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Multiple Myeloma

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Definition

Multiple myeloma is a neoplastic plasma-cell disorder that is characterized by clonal proliferation of malignant plasma cells in the bone marrow microenvironment, monoclonal protein in the blood or urine, and associated organ dysfunction.

Epidemiology

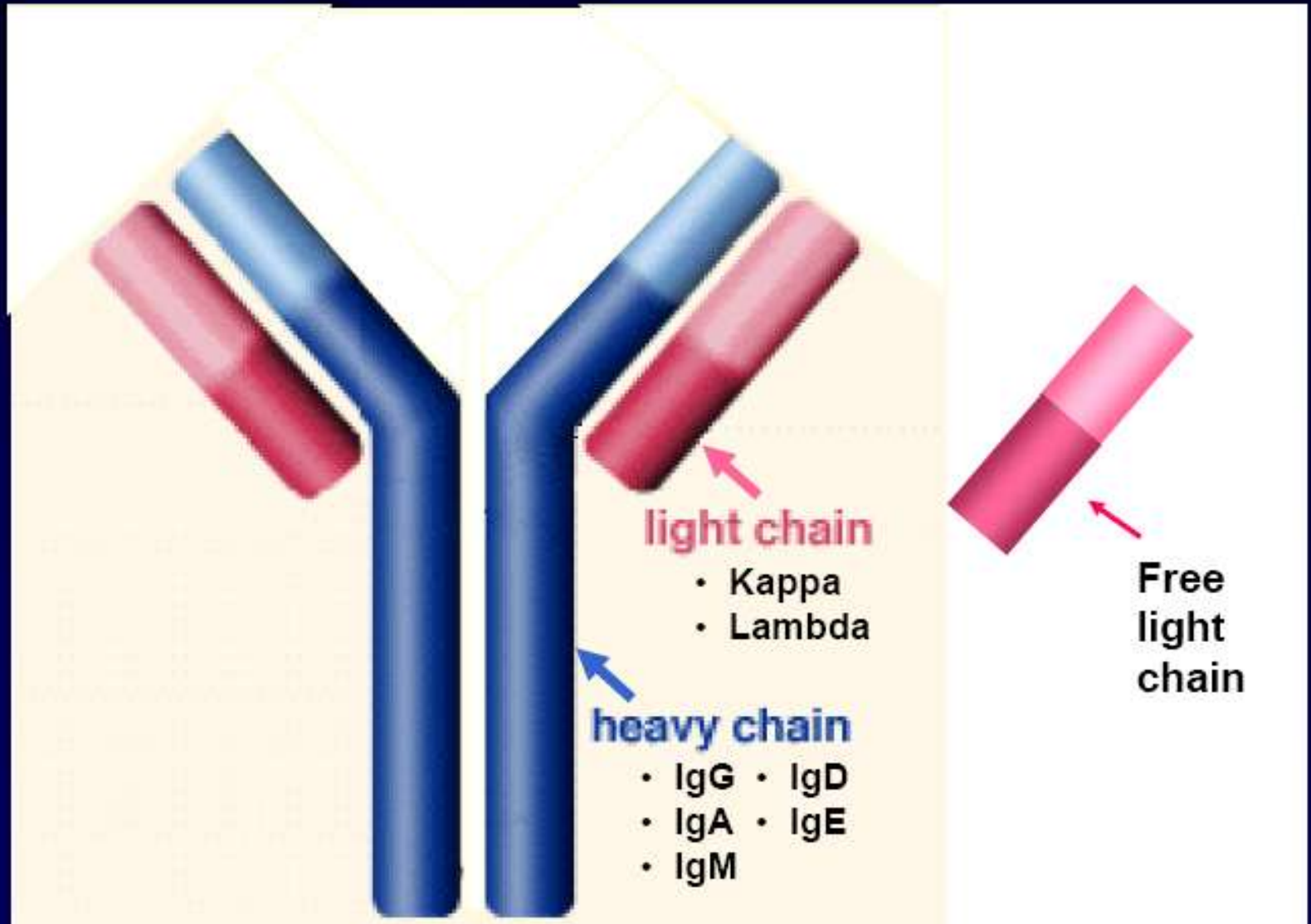
- It accounts for approximately 1% of neoplastic diseases and 13% of hematologic cancers. In Western countries, the annual age adjusted incidence is 5.6 cases per 100,000 persons.
- The median age at diagnosis is approximately 70 years; 37% of patients are younger than 65 years, 26% are between the ages of 65 and 74 years, and 37% are 75 years of age or older.
- In patients presenting at an age under 60 years, 10-year survival is approximately 30%

Age-adjusted Incidence per 100,000

	Male	Female
White	6.2	4.1
Black	11.8	10.0

Normal Ig structure

IgG κ
IgG λ
IgA κ
IgA λ
IgD κ
IgD λ
IgE κ
IgE λ
IgM κ
IgM λ

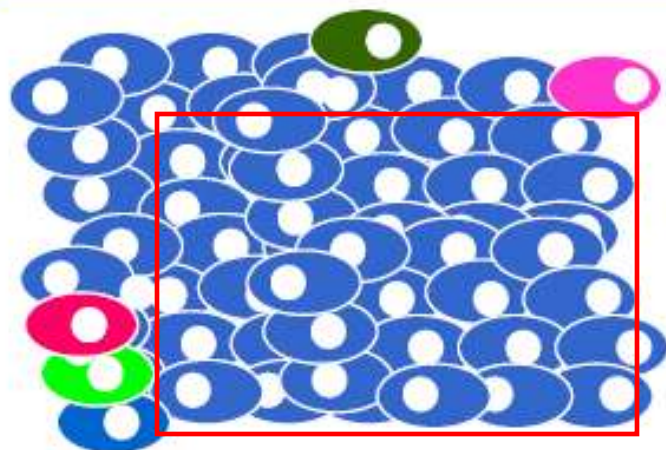




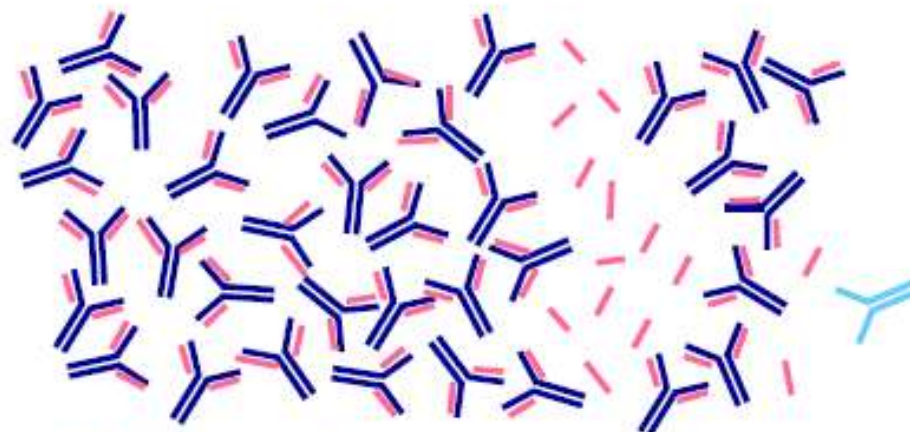
Normal



Many different types
of antibodies!

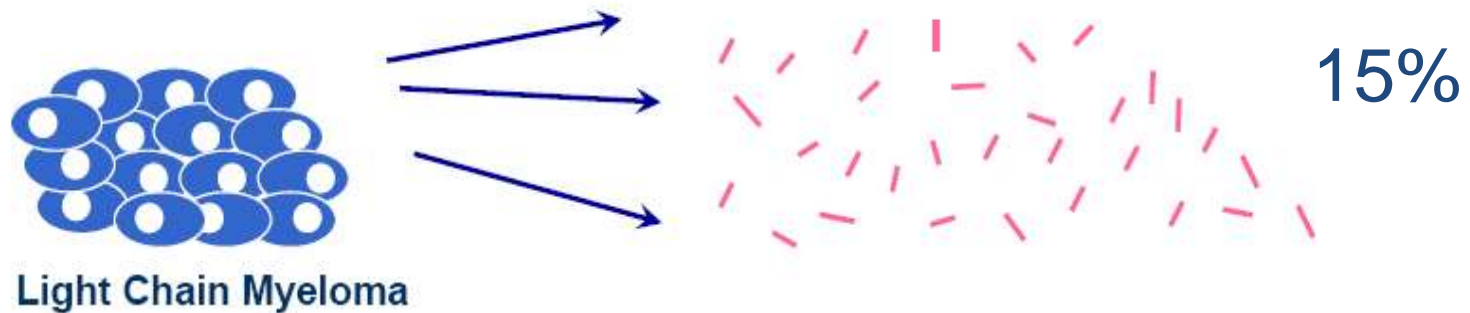
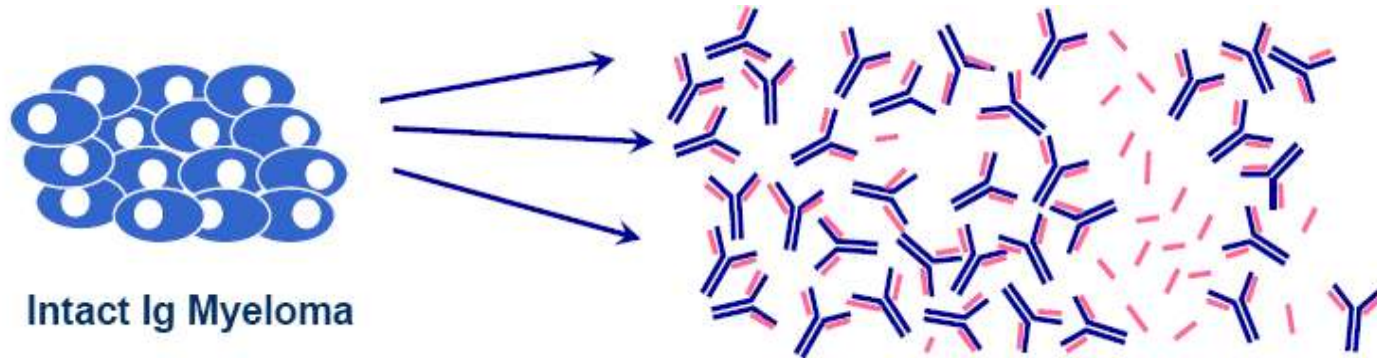


Myeloma



Mainly only one type of
antibody – and too many!

Different secreting patterns



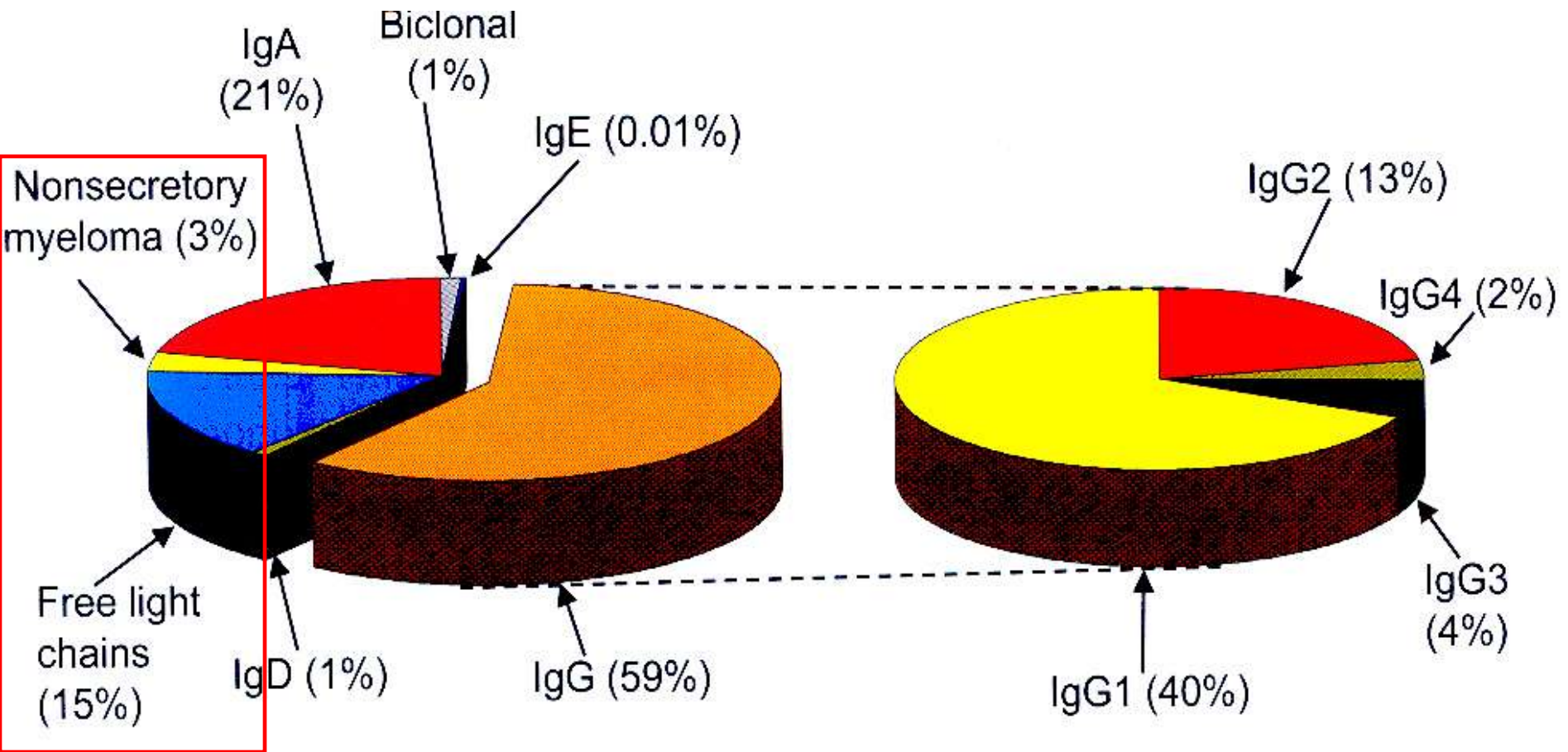
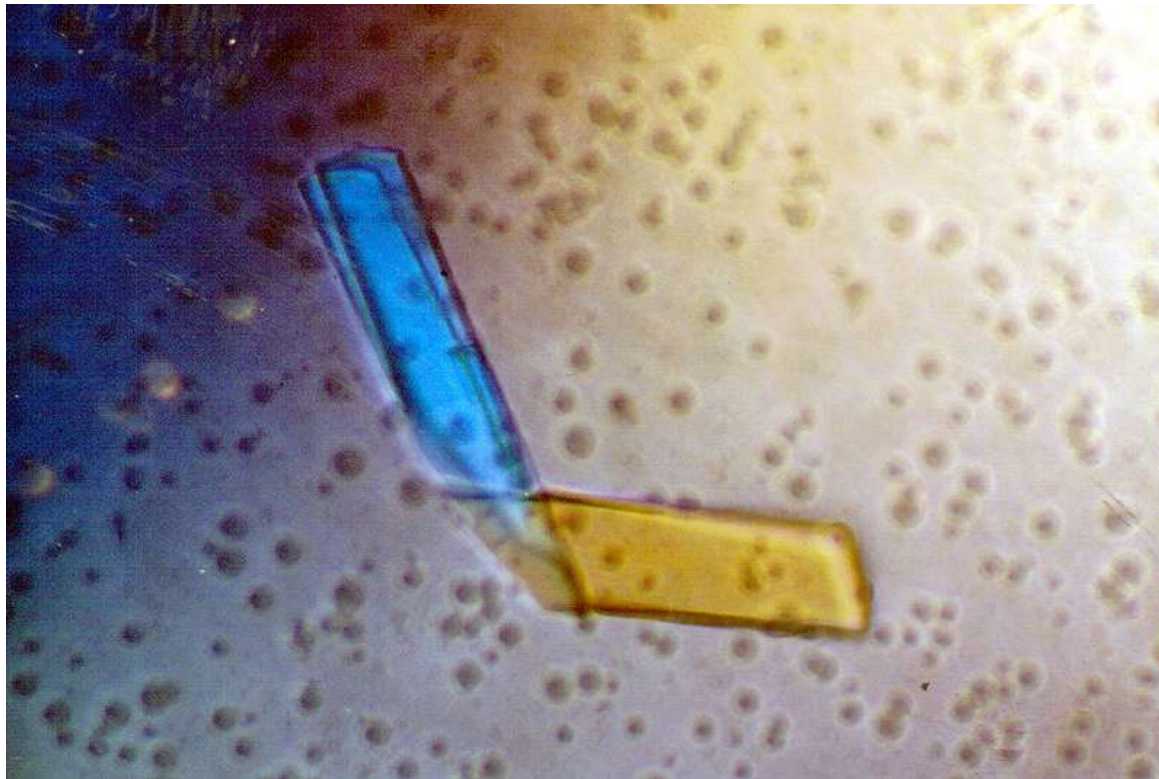


Figure 7.2. Classification of multiple myeloma based upon monoclonal protein production.

A crystal of Bence Jones protein

A crystal of Bence Jones protein created for X-ray crystallography, which can reveal detailed, three-dimensional protein structures. The proteins are immunoglobulin light chains (paraproteins) and are produced by neoplastic plasma cells. They can be kappa (most of the time) or lambda.





Henry Bence-Jones (1813-73).
British Physician (St George's
Hospital)

Patients & friends included Charles
Darwin, Florence Nightingale,
Thomas Huxley, Michael Faraday

Thomas McBean's urine was boiled.
A protein precipitated at 60° and re-
dissolved on boiling

World Health Organization Classification

- Monoclonal gammopathy of undetermined significance (MGUS)
- Plasma cell myeloma (multiple myeloma)

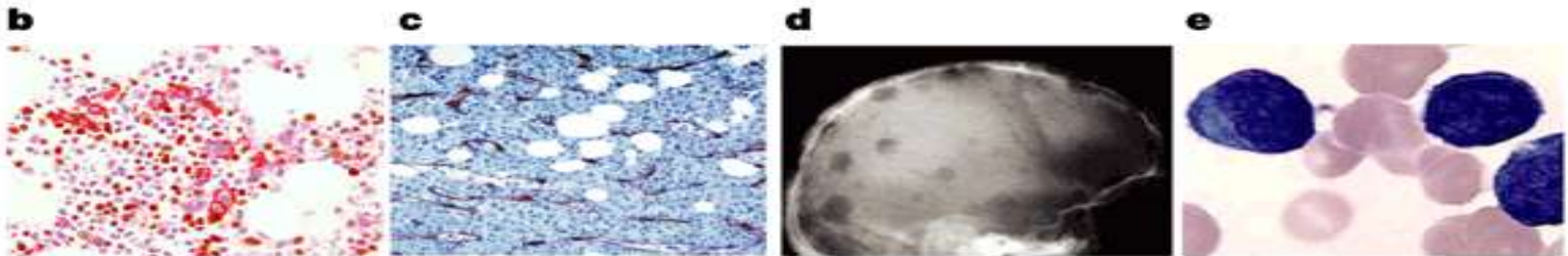
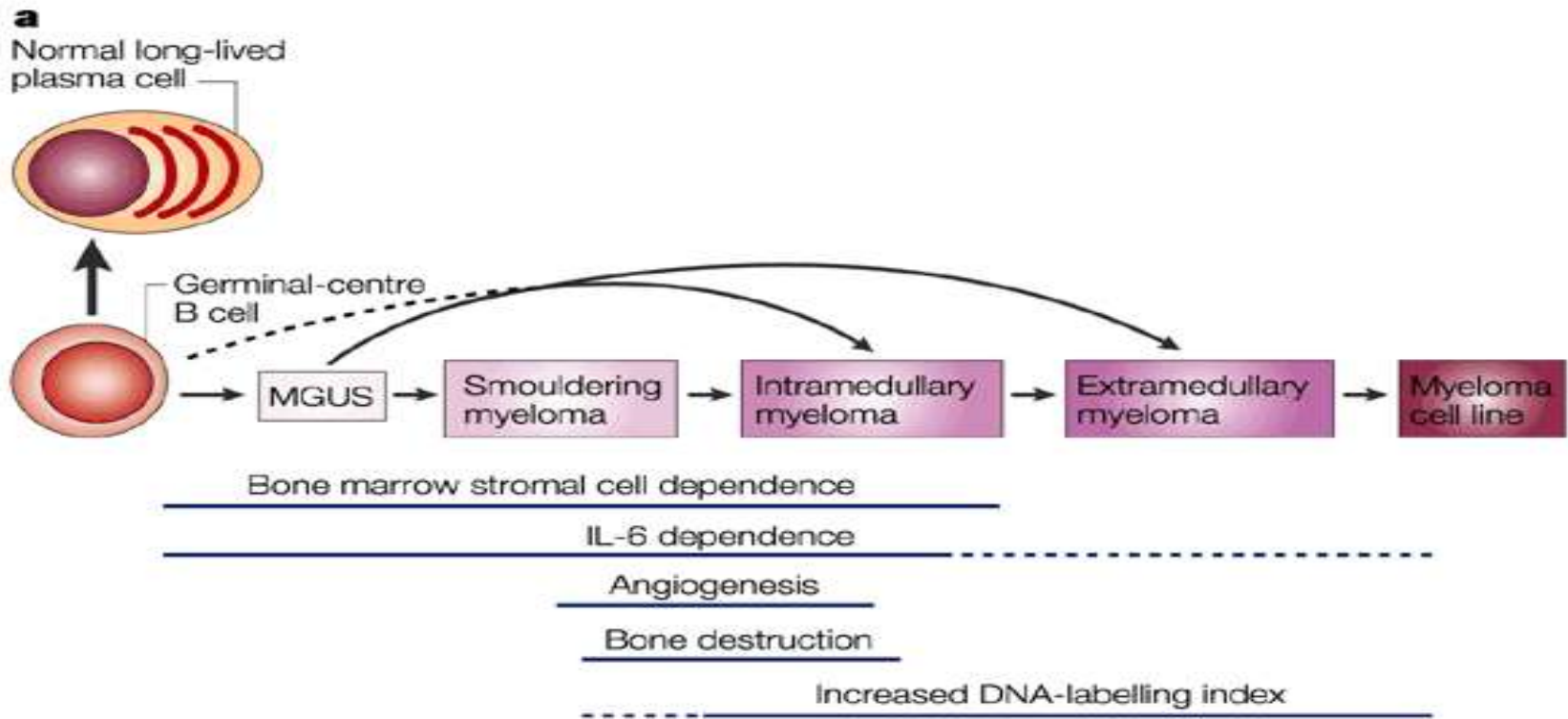
variants:

- Indolent myeloma
- Smoldering myeloma
- Osteosclerotic myeloma (POEMS syndrome)
- Plasma cell leukemia
- Non-secretory myeloma

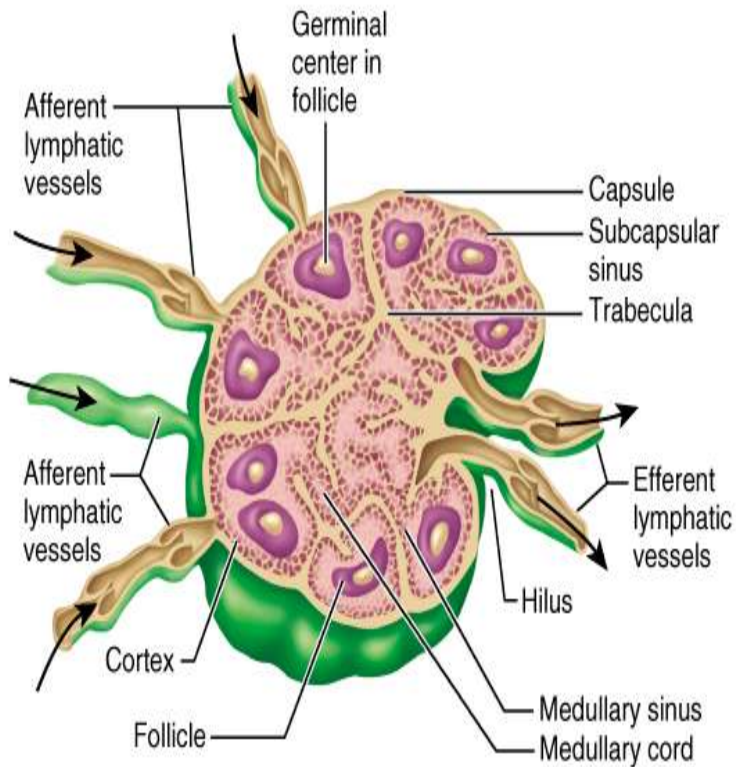
Monoclonal gammopathy of undetermined significance

- **MGUS is defined as having serum M-protein < 3 g/dL, clonal plasma cell population in bone marrow < 10%, and absence of end-organ damage (CRAB criteria of multiple myeloma) and has an average multiple myeloma progression risk of 1% per year.**

Natural development of myeloma

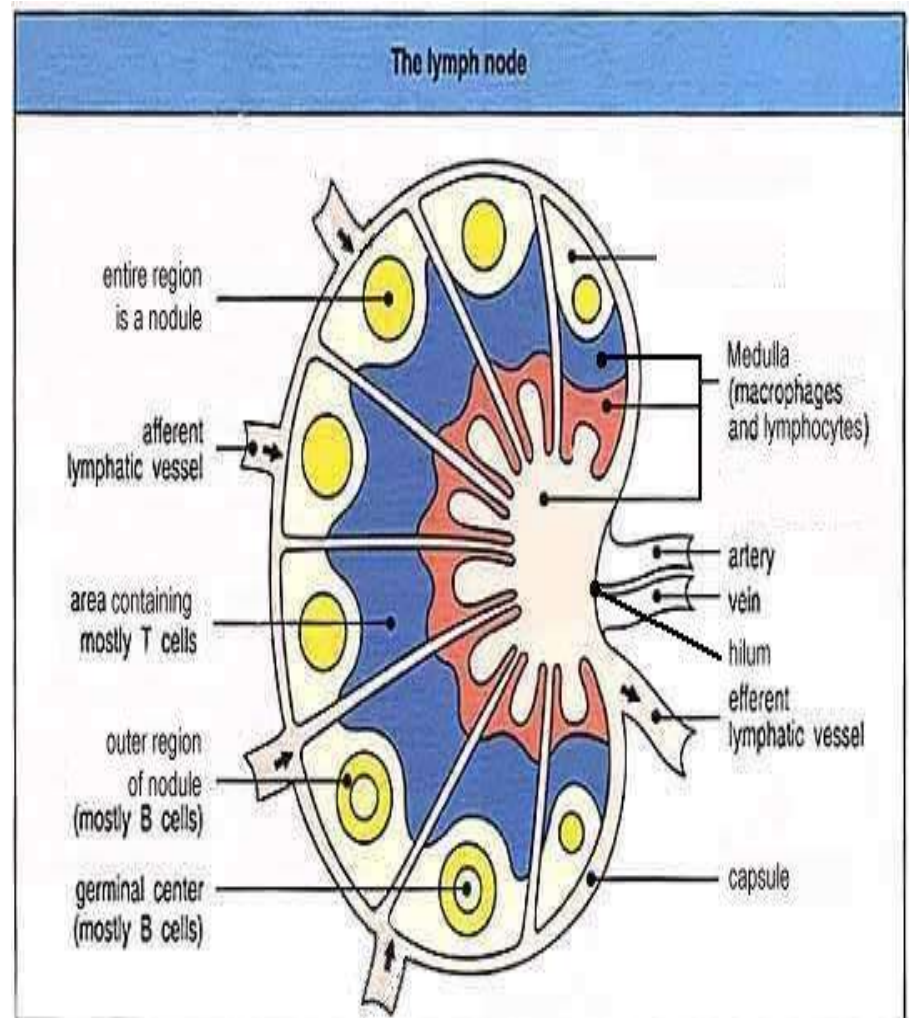


Lymph Nodes



(a)

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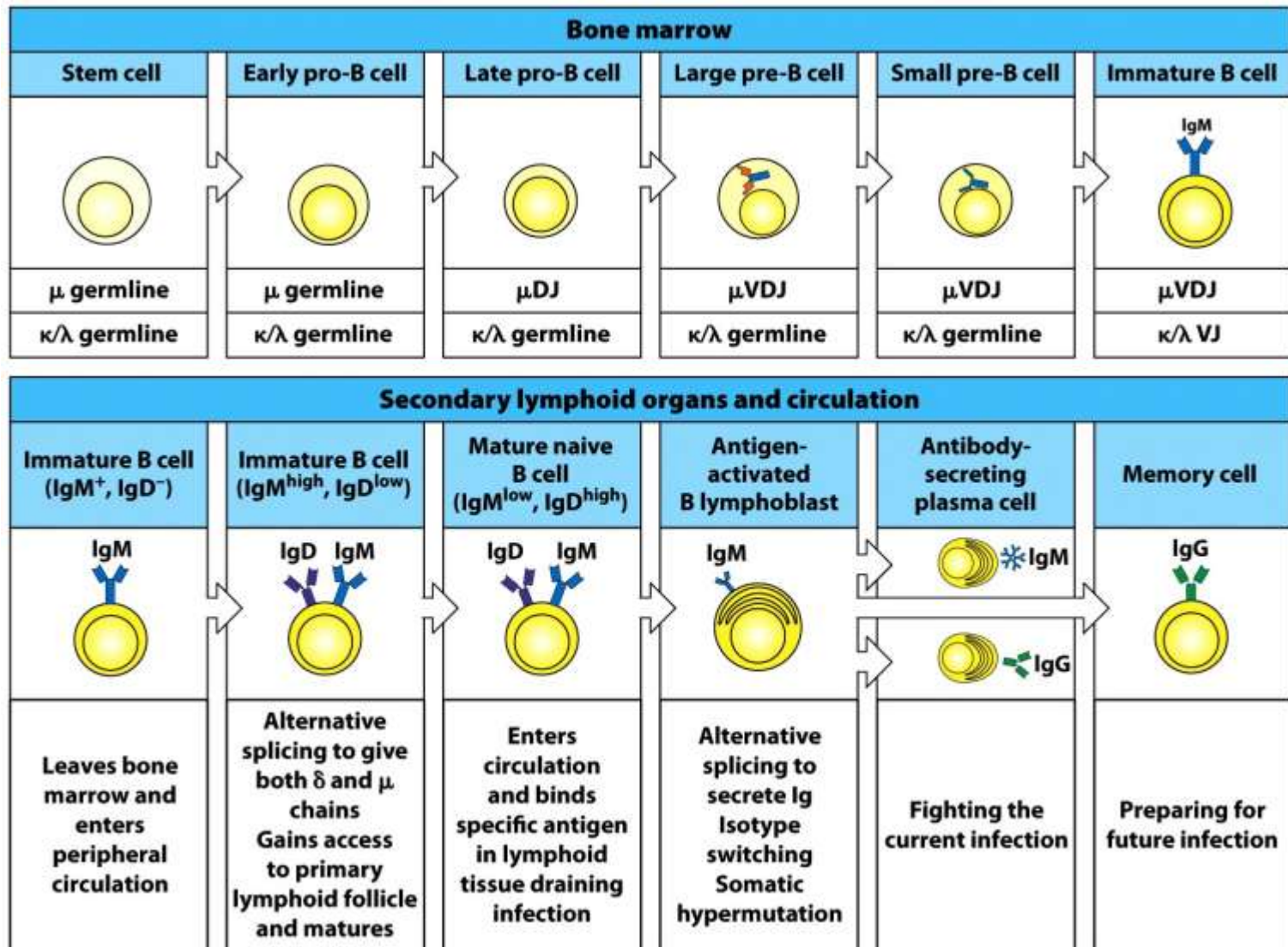
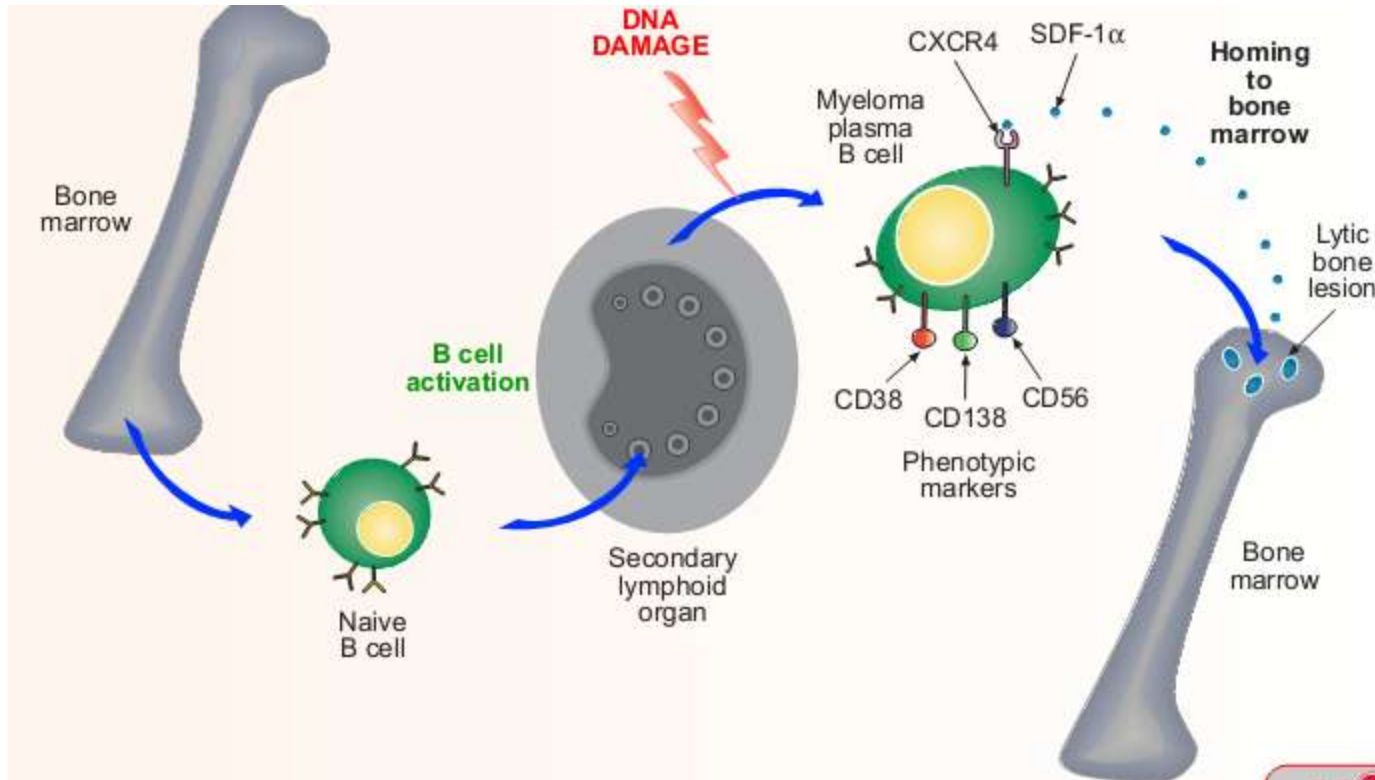


Figure 6.25 The Immune System, 3ed. (© Garland Science 2009)

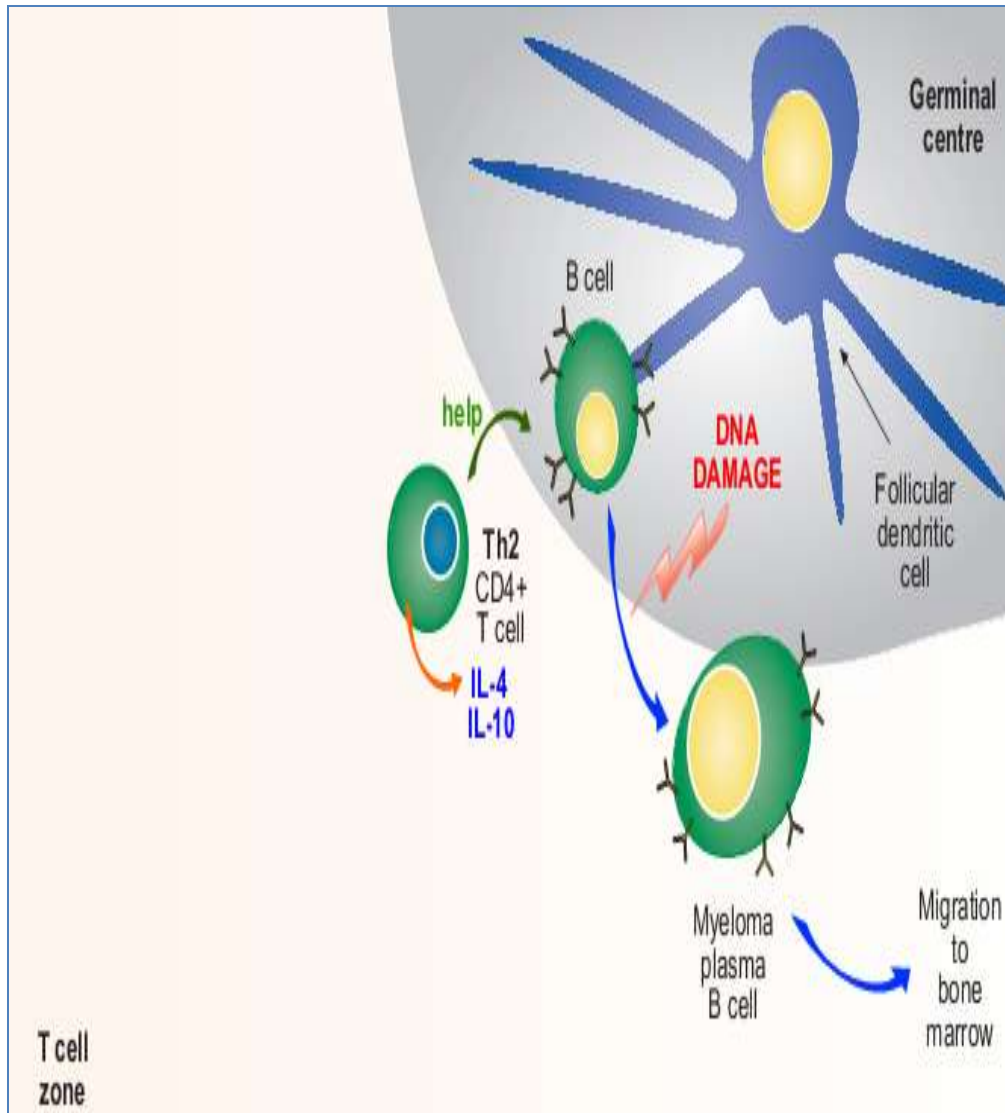
Pathogenesis



Multiple myeloma is a malignancy of plasma B cells caused by alterations to genetic material following B cell activation in the germinal centres of secondary lymphoid organs.

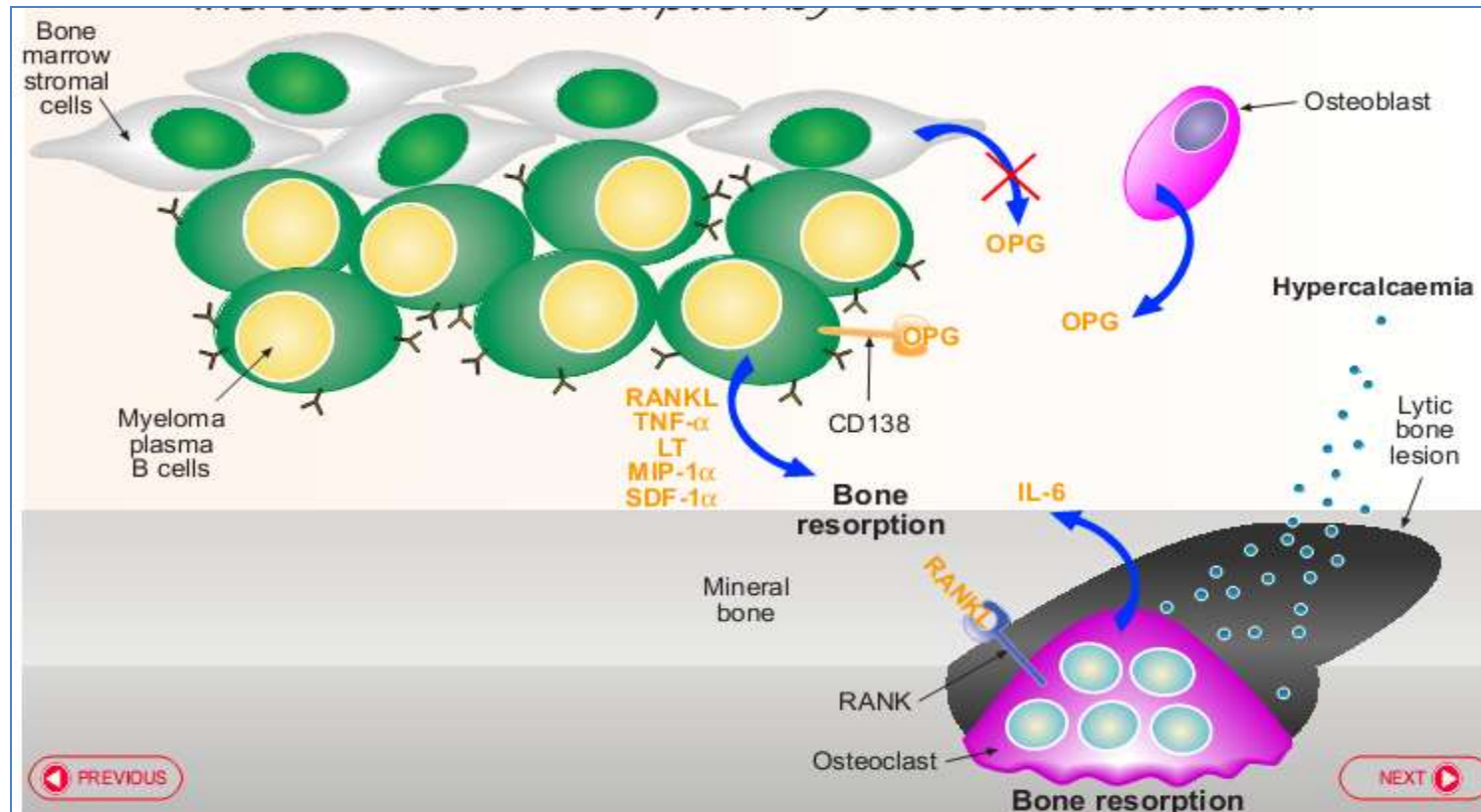
Myeloma plasma B cells also express CXCR4 receptors for SDF-1 α , a chemokine that regulates homing to the bone marrow where bone disease develops.

Pathogenesis



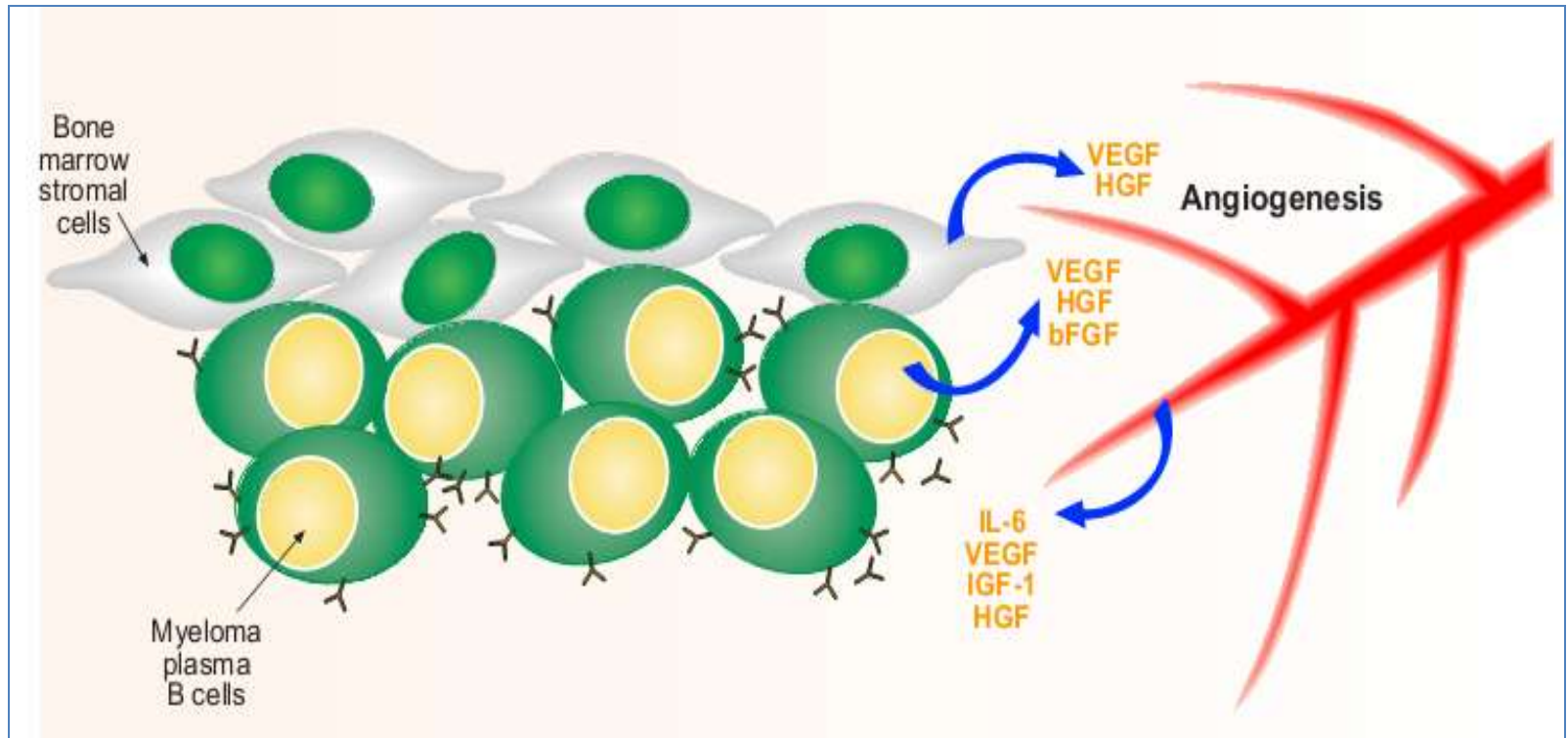
- B cells are primed by B cell receptor recognition of antigens presented by follicular dendritic cells in the germinal centres of secondary lymphoid organs.
- CD4⁺ helper T cell interaction activates B cells to differentiate into plasma cells and also induces isotype switching and affinity maturation. **During this process abnormal DNA recombination events translocate heavy and light immunoglobulin genes to other chromosomes and generate a malignant phenotype.**
- The myeloma plasma B cells continue to produce immunoglobulins resulting in a gammopathy and ultimately home to the bone marrow where bone disease develops.

Pathogenesis



- Bone destruction is mediated by the bone resorption activity of multinucleated osteoclasts. RANKL is a required activation signal for osteoclasts. RANKL is secreted along with other growth factors by myeloma plasma B cells..
- Activated osteoclasts secrete IL-6 that promotes the survival of myeloma plasma B cells

Pathogenesis



To improve oxygen and nutrient supply to the myeloma plasma B cells, the formation of new blood vessel is promoted by soluble factors secreted by both bone marrow stromal cells and myeloma plasma B cells. In addition, blood vessel endothelial cells also secrete growth factors that promote the survival of the myeloma plasma B cells.

The clinical picture

Proliferation of plasma cells



1. Osteolysis and osteodestruction
Neurological disorders
2. Syndrome of hypercalcemia
Renal failure
3. Inhibition of normal hematopoiesis
(anemia, pancytopenia)

M-protein secretion



1. Hyperviscosity syndrome
2. Myeloma nephropathy
3. Disproteinemia
Elevated levels of B2-microglobulin
Increased levels of IL6 and CRP
4. Reduction of normal Ig
Recurrent bacterial infections

Clinical features of bone disease

- Bone disease occurs in 80-90% of myeloma patients. The development of bone disease, either focal or diffuse, can result in pain, pathological fractures/spinal cord compression and hypercalcaemia
- Radiotherapy is useful to improve pain control and may also promote healing of the fracture site.

Hypercalcaemia

- Acute hypercalcaemia can present with central nervous system dysfunction (confusion, coma and obtundation), muscle weakness, pancreatitis, constipation, thirst, polyuria, shortening of the Q-T interval on ECG and acute renal insufficiency.
- All patients with moderate to severe hypercalcaemia should receive a bisphosphonate.

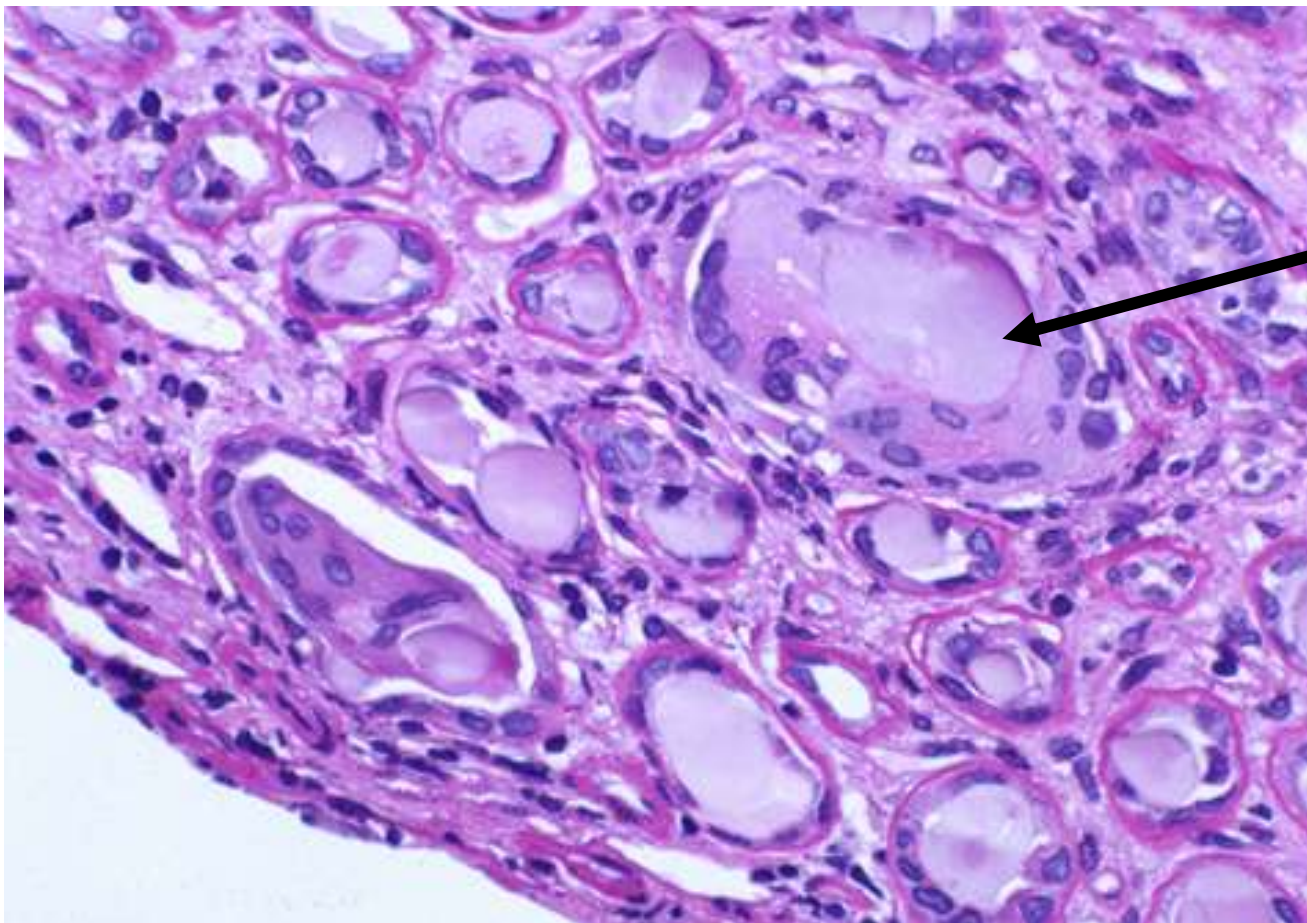
Hyperviscosity syndrome

- Hyperviscosity syndrome may develop in patients with high serum paraprotein levels, particularly those of IgA and IgG3 type.
- Symptoms include blurred vision, headaches, mucosal bleeding and dyspnoea due to heart failure.
- All patients with high protein levels should undergo fundoscopy which may demonstrate retinal vein distension, haemorrhages and papilloedema.
- Patients usually have raised plasma viscosity that usually corresponds to a serum IgM level of at least 30 g/l, an IgA level of 40 g/l and an IgG level of 60 g/l)

Renal impairment

- Renal impairment is a common and potentially serious complication of myeloma occurring at presentation in 20-25% of patients and in up to 50% of patients at some time during their disease.
- Renal failure occurs as a result of damage caused to renal tubules by free light chains (cast nephropathy, or “myeloma kidney”). A variety of other nephrotoxic processes may also contribute to this damage including dehydration, hypercalcaemia, nephrotoxic drugs, and infection

Myeloma Kidney



Protein cast
obstructs tubule
with syncytial giant
cell reaction
around it

Diagnostic criteria for MGUS, asymptomatic myeloma and symptomatic myeloma

(International Myeloma Working Group, 2003)

MGUS	Asymptomatic myeloma	Symptomatic myeloma
M-protein in serum <30 g/l	M-protein in serum >30 g/l and/or	M-protein in serum and/or urine**
Bone marrow clonal plasma cells <10 % and low level of plasma cell infiltration in a trephine biopsy (if done)	Bone marrow clonal plasma cells >10 %	Bone marrow (clonal) plasma cells or biopsy proven plasmacytoma
No related organ or tissue impairment ((no end organ damage including bone lesions)	No related organ or tissue impairment (no end organ damage including bone lesions) or symptoms	Myeloma-related organ or tissue impairment (including bone lesions)

Myeloma-related organ or tissue impairment (MWG, 2003)

Helpful

Mnemonic:

- **C** - calcium
- **R** - renal
- **A**-anemia
- **B** - bone

Clinical effects due to myeloma	Definition
Increased calcium levels	Corrected serum calcium >0.25mmol/l above the upper limit of normal or >2.75mmol/l
Renal insufficiency	Creatinine>173mmol/l
Anaemia	Haemoglobin 2 g/dl below the lower limit of normal or haemoglobin <10 g/dl
Bone lesions	Lytic lesions or osteoporosis with compression fractures (MRI or CT may clarify)
Other	Symptomatic hyperviscosity, amyloidosis, recurrent bacterial infections (> 2 episodes in 12 months)

International Staging System (ISS) for multiple myeloma

(adapted from Greipp *et al*, 2005)

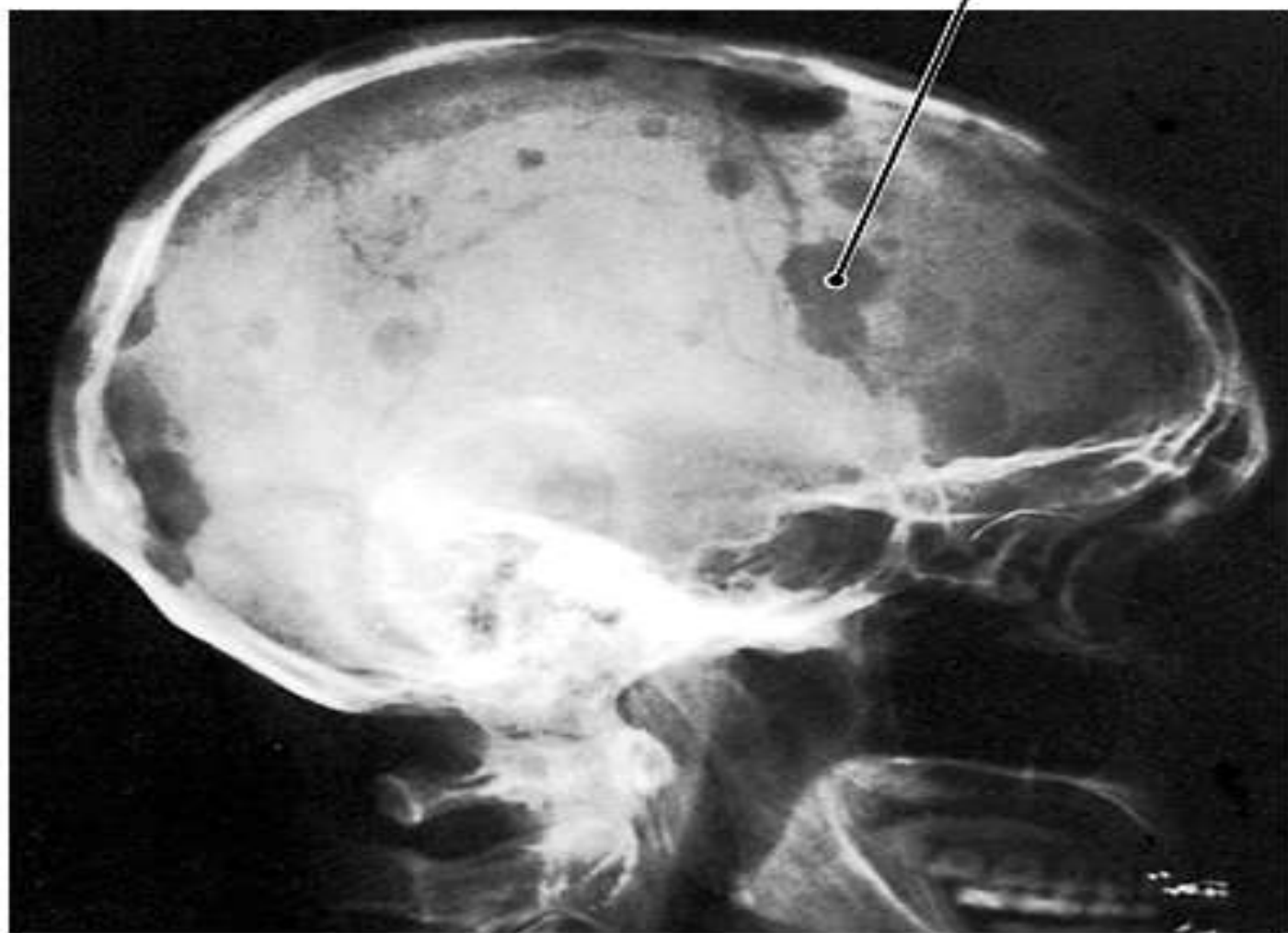
Stage	Criteria	Median survival in
I	Serum β 2 microglobulin < 3.5 mg/l (296 nmol/l) and serum albumin > 3.5 g/dl (35g/l or 532 μ mol/l)	62 months
II	Neither I or III*	45 months
III	Serum β 2 microglobulin > 5.5 mg/l (465 nmol/l)	29 months

Upper normal value for serum β 2 microglobulin is 2.0 mg/L
The normal range for serum albumin is 3.5 to 5.5 g/dL

Imaging techniques in myeloma

- **The skeletal survey** should include a postero-anterior (PA) view of the chest, antero-posterior (AP) and lateral views of the cervical spine, thoracic spine, lumbar spine, humeri and femora, AP and lateral view of the skull and AP view of the pelvis; other symptomatic areas should be specifically visualized with appropriate views
- **CT scanning or MRI** should be used to clarify the significance of ambiguous plain radiographic findings such as equivocal lytic lesions, especially in parts of the skeleton that are difficult to visualize on plain radiographs, such as ribs, sternum and scapulae
- **Urgent MRI** is the diagnostic procedure of choice to assess suspected cord compression in myeloma patients with or without vertebral collapse
- **Urgent CT scanning** is an alternative, when MR imaging is unavailable, intolerable or contraindicated
- CT or MR imaging is indicated to delineate the nature and extent of soft tissue masses and where appropriate, tissue biopsy may be guided by CT scanning

**"Punched out" lesions
of multiple myeloma**



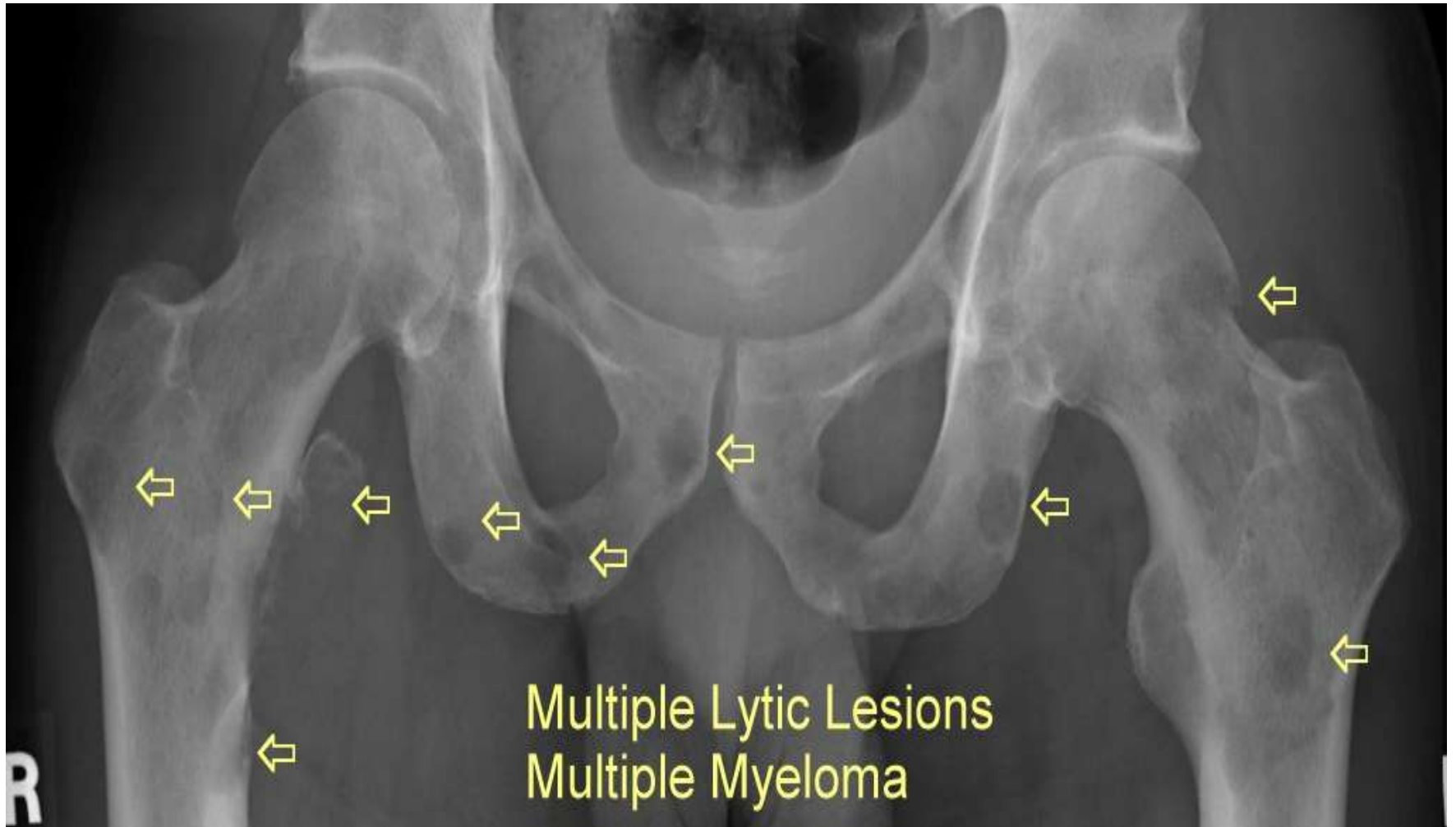
“Punched out” lesions in the bones



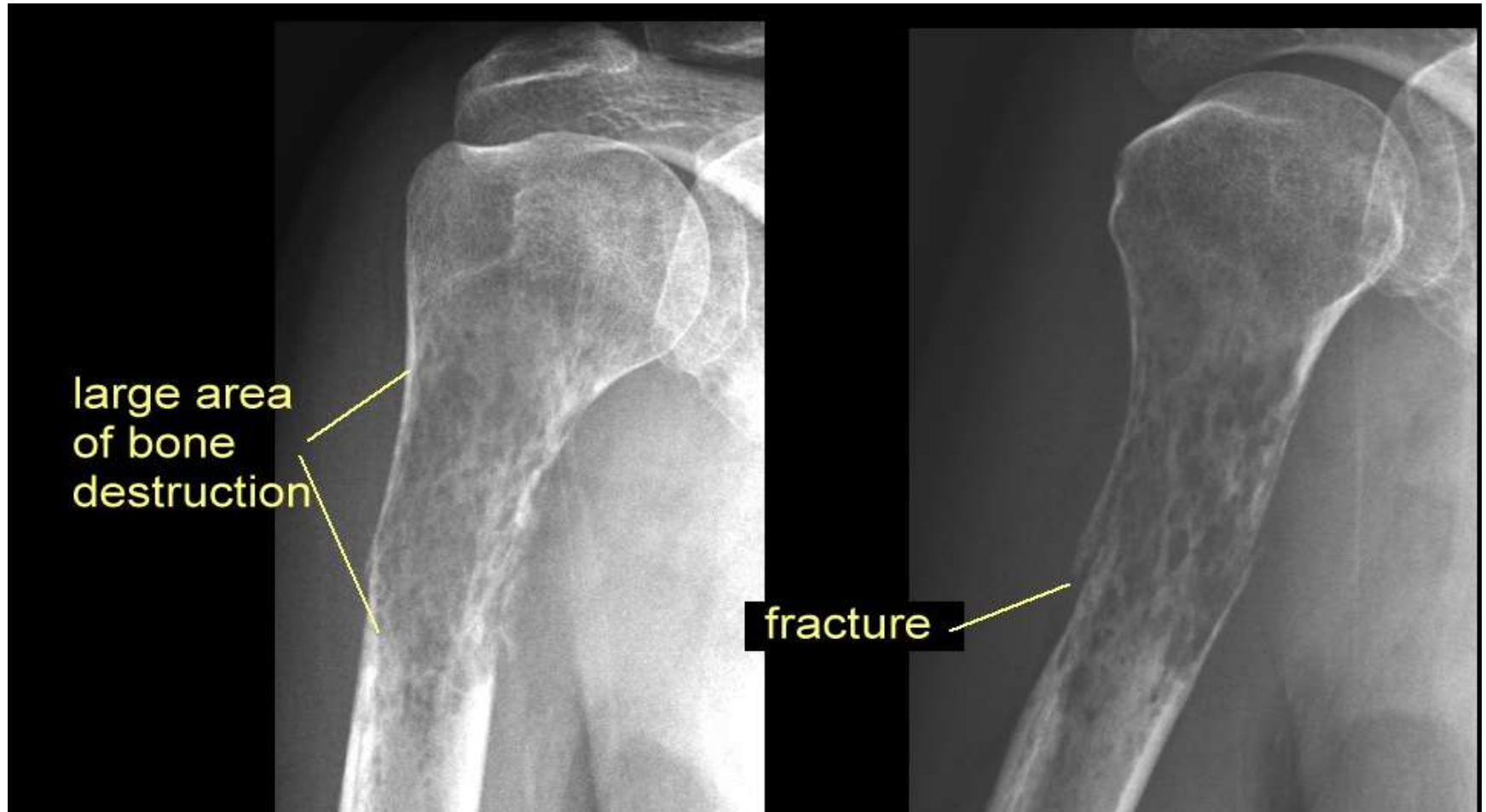
Поражение черепа (симптом «перечницы»)



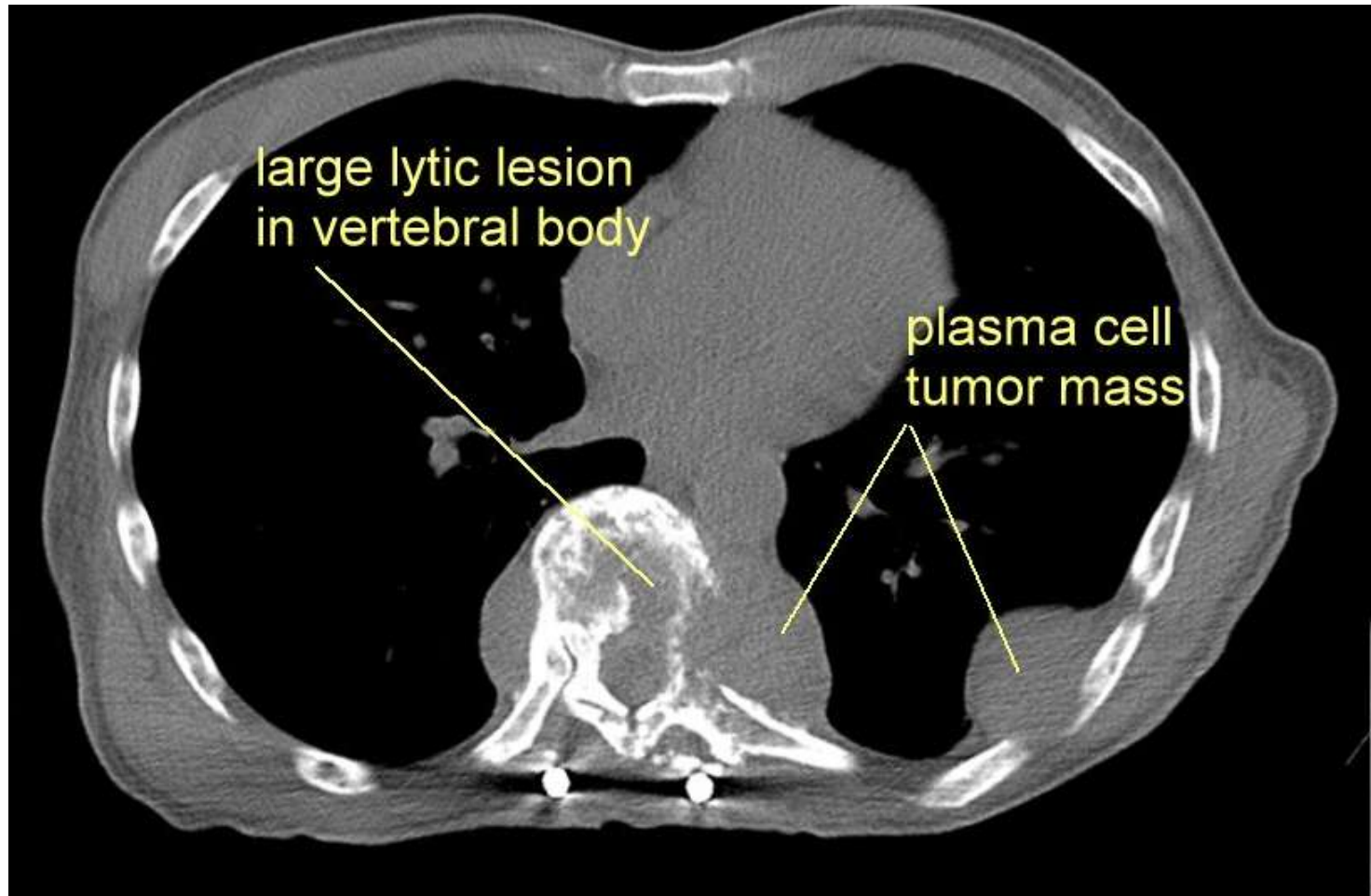
<http://www.aic.cuhk.edu.hk/web8/myeloma%20skull.htm>



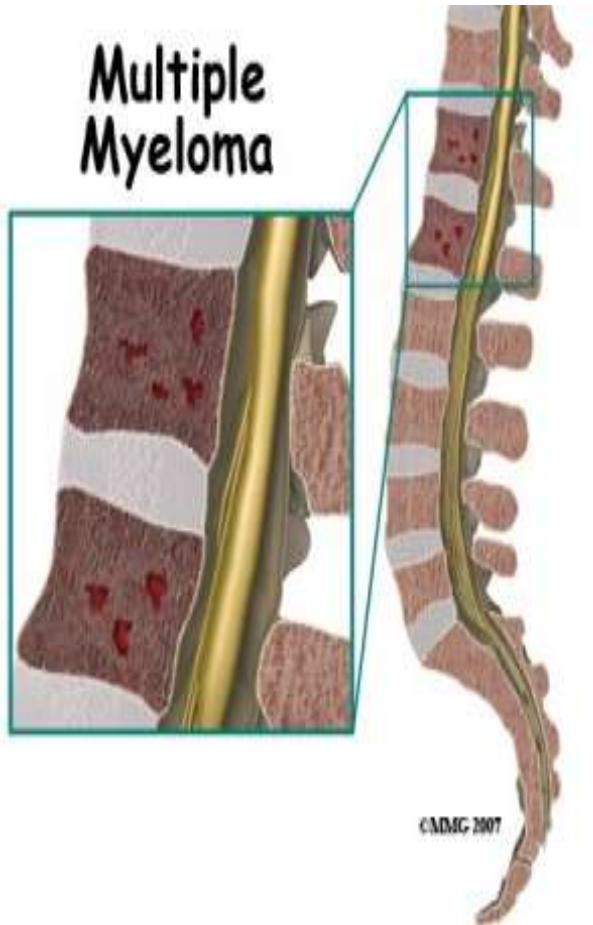
Radiography of the humerus



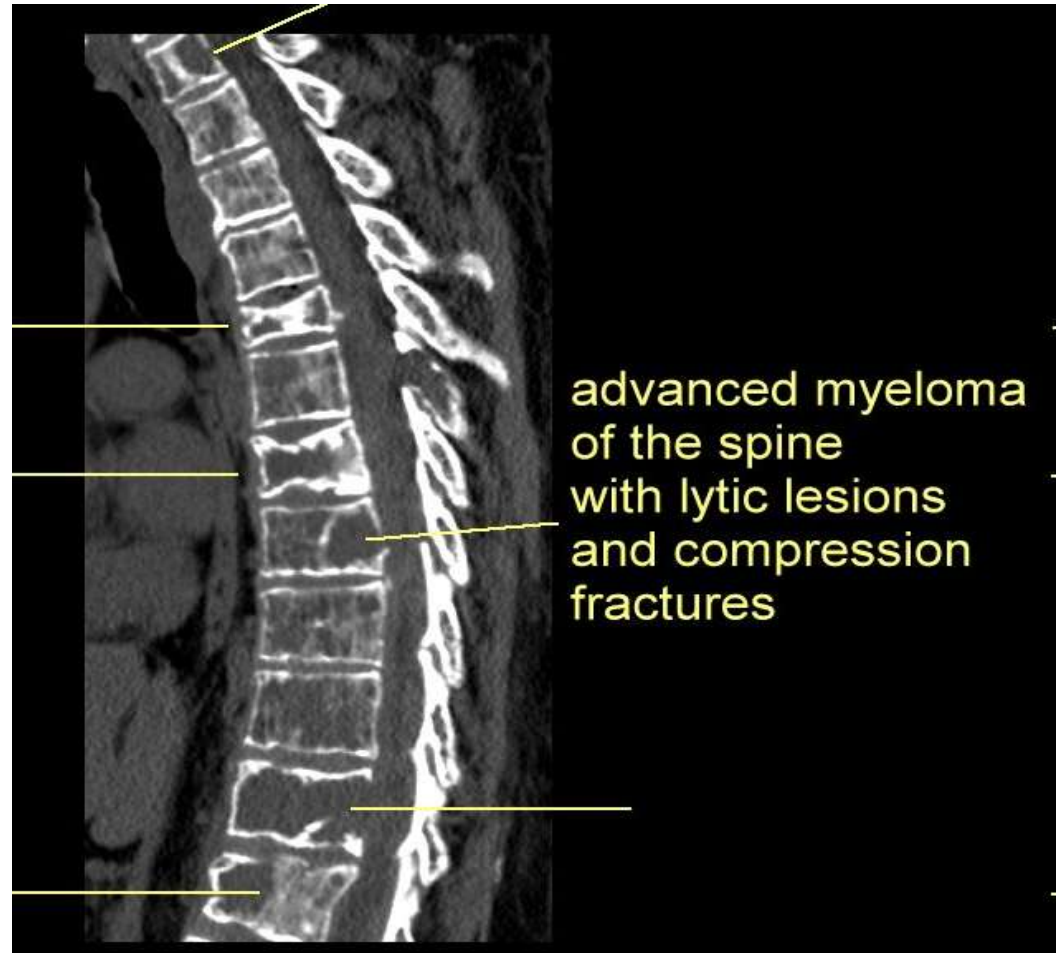
CT at the level of the thoracic spine



MRI of the thoracic spine

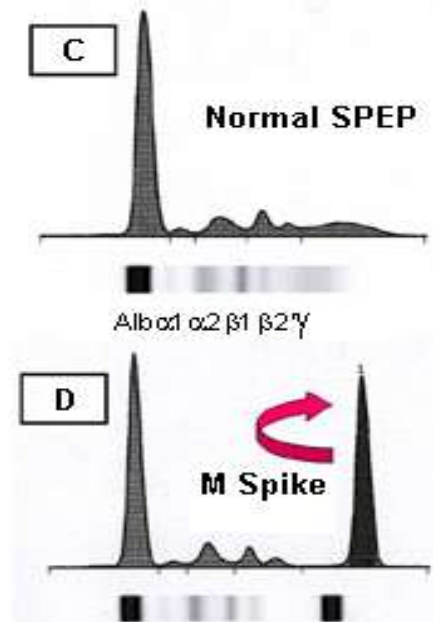
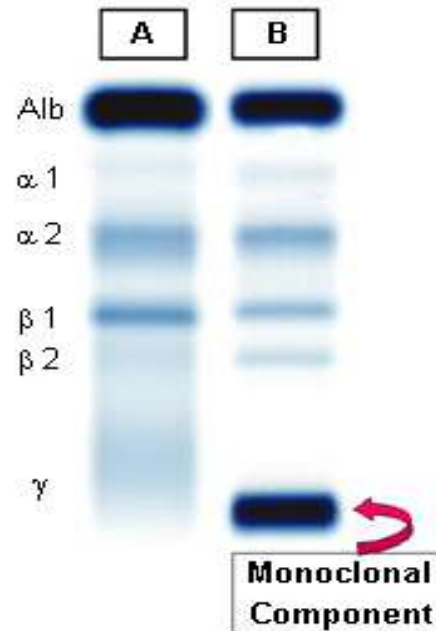
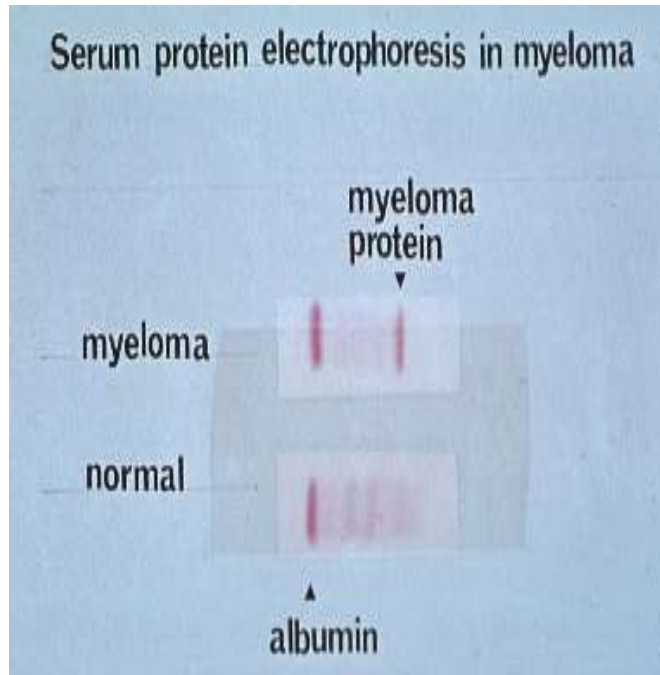


<http://trialx.com>



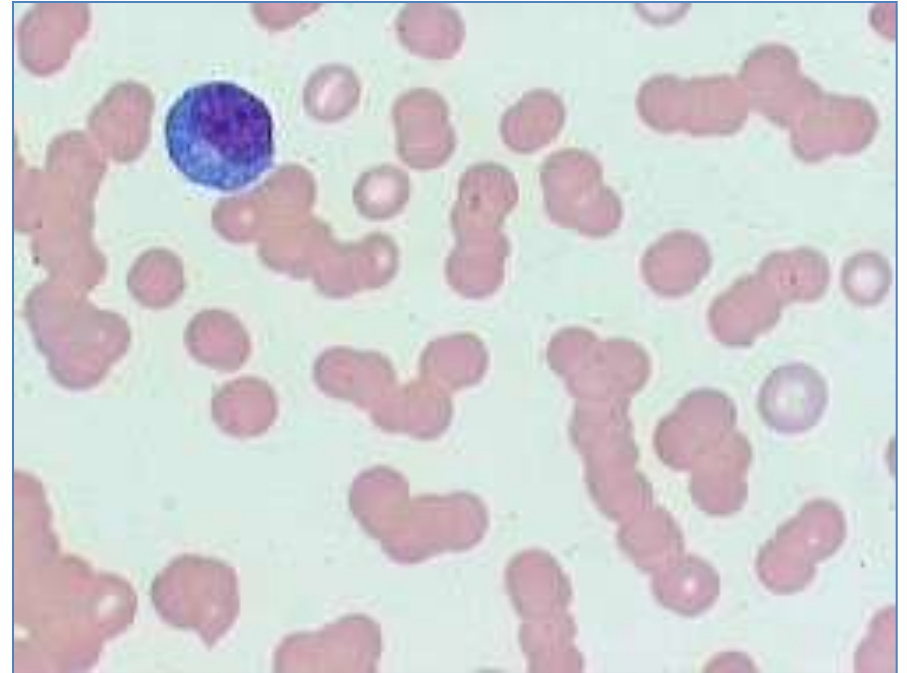
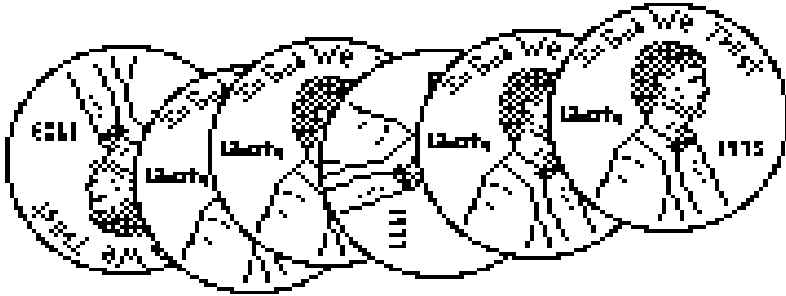
http://www.aboutcancer.com/myeloma_spine_bmc

Serum protein electrophoretic pattern in multiple myeloma

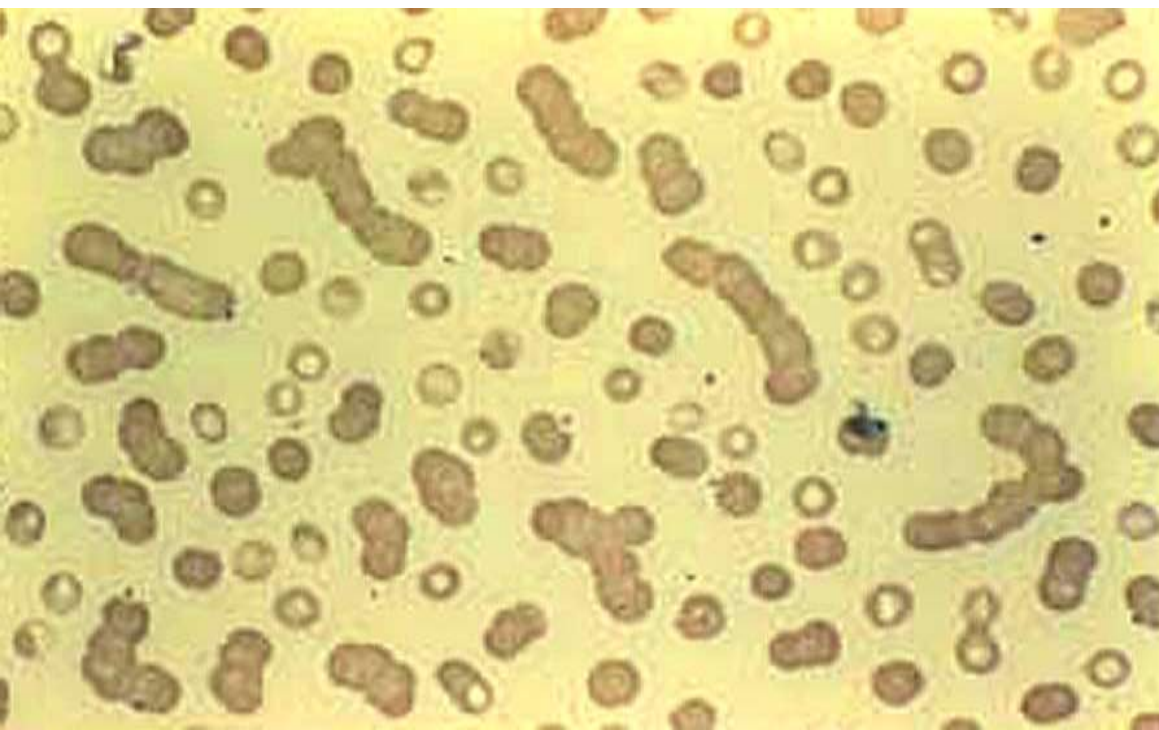
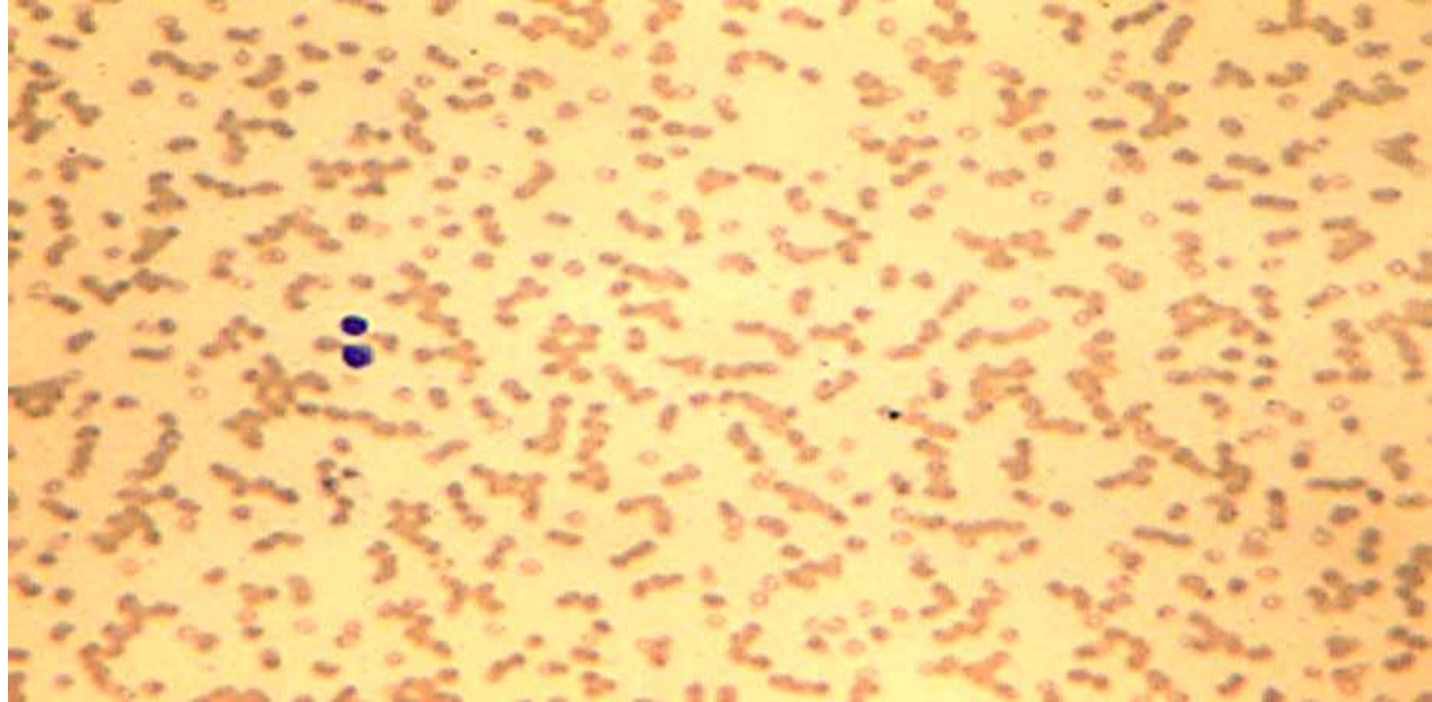


The normal plasma protein electrophoretic pattern shows a heavy albumin band (to the left) and lighter bands which are alpha, beta and gamma mobility globulins. The serum from the patient with multiple myeloma shows a heavy band which is the abnormal monoclonal immunoglobulin (referred to as a paraprotein). Because it is monoclonal (all molecules identical) it is a very narrow discrete band, which in this patient has gamma mobility.

Rouleaux formation

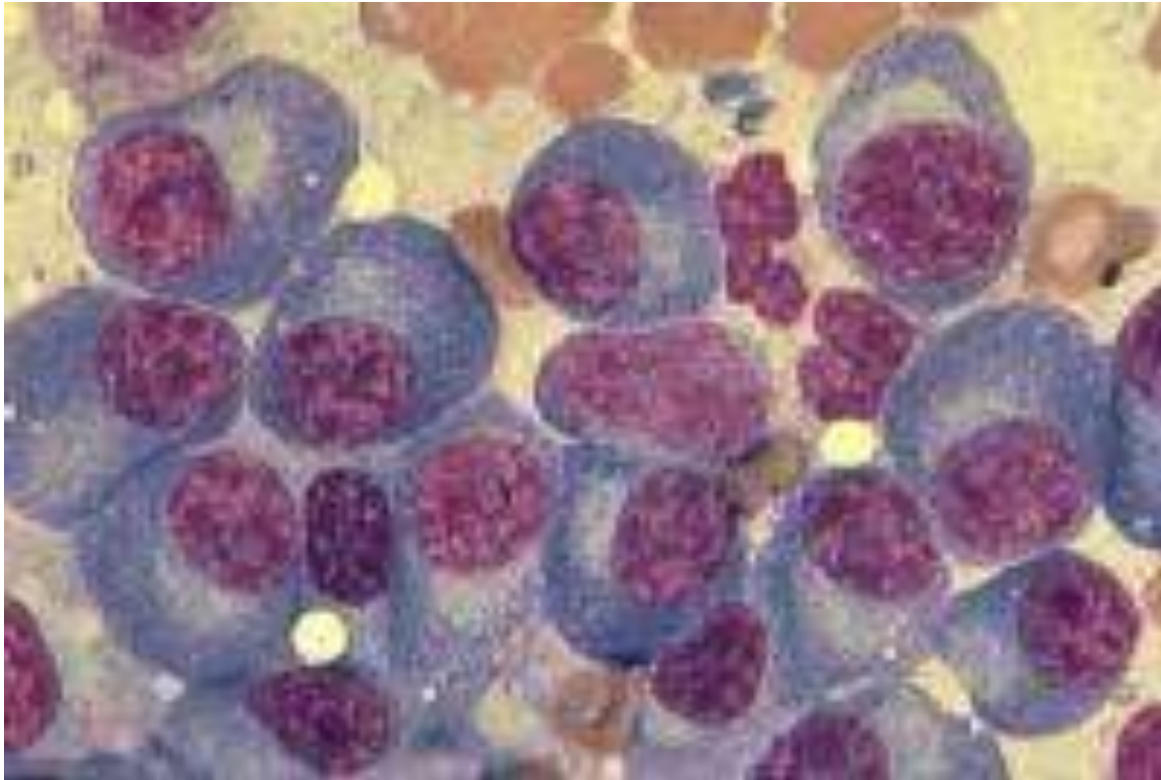


Excess Ig in the peripheral blood may result in Rouleaux formation in which immunoglobulin coated RBCs cling together (resembling overlapping pennies). The ESR may be increased secondary to hyperviscosity

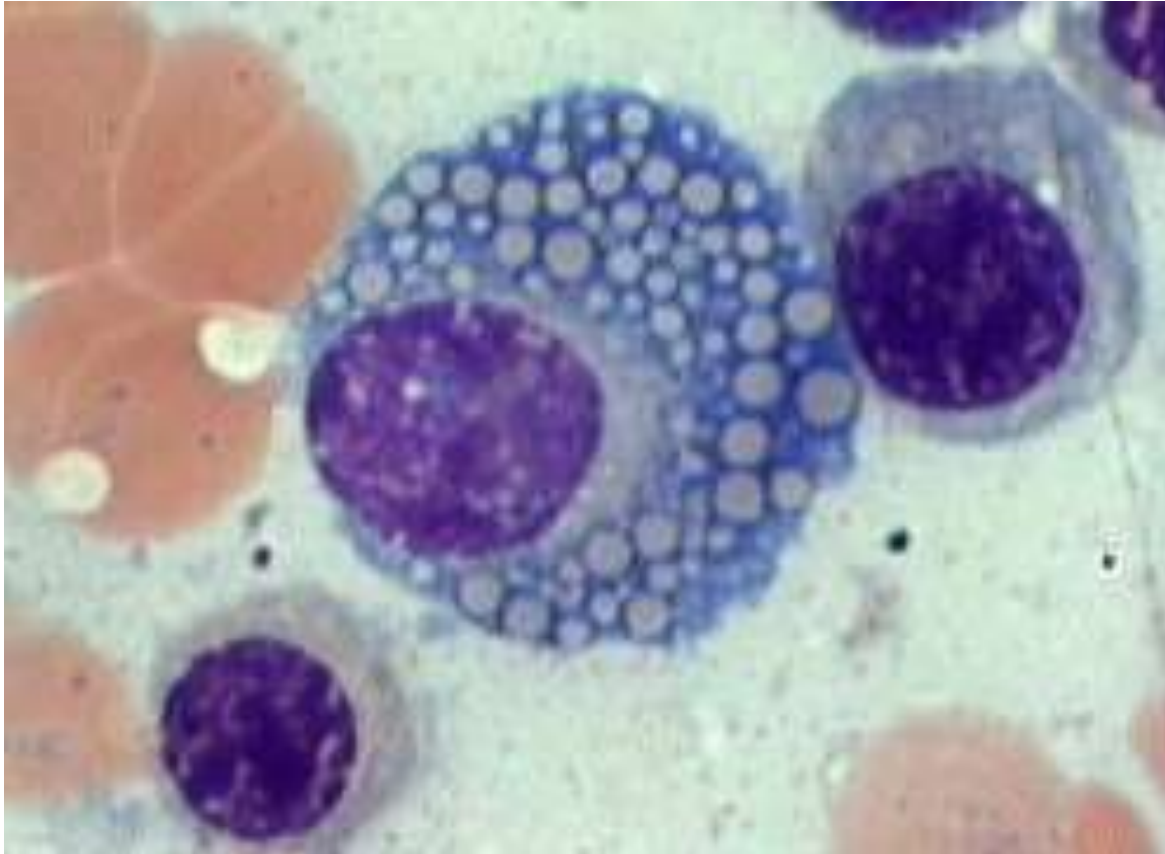


Rouleaux

- Bone marrow aspirate demonstrating plasma cells of multiple myeloma. Note the blue cytoplasm, eccentric nucleus, and perinuclear pale zone (or halo).
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Cells containing multiple immunoglobulin globules are known as Mott cells



Treatment options

- Chemotherapy (*Bortezomib, melphalan, thalidomide*)
- Dexamethasone
- High-dose chemotherapy with transplantation
- Radiation
- Alpha-interferon
- Erythropoietin
- Bisphosphonates
- Supporting therapy: antibiotics Emergency care (eg dialysis, plasmapheresis, surgery or radiation), pain management, growth factors, corsets/fixation, exercises, diet.

Indications for starting therapy

- Chemotherapy is only indicated in patients with symptomatic myeloma based on the presence of ROTI
- Early intervention in patients with asymptomatic myeloma is not required
- Patients with asymptomatic myeloma should be monitored under the supervision of a Consultant Haematologist
- Monitoring of patients with asymptomatic myeloma should include regular (typically 3 monthly) clinical assessment for the emergence of ROTI and measurement of serum and urinary M-protein

Till we meet again

