THE PATHOPHYSIOLOGY OF THE REFEEDING SYNDROME

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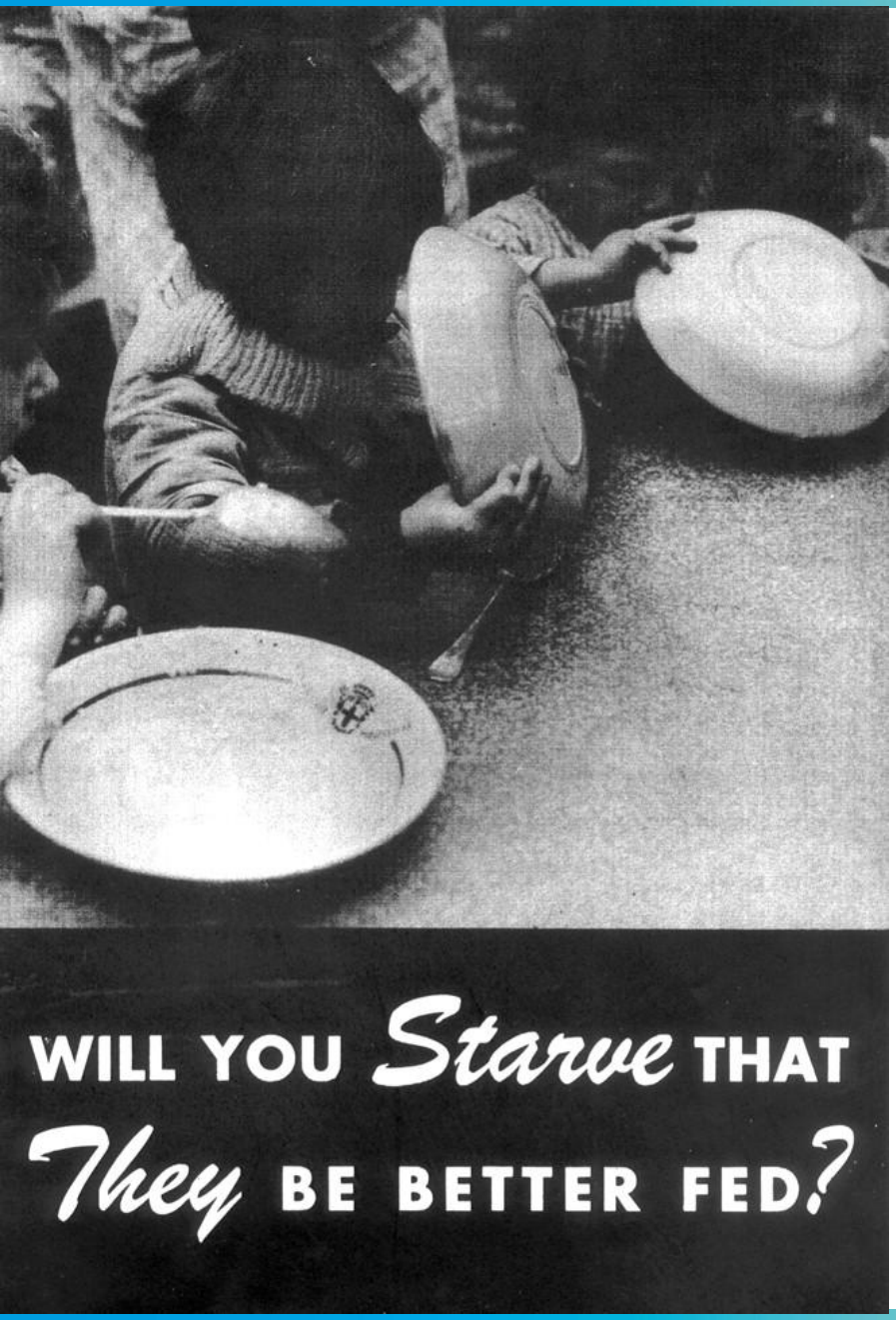


Minnesota Experiment

Aim

To guide the Allied assistance to famine victims in Europe at the end of the World War II ➔ impact of various rehabilitation strategies

n = 36 men selected from over 200 volunteers of the Civilian Public Service

Start → February 12th, 1945

Energy intake → "semi-starvation"

→ ca. 50% of the energy requirements

→ 2 meals, at 8 a.m. and at 6 p.m.

Objective

25% weight loss in 24 weeks (6 mts)

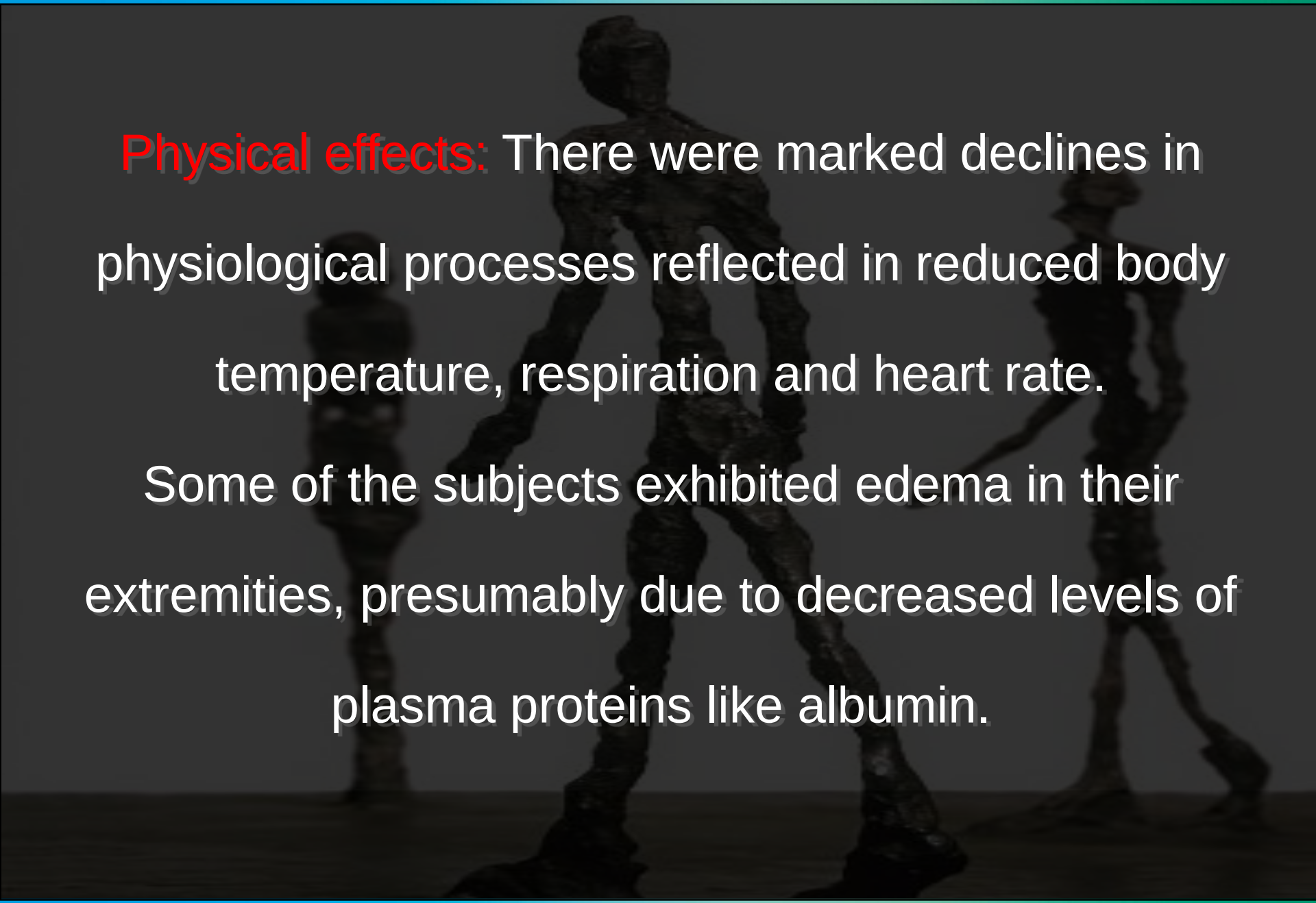
→ approx. 1 kg per week

Keys A et al. The Biology of Human Starvation.1950

The primary objective of the **Minnesota Starvation Experiment** was to study the physical and psychological effects of prolonged, famine-like semi-starvation on healthy men, as well as their subsequent rehabilitation from this condition.

Psychological effects: most of the subjects experienced periods of severe emotional distress and depression. Sexual interest was drastically reduced, and the volunteers showed signs of social withdrawal and isolation. The participants reported a decline in concentration, comprehension & judgment capabilities.

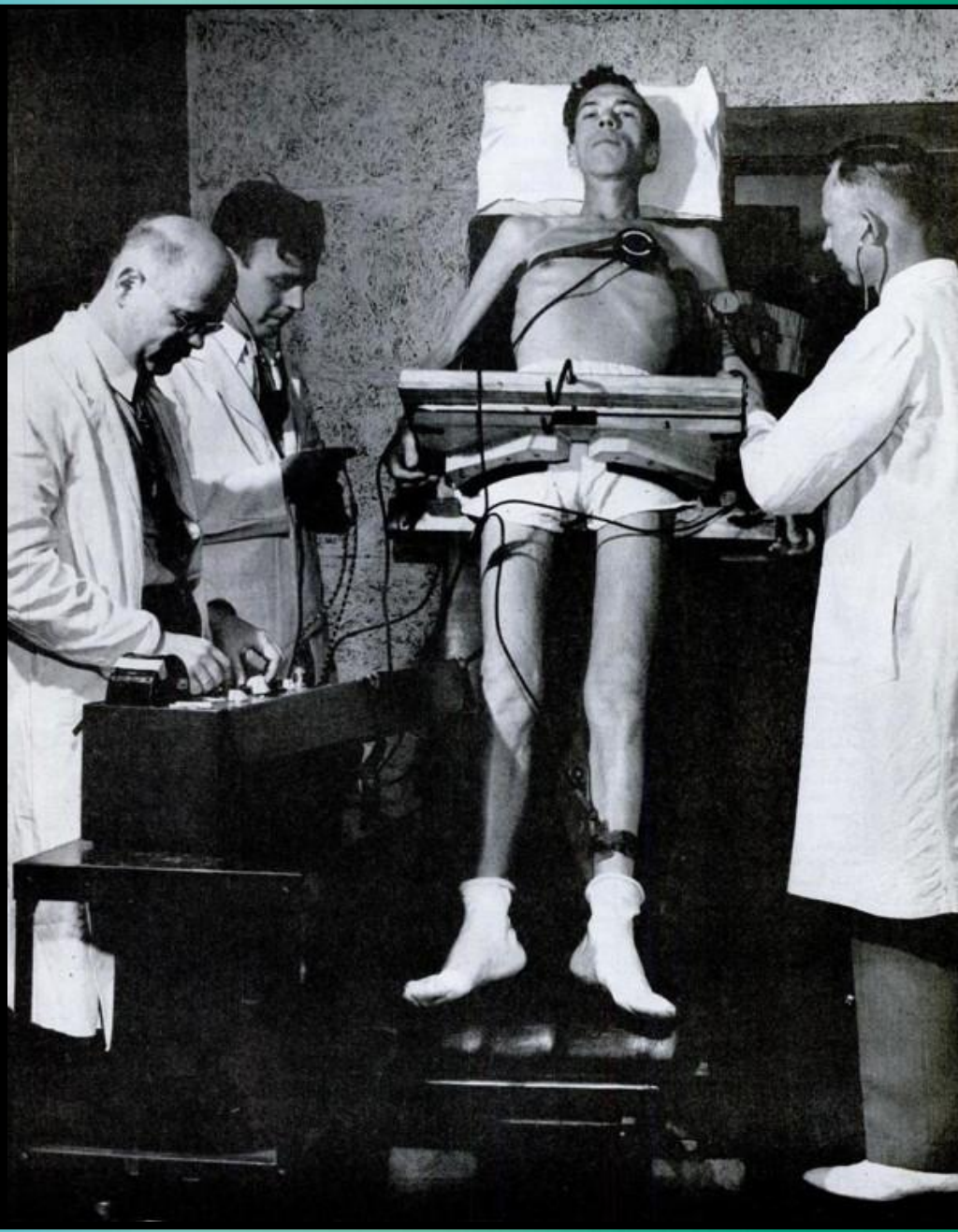
Keys A et al. The Biology of Human Starvation.1950



Physical effects: There were marked declines in physiological processes reflected in reduced body temperature, respiration and heart rate.

Some of the subjects exhibited edema in their extremities, presumably due to decreased levels of plasma proteins like albumin.

Keys A et al. The Biology of Human Starvation.1950

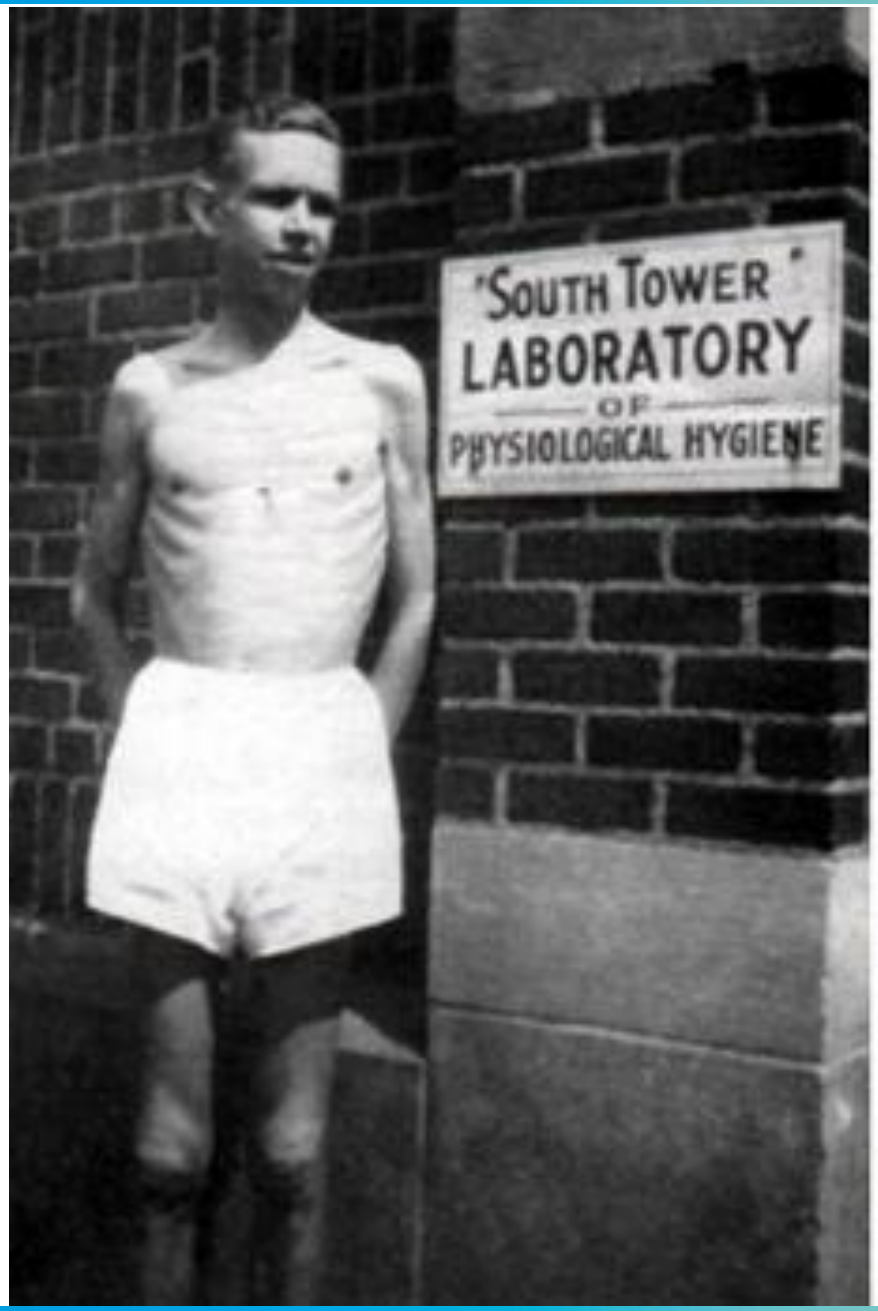


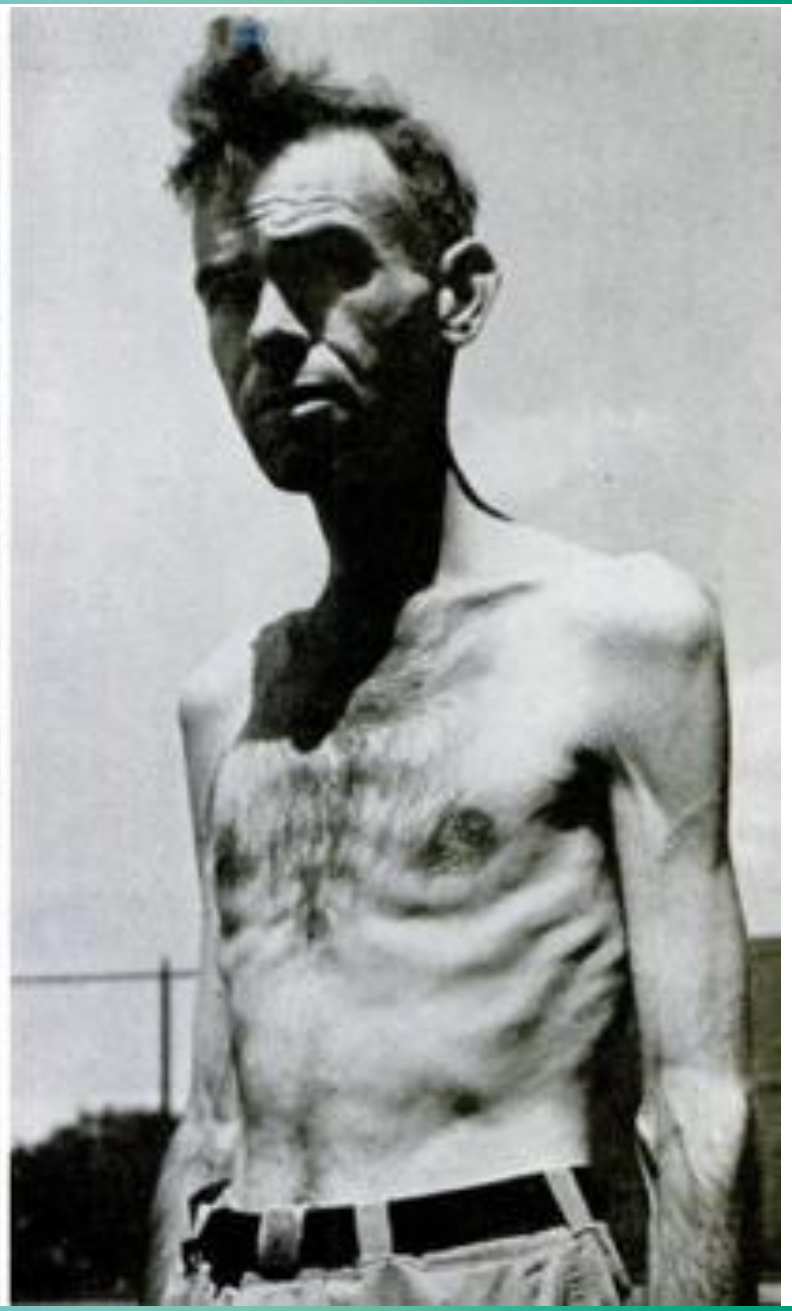
Keys A et al. The Biology of Human Starvation.1950

MEN STARVE IN MINNESOTA

CONSCIENTIOUS OBJECTORS VOLUNTEER FOR STRICT HUNGER TESTS TO STUDY EUROPE'S FOOD PROBLEM

Keys A et al. The Biology of Human Starvation.1950





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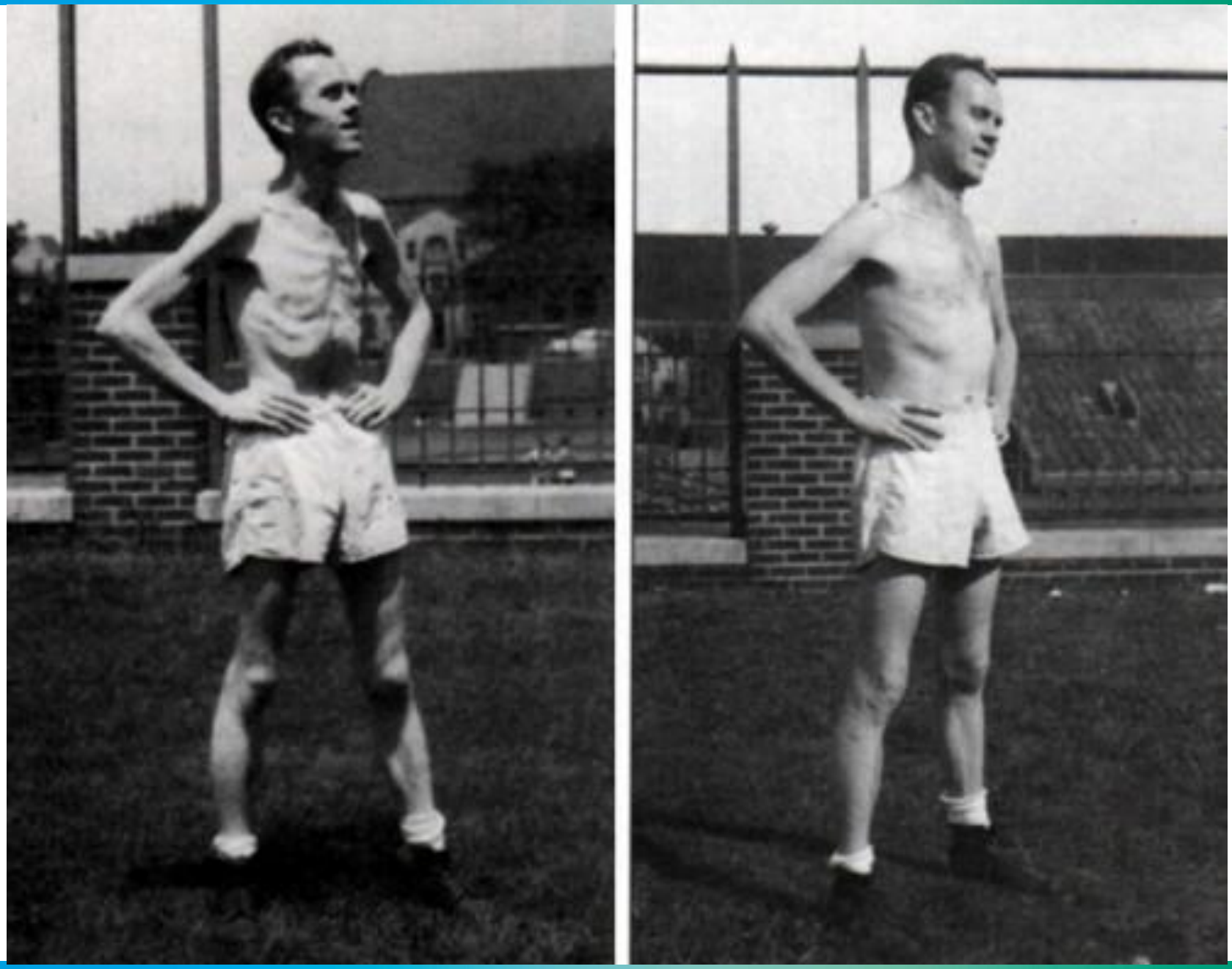
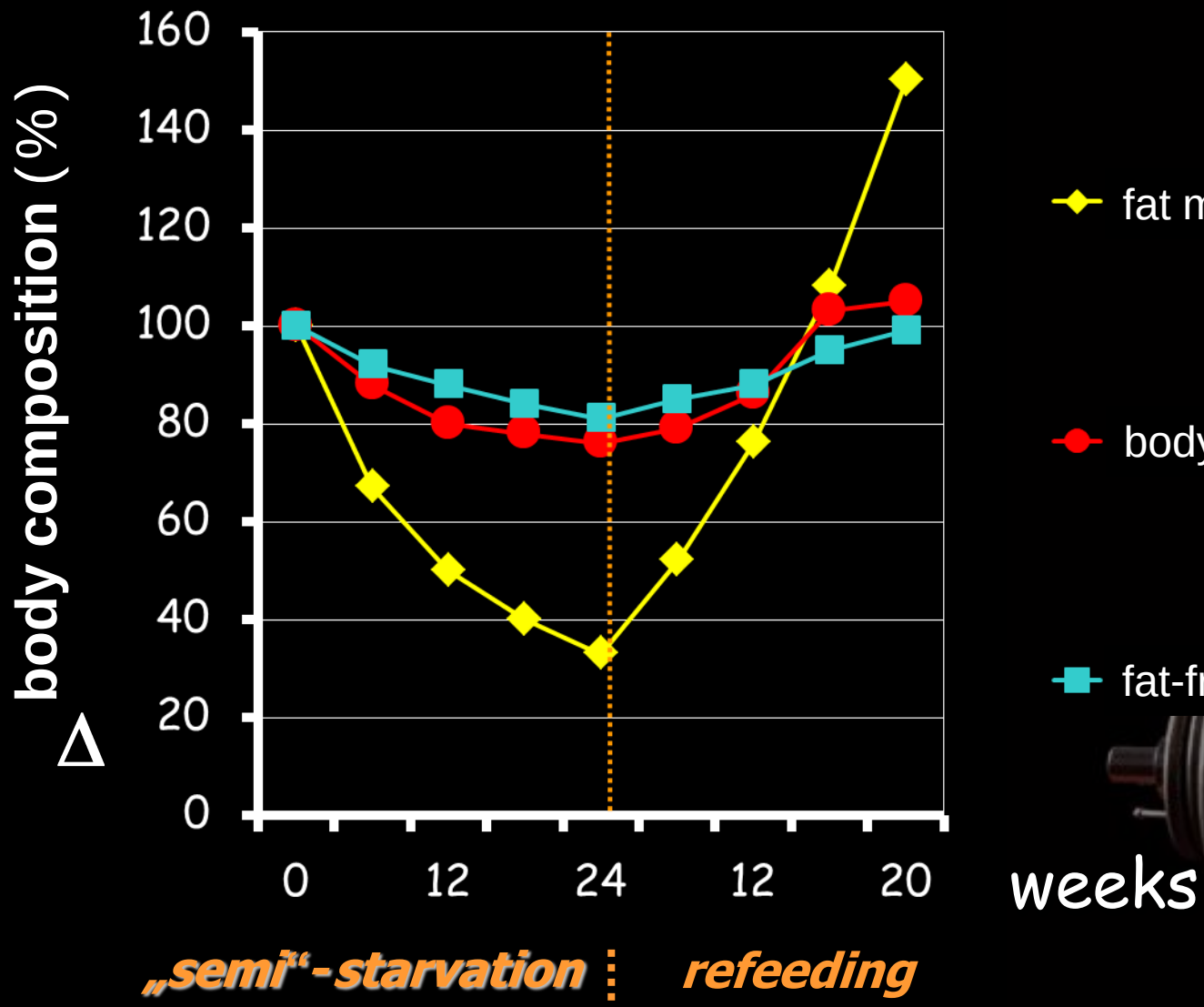


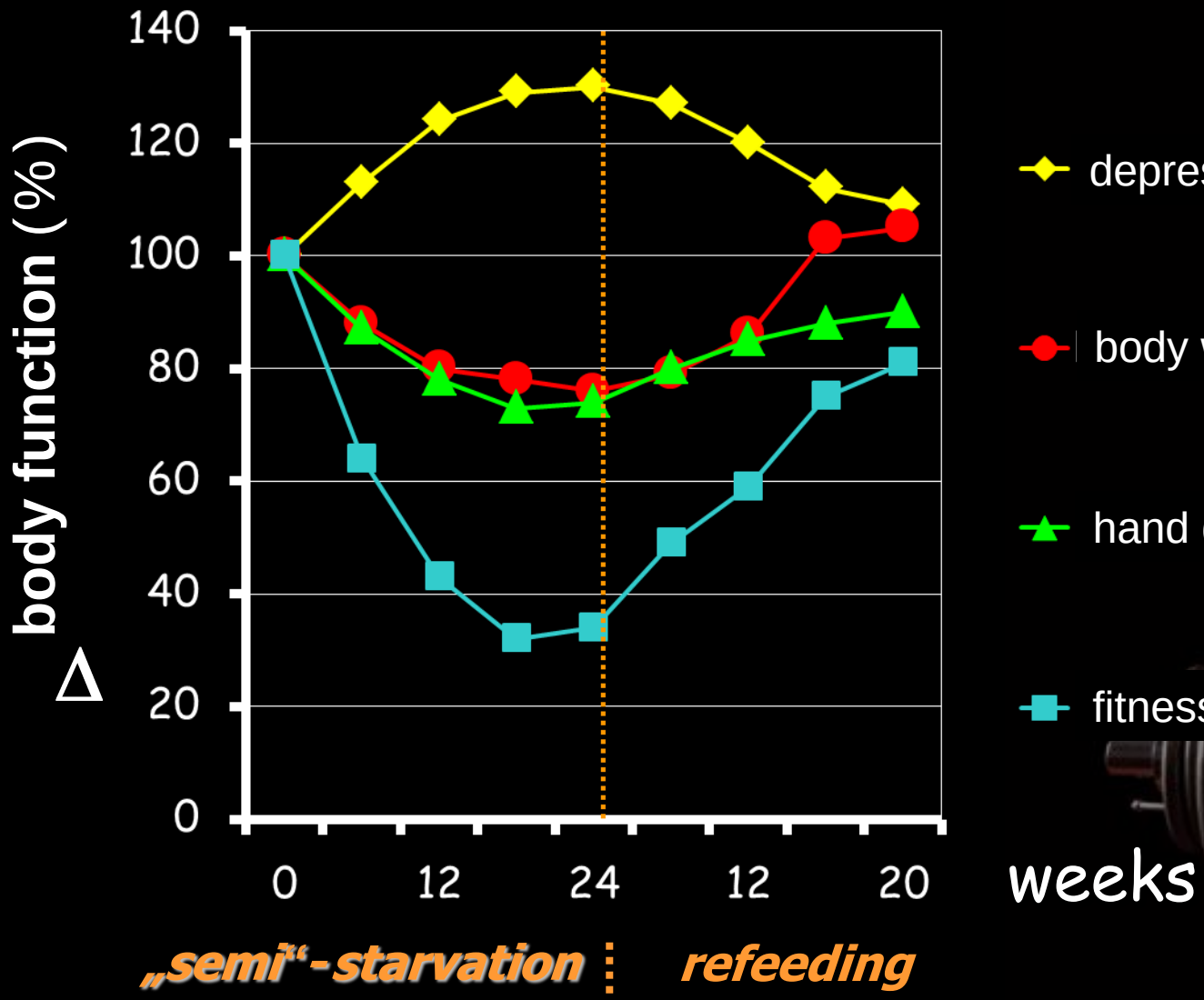
Keys A et al. The Biology of Human Starvation.1950

Δ body composition vs Δ body weight



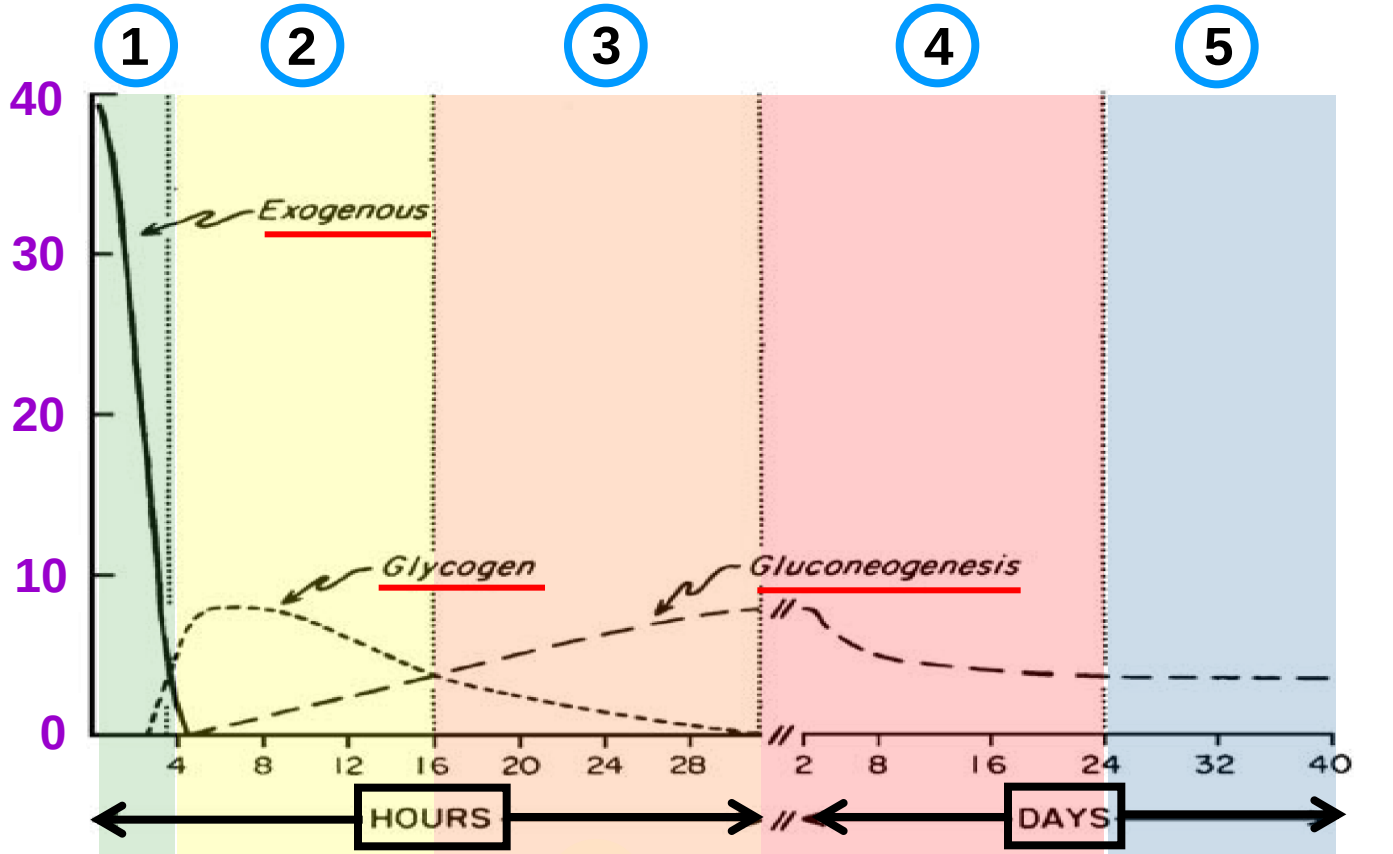
Keys A et al. The Biology of Human Starvation.1950

Δ body function vs Δ body weight



Keys A et al. The Biology of Human Starvation.1950

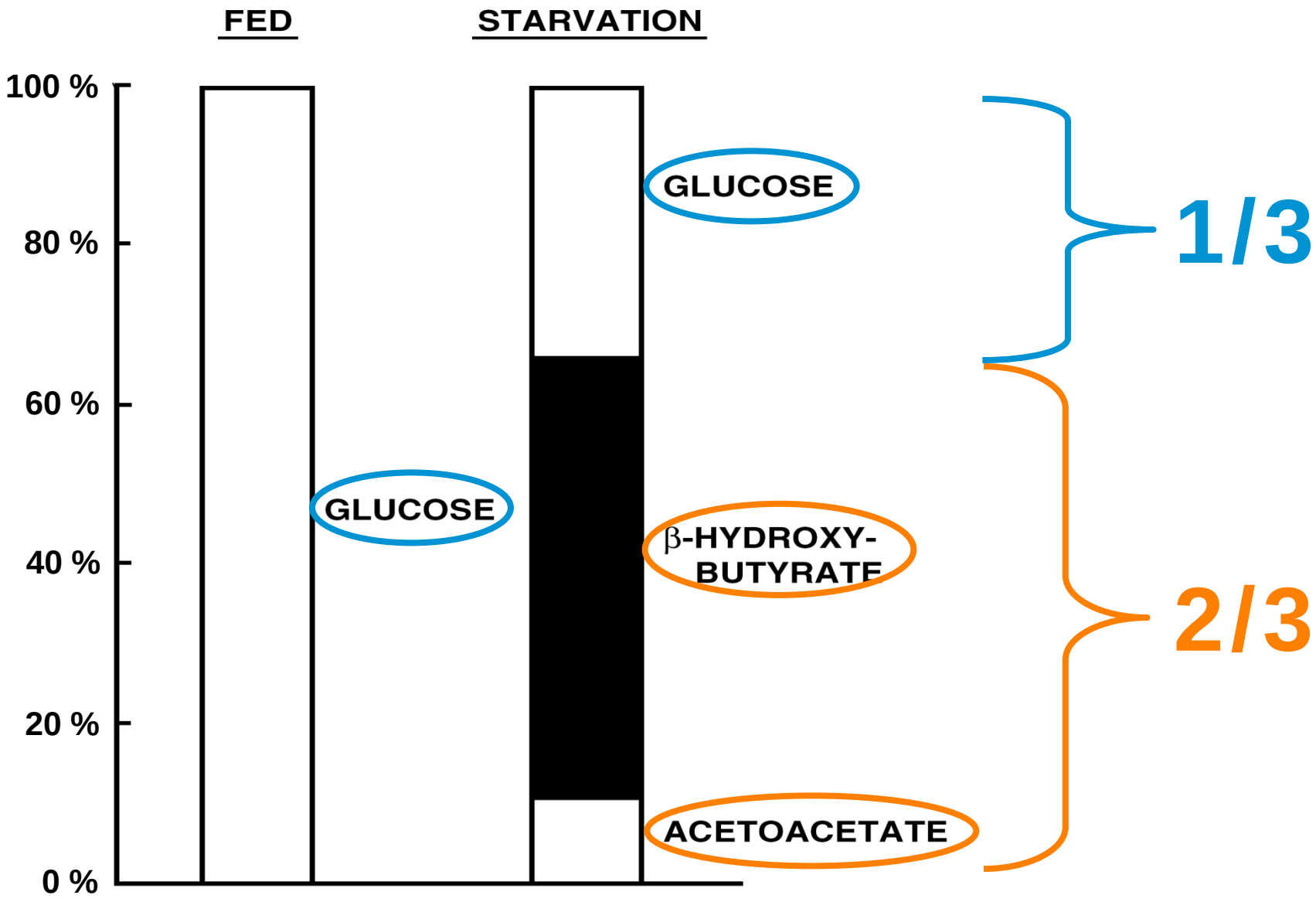
The five stages of metabolic adjustement during starvation



ORIGIN OF BLOOD GLUCOSE	Exogenous	Glycogen Hepatic gluconeogenesis	Hepatic gluconeogenesis Glycogen	Gluconeogenesis, hepatic and renal	Gluconeogenesis, hepatic and renal
TISSUES USING GLUCOSE	All	All except liver. Muscle and adipose tissue at diminished rates	All except liver. Muscle and adipose tissue at rates intermediate between II and IV	Brain, rbcs, renal medulla. Small amount by muscle	Brain at a diminished rate, rbcs, renal medulla
MAJOR FUEL OF BRAIN	Glucose	Glucose	Glucose	Glucose, ketone bodies	Ketone bodies, glucose

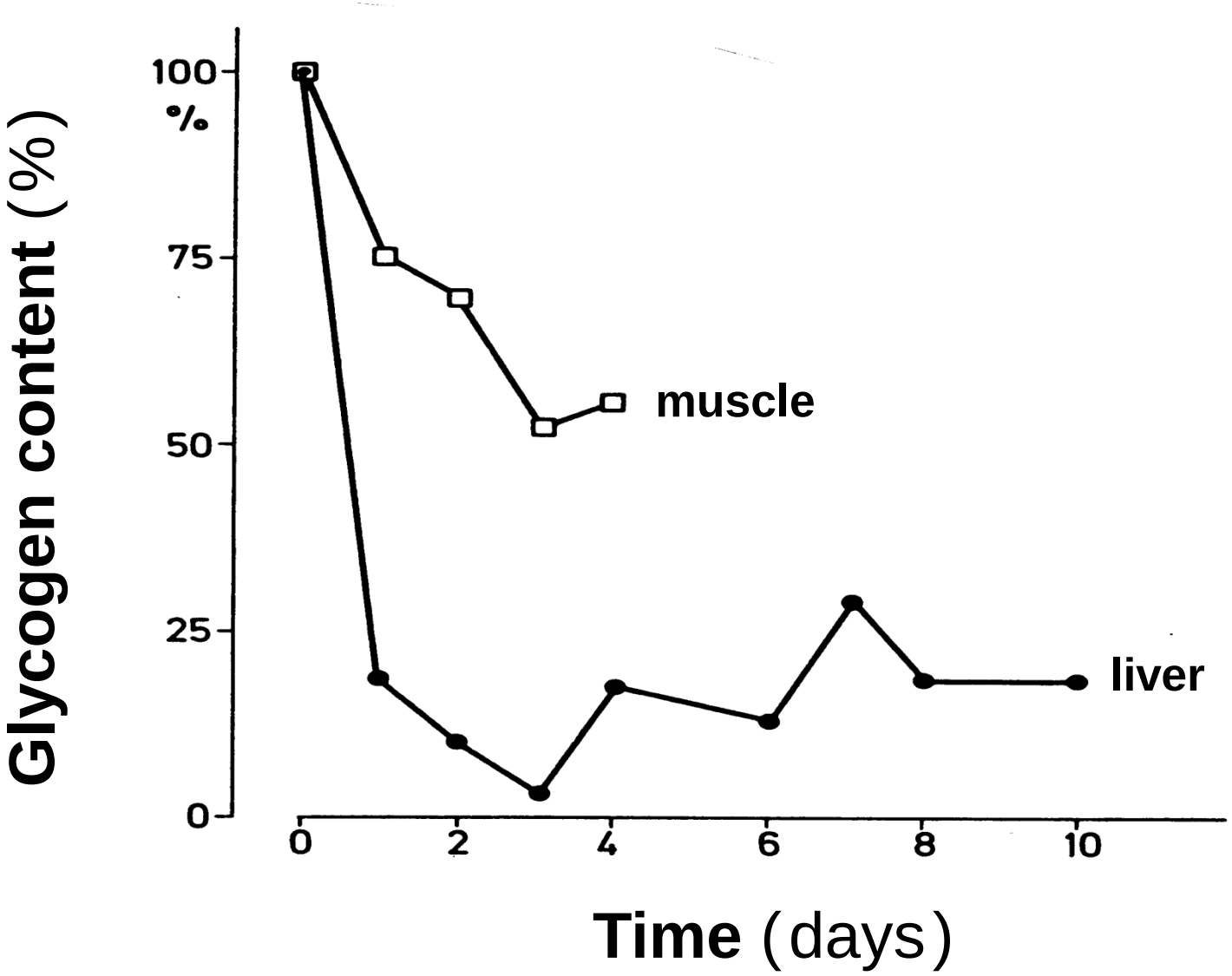
Cahill GF et al. Annu Rev Nutr 2006

Brain substrate utilisation during starvation



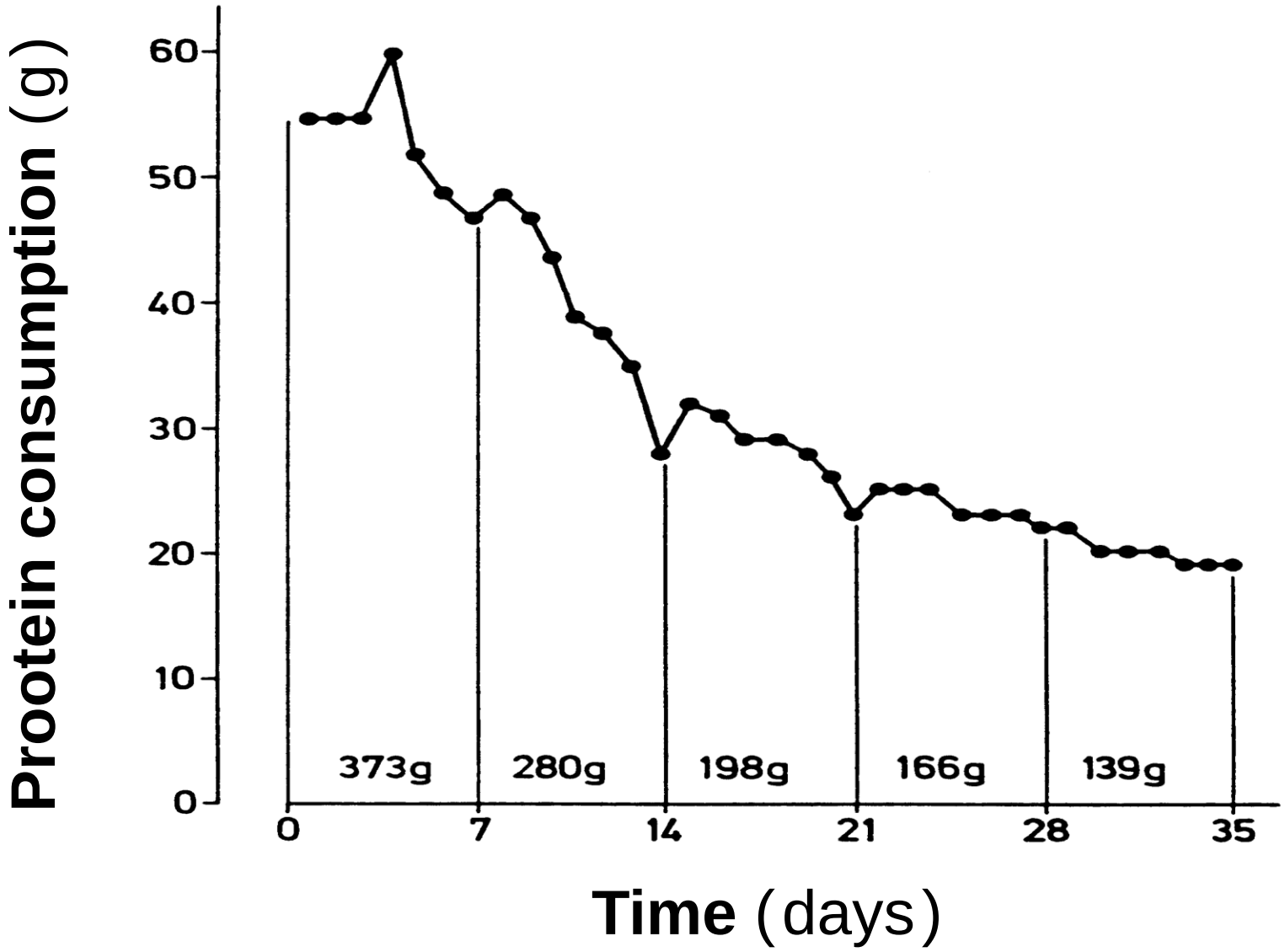
Owen OE et al. J Clin Invest 1967

Fall in glycogen content during fasting



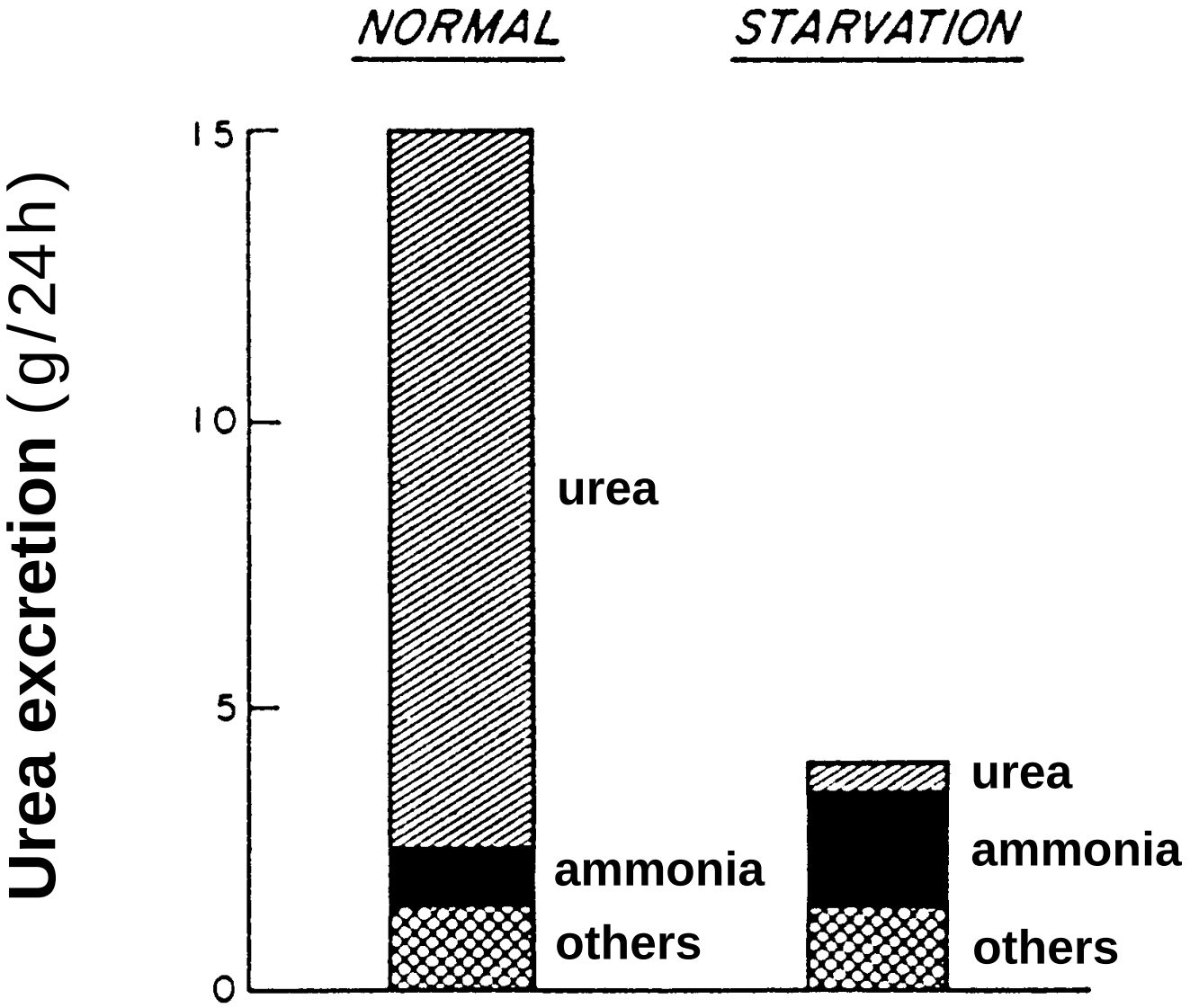
Owen OE et al. Am J Clin Nutr 1998

Protein mobilisation during fasting



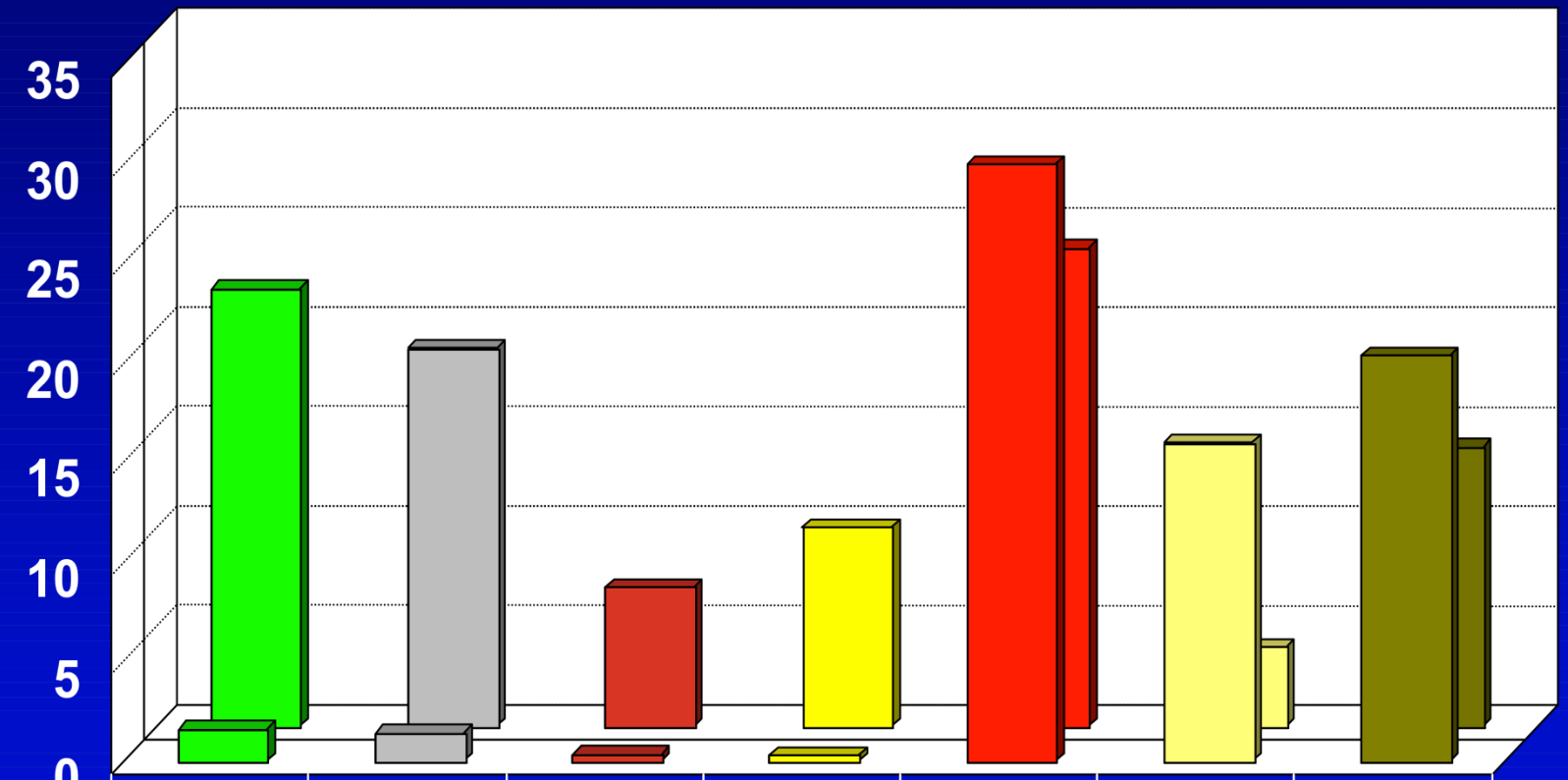
Owen OE et al. J Clin Invest 1969

Urinary urea excretion during fasting



Cahill GF et al. NEJM 1970

Organ-weight and -energy requirements

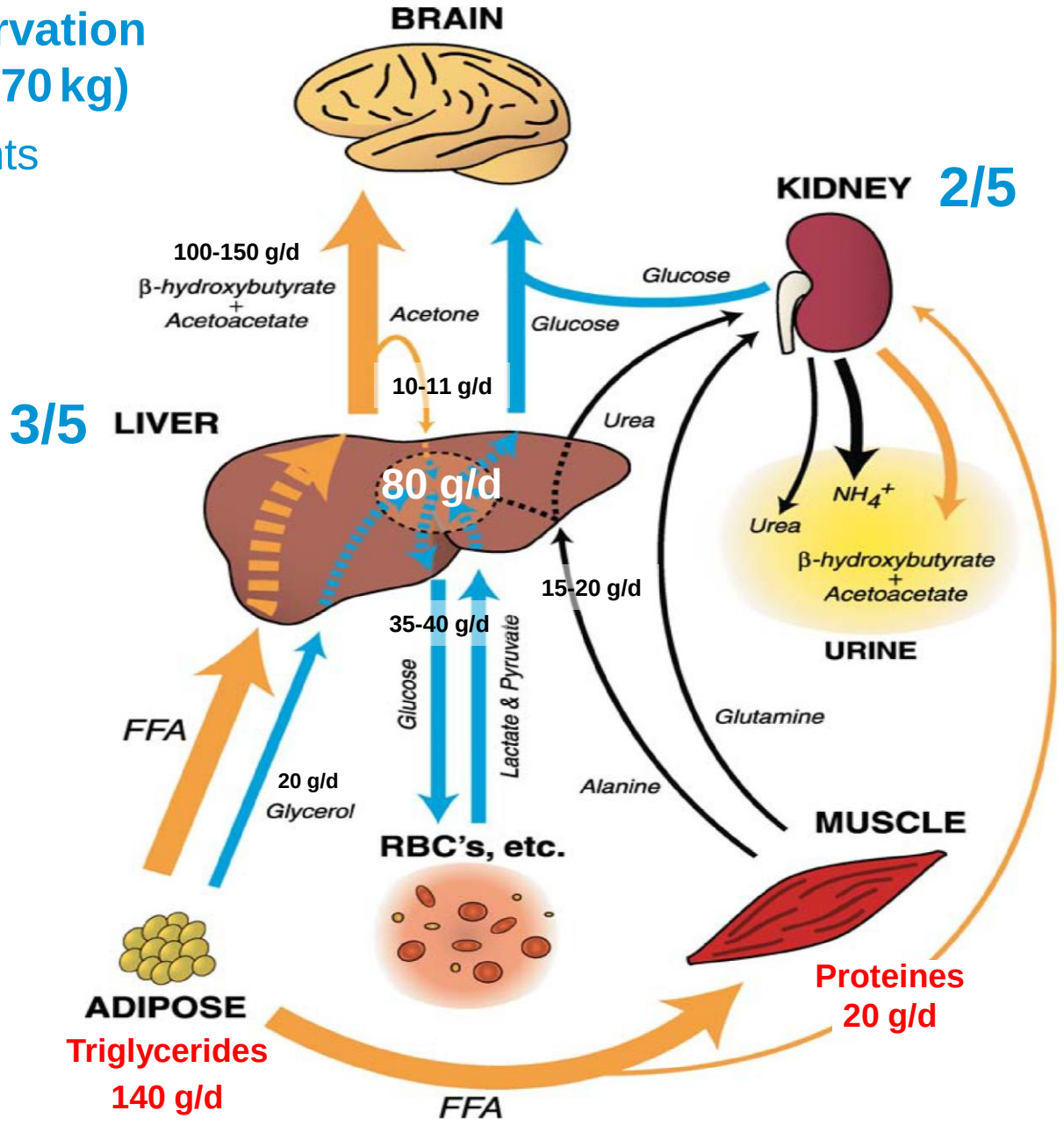


	liver	brain	heart	kidney	muscle	fat	others
Weight %	1,6	1,4	0,32	0,29	30	16	20,4
Energy %	22	19	7	10	24	4	14

Overall scheme of starvation fuel metabolism (man 70 kg)

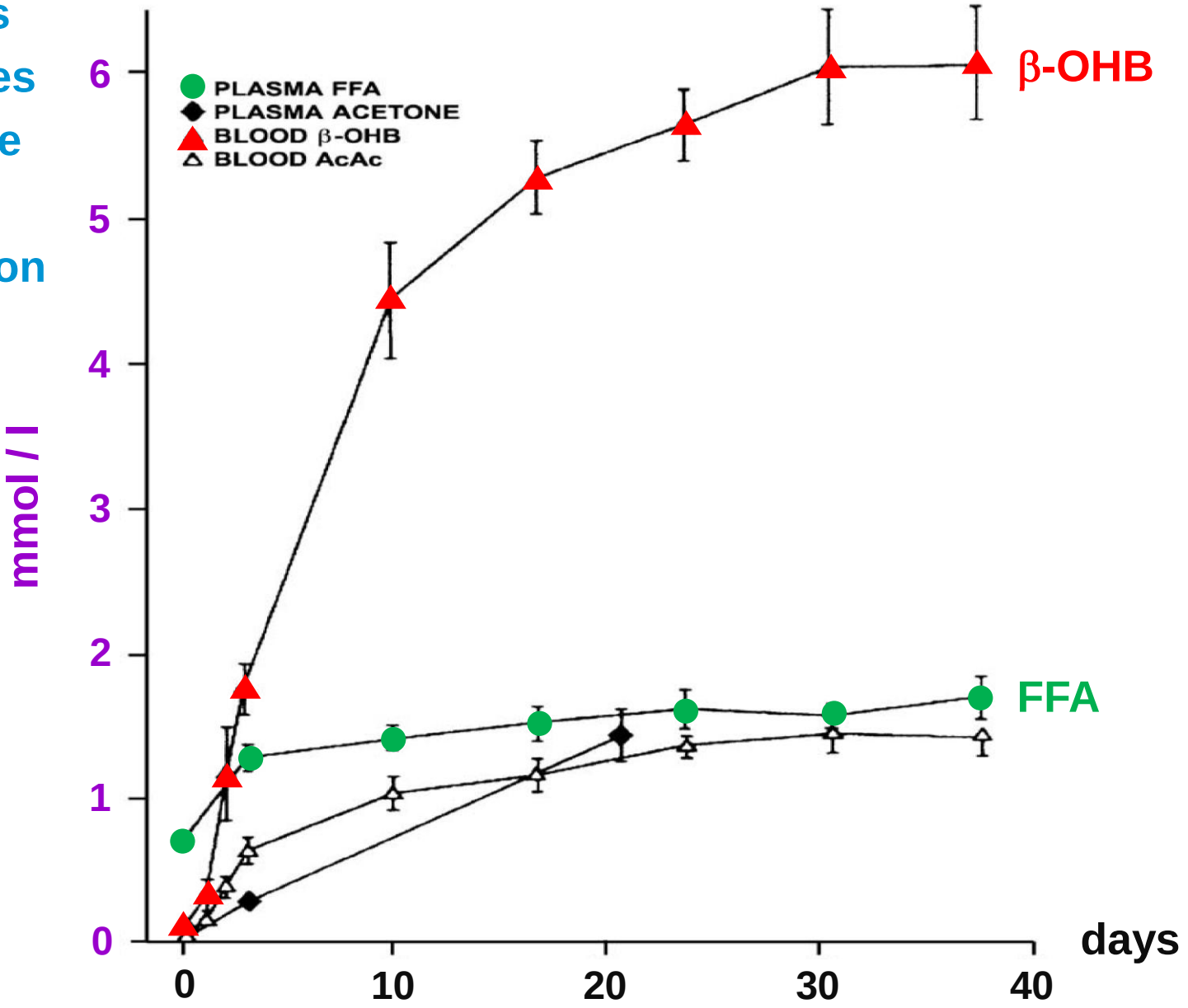
Basal energy requirements

24 h → ca. 1500 kcal



Cahill GF. NEJM 1970 & Annu Rev Nutr 2006

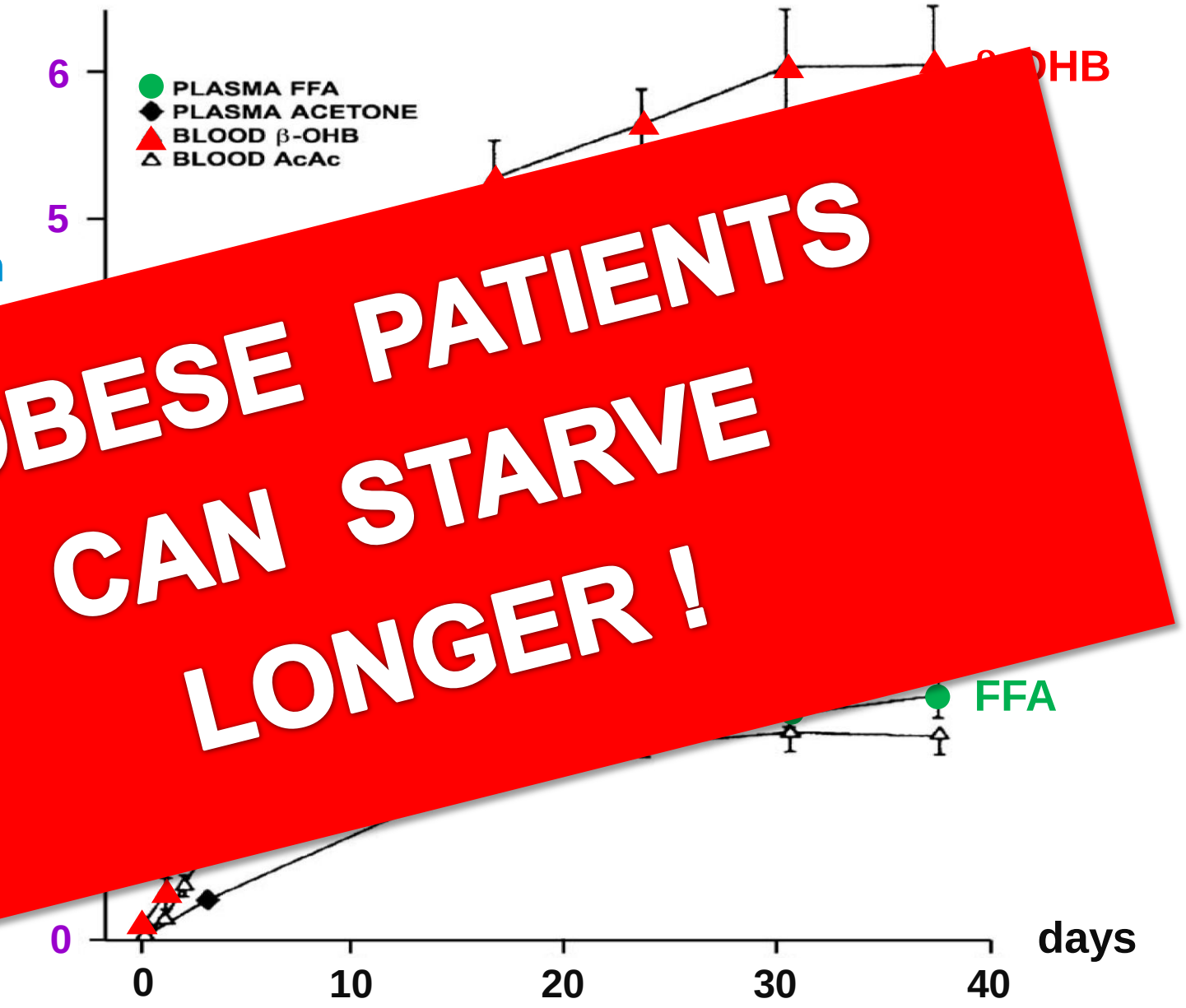
Concentrations of ketone bodies and plasma free fatty acids during starvation



3 obese patients

Cahill GF et al. Annu Rev Nutr 2006

Concentrations of ketone bodies and plasma free fatty acids during starvation



➔ OBESE PATIENTS CAN STARVE LONGER !

3 c… patients

Cahill GF et al. Annu Rev Nutr 2006

„Definition“ of the refeeding syndrome (RFS)

Life-threatening status with

- ➔ low-serum electrolyte and vitamin concentrations
- ➔ fluid imbalance
- ➔ sodium-retention
- ➔ disturbance of organ function

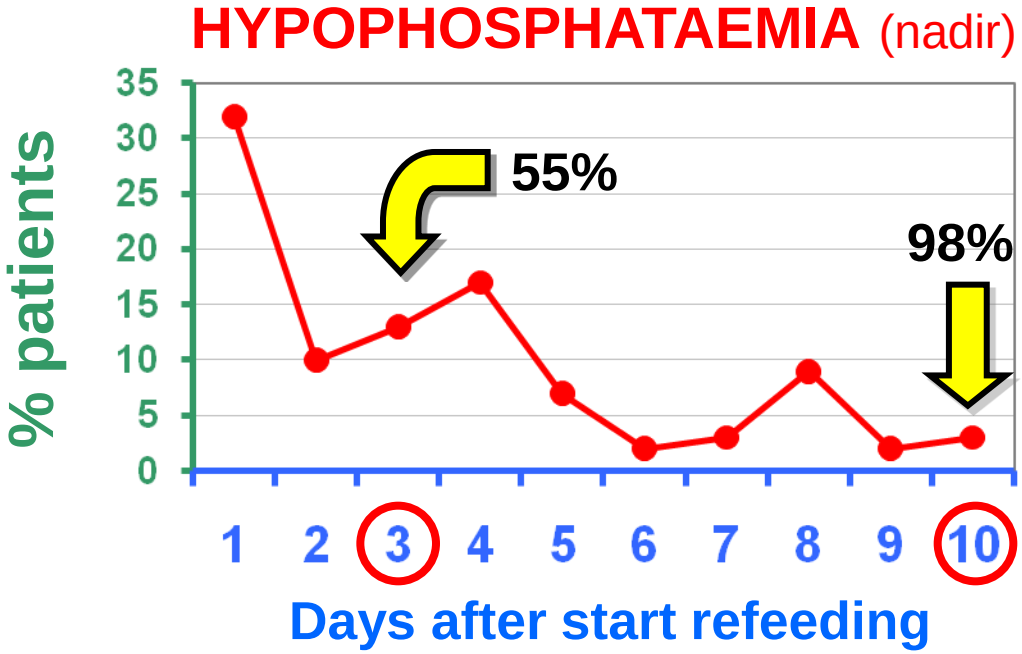
resulting from over-rapid or unbalanced refeeding of a malnourished catabolic patient.

NICE. Clin. Guidelines 2006 / Stanga Z. Eur J Clin Nutr 2008

Prevalence of RFS

- 10% → pat. with gastrointestinal fistulae — *Fan et al. Nutrition 2004*
- 14% → elderly patients (age ≥ 65 y) — *Kagansky et al. J Intern Med 2005*
- **25% → cancer patients** — *Gonzalez et al. Nutr Hosp 1996*
- **48% → malnourished patients** — *Hernandez-Aranda et al. Rev Gastroenterol Mex 1997*

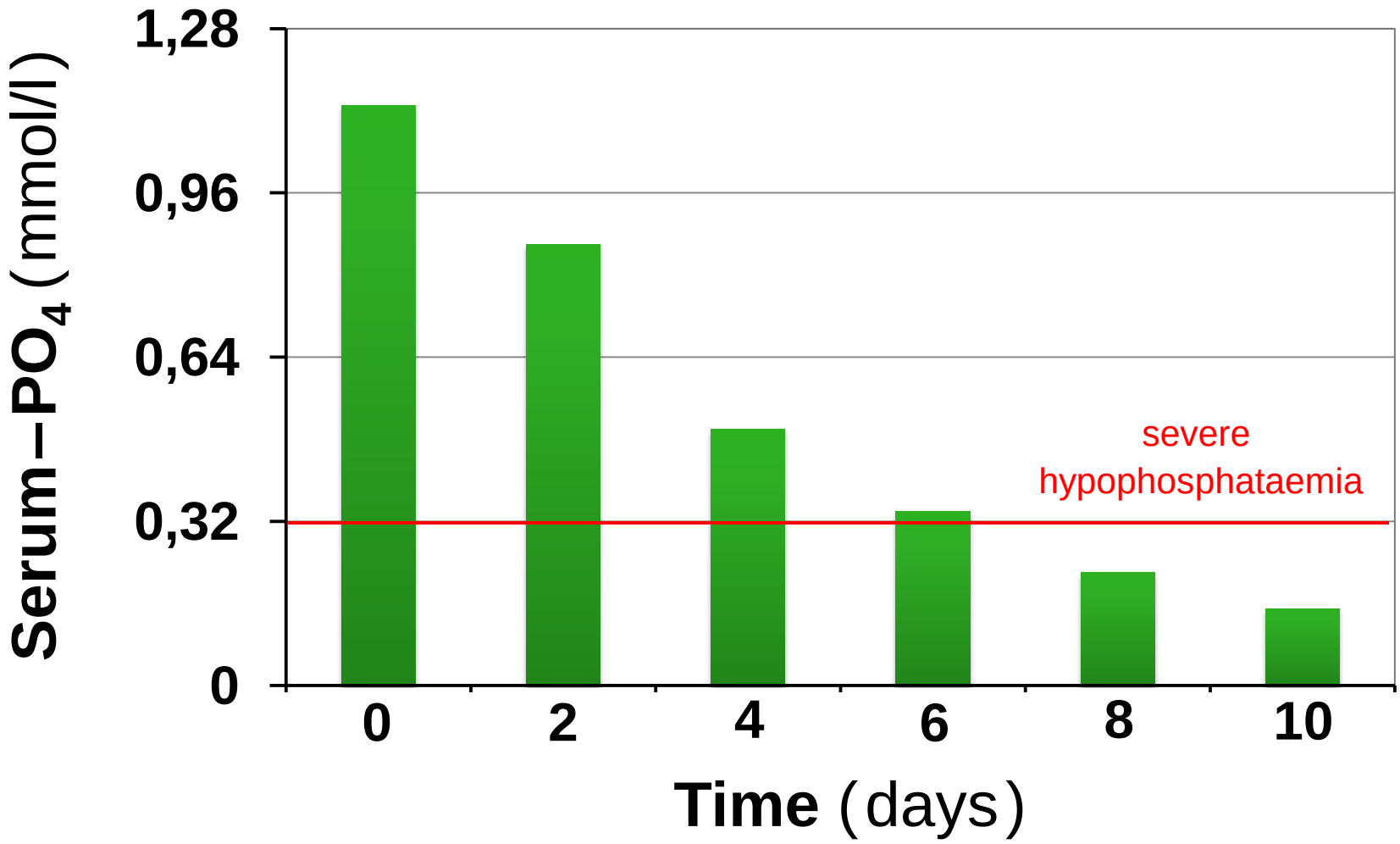
- 28% pat. affected by anorexia nervosa (*n* = 69, mean BMI 15 kg/m²) — *Ornstein. J Adolesc Health 2003*



NOTE

parenteral – enteral – oral

Impact of parenteral nutrition on S-PO_4 in malnourished ICU-patients (first 10 days)



Knochel JP et al. Arch Intern Med 1977

Pathophysiologic aspects of the RFS

Starvation or malnutrition ➔ catabolic state ➔ insulin ↓ glucagon ↑

↓

Gluconeogenesis, proteolysis ➔ loss of weight; depletion of vitamin & mineral stores

↓

REFEEDING ➔ **Glucose** ↑ ➔ lipogenesis ↑ → steatohepatitis; thiamine ↓ → Wernicke syn, met. acidosis; hyperosmotic state → neutrophil function ↓

↓

Insulin ↑ ➔ **Na** ↑ ➔ **ECV** ↑ ➔ heart failure; edema

↓

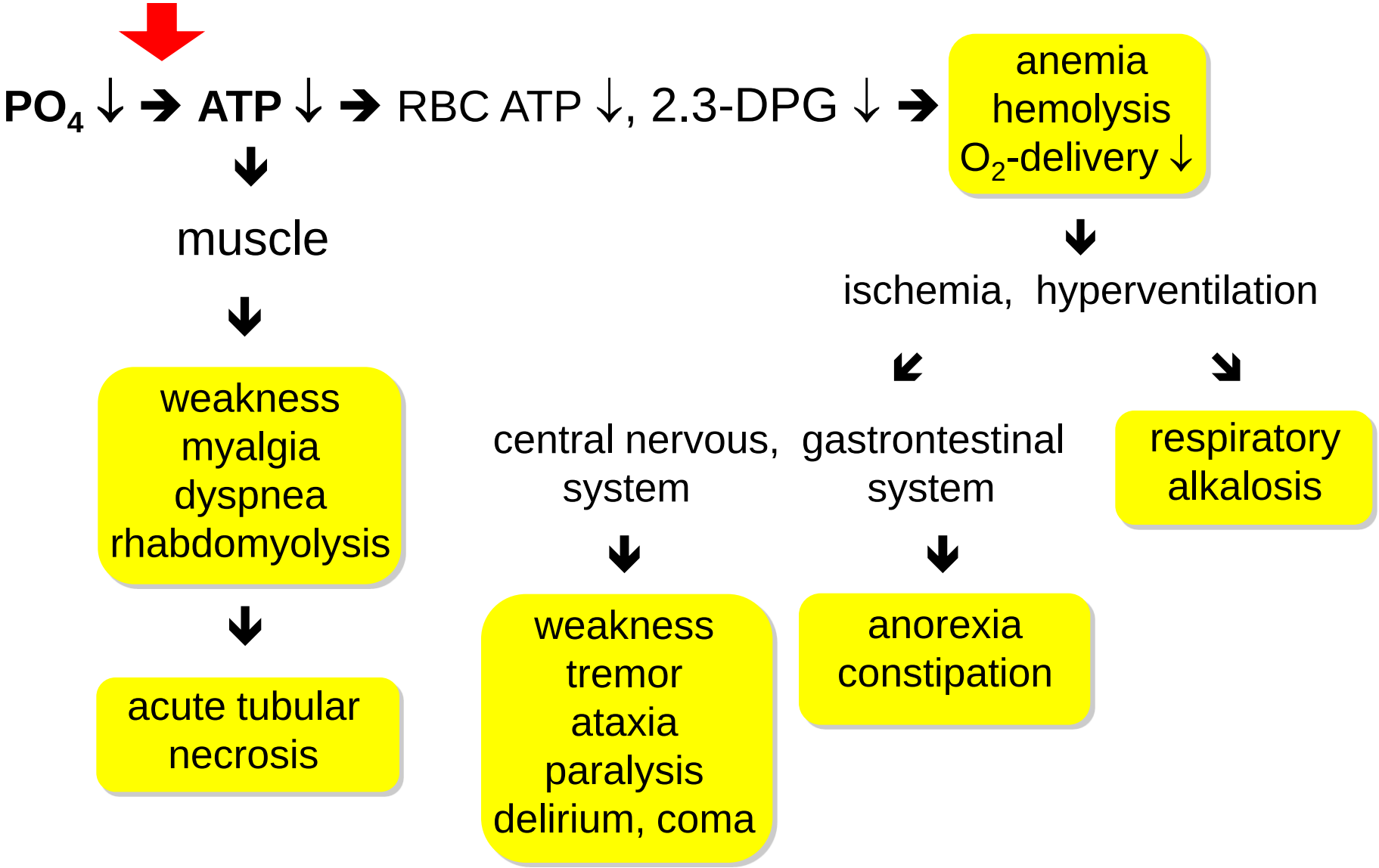
Transcellular shifts of

Glucose, PO_4, K, Mg ➔ **Mg** ↓, **K** ↓, **Ca** ↓ ➔ spasms; tetany; arrhythmias

↓

Boateng AA et al. Nutrition 2010

Pathophysiologic aspects of the RFS



Boateng AA et al. Nutrition 2010

Pathophysiologic aspect

PO

on

y

dium, coma

CLINICALLY MOST IMPORTANT SYMPTOMS

- ➔ tachykardia
- ➔ tachypnoea
- ➔ oedema

Boateng AA et al. Nutrition 2010

Pathophysiologie der Hypophosphatämie

Starvation OR malnutrition

Catabolism

- **Muscle- and fat-mass ↓**
- **PO_4-loss**

  NOTE: PO_4-concentration normal,

  fat-oxidation → without PO_4-products

Anabolism

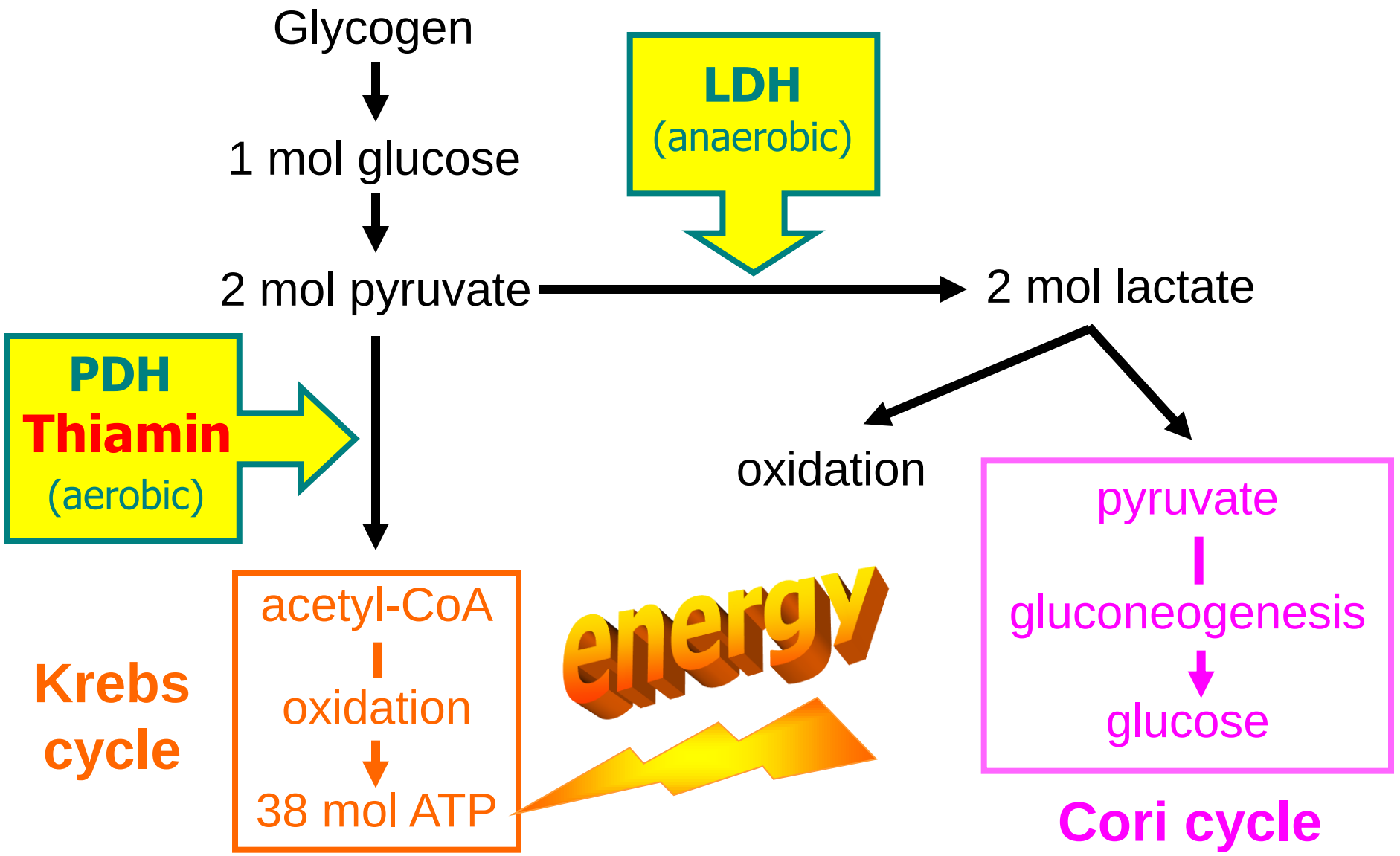
(glucose supply)

- **PO_4-requirements ↑** pro mol glucose

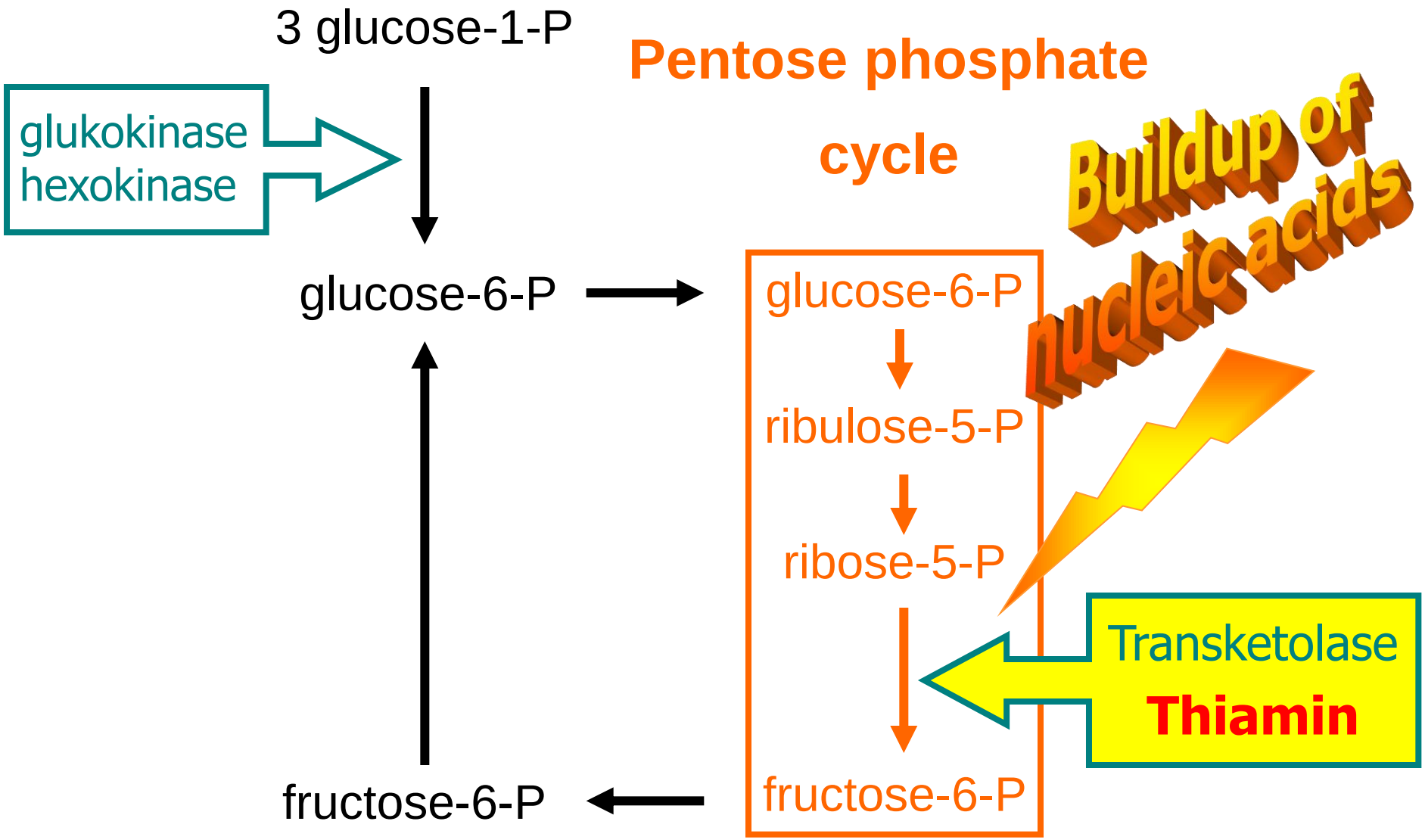
  2 mol (glycogen) resp. 4 mol (Krebs cycle)
- **Insulin ↑**

  → glucose / PO_4-transport in the cell ↑

Glucose metabolism and thiamine use



Glucose metabolism and thiamine use



Criteria for determination of patients at risk of RFS

ONE OF THE FOLLOWING	TWO OF THE FOLLOWING
BMI < 16 kg/m2	BMI < 18.5 kg/m2
Unintentional weight loss > 15% in the preceding 3 - 6 months	Unintentional weight loss > 10% in the preceding 3 - 6 months
Very little or no nutritional intake for more than 10 days	Very little or no nutritional intake for more than 5 days
Low levels of serum potassium, phosphate or magnesium prior to feed	History of alcool or drug abuse

FURTHER PATIENTS AT RISK

- hungerstrikers, anorexia nervosa
- After bariatric surgery, short bowel syndrome
- Oncology patients, elderly, chronic alcool or drug abuse

NICE. Clinical Guidelines 2006 / Stanga Z et al. EJCN 2007

Criteria for confirmation RFS

Severly low electrolytes

$PO_4 \rightarrow < 0.32$ mmol/l

$K \rightarrow < 2.5$ mmol/l

$Mg \rightarrow < 0.5$ mmol/l

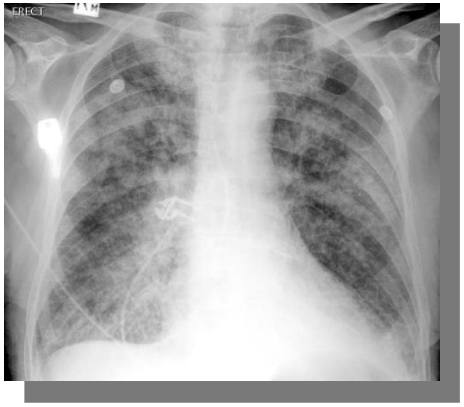
Fluid overload

Peripheral oedema or acute circulatory fluid overload

REFEEDING SYNDROME

Disturbance to organ function

respiratory failure,
cardiac failure or
pulmonary oedema



Rio A et al. BMJ Open 2013 / Crook MA et al. Nutrition 2001

CLINICAL CASE

Mr. HA, Tunisian, 27 years old

- Asylum seeker, in detention pending deportation
- **FH** unremarkable
- **PH** thalassemia minor
- **AP** hunger strike since 4 months (political reason)

  → he drinks only tea and coffee with sugar

  → 20 kg weight loss

Status at admission (prison at our university hospital)

- reduced general state, cachectic state
- 183 cm, 49.5 kg → BMI: 15 kg/m²
- BP 80/55 mmHg, P 56/min, T axilla 35.4 °C
- adynamic, dysphoric, orientated
- dry mucosae, skin turgor ↓
- Heart, chest and abdomen control → normal
- Neurostatus: reflexes weak, otherwise normal

Chronological follow-up

20.04. 49.5 kg refuses any nutrition, drinks only tea & coffee with sugar

03.05. further worsening of the general state, tired, aphatic

10.05. 46.1 kg **from day 20 after admission ➔ forced feeding**

→ insertion of a CVC (v. jugularis)

→ isocaloric **EN** (naso-gastral): 750 ml/day

→ **PN** : standard AIO-solution: 1‘250 ml/day

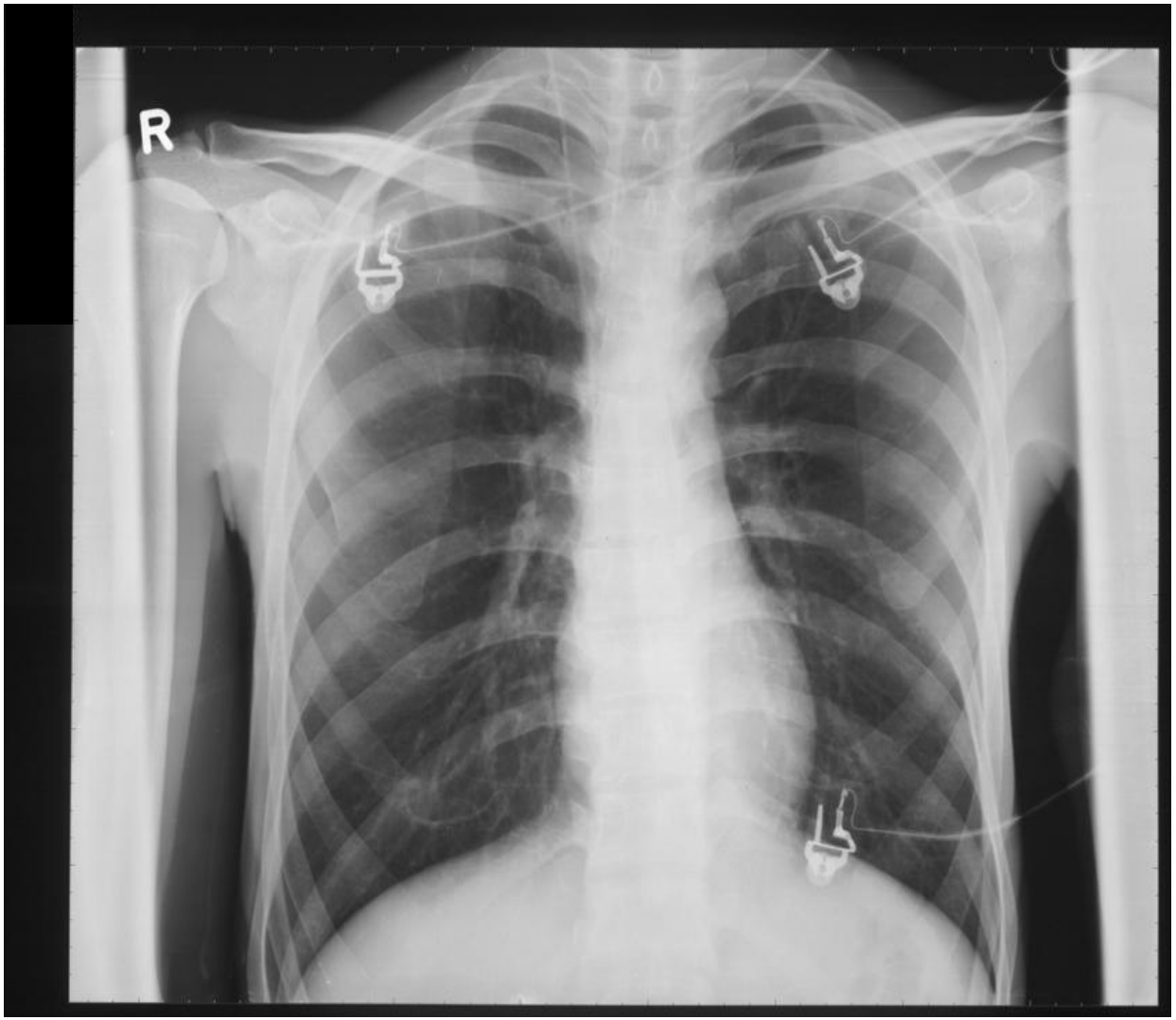
→ **NaCl 0.9%**: 1‘000 ml/d

→ **Additional** i.v./day:

KCl 20 mmol, 1 amp. water-soluble vitamins,

1 amp. fat-soluble vitamins, 1 amp. trace elements,

1 amp. zinc of 5 mg



X-ray control of the CVC

Laboratory parameters

Date		20.4	23.4	10.5
Hb	g/dl	10.6	11.3	9.5
Proteins	g/l	80		
Albumin	g/l			
Glucose	mmol/l	4.9		6.7
K	mmol/l	4	3.4	3.3
Na	mmol/l	140	134	131
PO_4	mmol/l		1.15	1.11
Ca	mmol/l	2.34		2.3
Mg	mmol/l	0.95		0.81
Urea	mmol/l	12.7	4.8	6.7
TSH	mU/l			
fT4	pmol/l			
Zinc	µmol/l			
Vit B1	nmol/l			
Vit B12	pmol/l			
Folate	nmol/l			

Refeeding

10.5 forced feeding

Chronological follow-up

20.04. 49.5 kg refuses any nutrition, dri s onl ea ee with sugar

03.05. furth rsenin her state, ired, aph atic

10.05. **20 af mission → for d fe**

sc tion of a CVC (v. i u s)

→ isocaloric s.- l, 50 ml/day

: star olution: 1‘250 ml/day

Cl 0.9 00 ml/d

ditional i.v./day:

KCl 20 mmol, 1 amp. water-soluble vitamins,

1 amp. fat-soluble vitamins, 1 amp. trace elements,

1 amp. zinc of 5 mg

3200 ml/d

2000 kcal/d

Laboratory parameters

Date		20.4	23.4	10.5	11.5	12.5	15.5
Hb	g/dl	10.6	11.3	9.5	8.9	7.9	7.1
Proteins	g/l	80					
Albumin	g/l						
Glucose	mmol/l	4.9		6.7	6.7	?	?
K	mmol/l	4	3.4	3.3	3.5	4.3	3.6
Na	mmol/l	140	134	131	?	137	142
PO_4	mmol/l		1.15	1.11	?	?	0.05
Ca	mmol/l	2.34		2.3	?	?	?
Mg	mmol/l	0.95		0.81	1.15	?	?
Urea	mmol/l	12.7	4.8	6.7			
TSH	mU/l					0.88	1.39
fT4	pmol/l						8
Zinc	µmol/l				12.9		9.5
Vit B1	nmol/l				?	?	?
Vit B12	pmol/l					239	
Folate	nmol/l				120		118

Refeeding

4 days later !

10.5 forced feeding

15.5 vertical nystagmus → phosphate

Chronological follow-up

15.05. 51.7 kg tired, apathic, suffer from vertigo

clinically: vertical rotating nystagmus

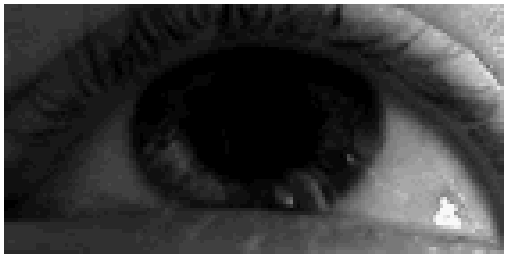
PN with unchanged additives

$KPO_4 \rightarrow$ 40 mmol/day

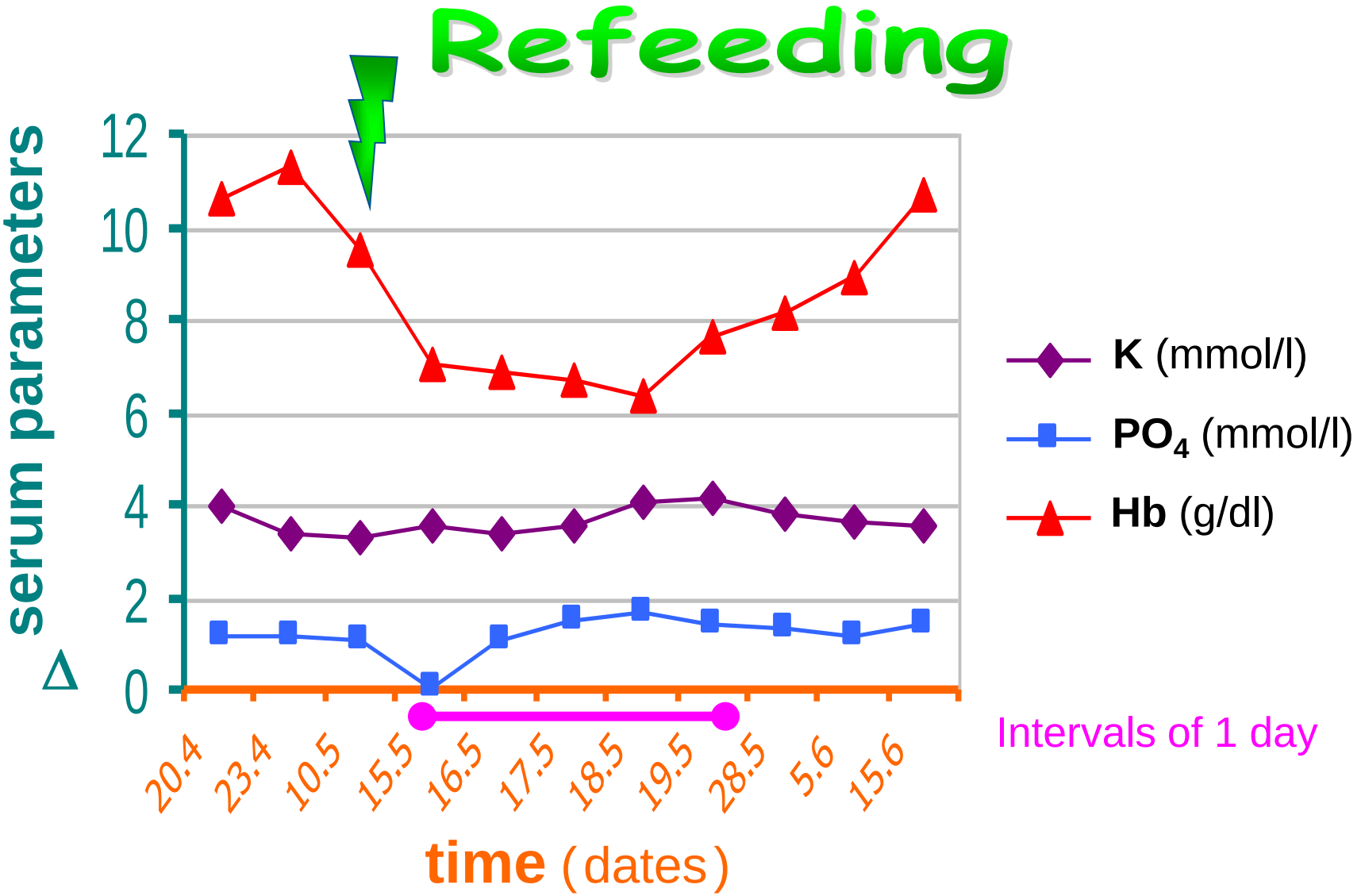
stop EN

ON (menu) + snacks between

17.05. 56.0 kg **vertical rot. Nystagmus → Wernicke encephalopathy**



Δ Serum parameters: starvation → refeeding



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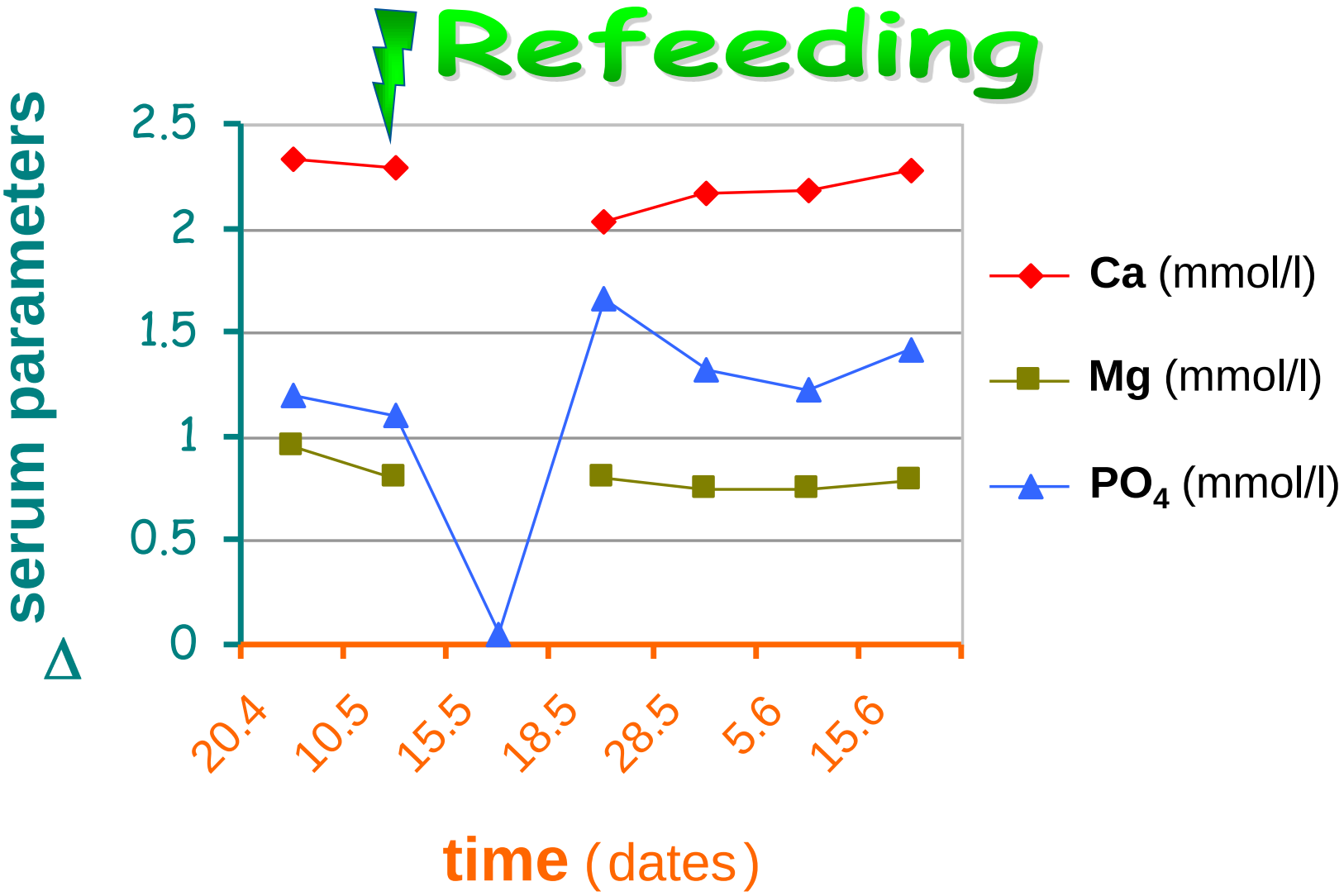
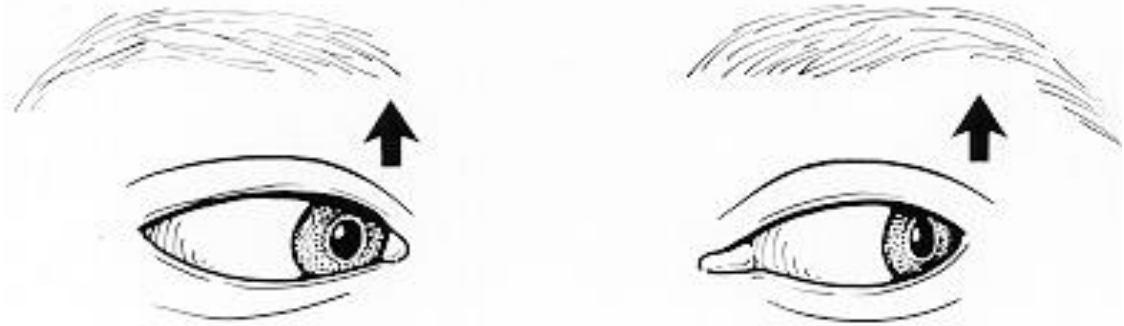
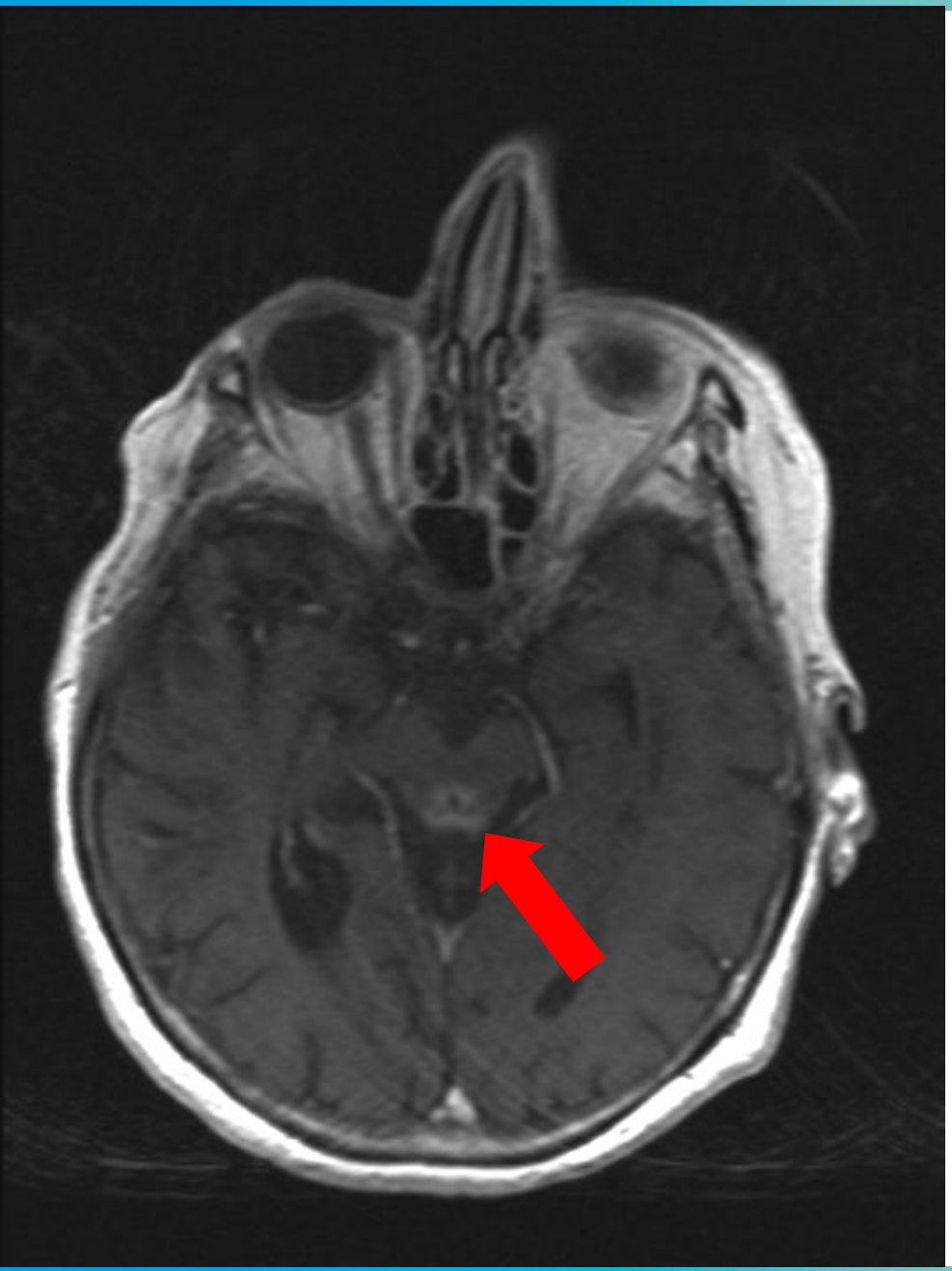


horizontal nystagmus



vertical nystagmus

rotating nystagmus



MR brain

Contrast enrichment

peri-aqueductal (medulla oblungata)

TYPICAL LESION OF

THIAMINE DEFICIENCY

→ **manifestation as**

Wernicke encephalopathy

diplopia, nystagmus, ataxia, consciousness troubles, apathy, confusion, somnolence, dysarthria, dysphagia, etc.

Chronological follow-up

15.05. **51.7 kg** tired, apathic, suffer from vertigo

clinically: vertical rotating nystagmus

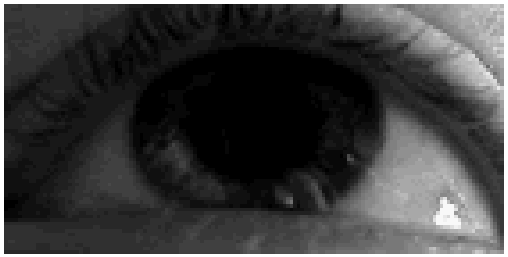
PN with unchanged additives

$KPO_4 \rightarrow$ 40 mmol/day

stop EN

ON (menu) + snacks between

17.05. 56.0 kg **vertical rot. Nystagmus → Wernicke encephalopathy**



Start **thiamine** substitution: 1 amp. 200 mg/day i.v.

Laboratory parameters

Date		20.4	23.4	10.5	11.5	12.5	15.5	16.5	17.5	18.5	19.5	21.5	28.5	16.6
Hb	g/dl	10.6	11.3	9.5	8.9	7.9	7.1			6.4	7.7		8.2	10.7
Proteins	g/l	80												
Albumin	g/l									27	29			36
Glucose	mmol/l	4.9		6.7	6.7	?	?	?	?					4.6
K	mmol/l	4	3.4	3.3	3.5	4.3	3.6	3.4	?	4.1	4.2		3.8	3.6
Na	mmol/l	140	134	131	?	137	142	?	?		141		141	143
PO4	mmol/l		1.15	1.11	?	?	0.05	1.14	1.52	1.66	1.44	1.81	1.32	1.42
Ca	mmol/l	2.34		2.3	?	?	?	?	?	2.04	2.16		2.17	2.28
Mg	mmol/l	0.95		0.81	1.15	?	?	?	?		0.85		0.75	0.79
Urea	mmol/l	12.7	4.8	6.7									5.6	4.9
TSH	mU/l					0.88	1.39							1.91
fT4	pmol/l						8							11
Zinc	µmol/l				12.9		9.5				10.5	10.8		14
Vit B1	nmol/l				?	?	?	?	?			219		
Vit B12	pmol/l					239						302		
Folate	nmol/l				120		118				113			

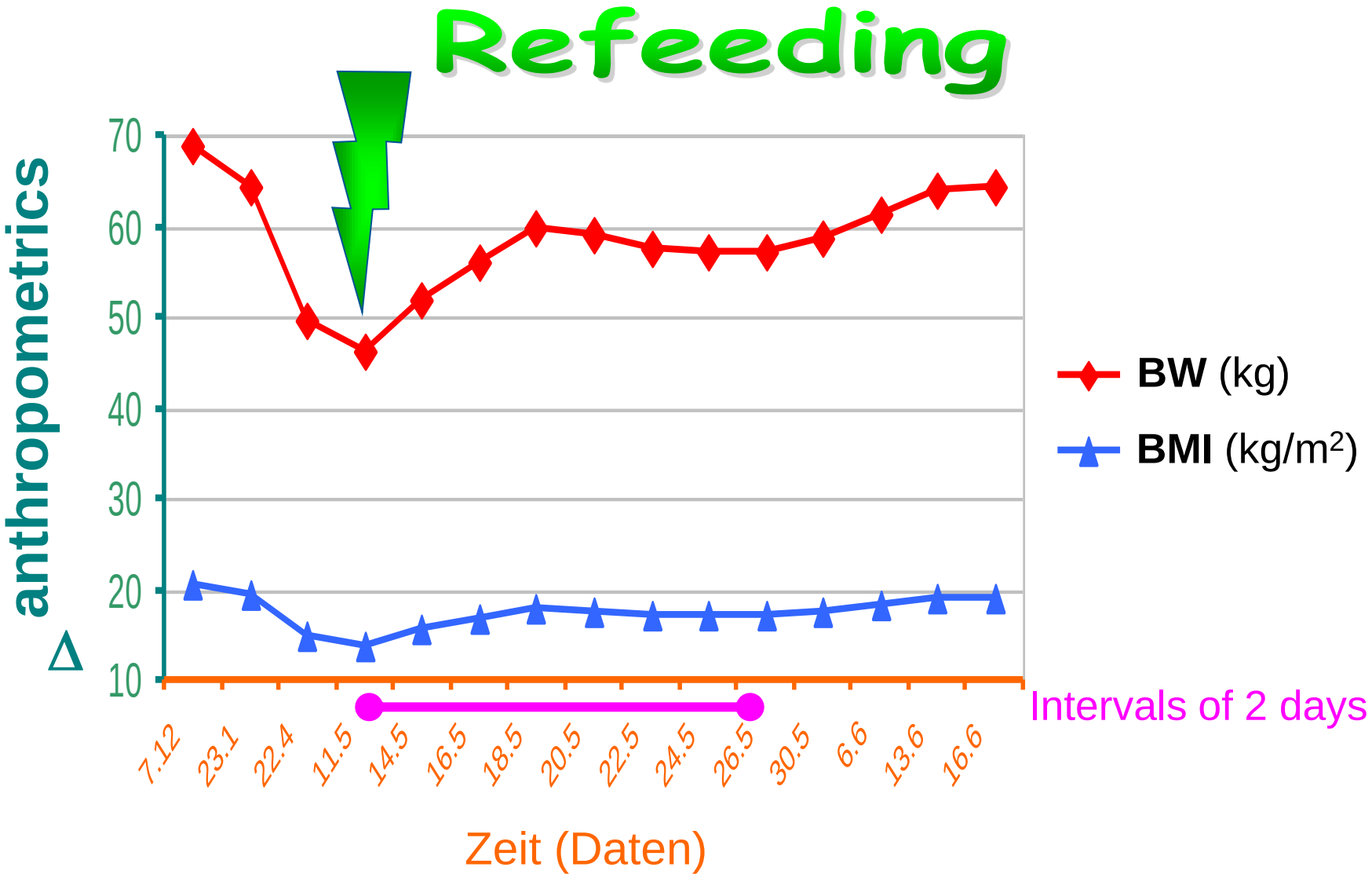
Refeeding

10.5 forced feeding

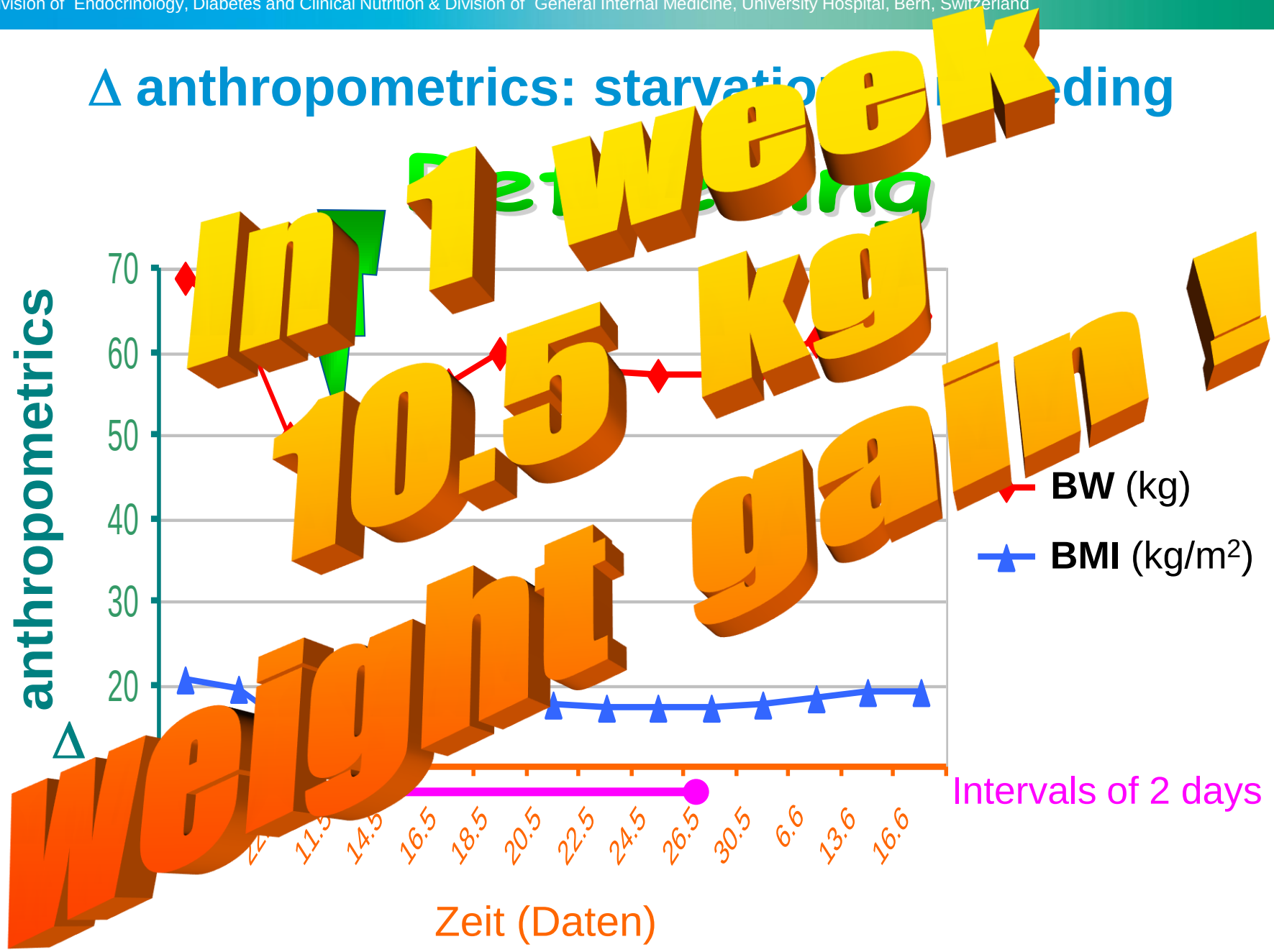
15.5 vertical nystagmus → phosphate

17.5 Wernicke encephalopathy → Vit B1 ↓

Δ anthropometrics: starvation → refeeding



Δ anthropometrics: starvation / refeeding



Chronological follow-up

15.05.	51.7 kg	tired, apathic, suffer from vertigo
		clinically: vertical rotating nystagmus
		PN with unchanged additives
		$KPO_4 \rightarrow$ 40 mmol/day
		stop EN
		ON (menu) + snacks between
17.05.	56.0 kg	**vertical rot. Nystagmus → Wernicke encephalopathy**
19.05.		stop PN, stop thiamine i.v.
24.05.	57.2 kg	build up strength, improvement of the general state
		→ rotating nystagmus only enhanced by fixation
		stop i.v. additives, vitamins tabl. orally till hospital discharge
16.06.	64.4 kg	**discharge, rotating nystagmus unchanged !**

Prevention and treatment of the RFS

DAY 1 – 10

- **Identification of patients at risk** → check PO_4, K, Mg
- **Energy:** day 1-3 → by all routes 10-15 kcal / kg / day

  day 4-6 → 15-20 kcal / kg /day

  day 7-10 → 20-30 kcal / kg /day
- **Electrolytes:** baseline, 6 h later, and daily till day 3 of refeeding → **supplementation** according to the plasma levels
- **Trace elements** (100% DRI) / **vitamins** (200% DRI)

  Give 200-300 mg **thiamine** i.v. or p.o. 30 min. before feeding

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Prevention and treatment of the RFS

DAY 1 – 10

- **Salt:** restrict sodium to <1 mmol / kg / day
- **Fluids:** day 1-3 → 20-30 ml / kg / day
  day 4-6 → 25-30 ml / kg / day
  day 7-10 → 30-35 ml / kg / day
- **Body weight:** 1x / day, after day 6 → 2x / week
- **Biochemistry:** PO_4, Mg, K, Na, Ca, glucose, creatinie, urea
  day 1-3 → 1x / day, after day 4 → 2x / week
- **Clinical examination:** 1x / day (hydration state? Objective: zero fluid balance)
- Preferably **ECG-monitoring** in severe cases (~24 h)

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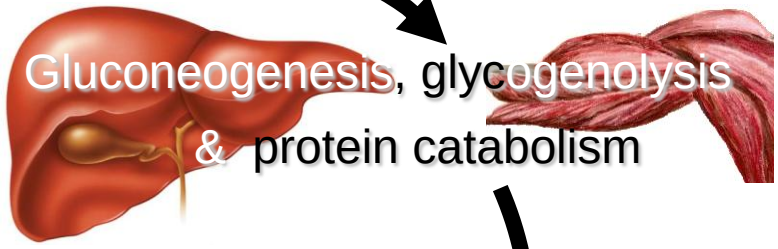
Hypokalaemia
Hypomagnesaemia
Hypophosphataemia
Thiamine deficiency
Salt & water retention

Starvation or malnutrition

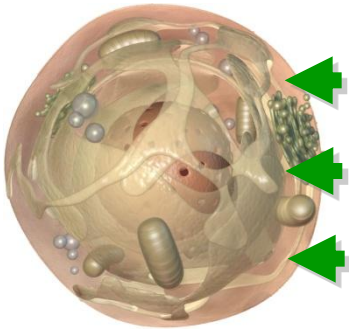


Gluconeogenesis, glycogenolysis & protein catabolism

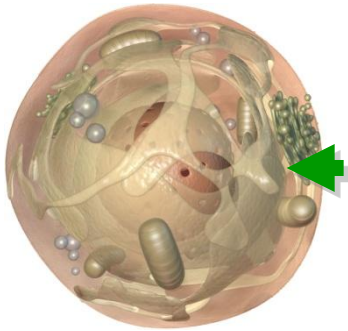
Depletion of mineral and vitamin stores

REFEEDING

REFEEDING SYNDROME



K^+
Mg^{2+}
PO_4^{2-}



↑ glucose uptake
↑ utilization of thiamine

Glucose major energy source

Insulin secretion

↑ protein synthesis
Na^+ retention → ↑ ECV

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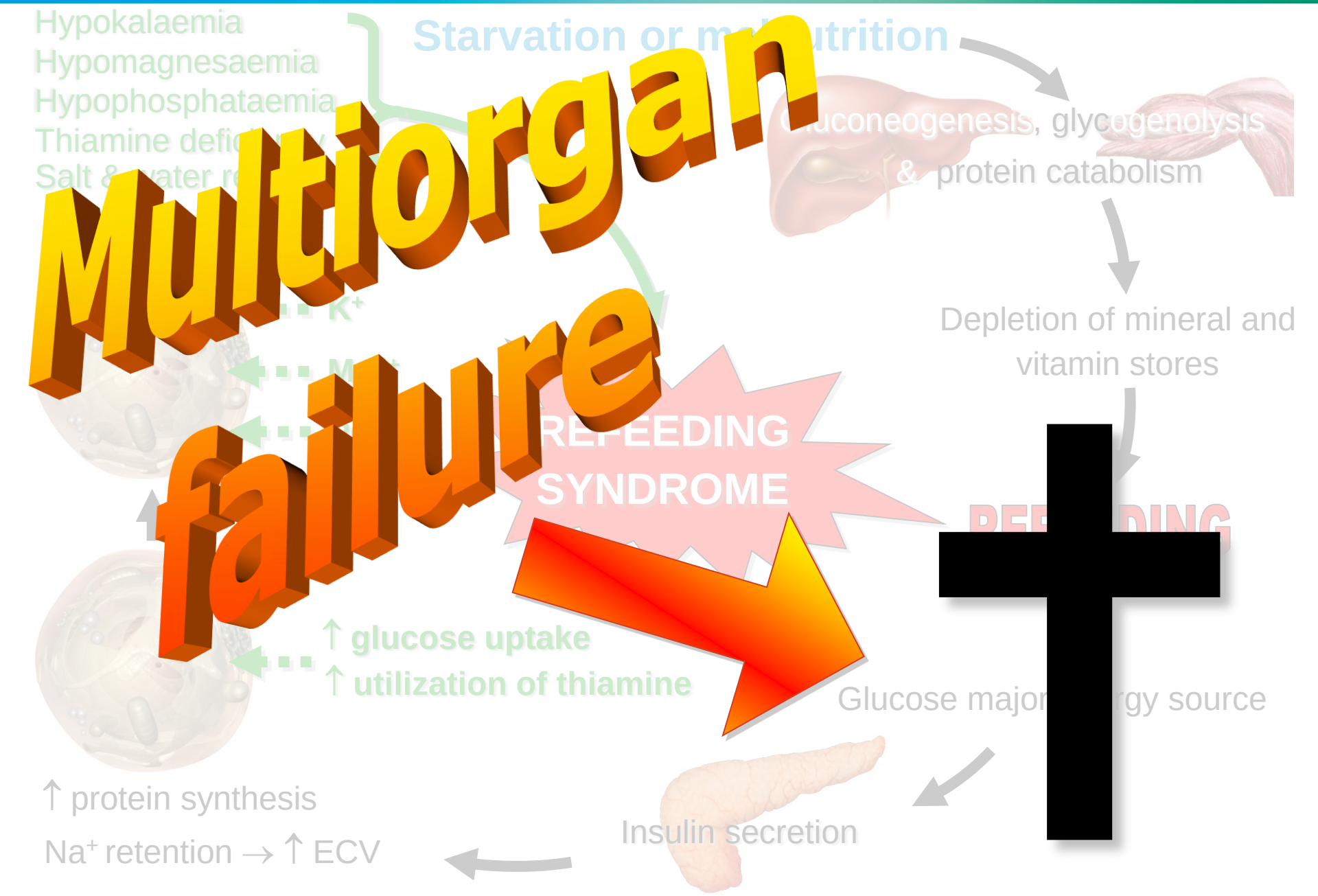

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Thanks for your attention !