Metabolic disease: A disease that disrupts metabolism.

Glycogen storage diseases (GSD):

- Genetic disorders . Result from a defect in an enzyme required for either synthesis or degradation.

Classified by a number (roman numerals), the name of the defective enzyme, the name of the doctor who described the disease.

Some cause few symptoms others are fatal.

GSD may affect the liver (enlarging it or damaging it due to increased glycogen amounts).

Or muscle (weakening muscle or breakdown during exercise due to inadequete glucose production.

Severe hypoglycemia ⟶ risk of brain damage

- affected organs either contain more glycogen or have abnormally structured glycogen;
- abnormally structured glycogen due to defects in either debranching enzyme or branching enzyme;

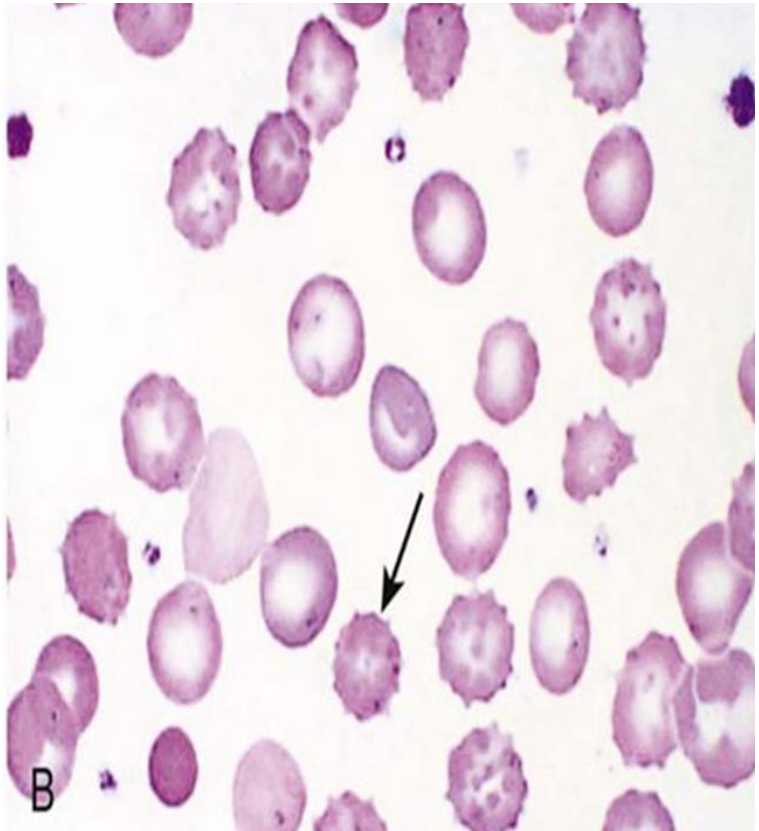
Glycogen-storage diseases

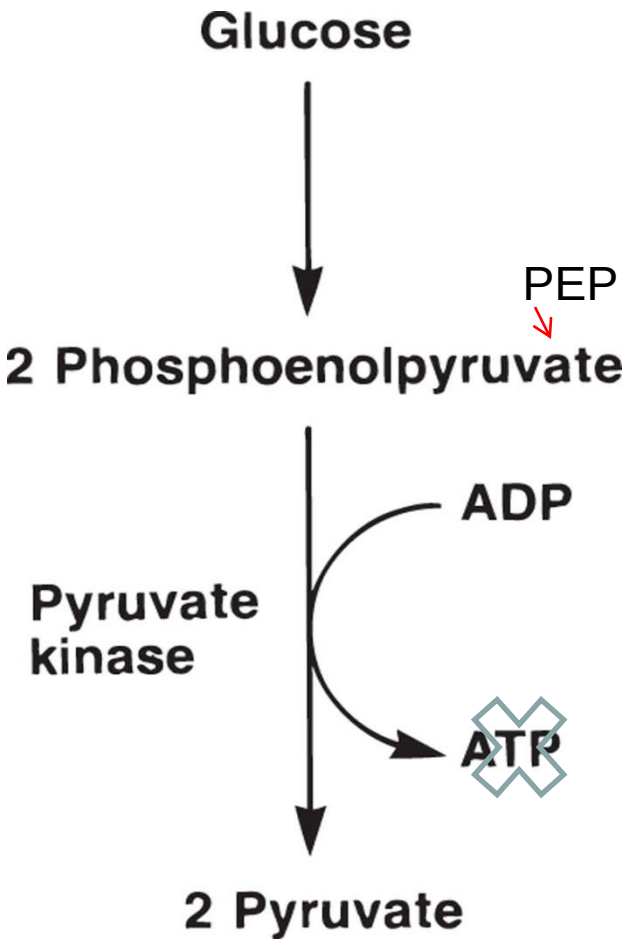
Type	Defective enzyme	Organ affected	Glycogen in the affected organ	Clinical features
I Von Gierke disease	Glucose 6-phosphatase or transport system	Liver and kidney	Increased amount; normal structure.	Massive enlargement of the liver. Failure to thrive. Severe hypoglycemia, ketosis, hyperuricemia, hyperlipemia.
II Pompe disease	α-1,4-Glucosidase (lysosomal)	All organs	Massive increase in amount; normal structure.	Cardiorespiratory failure causes death, usually before age 2.
III Cori disease	Amylo-1,6-glucosidase (debranching enzyme)	Muscle and liver	Increased amount; short outer branches.	Like type I, but milder course.
IV Andersen disease	Branching enzyme (α-1,4 $\longrightarrow$ α-1,6)	Liver and spleen	Normal amount; very long outer branches.	Progressive cirrhosis of the liver. Liver failure causes death, usually before age 2.
V McArdle disease	Phosphorylase	Muscle	Moderately increased amount; normal structure.	Limited ability to perform strenuous exercise because of painful muscle cramps. Otherwise patient is normal and well developed.
VI Hers disease	Phosphorylase	Liver	Increased amount.	Like type I, but milder course.
VII	Phosphofructokinase	Muscle	Increased amount; normal structure.	Like type V.
VIII	Phosphorylase kinase	Liver	Increased amount; normal structure.	Mild liver enlargement. Mild hypoglycemia.

Note: Types I through VII are inherited as autosomal recessives. Type VIII is sex linked.

Glycolytic Pathway: Pyruvte kinase deficiency

- Energy can not be produced, due to lack of ATP
- Results in alteration of membrane, dehydration, pump malfunction





Pyruvate dehydrogenase deficiency:

Inability to convert pyruvate to AcetylCoA , shunted to lactic acid.

Very rare but the most common E1

Symptoms: lactic acidosis, hypoglycemia , mental retardation,

Treatment : ketogenic diet with restricted carbohydrate intake.

,

diet rich in lysine and leucine.

Dietary Disaccharides are Hydrolyzed to Monosaccharides

Disaccharides cant directly enter cells without first being hydrolyzed to monosaccharides (extracellularly). Hydrolysis reactions are catalyzed by enzymes attached to outer surface of epithelial cells lining the small intestine.

$$\text{Maltose} + H_2O \xrightarrow[\text{maltase}]{} 2\ \text{D-glucose}$$

$$\text{Lactose} + H_2O \xrightarrow[\text{lactase}]{} \text{D-galactose} + \text{D-glucose}$$

$$\text{Sucrose} + H_2O \xrightarrow[\text{sucrase}]{} \text{D-fructose} + \text{D-glucose}$$

$$\text{Trehalose} + H_2O \xrightarrow[\text{trehalase}]{} 2\ \text{D-glucose}$$

The resulting monosaccharides enter cells lining the intestine via specific transport proteins. Then pass from cells into the blood, distributed to the liver, enter the glycolytic pathway.

Lactose intolerance

One in four adults is deficient in lactase.

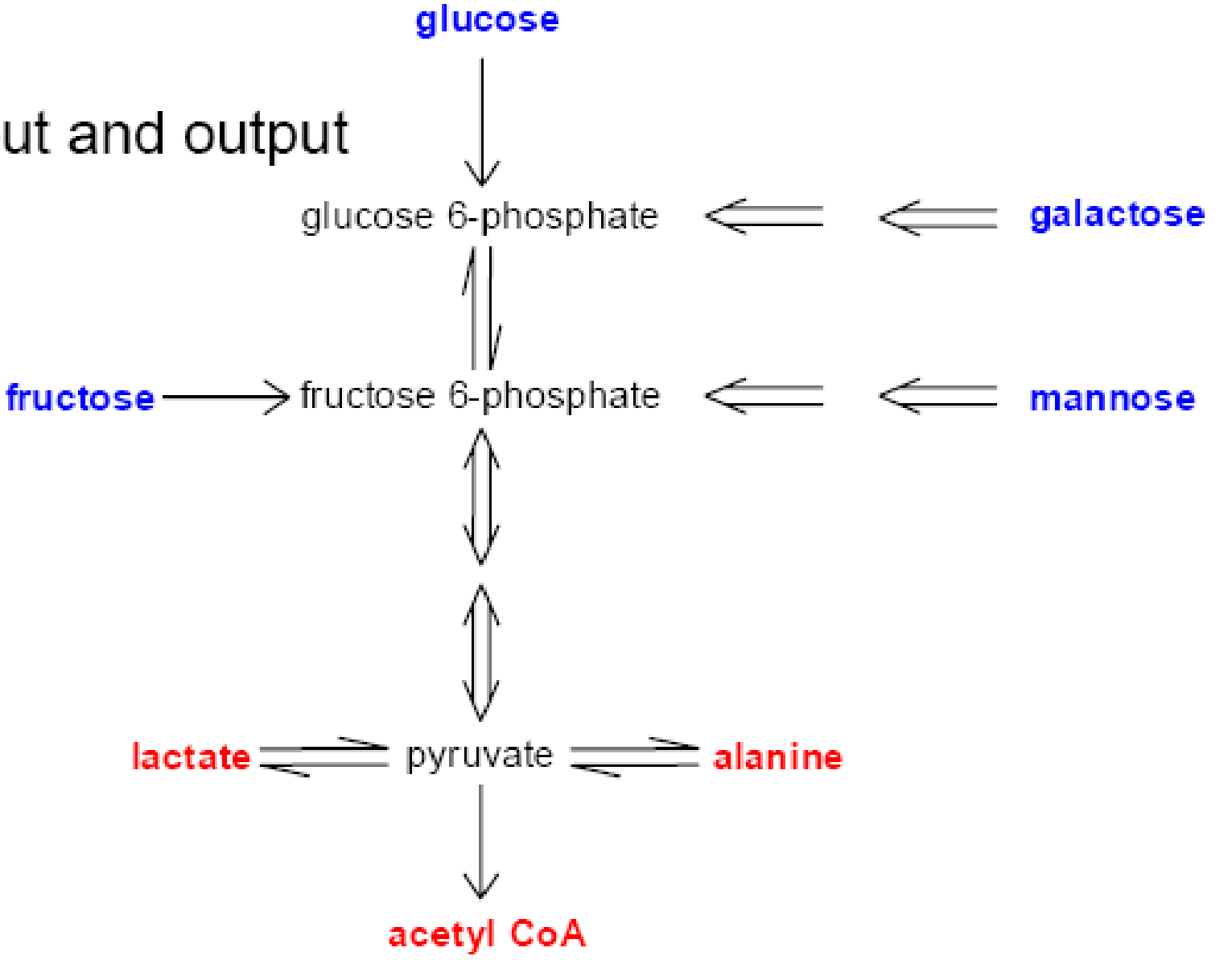
Lactose accumulates in the intestine, bacteria produce its own metabolites.

Results in cramping, diarrhea.

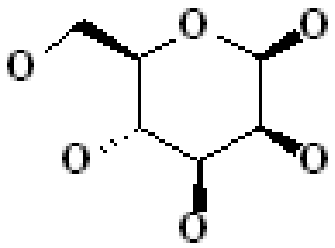
Lactose must be removed from diet.

Glycolytic background

- Input and output



Mannose degradation

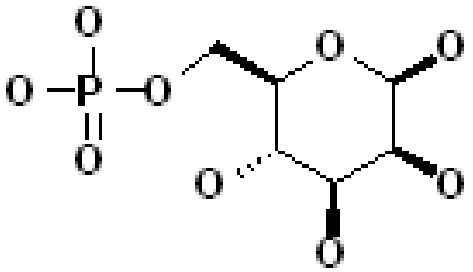


mannose

ATP

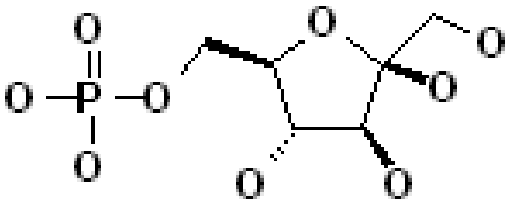
Hexokinase

ADP



mannose-6-phosphate

phosphomannose isomerase

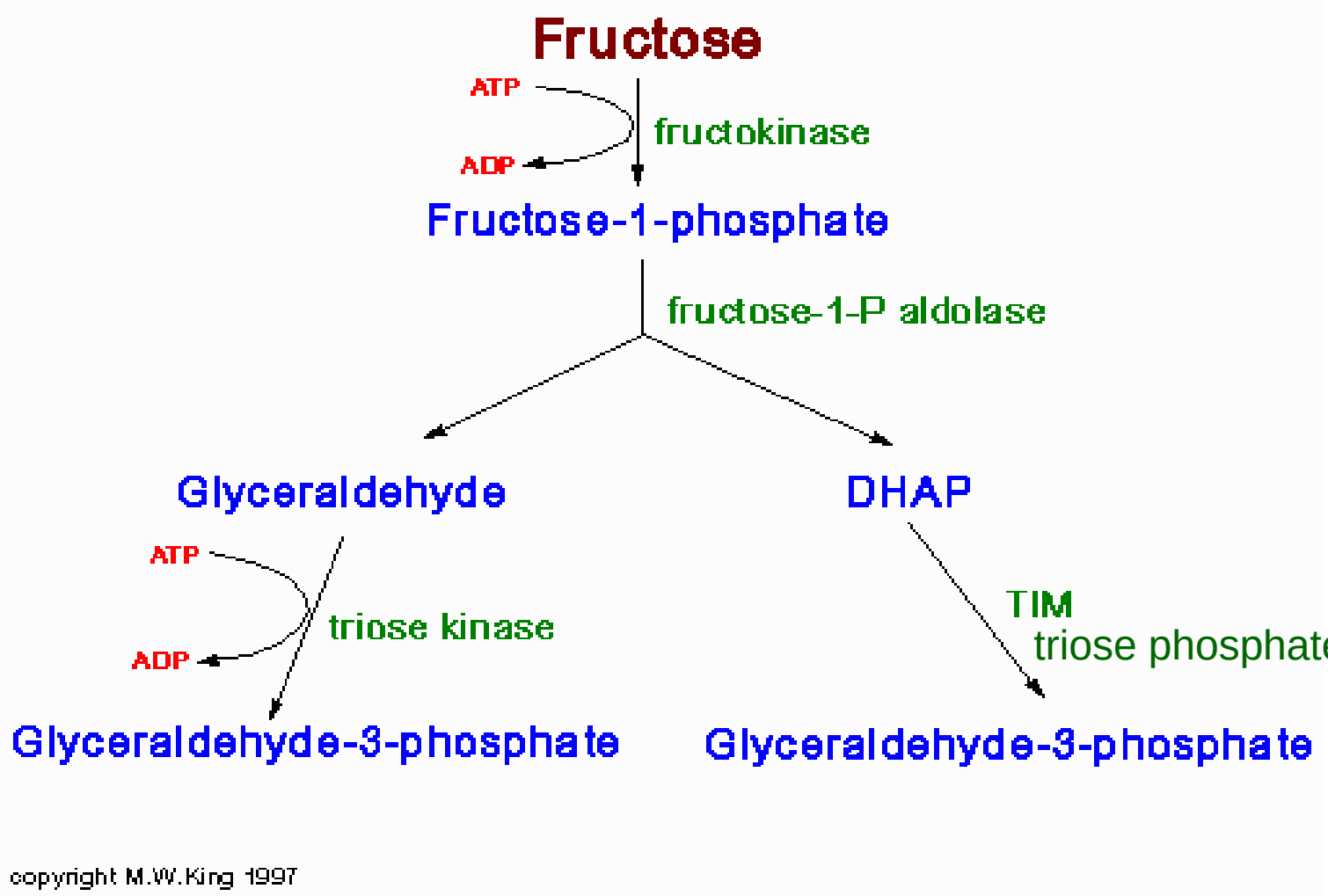


fructose-6-phosphate

Fructose absorption occurs via the GLUT-5 (fructose only) transporter, & GLUT2 transporter, for which it competes with glucose & galactose.

A typical daily intake 100g , much of it metabolized by the liver.

Hexokinase affinity 20x higher to glucose than fructose.



Three inherited abnormalities in fructose metabolism

- Essential fructosuria the lack of fructokinase (liver, pancreatic islets, kidney cortex).

  The fructosuria of this disease depends on the time and amount of fructose and sucrose intake.

  Since the disorder is harmless it may go undiagnosed.

- Hereditary fructose intolerance / fructosemia

  Prolonged intake of fructose by infants with this defect leads to hepatic failure & death →lethal disorder

  lack of aldolase (liver, small intestine & kidney cortex).

  severe hypoglycemia & vomiting following fructose intake→ jaundice , hepatomegaly

  hypoglycemia due to

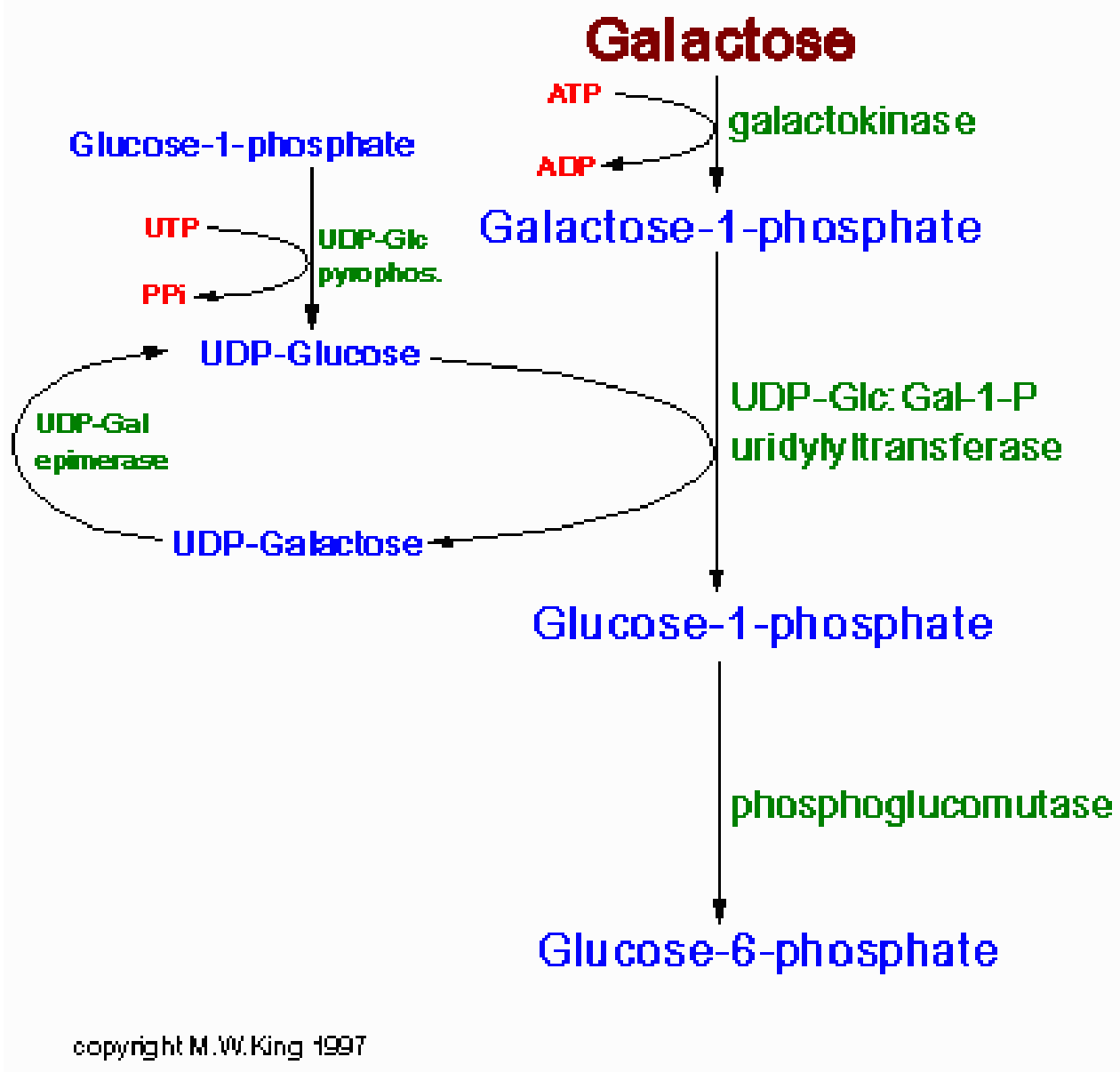
  1)fructose-1-phosphate inhibition of glycogenolysis, by interfering with the phosphorylase reaction

  2)inhibition of gluconeogenesis at the deficient aldolase step.

  Patients remain symptom free on a diet devoid of fructose & sucrose.

- Hereditary fructose-1,6-bisphosphatase deficiency results in severely impaired hepatic gluconeogenesis and leads to episodes of hypoglycemia.

UDP-glucose = the intermediate in the synthesis of glycosidic linkages
= activated donor for glucose



– **3 inborn errors related to galactose metabolism:**

1) of galactose-1-phosphate uridyl transferase deficiency →classic galactosemia)GALT)

2)Galactokinase deficiency (GALK).

3)UDP-galactose epimerase deficiency (GALE)

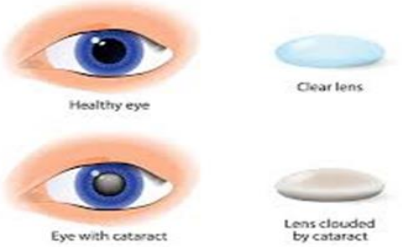
Galactosemia : autosomal recessive .

Vomiting and diarrhea occurs following ingestion of milk, impaired liver function, hypergalactosemia, Severe cases→blindness, mental retardation.

Blindness is due to the conversion of circulating galactose to the sugar alcohol galactitol, by an NADPH-dependent galactose reductase that is present in neural tissue and in the lens of the eye. At normal circulating levels of galactose this enzyme activity causes no pathological effects. However, a high concentration of galacitol in the lens causes osmotic swelling.

– Treatment = eliminate lactose, galactose from the diet.

Galactosemia (GAL)



- GAL is a condition in which the body is unable to process galactose, the sugar present in milk. Accumulation of excessive galactose in the body can cause many problems, including liver damage, brain damage and cataracts.