Short bowel syndrome:
Treatment at any length

Dr Simon Gabe

St Mark's Hospital, London

The Lennard-Jones Intestinal Failure Unit

St Mark's Hospital

Imperial College London

Overview

Definition, types & causes of IF

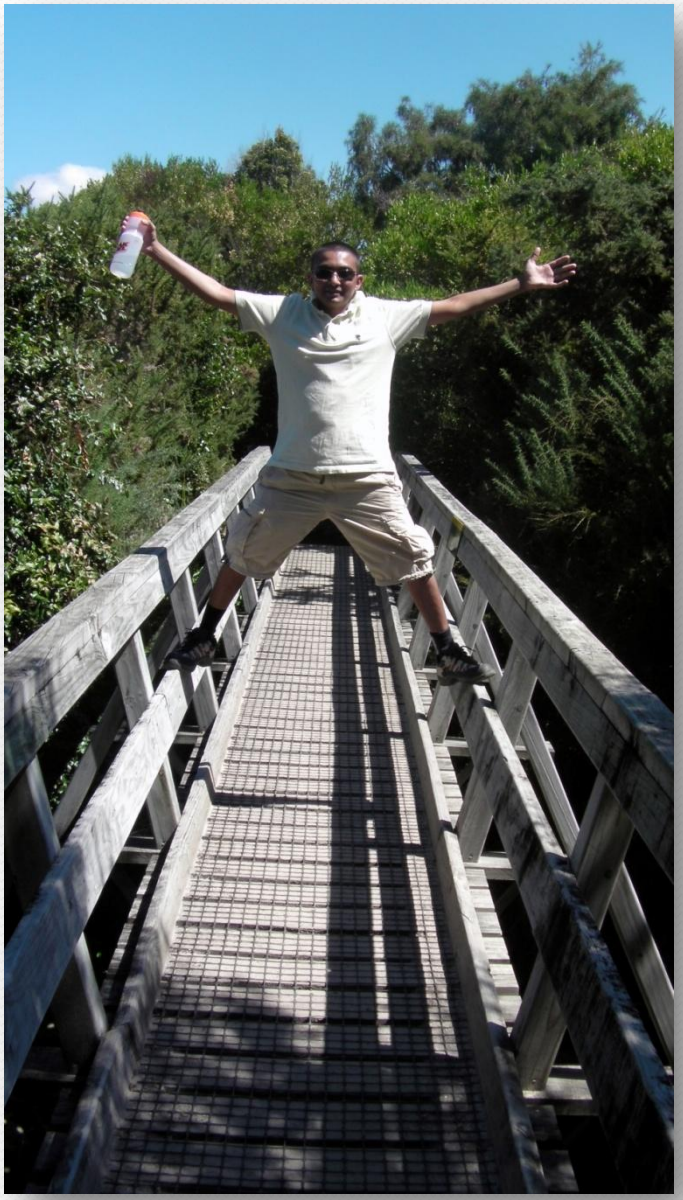
Physiology of SBS

Medical management

- Correct fluid management
- Pharmacological approaches
- Diet & enteral feeding

Emerging therapies

- Enteroclysis & fistuloclysis
- Intestinal lengthening
- GLP2 analogues
- Intestinal transplantation



Intestinal Failure: Definition

The reduction of functioning gut mass to below the minimum necessary for the absorption of nutrients and/or water & electrolytes

Nightingale, 2001

Fleming & Remington, 1981

Types of Intestinal Failure

Type 1

SHORT TERM

- Self-limiting intestinal failure
- Acute post-op ileus

Type 2

MEDIUM TERM

- Significant & prolonged PN support (>28 days)
- GI surgery complicated by EC fistulation

Type 3

LONG TERM

- Chronic IF (long term PN support)
- Short bowel syndrome
- Motility disorder

Lal et al. *AP&T 2006:*24;19-31

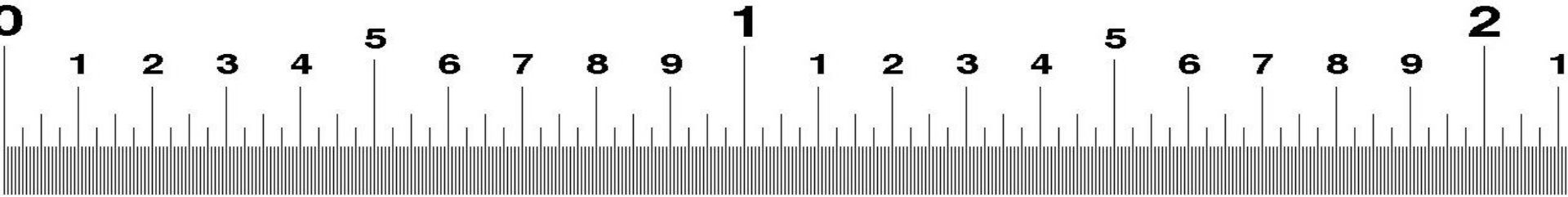
Causes of Short Bowel Syndrome

Group	Common	Uncommon
Small intestinal resections	Crohn's disease	Post irradiation enteritis
		Repeated surgery for surgical comps
Massive intestinal resection	Infarction (SMA/SMV thrombosis)	SMA embolus
		Massive volvulus
		Desmoid tumour
EC fistula	High output	
Bypass surgery		Gastric bypass (obesity)

Paediatric causes: NEC, gastroschisis, intestinal atresia

Short Bowel Syndrome

How long is the normal small bowel?



Variability of intestinal length

- Small intestinal length at autopsy
  - Bryant (1924): 3-8.5m

- Small intestinal length at laparotomy

	n	mean (cm)	range (cm)
Cook (1974)	6	421	320-521
Backman (1974)	32	643	400-846
Slater (1991)	38	500	302-782

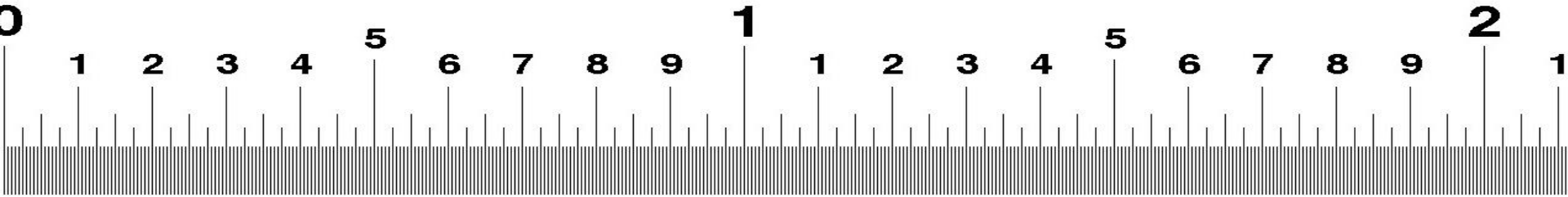
Short bowel syndrome: types

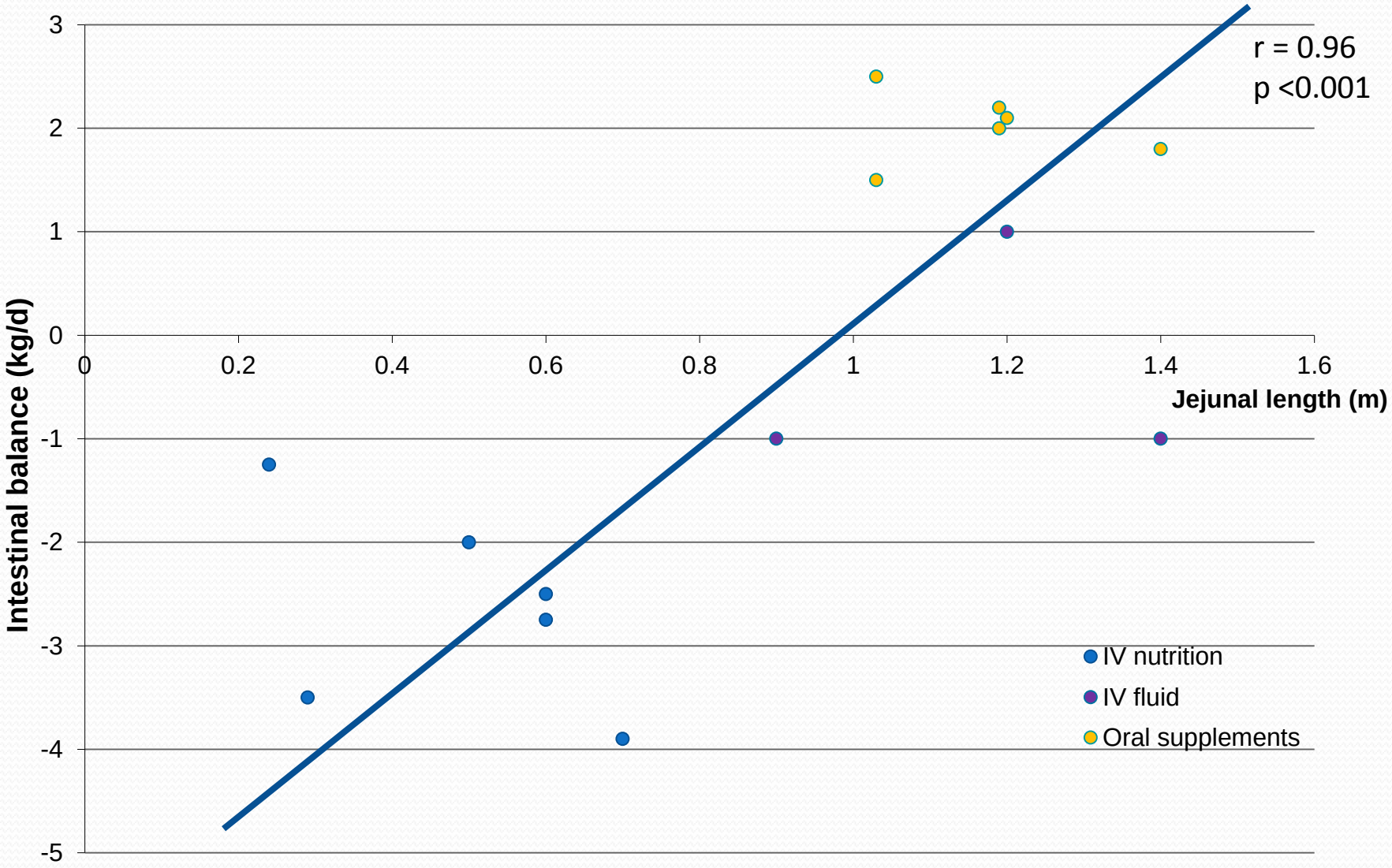
Mid small bowel resection	Jejuno-colic anastomosis	Jejunostomy or high output fistula
• Uncommon	• Usually fluid balance maintained	• Fluid balance – net secretors – net absorbers
• Rarely problems – Fluid balance – Nutrition	• Nutritional issues when jejunal length <100cm	• nutritional probs

Colonic digestion can salvage 700-950 kcal/day (carbohydrate fermentation & SCFA absorption)

Short bowel syndrome

What is the critical length of bowel that you need?

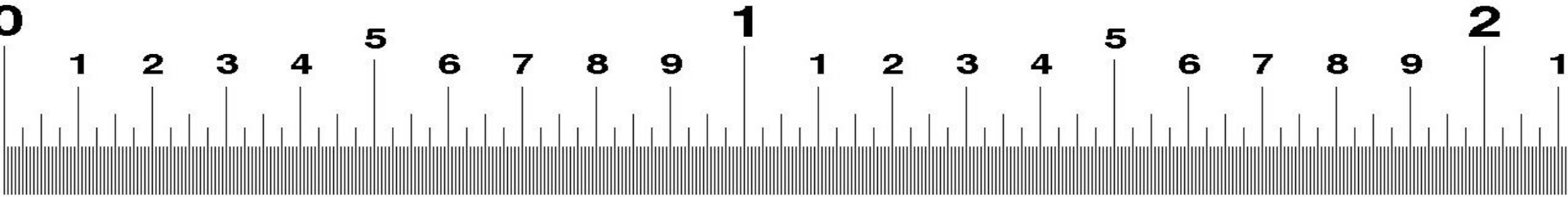




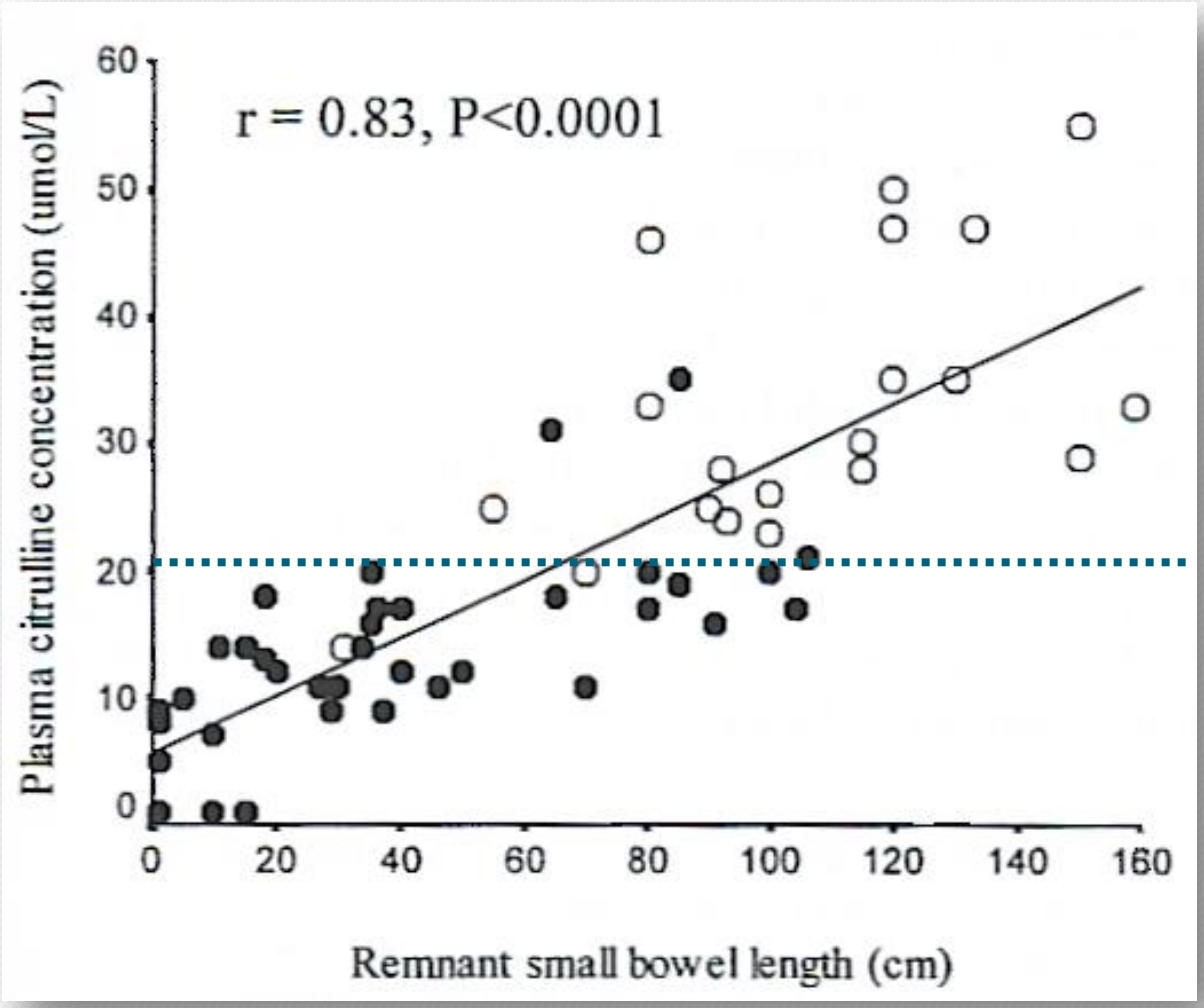
Nightingale, 1990

Length matters: critical lengths

SBS type	Critical SB length	Note
Jejunostomy or EC fistula	100 cm	More needed if diseased bowel
Jejunocolic anastomosis	Around 50 cm	Depends on amount of residual colon



Citrulline



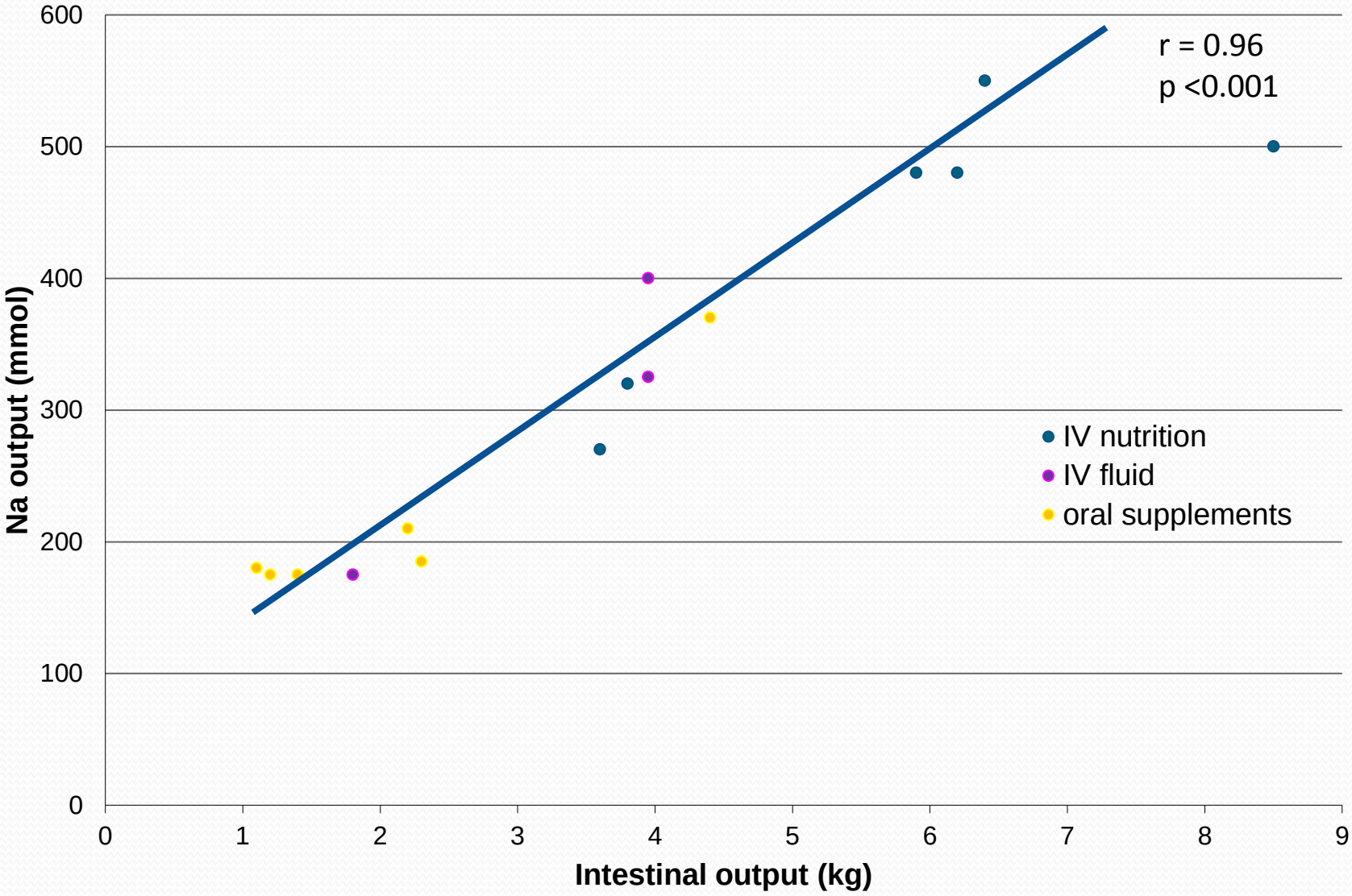
● Permanent IF
○ Transient IF

95% positive predictive value in distinguishing transient from permanent IF

Crenn P et al. Gastroenterology 2000; 119: 1496-1505

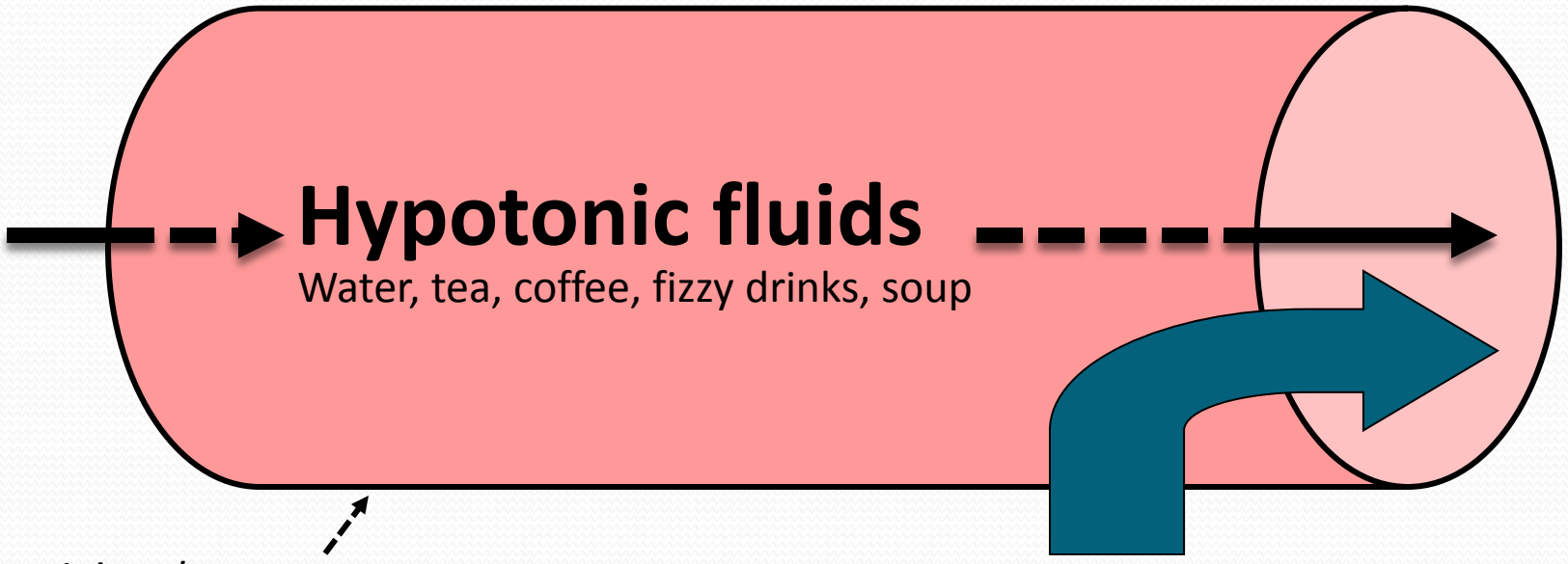
Short bowel syndrome

How much fluid does a patient need?



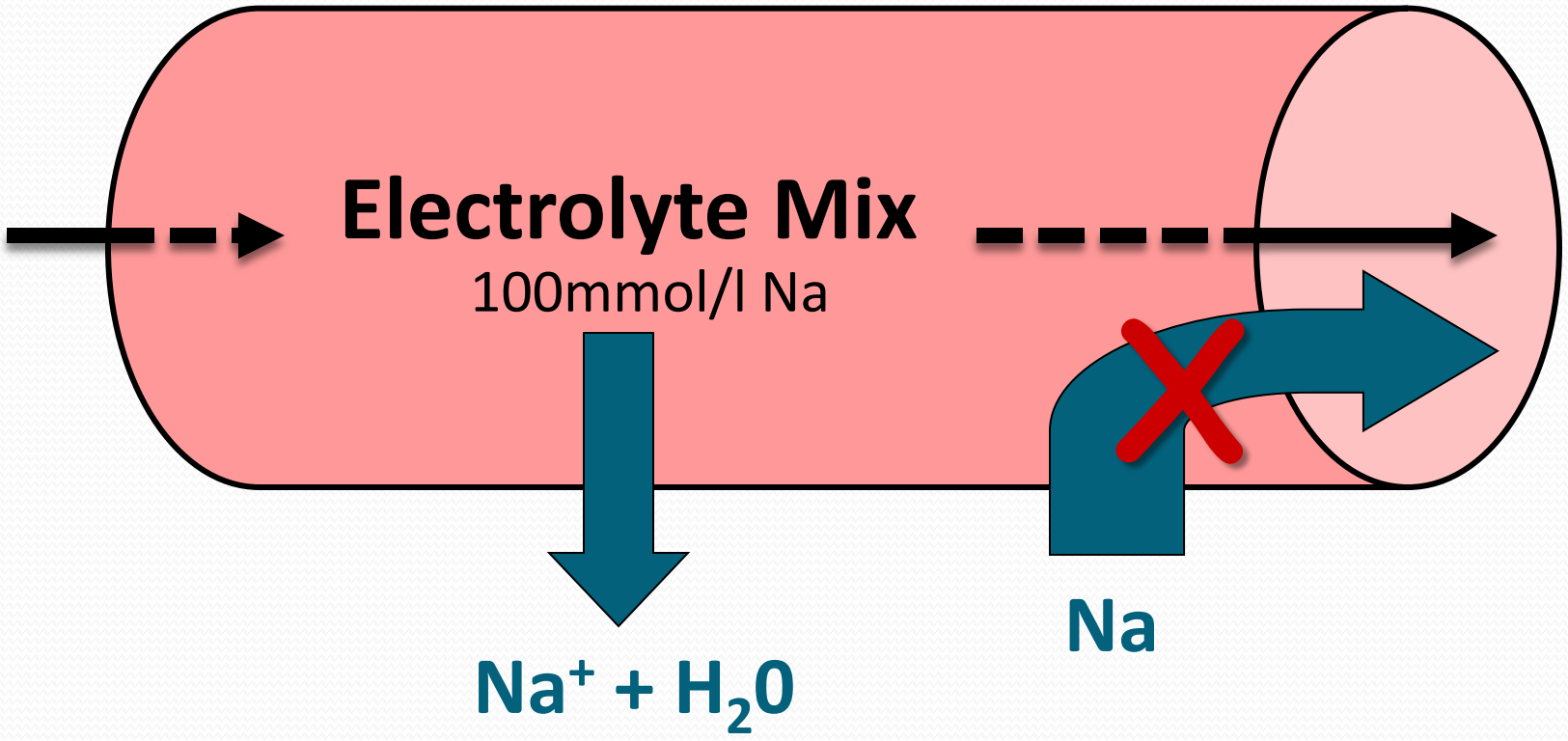
Nightingale, 1990

Jejunum


Hypotonic fluids
Water, tea, coffee, fizzy drinks, soup
Jejunal mucosa
Unable to maintain a Na gradient >30-40mmol/L
Na

Jejunum

Decreasing fluid losses & increasing absorption



Treatment: High Output State

Drink little hypotonic fluid	Maximum 1L/day
Drink a glucose-saline solution	Maximum 1L/day

	Na (mmol/l)	K (mmol/l)	Glucose (mmol/l)	Volume (ml)
WHO	90	20	111	1000
Electrolyte mix 	90	0	111	1000
Dioralyte	60	20	90	200

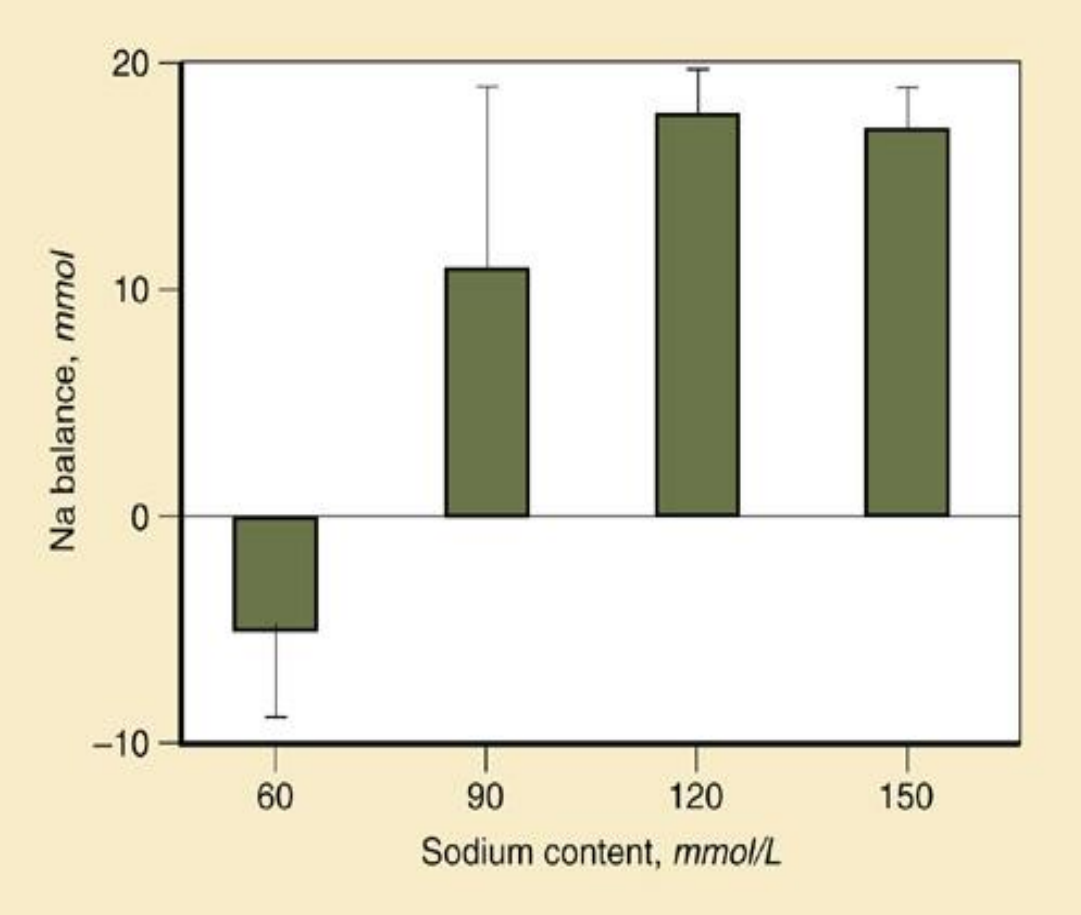
Oral hypertonic solutions

Water & sodium solutions <90mmol/L

- Negative Na balance[1]

Sodium solutions >90mmol/L

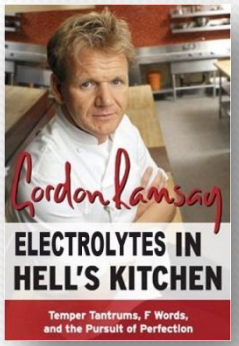
- Greater Na absorption
- But palatability an issue[2]



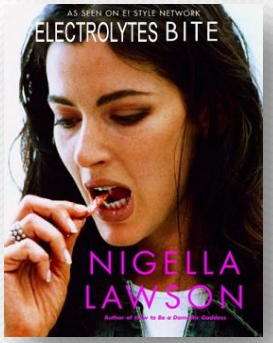
Rodrigues *et al*. (1988) Clin Sci;74:69P
Nightingale *et al* (1992) Gut; 33:759-761

E-mix recipe

Ingredient	Amount	Note
Glucose	20g	6 teaspoons
Salt	3.5g	1 level 5ml teaspoon
Sodium bicarbonate	2.5g	1 heaped 2.5ml teaspoon



Stir into 1L water & chill overnight
Enjoy the next day!

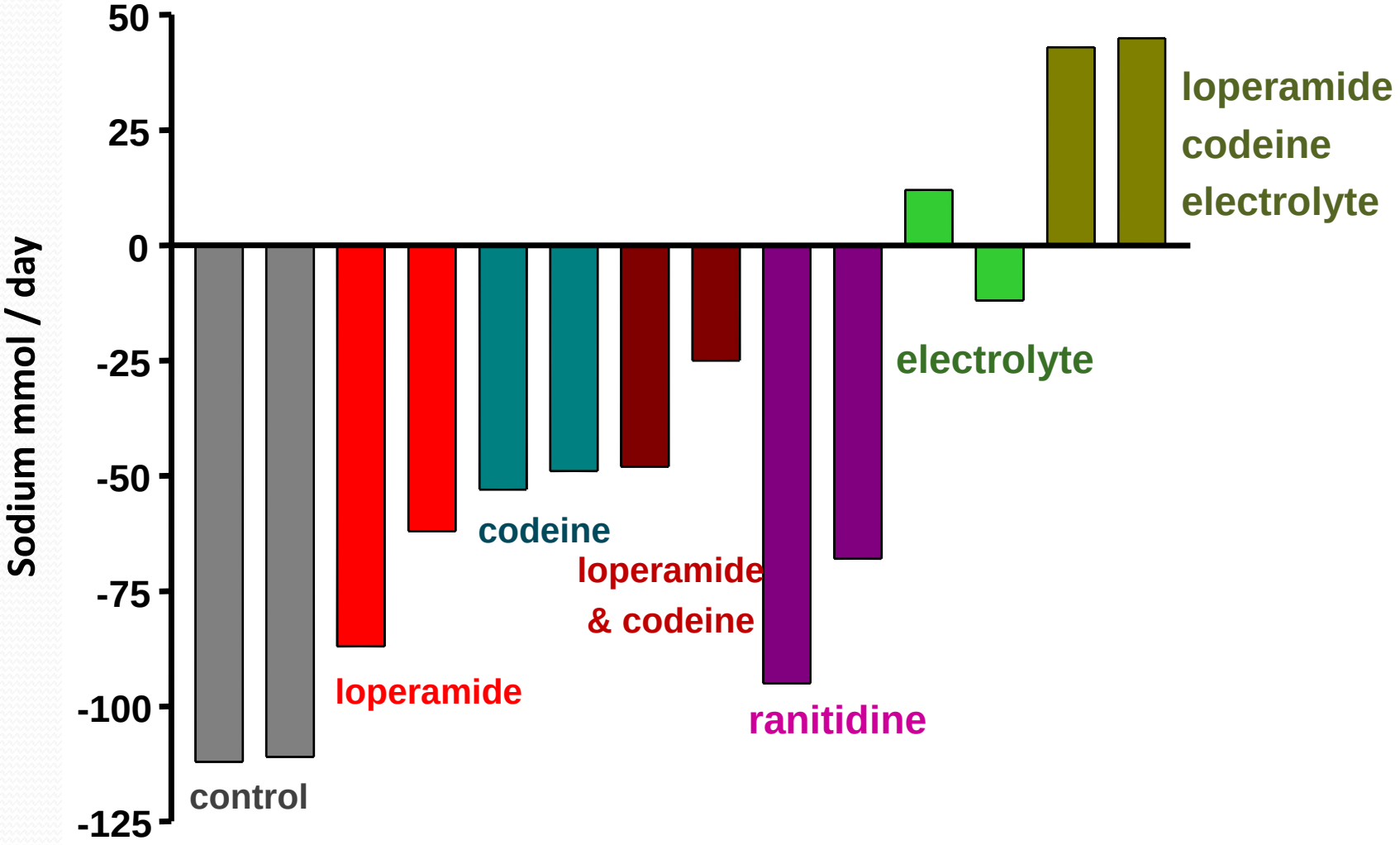


Treatment: High Output State

Drink little hypotonic fluid	Maximum 1L/day
Drink a glucose-saline solution	Maximum 1L/day

Drug therapy	Antimotility	Loperamide (up to 32mg QDS)
		Codeine phosphate (up to 60mg QDS)
	Antisecretory	Omeprazole (40mg BD)
		?Octreotide (50µg BD)
Magnesium supplements		Magnesium oxide Vitamin D
Nutrition		Low residue diet

Sodium Balance in Patient with Jejunostomy at 100 cm



Nightingale JMD et al. Clin Nutr 1992; 11: 101-5

Potassium & magnesium

Potassium

- Negative K balance when jejunum <50 cm
- Hyperaldosteronism in chronic Na deficiency

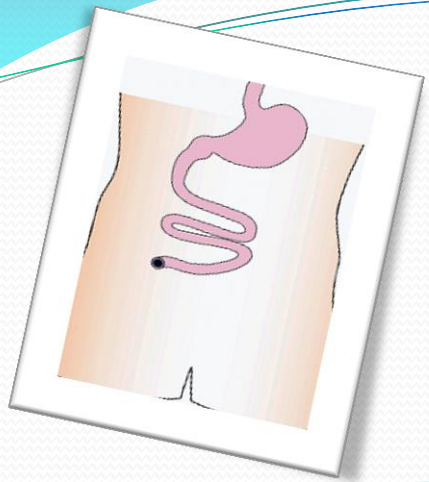
Magnesium

- Deficiency is common
  - 40% jejunum-colon pts
  - 70% jejunostomy pts
- No correlation between Mg balance & jejunal length

Parenteral fluids ± nutrition

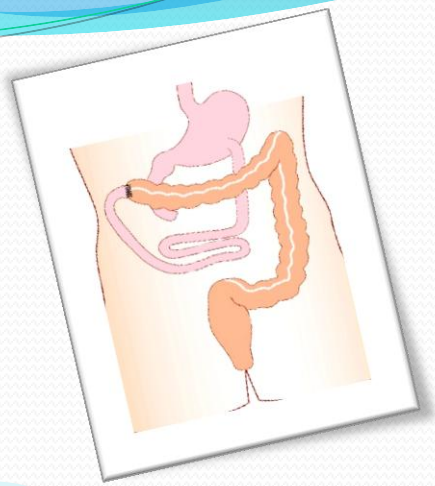
- Fluid & nutrition requirements are best considered separately
- “Standard IVN” bags will not be sufficient
- Bags need to be tailored to requirements
- Requirements alter daily until steady state

Random urine Na: best measure of dehydration



Gastric emptying

- ↑ with jejunostomy



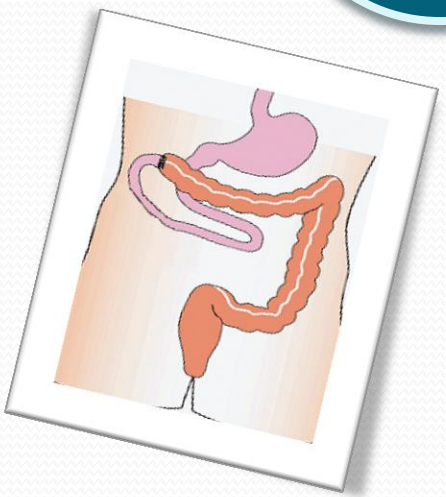
GI hormones

- ↑gastrin, ↑CCK, ↓PYY, ↓GLP-2

Physiological changes with SBS

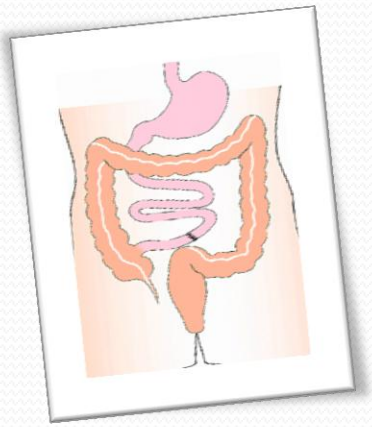
SB transit time

- ↓ with jejunostomy



↑Gastric secretions

- ↑gastric acid (hypergastrinaemia)



Recommended diet

Jejunostomy patients

Nutrient group	Amount	Note
Energy	High	30-60 kcal/kg/day
Protein	High	0.2-0.25g N_2/kg/day (80-100g protein)
Fat	High	
Fibre	Low	

Jejunocolic anastomosis

Nutrient group	Amount	Note
Energy	High	30-60 kcal/kg/day
Protein	High	0.2-0.25g N_2/kg/day (80-100g protein)
Fat	Low/moderate	according to degree of steatorrhoea
Fibre	Moderate/high	
Oxalate	Low	

Emerging therapies

Maximising GI function	Intestinal lengthening	Intestinal growth factors	Transplantation
Enteroclysis	Bianchi	Teduglutide (Revestive)	Intestinal
Fistuloclysis	STEP	Other growth factors	Modified multivisceral
			Multivisceral
			Abdominal wall

Maximising GI function

Fistuloclysis & enteroclysis

- Infusion of feed into distal limb of ECF or loop stoma
- Promotes intestinal adaptation before reconstructive surgery?
- Can replace IVN in selected patients




Fistuloclysis can successfully replace parenteral feeding in the nutritional support of patients with enterocutaneous fistula

A. Teubner, K. Morrison, H. R. Ravishankar, I. D. Anderson, N. A. Scott and G. L. Carlson

Intestinal Failure Unit, Department of Surgery, Hope Hospital, Salford, UK
Correspondence to: Mr G. L. Carlson, Department of Surgery, Hope Hospital, Salford M6 8HD, UK (e-mail: gcarlson@fs1.ho.man.ac.uk)

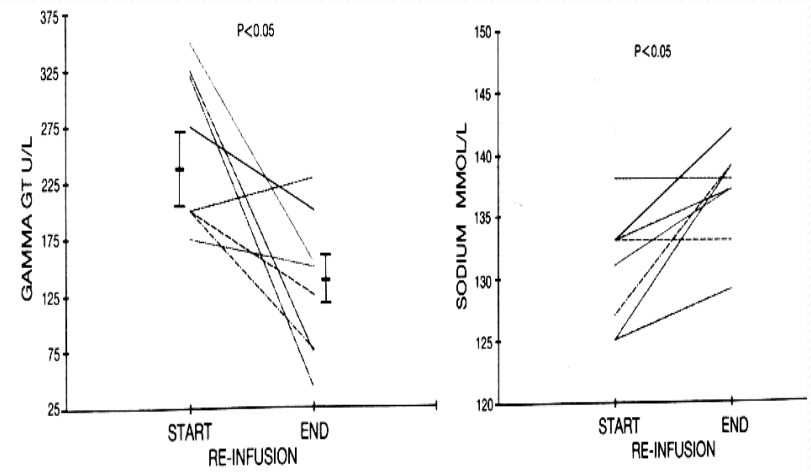
11/12 patients: fistuloclysis replaced PN

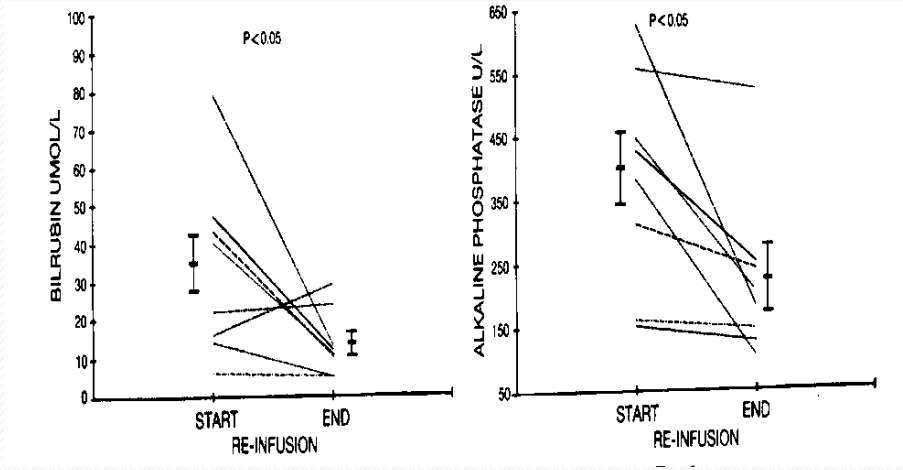
12 patients	Prox fistula output before fistuloclysis [median (range)]	1360 (690–3190) ml/day	
11 patients (successful fistuloclysis)	Time to stopping PN [median (range)]	28 (4–68) days	
	Prox fistula output before fistuloclysis [median (range)]	1170 (range 530–3440) ml/day	
	Change in prox fistula output with fistuloclysis (range)	↑ In 6 patients (40–330 ml/day)	↓ in 4 patients (290–1540 ml/day)
9 patients (reconstructive surgery)	Time to reconstructive surgery in (9/11 patients) [median (range)]	155 (range 19–422) days after starting fistuloclysis	

Teubner A et al. Br J Surg 2004; 91: 625-31

Reinfusion enteroclysis

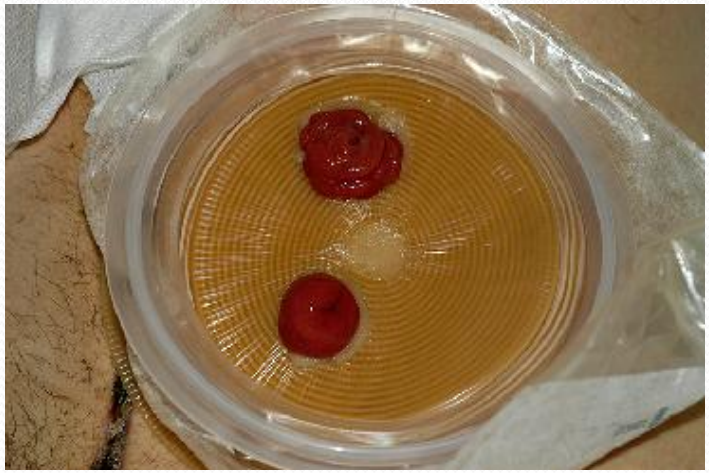
- Restoration of the enterohepatic cycle
- Possibly
  - Better absorption of nutrients
  - Prevent liver dysfunction & bacterial overgrowth





Rinsema *et al.* SGO 1988 167: 372-6

Reinfusion enteroclysis



Slide from: Prof Steven Damink, Maastricht University Medical Center

Bolus fistuloclysis / enteroclysis

- Do not need to meet nutritional requirements
- Not as difficult to perform
- Can use enteral feed/supplement or proximal effluent
- Possibly
  - Just as effective at maintaining GI integrity
  - Shorter recovery time after restorative surgery
  - Decreases post anastomotic complication rate

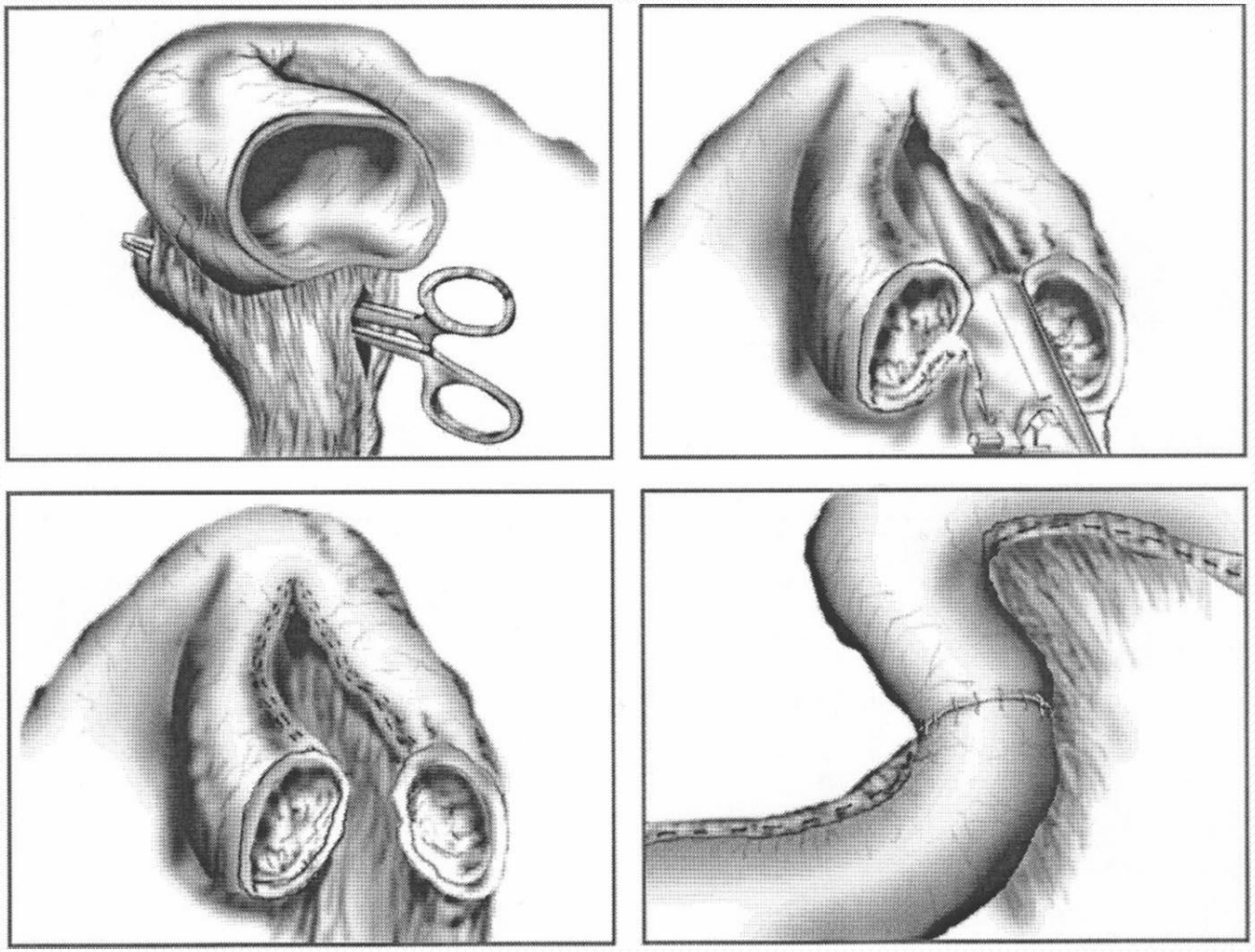
Caution (all forms of enteroclysis)

- ?patients with underlying mesenteric ischaemia

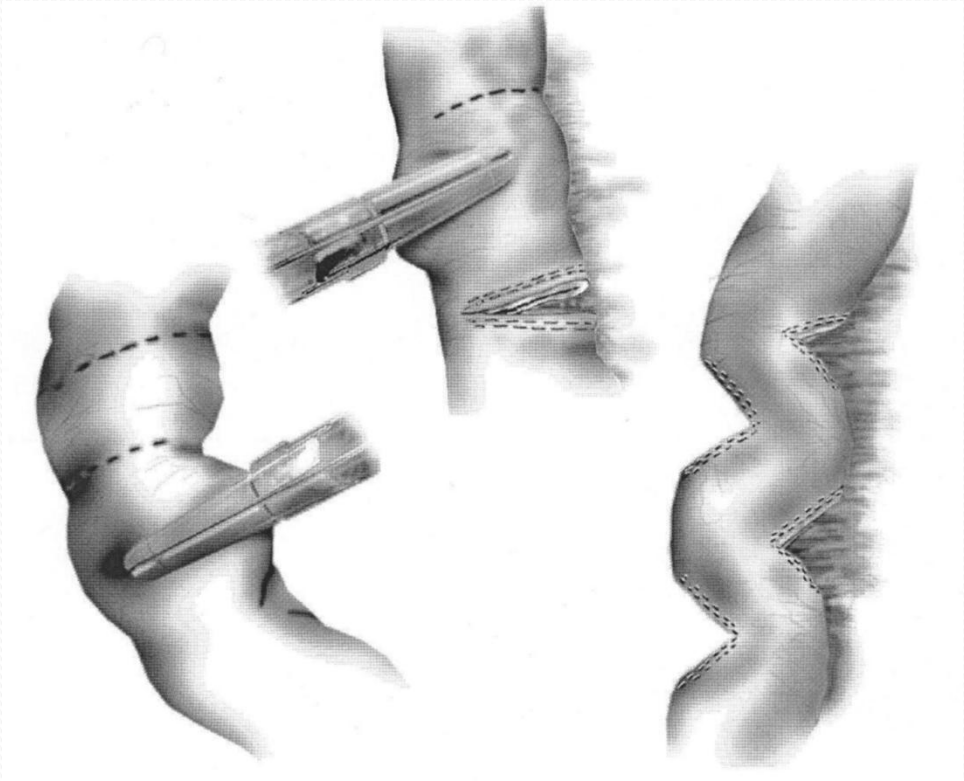
Emerging therapies

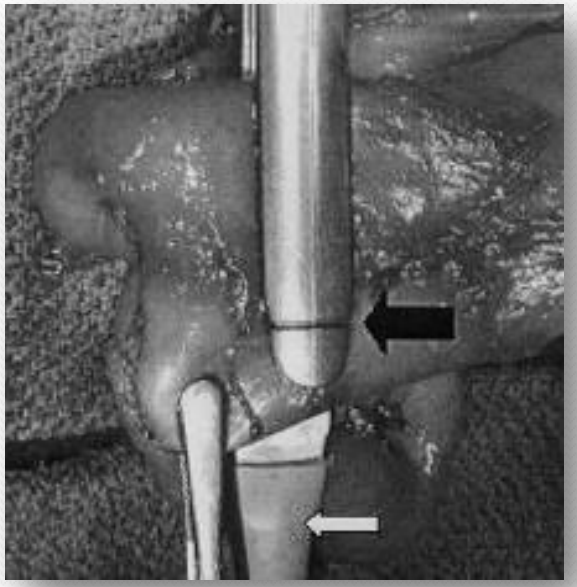
Maximising GI function	Intestinal lengthening	Intestinal growth factors	Transplantation
Enteroclysis	Bianchi	Teduglutide (Revestive)	Intestinal
Fistuloclysis	STEP	Other growth factors	Modified multivisceral
			Multivisceral
			Abdominal wall

The Bianchi technique



Serial transverse enteroplasty (STEP)



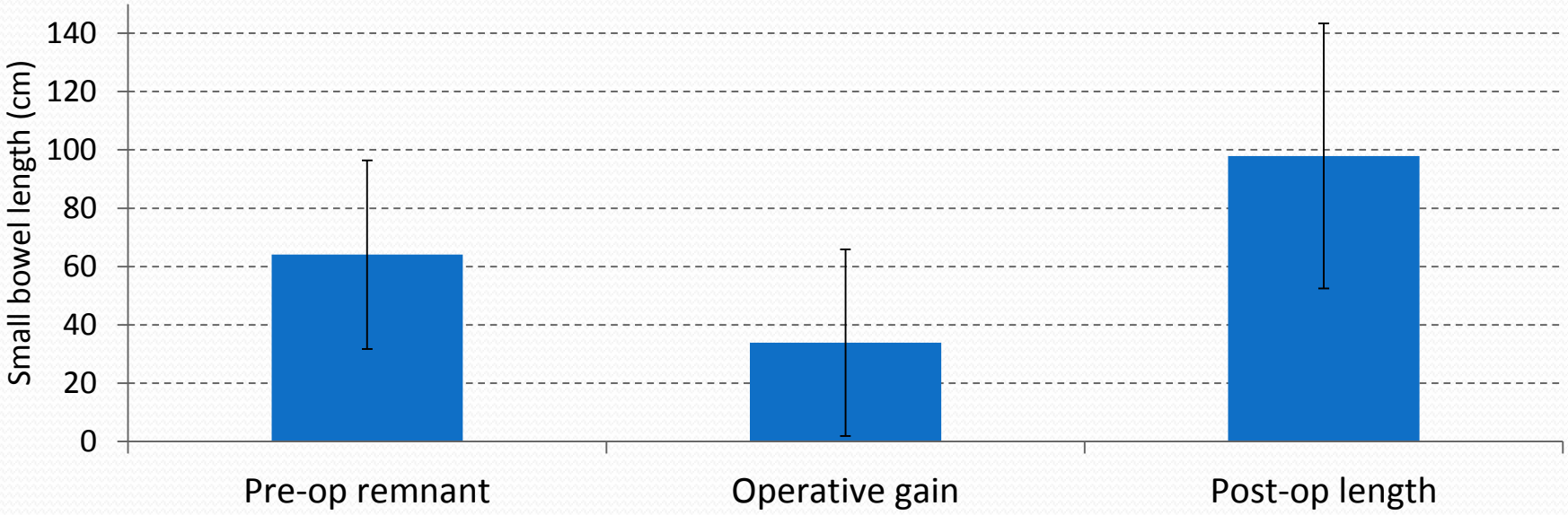


Intestinal lengthening

Retrospective case series

20 adults (6 Bianchi, 15 STEP)

Reason for surgery: 14 to wean off IVN, 6 for bacterial overgrowth



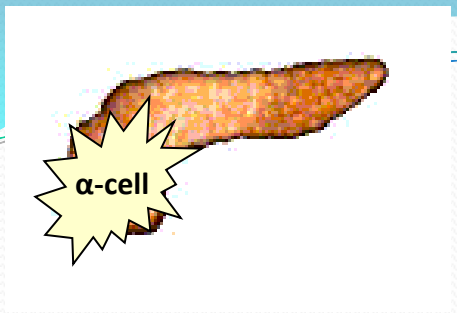
In the 14 patients to be weaned of IVN:

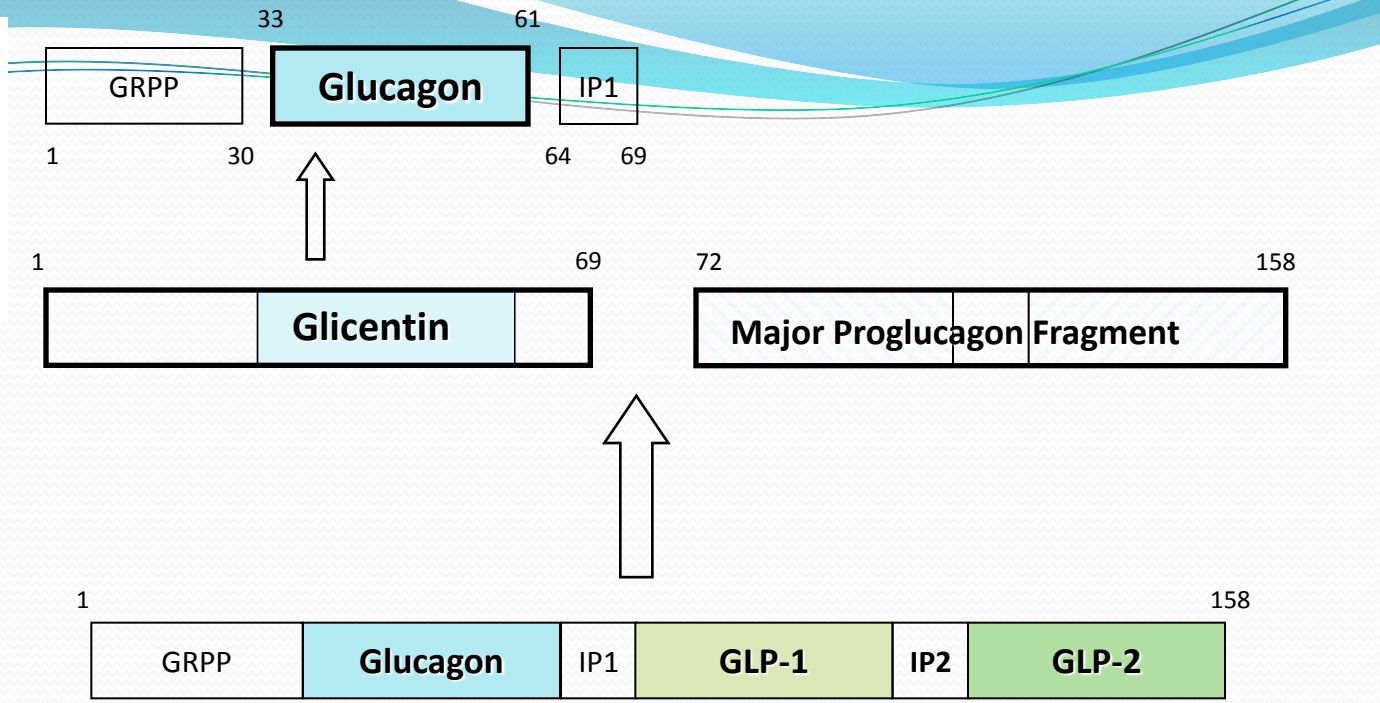
- 7 (50%) stopped after 2-25 months
- 2 (14%) died

Yannam GR et al. J Gastrointest Surg 2010;14:1931-6

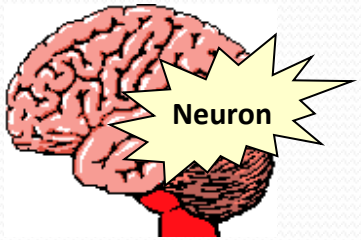
Emerging therapies

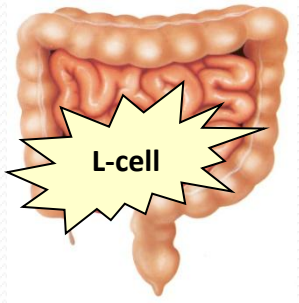
Maximising GI function	Intestinal lengthening	Intestinal growth factors	Transplantation
Enteroclysis	Bianchi	Teduglutide (Revestive)	Intestinal
Fistuloclysis	STEP	Other growth factors	Modified multivisceral
			Multivisceral
			Abdominal wall

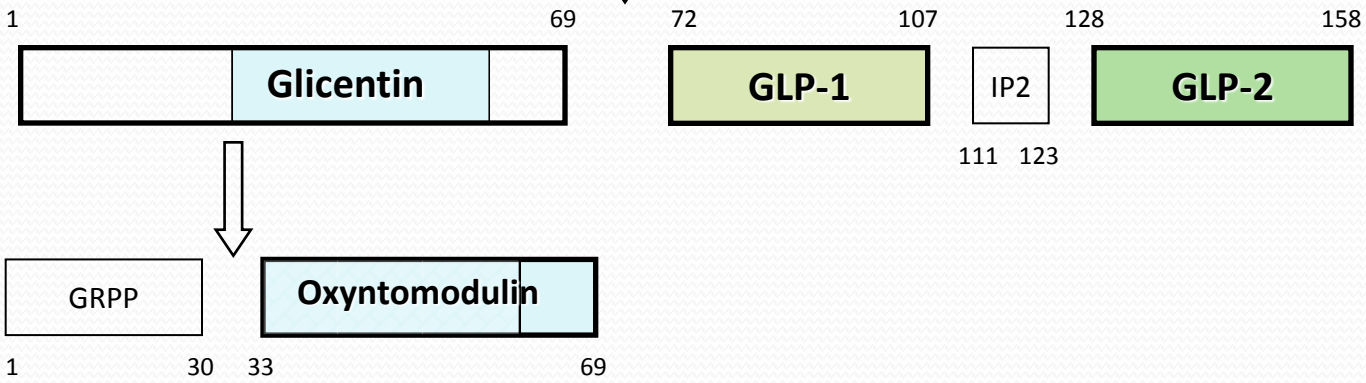




Proglucagon



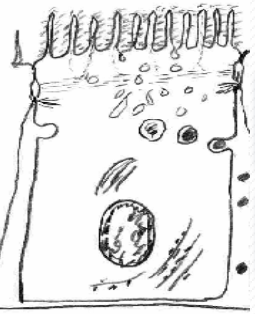




Glucagon-like Peptide 2

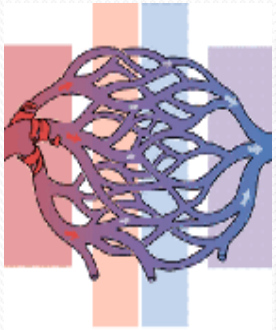
Naturally occurring 33 AA peptide

Production	Intestinal L cells (ileum & colon)
Release	stimulated by luminal nutrition
Receptors	Mainly in jejunum & proximal ileum
Action	Strong intestinotrophic properties



⇑ Mucosal proliferation

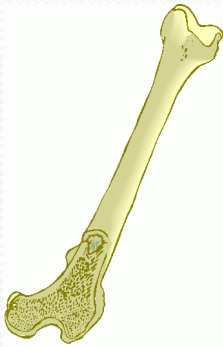
⇑ Nutrient absorption



⇑ Intestinal perfusion

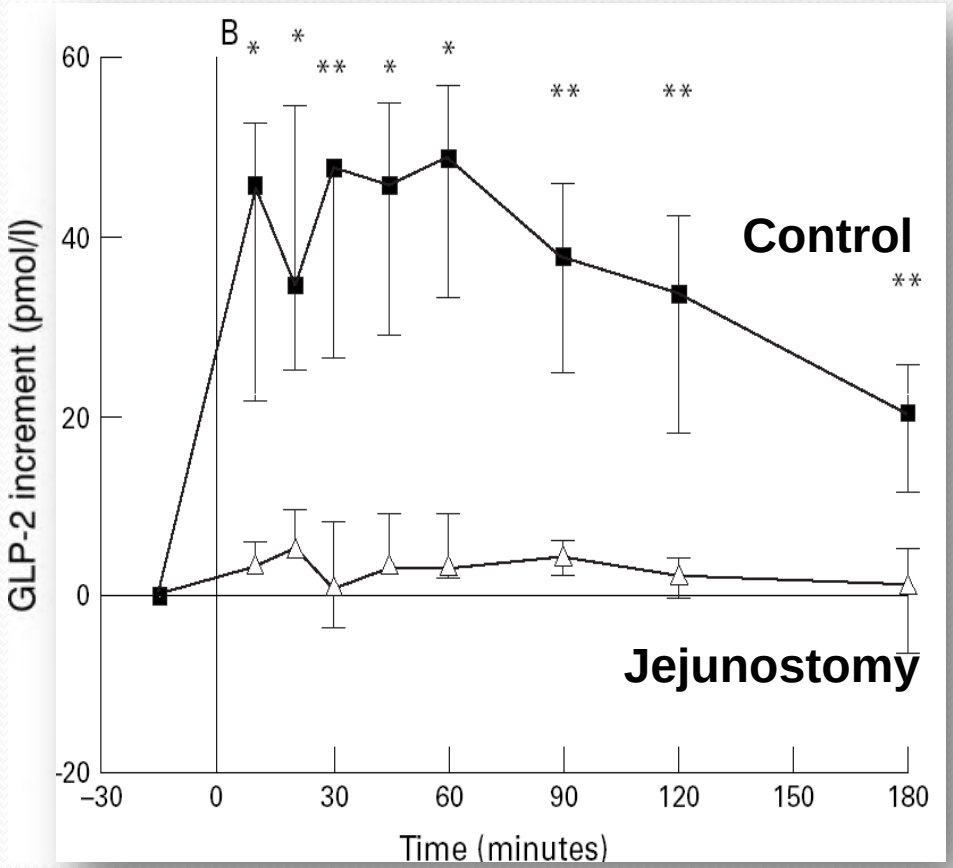
⇑ Cytoprotection

⇑ Bone density



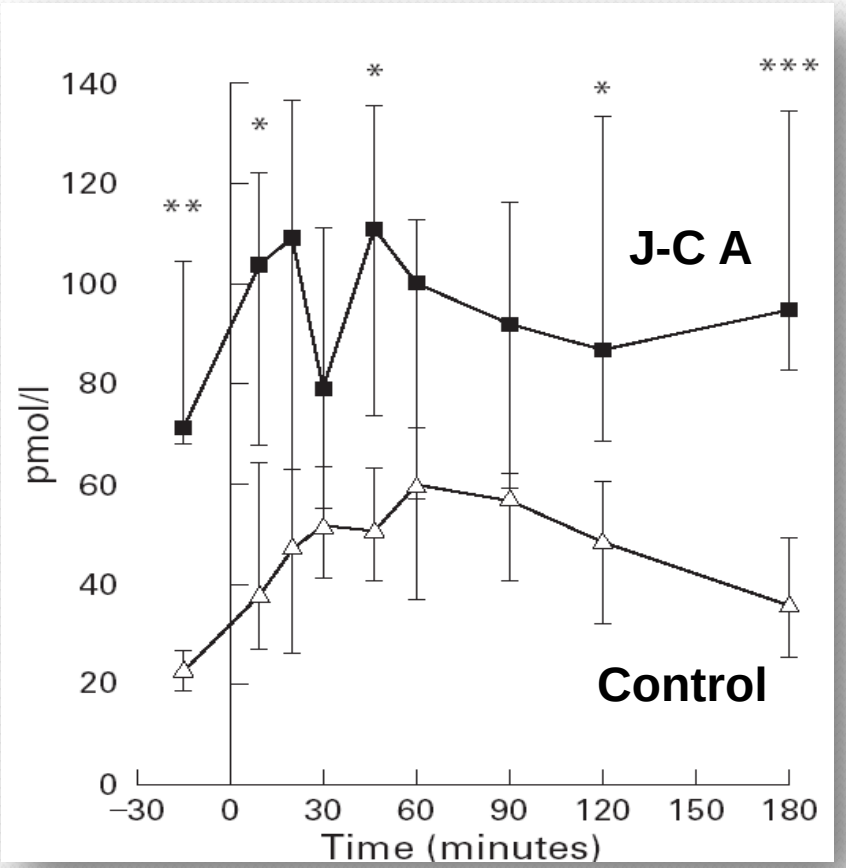
GLP-2 deficiency & SBS

Response to a meal



Jeppesen *et al*. 1999 Gut 45:559-563

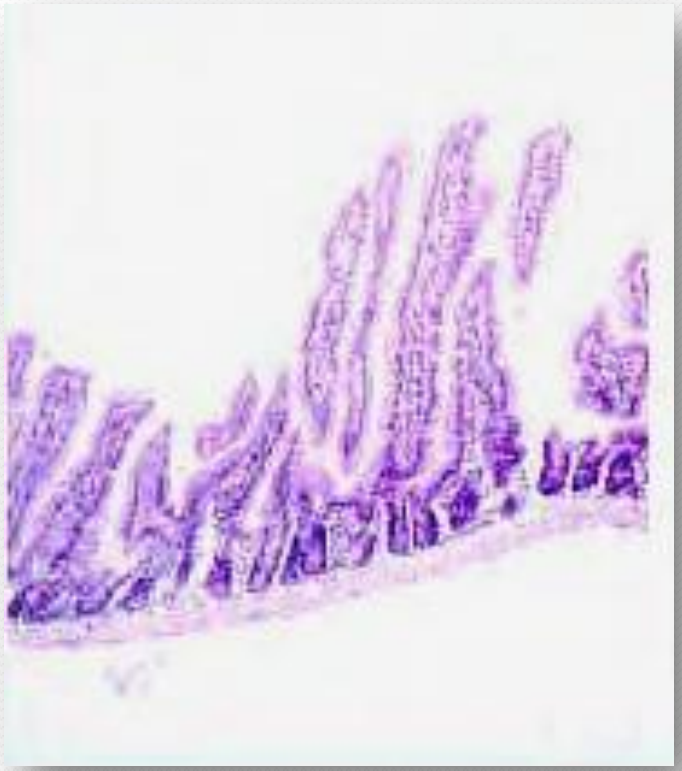
No meal given



Jeppesen *et al*. 2000 Gut 47:370-376

Glucagon-Like Peptide-2

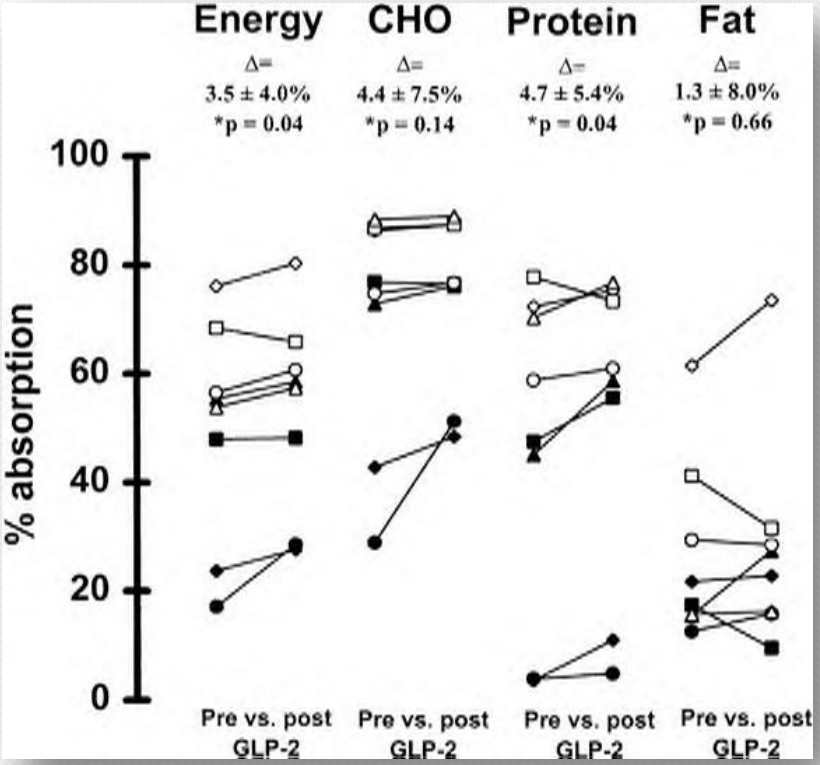
Control

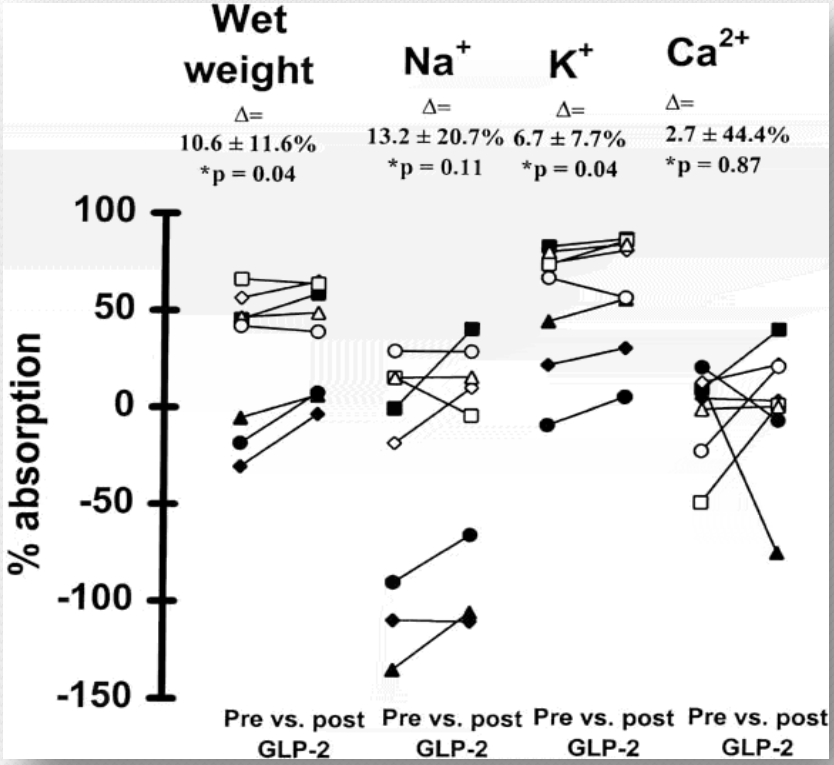


GLP-2

SB epithelium in GLP-2 treated mice

Exogenous GLP- 2 in SBS patients





Jeppesen *et al.* 2001 Gastroenterology 120:806-815

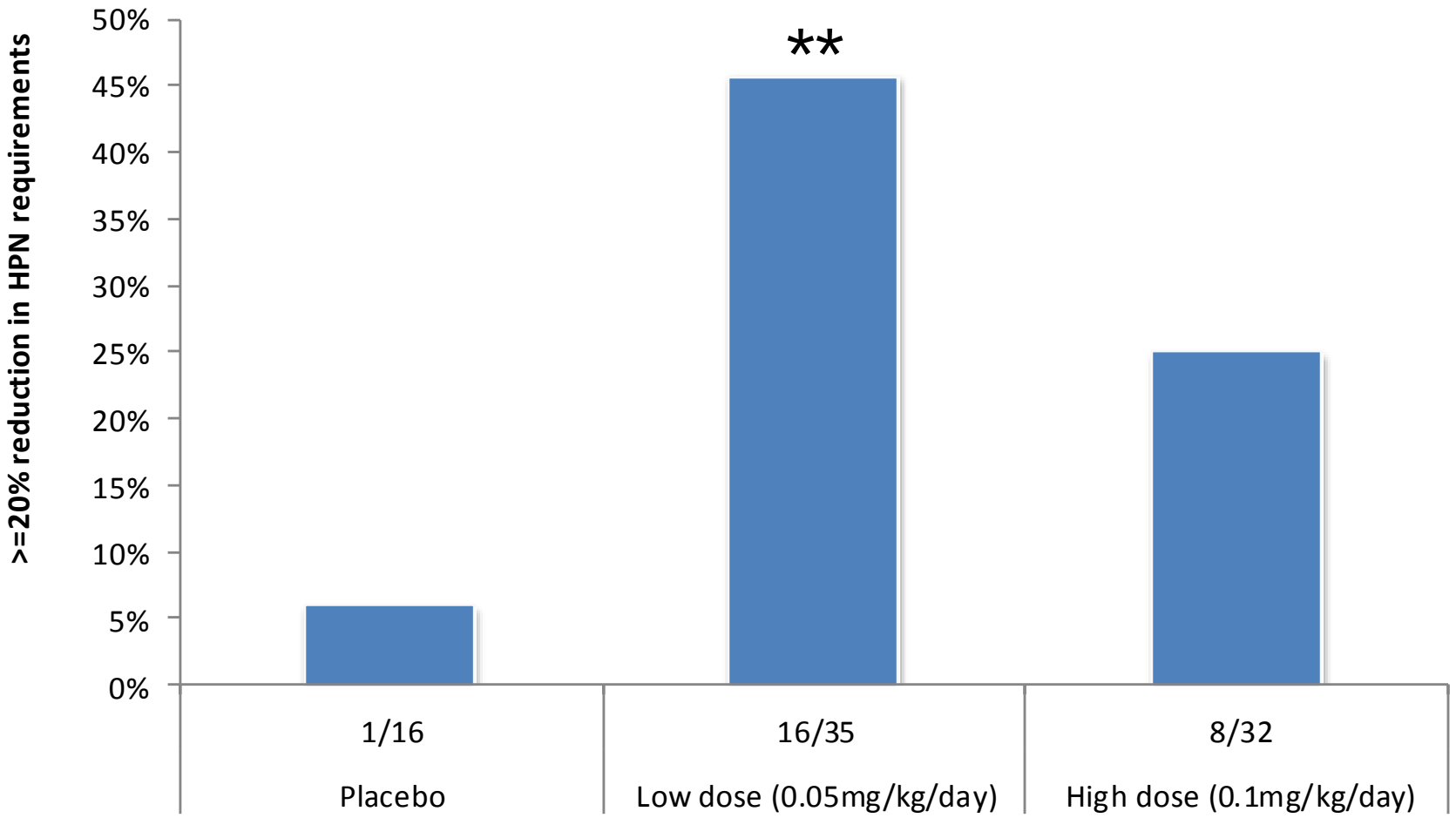
Teduglutide: [gly2]-hGLP-2

- Novel recombinant analogue of GLP-2 (orphan drug)
- 33 AA peptide that differs from GLP-2
  - Substitution of ALA by GLY at 2nd position (from N-terminus)
  - Resistance to *in vivo* degradation by dipeptidyl peptidase-IV

	Half life
GLP-2	7 minutes
Teduglutide	2 hours

Revestive

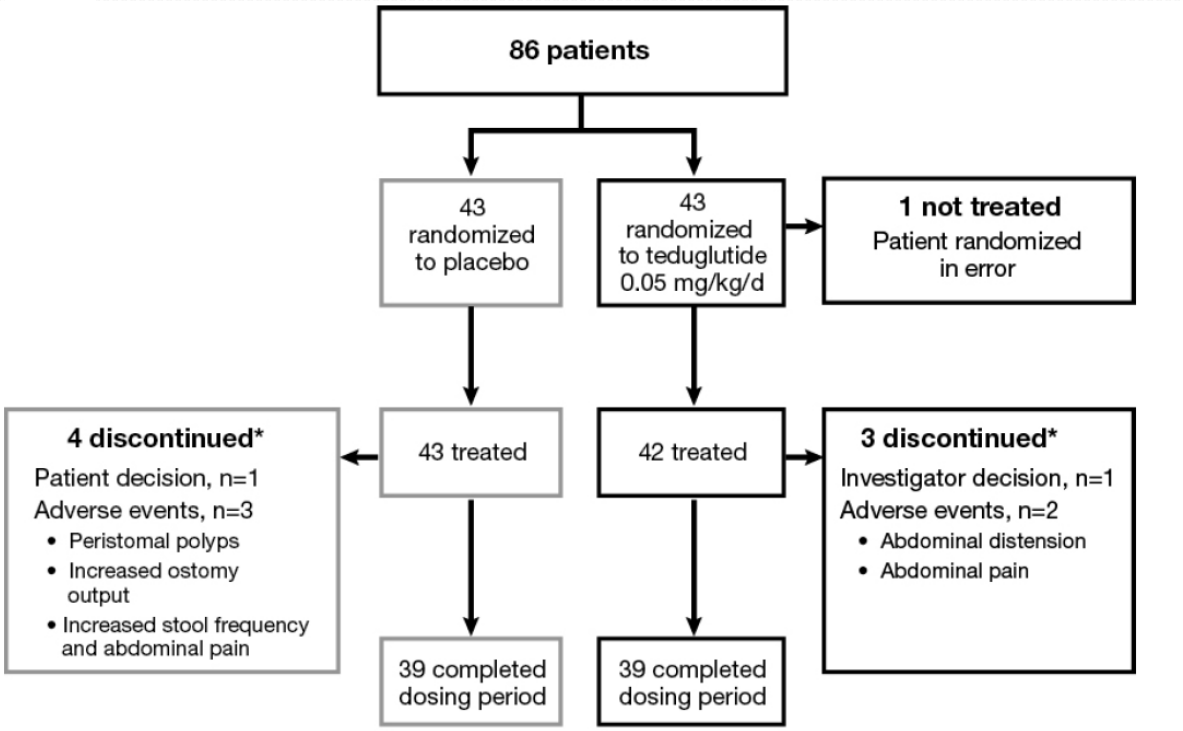
Teduglutide in HPN Patients



Jeppesen PB et al Gut 2011;60:902-14

Teduglutide reduces need for PN support among SBS patients with IF

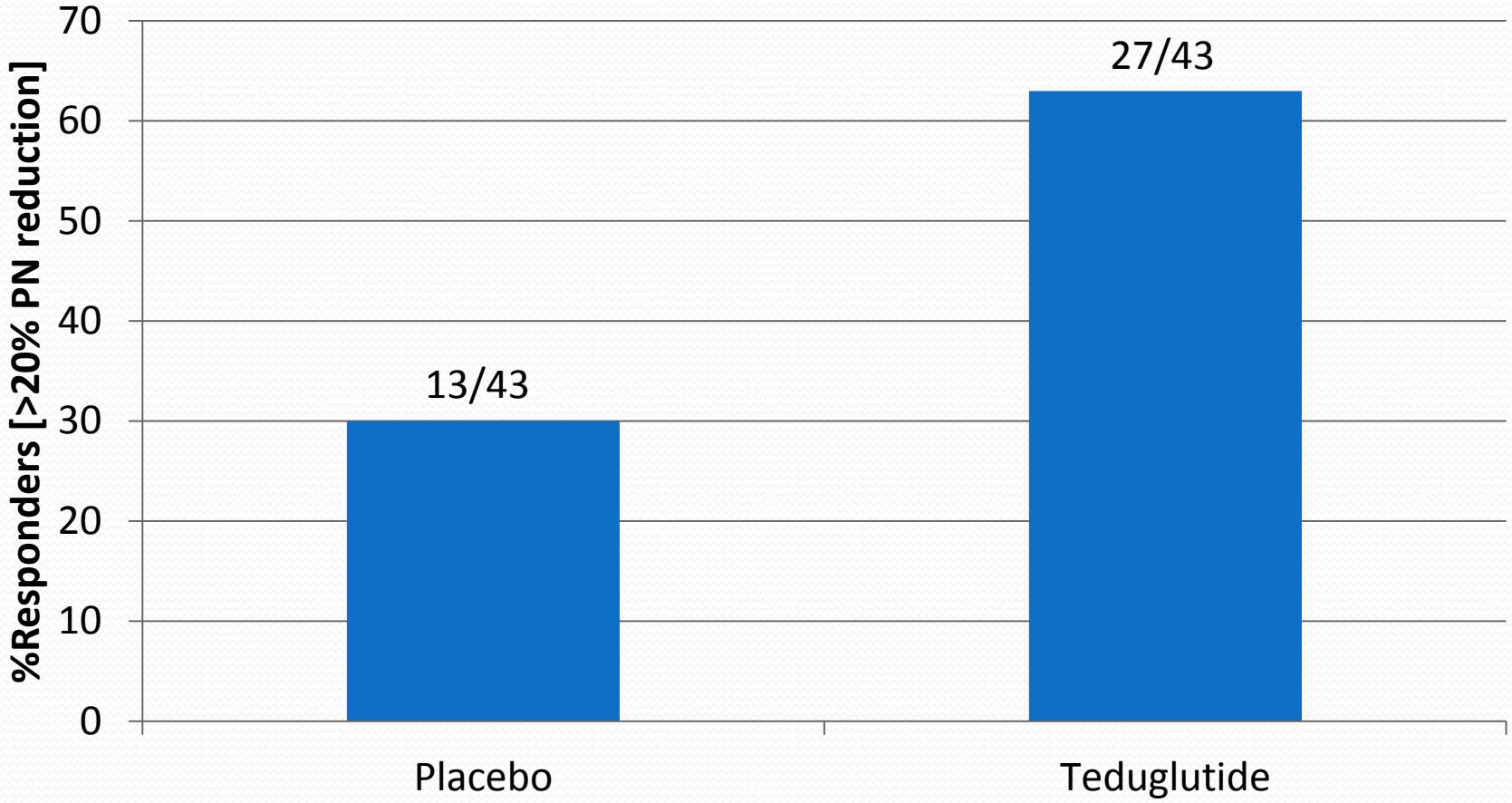
24-week study of patients with IF & SBS
S/c teduglutide (0.05 mg/kg/d; n=43) or placebo (n=43), once daily
Primary endpoint: number of responders (>20% reduction in PN volume at weeks 20 & 24)



*All adverse events resolved after discontinuation of study drug.

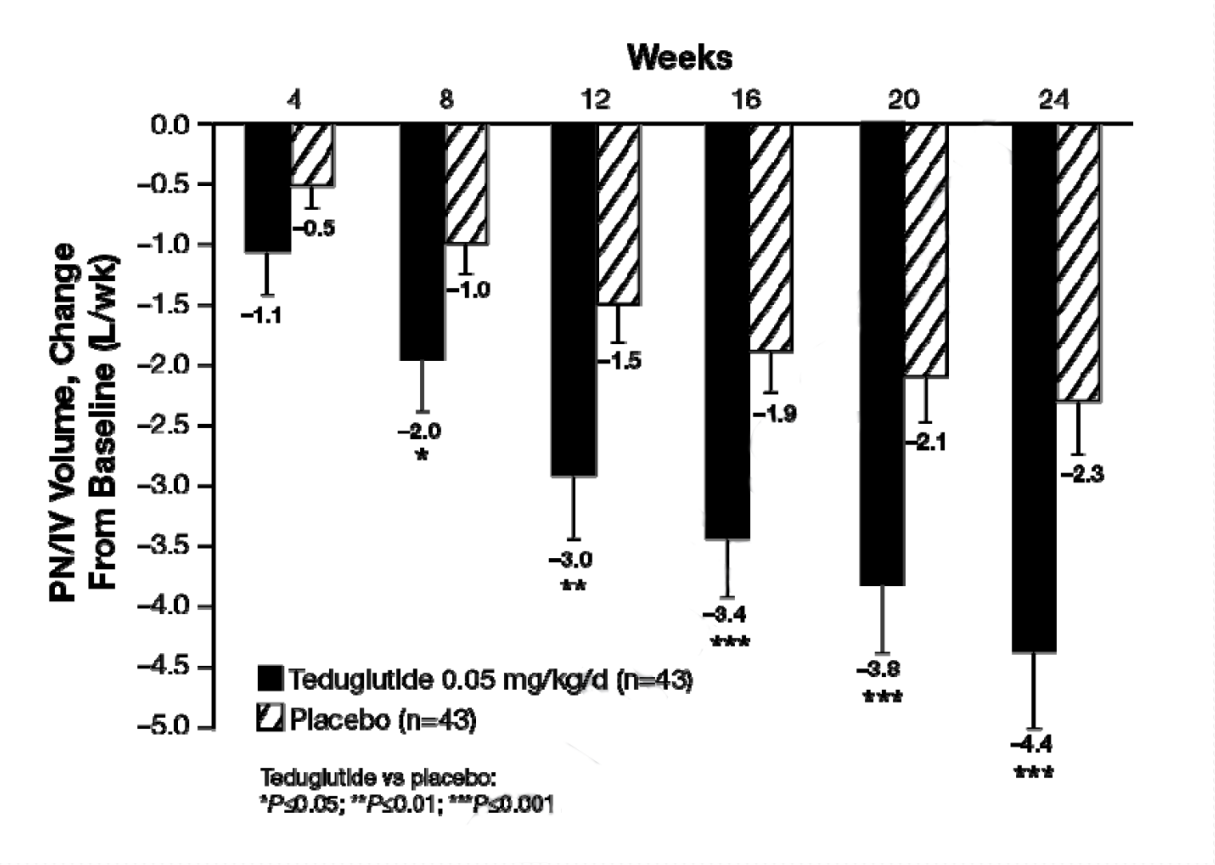
Jeppesen PB et al, Gastroenterology 2012 (in press)

Teduglutide reduces need for PN support among SBS patients with IF



Jeppesen PB et al, Gastroenterology 2012 (in press)

Teduglutide reduces need for PN support among SBS patients with IF



Jeppesen PB et al, Gastroenterology 2012 (in press)

R-Spondin Proteins

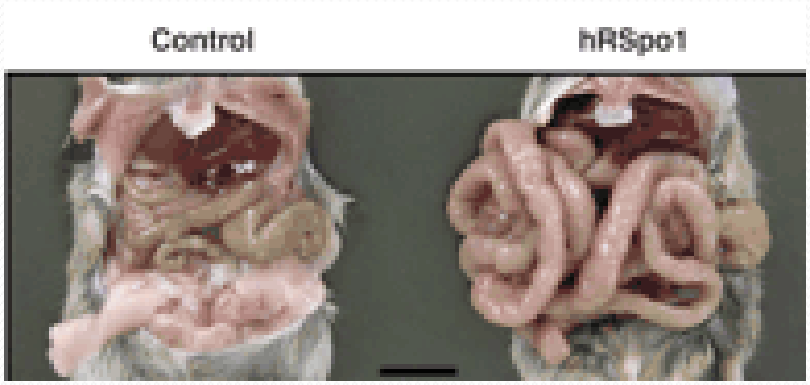
New group of human secreted proteins

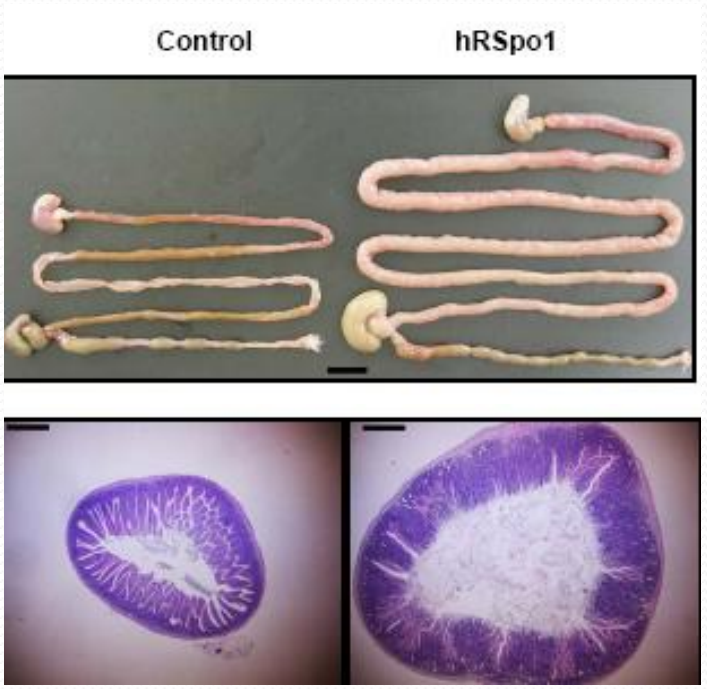
- 4 identified so far
- Controls transcription of genes involved in proliferation & differentiation
- R-spondin 1 is a potent & specific mitogen for the GI epithelium
- **Wnt/ β-catenin signaling pathway (↑ β-catenin)**

Dramatically enlarged small intestine discovered by chance in “knock in mouse”

Treatment effects

- Intestinal proliferation (small & large bowel)
- ↓ chemotherapy induced intestinal toxicity
  - without inducing tumour growth
- More dramatic effect than GLP-2 or KGF



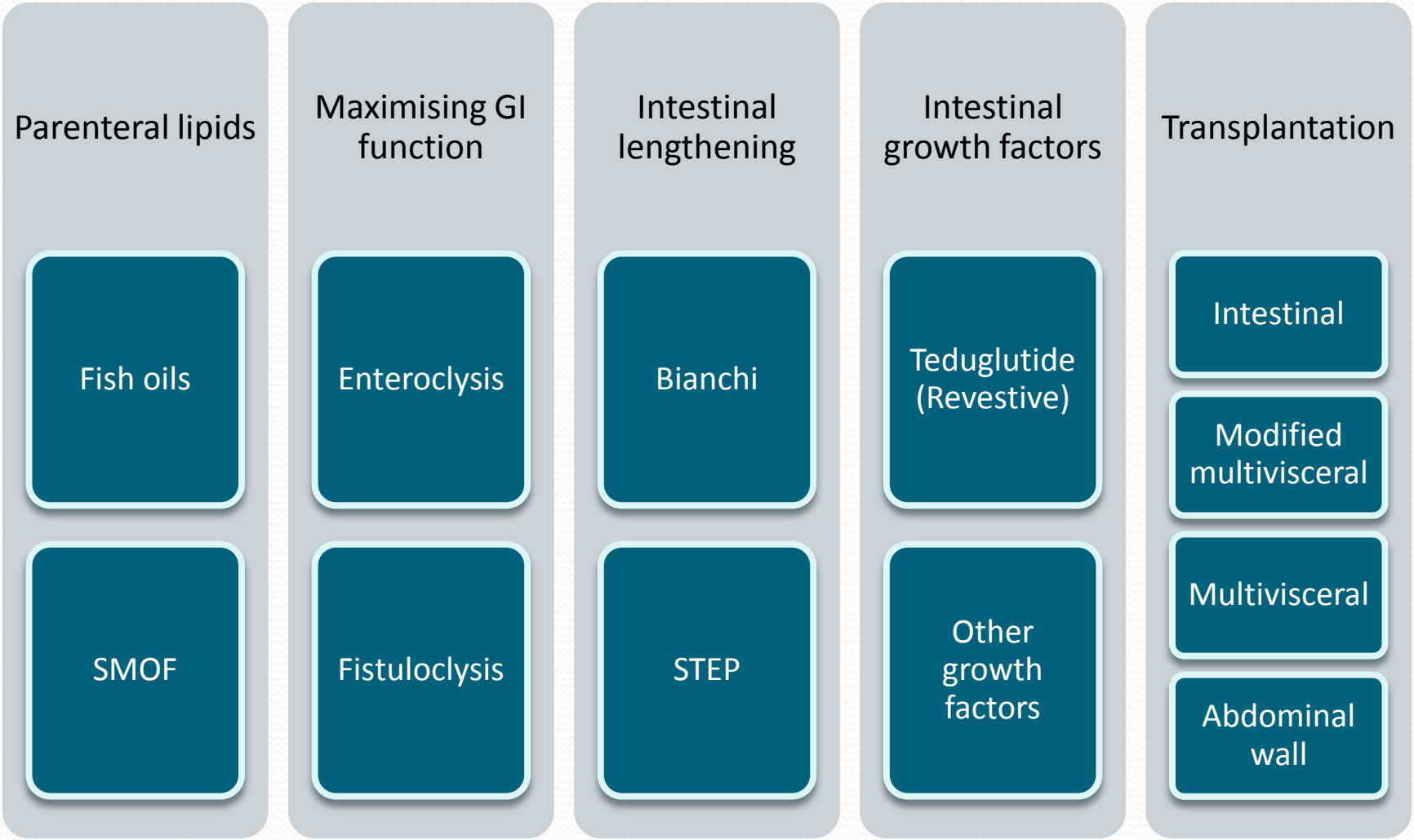


Growth factors in adaptation

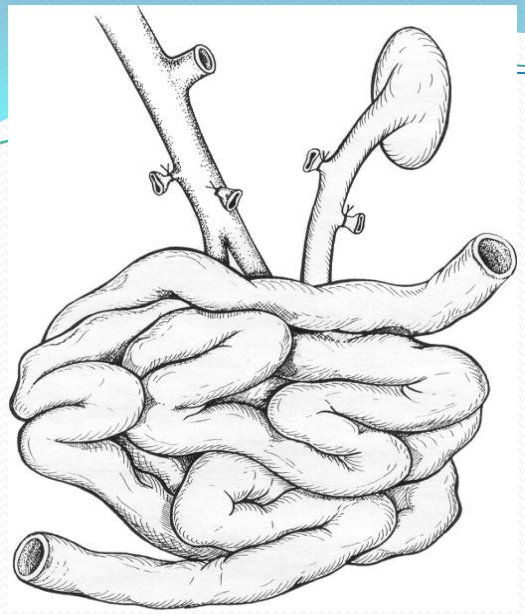
IGF-1	↑crypt cell & SM proliferation
EGF, TGFa	↑enterocyte proliferation ↓apoptosis
HGF	↑DNA content, mass & function of resected intestine
KGF	↑epithelial cell proliferation ↓apoptosis
Neurotensin	↑villus height
Leptin	↑CHO absorption
IL-11	↑epithelial proliferation, ↑absorption

No human trials yet for any of these factors

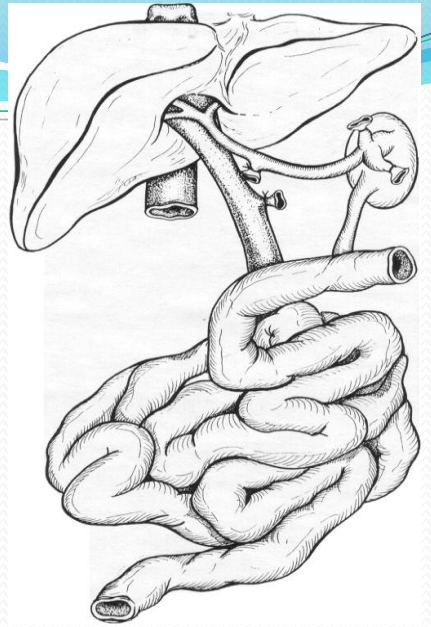
Emerging therapies



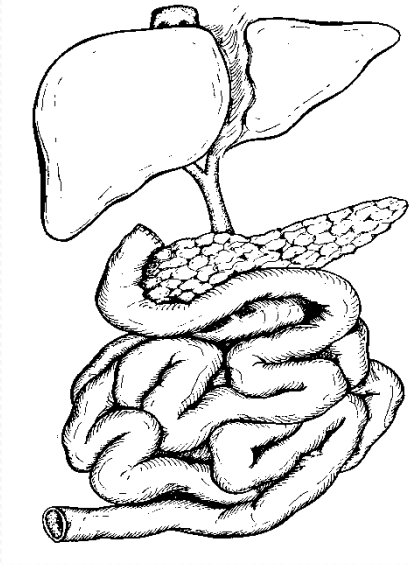
Intestinal transplantation

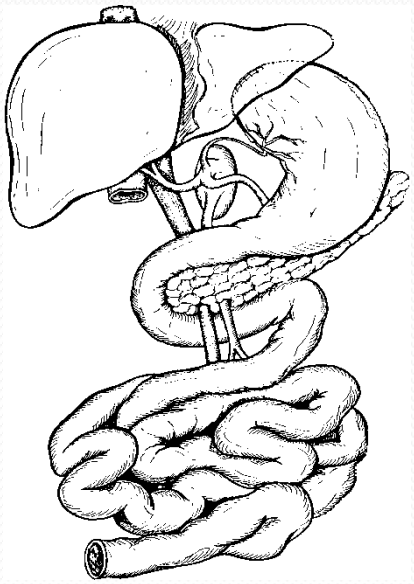


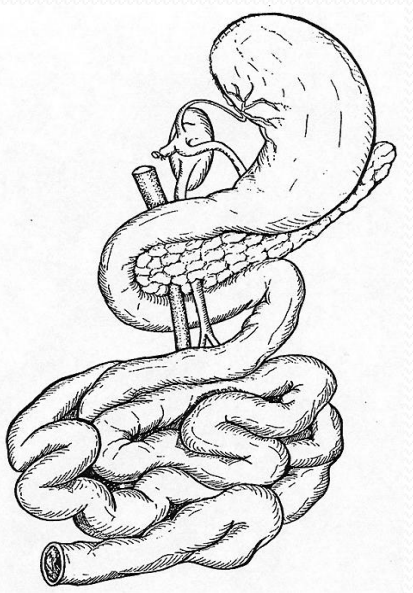
Isolated intestine



Liver + intestine





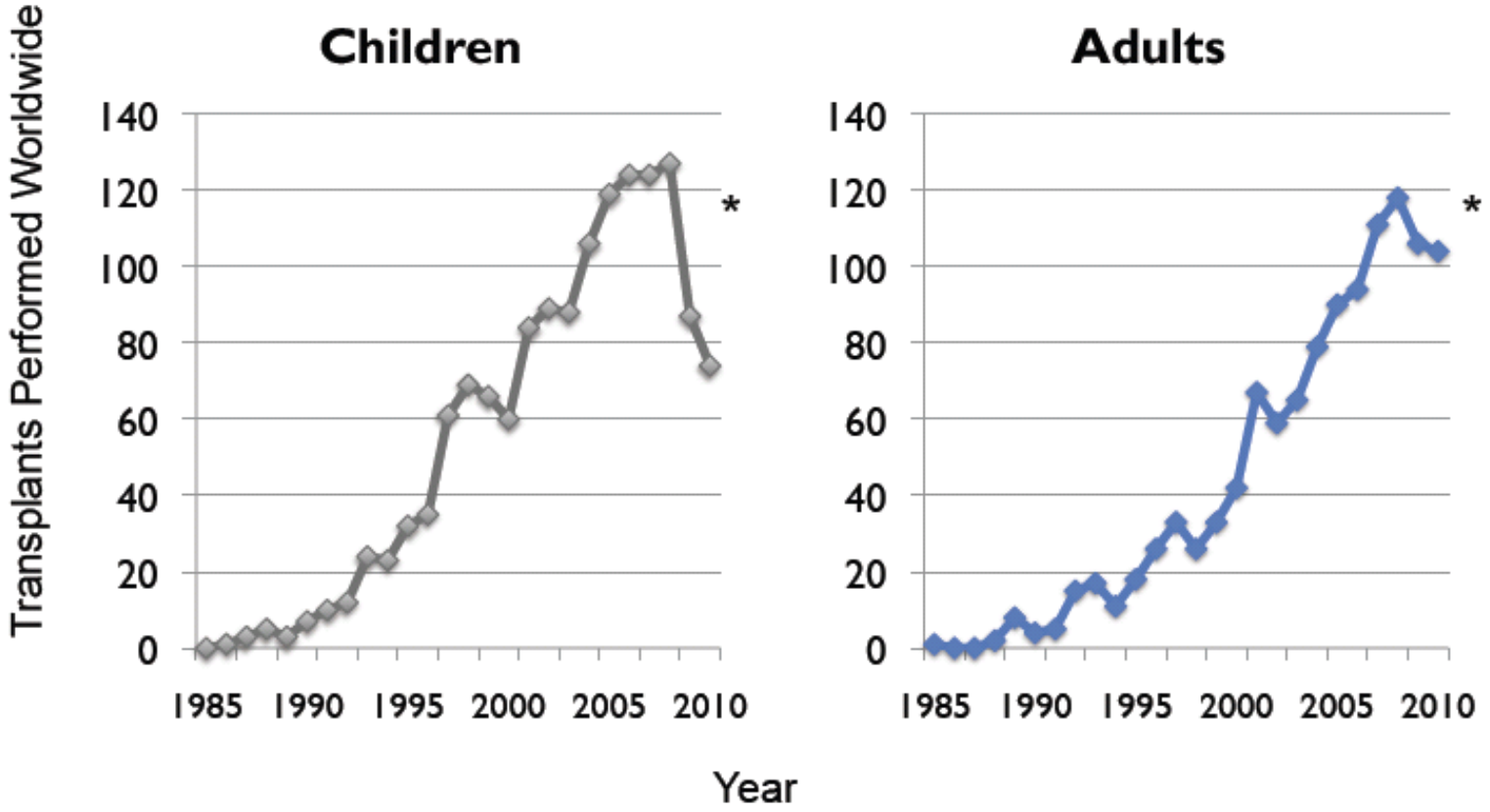


Multi-visceral

Overall Clinical Experience

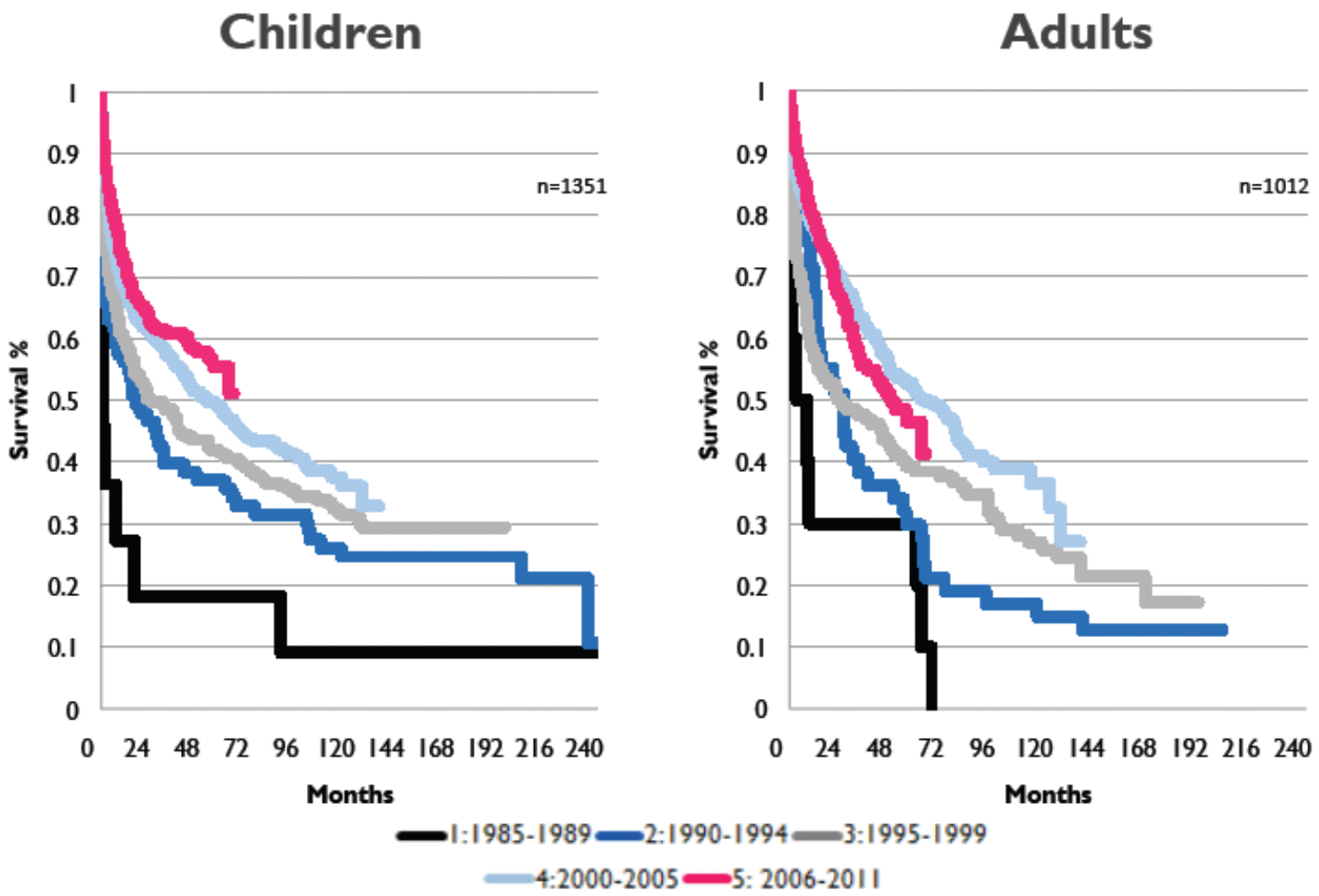
Total Number of Transplants:	**2611**
Centre Count	79
Active Centres	**35**
SB Alone	1148 (43.9%)
SB+Liver	845 (32.4%)
Multivisceral	619 (23.7%)
Current Survivors	**1341**

Intestinal Transplants Performed



*Preliminary 2011

Patient Survival by Era

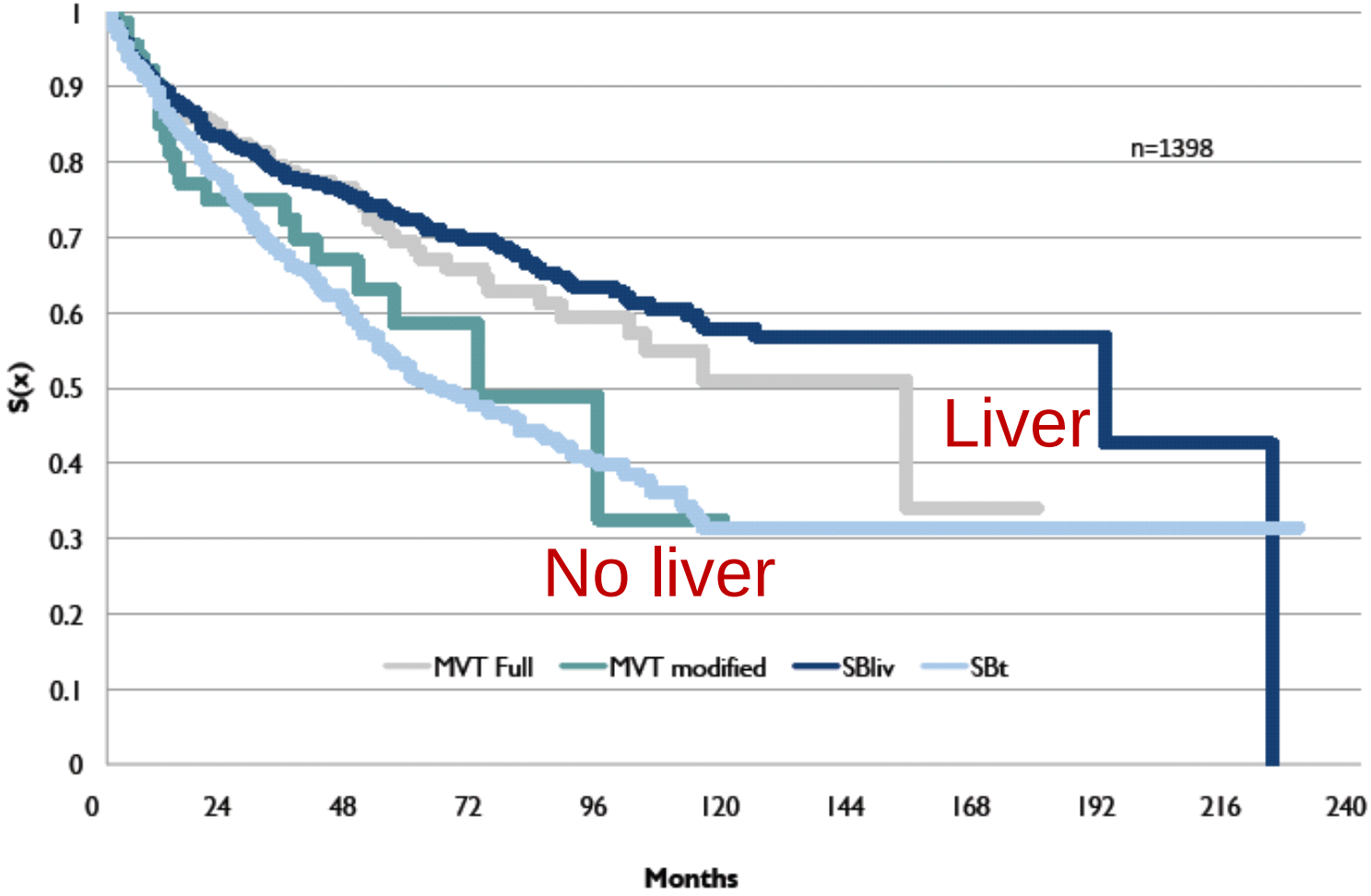


Multiple Variable Regression Analysis: Preliminary Results

End-point	Predictor	HR*	P value
Graft Survival 2006-11	Age < 1 yr	1.23	0.04
	Top 40% program case volume	0.66	0.02
	Home	0.68	0
Conditional graft survival (all eras)	+ Liver component	0.68	0

** Lower ratio = improved survival*

Conditional Long Term Survival by Transplant Type

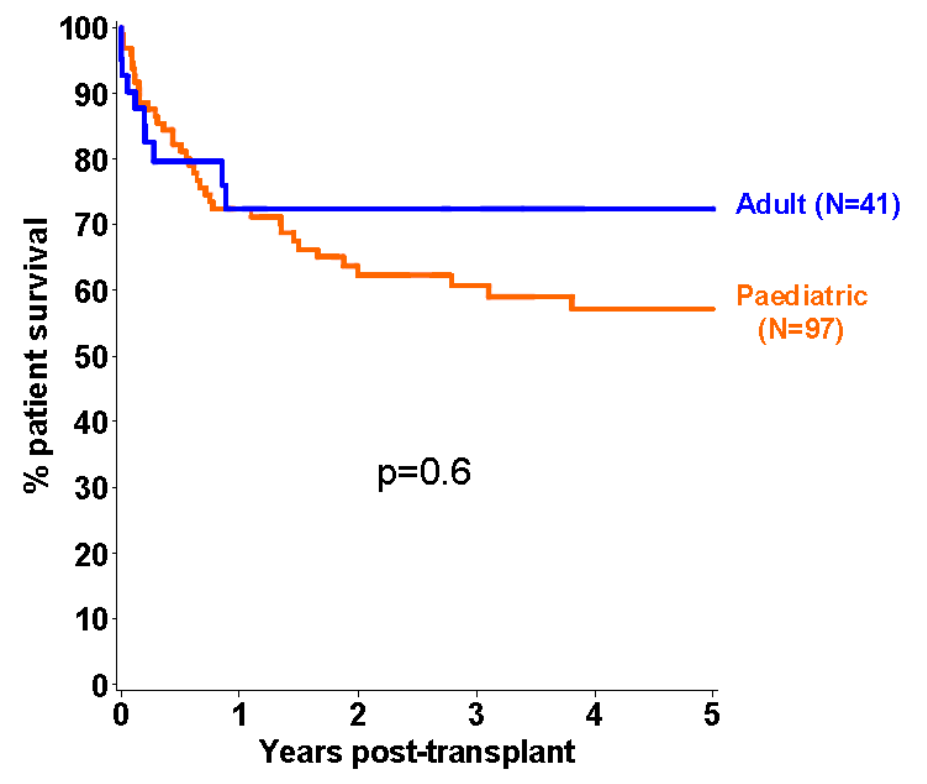


Intestinal Transplantation in UK

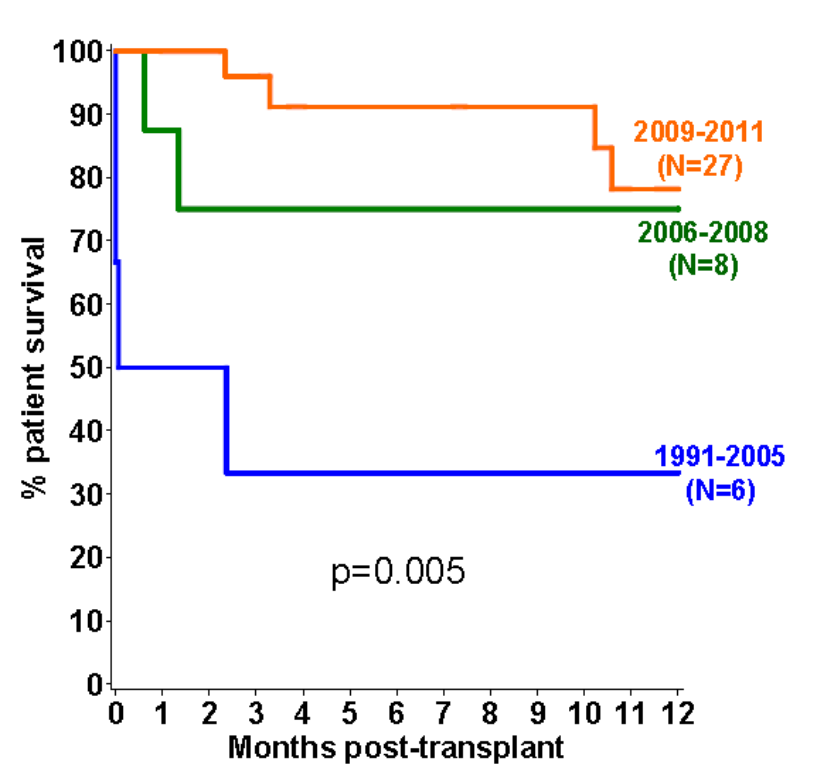
- First case 1991
- NHS funded (NSCAG) 1995
- 2008 – national service reconfigured
- Currently
  - 2 adult centres – Oxford, Cambridge
  - 2 paediatric centres – Birmingham, King's

UK Intestinal transplantation

5 year patient survival (1991-2011)



1 year survival by era



NHSBT data 2012

HPN or transplant?

			Survival		
			1 year	5 years	10 years
HPN			85–97%	58–83%	43–71%
ITx	International registry		75%	58%	40%
	best reported large cohort survival	All patients	85%	61%	42%
		Subgroup with lymphocyte depletion	91%	70%	

Lifelong HPN

Some patients can manage a good quality of life

Full time work

Holiday

Challenge

Manchester to London canoe

Summary: Short Bowel Syndrome

1. Understand the basic physiology
   - Makes the management easy / possible
2. Multidisciplinary approach essential
   - Medications, diet, fluid intake
   - Stoma care crucial
   - Psychological issues should not be overlooked
3. Optimise medical treatments
   - Including PN were needed
4. Surgical approaches
   - Assess if any bowel can be brought back into continuity
5. Long term outcome
   - Balance life expectancy with quality of life for that patient
   - Know your patients well to give them the best advice