BIOCHEMISTRY- BP203T

UNIT : 1 METABOLISM OF CARBOHYDRATES

CLASS:5

TOPIC: GLYCOGEN METABOLISM

GLYCOGEN:

Glycogen is the storage form of glucose in animals, as is starch in plants.

It is stored mostlyin liver (6-8%) and muscle (1-2%).

Due to more muscle mass, the quantity of glycogen in muscle(250 g) is about three times higher than that inthe liver (75 g).

Glycogen is stored as granules inthe cytosol, where most of the enzymes ofglycogen synthesis and breakdown are present.

Functions of glycogen

The prime function of liver glycogen is to maintain the blood glucose levels, particularly between meals.

Liver glycogen stores increase in a well-fed state which are depleted during fasting. Muscle glycogen serves as a fuel reservefor the supply of ATP during muscle contraction.

Why store glycogenas a fuel reserve?

As such, fat is the fuel reserve of the body. However, fat is not preferred, instead glycogen ischosen for a routine, and day to day use of energy for the following reasons

Glycogen can be rapidly mobilized

Glycogen can generate energy in the absence of oxygen

Brain depends on continuous glucose supply(which mostly comes from glycogen.)

On the other hand, fat mobilization is slow, needs O_2 for energy production and cannot produce glucose (to a significant extent).

GLYCOGENESIS

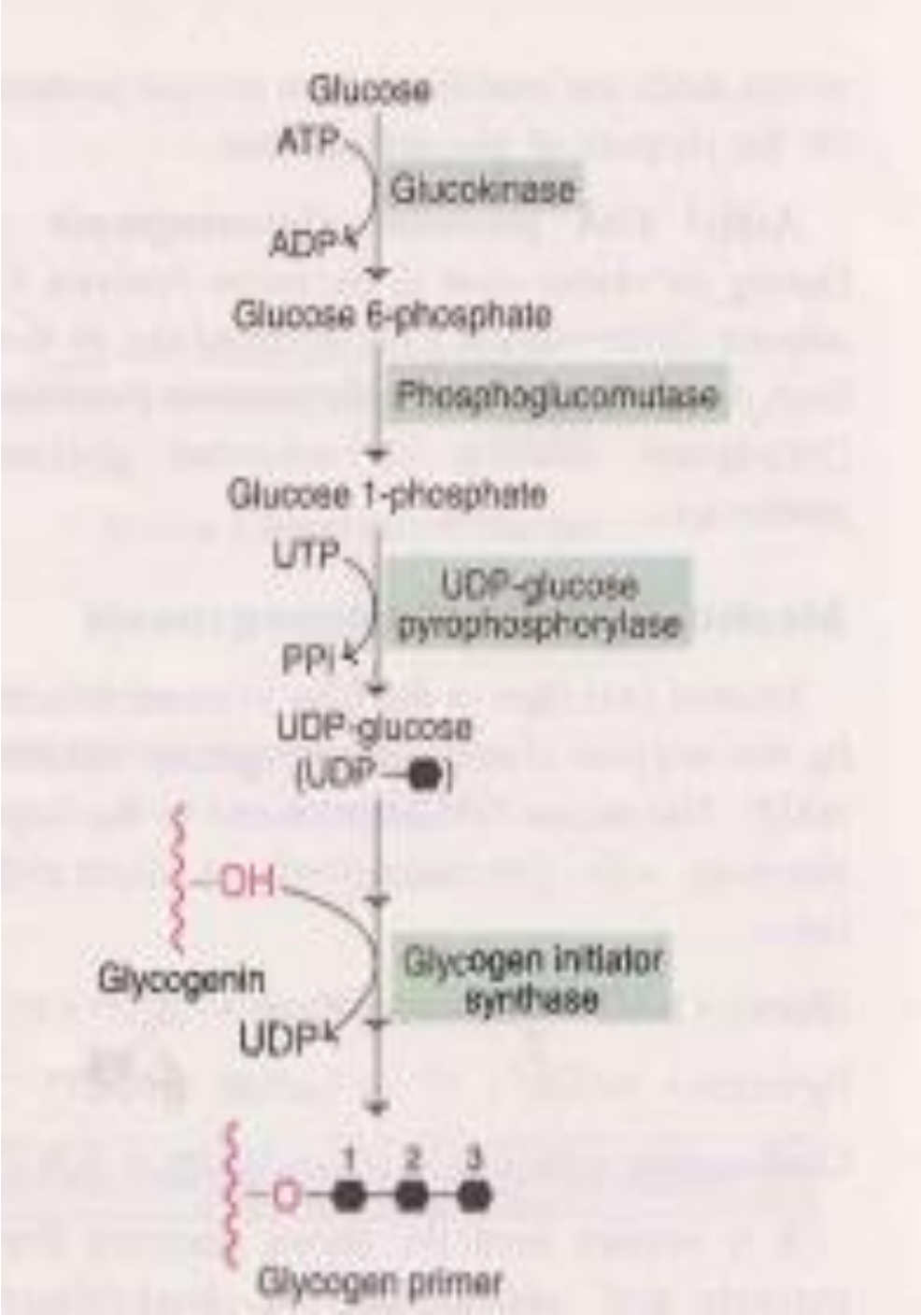
The **synthesis of glycogen** from glucose is glycogenesis (**Fig.13.14**). Glycogenesis takes place in the cytosol and requires ATP and UTP,besides glucose.

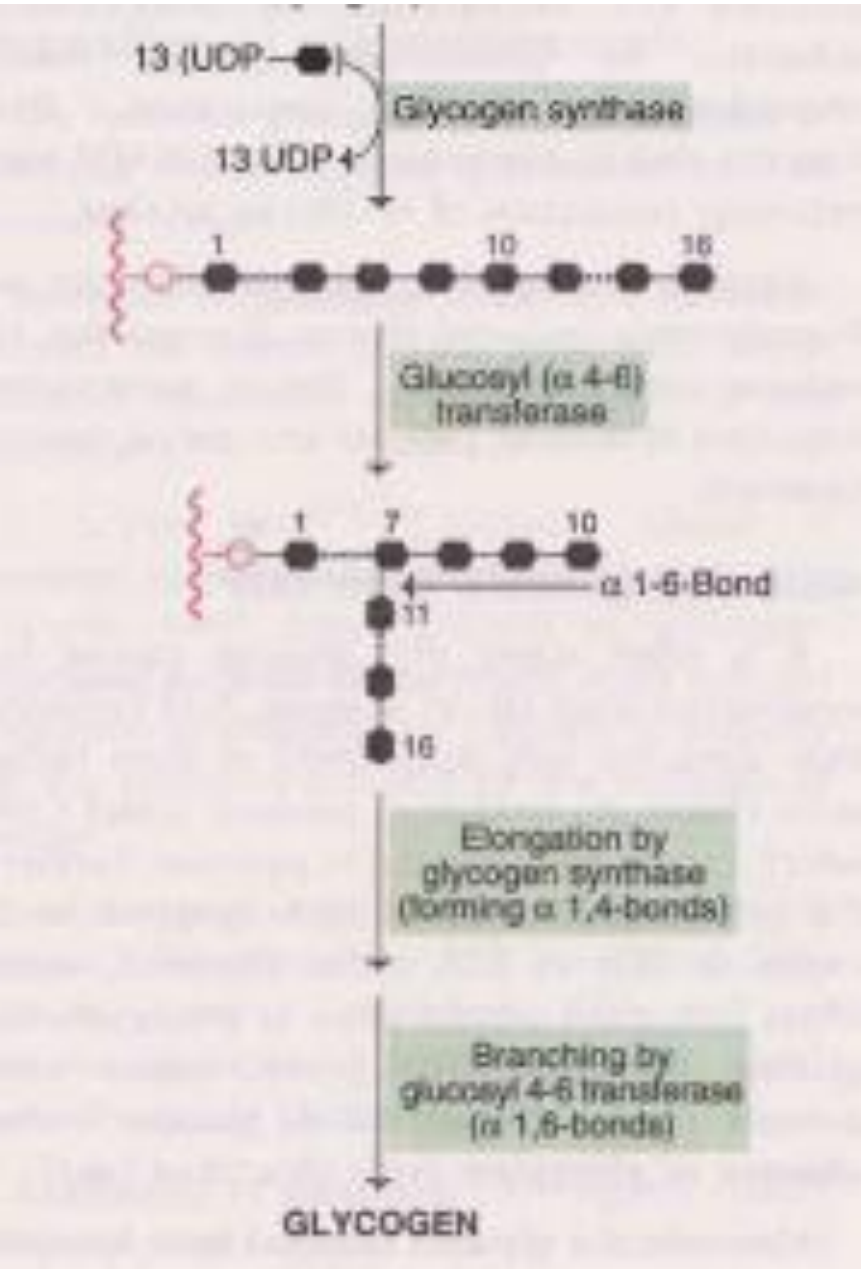
Synthesis of UDP-glucose :

The enzymeshexokinase (in muscle) and glucokinase (in liver)convert glucose to glucose 6-phosphate.

Phosphoglucomutase catalyses the conversion of glucose 6-phosphate to glucose 1-phosphate.

Uridine diphosphate glucose (UDPG) is synthesized from glucose 1-phosphate and UTP by UDP-glucose pyrophosphorylase.


Glucose
ATP
Glucokinase
ADP
Glucose 6-phosphate
Phosphoglucomutase
Glucose 1-phosphate
UTP
UDP-glucose pyrophosphorylase
PPi
UDP-glucose
(UDP
OH
Glycogenin
Glycogen initiator synthase
UDP
1
2
3
Glycogen primer


13 (UDP
Glycogen synthase
13 UDP
1
10
16
Glucosyl (α 4-6) transferase
1
7
10
α 1-6-Bond
11
16
Elongation by glycogen synthase (forming α 1,4-bonds)
Branching by glucosyl 4-6 transferase (α 1,6-bonds)
GLYCOGEN

2. Requirement of primer to initiate glycogenesis:

- A small fragment of pre-existing glycogen must act as a 'primer' to initiate glycogen synthesis.
- It is recently found that in the absence of glycogen primer, a specific protein—namely 'glycogenin'—can accept glucose from UDPG.
- The hydroxyl group of the amino acid tyrosine of glycogenin is the site at which the initial glucose unit is attached.
- The enzyme glycogen initiator synthase transfers the first molecule of glucose to glycogenin.
- Then glycogenin itself takes up a few glucose residues to form a fragment of primer which serves as an acceptor for the rest of the glucose molecules.

3. Glycogen synthesis by glycogen synthase :

- Glycogen synthase is responsible for the formation of 1,4-glycosidic linkages.
- This enzyme transfers the glucose from UDP-glucose to the non-reducing end of glycogen to form D1,4 linkages.

4. Formation of branches in glycogen :

- Glycogen synthase can catalyse the synthesis of a linear unbranched molecule with 1,4 D glycosidic linkages.
- Glycogen, however, is a branched tree-like structure. The formation of branches is brought about by the action of a branching enzyme, namely glucosyl D-4-6 transferase.
- (amylo D 1,4 o 1,6 transglucosidase):
- This enzyme transfers a small fragment of five to eight glucose residues from the non-reducing end of glycogen chain (by breaking D-1,4 linkages) to another glucose residue where it is linked by D-1,6 bond.
- This leads to the formation of a new non-reducing end, besides the existing one.
- Glycogen is further elongated and branched, respectively, by the enzymes glycogen synthase and glucosyl 4-6 transferase

$$(Glucose)n + Glucose + 2ATP \rightarrow (Glucose)n+1 + 2\ ADP + Pi$$

Of the two ATP utilized, one is required for the phosphorylation of glucose while the other is needed for conversion of UDP to UTP.

GLYCOGENOLYSIS:

The degradation of stored glycogen in liver and muscle constitutes glycogenolysis.

The pathways for the synthesis and degradation of glycogen are not reversible.

An independent set of enzymes present in the cytosol carry out glycogenolysis. Glycogen is degraded by breaking D-1,4- and D-1,6-glycosidic bonds .

1. Action of glycogen phosphorylase :

The D 1,4-glycosidic bonds (from the non-reducing ends) are cleaved sequentially by the enzyme glycogen phosphorylase to yield glucose 1-phosphate.

This process—called phosphorolysis—continues until four glucose residues remain on either side of branching point (D-1,6- glycosidic link).

The glycogen so formed is known as limit dextrin which cannot be further degraded by phosphorylase.

Glycogen phosphorylase possesses a molecule of pyridoxal phosphate, covalently bound to the enzyme.

2. Action of debranching enzyme :

The branches of glycogen are cleaved by two enzyme activities present on a single polypeptide called debranching enzyme, hence it is a bifunctional enzyme.

Glycosyl 4 : 4 transferase (oligo D-1,4 o 1,4 glucan transferase) activity removes a fragment of three or four glucose residues attached at a branch and transfers them to another chain.

Here, one D-1,4-bond is cleaved and the same D-1,4 bond is made, but the places are different.

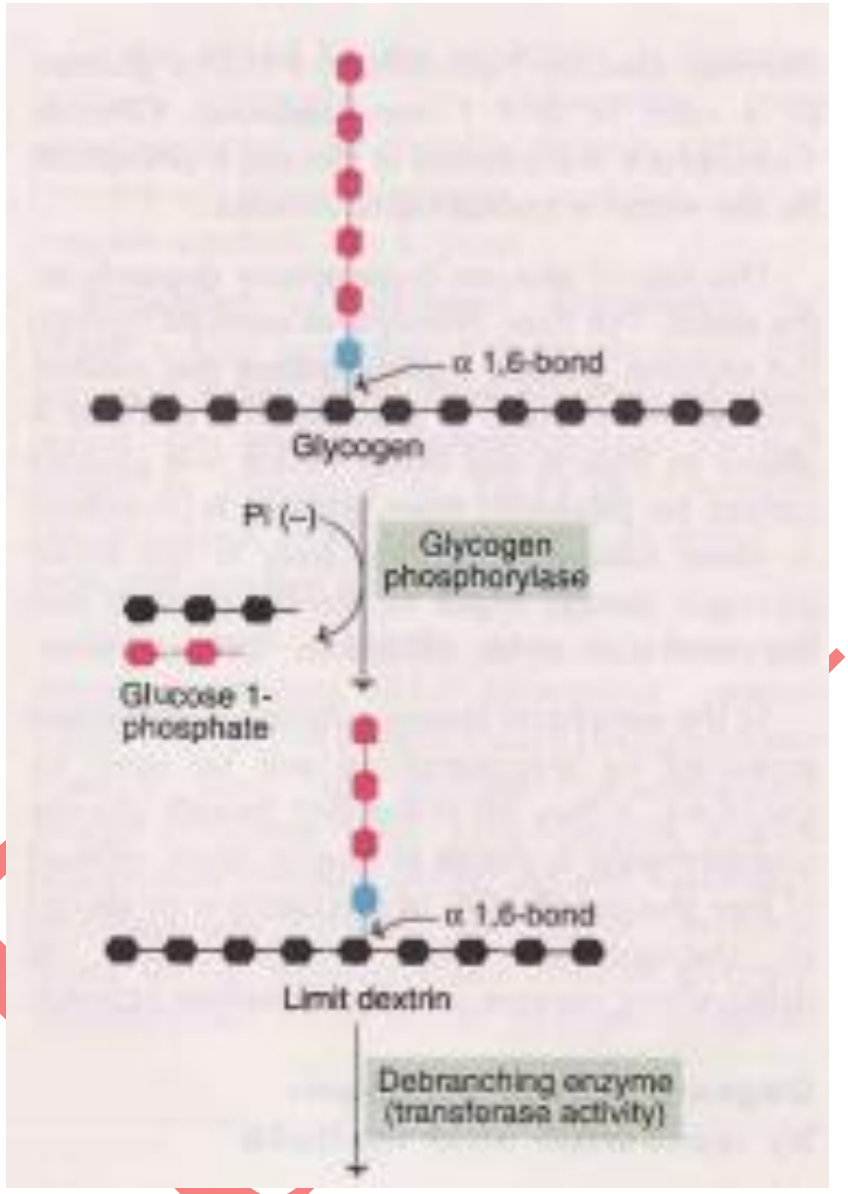
Amylo D-1,6-glucosidase breaks the D-1,6 bond at the branch with a single glucose residue and releases a free glucose.

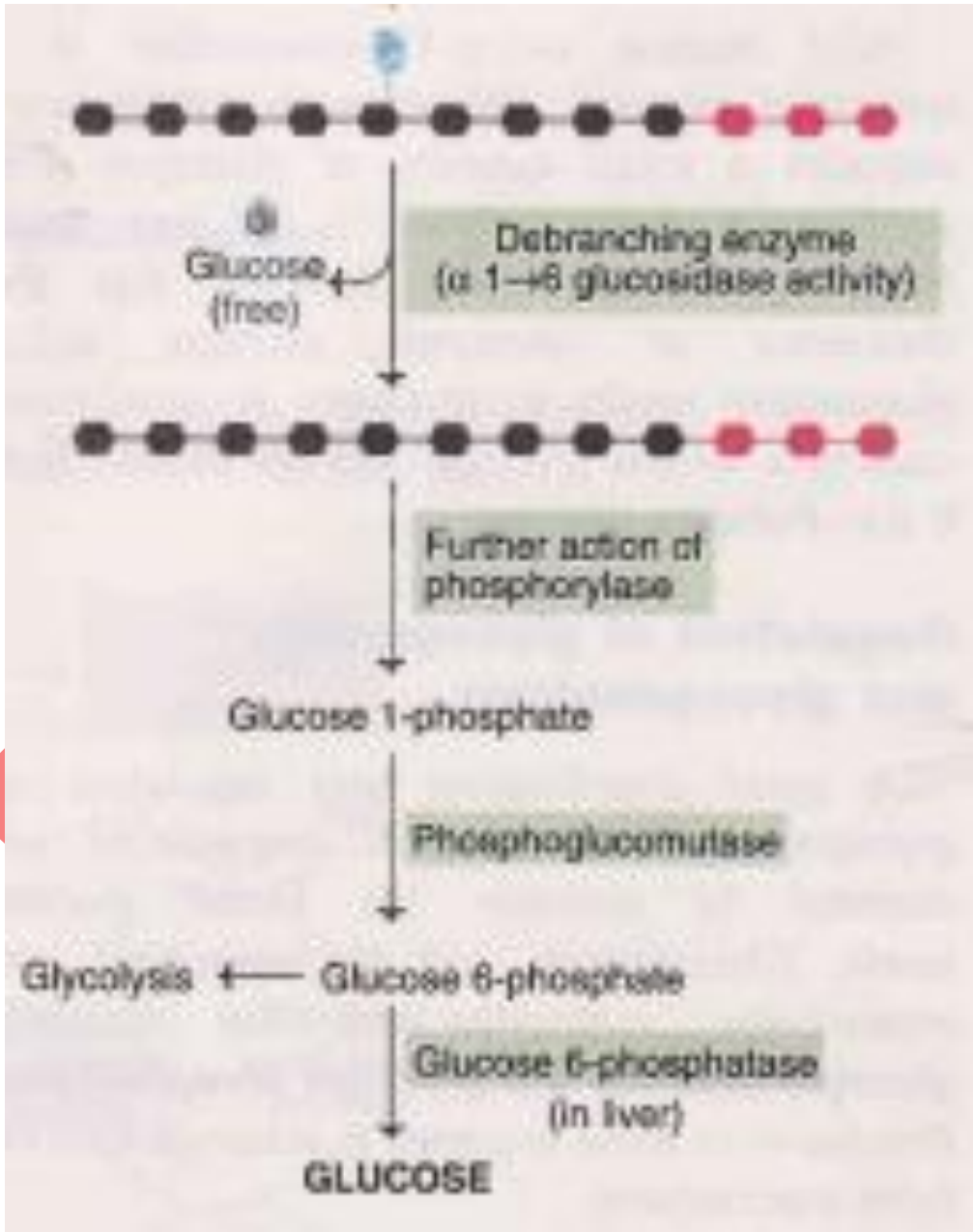
The remaining molecule of glycogen is again available for the action of phosphorylase and debranching enzyme to repeat the reactions stated in 1 and 2.

3. Formation of glucose 6-phosphate and glucose :

Through the combined action of glycogen phosphorylase and debranching enzyme, glucose 1-phosphate and free glucose in a ratio of 8 : 1 are produced.

Glucose 1-phosphate is converted to glucose 6-phosphate by the enzyme phosphoglucomutase.


α 1,6-bond
Glycogen
Pi (–)
Glycogen phosphorylase
Glucose 1-phosphate
α 1,6-bond
Limit dextrin
Debranching enzyme (transferase activity)


Glucose
(free)
Debranching enzyme
(α 1→6 glucosidase activity)
Further action of
phosphorylase
Glucose 1-phosphate
Phosphoglucomutase
Glycolysis
Glucose 6-phosphate
Glucose 6-phosphatase
(in liver)
GLUCOSE

GLYCOGEN STORAGE DISEASE:

The metabolic defects concerned with the glycogen synthesis and degradation are collectively referred to as glycogen storage diseases. These disorders are characterized by deposition of normal or abnormal type of glycogen in one or more tissues.

A summary of glycogen metabolism along with the defective enzymes in the glycogen storage disorders is depicted in Fig.13.19.

The biochemical lesions and the characteristic features of the disorders are given in Table 13.2.

Von Gierke's disease (type I)

The incidence of type I glycogen storage disease is 1 per 200,000 persons.

It is transmitted by autosomal recessive trait.

This disorder results in various biochemical manifestations.

1. Fasting hypoglycemia :

Due to the defect in the enzyme glucose 6-phosphatase, enough free glucose is not released from the liver.

2. Lactic acidemia :

Glucose is not synthesized from lactate produced in muscle and liver. Lactate level in blood increases and the pH is lowered (acidosis).

3. Hyperlipidemia :

There is a blockade in gluconeogenesis. Hence more fat is mobilized to meet energy requirements of the body.

This results in increased plasma free fatty acids and ketone bodies.

4. Hyperuricemia :

Glucose 6-phosphate that accumulates is diverted to pentose phosphate pathway, leading to increased synthesis of ribose phosphates which increase the cellular levels of phosphoribosyl pyrophosphate and enhance the metabolism of purine nucleotides to uric acid.

Elevated plasma levels of uric acid (hyperuricemia) are often associated with gouty arthritis (painful joints).

TABLE 13.2 Glycogen storage diseases - biochemical lesions and characteristic features

Type	Name	Enzyme defect	Organ(s) involved	Characteristic features
I	von Gierke's disease (type I glycogenosis)	Glucose 6-phosphatase	Liver, kidney and intestine	Glycogen accumulates in hepatocytes and renal cells, enlarged liver and kidney, fasting hypoglycemia, lactic acidemia; hyperlipidemia; ketosis; gouty arthritis.
II	Pompe's disease	Lysosomal α-1,4 glucosidase (acid maltase)	All organs	Glycogen accumulates in lysosomes in almost all the tissues; heart is mostly involved; enlarged liver and heart, nervous system is also affected; death occurs at an early age due to heart failure.
III	Cori's disease (limit dextrinosis, Forbe's disease)	Amylo α-1,6-glucosidase (debranching enzyme)	Liver, muscle, heart, leucocytes	Branched chain glycogen accumulates; liver enlarged; clinical manifestations are similar but milder compared to von Gierke's disease.
IV	Anderson's disease (amylopectinosis)	Glucosyl 4-6 transferase (branching enzyme)	Most tissues	A rare disease, glycogen with only few branches accumulate; cirrhosis of liver, impairment in liver function.
V	McArdle's disease (type V glycogenosis)	Muscle glycogen phosphorylase	Skeletal muscle	Muscle glycogen stores very high, not available during exercise; subjects cannot perform strenous exercise; suffer from muscle cramps; blood lactate and pyruvate do not increase after exercise; muscles may get damaged due to inadequate energy supply.
VI	Her's disease	Liver glycogen phosphorylase	Liver	Liver enlarged; liver glycogen cannot form glucose; mild hypoglycemia and ketosis seen.
VII	Tarui's disease	Phosphofructokinase	Skeletal muscle, erythrocytes	Muscle cramps due to exercise; blood lactate not elevated; hemolysis occurs.

Rare glycogen disorders VIII, IX, X and XI have been identified. They are due to defects in the enzymes concerned with activating and deactivating liver phosphorylase.