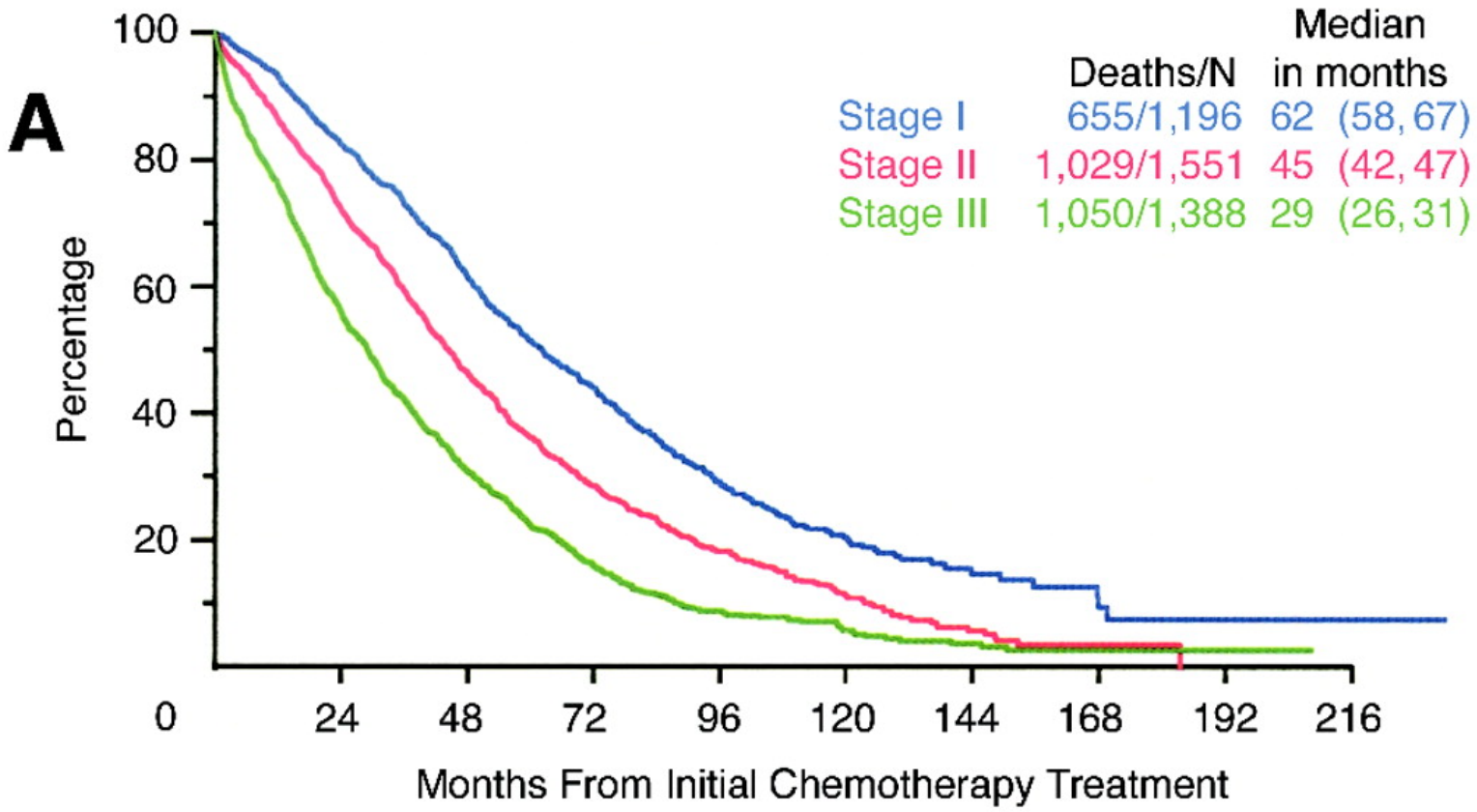
Table 2. New International Staging System

Stage	Criteria	Median Survival (months)
I	Serum β_2-microglobulin < 3.5 mg/L Serum albumin ≥ 3.5 g/dL	62
II	Not stage I or III*	44
III	Serum β_2-microglobulin ≥ 5.5 mg/L	29

*There are two categories for stage II: serum β_2-microglobulin < 3.5 mg/L but serum albumin < 3.5 g/dL; or serum β_2-microglobulin 3.5 to < 5.5 mg/L irrespective of the serum albumin level.

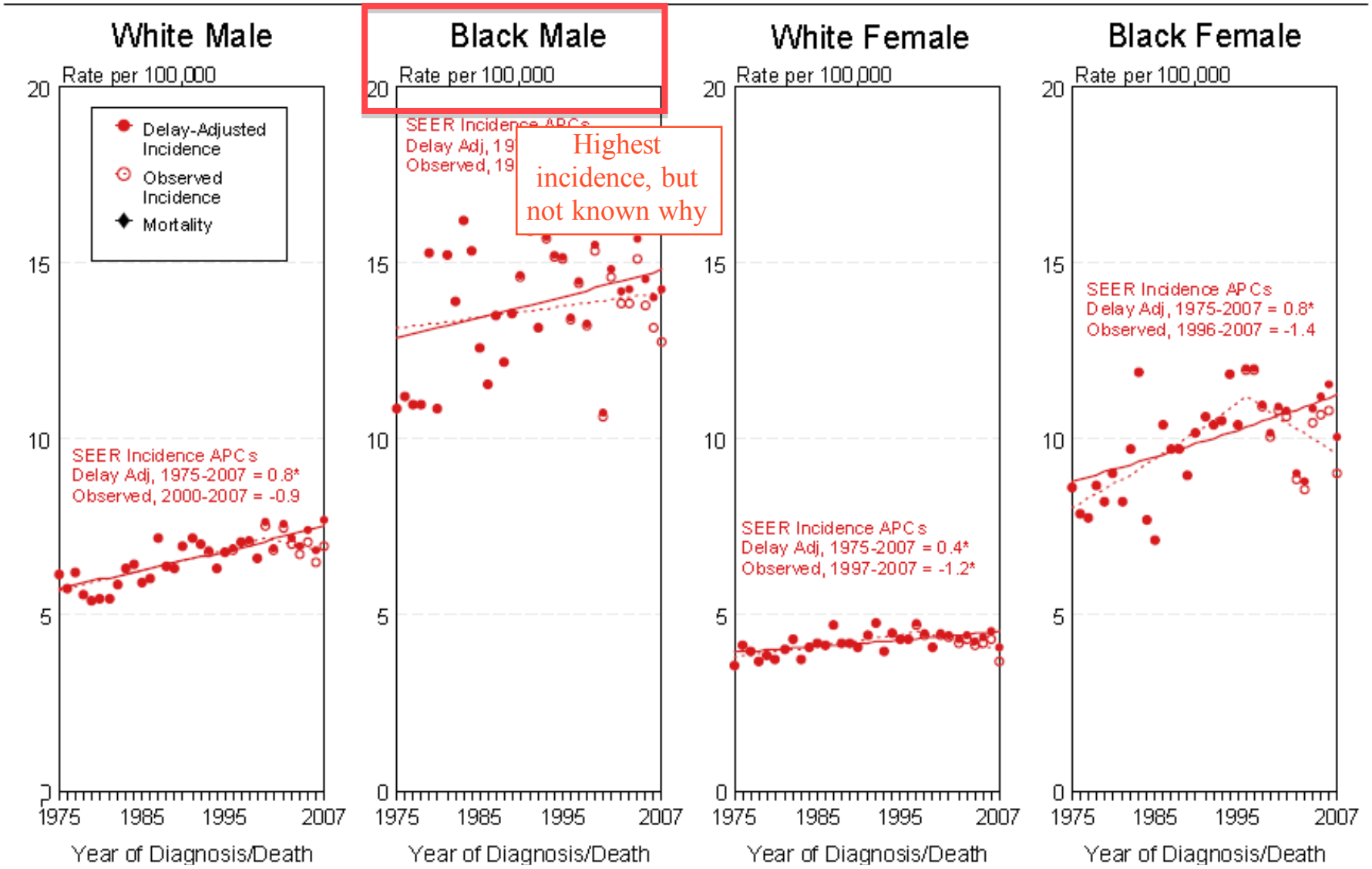
Greipp, J Clin Oncol 23:3412,2005

International Staging System Multiple Myeloma



Greipp, J Clin Oncol 23:3412,2005

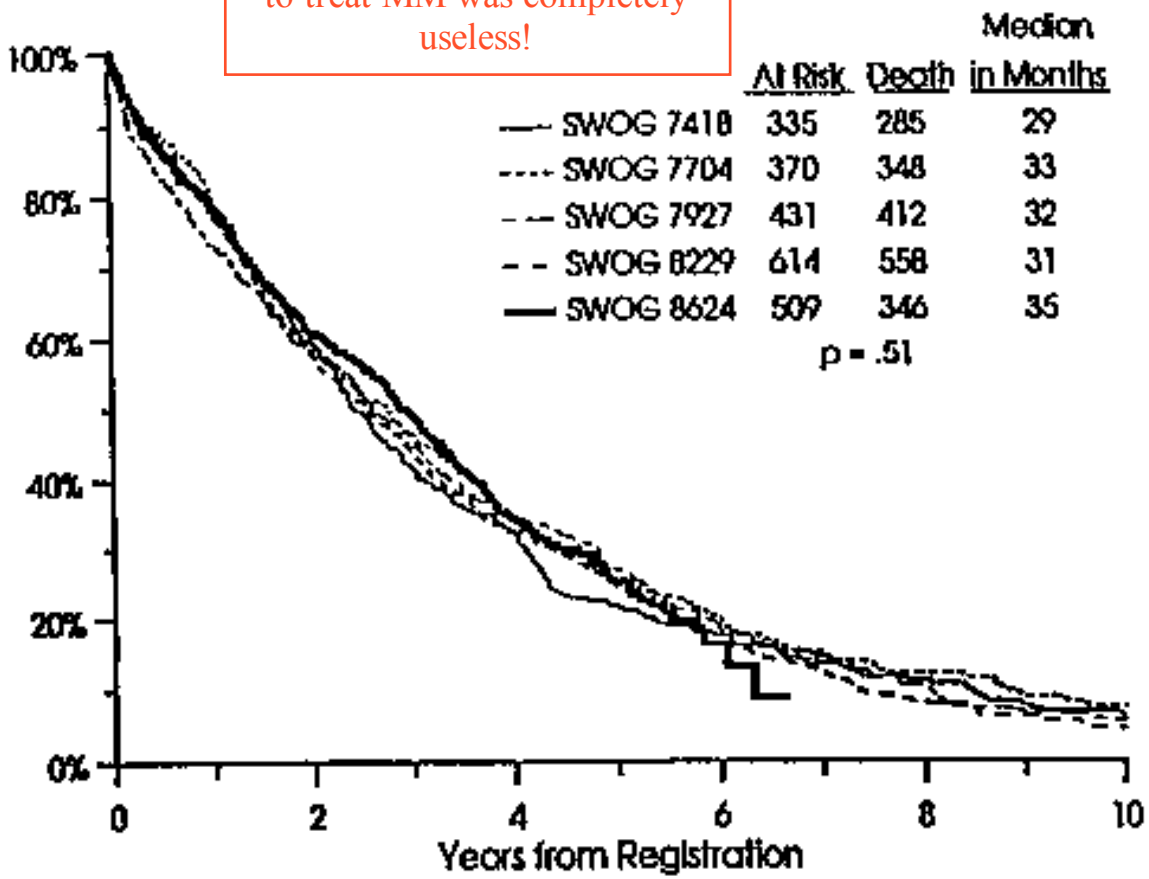
SEER Observed Incidence, SEER Delay Adjusted Incidence and US Death Rates[a] Myeloma, by Race and Sex



Treatment

Multiple Myeloma
Natural History: Treated

Putting together multiple drugs to treat MM was completely useless!

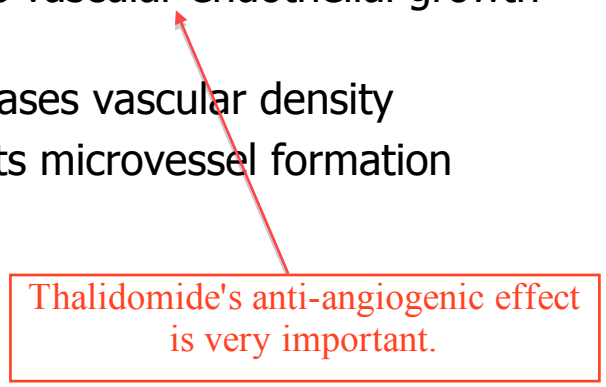


Vesole, SWOG, Cancer Investig 14:378-391, 1996

Thalidomide Mechanism of Action

- Immunomobulatory
  - inhibits TNF alpha production
    - increases TNF-alpha m-RNA degredation
    - increases alpha 1-acid glycoproteins which have anti TNF-alpha activity
  - increases cytotoxic T cell proliferation
  - Increases gamma interferon
  - increases IL-2
  - increases T-helpher cell type 2

- Antiangiogenic
  - blocks basic fibroblast growth factor
  - blocks vascular endothelial growth factor
  - decreases vascular density
  - inhibits microvessel formation



Kyle, Rajkumar Sem in Oncol 28:583, 2001

Thalidomide Response

This is in a trial that enrolled patients who FAILED bone marrow transplant.

M Protein	Percent
25%	7%
50%	9%
75%	8%
90%	10%
Complete response	2%

Desikan, SWOG, ASH #2685, 1999
Singhal NEJM 1999;341:1565-71.

Bortezomib

Here's another MM drug.

- Proteasome inhibitor
- Pharmacokinetics
  - Rapidly disappears from vascular compartment
  - Biologic half-life of 24 hours
- Mechanisms
  - Induces apoptosis
  - Down regulates adhesion molecule expression
  - Decreases transcription and secretion of cytokines
- Method of administration
  - IV over 3-5 seconds on days 1, 4, 8, 11 of 21 day cycle

Richardson, N Engl J Med 2003;348:2609-17

Bortezomib
Phase II Study

- 202 patients
- Multiple myeloma
- Relapsed and refractory

- Initial treatment with bortezomib
  - Dexamethasone added for suboptimal response

This drug got some good responses (see next slide).

Richardson, N Engl J Med 2003;348:2609-17

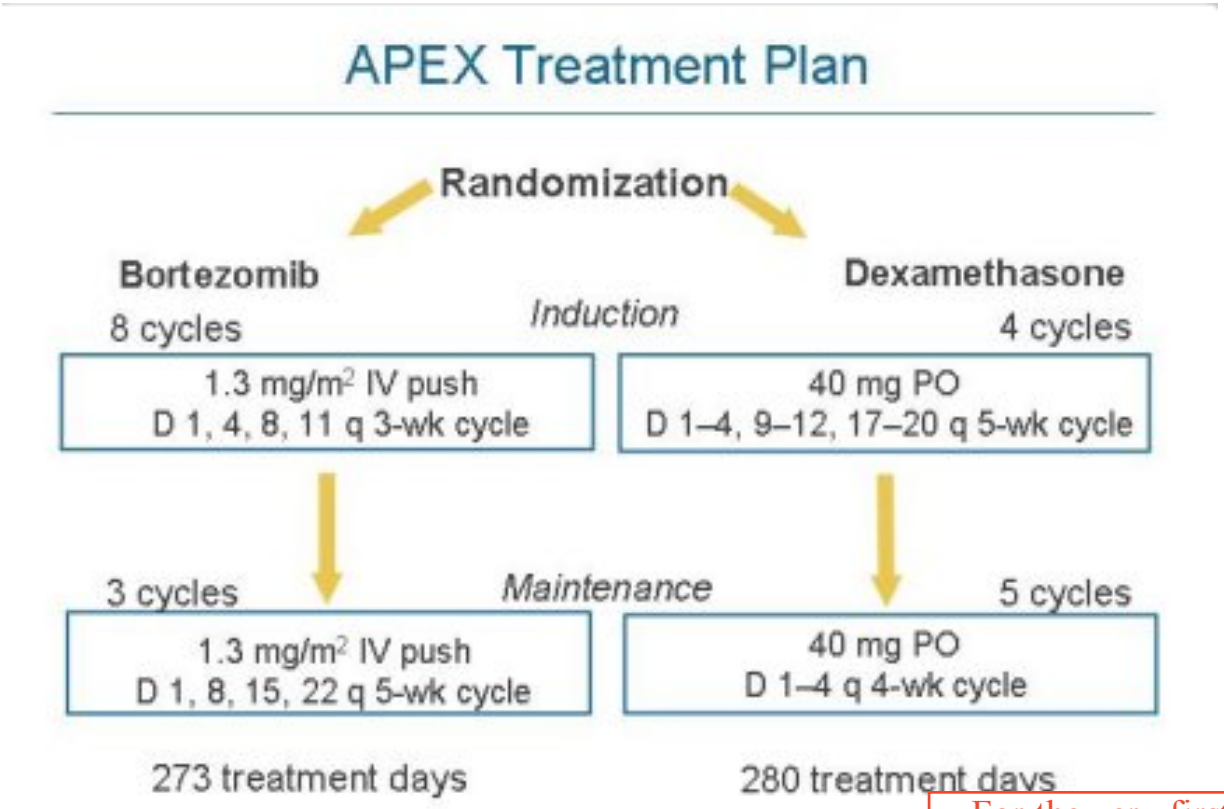
Bortezomib Response

This is considered a "magical" response in the multiple myeloma community.

Complete response SPEP and IFE	7/193 (4%)
Complete response SPEP alone	19/193 (10%)
Partial response	34/193 (18%)
Time to response	1.3 months
Time to progression Time to progression of responders	7 months 12 months

Richardson, N Engl J Med 2003;348:2609-17

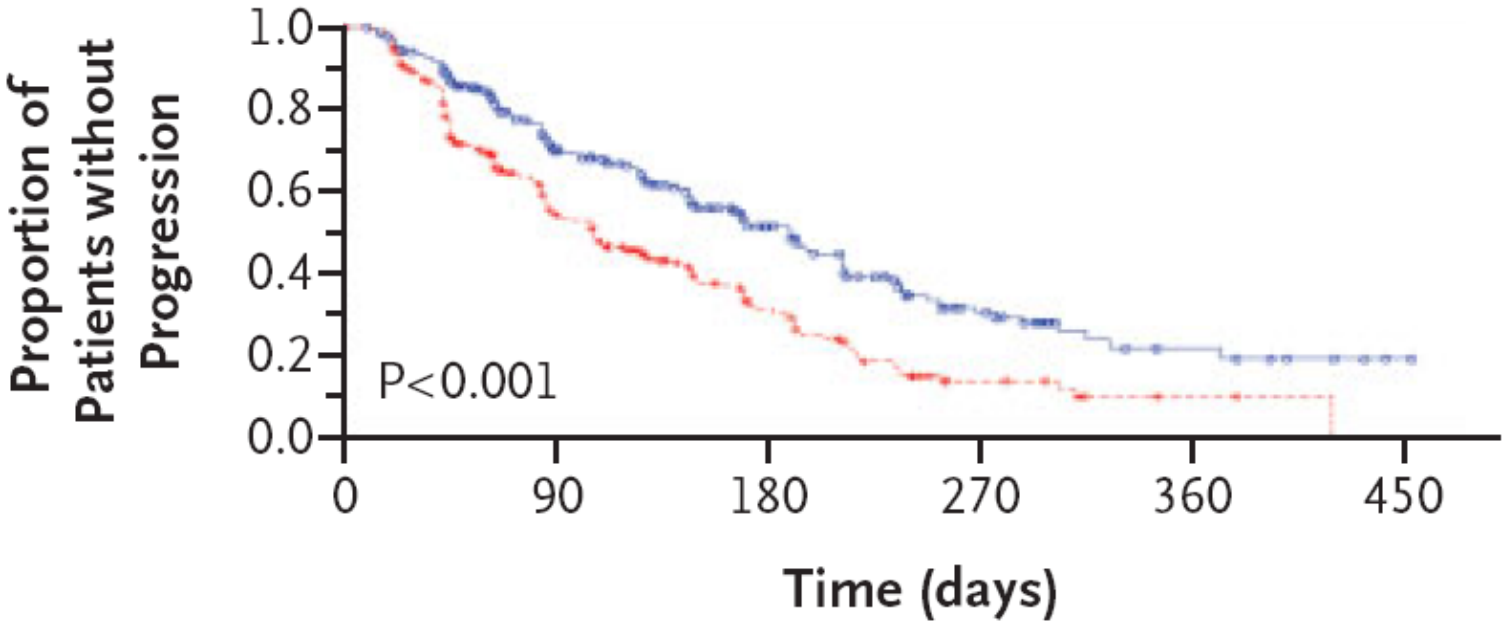
Bortezomib vs Dexamethasone Trial Structure



Source: Richardson P, et al. ASCO 2004. Abstract #6511.

For the very first time, a drug improved overall survival in multiple myeloma! (see the next slide for the graph showing this)

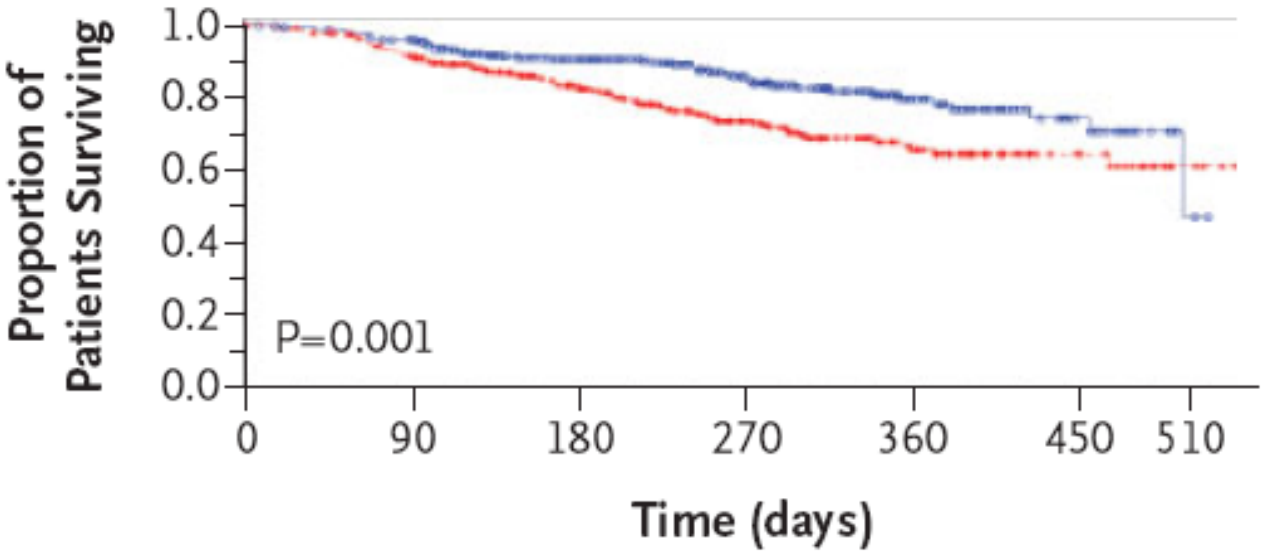
Bortezomib vs Dexamethasone Progression Free



No. at Risk					
Bortezomib	153	73	26	8	1
Dexamethasone	121	46	9	2	0

Richardson, N Engl J Med 352:2487-2498, 2005

Bortezomib vs Dexamethasone Overall Survival



No. at Risk						
Bortezomib	310	219	138	62	21	2
Dexamethasone	292	201	118	59	20	4

Richardson, N Engl J Med 352:2487-2498, 2005

Multiple Myeloma
HDCT + Auto graft vs Chemotherapy

i.e. stem cell transplant

- Multiple myeloma
- Age < 65
- Durie-Salmon stage II or III
- No prior treatment

- 204 patient
- 32 centers

The transplant is not actually what cures you. What the transplant does is allow the doctors to pump in you extremely high doses of chemo that kills EVERY native blood cell, which then gives you a higher chance of getting rid of more myeloma cells.

See the next slide for the protocols

Attal et al N Engl J Med 1996;335:91-7

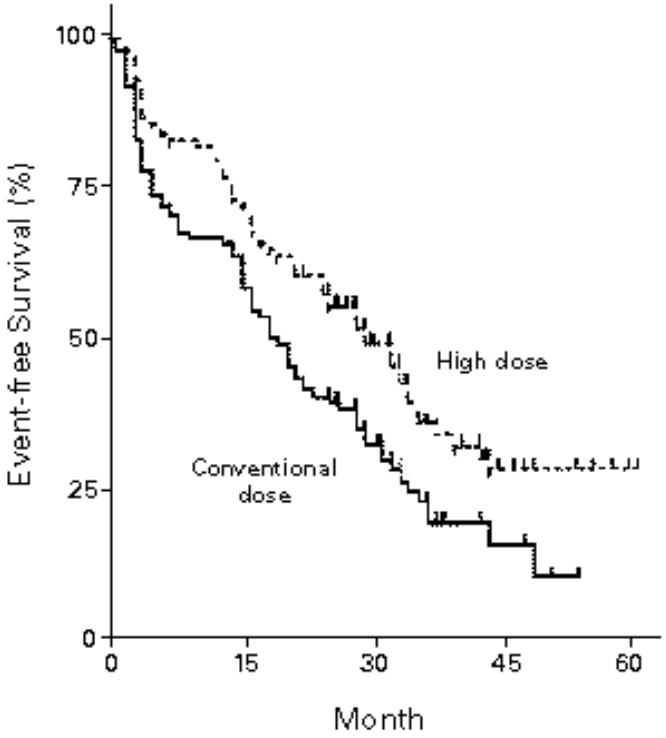
Multiple Myeloma
HDCT + Auto graft vs Chemotherapy

- Chemotherapy
  - VMCP and BVAP, alternating, 3 week interval, 12 months (18 cycles)
  - IFN 3 million IU TIW from cycle 9 until relapse
- High Dose Therapy
  - VMCP and BVAP alternating, 3 week interval, 4-6 cycles
  - Bone marrow collected after cycle #4
  - Unpurged marrow
  - Melphalan 140 mg/m2 + TBI (8 Gy)
  - IFN after recovery

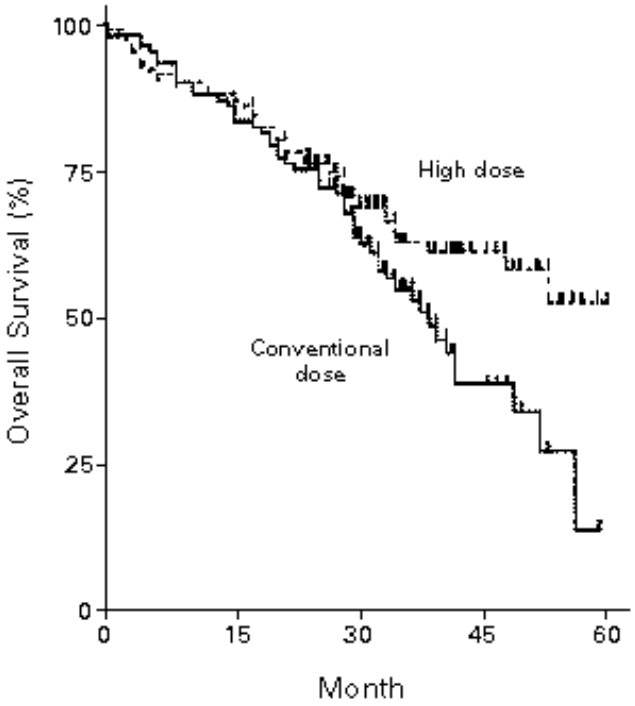
Attal et al N Engl J Med 1996;335:91-7

Multiple Myeloma
HDCT + Auto graft vs Chemotherapy

Results: transplant + chemo improved survival
(both event-free and overall)!



Conventional dose	58 (48–68)	32 (23–42)	15 (7–28)	10 (3–27)
High dose	71 (61–79)	50 (39–55)	28 (18–40)	28 (18–40)



Conventional dose	63 (53–73)	35 (22–50)	12 (1–40)	
High dose	69 (58–78)	61 (50–71)	52 (36–67)	

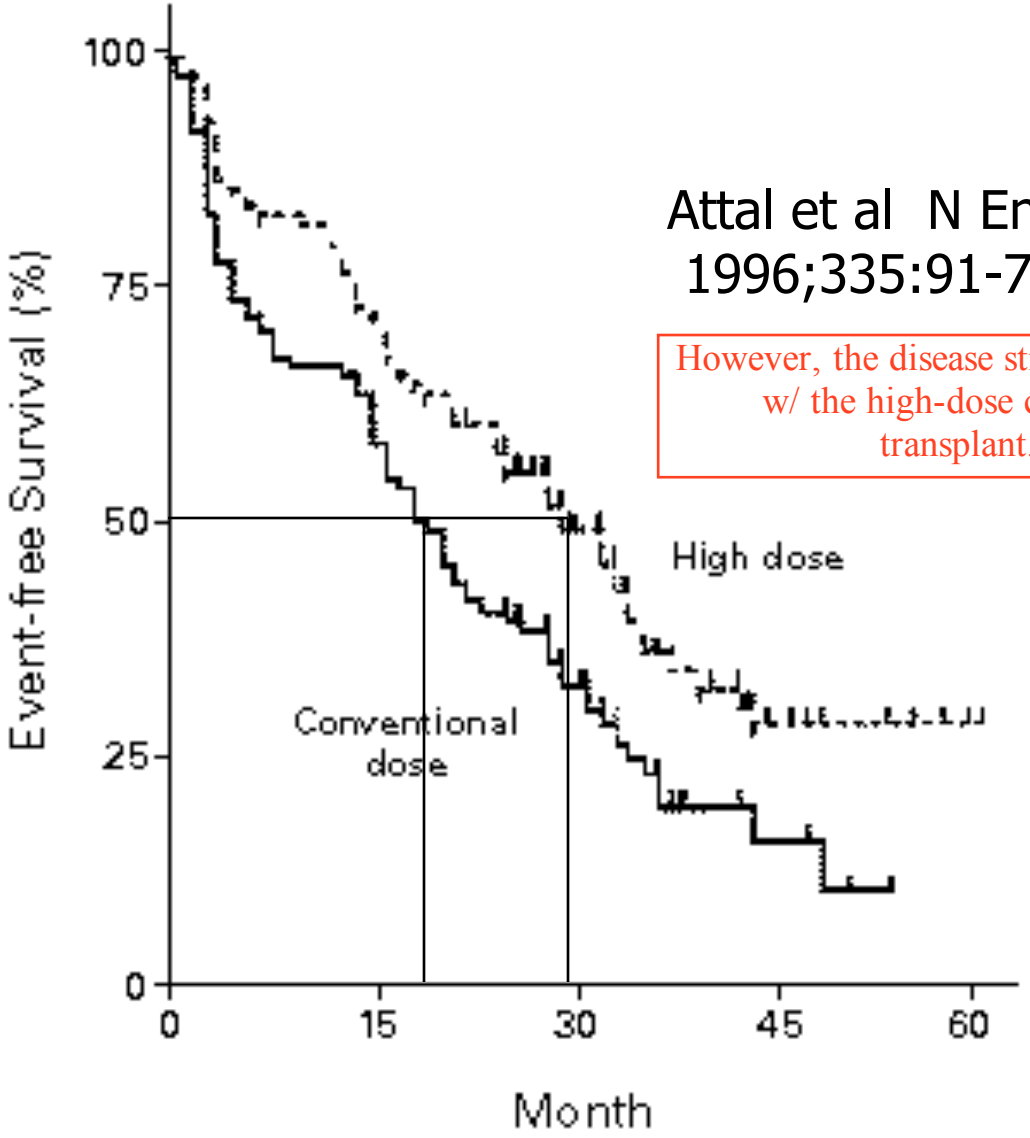
Attal et al N Engl J Med 1996;335:91-7

Attal et al N Engl J Med 1996;335:91-7

However, the disease still recurs even w/ the high-dose chemo + transplant.

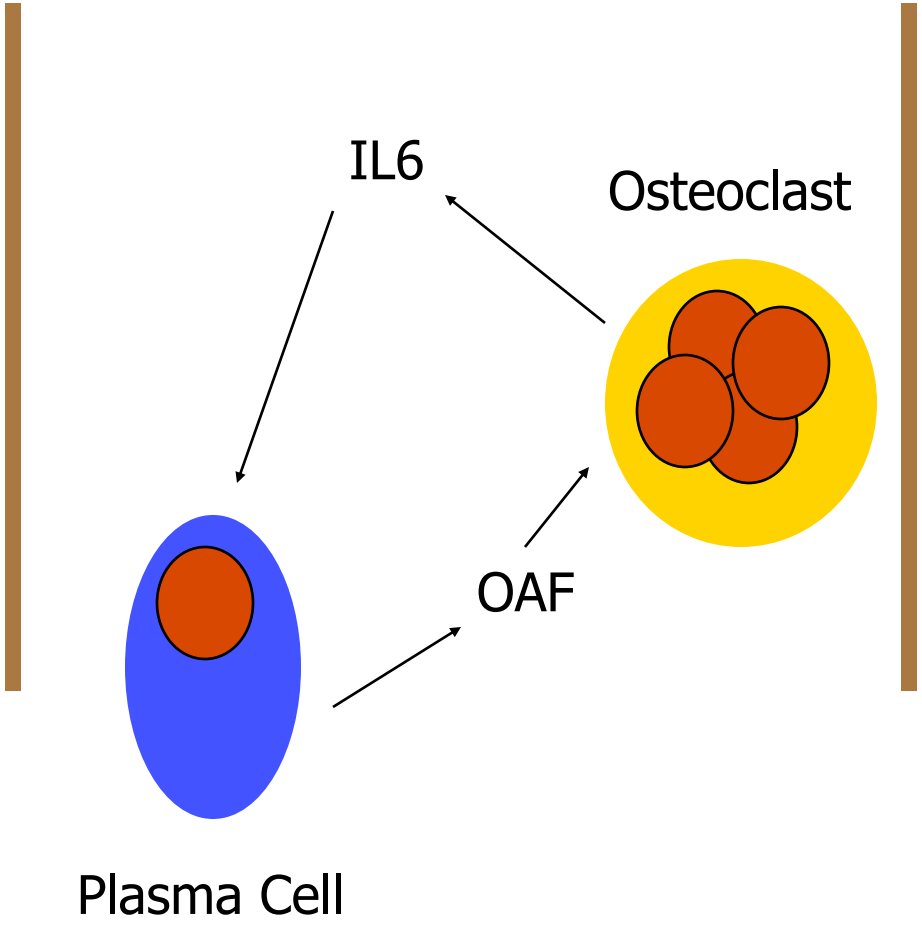
10.75 months
EFS Difference

Event = disease recurrence.

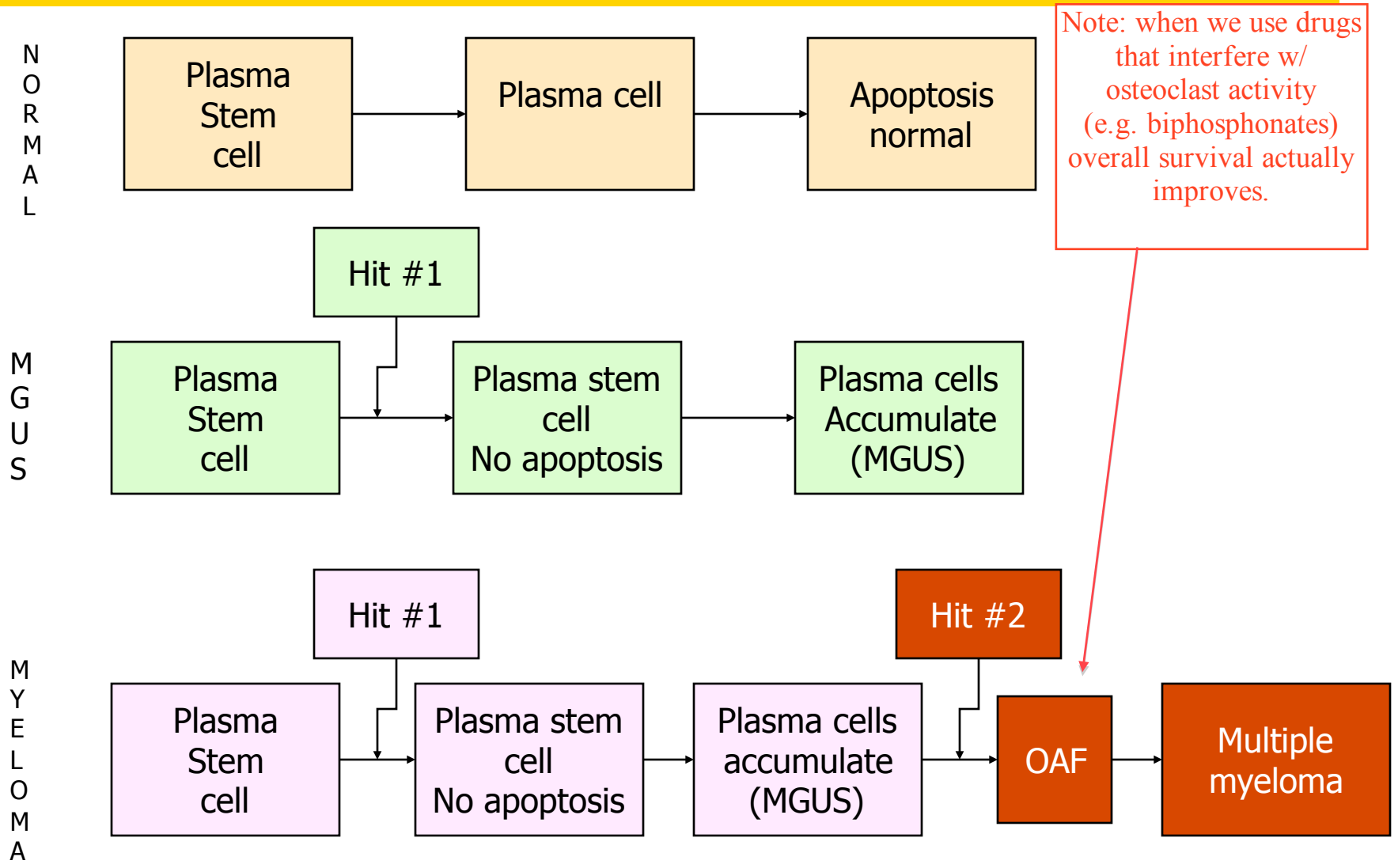


Conventional dose	58 (48–68)	32 (23–42)	15 (7–28)	10 (3–27)
High dose	71 (61–79)	50 (39–55)	28 (18–40)	28 (18–40)

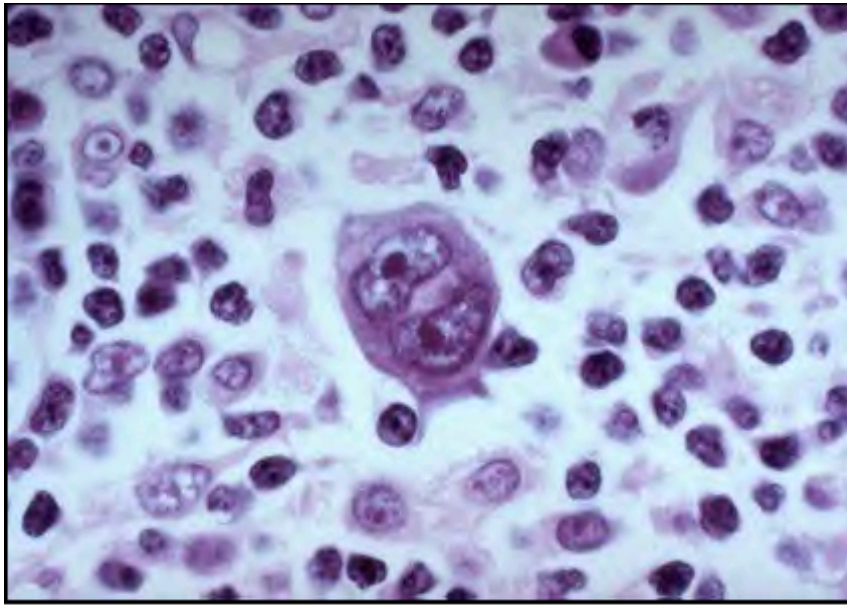
Concept Pathophysiology



Multi-hit hypothesis of multiple myeloma



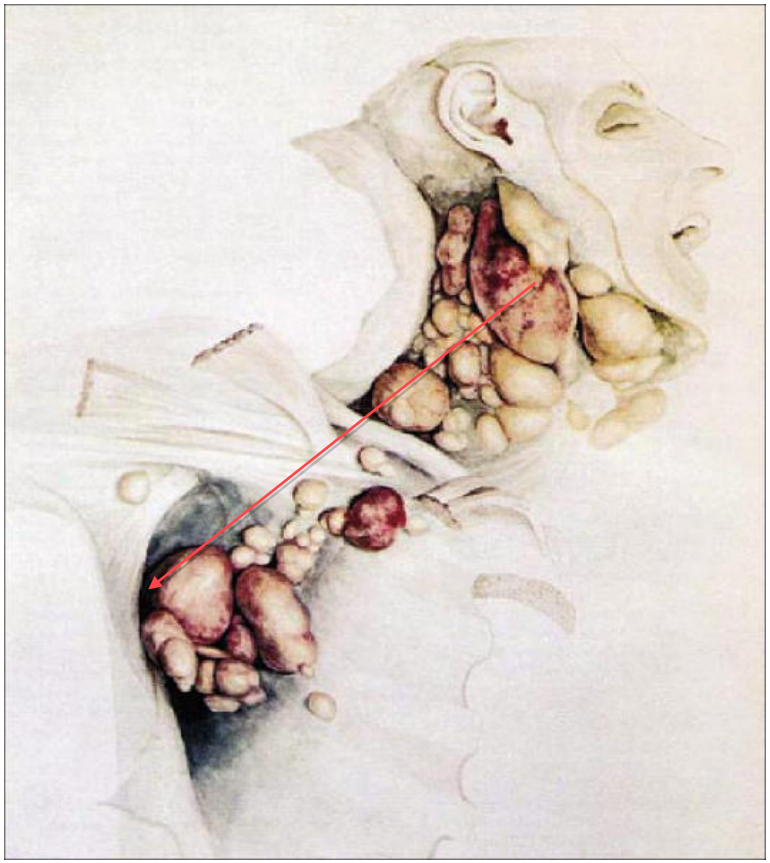
Hodgkin Lymphoma



Familiarize yourself with this image of the Reed-Sternberg cell, which is the neoplastic cell of HL (more on this in a bit)

Thomas Hodgkin

Hodgkin's disease watercolor drawing by Robert Carswell in 1828. This was case 7 in Hodgkin's report.



Hodgkin's lymphoma spreads predictably from one lymph node to the next. This is very unique for a lymphoma.

Case

- 23 year old man presented with increased shortness of breath and substernal chest pain. He had been losing some weight which he attributed to his new diet. He was otherwise without symptoms.
- PE: normal exam except for a 3 cm left supraclavicular lymph node and a 2.5 cm right anterior mid cervical lymph node.

Laboratory

Everything here is more or less normal except a slight leukocytosis

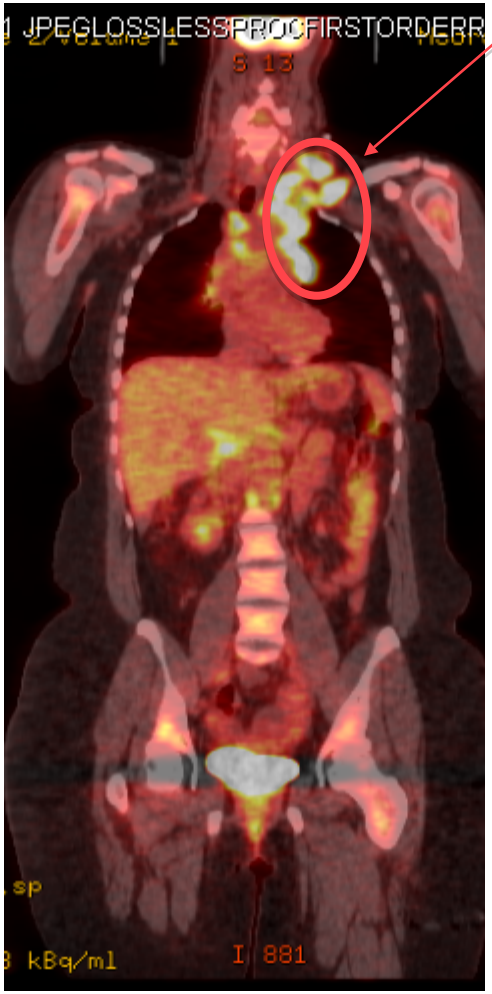
WBC	11,200
Hct	41%
Platelets	198,000

BUN	14
Creatinine	1.0
Calcium	8.8
Albumen	4.2

PET

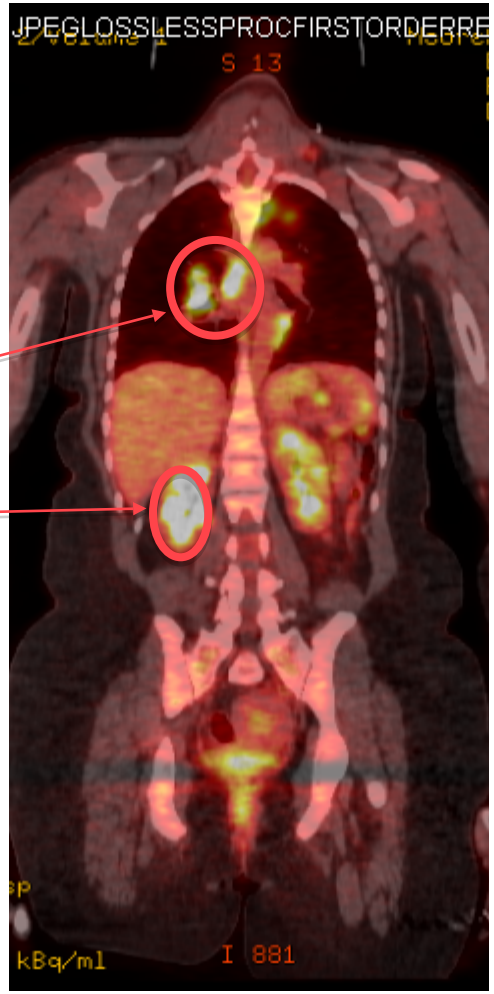
There is a lot of disease in the left neck, but also the right para-aoritc lymph nodes, and the right hilar nodes.

L. cervical/ supraclavicular nodes

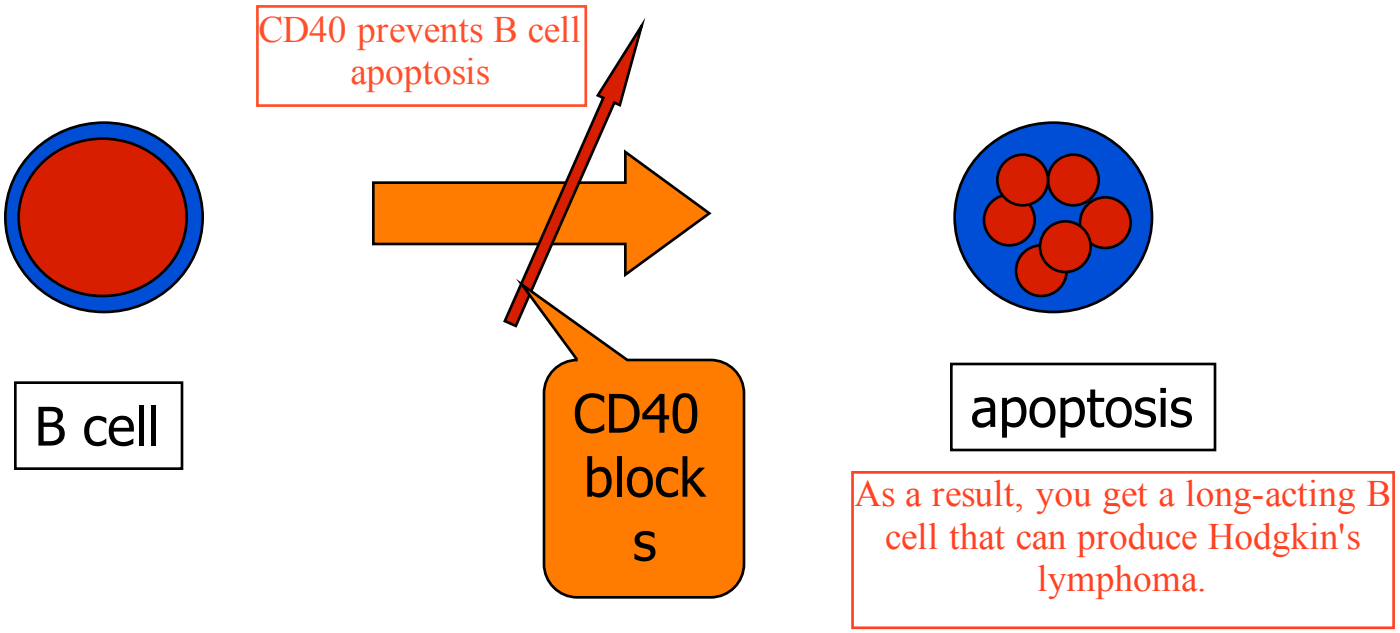


R. hilar nodes

R. para-aortic



Mechanism



LMP1 (from EBV) acts like CD40

This may explain the relationship with EBV, which is described in a bit.

Definition

- Reed-Sternberg cell, in the appropriate reactive background, which starts in a lymph node and progresses from lymph node to adjacent lymph node.

Hodgkin Lymphoma

Pathology

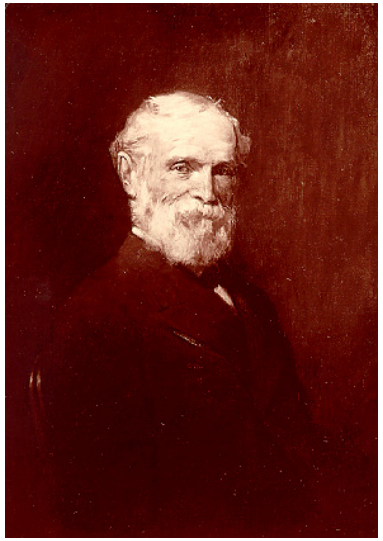
Again, the fundamental difference is that Hodgkin lymphoma progresses systematically from lymph node to lymph node. This is also the rationale behind the staging system for Hodgkin, which we wil discuss shortly.

Hodgkin Lymphoma
Histologic Classification (WHO)

Classical Hodgkin Lymphoma (95%)

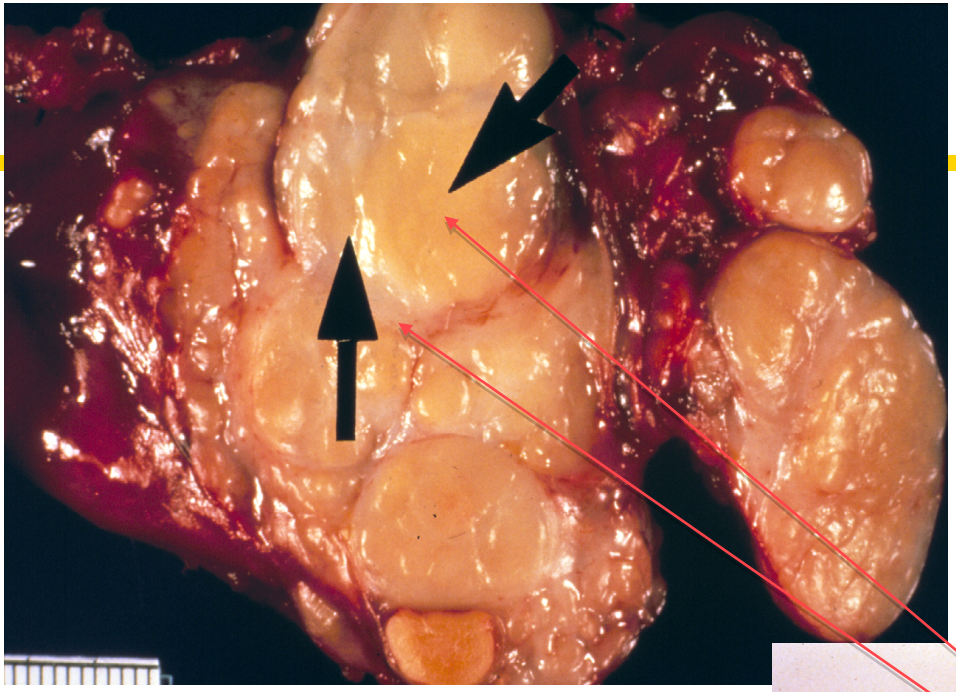
- Nodular sclerosis (70%)
- Mixed cellularity
- Lymphocyte-rich
- Lymphocyte depleted

Most common, and what we are about to discuss.



Nodular lymphocyte predominant (5%)

Reed-Sternberg cell



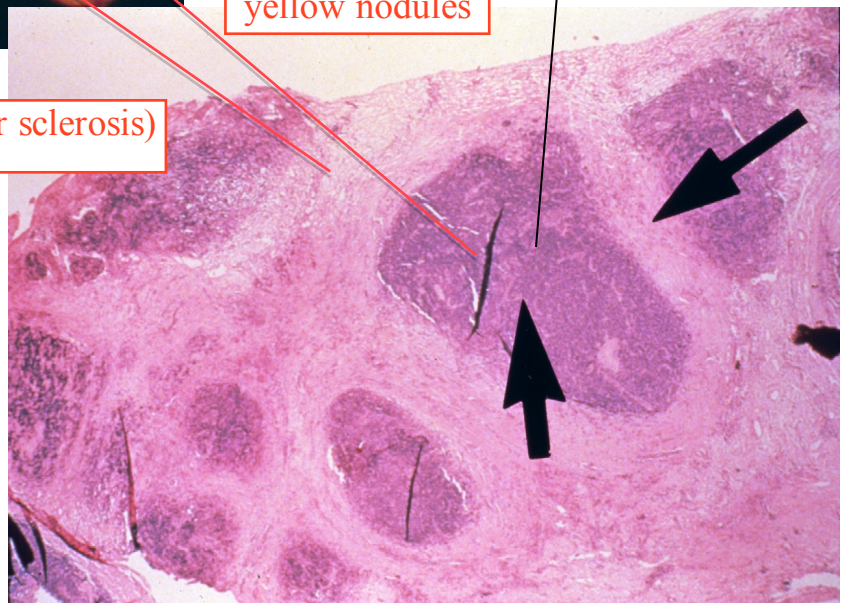
This tissue comes from the mediastinal mass of a young child.

This cell characterizes HL

This is a classic image of the RS cell.

yellow nodules

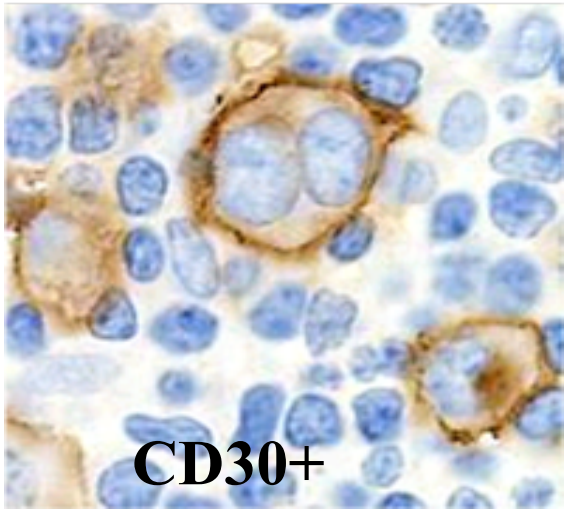
fibrosis (or sclerosis)



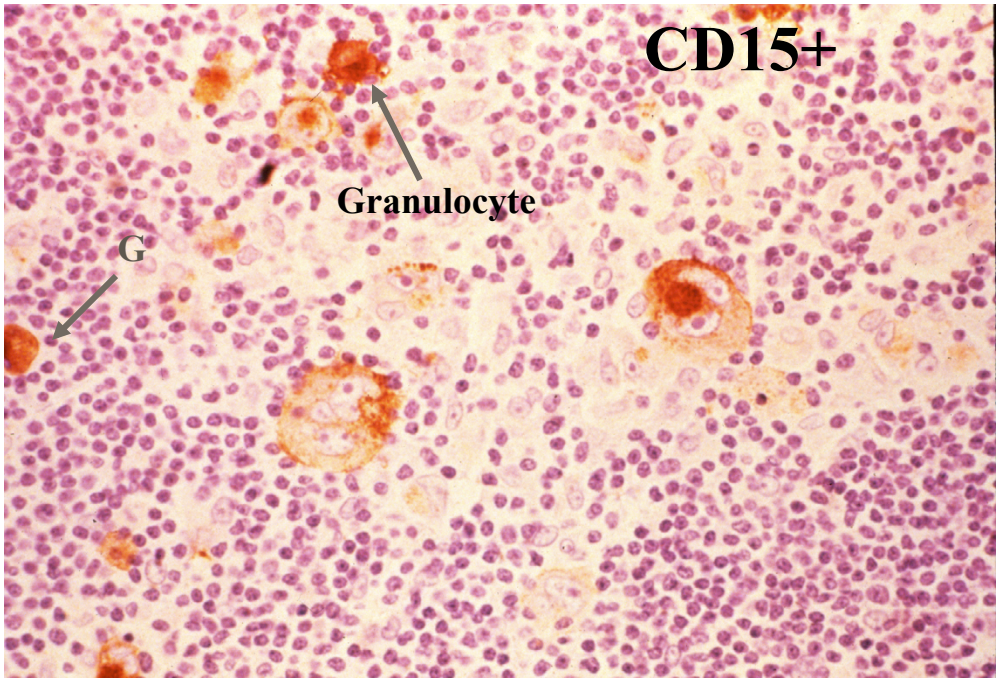
Nodular Sclerosis HL

Classical HL: Immunophenotype

Normally, granulocytes are CD15+, but HL is not caused by granulocytes. It's caused by B cells w/ aberrant CD15 expression.



CD30+/15+ (CD45-) Hodgkin and RS cells (unique immunophenotype)



HL is difficult to diagnose w/ small biopsies. The reason is that RS cells are tremendously immunogenic, which means there are ONLY A FEW RS CELLS surrounded, and possibly obscured, by a large quanitity of normal reactive leukocytes.

Staging

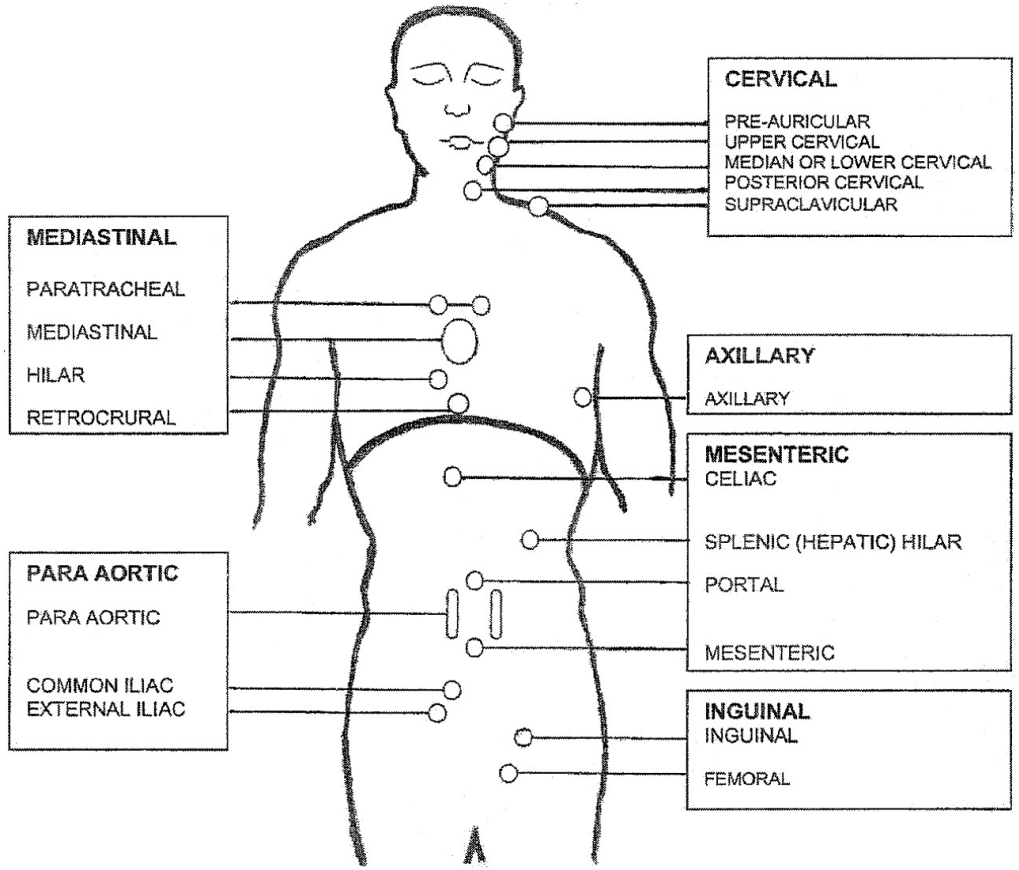
As mentioned before, Hodgkin lymphoma spreads in a systematic manner from lymph node to lymph node. This property is the basis of a unique staging system for Hodgkin lymphoma.

Stage	Disease
I	LN one location
II	LN 1+ locations, same side of diaphragm
III	LN on both sides of diaphragm
IV	Extranodal sites of disease

Symptoms A	No symptoms
Symptoms B	Fever, sweats, weight loss

E	Organ involvement adjacent to lymph node

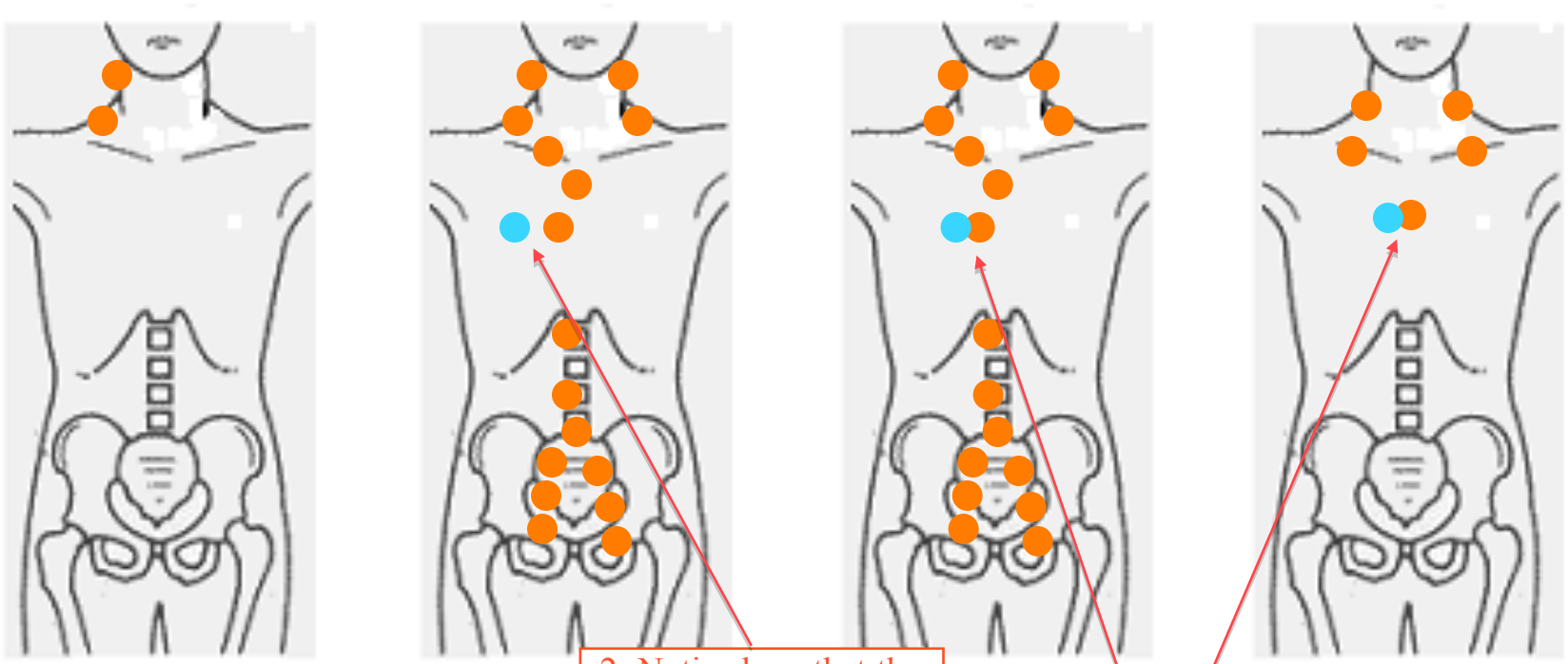
Manikin Used for Counting the Number of Involved Areas



OTHERS : EPITROCHLEAR, POPLITEAL

What is the stage? (All dots are lymphoma)

Finally, as opposed to non-Hodgkins lymphoma, for HL this staging system is actually useful!



Stage	I	IV	IIIE	IIE

2. Notice here that the lung nodule is NOT ADJACENT to the lymph nodule, so the Hodgkin lymphoma is Stage IV. A very subtle difference in this diagram.

1. The blue dot represents lung involvement. These two cases on the right are "E" because the lung involvement is adjacent to the lymph node.

Prognosis

Patient
Disease
Interaction

Disseminated
Factors

Cytokine

Especially important prognostically

Age
Sex

Stage IV

Albumin
Hemoglobin
WBC
Lymphocytes

Int Prog Factors Project, N Engl J Med 1998;339:1506-14

Multivariate Analysis

- Multivariate Analysis
  - Seven factors
  - All small effect
  - All same order of magnitude

This slide outlines the methodology behind establishing a scoring system to predict prognosis for Hodgkin lymphoma patients based on seven factors (see next slide).

- Freedom From Progression Curves
  - Equally spaced
  - Each factor worth 8 percentage points

Int Prog Factors Project, N Engl J Med 1998;339:1506-14

Final Cox Regression Model

Here are the 7 factors, each of which is worth ~8 points

Factor	Log Hazard Ratio	P Value	Relative Risk
Serum albumin, <4 g/dl	0.40±0.10	<0.001	1.49
Hemoglobin, <10.5 g/dl	0.30±0.11	0.006	1.35
Male sex	0.30±0.09	0.001	1.35
Stage IV disease	0.23±0.09	0.011	1.26
Age, ≥45 yr	0.33±0.10	0.001	1.39
White-cell count, ≥15,000/mm³	0.34±0.11	0.001	1.41
Lymphocyte count, <600/mm³ or <8% of white-cell count	0.31±0.10	0.002	1.38

Int Prog Factors Project, N Engl J Med 1998;339:1506-14

FFP and OS At 5 Years
Individual and Grouped Prognostic Score

Prognostic Score	No. of Patients (%)	Rate of Freedom from Progression	Rate of Overall Survival
		percent	
Individual			
0	115 (7)	84±4	89±2
1	360 (22)	77±3	90±2
2	464 (29)	67±2	81±2
3	378 (23)	60±3	78±3
4	190 (12)	51±4	61±4
≥5	111 (7)	42±5	56±5

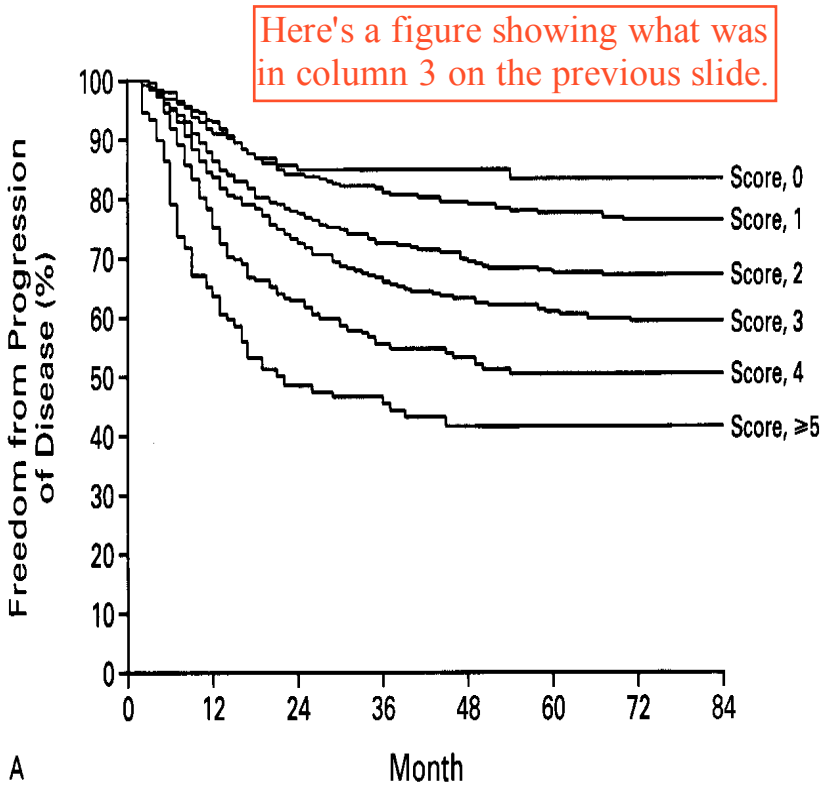
The multivariate analysis spits out a final scoring system based on the seven factors of the previous slide. 0 is good, 5 is bad.

Even w/ a score >=5, overal 5 yr survival is still pretty good.

Int Prog Factors Project, N Engl J Med 1998;339:1506-14

Freedom From Progression

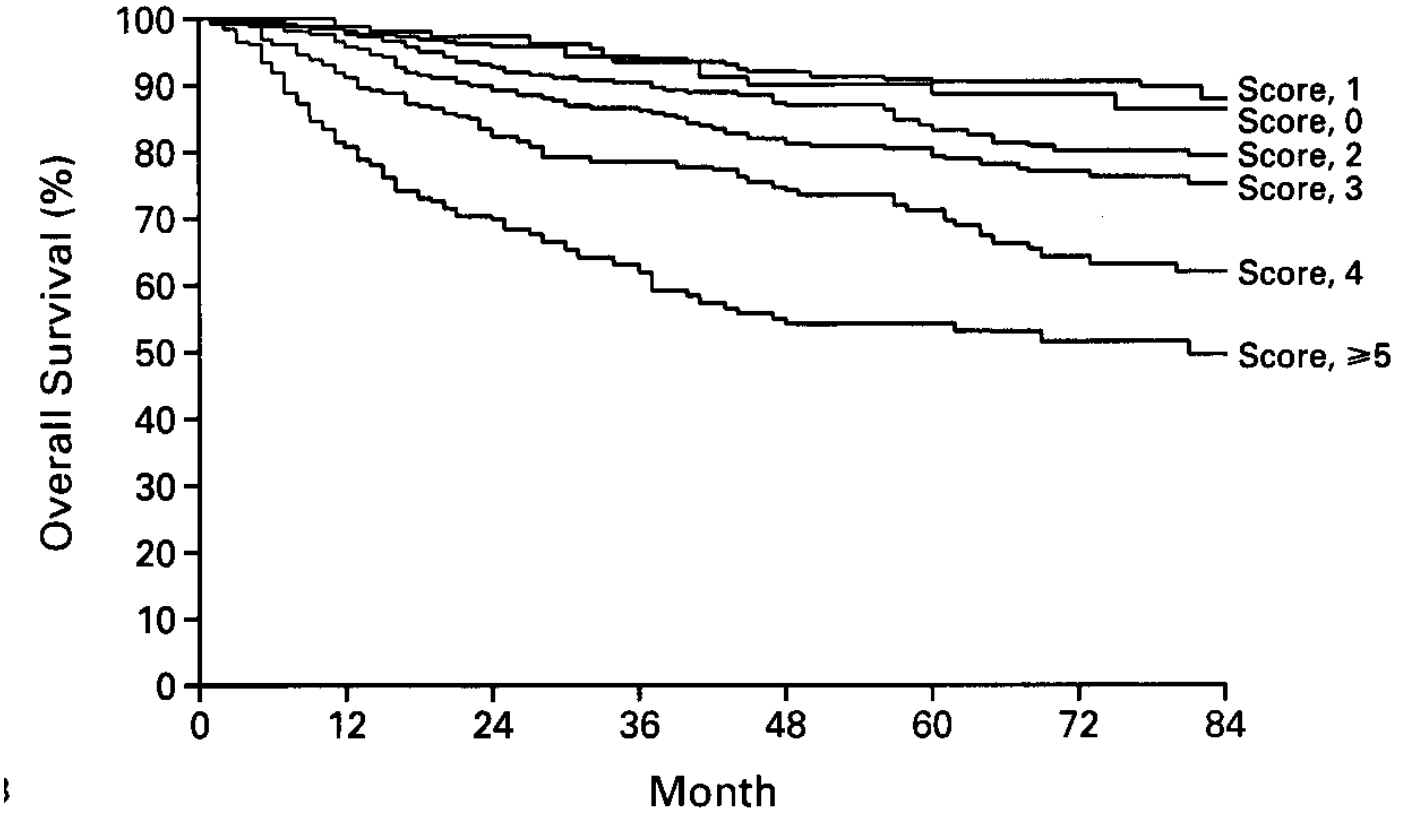
- Albumin < 4 g/dl
- Hemoglobin < 10.5 g/dl
- Male Sex
- Stage IV
- Age $\geq$ 45
- WBC > 15,000/mm3
- Lymphs < 600/mm3 or < 8% WBC



Int Prog Factors Project, N Engl J Med 1998;339:1506-14

Predict Overall Survival

Here's a figure showing what was in column 4 on slide 126



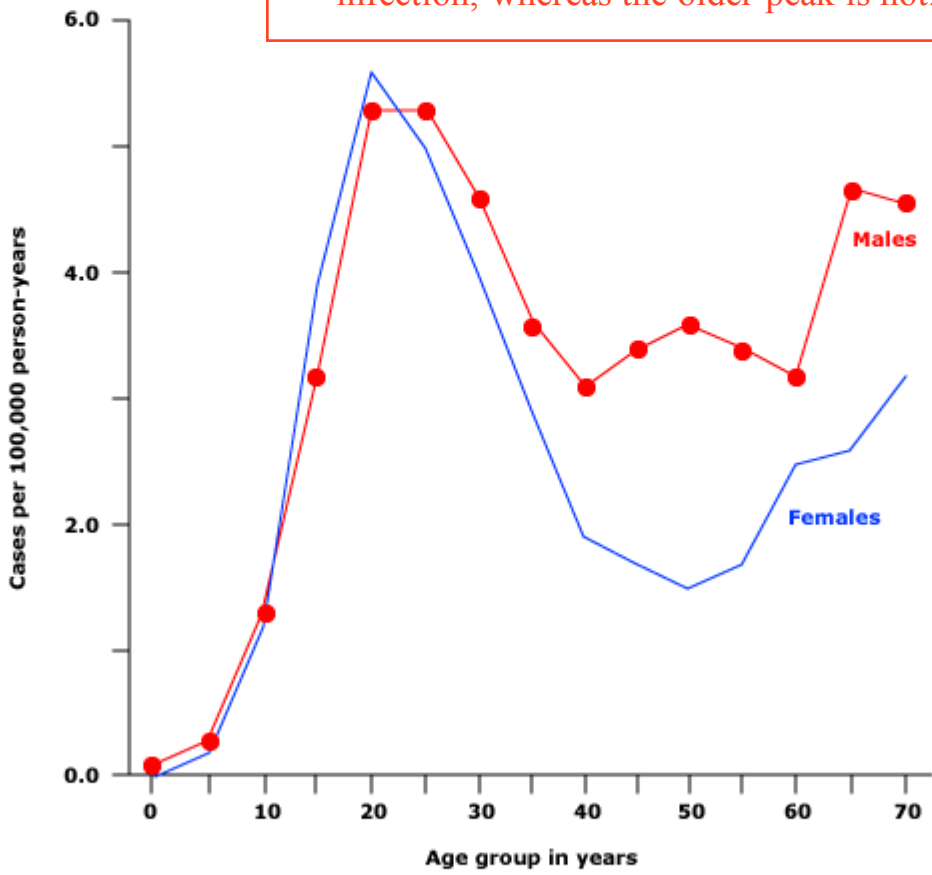
Int Prog Factors Project, N Engl J Med 1998;339:1506-14

Hodgkin Lymphoma

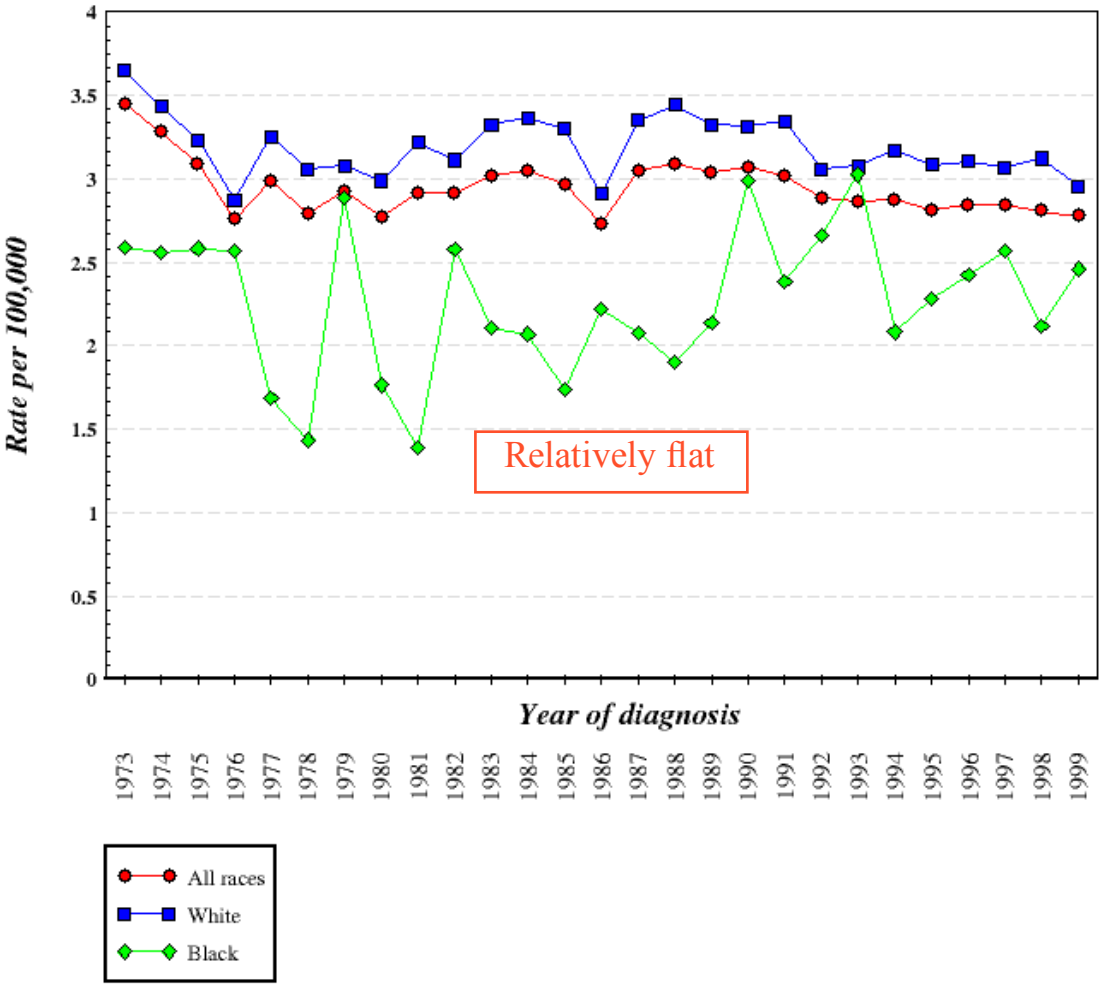
- Statistics

Hodgkin Lymphoma
Bimodal Age Distribution

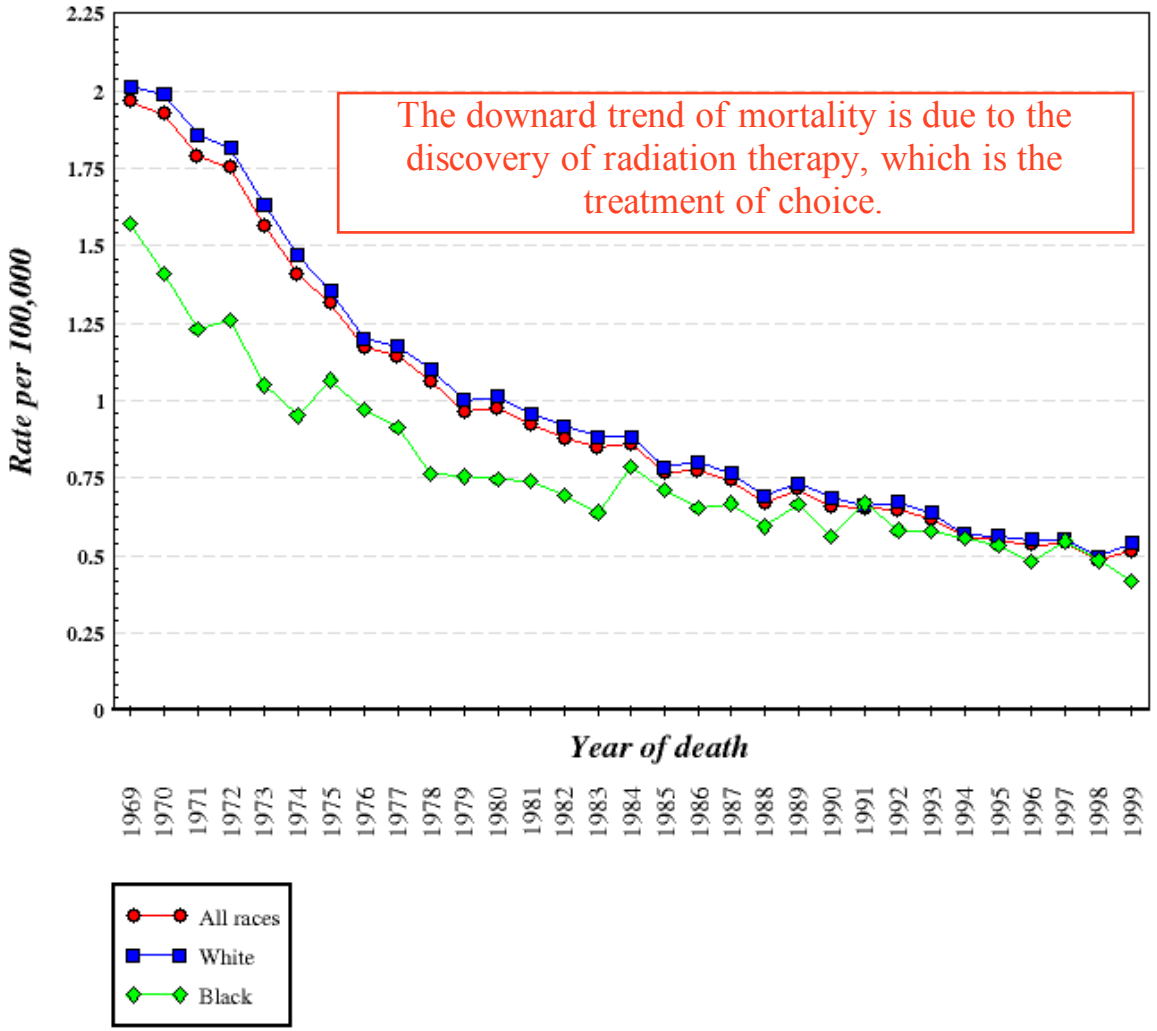
The younger peak may be associated with EBV infection, whereas the older peak is not.



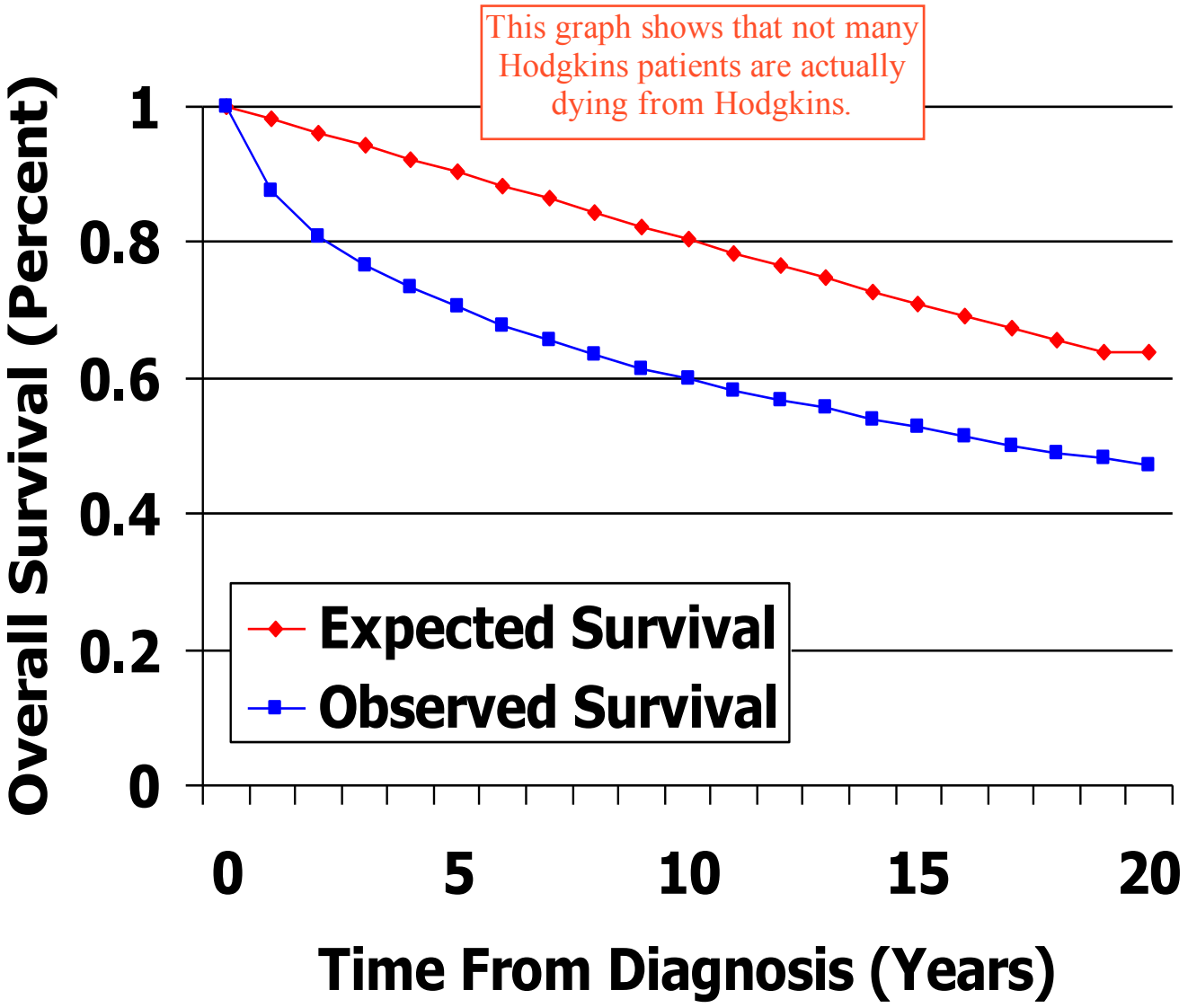
Age Adjusted Incidence from Hodgkin's Disease



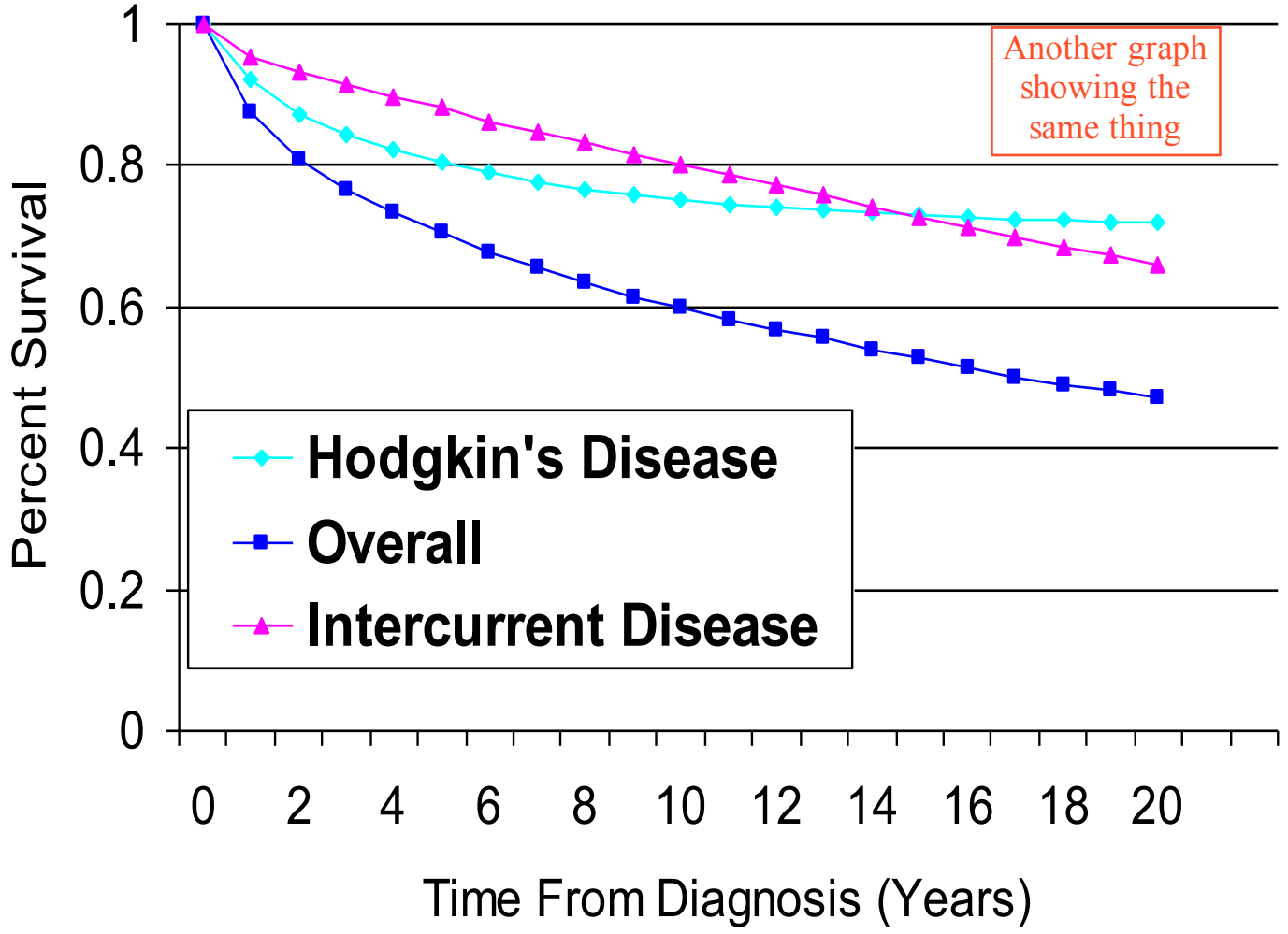
Age Adjusted Mortality from Hodgkin's Disease



Survival Hodgkin's Disease Expected vs Observed



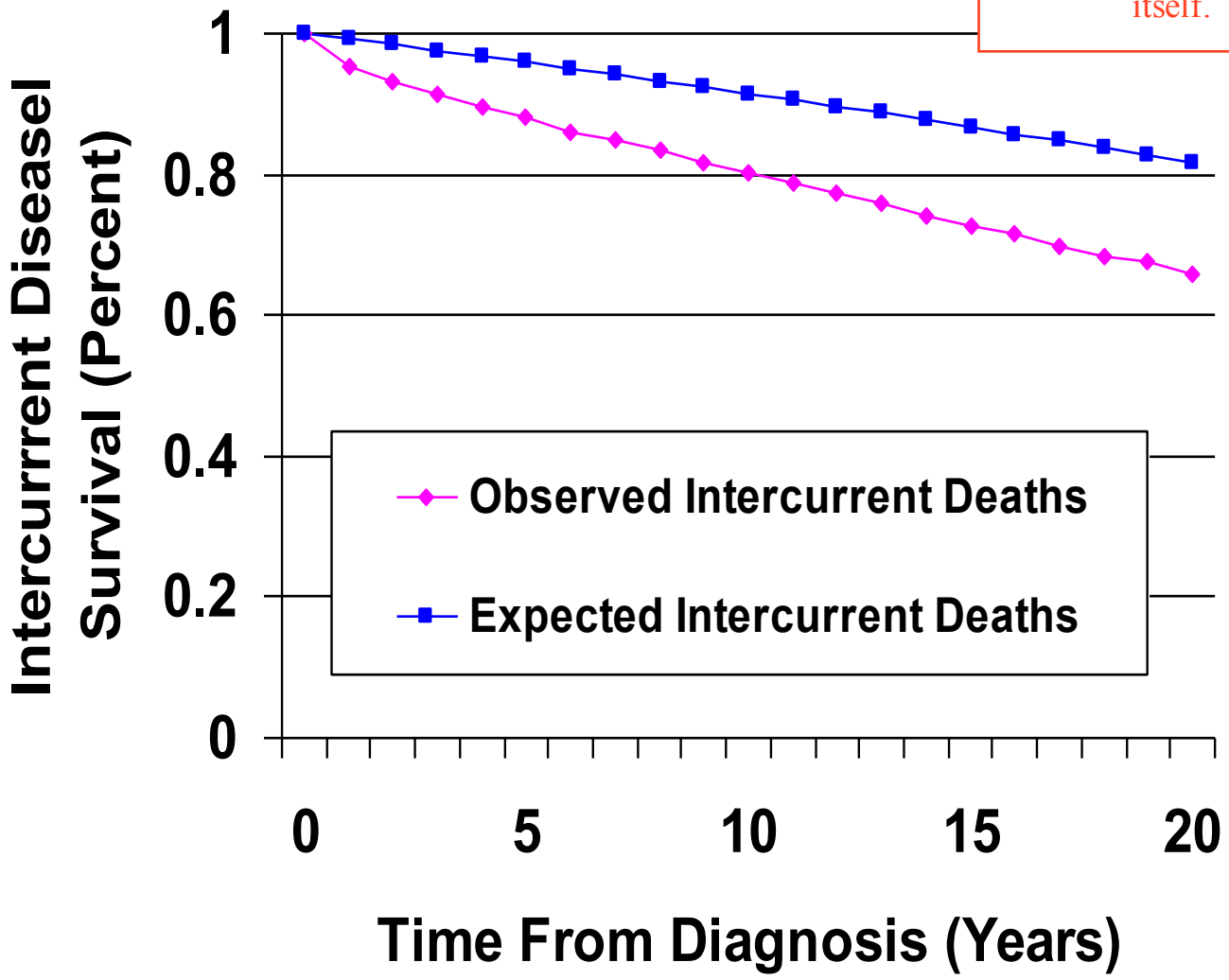
Overall Survival
Hodgkin's Disease vs Intercurrent Disease



SEER Data, ASCO, Abstract #36, 1999

Intercurrent Disease Survival Observed vs Expected

This data implies that more people are dying of other causes (which may be related to Hodgkin treatment) than Hodgkin itself.



Epidemiology
Childhood Social Environment

These are associated w/ increased incidence of HL

- Fewer siblings
- Late birth order
- Single vs multiple family homes
- Less educated mother

One explanation: If you get EBV very young, you won't get Hodgkin, but if you get EBV as an adolescent, young adult, you are at risk for Hodgkin.

This is analogous to the "poliovirus model." Infection of very young kids produces diarrhea, whereas infection of older individuals produces paralysis.

Gutensohn and Cole, N Engl J Med 304:135-40, 1981

Epidemiology
Childhood Social Environment

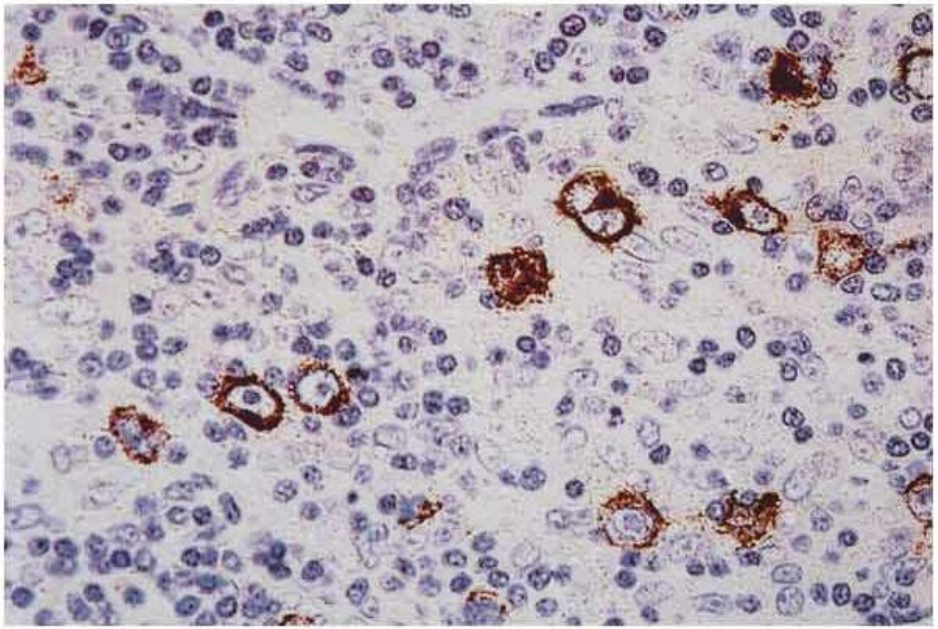
- Fewer siblings
- Late birth order
- Single vs multiple family homes
- Less educated mother

- Polio model

(see previous slide)

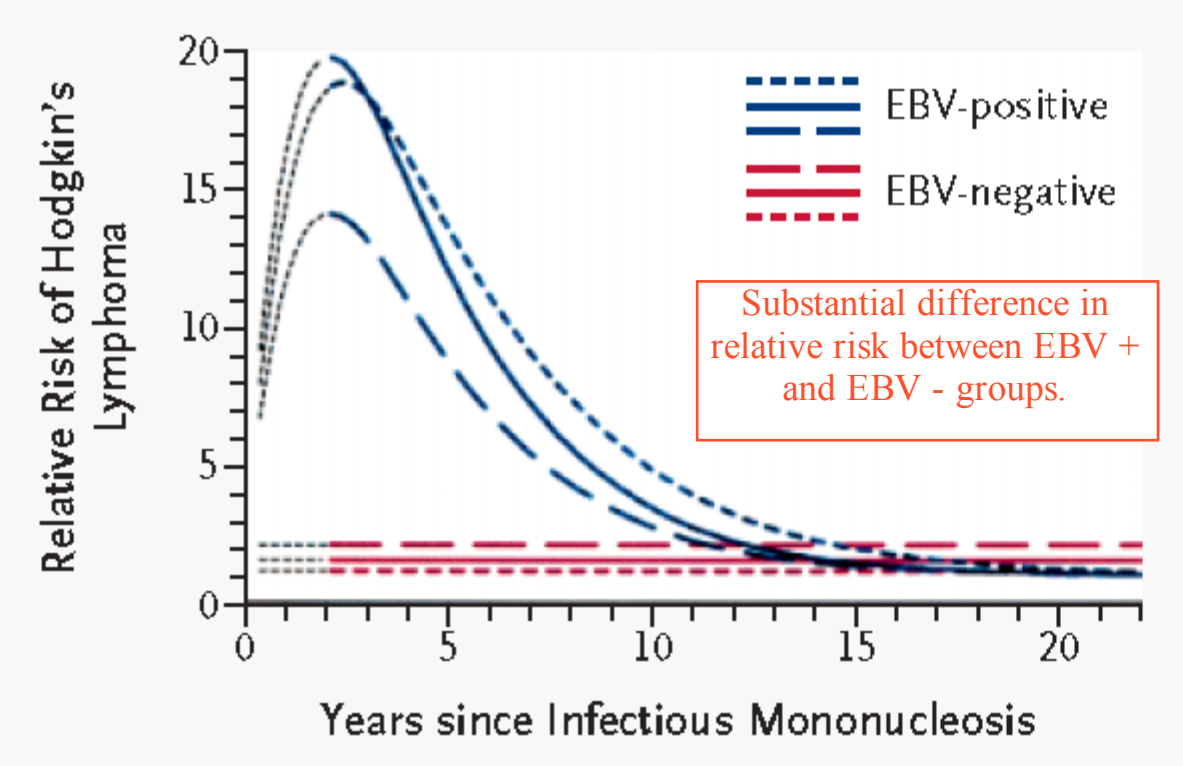
Gutensohn and Cole, N Engl J Med 304:135-40, 1981

Expression of Latent Membrane Protein 2 by Reed-Sternberg Cells



Murray, Blood 1998; 92:2477-83

Relative Risk of EBV – Positive and EBV-Negative Hodgkin's Lymphoma After Infection with Infectious Mononucleosis



Hjalgrim, N Engl J Med 349:1324, 2003

Relative Risk of EBV – Positive and EBV-Negative Hodgkin's Lymphoma After Infection with Infectious Mononucleosis

- Data
  - 446,757 person-years
  - Over 20 year period
  - 21 cases

- Conclusion
  - 1 Hodgkin's disease case per 21,274 person-years
  - If followed over a 20 year period, 1 case of Hodgkin's disease per 1064 infectious mononucleosis cases

This shows that HL is related to EBV infection

Jhalgrim, N Engl J Med 349:1324, 2003

Bari Harbor

Here, the lecturer decided to tell a story.
The next slide gives an outline of this tale.

Bari Harbor 2 December 1943 WWII

- German raid
- S.S. John Harvey, 2,000 chemical bombs holding 60-70 pounds of sulfur-mustard gas each
- 100 tons mustard gas exploded
- Disseminated mustard gas
- Mustard gas mixed with surface oil
- Dissolved in the oil
- Variable quantities of mustard in oil depending on distance from the ship

Science 103:409, 1946

Bari Harbor December 2, 1943

- Doses of mustard gas
  - Survivors in water with oil
  - Oil splashed on them
  - Rescue workers

Bari Harbor, 2 December 1943 Autopsies

- 83 hospital deaths
  - 53 autopsies
- Spleen was small and shrunken
- Lymph nodes were pale
- Sternal bone marrow was “dry”

There were lots of people who didn't die immediately and took 10-14 days to die at the hospital, which opened up this opportunity.

Thanks to Alexander's autopsies, it was discovered that mustard gas destroyed bone marrow and lymph tissue!

Alexander. The Military Surgeon 101:1, 1947

History of Nitrogen Mustard

- After World War I, however, medical researchers noticed an interesting effect of mustard gas—it destroyed lymphatic tissue and bone marrow. Perhaps, they reasoned, it could also kill cancer cells in the lymph nodes. But, Fischer said, this idea went nowhere. “They saw the relationship, but they didn’t do anything about it.”

Originally published in Yale Medicine, Summer 2005.

Alfred Gilman

Gilman figured out that if mustard gas caused bone marrow depletion and lymphoid destruction, it might be useful in treating Hodgkin!

Nitrogen Mustard Therapy

So people started giving cancer patients mustard

NITROGEN MUSTARD THERAPY

Use of Methyl-Bis(Beta-Chloroethyl)amine Hydrochloride and Tris(Beta-Chloroethyl)amine Hydrochloride for Hodgkin's Disease, Lymphosarcoma, Leukemia and Certain Allied and Miscellaneous Disorders

LOUIS S. GOODMAN, M.D., Salt Lake City
MAXWELL M. WINTROBE, M.D., Salt Lake City
WILLIAM DAMESHEK, M.D., Boston
MORTON J. GOODMAN, M.D., Portland, Ore.
MAJOR ALFRED GILMAN
Medical Corps, Army of the United States
and
MARGARET T. McLENNAN, M.D., Salt Lake City

Nitrogen Mustard Hodgkin's Disease

- 27 patients with Hodgkin's disease
- 24 had previous radiation
- "Nearly every case some benefit was obtained from chemotherapy

Louis S. Goodman, Maxwell M. Wintrobe, William Dameshek, Morton J. Goodman, Major Alfred Gilman and Margaret T. McLennan. Nitrogen Mustard Therapy. JAMA 132:126-132, 1946

Combination Chemotherapy Concepts (1966)

Next step: find out all the drugs that can benefit patients with HL!

Agent	Year Introduced	Tumor Regression % Patients
NH2	1943	60
Vinblastine	1959	60
Vincristine	1952	50
Prednisone	1950	30
Methylhydrazine	1962	60
Streptonigran	1961	50

Complete Response Rates Hodgkin's disease, 1970

Here's some more

Drug	Complete Response
Nitrogen mustard	13%
Cyclophosphamide	13%
Vincristine	36%
Vinblastine	33%
Procarbazine	37%

Quoted in Cancer 36:1227, 1975

MOPP Study

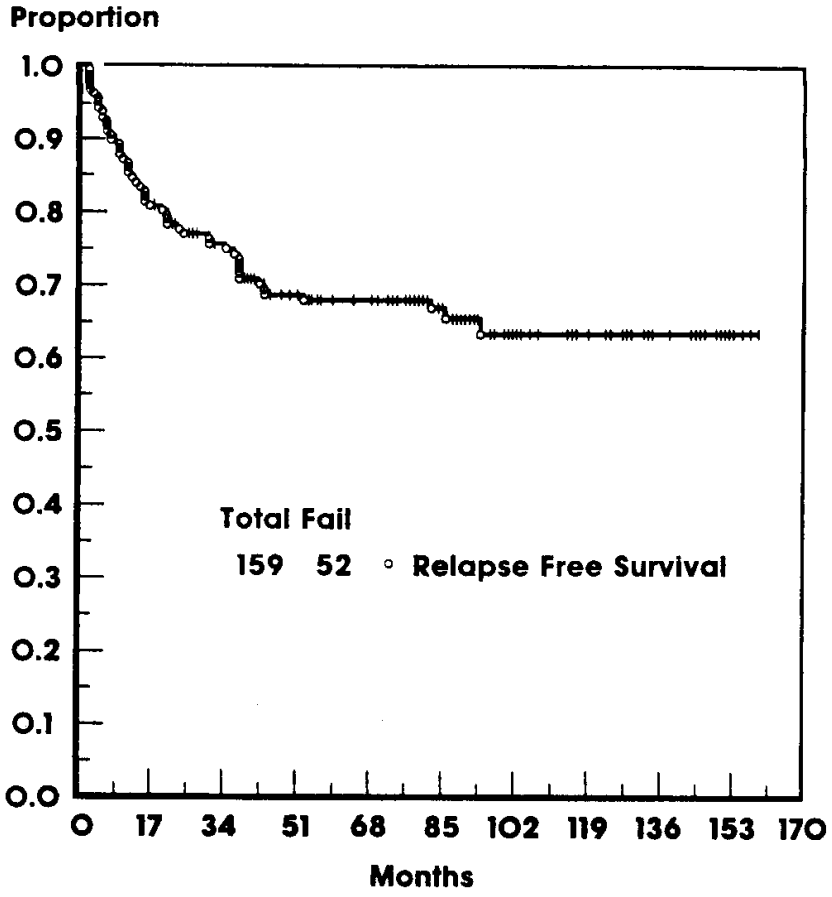
- Combination chemotherapy with non overlapping toxicity
  - Nitrogen Mustard
  - Vincristine
  - Prednisone
  - Procarbazine
- 1964 - 1967
- 44 patients at the NCI
- 81% complete responders

Oncologists decided to take the 4 most effective drugs with non-overlapping toxicity and use them together against Hodgkin lymphoma.

The result was fantastic

MOPP Chemotherapy
Relapse Free Survival of Complete Responders

- 198 patients
- Stage II, III, IV
- Minimum 6 cycles but CR + 2
- Adjuvant treatments
  - intermittent MOPP
  - intermittent BCNU
  - total lymphoid XRT



DeVita et al. Ann Int Med 1980;92:587-595

Causes of Death

These non-HL causes of death are higher rates than what they should be in patients at a young age. Thus, the treatment of Hodgkin lymphoma may cause greater damage than Hodgkin lymphoma itself!

Causes of Death	*Percent*	*Causes of Death*	*Percent*
Hodgkin's disease	52.5	Other heart disease	3.2
Non Hodgkin's Lymphoma	8.1	Acute leukemia	2.2
Second solid malignancy	6.8	Infection, not respiratory	2.1
Ischemic heart disease	6.7	Respiratory infection	1.9

SEER Data, ASCO, Abstract #36, 1999

Hodgkin's Disease Second Malignancies

Radiation and chemo treatment greatly increases risk of secondary malignancies.

Malignancy	Number	Standardized Incidence
Breast	17	77
Thyroid	10	32.7
Bone	4	24.6
Brain	4	10.5
Colorectal	3	38.9
Gastric	2	121.3

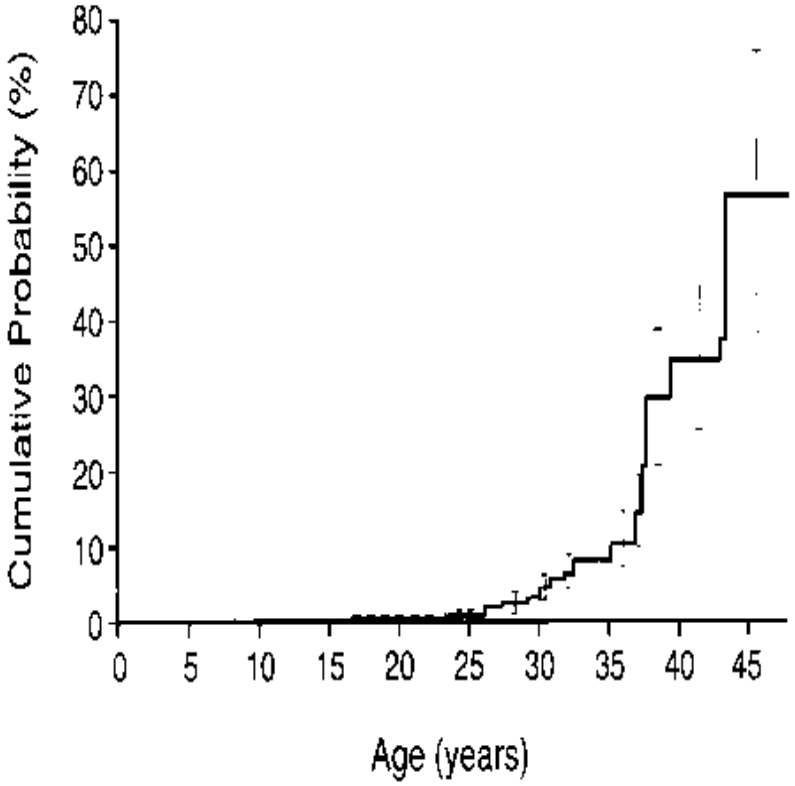
Second Neoplasms After Childhood Hodgkin's Disease: Breast Cancer

Here's some radiation-specific risk data.

- 17 Patient
- All XRT
- 16/17 in XRT field
- 5 bilateral
- Median Age 31.5

- 15 followed
  - 3 died
  - 8 alive with disease
  - 4 alive no disease

Not only do patients get breast cancer, but the cancer is also more malignant.



Bhatia S, et al. N Engl J Med 334:745, 1996

Late Psychosocial Sequelae in HD Survivors Symptom Scales

There's also a bunch of additional negative effects of post-Hodgkins to consider.

	Patient (n=91)	Controls (n=184)	P Value Adjusted
Fatigue	28.7	22.2	0.025
Nausea/emesis	2.9	2.8	0.22
Pain	14.3	15.1	0.94
Dyspnea	25.2	8.9	< 0.001
Sleep disturbances	21.3	20.1	0.54
Appetite loss	.1	4.3	0.54
Constipation	10	.9	0.27
Diarrhea	9.6	6.3	0.08
Financial difficulties	10.4	5.6	0.11

Joly et al (French) J Clin Oncol 14:2444, 1996

Late Psychosocial Sequelae in HD Survivors

Functioning	Patient (n=91)	Controls (n=184)	Adjusted P
Physical	86	93	0.001
Role	84	96	0.001
Emotional	55	57	0.24
Cognitive	80	90	0.015
Social	86	94	0.048
Global (QOL)	69	70	0.27

The lecture ended here.

Summary:

Epidemiology summary is on the next slide

Thank You

CML:
-Pathophys: bcr-abl -> no myeloid inhibition -> increased neutrophils, neutrophil precursors
-Findings: anemia, leukocytosis, thrombocytosis, splenomegaly
-Diagnosis: t(9:22) cytogenetics
-Staging: chronic, accelerated, blast crisis (acute leukemia due to 2nd hit)
-Treatment: imatinib

MM:
-Pathophys: 1st hit: apoptosis-resistant plasma cells (MGUS) 2nd hit: able to activate osteoclasts and cause bone damage (MM)
-Findings: back/bone pain, fractures, hypercalcemia, serum plasma cells, anemia, leukopenia, thrombocytopenia
-Diagnosis: excess plasma cells in BM, "punched out" skull lesions, pathologic fractures, monitor w/ serum protein electrophoresis
-Staging: 1. proliferation (MGUS) -> smoldering myeloma -> proliferation + bone damage (MM)
2. follow CRP and beta 2 microglobulin
-Treatment: super dose chemo + stem cell autograft

CLL:
-Pathophys: apoptosis-resistant lymphocytes -> lymphocytosis
-Findings: older patients, asymptomatic, lymphocytosis
-Diagnosis: CD5+/CD23+ cytometry, smudge cells
-Staging: 1. spread (0-II)
2. damage (III-IV)
-Treatment: FCR (rituximab is key)
-Misc: related to SLL, may transform to DLBCL via Richter's transformation.

HL (classical):
-Pathophys: excess CD40 prevents apoptosis -> long-lived B cells cause HL
-Findings: localized, systematically spreading lymphadenopathy (often neck or mediastinal region), slight leukocytosis
-Diagnosis: Reed-Sternberg cell, CD30+/CD15+/CD45- cytometry
-Staging: 1. systematic adjacent lymph node spread(I-III), adjacent organ tissue spread (E), extranodal spread (IV)
2. score 0-5 based on the 7 factors
-Treatment: radiation
-Misc: HL treatment can often cause more long-term problems than HL itself.

Epidemiology summary

CML:
-more often in males
-Asians are least susceptible race
-rare compared to other leukemias
-associated w/ ionizing radiation

MM:
-from the Mayo study, increased age increases incidence of MGUS and MM
-African Americans and males are more susceptible (unknown why)

Thank you

CLL:
-old people get this, very rare for a young person to have CLL
-possibly associated w/ agent orange, but otherwise not really associated with anything, which is unusual

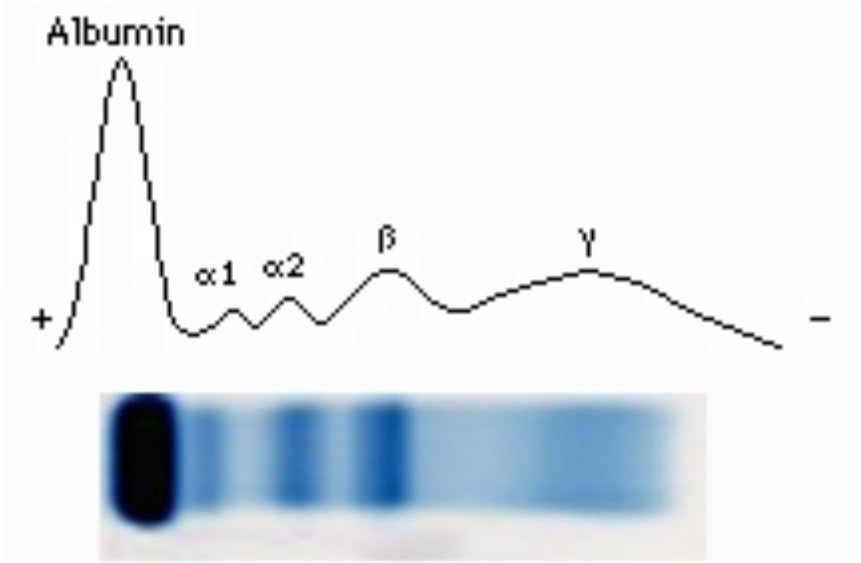
HL (classical):
-bimodal age distribution, males > females
-whites > blacks
-association w/ EBV. This association demonstrates the "poliovirus model."

The rest of the slides after this were not covered

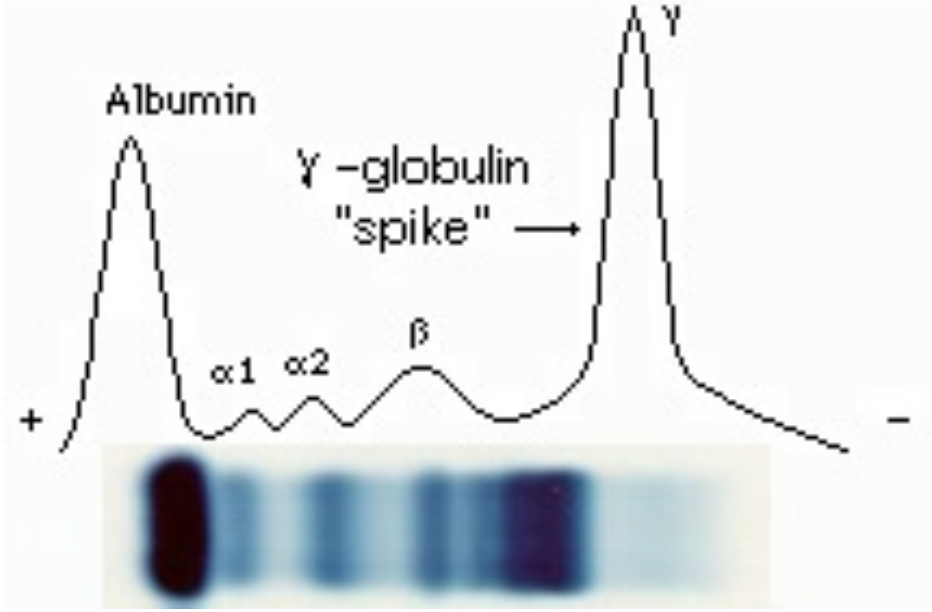
Extras

Serum Protein Electrophoresis

Normal



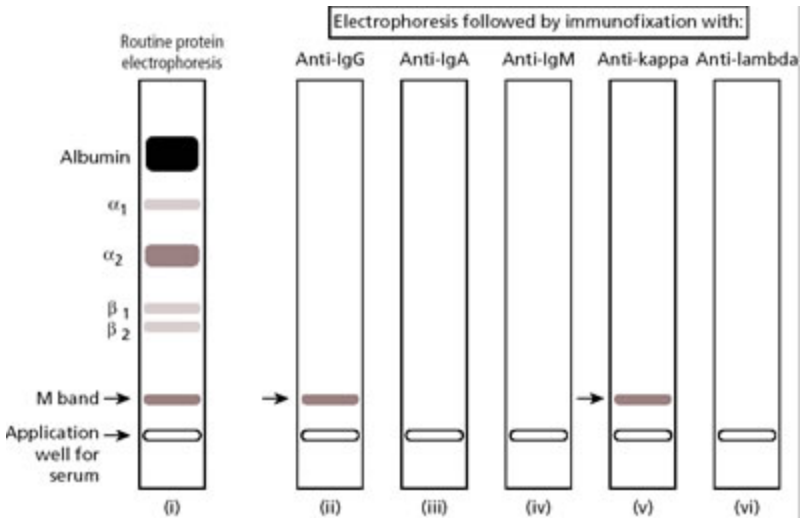
Monoclonal Spike



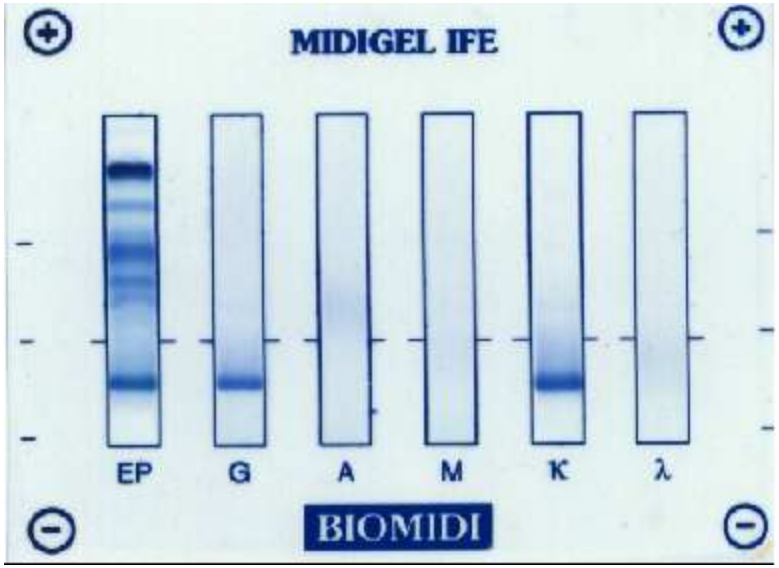
http://www.med-ed.virginia.edu/courses/path/innes/images/wcdjpeg/wcd%20spep%20monoclonal%20iga.jpeg

Immunofixation Electrophoresis

Drawing
(IgG kappa)



Actual Gel
(IgG kappa)



http://www.immunologyclinic.com/jpg/300_96dpi/19-5a.jpg

Individual Immunoglobulin Levels

- Measures actual individual immunoglobulin levels both normal and abnormal

- Example
  - IgG = 1631 mg/dL
  - IgA = 321 mg/dL
  - IgM = 42 mg/dL

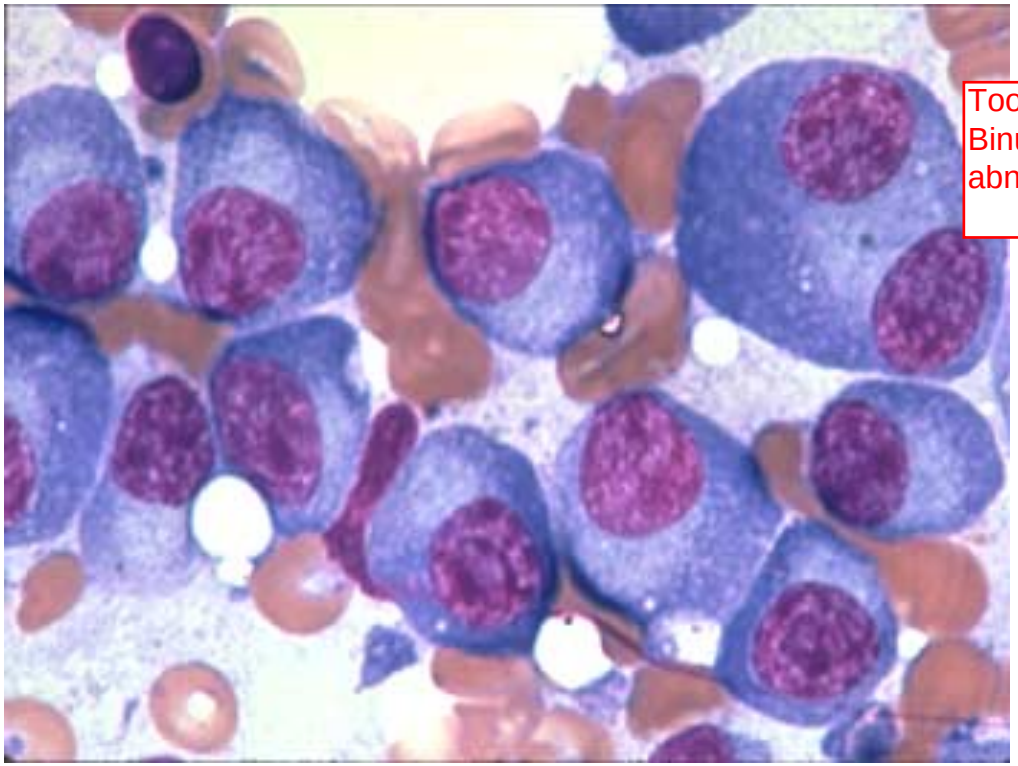
Example

SERUM PROTEIN ELECTROPHORESIS	IFE SERUM	IMMUNOGLOBULINS (IGG,IGM,IGA)
Reference SPE TOTAL PROTEIN 7.6 g/dL [6.0-8.0] SPE ALBUMIN % 54.0 % SPE ALBUMIN 4.10 g/dL [3.97-5.34] SPE ALPHA 1 % 2.8 % SPE ALPHA 1 0.21 g/dL [0.11-0.32] SPE ALPHA 2 % 15.1 % SPE ALPHA 2 * **1.15** g/dL [0.40-0.88] SPE BETA % 11.4 % SPE BETA 0.87 g/dL [0.60-1.02] SPE GAMMA % 16.7 % SPE GAMMA 1.27 g/dL [0.53-1.37] SPE M-SPIKE 1 % 12.2 % SPE M-SPIKE 1 0.93 g/dL	IFE SERUM MONOCLONAL IGG KAPPA COMPONENT BY IFE	**Reference** IMMUNOGLOBULIN G *1930 mg/dL [588-1573] IMMUNOGLOBULIN A *29 mg/dL [46-287] IMMUNOGLOBULIN M *23 mg/dL [57-237]

The M protein is present. It is 930 mg/dL.

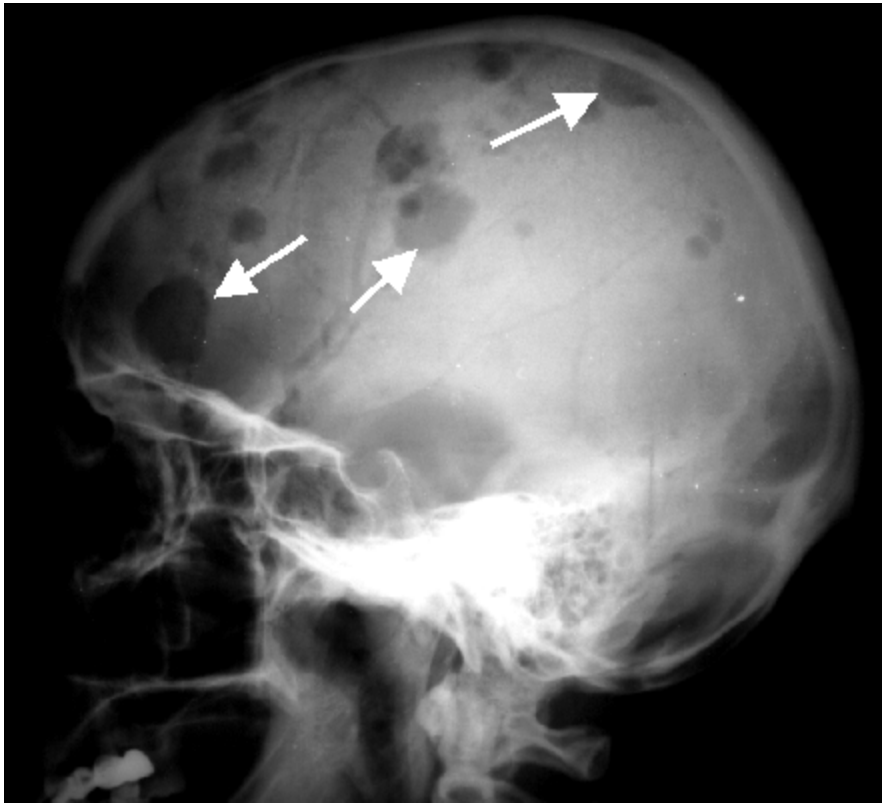
Monoclonal Protein

Bone Marrow

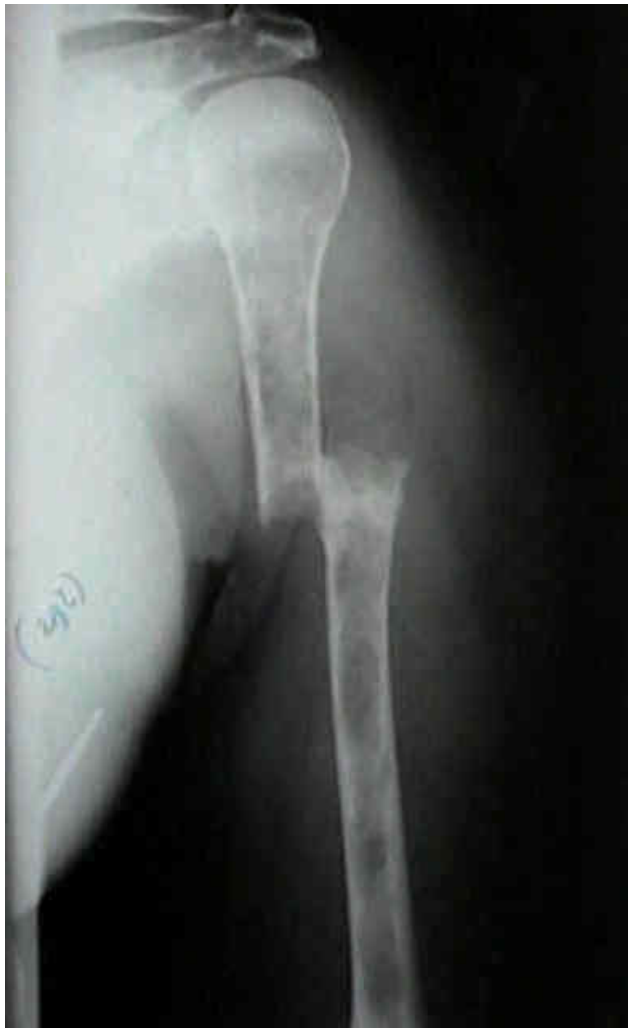


Too many plasma cells. Binucleate plasma cell is abnormal.

Lytic Bone Lesions



Pathological Fracture



Hodgkin's disease watercolor drawing by Robert Carswell in 1828. This was case 7 in Hodgkin's report.