

# Refeeding Syndrome

## History, pathology and guidelines

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# Expert panel

- Alison Culkin
- Mike Stroud
- Becky White
- Callum Livingstone
- Anna Hardman
- When were the first documented cases of refeeding syndrome (RFS)?

# History- Sieges

## *AD 70 Seige of Jerusalem by Romans (Flavius Josephus)*

Death in those who overindulged but not those who restrained their appetite.

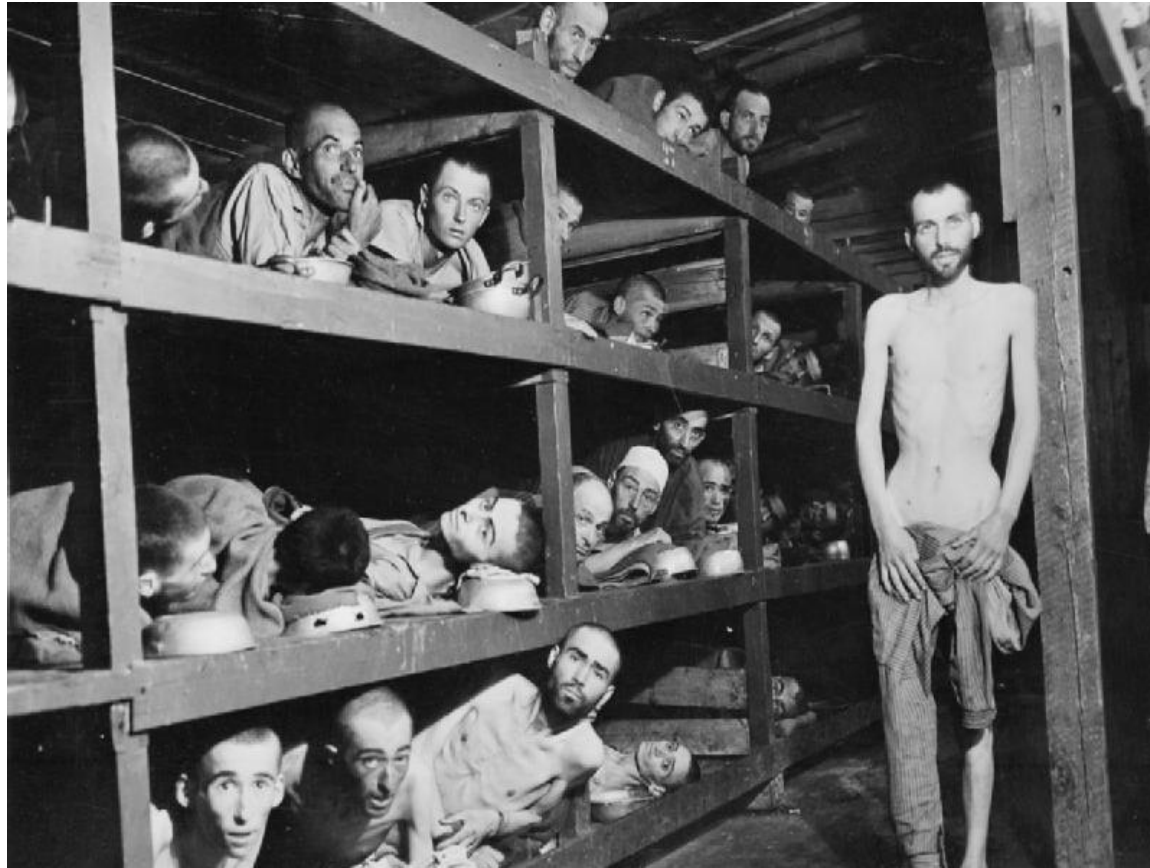
## *AD 543 Siege of Naples by the Ostrogoths*

Totila ordered the city be locked down and rations be given out gradually so the starving inhabitants wouldn't gorge themselves to death.



# Tortila of the Ostragoths

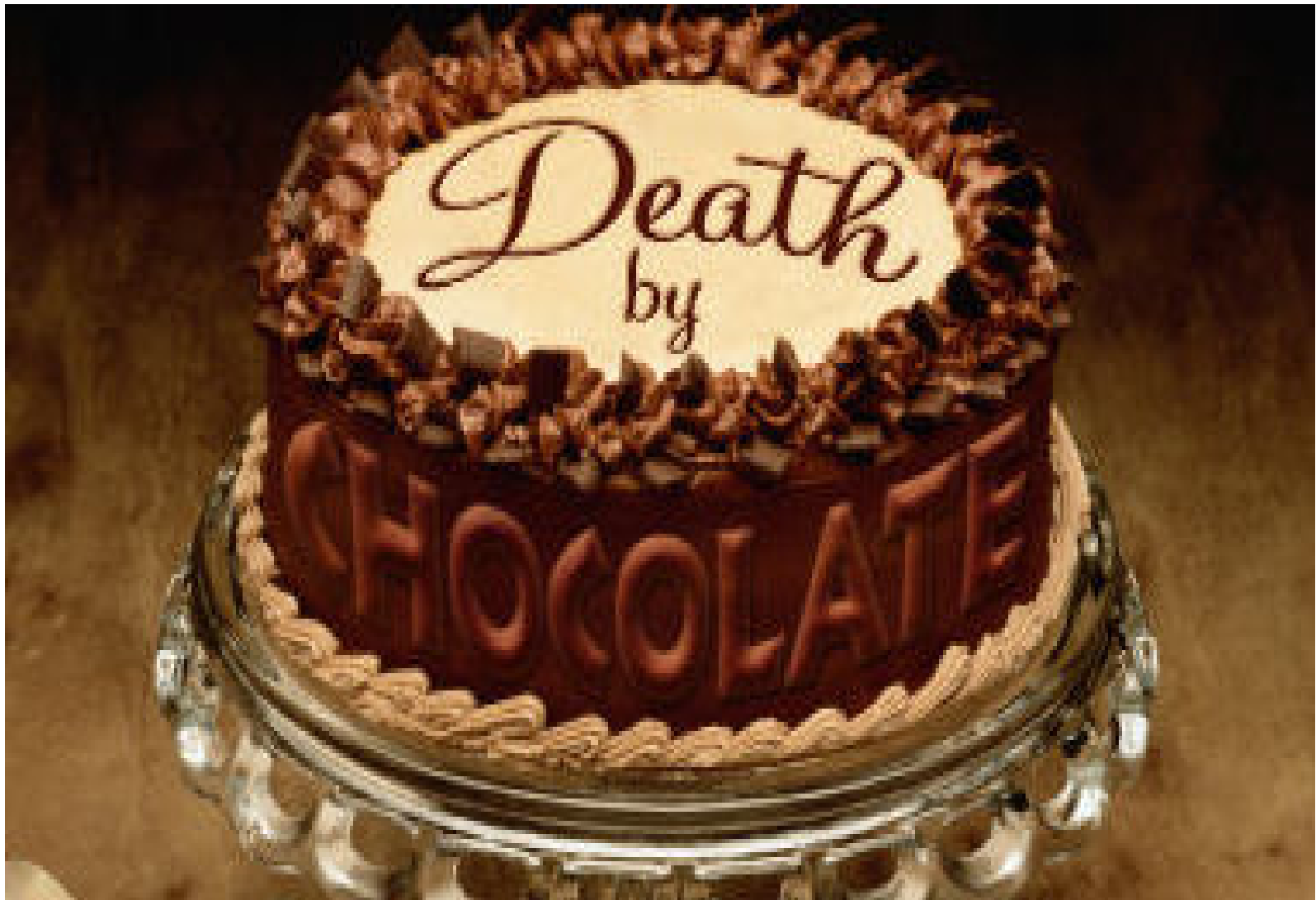




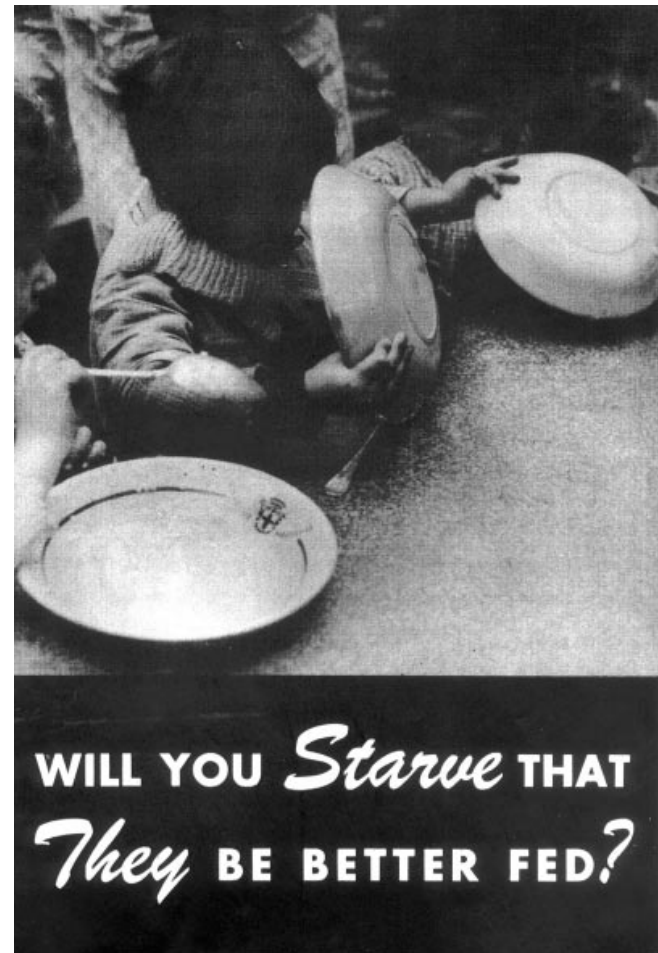
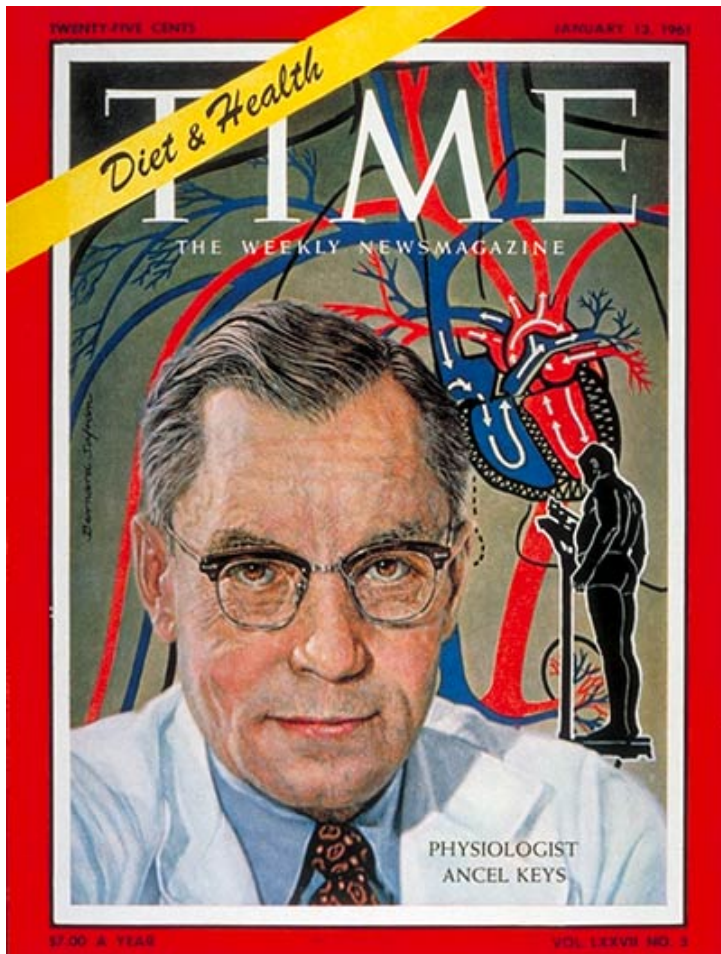
## BACKGROUND

Liberation of concentration camps  
after WWII





# Ansel Keys - Minnesota Experiment



# Minnesota Experiment



FIGURE 2 *Life* magazine photograph of conscientious objectors during starvation experiment. July 30, 1945. Volume 19, Number 5, p. 43. Credit: Wallace Kirkland/Time Life Pictures/Getty Images.

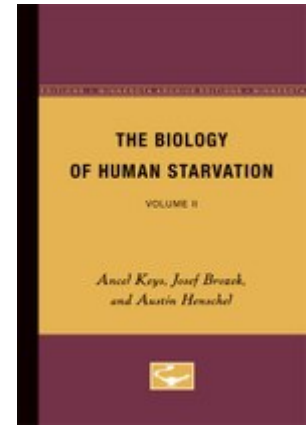
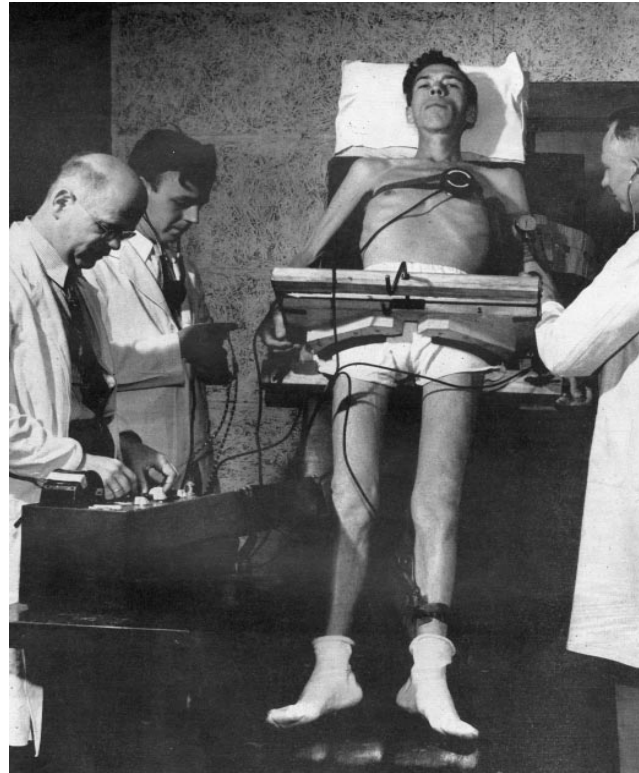


FIGURE 8.6. Minnesota volunteers after weight loss. Photo by Wallace Kirkland. Copyright 1950 by Life-Time-Warner.





**FIGURE 8.5.** Minnesota volunteers at mealtime. Copyright 1950 by the University of Minnesota Press. Reprinted by permission.



# Minnesota Experiment - findings

- 32 men completed the study
- 25% weight loss over 24 wks
- Apathy, depression, food obsession
- Refeeding – oedema, arrhythmias
- Biochemical changes
- Albumin – 39g/l
- What changes occur in starvation?





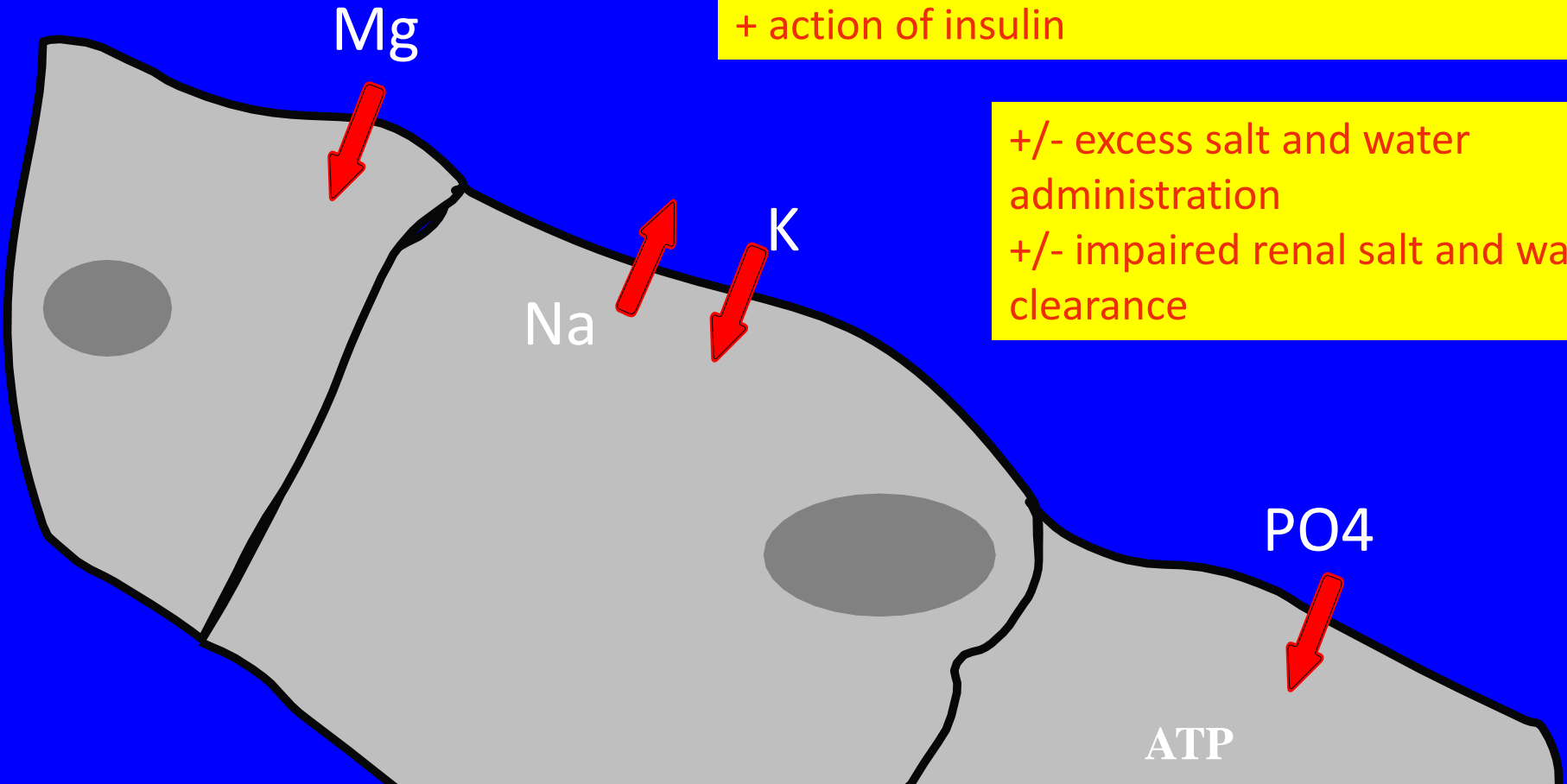
# Starvation

- ↓ Circulating insulin
- Catabolism
- Impaired cardiac and renal reserve
- ↓ Cell membrane pump activity
- Intracellular depletion of K, Mg, PO<sub>4</sub>
- ↑ intracellular Na and water
- Depletion of water soluble vitamins
  - » ↓ thiamine & other B vitamins

# THE REFEEDING SYNDROME

Restoration of trans-membrane pumps  
+ action of insulin

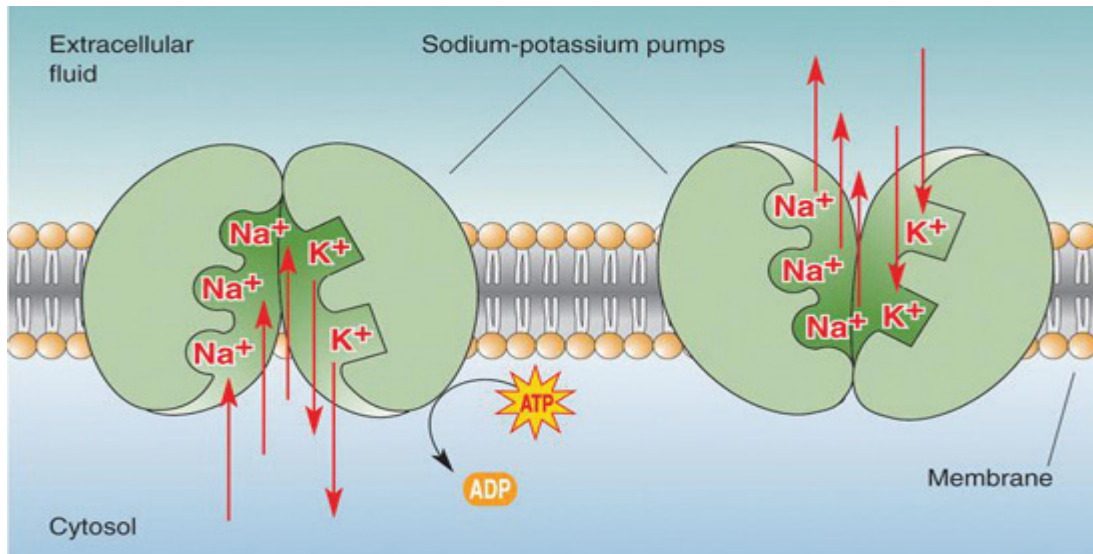
+/- excess salt and water  
administration  
+/- impaired renal salt and water  
clearance



= acute circulatory overload  
Severe electrolyte abnormalities with drop in K, Mg & PO4  
Cardiac Rhythm disturbances  
Death

# Cell Membrane Pumps

- What percentage of REE is accounted for by cell membrane pumps?



- 37%

# How much total body potassium?

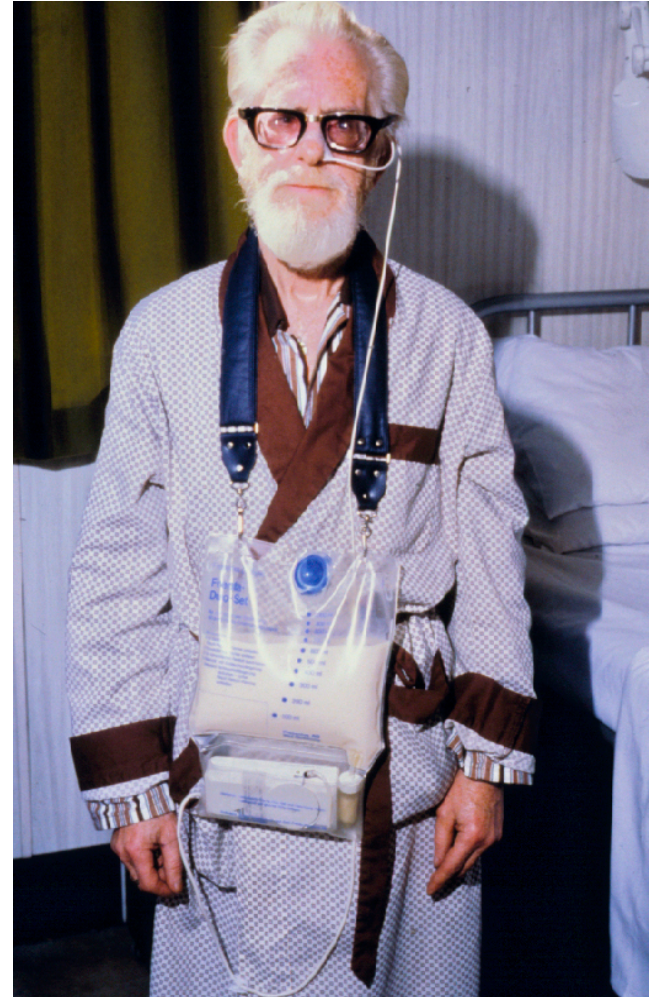
- 45 – 50mmol/kg
- 70kg 3500mmol
- 98% intracellular 3430mmol
- 3.4mols

# Effects of electrolyte abnormalities

<u>Electrolytes</u>	<u>Consequence</u>
↓ PO <sub>4</sub>	Acute ventilatory failure Arrhythmias Confusion Congesive heart failure Lethargy, weakness Rhabdomyolysis
↓ K <sup>+</sup>	Arrhythmias Cardiac arrest Constipation / ileus Polyuria / polydipsia Respiratory depression Weakness
↓ Mg <sup>2+</sup>	Anorexia Arrhythmias Confusion Diarrhoea / constipation Weakness

# Thiamine and refeeding (thiamin?)

- Water soluble
- Quickly depleted
- Carbohydrate metabolism
- Kreb's Cycle cofactor
- Feeding
- Lactic acidosis
- Wernike-Korsakoff Syndrome



# Wernicke-Korsakoff

- Apathy and disorientaion
- Nystagmus – eye movement disorders
- Ataxia
- Severe impairment of short term memory often with confabulation
- Treatment – high dose i.v B vitamins



# Prevalence

10% → Gastrointestinal fistulae *Fan et al (2004) Nutrition, 20, 346*

14% → Elderly (age  $\geq 65$ ) *Kagansky et al (2005) J Intern Med, 257: 461*

25% → Cancer *Gonzalez et al (1996) Nutr Hosp, 11:98*

48% → Malnourished *Hernandez-Aranda et al (1997) Rev Gastroenterol Mex, 62: 260*

28% → Anorexia nervosa *Ornstein (2003) Adolesc Health, 32: 83*



# Biochemical vs Symptomatic RFS

## Biochemical RFS

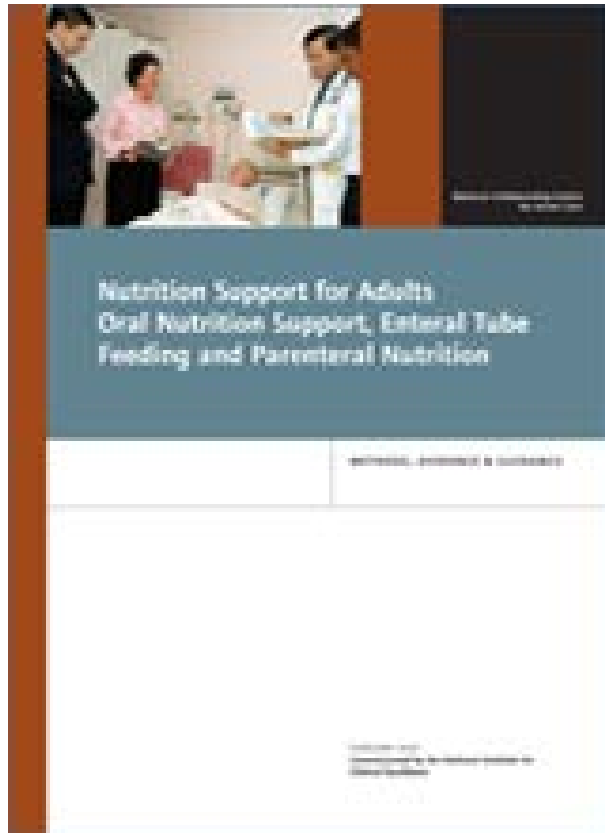
- ↓ potassium
- ↓ magnesium
- ↓ phosphate

## Symptomatic RFS

- Oedema
- Acute circulatory overload
- Disturbance to organ function
- Respiratory failure
- Cardiac failure
- Wernicke- Korsakoff
- Nystagmus (Stanga 2008)
- **Death** *Weinsier RL & Krumdieck CL. Am J Clin Nutr 1981; 34: 393-99*



# Refeeding Guidelines



European Journal of Clinical Nutrition (2008) 62, 687-694  
© 2008 Nature Publishing Group All rights reserved 0954-3007/08 \$30.00  
www.nature.com/ejcn

## REVIEW

### Nutrition in clinical practice—the refeeding syndrome: illustrative cases and guidelines for prevention and treatment

Z Stanga<sup>1,2</sup>, A Brunner<sup>1,3</sup>, M Leuenberger<sup>2</sup>, RF Grimble<sup>3</sup>, A Shenkin<sup>4</sup>, SP Allison<sup>5</sup> and DN Lobo<sup>5</sup>

<sup>1</sup>Department of Internal Medicine, University Hospital, Bern, Switzerland; <sup>2</sup>Clinical Nutrition Team, Division of Endocrinology, Diabetes and Clinical Nutrition, University Hospital, Bern, Switzerland; <sup>3</sup>Institute of Human Nutrition, Faculty of Medicine, Health and Life Sciences, University of Southampton, Southampton, UK; <sup>4</sup>Division of Clinical Chemistry, Faculty of Medicine, University of Liverpool, Liverpool, UK and <sup>5</sup>Division of Gastrointestinal Surgery, Wolfson Digestive Diseases Centre, Nottingham University Hospitals, Queen's Medical Centre, Nottingham, UK

# NICE CG32 Criteria

Box 1 Criteria for determining people at high risk of developing refeeding problems Patient has one or more of the following:

- **BMI less than 16 kg/m<sup>2</sup>**
- **unintentional weight loss greater than 15% within the last 3–6 months**
  - **little or no nutritional intake for more than 10 days**
- **low levels of potassium, phosphate or magnesium prior to feeding.**

Or patient has two or more of the following:

- **BMI less than 18.5 kg/m<sup>2</sup>**
- **unintentional weight loss greater than 10% within the last 3–6 months**
  - **little or no nutritional intake for more than 5 days**
- **a history of alcohol abuse or drugs including insulin, chemotherapy, antacids or diuretics.**

# Could we use urinary ketones?



# What to give Patients at High Risk of Developing Refeeding Problems

- Prescription for people at high risk of developing refeeding problems – consider: **D(GPP)**
  - starting nutrition support at a maximum of 10 kcal/kg/day, increasing levels slowly to meet or exceed full needs by 4–7 days
  - using only 5 kcal/kg/day in extreme cases
  - restoring circulatory volume and monitoring fluid balance and overall clinical status closely
  - providing immediately before and during the first 10 days of feeding: oral thiamin 200–300 mg daily, vitamin B co strong 1 or 2 tablets, three times a day (or full dose daily intravenous vitamin B preparation, if necessary) and a balanced multivitamin/trace element supplement once daily
  - providing oral, enteral or intravenous supplements of potassium (likely requirement 2–4 mmol/kg/day), phosphate (likely requirement 0.3–0.6 mmol/kg/day) and magnesium (likely requirement 0.2 mmol/kg/day intravenous, 0.4 mmol/kg/day oral) unless pre-feeding plasma levels are high. Pre-feeding correction of low plasma levels is unnecessary.

# Problems with guidelines?

- Does starting at 5 -10kcal/kg compound malnutrition?
- 50 kg patient – target 30kcal/kg = 1500kcal
- Daily increments 5,10,20,30kcal/kg
- 7,750 kcal in first week
- Daily increments 20, 30kcal/kg
- 10,000kcal in first week

# Problems with guidelines

- Deficit 2,250kcal = 350g adipose tissue
- Give adequate electrolytes and build up quickly  $\leq 4$  days
- Dietitians often reluctant to increase feed while electrolyte levels low.
- Is this a mistake?

# Barriers to electrolytes

- 70kg patient
- 2 – 4mmol K = 140 – 280mmol
- 12 – 24 tablets Sando K
- 1/3 multi-chamber PN bag with 400mmol K
- What if the whole bag is given by accident?
- No compounding unit?
- 5% Dextrose 200kcal/l
- Normal saline 154mmol Na and Cl

# Adverse Effects of 0.9% NaCl Lobo and Awad, *Kidney International* 2014 86(6): 1096–1105

Metabolic	<b>Hypoalbuminaemia Lobo et al 2001</b>
Body water	<ul style="list-style-type: none"><li>• Possible damage to the endothelial glycocalyx</li><li>• ↑ Interstitial fluid volume leading to edema</li></ul>
Renal	<ul style="list-style-type: none"><li>• Renal edema and capsular stretch leading to intrarenal tissue hypertension</li><li>• Renal vasoconstriction, ↓ renal blood flow and renal tissue perfusion</li><li>• ↓ Glomerular filtration rate, urine volume, and sodium excretion</li></ul>
Gastrointestinal	<ul style="list-style-type: none"><li>• Gastrointestinal edema, intestinal stretch</li><li>• Ileus, impaired anastomotic healing</li></ul>
Hematological	<ul style="list-style-type: none"><li>• ↑ Intraoperative blood loss</li><li>• ↑ Need for blood product transfusion</li></ul>
Clinical outcomes	<ul style="list-style-type: none"><li>• ↑ Postoperative complications</li><li>• ↑ Mortality</li><li>• ↑ Incidence of acute kidney injury and need for renal replacement therapy</li></ul>

# Who looks after these patients?

- People at high risk of developing refeeding problems should be cared for by healthcare professionals who have skills and training and expert knowledge of nutritional requirements and nutrition support.

D(GPP)



**DOOGIE HOWSER, M.D.**

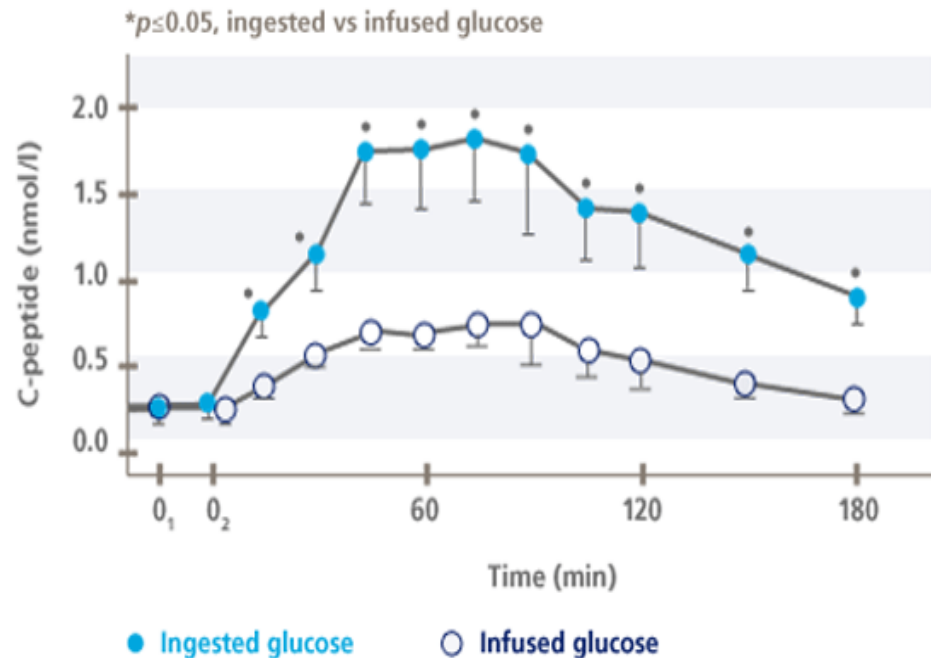


We have hospital policies for correction of electrolytes based on plasma levels and standard doses!!



# Are all routes equal?

- Enteral feeding higher risk than parenteral Zeki, Gabe, Culkin and Nightingale, Clinical Nutrition 2011,30 (3), 365–368
- Incretin effect
- GLP 1, GIP



Jejunal feeding is followed by a greater rise in plasma cholecystokinin, peptide YY, glucagon-like peptide 1, and glucagon-like peptide 2 concentrations compared with gastric feeding in vivo in humans: a randomized trial<sup>1,2</sup>

Joanna Luttikhoud,<sup>3,4\*</sup> Klaske van Norren,<sup>6</sup> Herman Rijna,<sup>7</sup> Nikki Buijs,<sup>4</sup> Marjolein Ankersmit,<sup>4</sup> Annemieke C Heijboer,<sup>5</sup> Jeannette Gootjes,<sup>8</sup> Bolette Hartmann,<sup>9</sup> Jens J Holst,<sup>9</sup> Luc JC van Loon,<sup>10</sup> and Paul AM van Leeuwen<sup>4</sup>

**TABLE 3**

Plasma glucose, insulin, and C-peptide concentrations: baseline, peak value, time to peak, iAUC, and insulinogenic index after either gastric feeding ( $n = 11$ ) or jejunal feeding ( $n = 12$ )<sup>1</sup>

	Glucose, $\mu\text{mol/L}$		Insulin, $\text{pmol/L}$		C-peptide, $\mu\text{mol/L}$	
	NGT	NJT	NGT	NJT	NGT	NJT
Baseline, $\mu\text{mol}$ or $\text{pmol/L}$	$5.4 \pm 0.2$	$5.5 \pm 0.2$	$37 \pm 34$	$36 \pm 33$	$0.38 \pm 0.1$	$0.36 \pm 0.1$
<u>Peak value, <math>\mu\text{mol}</math> or <math>\text{pmol/L}</math></u>	$7.0 \pm 0.2$	$7.2 \pm 0.2$	<u><math>326 \pm 54</math></u>	<u><math>392 \pm 53^*</math></u>	$1.2 \pm 0.1$	$1.2 \pm 0.1$
Time to peak, min	$194 \pm 85$	$297 \pm 80$	$174 \pm 68$	$162 \pm 63$	$185 \pm 85$	$311 \pm 80$
iAUC, $\mu\text{mol}$ or $\text{pmol/L} \cdot 720 \text{ min}$	$402 \pm 82$	$456 \pm 78$	$89 \pm 16$	$94 \pm 15$	$295 \pm 44$	$270 \pm 43$
Insulinogenic index, $T = 30 \text{ min}$	—	—	$105 \pm 21$	$102 \pm 20$	—	—

<sup>1</sup>All values are means  $\pm$  SEMs. \*Significantly different compared with gastric feeding,  $P < 0.05$ . iAUC, incremental AUC; NGT, nasogastric tube; NJT, nasojejunal tube.

Am J Clin Nutr 2016;103:435–43

# Order of RFS Risk?

1. Jejunal
  2. Gastric
  3. Parenteral
- Does this this have clinical implications?
  - Case scenarios

