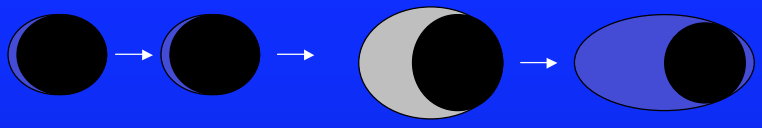
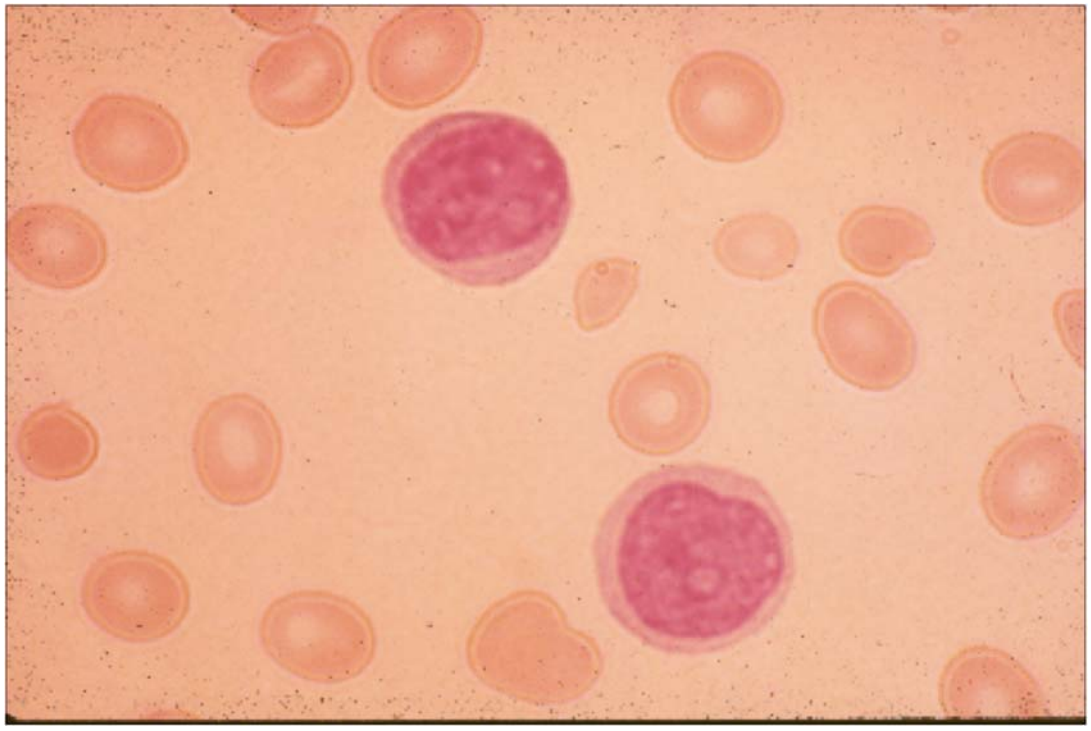
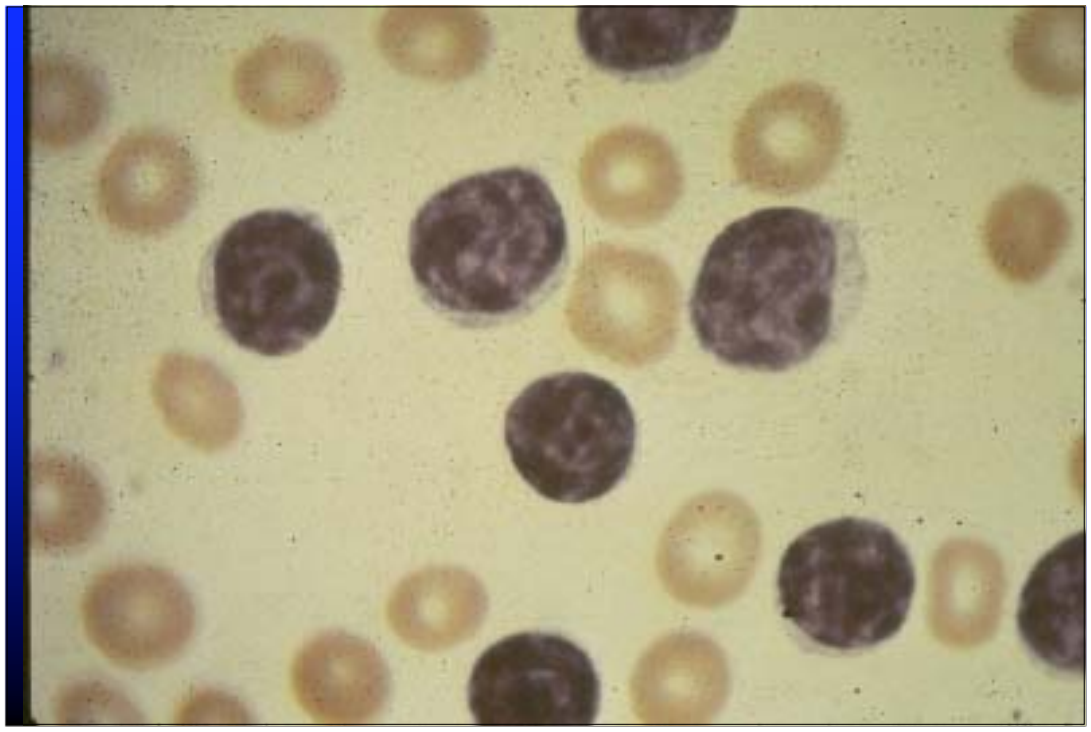
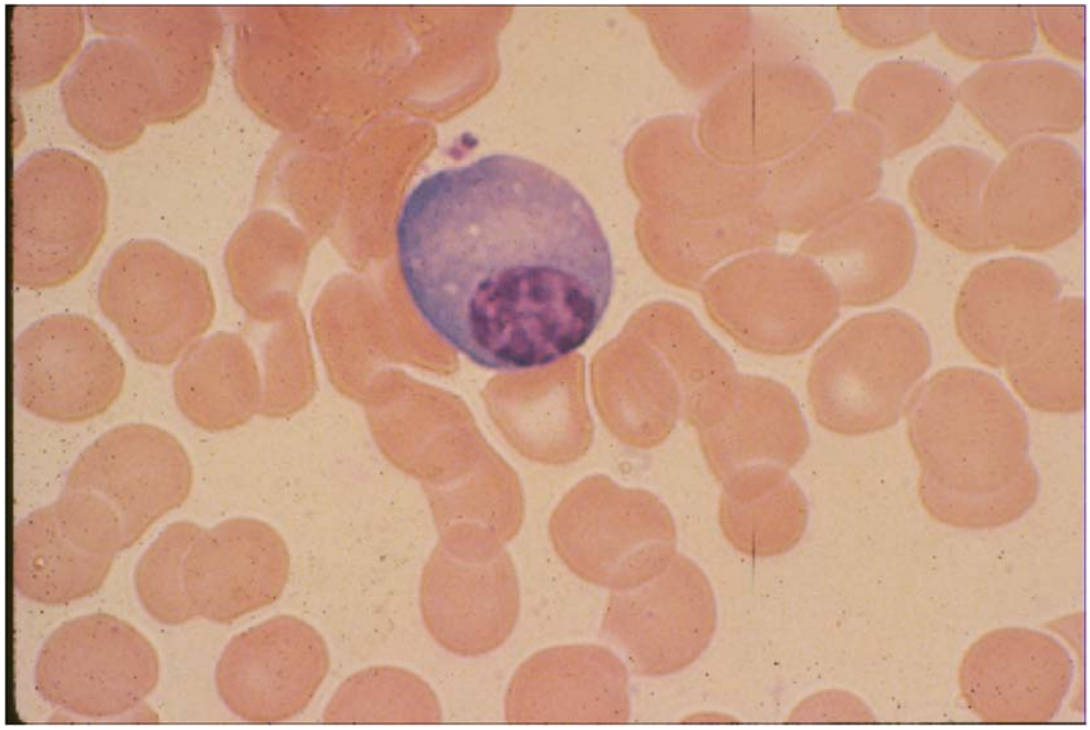
| Disease | Usual phenotype |
|---|---|
| acute leukemia | precursor |
| chronic leukemia<br>lymphoma<br>myeloma | differentiated |



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





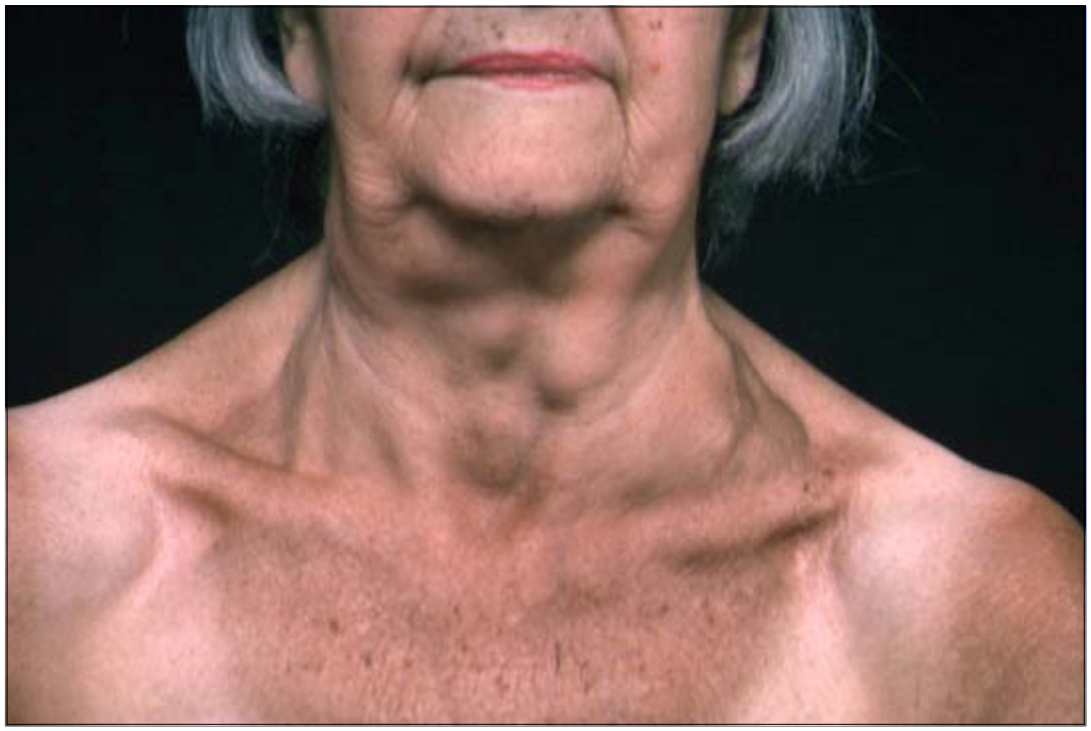


## Chronic Lymphocytic Leukemia

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

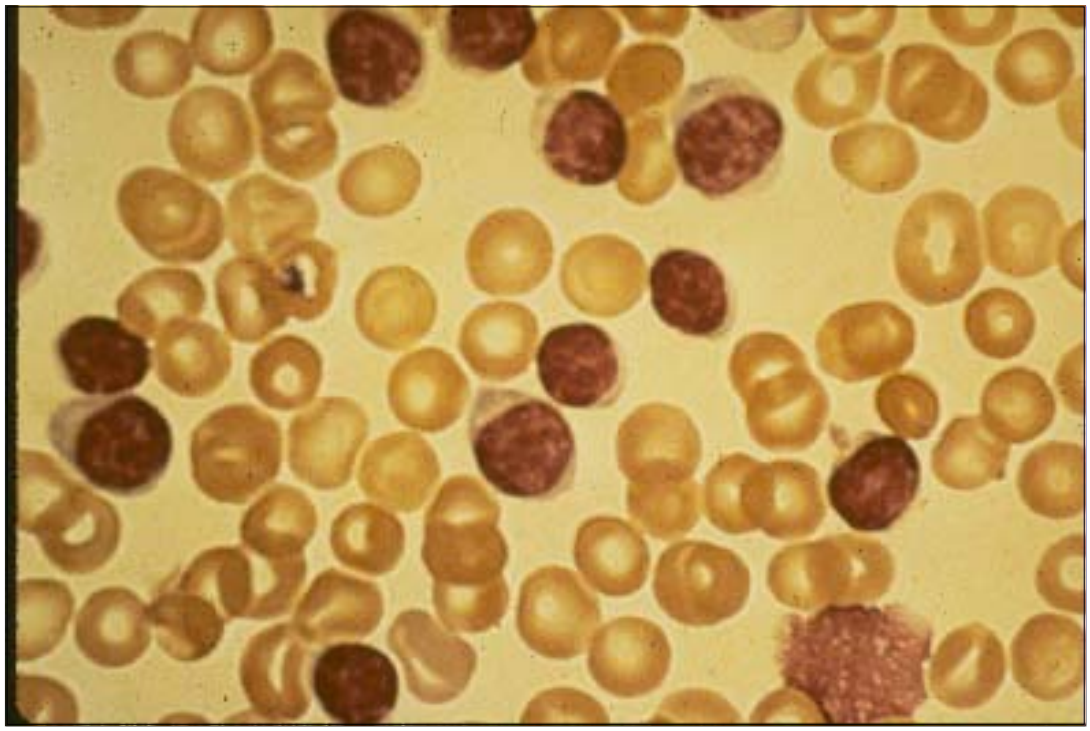
## *Clinical Features of CLL*

- **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

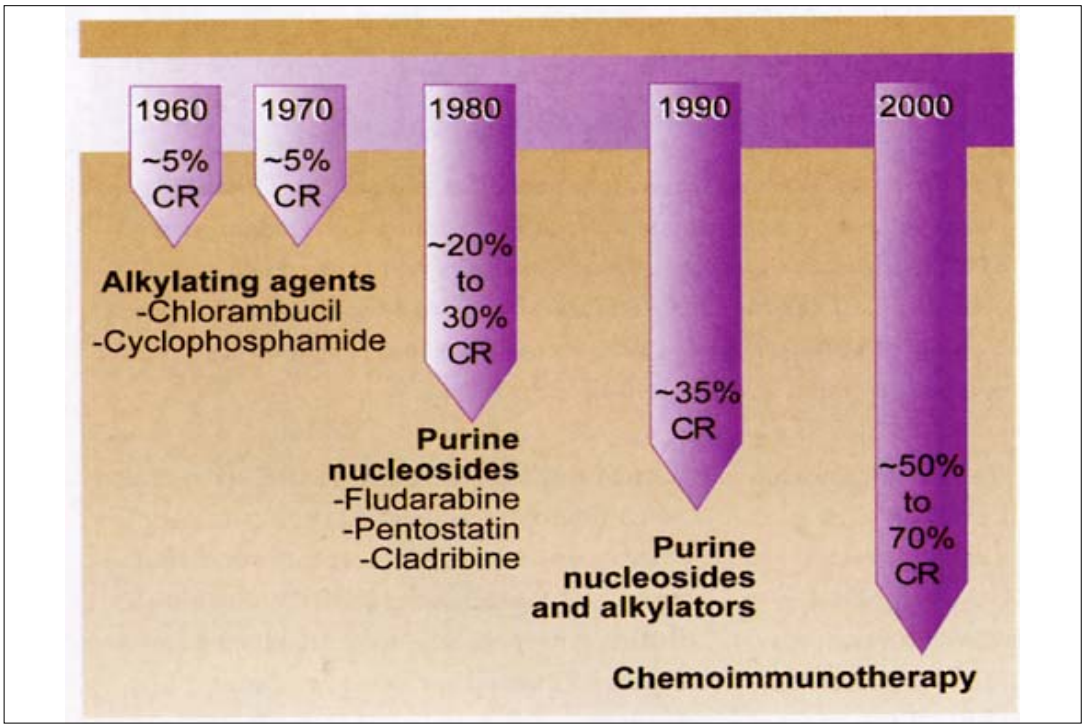
Progressive disease

## *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*

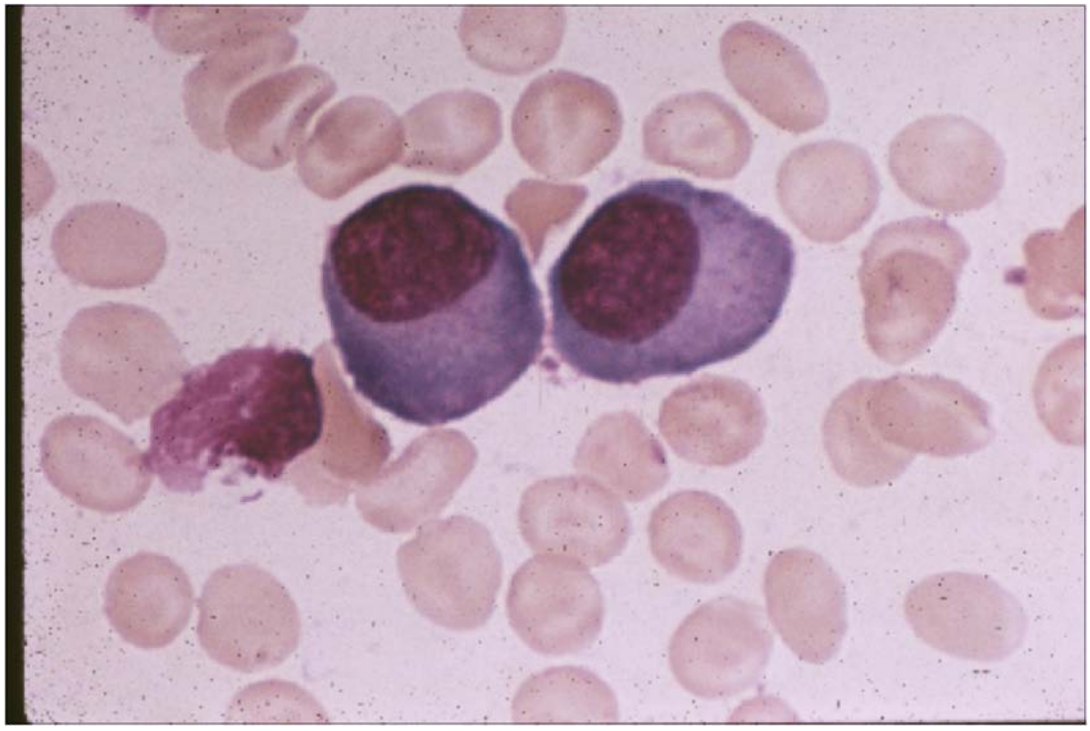
- **Clonal malignancy of plasma cells**
- **Increasing incidence**
- **Blacks:whites 2:1**
- **Age range 20-100 yrs (peak age 70 yrs)**
- **Cause unknown**
  **(Environmental/Genetic factors)**

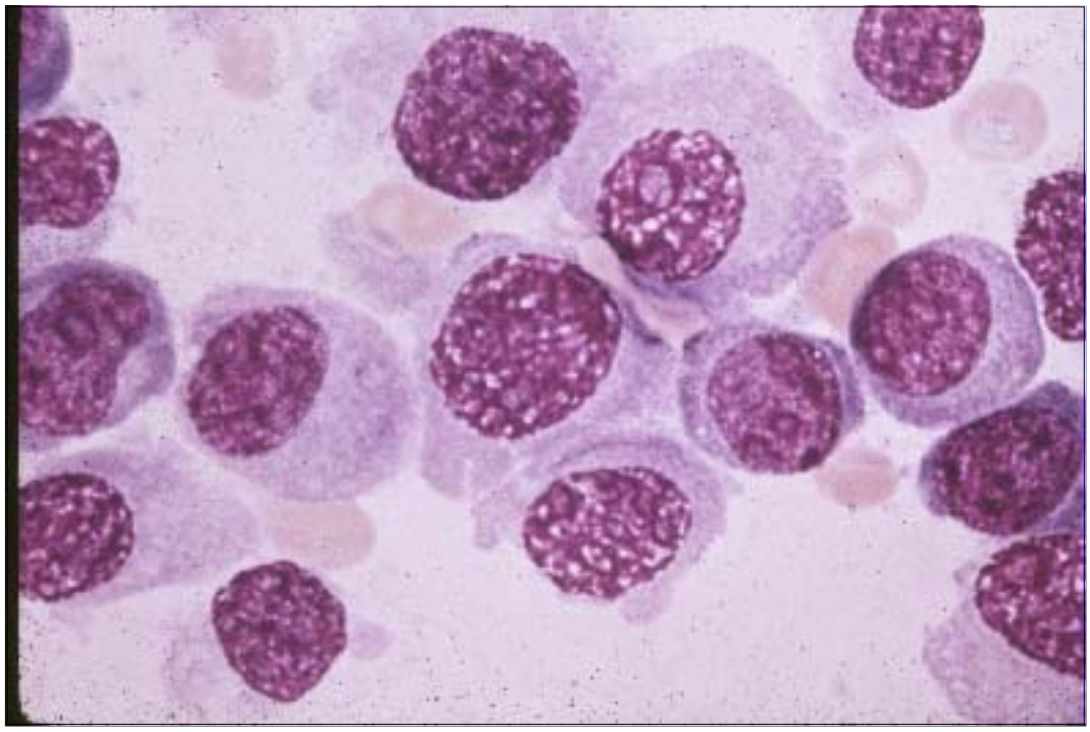
## *Classical Diagnostic Features of Myeloma*

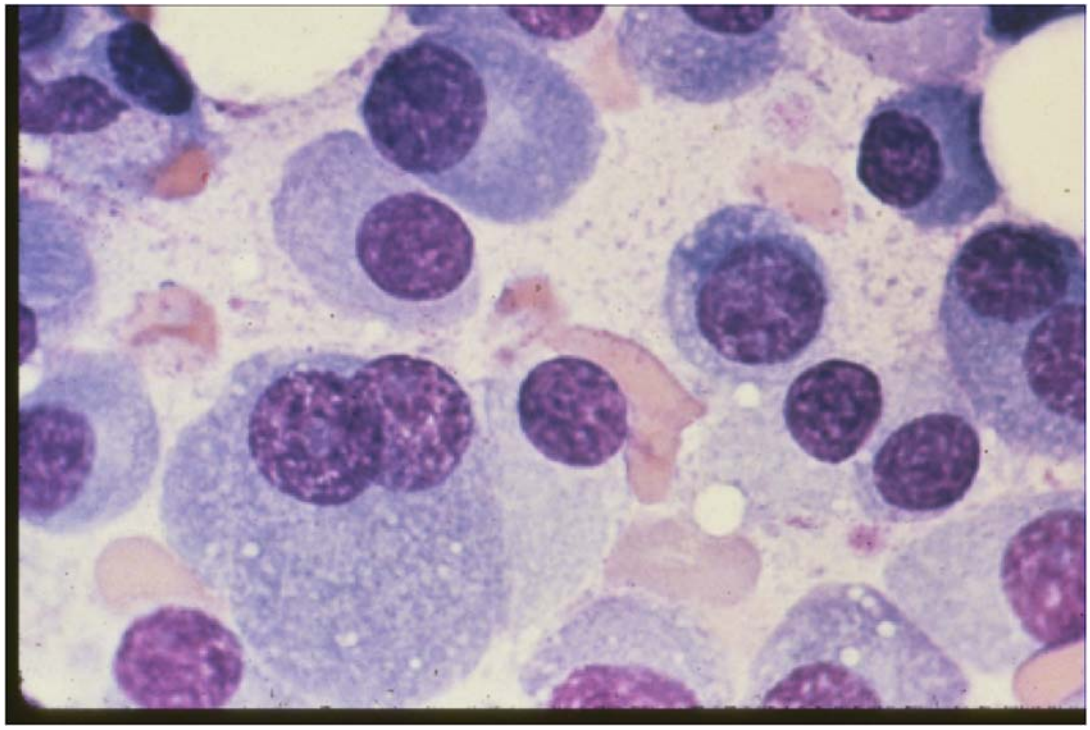
- Plasmacytosis in marrow
- Monoclonal protein in serum or urine
- Lytic disease of bone

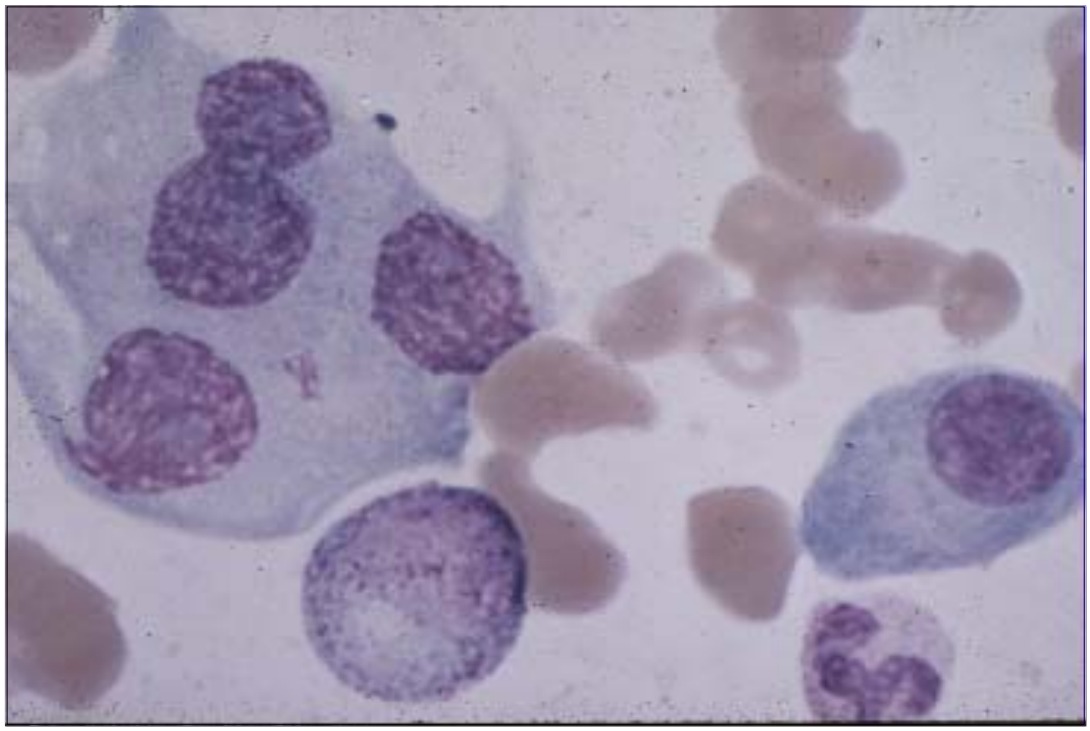
## *Marrow Plasmacytosis in Myeloma*

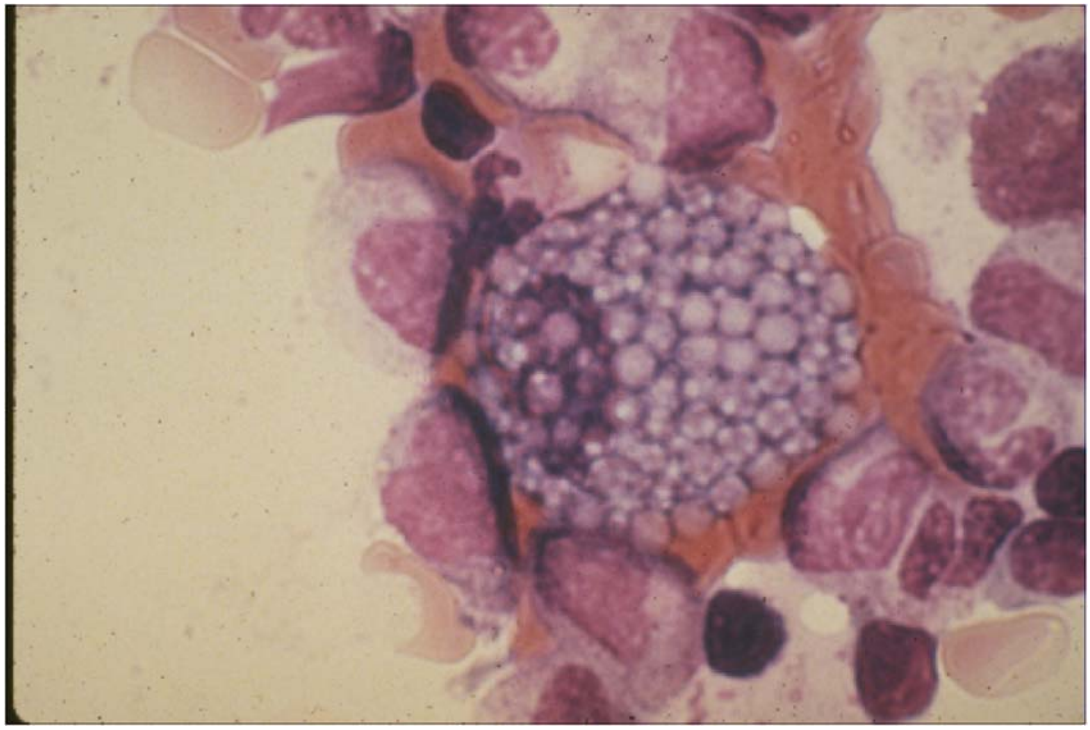
- **Plasma cells > 10%**
- **Usually much higher**
- **Often present in 'sheets'**
- **Alternatively, biopsy-proven plasmacytoma**
- **Other causes of plasmacytosis:**
  - **inflammation, cirrhosis, AIDS**

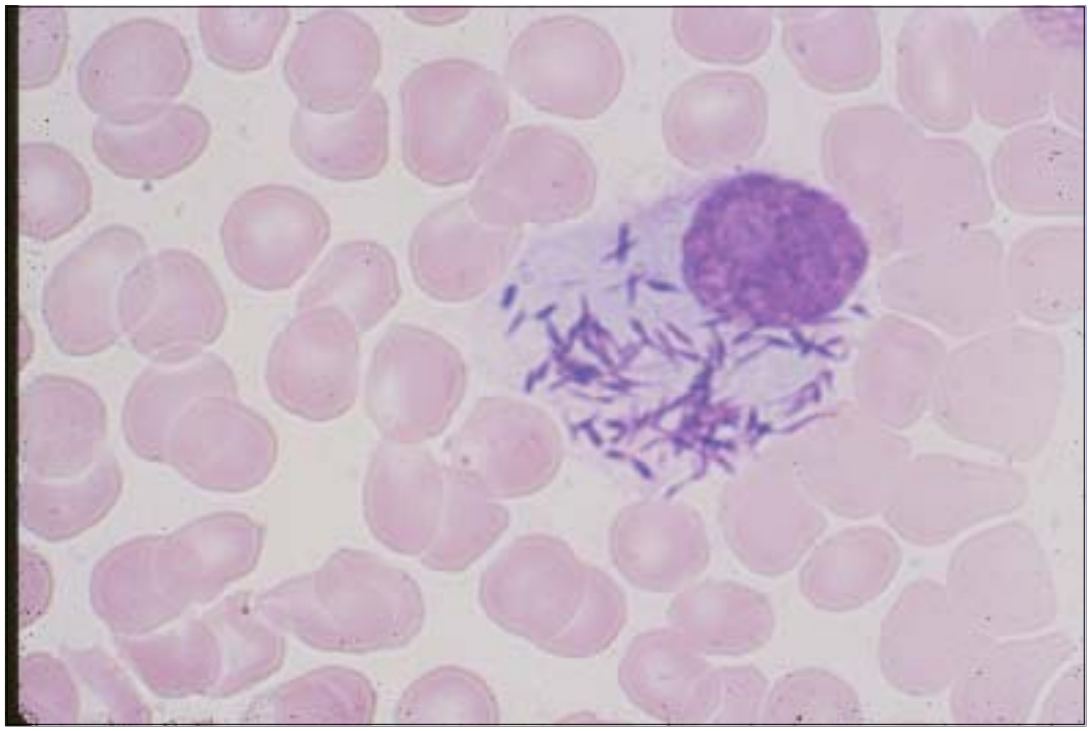


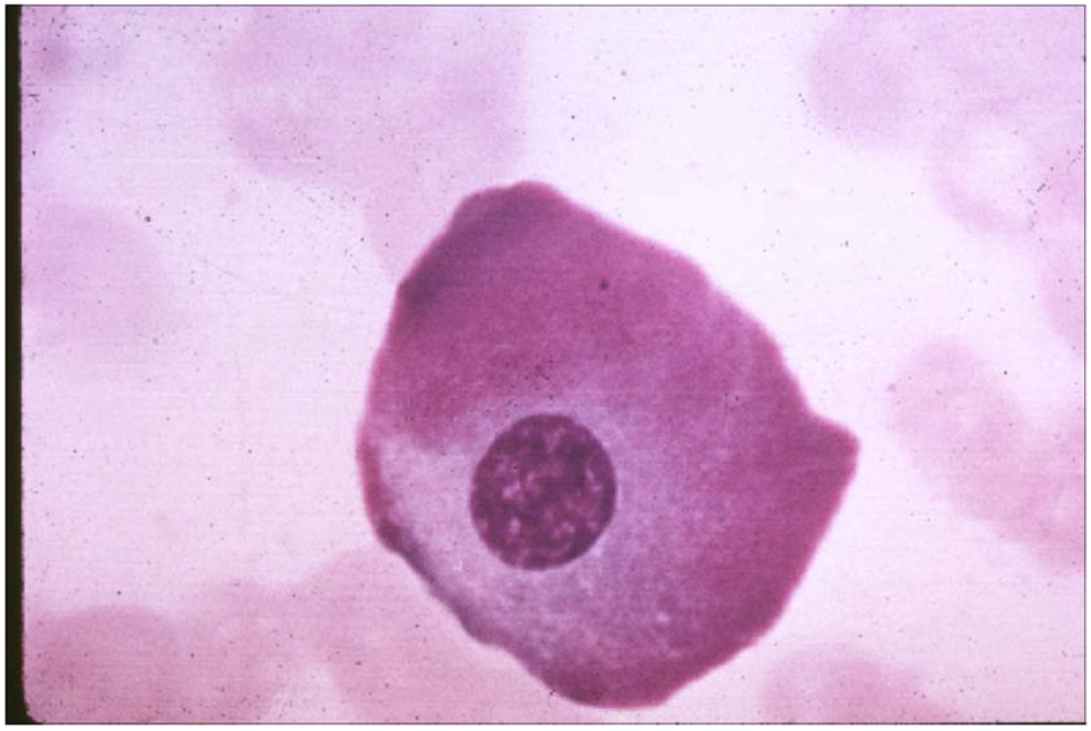


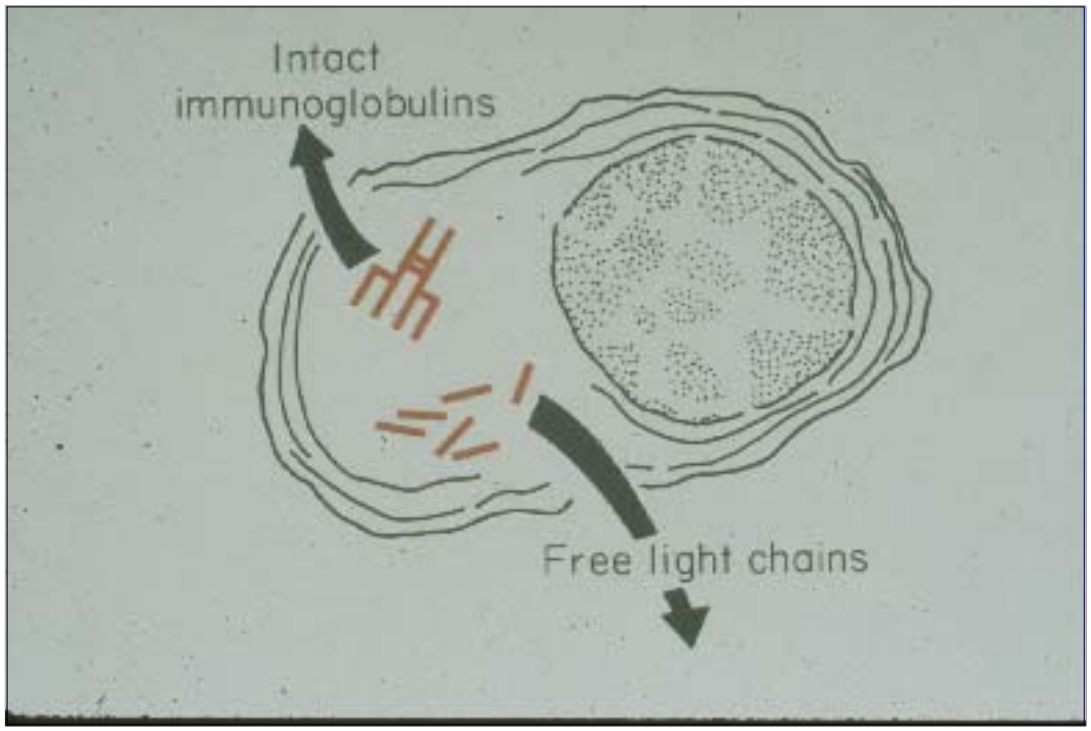






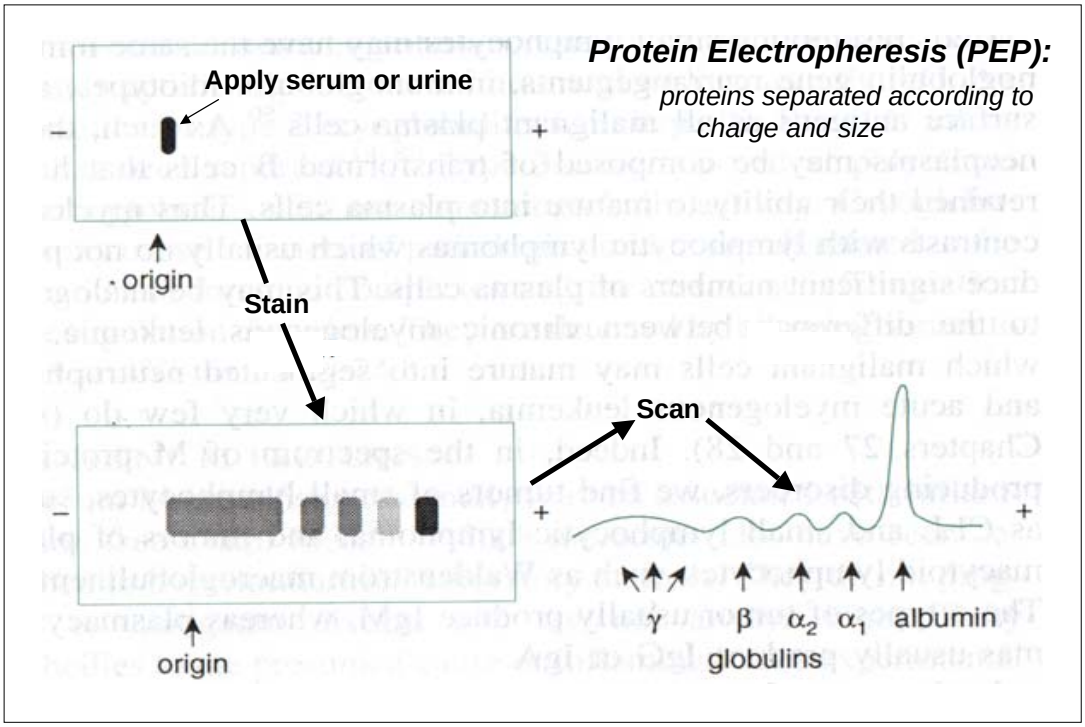




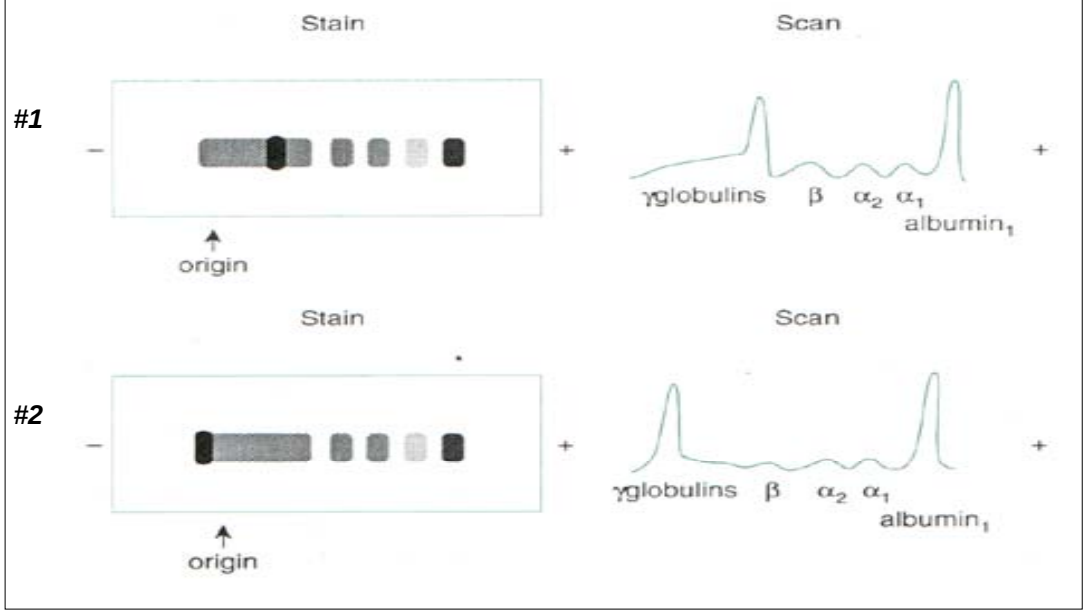

Intact
immunoglobulins
Free light chains

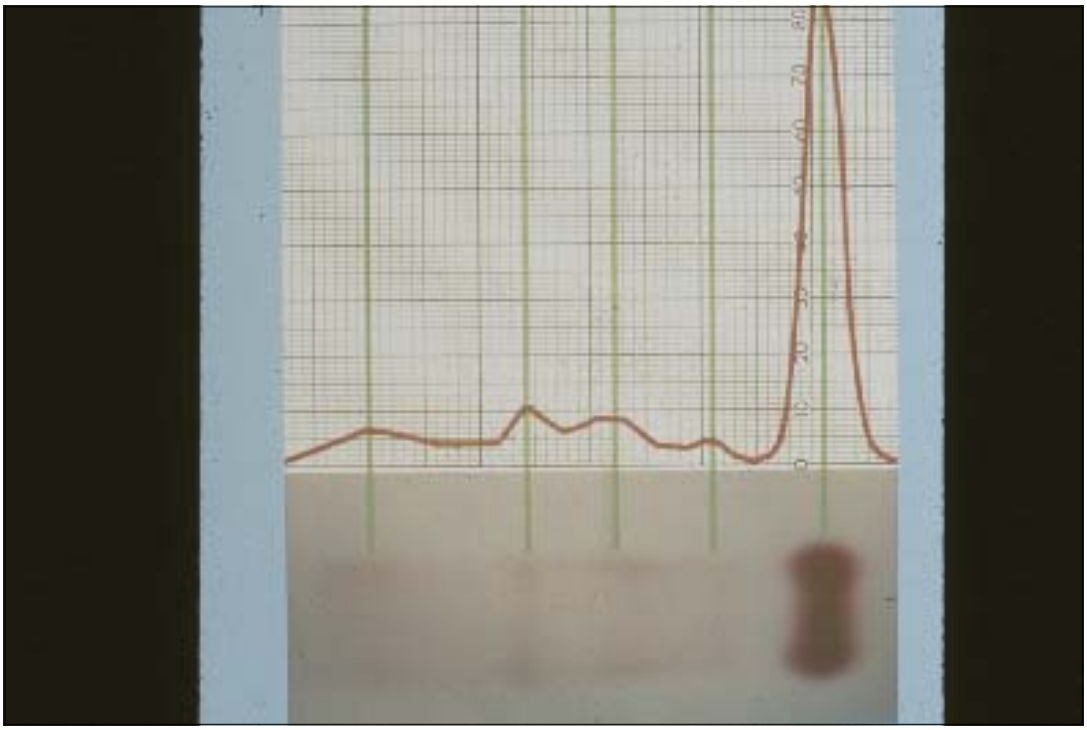
## *Diagnosis of Myeloma: Monoclonal Proteins*

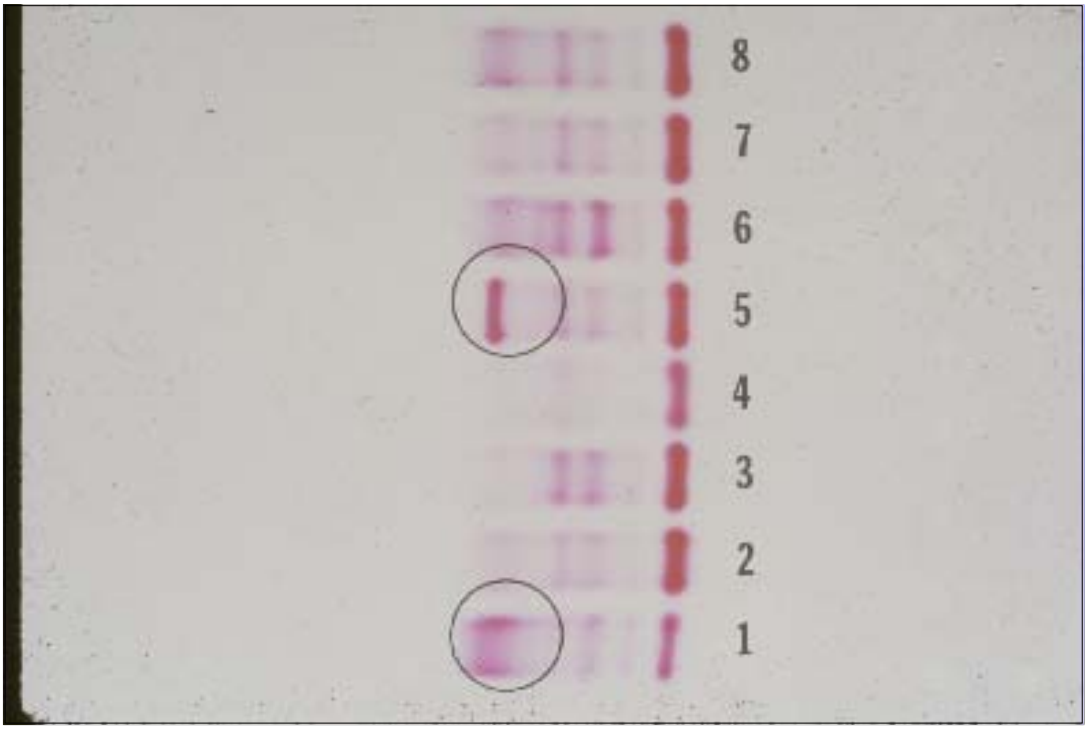
- **75-80% have serum monoclonal Ig**
  **(M-component, paraprotein, or 'spike' on electropheresis)**
- **10-20% make light chains only → rapid renal excretion → no paraprotein on serum protein electropheresis**
- **Non-secretory myeloma rare (< 1%)**
- **Other causes of monoclonal proteins**
  **(eg,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



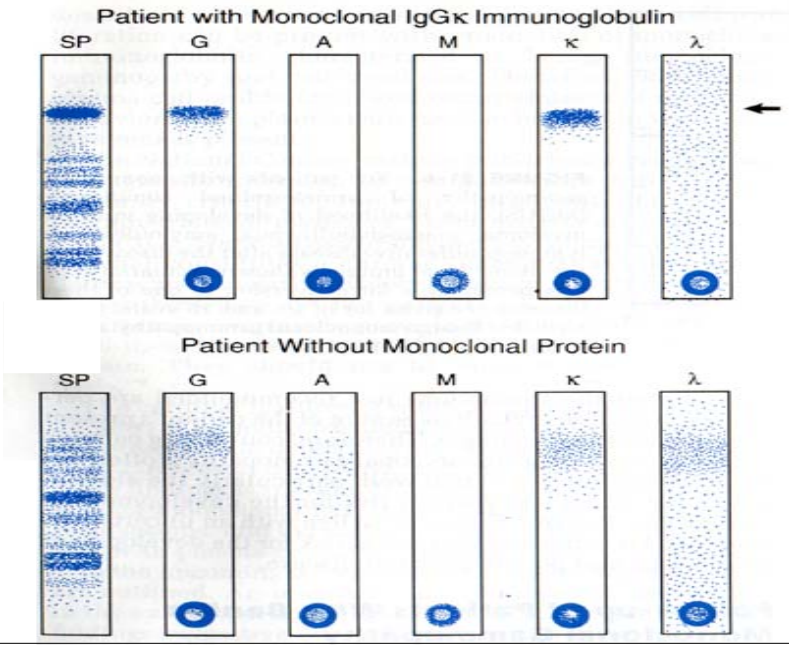
***Serum Protein Electrophereses in 2 Patients with Myeloma***



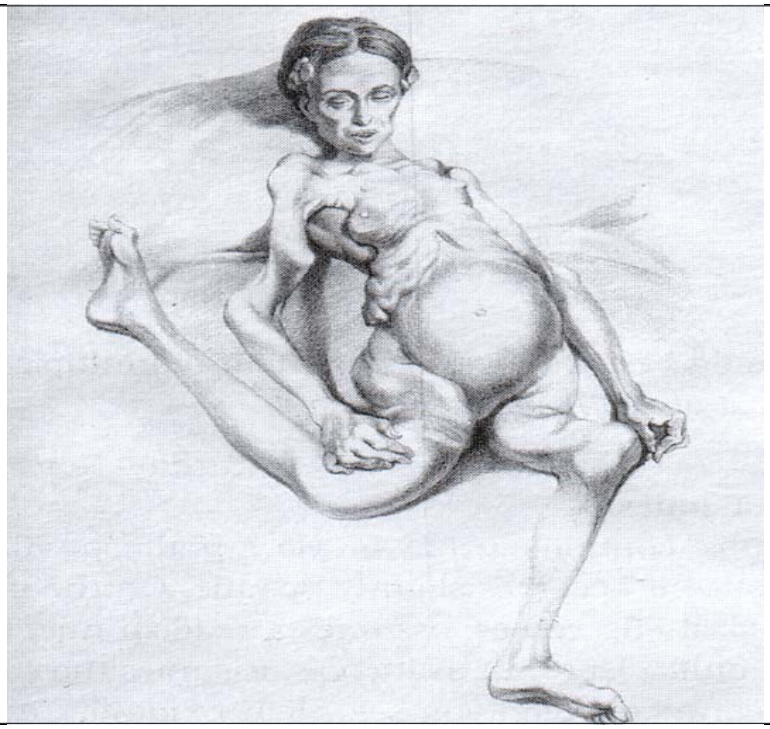


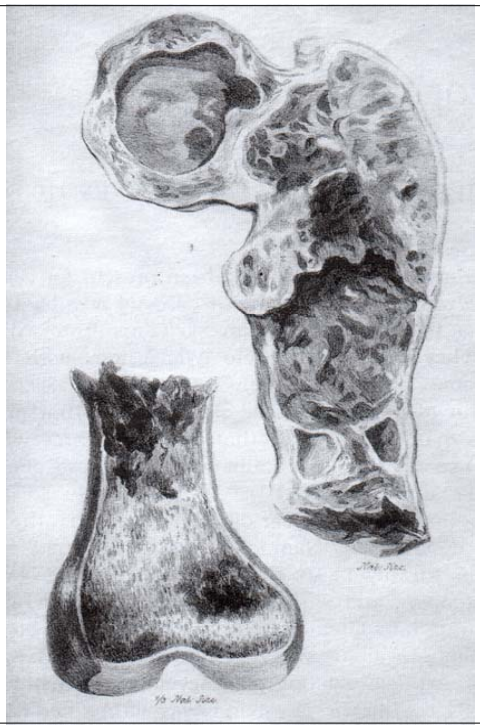

***Immunofixation Electropheresis***

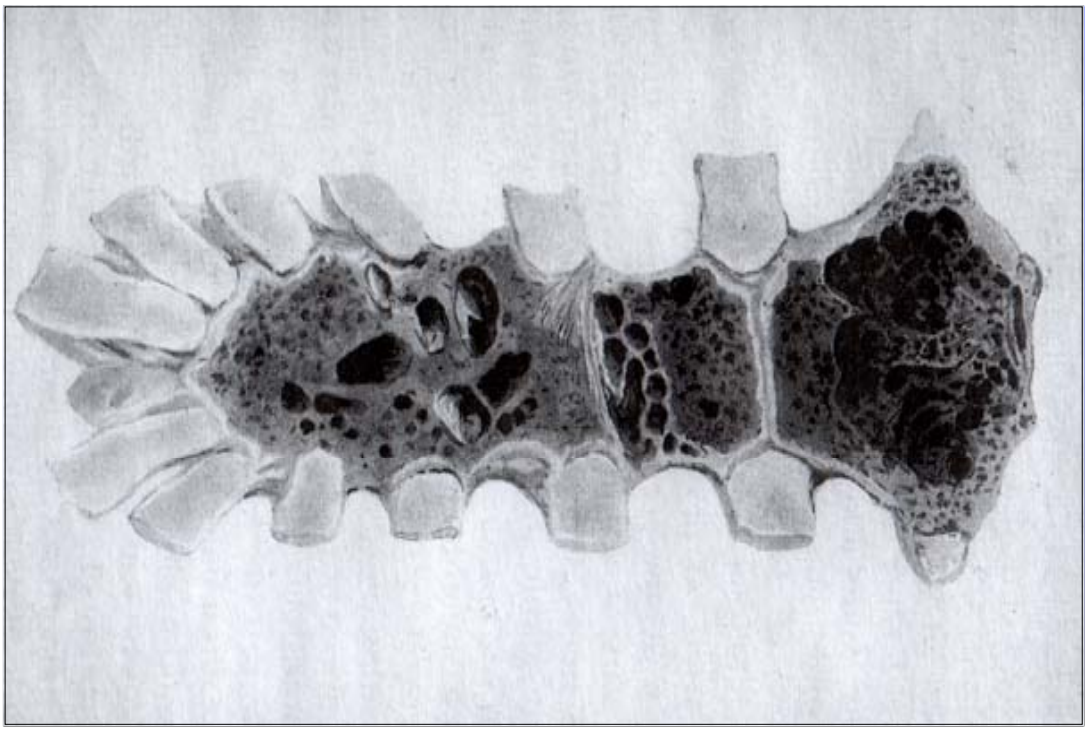


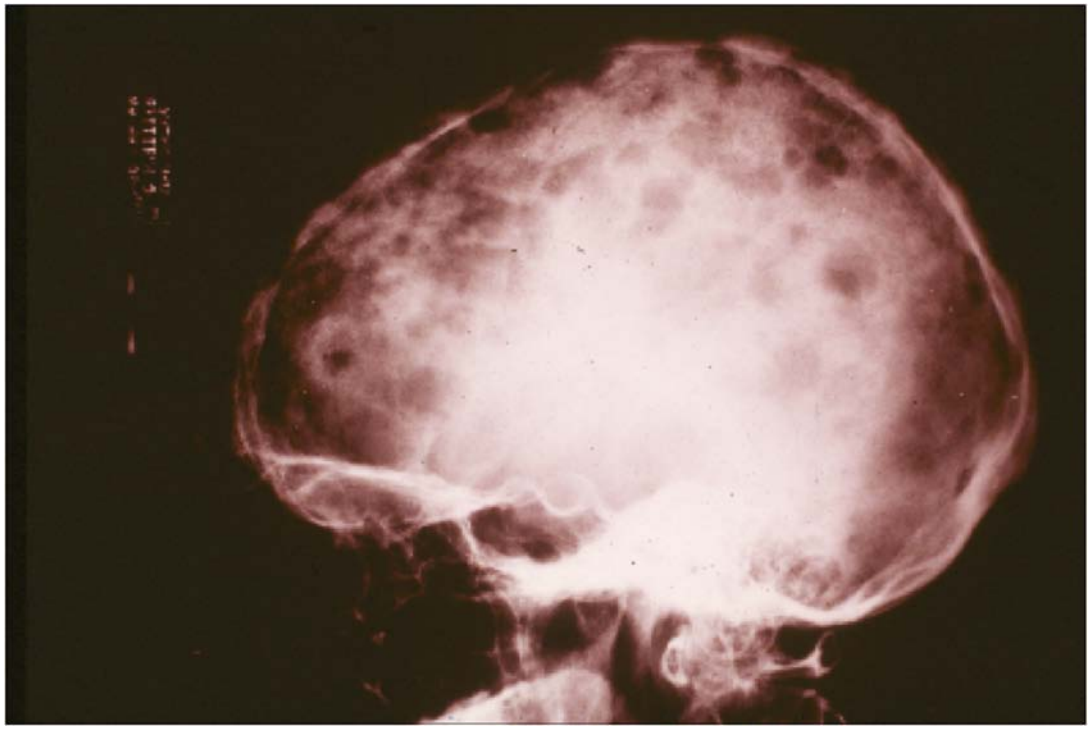
## *Bone Disease in Myeloma*

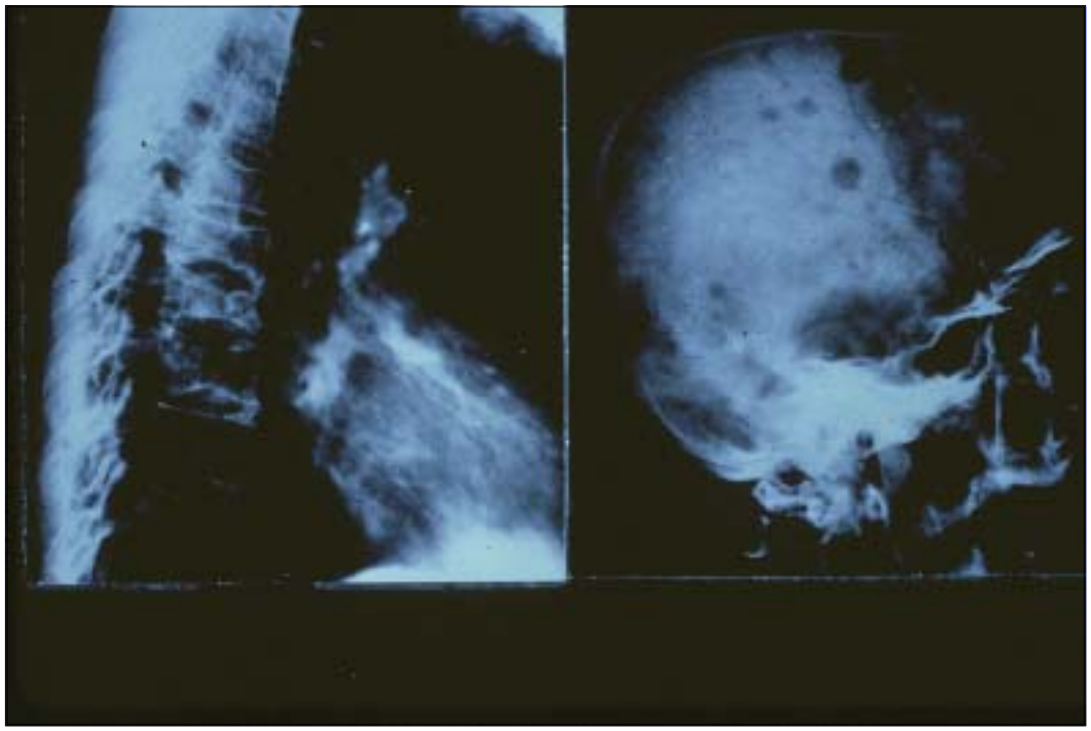
- Unbalanced osteoclast activity
- Radiographic manifestations
  - Osteoporosis almost invariable
  - Usually multiple lytic lesions
  - Axial skeleton involved (active marrow)
  - Osteoblastic reaction minimal
- Hypercalciuria and hypercalcemia

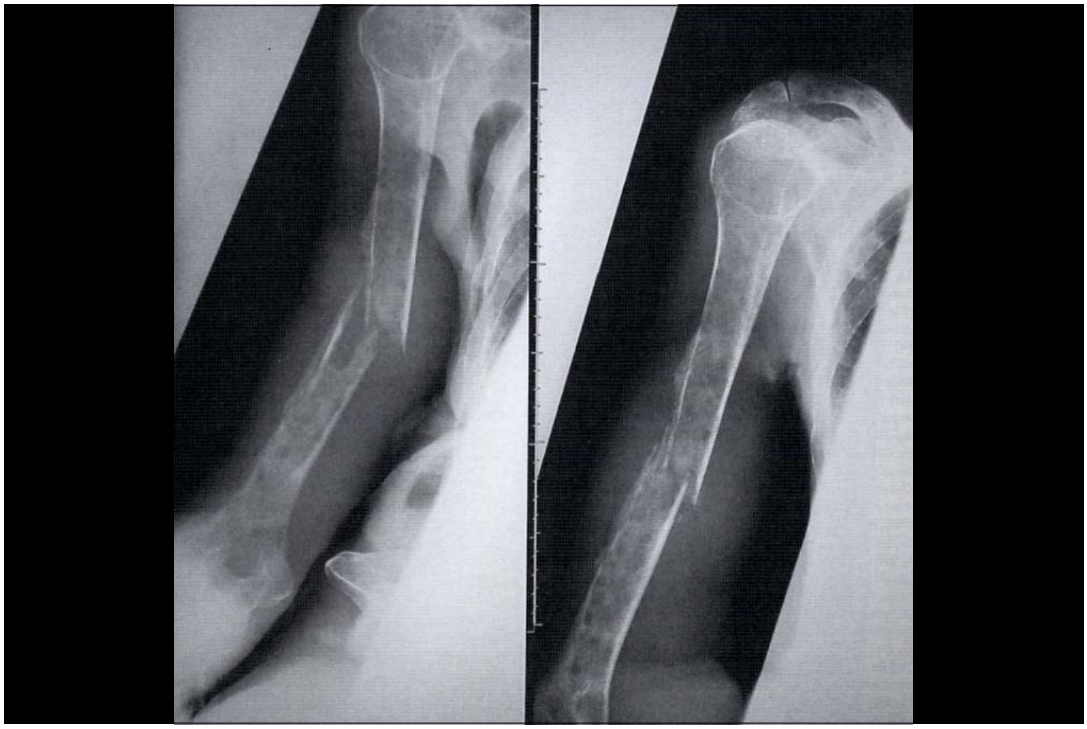


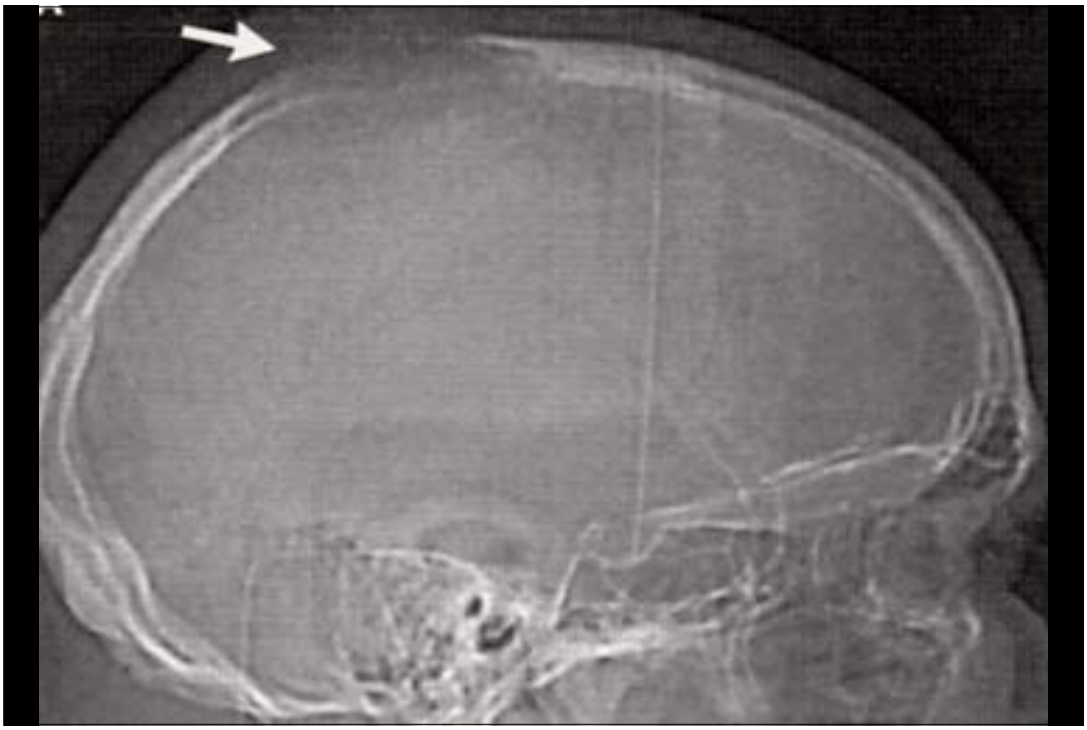


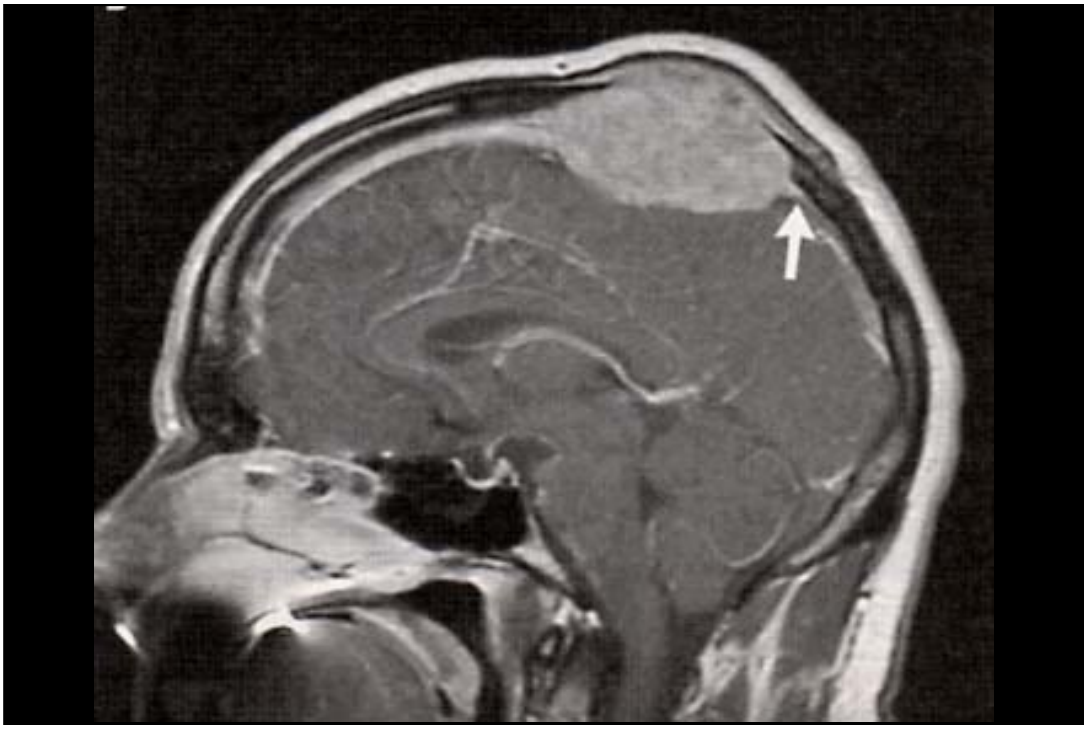












## Benign Monoclonal Gammopathy

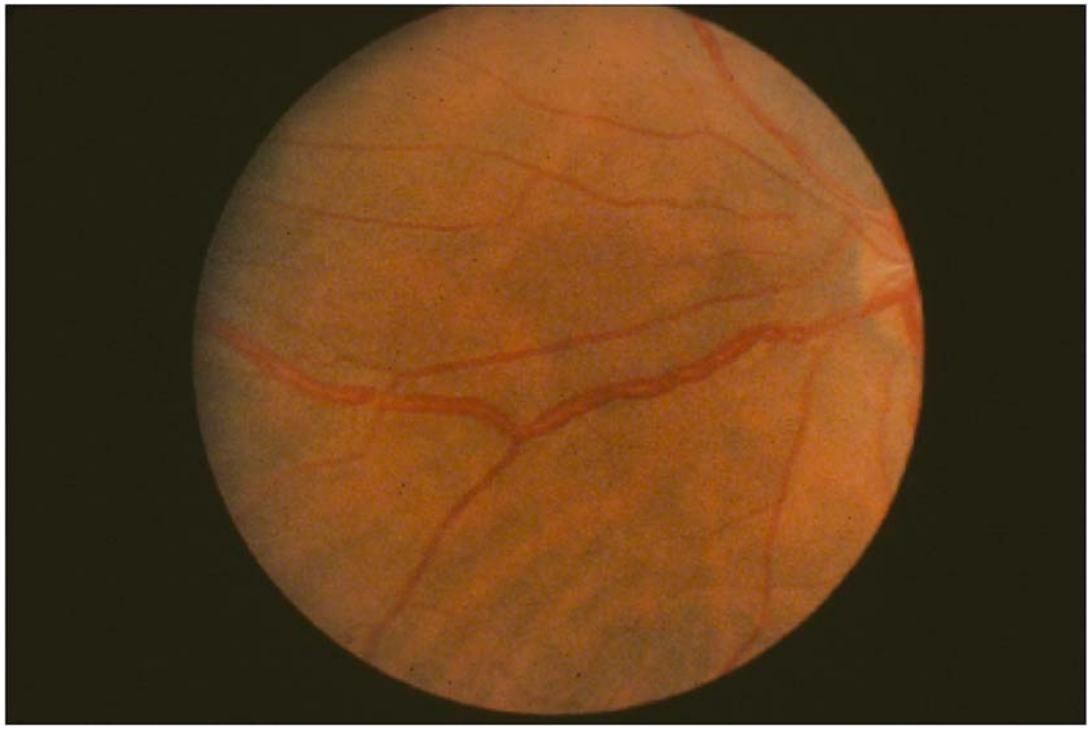
- Monoclonal Ig as isolated finding
- More common than myeloma
- No bone disease, anemia, renal dysfunction
- Most remain stable
- About 10% eventually develop classical myeloma

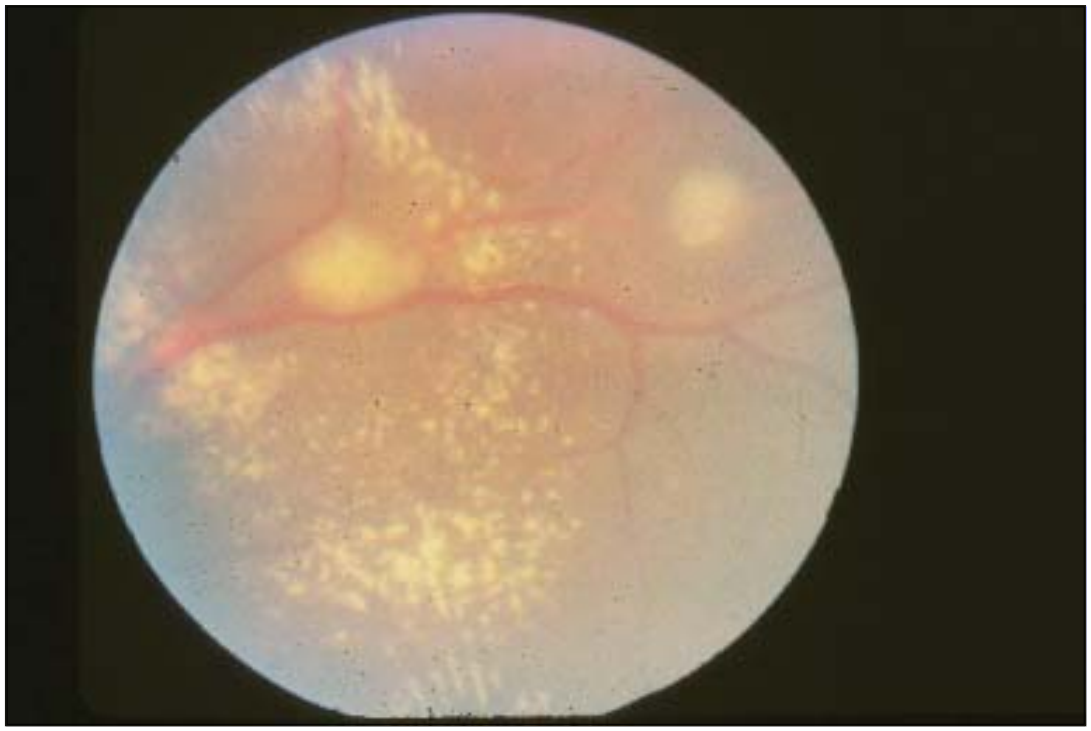
## *Myeloma at Presentation*

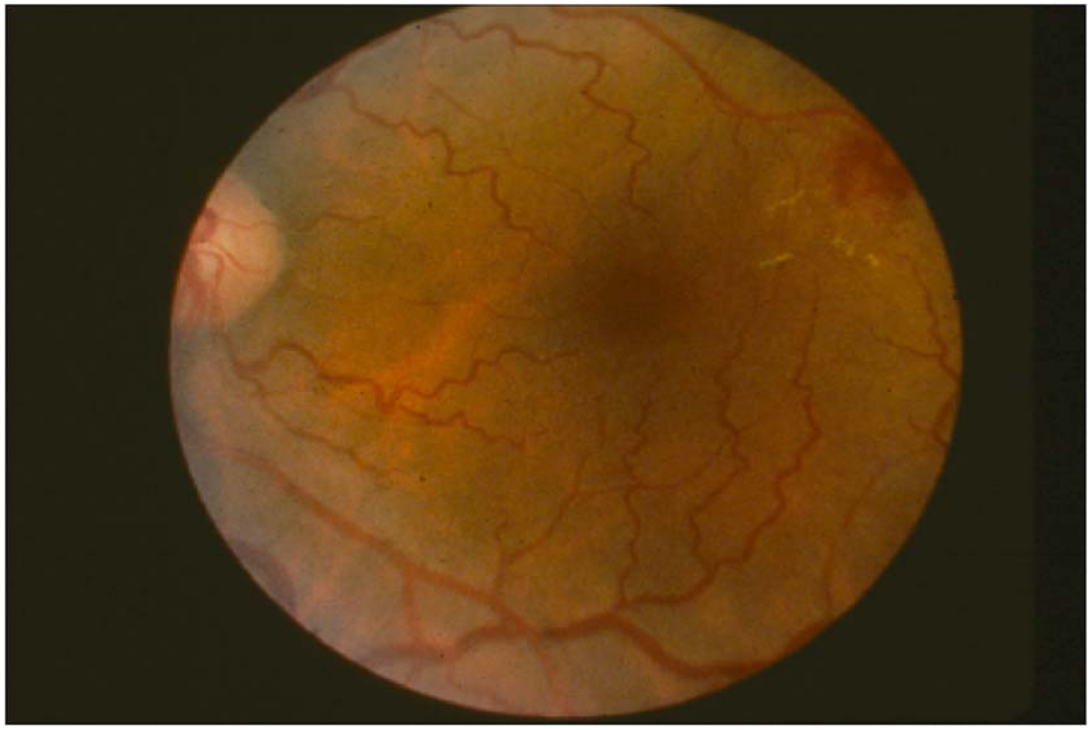
- Early - asymptomatic, incidental diagnosis
  - Paraprotein on electropheresis
  - Mild marrow plasmacytosis
  - Solitary plasmacytoma (10% of cases)
- Late - symptomatic
  - Bone pain (usually lower back)
  - Pneumococcal infection
  - Systemic symptoms (eg, weakness, weight loss)
    - Related to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

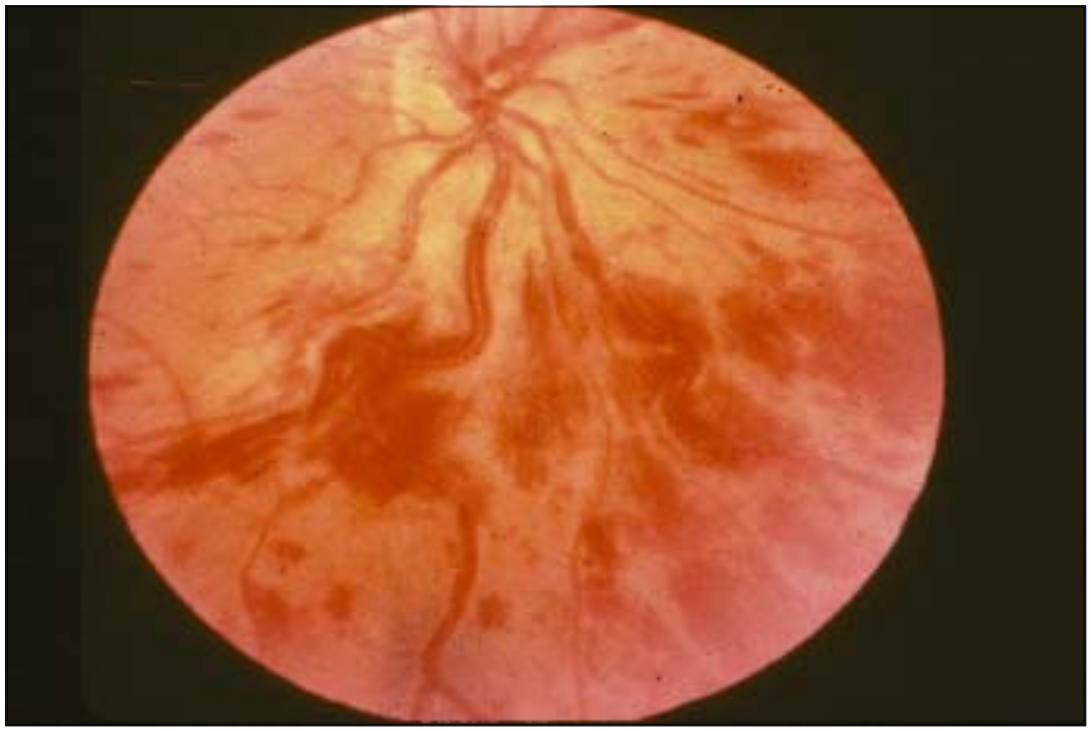
## Hyperviscosity Syndrome

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







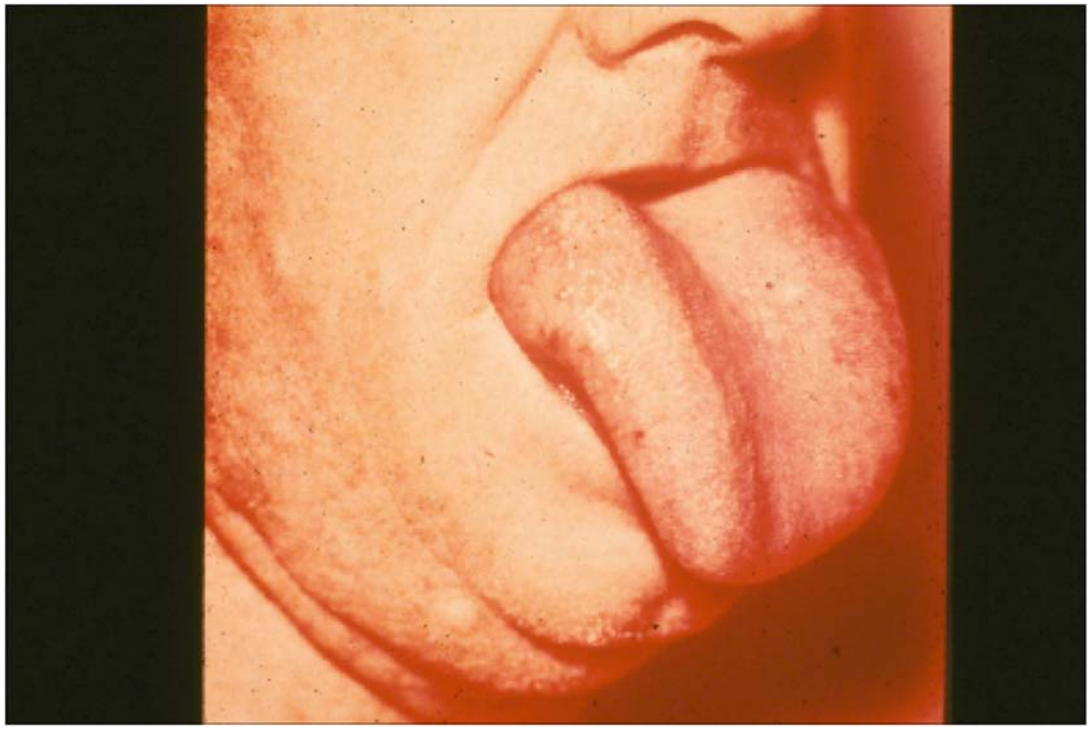


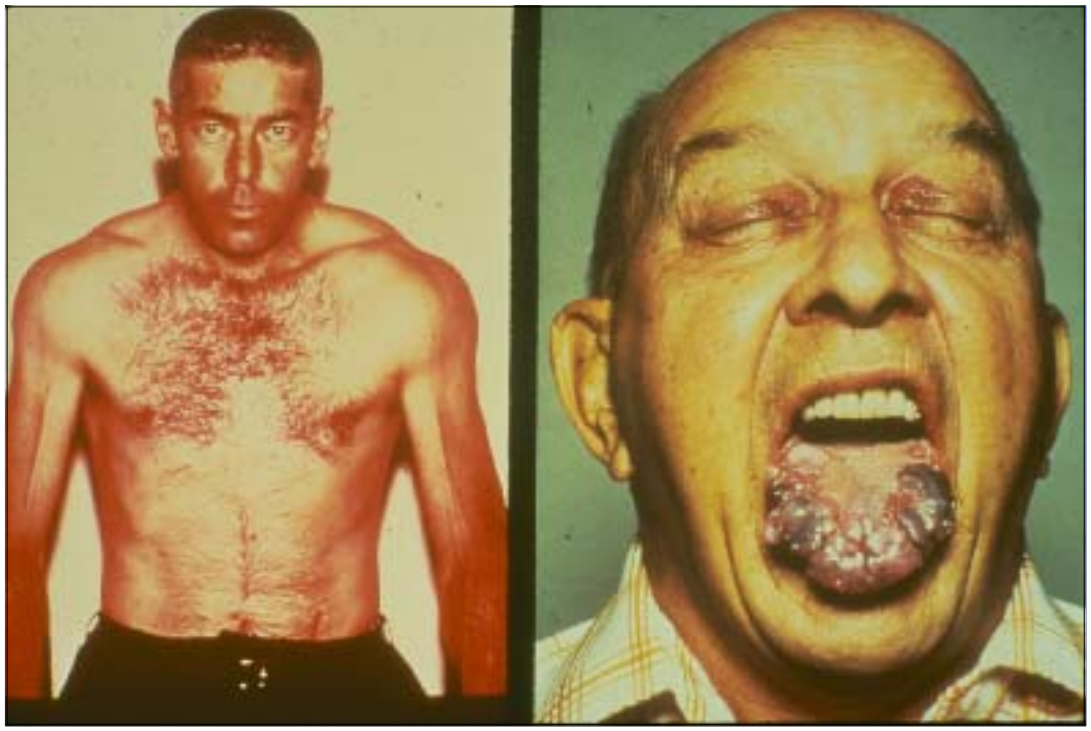
## *Immunological Features of Myeloma*

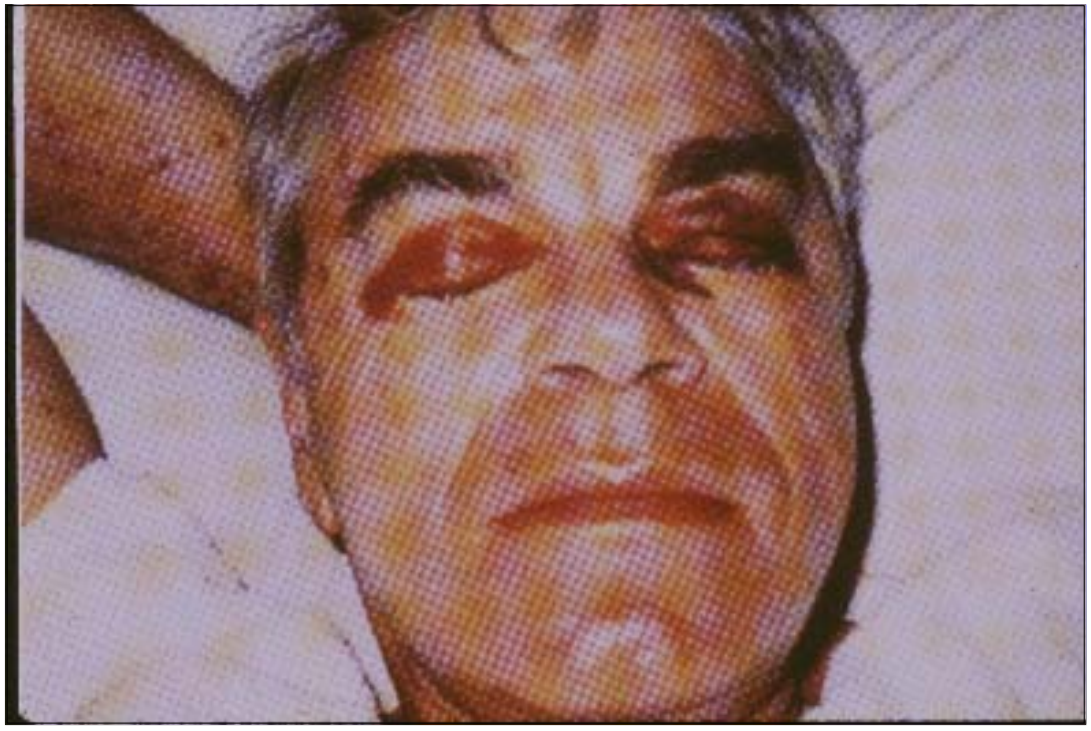
- Monoclonal Ig and/or monoclonal light chain
- ↓Levels of normal Ig's (hypogammaglobulinemia)
- Cellular immune responses usually preserved
- Bacterial infections common
  Early: S pneumoniae
  Late: S aureus, Gram negative rods

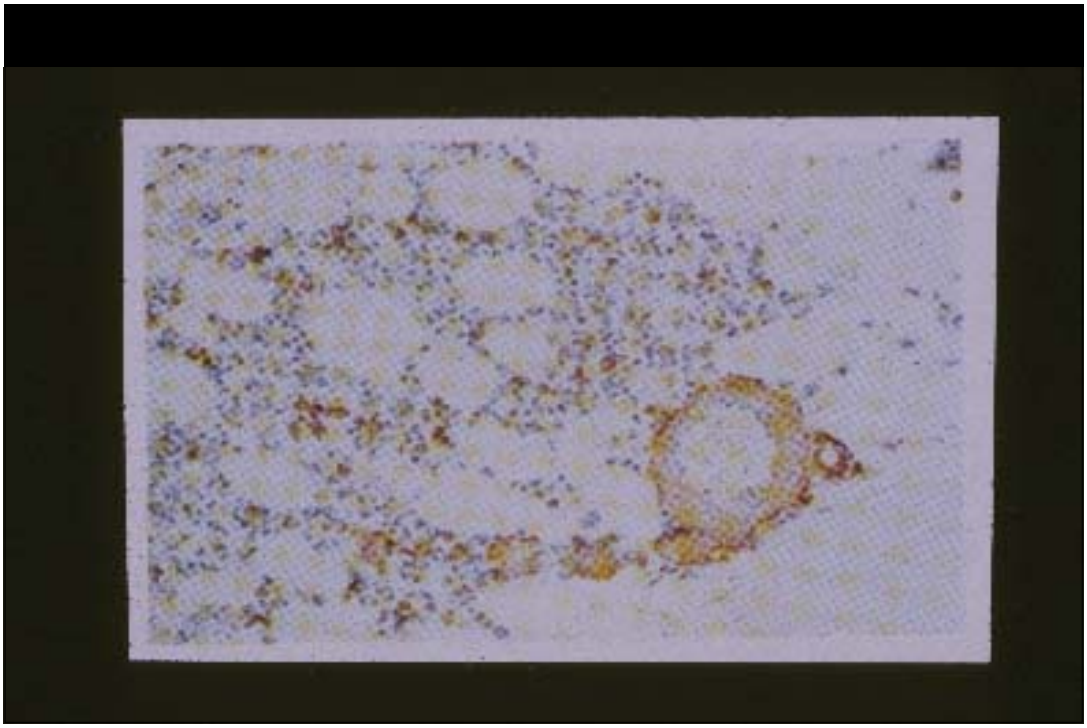
## *Amyloidosis in Myeloma*

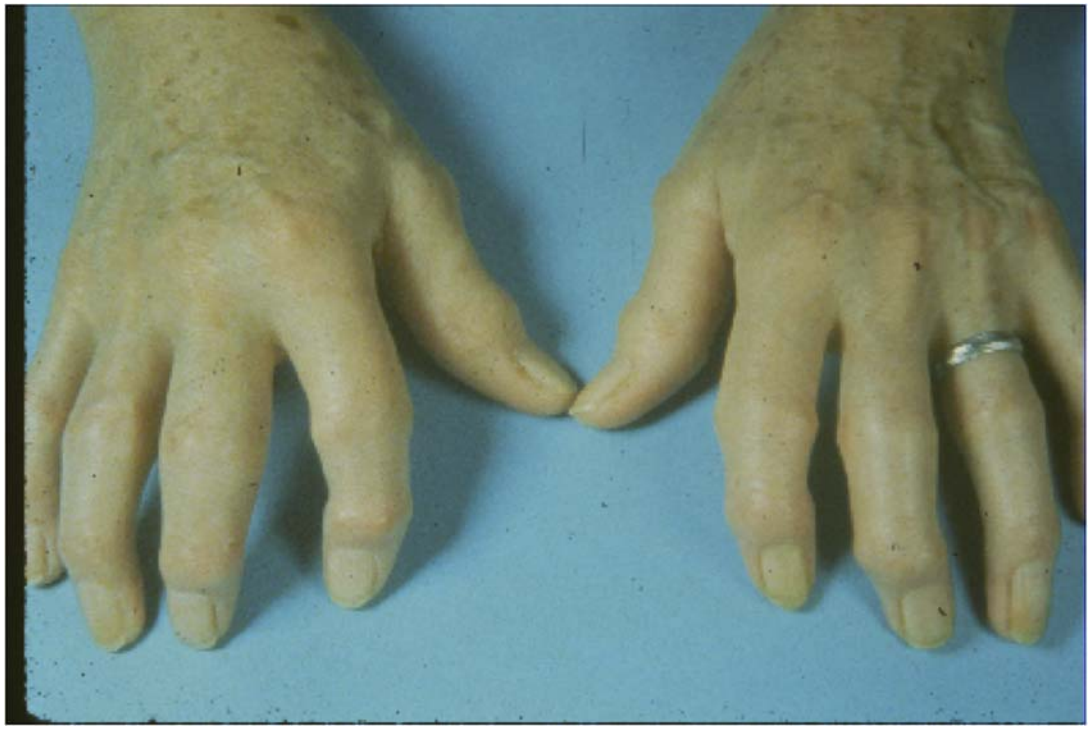
- Due to light chain deposition in tissues
- Incidence: λ amyloid > κ amyloid
- Organs commonly involved:
  Skin
  Tongue and GI
  Heart
  Peripheral nerves
  Kidneys
  Soft tissues
- No effective therapy, except ?stem cell transplant

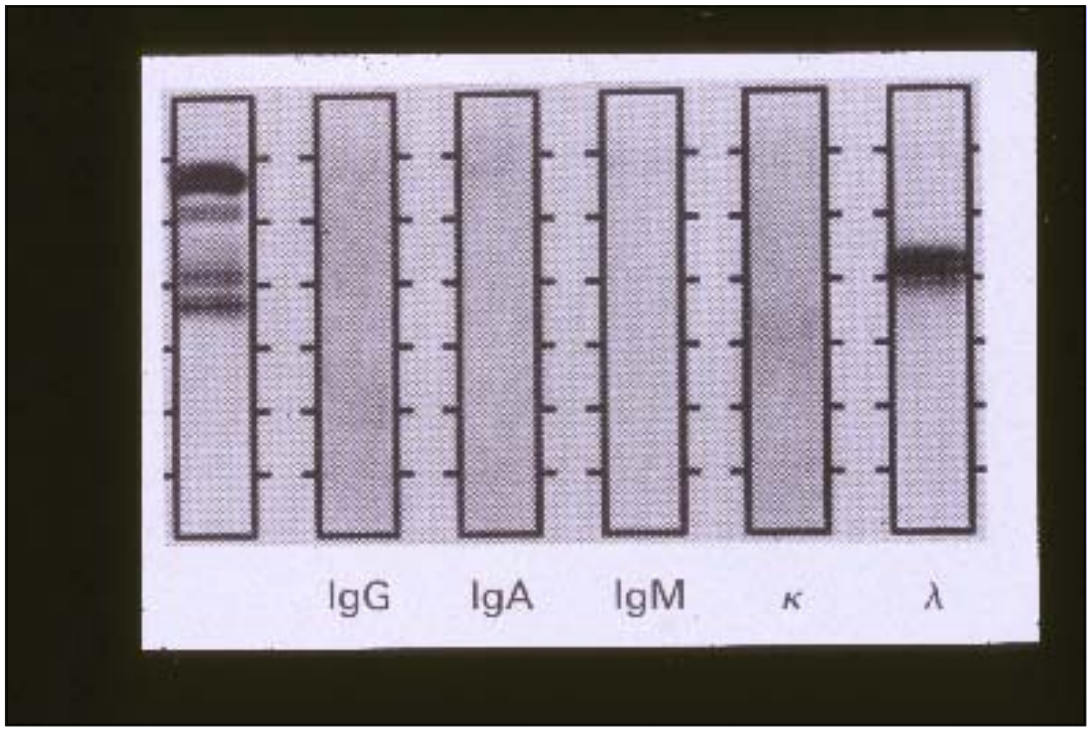











IgG
IgA
IgM
κ
λ

## *Therapy for Myeloma*

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