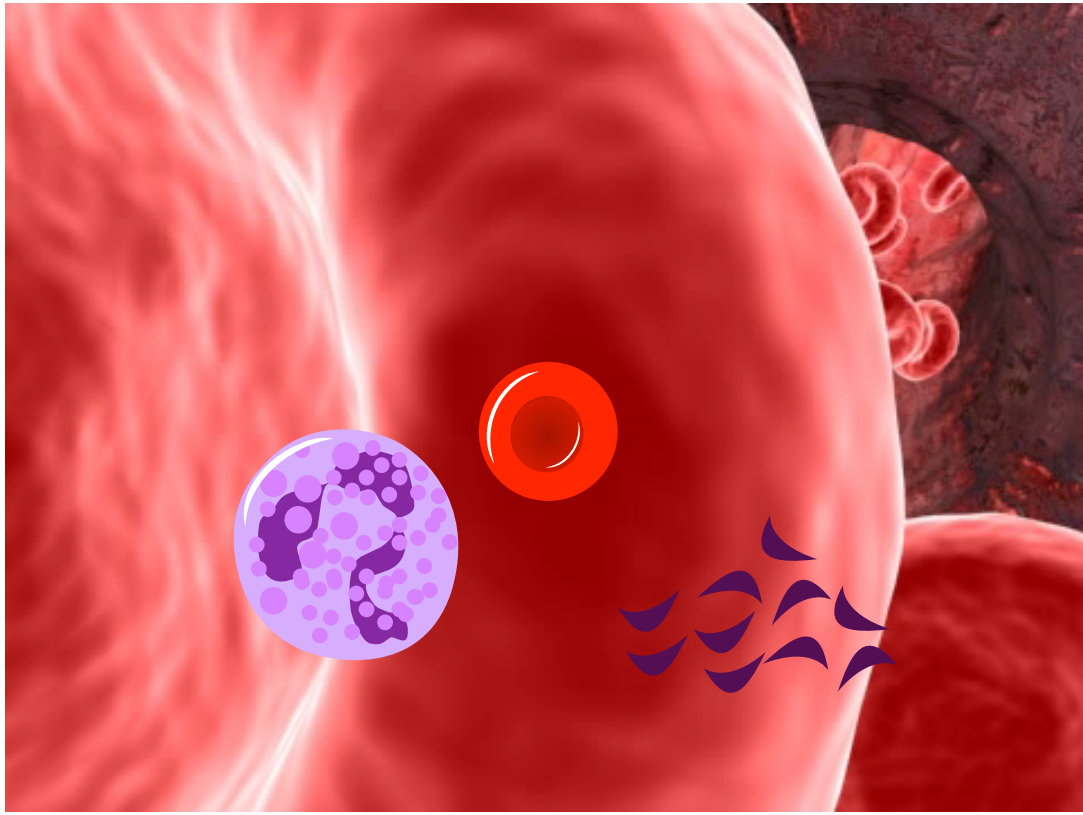
Bone marrow disorders

Dick Wells
Sunnybrook MDS Program

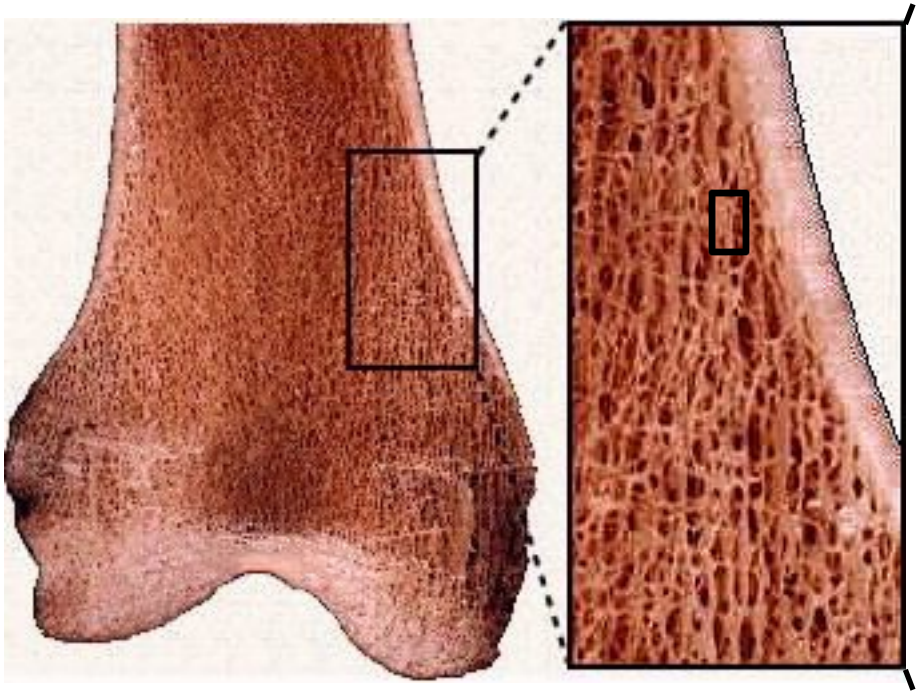
Red blood cell:
Carries oxygen

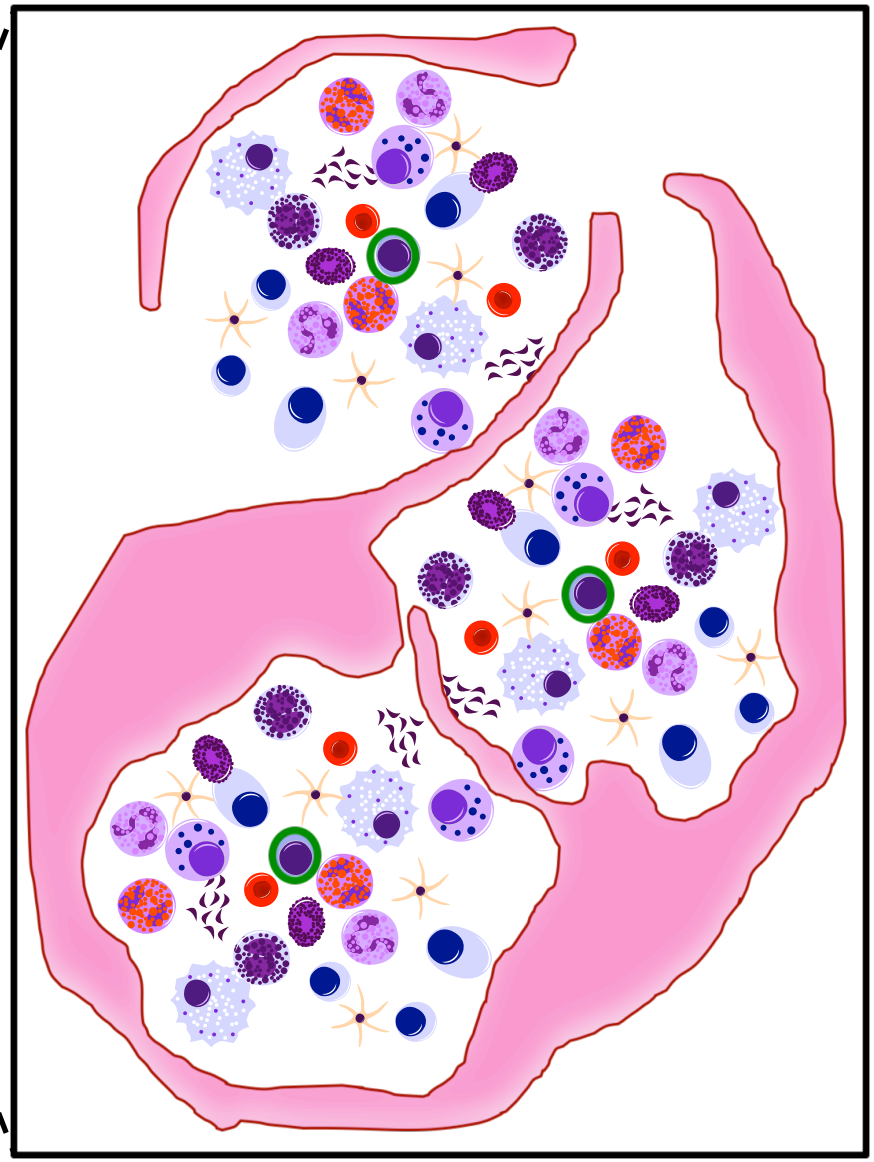
White blood cell:
Fights infection

Platelets:
Stop bleeding

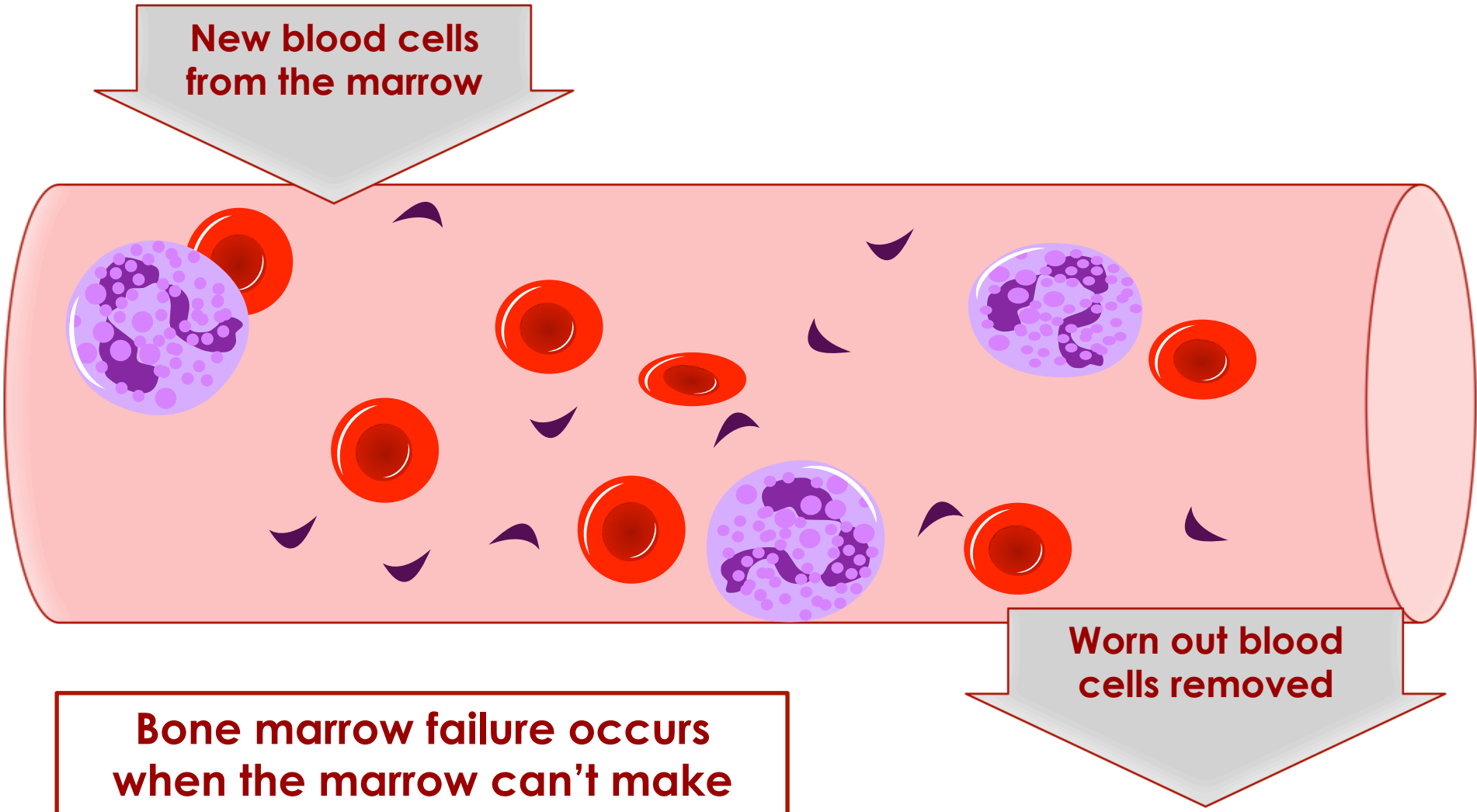


New blood cells are made in the bone marrow





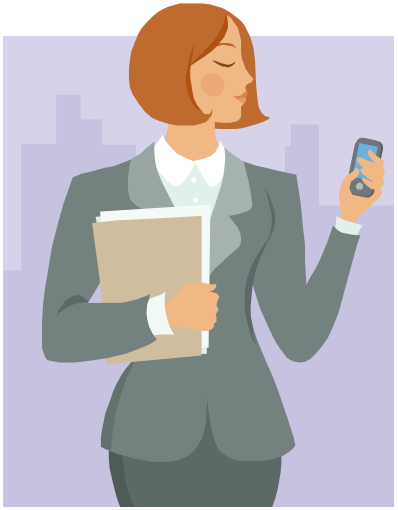
New blood cells come from "stem cells"



Bone marrow failure occurs when the marrow can't make enough new cells to replace the ones that wear out

Bone marrow failure Patient #1

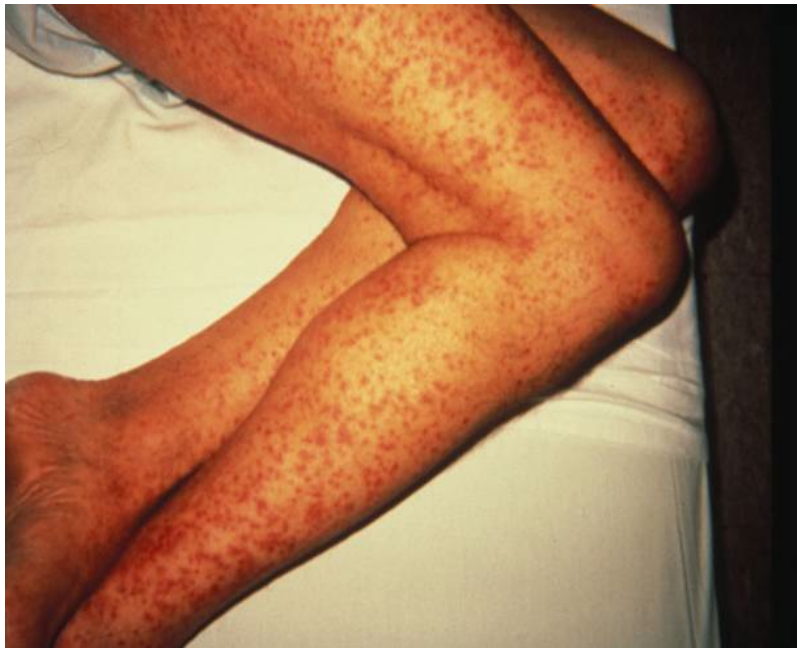
- Jenna is a 49 year old woman who has always been healthy
- Over the past two months she has felt very tired, but blamed it on her busy schedule



- For two weeks she has noticed bruises on her legs
- Today she has a high fever

Bone marrow failure: pancytopenia

- Examination:
  - Pale
  - Petechiae on legs



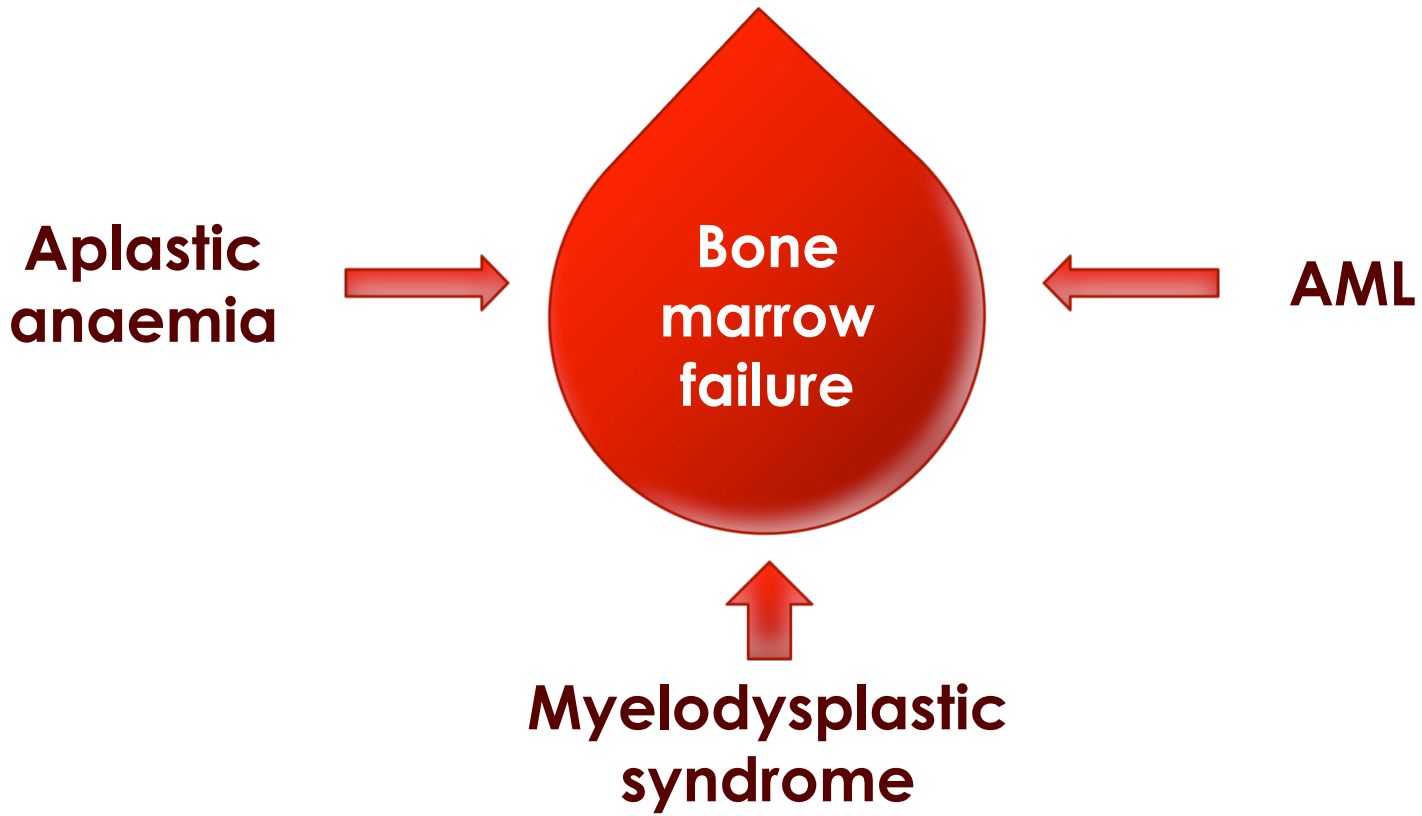
- Labs:
  - Pancytopenia
    - **Hb 43 g/L** (130-160)
    - **WBC 0.4x10^9/L** (3-9.5)
    - **Plt 12x10^9/L** (150-400)

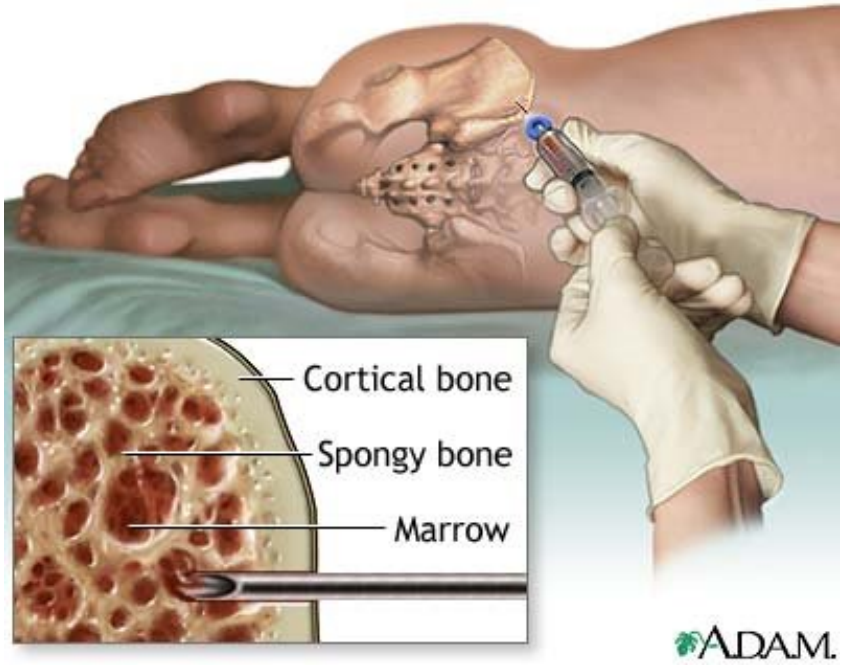
Why has Jenna's bone marrow failed?

Consequences of bone marrow failure

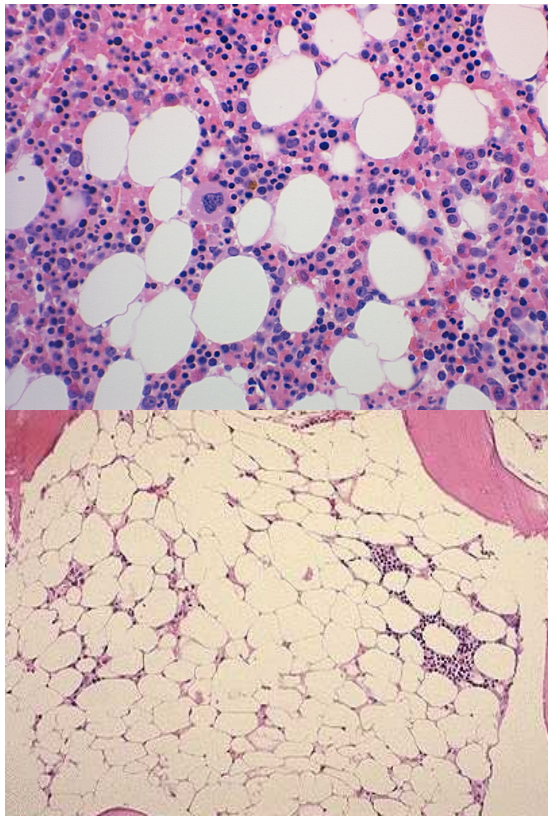
- Anaemia: not enough red blood cells
  - Fatigue
  - Breathlessness
  - Heart failure
- Thrombocytopenia: not enough platelets
  - Bruising with minimal trauma (or spontaneous)
  - Catastrophic bleeding (e.g. intracranial)
- Leukopenia: not enough white blood cells
  - Increased frequency and severity of infection

Causes of bone marrow failure

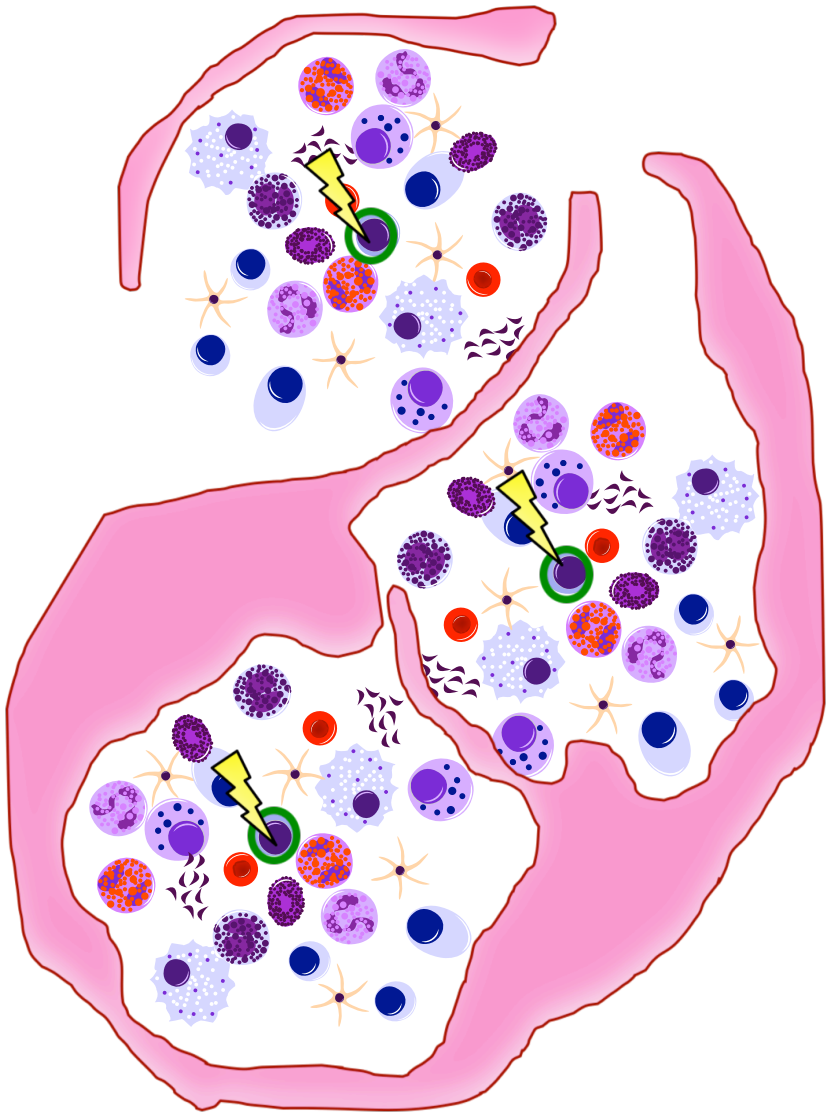




Normal marrow



Aplastic anaemia



Aplastic Anaemia

Immune system attacks the stem cells

Stem cells are destroyed

New blood cells are not made

–

Marrow becomes empty

Aplastic anaemia facts

- Rare: 5 cases per million per year
- Can affect all ages
- Stem cells are lost/destroyed due to immune system, toxins, or inherited problems
- The bone marrow cannot meet the body's needs for new blood cells

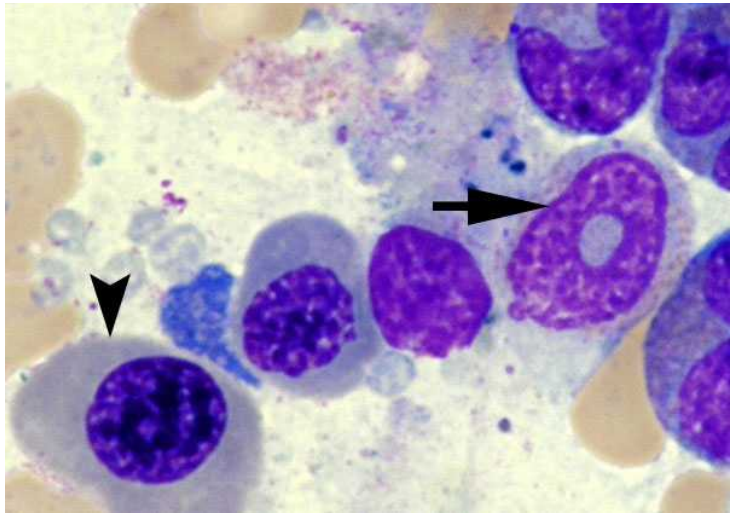
Bone marrow failure Patient #2

- Robert is an 86 year old man who has a history of heart disease and a knee replacement
- His doctor has noted a drop in all his blood counts over the past 10 months

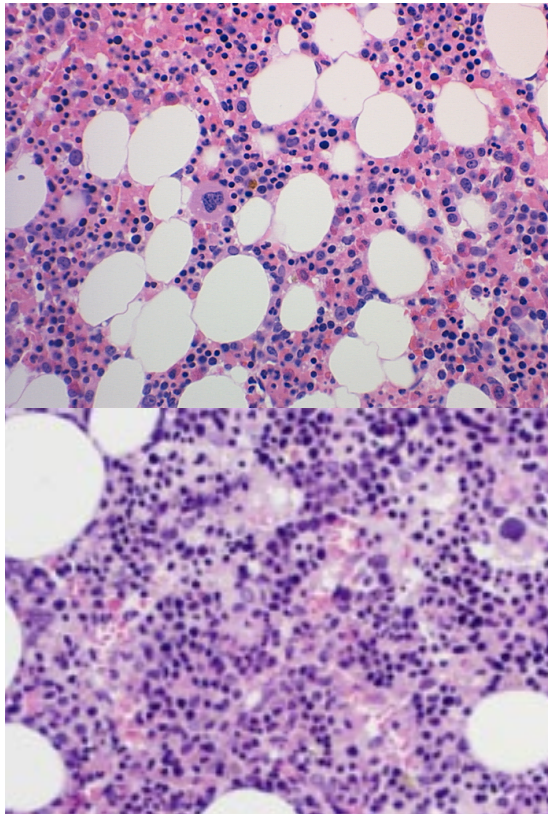
- He now needs a blood transfusion and is sent to a haematologist

Bone marrow biopsy: MDS

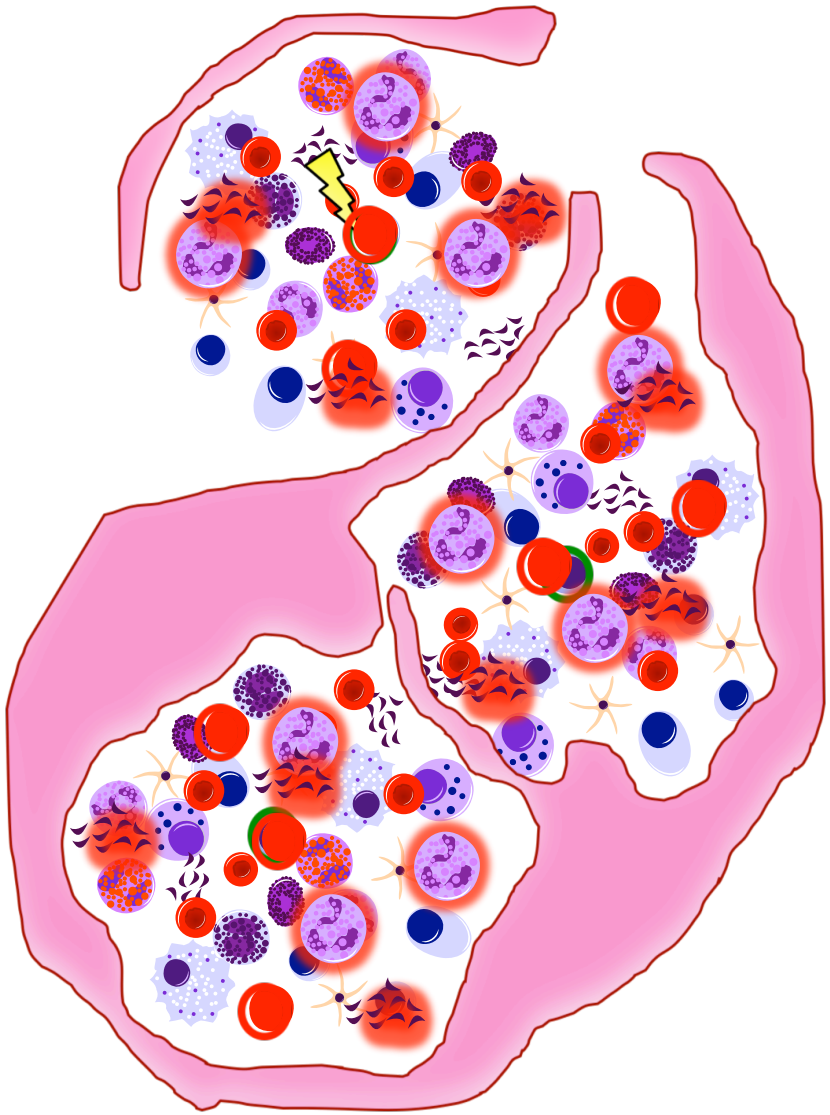
- Unlike aplastic anaemia, the marrow is full of cells (even more than normal)
- Plenty of blood cells are made, but they are too abnormal to be released into the blood



Normal marrow



MDS



Myelodysplastic syndrome

Single stem cell is mutated

The mutant stem cell takes over

Dysplastic blood cells made – Not enough normal cells

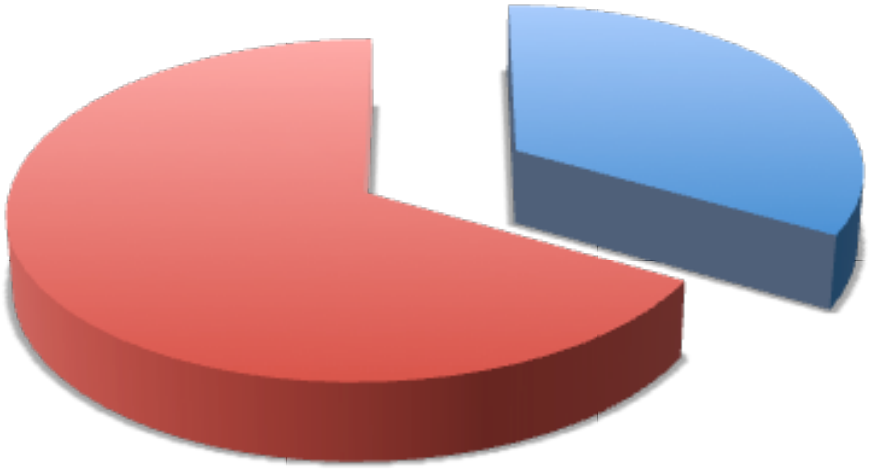
MDS facts

- 50-100 per million per year
- Rare in children and young adults
- Causes: radiation, chemo, organic solvents
- Usually the cause cannot be identified
- Blood cells develop abnormally and fail to exit the bone marrow

All cases of MDS are NOT created equal

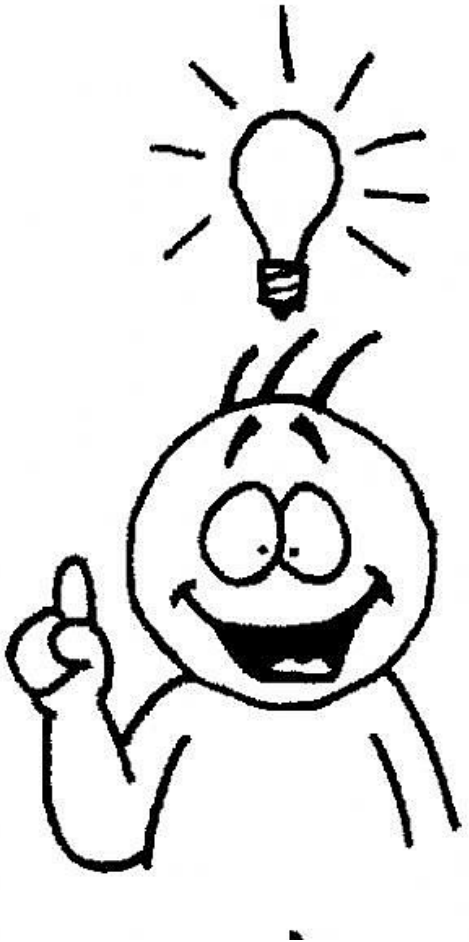
Two kinds of MDS

High-risk
Life expectancy 1-2 years
Rapid development of leukaemia
Treatment aimed extending survival



Low-risk
Life expectancy 5-10 years
Leukaemia is rare
Treatment aimed at improving blood counts

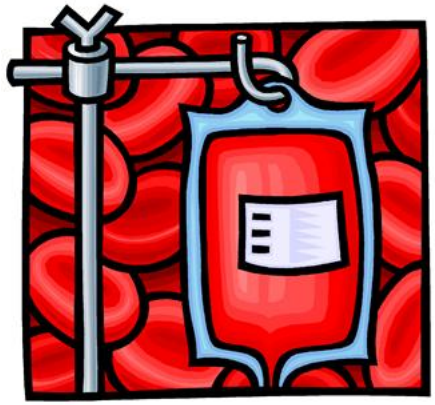
Progress!



- Two major therapeutic breakthroughs in the past 5 years (Lenalidomide and Vidaza)
- Huge advances in our understanding of genetic mutations in MDS in last 2 years
- Research continues – more breakthoughs coming!

Bone marrow failure Patient #3

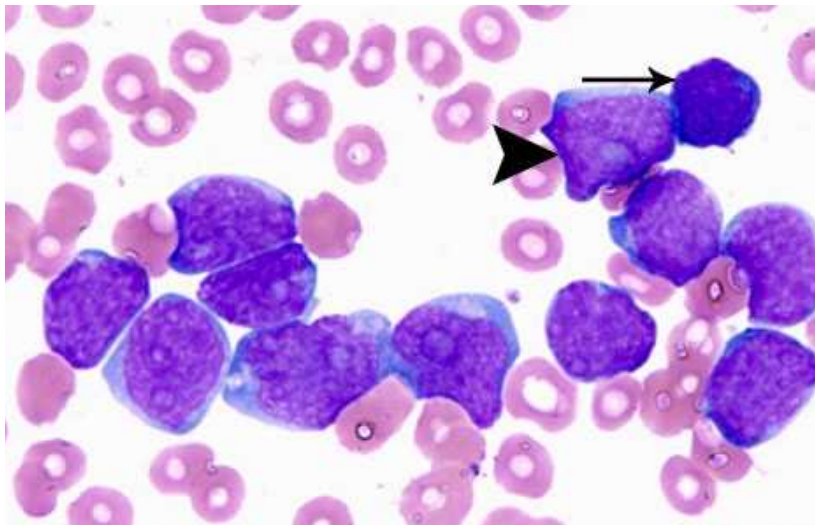
- Steven is a 74 year old man who was diagnosed with MDS 3 years ago
- His condition has been stable on treatment, but now he has begun to need more frequent transfusions



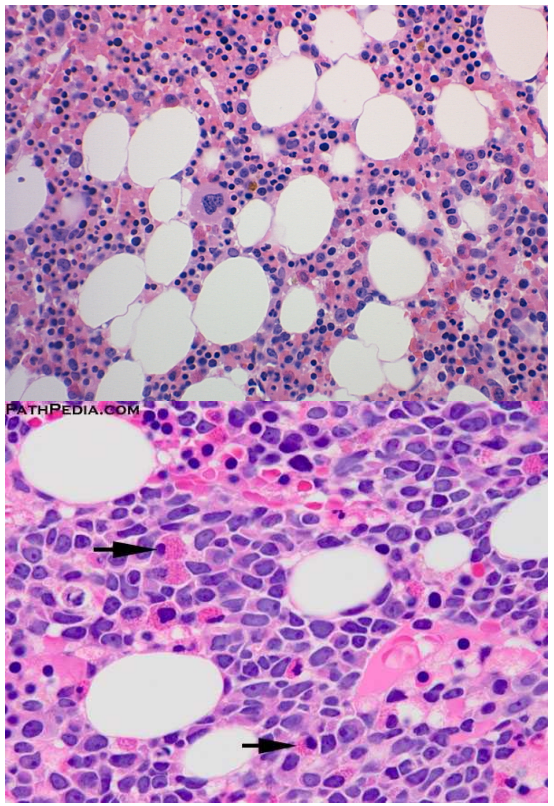
- For a few days he has noticed bruises all over. Now he has a fever.

Bone marrow biopsy: AML

- Blood cells completely fail to develop
- The bone marrow is full of blasts – no normal cells are made



Normal marrow



AML

AML facts

- About 30% of cases of MDS will progress to AML
- AML can also arise in a previously healthy bone marrow
- In the past AML was always fatal without intensive chemotherapy treatment
- New approaches have been developed which provide an alternative

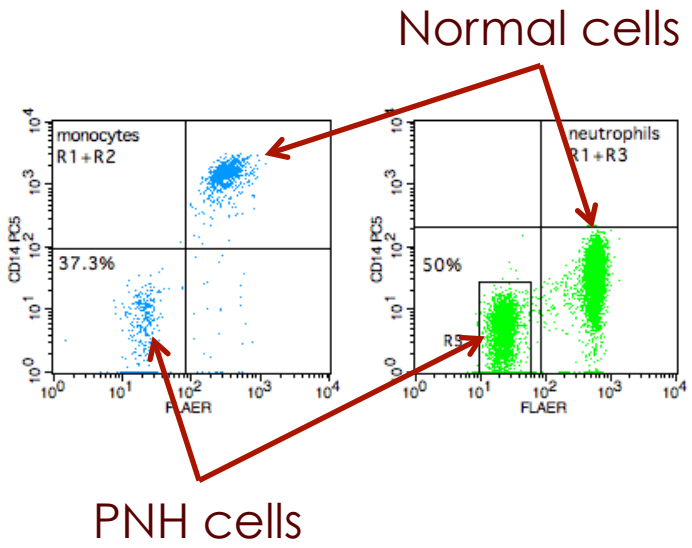
Bone marrow failure Patient #4

- Nadia is a 29 year old new mom.
- During her pregnancy her haemoglobin and platelet counts dropped. After her son was born, her counts continued to get worse.

- She suddenly develops chest pain and goes to the emergency room
- She is found to have a blood clot in her lung, and is very anaemic but has a high reticulocyte count

FLAER assay: PNH

- FLAER assay detects a structure called the GPI anchor on the surface of blood cells
- In PNH the GPI anchor is missing



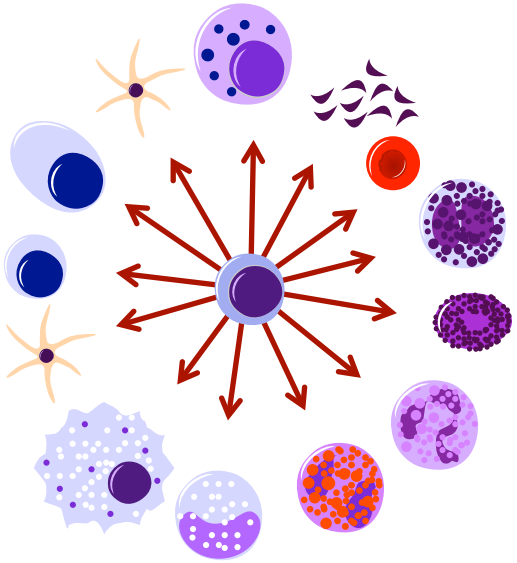
Paroxysmal Nocturnal Haemoglobinuria
Poor branding?

- It's not necessarily paroxysmal
- It's not exclusively nocturnal
  - Haemolysis in PNH is subtle and constant, 24 hours a day
- Haemoglobinuria is infrequently seen
  - ¾ patients present without haemoglobinuria[1]

PNH facts

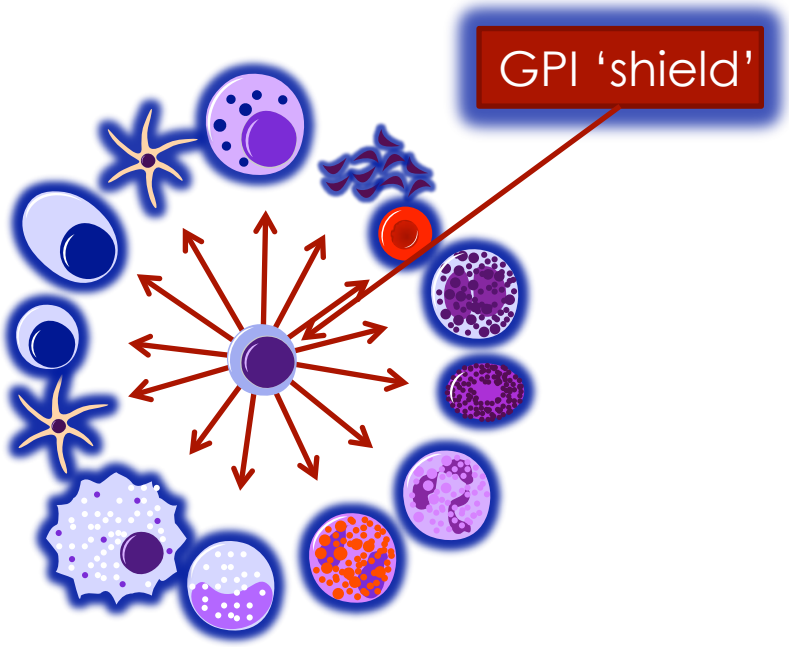
- Incredibly rare. Incidence is about 1 per 1 million per year
- Caused by a specific gene mutation that occurs in a single bone marrow stem cell
- Often found in combination with AA or MDS

PNH starts in a single HSC

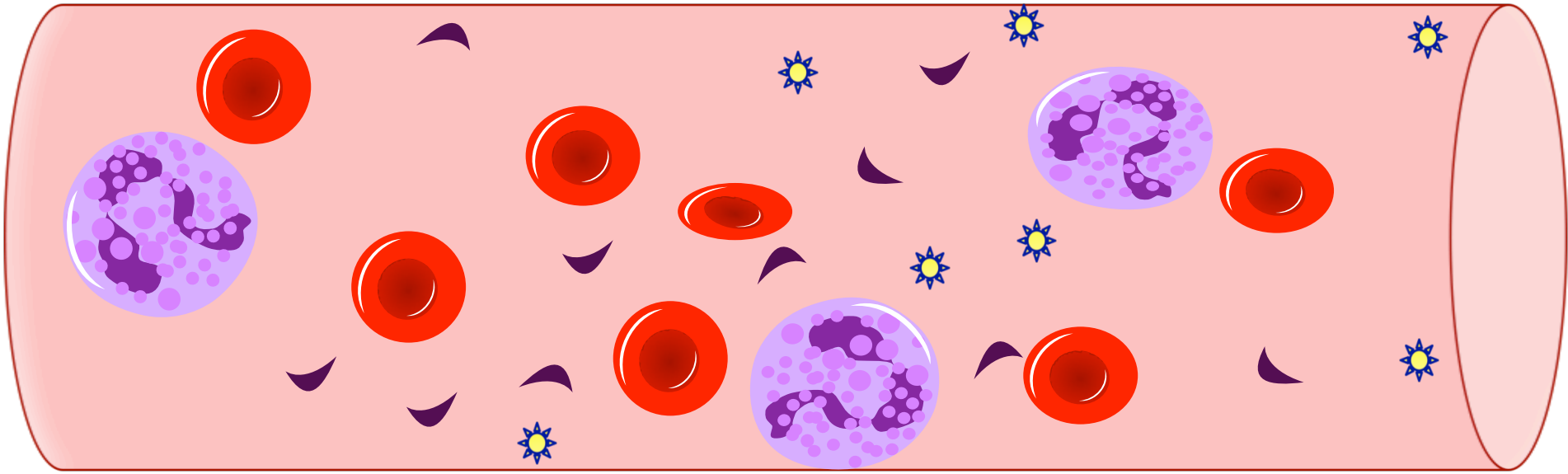


PIGA mutation in HSC:

All descendants lack GPI anchor



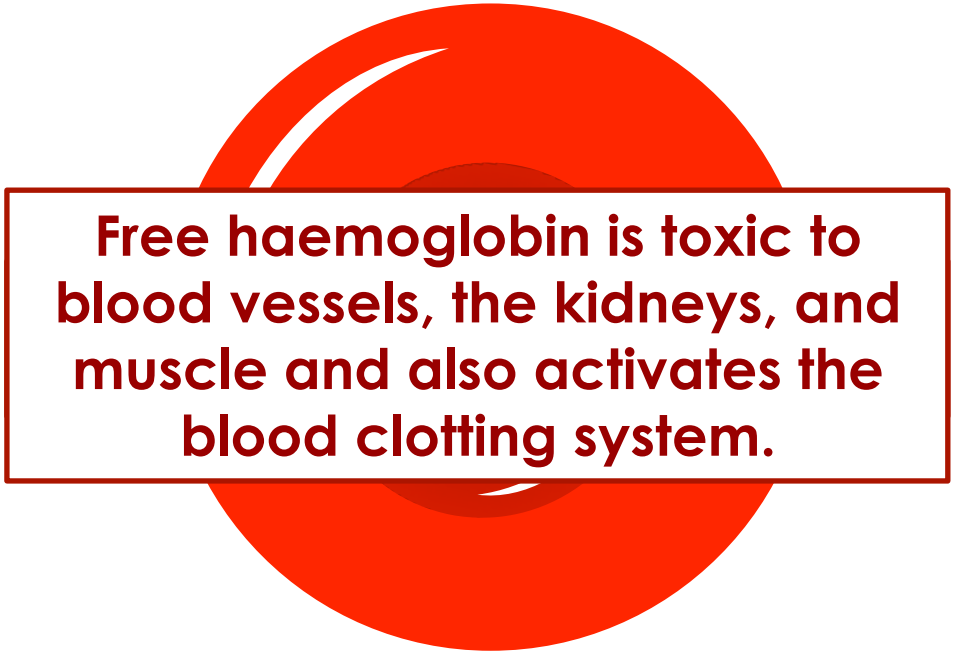
Normal HSC



complement

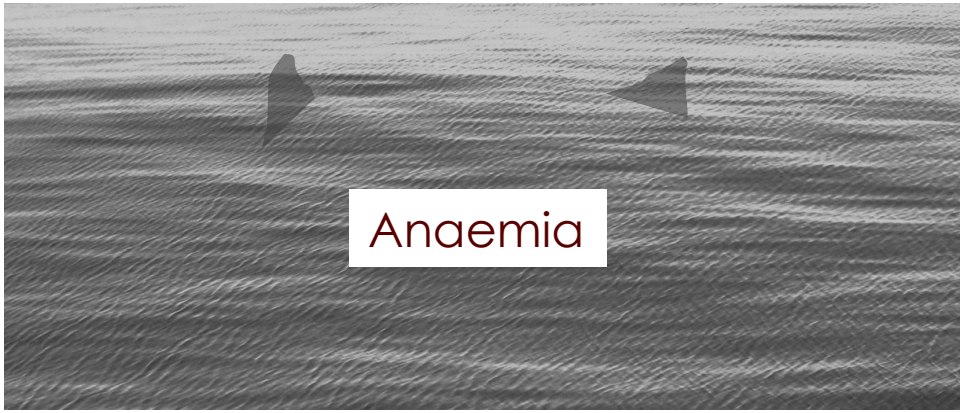
PNH red blood cells are burst by the complement system

When PNH cells burst…



Free haemoglobin is toxic to blood vessels, the kidneys, and muscle and also activates the blood clotting system.

Anaemia in PNH: Just the ears of the hippo

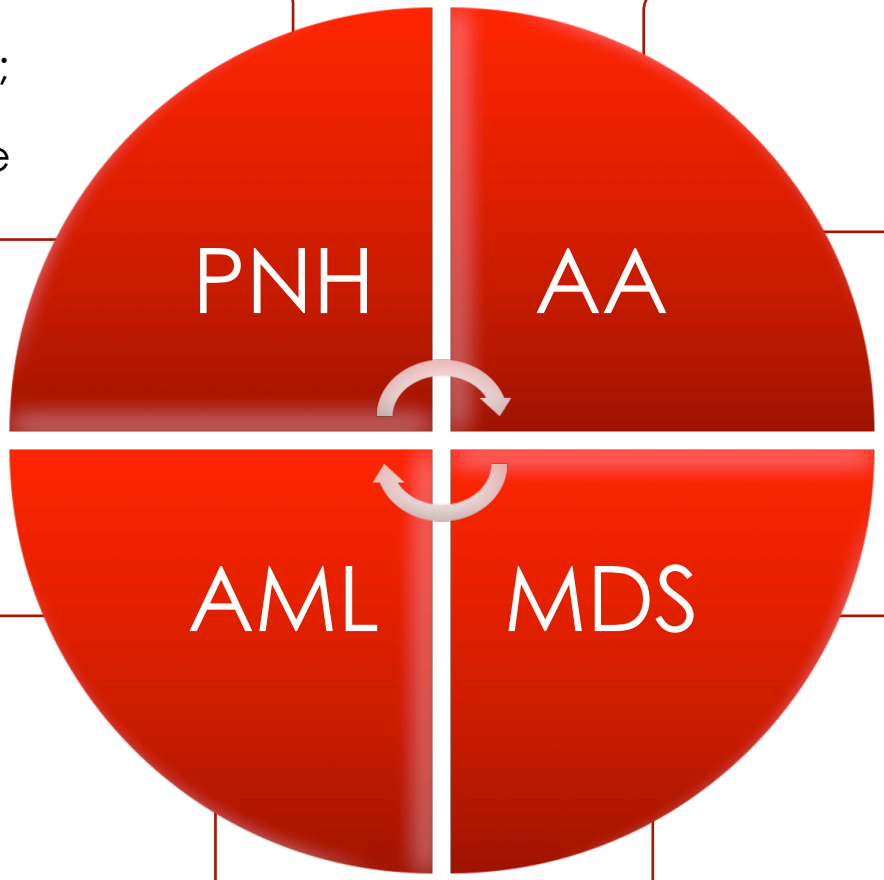


Modern PNH therapy is designed to block the destruction of red blood cells and prevent the damage caused by haemoglobin

Bone marrow failure

- Lack of GPI shield makes RBC vulnerable; free haemoglobin causes organ damage

- Attack by immune system or toxins depletes stem cells



- Further mutation creates a bone marrow cancer

- Mutation impairs ability of stem cells to make normal marrow

Any questions?