

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ
(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)



HLS Physiology | MID 3

RBCs

Pt.2



Written by : Salma Obeidat (s.holmes)

Mousa Al-Neimat

Reviewed by : Sara Qatatshah

Important Notes Regarding The Previous Lecture

1. Reticulocytes:

- Reticulocytes are **immature red blood cells (RBCs)** that leave the bone marrow and enter the circulation before **completing their maturation into erythrocytes**.
- Textbook note: At the Reticulocyte stage, the reticulocyte **starts leaving the bone marrow to circulate in the blood**. However, some reticulocytes **may leave the bone marrow before maturing into erythrocytes**, making up approximately **2%** compared with RBCs.

Important Notes Regarding Reticulocyte

1. Reticulocytes:

❑ Clinical significance

- When a person experiences blood loss (hemorrhage), the red bone marrow increases hematopoiesis to compensate for the loss of RBCs. As a result, the number and percentage of reticulocytes increase.
- Increased reticulocyte count: Indicates increased RBC production by the bone marrow, as seen in hemorrhage and hemolytic anemia.
- Decreased reticulocyte count: Suggests decreased RBC production or an impaired bone marrow response, as seen in aplastic anemia.
- Summary: Reticulocytes reflect the bone marrow's response to RBC loss. An increased count generally indicates increased production, whereas a decreased count may indicate impaired production.

RBC

Reticulocyte count

<2% in normal adult

The normal count or concentration of Reticulocyte should be between 1-2% of the RBCs count.

$$\text{Reticulocyte count} = \frac{\text{Number of reticulocyte}}{\text{Number of RBCs}} \times 100\%$$

Importance: Reticulocytes count help in diagnosis and typing of anemia

Decreased

Aplastic anemia

Increased

Hemolytic anemia
Post hemorrhage

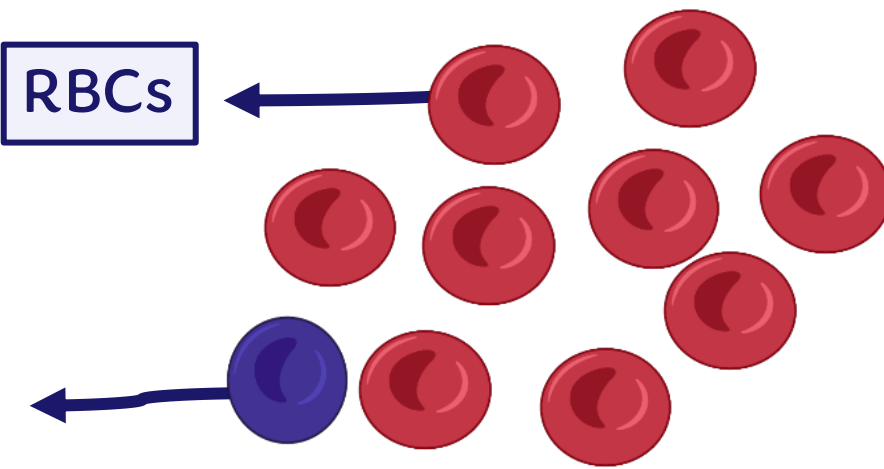
Reticulocyte Count

❑ Why is the reticulocyte count important?

- It helps in diagnosing different types of anemia.
 - All types of anemia have decreased RBCs Count, but to classify them we need to take a look at Reticulocyte count.
 - for example a person has a blood loss (hemorrhage), the bone marrow tries to induce erythropoiesis causing more production for RBCs → **the percentage of reticulocyte will increase in the circulation as a compensative response of losing the RBCs.**
 - If the reticulocyte percentage is decreased the problem in this case is in the bone marrow causing Aplastic anemia (Decreased RBCs production due to a problem in Red bone marrow).
- ✓ Further explanation : a reticulocyte is an immature RBC originated from the bone marrow, it enters the blood circulation and within 1-2 days it becomes a mature RBC. Knowing the percentage of the reticulocytes helps in determining some types of anemia.
- ✓ So we have 2 cases :
 - 1) Decreased reticulocyte count : the bone marrow fails in producing enough RBCs--->aplastic anemia
 - 2) Increased reticulocyte count:
 - in hemolytic anemia case (when RBCs get broken down early *remember the lifespan of RBCs is ~120 days *).
 - in post-hemorrhage anemia case
- ✓ so the bone marrow increases the RBCs production to compensate the lost RBCs .

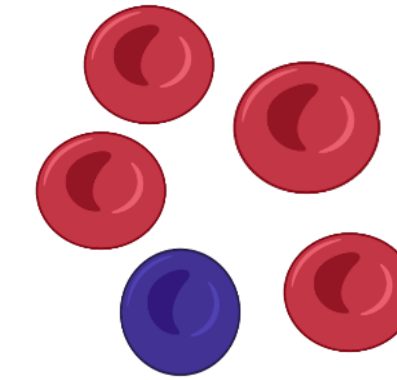
RBC

Corrected Reticulocyte count



Retic = 1%

Hct = 45



Retic = 2%

Hct = 22.5

We cannot depend on reticulocyte count only to determine the anemia case because the percentage depends on number of reticulocytes and number of RBCs (the dominator)

We have to make a correction by returning the Hct to its reference (the normal reference=45)

Corrected reticulocyte count = Reticulocyte count $\times \frac{\text{Actual Hct}}{\text{Normal Hct}}$

$$= 1\% \times \frac{45}{45}$$

= 1%

An anemic person with abnormal Hct but with normal reticulocyte count.

This indicates Aplastic anemia and the problem is BM,
Even the percentage is normal but think about it as a ratio

$$= 2\% \times \frac{22.5}{45}$$

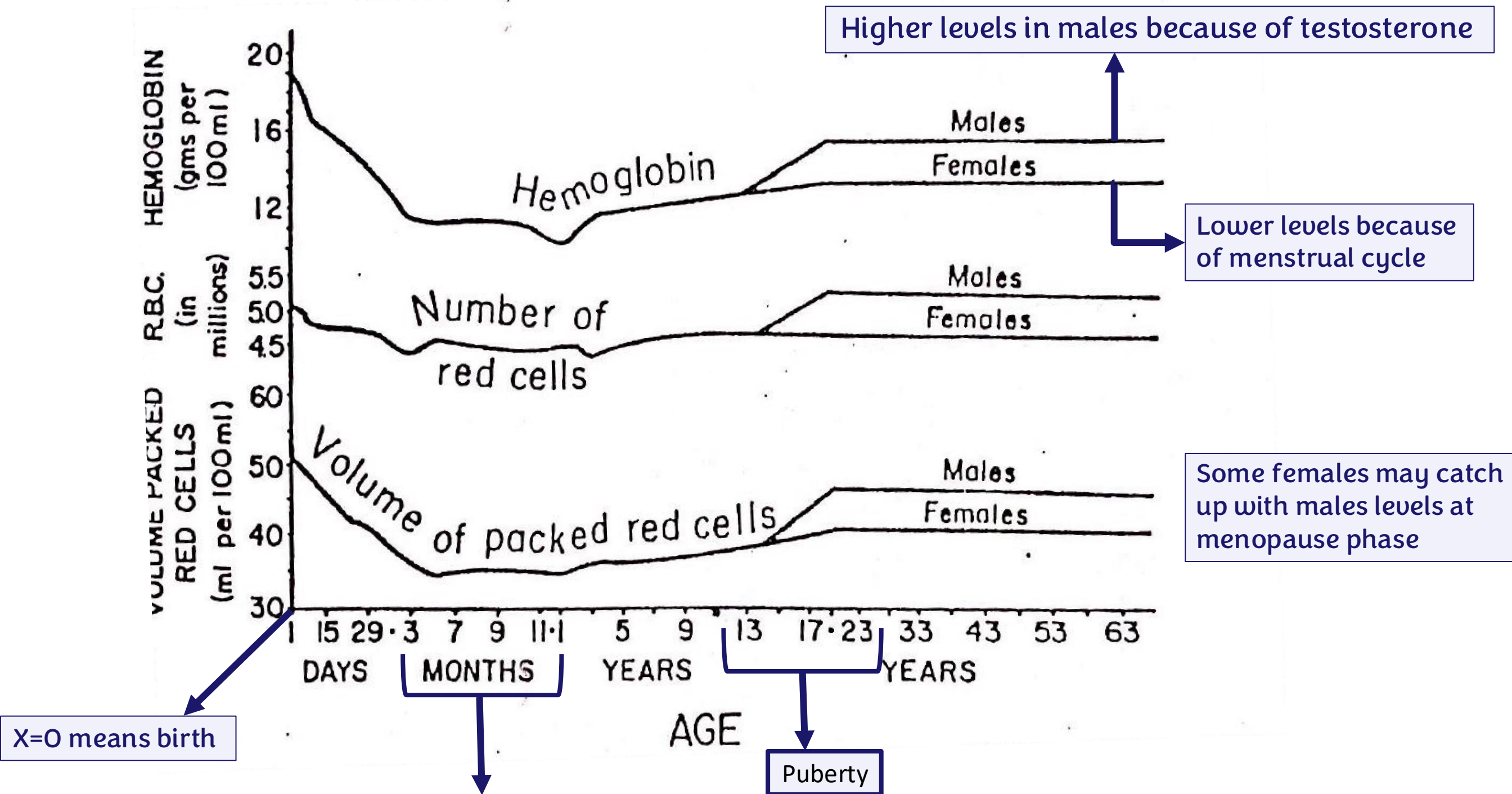
= 1%

Dr. Notes Regarding the Previous Slide

- In the state of anemia, reticulocyte % is not a true reflection of reticulocyte production.
- A correction factor must be applied to not overestimate marrow production because each reticulocyte is released into whole blood containing few RBCs, which means low Hct, thus increasing the percentage.
- Because a patient with anemia has a decreased hematocrit (Hct), which represents the percentage of blood volume occupied by red blood cells (RBCs), the reticulocyte percentage may appear relatively elevated even if reticulocyte production is not actually increased to the extent suggested by the percentage.
- Therefore, the reticulocyte percentage must be corrected according to the severity of anemia to obtain a more accurate assessment of bone marrow production.

RBC

RBCs parameters



The lowest point of all RBCs parameters due to increased oxygen availability which inhibit EPO leading to a decrease in RBCs levels + because of the baby's growth and the increase in plasma volume ----> RBCs dilution

❑ An important note: about RBCs production sites ::

- Early stages → yolk sac
- Then in the liver,,spleen → then in the bone marrow (before birth, during the 8th month of pregnancy)

❑ **Decline after birth**

- After birth, improved oxygenation suppresses EPO and reduces RBC production. Neonatal RBCs also have a shorter lifespan, and rapid growth expands blood volume. Together, these lower hemoglobin, producing the physiological nadir at about **2-3 months in term infants**.

RBC

RBCs parameters

RBC count ($10^6/\mu\text{L}$ blood)	4.0 (female); 4.5 (male)
Hematocrit (%)	40 (female); 45 (male)
Hemoglobin (g/dL blood)	14.0 (female); 15.5 (male)
Mean red cell volume, MCV (fL/cell)	90
Mean red cell hemoglobin, MCH (pg/cell)	30
Mean cell hemoglobin concentration, MCHC (g/dL RBCs)	35
Red cell distribution width, RDW (%)	13

RBC

RBCs parameters

RBC count

- **RBC count: the number of cells**
- This is the number of RBCs in **one microliter of whole blood**.
- For example, $5 \times 10^6/\mu\text{L}$ means **5 million RBCs per microliter**.



RBC

RBCs parameters

MCV

Mean cell volume (fL/cell) Reflect the size of RBCs.

- Is the average volume (size) of the RBCs.
- It can be measured, as it is in automated cell counters, or calculated:

$$= \frac{\text{Hct [\%]} \times 10}{\text{RBC count [in millions}/\mu\text{L}]}$$

Reflect the volume of RBCs

For units regards

- MCV measures the average volume or size of an RBC.
- **Classification according to MCV:**
 - Microcytic: MCV below 80 fL.
 - Normocytic: MCV from 80 to 100 fL.
 - Macrocytic: MCV above 100 fL.



**Macrocytic
(>100)**



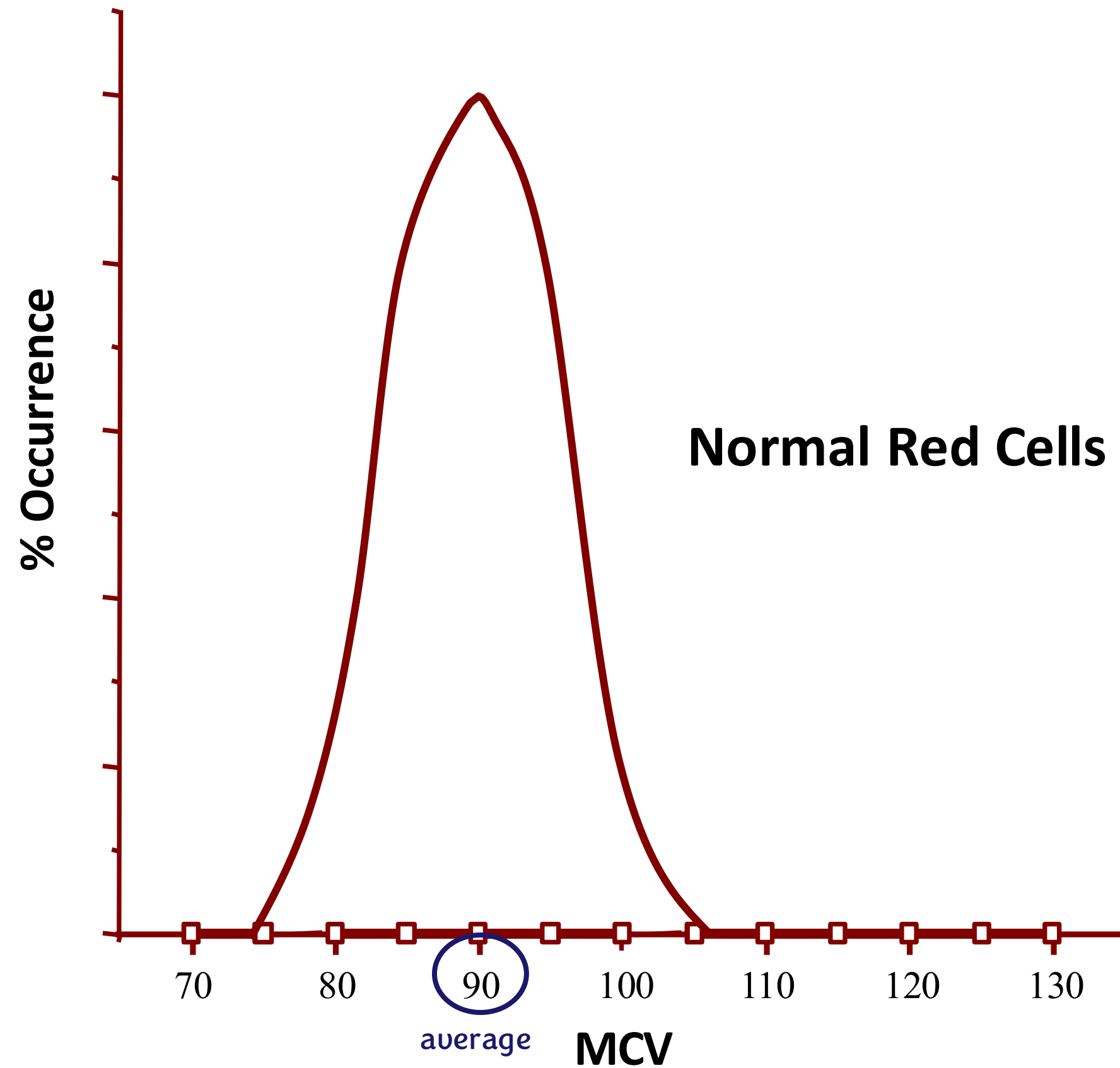
**Normocytic
(80-100)**



**Microcytic
(<80)**

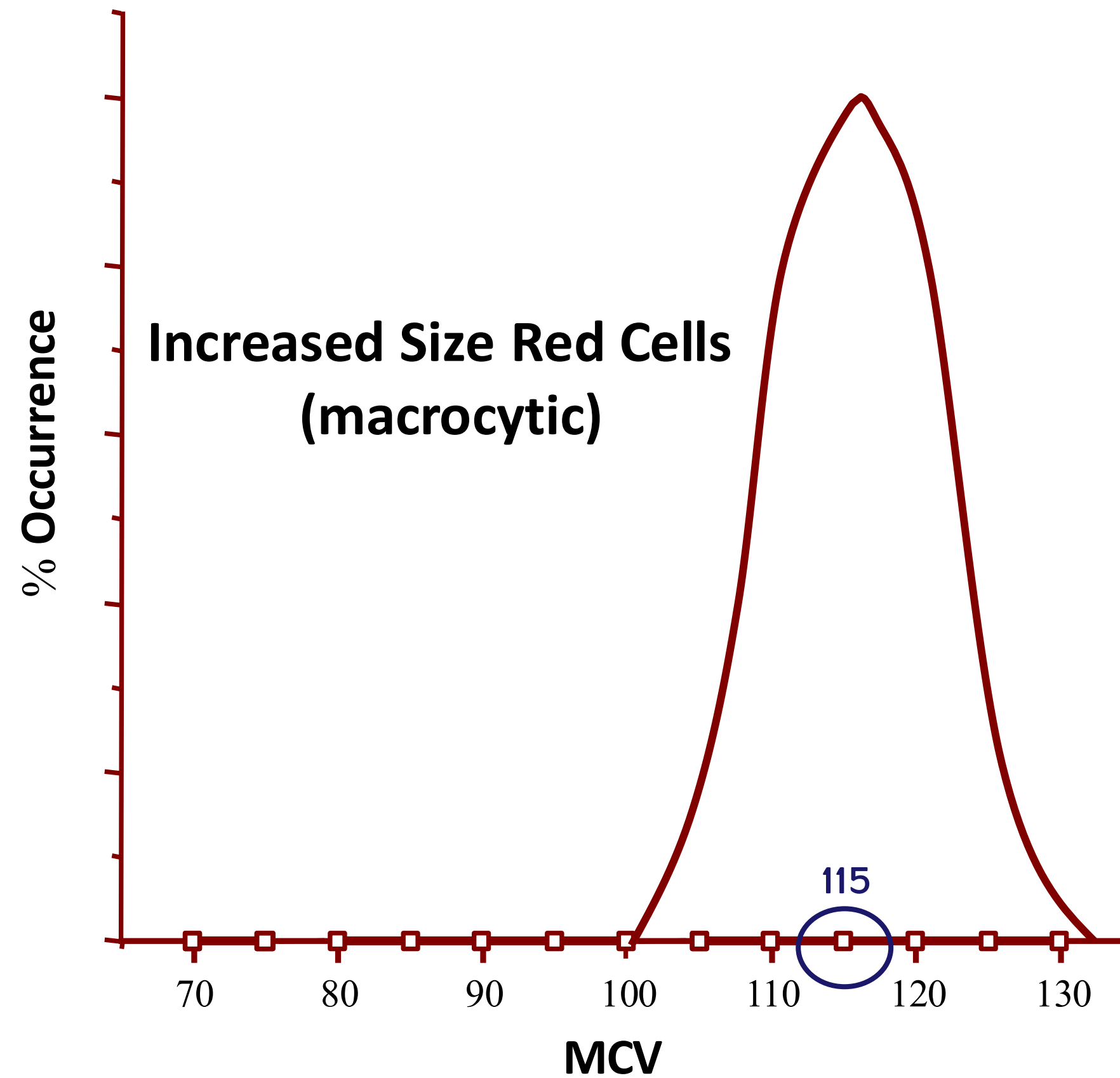
RBCs parameters

Distribution of RBCs sizes



RBCs parameters

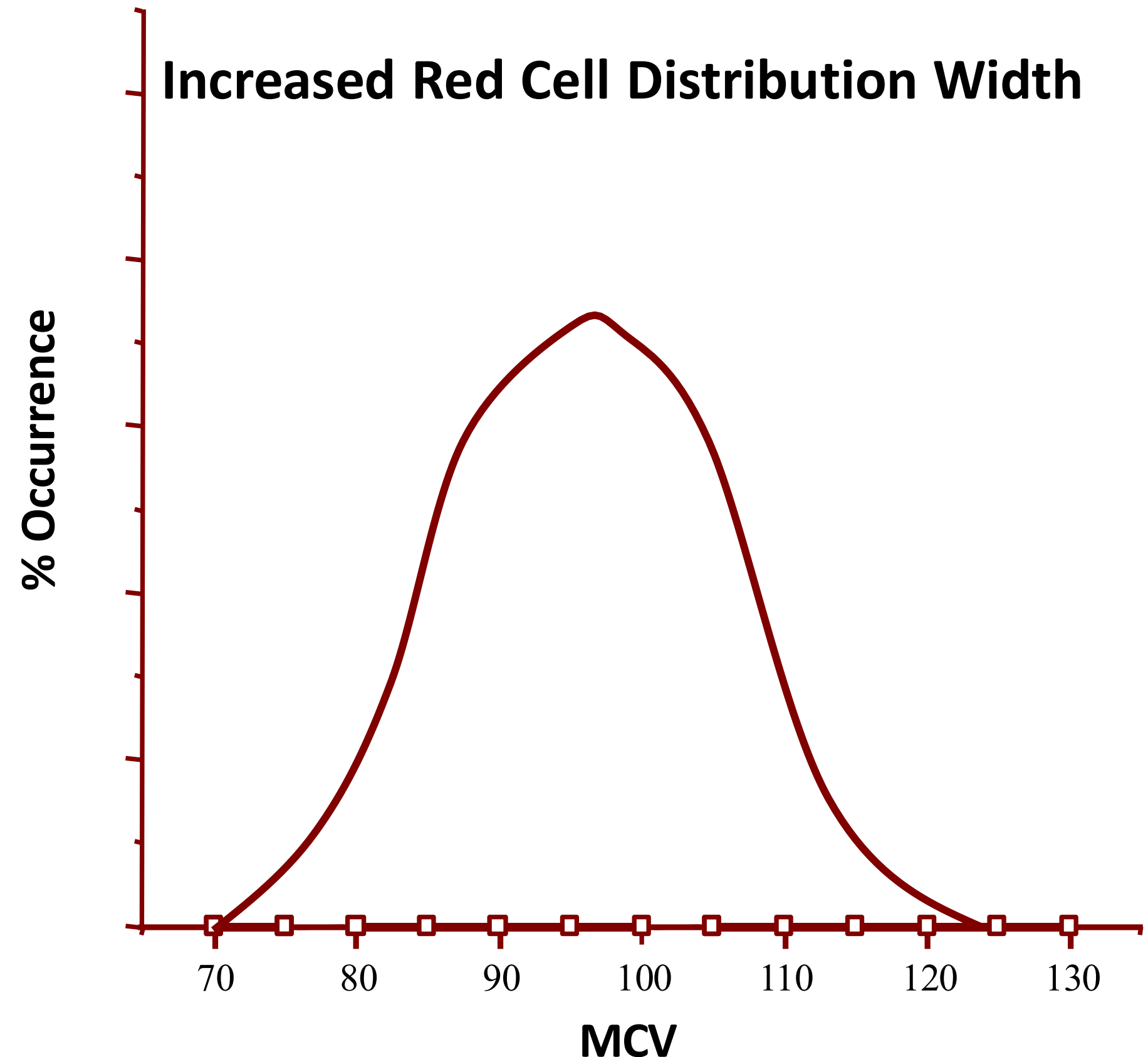
Distribution of RBCs sizes



RBCs parameters

Red cell Distribution Width (RDW)

- The average=95 but the width of the distribution of MCV values vary means we have micro/macro/normo-cytic,
- a high standard deviation indicates high variation
- Measurement of RBC size variation (anisocytosis).
- $RDW = [\text{standard deviation}/MCV] \times 100$.
- High RDW $\rightarrow$ large variation in RBC sizes
- Normal RDW $\rightarrow$ more homogeneous population of RBCs.
- A high RDW can be seen in a number of anemias, including iron deficiency, vitamin B12 or folate deficiency.
- E.g: a 20 year-old female, her Hb level=10g/dL, Hct=35% (means she is an anemic) , MCV=70 (microcytic) $\rightarrow$ iron deficiency anemia cause microcytic anemia



Dr. Notes Regarding the Previous Slide

□ Anisocytosis

- Anisocytosis refers to the presence of RBCs of different sizes.
- The RBC size-distribution curve shows a wider width. This reflects increased variation in RBC size, associated with an increased standard deviation.
- A high proportion of microcytic and macrocytic RBCs compared with normal cells can contribute to this variation.
- High Red Blood Cell Distribution Width (RDW) Why does RDW increase? In iron deficiency, fluctuations in RBC production can result in cells of different sizes.
- Some RBCs may have a relatively normal hemoglobin content, while others have reduced hemoglobin content and are smaller.

Dr. Notes Regarding the Previous Slide

□ Anisocytosis

- causes:

- 1) Iron deficiency: causes some RBCs to become small due to impaired hemoglobin production.
- 1) Vitamin B12 or folate deficiency: causes some RBCs to become large.

□ Minor Thalassemia:

- Thalassemia is associated with a decreased ability to produce hemoglobin due to a genetic disorder.
- It can result in microcytosis and may produce a different RDW pattern from iron deficiency:
Thalassemia trait (minor): RBCs tend to be relatively uniform in size, so RDW may remain normal or only mildly increased while Iron deficiency anemia have more variation in RBC size is often more pronounced, resulting in a higher RDW. Other methods for differentiating thalassemia minor from iron deficiency anemia: Measurement of iron concentration and related iron studies.

RBC

RBCs parameters

MCH

Mean cell hemoglobin concentration (pg/ cell)

- **MCH represents the average mass of hemoglobin in each RBC, measured in picograms per cell (pg/cell).**
- Is the average hemoglobin content in a RBC.

$$= \frac{\text{Hemoglobin [g/dL]} \times 10}{\text{RBC count [in millions}/\mu\text{L}]}$$

- A low MCH is typically reflected in an enlarged area of central pallor in RBCs on the peripheral blood smear (greater than one-third of the RBC diameter)



**Normochromic
(30-34)**



**Hypochromic
(<30)**

Dr. Notes Regarding the normochromic and Hypochromic

Hemoglobin concentration and RBC staining

- ❑ Normal concentration of hemoglobin: Produces normal eosinophilic staining. The RBC is described as normochromic.
 - Normal MCH is approximately 30–34 pg/cell, according to the handwritten notes.
- ❑ Low concentration of hemoglobin: Produces decreased staining intensity.
 - The RBC is described as hypochromic → MCH below 30 pg/cell.
 - Central pallor of RBCs : When we examine a blood smear under a light microscope (LM), we notice a central pale–staining region in the RBC.
 - ✓ This central pallor is explained by the distribution of hemoglobin within the RBC. The center of a normal biconcave RBC is thinner than its periphery, **so less hemoglobin is present along the light path through the center**, resulting in less staining. The notes state that the width at the center is approximately 1 μm , **which is too small to contain as much hemoglobin as the thicker peripheral region.**

$$\text{MCHC} = \text{MCH} / \text{MCV}$$

****Mean corpuscular hemoglobin concentration** expresses the amount of hemoglobin **relative to the volume of RBCs**

****For example, if a cell becomes larger and its hemoglobin amount increases proportionally, MCH rises but MCHC stays the same.**

RBC

RBCs parameters

MCHC

Mean cell hemoglobin concentration (g/dL RBC)

- Is the average hemoglobin concentration per RBC.
- expresses the amount of hemoglobin **relative to the volume of RBCs**

$$= \frac{\text{Hemoglobin [g/dL]} \times 100}{\text{Hct [\%]}}$$

- MCHC represents the average concentration of hemoglobin per unit volume of RBCs, measured in g/dL.

$$\text{MCHC} = \frac{\text{MCH}}{\text{MCV}}$$



**Normochromic
(30-36)**



**Hypochromic
(<30)**

RBC

RBCs parameters

Hb = 8 g/dL

Hct = 28%

RBC count = 4 million/ μ L

$$MCV = \frac{Hct \times 10}{RBC \text{ count}} = \frac{28 \times 10}{4} = 70 \text{ fL}$$

Small RBCs — microcytic

$$MCH = \frac{Hb \times 10}{RBC \text{ count}} = \frac{8 \times 10}{4} = 20 \text{ pg}$$

Reduced hemoglobin amount per RBC

$$MCHC = \frac{Hb \times 100}{Hct} = \frac{8 \times 100}{28} = 28.6 \text{ g/dL}$$

Reduced hemoglobin concentration — hypochromic

RBC

Anemia

Anemia

Production

Destruction

*Less EPO
* BM damage
*Iron deficiency

* Blood loss
*Hemolysis

Low RI

High RI



Dr. Notes Regarding the Previous Slide

□ **Anemia** is a condition characterized by a **decrease in hemoglobin (Hb) concentration below the normal range for a person's age, sex, and physiological status.**

- This reduces the oxygen-carrying capacity of the blood. Anemia can result from two main mechanisms:

A. Decreased RBC Production

- The bone marrow fails to produce enough red blood cells. Causes include: Decreased erythropoietin (EPO): EPO is a hormone produced mainly by the kidneys that stimulates RBC production.
- Bone marrow damage: Impaired bone marrow function decreases RBC production. Iron deficiency: Iron is essential for hemoglobin synthesis; its deficiency impairs RBC production.
- Vitamin B12 or folate deficiency: These deficiencies impair DNA synthesis and RBC maturation.
- Chronic inflammation: Inflammation can impair iron availability and RBC production.

B. Increased RBC Loss or Destruction

- Red blood cells are lost or destroyed faster than the body can replace them.
 - Causes include:
 - Blood loss: Such as acute hemorrhage.
 - Hemolysis: Premature destruction of RBCs before the end of their normal lifespan.

Dr. Notes Regarding the Previous Slide

❑ Anemia is a condition characterized by a **decrease in hemoglobin (Hb) concentration below the normal range for a person's age, sex, and physiological status.**

❑ Role of the Reticulocyte Count:

- Reticulocytes are immature red blood cells recently released from the bone marrow into the circulation. Their number helps assess the bone marrow's response to anemia. The reticulocyte response is interpreted in relation to the severity of anemia.
- The corrected reticulocyte count or reticulocyte production index (RPI) may be used for a more accurate assessment.

A. Increased Reticulocyte Response

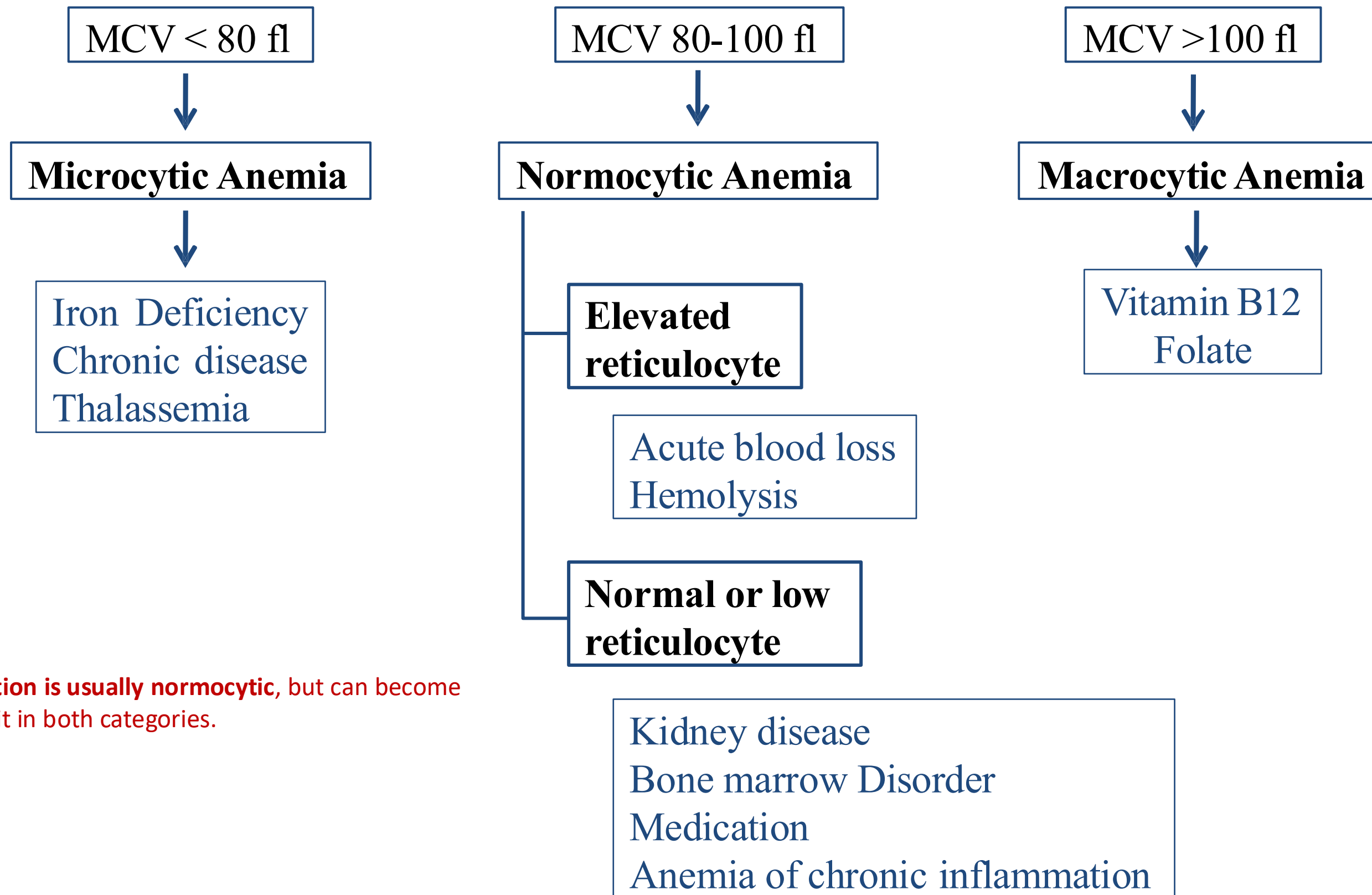
- An increased reticulocyte response indicates that the bone marrow is attempting to compensate for RBC loss or destruction.
- Common causes include:
 - Acute blood loss (hemorrhage).
 - Hemolytic anemia.

Dr. Notes Regarding the Previous Slide

- B. Low or Inadequate Reticulocyte Response : A low or inappropriately normal reticulocyte response indicates that the bone marrow is not producing enough RBCs to compensate for the anemia.
- Possible causes include:
 - Kidney disease due to decreased EPO production.
 - Bone marrow disorders.
 - Iron deficiency.
 - Medication-related suppression of RBC production.
 - Anemia of chronic inflammation.
 - ✓ Important: A reticulocyte percentage that appears normal may still represent an inadequate response in an anemic patient.

Anemia classification

Anemia confirmed by low hemoglobin → classify by MCV



****chronic inflammation is usually normocytic, but can become microcytic—include it in both categories.**

Dr. Notes Regarding the Previous Slide

Classification of Anemia According to MCV

Mean Cell Volume (MCV) measures the average volume of an RBC. Once anemia is confirmed by a low hemoglobin concentration, MCV is used to classify anemia into three main categories.

A. Microcytic Anemia:

- **MCV less than 80 fL**
- Microcytic anemia is characterized by red blood cells that are smaller than normal.
- Common causes include:
 - **Iron deficiency anemia:** Insufficient iron impairs hemoglobin synthesis.
 - **Anemia of chronic inflammation:** Inflammation can restrict iron availability and impair erythropoiesis.
 - **Thalassemia:** An inherited disorder characterized by reduced synthesis of one or more globin chains of hemoglobin.

B. Normocytic Anemia :

MCV 80–100 fL

- Normocytic anemia is characterized by RBCs of normal average size but a reduced hemoglobin concentration.
- The reticulocyte response helps narrow down the cause.

1. Increased reticulocyte response

- Suggests that RBCs are being lost or destroyed and that the bone marrow is responding appropriately.
- Examples:
 - Acute blood loss.
 - Hemolysis.

Dr. Notes Regarding the Previous Slide

2. Low or inadequate reticulocyte response

- Suggests decreased RBC production.
- Examples:
 - Kidney disease.
 - Bone marrow disorders.
 - Medication-related suppression.
 - Anemia of chronic inflammation.

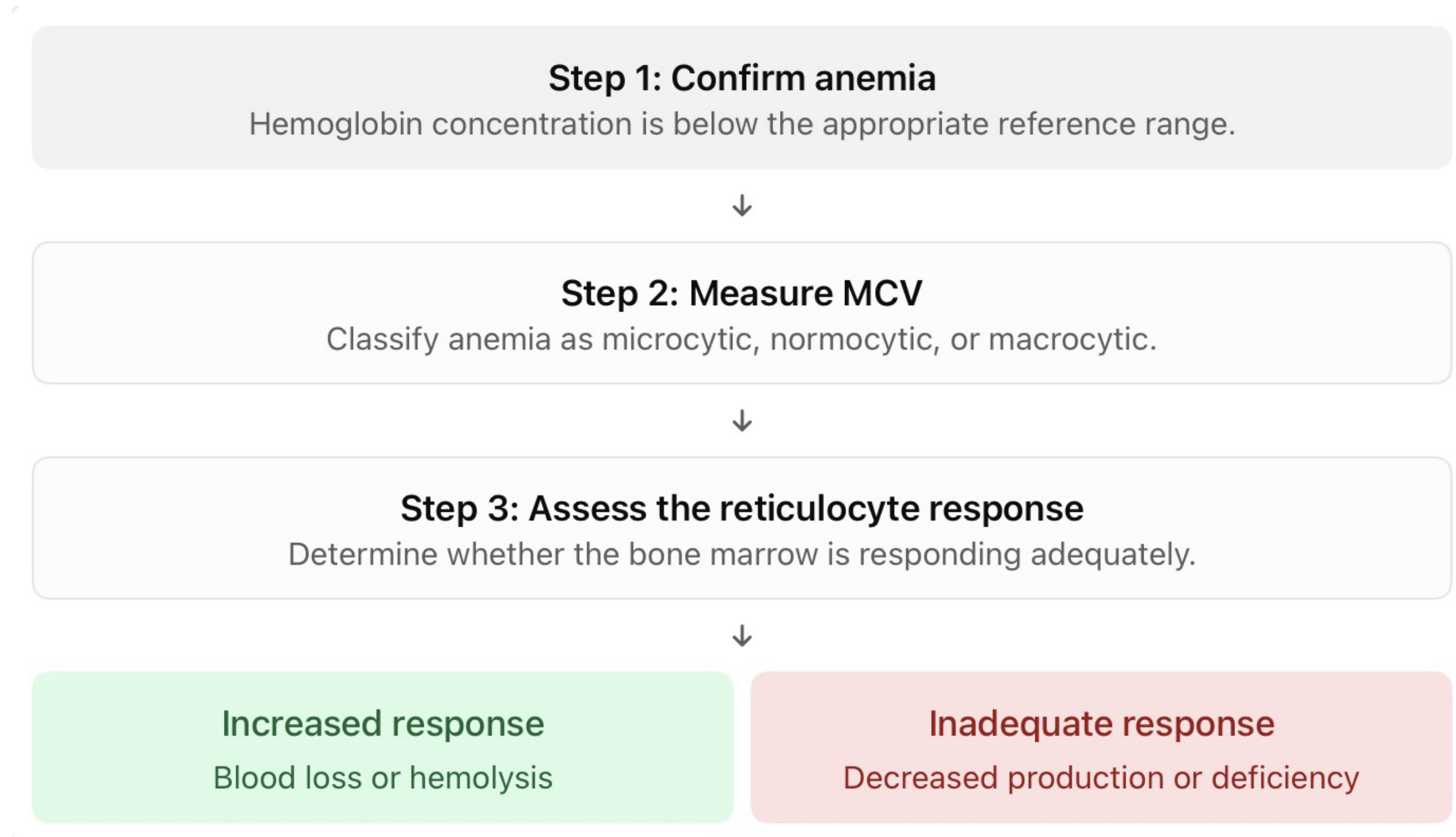
C. Macrocytic Anemia

- **MCV greater than 100 fL**
- Macrocytic anemia is characterized by RBCs that are larger than normal.
- Common causes include:
 - **Vitamin B12 deficiency:** Impairs DNA synthesis, resulting in abnormal RBC maturation.
 - **Folate deficiency:** Also impairs DNA synthesis and RBC maturation.
 - Other causes of macrocytosis include alcohol use, liver disease, certain medications, and hypothyroidism.

Dr. Notes Regarding the Previous Slide

❑ Diagnostic Approach to Anemia :

- A systematic approach can help identify the underlying cause.



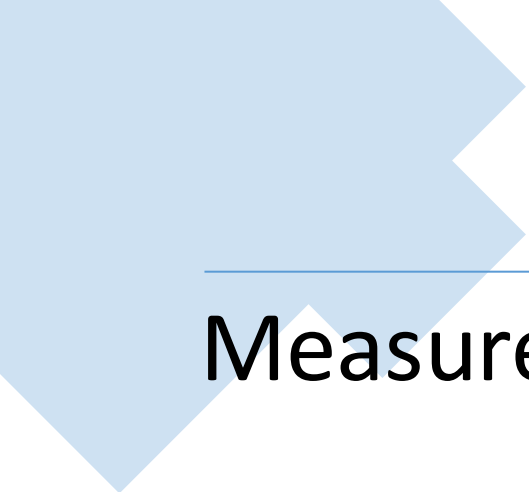
RBC

Anemia classification

(MCV)	(MCHC)	Typical causes
Normocytic	Usually normochromic	Chronic kidney disease, anemia of chronic inflammation, acute blood loss, many hemolytic anemias, marrow failure
Macrocytic	Usually normochromic	Vitamin B12 or folate deficiency; also liver disease, alcohol use, certain medications
Microcytic	Often hypochromic	Iron deficiency, thalassemia, sometimes anemia of chronic inflammation

Summary

Parameter	Interpretation	Common associations
MCV below 80 fL	Microcytic anemia	Iron deficiency, thalassemia
MCV 80–100 fL	Normocytic anemia	Acute blood loss, hemolysis, kidney disease
MCV above 100 fL	Macrocytic anemia	Vitamin B12 or folate deficiency
Increased reticulocyte response	Increased RBC production	Hemorrhage, hemolysis
Low or inadequate reticulocyte response	Impaired RBC production	Kidney disease, marrow disorders, deficiencies



Measurement

Main question it answers

RBC count

How many red cells are present?

Hematocrit (Hct)

How much of the blood's volume is occupied by RBCs?

Hemoglobin (Hb)

How much hemoglobin is present in whole blood?

MCV

How large is the average RBC?

MCH

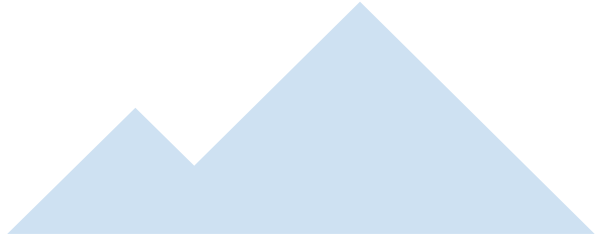
How much hemoglobin is in the average RBC?

MCHC

How concentrated is hemoglobin inside the RBCs?

RDW

How much do RBC sizes differ from one another?



In anemia, each milliliter of blood carries less oxygen, so the body compensates by circulating more blood per minute. This increases the heart's workload

$$\text{Oxygen delivery} = \text{Cardiac output} \times \text{Blood oxygen content}$$

Change in anemia	Effect on circulation
Lower hematocrit → lower blood viscosity	Blood flows more easily, reducing resistance in the circulation.
Reduced oxygen delivery → tissue arterioles dilate	Wider vessels further reduce resistance and allow more blood through the tissues.

This compensation can maintain adequate oxygen delivery **at rest**, despite the anemia.

Why does exercise become difficult?

****Exercise increases the muscles' oxygen requirements. Normally, the heart responds by increasing cardiac output. In severe anemia, however, cardiac output is **already elevated at rest**, leaving less capacity to increase it further—called **reduced cardiac reserve**. Consequently, oxygen delivery may fail to meet demand, causing **fatigue, breathlessness, and palpitations**.**

Text Book Notes Regarding Previous Slide (Required)

1. Decreased Blood Viscosity

- Blood viscosity depends largely on the concentration of RBCs in the blood.
- In severe anemia, blood viscosity may decrease to approximately **1.5 times the viscosity of water**, compared with the normal value of about **3 times that of water**.
- Decreased viscosity reduces resistance to blood flow in peripheral blood vessels.

2. Increased Cardiac Output

- Decreased peripheral resistance allows more blood to flow through the tissues and return to the heart, resulting in increased cardiac output.
- Additionally, anemia reduces the oxygen-carrying capacity of blood, causing tissue hypoxia. In response, peripheral blood vessels dilate, further increasing venous return and cardiac output.
- Cardiac output may increase to **3–4 times the normal level** in severe cases.
- The heart experiences an increased pumping workload.

3. Compensation for Reduced Oxygen Delivery

- In anemia, each unit of blood carries less oxygen because hemoglobin concentration is reduced.
- However, increased cardiac output partially compensates for this reduction by delivering blood to the tissues more rapidly. Consequently, oxygen delivery to tissues may remain near normal at rest in some patients.

4. Effects During Exercise

- During exercise, tissue oxygen demand increases significantly.
- However, the heart is already pumping an increased volume of blood to compensate for anemia, so its ability to increase cardiac output further may be limited.
 - As a result:
 - Tissue hypoxia becomes more severe.
 - Oxygen delivery may become insufficient to meet tissue demands.
 - In severe cases, acute cardiac failure may occur.

Polycythemia means an increased concentration of RBCs in the blood. The higher hematocrit makes blood more viscous “thicker” and harder to move through blood vessels.

1. Cardiac output: two opposing effects

Change	Effect on blood returning to the heart
Increased viscosity	Increases resistance to flow → tends to decrease venous return
Increased blood volume, as can occur in polycythemia vera	Increases the pressure driving blood back to the heart → tends to increase venous return

2. Blood pressure: thicker blood does not automatically mean hypertension

Mean arterial pressure $\approx$ Cardiac output $\times$ Systemic vascular resistance

Higher viscosity tends to increase vascular resistance and therefore blood pressure. However, adjustments in vessel diameter, cardiac output, and fluid balance can compensate. **Hypertension develops when compensation is insufficient.**

Skin color: why it may look reddish or dusky

The **subpapillary venous plexus** is a network of small veins just beneath the skin's surface.

In polycythemia vera:

- More blood and hemoglobin in these vessels give the skin a **ruddy or reddish appearance**.
- Sluggish flow allows tissues to extract more oxygen from passing blood.
- The increased amount of **deoxygenated hemoglobin** can add a **dusky or bluish tinge**.

Text Book Notes Regarding Previous Slide (Required)

1. Increased Blood Viscosity

- In polycythemia, the increased RBC concentration causes **increased blood viscosity**.
- Increased viscosity makes blood flow more sluggish through peripheral blood vessels.
- This increases resistance to blood flow, decreasing tissue blood flow, venous return, and cardiac output.

2. Effect on Cardiac Output

- Two opposing factors affect cardiac output in polycythemia:
 - **Increased blood viscosity:** Decreases tissue blood flow and venous return, tending to decrease cardiac output.
 - **Increased blood volume:** Increases venous return, tending to increase cardiac output.
- ✓ These two effects partially counterbalance each other. Therefore, **cardiac output is often close to normal** in polycythemia.

3. Effect on Arterial Blood Pressure

- Arterial blood pressure is normal in most people with polycythemia.
- Approximately one-third of patients may develop elevated arterial pressure.
- Increased blood viscosity raises peripheral vascular resistance, which tends to increase blood pressure.
- Blood pressure regulatory mechanisms can usually compensate for this effect.
- When these compensatory mechanisms are insufficient, **hypertension may develop**.

4. Effect on Skin Color in Polycythemia Vera

- The color of the skin depends partly on the amount of blood in the subpapillary venous plexus.
- In polycythemia vera:
 - The amount of blood in the subpapillary venous plexus increases.
 - Blood flows sluggishly through the skin capillaries, allowing a greater proportion of hemoglobin to become deoxygenated.
 - The increased amount of deoxygenated hemoglobin produces a bluish tint that combines with the red appearance of the increased blood volume.
 - Consequently, patients with polycythemia vera typically develop a **ruddy complexion with a bluish (cyanotic) tint**.

Did you know by S.Holmes



Luminol

What is Luminol

Luminol is a chemical compound used in forensic investigations to detect traces of blood at crime scenes, even when the blood is not visible to the naked eye. It can reveal blood traces that have been washed away or cleaned.

Luminol works through a chemical reaction called **chemiluminescence**, which is the production of light as a result of a chemical reaction.

For any feedback, scan the code or click on it.



Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			