# Glucose-6-Phosphate Dehydrogenase Deficiency (G6PDD)

# 5th Lecture Objectives
# (Glucose-6-Phosphate Dehydrogenase deficiency)
# (G6PDD)

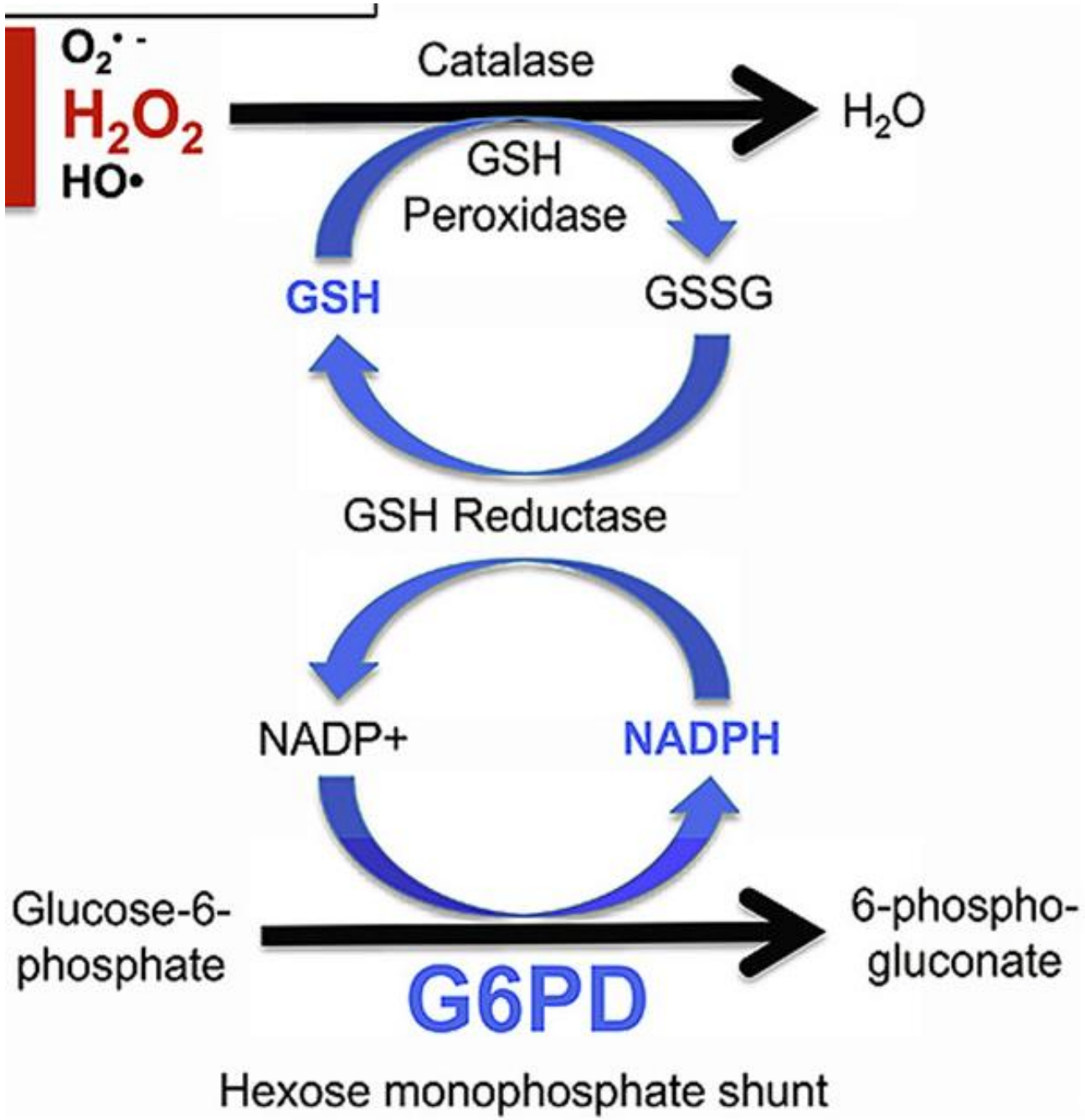
1-to understand the definition of (G6PDD) and recognize its etiology

2- to be able to approaches to patient with (G6PDD) (investigations and treatment)

3- to be able to advice mother about prevention of G6PDD aggravating factors (especially food items)

The **glycolytic pathway** is the main source of energy (ATP)

The **hexose monophosphate 'shunt' pathway** provides the main source of reduced nicotinamide adenine dinucleotide phosphate (NADPH), which maintains reduced glutathione (GSH) and **protects haemoglobin and the membrane proteins against oxidant damage**.

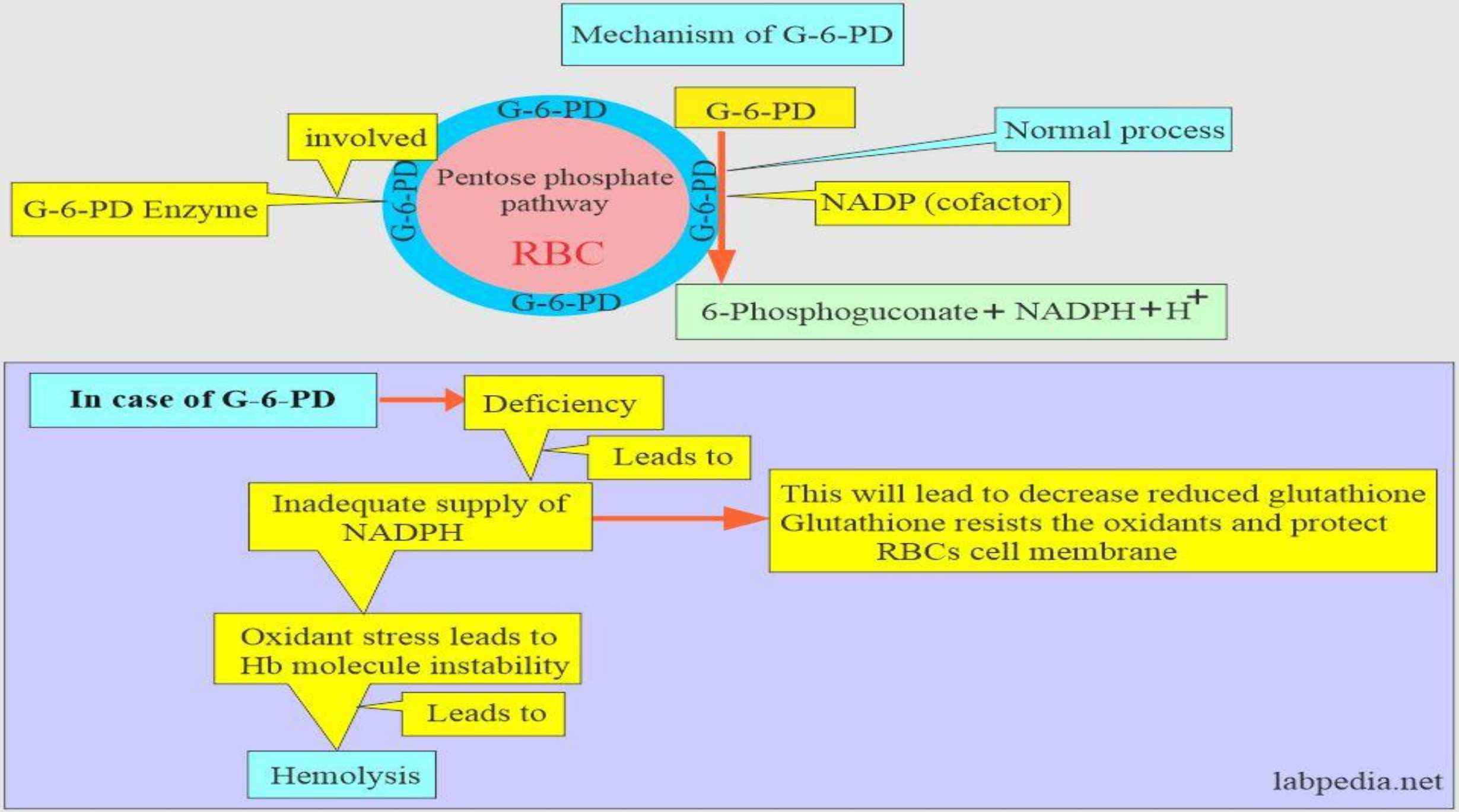


# Pathogenesis

The main role of pentose phosphate pathway is related to metabolism of **glutathione (GSH)** through production of reduced form of nicotinamide adenine dinucleotide phosphate (NADPH).

GSH is important for preservation of sulfhydryl group in many proteins including hemoglobin and to prevent the damage from oxidative radicals in general. Thus, GSH should be constantly available in the reduced form which is effected by, GSH reductase through NADPH, the later is provided by G6PD.

1) an oxidative agent causes **conversion of GSH to oxidized glutathione**;
2) because of the limited capacity of G6PD-deficient red blood cells to regenerate GSH, their **GSH reserve is rapidly depleted**
3) once GSH is exhausted, the **sulfhydryl groups of hemoglobin and probably other proteins are oxidized** to disulfides or sulfoxides
4) **coarse precipitates of denatured hemoglobin** cause irreversible damage to the membrane, and the red blood cells lyse


Mechanism of G-6-PD
G-6-PD
involved
G-6-PD Enzyme
G-6-PD
Pentose phosphate pathway
RBC
G-6-PD
G-6-PD
G-6-PD
Normal process
NADP (cofactor)
6-Phosphoguconate + NADPH + H+
In case of G-6-PD
Deficiency
Leads to
Inadequate supply of NADPH
This will lead to decrease reduced glutathione
Glutathione resists the oxidants and protect RBCs cell membrane
Oxidant stress leads to Hb molecule instability
Leads to
Hemolysis
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a substantial proportion of the hemolysis is **extravascular (as shown by the enlarged spleen)**.
Probably the most severely damaged red blood cells hemolyze in the blood stream on their own, whereas less severely damaged red blood cells will be recognized as abnormal by macrophages and will undergo extravascular hemolysis in the reticuloendothelial system.
The oldest red blood cells with the least G6PD are the first to hemolyze, and the hemolytic process progresses upstream toward cells with more and more G6PD.

# Genetics

1. **Sex-linked recessive** mode of inheritance by a gene located on the X chromosome (similar to hemophilia).

2. Disease is fully expressed in hemizygous males and homozygous females.
There is an advantage of resistance to falciparum malaria in heterozygous females.

# CLINICAL MANIFESTATIONS OF G6PD DEFICIENCY

The most classic manifestation of G6PD deficiency is **acute hemolytic anemia (AHA)**;
another syndrome of great clinical and public health importance is **neonatal jaundice (NNJ)**.

# Acute Hemolytic Anemia

A child with G6PD deficiency is clinically and hematologically normal most of the time, and this status can be designated as a steady-state condition. However, a rather dramatic clinical picture can develop upon

- **ingestion of fava beans (favism)**
- **during the course of infection**
- **after exposure to certain oxidative agents**

# Triggers and Mechanism of Hemolysis

After primaquine, numerous other **drugs** have been reported as being potentially dangerous in G6PD-deficient persons .
There is no obvious similarity in chemical structure among all of these substances, but they have in common the ability to stimulate the pentose phosphate pathway in red blood cells, which must mean that they are able to oxidize NADPH directly or indirectly.

**TABLE 18-3 Drugs That Can Trigger Hemolysis in Glucose-6-Phosphate Dehydrogenase–Deficient Subjects***

| Category of Drug | Definite Hemolysis | Possible Hemolysis |
|---|---|---|
| Antimalarial | Dapsone<br>Primaquine<br>Methylene blue† | Chloroquine<br>Quinine |
| Analgesic | Phenazopyridine | Aspirin (high doses) |
| Antibacterial | Sulfamethoxazole/co-trimoxazole‡<br>Sulfadiazine<br>Ciprofloxacin<br>Moxifloxacin<br>Norfloxacin<br>Ofloxacin<br>Nalidixic Acid<br>Nitrofurans:<br>Nitrofurantoin | Sulfasalazine<br><br><br><br><br><br><br><br>Chloramphenicol<br>Isoniazid |
| Other | Rasburicase<br>Toluidine blue | Ascorbic acid<br>Glibenclamide<br>Vitamin K |

# Favism

After a lag of hours since eating fava beans, the child may become fractious and irritable or subdued and even lethargic.

**within 6 to 24 hours**, the telltale and rather frightening sign of discolored urine .The urine will be reported as dark; as **red, brown, or black; or as "passing blood instead of water."** Depending on experience, culture, and socioeconomic background, it will be said to resemble Coca-Cola, strong tea, or port wine.
At about the same time, **jaundice** will become obvious.

**Within 24 to 48 hours** the child's temperature is often moderately elevated. Nausea, abdominal pain, diarrhea, and rarely vomiting may be present.

**Physical examination** The child will be pale and tachycardic, and in severe cases evidence may be seen of hypovolemic shock or, less likely, heart failure.
The spleen is usually moderately enlarged, and the liver may also be enlarged; either or both may be tender.

The components of **fava beans** responsible for hemolysis have been identified as **vicine** and **convicine**, two β-glycosides that generate the aglycones **divicine** and **isouramil**.
These compounds, in the course of their auto-oxidation, produce free radicals, which in turn oxidize GSH and thereby activate the chain reaction of events previously outlined.
One obvious factor must be the **amount of fava beans ingested** (in relation to body mass). Another is the **quality, with raw fava beans more likely to cause favism than cooked, frozen, or canned fava beans**.

**Henna dyes**, which are used as cosmetics in several populations, mainly in Asia, can also cause serious hemolysis after absorption through the skin

# Drugs

The drop in hemoglobin averaged about 2 g/dL over 3 days, with a nadir on day 7.
An increase in neutrophils and a brisk reticulocyte response were noted, and the bilirubin peaked on day 3.

## Laboratory Findings

Anemia may range from moderate to extremely severe (hemoglobin values of 2.5 g/dL have been recorded). In the absence of other preexisting hematologic abnormalities, the anemia is normocytic and normochromic.

# Infection

the best documented precipitants are hepatitis, pneumonia, typhoid fever, brucellosis and *Clostridium difficile* (in newborns); however, viral infections of the upper respiratory or gastrointestinal tract may also cause hemolysis.
Release of peroxides during pahagocytosis of bacteria by granulocytes might explain the hemolytic process in persons with bacterial infections.
In this respect it is possible that hemolysis has sometimes been attributed to drugs used for treating infection when it should have been blamed on the infection itself.

Apparently, trauma also can be a trigger. It has been reported that in a group of patients who had been involved in major road traffic accidents, the frequency and severity of infection were significantly higher in patients who were G6PD deficient, and more severe anemia also occurred in this group.

# Neonatal Jaundice

G6PD deficiency is an important etiologic factor of severe NNJ, including kernicterus

## Clinical Features

NNJ related to G6PD deficiency is very rarely present at birth; it has a peak incidence between day 2 and day 3.
The severity of G6PD-related NNJ varies from being subclinical to imposing the threat of kernicterus if not treated, and thus prompt recognition of the problem is extremely important to avoid crippling neurologic sequelae.

# Clinical Course

In the majority of cases the hemolytic attack, even if severe, is **self-limited** and tends to resolve spontaneously .
Depending on the proportion of red blood cells that have been destroyed, the anemia will be more or less severe, but the hemoglobin level may be back to normal in **3 to 6 weeks**.
However, in some cases the decrease in hemoglobin is so precipitous that blood transfusion is required to save the child's life. The proportion of such cases will depend primarily on

**(1)the dose of the offending agent**
**(2)concomitant pathology**
**(3)the previous hemoglobin level.**

Although the blood urea level may be transiently elevated, the development of renal failure in children is exceedingly rare, even in the presence of massive hemoglobinuria

# Differential Diagnosis

With a history of fava bean ingestion or of administration of a potentially hemolytic drug followed by hemoglobinuria ,the diagnosis is almost always straightforward.

If the hemoglobinuria has already subsided and the history is uncertain, one is faced instead with the much wider differential diagnosis.

Negative findings of a direct antiglobulin test will militate against **autoimmune hemolytic anemia**.

In endemic areas it will be important to exclude **malaria** .

In persons with **hemolytic-uremic syndrome**, the red blood cell structure is different, and evidence of impaired renal function will be seen.

# Congenital Nonspherocytic Hemolytic Anemia

A small minority of children with G6PD deficiency have hemolytic anemia not only when it is triggered by an exogenous factor but even in the steady state. These children have special G6PD mutations ,all of them are rare, but they are scattered worldwide, regardless of whether G6PD deficiency is endemic in the region.

The patient is almost invariably male and in general is evaluated because of unexplained jaundice, frequently presenting at birth (NNJ). Unfortunately, anemia recurs and the jaundice fails to clear completely, thus requiring further investigation.

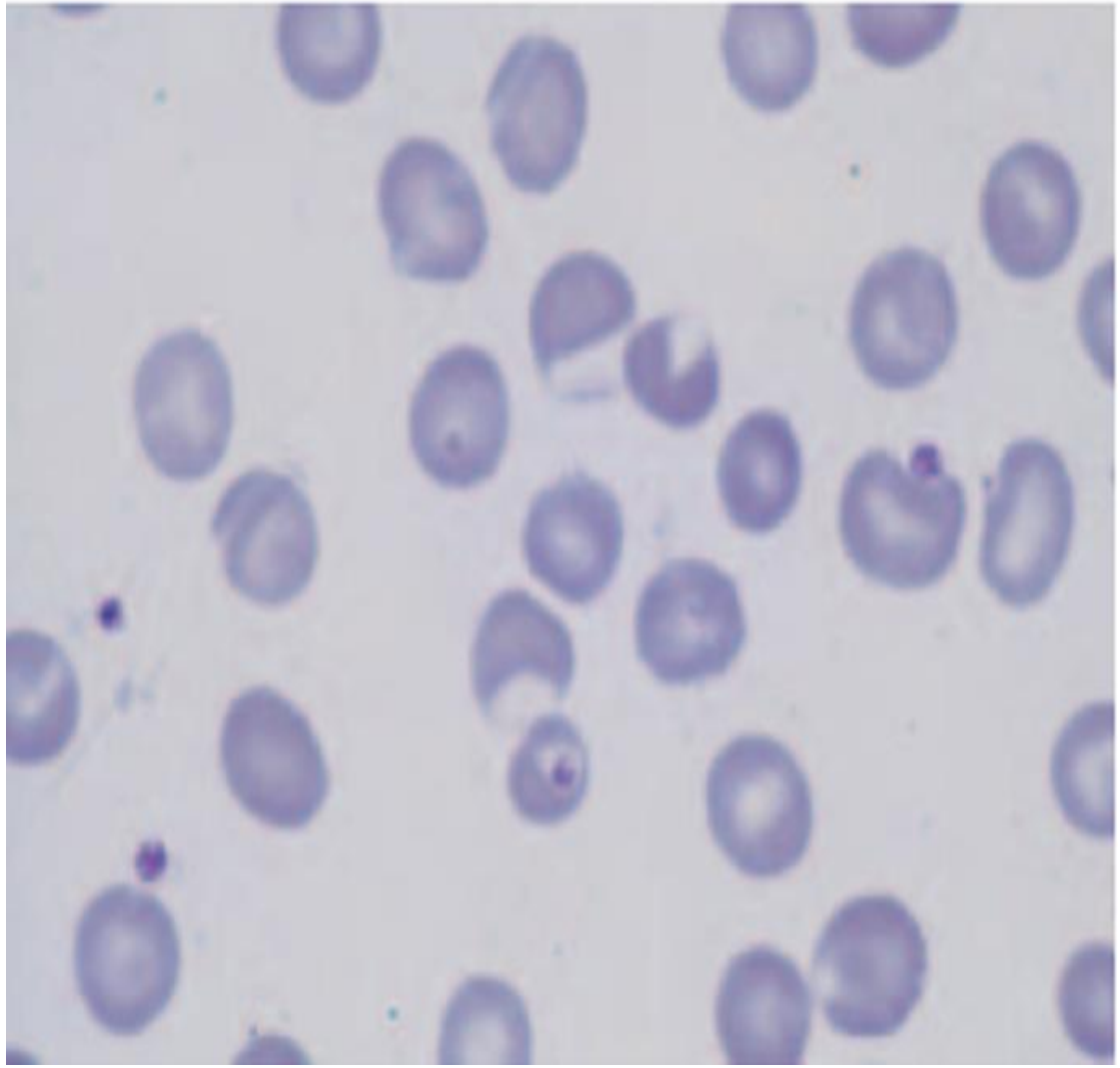
The severity of the anemia ranges from being borderline to being transfusion-dependent in different patients .The anemia is usually normochromic but somewhat macrocytic because a large proportion of reticulocytes (up to 20% or more) will cause an increased mean corpuscular volume.

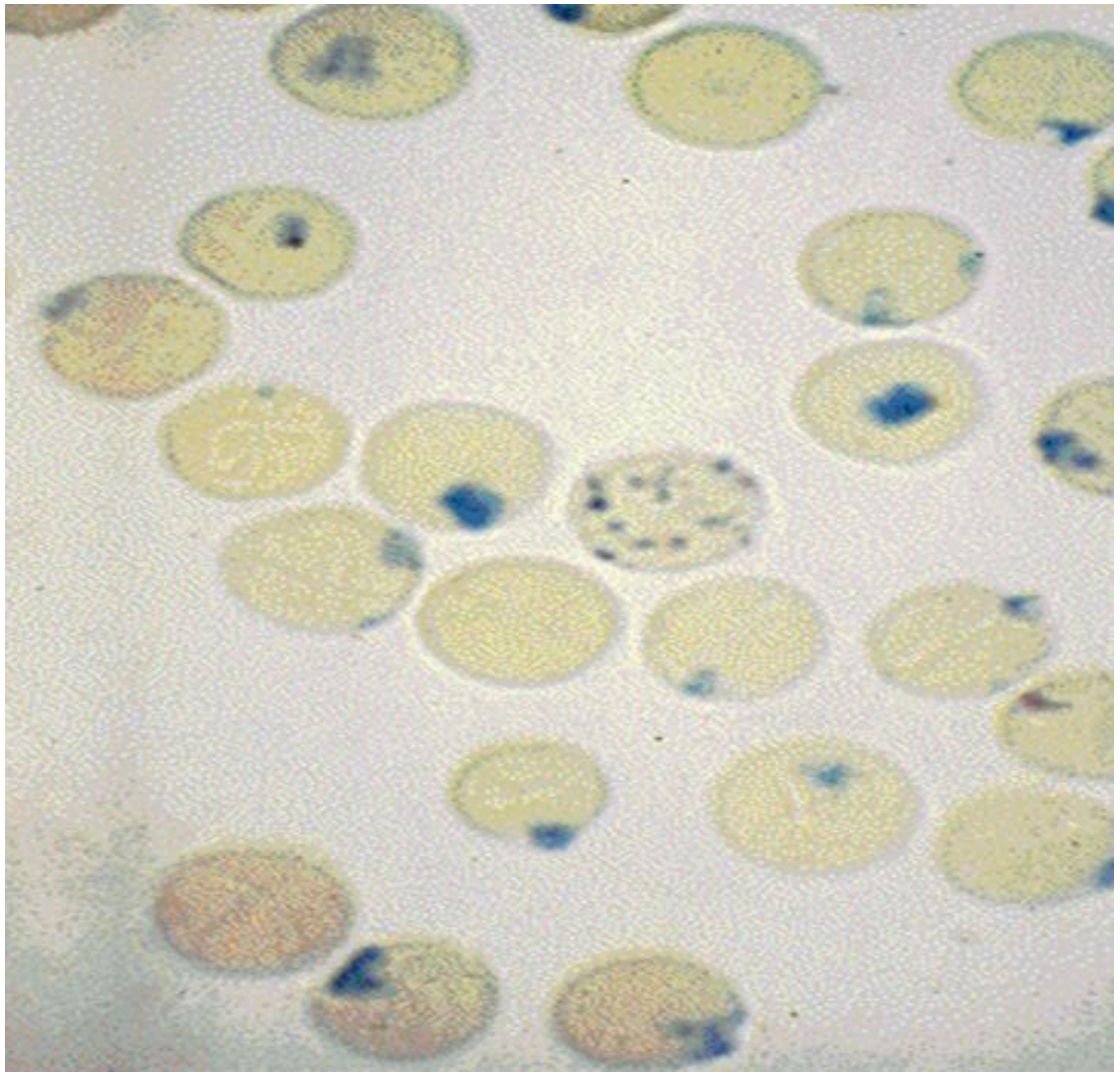
## Treatment 0f Congenital Nonspherocytic Hemolytic Anemia

If the anemia is not severe, regular folic acid supplements .
It is important to avoid exposure to potentially hemolytic drugs, and blood transfusion may be indicated when exacerbations occur, mostly in concomitance with intercurrent infection.

# laboratory findings 0f G6PD deficiency

- **(Blood film): Heinz bodies** They consist of precipitates of denatured hemoglobin and are the vivid manifestation of the oxidative insult that this protein and the cell itself has experienced. However, Heinz bodies are a very transient finding because they tend to be promptly “pinched off” by the spleen(thus giving rise to **bite cells**), and the red blood cells that contain them are very rapidly removed from the circulation.
- **Haptoglobin** is reduced to the point of being undetectable.
- In severe cases it is possible to demonstrate **free hemoglobin in plasma (*hemoglobinemia*).**
- The **white blood cell count** is usually moderately elevated, with a predominance of granulocytes.
- The **platelet count** may be normal, increased, or moderately decreased.
- The **unconjugated bilirubin** level is elevated, but “liver enzyme” levels are generally normal.
- Test results of the **dark urine** are strongly positive for blood because of the presence of free hemoglobin





## LABORATORY DIAGNOSIS OF G6PD DEFICIENCY

The final diagnosis of G6PD deficiency must rely on an enzyme essay, which is fortunately easy to perform, and numerous “screening tests”

### Tests for G6PD Deficiency

The classic spectrophotometric method directly measures the rate of formation of NADPH. Because G6PD activity is much higher in leukocytes (particularly in granulocytes) than in erythrocytes, for accurate measurements it is essential to remove all leukocytes. In normal red blood cells, the range of G6PD activity, measured at 30° C, is 7 to 10 international units/g of hemoglobin.

Several “screening tests” for G6PD deficiency are useful and reliable
**The dye decolorization test** and the **methemoglobin reduction test** are not used much anymore
**fluorescence spot test** and a **formazan-based spot test** are meant to classify a sample simply as **“normal” or “deficient.”**.
One should aim to classify as deficient any sample having **less than 30% of normal** activity, because above this level it is unlikely that serious clinical manifestations will occur.
They are also perfectly adequate for diagnostic purposes in patients who are in the steady state but *not* for patients in the post-hemolytic period or with other complications; in addition, they cannot be expected to identify all heterozygotes.

## The Effect of Red Blood Cell Age and Selective Hemolysis

Because G6PD decreases gradually as red blood cells age, any condition associated with reticulocytosis will entail an *increase* in G6PD activity , and the patient might therefore be misclassified as being G6PD normal .
Test is delayed for a few weeks, when the situation will be evolving toward the steady state, and a repeat test will prove whether the patient is indeed deficient in G6PD.

# Treatment

The most urgent question is whether a blood transfusion is needed. It is difficult to give absolute directives, but the following guidelines may be useful

1) If the hemoglobin level is **less than 7 g/dL**, the child should undergo a transfusion immediately.
2) If the hemoglobin level is **between 7 and 9 g/dL** and evidence indicates persistent brisk hemolysis (hemoglobinuria), immediate blood transfusion is also indicated.
3) if the hemoglobin level is **between 7 and 9 g/dL** but the child has no hemoglobinuria, the child should be kept under close observation for at least 48 hours and should undergo a transfusion if either condition 1 or 2 develops.
4) If the hemoglobin level is **greater than 9 g/dL** but hemoglobinuria persists, the child should be kept under close observation for at least 48 hours and should undergo a transfusion if either condition 1 or 2 develops.

The most important complication that may require treatment is **acute renal failure**, which is exceedingly rare in children.


Any
Questions ?