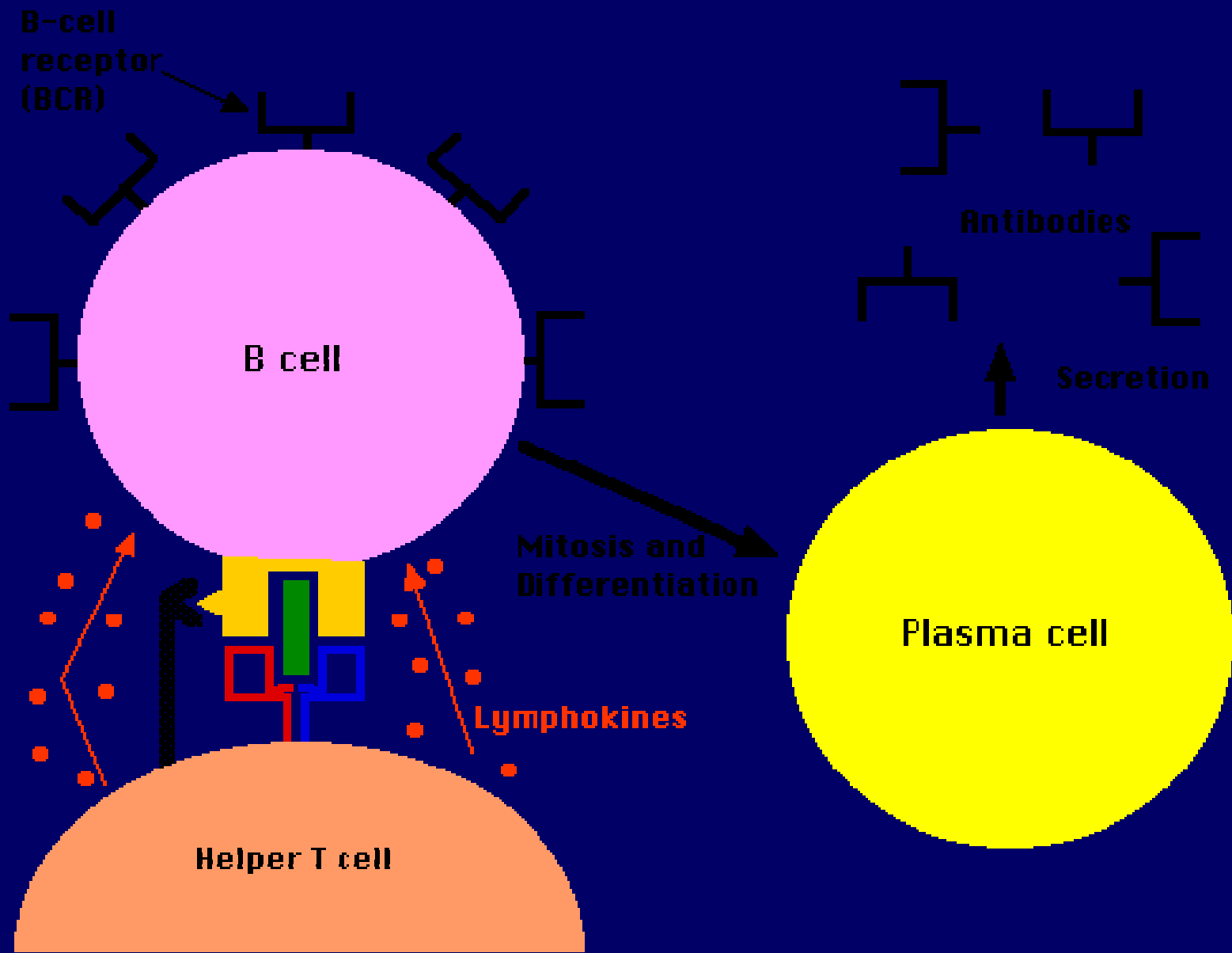
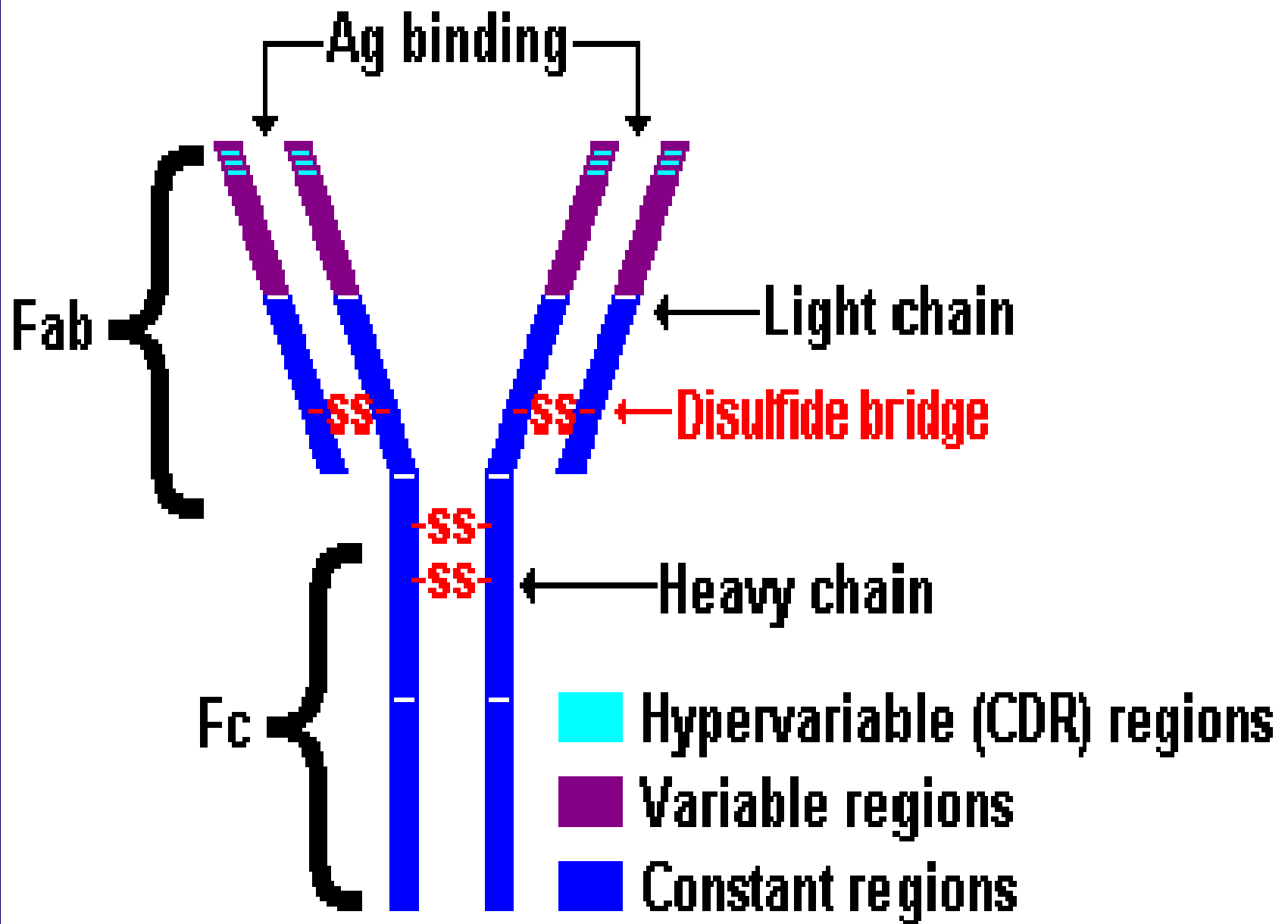


# MGUS

Is it Myeloma?

**PLASMA CELLS** are the mature form of B-lymphocytes that have acquired the complex skill of producing immunoglobulin molecules, better known as antibodies

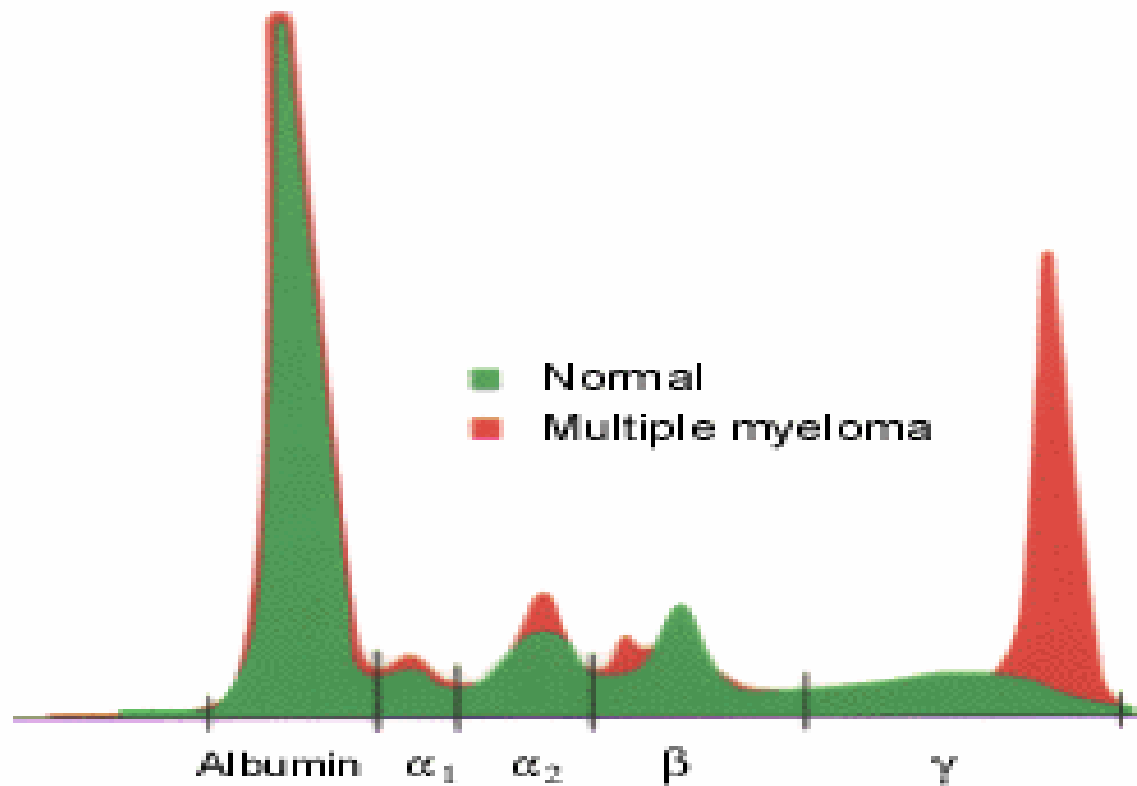




# Plasma cell neoplasms

- Result from expansion of a single clone of Ig-secreting B cells
- Characterized by the secretion of a single homogenous Ig product known as the **M-component**
- Wide spectrum, benign/ premalignant: MGUS & malignant: myeloma & Waldenstrom macroglobulinemia

## Serum Protein Electrophoresis

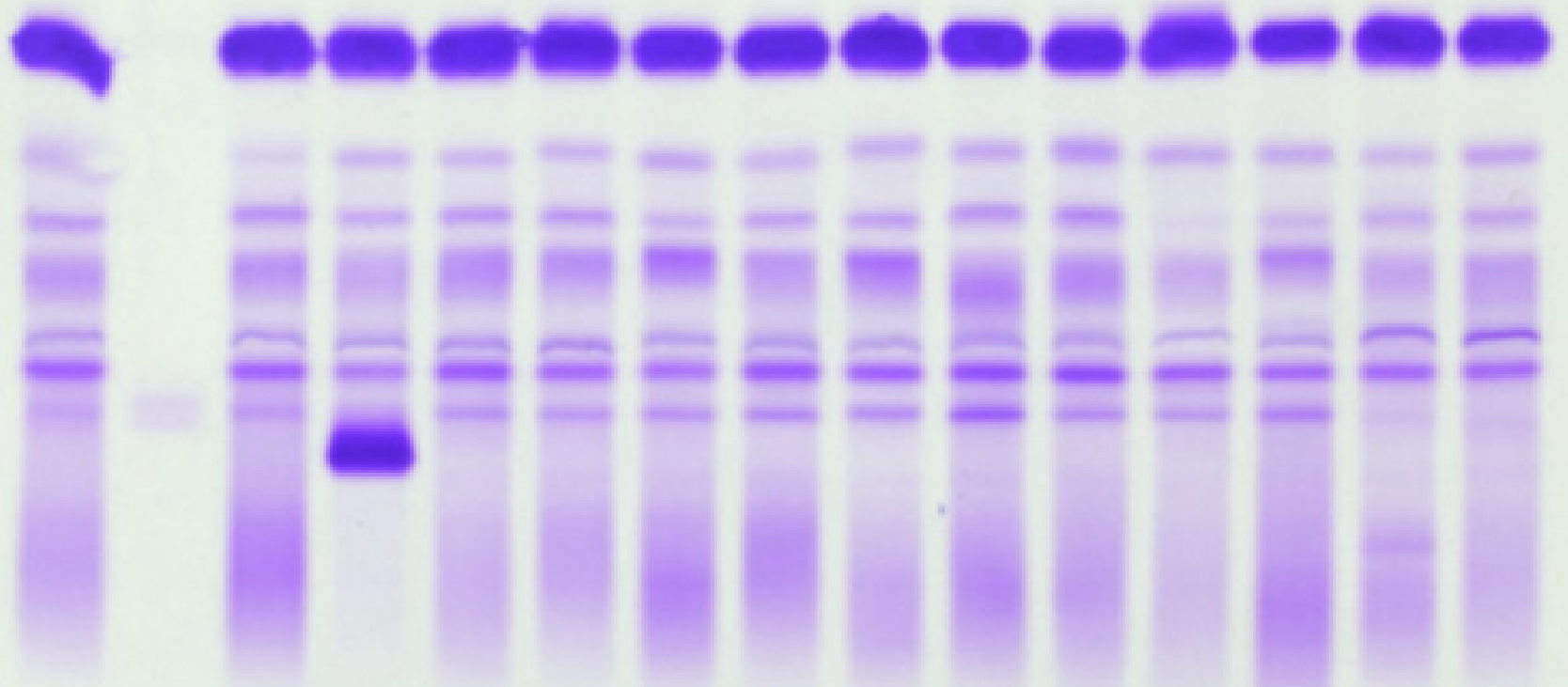


HYDRAGEL 15 HR

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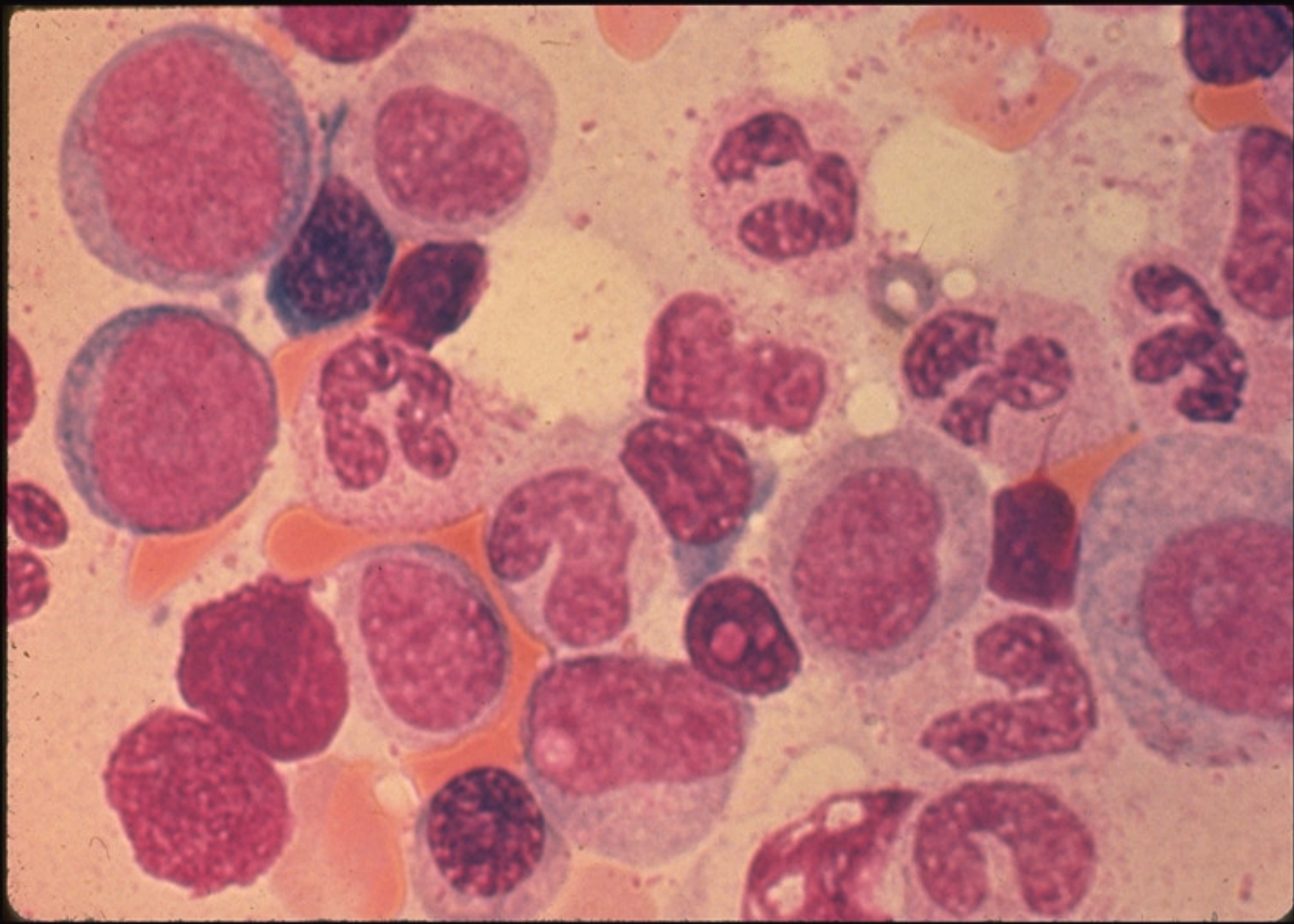
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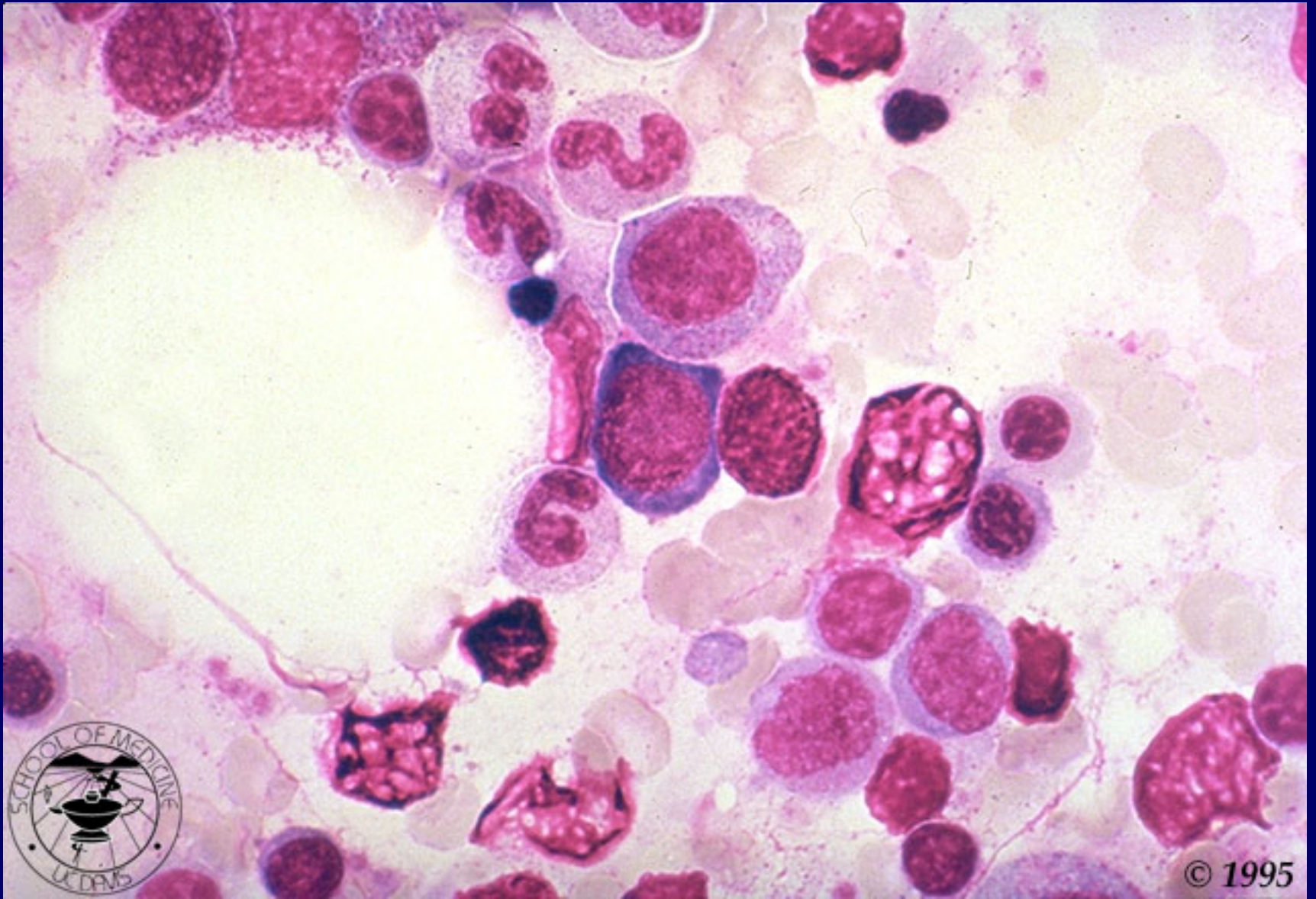
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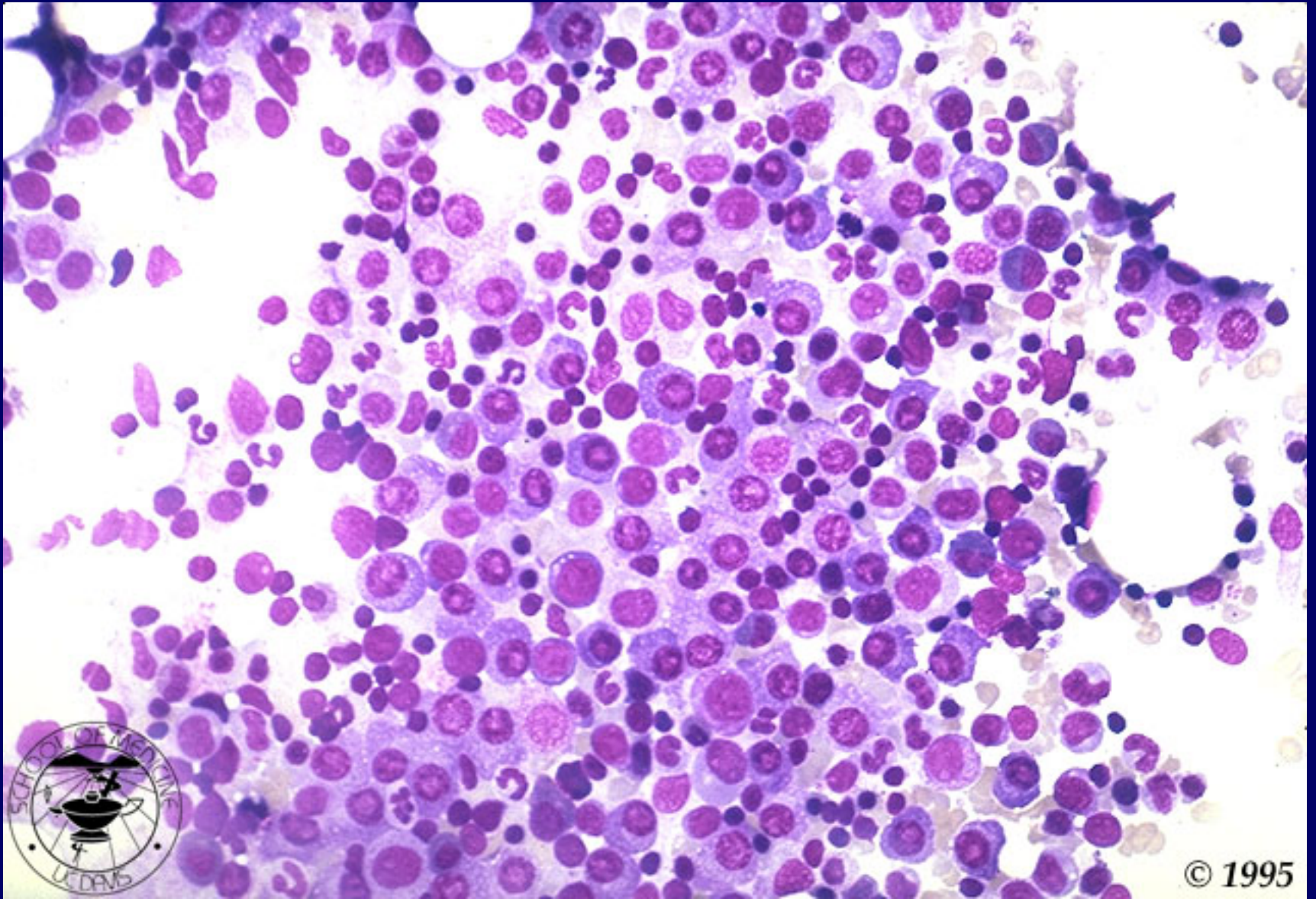
# Multiple myeloma

- **Characterized by a serum monoclonal protein, skeletal destruction, hypercalcemia, anemia & renal impairment**
- **Spectrum: localized, smoldering, indolent to aggressive multiple myeloma**
- **Diagnosis based on combination of pathological, radiological & clinical features**

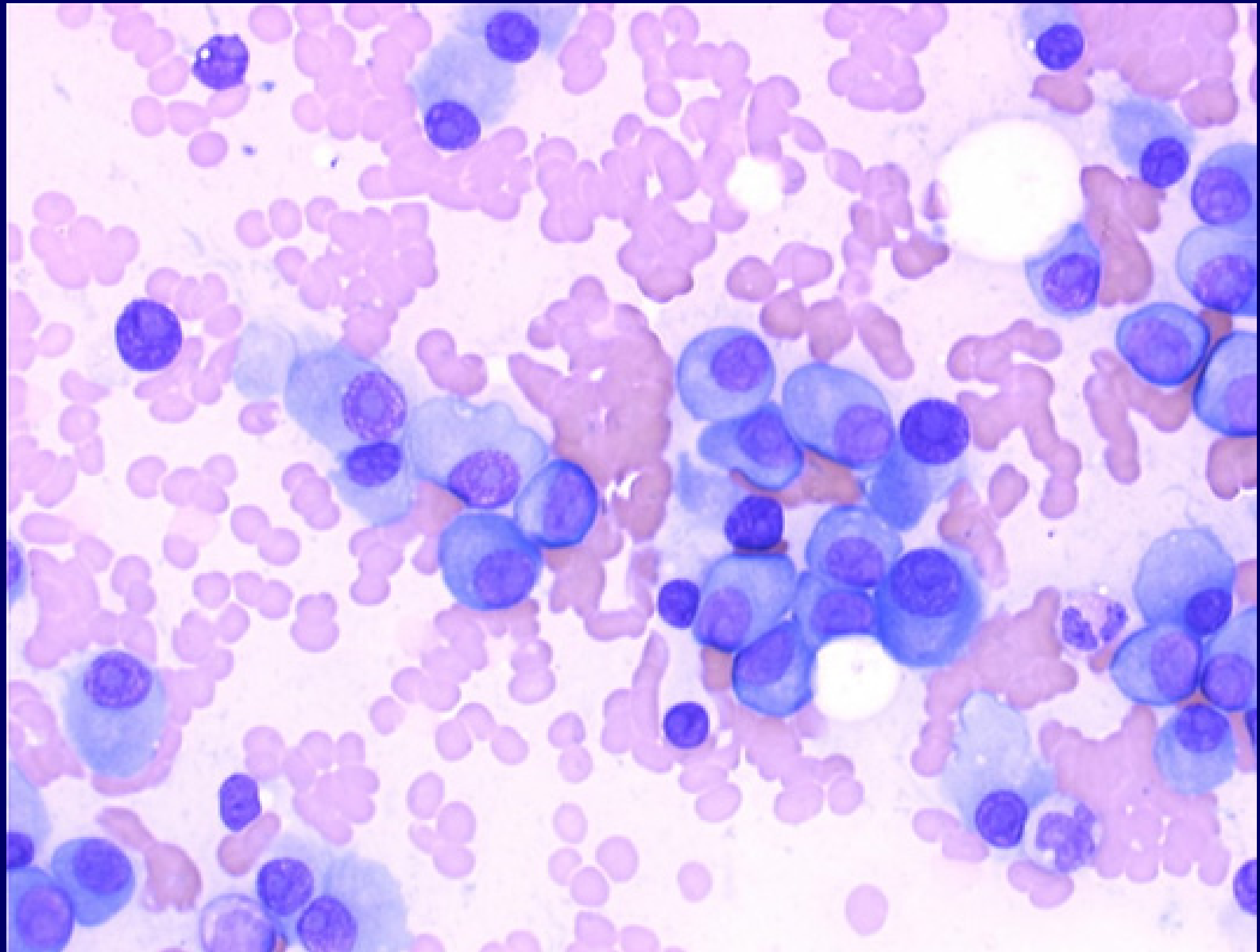




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# Diagnostic criteria for Multiple myeloma

- **Major**

- Marrow plasmacytosis > 30%
- Plasmacytoma on biopsy
- M component
  - Serum: IgG > 35 gm/l, IgA > 20 gm/l
  - Urine > 1 gm/24 hour B<sub>2</sub> protein

- **Minor**

- Marrow plasmacytosis: 10%-30%
- M component present but less than above
- Lytic bone lesions
- Reduced normal Igs less 50% normal

- **Diagnosis require a minimum of : one major and one minor or three minor criteria which must include the first two**
- **These criteria must be manifest in a *symptomatic patient* with progressive disease**

# Characteristics of plasma cell neoplasms

	MGUS	Smoldering myeloma	Indolent Myeloma
Plasma Cells(BM)	<10%	10-30%	>30%
M-component	IgG<35 IgA<20	IgG>35 IgA>20	IgG 35-70 IgA 20-50
Lytic bone lesions	None	None	<4
Symptoms Infection	None	None	None

\*Patients are asymptomatic

\*Creatinine & Ca are normal

# Case One

MGUS

- 55 year old *asymptomatic* male was referred by GP in 1987 for assessment re abnormal protein electrophoresis
- **Investigations**
  - IgG kappa paraprotein 20g/L
  - Normal calcium & creatinine
  - Normal skeletal survey

## Follow up

Remained *asymptomatic* upon annual clinical review  
IgG levels around 23.9 (Normal up to 16 & myeloma  
levels > 35)

All tests are otherwise normal

# Characteristics

- **The presence of a serum monoclonal protein(IgA,IgG or IgM) usually at a conc <30 gm/L**
- **Fewer than 10% plasma cells in marrow**
- **No or only small amount of BJP in urine**
- **Absence of lytic lesions, anemia, hypercalcemia and renal insufficiency**
- **Stability of the M protein & failure to develop other abnormalities on follow up**

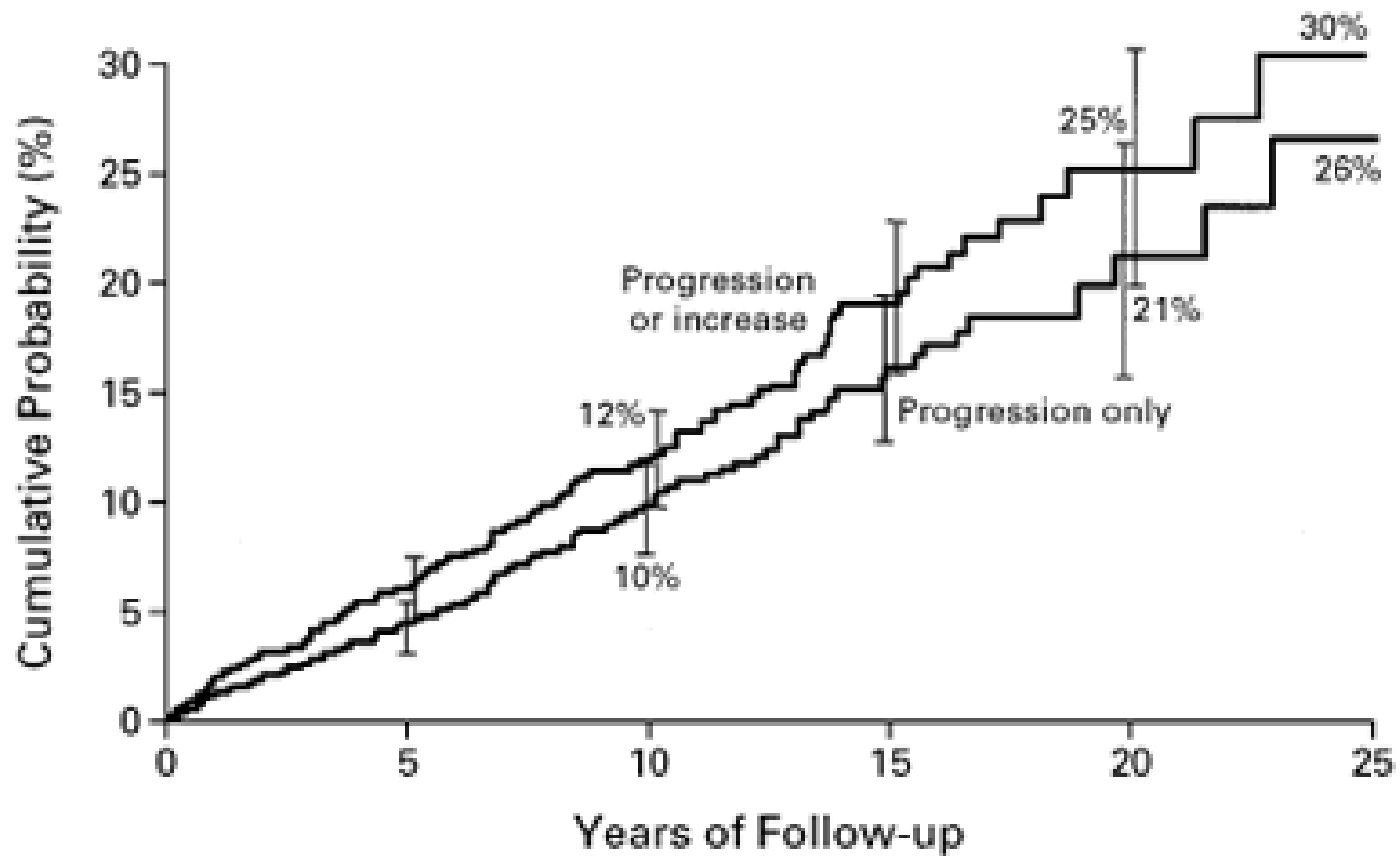
# Prevalence

- *Kyle et al. NEJM, vol.354, no.13 .FEB.2006* identified all living residents of Olmsted County, Minnesota. SPE done on 21,463 of the 28,038 residents 50 yrs of age or older (76.6 %)
- MGUS in 694 (3.2 %). 5.3 % in 70 yrs or older and 7.5% in 85 yrs persons
- higher in men (4.0 % vs. 2.7%,  $P < 0.001$ )
- Ig level less than 10 g /L in 63.5 % and at least 20 g /L in 4.5%
- Immunoparesis in 27.7 % of 447
- 21.5% of 79 had a monoclonal urinary light chain
- IgG in 68.9%, IgM in 17.2%, IgA in 10.8%, and biclonal in 3.0%
- kappa in 62.0%

- In another study published at the *NEJM* by Kyle *et al* Vol. 346 (8);Feb 02
- 1384 patients with a serum monoclonal prot. conc. of 30 gram/l or less , were followed up for 11,009 person-year (median 15.4 years,range 0 to 35 years)
- The initial monoclonal prot. Values ranged from unmeasurable (visible as small band on SPE but not quantifiable on densitometry ) to 30 g/L

# Outcomes of MGUS

- During follow up , *multiple myeloma, lymphoma with an IgM serum monoclonal prot., primary amyloidosis, macroglobulinemia, CLL, or plasmacytoma developed in 115 patients (8%)*
- the cumulative probability of progression to one of those disorders was :10% at 10 yrs , 21% at 20 yrs , 26% at 25 yrs
- **The overall risk of progression is 1% /yr**



NO. AT RISK    1384                    867                    423                    177                    56                    17

# Risk factors for progression

- The only predictors of progression are *concentration & the type of the M protein*
- IgM or IgA had an increased risk of progression
- Reduced conc. of uninvolved Igs was **not** a risk factor

# Management of MGUS

- *It is essential to differentiate a patient with stable MGUS from one who develops MM*
- A **careful history & physical examination** should be performed
- **Initial studies** necessary for evaluation of MGUS in an asymptomatic patient include :
  - **FBC**
  - **Serum Ca & Cr**
  - **SPE**
  - **Quantitation of Igs**
  - **Urine analysis for B-J prot**

- *If the above test results are normal* :SPE should be repeated in 3-6 m, and if stable at annual intervals thereafter
- *If the initial M prot. value is >20 g/l* : a 24 h urine specimen should be obtained for electrophoresis and immunofixation, a skeletal bone survey and a bone marrow may be considered( if clinically indicated), *if no evidence of MM is found*; SPE should be repeated in 3-6 m and , if stable; followed annually

# Summary

- Patients with MGUS should be monitored **annually** with *careful clinical assessment & SPE to detect progression to MM*
- Early detection of disease progression should improve quality of life & prevent complications like renal failure & pathological fractures

# Case Two

- 49 year old *asymptomatic* male was referred by GP in 1998 for assessment re abnormal protein electrophoresis
- **Investigations**
  - IgG kappa paraprotein 28gm/l, IgM 0.3gm/l, IgA 0.2 gm/l
  - Normal calcium & creatinine & Hb
  - Normal skeletal survey
  - Negative BJ protein on casual urine testing
  - Bone marrow showed 60% plasma cells

## Diagnosis?

- 1) MGUS
- 2) Smoldering myeloma
- 3) Indolent myeloma
- 4) Multiple myeloma

## Action?

- 1) Discharge from clinic
- 2) Regular follow-up
- 3) Start treatment

# Follow up

	IgG levels	Hb	Lytic lesions	Bone Marrow
1999	27	124	No	
2000	29	124	No	
2001	30.8	114	No	
2002	41.3	103	No	55%

- Patient developed recurrent *S. pneumoniae* in 2002
- Creatinine & Ca remained normal

- This man developed symptoms in the form of recurrent *S. pneumoniae* sepsis
- His disease has progressed from Indolent myeloma to Multiple myeloma
- The haematologist is considering treatment with chemotherapy

# Case Three

- 63 year old *asymptomatic* female was referred by GP in 1989 for assessment re abnormal protein electrophoresis
- **Investigations**
  - IgG kappa paraprotein 40.7gm/l, IgM 0.8gm/l, IgA 1 gm/l
  - Normal calcium & creatinine & Hb
  - Normal skeletal survey
  - Negative BJ protein on 24 hour urine collection
  - Bone marrow showed 20% plasma cells

## **Diagnosis?**

- 1) MGUS
- 2) Smoldering myeloma
- 3) Indolent myeloma
- 4) Multiple myeloma

## **Action?**

- 1) Discharge from clinic
- 2) Regular follow-up
- 3) Start treatment

year	IgG	Hb	lytic lesions
1990	55 gm/l	123	none
1995	62 gm/l	115	none
1996	68 gm/l	112	One lytic lesion right mid femoral shaft
1997	65 gm/l	111	THJR. Femoral head biopsy showed myeloma

\*Calcium & creatinine remained normal

\*The patient remained asymptomatic

As a consequence of the development of a pathological fracture should this patient be commenced on chemotherapy?

year	IgG	Hb	lytic lesions
1990	55 gm/l	123	none
1995	62 gm/l	115	none
1996	68 gm/l	112	One lytic lesion right mid femoral shaft
1997	65 gm/l	111	THJR. Femoral head biopsy showed myeloma. Had RT
1999	66 gm/l	112	Two new bony lesions
2002	68.5 gm/l	108	No new lesions

\*Calcium & creatinine remained normal

\*The patient remained asymptomatic

\*Patient had no chemotherapy at any stage

# Summary

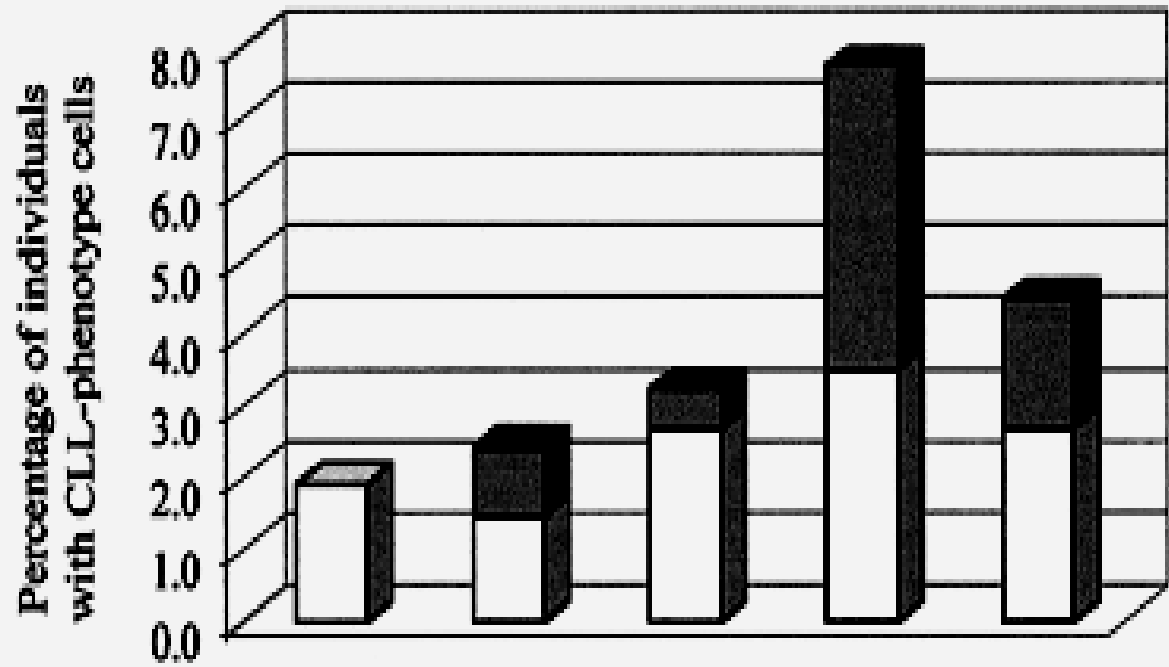
- *Early myeloma* includes smoldering & indolent myeloma
- *Treatment* is reserved for patients with *symptomatic disease* or disease where short term complications can be anticipated, otherwise follow up is recommended

# Monoclonal B Cell Lymphocytosis

- **CLL is the most common leukemia in the Western world, affecting 2- 6 individuals per 100 000/yr**
- **Diagnosis requires  $>5 \times 10^9/L$  circulating monoclonal B lymphocytes with a  $CD5^+CD23^+$  phenotype and weak or no surface Ig expression**
- **Diagnosis requires morphology, immunophenotype and/or PCR amplification of Ig heavy-chain gene rearrangement**

- 910 outpatients > 40 yrs, age- and sex-matched to the general population with normal hematological parameters
- Monoclonal B lymphocytes with the characteristics of "indolent" CLL are present in 3.5% of adults with normal FBC

*Rawstron et al, Blood, 15 July 2002, Vol. 100, No. 2, pp. 635-639*



Age group:		40-49	50-59	60-69	70-79	80-89
Number with CLL cells present/Total	Male:	5/132	3/103	5/88	5/61	3/41
	Female:	0/130	2/103	1/99	6/82	2/71

*Ghia et al (Blood, March 2004, Vol. 103, No. 6, pp. 2337-2342)*, phenotyped PB cells from 500 healthy subjects > 65 yrs with no history or suspicion of malignancies and no evidence of lymphocytosis, Monoclonal population of lymphocytes found in 3.8% (19 cases)

# **Diagnostic criteria of CLL (all of the following)**

- 1. Lymphocytes  $> 5 \times 10^9/l$**
- 2. Duration of lymphocytosis  $> 2$  months**
- 3. Bone marrow lymphocytes  $> 30\%$**
- 4. Flow cytometry findings in the majority of lymphocytes**
  - A. Kappa or lambda monoclonality**
  - B. CD5<sup>+</sup>, CD19<sup>+</sup>, CD23<sup>+</sup>, CD20 weak or positive**
  - C. Cyclin D1 negative, CD22 weak or negative**