
Grand Rounds
Rigshospitalet
rigshospitalet.dk/grandrounds

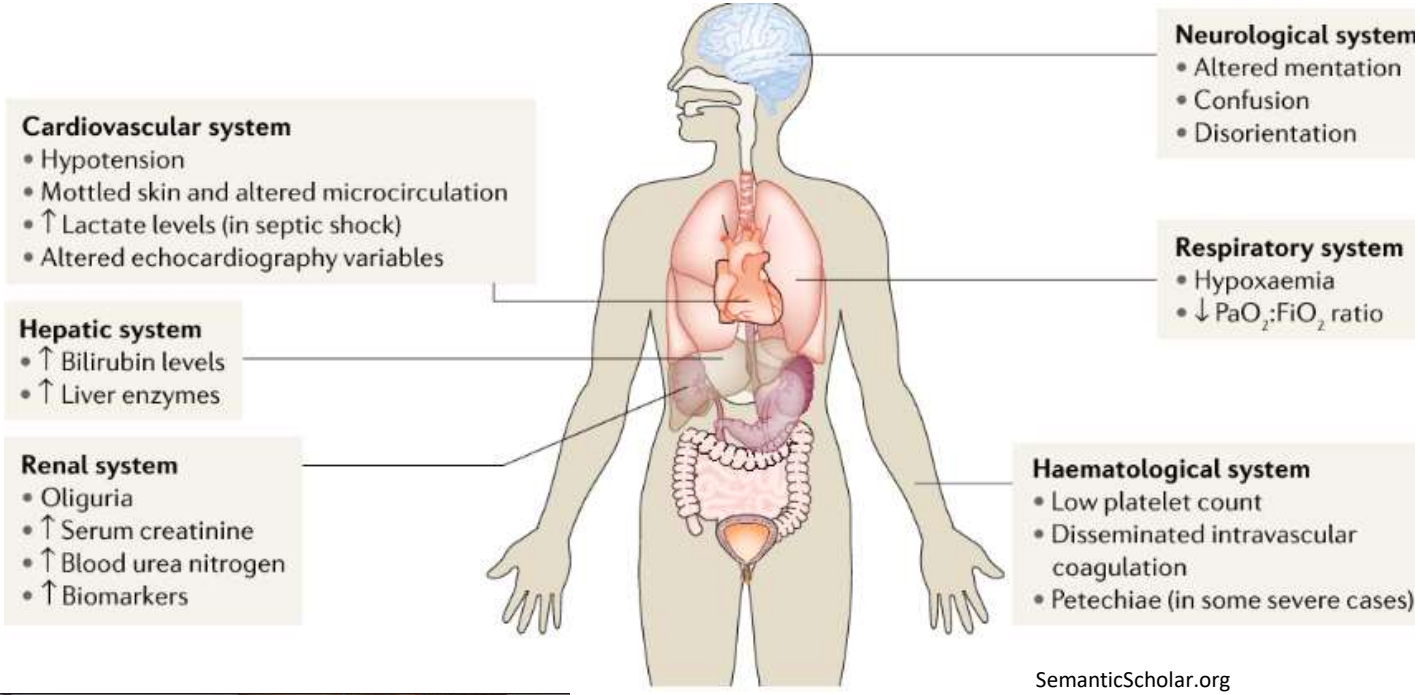
Grand Rounds om tarmsvigt

Globale pionerer for den tværfaglige og interdisciplinære behandling af tarmsvigt

Cheflæge, Prof. Palle Bekker Jeppesen, dr. med., Ph.D., Dls.
Overlæge, Michael Staun, dr. med.
Afdeling for Tarmsvigt og Leversygdomme

Palle.bekker.Jeppesen@regionh.dk
Michael.Staun@regionh.dk

Organ Failures



SemanticScholar.org

Where is ”Intestinal Failure” ????

What is Intestinal Failure & Short Bowel Syndrome?

Intestinal failure vs insufficiency:
ESPEN Definitions 2015

Intestinal failure *is defined as the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation is required to maintain health and/or growth.*

The reduction of gut absorptive function that doesn't require intravenous supplementation to maintain health and/or growth, can be considered as ***"intestinal insufficiency".***

ESPEN endorsed recommendations. Definition and classification of intestinal failure in adults

Loris Pironi [a,*], Jann Arends [b], Janet Baxter [c], Federico Bozzetti [d], Rosa Burgos Peláez [e], Cristina Cuerda [f], Alastair Forbes [g], Simon Gabe [h], Lyn Gillanders [i], Mette Holst [j], Palle Bekker Jeppesen [k], Francisca Joly [l], Darlene Kelly [m], Stanislaw Klek [n], Øivind Irtun [o], SW Olde Damink [p], Marina Panisic [q], Henrik Højgaard Rasmussen [j], Michael Staun [k], Kinga Szczepanek [n], André Van Gossum [r], Geert Wanten [s], Stéphane Michel Schneider [t], Jon Shaffer [u], the Home Artificial Nutrition & Chronic Intestinal Failure and the Acute Intestinal Failure Special Interest Groups of ESPEN

Pironi, et al. *Clin Nutr.* 2015;34:171–80.

Gut 2000;46:701–706

Intestinal failure defined by measurements of intestinal energy and wet weight absorption

P B Jeppesen, P B Mortensen

Classification according to: The patophysiological causes of intestinal insufficiency and failure

- Short Bowel

- Intestinal Fistula

- Intestinal Dysmotility

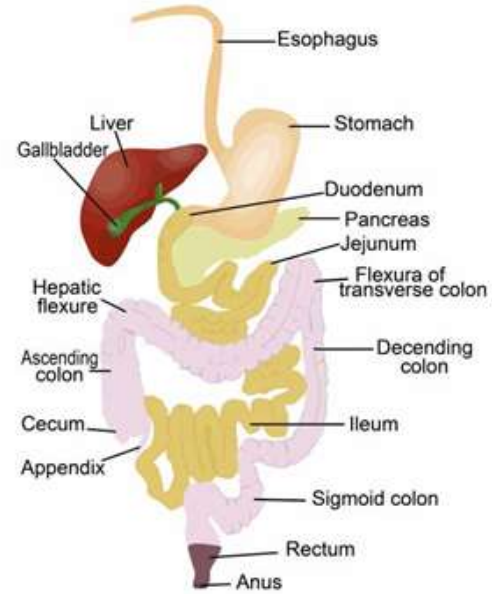
- Mechanical Obstruction

- Extensive small bowel mucosal disease

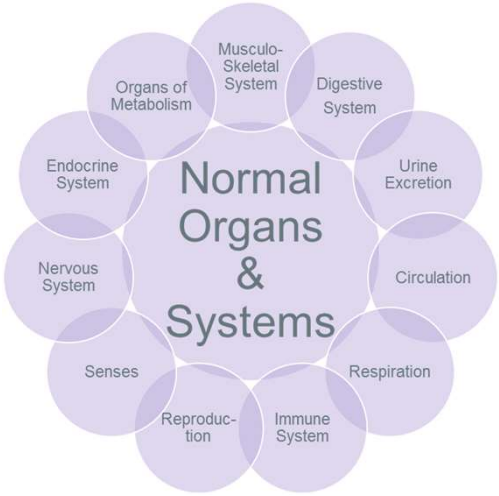
Normal vs. Pathophysiology

Macronutrients, Fluid, Electrolytes, Trace elements, Vitamins

Homeostasis



INTESTINAL ABSORPTION



NORMAL METABOLISM

Macronutrient, Fluid, Electrolyte, Trace element, Vitamin

Dys-homeostasis

INTESTINAL DISEASE

Macronutrient, Fluid, Electrolyte, Trace element, Vitamin

Dys-homeostasis

INTESTINAL DISEASE

INTESTINAL RESECTION

Macronutrient, Fluid, Electrolyte, Trace element, Vitamin

Dys-homeostasis

INTESTINAL DISEASE

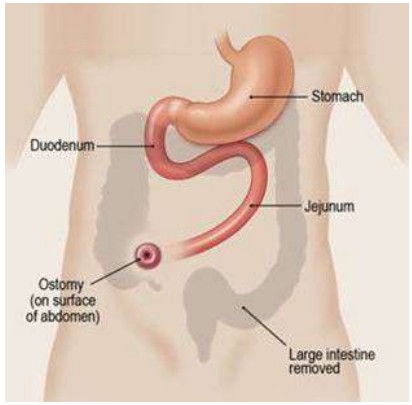
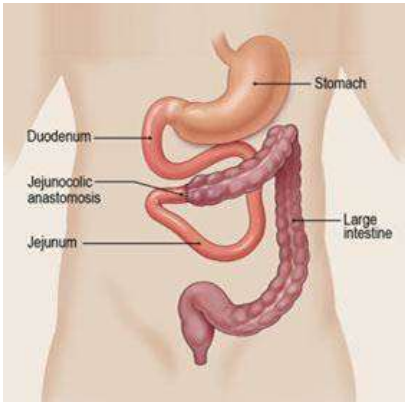
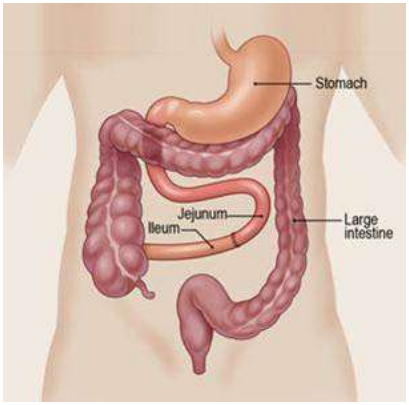
INTESTINAL RESECTION

(Anatomy group 1) (Anatomy group 2) (Anatomy group 3)

SHORT BOWEL SYNDROME & IMPAIRED INTESTINAL FUNCTION

Short Bowel Syndrome

Intestinal Failure by Anatomy

	JEJUNO(-ILEO) -STOMY	JEJUNO(-ILEO)- COLIC ANASTOMOSIS	
			
	Group 1	**Group 2**	**Group 3**
Small Bowel Length	**<115 cm**	**<60 cm**	**<35 cm**

Messing et al. Gastroenterology 1999

The Spectrum of Intestinal Function

Normal

Jeppesen P. Short Bowel Syndrome:
Practical Approach to Management (2016). Editor DiBaise JK. Chapter 1.

The Spectrum of Intestinal Function

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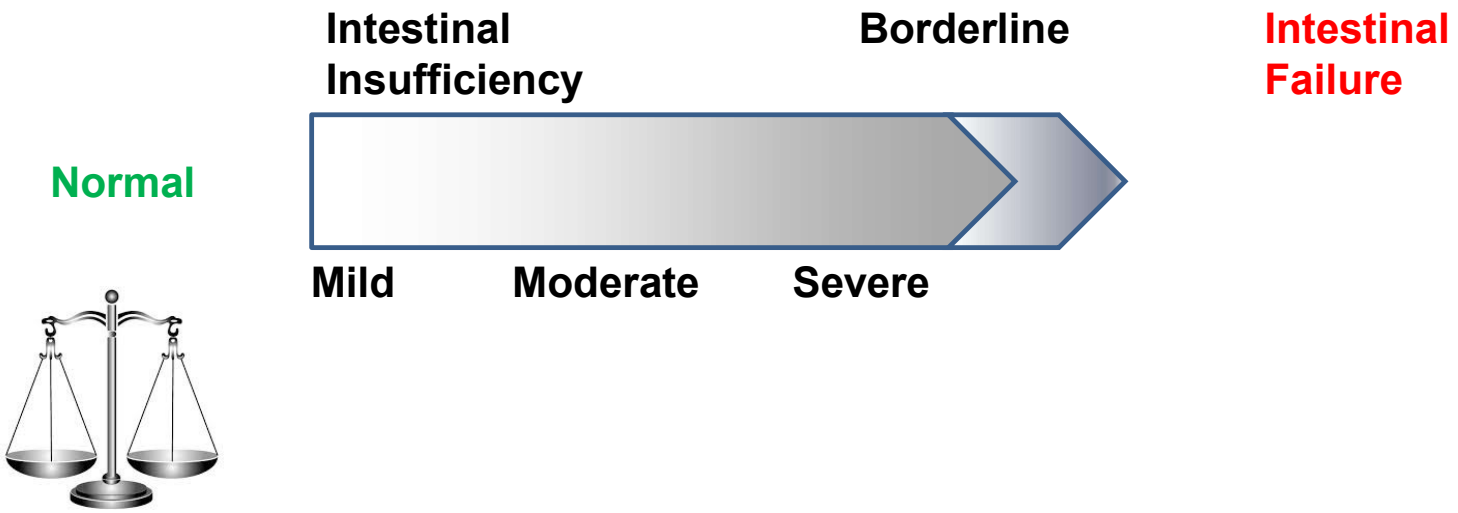


Jeppesen P. Short Bowel Syndrome:
Practical Approach to Management (2016). Editor DiBaise JK. Chapter 1.

The Spectrum of Intestinal Function

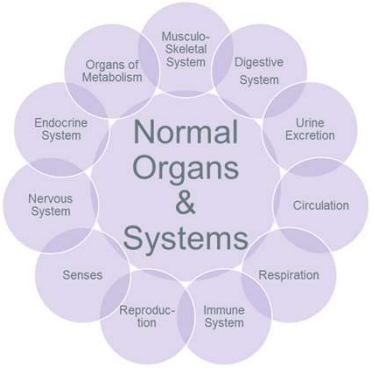
Normal

Intestinal Insufficiency

Borderline

Intestinal Failure

Mild **Moderate** **Severe**



Metabolic Adaptation

Jeppesen P. Short Bowel Syndrome:
Practical Approach to Management (2016). Editor DiBaise JK. Chapter 1.

The Spectrum of Intestinal Function

Normal

Intestinal Insufficiency

Borderline

Intestinal Failure

Mild

Moderate

Severe

PROMOTE INTESTINAL ADAPTATION

Metabolic Adaptation

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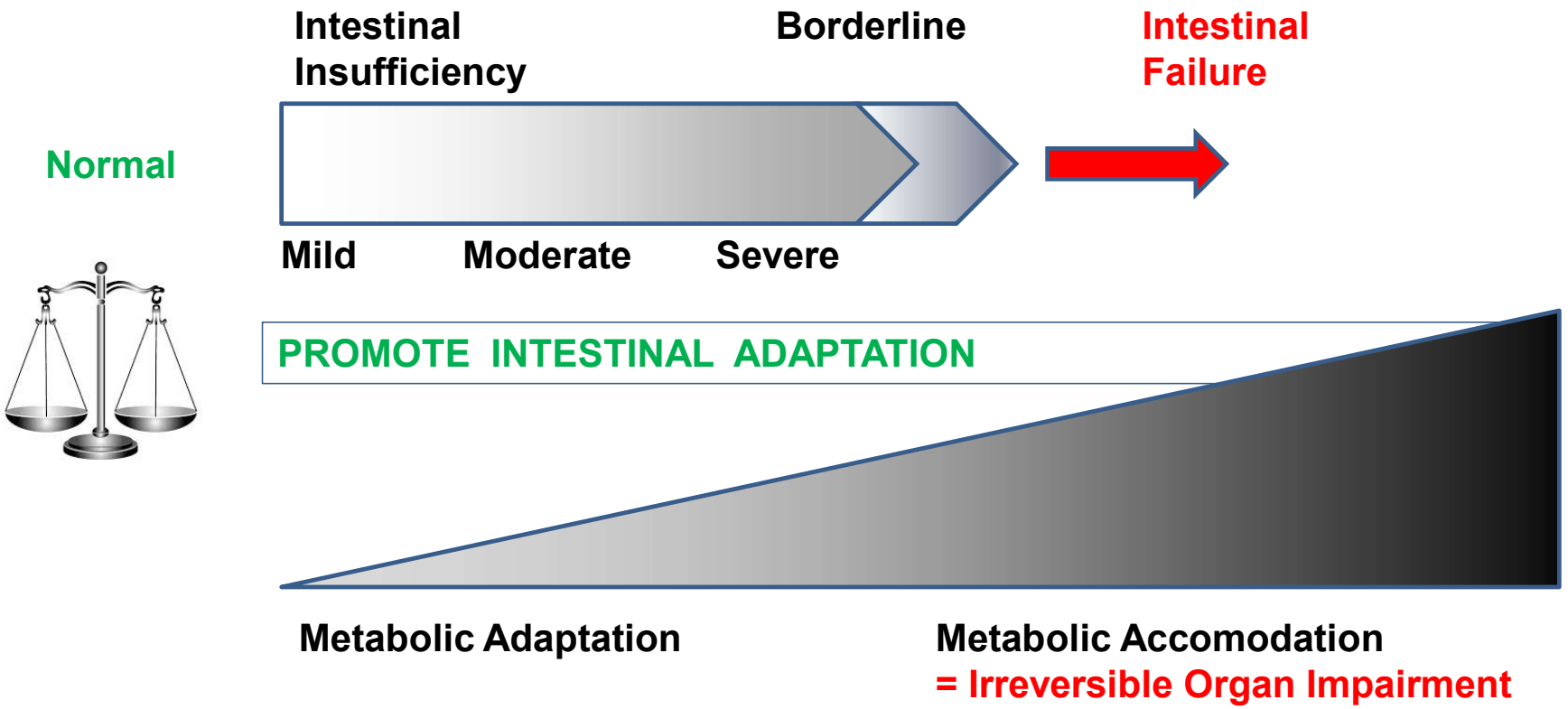
The Spectrum of Intestinal Function



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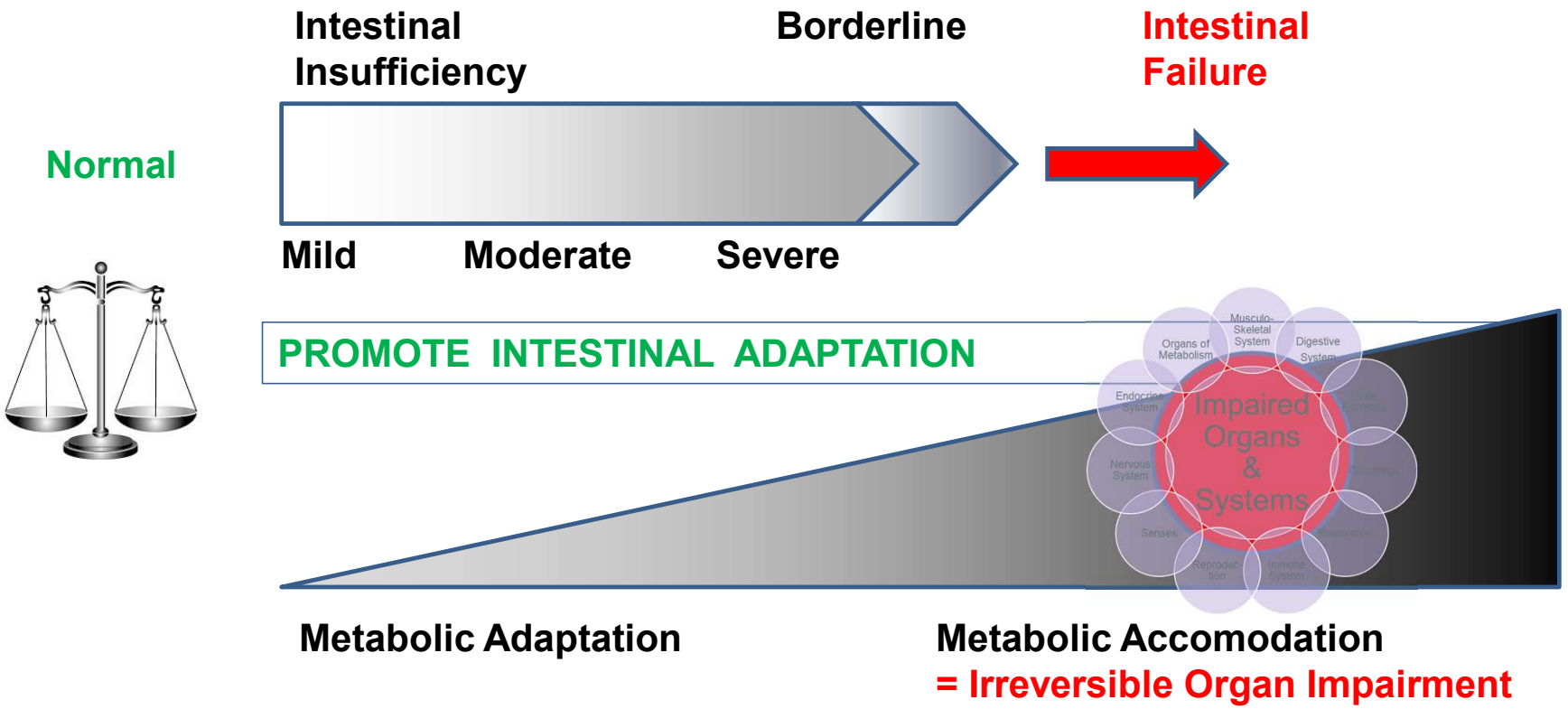

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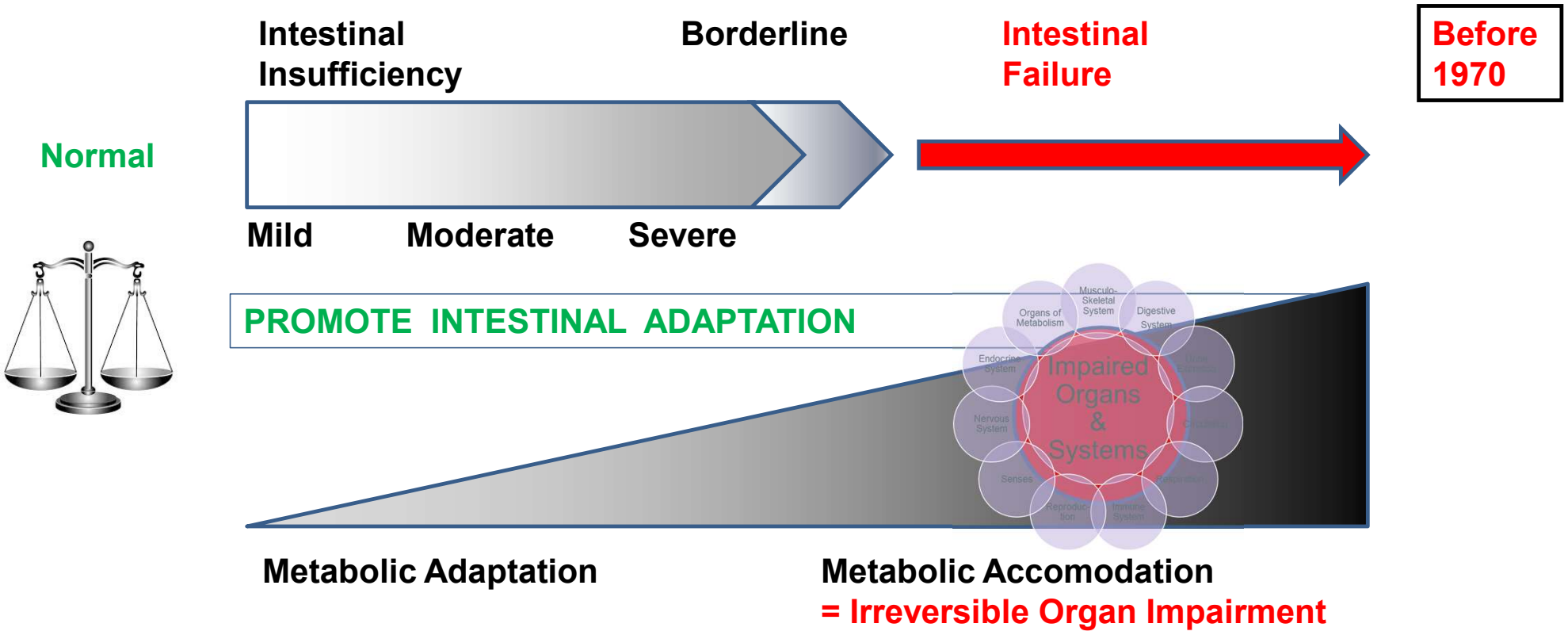

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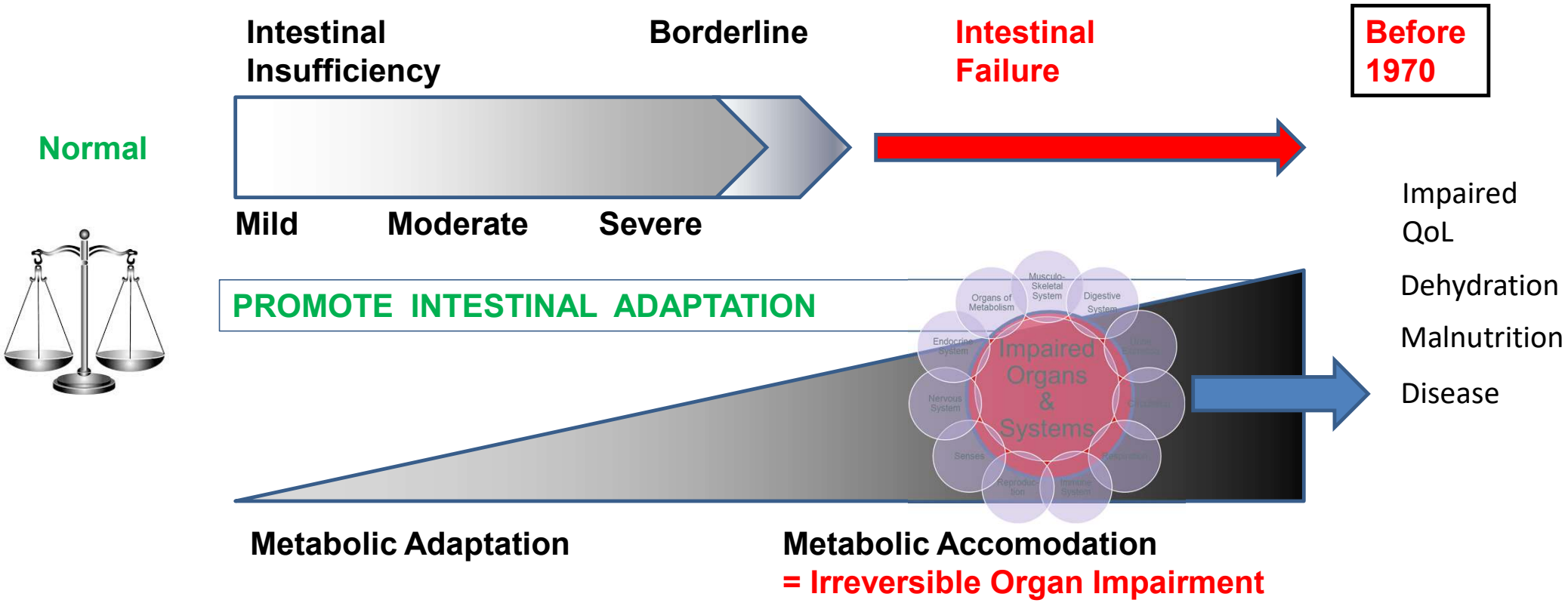

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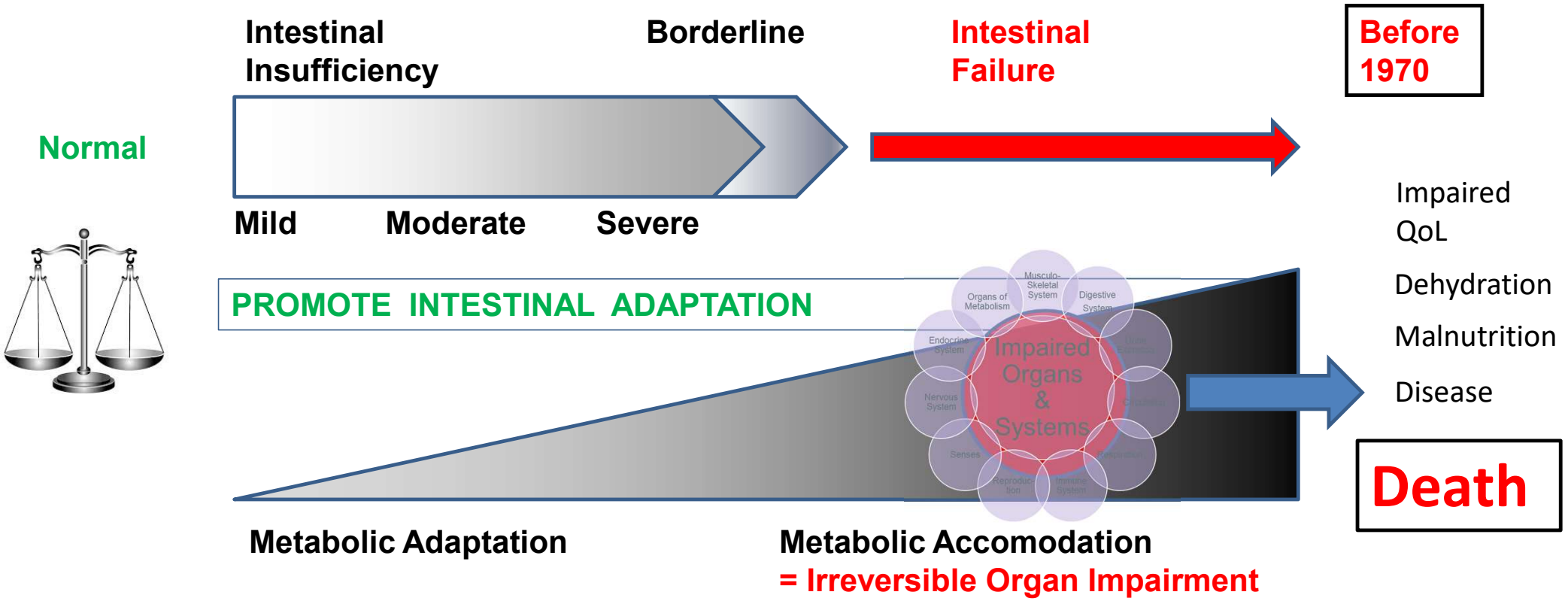

Jeppesen P. Short Bowel Syndrome:
Practical Approach to Management (2016). Editor DiBaise JK. Chapter 1.

The History of Intestinal Failure in Denmark: Stig Jarnum (1/7-1926 - 16/12-1994)

1952: MD, University of Copenhagen
1964: Specialist in Medical Gastroenterology at Rigshospitalet (Dept P)
1965: Head of Department; Rigshospitalet

Scientific Interest; Protein-losing enteropathy

The History of Intestinal Failure in Denmark: Stig Jarnum (1/7-1926 - 16/12-1994)

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Scientific Interest; "Protein-losing enteropathies"

Am J Physiol. 1956 Apr;185(1):185-94.
Water balance of the camel.
SCHMIDT-NIELSEN B, SCHMIDT-NIELSEN K, HOUPT TR, JARNUM SA.

The Early History of Parenteral Support (PS) in Denmark: 1958 & 1961

6 marts 1958 **UGESKRIFT FOR LÆGER** 120 årg. - nr 10
UDGIVET AF DEN ALM. DANSKE LÆGEFORENING

VIDENSKAB OG PRAKSIS

PARENTERAL KVÆLSTOFTILFØRSEL MED PROTEINHYDROLYSAT OG HUMANT SERUM

Af STIG JARNUM og ERIC THING

Patienter med anorexi, dyspepsi og stenose i fordøjelseskanalen eller med mangelfuld resorption i tarmen giver anledning til specielle ernæringsfysiologiske vanskeligheder. Det kan hos disse patienter være umuligt peroralt at tilføre sådanne mængder protein, at organismen er i kvælstofligevægt.

I mange år har man anvendt parenteral indgift af mere eller mindre rene blandinger af aminosyrer. Henriques & Andersen (39) viste i 1913, at det var muligt at holde en ged på positiv kvælstofbalance gennem lange perioder med parenteralt indgivet, enzymatisk spaltet protein. Elman's arbejder (17, 18, 19) fra slutningen

I det foreliggende arbejde har man ønsket at undersøge virkningen på kvælstofomsætningen af parenteralt indgivet kvælstof i form af proteinhydrolysat og serum.

EGNE UNDERSØGELSER

Forsøgspersoner.

De undersøgte patienter har alle været indlagt på Bispebjerg Hospital, kirurgisk afdeling A, og har frivilligt medvirket til undersøgelsen.

De første kvælstofbalanceforsøg blev foretaget på patienter med underextremitetsfraktur. Patienterne var raske mænd i alderen 17—64 år.

Som modsætning til disse valgte man desuden at undersøge patienter med cancer ventriculi for dennem

3 februar 1961 **UGESKRIFT FOR LÆGER** 123 årg. - nr 5
UDGIVET AF DEN ALM. DANSKE LÆGEFORENING

VIDENSKAB OG PRAKSIS

PARENTERAL ERNÆRING

SÆRLIGT MED HENBLIK PÅ TILFØRSLEN AF KALORIER OG KVÆLSTOF

Af STIG JARNUM

Rationel parenteral vædsketerapi introduceredes i klinikken for mere end 100 år siden, da englænderen Latta (77) i 1831 med held behandlede kolera med intravenøse infusioner af vand med natriumklorid og natriumbikarbonat. I lighed med andre betydningsfulde opdagelser gik hans terapi i glemmebogen i mange år. Først indenfor de sidste 50 år har den udvikling fundet sted, som i dag tillader et næsten komplet parenteralt regime, der kvalitativt og kvantitativt tilgodeser alle hidtil kendte behov i ernæringen.

Et generelt skema (25, 76) for parenteral ernæring er ikke ulig driftsregnskabet for en større virksomhed. Således skal den samlede indtægt eller tilførsel, hvis status skal holdes, dække 3 hovedposter:

1. Vedligeholdelsesudgifter eller opfyldelsen af det *basale behov* for kalorier, kvælstof, vand,

udfra kendskabet til hans overflade. Dette er utvivlsomt den mest rationelle doseringsmåde for voksne individer, mens den ikke bør anvendes skematisk hos børn (25), spec. ikke straks efter fødslen, hvor behovet (per m^2) er betydeligt (30 %) lavere end hos voksne.

I praksis benytter man sjældent overfladeberegningen, men tilpasser efter skøn og vægt terapien udfra kendskabet til behovet hos et gennemsnitsindivid på f. eks. 70 kg med en overflade på 1.73 m^2*).

I det følgende gøres der først rede for indikationer for og midler til parenteral *kalorietilførsel*. Herunder vil en nærmere omtale blive viet fedtemulsioner, som efter alt at dømme vil vinde stor udbredelse som parenteral kaloriekilde i løbet af få år.

Derefter omtales på tilsvarende måde *kvælstof*.

International Collaboration

Long-term total parenteral nutrition with growth, development, and positive nitrogen balance*

Stanley J. Dudrick, M. D.; Douglas W. Wilmore, M. D.; Harry M. Vars, Ph. D.; Jonathan E. Rhoads, M. D.

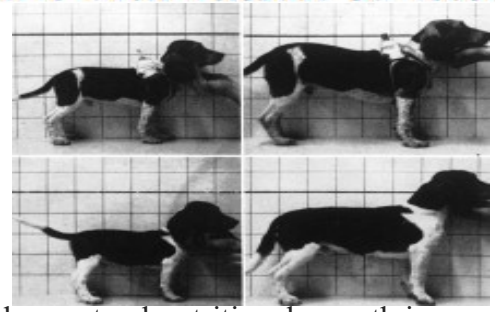
Philadelphia, P.A. From the Department of Surgery and the Harrison Department of Surgical Research, School of Medicine, University of Pennsylvania

The best route for satisfying nutritional requirements is the gastrointestinal tract. However, when its use is precluded for prolonged periods, parenteral alimentation becomes necessary and is common clinical practice with the use of carbohydrate, amino acid, vitamin, and electrolyte solutions. Limited positive nitrogen balance has been achieved in several short-term periods of total intravenous feeding [1, 5]

From 1964 to 1966, Dudrick worked with his mentor, Dr. Jonathon Rhoads, in developing TPN.

Laboratory studies

Six male pedigreed beagle puppies were fed entirely intravenously for 72 o 256 days and compared with their orally fed littermates. After weaning at 8 weeks of age, the puppies were paired according to their size and compared with their orally fed litterately in metabolic cages, and fed a standard oral ration to determine their



Dudrick SJ et al. Longterm total parenteral nutritional growth in puppies and positive nitrogen balance in patients. Surgical forum 18(1967), 134-142.

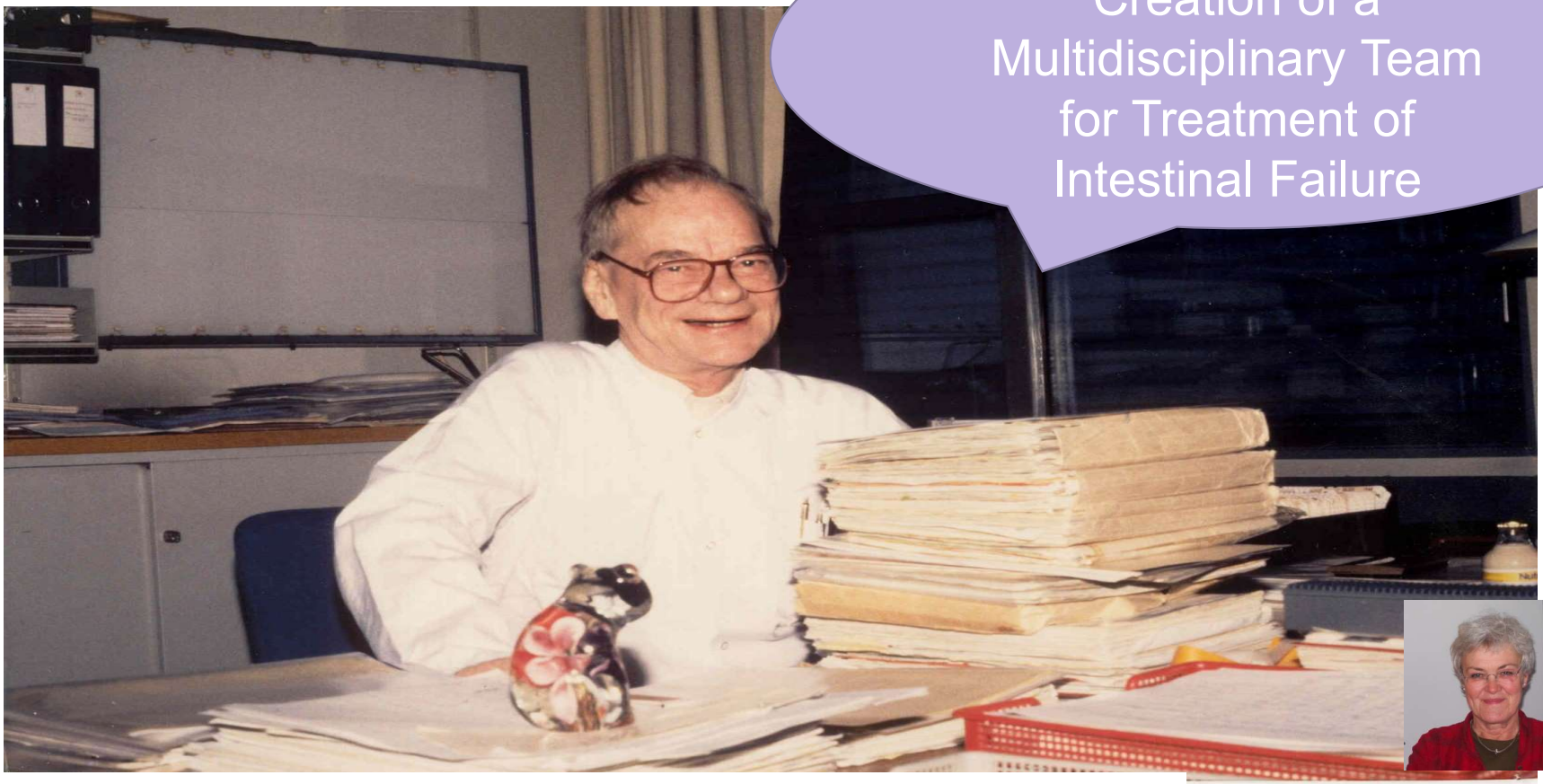
American/JFK:Ambitions

"We choose to go to the moon"

Sept 12th, 1962

Jarnum Ambitions

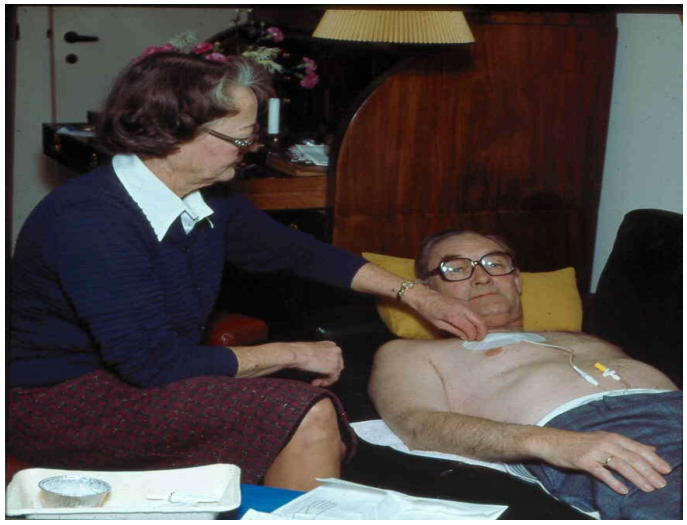
We Choose to Initiate the Creation of a Multidisciplinary Team for Treatment of Intestinal Failure



Karin Ladefoged
Research Fellow

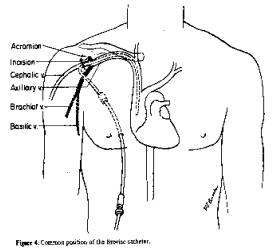
Jarnum S. Parenteral Nutrion in the Short-Bowel-Syndrome. Infusionstherapie Sonderheft (1973) 2: 53-58

First IF patient Discharged with Home Parenteral Support from Rigshospitalet August 25th, 1970



Karin Ladefoged

The Spectrum of Intestinal Function



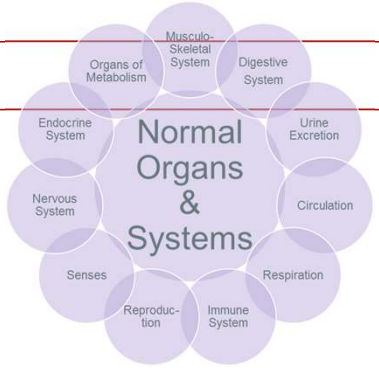
Intestinal Insufficiency | **Borderline** | **Intestinal Failure**

Normal

LIFESAVING PARENTERAL SUPPORT

Mild **Moderate** **Severe** **Mild** **Moderate** **Severe**

PROMOTE INTESTINAL ADAPTATION



Normal

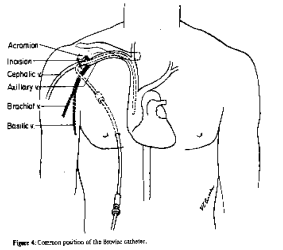
NO Metabolic Adaptation **NO Metabolic Accomodation**

Jeppesen P. Short Bowel Syndrome:
Practical Approach to Management (2016). Editor DiBaise JK. Chapter 1.

The Spectrum of Intestinal Function

IF/HPS & Complications

Intestinal Insufficiency | **Borderline** | **Intestinal Failure**



Normal

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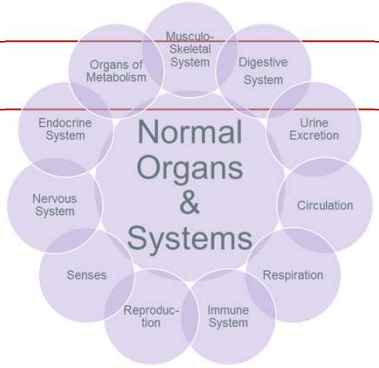
Mild **Moderate** **Severe** **Mild** **Moderate** **Severe**

Normal

PROMOTE INTESTINAL ADAPTATION



NO Metabolic Adaptation **NO Metabolic Accomodation**

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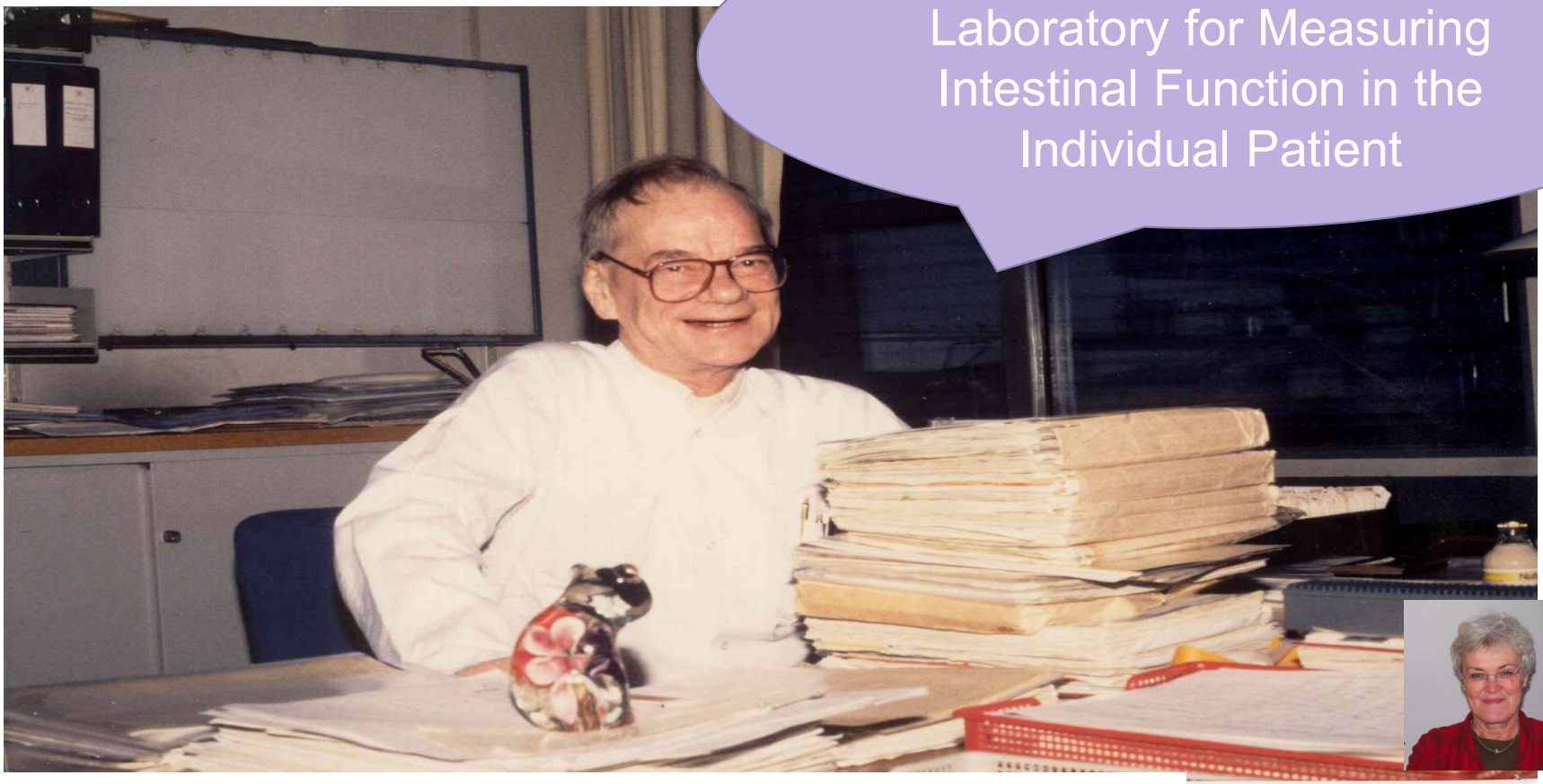
Stig Jarnum - ambitions

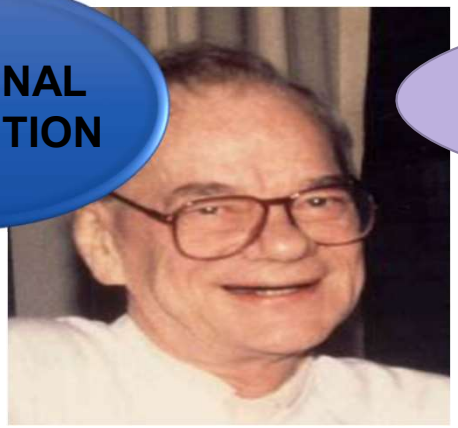
We Choose to set up a Clinical Laboratory for Measuring Intestinal Function in the Individual Patient



Karin Ladefoged
Research Fellow

Jarnum S. Parenteral Nutrion in the Short-Bowel-Syndrome. Infusionstherapie Sonderheft (1973) 2: 53-58

INTESTINAL ABSORPTION



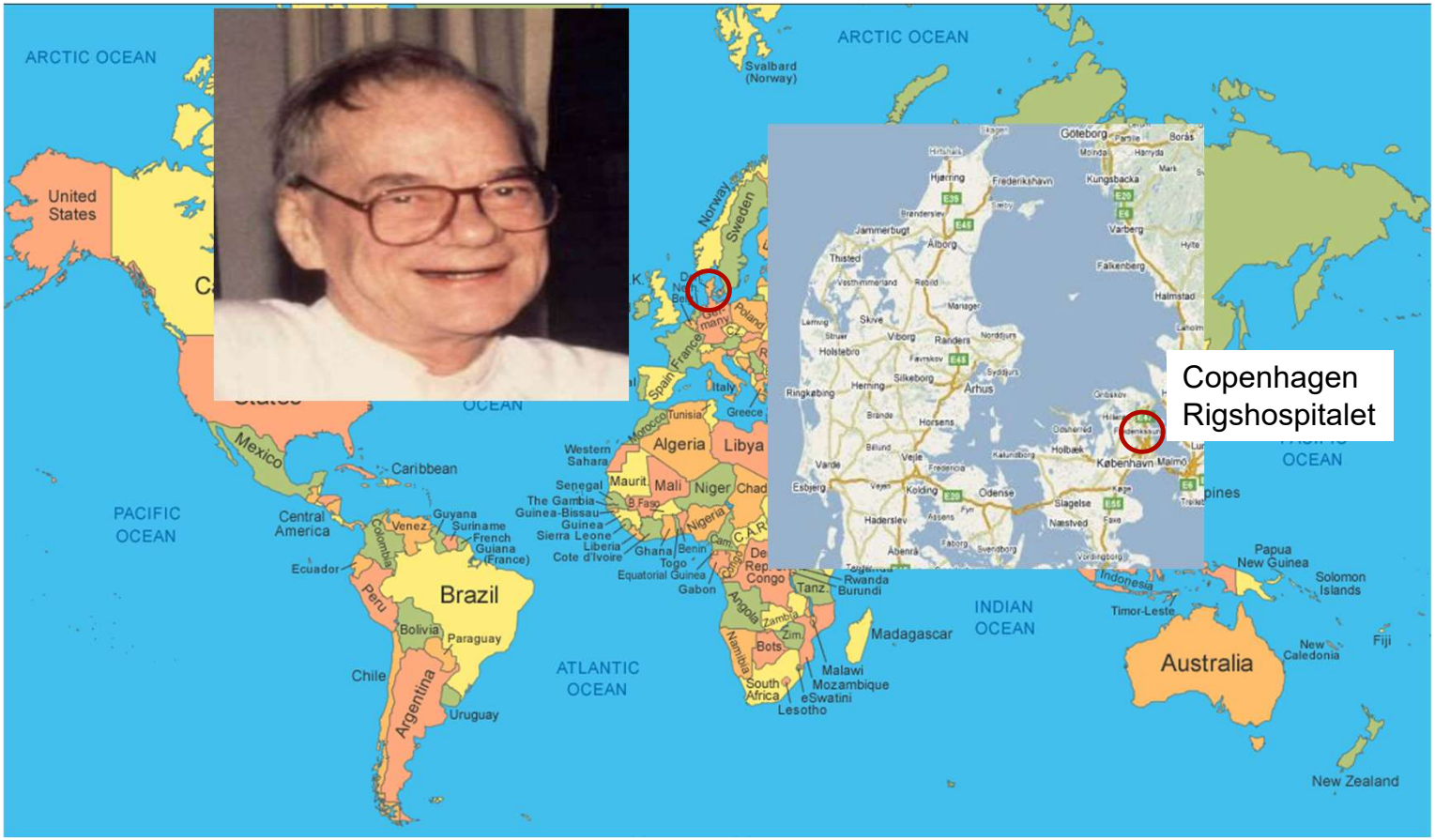
Jarnum/Karin/Jette:
"We want an evidence based approach "

Gold Standard: Metabolic Balance Studies =
Objective Measurements of
The Remnant Intestinal Absorptive Capacity

Jette Christiansen
Lab technician

Balance Studies: Diet – Faeces = Absorption

Karin Ladefoged



Jette Christiansen
Lab technician

The Pioneers

Karin Ladefoged

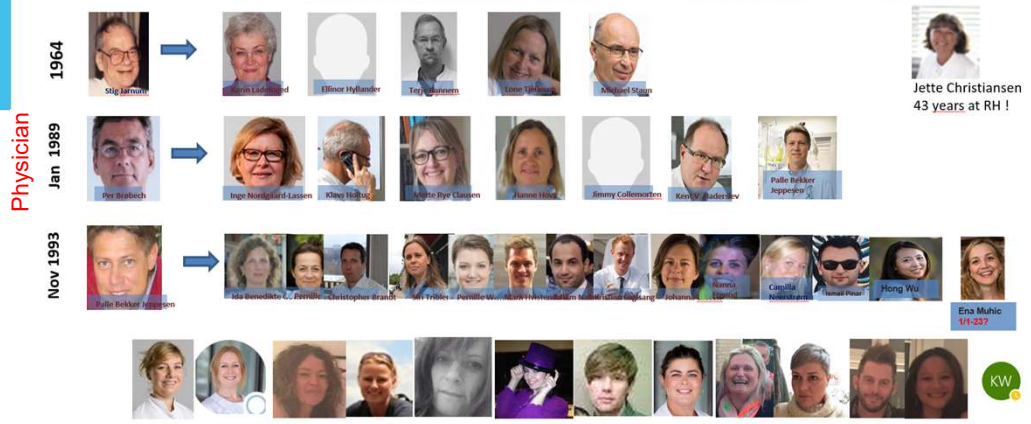
Copenhagen

Department of Intestinal Failure and Liver Disease/ (26-28 Beds)
Rigshospitalet (1000 beds)

Copenhagen

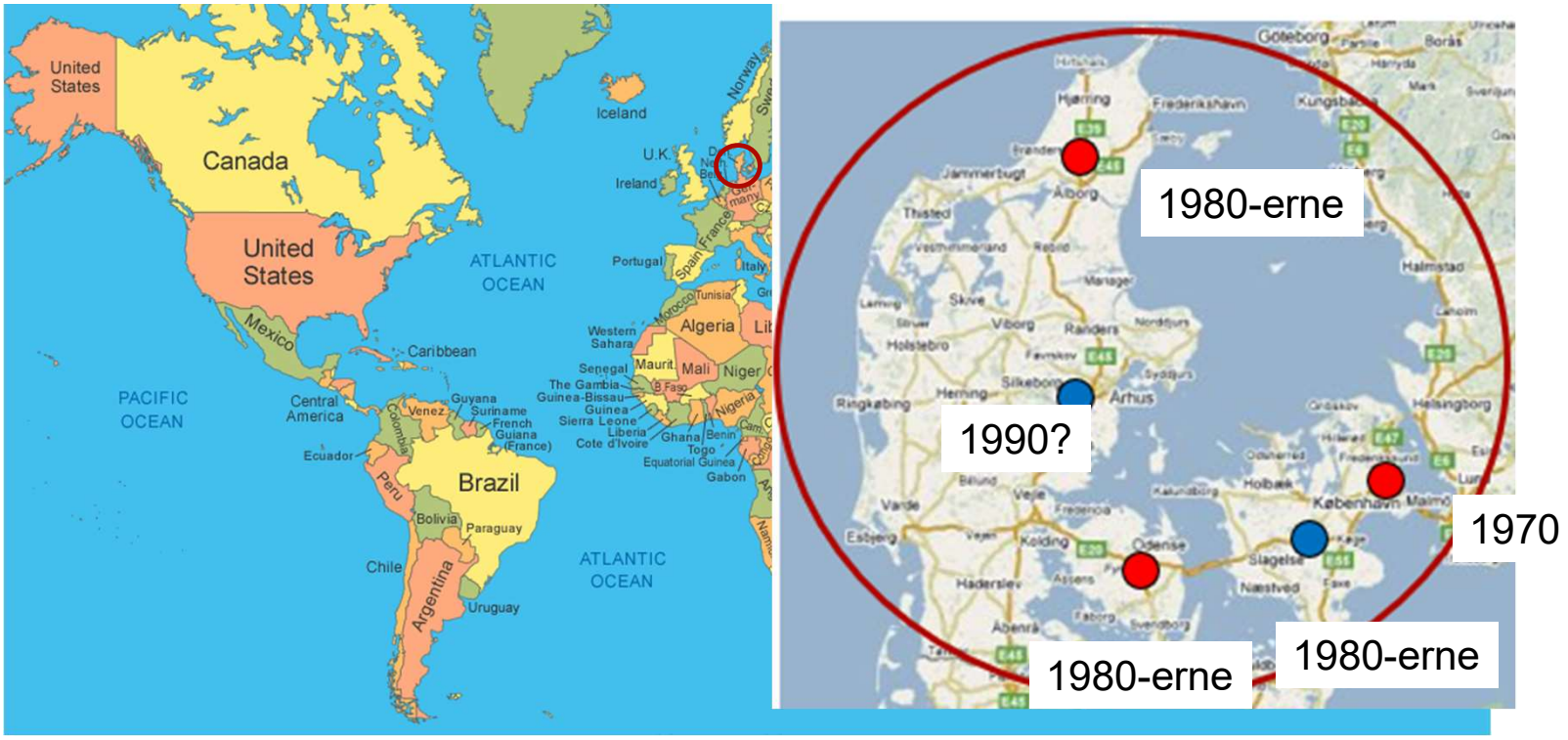
A Key to Clinical Success is:

Knowledge = Dedicated Phycisians (Ph.d.-students), Nurses, Secretaries , Lab. Tech's etc…



The Settlers

Spread of IF-Treatment in Denmark



Key Factors in the Successful IF Treatment in Denmark?

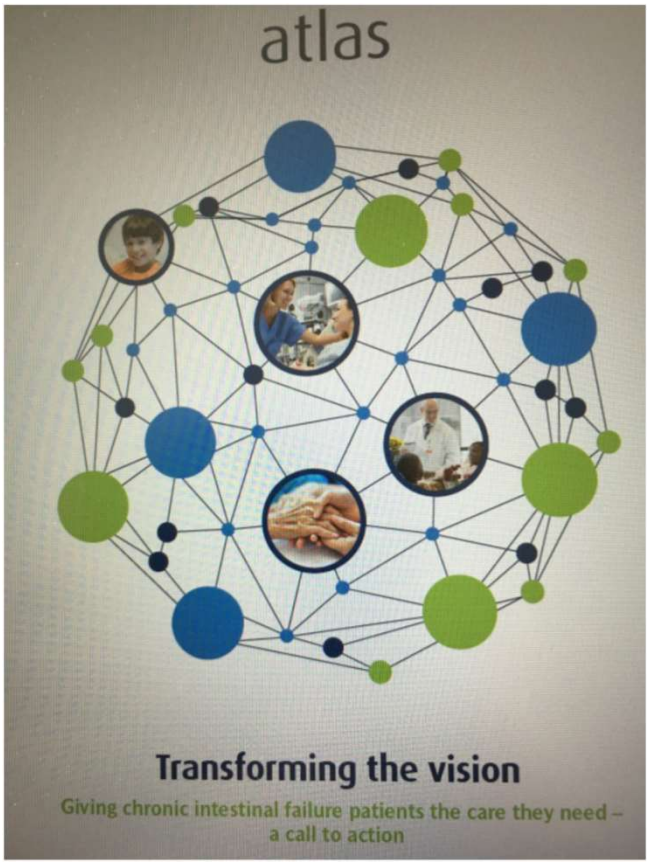
Awareness and Recognition

The Political and Ethical challenge (National)

- **Intestinal Failure Patients** should have **Equal Rights** regarding **Access to Treatment** in Centres of Experience compared to patients with other Organ Failures

Jeppesen PB.
Dig Dis Sci. 2019 Oct;64(10):2717-2735.

EU Policy Paper 2017

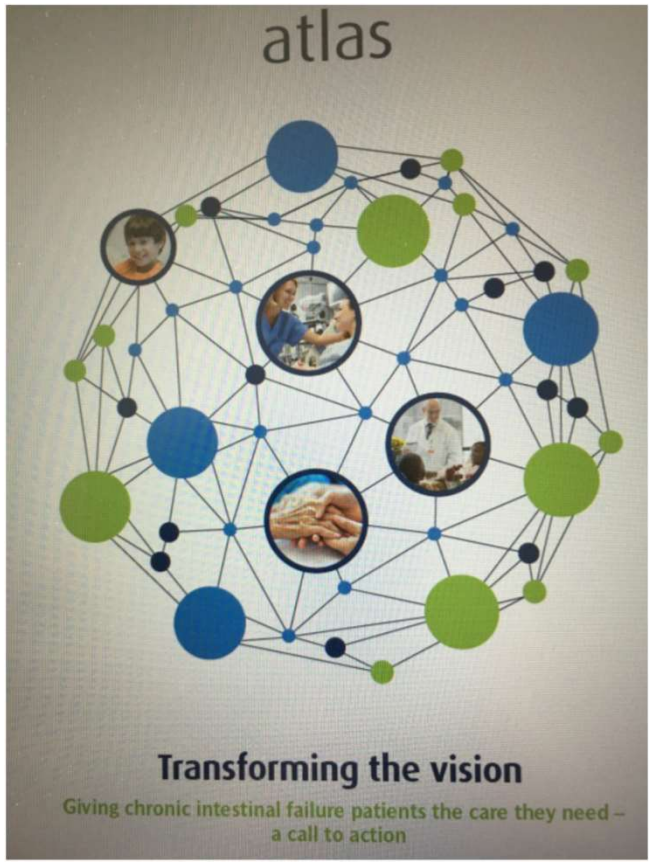


Improving standards of care in Chronic Intestinal Failure

Much more needs to be done to reduce inequalities of care for people suffering from Chronic IF, a rare disease and organ failure, MEPs have been told.

The event's main speakers, from left to right: Professor Palle Jeppesen, Professor Simon Lal, José Inácio Faria MEP, XChronic IF expert patient Marek Lichota, Cristian Busoi MEP & Professor Stéphane Schneider | Photo credit: Jean-Yves Limet

Acceptance of ICD *-11 Codes for SBS and IF !



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Keys to Clinical Success

Clinical Classification according to: The post-surgical outcome (Type I, II and III)

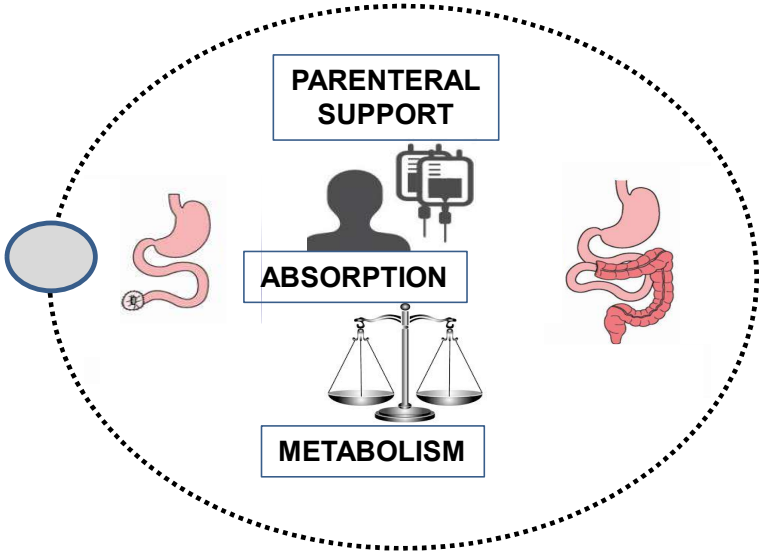
On the basis of onset, metabolic and expected outcome criteria, IF is classified as:

- Type I
  - Acute, short-term and often self limiting condition
- Type II
  - Prolonged acute condition, often in metabolically unstable patients, requiring complex multi-disciplinary care and intravenous supplementation over periods of weeks or months
- Type III
  - Chronic condition, in metabolically stable patients, requiring intravenous supplementation over months or years. It may be reversible or irreversible.

Management strategy and and multidisciplinary team in Intestinal Rehabilitation (IR):

Acute IF

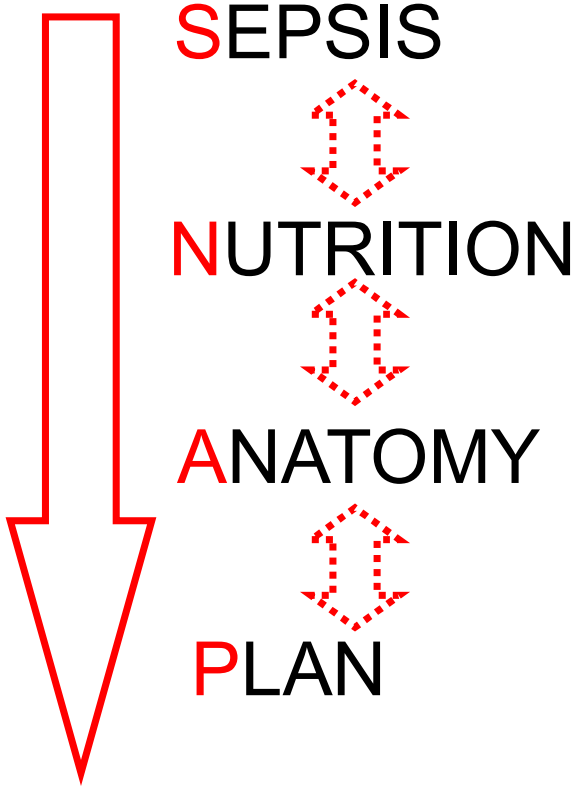
Surgery:
GI Surgeon/
"Liaison Gastroenterologist"
Transplantation Team



IR Clinic Team

Local/Home Healthcare

MANAGEMENT OF ACUTE INTESTINAL FAILURE



*'Resolving **S**epsis is vital before intestinal function and **N**utritional status can be restored. Nutritional repletion is vital before considering reconstructive surgery. Intestinal **A**natomy must be defined so that we can formulate a definitive management **P**lan.'*

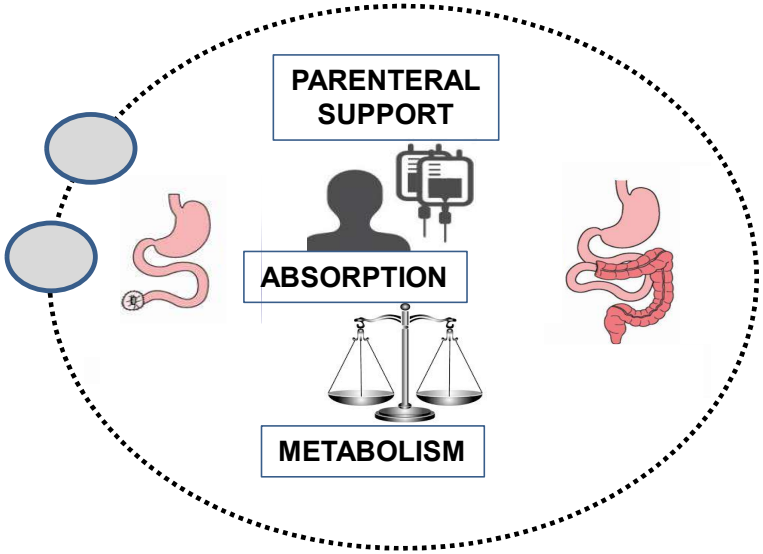
Lal S, Teubner A, Shaffer J. *Alimen Pharm Ther* 2006; 24: 19-31

Management strategy and and multidisciplinary team in Intestinal Rehabilitation (IR):

IF Type 2

Sepsis Resolving Team:
Surgeon/Interventional Radiologist/
Microbiologist/Gastroenterologist

Surgery:
GI Surgeon/
"Liaison Gastroenterologist"
Transplantation Team



IR Clinic Team

Local/Home Healthcare

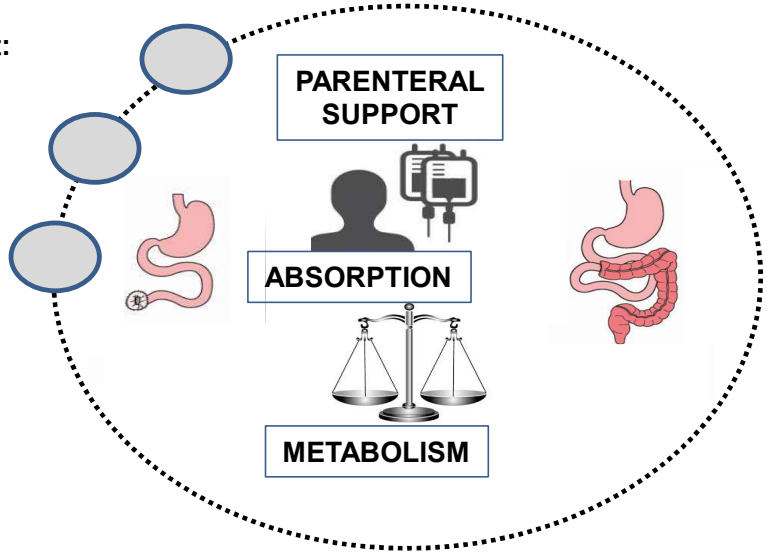
Management strategy and and multidisciplinary team in Intestinal Rehabilitation (IR):

IF Type 2

Pain Management:
Anesthesiologist/nurse

Sepsis Resolving Team:
Surgeon/Interventional Radiologist/
Microbiologist/Gastroenterologist

Surgery:
GI Surgeon/
"Liaison Gastroenterologist"
Transplantation Team



IR Clinic Team

Local/Home Healthcare

Management Strategy and and Multidisciplinary Team in Intestinal Rehabilitation (IR):

IF Type 2

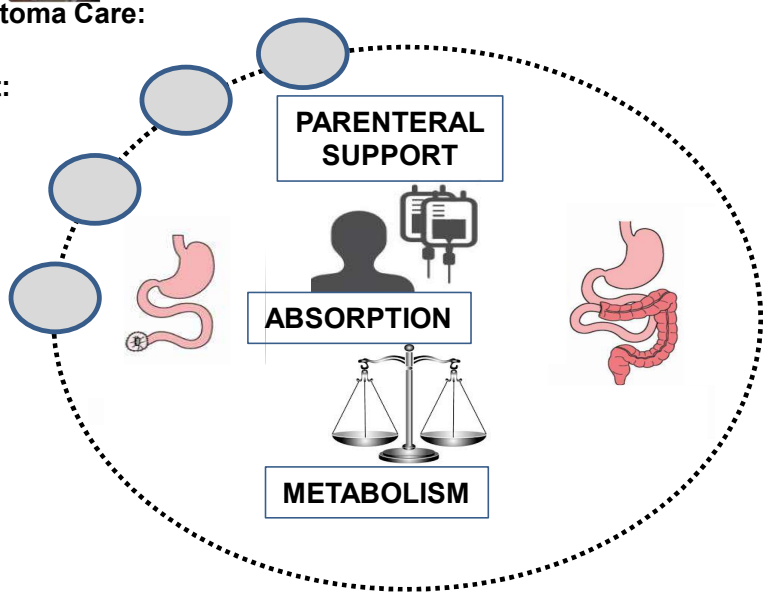


Wound and Stoma Care:
Nurse

Pain Management:
Anesthesiologist/nurse

Sepsis Resolving Team:
Surgeon/Interventional Radiologist/
Microbiologist/Gastroenterologist

Surgery:
GI Surgeon/
"Liaison Gastroenterologist"
Transplantation Team



IR Clinic Team

Local/Home Healthcare

Educating the patient in stoma care

Management Strategy and and Multidisciplinary Team in Intestinal Rehabilitation (IR):

IF Type 2

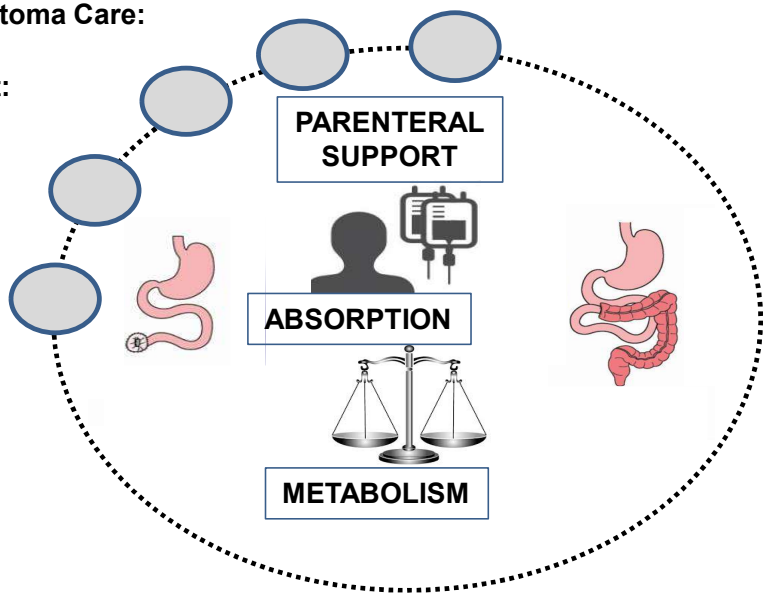
Anatomy Mapping:
Radiologist, Gastroenterologist

Wound and Stoma Care:
Nurse

Pain Management:
Anesthesiologist/nurse

Sepsis Resolving Team:
Surgeon/Interventional Radiologist/
Microbiologist/Gastroenterologist

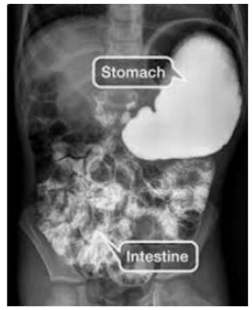
Surgery:
GI Surgeon/
"Liaison Gastroenterologist"
Transplantation Team



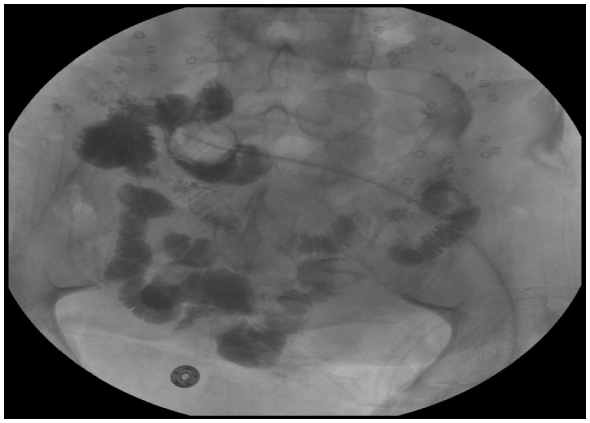
IR Clinic Team

Local/Home Healthcare

ANATOMY MAPPING



- Define health functional intestine, fistulae, identify strictures, /diseased segments.



- Water soluble contrast>Barium:
  - Small Intestinal enema/meal follow through
  - Fistulography
  - Proctogram
  - Urostography/vaginography etc.
  - Tubogram
- CT, MR ect

- Determine long-term nutritional support & timing for reconstructive surgery.

Management Strategy and and Multidisciplinary Team in Intestinal Rehabilitation (IR):

IF Type 2

Anatomy Mapping:
Radiologist, Gastroenterologist

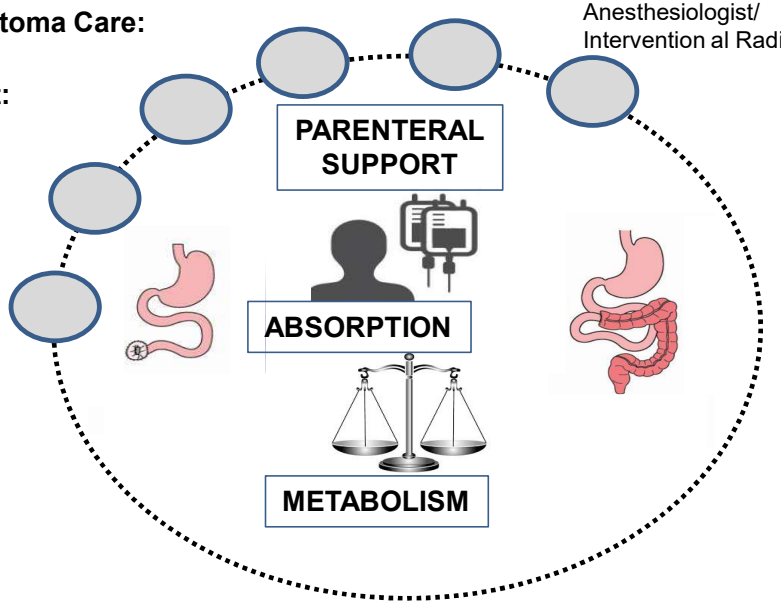
Catheter Placement:
Anesthesiologist/
Intervention al Radiologist/ Surgeon

Wound and Stoma Care:
Nurse

Pain Management:
Anesthesiologist/nurse

Sepsis Resolving Team:
Surgeon/Interventional Radiologist/
Microbiologist/Gastroenterologist

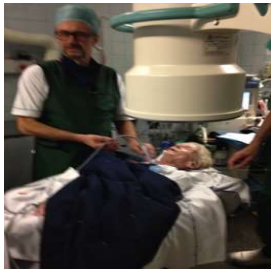
Surgery:
GI Surgeon/
"Liaison Gastroenterologist"
Transplantation Team



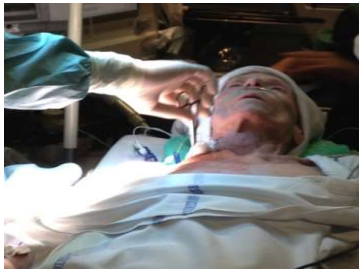
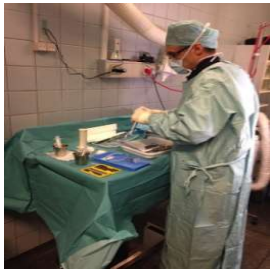
IR Clinic Team

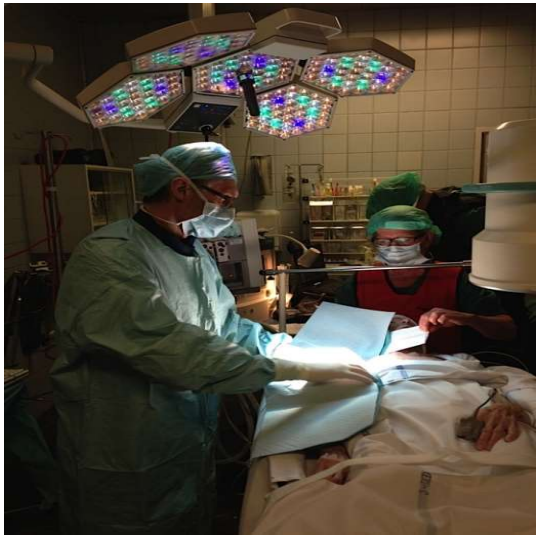
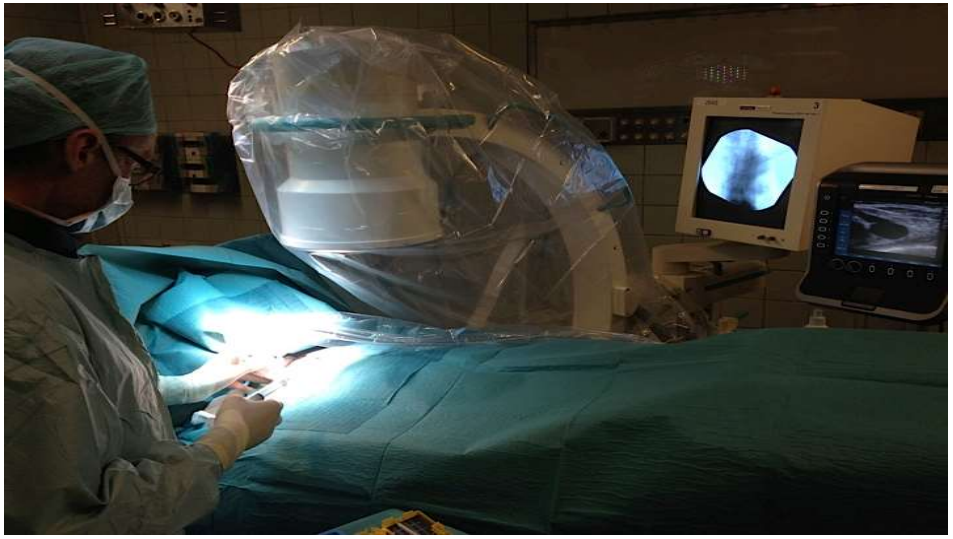
Local/Home Healthcare

HIGH QUALITY OF CATHETER PLACEMENT AND CARE





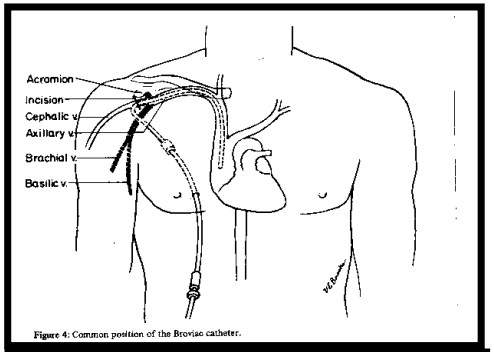
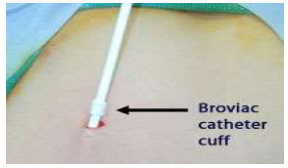


Figure 4: Common position of the Broviac catheter.

Single lumen, dedicated for PS only, SCV/IJV, PICC?, Silicone, Cuffed and Tunnelled, Implanted ports?



Management Strategy and and Multidisciplinary Team in Intestinal Rehabilitation (IR):

IF Type 2

Anatomy Mapping:
Radiologist, Gastroenterologist

Wound and Stoma Care:
Nurse

Pain Management:
Anesthesiologist/nurse

Sepsis Resolving Team:
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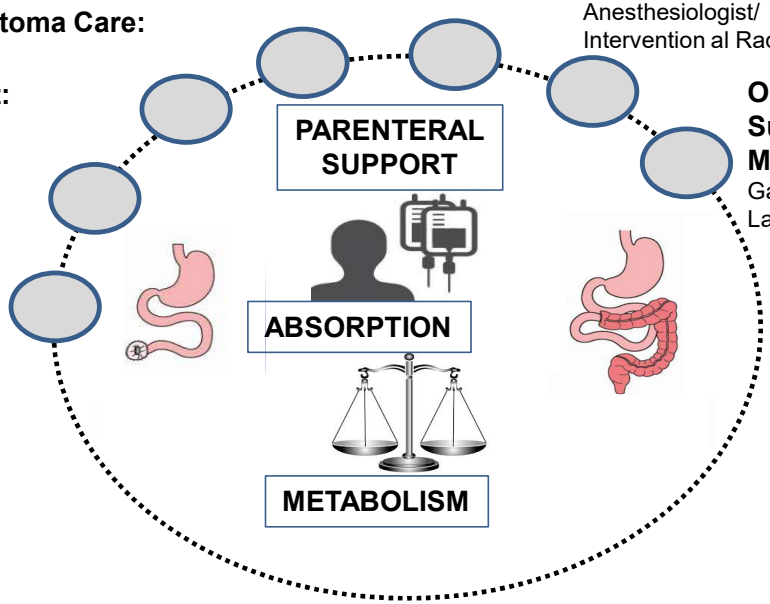
Microbiologist/Gastroenterologist

Surgery:
GI Surgeon/
"Liaison Gastroenterologist"
Transplantation Team

Catheter Placement:
Anesthesiologist/
Intervention al Radiologist/ Surgeon

Oral, Enteral, Parenteral Support and Pharmacological Management:
Gastroenterologist, Dietician, Pharmacist,
Lab. technicians



IR Clinic Team

Local/Home Healthcare

Design and compounding of Parenteral Support

Management Strategy and and Multidisciplinary Team in Intestinal Rehabilitation (IR):

IF Type 2

Anatomy Mapping:
Radiologist, Gastroenterologist

Wound and Stoma Care:
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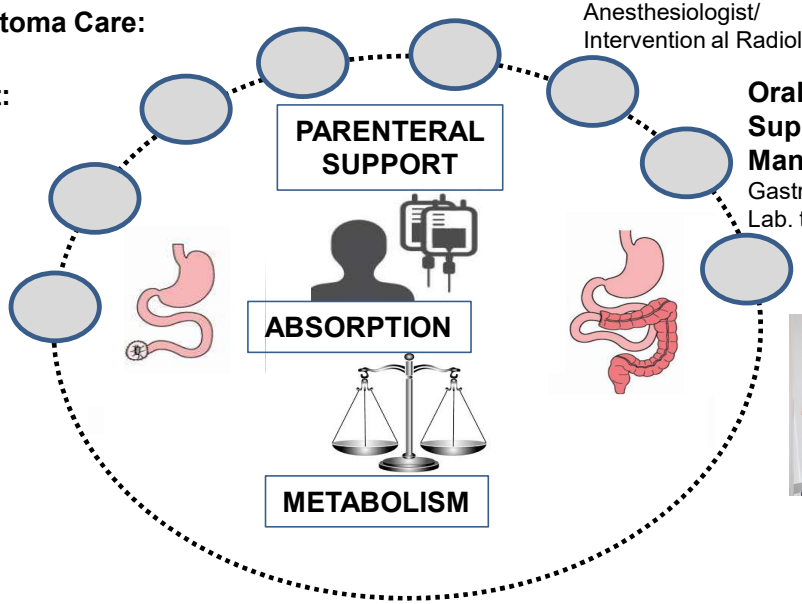
Microbiologist/Gastroenterologist

Surgery:
GI Surgeon/
"Liaison Gastroenterologist"
Transplantation Team

Catheter Placement:
Anesthesiologist/
Intervention al Radiologist/ Surgeon

Oral, Enteral, Parenteral Support and Pharmacological Management:
Gastroenterologist, Dietician, Pharmacist, Lab. technicians

General Hospital Care:
Nurse, Physiotherapy



IR Clinic Team

Local/Home Healthcare

Management Strategy and and Multidisciplinary Team in Intestinal Rehabilitation (IR):

IF Type 2

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Radiologist, Gastroenterologist

Wound and Stoma Care:
Nurse

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Microbiologist/Gastroenterologist

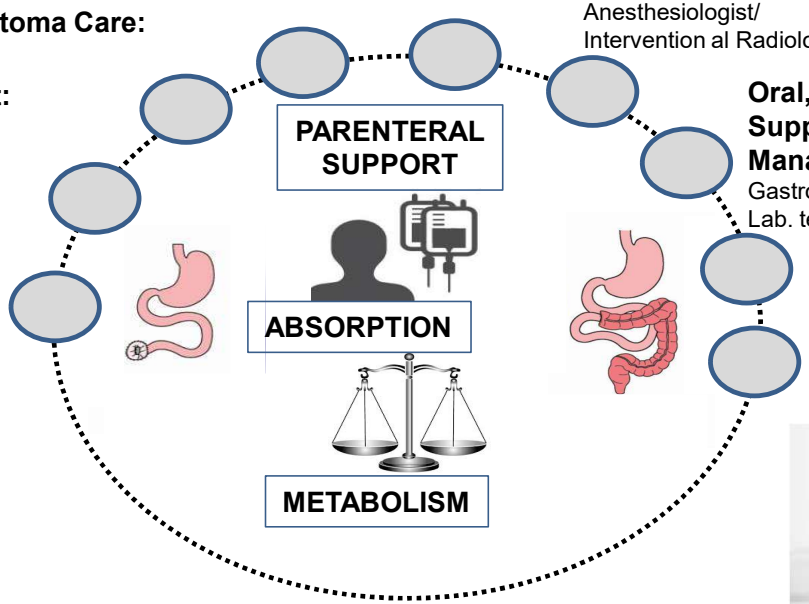
Surgery:
GI Surgeon/
"Liaison Gastroenterologist"
Transplantation Team

Catheter Placement:
Anesthesiologist/
Intervention al Radiologist/ Surgeon

Oral, Enteral, Parenteral Support and Pharmacological Management:
Gastroenterologist, Dietician, Pharmacist, Lab. technicians

General Hospital Care:
Nurse, Physiotherapy

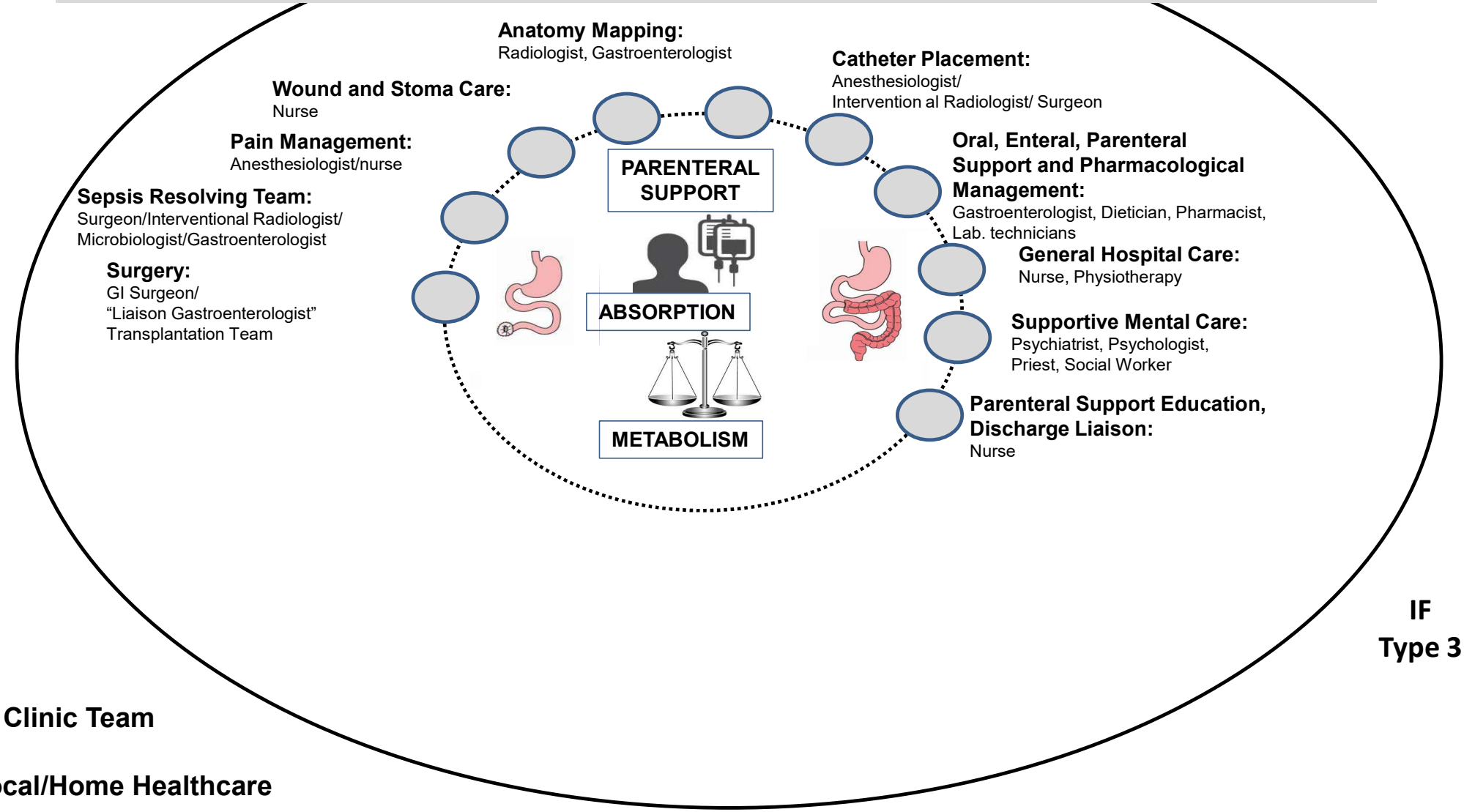
Supportive Mental Care:
Psychiatrist, Psychologist,
Priest, Social Worker



IR Clinic Team

Local/Home Healthcare

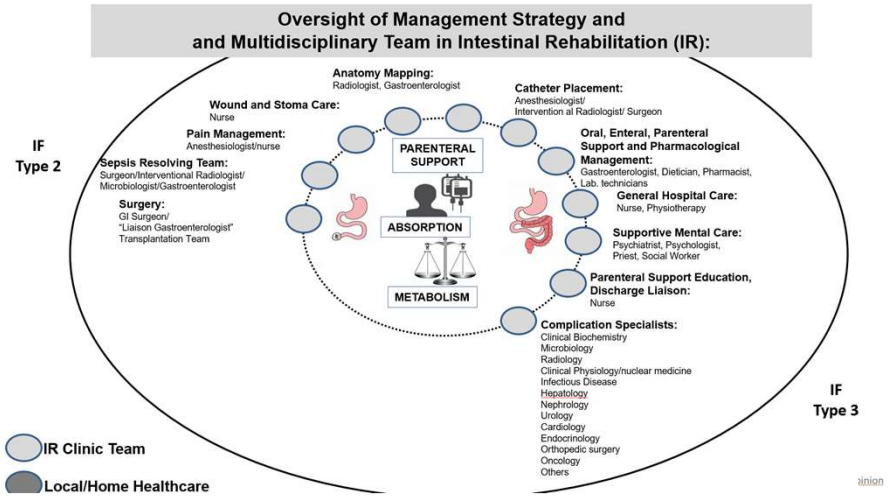
Management Strategy and and Multidisciplinary Team in Intestinal Rehabilitation (IR):



Patient education for Home Parenteral Support

HPS/IF Challenges

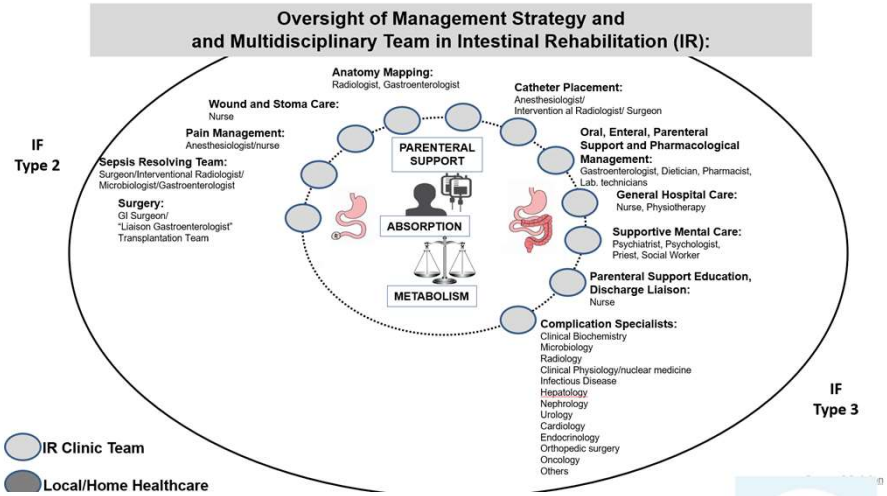
Hospital



Chronic
Life-Long
Diseases

HPS/IF Challenges

Hospital

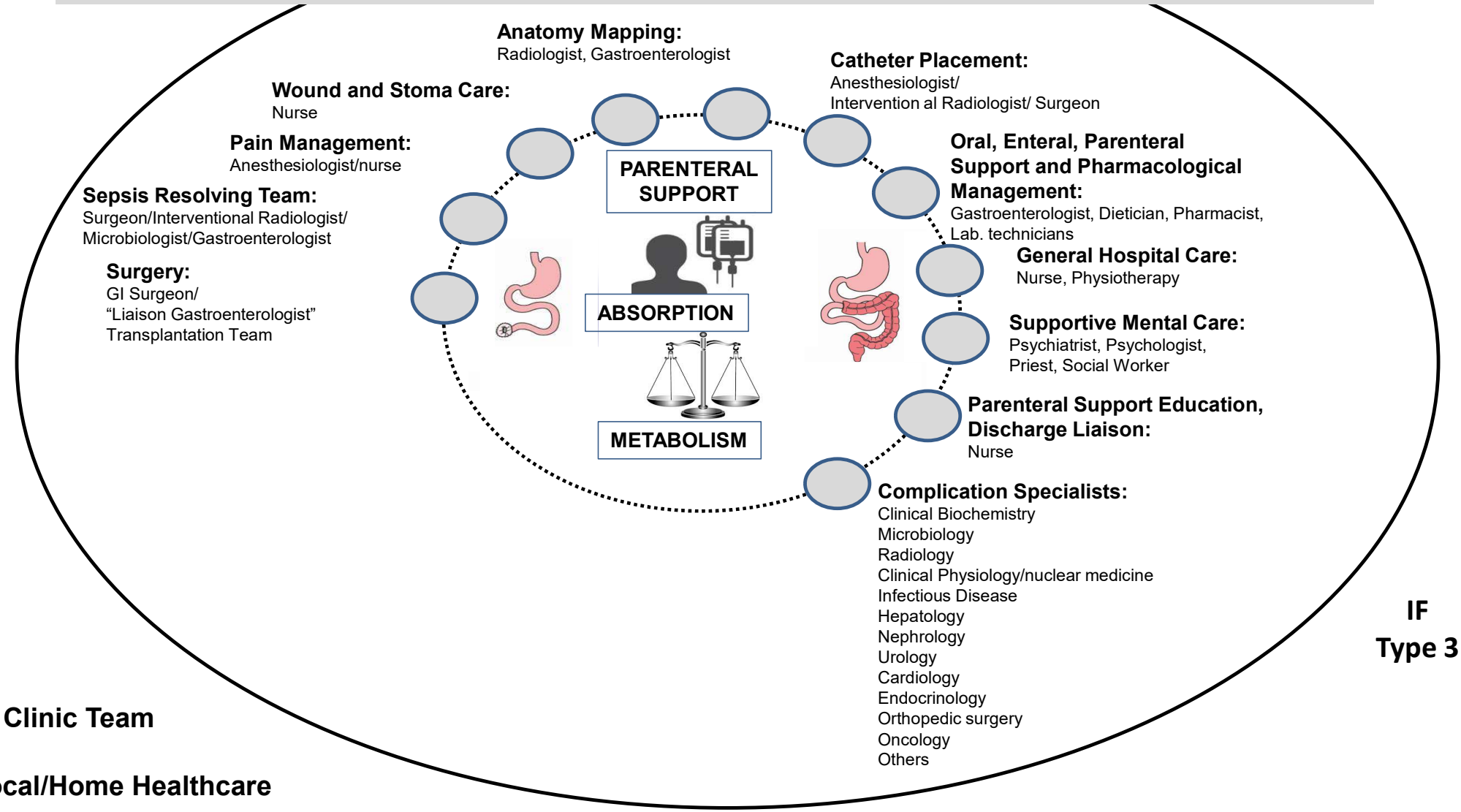


Home Care

Chronic
Life-Long
Diseases

How to plan a successful discharge of patients for home treatment?

Management strategy and and multidisciplinary team in Intestinal Rehabilitation (IR):



Support of Patients, Relatives and Healthcare Professionals in the Home Environment

Management strategy and and multidisciplinary team in Intestinal Rehabilitation (IR):

IF Type 2

Anatomy Mapping:
Radiologist, Gastroenterologist

Wound and Stoma Care:
Nurse

Pain Management:
Anesthesiologist/nurse

Sepsis Resolving Team:
Surgeon/Interventional Radiologist/
Microbiologist/Gastroenterologist

Surgery:
GI Surgeon/
"Liaison Gastroenterologist"
Transplantation Team

Catheter Placement:
Anesthesiologist/
Intervention al Radiologist/ Surgeon

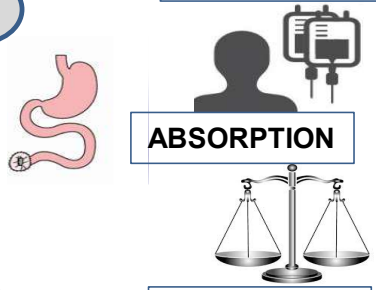
Oral, Enteral, Parenteral Support and Pharmacological Management:
Gastroenterologist, Dietician, Pharmacist,
Lab. technicians

General Hospital Care:
Nurse, Physiotherapy

Supportive Mental Care:
Psychiatrist, Psychologist,
Priest, Social Worker

Parenteral Support Education, Discharge Liaison:
Nurse

Complication Specialists:
Clinical Biochemistry
Microbiology
Radiology
Clinical Physiology/nuclear medicine
Infectious Disease
Hepatology
Nephrology
Urology
Cardiology
Endocrinology
Orthopedic surgery
Oncology
Others



IR Laboratory/ Quality Assurance/ Database/Research/ Development:
Head of Laboratory/
Gastroenterologist/
Laboratory Technicians/
Ph.D.-students/ Post-docs

Palle Bekker Jeppesen

IF Type 3

IR Clinic Team

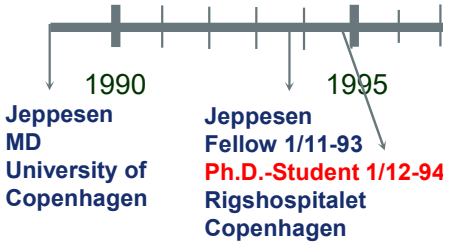
Local/Home Healthcare

”Anvendelse og udviklingen af intestinale vækst-faktorer i behandlingen af tarmsvigt”

Cheflæge Palle Bekker Jeppesen,

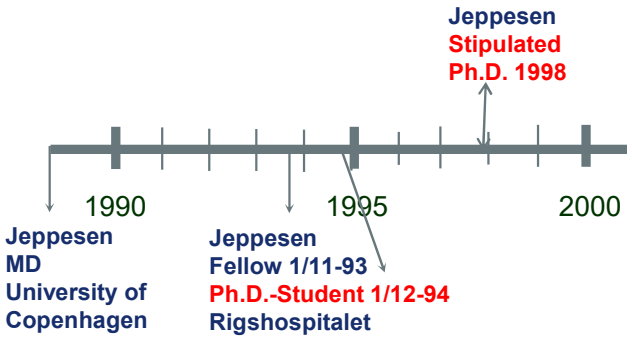
Afdeling for Tarmsvigt og Leversygdomme,
Rigshospitalet.

Fellow at Rigshospitalet 1993, Ph.d.-Student 1994



Per Brøbech Mortensen Vejleder/Mentor

Ph.d.-Student



Initial Reseach Themes:

Measurement of Intestinal Function

Intestinal Adaptation

Intestinal Rehabilitation

Balance Studies: Diet – Faeces = Absorption

The ”Whip”

Jette Christiansen
Lab technician

HPN/IF EPIDEMI-OLOGY

Denmark:
"A Fairy Tale Country and a Heaven for Clinical and Epidemiological Intestinal Failure (IF) Research….."

- Centralised referral of IF patients
  - IF History since 1970
  - Well established network
- All Danes are entitled to Social Security
  - Free access to HPN, if needed…
- Small Population 5.8 million
- Small Distances
- Little Emigration/"Lost to follow-up"
- Centralised Registries
  - Death, infections etc.

IF Center Satelite IF Center

HPN/IF

EPIDEMI-OLOGY

Adult Patients Receiving Home Parenteral Nutrition in Denmark from 1991 to 1996: Who Will Benefit from Intestinal Transplantation?

P. BEKKER JEPPESEN, M. STAUN & P. BRØBECH MORTENSEN
Dept. of Medicine CA, Division of Gastroenterology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

P. B. Jeppesen et al.

Scand.J.Gastroenterol. 1998;338:839-846.

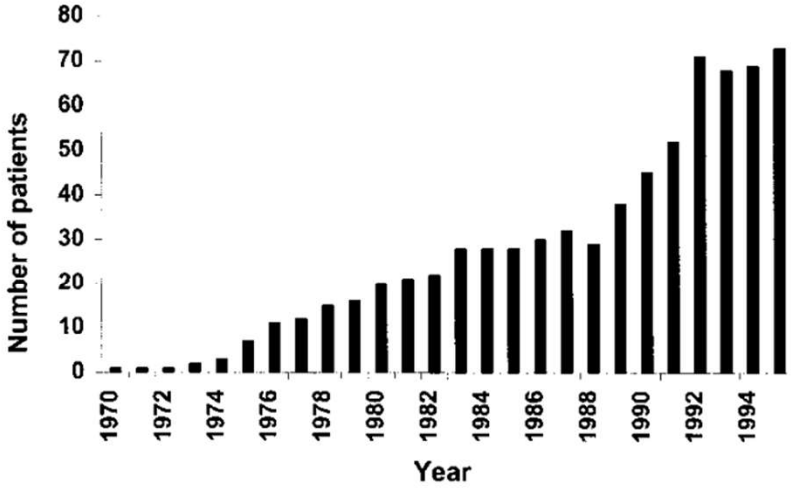


Fig. 1. The number of patients receiving home parenteral nutrition in Denmark from 1970 to 1996.

A total of 73 patientswere receiving HPN at the end of December 1995, a prevalence of 13.9 patients per million in a population of 5.2million. Fifty-seven (78%) were monitored at the Copenhagen centre, and 12, 2, and 2 were seen in hospitals in Aalborg,Odense, and Køge, respectively.

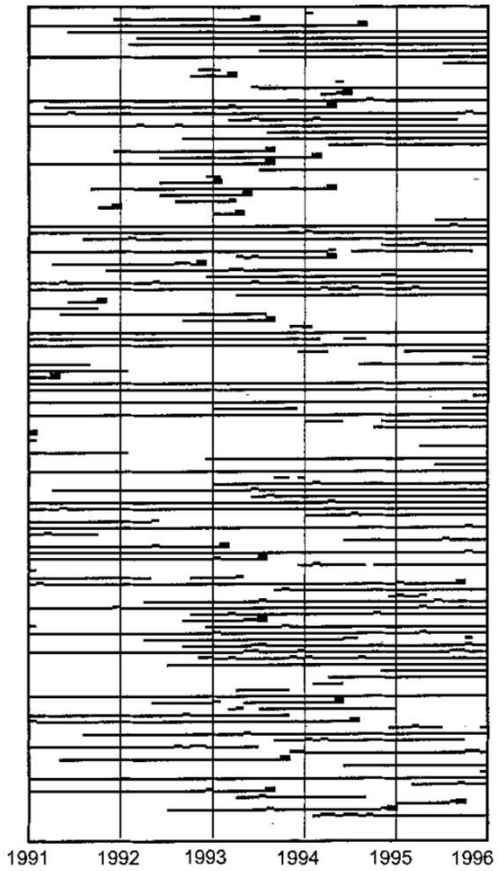


Fig. 2. The individual time course of home parenteral nutrition for all 129 patients in the period 1991 to 1996 (313.5 catheter-years). Black squares indicate death. Elevated grey squares indicate episode of sepsis.

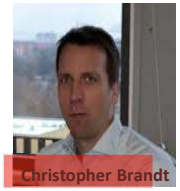
HPN/IF

EPIDEMI-OLOGY

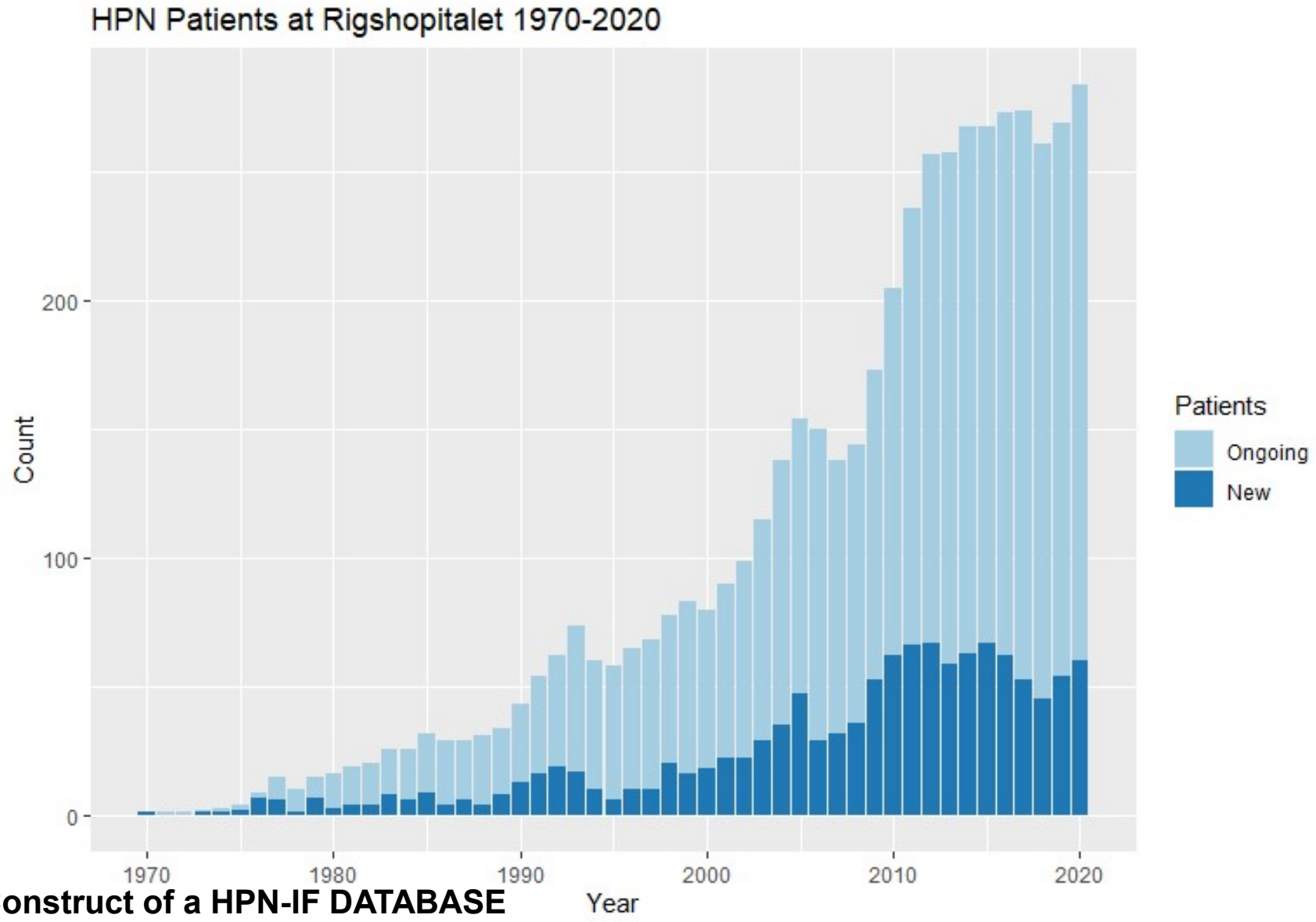
The Construct of a HPN-IF DATABASE

HPN/IF

EPIDEMI-OLOGY



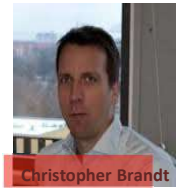
2013-2016



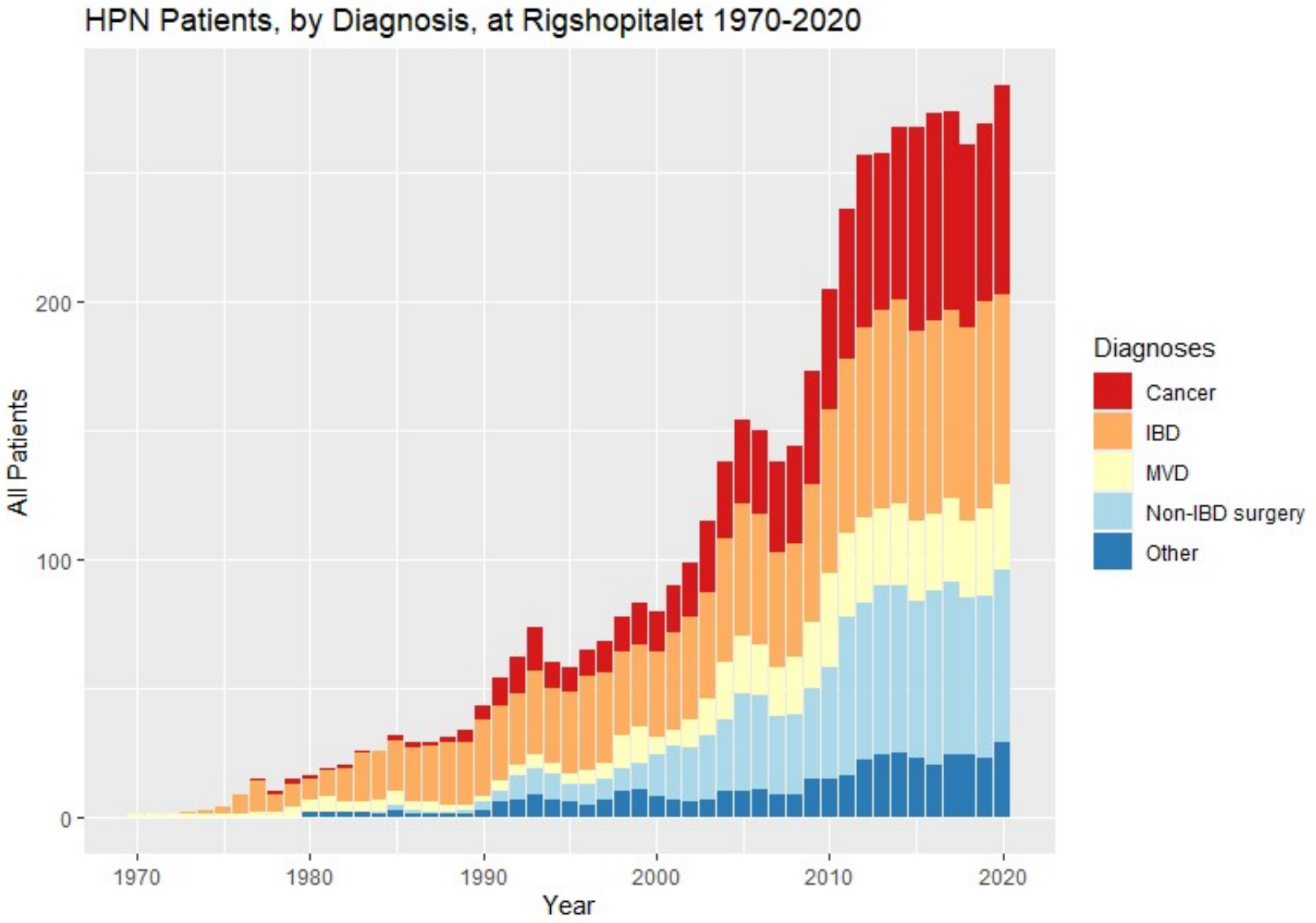
The Construct of a HPN-IF DATABASE

Brandt CF et al. JPEN J Parenter Enteral Nutr. 2018 Jan;42(1):95-103.

HPN/IF EPIDEMI-OLOGY



2013-2016



Brandt CF et al. JPEN J Parenter Enteral Nutr. 2018 Jan;42(1):95-103.

HPN/IF EPIDEMI-OLOGY

Denmark:
"A Fairy Tale Country and a Heaven for Clinical and Epidemiological Intestinal Failure (IF) Research….."

IF Center Satelite IF Center

1/9-22
Rigshospitalet = 240 IF Patients
Aalborg = 200 IF Patients
Odense = 120
Køge = 60

In total = 620 IF Patients in DK = **Prevalence 106/MIO**

The highest prevalence in the world!

Home Parenteral Support Outcomes at Rigshospitalet

Survival in adult non-Malignant SBS-IF: 76% and 65% at 5 and 10 years

HPN/IF EPIDEMI-OLOGY

2016-2020

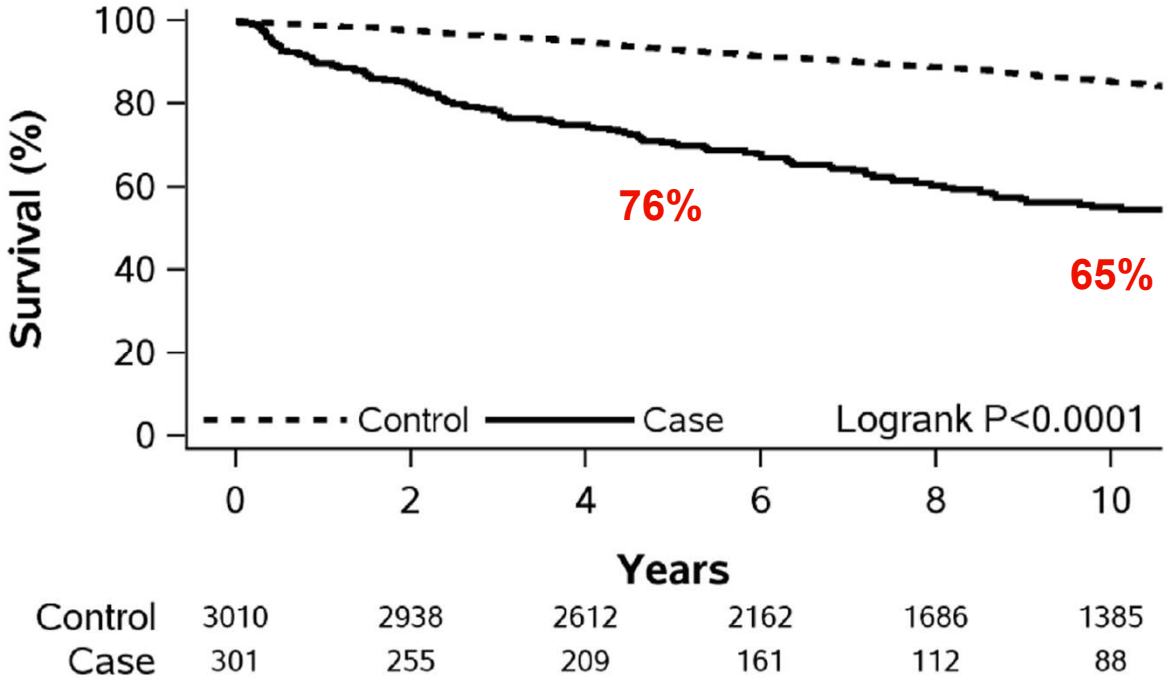


Fig. 1. Overall survival for cases and matched controls. Years: Time from home parenteral support initiation for cases and from observation start for controls. N at risk below figure.

Survival in patients initiating home parenteral support due to nonmalignant short bowel syndrome compared with background population.
Fuglsang KA, Brandt CF, Jeppesen PB.Clin Nutr ESPEN. 2022 Aug;50:170-177.

Survival in adult non-Malignant SBS-IF: 76% and 65% at 5 and 10 years

HPN/IF EPIDEMI-OLOGY

2016-2020

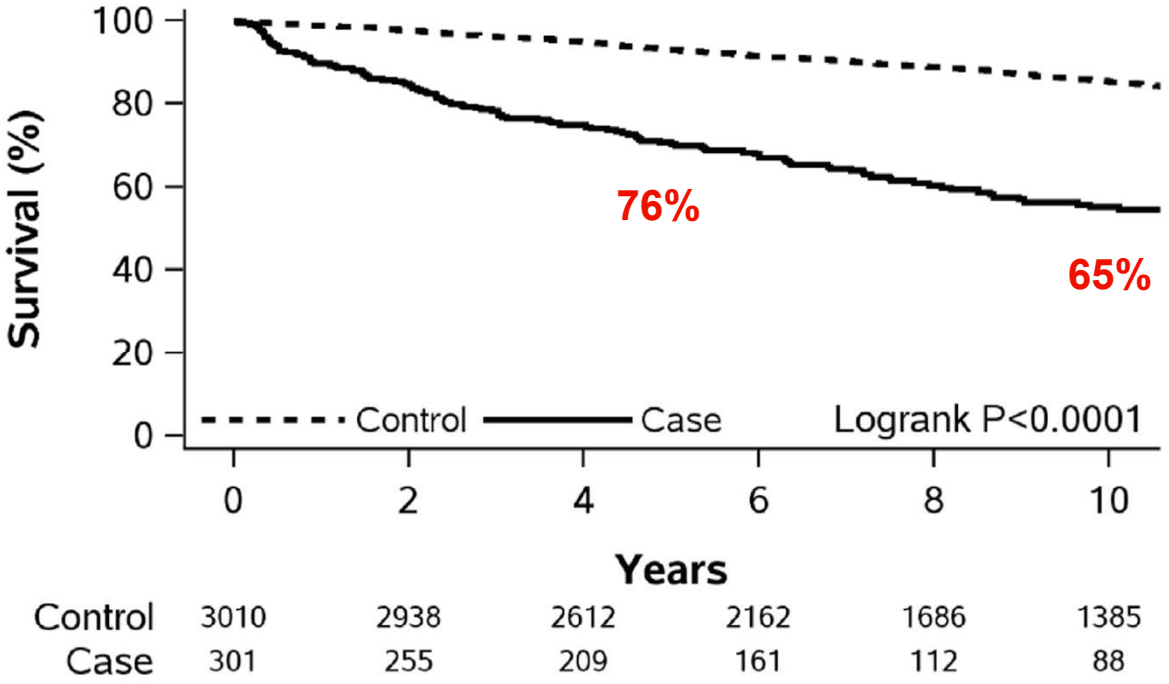


Fig. 1. Overall survival for cases and matched controls. Years: Time from home parenteral support initiation for cases and from observation start for controls. N at risk below figure.

Only 13 (11%) of the registered deaths were related to HPS complications:
10 Intestinal Failure Associated Liver Disease/3 Catheter Related Sepsis

Survival in patients initiating home parenteral support due to nonmalignant short bowel syndrome compared with background population.
Fuglsang KA, Brandt CF, Jeppesen PB.Clin Nutr ESPEN. 2022 Aug;50:170-177.

HPN/IF

EPIDEMI-OLOGY

Admission time ~ 6.5% of Life on HPS

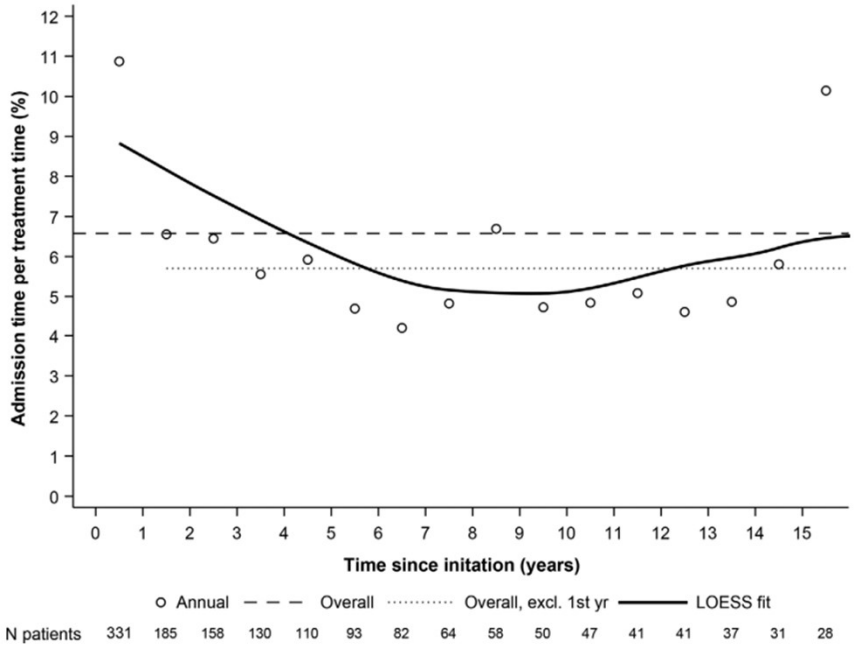


Figure 2. Admission time per treatment time. Calculated as the time admitted while on HPS per HPS treatment time. excl. excluding; HPS, home parenteral support; LOESS fit, locally estimated scatterplot smoothing fit (weighted by the annual treatment time, smoothing 0.4 and with cubic interpolation).

Annual Admissions ~ 2.5 per year

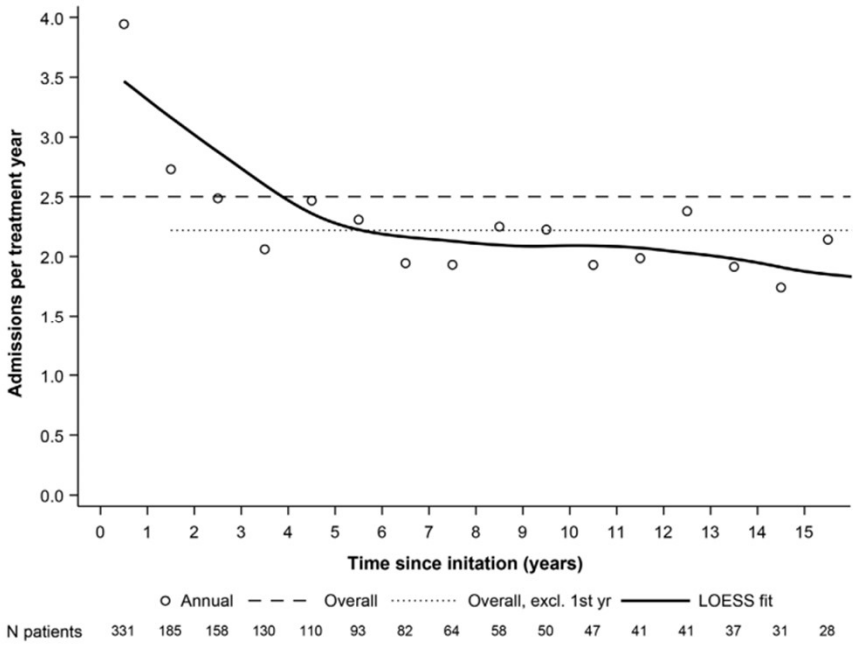


Figure 3. Hospitalizations per treatment year. Calculated as the number of admissions while on home parenteral support per treatment time not spent readmitted. excl., excluding; LOESS fit, locally estimated scatterplot smoothing fit (weighted by the annual treatment time, smoothing 0.3 and with cubic interpolation).

Fuglsang KA, Brandt CF, Scheike T, Jeppesen PB. Hospitalizations in Patients With Nonmalignant Short-Bowel Syndrome Receiving Home Parenteral Support. Nutr Clin Pract. 2020 Oct;35(5):894-902.

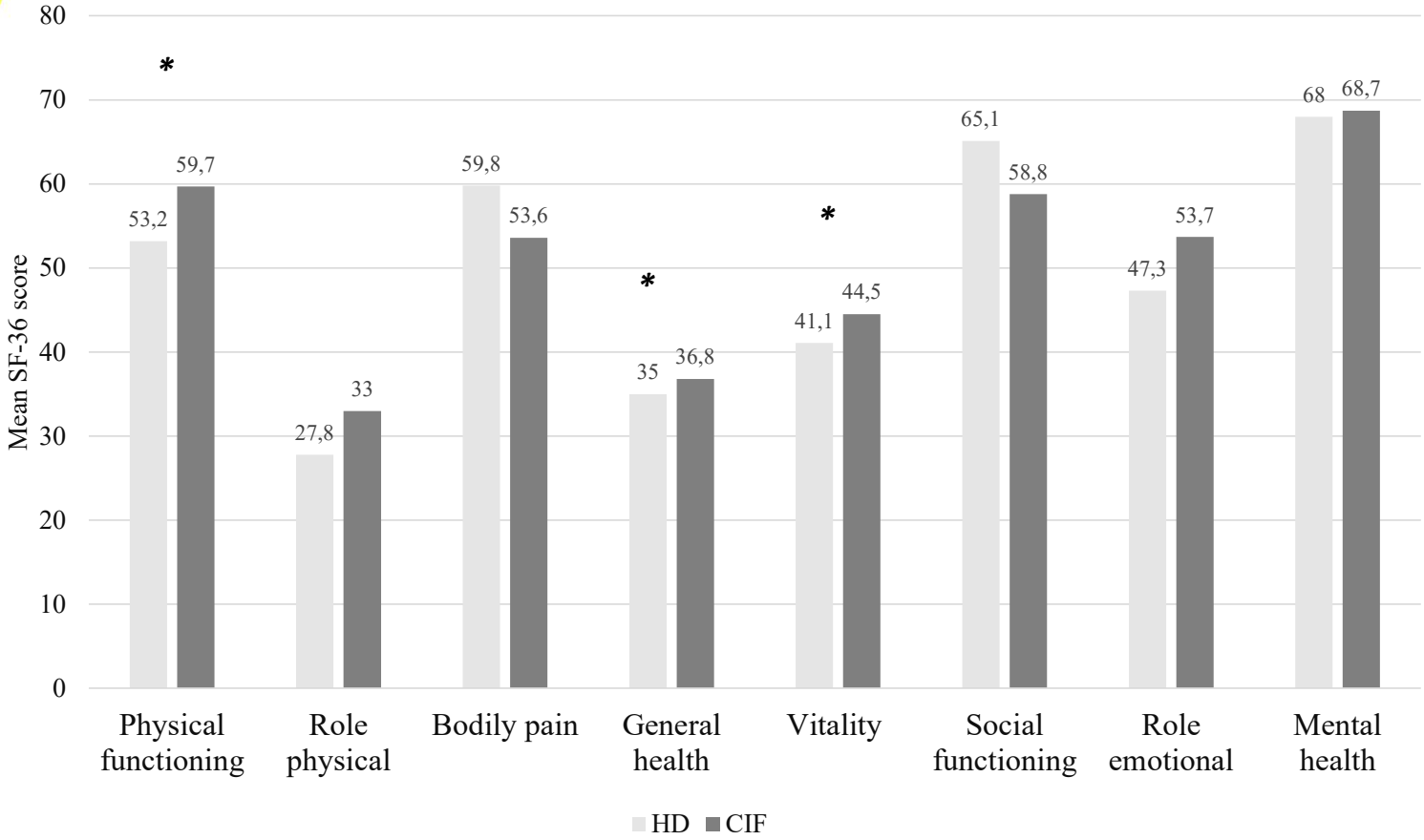
QUALITY OF LIFE

SBS QoL PRO etc.

2018-2021

Quality of Life:

Chronic Intestinal Failure/HPS vs. Renal Failure/Hemodialysis



A Comparison of Health-related Quality of Life in Chronic Intestinal Failure and Chronic Renal Failure: Equal Needs Require Equal Attention.

Johanna Eliasson MD, PhD[1], Louise Bangsgaard Antonsen RN, MSc[1], Stig Molsted PhD[5], Ylian Serina Liem MD, PhD[2], Inge Eidemak MD, PhD[3], Sille Larsen RN, Per Sjøgren MD, PhD[3], Geana Paula Kurita PhD[3,4,6], Palle Bekker Jeppesen MD, PhD[1,] Submitted Gut 2023.

Evaluation of Organ Function and Failure Well-Established

Kidney ~ Creatinine Clearence

Heart ~ Cardiac output

Lung ~ Blood gasses

Liver ~ Coma scale

Evaluation of Organ Function and Failure Well-Established

Kidney ~ Creatinine Clearence

Heart ~ Cardiac output

Lung ~ Blood gasses

Liver ~ Coma scale

Gut ?

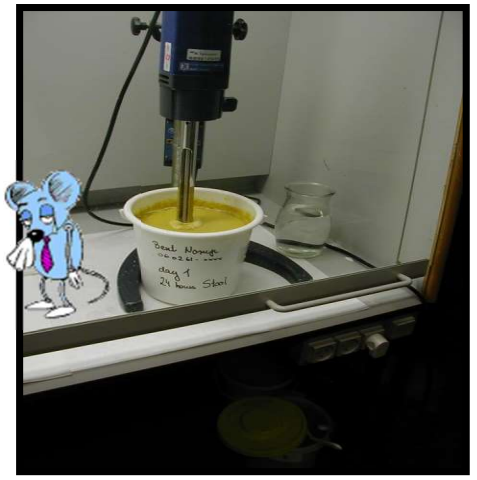
Intestinal Failure Evaluated/Defined by Metabolic Balances?

INTESTINAL ABSORPTION

Jette Christiansen
Lab technician

Classification according to: The remnant intestinal absorptive capacity

Balance Studies: Diet – Faeces = Absorption



Gut 2000;46:701–706

Intestinal failure defined by measurements of intestinal energy and wet weight absorption

P B Jeppesen, P B Mortensen

INTESTINAL ABSORPTION

Methods in Balance Studies

Jette Christiansen
Lab technician

Weights by simple measurements

Electrolytes by Spectrometry

Energy by bombcaloriemetry

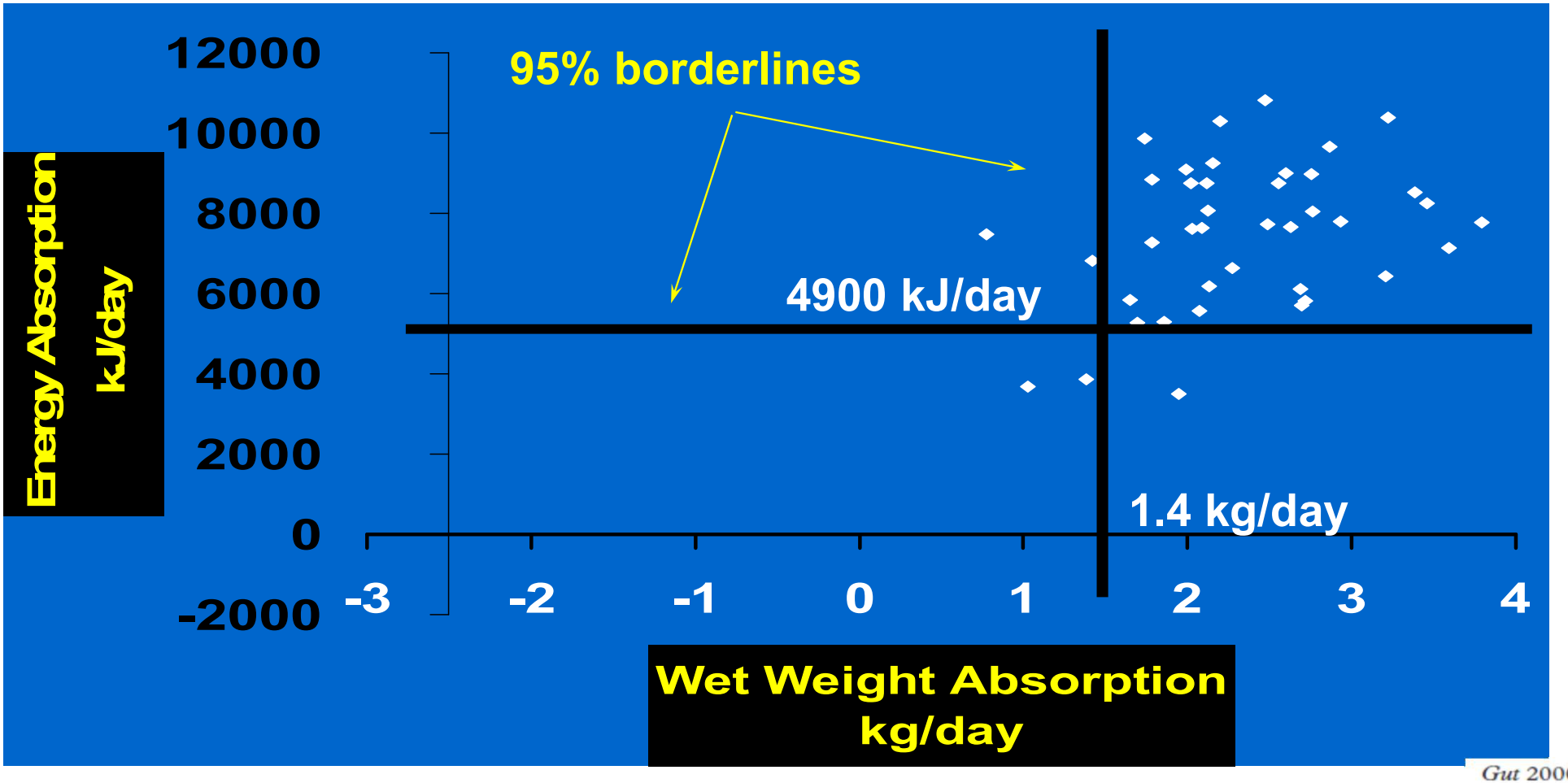
Fat by gas-chromatography/titration

Nitrogen by method of Kjeldahl

Carbohydrate by method of Englyst

Balance Studies: Diet – Faeces = Absorption

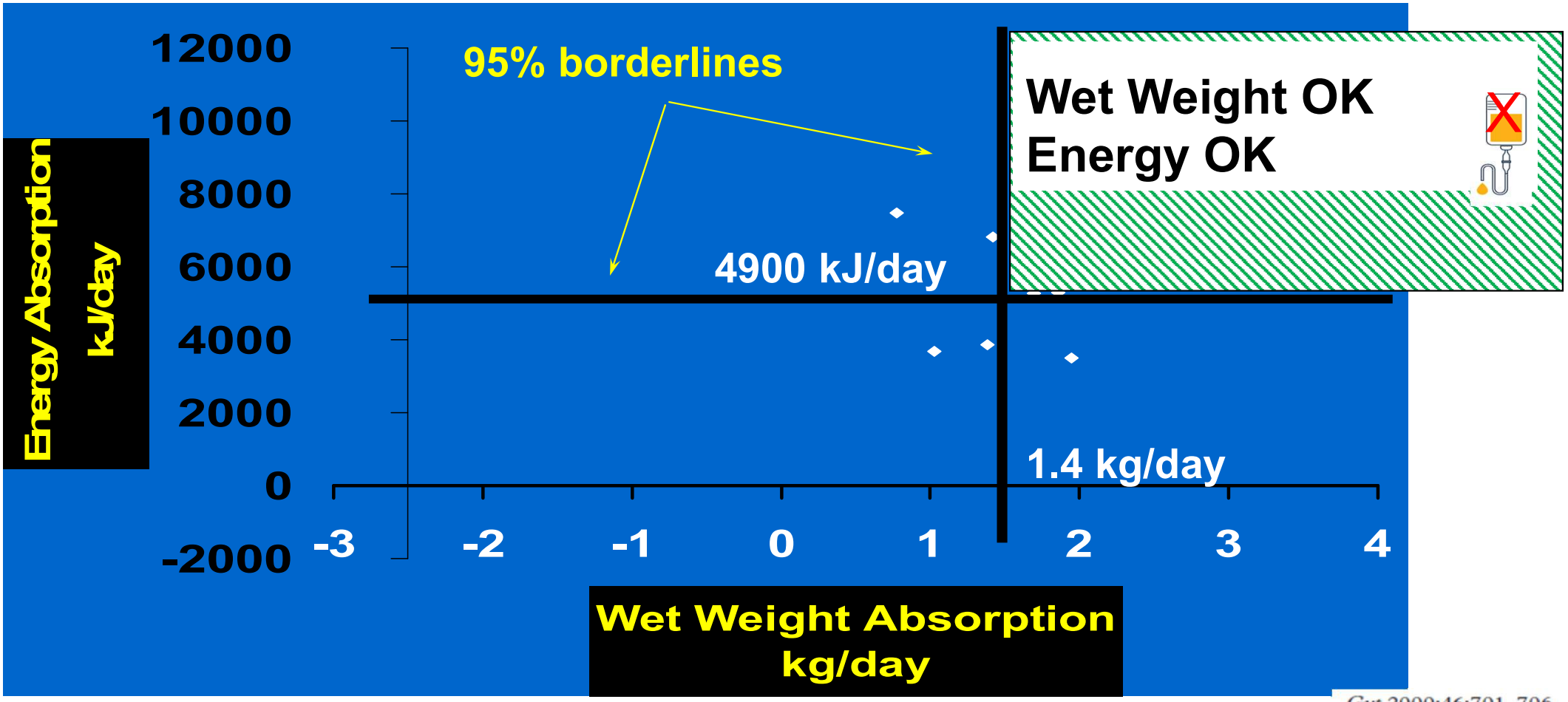
Intestinal Insufficiency (n=45)
~ Non-HPN Patients



Gut 2000;46:701–706

Jeppesen & Mortensen

Intestinal Insufficiency (n=45)
~ Non-HPN Patients

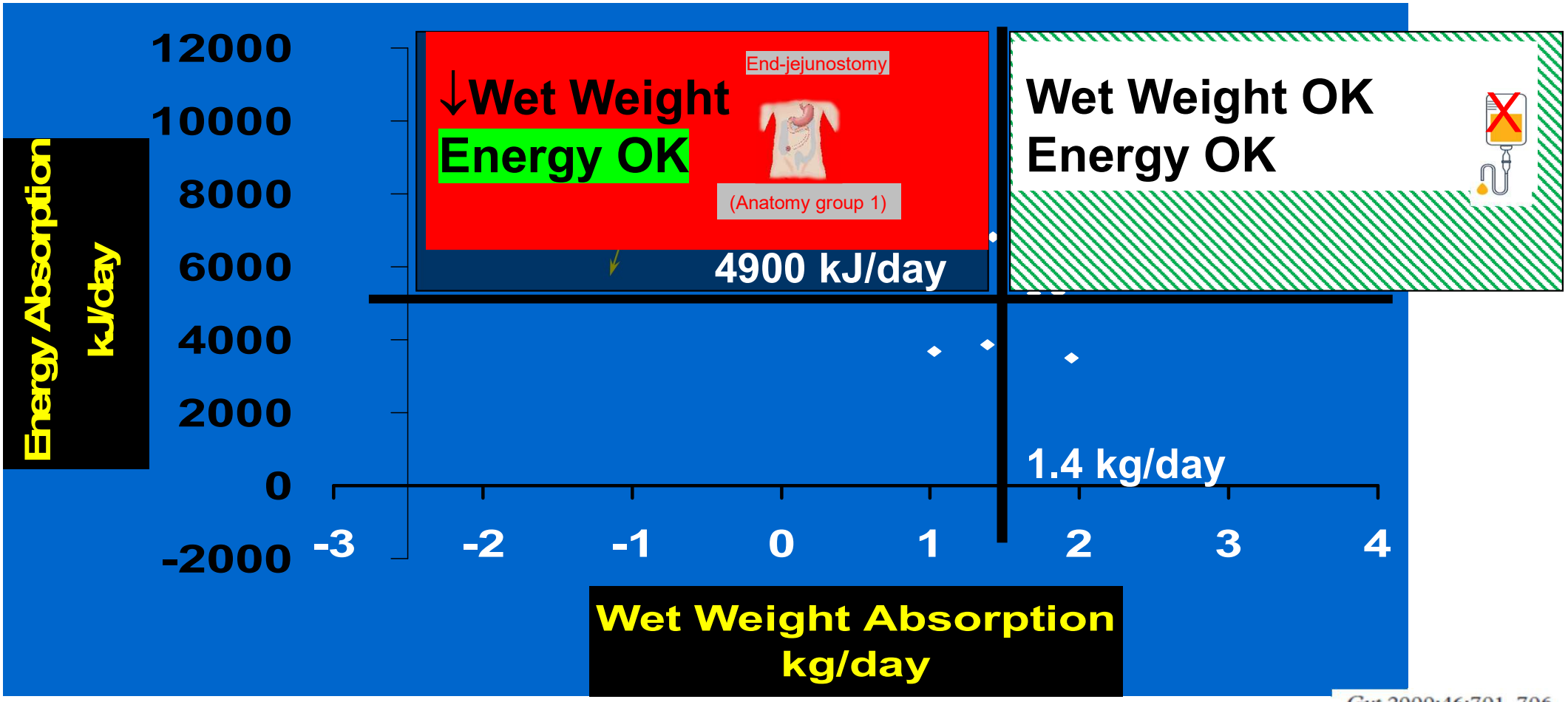


Gut 2000;46:701–706

Jeppesen & Mortensen

Intestinal Failure (n=46)
~ HPN Patients

Intestinal Insufficiency (n=45)
~ Non-HPN Patients

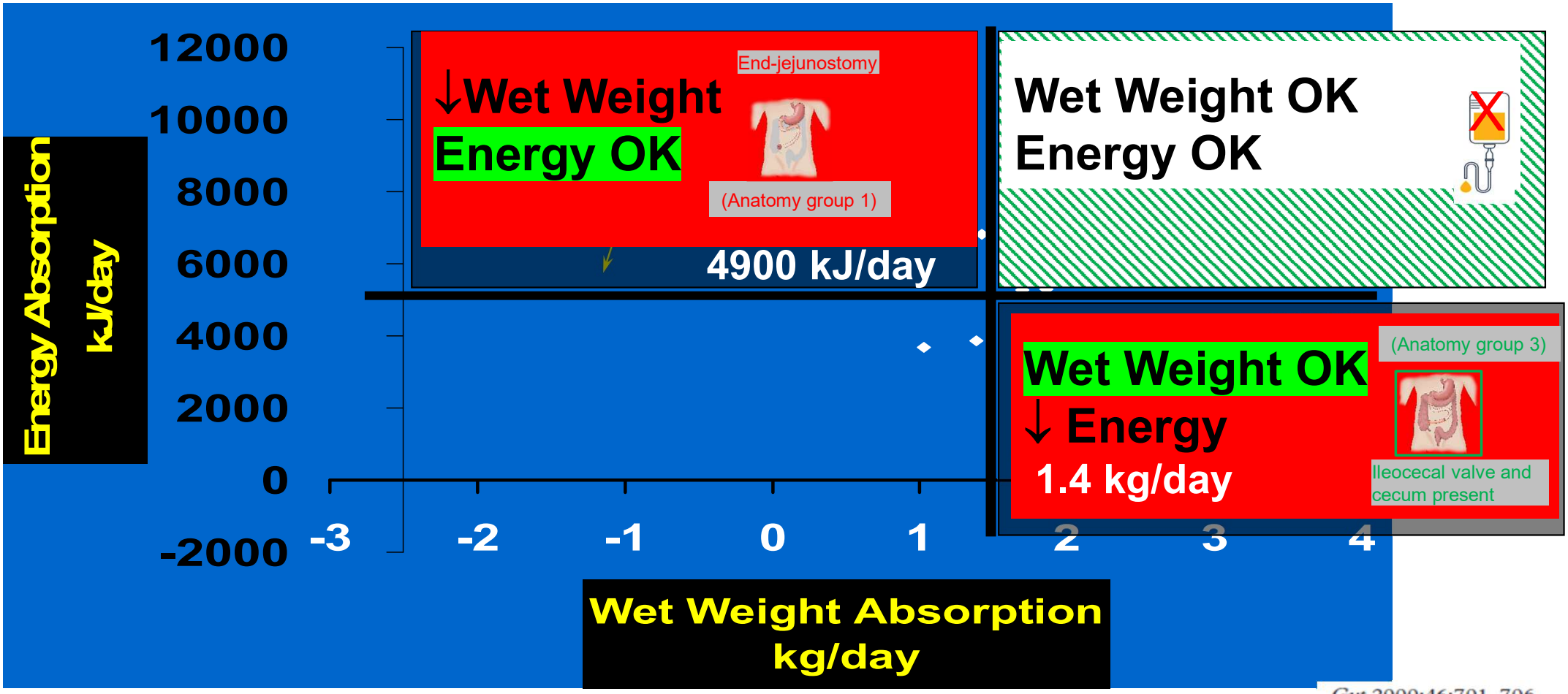


Gut 2000;46:701–706

Jeppesen & Mortensen

Intestinal Failure (n=46)
~ HPN Patients

Intestinal Insufficiency (n=45)
~ Non-HPN Patients

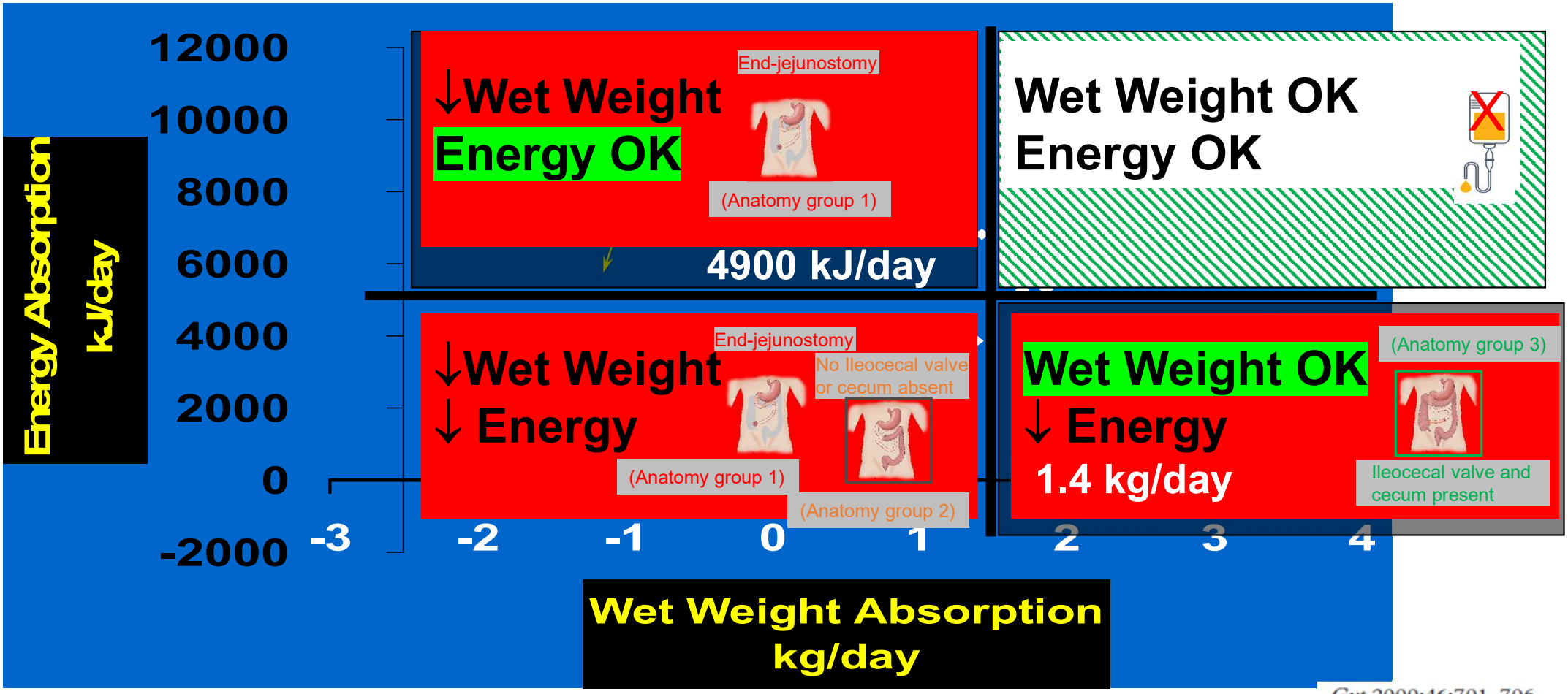


Gut 2000;46:701–706

Jeppesen & Mortensen

Intestinal Failure (n=46)
~ HPN Patients

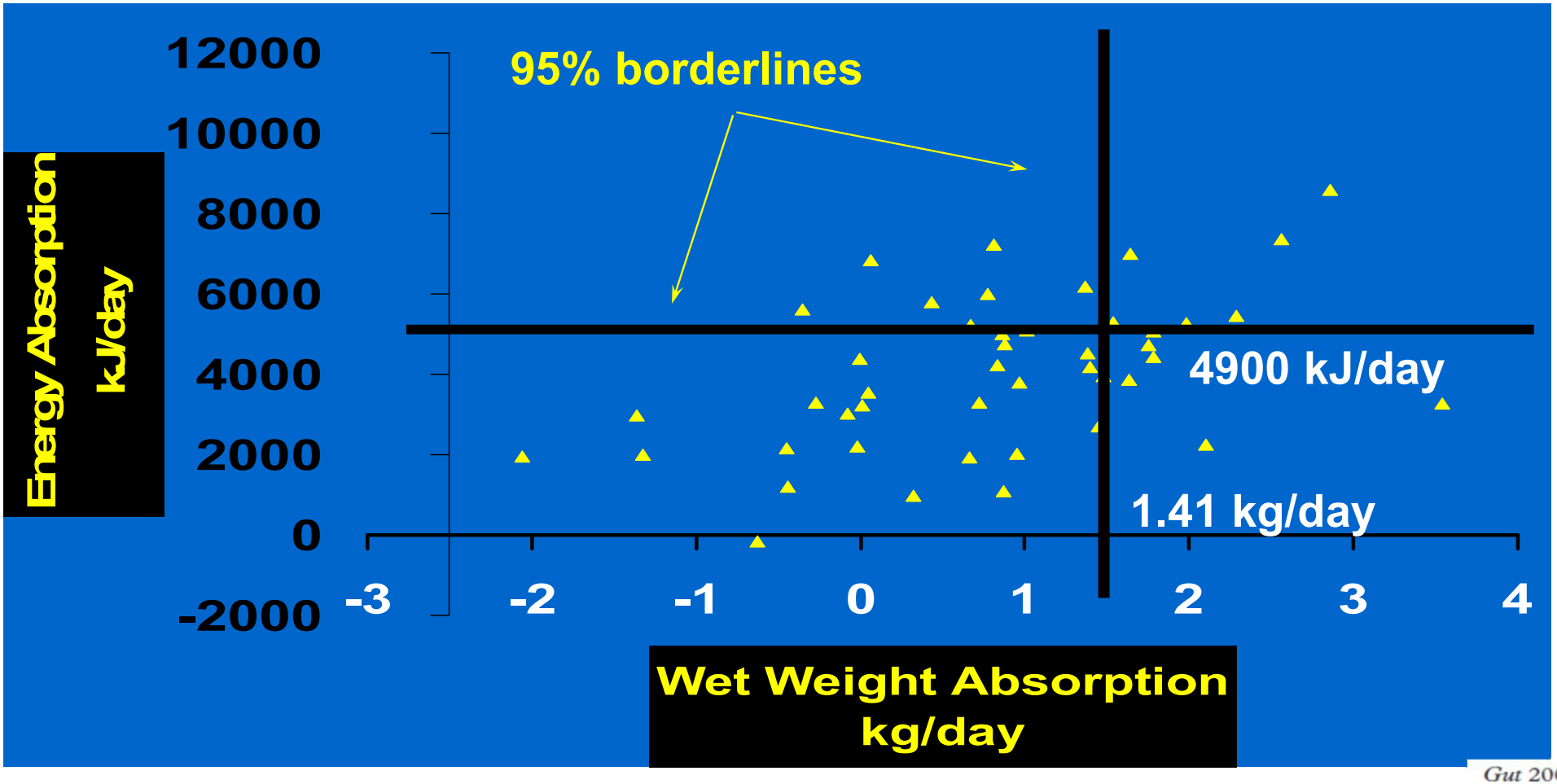
Intestinal Insufficiency (n=45)
~ Non-HPN Patients



Gut 2000;46:701–706

Jeppesen & Mortensen

Intestinal Failure (n=46)
~ HPN Patients

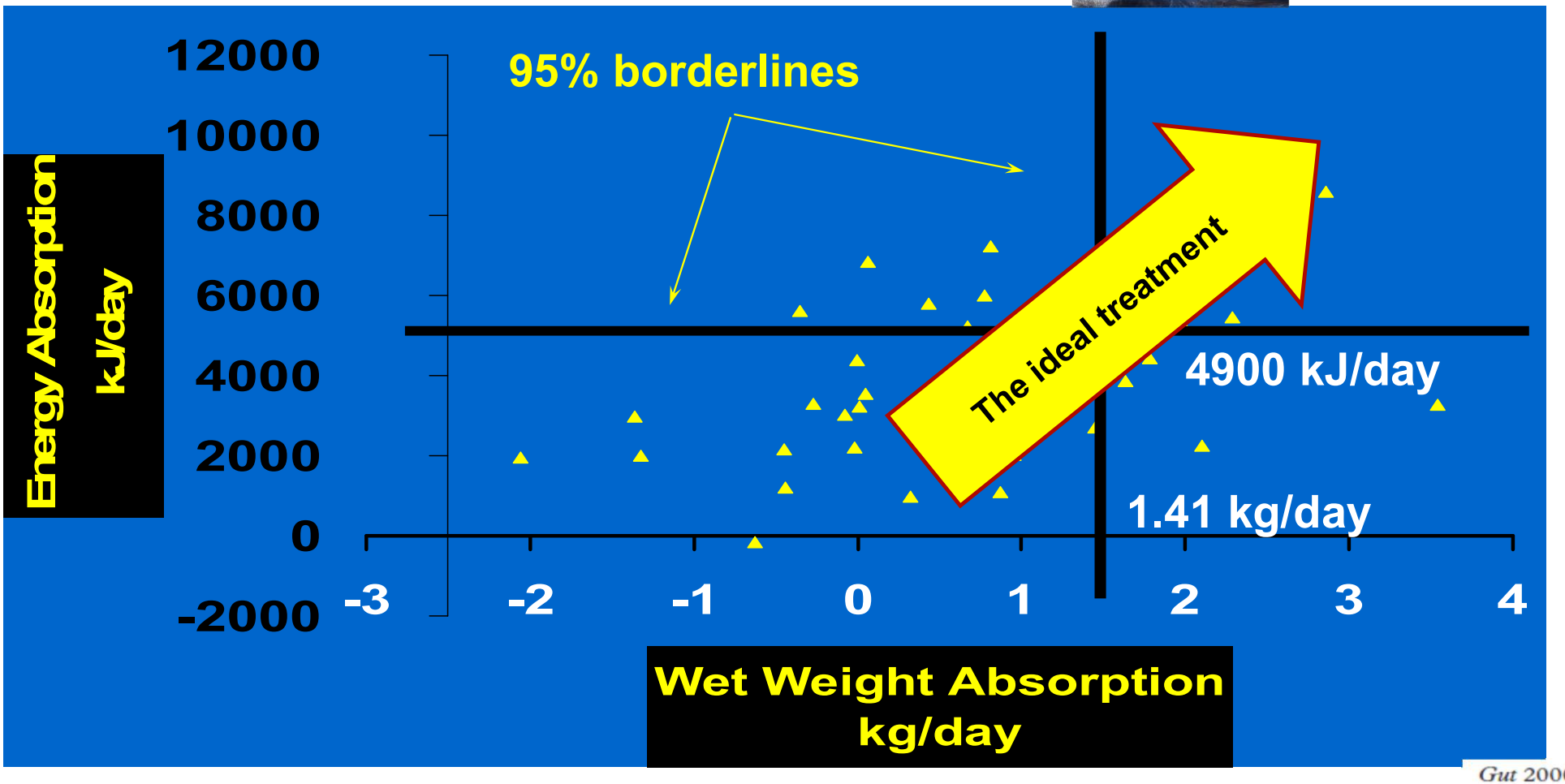


Gut 2000;46:701–706

Jeppesen & Mortensen

Intestinal Failure (n=46) ~ HPN Patients

Oral/Enteral Autonomy =
”Getting rid of the Catheter and need for PS infusions”



Gut 2000;46:701–706

Jeppesen & Mortensen

Intestinal Rehabilitation

Intestinal Rehabilitation

Oral Rehydration Solutions

Dietary Manipulation

} Spontaneous Adapatation

Intestinal Rehabilitation: Polydipsia

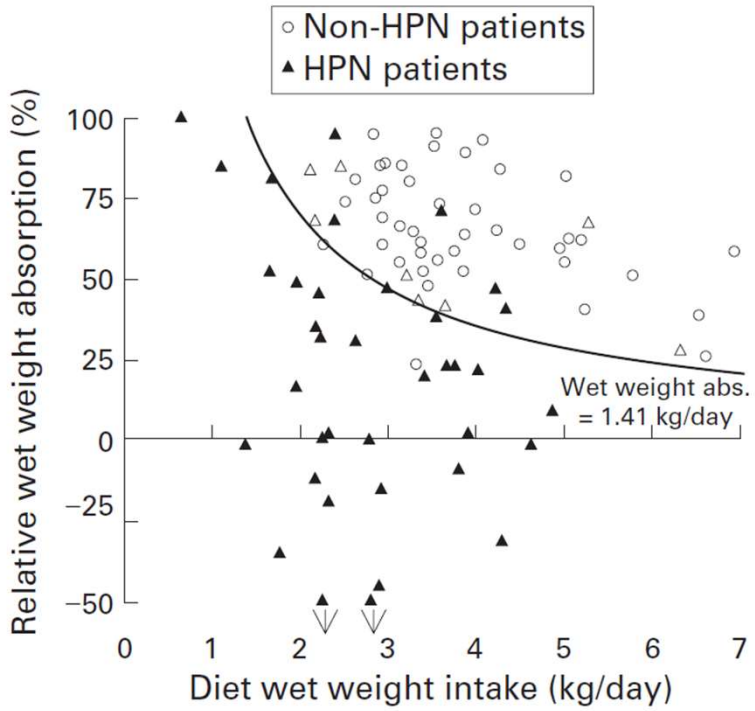
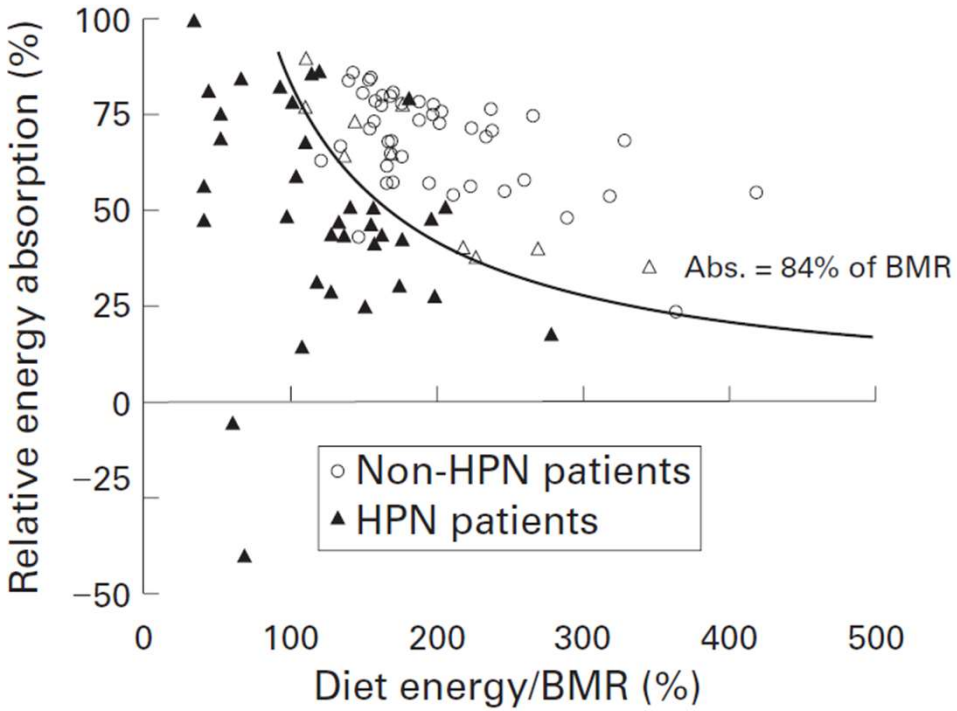


Figure 3 Relative wet weight absorption in relation to the dietary wet weight intake in 44 non-HPN patients and 45 HPN patients. The open triangles indicate HPN patients who received HPN because of energy absorption less than the 5% limit for basal metabolic rate (BMR) (84%).

Gut 2000;46:701–706

Jeppesen & Mortensen

Intestinal Rehabilitation: Hyperphagia



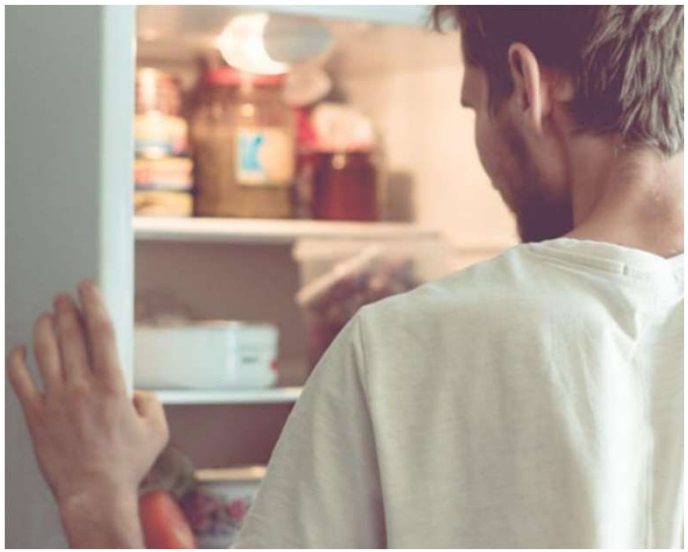
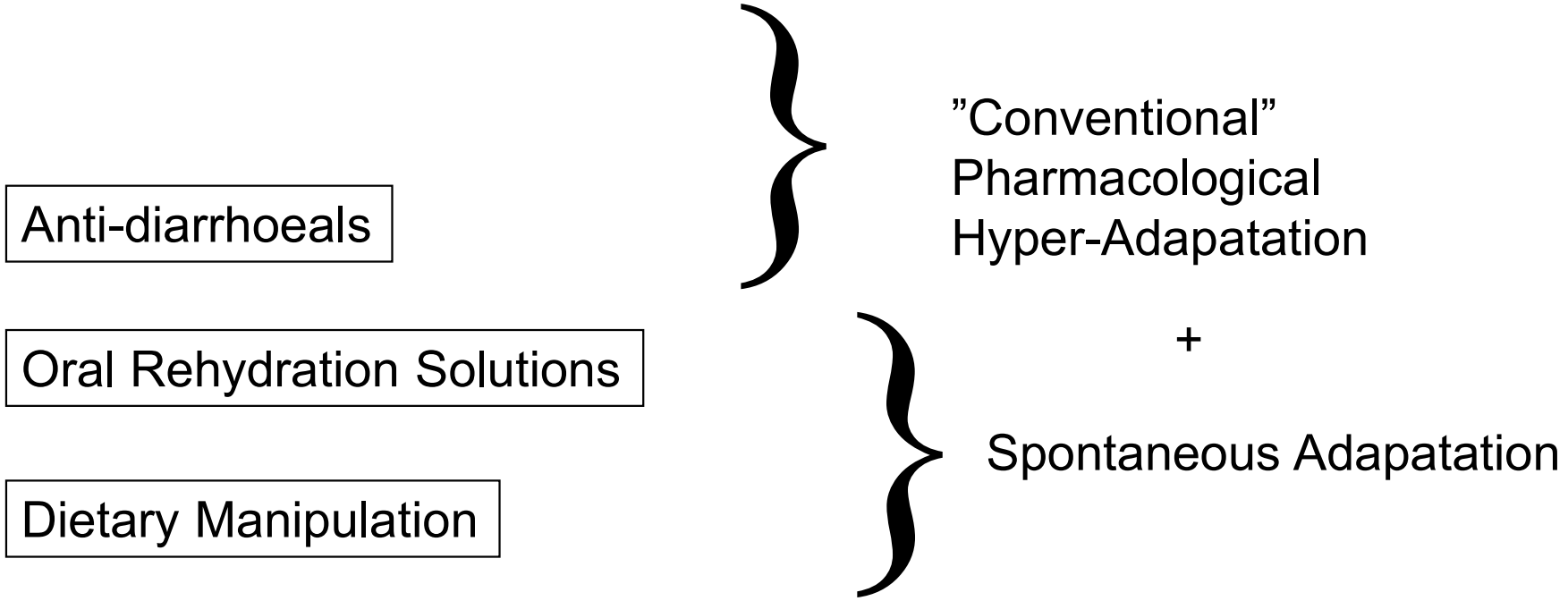


Figure 2 Relative energy absorption in relation to dietary energy intake/basal metabolic rate (BMR) in 44 non-HPN patients and 45 HPN patients. The open triangles indicate HPN patients who received HPN due to a wet weight absorption of less than the 5% limit (1.41 kg/day).

Gut 2000;46:701–706

Jeppesen & Mortensen

Intestinal Rehabilitation



Intestinal Rehabilitation

- Anti-secretory Agents
- Anti-diarrhoeals
- Oral Rehydration Solutions
- Dietary Manipulation

} ”Conventional” Pharmacological Hyper-Adapatation

+

} Spontaneous Adapatation

Intestinal Rehabilitation

INTESTINAL ABSORPTION & Growth Factors

”Pro-adaptive Factors”

“Neuro-Endocrine” Hyper-Adaptation

The ideal Treatment

+

Anti-secretory Agents

Anti-diarrhoeals

”Conventional” Pharmacological Hyper-Adapatation

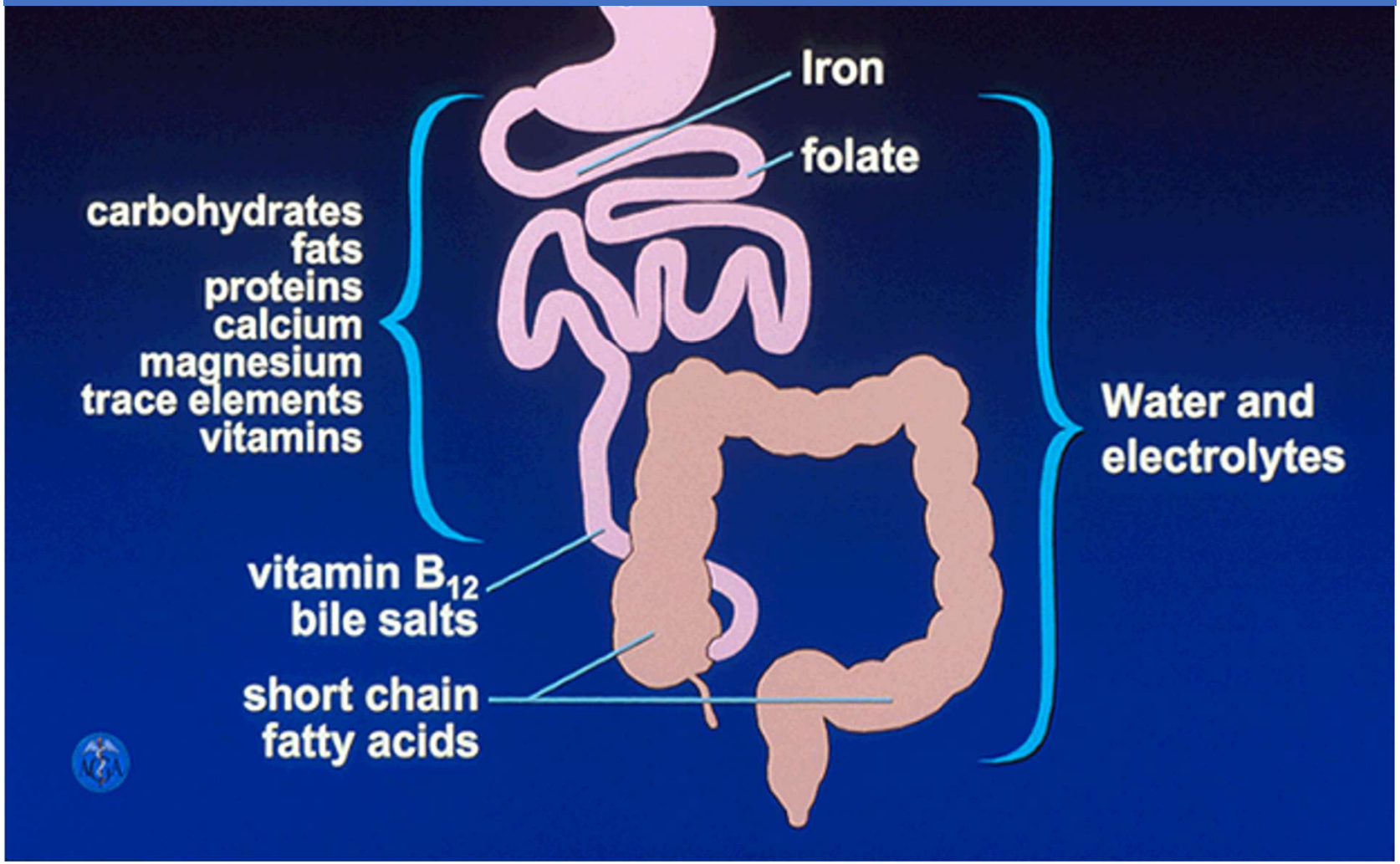
+

Oral Rehydration Solutions

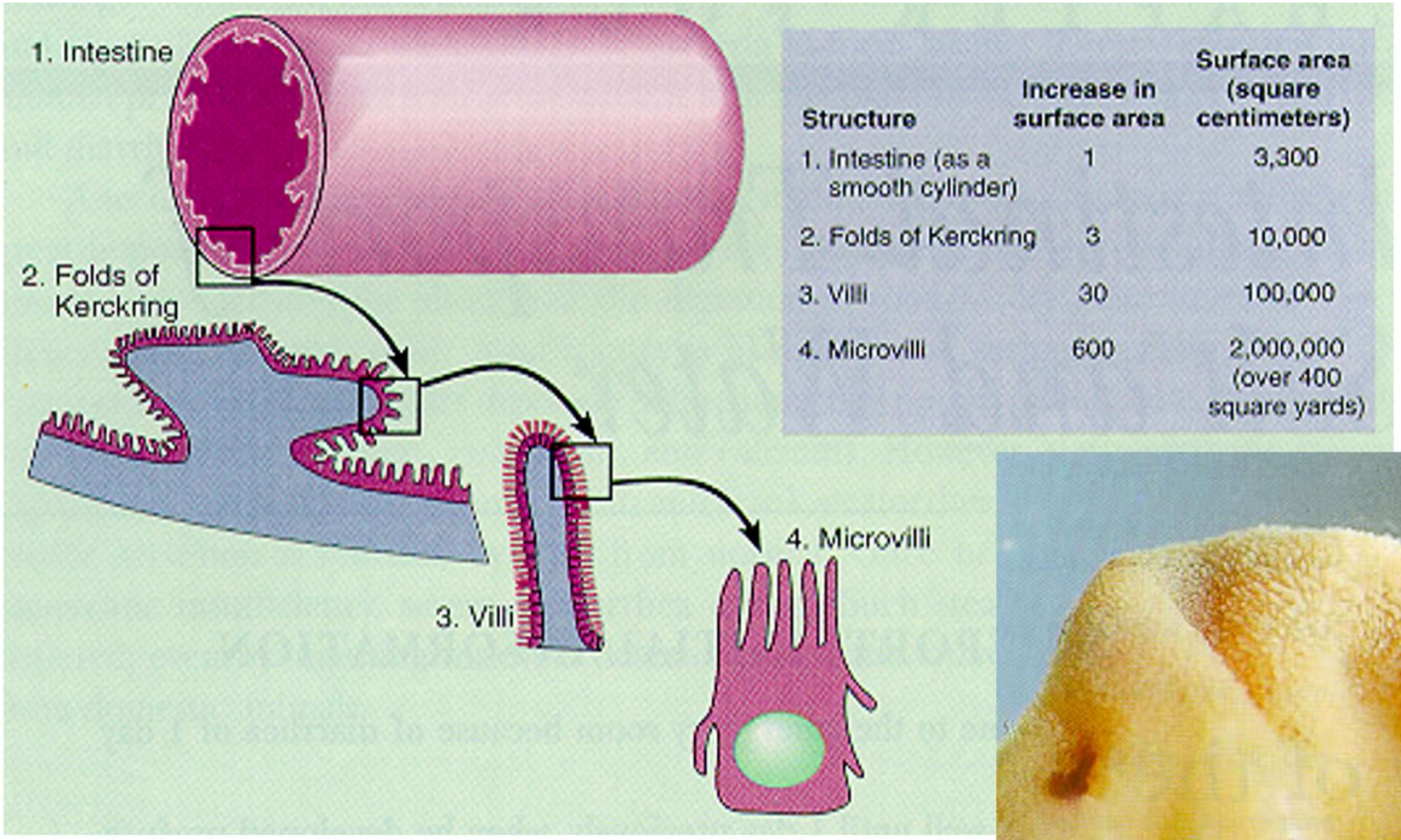
Dietary Manipulation

Spontaneous Adapatation

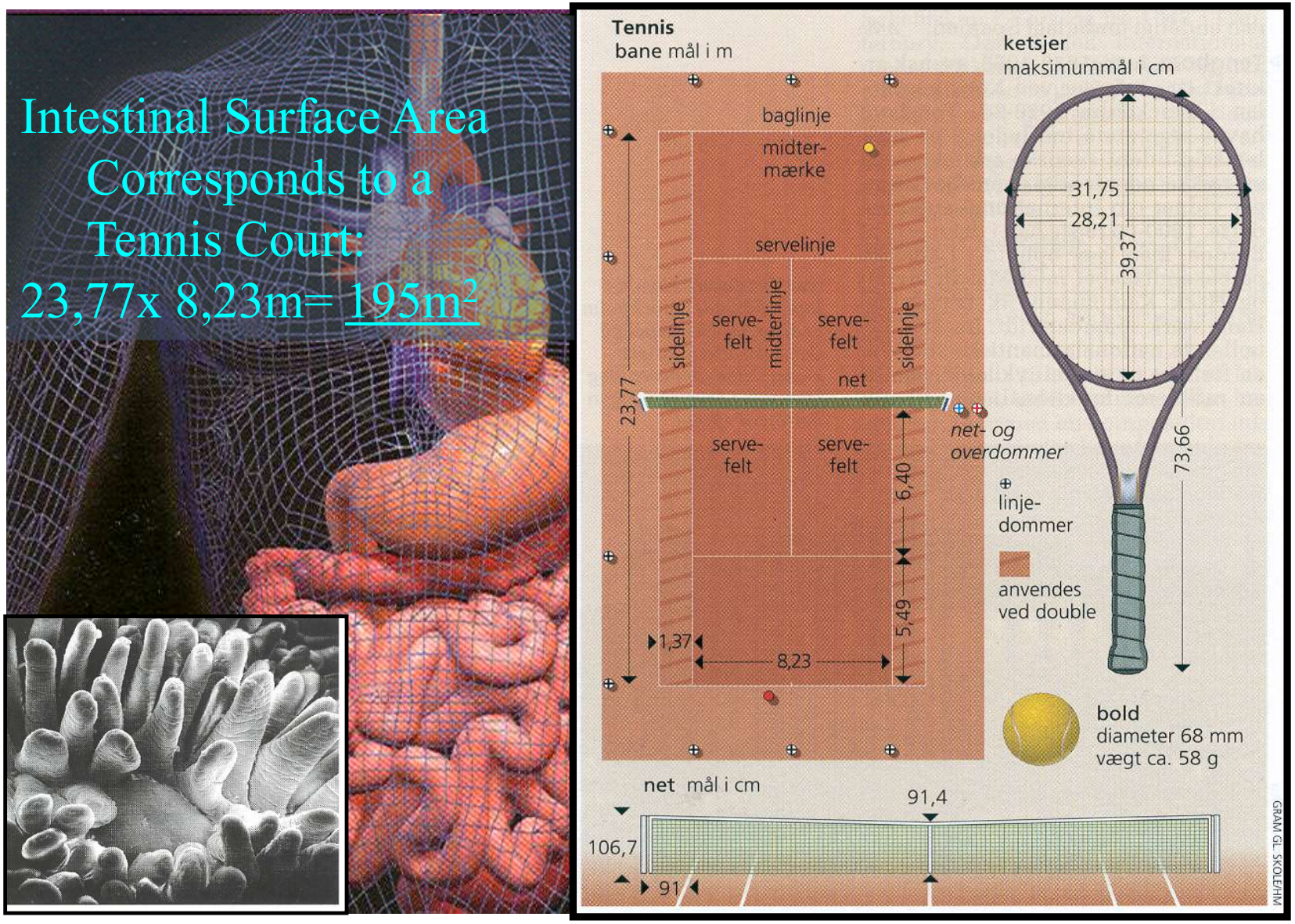
Normal Intestinal absorption



The Intestinal Anatomy and Architecture facilitates the Functional Capacity

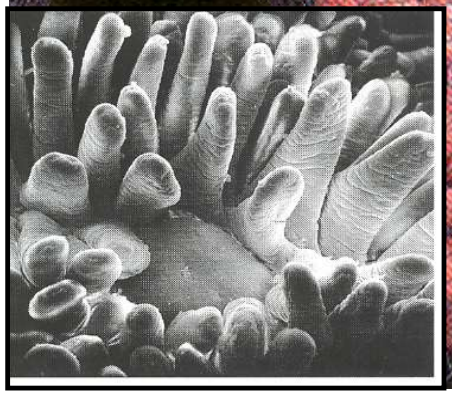


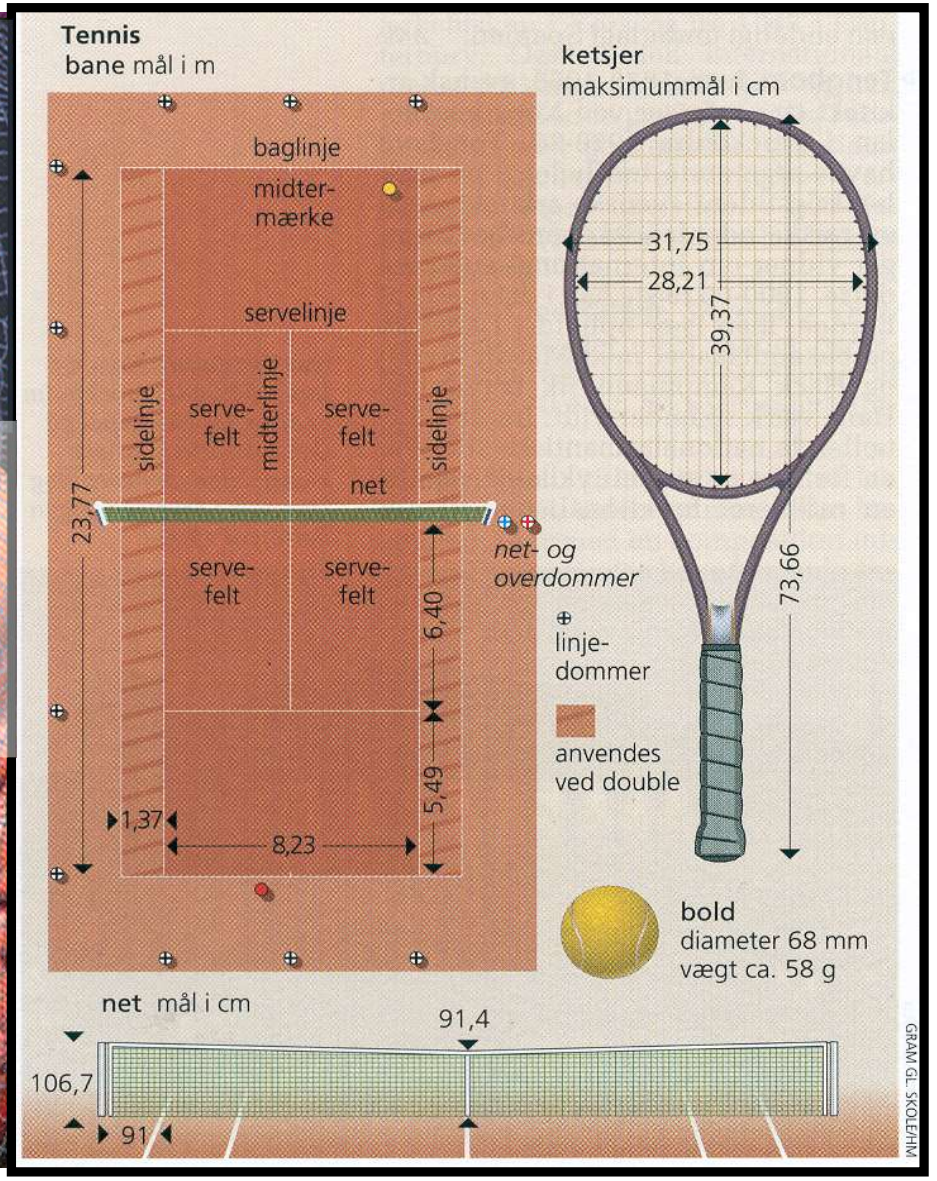
Structure	Increase in surface area	Surface area (square centimeters)
1. Intestine (as a smooth cylinder)	1	3,300
2. Folds of Kerckring	3	10,000
3. Villi	30	100,000
4. Microvilli	600	2,000,000 (over 400 square yards)


Intestinal Surface Area
Corresponds to a
Tennis Court:
23,77x 8,23m= 195m²
Tennis
bane mål i m
baglinje
midter-
mærke
servelinje
sidelinje
serve-
felt
midterlinje
serve-
felt
sidelinje
net
23,77
serve-
felt
serve-
felt
6,40
5,49
1,37
8,23
net- og
overdommer
linje-
dommer
anvendes
ved double
ketsjer
maksimummål i cm
31,75
28,21
39,37
73,66
bold
diameter 68 mm
vægt ca. 58 g
net mål i cm
91,4
106,7
91
GRAM GL SKOLEHM

Intestinal Surface Area
Corresponds to a
Tennis Court:
23,77x 8,23m= 195m²

A New Mucocal Surface Area is Generated Every Week!

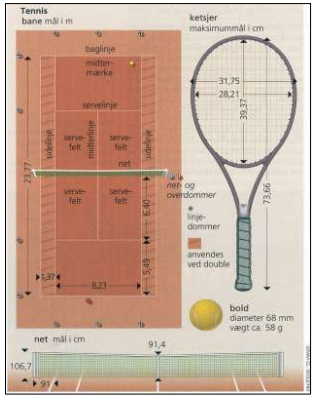




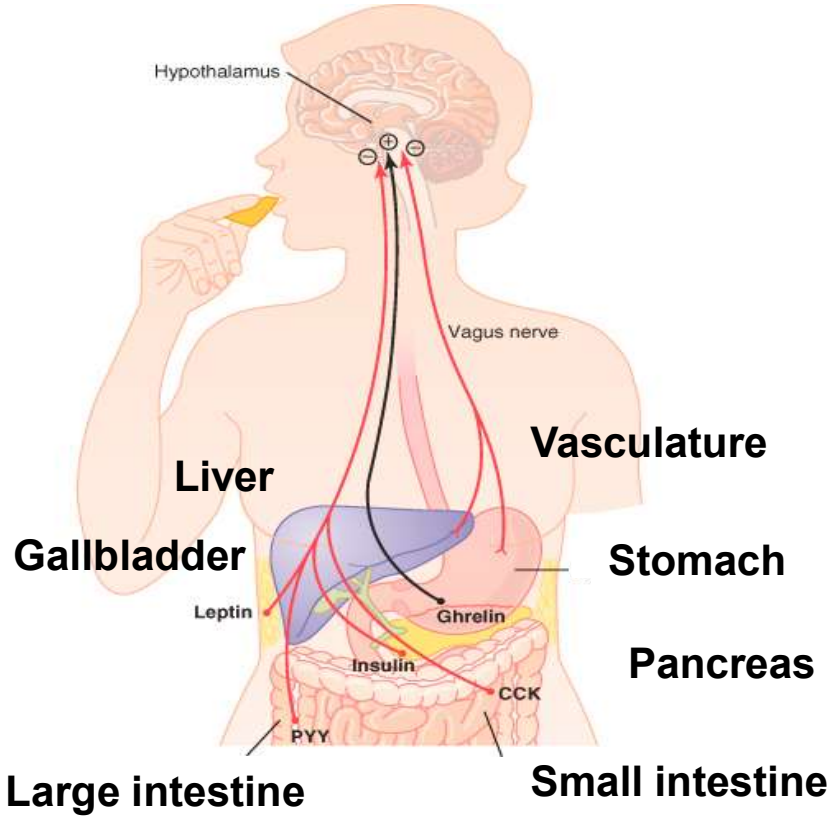
A Better Understanding of SBS-IF Pathophysiology will Improve Rehabilitation Efforts

Over the past decades, it has become increasingly clear, that the malassimilation seen in SBS patients relates not only to the diminished absorptive surface-area of the remnant bowel…

…but also to:



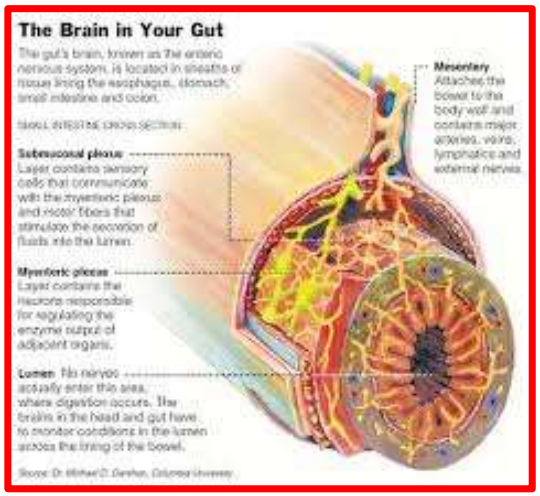
GI Neuro-endocrine regulation: "Feedback loops"



Motility
Secretions
Mucosal function
Blood/lymph-flow

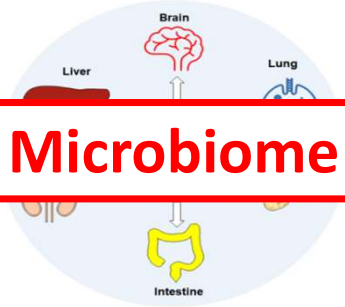
& "Inter-organ-axis communication"⇒
Optimal Intestinal Absorption

Cummings DE and Overduin. *J of Clin Investig.* 2007;1:13–23



Secretion/
Digestion/
Absorption

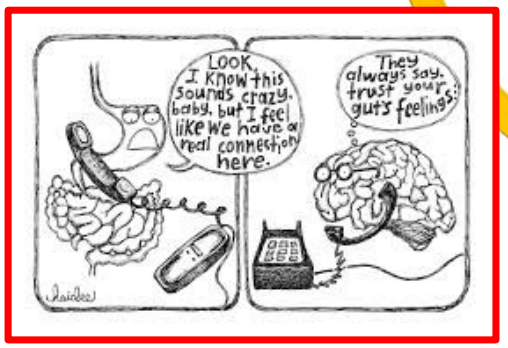
Barrier/
Immunity



Microbiome

Motility

Bloodflow



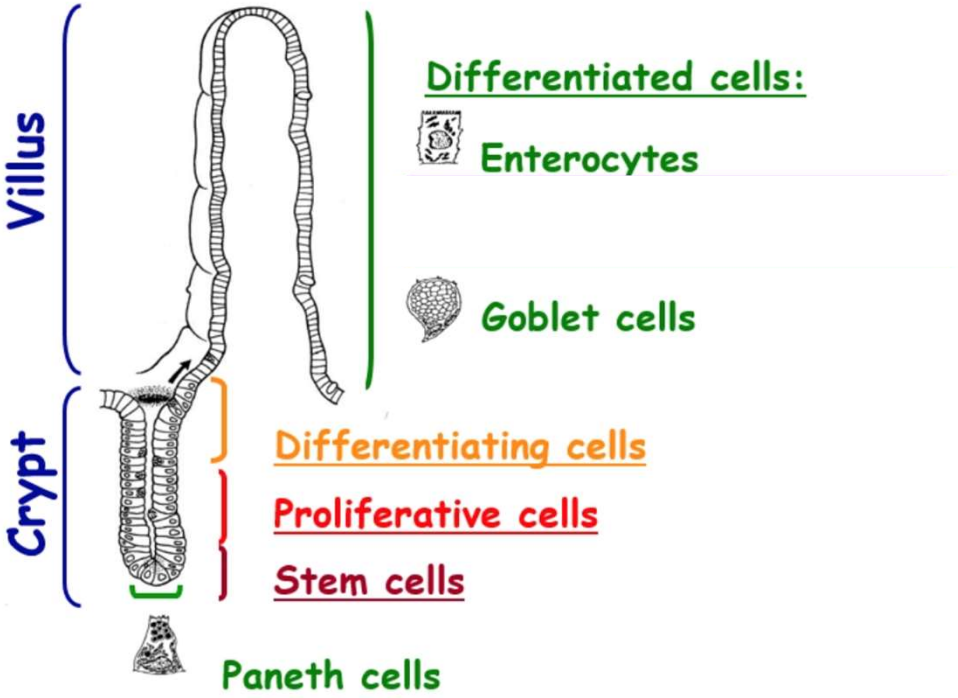
Normal Bowel Function

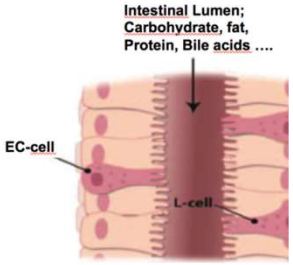
>95% Macronutrient Abs.

>95% Wet Weight Abs.

Digestion and Absorption = Many organs involved in optimal performance
Symphony = Many mucisians involved in optimal performance (Melody, Rythm, Harmony…..)

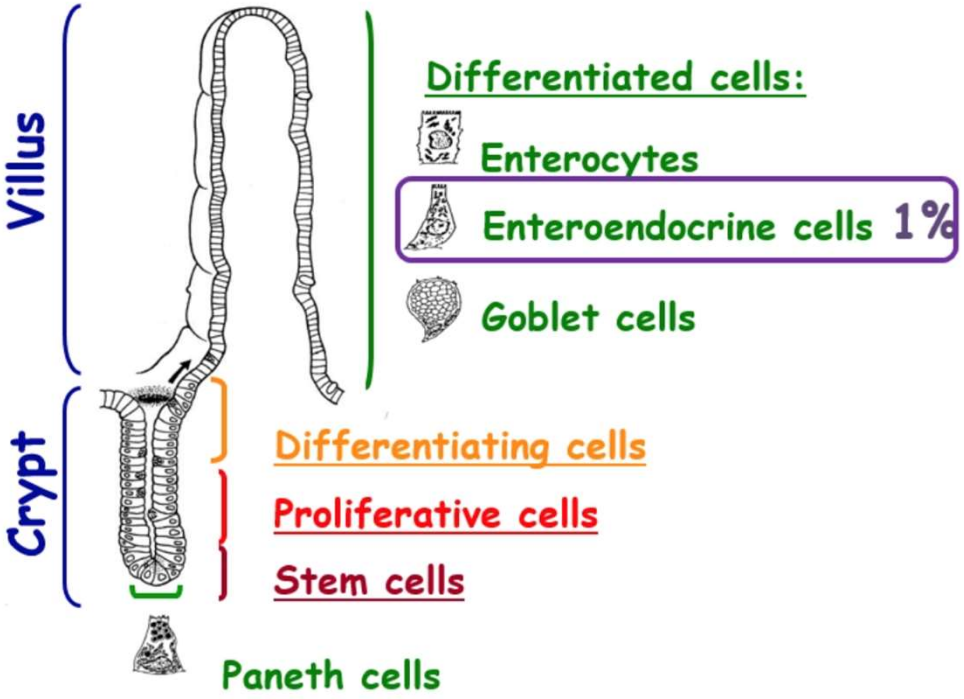
Recognition of the intestine

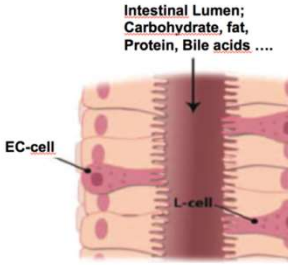




De Santa Barbara P et al. Cell Mol Life Sci 2003;7:1322-32;
Chaudhri O et al. *Phil Trans R Soc B.* 2006;361:1187–1209

Recognition of the intestine
as the Largest Endocrine Organ in the Body





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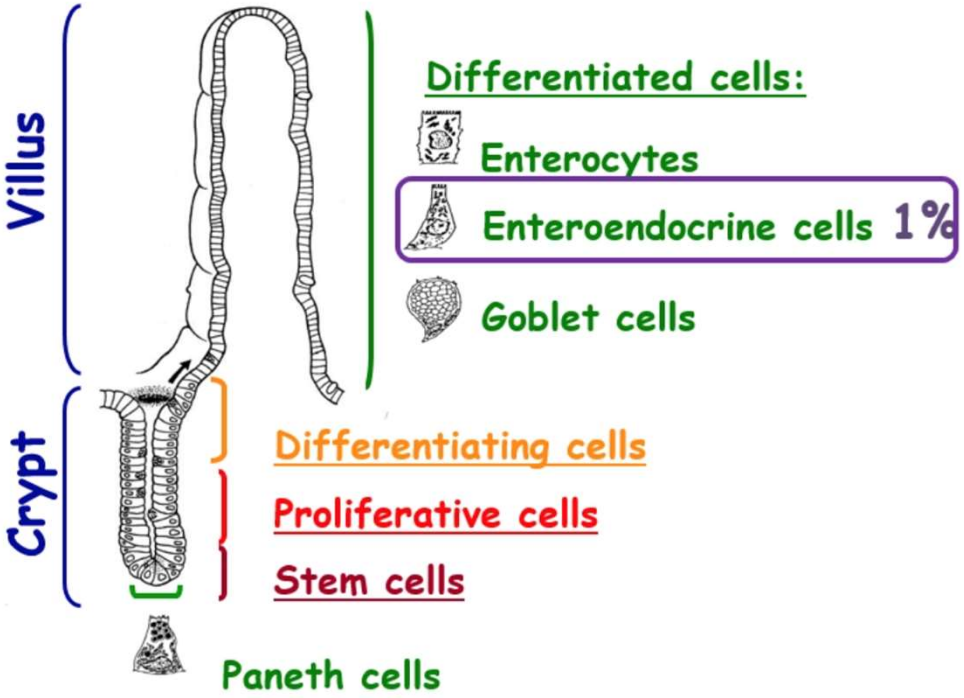
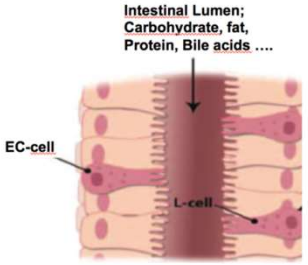
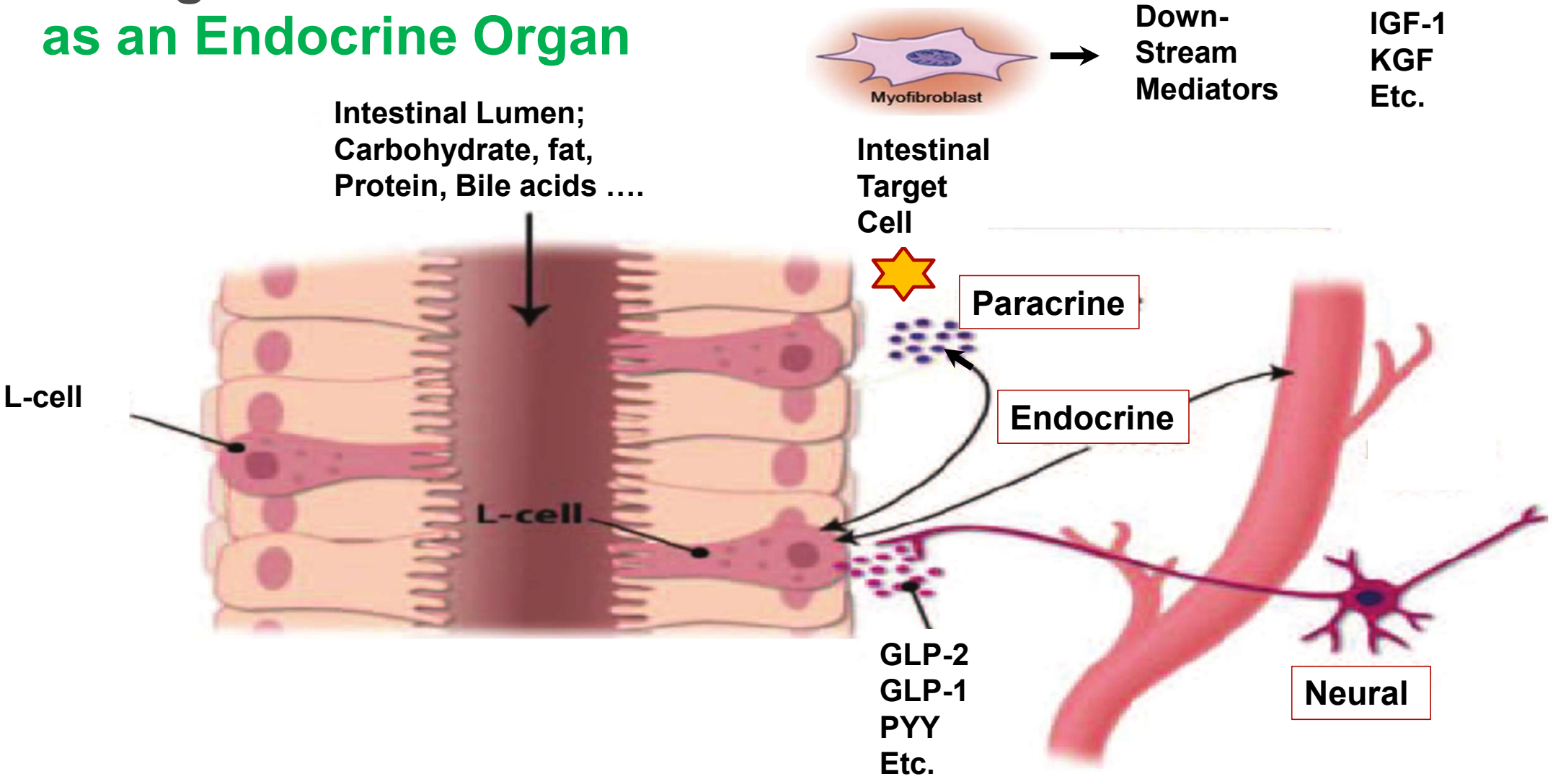




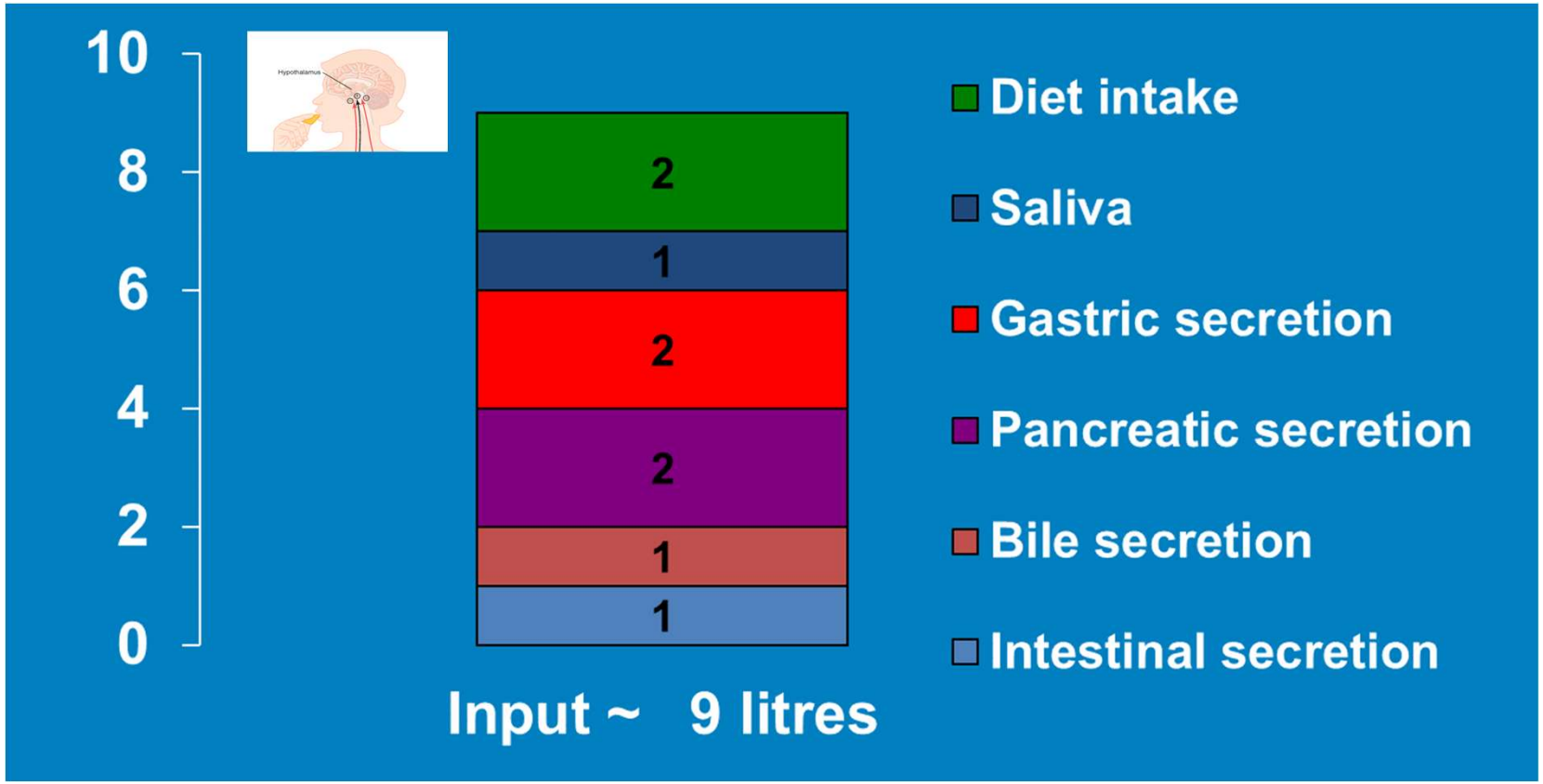
Entero-Endocrine Cells	Secreted Hormones
L cell	GLP-1/GLP-2/PYY
K cell	GIP
I cell	CCK
S cell	Secretin
N cell	Neurotensin
EC cell	Serotonin
ECL cell	Histamin
G cell	Gastrin
D cell	Somatostatin
M cell	Motilin/Ghrelin

De Santa Barbara P et al. Cell Mol Life Sci 2003;7:1322-32;
Chaudhri O et al. *Phil Trans R Soc B.* 2006;361:1187–1209

Recognition of the intestine
as an Endocrine Organ

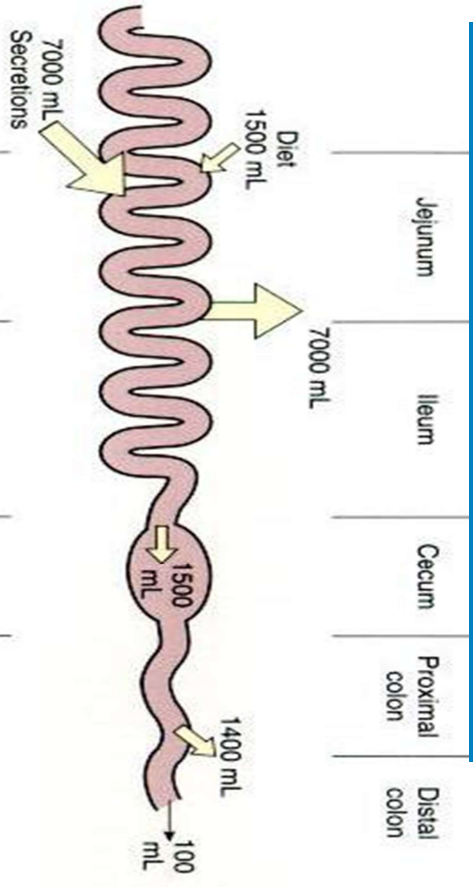


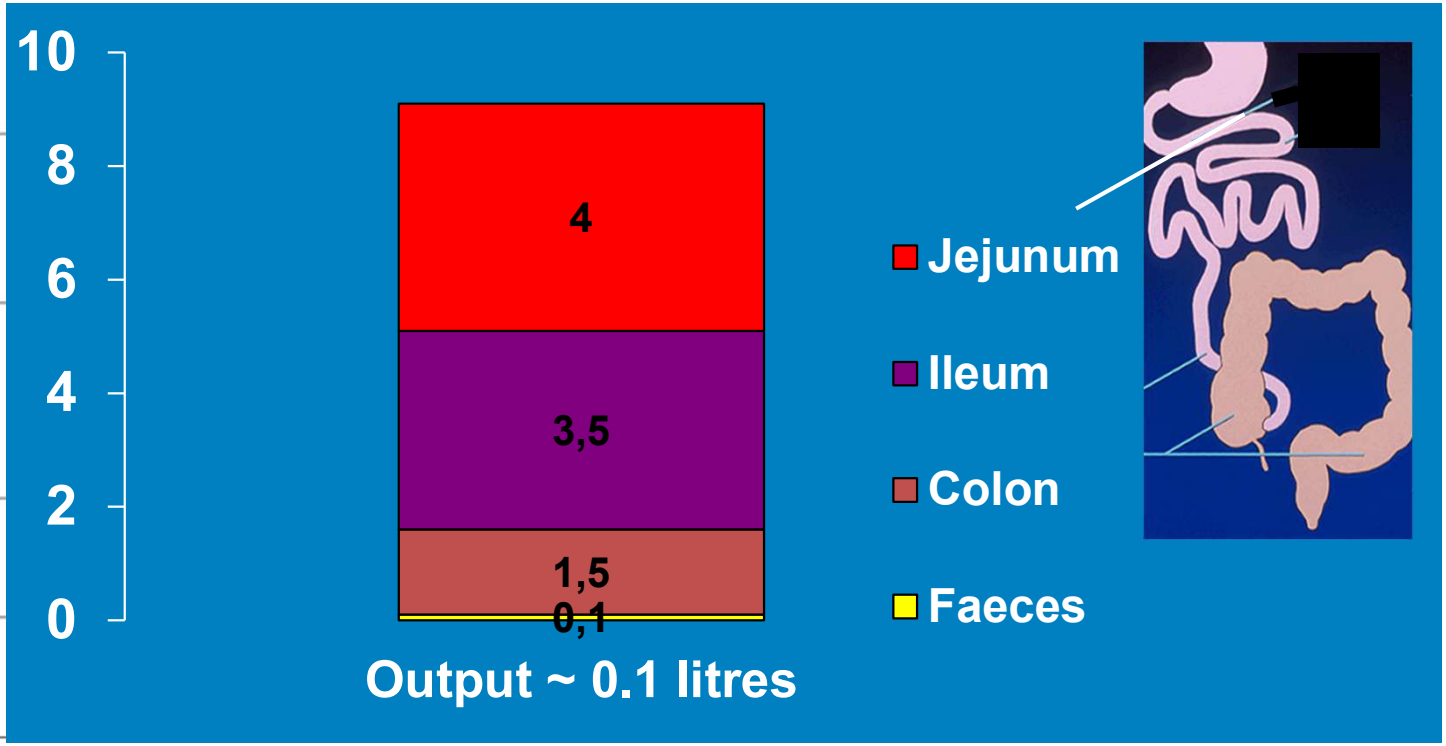
Normal Oral Wet Weight intake and Upper Gastrointestinal Secretions



Normal Intestinal Fluid Absorption & Output

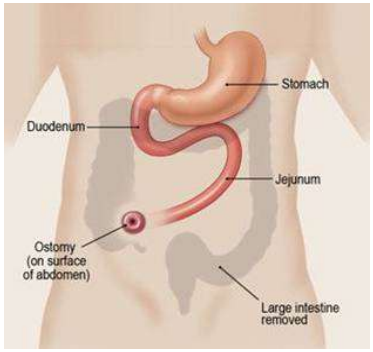
No Intestinal Resection





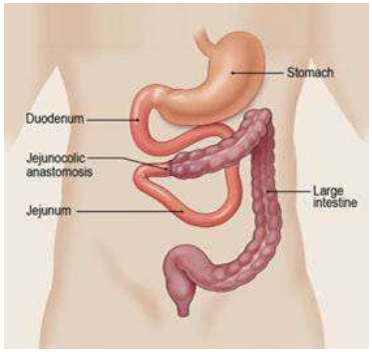
Short Bowel Syndrome:
Neuro-Endocrine Dysregulation and Adaptive Regulation

JEJUNO(-ILEO) -STOMY



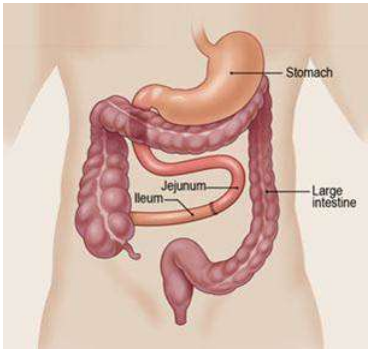
Group 1

JEJUNO-COLIC ANASTOMOSIS



Group 2

JEJUNO-ILEO-COLIC ANASTOMOSIS

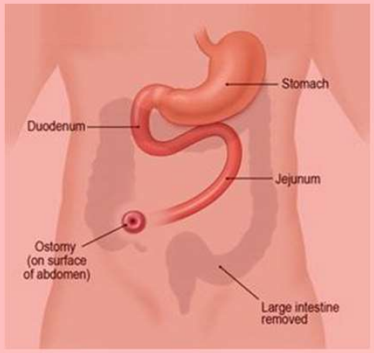


Group 3

The Human ”Intestinal Knockout Model”

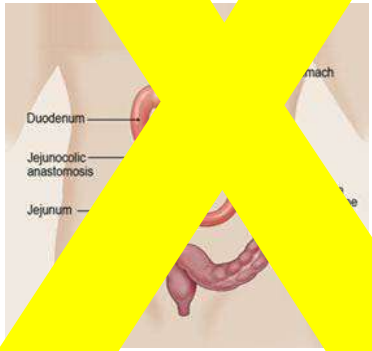
Short Bowel Syndrome:
Neuro-Endocrine Dysregulation and Adaptive Regulation

JEJUNO(-ILEO)
-STOMY



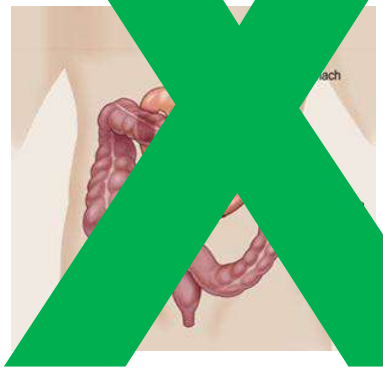
Group 1

JE O-CO
ANA OMO



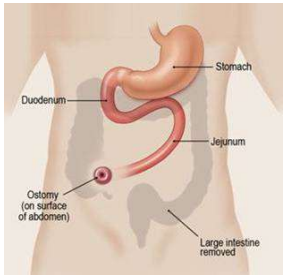
Group 2

JEJU ILEO-C C
ANA OMO

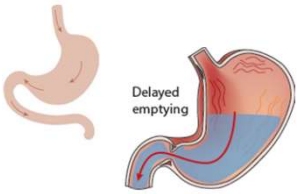


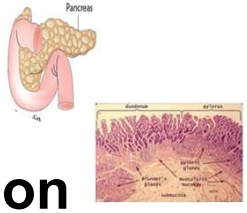
Group 3

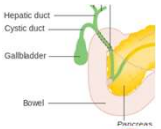
Phenotype/Pathophysiology
End-Jejunostomy, SBS-IF
Anatomy Group I

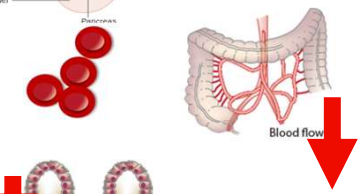


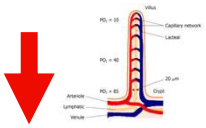
	Increased/ Accelerated	Normal	Diminished/ Delayed
Gastric emptying	XXX		
Gastric secretion	XXX		
Pancreatic exocrine secretion	? (X)		
Brunner gland secretion	XX		
Bile secretion	XXX		
Intestinal blood flow			X
Intestinal growth			X

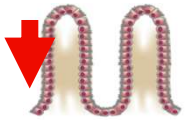




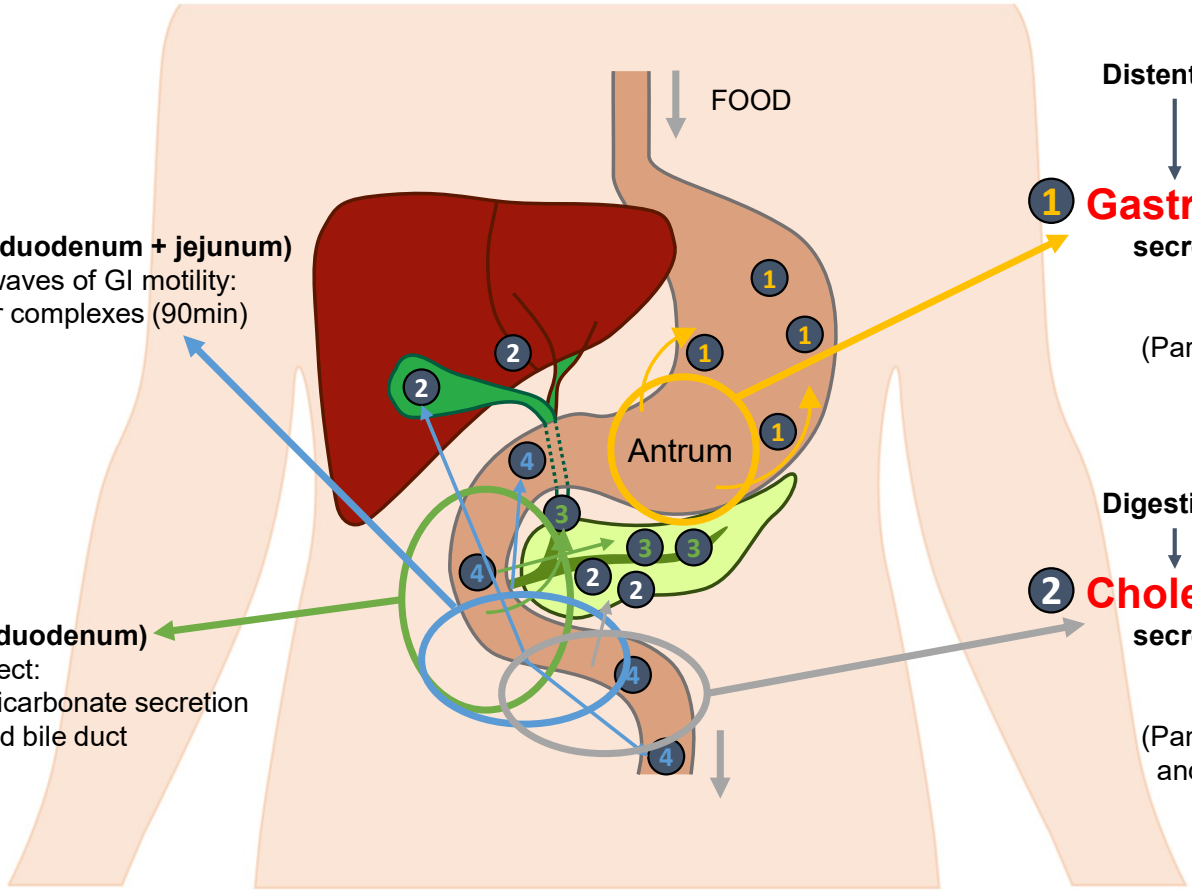








Pro-secretory and pro-motility hormones involved



Fasting state

High pH

4 Motilin

secretion by "M" cells (duodenum + jejunum)

Stimulation of waves of GI motility:
migrating motor complexes (90min)

Distention of stomach

Protein products

Vagal stimulation:
gastrin releasing peptide (GRP)

1 Gastrin

secretion by "G" cells

Stimulation of:
gastric acid secretion
(Parietal cells: HCl & ECLs: histamine)

Acid gastric juice

3 Secretin

secretion by "S" cells (duodenum)

Neutralizing effect:
stimulation of bicarbonate secretion
by pancreas and bile duct

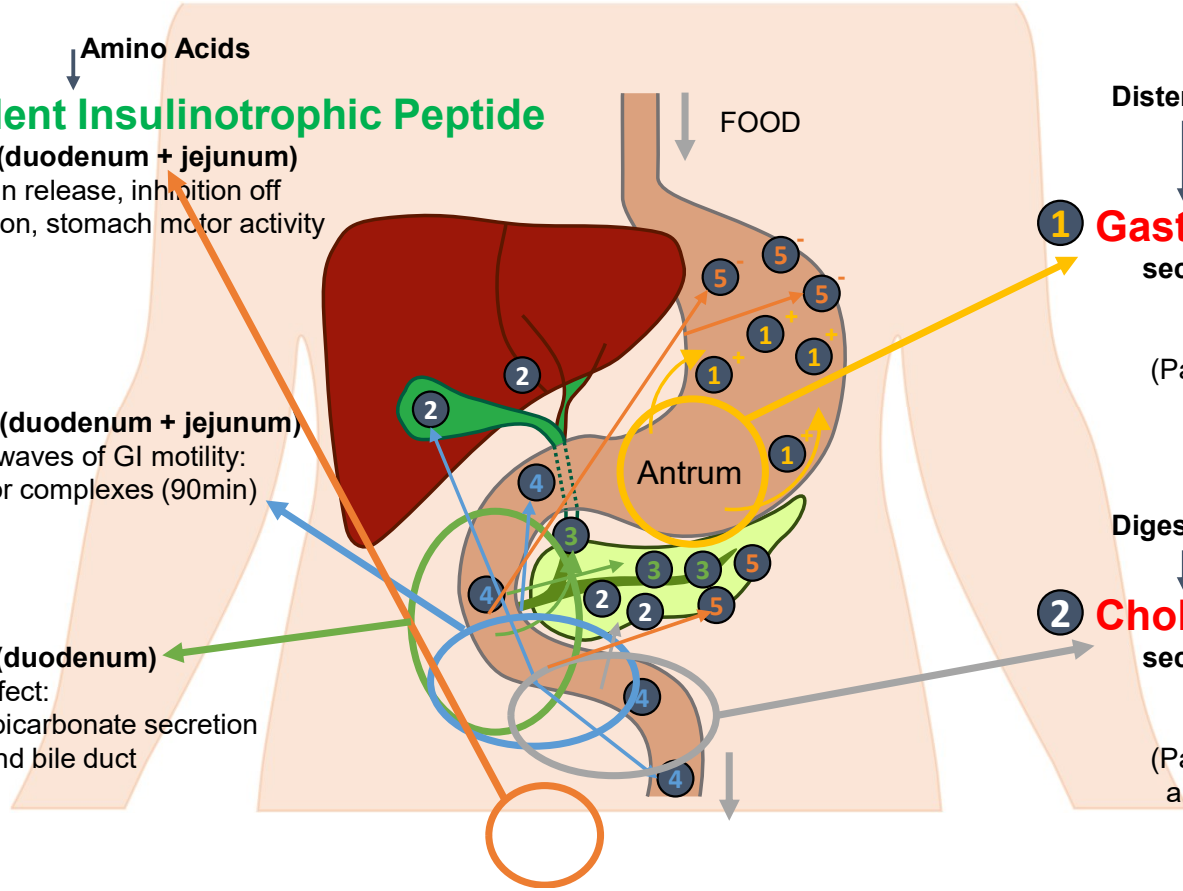
Digestive products of fat

2 Cholecystokinin

secretion by "I" cells (duodenum & jejunum)

Stimulation of:
Delivery of bile + Pancreatic Enzymes
(Pancreas: digestive enzymes, bile secretion
and gall bladder contraction)

Anti-secretory and anti-motility hormones in proximal GI tract



Fatty acids | Carbs | Amino Acids

5 / Glucose-dependent Insulinotrophic Peptide

secretion by "K" cells (duodenum + jejunum)

Stimulation of insulin release, inhibition off gastric acid secretion, stomach motor activity

Fasting state | High pH

4 Motilin

secretion by "M" cells (duodenum + jejunum)

Stimulation of waves of GI motility: migrating motor complexes (90min)

Acid gastric juice

3 Secretin

secretion by "S" cells (duodenum)

Neutralizing effect: stimulation of bicarbonate secretion by pancreas and bile duct

Distention of stomach | Protein products | Vagal stimulation: gastrin releasing peptide (GRP)

1 Gastrin

secretion by "G" cells

Stimulation of: gastric acid secretion

(Parietal cells: HCl & ECLs: histamine)

Digestive products of fat

2 Cholecystokinin

secretion by "I" cells (duodenum & jejunum)

Stimulation of: Delivery of bile + Pancreatic Enzymes

(Pancreas: digestive enzymes, bile secretion and gall bladder contraction)

Anti-secretory and anti-motility hormones in proximal GI tract

6 Stomatostatin
secretion by "D" cells (stomach)

Slows gastric emptying and small bowel transit and reduces salivary, gastric and pancreaticobiliary secretions.

Fatty acids | Carbs | Amino Acids

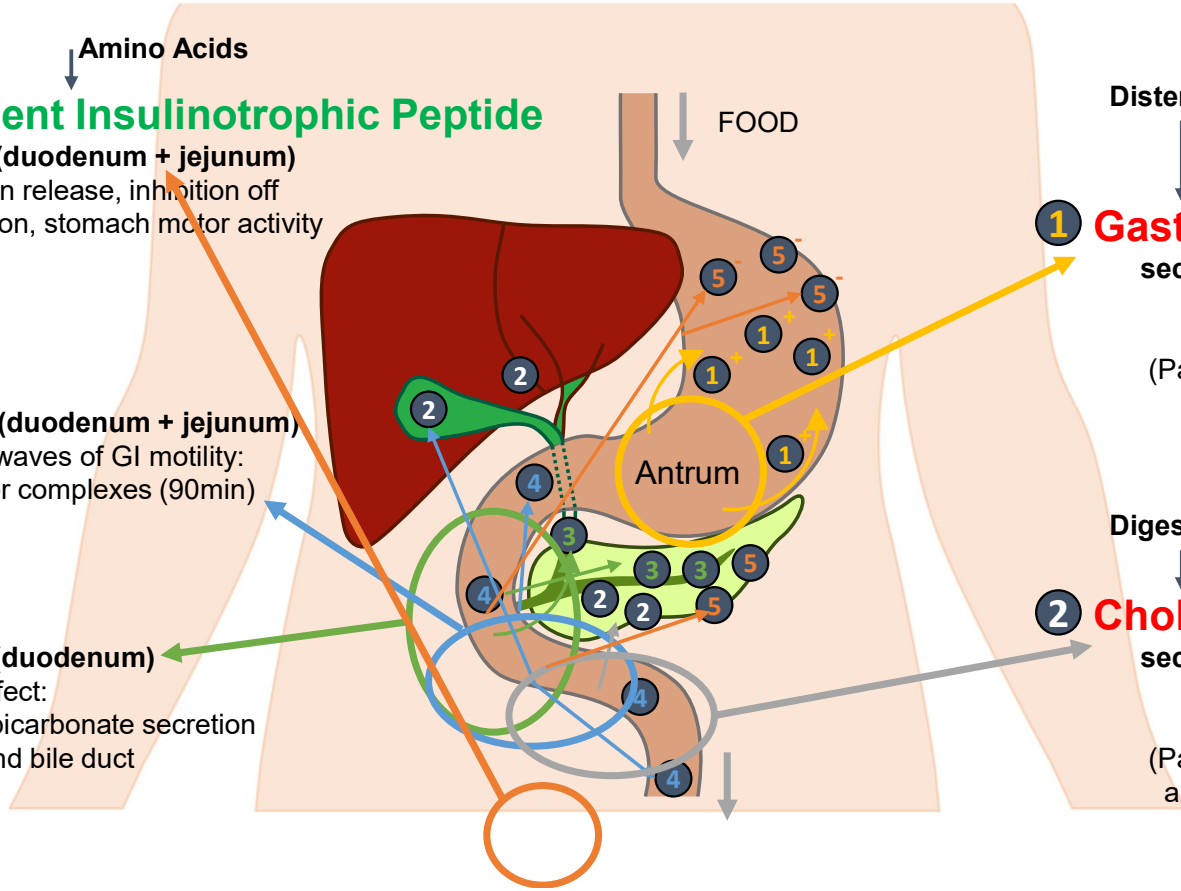
5 / Glucose-dependent Insulinotrophic Peptide
secretion by "K" cells (duodenum + jejunum)
Stimulation of insulin release, inhibition off gastric acid secretion, stomach motor activity

Fasting state | High pH

4 Motilin
secretion by "M" cells (duodenum + jejunum)
Stimulation of waves of GI motility: migrating motor complexes (90min)

Acid gastric juice

3 Secretin
secretion by "S" cells (duodenum)
Neutralizing effect: stimulation of bicarbonate secretion by pancreas and bile duct



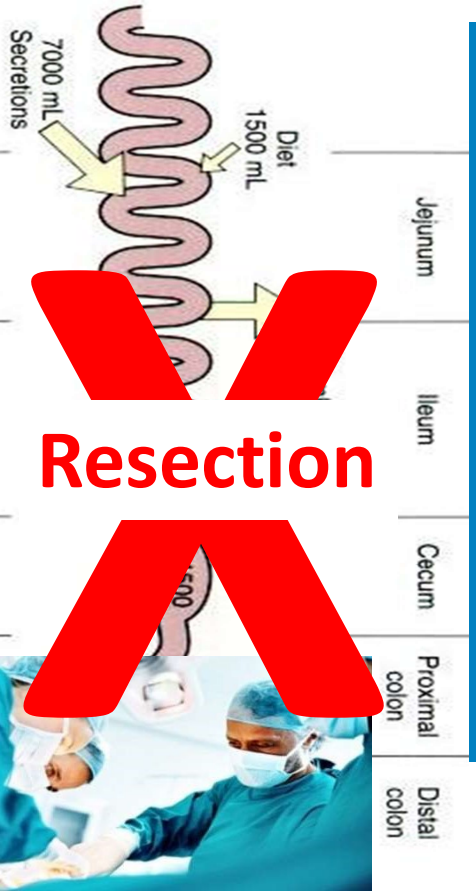
Distention of stomach | Protein products | Vagal stimulation: gastrin releasing peptide (GRP)

1 Gastrin
secretion by "G" cells
Stimulation of: gastric acid secretion
(Parietal cells: HCl & ECLs: histamine)

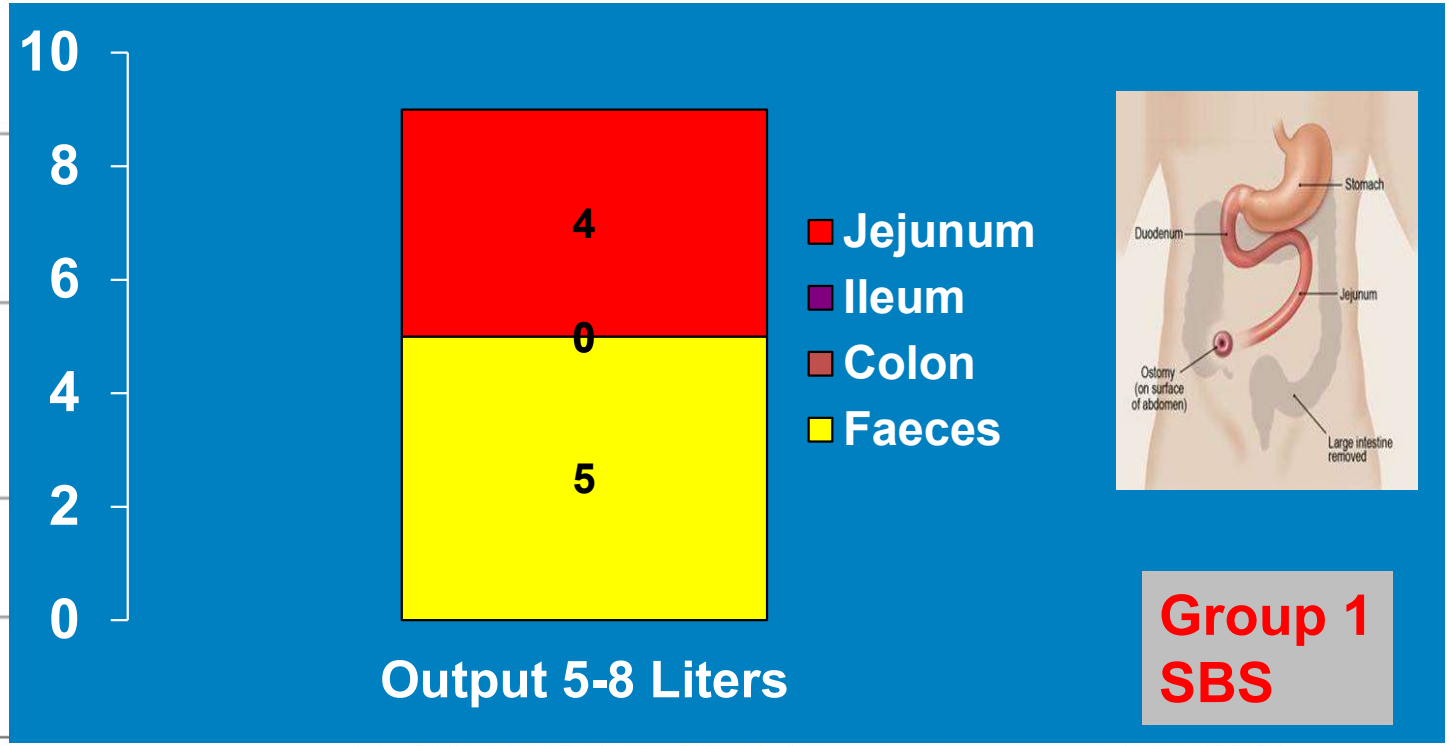
Digestive products of fat

2 Cholecystokinin
secretion by "I" cells (duodenum & jejunum)
Stimulation of: Delivery of bile + Pancreatic Enzymes
(Pancreas: digestive enzymes, bile secretion and gall bladder contraction)

Consequeces of high end-jejunostomy



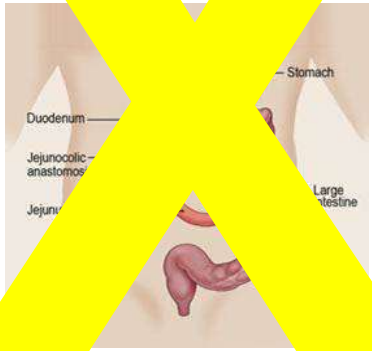
Resection



Group 1 SBS

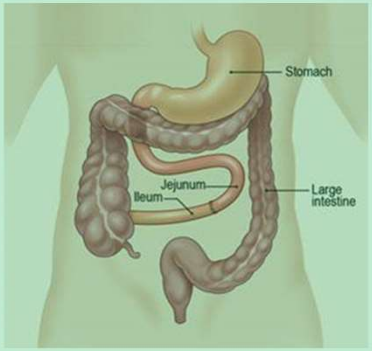
Short Bowel Syndrome:
Neuro-Endocrine Dysregulation and Adaptive Regulation

Group 1



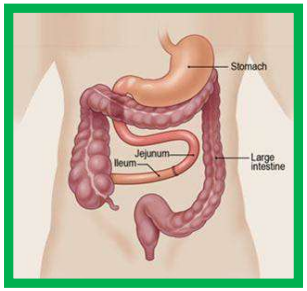
Group 2

JEJUNO-ILEO-COLIC ANASTOMOSIS

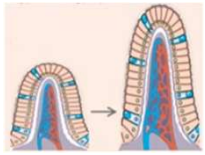


Group 3

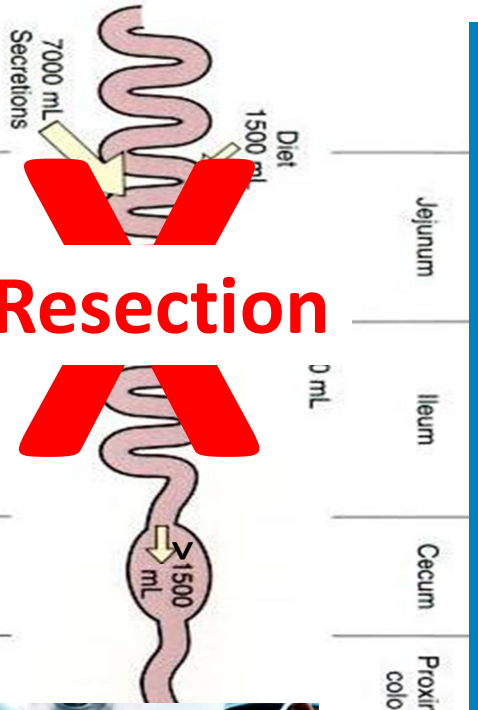
Phenotype/Pathophysiology
Jejuno-ileo-anastomosis SBS-IF, Anatomy Group 3

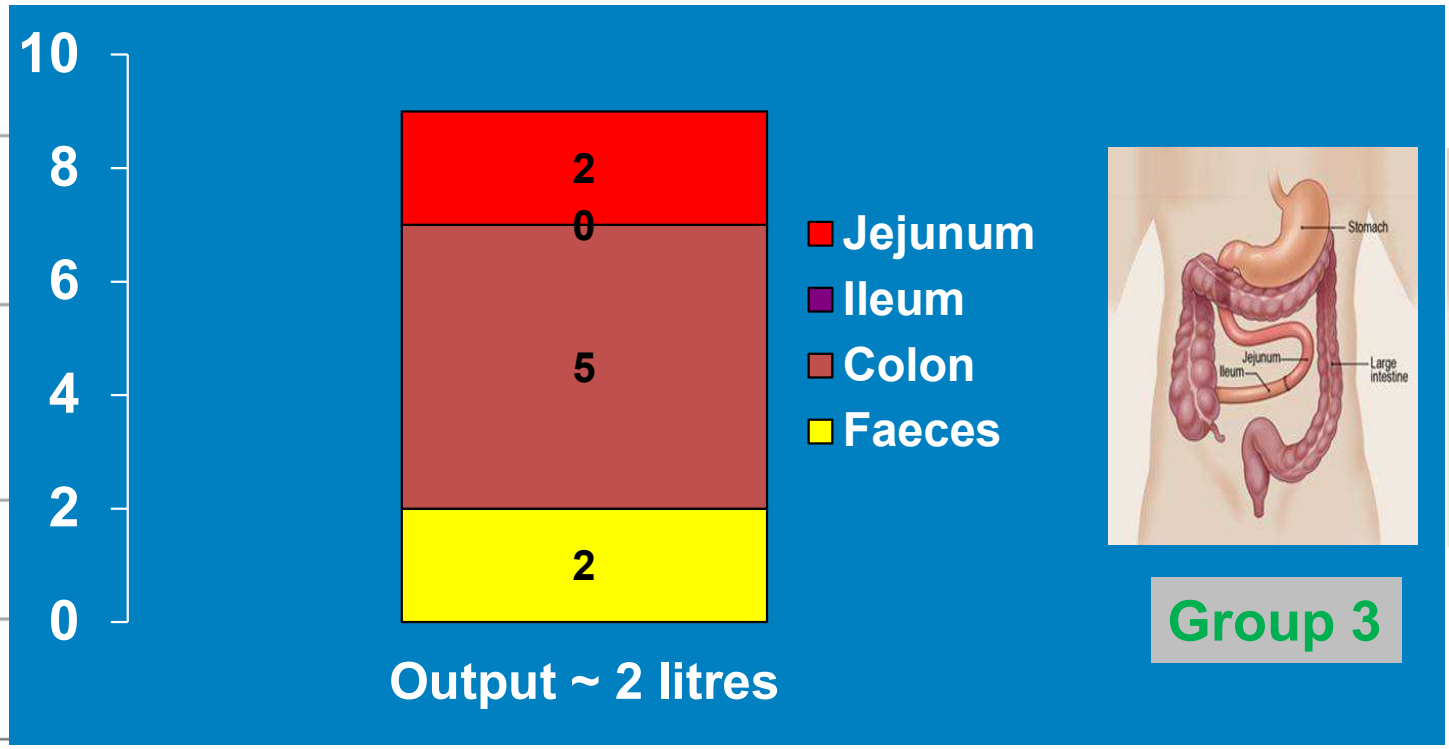


	Increased/ accelerated	Normal	Diminished/ Delayed
Gastric emptying	?X		
Gastric secretion	?X		
Pancreatic exocrine secretion	?		
Brunner gland secretion	?		
Bile secretion	?		?X
Intestinal blood flow	X		
Intestinal growth	XXX		

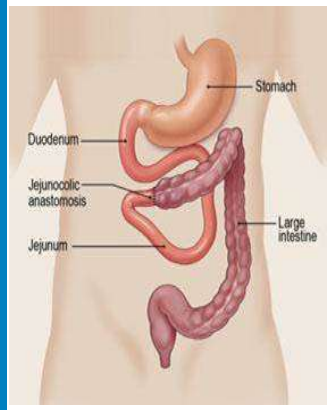


Consequeces Mid-Small Bowel Resection with jejuno-(ileo)-colonic anastomosis



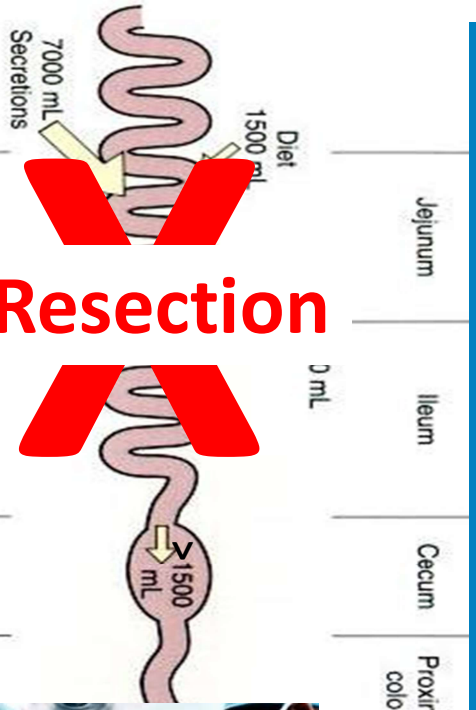


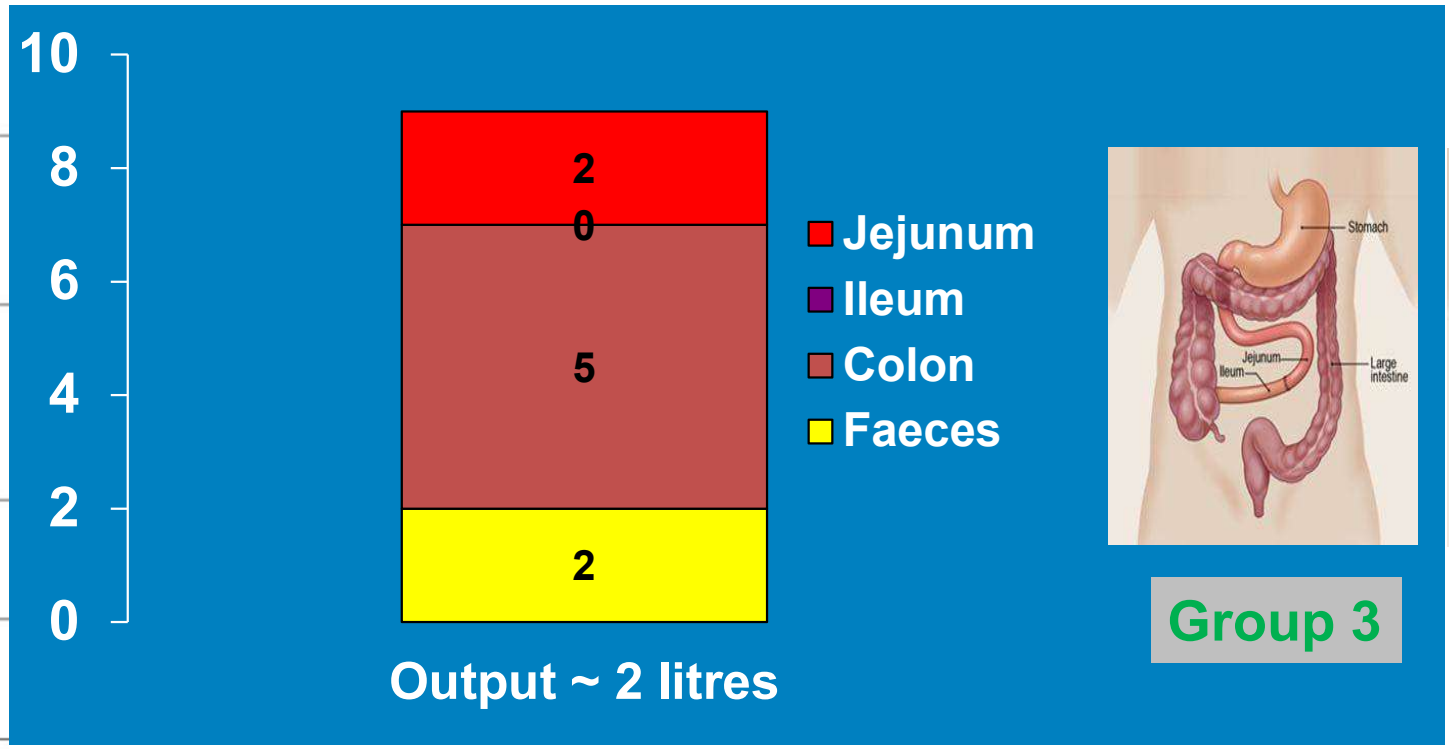
Group 3



Group 2

Consequeces Mid-Small Bowel Resection with jejuno-(ileo)-colonic anastomosis





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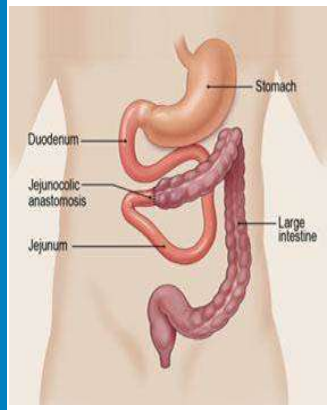


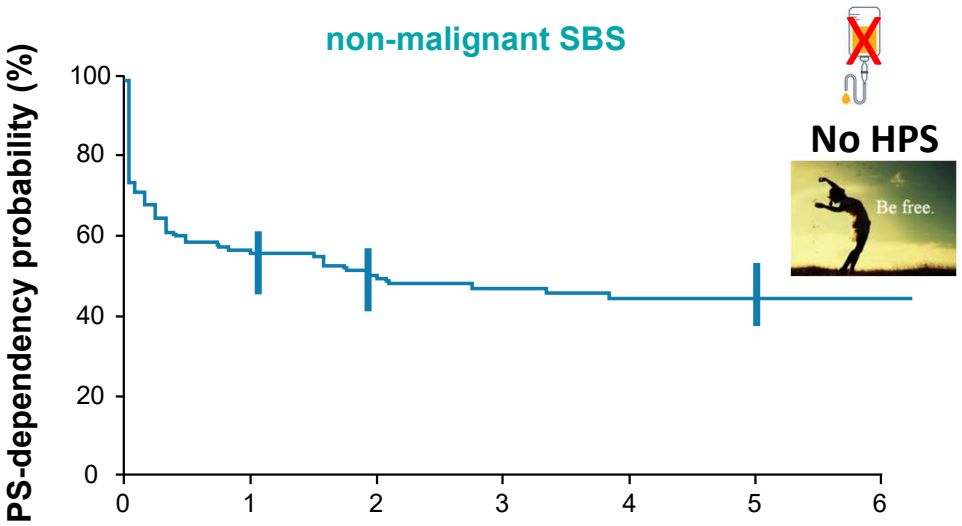
Group 2

Reserve capacity of the human colon to absorb :
(5.7 L fluid* + 816 mmol sodium* + 4.2 MJ# per day)

*Debongnie &Phillips Gastroenterology/ #Nordgaard-I Lancet 1994

Adaptation: PS dependency (IF) in non-malignant SBS

Probability of PS dependence in 124 adult patients with non-malignant SBS



No HPS

No. patients at risk	124	51	45	39	29	20	14

Vertical bars indicate 95% CIs at 1, 2 and 5 years of follow-up. PS dependence probabilities were 53% (95% CI, 44–62), 49% (95% CI, 40–58) and 45% (95% CI, 35–55) at 1, 2 and 5 years, respectively.

Digestive characteristics of 124 patients with non-malignant SBS

Characteristics	No. patients (%)
Remnant small bowel length (cm)	
<50	43 (35)
50–99	39 (31)
100–150	42 (34)
Digestive circuit type of anastomosis	
End-enterostomy (Anatomy group 1)	18 (14)
Jejunocolic anastomosis (Anatomy group 2)	78 (63)
Jejunoileocolic anastomosis (Anatomy group 3)	28 (23)
Radiographic abnormal pattern of remnant small bowel	
Present*	24 (19)
Absent	100 (81)
Other digestive features	
Left colostomy	12 (10)
Duodenopancreatectomy	3 (2)

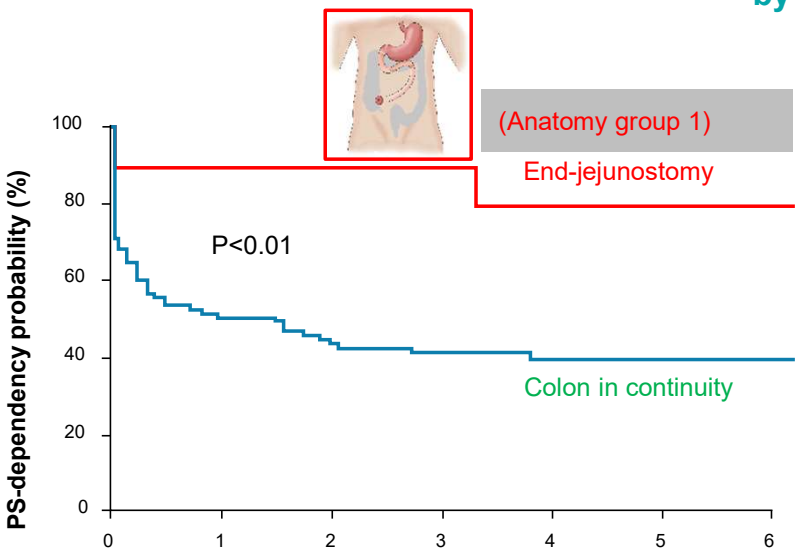
*Modified mucosal folds and/or non-occlusive stenoses in 14 of 28 patients with radiation enteritis, 4 of 11 with CD, 3 of 41 with arterial ischaemic enteritis as cause of bowel resection and 3 of 13 with miscellaneous diseases; none of the patients had occlusive stenoses.

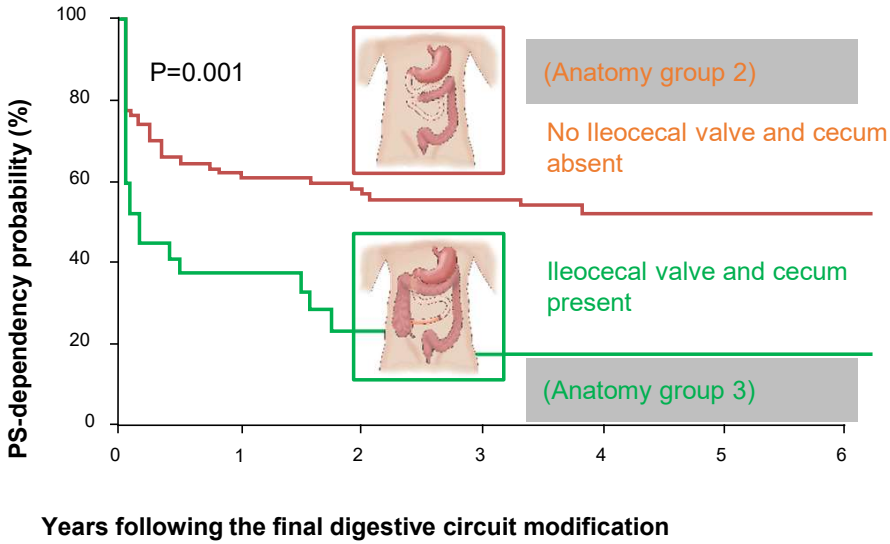
CD: Crohn's disease; CI: confidence interval; IF: intestinal failure; Ps: parenteral Support; SBS: short bowel syndrome; SBS-IF: short bowel syndrome due to intestinal failure.

Messing B, et al. *Gastroenterology* 1999;117:1043–50.

PS dependency according to anatomy group in non-malignant SBS

Probability of PS dependence in 124 adult patients with non-malignant SBS by anatomy group

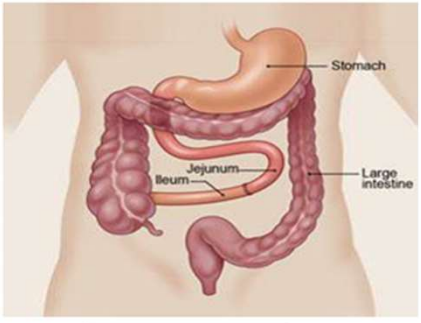




PS: parenteral support; SBS: short bowel syndrome.
Messing B, et al. *Gastroenterology* 1999;117:1043–50. Anatomy figures adapted from Tappenden KA, et al. *JPEN J Parenter Enteral Nutr*. 2014;38(suppl 1):14S–22S.

The Benefits of a Colon for Fluid, Electrolyte and Energy Absorption are well known in SBS Group 3...

...But could signals from the distal small bowel & colon also positively improve upper small bowel adaptation (**"Calm Down"** **the "Hyper-Reactive Proximal GI Tract"**)?



Group 3

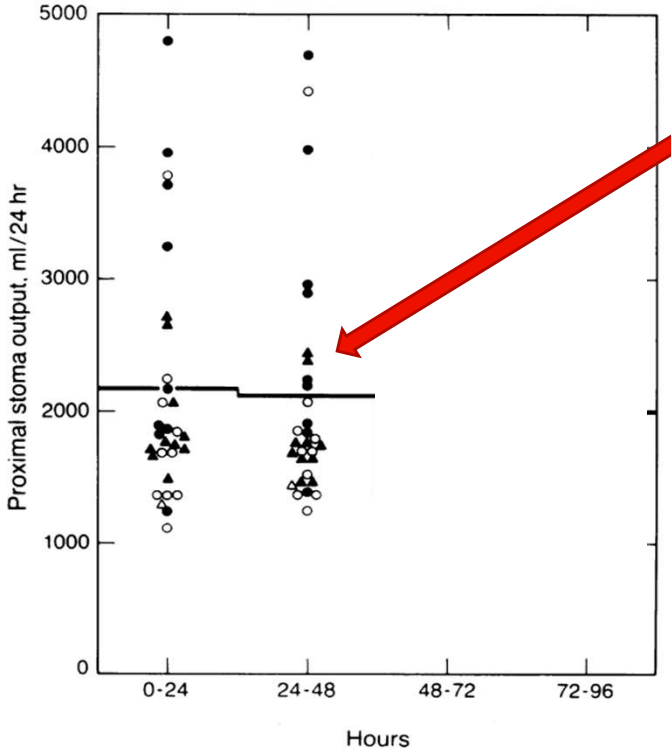
Communication from Distal to Proximal Intestine by Reinfusion of succus entericus into the distal small bowel: Inhibition of upper GI hypersecretions

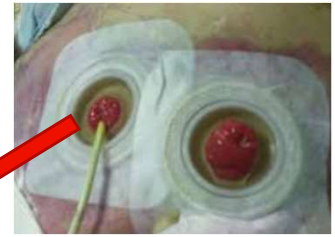
Clinical study of 30 patients;

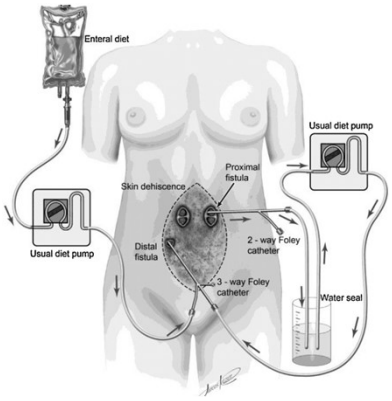
Peritonitis and temporary enterostomy: Diversion of intestinal continuity by stoma, fistula, or both

Proximal intestinal effluent collected and recycled into the distal small bowel

During reinfusion of succus entericus, a significant reduction in the output of the proximal stoma was observed (mean 30.2%, *P*<0.001)







Daily proximal stoma output in patients having succus entericus reinfusion. Key for reinfusion level: • within 100 cm of dudenojejunal flexure; mid small bowel; O within 100 cm of ileocecal valve; ♦ colon

Lévy et al. *Ann Surg*. 1983;198:596–600

GI, gastrointestinal

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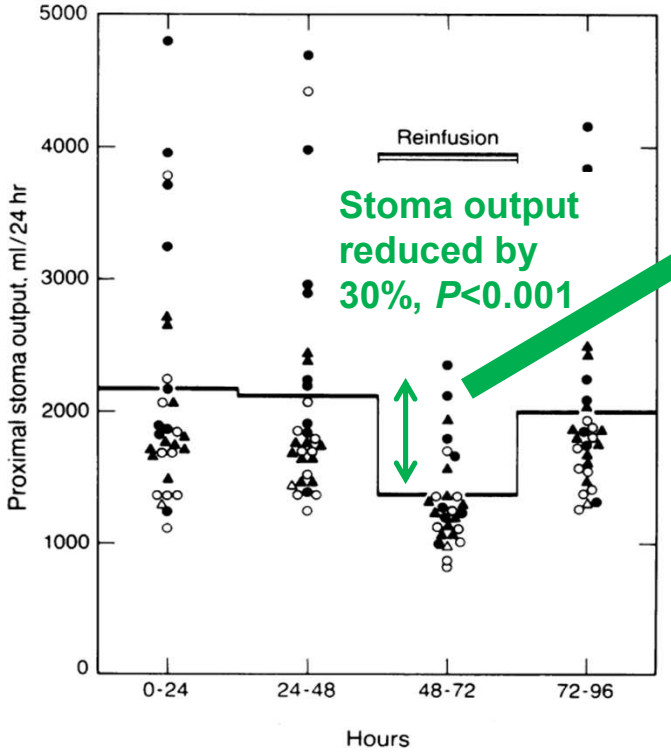

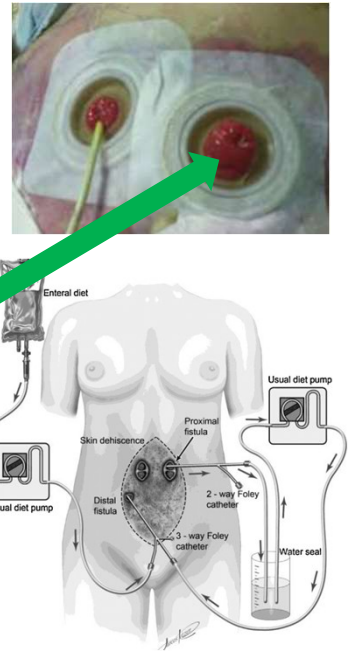

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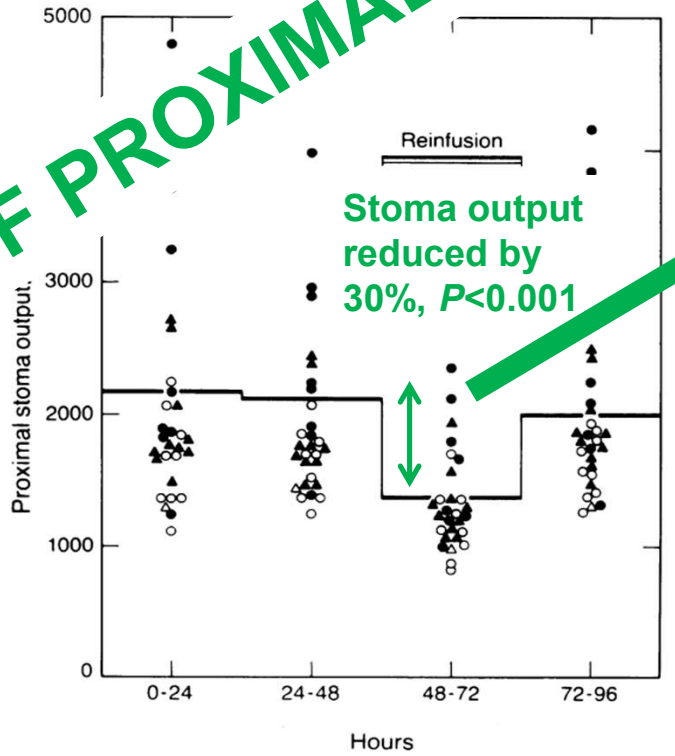
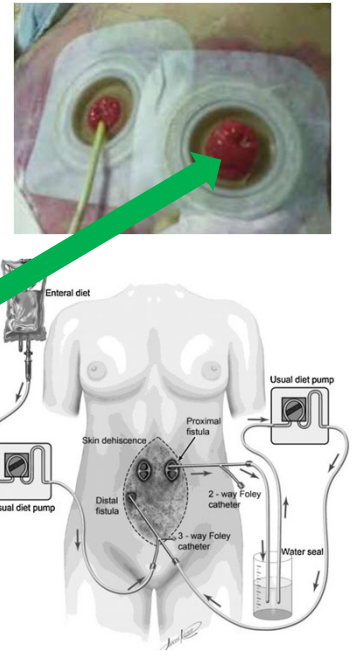
FEEDBACK REGULATION OF PROXIMAL BOWEL





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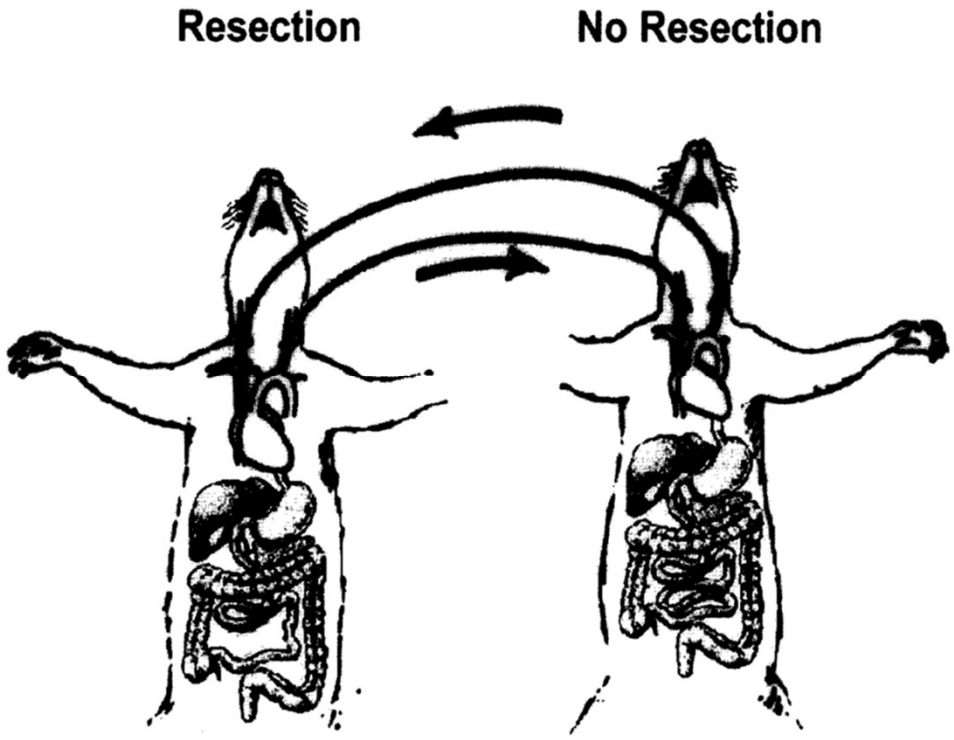
Lévy et al. *Ann Surg*. 1983;198:596–600

GI, gastrointestinal

Hormonal Factors Involved…. But which?



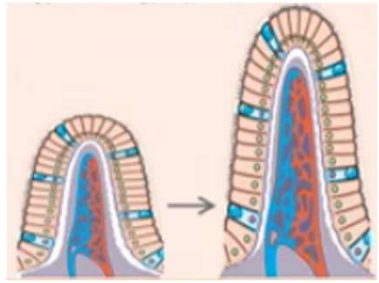
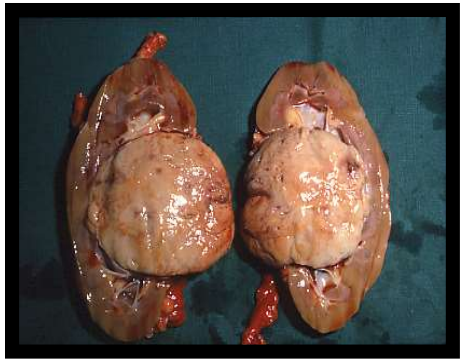
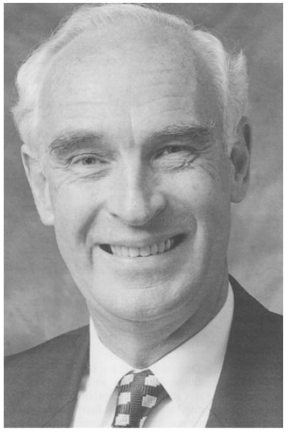


Fig 4. Vascular parabiosis. In animals sharing a common circulation intestinal resection in one animal induces adaptive changes in the intestine of the unoperated animal.

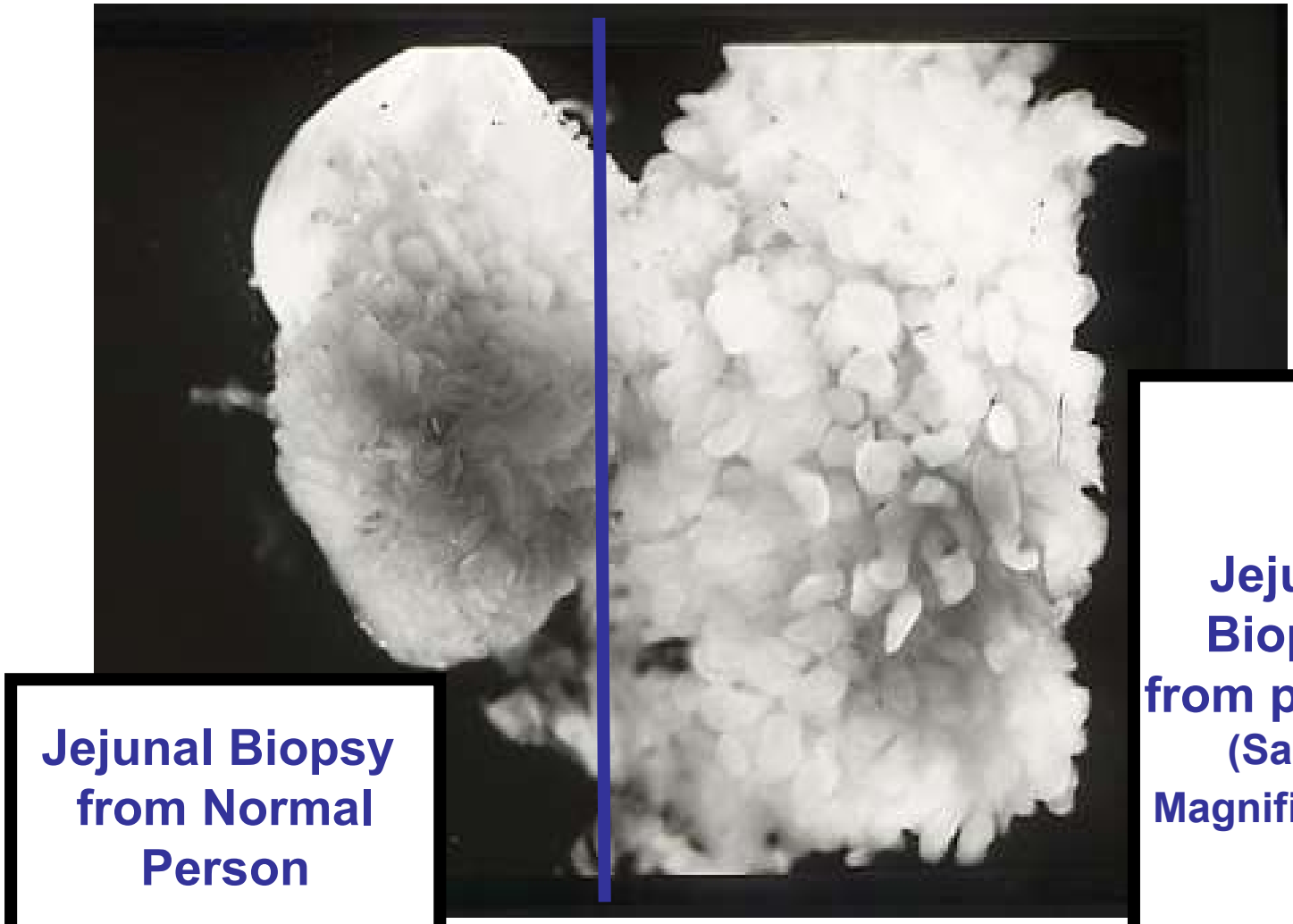
Williamson et al. *Gastroenterology*. 1978;75:249–254

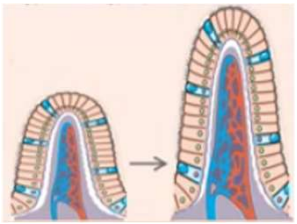
Endocrine tumor in kidney affecting small bowel structure, motility and absorptive function. 1971





Gleeson MH, Bloom SR, Polak JM, Henry K, Dowling RH. Endocrine tumour in kidney affecting small bowel structure, motility, and absorptive function. *Gut.* 1971 Oct;12(10):773–782.





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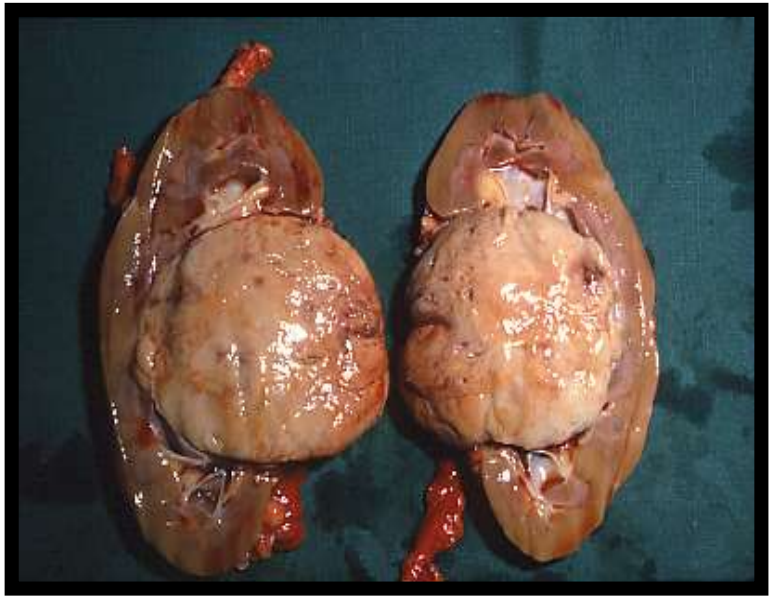
Gut, 1972, **13**, 520-523

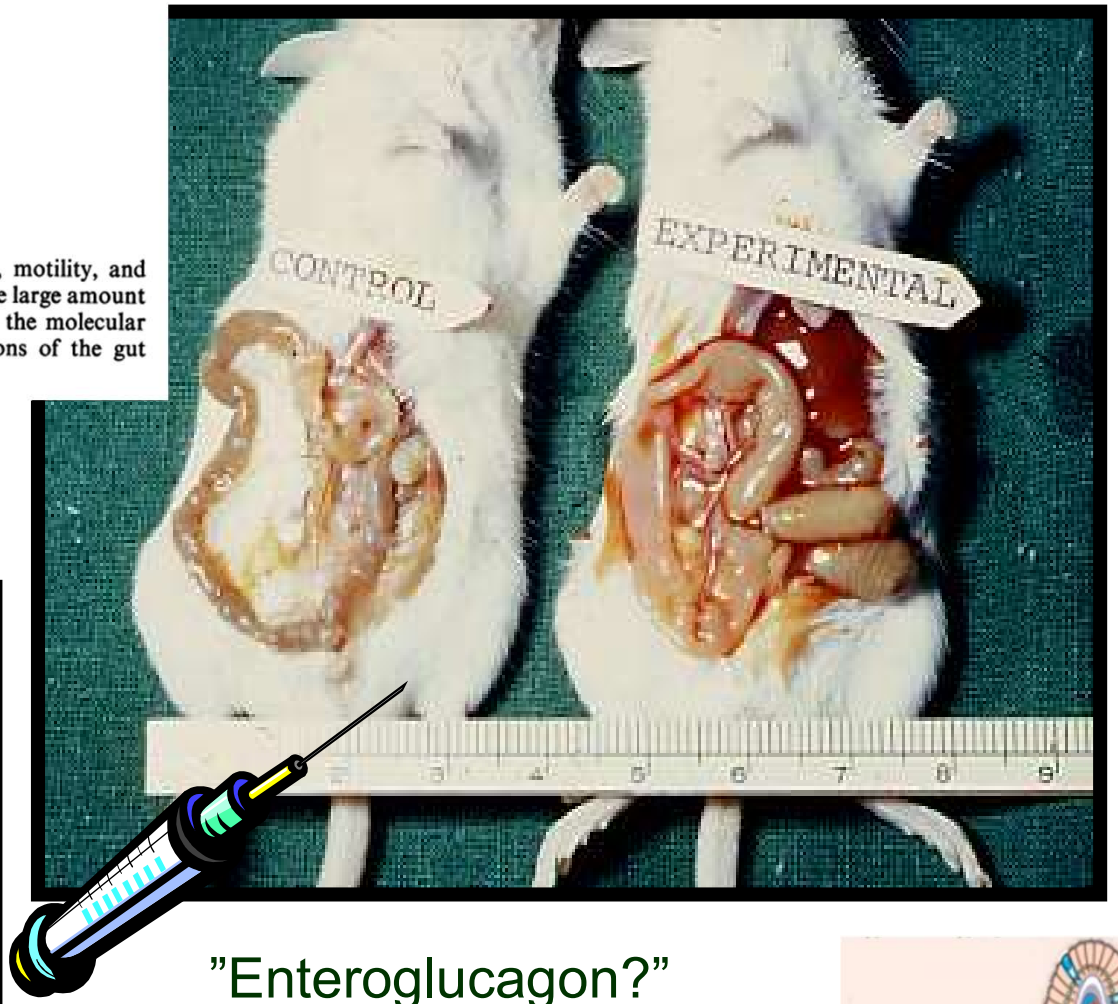
An enteroglucagon tumour

S. R. BLOOM

From the Institute of Clinical Research, The Middlesex Hospital, London

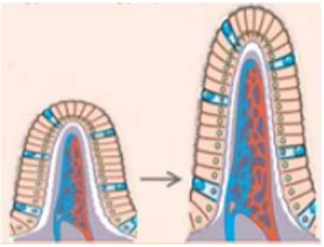
SUMMARY A hormone-secreting renal tumour that affected small bowel structure, motility, and function has been described by Gleeson *et al* (1971). The present studies show that the large amount of glucagon-like immunoreactivity which could be extracted from this tumour had the molecular weight, action on plasma insulin and glucose *in vivo*, and immunological reactions of the gut hormone enteroglucagon. This is the first enteroglucagonoma to be reported.



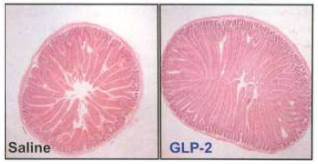


”Enteroglucagon?”

Gleeson MH



1996:
Drucker



Proc. Natl. Acad. Sci. USA
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Induction of intestinal epithelial proliferation by glucagon-like peptide 2

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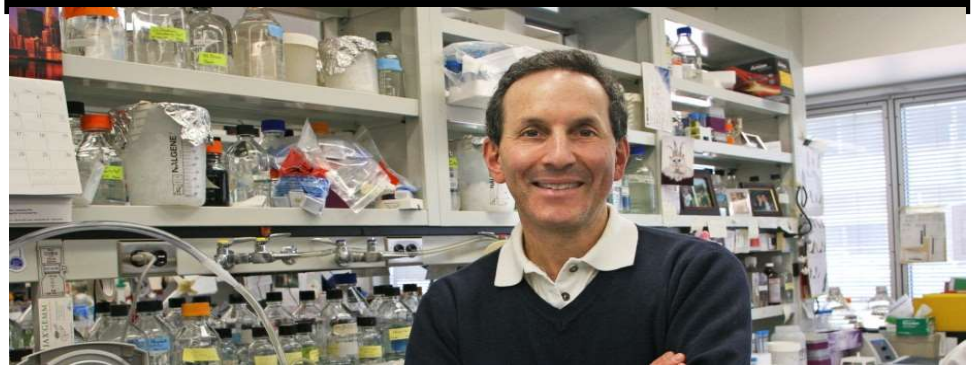
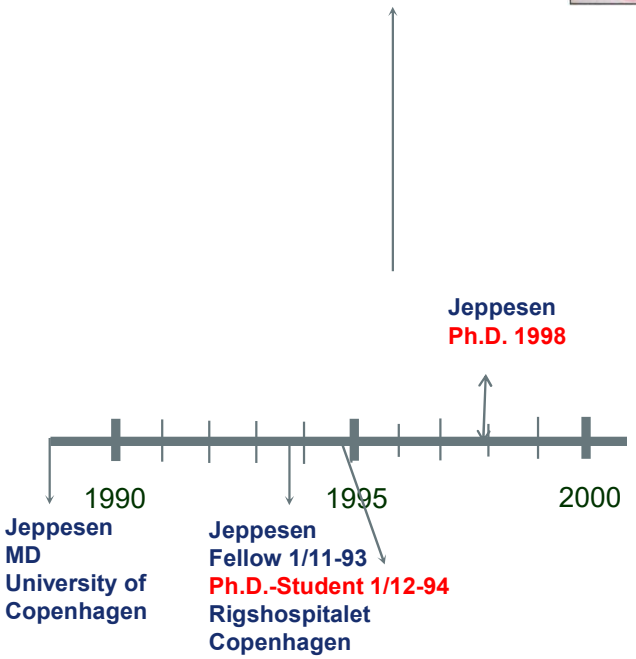


The Seminal Paper



Glucagon-Like Peptide 2 (GLP-2)

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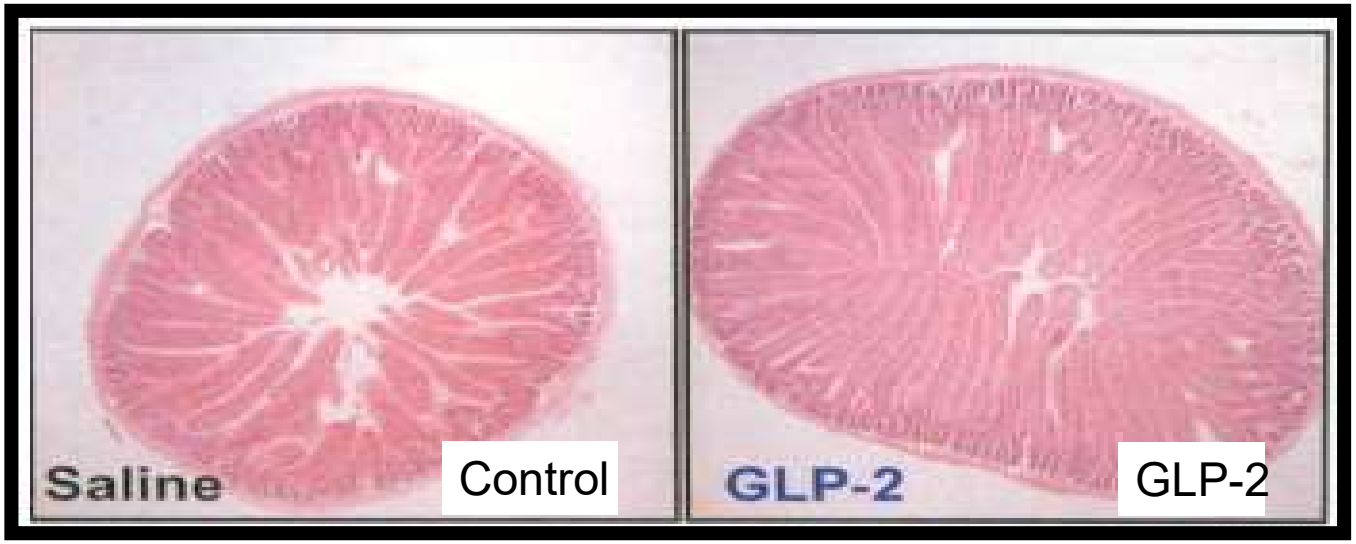
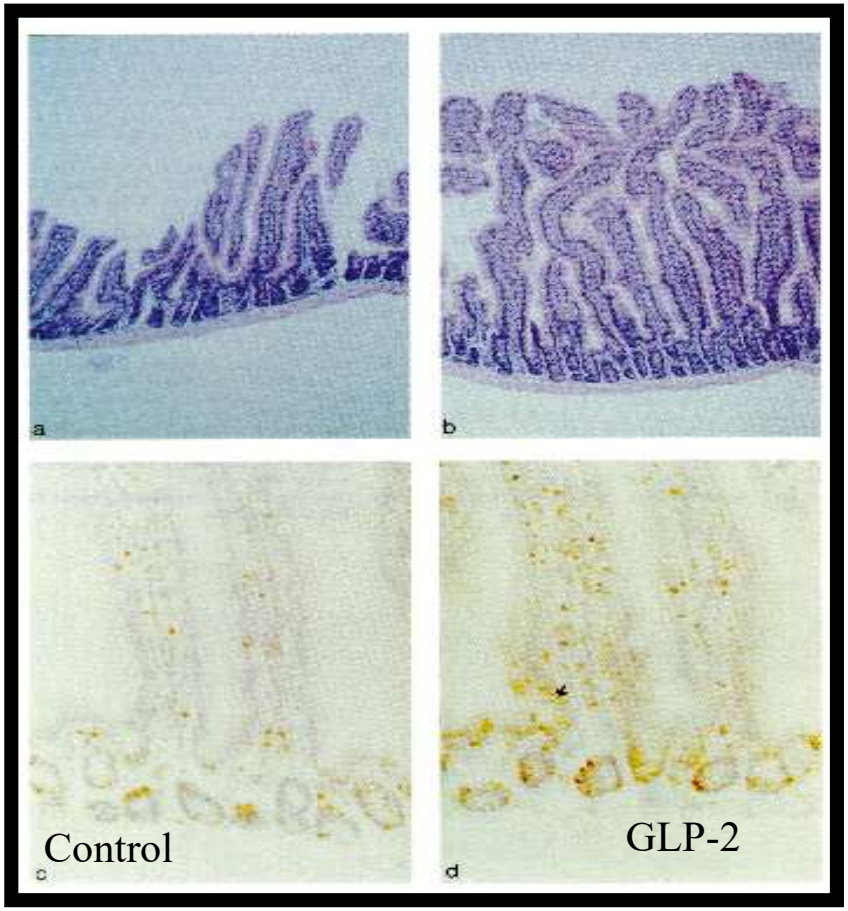
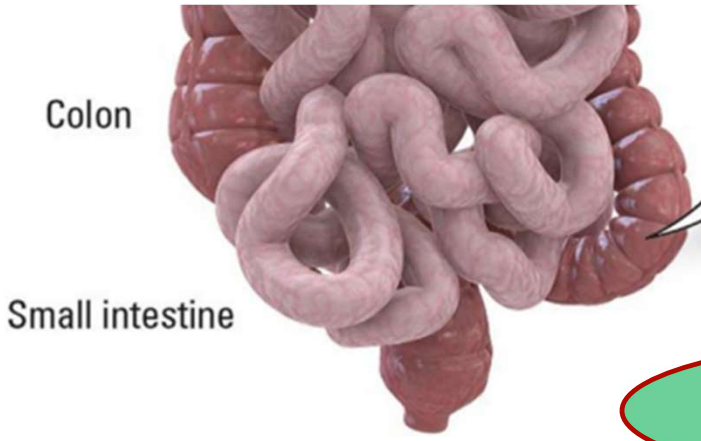


Drucker et al., PNAS 93:7911-7916,1996



Lower GI hormones
(‘Feedback’ or ‘brake’ hormones)



Hormone hyper-secretion

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↓ Bile acids, glucose production
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GLUCAGON LIKE PEPTIDE-2 (GLP-2):
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OXYNTOMODULIN:
↑ With eating
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↓ Hunger

PEPTIDE YY (P-YY):
↑ With eating
↓ Gallbaldder & pancreatic secretions
↓ Intestinal motility
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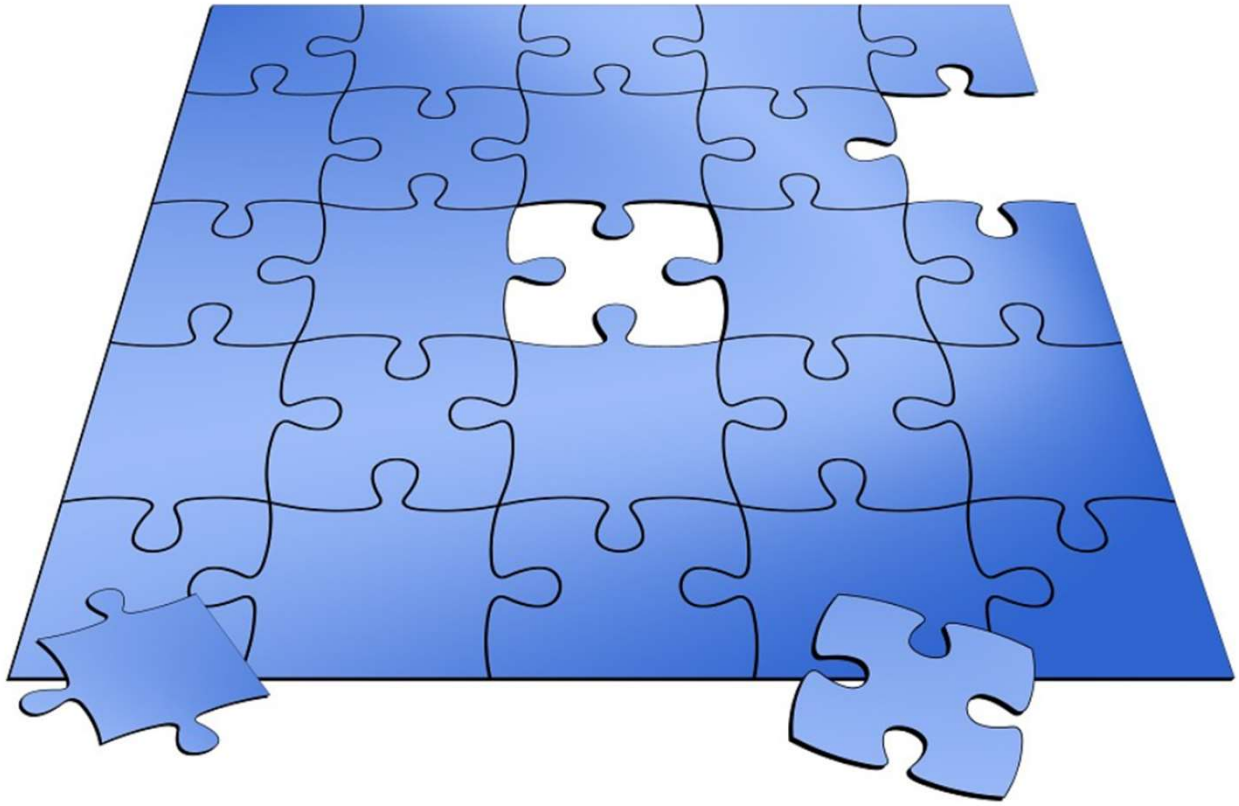
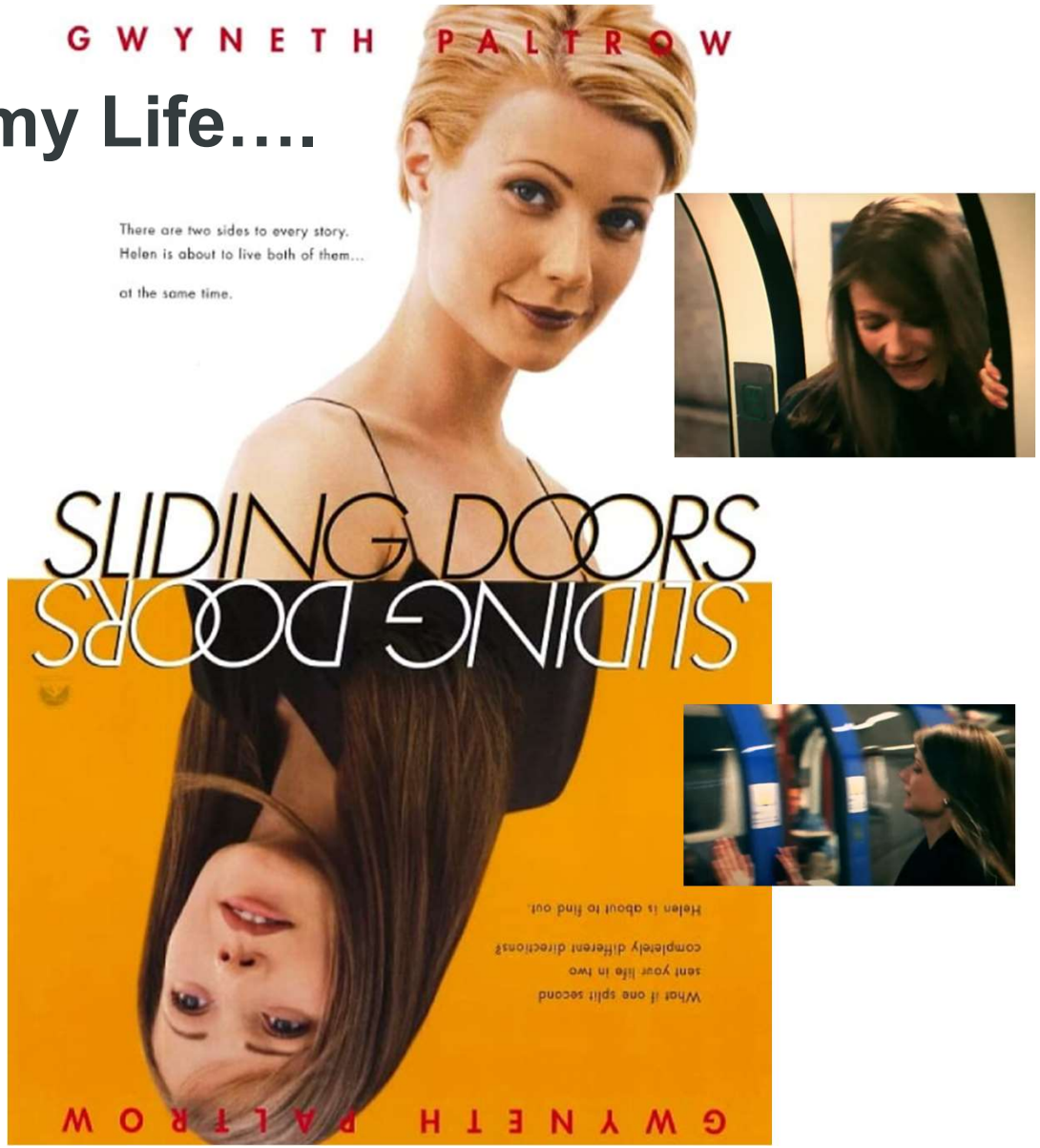
Meal-stimulated GLP-2 secretion from intestinal L-cells predonimantly secreted from terminal ileum and colon

GLP-2: One of The Missing Pieces in the **“Adaptation Jigsaw Puzzle”?**



The Sliding Doors Moment of my Life….

- In 1998, writer-director Peter Howitt incepted a whole generation with this recurring-nightmare-fantasy scenario, by way of the romantic comedy *Sliding Doors*.
- An examination of how tiny, seemingly inconsequential moments can alter the trajectories of our lives, *Sliding Doors* is a perfectly light, frothy rom-com that improbably shoves you down into a bottomless funk of self-doubt right after the credits.



A Career with GLP-2

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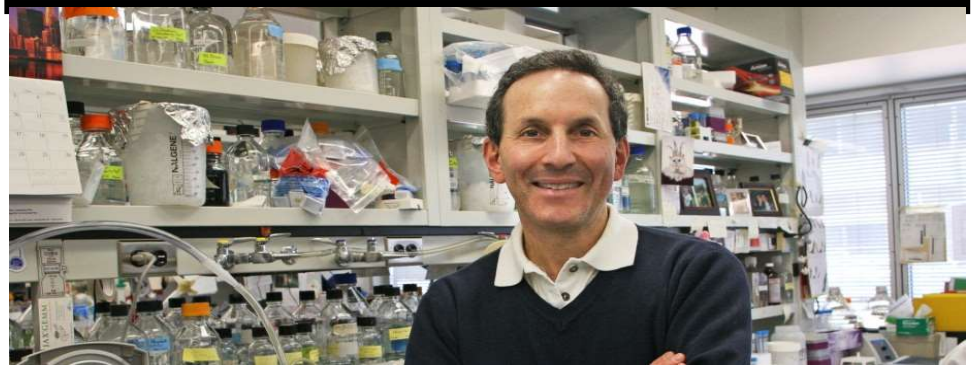

1996:
Drucker

Holst
Mortensen
Jeppesen
Meeting

Jeppesen
Ph.D. 1998

1990 — 1995 — 2000

Jeppesen
MD

Jeppesen
Fellow 1/11-93
Ph.D.-Student 1/12-94
Rigshospitalet

"The Sliding Door Moment" Meeting

Jens Juel Holst, Bolette Hartmann Steeen Seier Poulsen og H. Kissow

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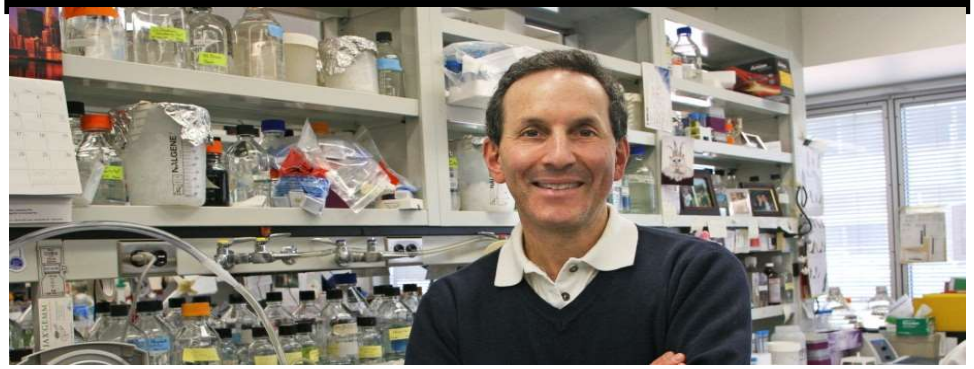

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Assay for Plasma GLP-2 Measurements

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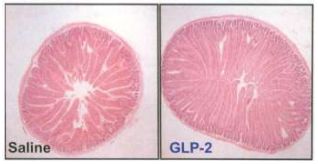

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"The Sliding Door Moment" Meeting

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Assay for Plasma GLP-2 Measurements

Funding for & Access to Native GLP-2

A Career with GLP-2

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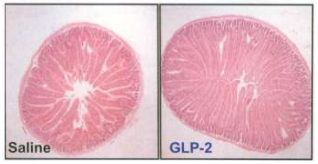

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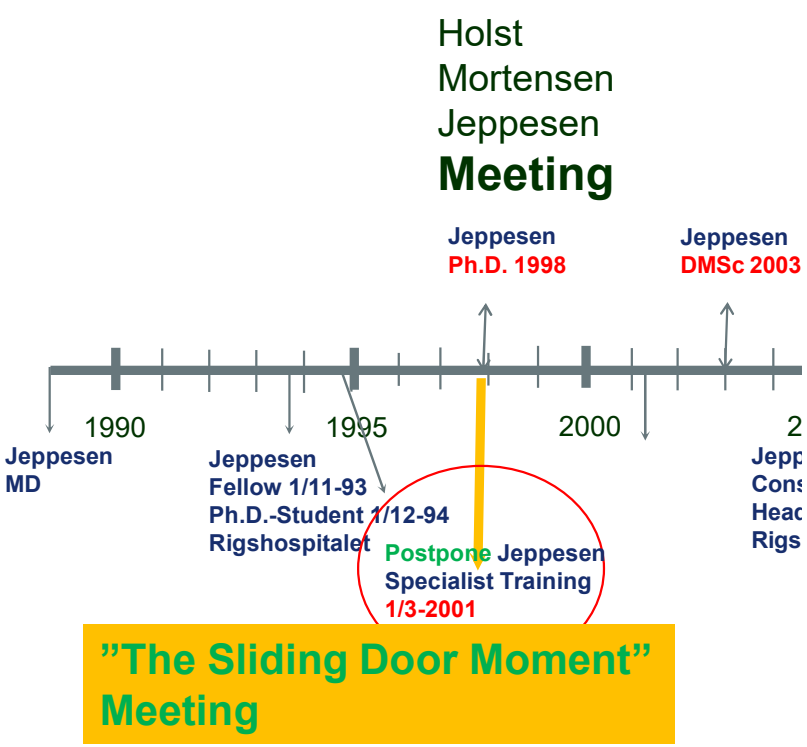
Assay for Plasma GLP-2 Measurements

Funding for & Access to Native GLP-2

A Career with GLP-2

Post-doc

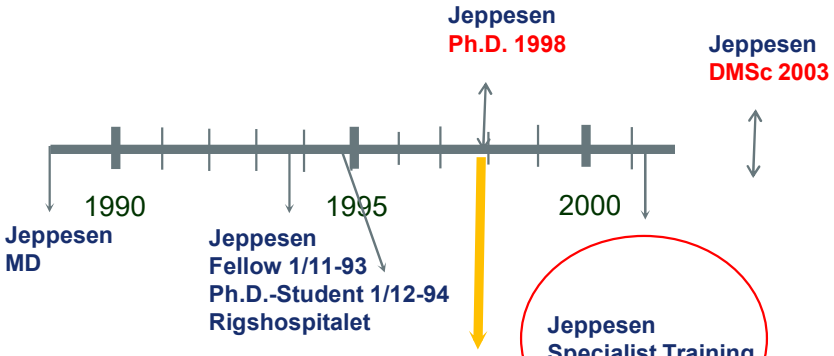


"The Sliding Door Moment" Meeting

A Career with GLP-2

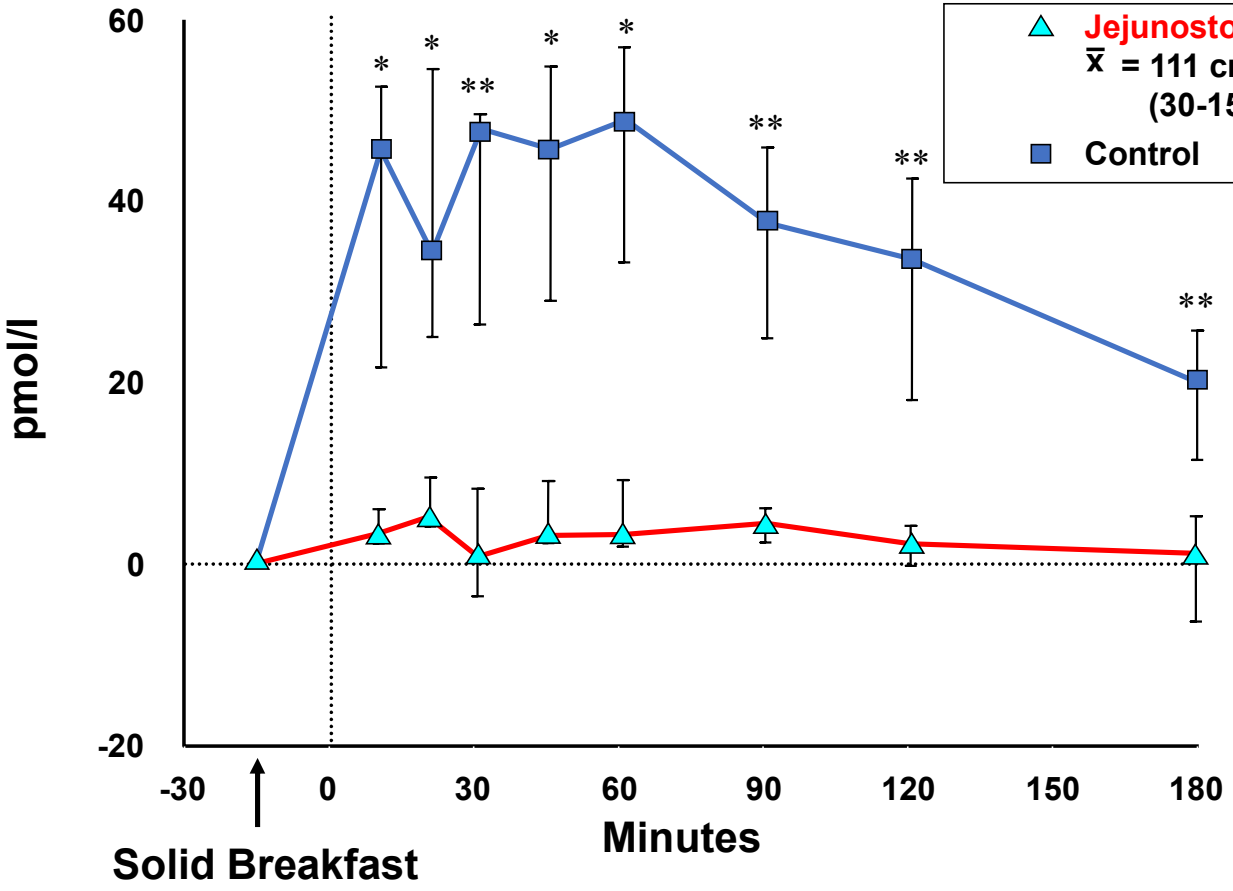
Post-doc

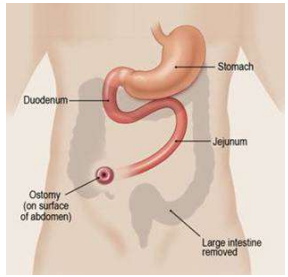
- Native GLP-1, GLP-2 & GLP-2 + GLP-1 studies
- 2-year Native GLP-2 studies
- Teduglutide Phase 2
- GLP-2 and Mesenteric Bloodflow
- GLP-2 and Bone
- Native GLP-2 in SBS
- Lack of GLP-2 in end-jejunostomy
- Elevated GLP-2 in SBS CiC



"The Sliding Door Moment" Meeting

End-Jejunostomy, Group 1 anatomy
Lack of Meal-Stimulated GLP-2 Secretion

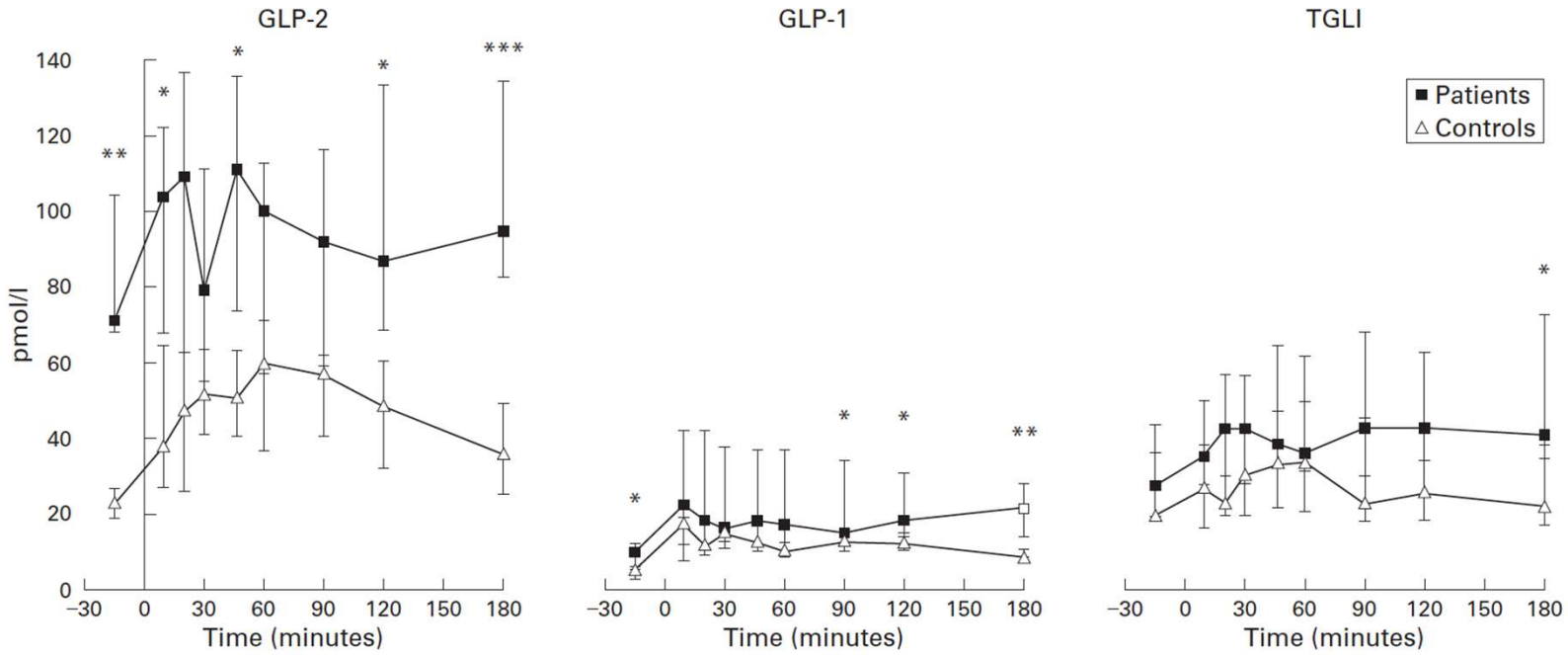


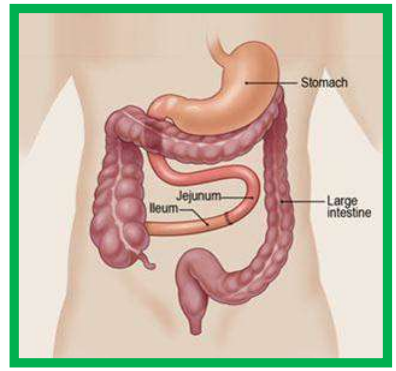


Reduced L-cells stimulation due to resection of terminal Ileum and colon

Jeppesen et al, Gut 45:559-63, 1999

Elevated plasma GLP-1 and -2 concentrations in Jejunum resected SBS patients with a preserved colon





Increased L-cells stimulation due to hyperstimulation of terminal Ileum and colon

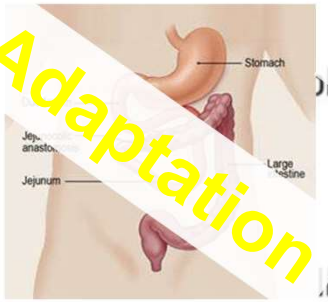
Meal stimulated GLP-1 and -2, and total glucagon-like immunoreactivity (TGLI) responses (pmol/L) in patients and controls.

*P<0.05, **P<0.01, ***P<0.001, Mann-Whitney rank sum test; results are median (25–75%).

Jeppesen et al. *Gut*. 2000;47:370–376

Lower GI hormones
(‘Feedback’ or ‘brake’ hormones)

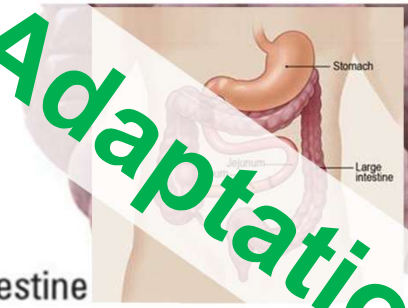
JEJUNO-COLIC ANASTOMOSIS



Adaptation

Group 2

JEJUNO-ILEO-COLIC ANASTOMOSIS



Adaptation

Group 3

Hormone hyper-secretion

FIBROBLAST GROWTH FACTOR (FGF19):
↑ With eating
↓ Bile acids, glucose production
↑ Insulin sensitivity, glycogen synthesis
↓ Hunger

GLUCAGON LIKE PEPTIDE-1 (GLP-1):
↑ With eating
↑ Insulin
↓ Glucagon, gastric emptying
↓ Hunger

GLUCAGON LIKE PEPTIDE-2 (GLP-2):
↑ With eating
↑ Intestinal mucosal growth
↓ Gastric secretions

OXYNTOMODULIN:
↑ With eating
↓ Gastric acid and motility
↓ Hunger

PEPTIDE YY (P-YY):
↑ With eating
↓ Gallbaldder & pancreatic secretions
↓ Intestinal motility
↓ Hunger

Jeppesen et al. Gut. 2000;47:370–376;

Lower GI hormones
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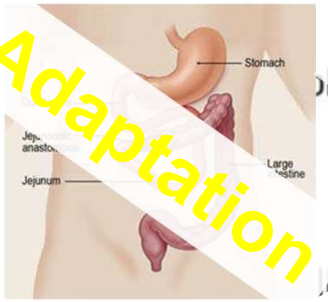

Group *2*

JEJUNO-ILEO-COLIC ANASTOMOSIS

Group 3

-secretion

BROBLAST GROWTH FACTOR (FGF19):
↑ With eating
↓ Bile acids, glucose production
↑ Insulin sensitivity, glycogen synthesis
↓ Hunger

GLUCAGON LIKE PEPTIDE-1 (GLP-1):
↑ With eating
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↓ Hunger

GLUCAGON LIKE PEPTIDE-2 (GLP-2):
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↓ Gastric secretions

OXYNTOMODULIN:
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PEPTIDE YY (P-YY):
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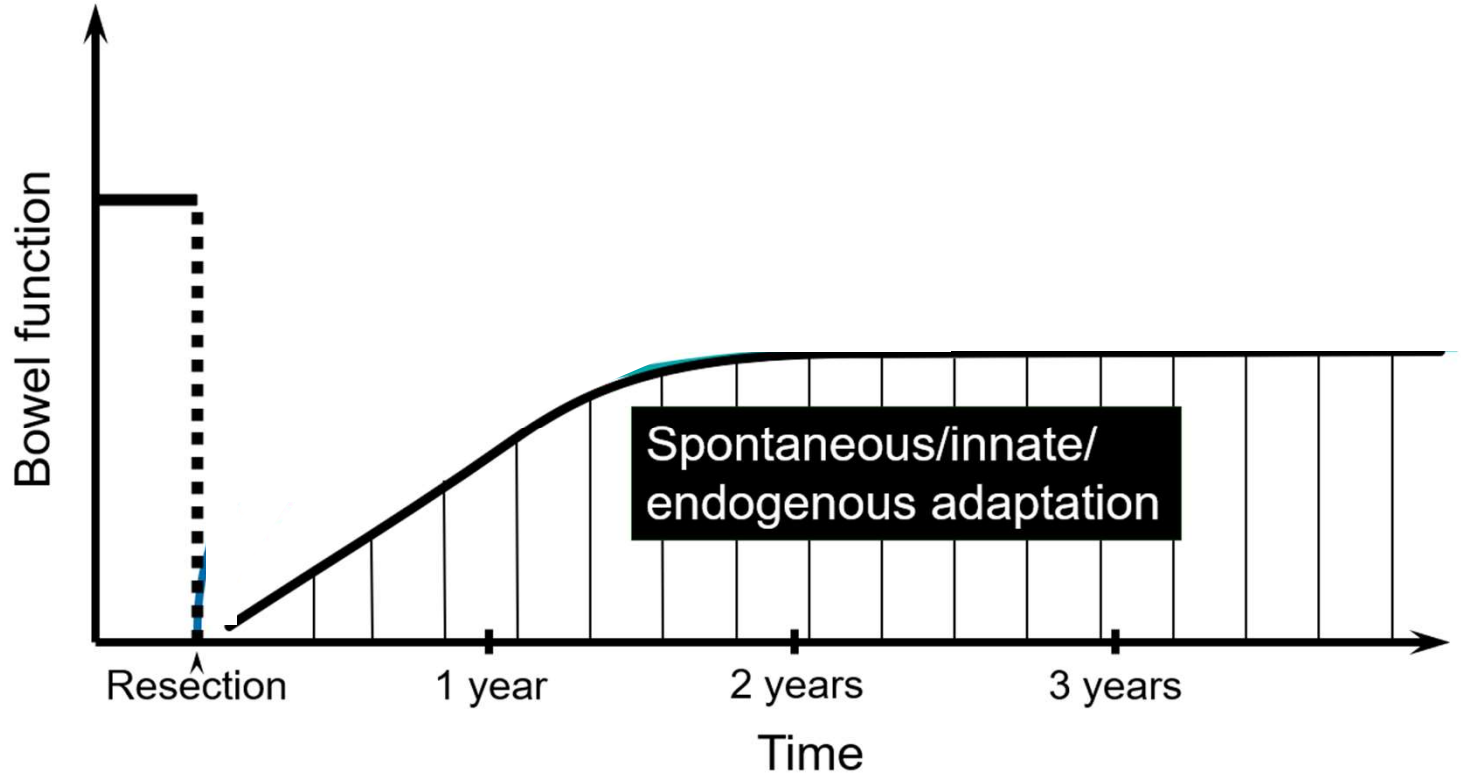
Adaptation

Ada tation

FEEDBACK REGULATION OF PROXIMAL BOWEL

Jeppesen et al. Gut. 2000;47:370–376;

Pro-adaptive/Enterohormone therapy following resection may facilitate hyperadaptation in patients with SBS-IF



Jeppesen-PB. Gastroenterol Clin N Am 36 (2007) 109–121.

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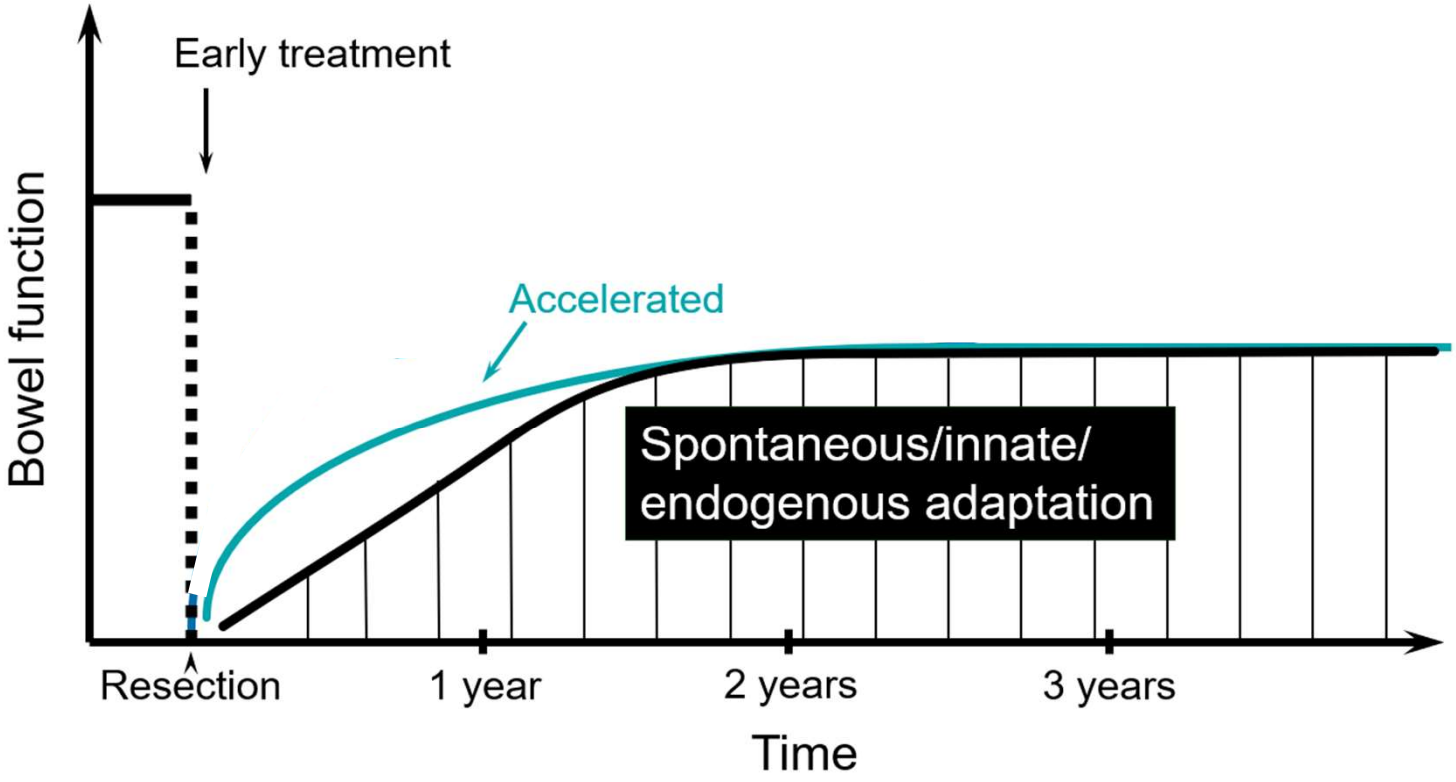

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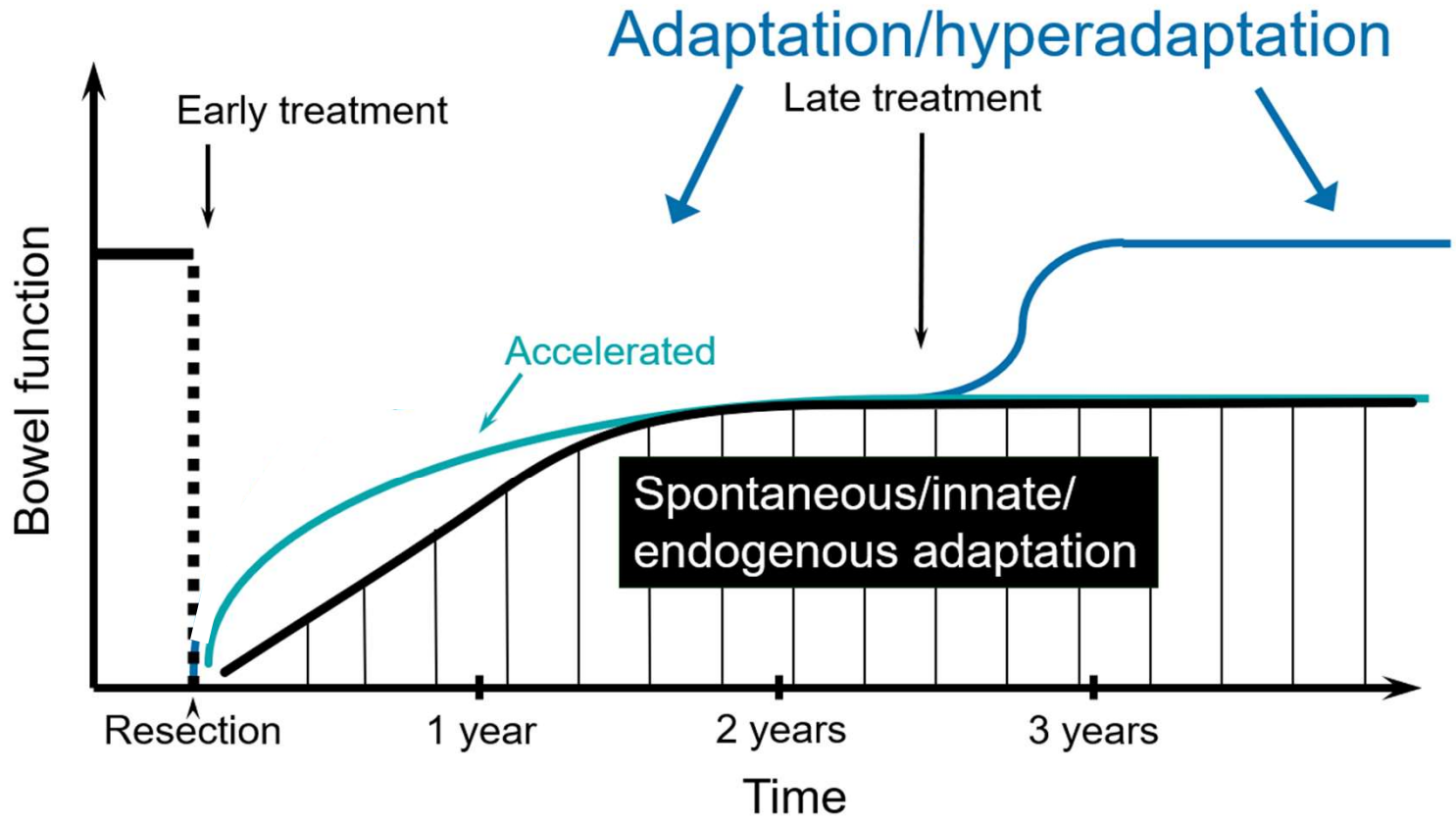

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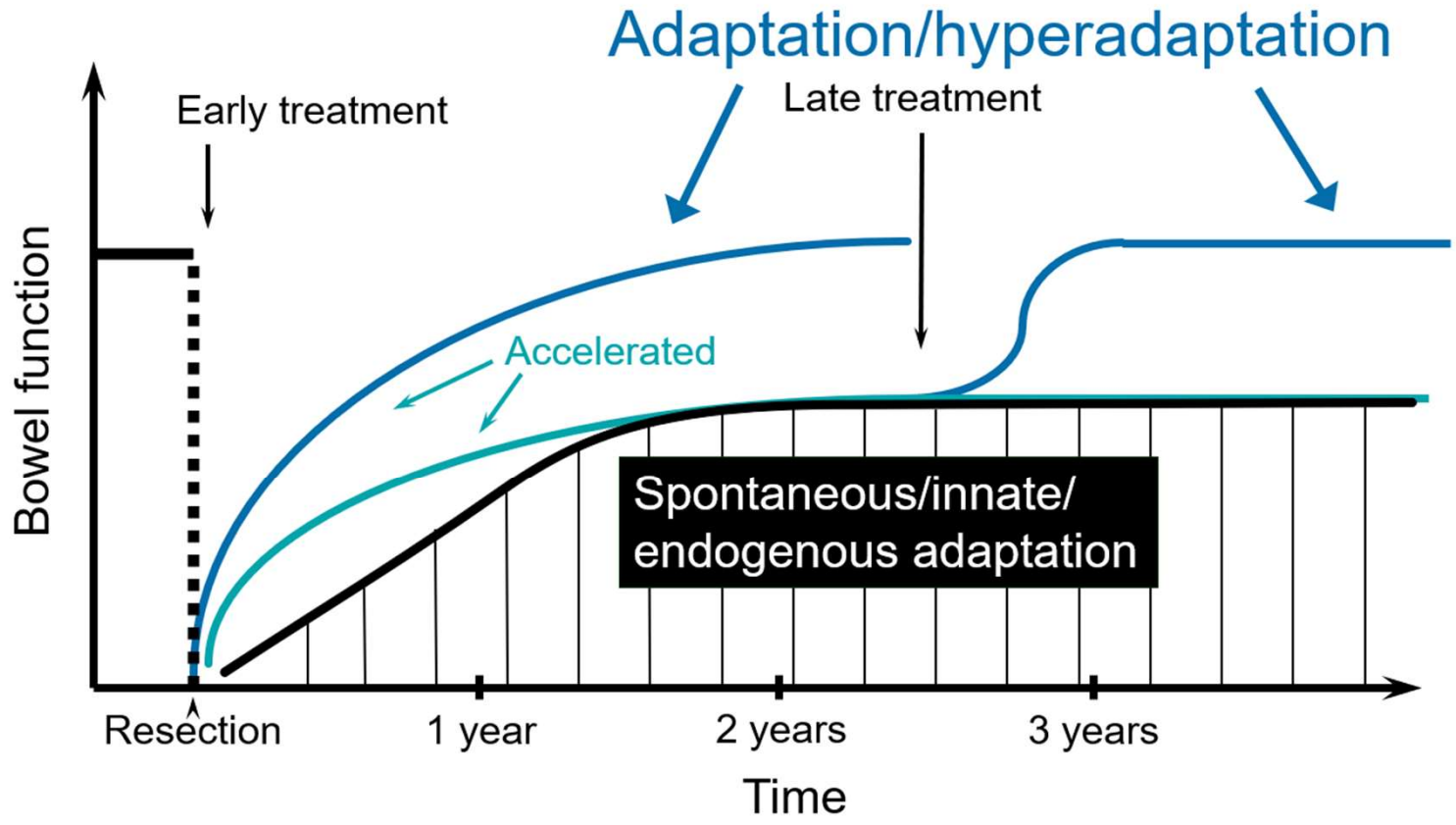


Jeppesen-PB. Gastroenterol Clin N Am 36 (2007) 109–121.

GASTROENTEROLOGY 2001;120:806–815

Glucagon-like Peptide 2 Improves Nutrient Absorption and Nutritional Status in Short-Bowel Patients With No Colon

PALLE BEKKER JEPPESEN,* BOLETTE HARTMANN,† JESPER THULESEN,§ JESPER GRAFF,‖ JETTE LOHMANN,¶ BIRTHE STENBÆK HANSEN,* FLEMMING TOFTENG,* STEEN SEIER POULSEN,§ JAN LYSGAARD MADSEN,‖ JENS JUUL HOLST,† and PER BRØBECH MORTENSEN*

*Department of Medicine, Section of Gastroenterology, Rigshospitalet, University Hospital of Copenhagen, Denmark; Departments of †Medical Physiology and §Medical Anatomy, The Panum Institute, University of Copenhagen, Denmark; ‖Department of Clinical Physiology and Nuclear Medicine, Hvidovre Hospital, University Hospital of Copenhagen, Denmark; and ¶H.S. Pharmacy, Copenhagen Hospital Corporation, Denmark

See editorial on page 1041.

The intestinal proglucagon-derived peptides (PGDPs), comprising glicentin, oxyntomodulin, and the 2 glucagon-like peptides (GLP-1 and GLP-2) are secreted from

Balance Studies: Diet – Faeces = Absorption

First In Human Proof of Concept Trial

Intestinal absorption

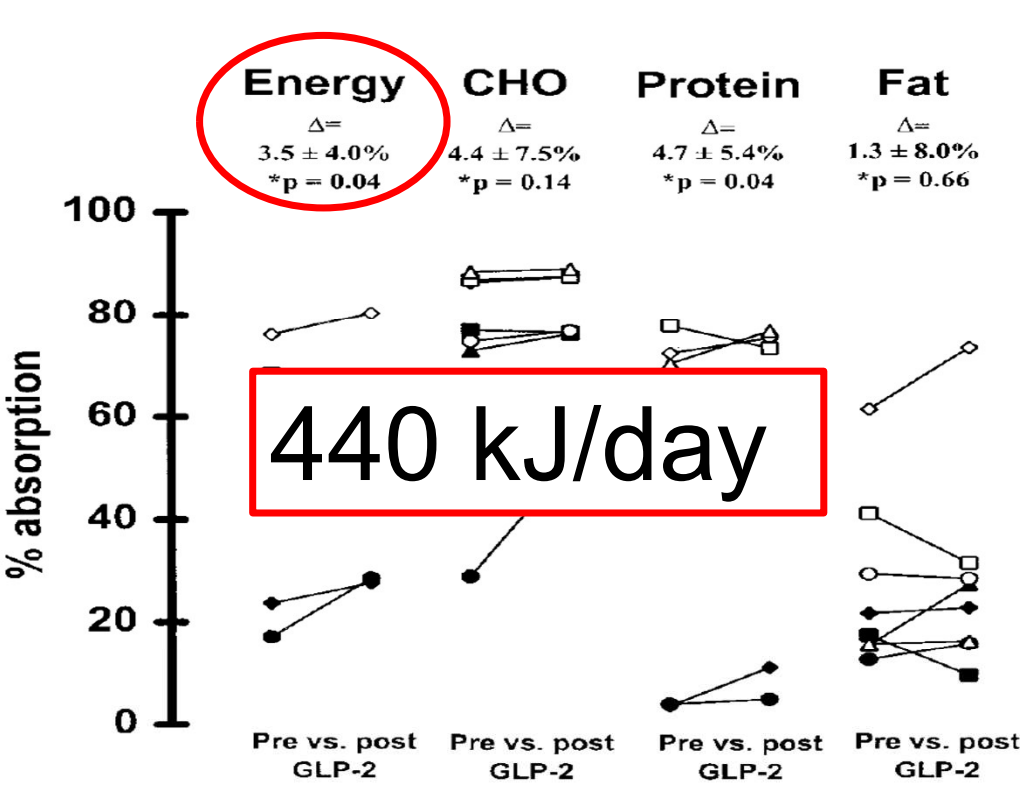


Figure 1. Relative absorption of energy and macronutrients before and after 5 weeks of GLP-2 treatment in 8 patients with the short-bowel syndrome. *Closed symbols* represent patients receiving HPN. *Paired Student *t* test. Δ, Mean ± SD effect of treatment with GLP-2 compared with baseline.

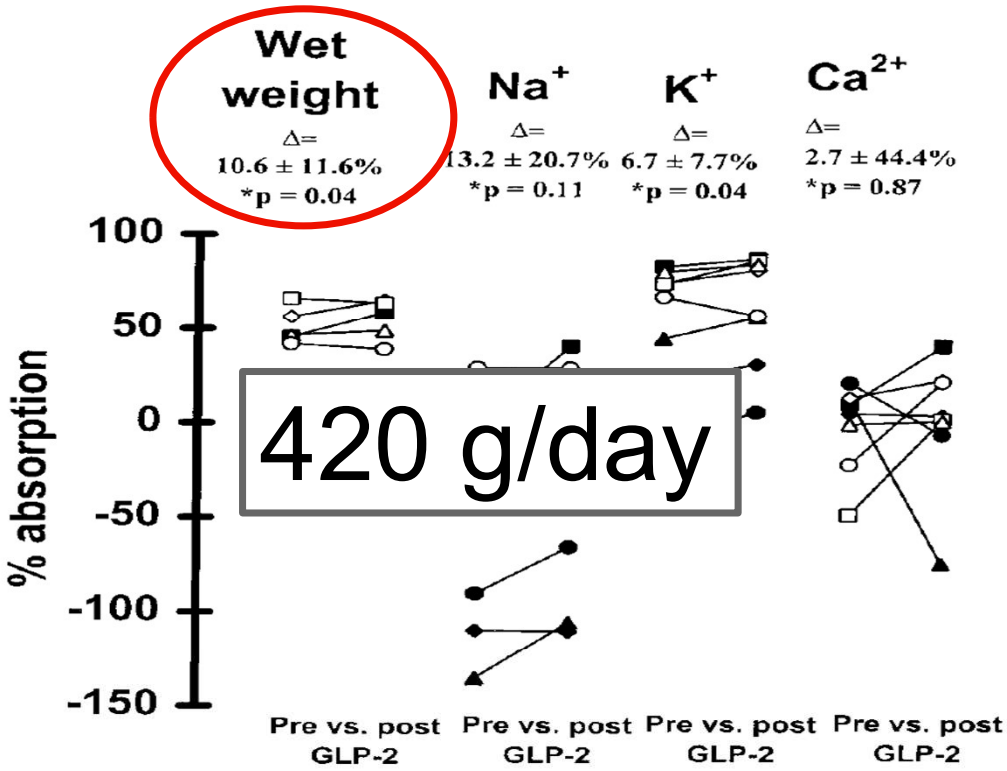
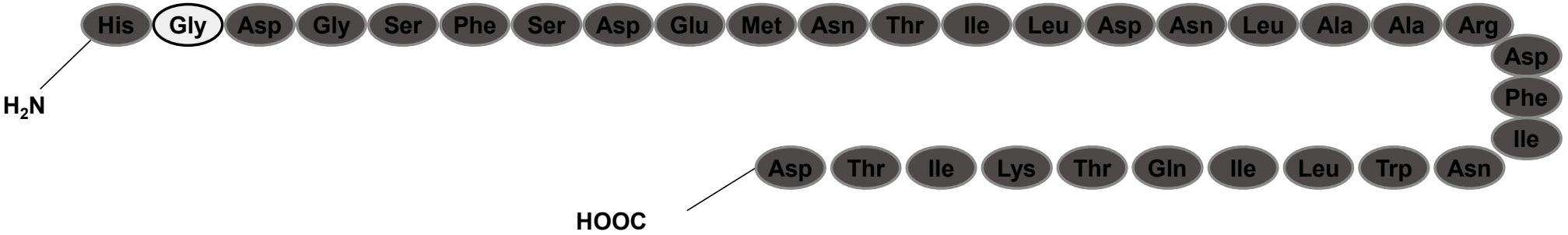


Figure 2. Relative absorption of wet weight, sodium, potassium, and calcium before and after 5 weeks of GLP-2 treatment in 8 patients with the short-bowel syndrome. *Closed symbols* represent patients receiving HPN. *Paired Student *t* test. Δ, Mean ± SD effect of treatment with GLP-2 compared with baseline.

Jeppesen et al. Gastroenterology 2001

Teduglutide

Salt Lake City, Utah.



Recombinant analogue of GLP-2[1,2]

Resistant to degradation by DPP-IV[1,2]

- $T_{½}$ ~2 hours compared to ~7 minutes for GLP-2[1,2]

In preclinical studies, teduglutide has been shown to:

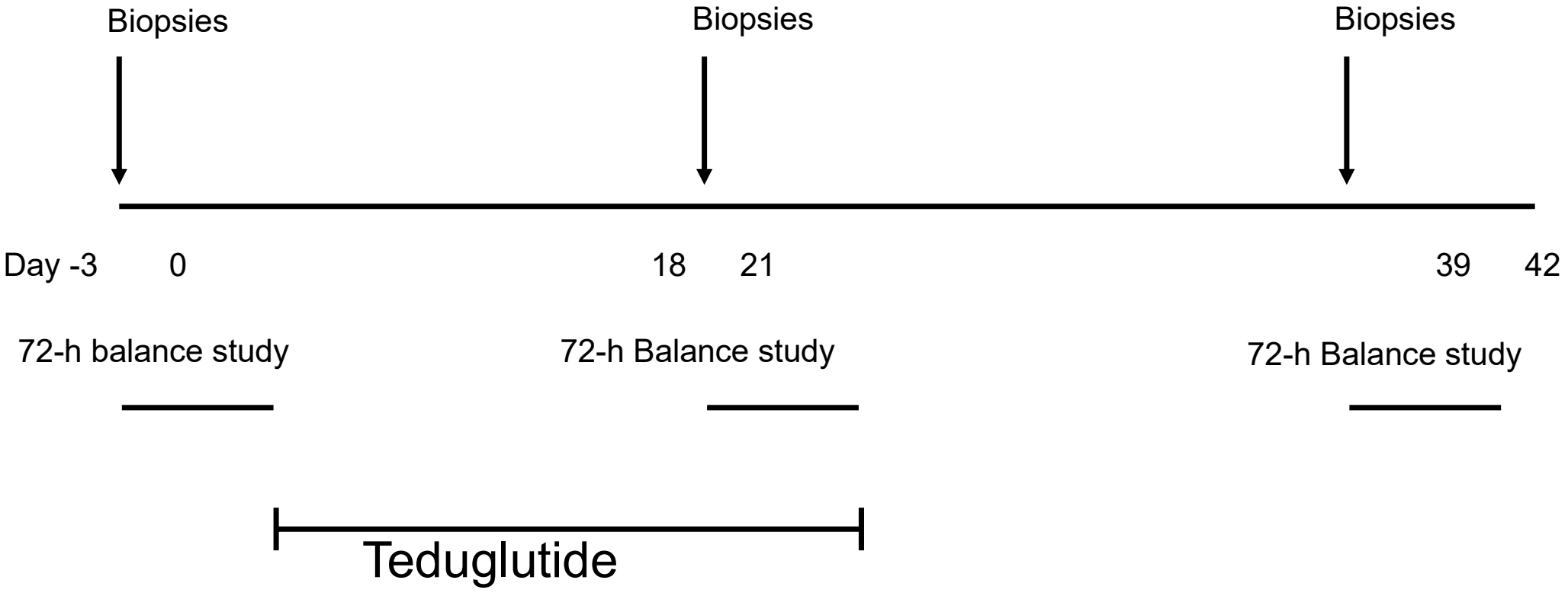
- Increase small intestine weight[3,4]
- Promote hyperplasia of superficial mucosa (villous height and crypt depth)[3,5]
- Increase small bowel length[6]

DPP-IV=dipeptidyl peptidase-4; $T_{½}$=half-life

[1]Jeppesen et al. Gut 2005; 54: 1224–1231; [2]Jeppesen et al. Gut 2011; 60: 902–914;
[3]Scott et al. Am J Physiol 1998; 275 (5 Part 1): G911–G921; [4]Drucker et al. Am J Physiol 1997; 273 (6 Part 1): G1242–G1262; [5]Drucker et al. Nat Biotechnol 1997; 15 (7): 673–677;
[6]Lovshin et al. Endocrinology 2000; 141 (11): 4194–4201

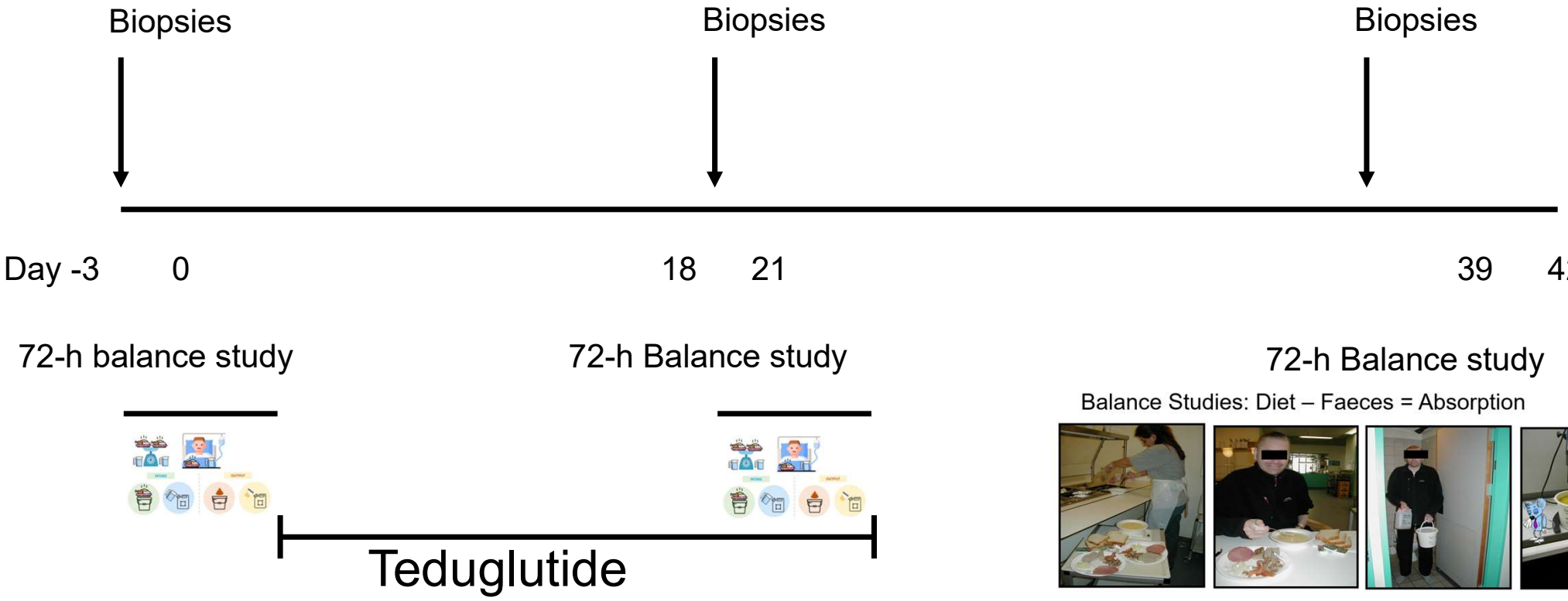
“The main clinical trials of teduglutide in Adults ”

Phase II Study Design – Treatment Phases



Jeppesen et al., Gut 2005

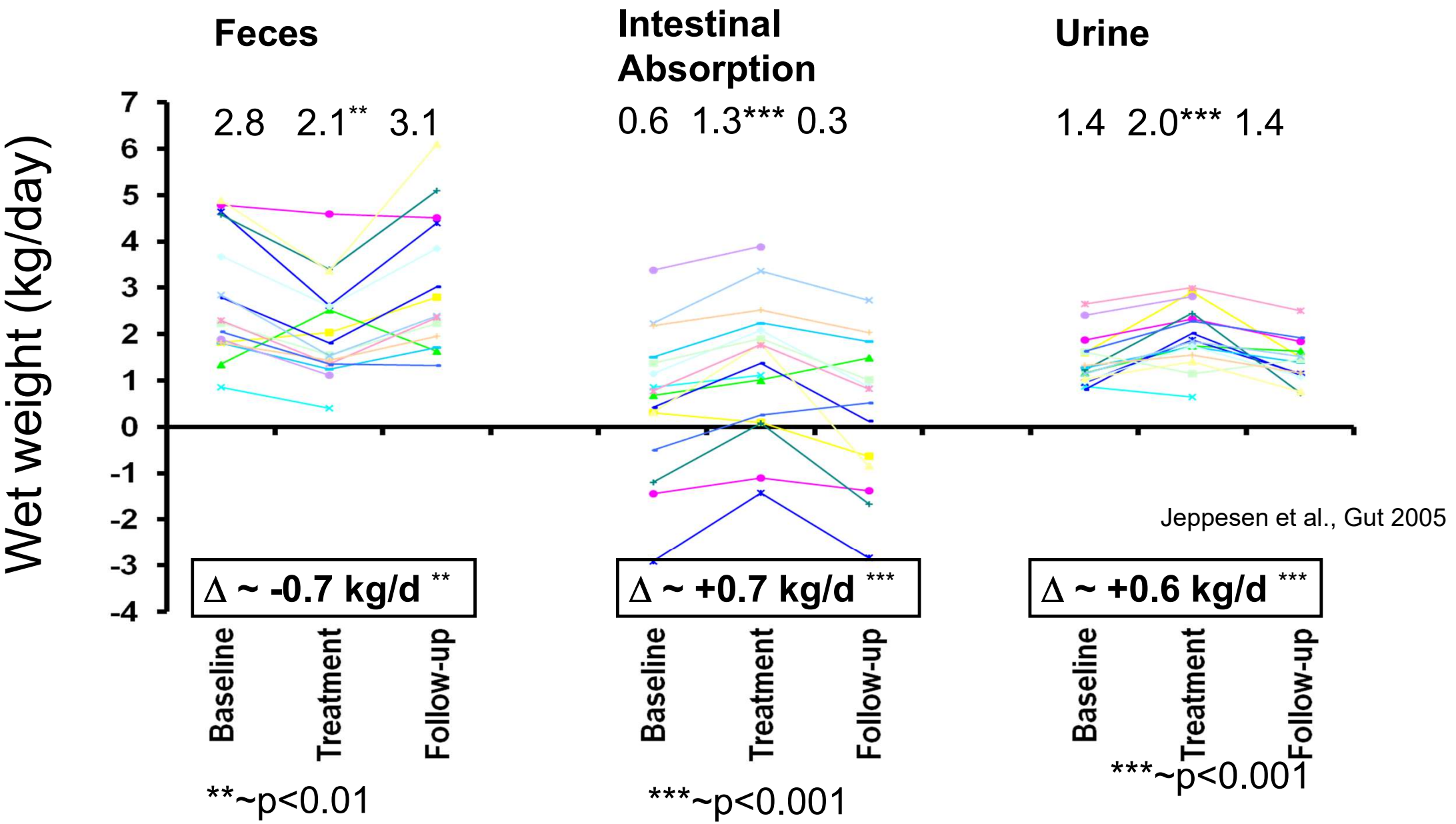
Phase II Study Design – Treatment Phases

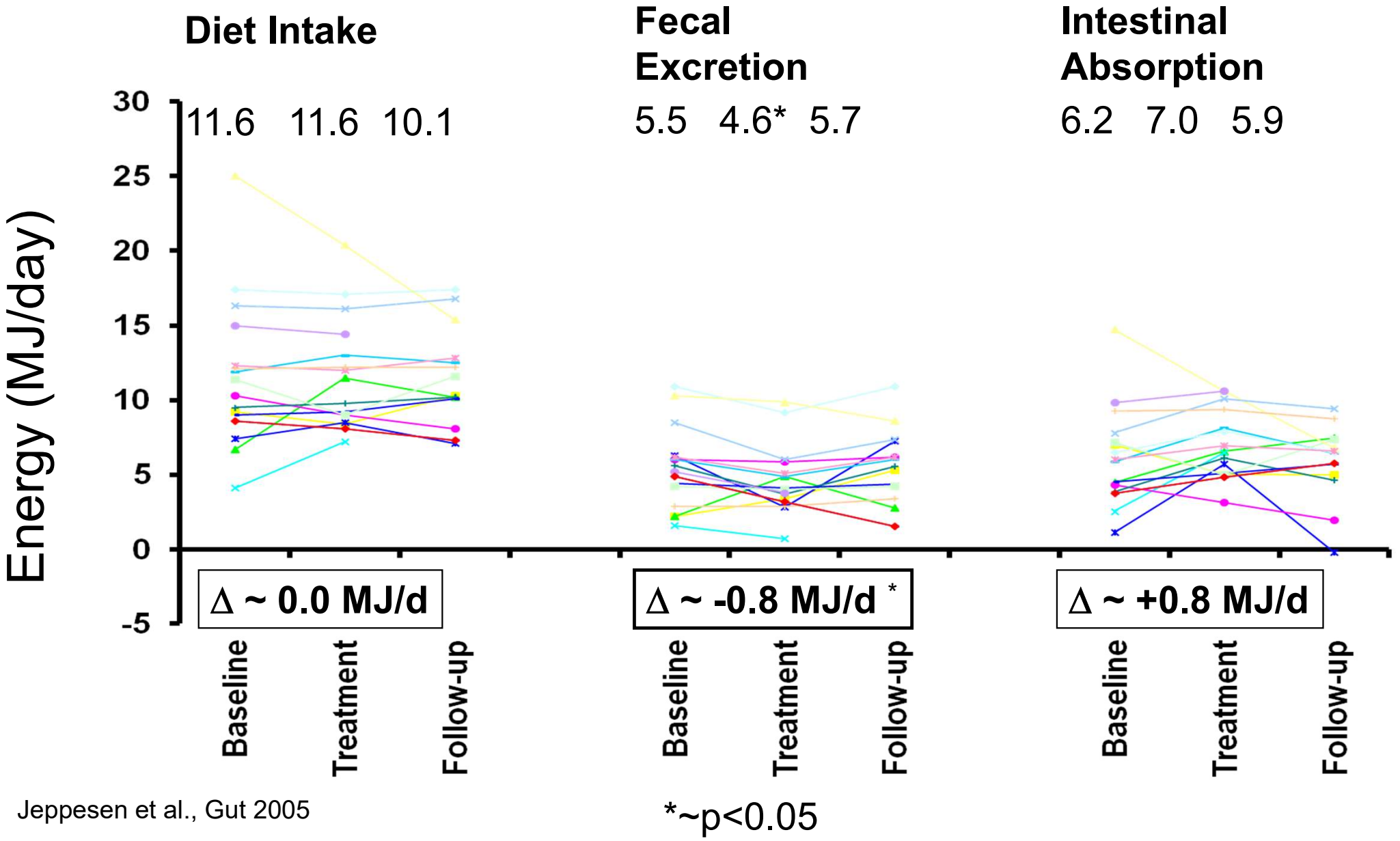


Balance Studies: Diet – Faeces = Absorption

Jeppesen et al., Gut 2005

Fixed/Controlled Oral Intake

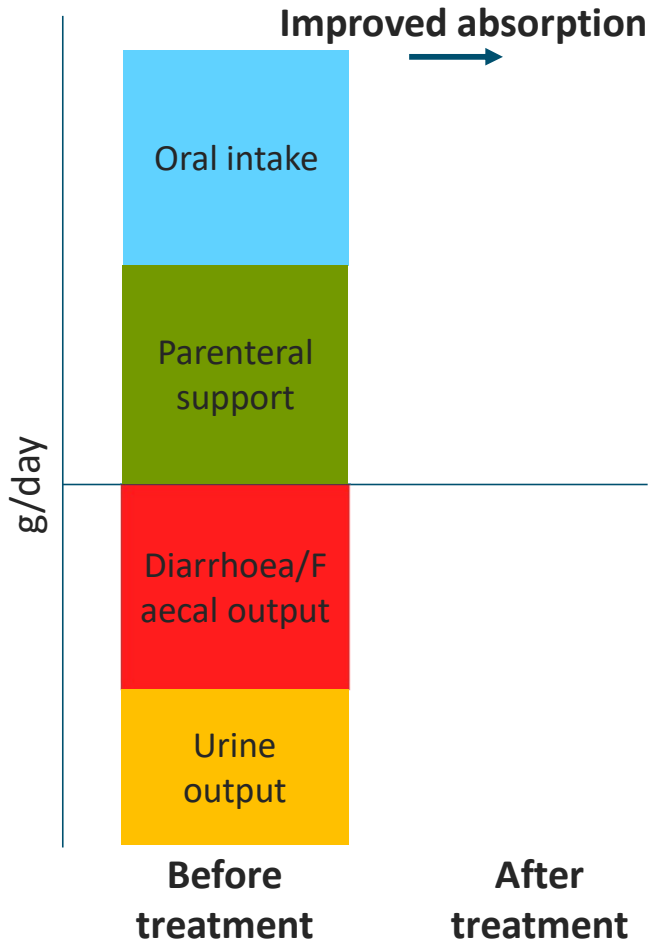

Feces
Intestinal Absorption
Urine
2.8 2.1** 3.1
0.6 1.3*** 0.3
1.4 2.0*** 1.4
Wet weight (kg/day)
7
6
5
4
3
2
1
0
-1
-2
-3
-4
Δ ~ -0.7 kg/d **
Δ ~ +0.7 kg/d ***
Δ ~ +0.6 kg/d ***
Baseline
Treatment
Follow-up
Baseline
Treatment
Follow-up
Baseline
Treatment
Follow-up
Jeppesen et al., Gut 2005
**~p<0.01
***~p<0.001
***~p<0.001



Jeppesen et al., Gut 2005

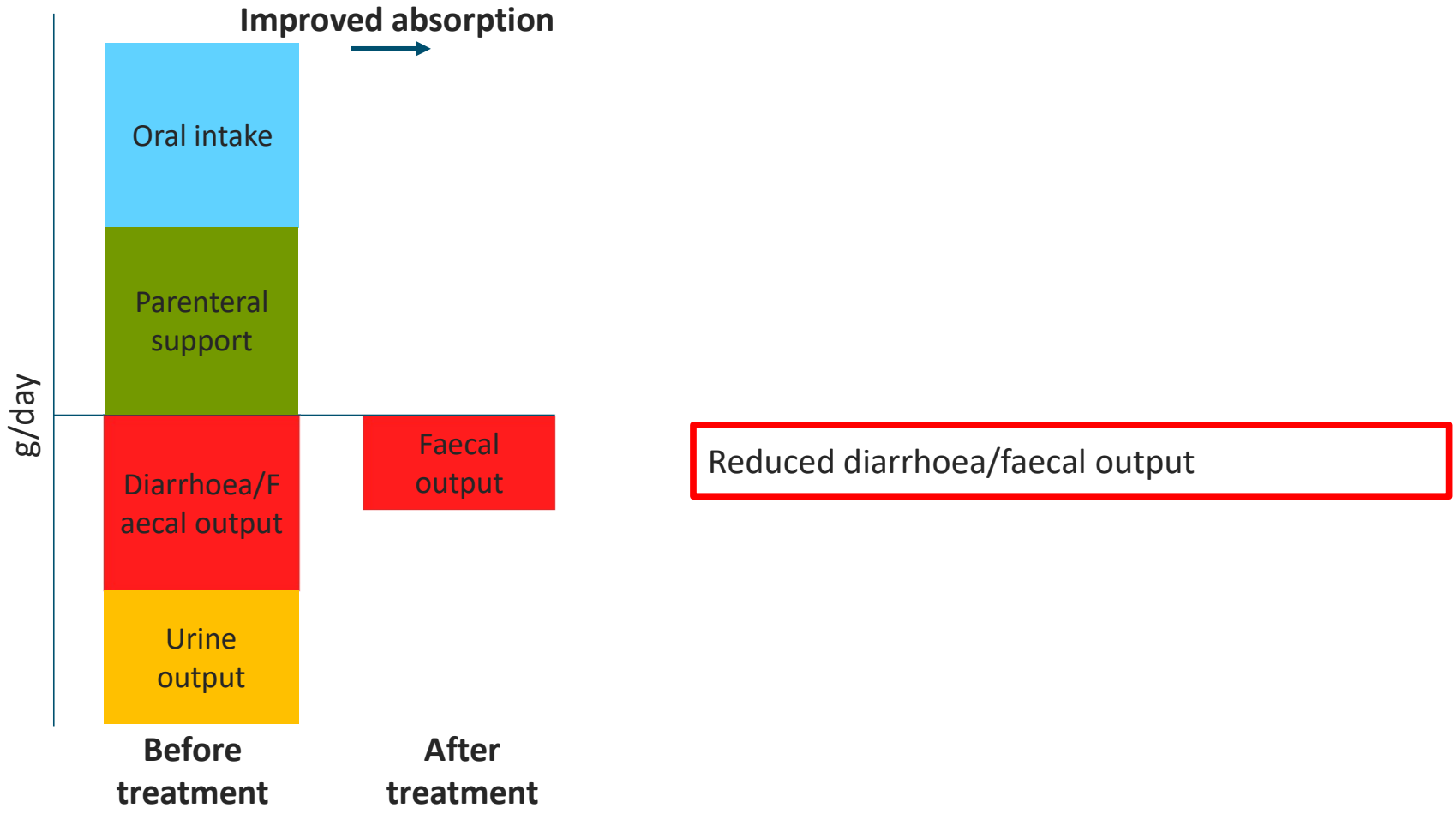
*~p<0.05

Expected benefits of improved absorption



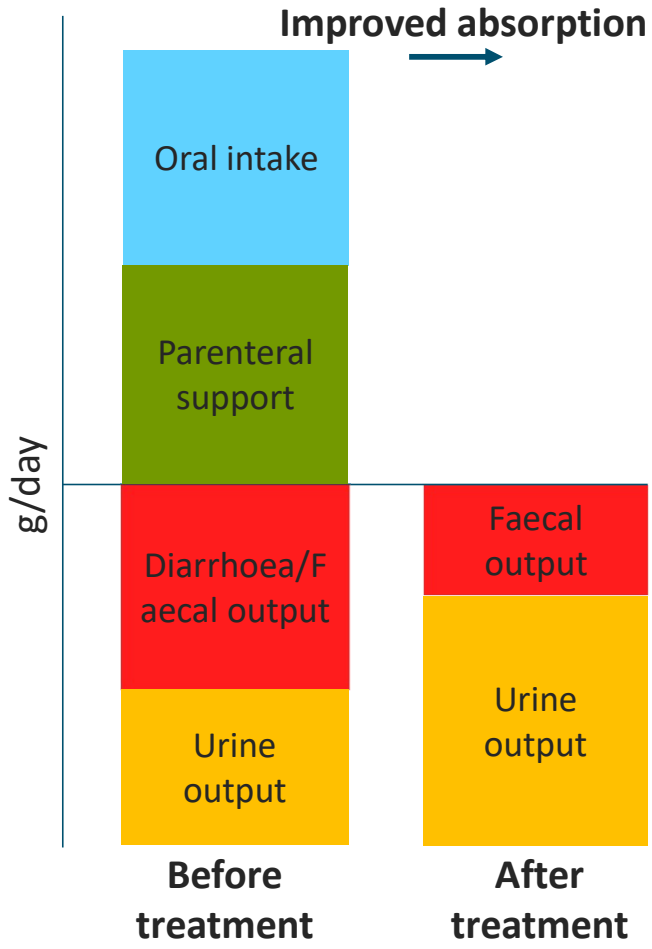
Jeppesen PB. *Dig Dis Sci.* 2019;64:2717–35.

Expected benefits of improved absorption



Jeppesen PB. *Dig Dis Sci.* 2019;64:2717–35.

Expected benefits of improved absorption

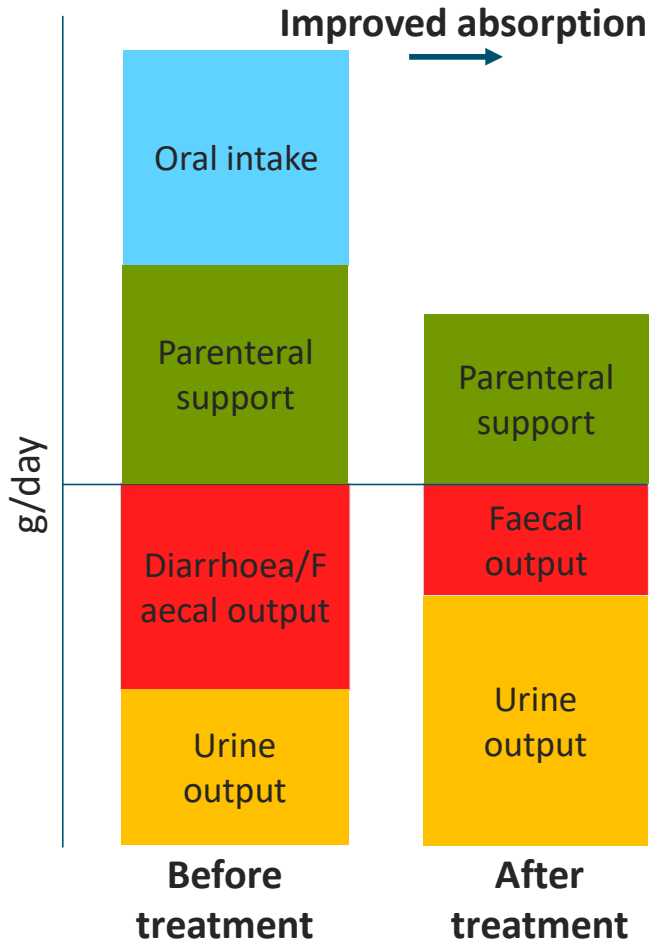


Reduced diarrhoea/faecal output

Increased urine production

Jeppesen PB. *Dig Dis Sci.* 2019;64:2717–35.

Expected benefits of improved absorption



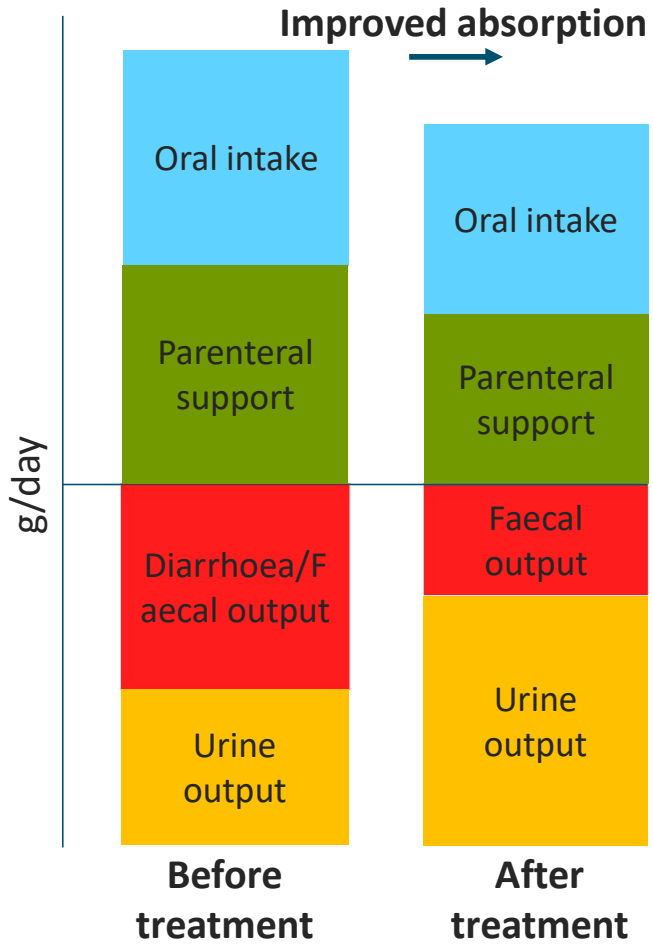
Reduced need for parenteral support

Reduced diarrhoea/faecal output

Increased urine production

Jeppesen PB. *Dig Dis Sci.* 2019;64:2717–35.

Expected benefits of improved absorption



Reduced need for oral intake

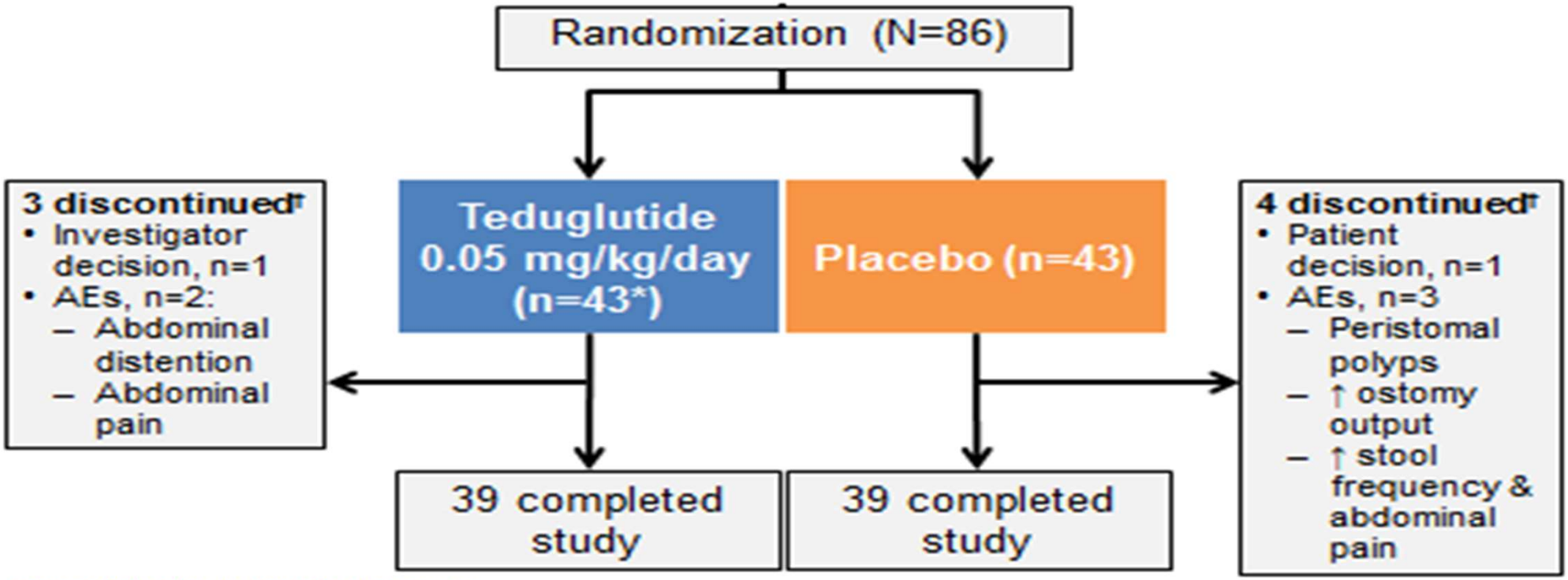
Reduced need for parenteral support

Reduced diarrhoea/faecal output

Increased urine production

Jeppesen PB. *Dig Dis Sci.* 2019;64:2717–35.

Pivotal Study (STEPS)
Patient Disposition



*One not treated (randomized in error)
†All AEs resolved after discontinuation of study drug

AE= adverse event
Jeppesen PB, et al. Gastroenterology. 2012;143:1473-1481

STEPS 020 Demography

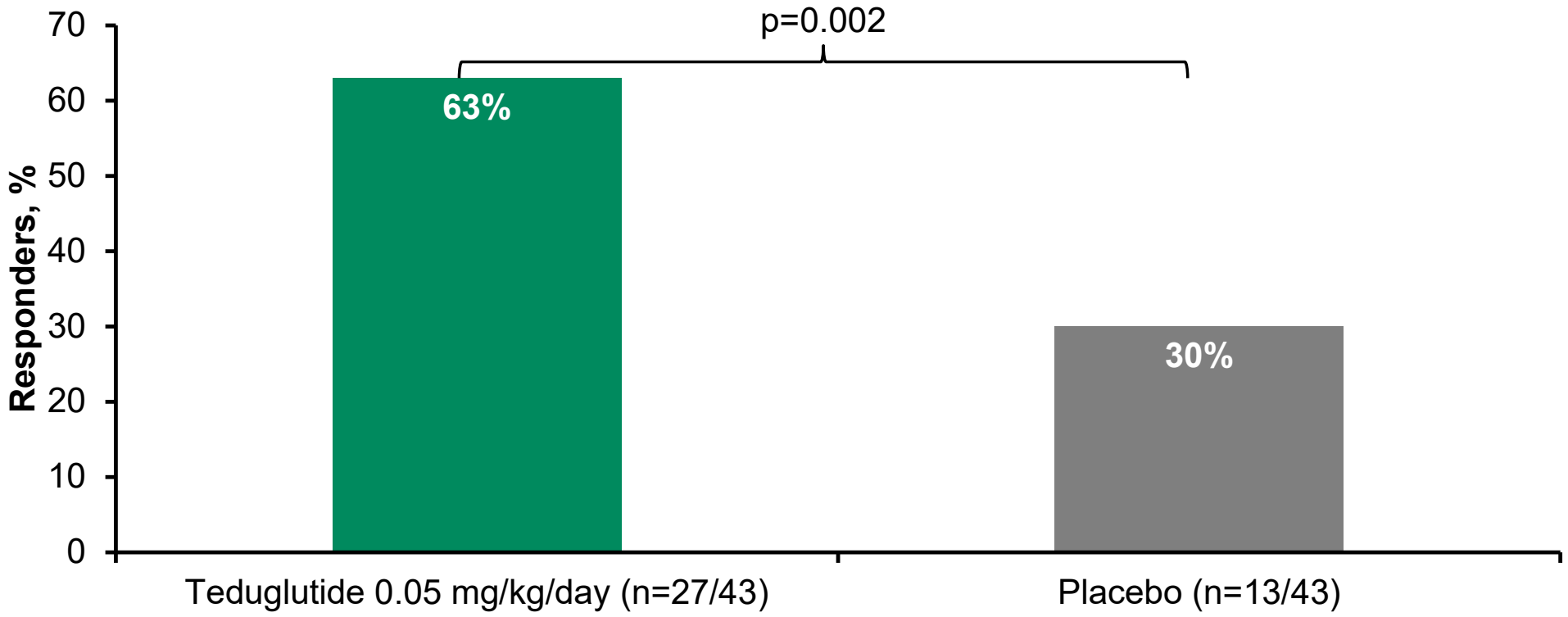
	Teduglutide 0.05 mg/kg/day (n=43)	Placebo (n=43)
Age, years (mean ± SD)	51 ± 13	50 ± 16
Gender (male/female)	21/22	19/24
Weight, kg (mean ± SD)	63 ± 11	62 ± 13
Reason for resection, Mes. Inf./CD/other	13/10/20	16/8/19
Estimated small bowel length, cm (mean ± SD)	86 ± 65[#]	69 ± 64
Patients with colon in continuity, % remaining	26, 56	23, 70
Stoma present, %	49	40
Actual PS L/week (mean ± SD)	12.5 ± 7.8	13.4 ± 7.4

No clinically or statistically significant differences were seen between treatment groups

Mes. Inf.=mesenteric infarction; CD=Crohn's disease; SD=standard deviation
ITT population; [#]n=42

Jeppesen *et al*. *Gastroenterology* 2012;143(6):1473–1481

STEPS primary endpoint: Responder analysis

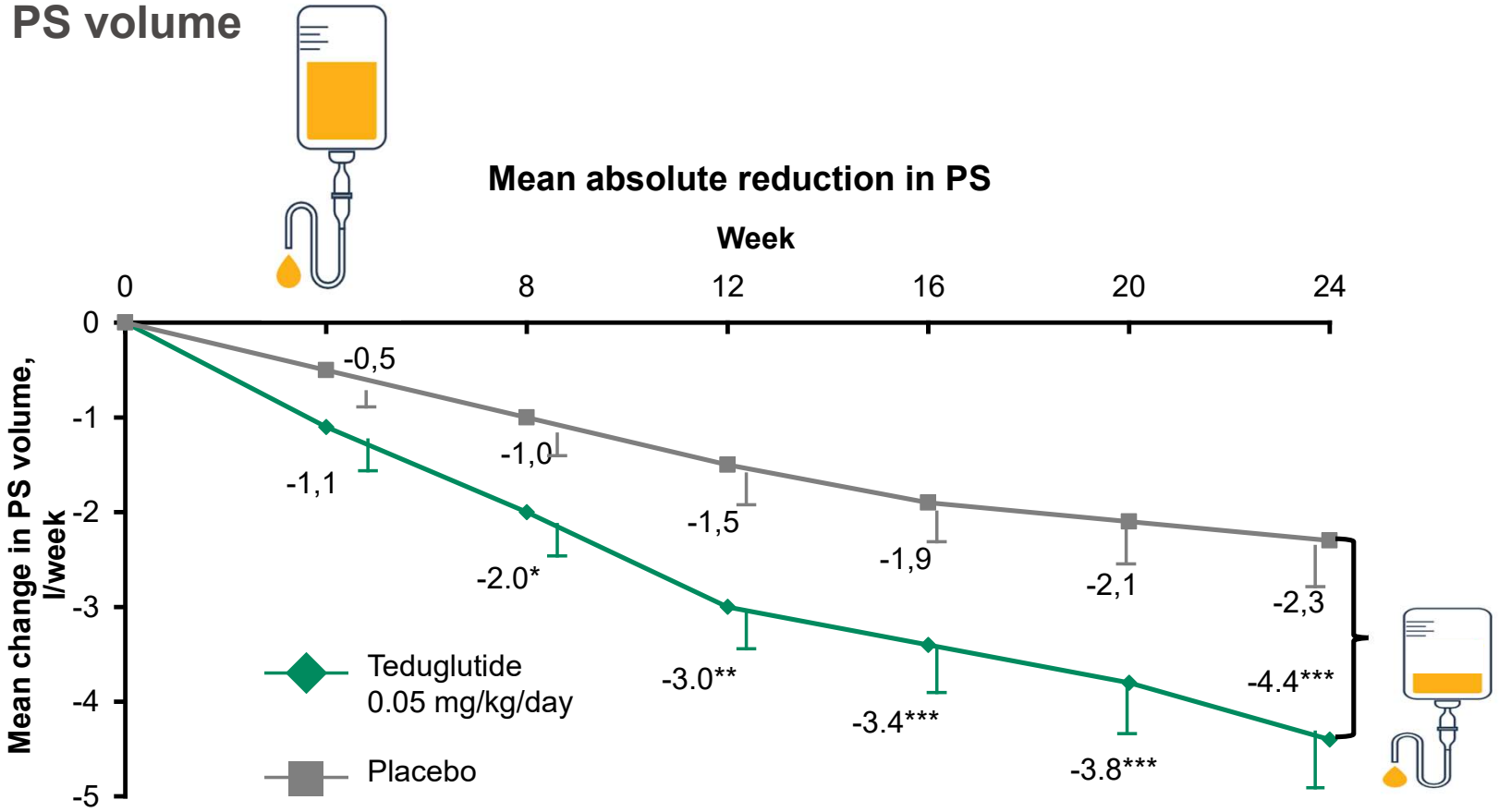


Response was defined as 20–100% reduction in weekly PS volume at Weeks 20 and 24

Jeppesen *et al*. *Gastroenterology* 2012;143(6):1473–1481

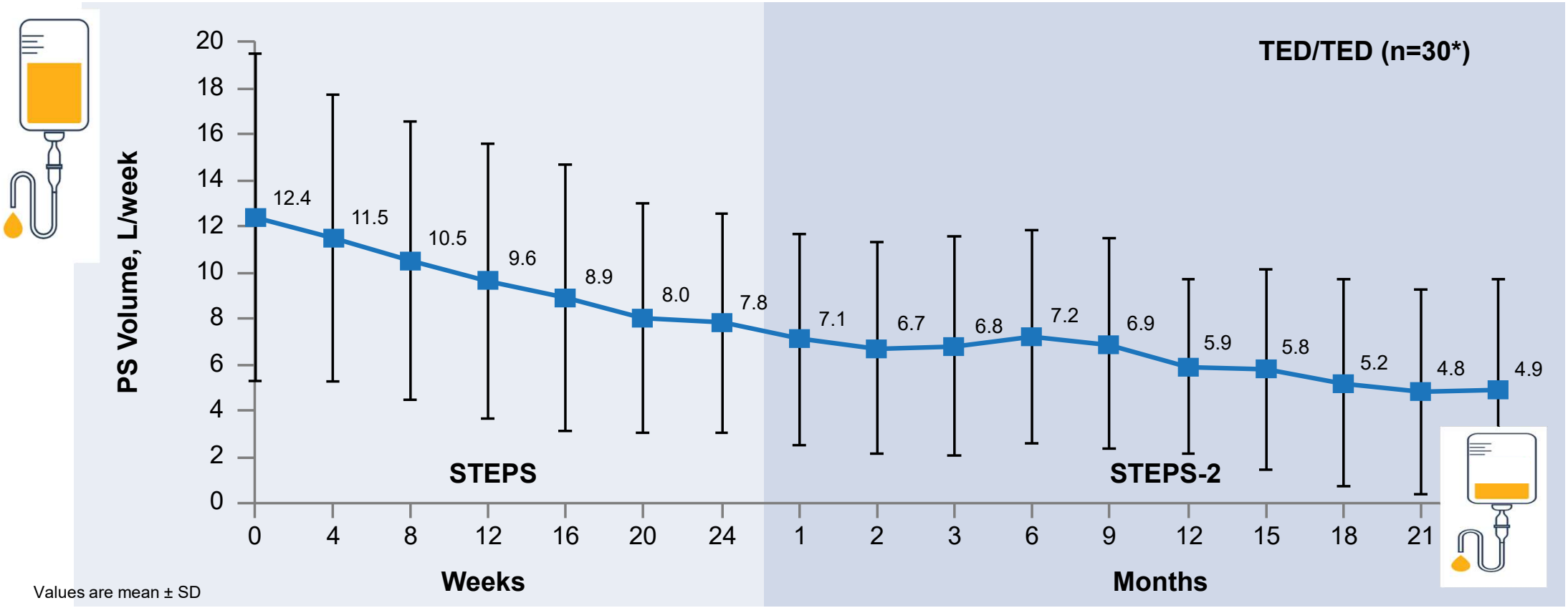
STEPS study:
Mean reduction in PS volume

Primary endpoint: teduglutide resulted in significantly more patients achieving response (20%–100% reduction from baseline in weekly PN/IV volume at weeks 20 and 24) vs placebo (63% vs 30% respectively)



Jeppesen PB, et al. Gastroenterology 2012;143:1473–1481

RESULTS
PS Volume Reductions Over 30 Months



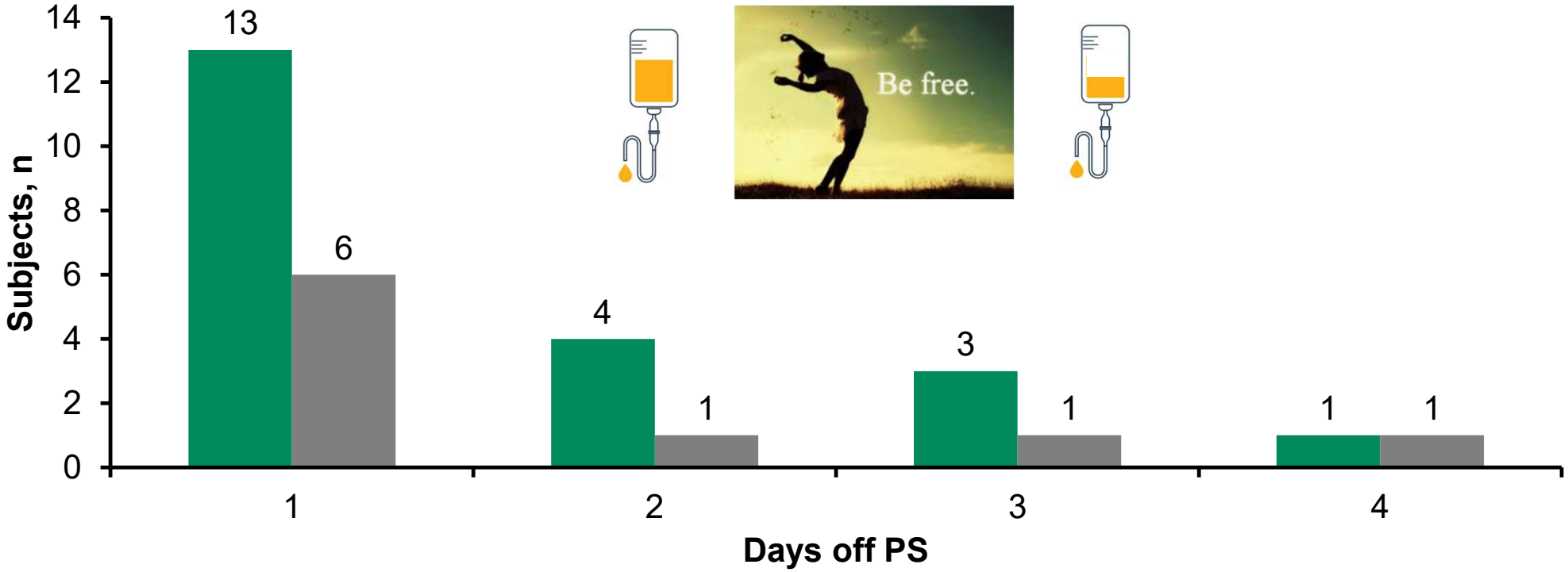
Values are mean ± SD

- Sustained reductions in PS volume requirements were observed over 30 months of treatment in among TED/TED patients who completed the study

*30/37 TED/TED patients who completed the 24-month study

PPS=parenteral nutrition and/or intravenous fluids; TED=teduglutide

STEPS study: Number of patients achieving at least one day off PS per week



Jeppesen *et al*. *Gastroenterology* 2012;143(6):1473–1481;

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NEWS RELEASES

powered by BusinessWire

Takeda Receives Positive CHMP Opinion for Teduglutide (Revestive®) for Patients with Short Bowel Syndrome

BusinessWire - Jun. 22, 2012 | Last Updated: Jun. 22, 2012

Takeda Pharmaceutical Company Limited (TSE:4502, "Takeda") and NPS Pharmaceuticals, Inc. (NASDAQ: NPSP, "NPS"), jointly announced today that the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency has adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product teduglutide (tradename in Europe: Revestive®) as a once-daily treatment for adult patients with short bowel syndrome (SBS). The marketing authorisation application was submitted in March 2011.

SBS is a rare and debilitating disease characterized by the body's severely impaired ability to absorb nutrients and fluids through the gastrointestinal tract in people who have had a significant portion of their small intestine removed. SBS typically arises after extensive surgical resection of the bowel due to Crohn's disease, ischemia or other conditions. Many patients with SBS depend on

Tools

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June 22nd, 2012: "The Committee for Medicinal Products for Humans, CHMP, on the basis of quality, safety and efficacy data submitted, considers there to be a favourable benefit-to-risk balance for Revestive and therefore recommends the granting of the marketing authorisation."

“QOL data will be crucial to determine the cost to benefit profile but this may be difficult to evaluate”, **said Palle Bekker Jeppesen,** gastroenterologist at the University Hospital of Copenhagen. “One problem with a QOL measurement is that with chronic diseases, patients tend to normalize their QOL after having adapted to a difficult situation so their QOL becomes very subjective”, **Jeppesen added.**

“In order for Gattex to be cost neutral, a daily injection a year would have to be no more than USD 20,000, which would equate to around USD 55 an injection”, he estimated.

Biopharm Insight 21/1-11

Last night, NPS Pharmaceuticals announced that it was pricing Gattex, its drug for short bowel syndrome, at $295,000 per patient per year, about triple what analysts on Wall Street expected.

Forbes 1/3-2013

Shire to acquire NPS Pharmaceuticals

Further step in building a leading biotech

Transaction valued at $5.2 billion

Enhances growth profile

Flemming Ornskov, MD, MPH
CEO, Shire plc

Francois Nader, MD, MBA
CEO, NPS Pharmaceuticals, Inc.

January 11, 2015

Our purpose
We enable people with life-altering conditions to lead better lives.

Shire

Introduction of Teduglutide in Denmark 2022
After evalation in Medicinrådet

”Me-search”: A Career with native GLP-2 & Teduglutide

1996: Drucker

Jul 1999: Jeppesen, native GLP-2 Study initiated

- August 2000: Teduglutide awarded ***orphan*** drug status, NPS

2001: Jeppesen, native GLP-2, Gastroenterology

2002: Teduglutide Phase 2 initiated

2005: Jeppesen Teduglutide Phase 2 Gut

2007: Nycomed Aquire Europe Licencing

2008: ’STEPS 020’ Study initiation

2011: Takeda to Aquire Nycomed

2012: 020 Submitted Gastroenterology

020 Jeppesen, Gastroenterology

2020: Pediatric Study; Kocoshis SA, JPEN

Holst Mortensen Jeppesen Meeting

1990 1995 2000 2005 2010 2015 2020

Jeppesen MD

Jeppesen Fellow 1/11-93 Ph.D.-Student 1/12-94 Rigshospitalet

Jeppesen Ph.D. 1998

Jeppesen DMSc

Jeppesen Consultant/ Head of Lab Rigshospitalet

Jeppesen Assistant Professor

Jeppesen Professor

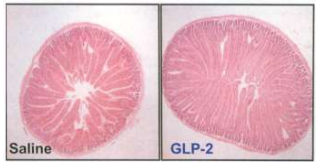
Jeppesen Head of Department/Professor

NPS Reaquire worldwide rights from Takeda

Jun 2012: Pos. EMA CHMP opinion

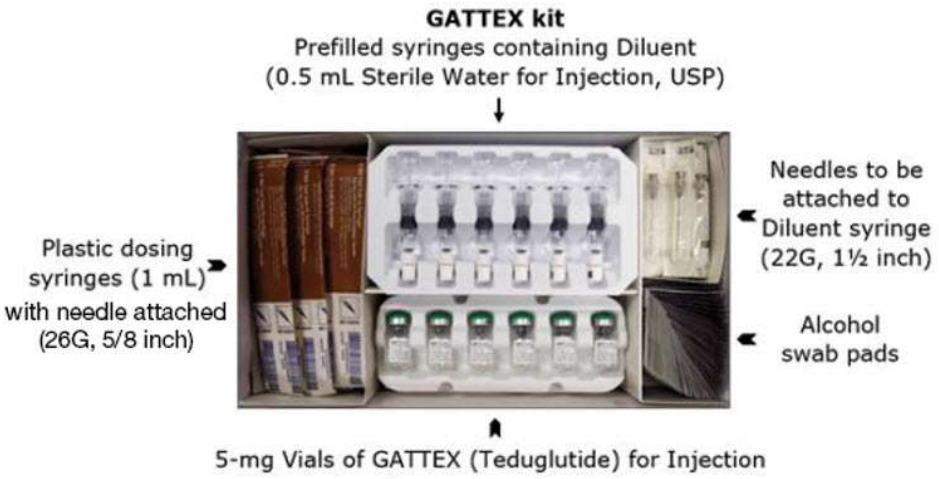
2011: Pos. Results from ”STEPS 020” study

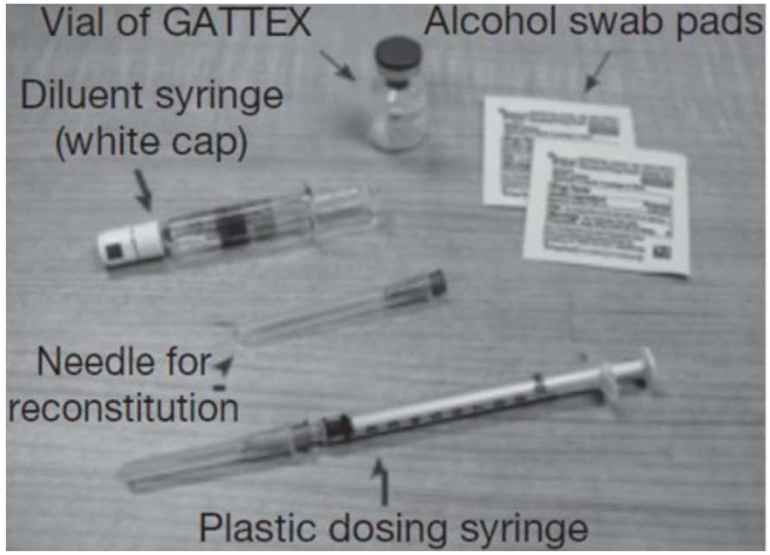
2007: Jeppesen:,Results from Phase 3 study (004/005), Gut



Jeppesen Specialist Training 1/3-2001

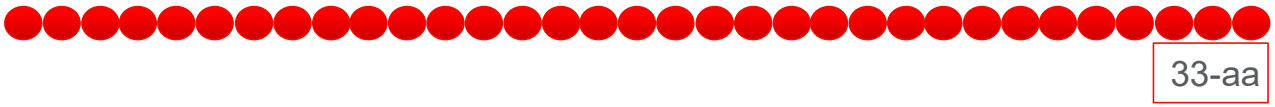
Cumbersome Daily Injection Procedures (25 minutes)



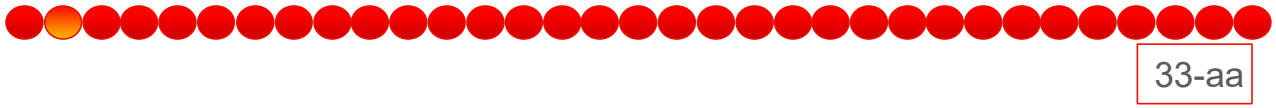


GLP-2 and the Analogs

T½

hGLP-2 — 

<10 min

Gly-GLP-2
Teduglutide — 

1.3-2 h

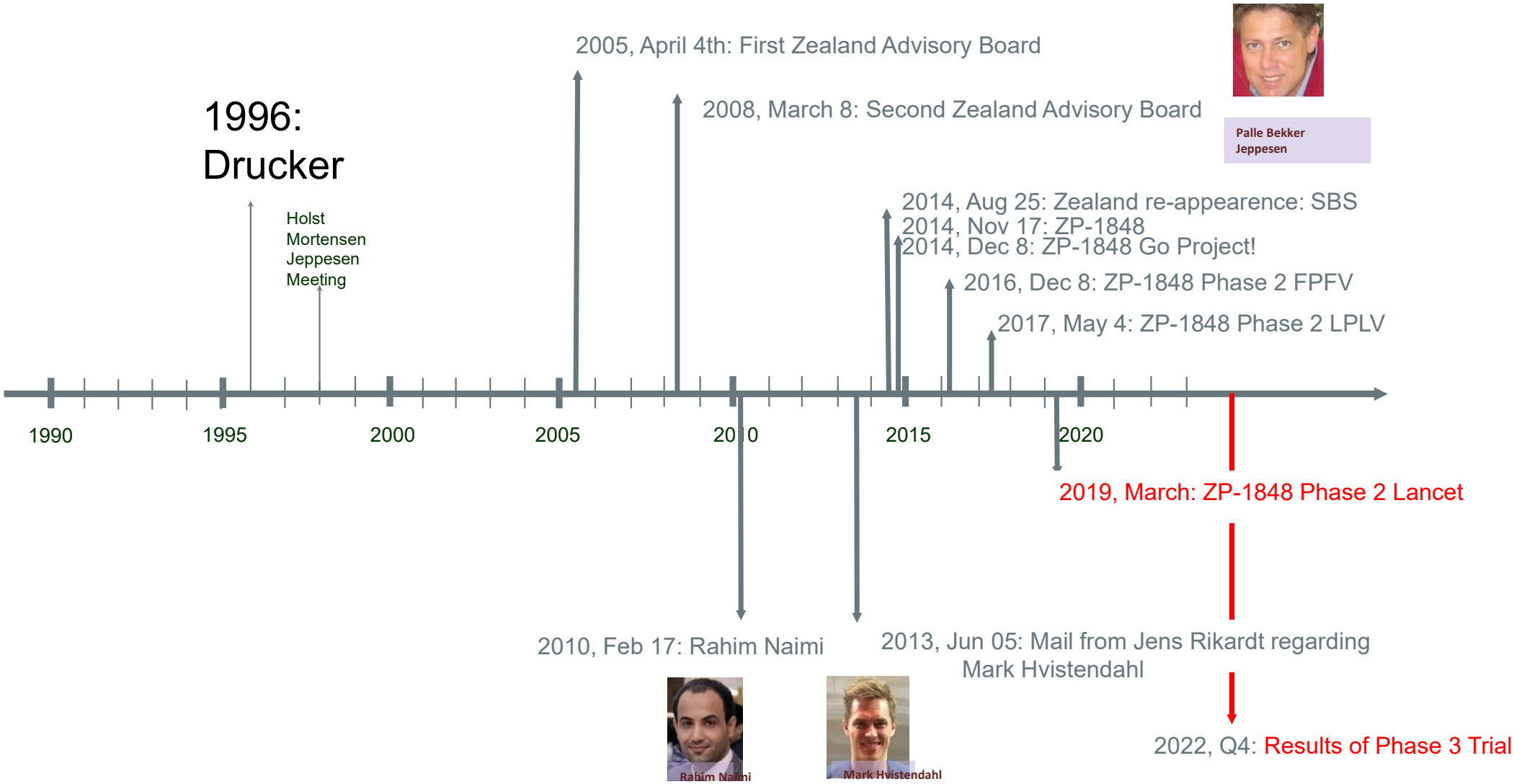
Glepaglutide — 

>88 h?

Phase 2: Once Daily, Phase 3: Once or Twice Weekly

Glepaglutide's long half-life is the result of nine amino acid modifications to human GLP-2 and a SIP tail

The Development of Orphans (Glepaglutide, ZP18/46-48)



ASPEN April 2023

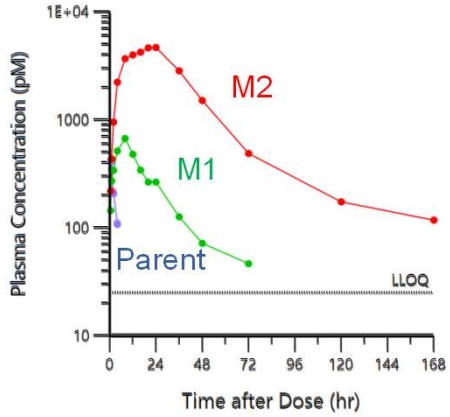
GLEPAGLUTIDE, A LONG-ACTING GLP-2 ANALOG, SIGNIFICANTLY REDUCES NEED FOR PARENTERAL SUPPORT IN PATIENTS WITH SHORT BOWEL SYNDROME: RESULTS OF EASE SBS-1, A RANDOMIZED, DOUBLE-BLIND, 24-WEEK PHASE 3 TRIAL

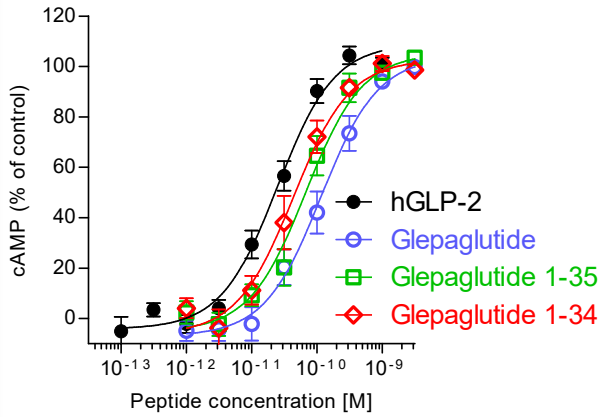
Palle B Jeppesen[1], Tim Vanuytsel[2], Sukanya Subramanian[3], Francisca Joly[4], Geert Wanten[5], Georg Lamprecht[6], Marek Kunecki[7], Farooq Rahman[8], Birgitte B Rønn[9], Mikkel A Agersnap[9], Mark Berner-Hansen[9], Ulrich F Pape[10], David F Mercer[11]

[1]Rigshospitalet, Copenhagen, Denmark; [2]University Hospital, Leuven, Belgium; [3]MedStar Georgetown University Hospital, Washington DC, USA; [4]Beaujon University Hospital, Paris, France; [5]Radboud University Medical Centre, Nijmegen, Netherlands; [6]Rostock University Medical Center, Rostock, Germany; [7]M. Pirogow Hospital, Lodz, Poland; [8]University College London Hospitals NHS Foundation Trust, London, UK; [9]Zealand Pharma, Copenhagen, Denmark; [10]Asklepios Medical School, Hamburg and Charité University Hospital, Berlin, Germany; [11]University of Nebraska Medical Center, Omaha, NE, USA

On behalf of the EASE Investigators

Glepaglutide: A Long-Acting GLP-2 Analog in Development for SBS as a Liquid Formulation for Subcutaneous Injection





Effective half-life:

88 hours

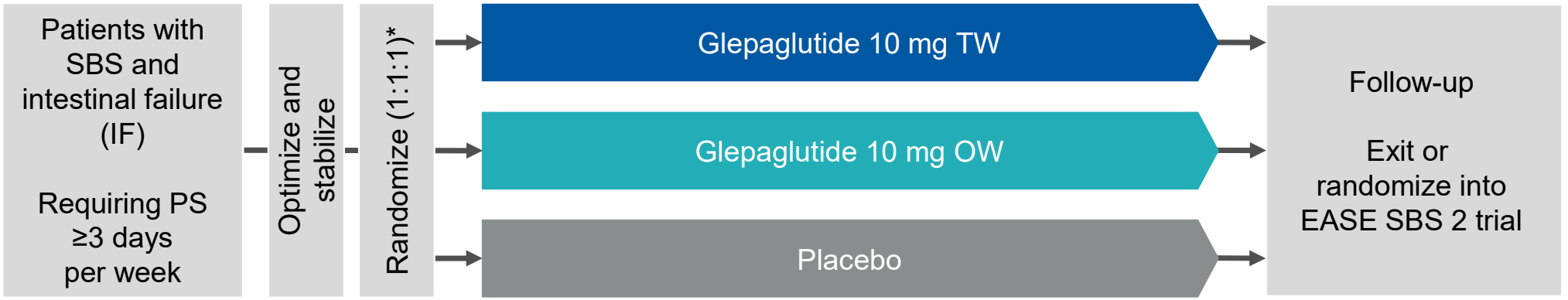
39-amino-acid peptide forms a depot at the injection site

The long half-life is the result of nine amino acid modifications to human GLP-2 (hGLP-2) and a SIP tail

The sequence similarity of the backbone is about 64% that of native GLP-2.
LLOQ=lower limit of quantification; M1& M2=glepaglutide metabolites; SIP=structural inducing probe.
Data on file and Agersnap MA *et al*. *Clin Pharmacokinet* 2023;DOI: https://doi.org/10.1007/s40262-023-01215-9.

EASE SBS 1 Trial Design

- Randomized, double-blind, 29-center, international, placebo-controlled Phase 3 trial

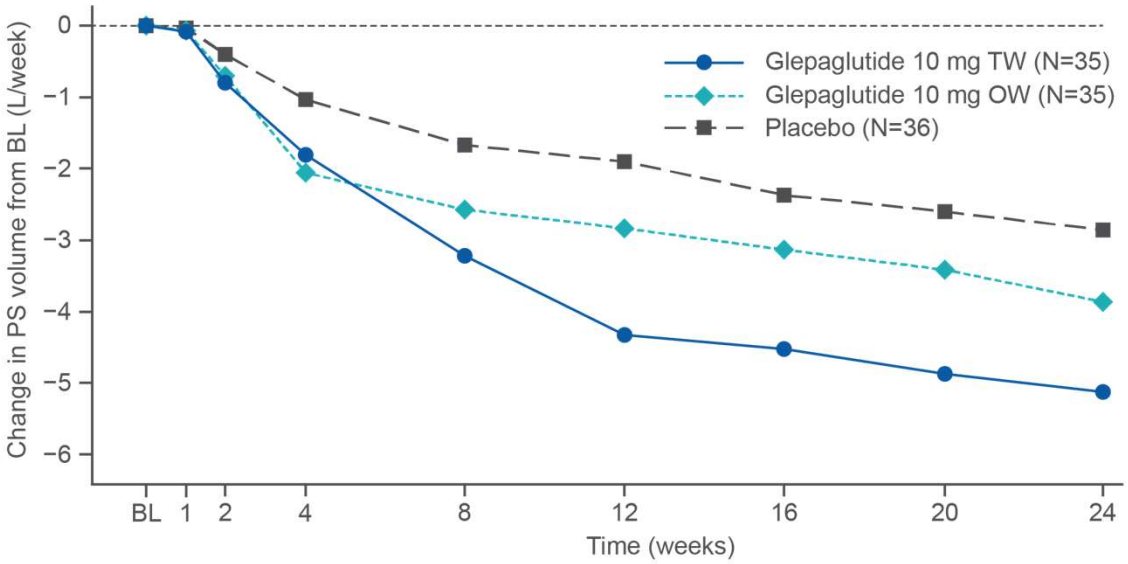


EASE 2 + EASE 3
AUTO-INJECTOR

*Stratified by patient's weekly PS volume requirements (<12 L/week vs ≥12 L/week).
OW=once weekly; TW=twice weekly.

Primary efficacy endpoint: change in PS volume (L/week) from baseline to week 24

Glepaglutide 10 mg TW Significantly Reduced PS Volume in Patients With SBS-IF



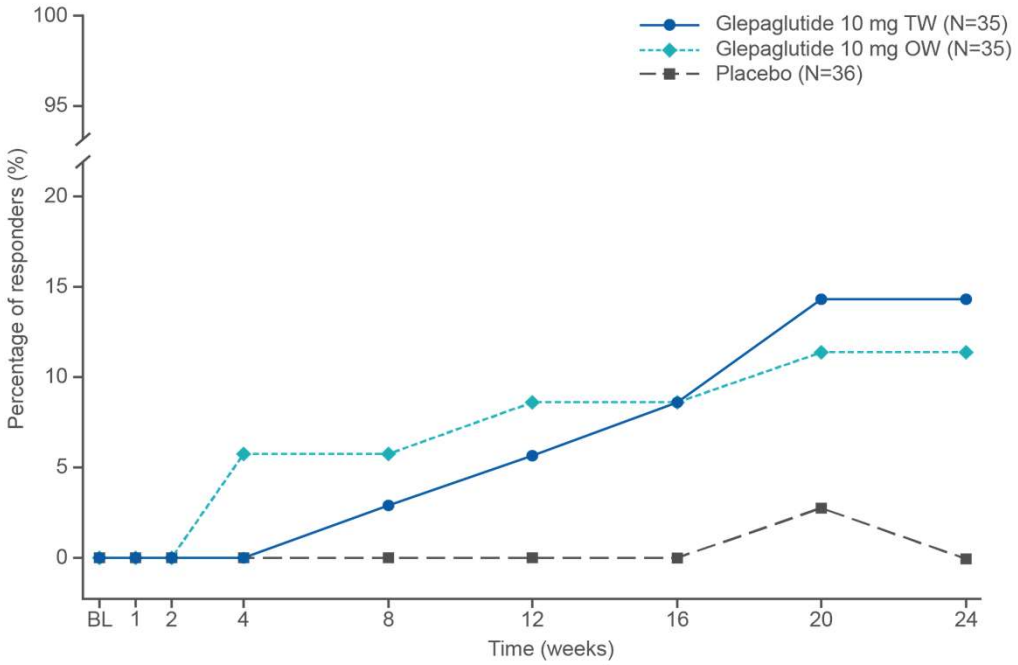
	Glepaglutide 10 mg TW (N=35)*
Least-squares mean [95% CI]	−5.13 [−6.24, −4.02]
Difference vs placebo [95% CI]	−2.28 [−3.83, −0.73]
p value	0.0039

*In anatomical subgroup analysis for patients without and with colon-in-continuity, the mean PS volume reduction at week 24 was −5.63 L/week and −4.77 L/week, respectively.
BL=baseline; SBS-IF=SBS with IF.

Secondary endpoint: 100% reduction in weekly PS volume from baseline to week 24

Glepaglutide-Induced Oral/Enteral Autonomy (Total Weaning Off PS)

Reduction in weekly PS volume of 100% at week 24



	Glepaglutide 10 mg TW (N=35)
n/N (%)	5/35 (14.3)
Difference vs placebo [95% CI]	14.1 [2.5, 25.6]
Nominal p value	0.0160

Summary and Conclusions

Treatment with glepaglutide 10 mg TW

- Significantly reduced PS requirements in patients with SBS and IF
  - **Overall reduction of 5.2 L/week (~45% reduction from baseline)**
  - 66% of patients achieved clinical response (≥20% reduction in PS from baseline)
  - **51% of patients had a reduced number of days off PS by 1 day or more**

- Five of 35 patients (**14%**) achieved **enteral autonomy (vs 0% of patients treated with placebo)**
  - 11% of those treated with glepaglutide 10 mg OW also achieved enteral autonomy
- Was well-tolerated and had an acceptable safety profile over the 24 weeks of treatment

Glepaglutide is a novel long-acting GLP-2
that can reduce the burden of PS in patients with SBS-IF
and represents an attractive potential treatment option for the management of SBS

Where do we go from here ?

- Growth Hormone
- Insulin-Like Growth Factor –1 (IGF-1)
- Glucagon-like Peptide 2
- Long-acting GLP-2 analogs (Tedu/Glepa/Apra/….)
- Dipeptidyl-peptidase-IV inhibitors
- GLP-1 (Liraglutide/Exenatide)
- Dual Agonist (GLP-1/GLP-2 Dapiglutide)
- GIP (or GIP/GLP-2)
- Peptide YY
- Fibroblast Growth Factor 19 (FGF)
- Neurotensin
- Keratocyte Growth Factor (KGF)
- Transforming Growth Factor (TGF alfa + beta)
- Hepatocyte Growth Factor (HGF)
- Epidermal Growth Factor (EGF)
- Etc……

} Past

} Present

} Future

A Key to Clinical Success is:

Knowledge = Dedicated Phycisians, **Ph.d.-students**

1964

> 10 Doctorial Theses
>15 Ph.D.-Dissertations

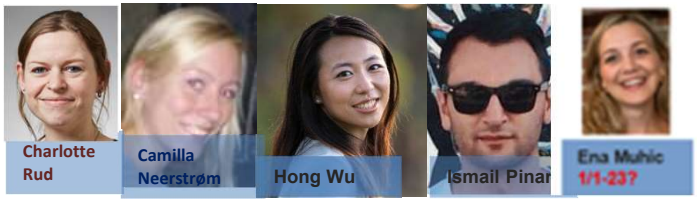
November 1st, Januar 1st, 1989

Previous:

November 1st, 1993

Current:

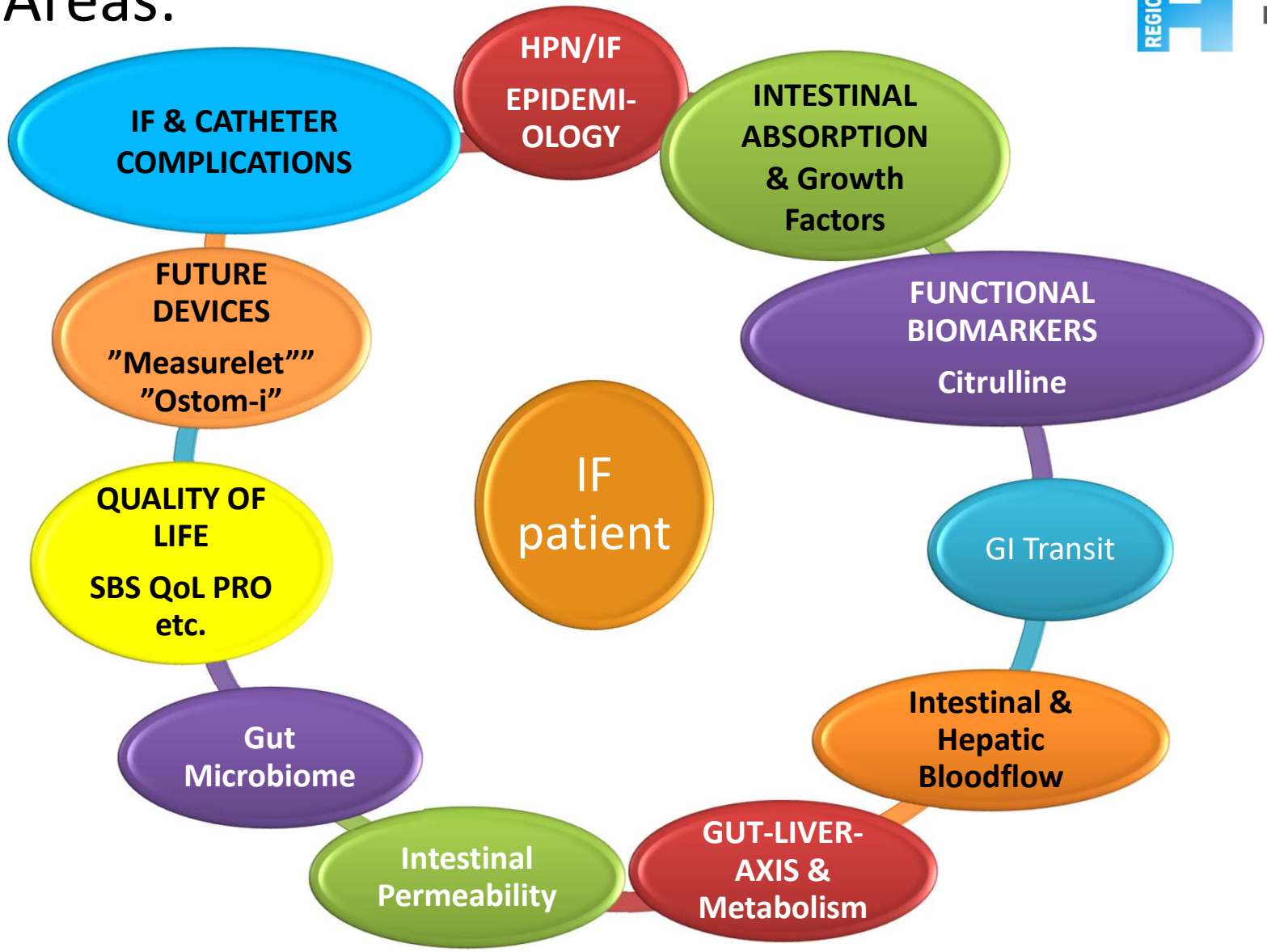
2006: Consultant/ Head of Lab



2023 2024 2025 2025 2026

Employ people who have more endurance and who potentially can become smarter than yourself….

Research Areas:



The Intestinal Failure Unit, Rigshospitalet, Copenhagen, Denmark

Keys to Successful Intestinal Failure Management:

Centralisation
Organisation
Multi- and Inter-disciplinary Teamwork
Vision, Strategy, Collaboration and Research!!

We Believe we can convert ”Ugly Ducklings” into ”Beautiful Swans”…….

H. C. Andersen 1805-75


Grand Rounds
Rigshospitalet
Tak for i dag