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**GLUCOSE-6
PHOSPHATE
DEHYDROGENASE
DEFICIENCY**

Physiology of G6PD- Deficiency



fig 1.

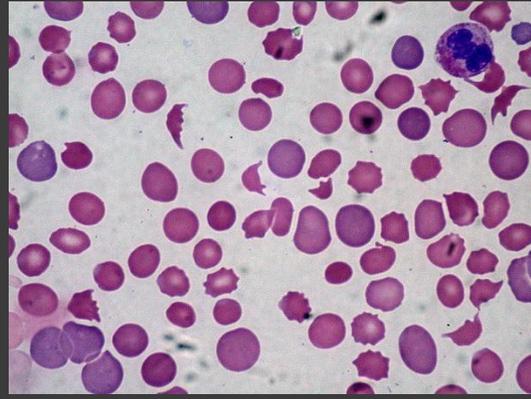


fig 2.



fig 3

- Most common enzyme-deficiency disorder in the world, with rates reaching around 25%
- Indication of symptoms only upon a reaction, or a “trigger”
- Symptoms usually manifest as either neonatal jaundice (infant) or acute hemolytic anemia
- Jaundice is the yellowing of skin and whites of eyes (bilirubin levels exceed normal)
- Hemolytic anemia is anemia stemming from excess hemolysis, which is the rupturing of erythrocytes
- Chronic Nonspherocytic Hemolytic Anemia can arise, a condition where anemic symptoms can develop even without a “trigger”:
- Patients, if correct substances are avoided, are capable of living perfectly normal lives.
- Favism is a specific condition, where fava beans will cause a serious reaction

Molecular Cause

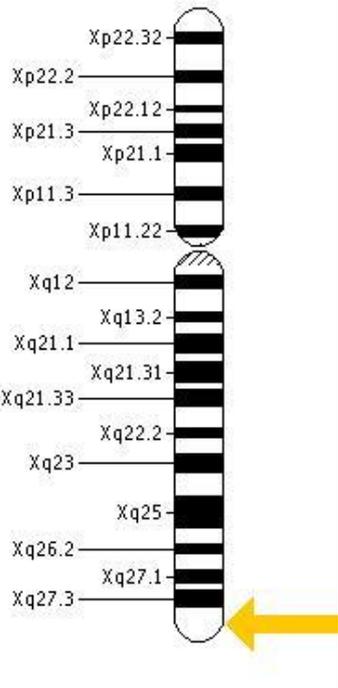


fig 4.

- The G6PD gene is located on the long arm, at position 28
- There are over 400 known variants of the mutation, usually in the form of substitutions or deletions of single nucleotides.
- The most common variant is the G6PD B-, or the G6PD Mediterranean variant (also displays most severe symptoms)
- G6PD is the first enzyme in the hexose monophosphate shunt
- This is critical for generating nicotinamide adenine dinucleotide phosphate, which is used to regenerate reduced glutathione
- Reduced glutathione is used to detoxify oxidants created from the interaction of hemoglobin/oxygen, as well as drugs, infection, and metabolic acidosis
- Without the presence of reduced oxidants, oxidative stress is generated, which aggregates Heinz bodies (denatured hemoglobin)

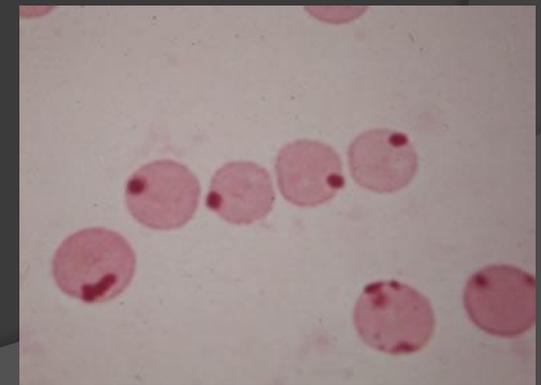
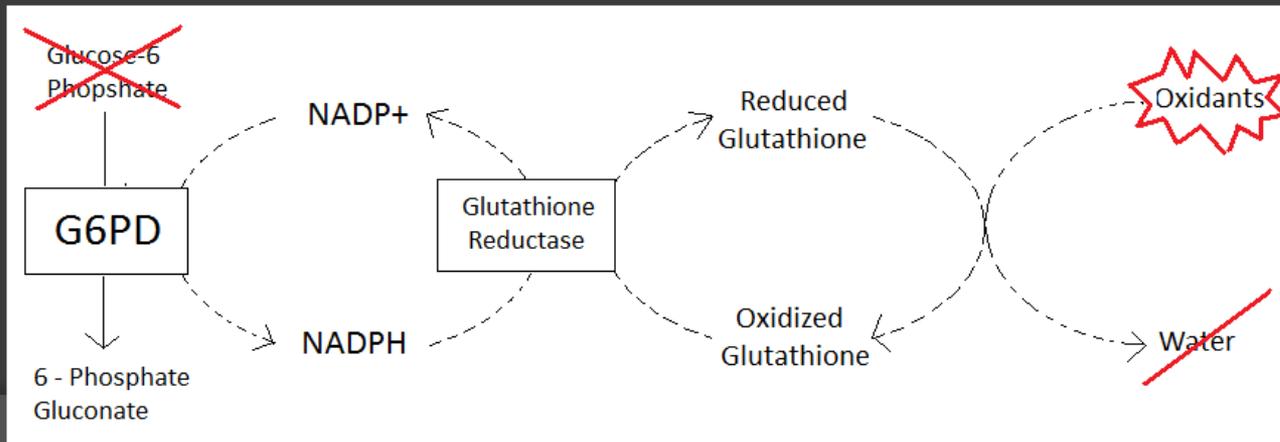


fig 5.

Current Therapies

- The most common and efficient 'solution' to G6PD-Deficiency is a modified diet
- Hemolytic reactions are not often serious enough to provoke physical manifestation of symptoms
- Symptoms are treated individually; patients with jaundice respond positively to phototherapy and hydration. If symptoms worsen to the point of hemolytic anemia, blood transfusions/resuscitation will be required.
- For babies display neonatal jaundice, frequent feedings are encouraged to facilitate removal of bilirubin through the stool
- Immediate treatment of any open wounds and cuts are also mandatory
- Being aware of all potential triggers is very difficult. Patients with different variants suffer various degrees of G6PD deficiency, hence forth varying degrees of reactions
- Fava beans (the main culprit trigger) is a staple in a number of nations with peaking rates
- Blood transfusions can be very difficult to deliver, as well as a number of complications.

Proposed Cure & Limitations

- Scientists have managed to utilize retroviral vectors pseudotyped with vesicular stomatitis virus G glycoprotein that harbors complimentary DNA for the G6PD gene.
- Upon transduction in human stem cells, and introducing it to mice for testing, a majority of G6PD-Deficient mice demonstrated a corrected-phenotype, with sufficient levels of G6PD created
- Using extracted stem cells from a patient (stem cell aspiration), the cells are to be transduced with the MPSV-G6PD A vector. They are then to be delivered via stem cell transplant.
- A minority of mice (1 of 26 mice did not show signs of G6PD, and 9 out of the other 25 lost expressions within weeks). Applied globally, efficiency and effectiveness of the proposal may be severely flawed.
- In the successful experiments, G6PD expression was only 5-10% of the normal expression rate, but it was enough to relieve the phenotype.
- The successful test results were in respect to a mouse's physiology; whether or not sufficient G6PD within a human environment is under question
- Delivery of cells is also dangerous; stem cell transplant has the potential of leading a multitude of complications, including death.

