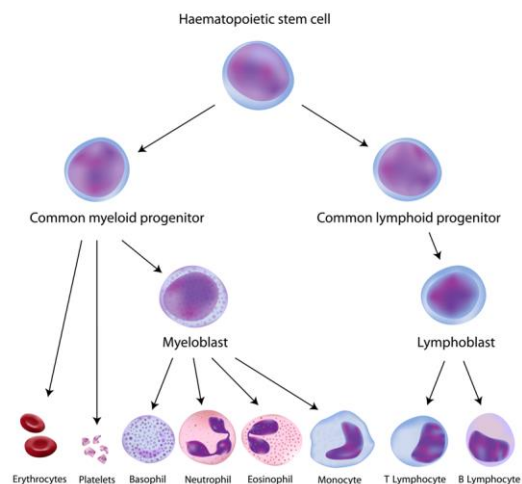
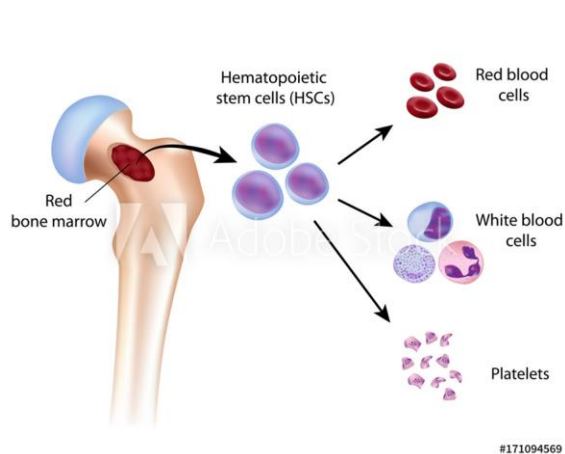
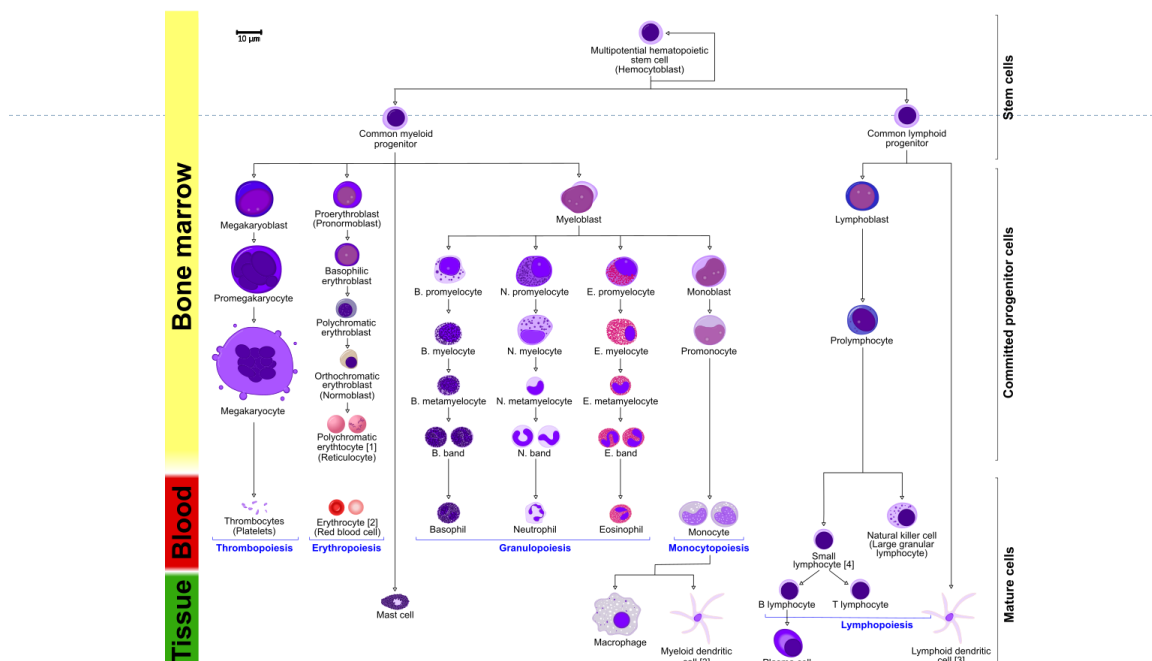


Linking Vitamin B12 with Auto-immunity and Related Conditions

PART 1 – LETS GO BACK TO THE BASICS

Blood – The Basics





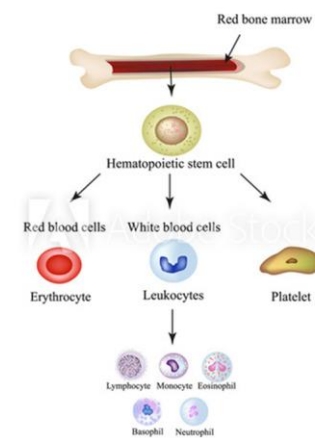
By original: User:A. Rad, svg file drawn with FlashMX by birdyderivative work: RexxS (talk) - Hematopoiesis_(human)_diagram.svg, CC BY-SA 3.0, <https://commons.wikimedia.org/w/index.php?curid=9420824>

Blood... The Basics

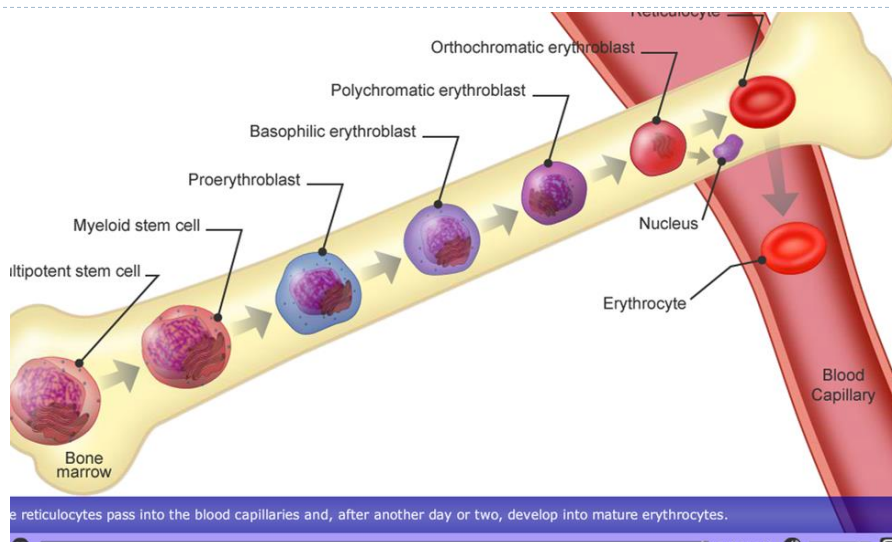
Haematopoiesis = the production of all blood cells including formation, development, and differentiation.

Where Do Blood Cells Come From?

- ❑ Blood cells develop from **haematopoietic stem cells** and are formed in the bone marrow via haematopoiesis.
- ❑ These stem cells transform into red blood cells (RBC), white blood cells (WBC), and platelets.
- ❑ Ineffective haematopoiesis results in insufficient numbers of RBC and results in one of several forms of **anaemia**.



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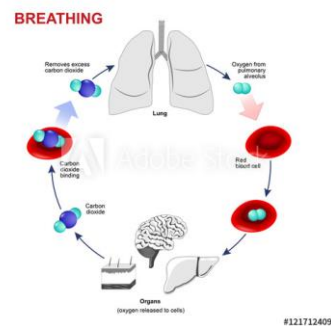
Blood... The Basics

Composition of whole blood:

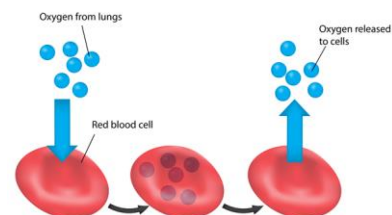
plasma	55%
red blood cells (RBC)	41%
white blood cells (WBC)	4%

Functions of blood:

- ☐ transporting oxygen to tissues and organs
- ☐ transporting waste to the lungs
- ☐ forming blood clots to prevent excess blood loss
- ☐ carrying cells and antibodies that fight infection
- ☐ bringing waste products to kidneys and liver for filtration
- ☐ regulating body temperature



Oxygen Transport

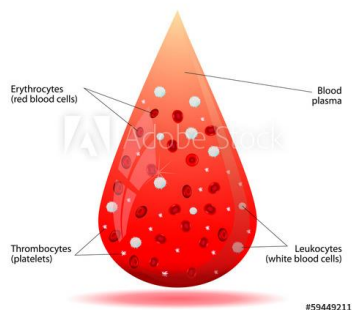


Plasma

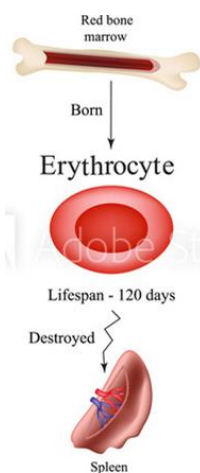
Plasma is a mixture of water, sugar, fat, protein, and salts.

- ❑ Plasma transports the following substances around the body:
 - ❑ blood cells
 - ❑ nutrients
 - ❑ waste products
 - ❑ antibodies
 - ❑ clotting proteins
 - ❑ chemical messengers (hormones, proteins) to maintain fluid balance.

FORMED ELEMENTS OF BLOOD



Red Blood Cells (RBC)/Erythrocytes



Most abundant cell in the blood, (40-45 % of total blood volume).

- ❑ RBC start as immature cells in bone marrow
- ❑ Released into blood stream after about seven days.

RBC have **no nucleus** meaning they can easily change shape and fit through the various blood vessels in your body.

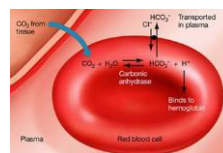
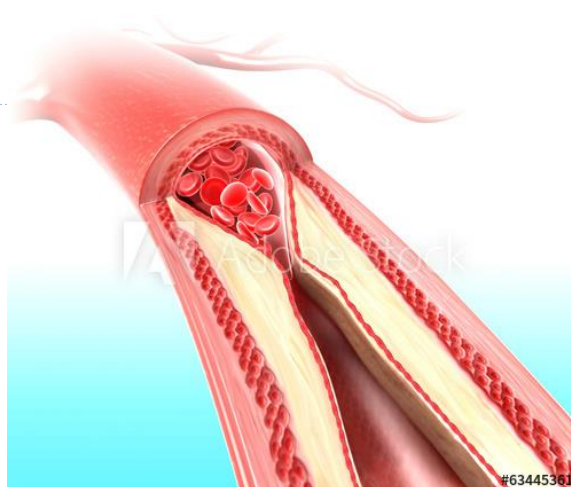
- ❑ **Average RBC lifespan 120 days.**

As RBC travel through small blood vessels their **cell membranes may be damaged**.

Erythrocytes are **biconcave discs** with very shallow centres.

This shape:

- ❑ optimises the ratio of surface area to volume, facilitating gas exchange.
- ❑ enables them to fold up as they move through narrow blood vessels.



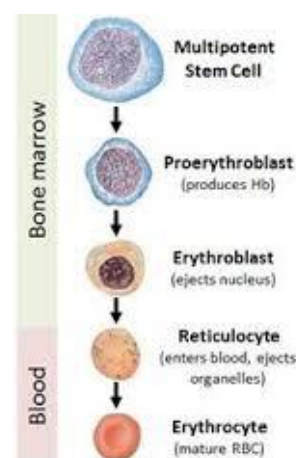
Erythropoiesis

RBC production is called **erythropoiesis** which:

- ❑ occurs in bone marrow via a complex sequence of tightly regulated steps.
- ❑ stimulated by the hormone **erythropoietin (EPO)**.

EPO is largely produced and **secreted by the kidneys**, with about 10% produced and secreted by the liver.

- ❑ EPO secretion is up-regulated in response to low oxygen levels (**hypoxia**) in the blood, as a compensatory mechanism.
- ❑ In a **negative-feedback loop**, as oxygen saturation rises, EPO secretion falls, and vice versa, **maintaining homeostasis**.
- ❑ An overproduction of RBC produces **polycythaemia**.



White Blood Cells (WBC) / Leukocytes

WBC protect the body from infection - account for approximately 1% of total blood volume

Neutrophils 40-60% of total WCC

Kill and digest **bacteria** and **fungi**.

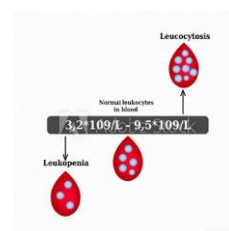
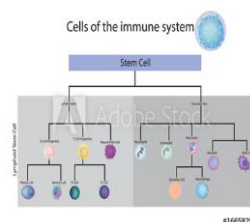
First line of defence when infection strikes. **"immediate response"** Live <24 hours

Lymphocytes (B & T Cells) 20-40% of total WCC

Create **antibodies** to defend against **bacteria**, **viruses**, and other harmful invaders

T lymphocytes regulate function of other immune cells and directly attack infected cells and tumours

B lymphocytes make antibodies (proteins that specifically target bacteria, viruses, and other foreign materials)



White Blood Cells (WBC) / Leukocytes

Monocytes 2-8% total WCC

longer lifespan

break down **bacteria**

Eosinophils 1-4% total WCC

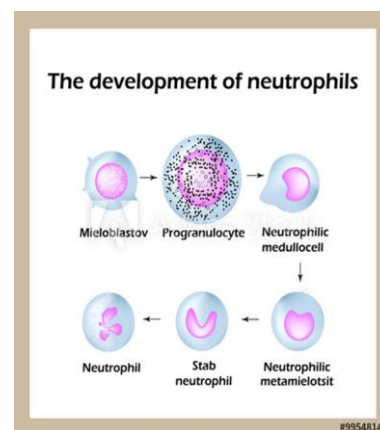
attack and kill **parasites**, destroy **cancer cells** and help with **allergic responses**

Basophils 0.5-1% total WCC

Small cells that sound an alarm when infectious agents invade the blood

Secrete chemicals including **histamine**

Band 0% to 3% (Young neutrophils)

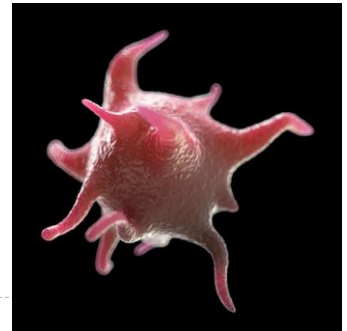


Platelets / Thrombocytes

Major function of platelets = **aiding coagulation** or clotting by gathering at injury sites

- ❑ Platelets **stick to the lining** of the injured blood vessel and form a platform for coagulation
- ❑ A **Fibrin clot** then forms, covering the wound to prevent blood from leaking out
- ❑ Fibrin clot forms the initial scaffolding upon which new tissue forms
- ❑ Increased platelets
- ❑ Cause unnecessary clotting and increased risk of strokes and heart attack

Decreased platelets - Cause extensive bleeding



Haemoglobin (Hb)

Haemoglobin is comprised of

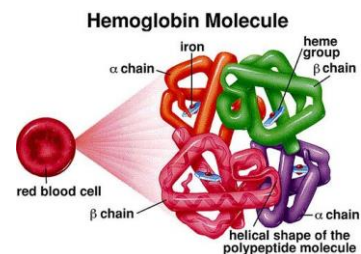
Haem = iron & protoporphyrin

Globin = protein

Hb is contained in the RBC and gives blood its red pigment

Primary functions:

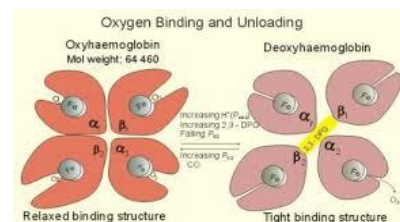
- ❑ **Transports oxygen** from the lungs to the rest of the body
- ❑ **Transports carbon dioxide** from the body to the lungs for exhalation



Haemoglobin (Hb)

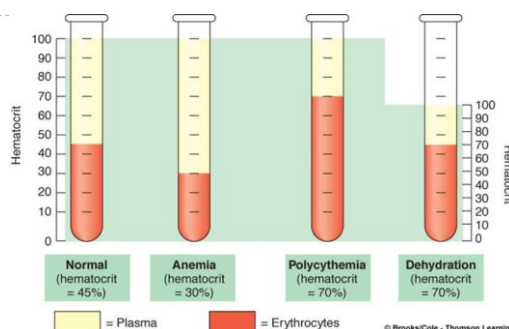
In the lungs, Hb picks up oxygen, which binds to the iron ions, forming **oxyhaemoglobin**.

- The bright red, oxygenated Hb travels to the body tissues, where it releases some of the oxygen molecules, becoming darker red **deoxyhaemoglobin**, sometimes referred to as reduced Hb.
- Oxygen release depends on the need for oxygen in the surrounding tissues, so Hb rarely if ever leaves all of its oxygen behind.

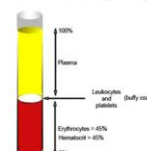


Haematocrit (Hct)

- Haematocrit is the **ratio of RBC to total blood volume** (cells and plasma).
- Hct is useful in the determination of **oxygen deprivation states** including **anaemias**, **altered blood volume states**, **nutritional deficiencies**, haemoglobinopathies and certain chronic diseases.



Haematocrit (PCV) tube



Oxygenation and Saturation

Hb is vital for oxygenation

- Oxygen saturation refers to the percentage of Hb sites occupied by oxygen in a patient's blood, and may be monitored using a **pulse oximeter**, applied to the patient's finger.

An oximeter:

sends two wavelengths of light (one red, one infrared) through the finger
a photodetector measures the light as it exits, (Hb absorbs light differentia depending upon its oxygen saturation).

the oximeter measures the amount of light received against the amount absorbed by the partially oxygenated Hb

presents the data as percent saturation.



Normal pulse oximeter range is 98–100%.

- Decreased saturation % reflects hypoxemia, or low blood oxygen.

Deoxygenated Blood Vs Oxygenated Blood



Vital Nutrients for Erythropoiesis

Healthy **Erythropoiesis** produces a staggering 2 million+ cells per second.

A number of raw materials must be present in adequate amounts for healthy RBC production.

These include

- ❑ Nutrients essential for production and maintenance of all cells (glucose, lipids, amino acids)
- ❑ As well as
 - ❑ Iron
 - ❑ Copper, Zinc
 - ❑ **B12**
 - ❑ Folate, B6, B2



Iron (Fe)

Each haem group in a Hb molecule contains an ion of the trace mineral Fe.

On average <20% of ingested Fe is absorbed.

- ❑ Haem Fe, (animal foods), is absorbed more efficiently than non-haem Fe (plant foods).
- ❑ **Fe²⁺ (Ferrous)** = a salt containing iron in its lowest valence state, Fe²⁺.
- ❑ **Fe³⁺ (Ferric)** = form of Fe that can be bound to its **transport protein transferrin**, for transport to body cells.

Upon absorption, Fe becomes part of the body's total iron pool.



Iron (Fe)

The bone marrow, liver, and spleen can store Fe in the protein compounds *ferritin* and *haemosiderin*

- ❑ *Ferroportin* transports Fe across the intestinal cell plasma membranes and from its storage sites into tissue fluid where it enters the blood.
- ❑ When **EPO** stimulates the production of erythrocytes, iron is released from storage, bound to *transferrin*, and carried to the red marrow where it attaches to erythrocyte precursors.
- ❑ **Iron deficiency will cause low Hb.**



Copper (Cu)

Cu is a trace mineral, and a component of two plasma proteins, *hephaestin* and *ceruloplasmin*.

- ❑ Hephaestin and ceruloplasmin are vital for Hb production.
- ❑ Hephaestin enables Fe to be absorbed by intestinal cells, and is located in the intestinal villi.

Ceruloplasmin transports Cu.

Both hephaestin and ceruloplasmin enable the oxidation of Fe from *Fe²⁺* (*ferrous*) to *Fe³⁺* (*ferric*).

- ❑ Cu deficiency causes decreased levels of the Fe transporter molecules, meaning iron can accumulate in tissues, where it can eventually lead to organ damage. Haem synthesis also decreases.



Zinc (Zn)

- ❑ The trace mineral Zn functions as a co-enzyme that **facilitates the synthesis of the *haem* portion of Hb.**



B12 & Folate – partners for life!

- ❑ Vitamin B12 functions as a **co-enzymes that facilitates DNA synthesis..**
- ❑ B12 is critical for the synthesis of new cells, including erythrocytes.
- ❑ Methylcobalamin is required for the function of the ***folate-dependent enzyme methionine synthase***.
 - ❑ ***Methionine synthase*** is an **enzyme** required for the synthesis of the amino acid **methionine from homocysteine**.
 - ❑ Vitamin B-12 contributes to Hb synthesis by activating ***succinyl CoA***
 - ❑ Succinyl CoA is a haem precursor.

Without vitamin B12, you cannot make enough haem to produce functional RBC!!!

Folate



Folate functions as a **coenzymes that facilitate DNA synthesis**.

Erythroblasts require folate for proliferation during their differentiation.

Erythrocyte Lifespan

Erythrocytes live up to 120 days in the circulation.

After 120 days worn-out cells are removed by **macrophages**.

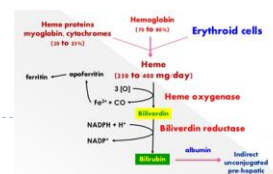
The components of the degraded erythrocytes are further processed as follows:

- ❑ **Globin**, the protein portion of Hb, is broken down into amino acids, sent back to the bone marrow to be used in erythropoiesis.
- ❑ The remaining (non-phagocytized) Hb is broken down in the circulation, releasing its alpha and beta chains that are removed from circulation by the kidneys.
- ❑ The **Fe** contained in the haem portion of Hb may be stored in the liver or spleen, primarily as **ferritin** or **hemosiderin**, or carried through the bloodstream by **transferrin** to the red bone marrow for recycling into new erythrocytes.

Bilirubin

The non-Fe portion of haem is degraded into the waste product **biliverdin**, (green pigment), and then **bilirubin** (yellow pigment).

Bilirubin binds to **albumin** and travels in the blood to the liver



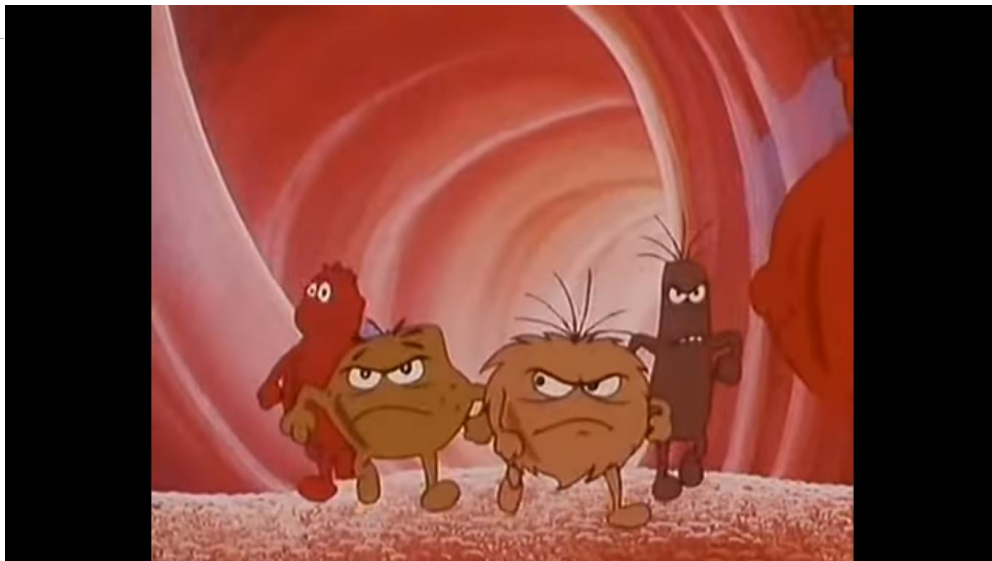
- ❑ In the liver **bilirubin** is used to manufacture **bile**, which is released into the intestines to emulsify dietary fats.
- ❑ In the large intestine, bacteria breaks the bilirubin apart from the bile and converts it to **urobilinogen** and then **stercobilin**, which is then eliminated in the faeces.
 - ❑ (Broad-spectrum antibiotics typically eliminate these bacteria and subsequently alter the colour of the faeces).
- ❑ The kidneys also remove circulating **bilirubin** and other related metabolic by products such as **urobilins** and secrete them into the urine.

Pigment Breakdown

The breakdown pigments formed from the destruction of Hb can be seen in a variety of presentations:

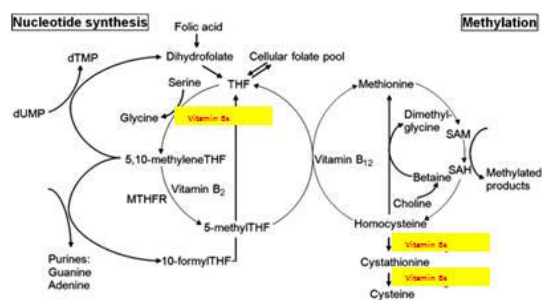
- ❑ **Biliverdin** from damaged RBCs produces some colouration in **bruising**
- ❑ If **bilirubin** cannot be removed effectively from circulation it causes the yellowish tinge of **jaundice**.
- ❑ **Stercobilins** within **faeces** produce the typical brown colour.
- ❑ Yellow colour of **urine** is associated with the **urobilins**.





Vitamin B6

- As well as Folate, B12, and iron, **vitamin B6** also has a crucial role in erythropoiesis.
- Vitamin B6 is also essential for RBC metabolism.



<http://pi.oregonstate.edu/mic/vitamins/vitamin-B6>

Hop on Hop off – The Little Red Bus

Think of the RBC as a bus. Once made it takes on board Hb it sets off for the the tissues and then returns back to the lungs.

(**B12**, folate, Fe, Zn, B6 & B2 are like the **building materials for the bus** (RBC), essential for **healthy erythropoiesis**).

Waiting in the **lungs** are **oxygen molecules** which hop on the bus (into the RBC) and immediately **bond to the iron in the Hb** (oxygen sits next to Fe & they hold hands).

The bus carries on to tissues/organs and when it arrives, the doors open, the **oxygen molecules separate from the Hb** and exit the bus.

The **RBC then return to the lungs**, taking with them some **waste proc**

The bus drives this same route endlessly, repeating the process.



Take Home Summary of B12 and RBC Health

Without adequate supplies of iron, folate, B6, Zn, B2 and **B12, individuals are unable to make healthy RBC!**

- ❑ B12 deficiency deforms the shape of the RBC's, typically making them bigger (**Macrocytosis**), however there are exceptions to this (for example in concurrent B12 and iron deficiency).
- ❑ If an individual has **low or very low B12 levels**, they won't be able to make healthy RBC, and the strangely shaped RBC **won't be able to carry Hb**.
- ❑ The decreased oxygenation in the body causes fatigue, impaired concentration and so on.