2012

KING SAUD UNIVERSITY
COLLEGE OF MEDICINE
HAEMATOLOGY TEAM
GIT BLOCK

Haematology Block

Haematology: Lecture 2

Anemia

HEREDITARY HAEMOLYTIC ANAEMIAS

ENZYMOPATHIES

GLUCOSE - 6 – PHOSPHATE DEHYDROGENASE DEFICIENCY

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ANAEMIA

HEREDITARY HAEMOLYTIC ANAEMIAS

ENZYMOPATHIES

GLUCOSE - 6 – PHOSPHATE DEHYDROGENASE DEFICIENCY

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Location: (OBG03) Booking Clinic
Doctor: [redacted] *

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EDTA Whole Blood

	Full Blood Count				
[*]	WBC	10.2		4 - 11	x10.e9/L
[*]	RBC	4.59		4.2 - 5.5	x10.e12/L
[*]	HGB	132		120 - 160	g/L
[*]	HCT	39.5		37 - 47	%
[*]	MCV	86.0		80 - 94	fl
[*]	MCH	28.8		27 - 32	pg
[*]	MCHC	335		320 - 360	g/L
[ ]>	RDW	14.9	H	11.5 - 14.5	%
	PLT	PEND		140 - 450	x10.e9/L
Low Platelet W Giant platelets seen					
[*]	MPV	9.4		7.2 - 11.1	fl
	Differential				
[ ]>	%NEUT	76.7	H	40 - 75	%
<[ ]	%LYMP	19.0	L	20 - 45	%
<[ ]	%MONO	2.3	L	3 - 9	%
[*]	%EOS	1.8		0 - 6	%
[*]	%BASO	0.2		0 - 1	%
[ ]>	#NEUT	7.8	H	2 - 7.5	x10.e9/L
[*]	#LYMP	1.9		1 - 5	x10.e9/L
[*]	#MONO	0.2		0.2 - 0.8	x10.e9/L
[*]	#EOS	0.2		0.0 - 0.8	x10.e9/L
	Morophology				
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	ANISO				
	MICRO				
	MACRO				
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	HYPO				
	Polychromasia				
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REQUEST COMMENTS:
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Technician on Duty

Consultant

HEREDITARY HAEMOLYTIC ANAEMIA

Hereditary Haemolytic Anemia

- Membrane Defects
- Metabolic Defects
- Haemoglobin Defects

MEMBRANE DEFECTS:

- Hereditary Spherocytosis
- Hereditary Elliptocytosis
- Hereditary Stomatocytosis

METABOLIC DEFECTS:

Deficiency of:

* **Glucose-6-phosphate dehydrogenase (most common)**
* Pyruvate kinase
* Triose phosphate isomerase
* Pyrimidine-5-nucleotidase
* Glutathione synthetase

Note: G6PD difeciency --> Most common dificiency here in KSA

HAEMOGLOBIN DEFECTS:

* Defective synthesis

e.g. Thalassaemia (Alpha or Beta)

* Abnormal variants

e.g. Hb S, Hb C, Unstable Hb

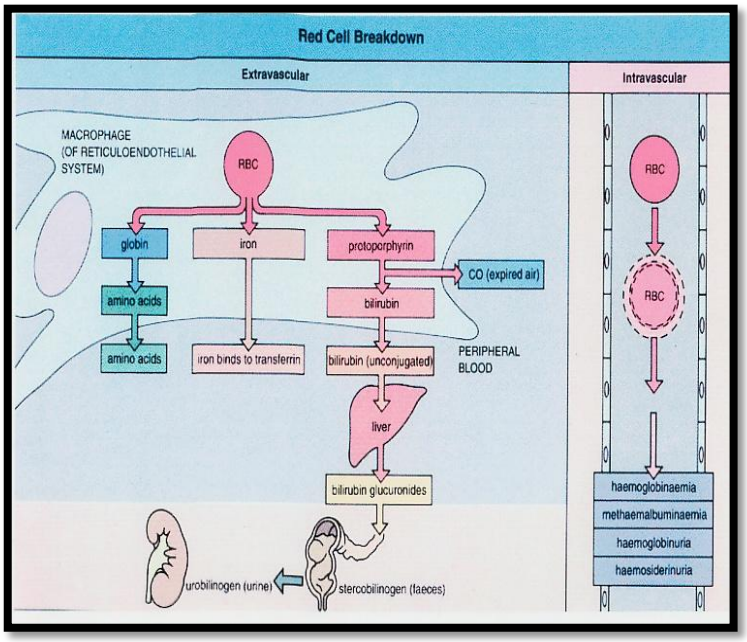
Spherocyte: A small spherical red blood cell, characteristic of hereditary spherocytosis and of certain hemolytic anemias.

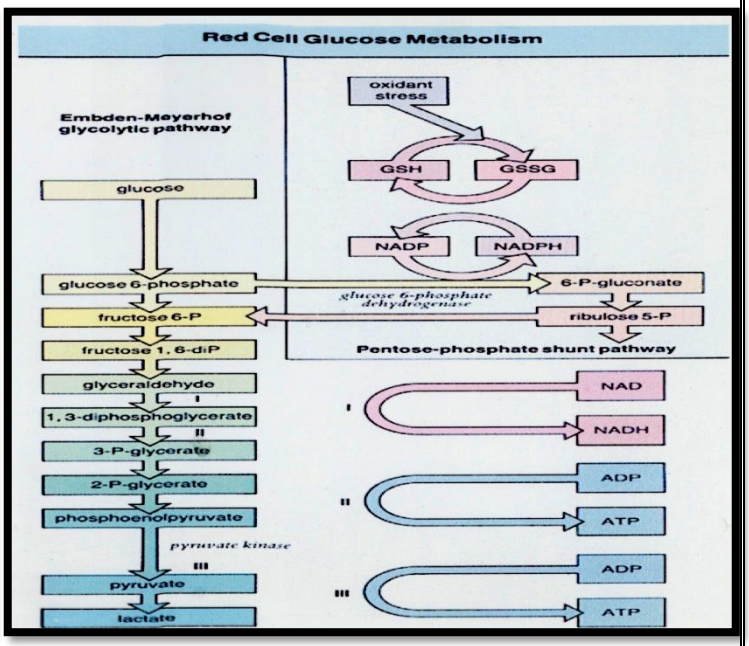
Elloptocye: Elliptocytes, also known as ovalocytes are abnormally shaped red blood cells that appear oval or elongated

Hereditary stomatocytosis : describes a number of inherited autosomal dominant human conditions which affect the red blood cell, in which the membrane or outer coating of the cell 'leaks' sodium and potassium ions.

Types of Anemia:

- Normocytic (MCRV: 80-94)
- Microcytic (MCV <80)
- Macrocytic (MCV >100)

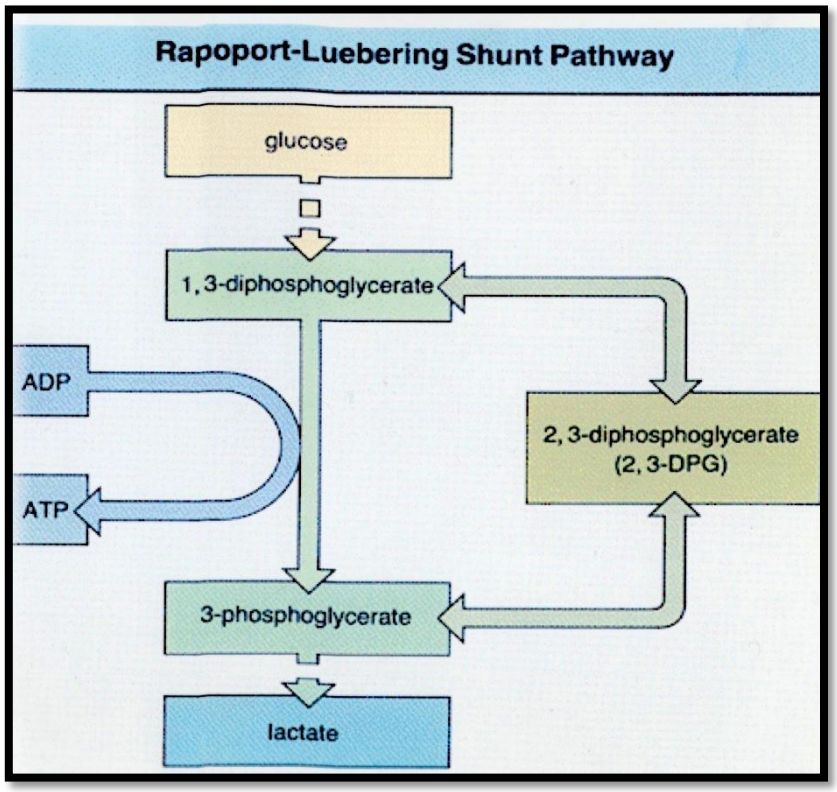




RBC Breakdown:
Intravascular → Blood Vessels
Extravascular → Liver & Spleen

NADPH → Very important in this cycle

Without it there would be no enzyme activation → G6PD deficiency → No cycle → No RBC metabolism



GLUCOSE - 6 – PHOSPHATE DEHYDROGENASE DEFICIENCY

- G-6-PD (MOL .WT. 50,000 – 55, 000)
- There are electrophoretic variants with normal activity.
- G6PD B is the most common normal type (historically). (Commonly found in the middle east)
- G6PD A is a fast moving non-deficient variant (common in Africa) and has no clinical significance.
- G6PD A should not be confused with the G6PD deficient variant G6PD A^- (seen in Nigeria).
- All variants other than B, A and A^- are designated by geographical and trivial names.
- Over 400 variants are now known.
- High incidence in endemic malarious areas.
- **It is thought to confer a selective protection against Plasmodium Falciprum Malaria** (In G6PD Deficiency, RBCs are broken down fastly, so plasmoduim falciprum will not be able to accomodate in the body)
- G6PD ↓ is the most common metabolic disorder of red blood cells.
- Almost 200 million people are affected mainly in Tropical & Subtropical areas.
- Due to recent migrations G6PD ↓ has become widespread in many other areas.

You need to know that there are different types of G6PD deficiency

The most important 3 are B, A, A- :

- B → KSA & Middle East
- A → Africa
- A - → Nigeria

Very Rare

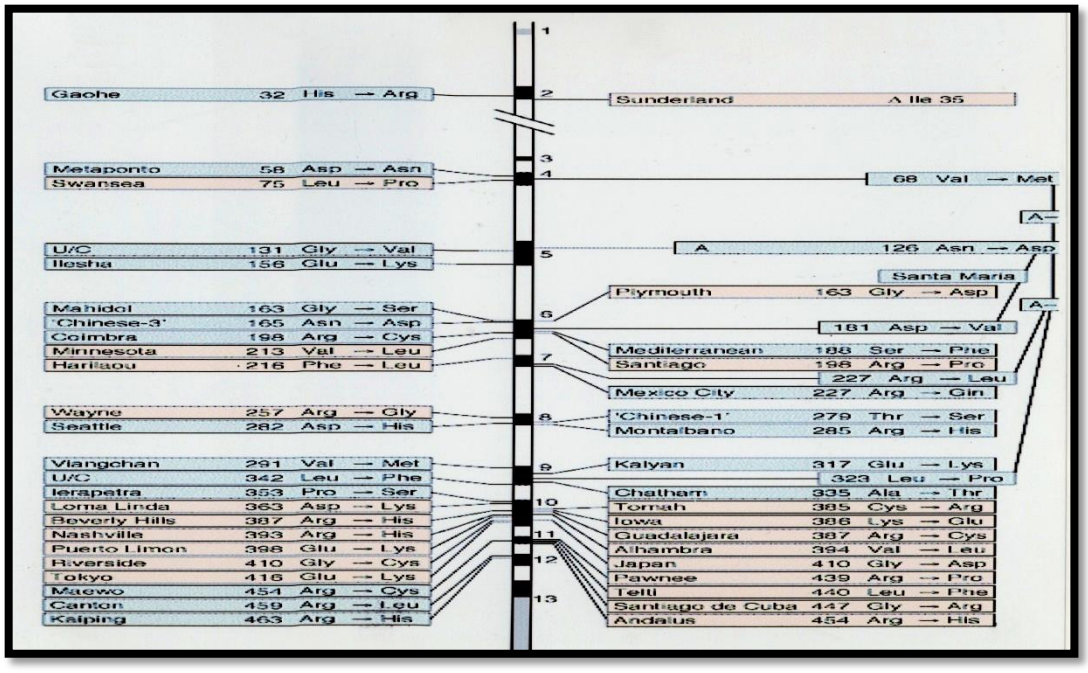
- in indigenous population in Northern Europe

20%

- in parts of:
  - Southern Europe
  - Africa
  - Asia

40%

- in certain areas of the Middle East



In some human populations:

Country	Frequency in Males	Most Common Variants
Greece	4 – 35	Mediterranean Athens-like Orchomenos Union-Markham
Southern Italy	2 – 22	Mediterranean Sassari Cagliary, Seatle-like
Nigeria	18 – 25	A^-
Thailand	3 – 14	Mahidol, Canton, Union, Hong Kong
Papua new Guinea	1-29	Markham, Many Others

Genetics

All variants result from point Mutations within the X-linked structural gene

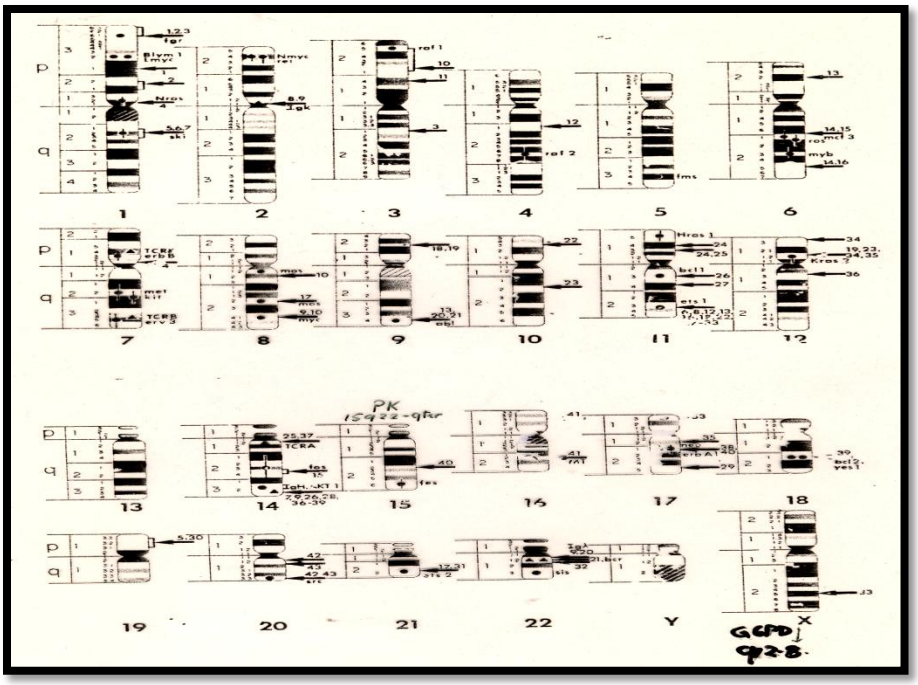
- Decreased activity
- Decreased stability
- Both (Decreased activity & stability)

The genes controlling G6PD structure and synthesis are located on the X-chromosome very close to the genes of factor VIII genes and for color blindness.

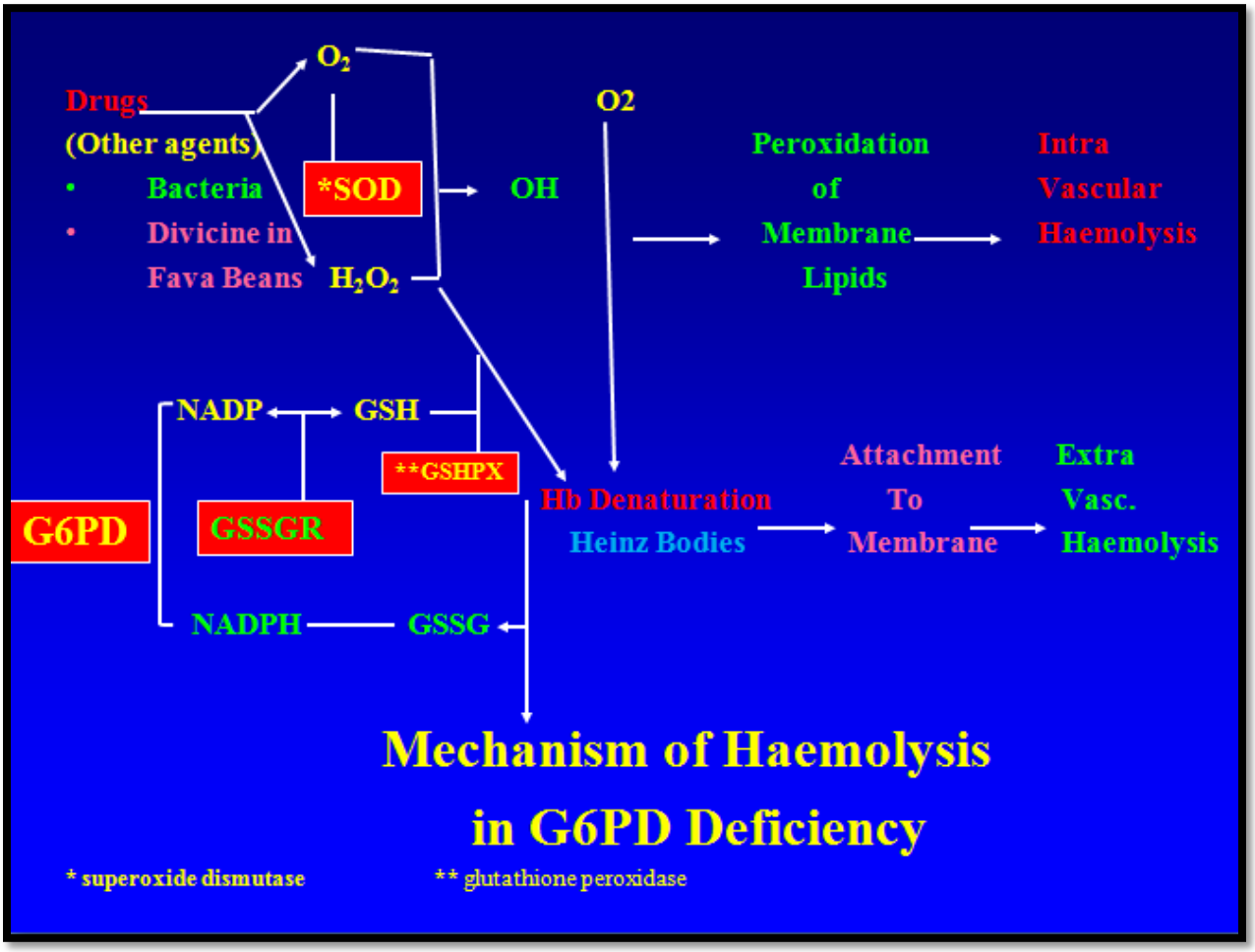
Males are the ones affected. (Because they have one X chromosome)

Females are more rarely affected in the homozygous state in particular.

Heterozygote females can have clinical manifistations (because of X-chromosome inactivation).



Gene affected → **G6PD q2.8**
On the long arm of the X chromosome



Clinical Features

- Clinical manifestation can be either
  - Acute (Haemolysis)
  - Chronic (Haemolysis)
- Most affected individuals are asymptomatic until acute attack takes place. (In prevailing variants in various populations).
- Few show mild to moderate or severe chronic hemolytic anemia. (In other rare variants).

Acute Hemolytic Anemia

Under normal circumstances G6PD enzyme activity of 20% of normal (even as low as 3%) is sufficient for normal red cell function.

Triggering Factors

- **Fava Beans** (Most important trigger)
- Infection
- Drugs

Haemolytic Attack (Cont.)

In blue (Important)

- In general **haemolysis is less severe with the African type (variant) A^-** than with the variant more prevalent in the Mediterranean, the Middle East and South East Asia. (Sometimes it subsides even when the trigger is still present)
- **Massive haemoglobinuria is seen most frequently in children with favism.** (Due to breakdown of RBC's)
  (Some degree of haemoglobinuria is always seen in an attack)
- Renal failure is very rare in children but not uncommon in adults.
- In some cases haemolysis can be self limiting.
  (This is not necessary true for all drugs or for all variants)

Favism

- Fava beans ingestion is not always followed by a haemolytic attack in G6PD↓ individuals.
- The offending agent may be the **glucoside divicine or aglycone isouramil.** (Important)
- Those agents vary widely in different caltivars of vicia faba and with the way fava beans are consumed.
- Favism has been precipitated with fresh beans, dried beans, canned and frozen beans.
  (It is commonest with fresh and raw beans)
- Oxidative damage may depend on how much isouramil is released by glycosidases present in the beans or in the intestinal tract of the consumer.

Features of a Hemolytic Attack

Acute Phase

- Sudden Onset
- Malaise, Prostration
- Pallor
- Fever
- Abdominal Pain
- Hypotension
- Dark Urine
- Jaundice
- Renal Failure

Recovery Phase

- Gradual But Rapid
- Urine Clears in Few Days
- Jaundice Clears in 1-2 weeks

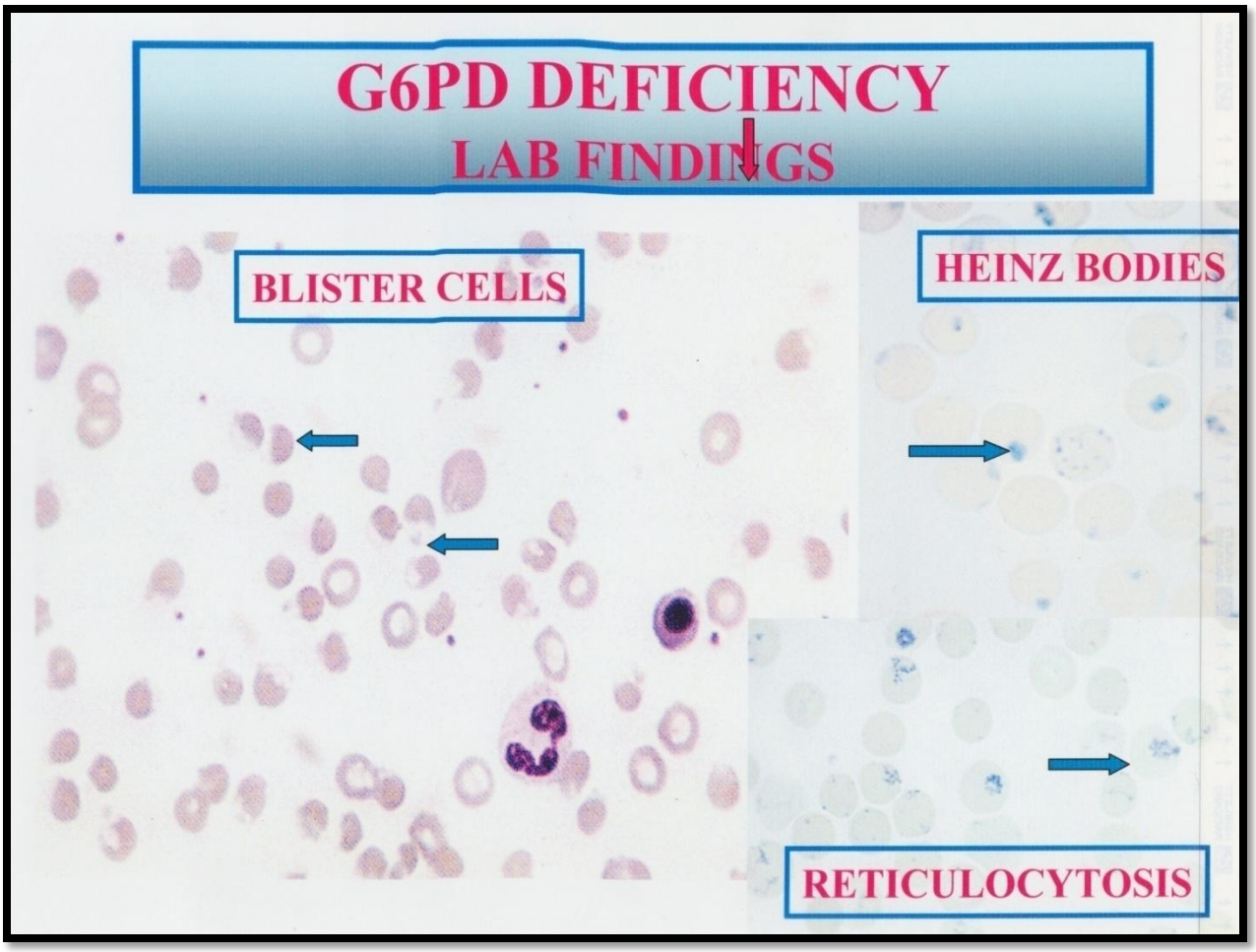
Characteristic Lab. Features of a Haemolytic Attack

Acute Phase

- Anaemia
- Reticulocytosis
- Heinz Bodies
- **G6PD deficient ***
- Leukocytosis
- Haemoglobinaemia
- Haemoglobinuria
- Haptoglobin absent
- Methaemalbuminaemia
- Hyperbilirubinaemia
- Raised Urea & Creatinine Levels

Recovery Phase

- Reticulocytes peak day 5-8
- G6PD but rarely to normal range



Heinz Bodies & Blister cells are a characteristic of G6PD deficiency (Important)

Reticulocytosis (less important)

Laboratory Diagnosis

G6PD screening tests:

- Nitro blue tetrazolium (NBT) **spot test** (Important)
- Fluorescent spot test
- Cytochemical demonstration of G6PD↓

Quantitative Assay:

- G-6-P + NADP --> ^{G6PD} --> 6PG + NADPH
- 6PG + NADP --> ^{6pGD} --> 6PGD R5P + CO2 + NADPH
- Spectrophotometrically
- Normal range at 37°C
- WHO G6PD IU/10 ^{10} RBC = 3.6±0.6
- ICSH G6PD IU/10^{10} RBC = 2.5±0.5
- NB:In acute attacks normal false screening test & assay results can be seen and a repeat between attacks is needed

Neonatal Jaundice (NNJ)

- Strong association is known between G6PD ↓ and NNJ.
- **G6PD↓ can be considered the most common cause of NNJ in Nigeria** and probably in other parts of the world. (Important)
- ½ of G6PD↓ babies do not develop NNJ.
- Thus there have to be additional genetic, developmental or acquired factors interact with G6PD↓.
- Hyperbilirubinaemia develops usually late if compared with NNJ caused by Rh isoimmunization.
- Hyperbilirubinaemia is usually more than what expected in relation to the degree of haemolysis.

  (This may be due to ↓ liver function in handling unconjugated bilirubin as a result of perhaps low G6PD in the hepatocytes).

Drugs which may cause haemolytic anaemia in subjects with G6PD deficiency	Drugs that can be given safely in therapeutic doses to subjects with G6PD deficiency without non-spherocytic haemolytic anaemia.
Antimalarials **Fansidar** **Maloprim (contains dapsone)** **Pamaquine** **Pentaquine** **Premaquine** **? Chloroquine** **Sulphonamides** **Sulphamethoxazone** **Some other sulphonamides** **Sulphones** **Dapsone** **Thiazolesulphone** **Other antibacterial compounds** **Nitrofurans** **Naladixic acid** **Antihelminthic-naphthol** **Sitophan** **Miscellaneous** **? Vitamin K** **Napthalene (moth balls)** **Methylene blue** **Doxorubicin**	**Ascorbic acid** **Aspirin** **Colchicine** **Isoniazid** **Menadione** **Phenytoin** **Probenecid** **Procainamide** **Pyrimethanine** **Quinidine** **Quinine** **Sulphamethoxypyridazine** **Trimethoprim**
? – there is some dispute with these compounds	

TREATMENT OF ACUTE HAEMOLYTIC ANAEMIA

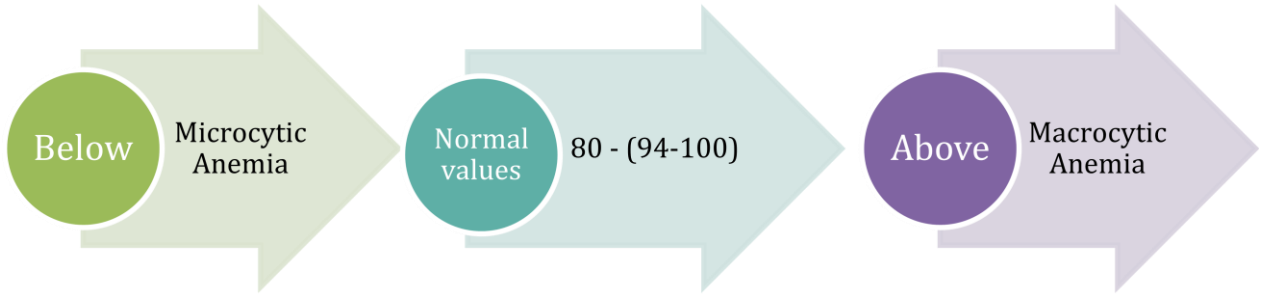
- Withdrawal of the triggering agent or avoiding it.
- In pregnant & nursing women known to be heterozygous (Carriers) should avoid drugs with oxidant potential or use them cautiously.
- Phototherapy and exchange blood transfusion is used in NNJ as in other cases of NNJ due to other causes.
- Transfusion therapy is unnecessary unless haemolytic episodes are complicated by concurrent arrest of erythropoiesis.

Information mentioned but is not in the lecture:

- G6PD deficiency is the most common hereditary hemolytic anemia here in KSA (Variant B)
- Patients with G6PD deficiency are protected against Malaria → Because RBC's have a shorter life span than normal → RBC's break down early → Malaria cannot survive.
- Point mutations (X Chromosome, Long arm, G6PD q2.8) → decreased enzyme availability and activity (G6PD deficiency)
- It is wrong to perform a blood transfusion if the patient is not in a critical condition (Blood transfusion are a last resort)

Points you must know and possible MCQ's

- We know the type of anemia from the **MCV** (MCQ)
  *Mean corpuscular volume (MCV) is a measurement of the average size of your RBCs.



- There are over 400 variants of G6PD deficiency
  - **B → KSA and The Middle** East (MCQ)
  - **A → Africa** (MCQ)
  - **A- → Nigeria** (MCQ)
- G6PD deficiency → (X Chromosome, Long arm, G6PD q2.8)
- **Heinz bodies& Blister cells** are a characteristic of G6PD deficiency (MCQ)
- G6PD screening test is the **Spot Test** (MCQ)