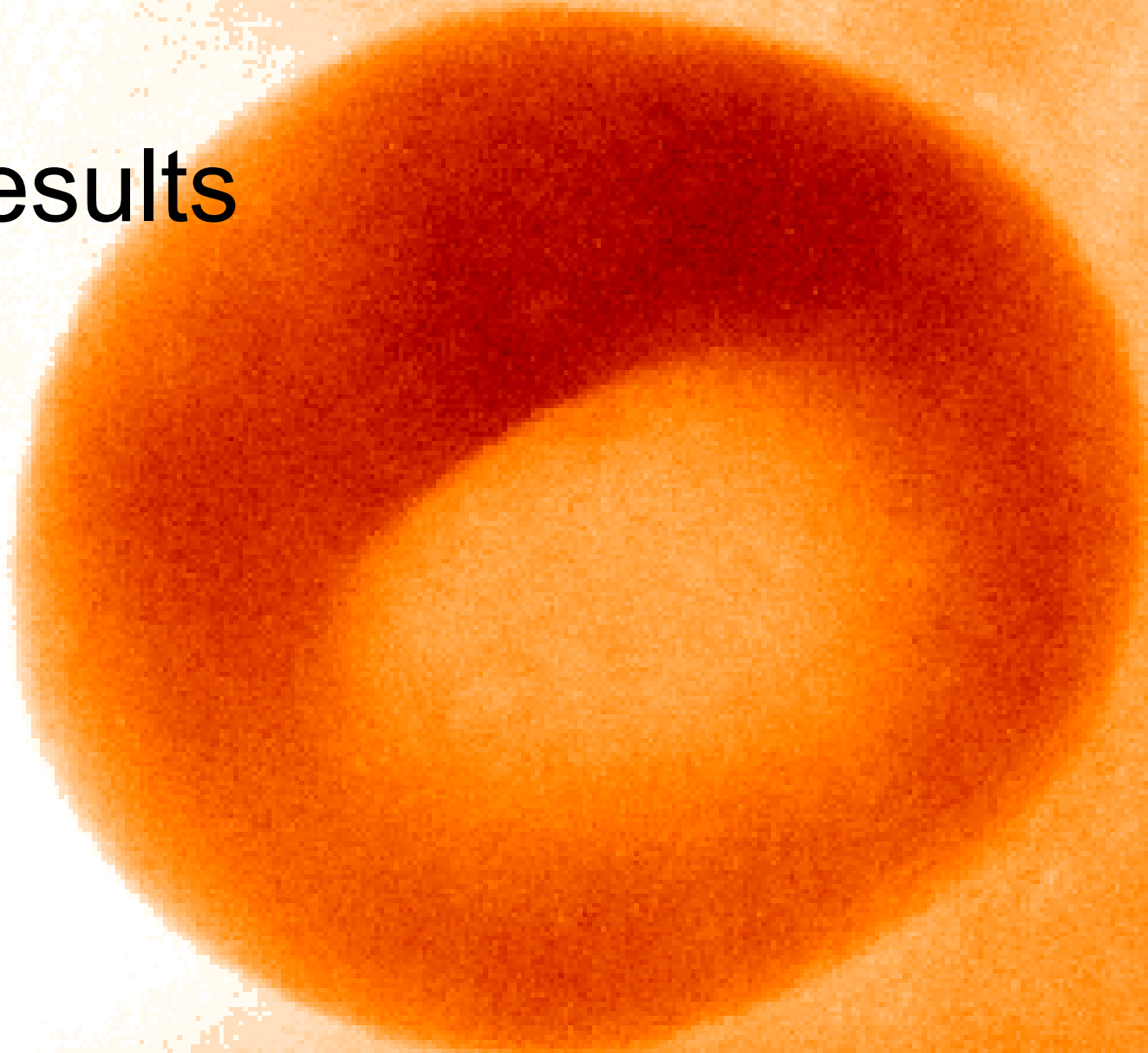
Lab results



Case study

- 47 year old man complains of tiredness and joint aches
- O/E mildly increased BMI, nil else
- What tests?
- FBC
- U&Es
- Glucose
- LFTs
- TFTs
- Iron studies

Case study

- Serum Iron high (other studies normal)
- Iron binding capacity normal
- Ferritin 483
- What now?
  - Soluble transferrin receptor?
  - Fasting iron? (and maybe fasting glucose and lipids?)
  - Venesection?
  - Gene studies?
  - Haematology referral?

	serum iron	IBC	ferritin
IDA	low	high	low
Inflammation	low	low	high
Both	low	normal	high/N

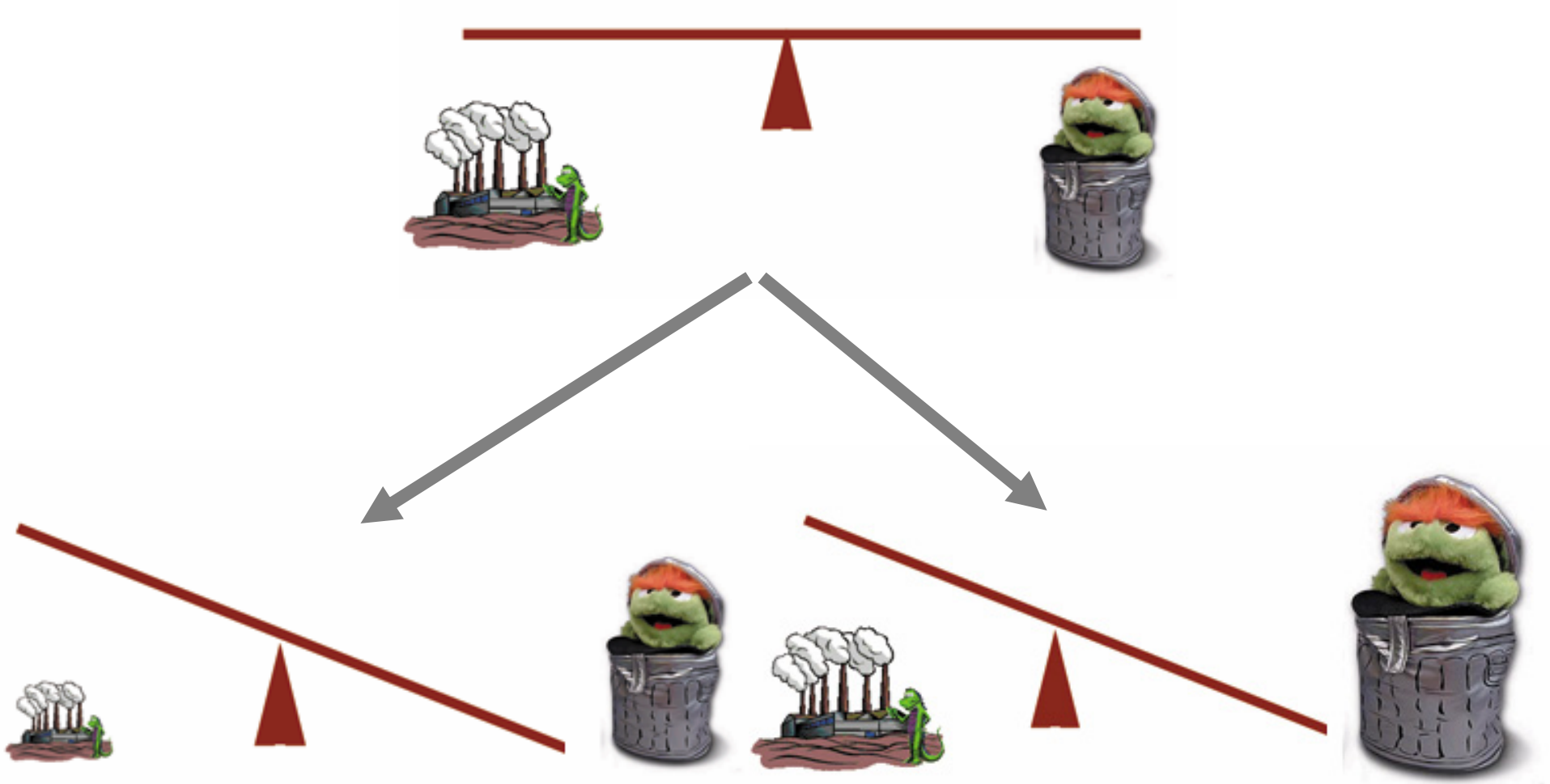
Case study

- Fasting iron still high; what now?
- Gene studies undertaken:
- HFE C282Y heterozygote: what now?
- Other gene studies? (H63D, S65C)
- Venesect?
- Just monitor ferritins?
- Liver qMRI?

Case study

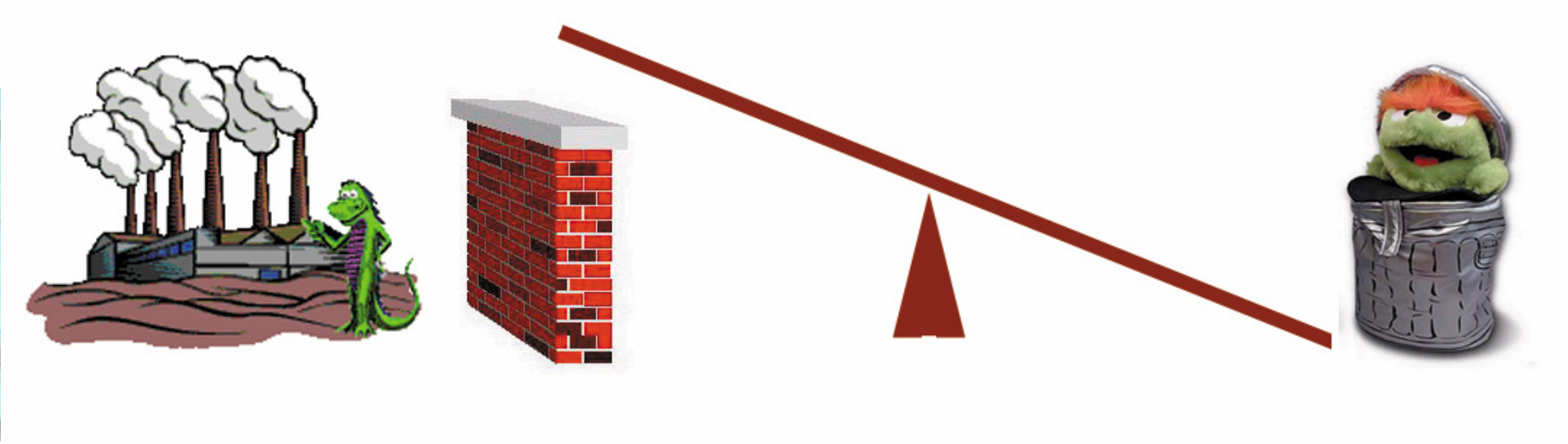
- Other gene studies normal (implies not compound heterozygote)
- Probably involve Haematology department at this stage
- Venesection reasonable as symptoms, BUT:
  - Danger of focussing on possible iron overload and ignoring more likely causes of symptoms; **genotype does not equal phenotype.**
  - NB: this genotype occurs in approx 1 in 10 Caucasians, so could be an incidental finding.
- If over 3g (approx12 units), implies iron overload
- Monitoring ferritins also reasonable
- qMRI liver helps establish/exclude iron overload

Production/destruction imbalance



Myelodysplasias (MDS)

- characterized by lots of action in the marrow but little production



Symptom + Signs

- Koilonychia = nail change, usually seen in Fe deficiency. Nails become brittle, spoon shaped, and ridged.
- angular cheilosis = painful inflammation at angles of mouth, seen in Fe, B12, or folate deficiency.
- Jaundice = due to increased bilirubin production as a result of increased haemolysis (haemolytic anaemia)

Investigation for Suspected Anaemia

- Hb concentration: confirms anaemia + assesses severity
- MCV: is this microcytic, normocytic, or macrocytic?

  Microcytic = MCV < normal (76)

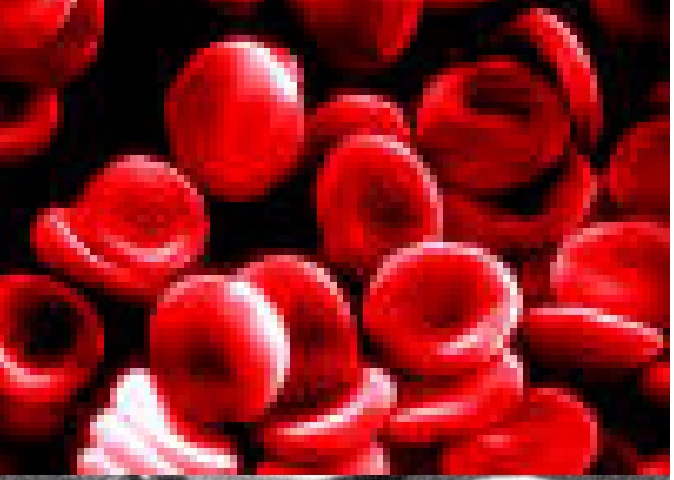
  Normocytic = MCV normal (76 – 96)

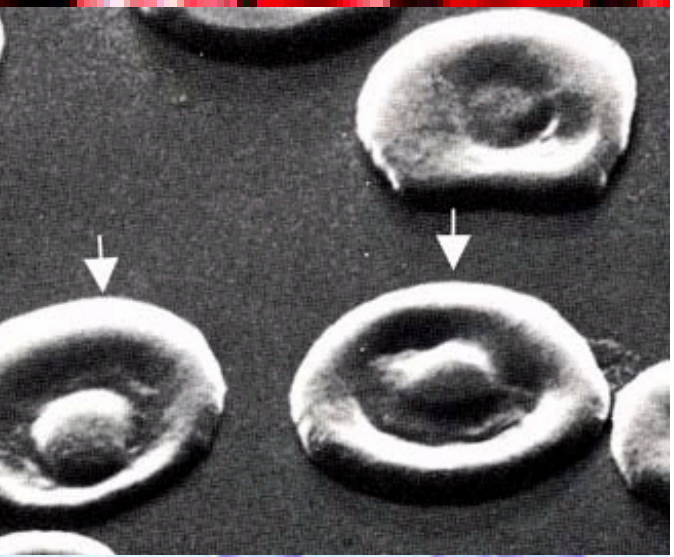
  Macrocytic = MCV > normal (> 96)

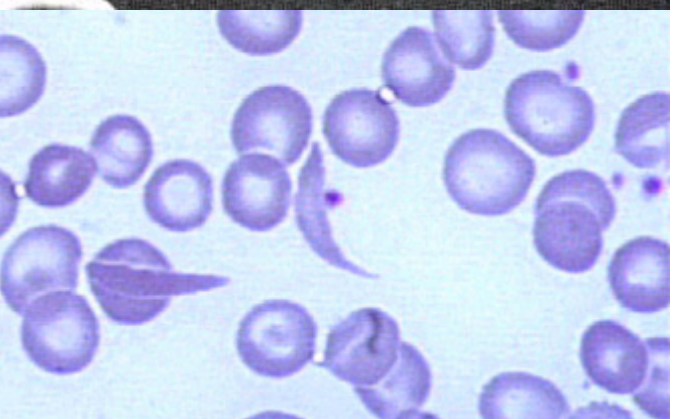
- Other cell counts: is this isolated anaemia or pan-cytopenia?
- Blood film appearance: pencil cells, target cells, spherocytes, hypersegmented neutrophils, etc

Classification Based on MCV

Microcytic ~	Normocytic ~	Macrocytic ~
•Fe deficiency	•Chronic disease	•B12/folate deficiency
•Thalassaemia	•Haemolysis	•Liver disease
•Chronic disease	•Marrow disease (including myelodysplasia)	•Marrow disease (MDS)
		•Haemolysis (if MCV pushed up by reticulocytosis)







Microcytic Anaemias

Red cell is a bag of Haemoglobin - if deficit, cells are small and pale (micro/hypo) and may have excess of membrane (target cells)

- Hb = Haem + globin - so iron deficiency or globin deficiency (thalassaemias) cause micro/hypo
- cf Haemoglobinopathies

Thalassaemia

α

- Impaired production of α chain in the globin.
- Severity depends on number of genes deleted
- 4/4 = hydrops fetalis (intrauterine death)
- 3/4 = haemoglobin H disease (severe anaemia)
- 1- 2/4 = α trait (mild anaemia, or microcytosis with normal Hb)

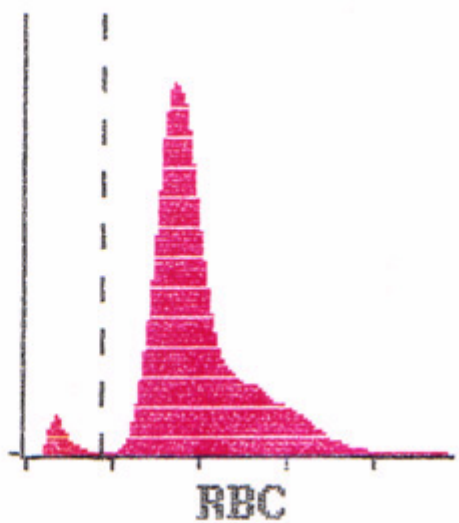
β

- Impaired production of β chain in the globin
- Major = complete failure of production (severe anaemia)
- Intermedia = partial failure (moderate anaemia)
- Minor = asymptomatic or mild anaemia

Investigating Microcytic Anaemia

- Thalassaemia vs iron deficiency -
  - has MCV ever been normal?
  - Pencil cells on blood film?
- RDW:
  - high => iron deficiency rather than thalassaemia

RBC	4.63	M/uL
HGB	13.7	g/dL
HCT	40.3	%
MCV	87.1	fL
MCH	29.6	pg
MCHC	34.0	g/dL
RDW	15.1	%



Investigating Microcytic Anaemia

Iron Studies

- Serum Iron (free Fe)
- Iron Binding Capacity IBC (transferrin)
- Ferritin

Do iron studies before thalassaemia screen

- commoner
- cheaper
- false negatives

Investigating Microcytic Anaemia: iron studies:

Fe Deficiency:	Chronic Disease:	Iron overload:
•Low serum Fe •Increased IBC •Low ferritin	•Low serum Fe •Reduced IBC •Normal ferritin	•High serum Fe •Normal IBC •High ferritin
	NB: Problem here is a block in the utilisation of Fe.	NB: May reflect defects in Hb production, or iron overload from transfusion.

Investigating Microcytic Anaemia

Special Tests

- soluble transferrin receptor (sTfR)

  main role is excluding iron deficiency in patient with anaemia of chronic disease
- thalassaemia: Haemoglobinopathy/thalassaemia screen and DNA analysis
- iron status remains unclear: Bone marrow biopsy

Soluble transferrin receptor

- soluble transferrin receptor levels parallel cell surface expression levels
- Increased transferrin receptor expression with onset of iron deficiency (80-95% transferrin receptors are on erythropoietic cells)
- rise predates fall in Hb

Soluble transferrin receptor

- Main role is in anaemia of chronic disease (ACD), to exclude concomitant iron deficiency
- mirrors marrow iron deficiency and is not elevated by ACD *per se*
- performed at A+

Fe Deficiency

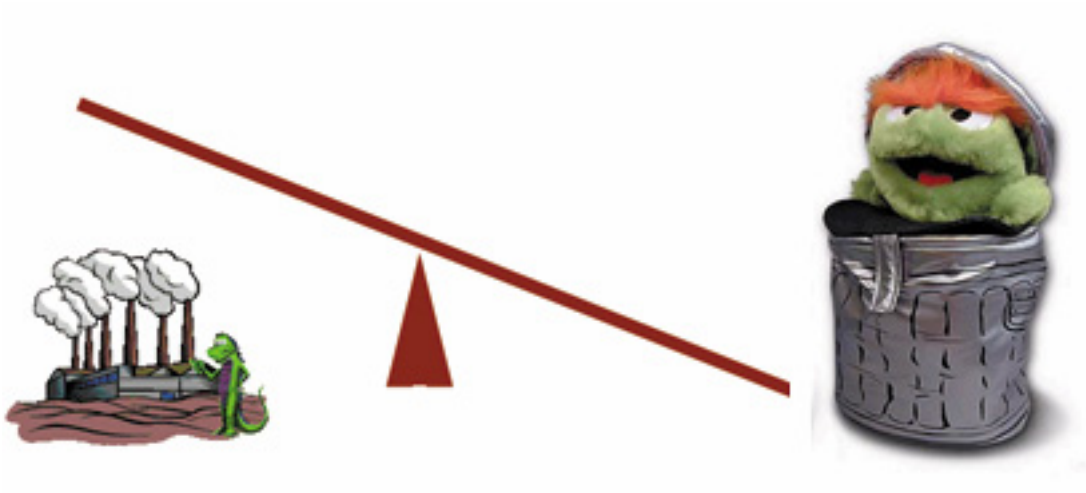
- Treat underlying cause if possible (e.g. bleed)
- Oral Fe replacement – Ferrous sulphate cheap but may be problematic; try ferrous gluconate or fumarate
- Continue for 4-6/12
- Reticulocytosis typically begins 7 days after Rx
- Fe replacement IV if oral not possible - 2 preparations available
- Debate over role of IM iron

Classification Based on MCV

Microcytic ~	Normocytic ~	Macrocytic ~
•Fe deficiency	•Chronic disease	•B12/folate deficiency
•Thalassaemia	•Haemolysis	•Liver disease
•Chronic disease	•Marrow disease (including MDS)	•Marrow disease (MDS)
		•Haemolysis (if MCV pushed up by reticulocytosis)

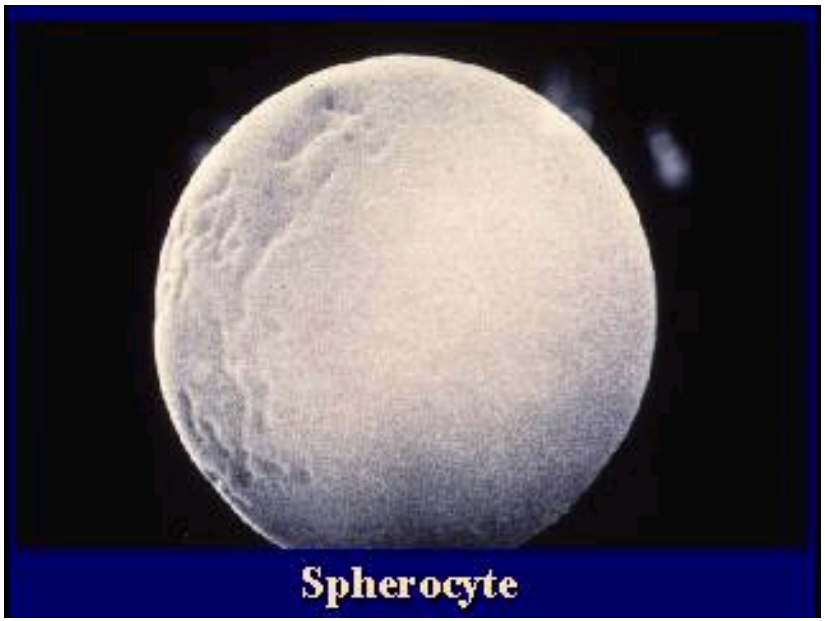
Red cell destruction - how it's done

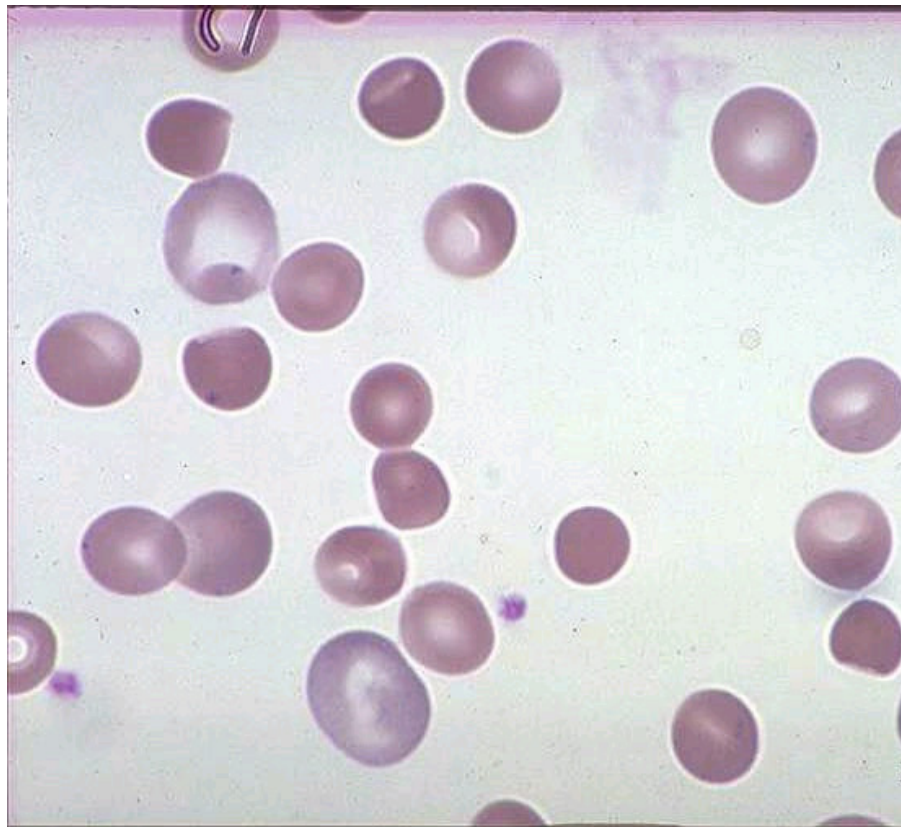
- Immunological - may form spherocytes
- by mechanical fragmentation



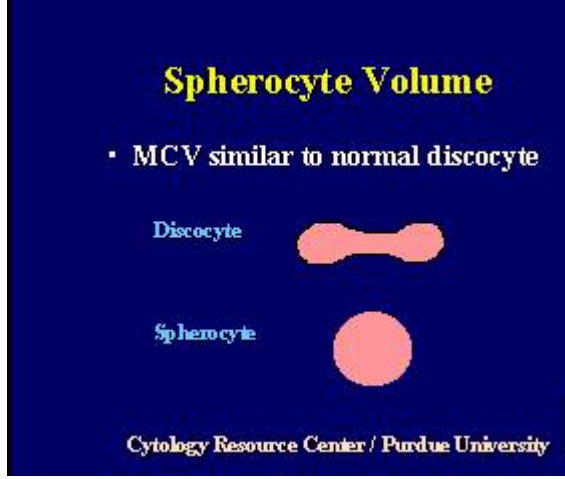
Red cell destruction

- Immunological
  - ‘warm’/IgG
    - spleen
    - spherocytosis

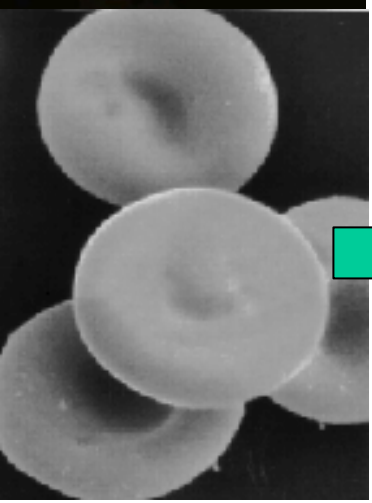


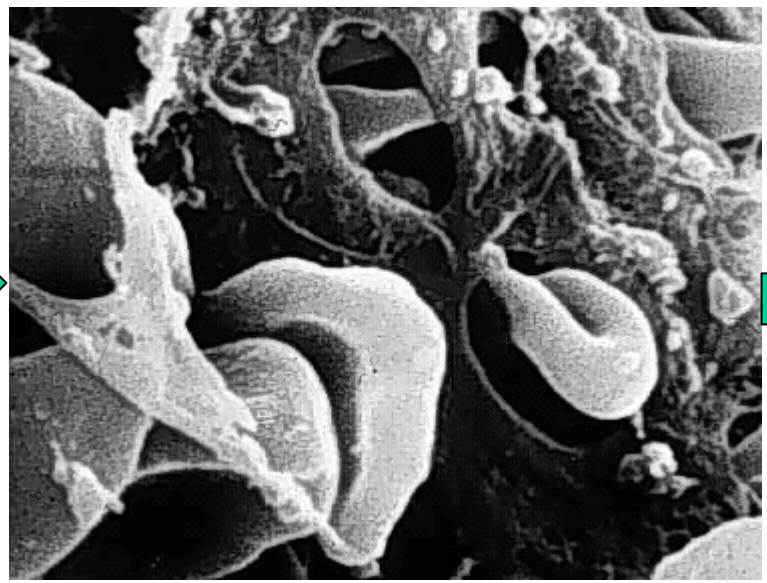


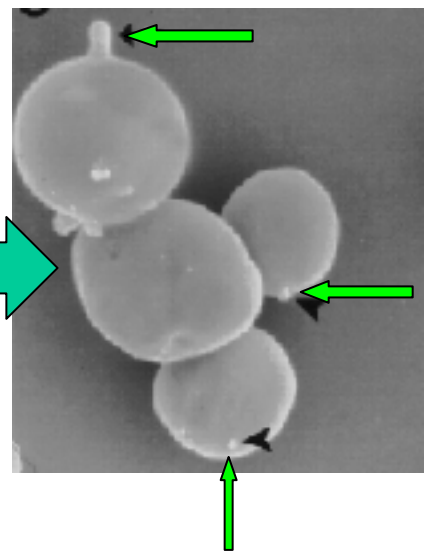
Red cell destruction -



- mechanism of formation of spherocytes





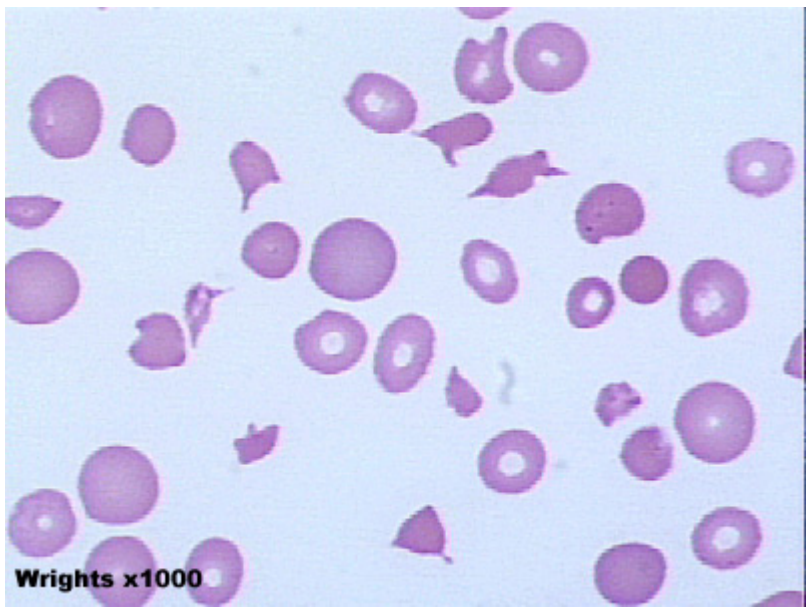


Red cell destruction

- Immunological
  - ‘cold’ / IgM
    - red cell agglutination

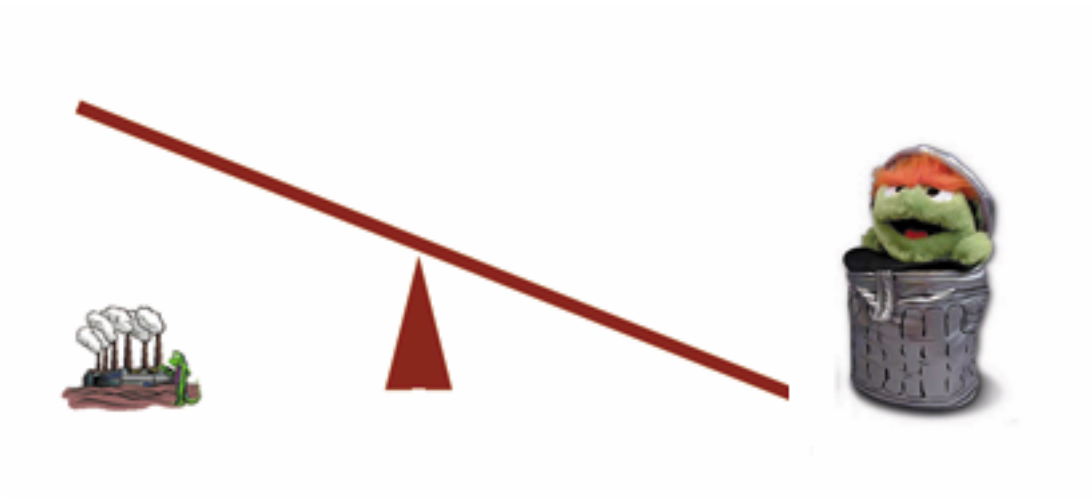
Red cell destruction

- By mechanical fragmentation



- Other forms of haemolysis:
  - congenital (spherocytic and non-)
  - PNH (=Paroxysmal Nocturnal Haemoglobinuria - clonal, C’)

- Pure red cell aplasia
  - rare
  - immune
  - thymoma



Investigating Normocytic Anaemia

Reticulocyte Count

Increased → Haemolysis

- Normal or decreased → Chronic disease

  Marrow disease
  (MDS or infiltration)

Haptoglobins

Present: excludes significant haemolysis

coombs test:

detects presence of antibody on cell surface

bilirubin

Investigating Normocytic Anaemia

Other Cell Counts

- Normal → Chronic disease likely
- Abnormal → Marrow disease should be considered

Investigating Normocytic Anaemia

Further Tests

- Bone marrow biopsy to exclude infiltration, dysplasia, or aplasia
- Other tests for underlying chronic disease
    1. ESR, CRP
    2. U&E's, creatinine
    3. LFTs
    4. Thyroid function …etc.

Investigating Macrocytic Anaemia

Target cells: suggests liver disease

Oval macrocytes and concomitant cytopenias: suggest B12/folate deficiency or MDS

Dysplastic features eg hypogramular neutrophils: suggests MDS

- → confirm with marrow biopsy, chromosomes, etc.)

Macrocytic Anaemias

- cell division requires DNA; T made from U (fidelity) - needs B12 and folate otherwise cell can't divide, gets larger: macrocytic red cells, hypersegmented neutrophils
- liver disease (lipid)
- Myelodysplasias

Investigating Macrocytic Anaemia

LFTs.

B12/folate (NB red cell folate).

Reticulocyte Count

Investigating Macrocytic Anaemia

B12 / Folate Level

- note that normal folate reflects current status and does not exclude folate-deficient haemopoiesis in the recent past - need red cell folate