Metabolism of glycogen

Ahmed Salem, MD, MSc, PhD, FRCR

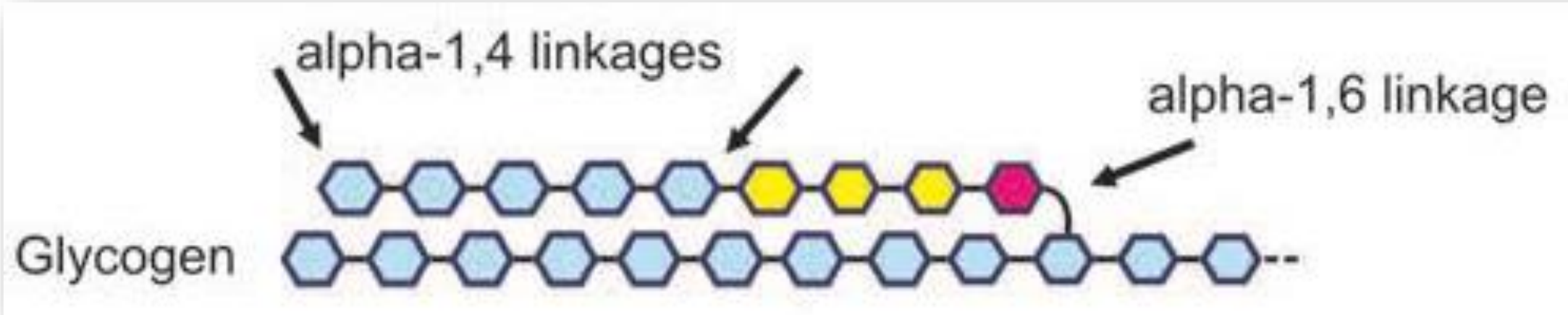
CHO metabolism	*1. Glycolysis* *a. First phase* *b. Second phase* *2.Pentosephosphate pathway* *3.Metabolism of non-glucose sugars* *a.metabolism of fructose.* *b.metabolism of galactose* *c.metabolism of glucuronic acid* 3. Glycogen metabolism a. Glycogen synthesis b. Glycogen breakdown

GLYCOGEN METABOLISM

- Glycogen is the major storage form of carbohydrates in cells
- It is stored in the cytosol as **granules** (all enzymes are cytoplasmic)
- It is present in every cell (but more abundant in liver, muscle):
  - **Muscle glycogen (1-2g/100g; appx 400-500g in total):** provide rapidly available supply of glucose as fuel for glycolysis during contraction (muscle use only)
  - **Liver glycogen (6-10g/100g; appx 100-120g in total):** maintaining blood glucose levels during fasting (for whole body)

Its metabolism involves two processes:

I- Glycogenolysis (Glycogen breakdown)
II- Glycogenesis (Glycogen formation)


alpha-1,4 linkages
alpha-1,6 linkage
Glycogen

Glycogen breakdown (glycogenolysis)

- Starts 4 h after meal (fasting), lasts 12-18h

- Occurs in cytoplasm of cells (except RBCs; does not store glycogen):
  - ***In liver:*** glycogen is hydrolysed to **glucose** to maintain blood glucose level
  - ***In muscle:*** glycogen is hydrolysed to **glucose 6-P** → glycolytic pathway to generate ATP

- Glycogenolysis is catalysed:
  - 1st by ***glycogen phosphorylase*** → glucose 1-P
  - Then by ***debranching enzyme*** → liberate free glucose

Steps of glycogenolysis (enzymes)

1. Glycogen phosphorylase

2. Debranching enzyme (bi-functional)
    A. Glucan transferase
    B. α 1,6 glucosidase

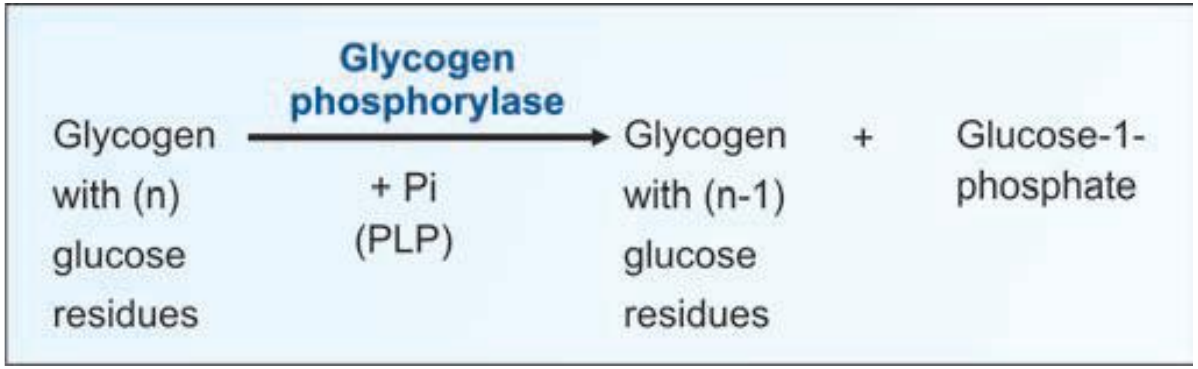
3. Phosphoglucomutase

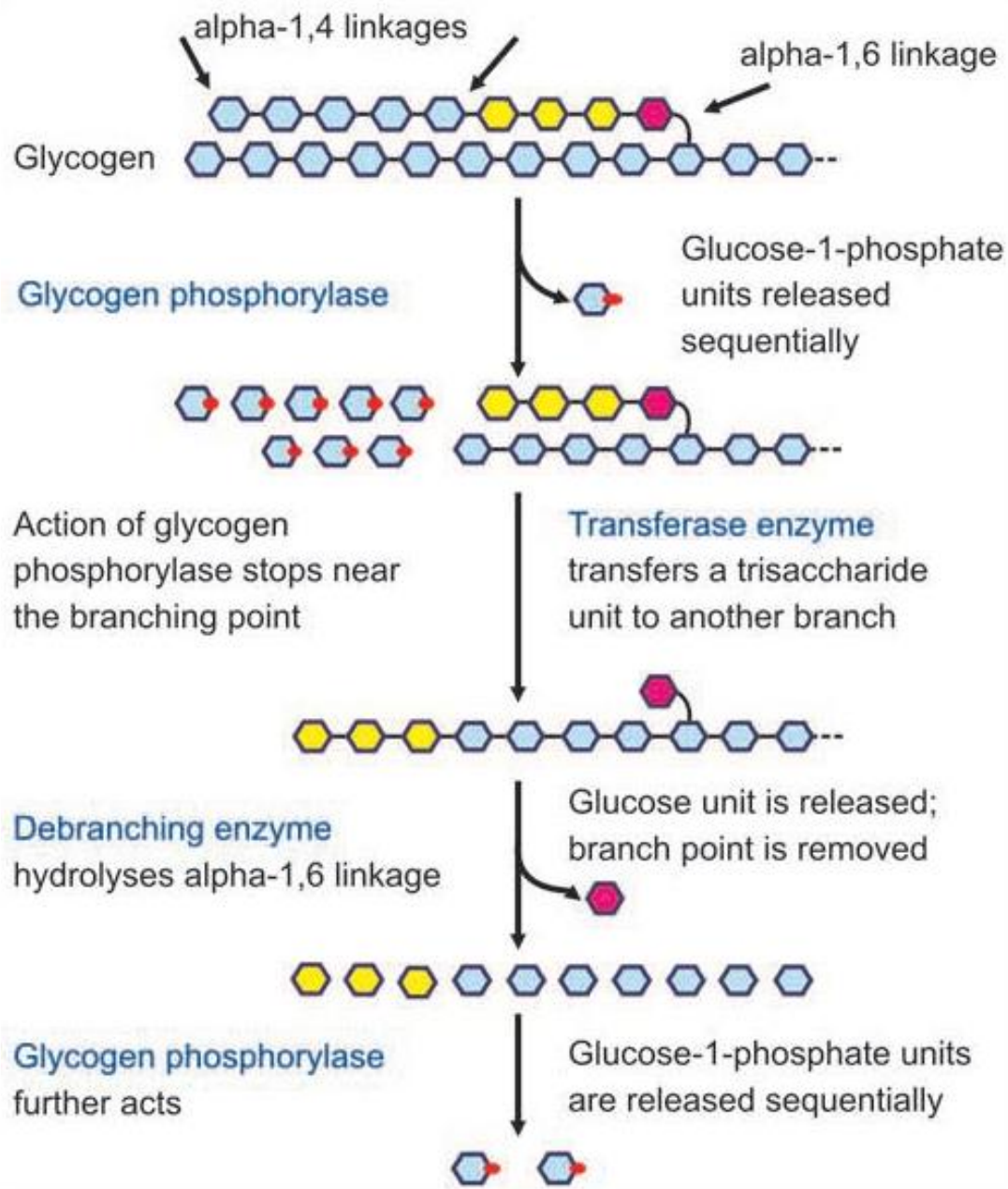
4. Glucose-6 phosphatase

1. Glycogen phosphorylase

- Catalyses release of glucose 1-P from terminal residue of glycogen by adding inorganic phosphate (phosphorolysis)
    - Glycogen phosphorylase contains pyridoxal phosphate as an integral coenzyme

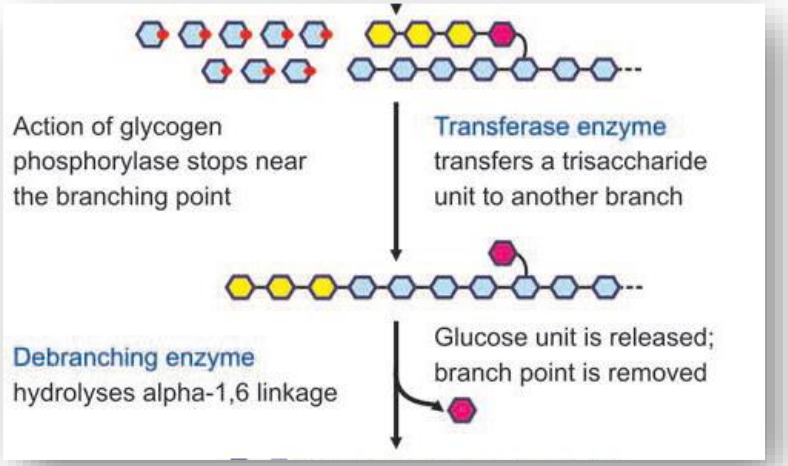
- The action of glycogen phosphorylase stops when 4 glucose residues are left from the branching point




alpha-1,4 linkages
alpha-1,6 linkage
Glycogen
Glycogen phosphorylase
Glucose-1-phosphate units released sequentially
Action of glycogen phosphorylase stops near the branching point
Transferase enzyme transfers a trisaccharide unit to another branch
Debranching enzyme hydrolyses alpha-1,6 linkage
Glucose unit is released; branch point is removed
Glycogen phosphorylase further acts
Glucose-1-phosphate units are released sequentially

2. Debranching enzymes

- Glucan transferase
  - It transfers the outer 3 glucose units from the branching point & attaches them to the nearest straight chain
    - This is important to unmask the α 1,6 glucosidic bond at the branching point

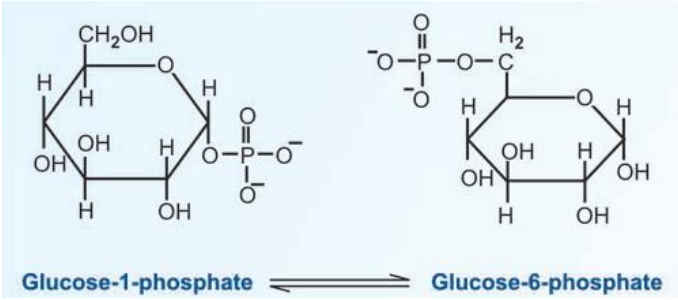


- α 1,6 glucosidase
  - This enzyme removes the last glucose residue at the branch point
    - » This glucose residue is released as **free glucose**

- → both these enzymes will together convert the branched chain into a linear one
  - » With removal of branches, phosphorylase can proceed with its action

3. Phosphoglucomutase

- This enzyme converts glucose 1-P to glucose 6-P

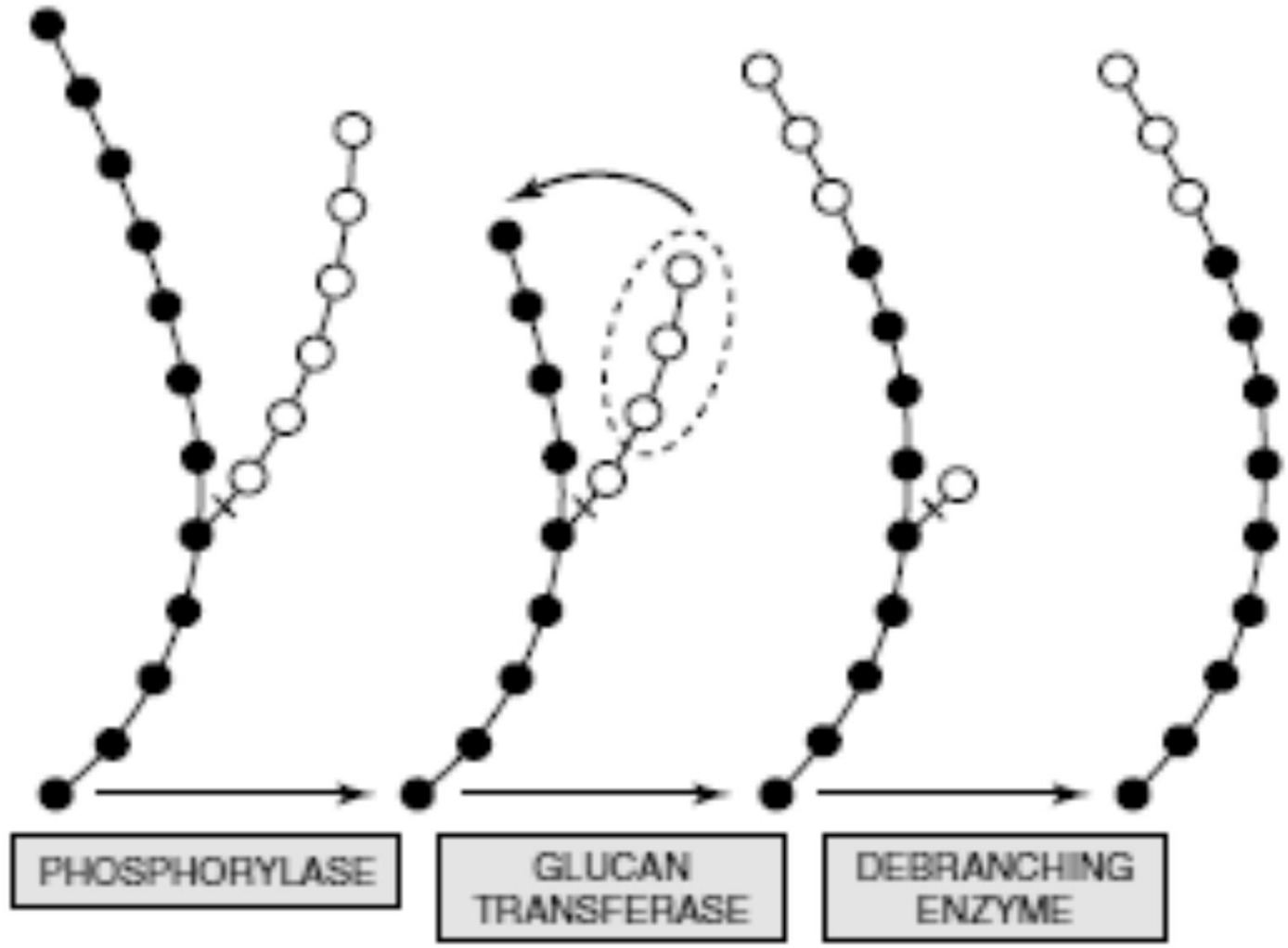


4. Glucose 6-phosphatase

- Converts glucose 6-P to free glucose
    - **<u>It is present mostly in the liver</u>**
    - The product of glycogenolysis is free glucose which is released in the blood
- **<u>Muscle lacks this enzyme:</u>**
    - » Glucose will not be released into blood
    - » Glucose 6-P undergoes glycolysis to produce lactate and ATP <u>for ms contraction</u>

Energy yield (anaerobic):

- Glucosyl unit derived from glycogen → 3 ATP
- Glycolysis starts from glucose → 2 ATP


PHOSPHORYLASE
GLUCAN TRANSFERASE
DEBRANCHING ENZYME

GLYCOGENESIS

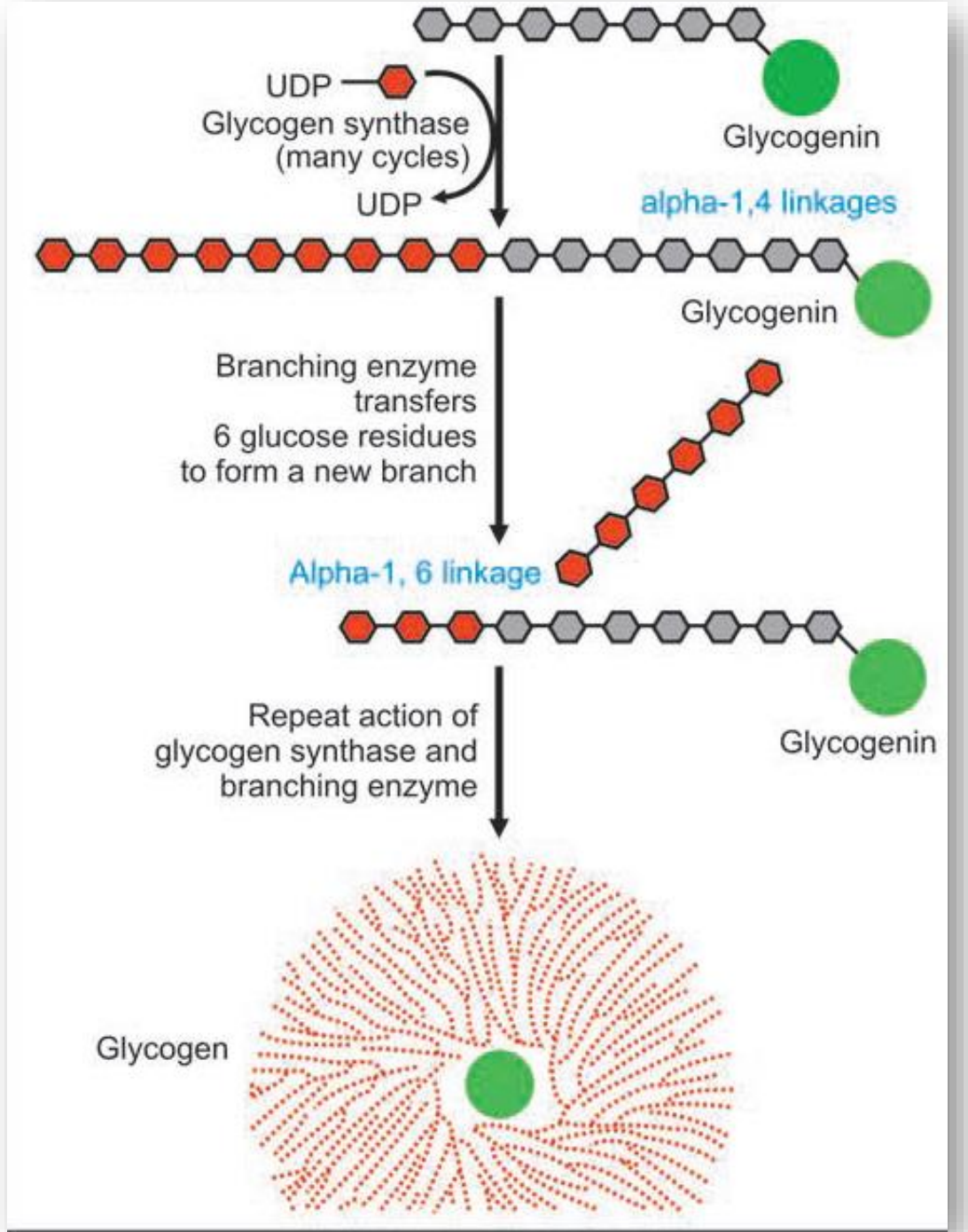
- It is the formation of glycogen from glucose or other hexoses
- It occurs in the cytosol of cells (except RBCs) especially in *liver* & *muscles*
- **Importance:** Storage of excess glucose, or other hexoses taken in food

Steps of glycogenesis

1. Activation of glucose + formation of UDP glucose*
2. Addition of glucosyl residues
3. Formation of branches

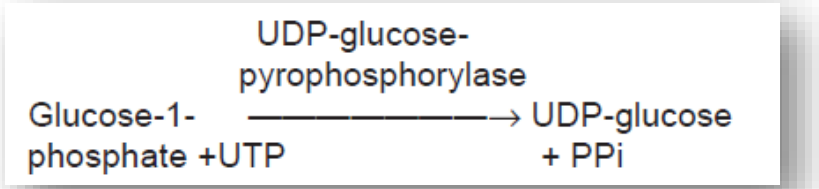
*UDP glucose: uracil diphosphate glucose → nucleotide sugar made from pyrophosphate group, pentose sugar ribose, glucose, and nucleobase uracil

- involved in formation of glycoproteins
- glycogen precursor
- nucleotide sugar metabolism


UDP
Glycogen synthase
(many cycles)
UDP
Glycogenin
alpha-1,4 linkages
Glycogenin
Branching enzyme
transfers
6 glucose residues
to form a new branch
Alpha-1, 6 linkage
Glycogenin
Repeat action of
glycogen synthase and
branching enzyme
Glycogen

1. Formation of UDP glucose:

- Glucose is phosphorylated to G-6-P by **glucokinase** (liver) or hexokinase (muscle)
- G-6-P is then converted to G-1-P by **phosphoglucomutase**
- **G-1-P uridyl transferase** catalyzes formation of UDP-G from G-1-P and UTP with liberation of pyrophosphate (irreversible reaction)
    - UDP glucose is called ***activated glucose*** and serves as a **glucose donor** for glycogen synthesis



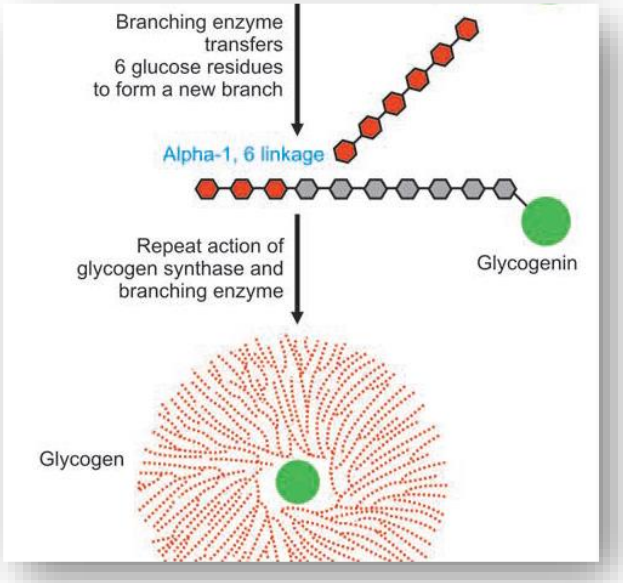
2. Addition of glucosyl residues

- **Glycogen primer:** oligosaccharide chain linked by α1,4 glucosidic links attached to *protein-CHO nucleus* called **glycogenin**
  - Glycogen primer may be an old incompletely broken glycogen molecule or a newly formed glycogen primer
  - **Glycogenin** can undergo autoglycosylation (i.e. bind glucose to its tyrosine residue via OH group)
  - **Glycogenin** binds more glucose units in form of UDPG one by one through α1,4 glucosidic links → up to 8 units (primer)

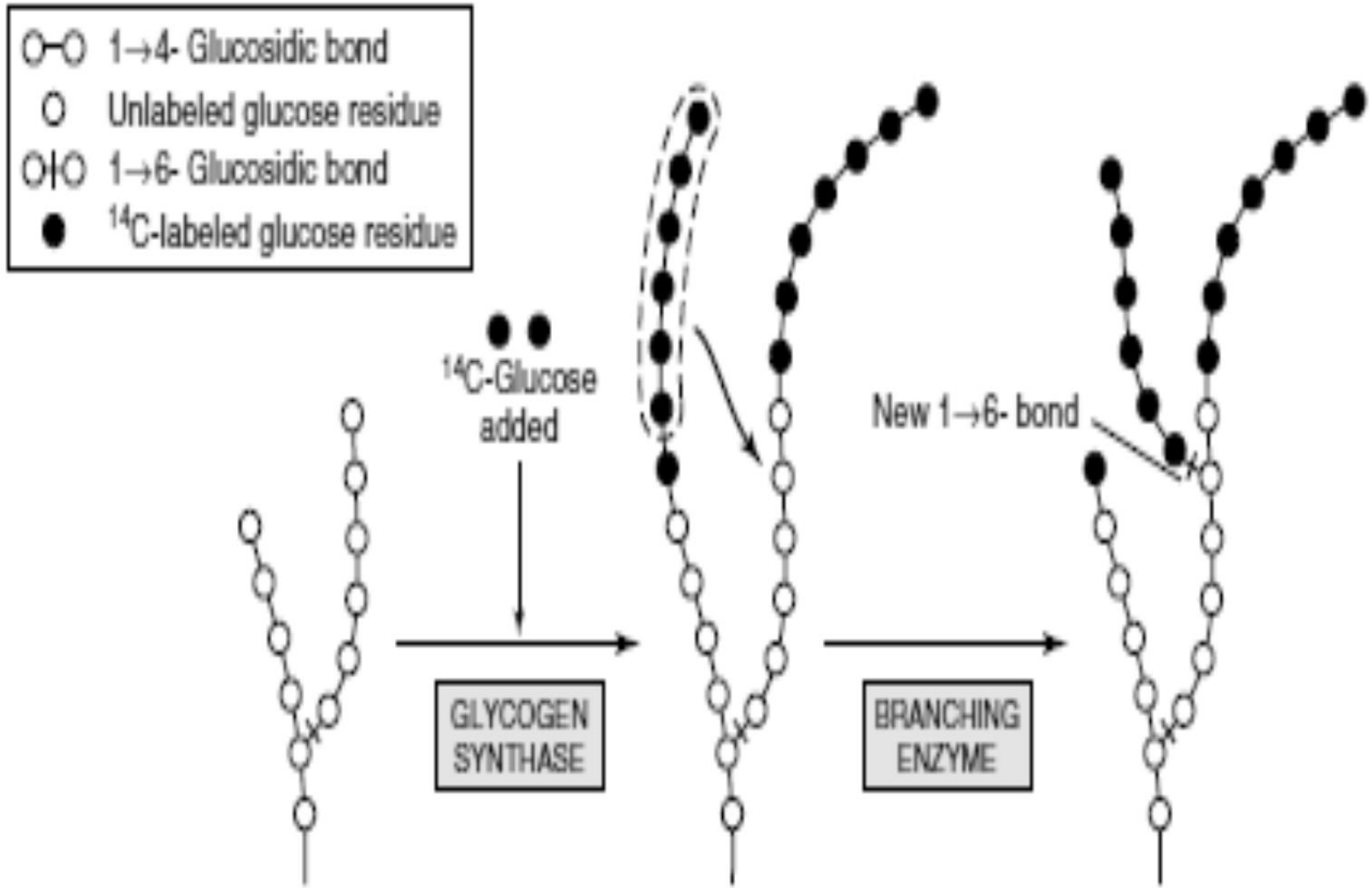
- → Glycogen synthase (key enzyme) transfers more activated glucose units from UDPG to the end of glycogen primer (and UDP is removed)
  - This repeats until about 12 glucose residues are added

3. Formation of branches

- When chain length is 11-12 residues:
  - A **branching enzyme** (AKA amylo 1,4 → 1,6 transglucosidase) transfers a block of 6-8 glucose units from the end of glycogen to C6 of glucose:
    - Creating a new α-1, 6-glucosidic bond
    - A new branch appears on which glycogen synthase can act again



The combined action of glycogen synthase and branching enzyme → a highly branched glycogen structure


1→4- Glucosidic bond
Unlabeled glucose residue
1→6- Glucosidic bond
14C-labeled glucose residue
14C-Glucose added
GLYCOGEN SYNTHASE
New 1→6- bond
BRANCHING ENZYME

Biological impotence of branching

- Makes glycogen more stable
- Increases number of ends → increases number of sites accessible to glycogen synthase (**amplifying cascade**)
- Increase sites of breaking attacks by phosphorylase → facilitating glycogen breakdown

Regulation of glycogen metabolism

- Principle enzymes controlling this are:
  - Glycogen synthase
  - Phosphorylase

  } Reciprocally regulated

- They are controlled by:
  - Allosteric control
  - Covalent modification

Regulation of glycogen metabolism

- Allosteric control
  - Glycogen synthase
    - Stimulated by glucose 6-P & ATP
    - Inhibited by glycogen (product)
  - Glycogen phosphorylase
    - Stimulated by AMP
    - Inhibited by glucose & ATP

Regulation of glycogen metabolism

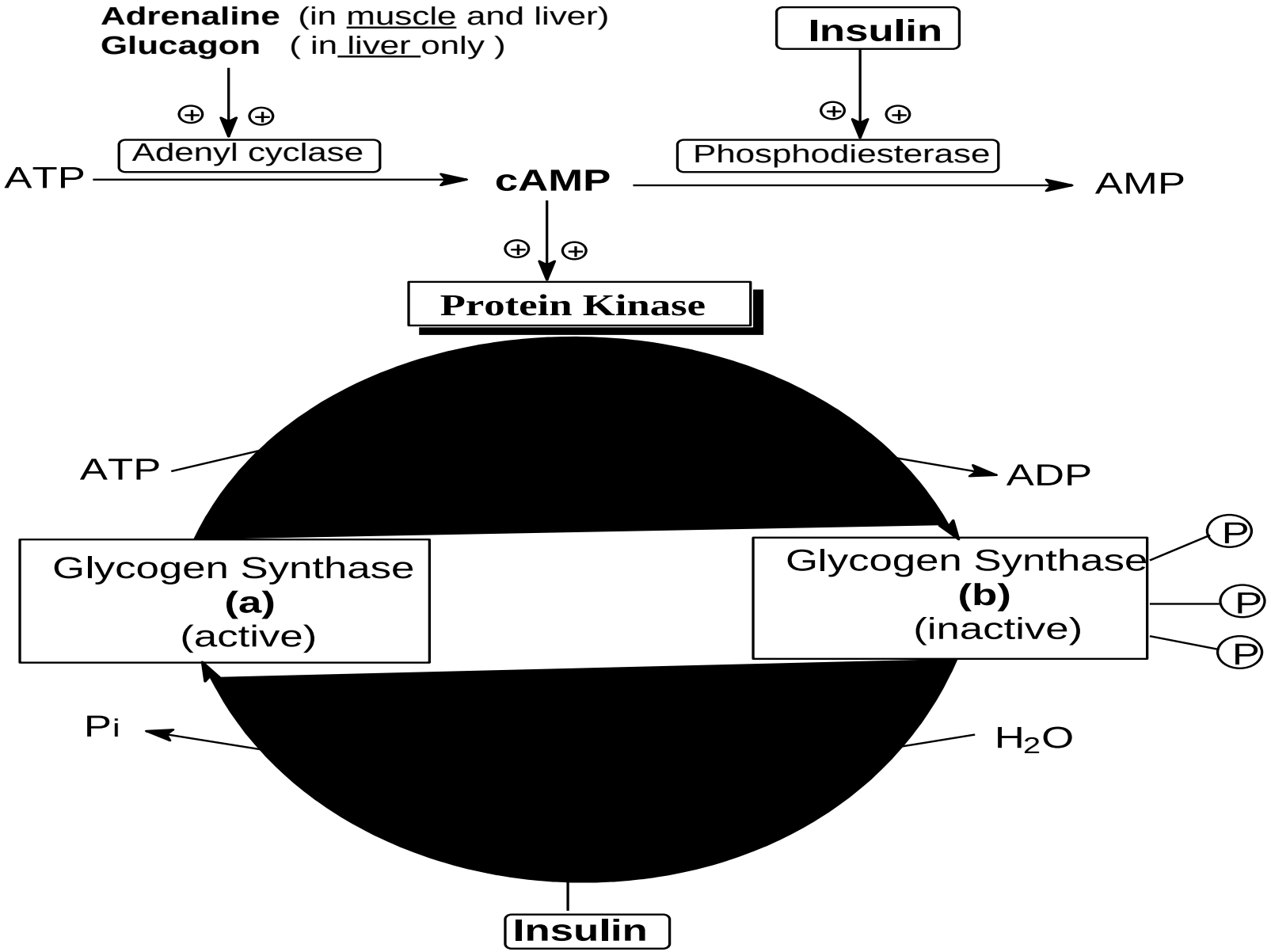
- Covalent modification
  - Glycogen synthase: active in ***dephosphorylated*** form
  - Glycogen phosphorylase: active in ***phosphorylated*** form
  - Covalent modification of these enzymes is through hormones that act through the 2nd messenger cAMP
  - Glycogen synthase exists in 2 forms (interconverted by specific enzyme):
    - Less active phosphorylated form (glycogen synthase b)
    - More active ***dephosphorylated*** form (glycogen synthase a)
  - Glycogen phosphorylase exists in 2 forms:
    - Less active ***dephosphorylated*** form (phosphorylase b)
    - More active phosphorylated form (phosphorylase a)

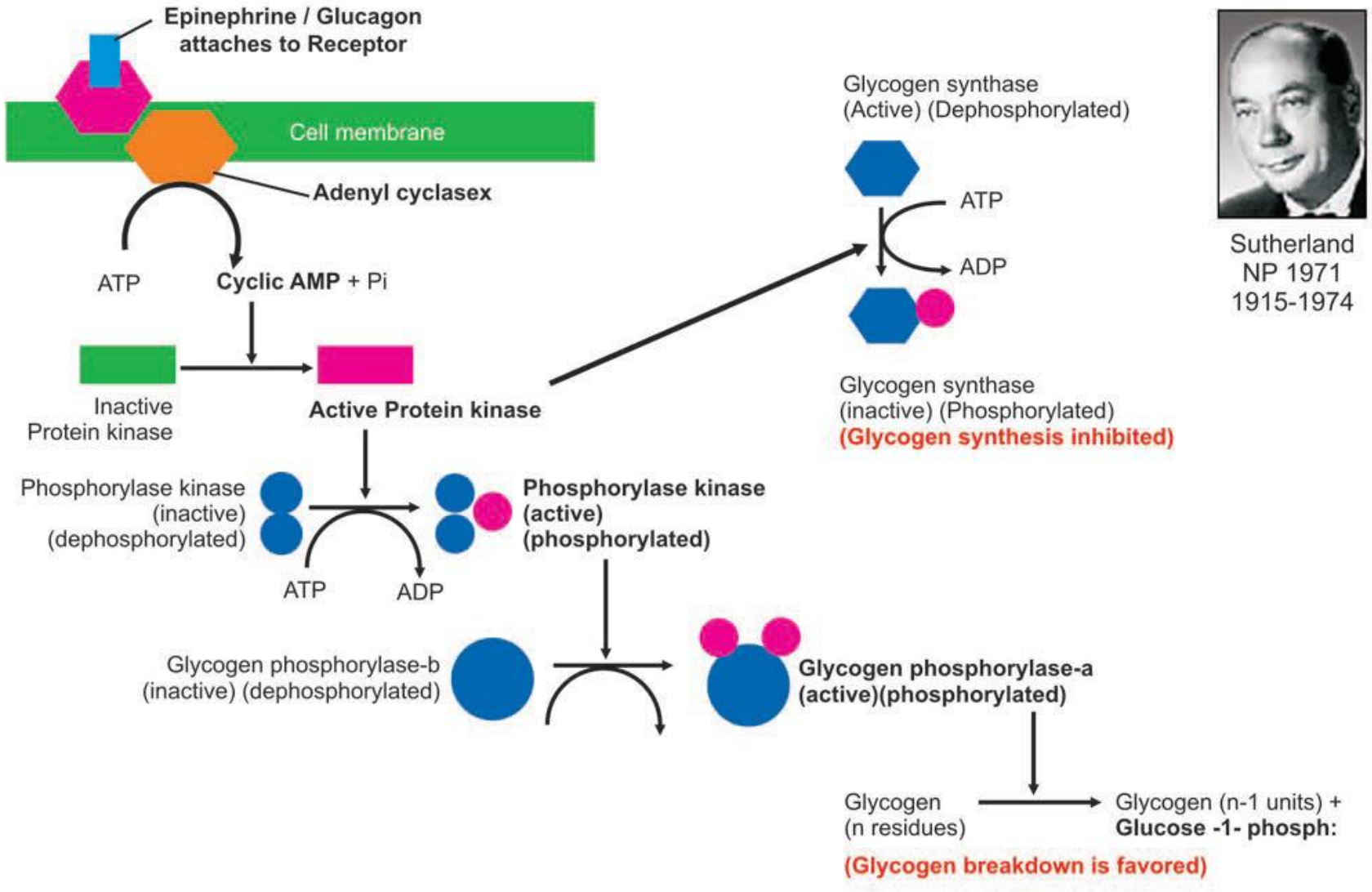
During fed state

- Insulin dephosphorylates both glycogen synthase and glycogen phosphorylase via 2 mechanisms:
    - Activation of phosphodiesterase enzyme → inactivates cAMP to AMP → inhibits protein kinase
    - Activation of phosphatase enzyme which removes P:
        - » Dephosphorylation of glycogen synthase → its activation → GLYCOGENESIS
        - » Dephosphorylation of glycogen phosphorylase → its inactivation → inhibition of glycogenolysis

During fasting state

- Glucagon (in liver) & epinephrine (in liver & muscle):
  - Activate a membrane receptor (G protein) → activates adenyl cyclase (a membrane linked enzyme) → converts ATP to cAMP
  - cAMP activates cAMP dependent protein kinase → phosphorylates (inactivates) glycogen synthase → inhibits glycogensis
    - Activation of protein kinase → activate phosphorylase kinase enzyme → stimulation of glycogen phosphorylase → glycogenolysis


Adrenaline (in muscle and liver)
Glucagon (in liver only)
Insulin
Adenyl cyclase
Phosphodiesterase
ATP
cAMP
AMP
Protein Kinase
ATP
ADP
Glycogen Synthase
(a)
(active)
Glycogen Synthase
(b)
(inactive)
P
P
P
Pi
H2O
Insulin


Epinephrine / Glucagon
attaches to Receptor
Cell membrane
Adenyl cyclasex
ATP
Cyclic AMP + Pi
Inactive
Protein kinase
Active Protein kinase
Phosphorylase kinase
(inactive)
(dephosphorylated)
ATP
ADP
Phosphorylase kinase
(active)
(phosphorylated)
Glycogen phosphorylase-b
(inactive) (dephosphorylated)
Glycogen phosphorylase-a
(active)(phosphorylated)
Glycogen
(n residues)
Glycogen (n-1 units) +
Glucose -1- phosph:
(Glycogen breakdown is favored)
Glycogen synthase
(Active) (Dephosphorylated)
ATP
ADP
Glycogen synthase
(inactive) (Phosphorylated)
(Glycogen synthesis inhibited)
Sutherland
NP 1971
1915-1974

Allosteric regulation in muscle exercise:

- Muscle phosphorylase is allosterically activated by AMP → glycogenolysis

- AMP is increased during muscular exercise and allosterically inhibited by:
  - ATP & G-6-P because their elevated levels indicate that the cell is not in need of more energy and there is no need to breakdown glycogen.

During muscle exercise:
↑ release of Ca from sarcoplasmic reticulum → activates glycogen phosphorylase → glycogenolysis

Induction and repression of the key enzyme:

- Carbohydrate feeding → induce insulin → ↓ synthesis of key enzyme (**repression**) so glycogenolysis is inhibited.

- Fasting → ↓ insulin and ↑ anti-insulin which increase synthesis of key enzyme (**induction**) so glycogenolysis is stimulated.

Glycogen storage diseases

Inborn errors of glycogen metabolism

Classified into different types according to the deficient enzyme

Most common

Type	Disease Name	Defective enzyme	Glycogen levels	Glycogen structure	Principal tissue affected
I	Von Gierke's disease	Glucose-6-phosphatase (G6pase)	High	Normal	Liver, kidney
II	Pompe's disease	α-1,4 Glucosidase	Very high	Normal	All organs
III	Cori's Forbes' disease	Debranching enzyme	High	Short outer branches	Liver, Heart, Muscle
IV	Andersen's disease	Branching enzyme	Normal	Long outer branches	Liver, Spleen, Muscle
V	McArdle's disease	Muscle Phosphorylase	High	Normal	Muscle
VI	Hers' disease	Liver Phosphorylase	High	Normal	Liver
VII	Tarui's disease	Phosphofructokinase	High	Normal	Muscle
VIII	Hepatic phosphorylase kinase deficiency	Phosphorylase kinase	High	Normal	Liver

Characteristic feature

I: Fasting hypoglycaemia (not responding to adrenaline), hepatomegaly

II: early death before 2 years

III: mild fasting hypoglycaemia

IV: hepatosplenomegaly, mild hypoglycaemia, results in synthesis of straight chain glycogen only

V: exercise intolerance, painful muscle cramps during exercise