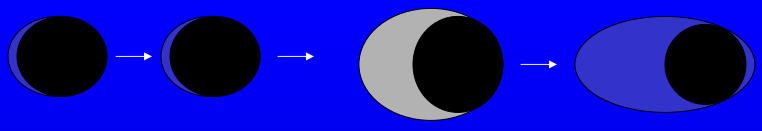
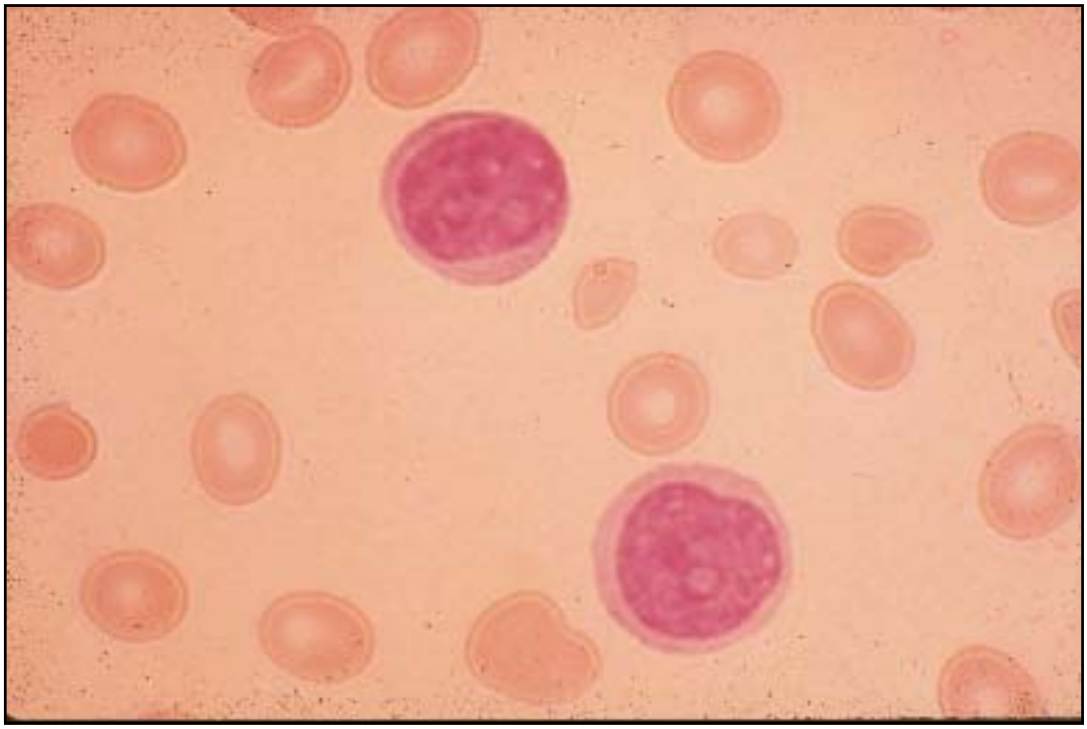
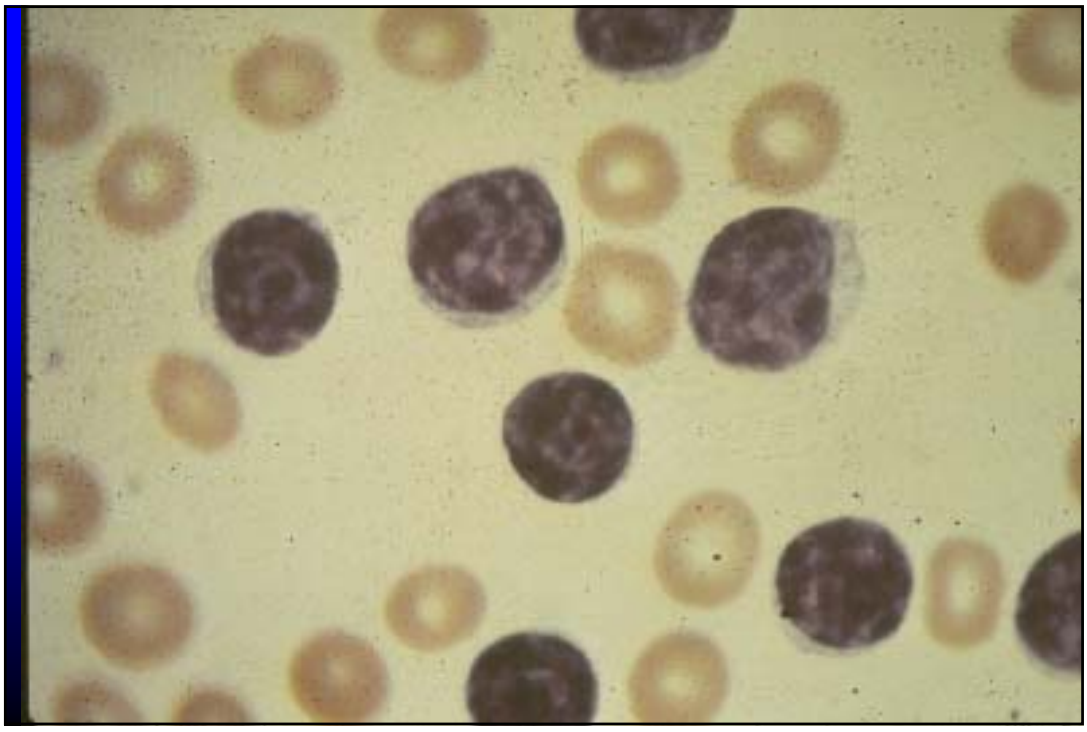
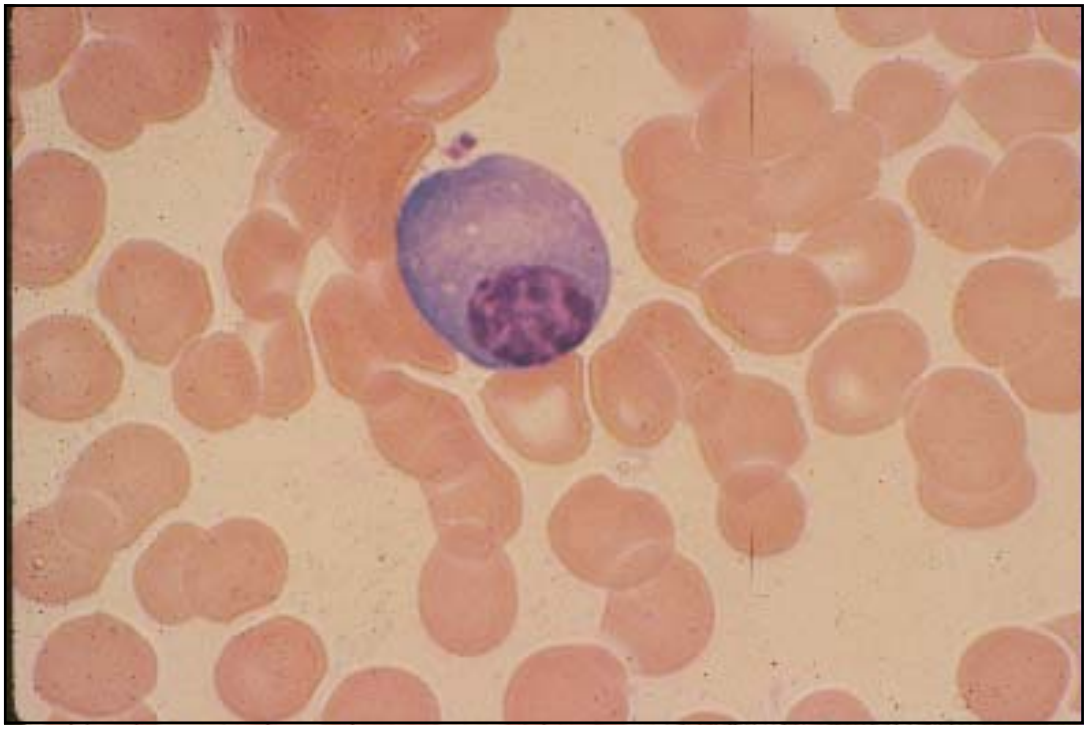
Disease	Usual phenotype
acute leukemia	precursor
chronic leukemia lymphoma myeloma	differentiated



	Pre-B-cell	B-cell	Transformed B-cell	Plasma cell
Ig		Surface	Surface	Secreted
Major malignant counterpart	B-ALL	CLL	Macroglobu-linemia	Myeloma
Major immunological abnormality		↓Gamma globulins	Monoclonal IgM	Monoclonal Ig or light chain





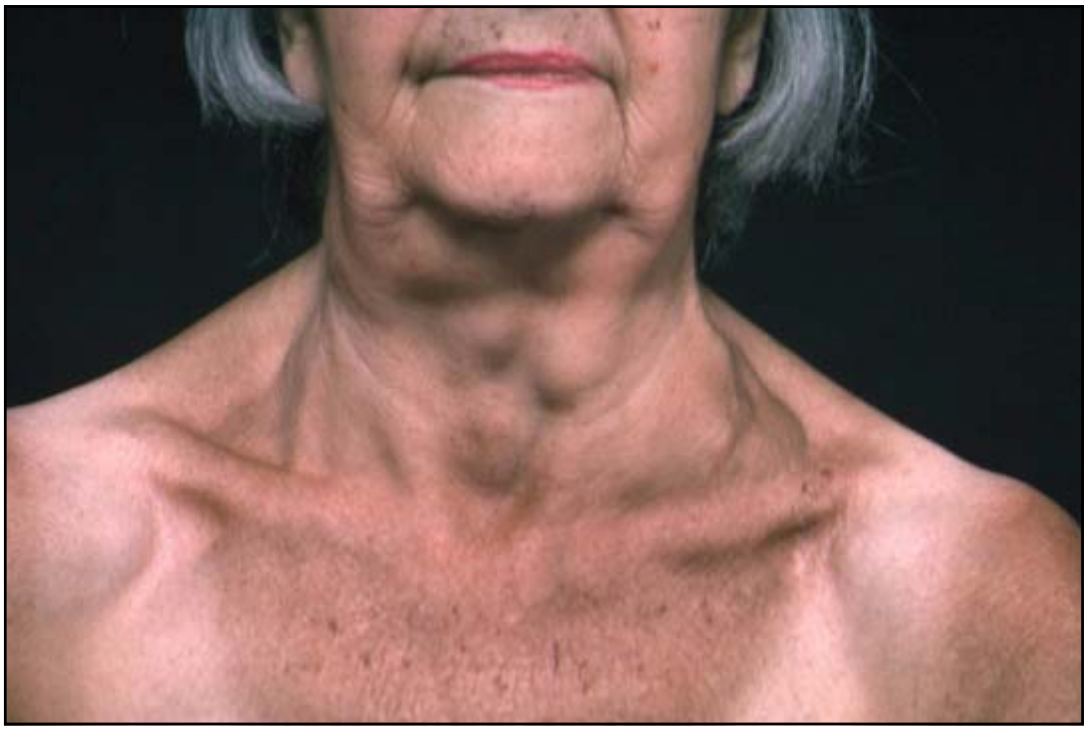


Chronic Lymphocytic Leukemia

- **Most common leukemia**
- **Usual age > 50 yrs**
- **Increased proliferation and progressive accumulation of neoplastic, immunologically incompetent, clonal lymphocytes**
  - **B cell origin > 99%**

Clinical Features of CLL

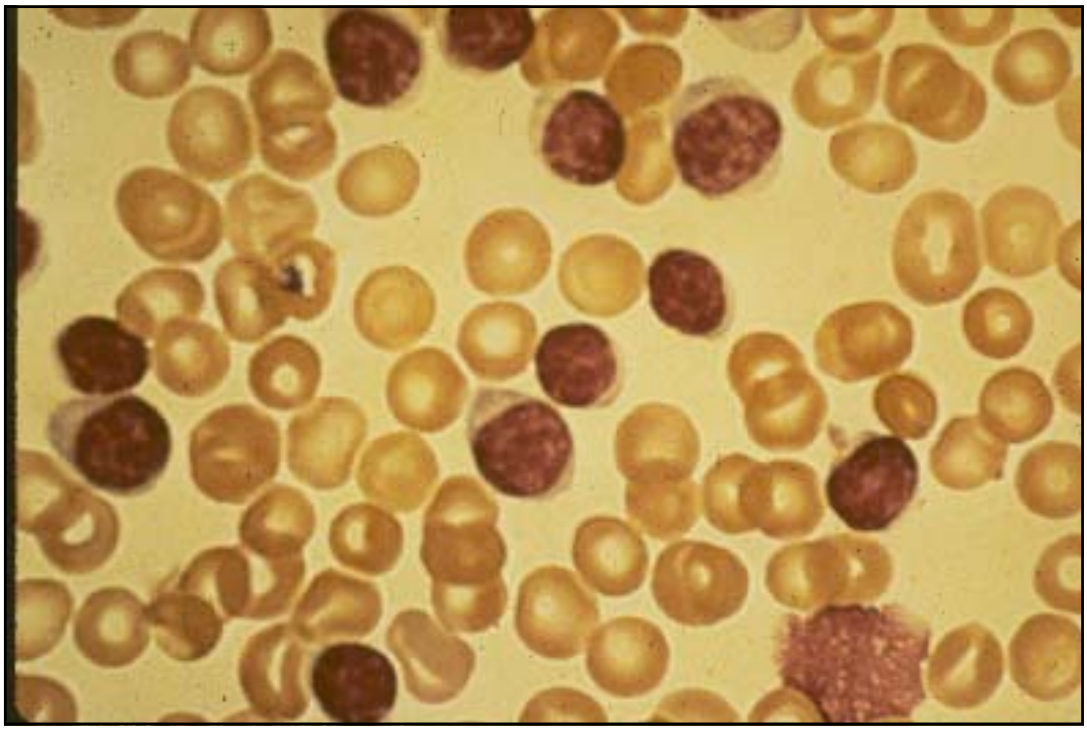
- **Highly variable presentation**
  - **Asymptomatic, or vague, non-specific complaints**
  - **Recurrent infection 10% (often pneumococcus)**
- **Signs**
  - **Lymphadenopathy (60%)**
  - **Splenomegaly (50%)**
  - **Hepatomegaly (< 40%)**



Clinical Features of CLL

- **Laboratory**
  - **blood and marrow lymphocytosis**
  - **B cell monoclonality:**
    - **κ vs λ surface light chain**
    - **single Ig gene rearrangement**
  - **hypoimmunoglobulinemia**

- **Prognosis**
  - **Mean survival = 50-60 months**
  - **Range = few months to > 20 yrs**



Immunological Abnormalities in CLL

- **Disturbed Ab production**
  - **Hypogammaglobulinemia (50%) → bacterial infection**
  - **Monoclonal Ig paraprotein in serum (10%)**
  - **Autoantibodies (10%)**
- **Minor impairments in cell-mediated immunity**
- **Neoplastic lymphocytes**
  - **Monoclonal surface Ig**
  - **Abnormal response to Ig challenge**

Complications of CLL

Recurrent infections

Immune hemolysis

Immune thrombocytopenia

Progressive disease

Rai Staging System for CLL

Stage	Features	Median survival (years)
I	Lymphocytosis	13
II	Lymphocytosis + lymphadenopathy	8
III	Lymphocytosis + splenomegaly	6
IV	Lymphocytosis + anemia	1-2
V	Lymphocytosis + thrombocytopenia	1-2

Treatment of CLL

- No evidence that therapy prolongs survival
- Asymptomatic: watch and wait
- Symptomatic:
  - Radiation for local complications
  - Chemotherapy: fludarabine, alkylators, combinations
  - Monoclonal antibodies (eg, Campath)
  - Stem cell transplantation

Multiple Myeloma

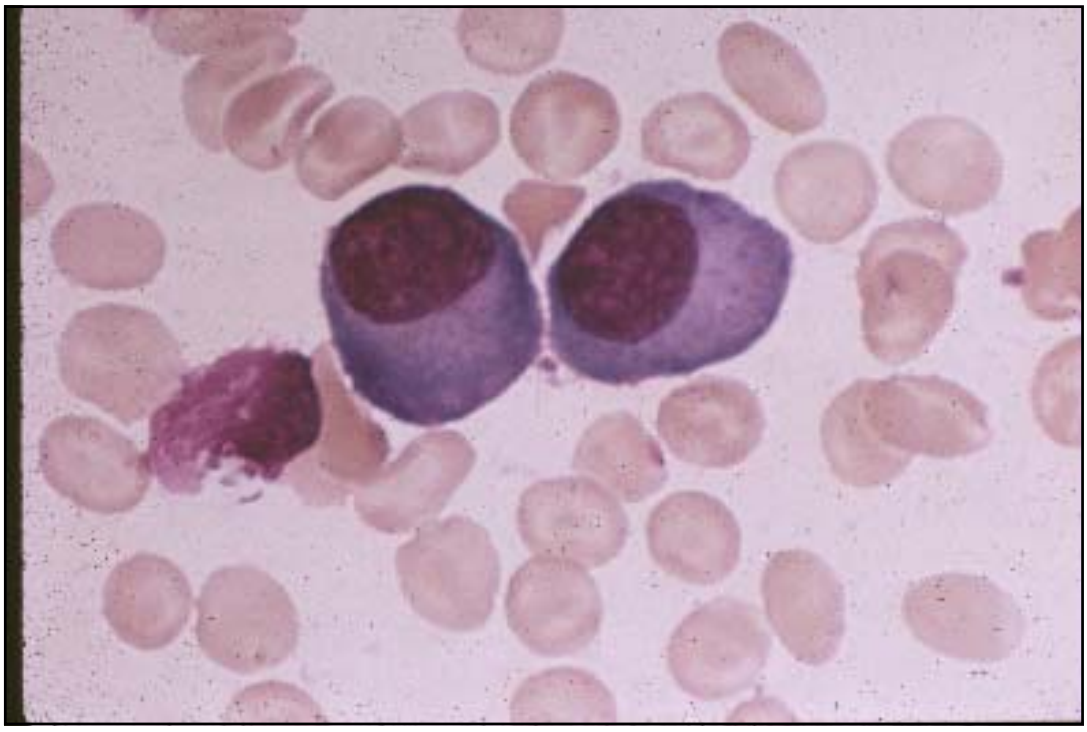
- **Clonal malignancy of plasma cells**
- **Increasing incidence**
- **Blacks:whites 2:1**
- **Age range 20-100 yrs (peak age 70 yrs)**
- **Cause unknown**
  (Environmental/Genetic factors)

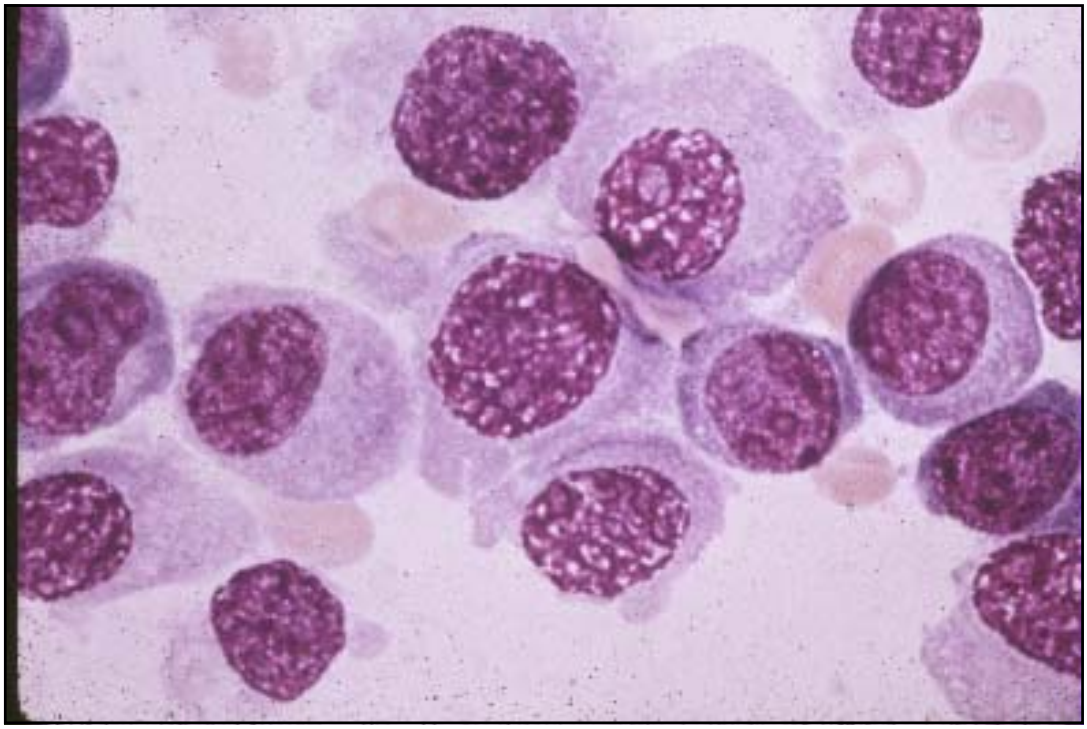
Classical Diagnostic Features of Myeloma

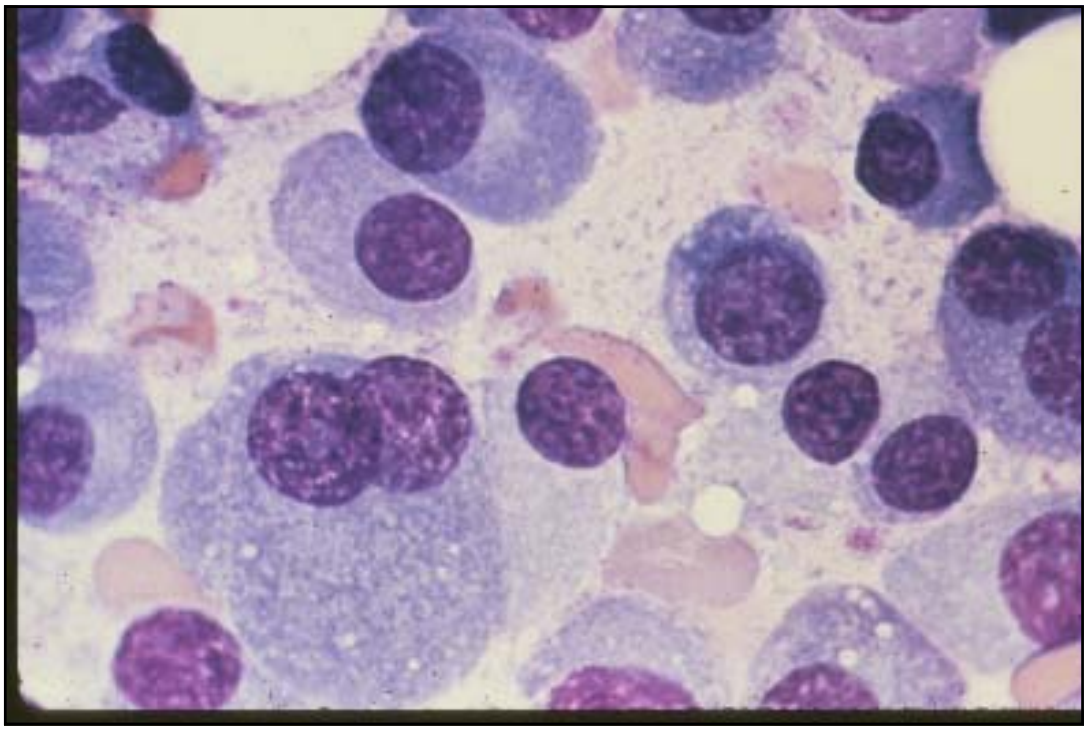
- Plasmacytosis in marrow
- Monoclonal protein in serum or urine
- Lytic disease of bone

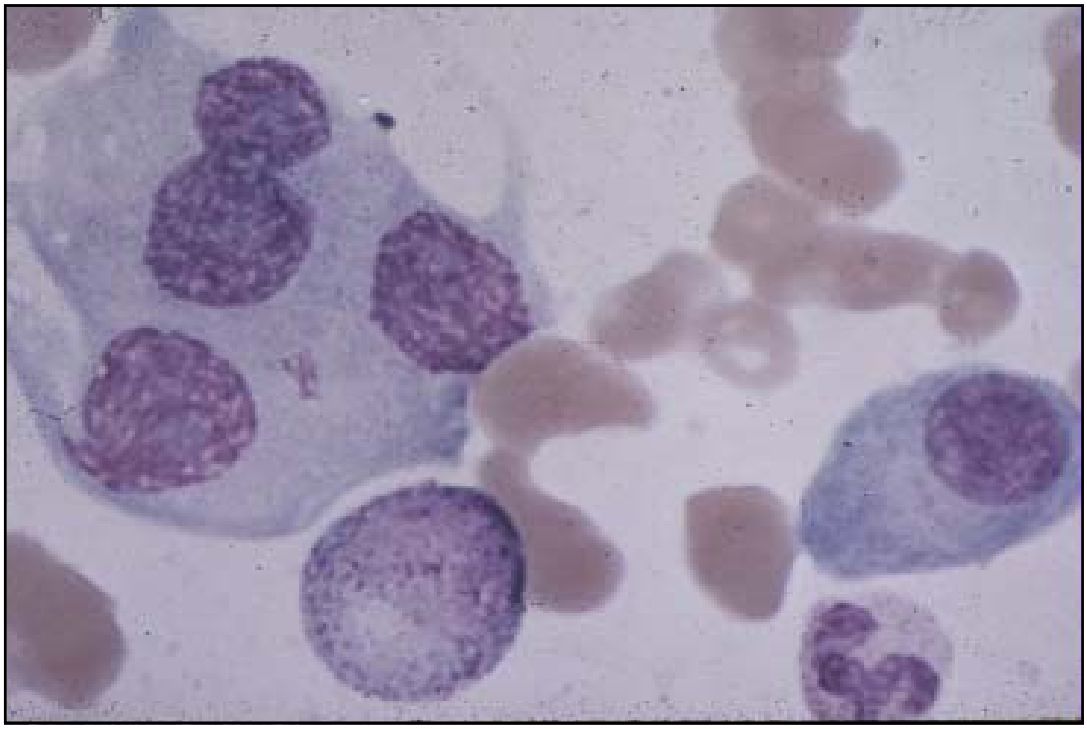
Marrow Plasmacytosis in Myeloma

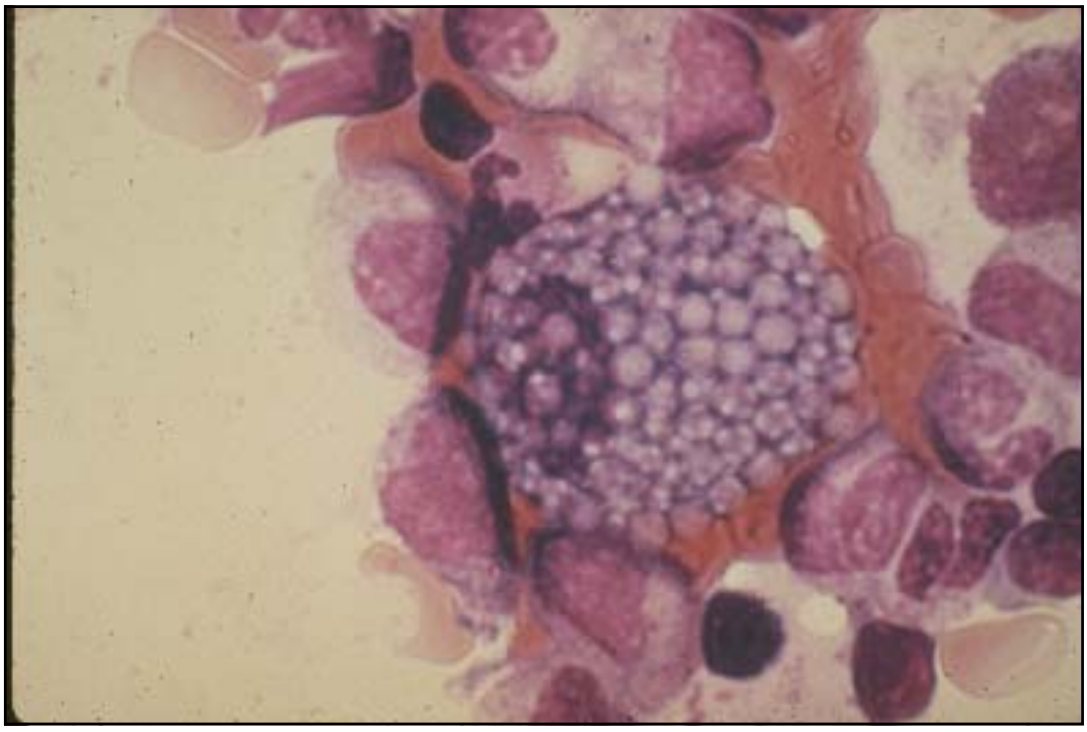
- **Plasma cells > 10%**
- **Usually much higher**
- **Often present in 'sheets'**
- **Alternatively, biopsy-proven plasmacytoma**
- **Other causes of plasmacytosis:**
  - **inflammation, cirrhosis, AIDS**

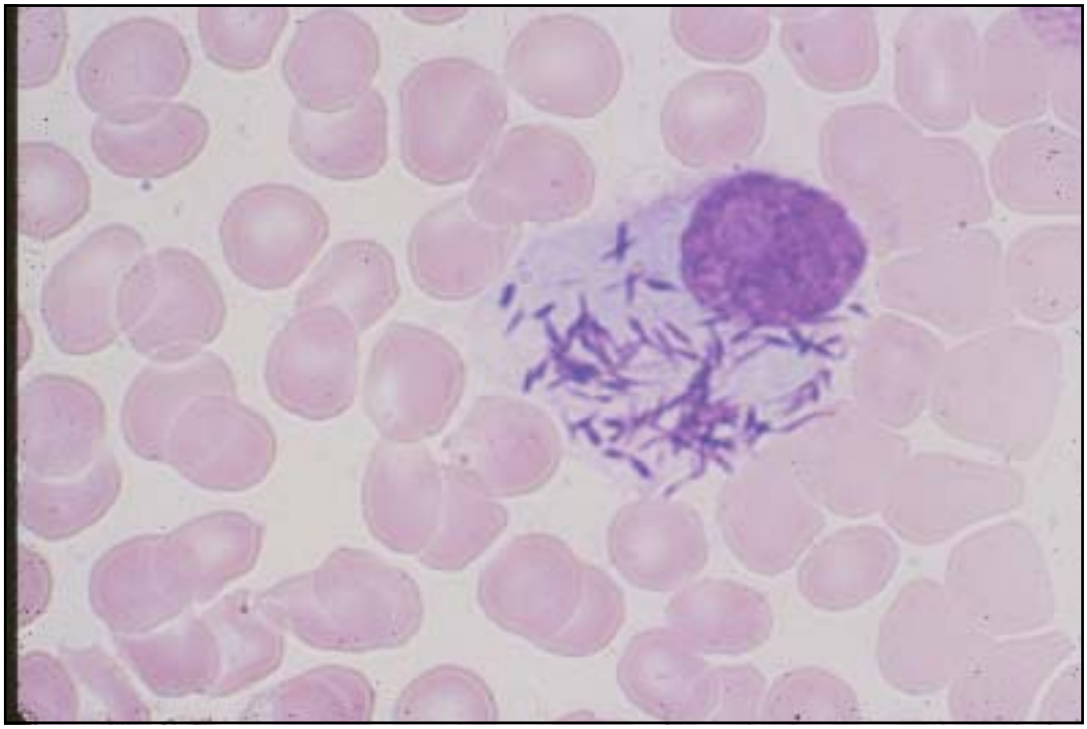


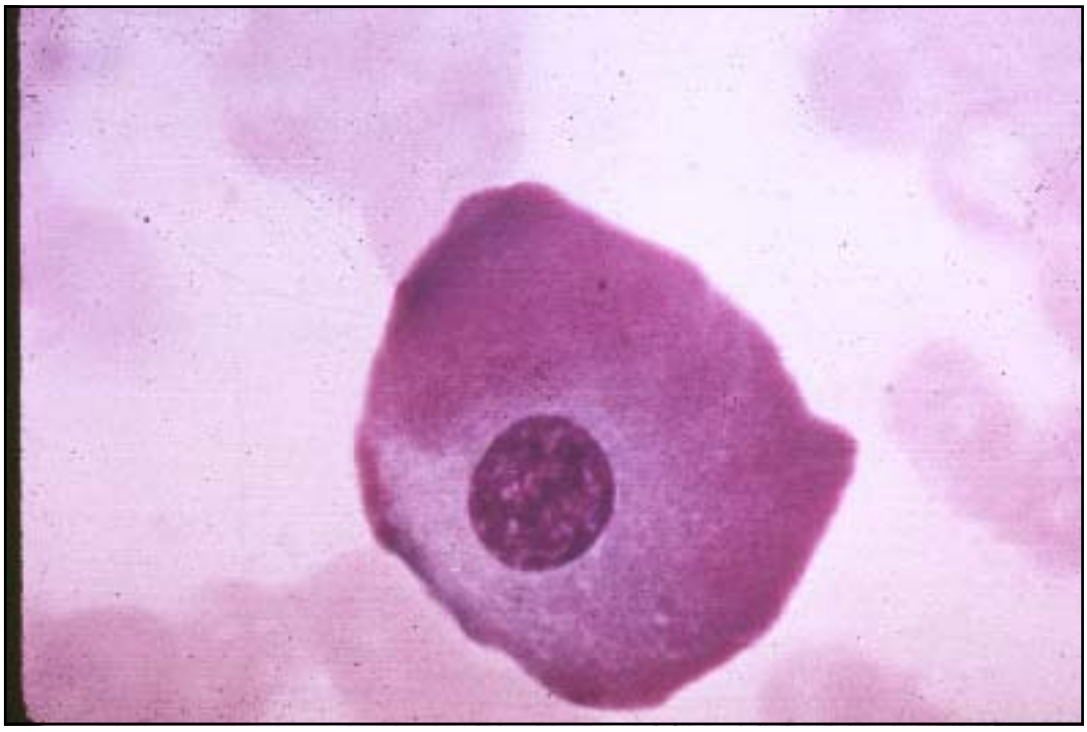


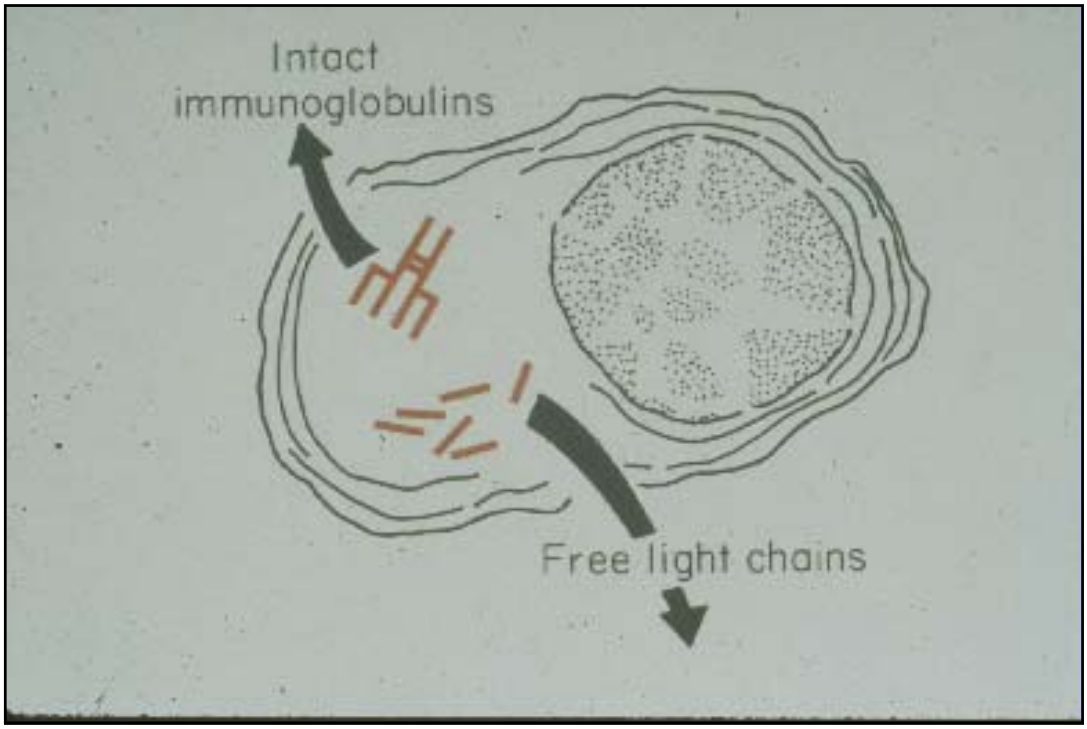






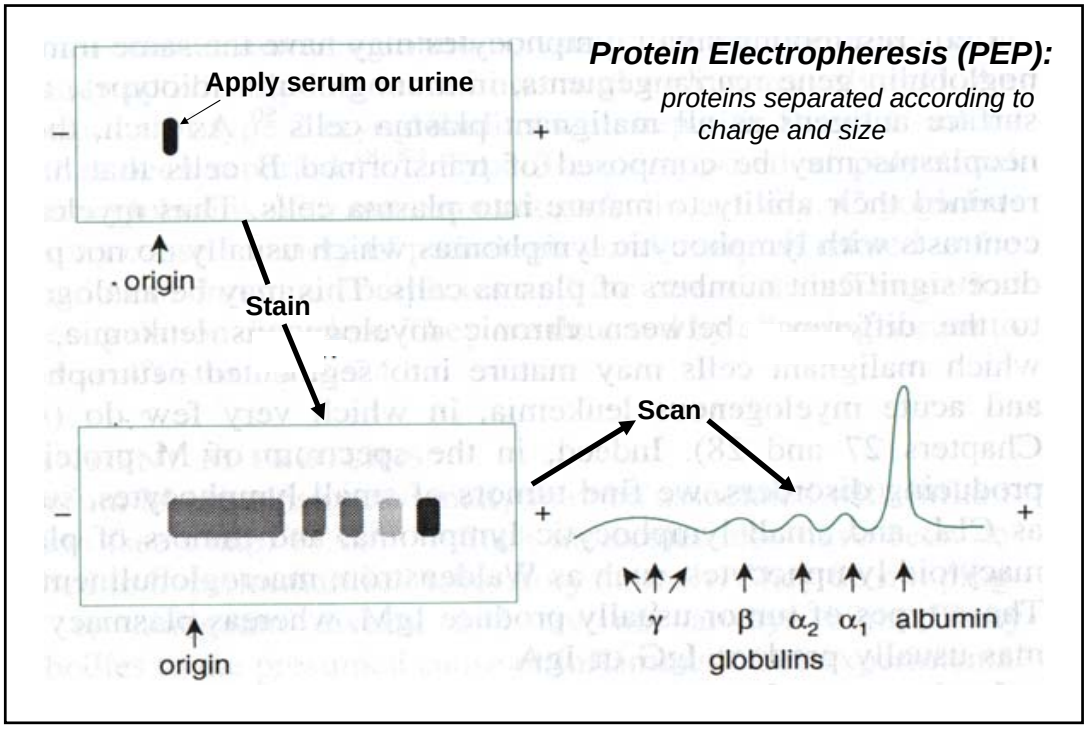


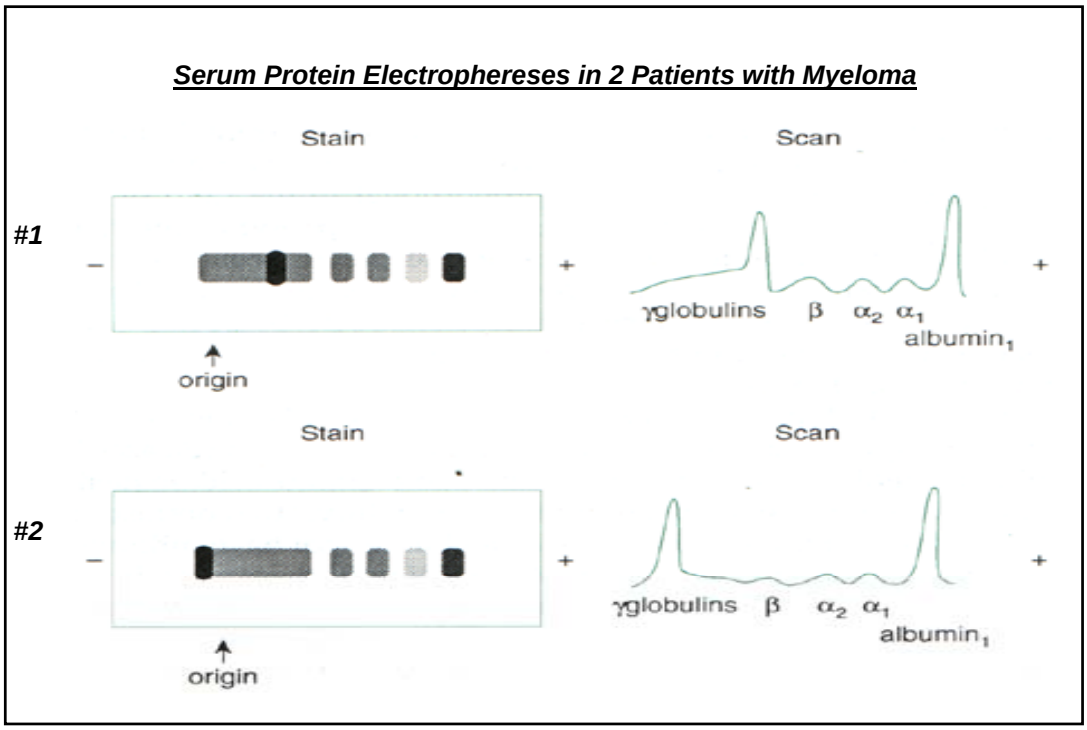


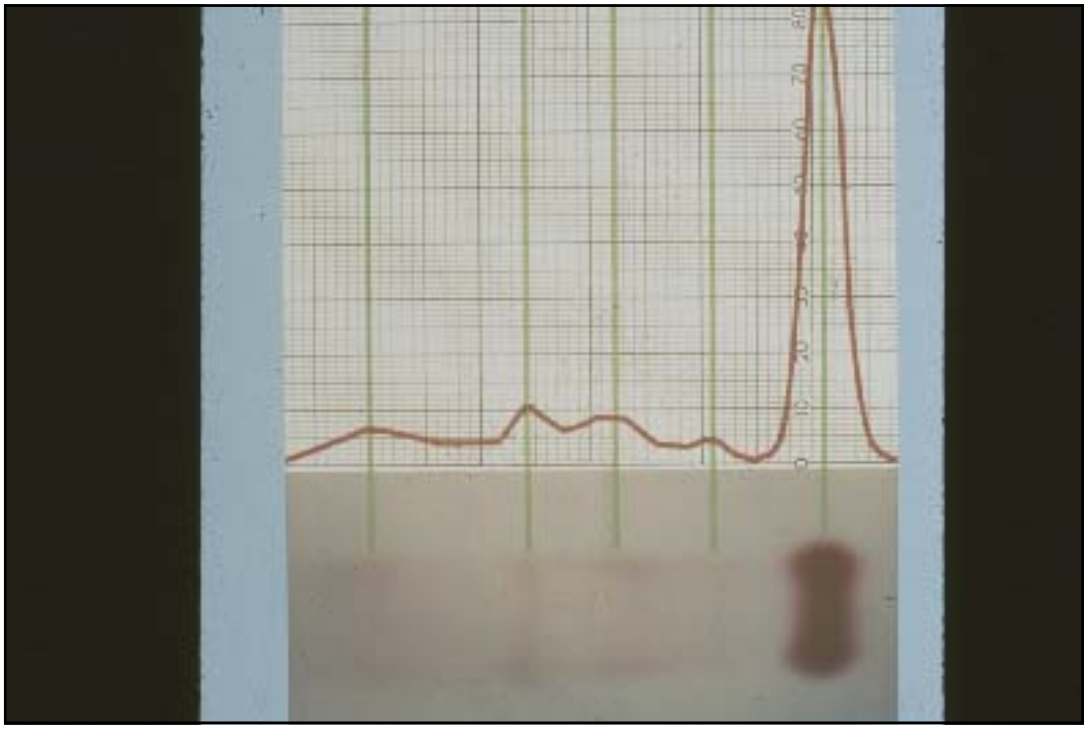


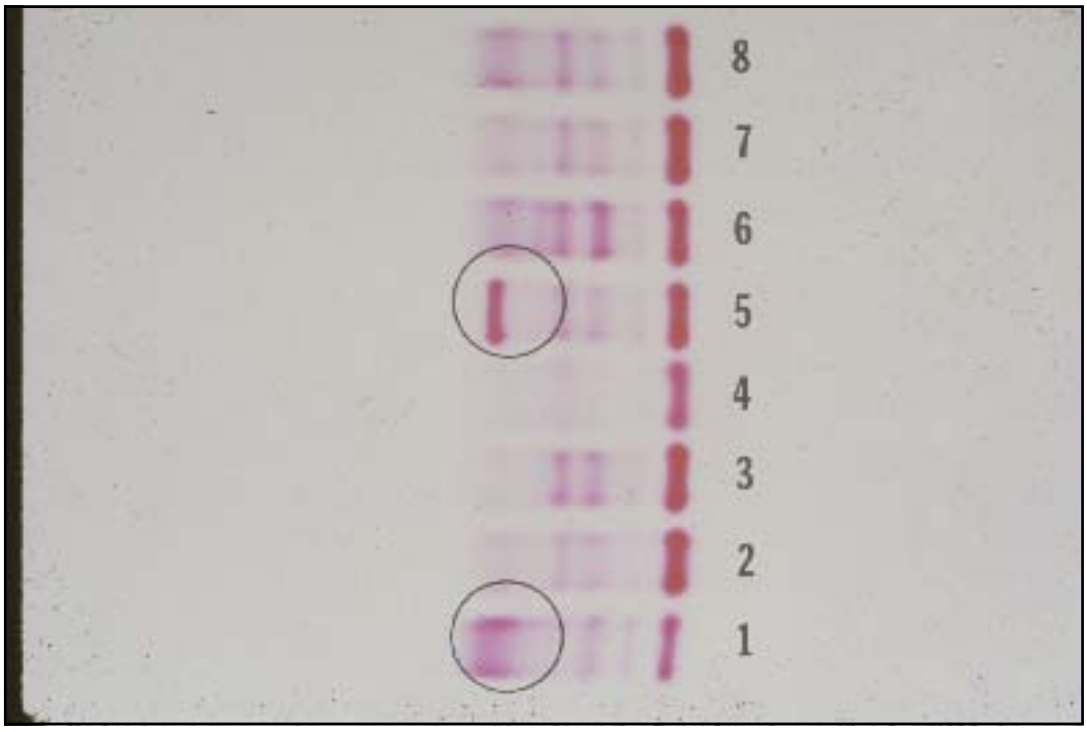
Diagnosis of Myeloma: Monoclonal Proteins

- **75-80% have serum monoclonal Ig**
  (M-component, paraprotein, or 'spike' on electropheresis)
- **10-20% make light chains only → rapid renal excretion → no paraprotein on serum protein electropheresis**
- **Non-secretory myeloma rare (< 1%)**
- **Other causes of monoclonal proteins**
  (eg, CLL, lymphoma, benign monoclonal gammopathy)


Protein Electropheresis (PEP):
proteins separated according to charge and size
Apply serum or urine
–
+
origin
Stain
Scan
–
+
+
origin
γ
β
α2
α1
albumin
globulins


Serum Protein Electrophereses in 2 Patients with Myeloma
Stain
Scan
#1
–
+
+
origin
γglobulins
β
α2
α1
albumin1
Stain
Scan
#2
–
+
+
origin
γglobulins
β
α2
α1
albumin1




8
7
6
5
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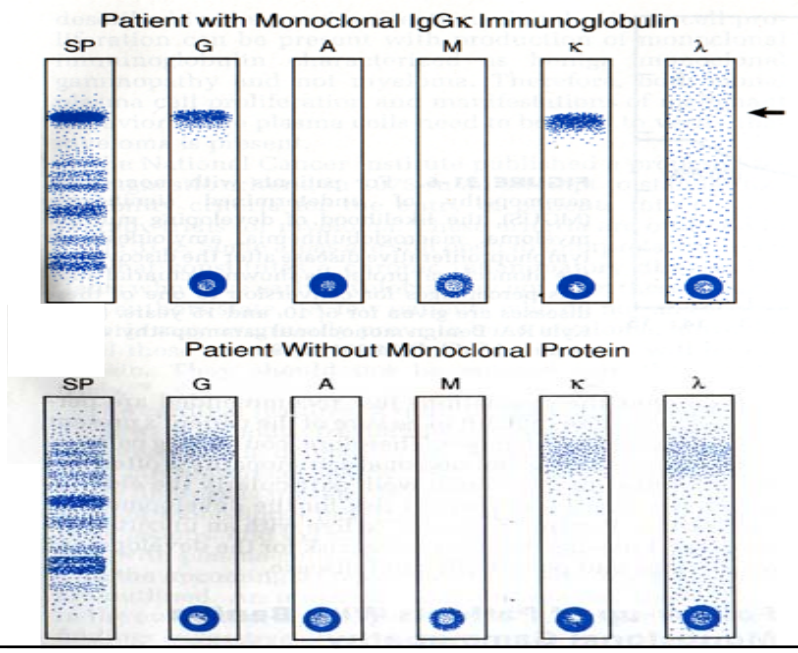
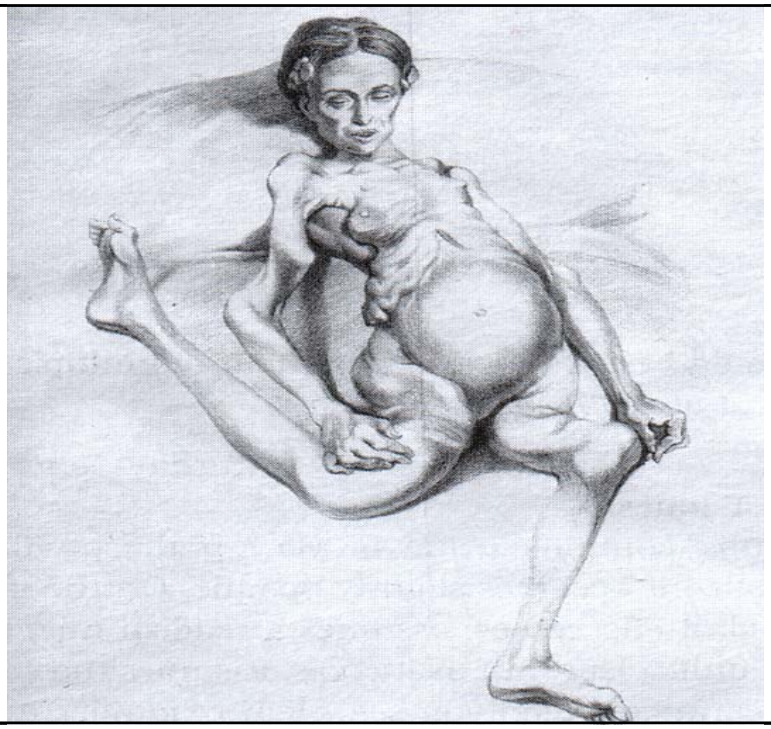
3
2
1

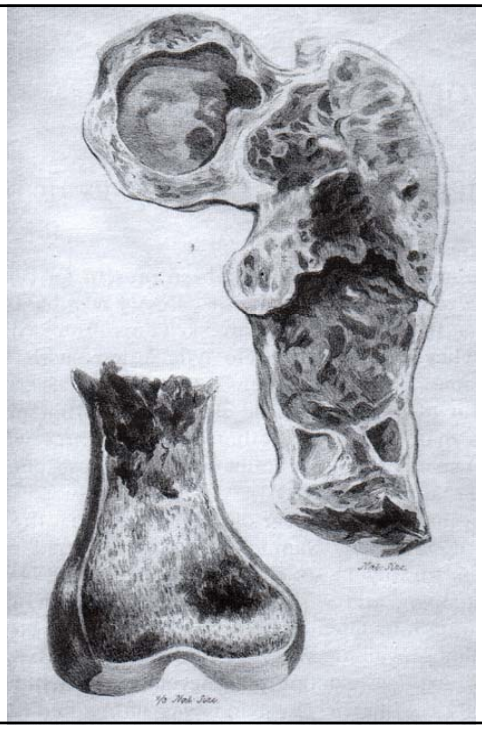
Immunofixation Electropheresis

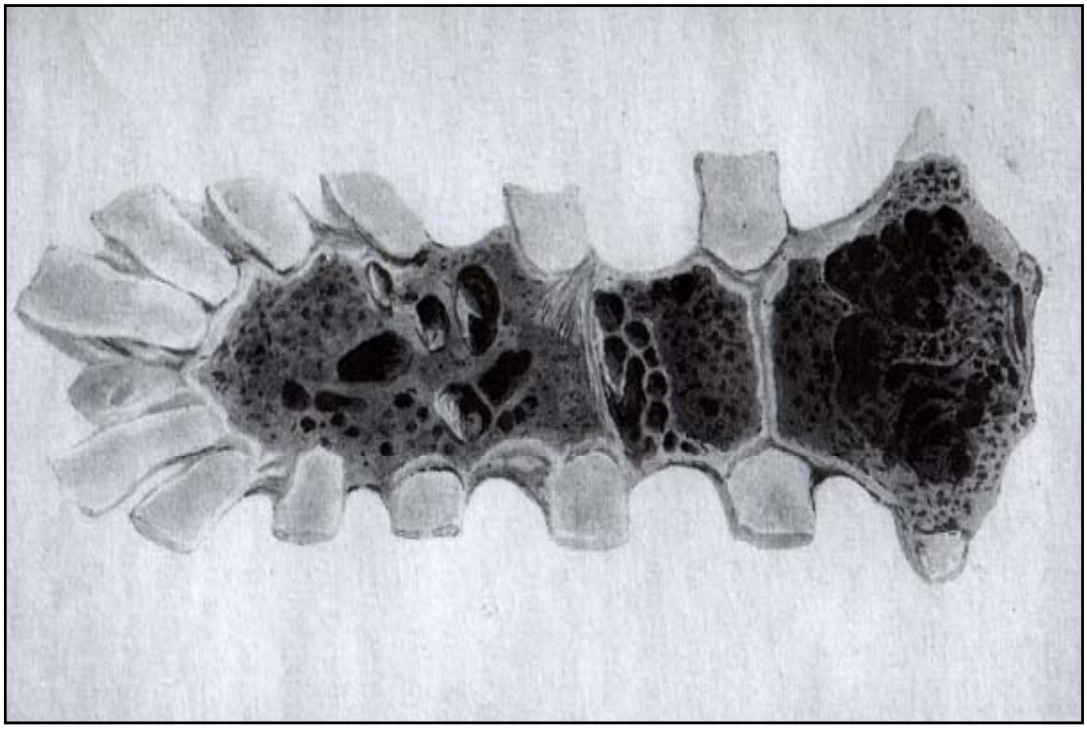


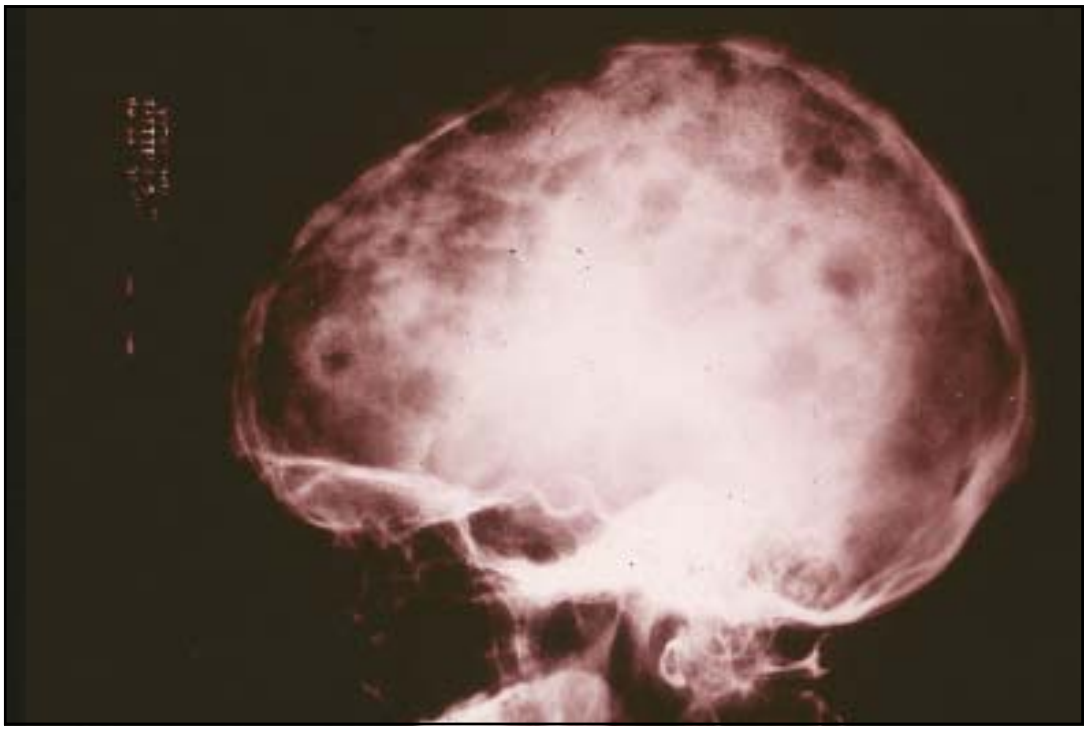
Bone Disease in Myeloma

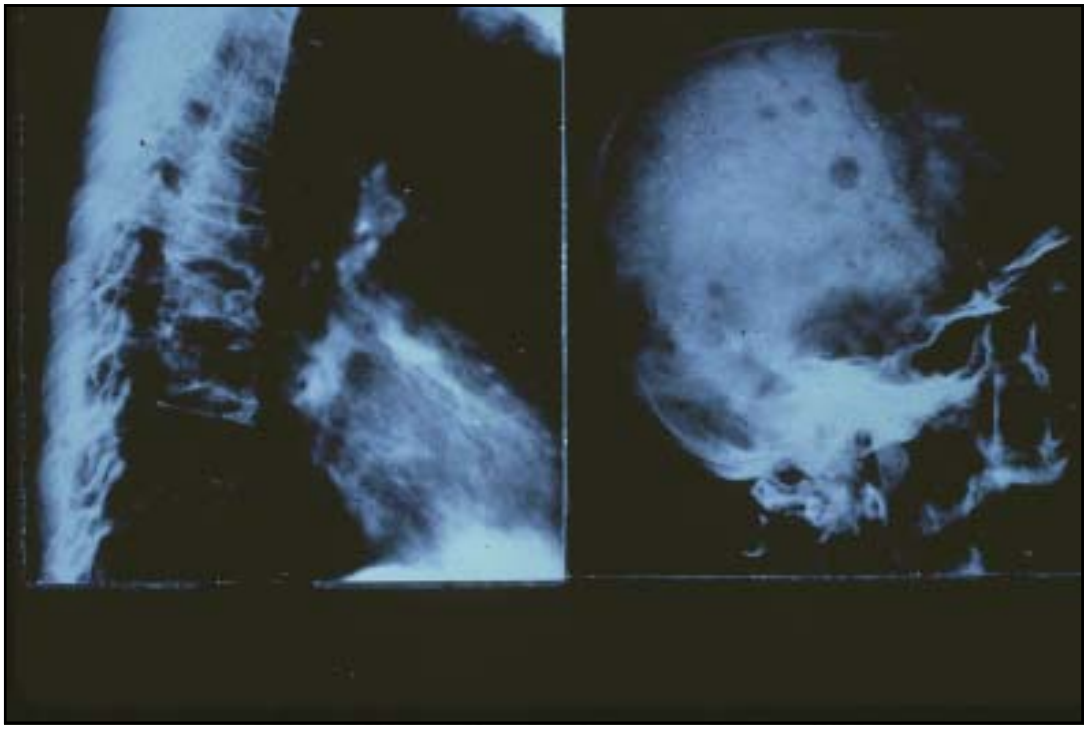
- Unbalanced osteoclast activity
- Radiographic manifestations
  - Osteoporosis almost invariable
  - Usually multiple lytic lesions
  - Axial skeleton involved (active marrow)
  - Osteoblastic reaction minimal
- Hypercalciuria and hypercalcemia

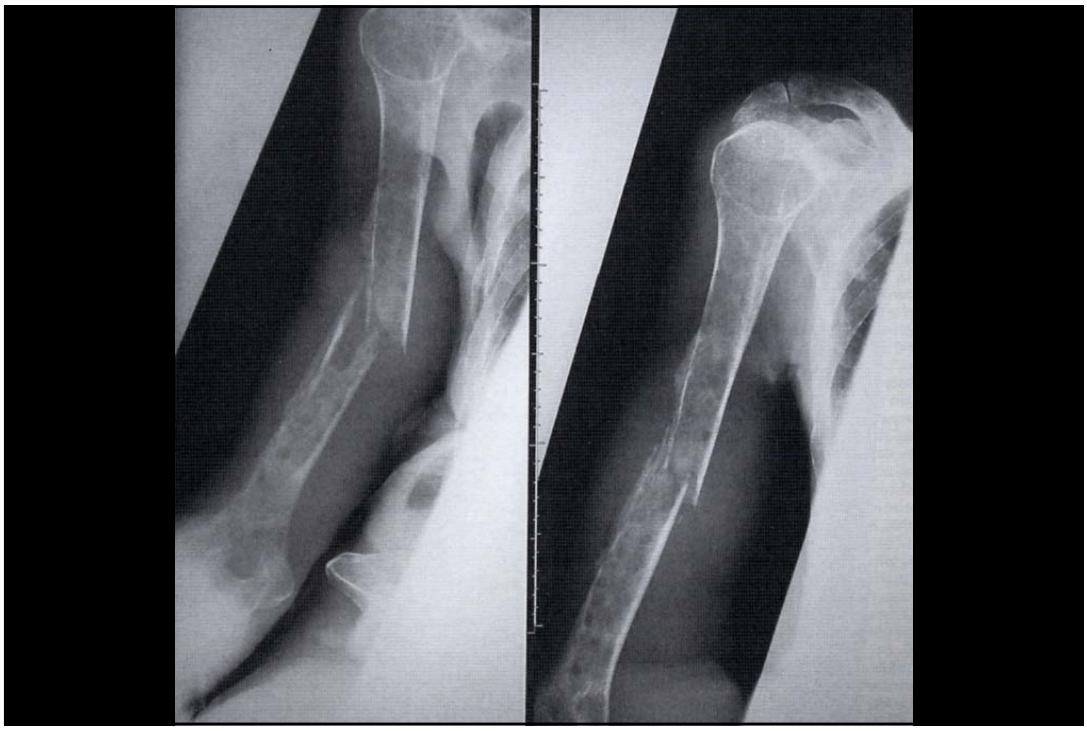


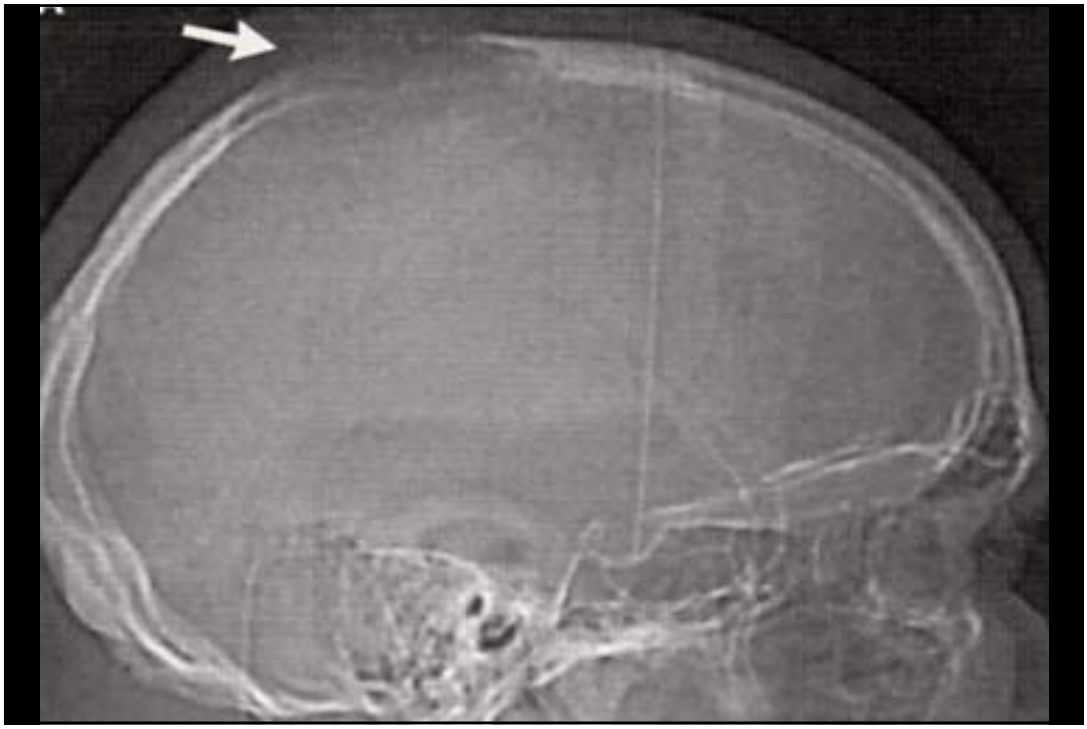


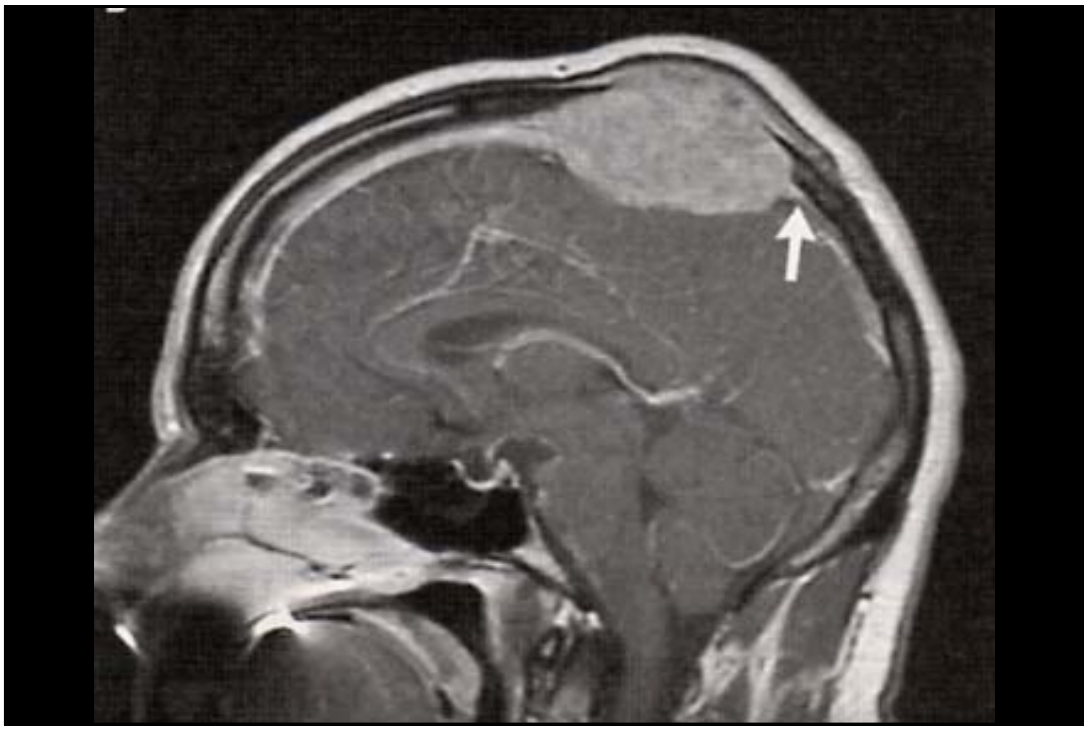












Benign Monoclonal Gammopathy

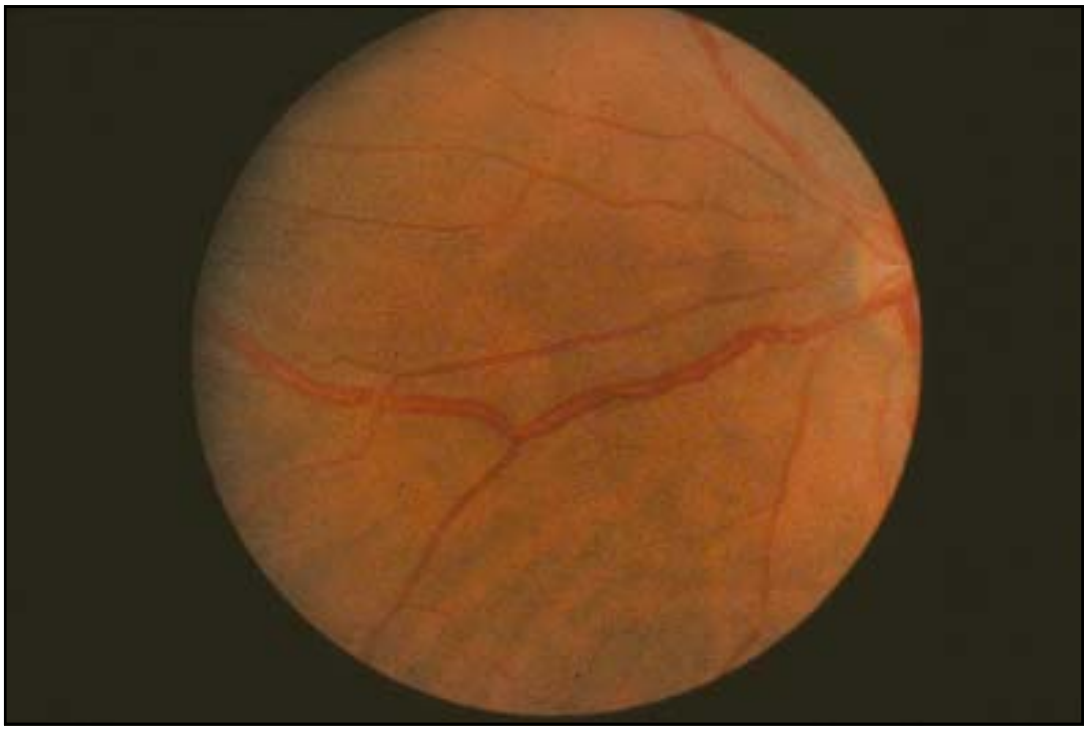
- **Monoclonal Ig as isolated finding**
- **More common than myeloma**
- **No bone disease, anemia, renal dysfunction**
- **Most remain stable**
- **About 10% eventually develop classical myeloma**

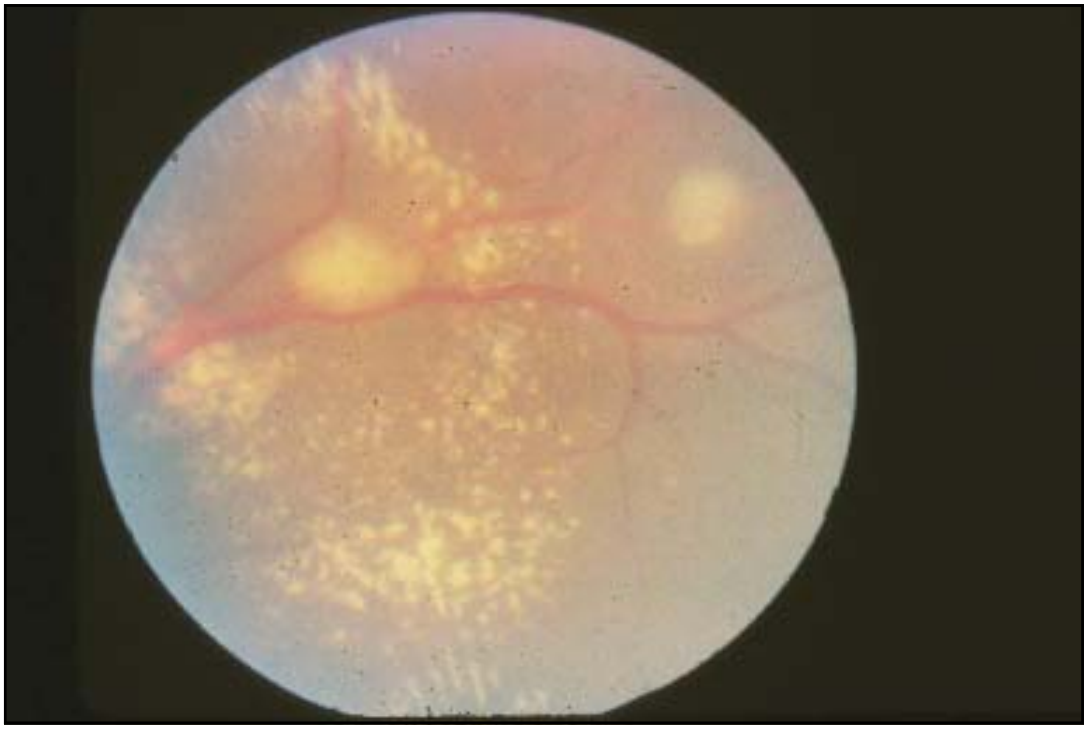
Myeloma at Presentation

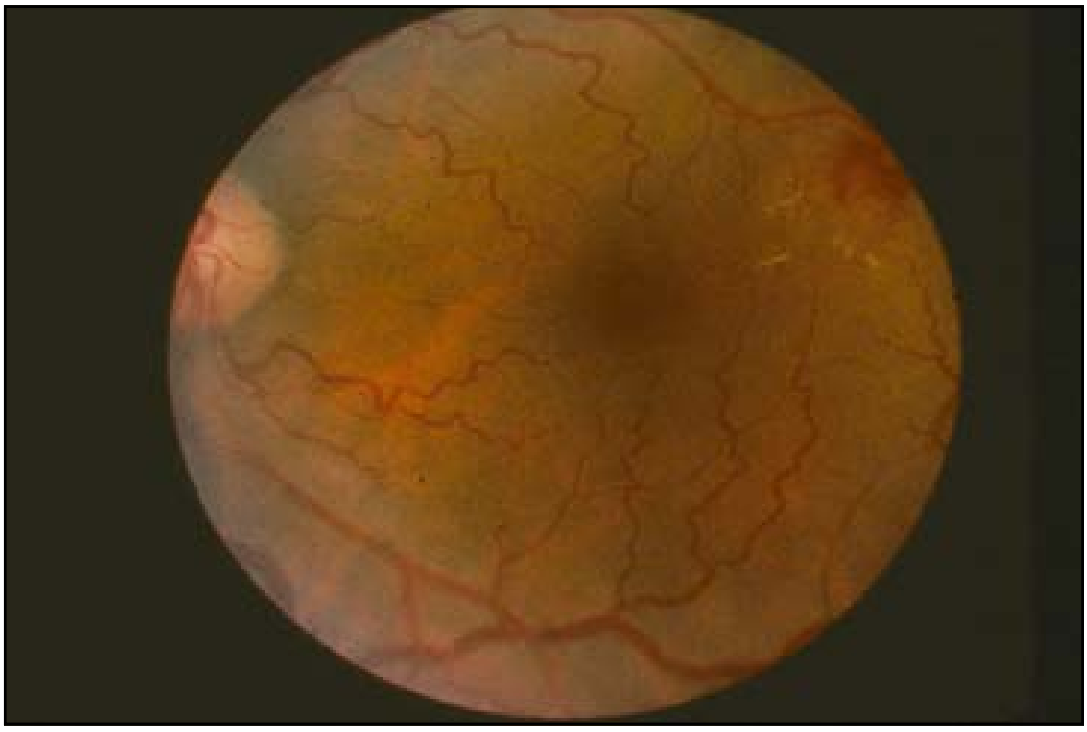
- Early - asymptomatic, incidental diagnosis
  - Paraprotein on electropheresis
  - Mild marrow plasmacytosis
  - Solitary plasmacytoma (10% of cases)
- Late - symptomatic
  - Bone pain (usually lower back)
  - Pneumococcal infection
  - Systemic symptoms (eg, weakness, weight loss)
    - Related to anemia, renal failure, hypercalcemia

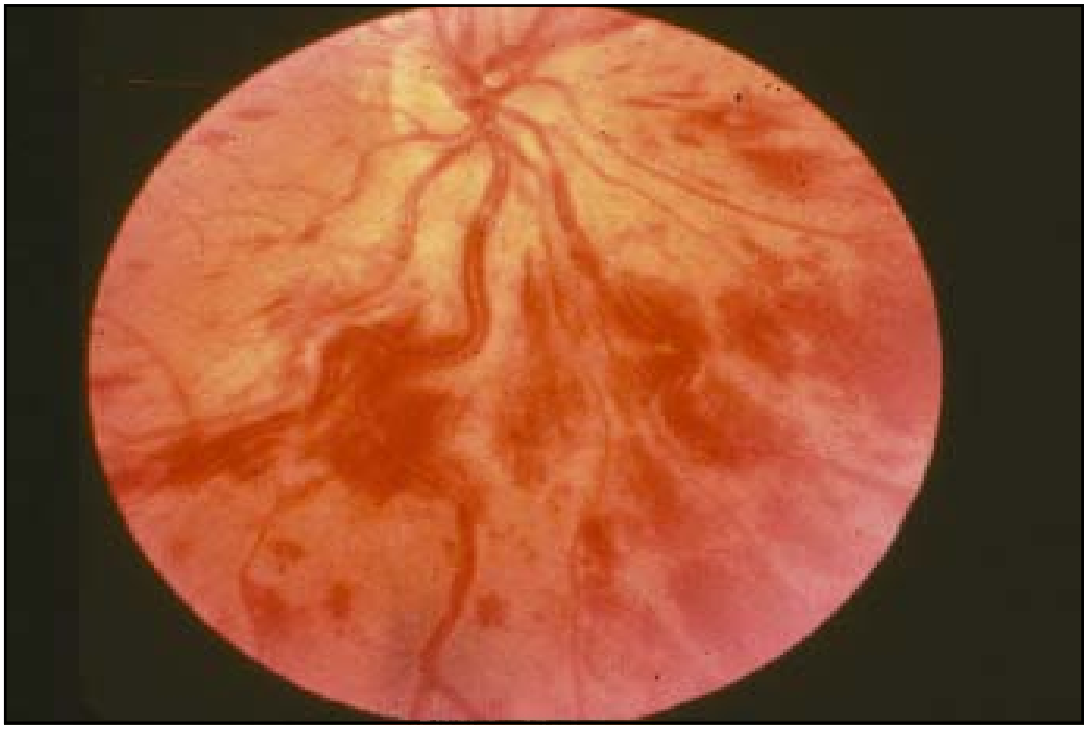
Hyperviscosity Syndrome

- Due to aggregating paraprotein
- Pathogenesis
  - Circulatory insufficiency, abnormal hemostasis
- Manifestations
  - Bleeding
  - Dyspnea (congestion on CXR)
  - Encephalopathy and visual disturbances







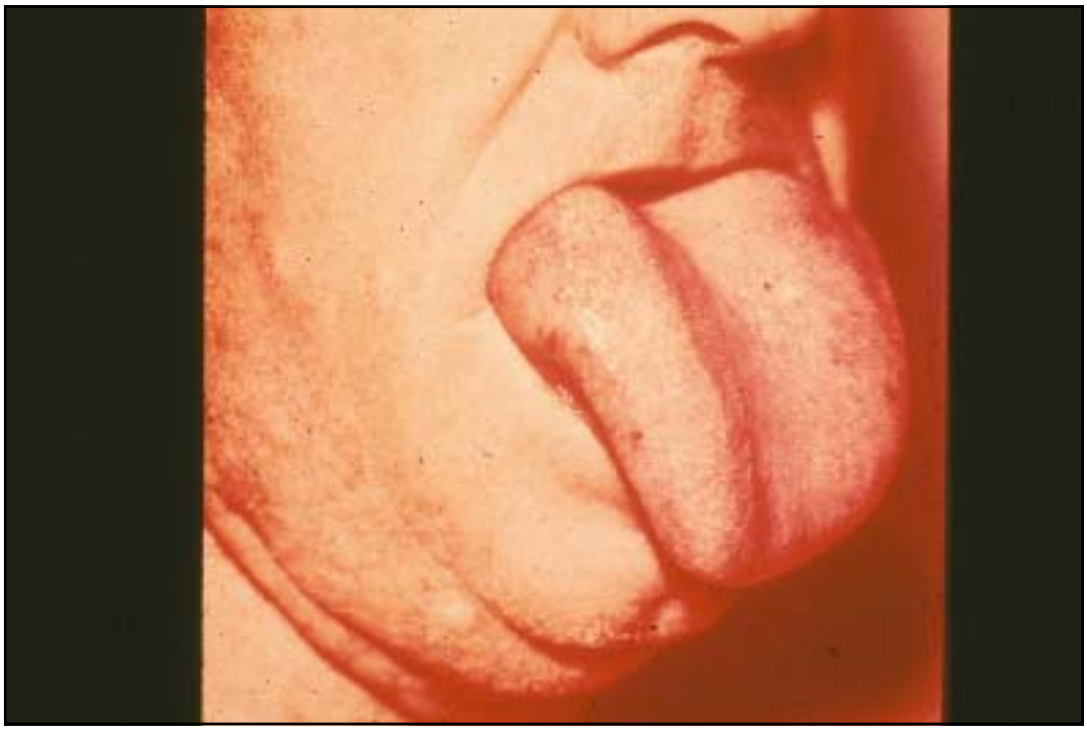


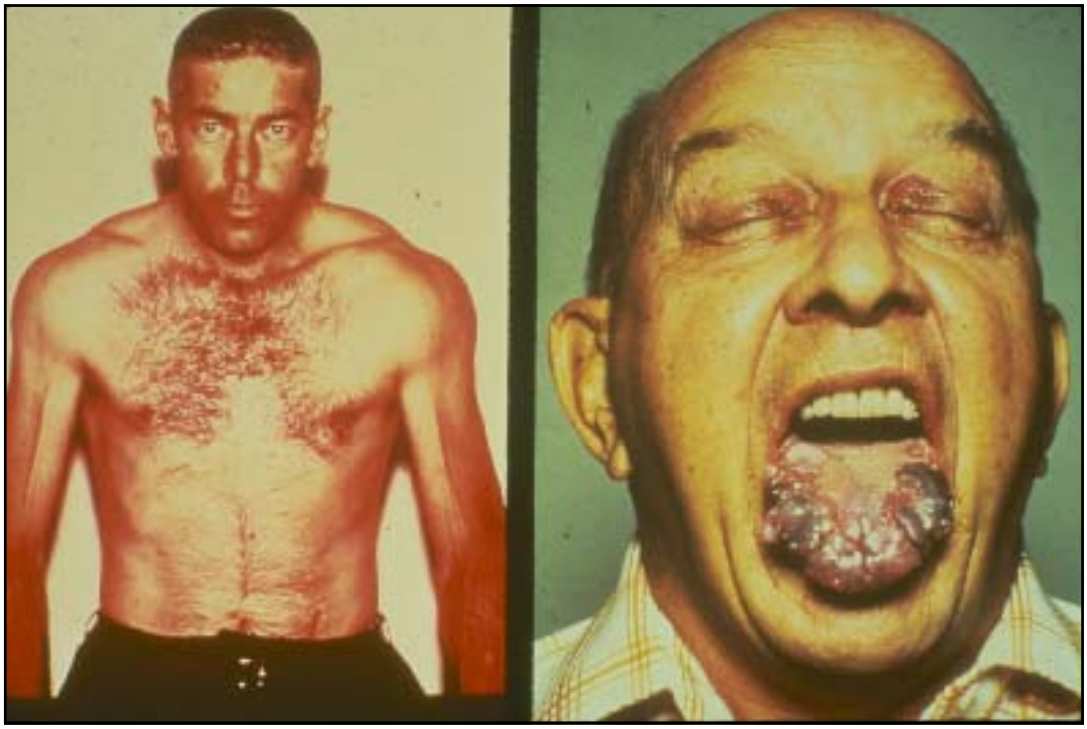
Immunological Features of Myeloma

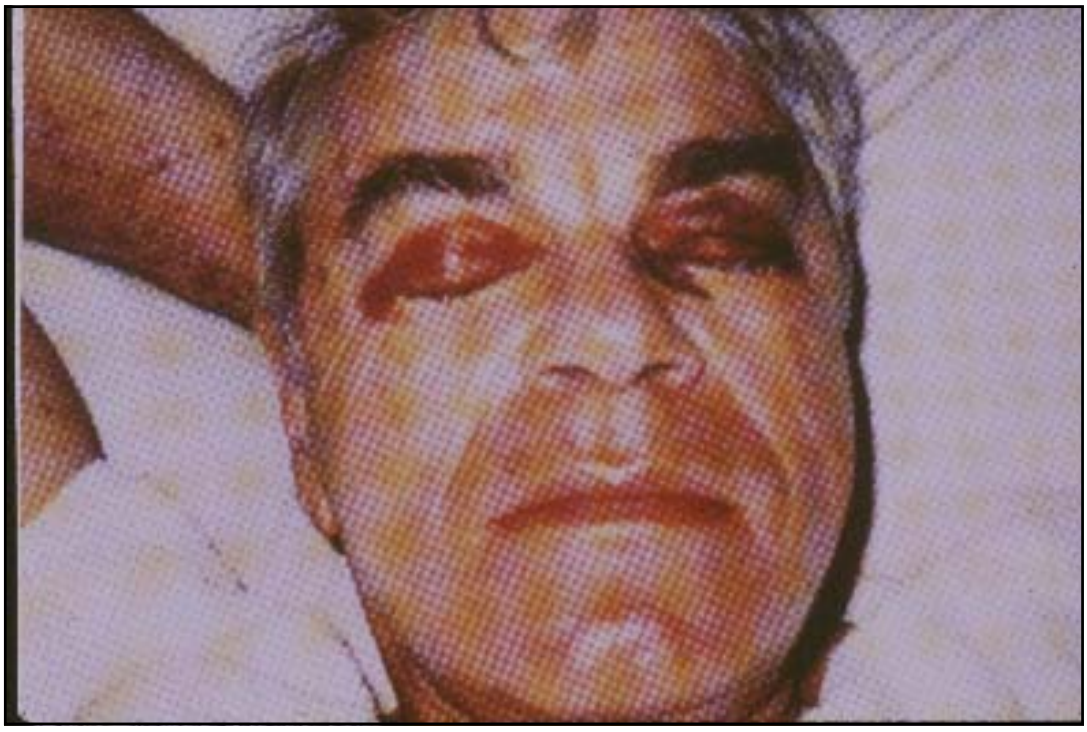
- **Monoclonal Ig and/or monoclonal light chain**
- **↓Levels of normal Ig's (hypogammaglobulinemia)**
- **Cellular immune responses usually preserved**
- **Bacterial infections common**
  Early: S pneumoniae
  Late: S aureus, Gram negative rods

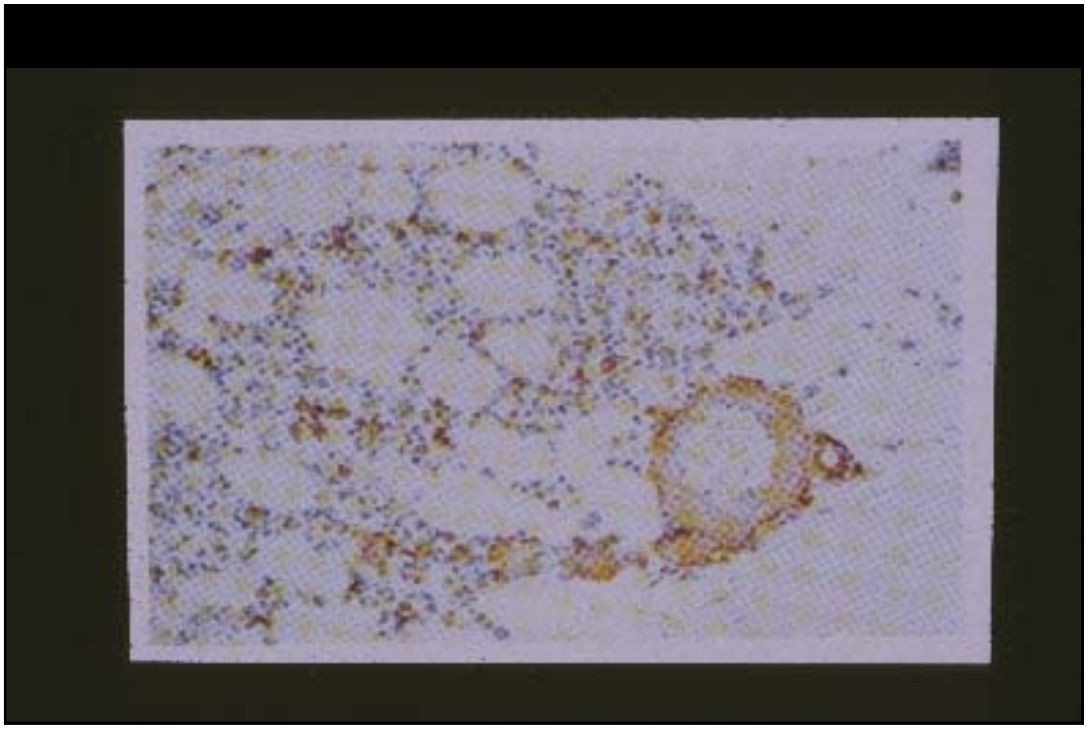
Amyloidosis in Myeloma

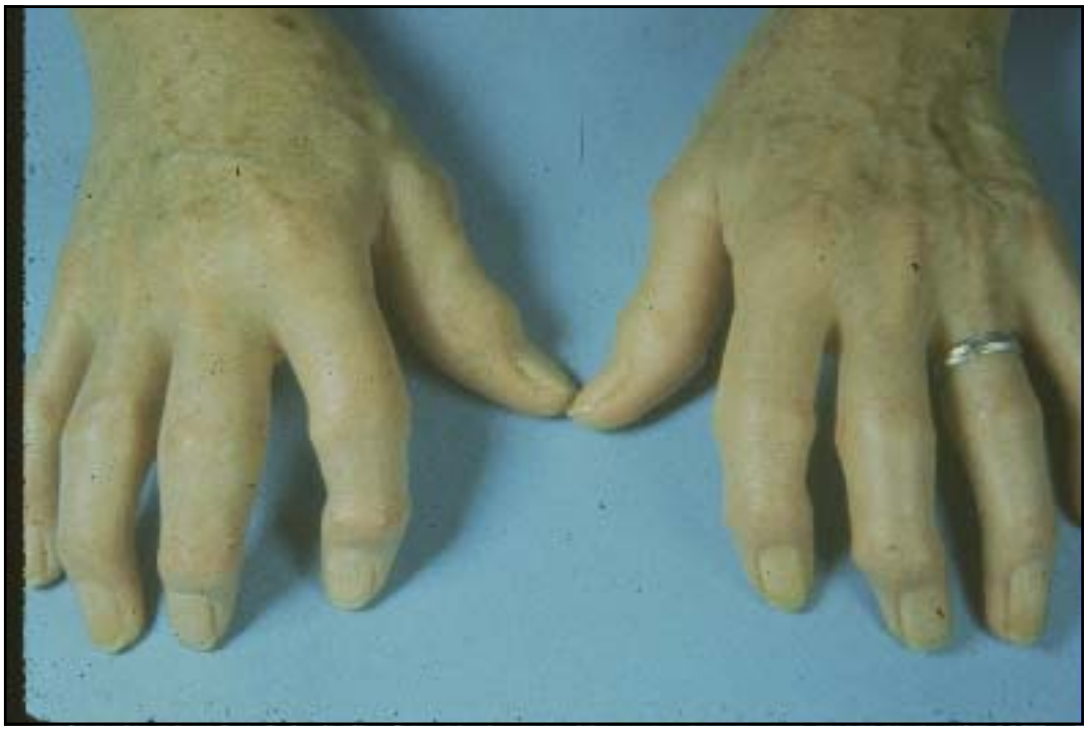
- **Due to light chain deposition in tissues**
- **Incidence: λ amyloid > κ amyloid**
- **Organs commonly involved:**
  - **Skin**
  - **Tongue and GI**
  - **Heart**
  - **Peripheral nerves**
  - **Kidneys**
  - **Soft tissues**
- **No effective therapy, except ?stem cell transplant**

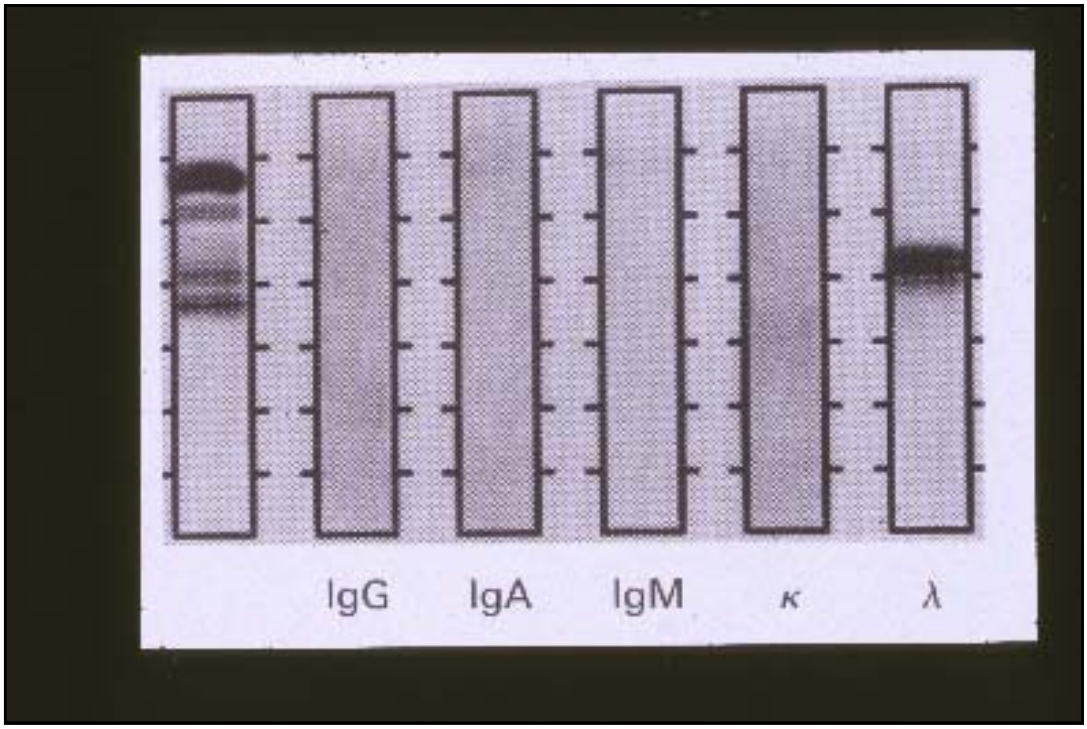












Therapy for Myeloma

- **Biphosphonates (pamidronate, zoledronate)**
- **Radiotherapy**
- **Corticosteroids and conventional chemotherapy**
- **Thalidomide (anti-angiogenesis)**
- **Bortezomib (proteasome inhibitor)**
- **Stem cell transplantation**