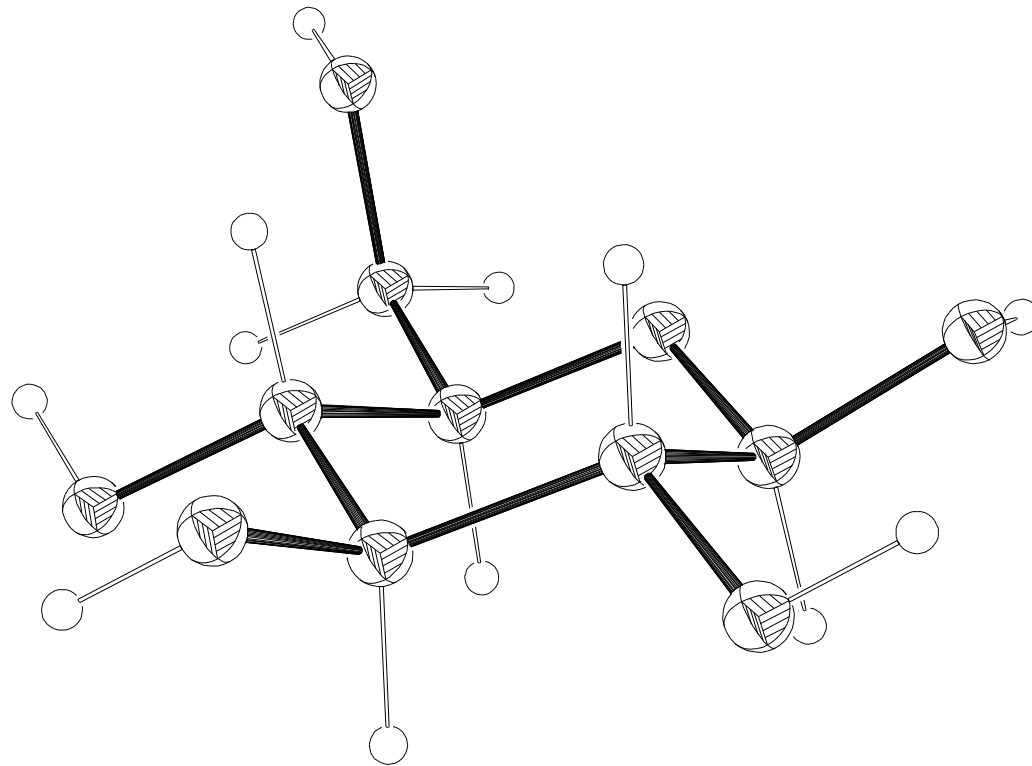# Glucose in blood

Seminar No. 3
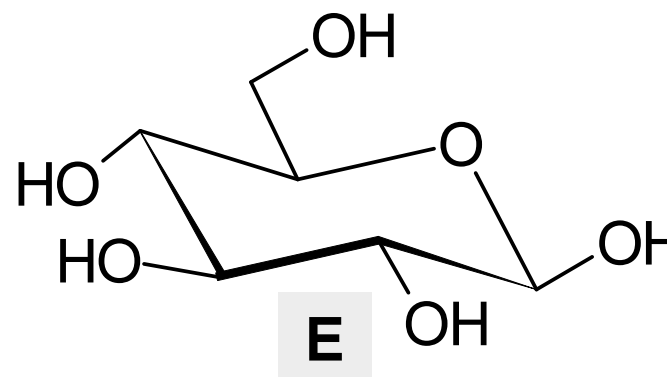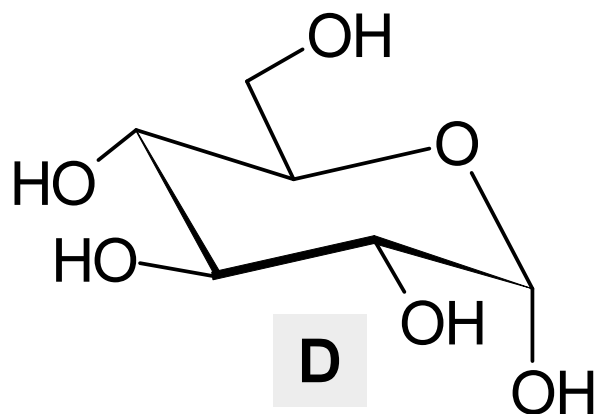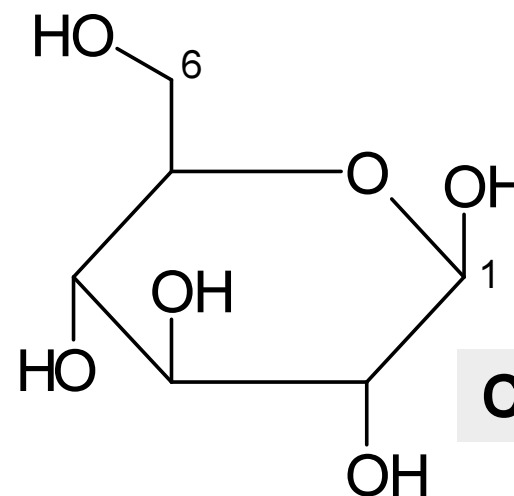
- Chapter 8 -

What is glucose?

- the most common monosaccharide, aldohexose

- $C_6H_{12}O_6$ (M_r 180)

- grape sugar, blood sugar, dextrose

- the most important sugar in the human body

- the source of chemical energy (17 kJ/g)

- metabolic nutrient for most tissues

- prominent fuel for the brain and RBC

Different formulas of D-glucose

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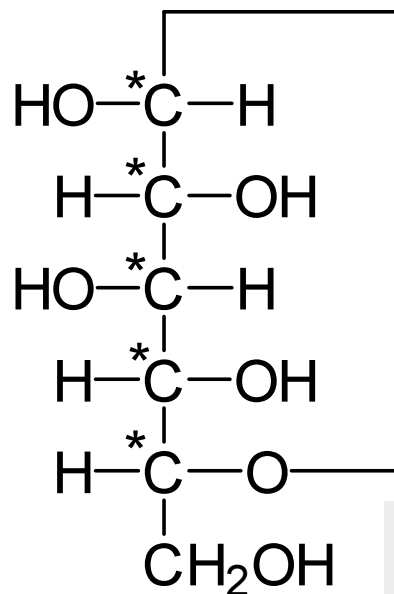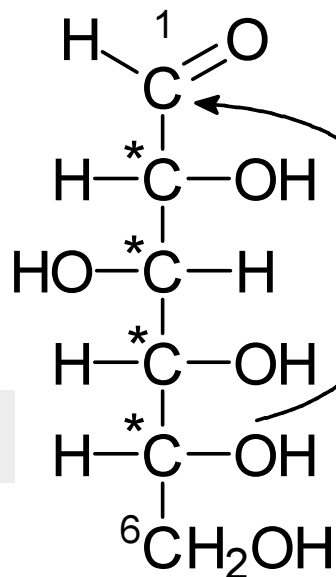
A = D-glucose (Fischer formula)

B = β-D-glucopyranose (Fischer formula)

C = β-D-glucopyranose (Haworth formula)

D = α-D-glucopyranose (chair conformation)

E = β-D-glucopyranose (chair conformation)

Sources of glucose in blood

- **Resorption phase = just after meal**

  Exogenous saccharides (food)

- **Postresorption phase = in the obvious fasting**

  Endogenous storage and/or non-saccharide precursors of Glc

Glucose sources in resorption phase

➤ **Starch** (polysaccharide from glucose: amylose + amylopectin)

Starch-based food: cereals, bread, rolls, pastry, cakes, biscuits, dumplings, rice, pasta, semolina, legumes, potatoes, banana

➤ **Sugar** (table sugar, sucrose, disaccharide: glucose + fructose) commercially available in 100% purity

----

- Lactose (disaccharide: galactose + glucose) – milk

- Glucose – free glucose is very rare in common food

- Fructose – fresh fruits (5-10 %), honey (cca 60 %)

- Honey $\approx$ 30 % glucose, 60 % fructose, 10 % sucrose

Starch content in some food

Foodstuff	Starch (%)[a]
Flour	75
Rice	75
Pasta	70
Rolls	60
Legumes	60
Bread	50
Wholemeal bread	40
Potatoes	15
Banana	15
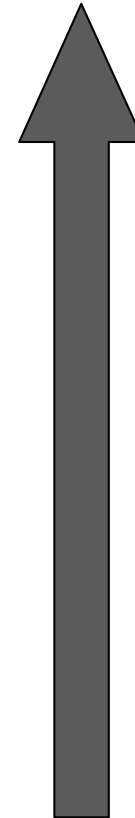
[a] mass percentage, average values

Free glucose is rare in food

Food	Glucose (%)[a]
Glukopur[b]	100
Raisins	50
Honey	30
Grapes	6-10
Other fresh fruits	1-5
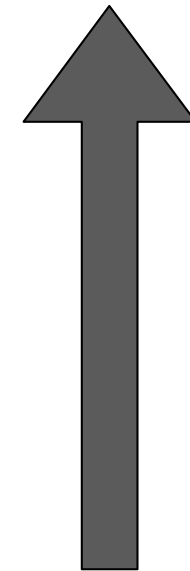
[a] mass percentage, average values

[b] pure crystalline glucose, Czech made, sold in pharmacy

Glucose sources in postresorption phase

- **Liver glycogen** is degraded by phosphate (phosphorolysis)

$$\text{glycogen} \xrightarrow{\text{P}_i} \text{Glc-1-P} \rightarrow \text{Glc-6-P} \rightarrow \text{glucose in blood}$$

- **Gluconeogenesis** from non-saccharide substrates:

    Lactate (60 %)

    Alanine (30 %)

    Glycerol (10 %)

Five stages of glucose homeostasis

Feature	I	II	III	IV	V
Stage description	well-fed	post resorption	early starvation	prolonged starvation	extreme starvation
Time interval[a]	0-4 h	4-16 h	16-30 h	2-24 d	over 24 d
Origine of Glc in blood	food	liver glycogen gluconeogenesis	gluconeogenesis liver glycogen	gluconeogenesis	gluconeogenesis
Utilization of Glc	all tissues[b]	all tissues[b] muscle, ad.t. limited	all tissues[b] muscle, ad.t. limited	brain, Ercs, kidney	Ercs, kidney, brain - limited
Energy for brain	Glc	Glc	Glc	Glc, ketone bodies	ketone bodies, Glc

[a] Approximate values, time 0 = any main meal (e.g. lunch).

[b] Except of liver.

Five stages of glucose homeostasis

- Stage I – glucose comes from food (mainly starch)

- Stage II – glycogenolysis in liver

- Stage III – gluconeogenesis in liver starts to work

- Stage IV – in addition to liver, kidney starts to make Glc

- Stage V – liver and kidney gluconeogenesis diminishes, energy needs of most tissues are met by FA + KB

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Q. 1 (p. 45)

What is reference range of glucose
concentration in blood?

A. 1

3.3 – 5.6 mmol/l

capillary blood

Transport of glucose into cells

- Glucose is highly polar compound, does not pass freely across hydrophobic cell membranes
- Requires specific protein transporters
- GLUT = glucose transporter

GLUT 1	**most cells**
GLUT 2	**liver**
GLUT 3	**brain**
GLUT 4	**muscle, adip. tissues – insulin dependent**

Insulin-independent transporters

- In most tissues (liver, CNS, Ery)

- Passive transport – facilitated diffusion

- Transporter – integral protein

- After binding Glc it changes conformation and releases glucose into ICF

Passive transport (facilitated diffusion) – no energy required

see also Chapter 17 !!

Insulin-dependent transporters

- In muscles, adipose tissue – peripheral tissues

- After binding Glc it changes conformation and releases glucose into ICF

- Free transporters are then transferred inside the cell by endocytosis

- **Insulin stimulates their incorporation into cell membrane when necessary**

Passive transport (facilitated diffusion) – no energy required
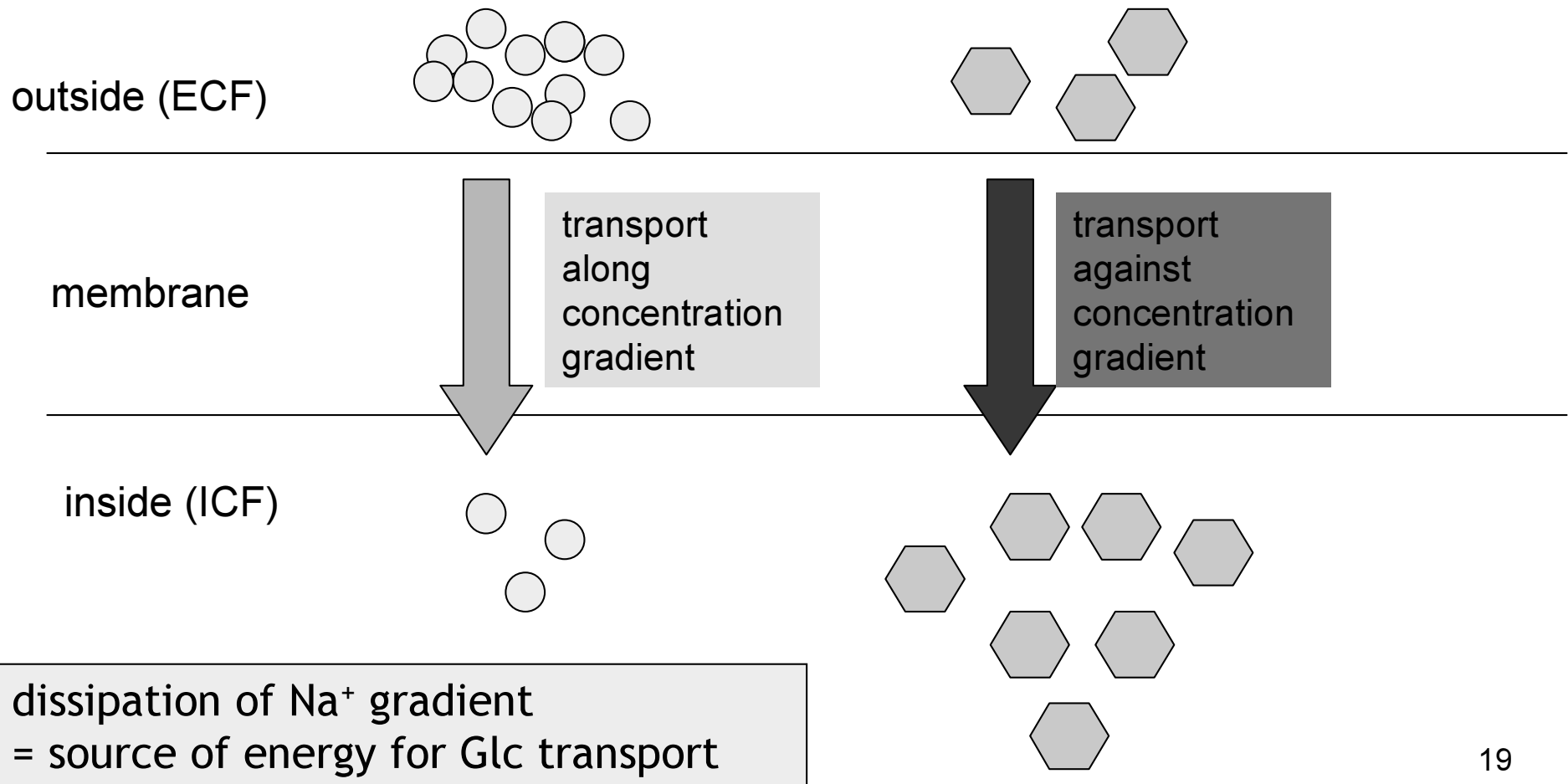
Symport (co-transport) with Na$^+$ ions

- In enterocytes, renal tubules

- Transporter binds together Glc and Na$^+$

- Na$^+$ ions move from high conc. space to low conc. space

- Glc remains in cell and it is metabolized

- Na$^+$ ions are expelled from cell *via* Na$^+$,K$^+$-ATPase pump

Secondary active transport – energy **is** required (p. 99)

Symport of Glucose with Na$^+$

○ Na$^+$ ⬡ glucose

outside (ECF)

membrane

transport along concentration gradient

transport against concentration gradient

inside (ICF)

dissipation of Na$^+$ gradient
= source of energy for Glc transport

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Hormonal regulation of Glc metabolism

- „Resting state" hormones: insulin, glucagon

- Stress hormones: adrenalin, cortisol

Insulin (after meal)

- High blood glucose level is the signal for insulin secretion

- Stimulates glycolysis in liver, muscles and other tissues

- Increases glucose transport into adipose tissues and muscles

- Stimulates synthesis of glycogen, TAG, proteins

Insulin is generally anabolic hormone

Insulin is **inductor** of key enzymes of glycolysis and glycogenesis

Glucagon (after meal)

- Antagonist of insulin

- Low blood glucose level is the signal for glucagon secretion

- Stimulates breakdown of glycogen in liver (**not in muscles**)

- Stimulates gluconeogenesis from aminoacids

Glucagon is **<u>inductor</u>** of key enzymes of gluconeogenesis
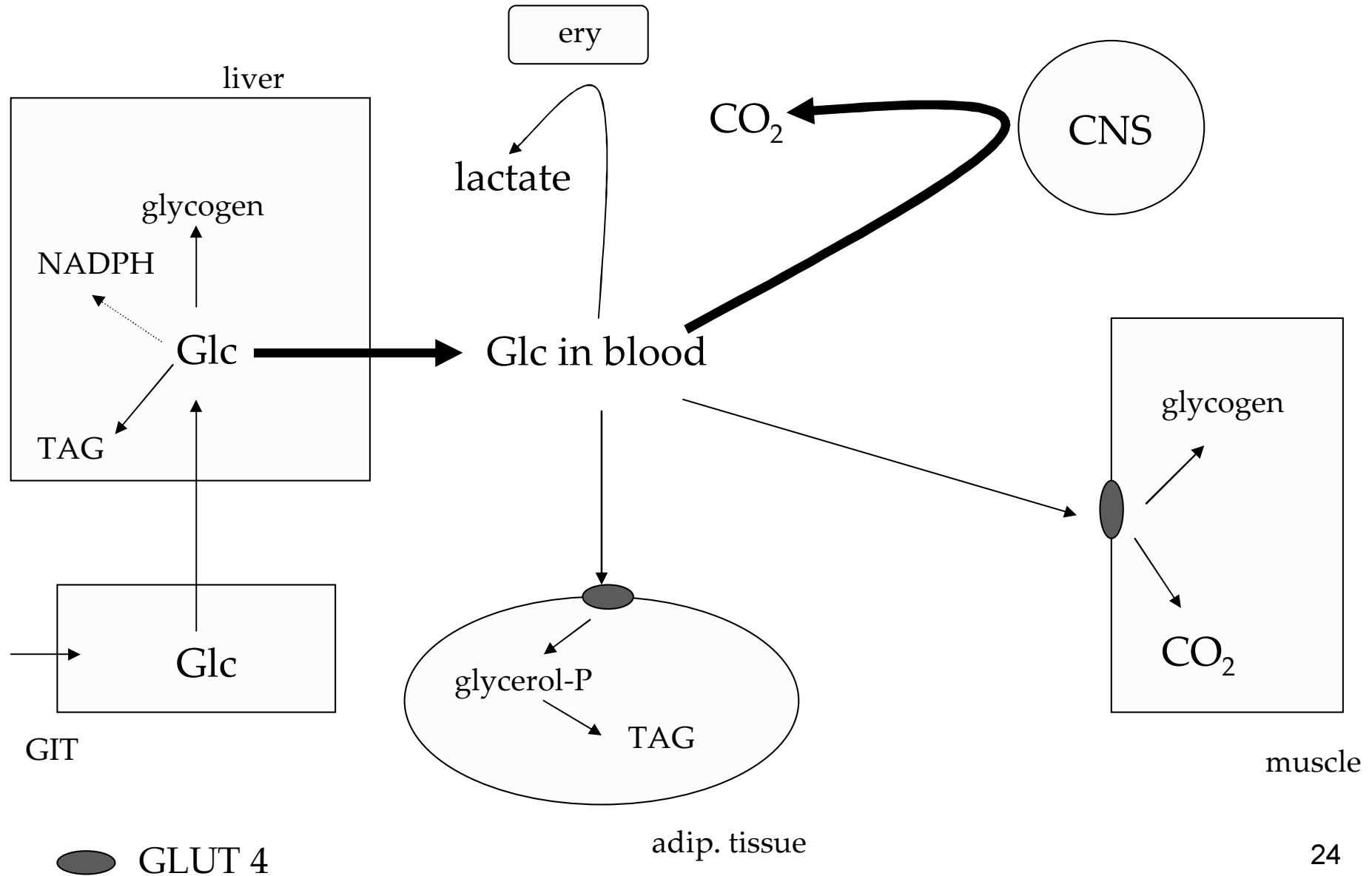
Adrenaline (in stress)

- Signal that energy is needed immediately
- Very quick action
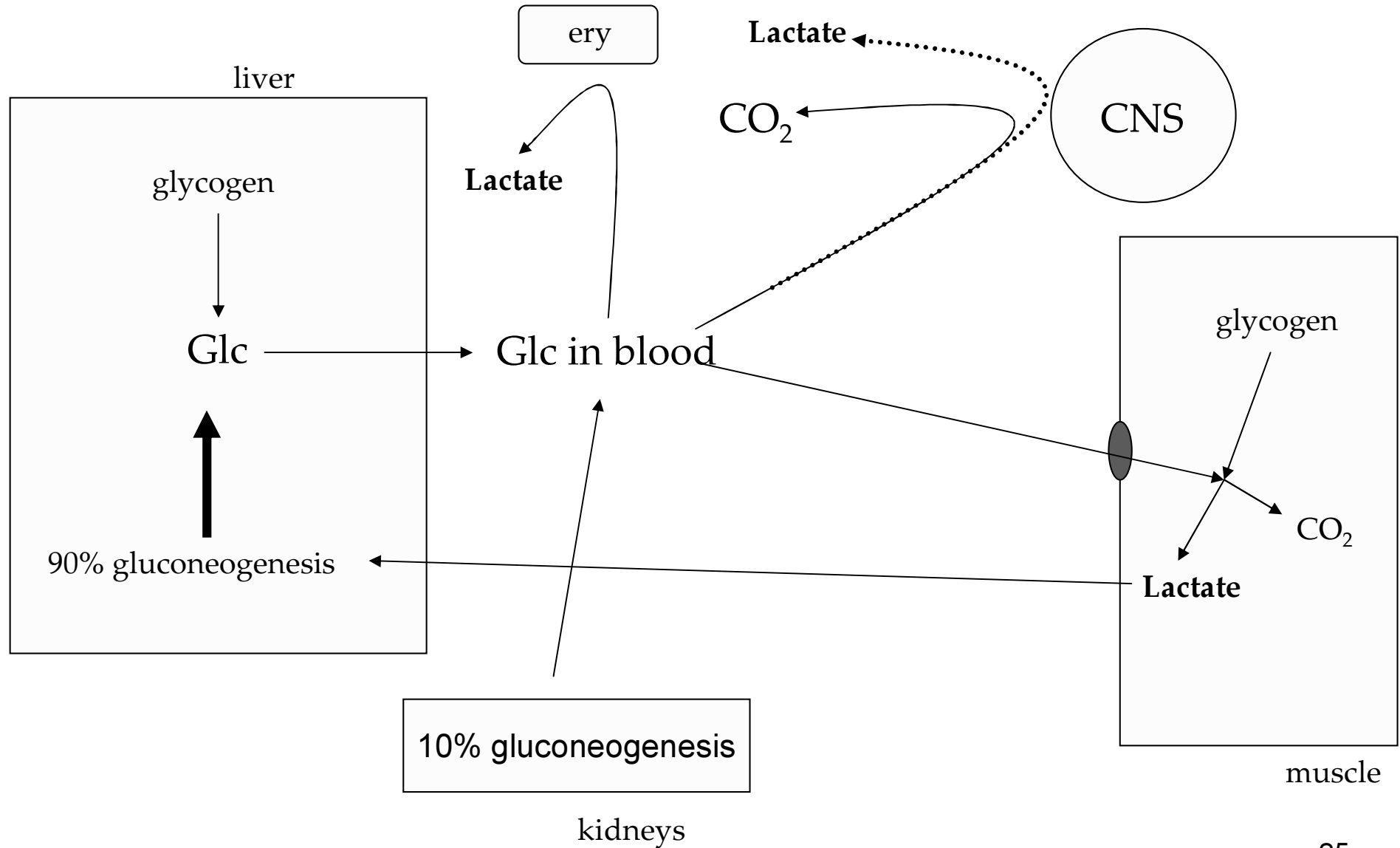- Stimulates the breakdown of glycogen (in liver and muscles) and TAG

Cortisol – adaptation to stress

- Stimulates proteolysis in muscles
- Released AA are substrates for gluconeogenesis

Processes in resorption phase (insulin)

ery

liver

CO_2

CNS

glycogen

NADPH

Glc → Glc in blood

lactate

TAG

glycogen

Glc

glycerol-P

CO_2

TAG

GIT

adip. tissue

muscle

⬤ GLUT 4

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Processes in postresorption phase (glucagon)

liver

ery

Lactate

CO$_2$

CNS

glycogen

Lactate

Glc → Glc in blood

glycogen

CO$_2$

90% gluconeogenesis

Lactate

10% gluconeogenesis

muscle

kidneys

25

Q. (p. 42)

The important intermediate of Glc is Glc-6-phosphate.

What enzymes catalyze its formation?

A.

hexokinase
glucokinase

$$\text{Glc} + \text{ATP} \rightarrow \text{Glc-6-P} + \text{ADP}$$

Q. (p. 42)

What enzyme catalyzes the conversion of Glc-6-P to glucose?

In which organs is it located?

A.

glucose-6-phosphatase

$$Glc\text{-}6\text{-}P \ + \ H_2O \ \rightarrow \ Glc \ + \ P_i$$

occurs in liver, kidney, intestine but **not in muscles**

Metabolic Features of Diabetes (IDDM)

see the scheme on the page 43

metabolic processes occur **under influence of glucagon**

Metabolic Features of Diabetes (IDDM)

- **The lack of insulin** $\Rightarrow$ Glc cannot enter adipose and muscle cells $\Rightarrow$ elevated blood Glc

- **The release of glucagon** $\Rightarrow$ glycogenolysis + lipolysis $\Rightarrow$ elevated blood glucose + elevated blood FA

- **The excess of FA** $\Rightarrow$ excess of acetyl-CoA (over CAC capacity) $\Rightarrow$ synthesis of KB $\Rightarrow$ elevated blood KB

- **Limited glycolysis in liver** $\Rightarrow$ not enough pyruvate $\Rightarrow$ not enough oxaloacetate to run CAC $\Rightarrow$ excess of acetyl-CoA (over CAC capacity) $\Rightarrow$ synthesis of KB $\Rightarrow$ elevated blood KB

- **The lack of insulin** $\Rightarrow$ not enough LPL (insulin is inductor of its synthesis) $\Rightarrow$ elevated blood CM + VLDL

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The metabolic consequences of insuline << glucagon ratio

Process	Change	Consequence
Transport of glucose into periph. tiss.	⇩	
Glycolysis in liver	⇩	
Gluconeogenesis in liver	⇧	
Lipolysis in adipocytes	⇧	
β-Oxidation of FA in liver	⇧	
Production of ketone bodies	⇧	

The metabolic consequences of insuline << glucagon ratio

Process	Change	Consequence
Transport of glucose into periph. tiss.	⇩	elevated blood glucose
Glycolysis in liver	⇩	elevated blood glucose
Gluconeogenesis in liver	⇧	elevated blood glucose
Lipolysis in adipocytes	⇧	elevated blood fatty acids
β-Oxidation of FA in liver	⇧	increased prod. acetyl-CoA
Production of ketone bodies	⇧	elevated blood KB, acidosis

Complications of diabetes

<u>Acute</u>

- ketoacidosis (pH of blood < 7.36)

- hyperosmolarity of blood plasma (> 310 mmol/l)
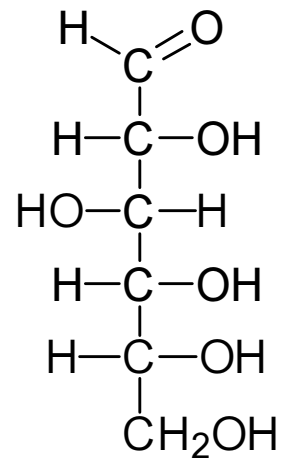
<u>Long-term</u>

- non-enzymatic glycation of proteins

- AGE production (<u>a</u>dvanced <u>g</u>lycation <u>e</u>ndproducts)
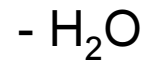
- activation of sorbitol (glucitol) production

Glycated hemoglobin HbA$_{1c}$

- it is formed non-enzymatically in RBC
- reaction of globin NH$_2$-terminal group with aldehyde group of glucose
- **the concentration of HbA$_{1c}$ depends on:**

  concentration of glucose in blood

  duration of hyperglycemia

  concentration of hemoglobin (less important factor)

- normal values: 6-8 %
- **the value of HBA$_{1c}$ gives cumulative information on glucose level in recent 6-8 weeks**
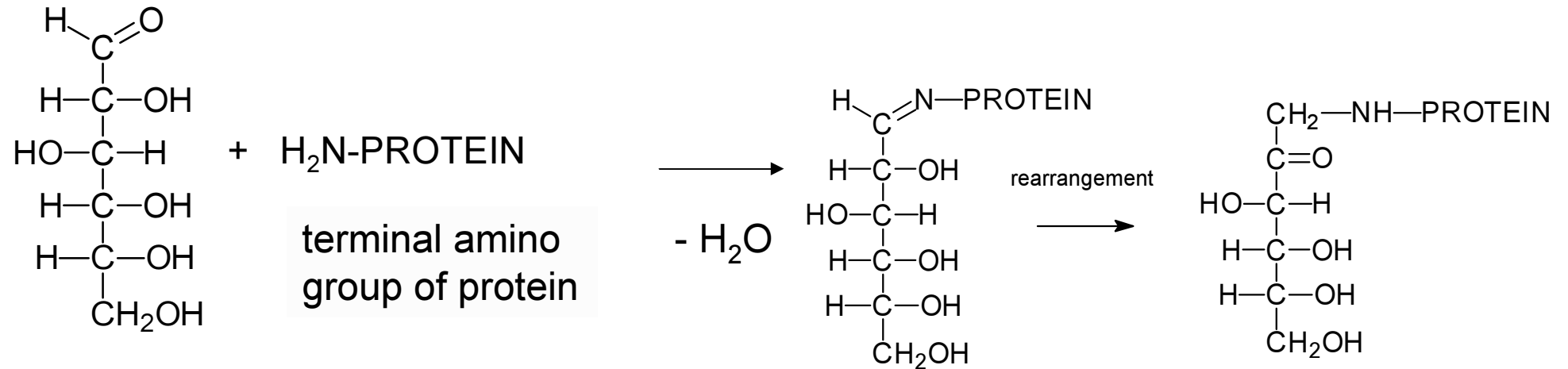
Glycation of proteins

H−C=O
H−C−OH
HO−C−H
H−C−OH
H−C−OH
CH_2OH

+ H_2N-PROTEIN ⟶

terminal amino
group of protein

- H_2O

glucose
aldehyde form

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Glycation of proteins

glucose

aldehyde form

+ H₂N-PROTEIN

terminal amino group of protein

- H₂O

aldimine

Schiff's base

unstable

rearrangement

ketoamine

glycated protein
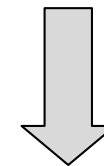
AGE

see page 14

Determination of Glc in body fluids

$$\text{glucose} + O_2 \xrightarrow{\text{glucose oxidase}} \text{gluconolactone} + H_2O_2$$

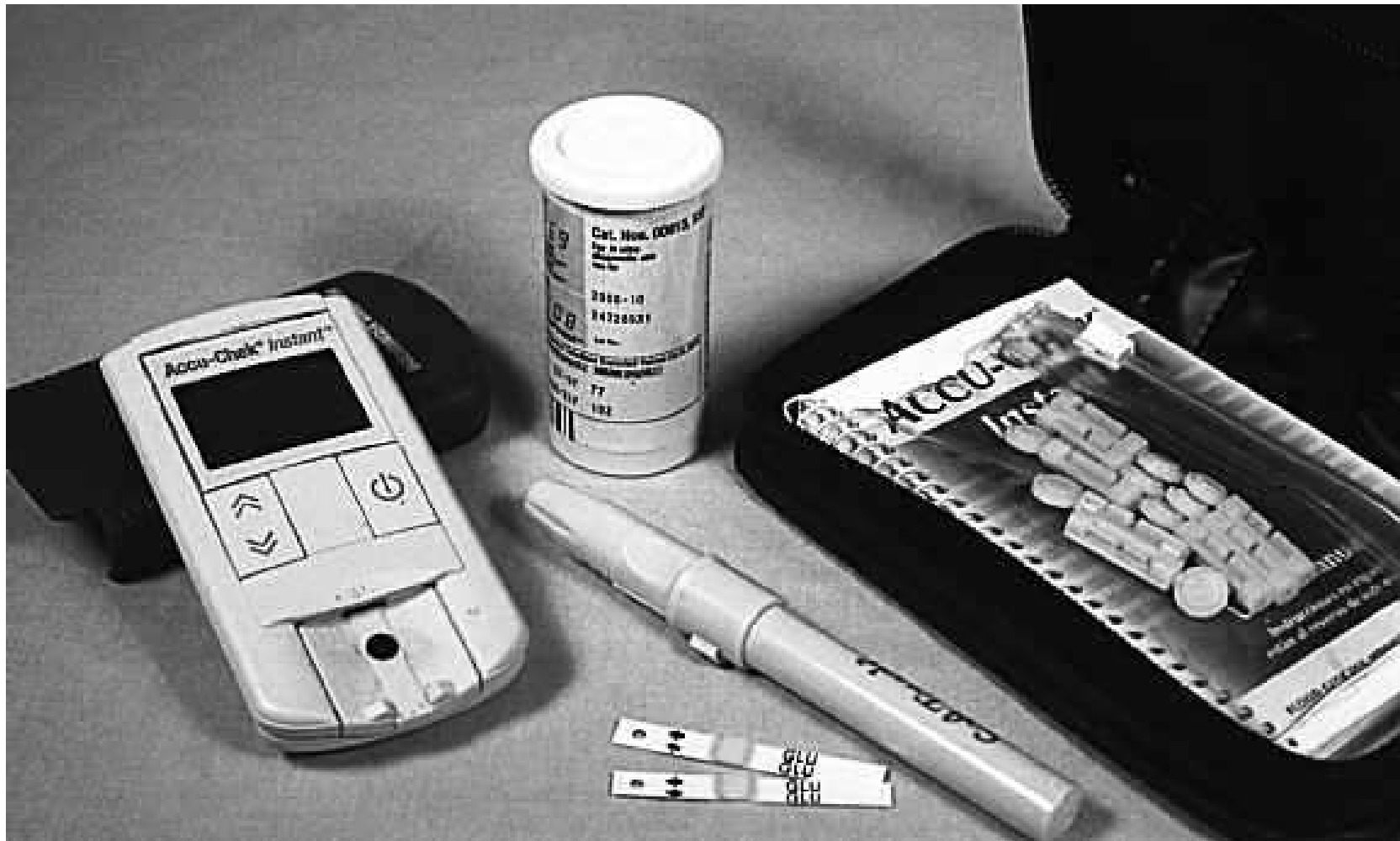$$H_2O_2 + H_2A \xrightarrow{\text{peroxidase}} 2\,H_2O + A$$
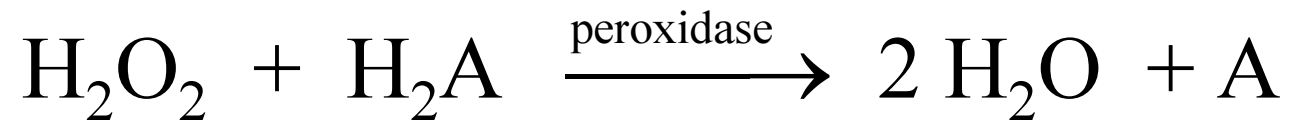
colorless
chromogen

coloured product
(spectrophotometry)

Personal glucometer

(you will see in the labs)

Three diabetics, supervised after 6 weeks (p. 44)

Patient No. 1 (left picture)

glucose level .... little elevated

HbA_1 .... OK

conclusion .... good dietary regime

Patient No. 2 (middle picture)

glucose level .... OK

HbA_1 .... significantly elevated

conclusion .... bad dietary regime

Patient No. 3 (right picture)

glucose level .... OK

HbA_1 .... little elevated

conclusion .... acceptable dietary regime