



ESPEN Congress Lisbon 2004

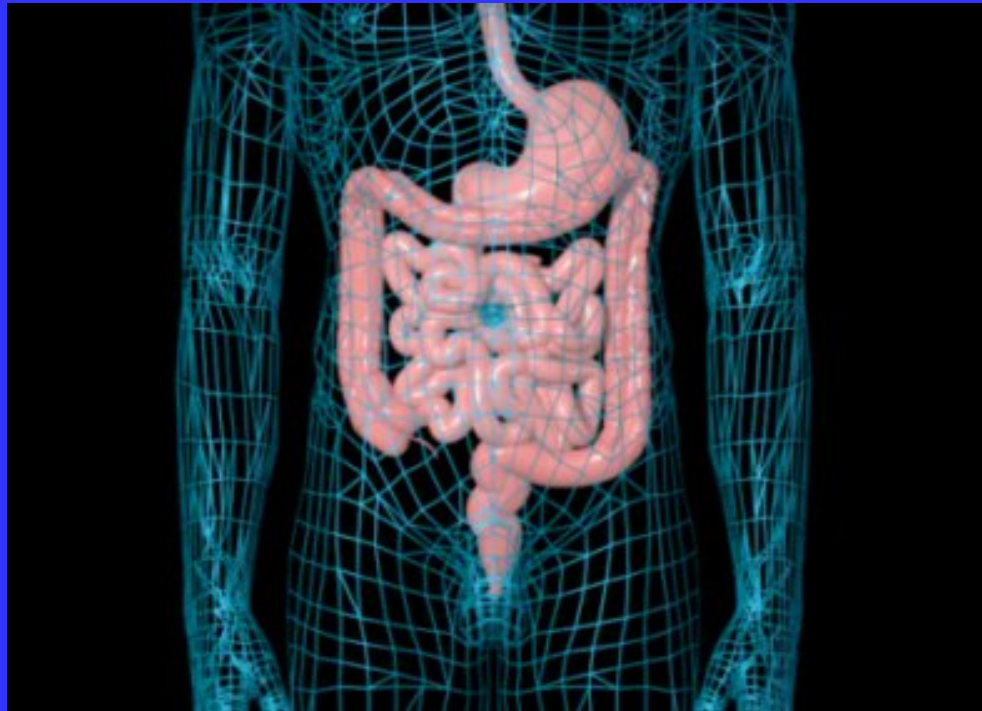
Enteral nutrition and gut function

**Starvation, gut permeability and
bacterial translocation**

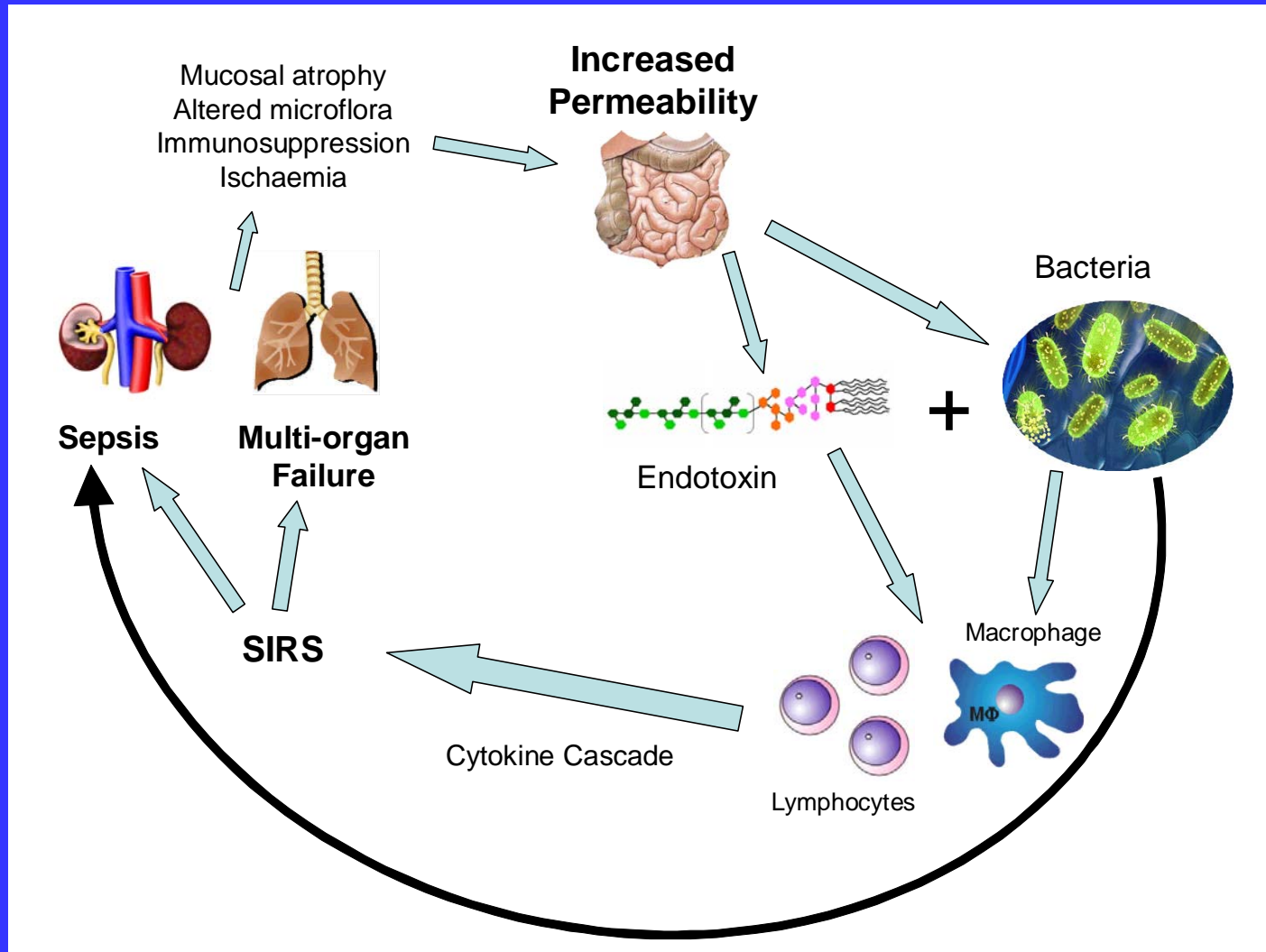
John MacFie

ESPEN 2004

Starvation, Intestinal Permeability and Bacterial Translocation

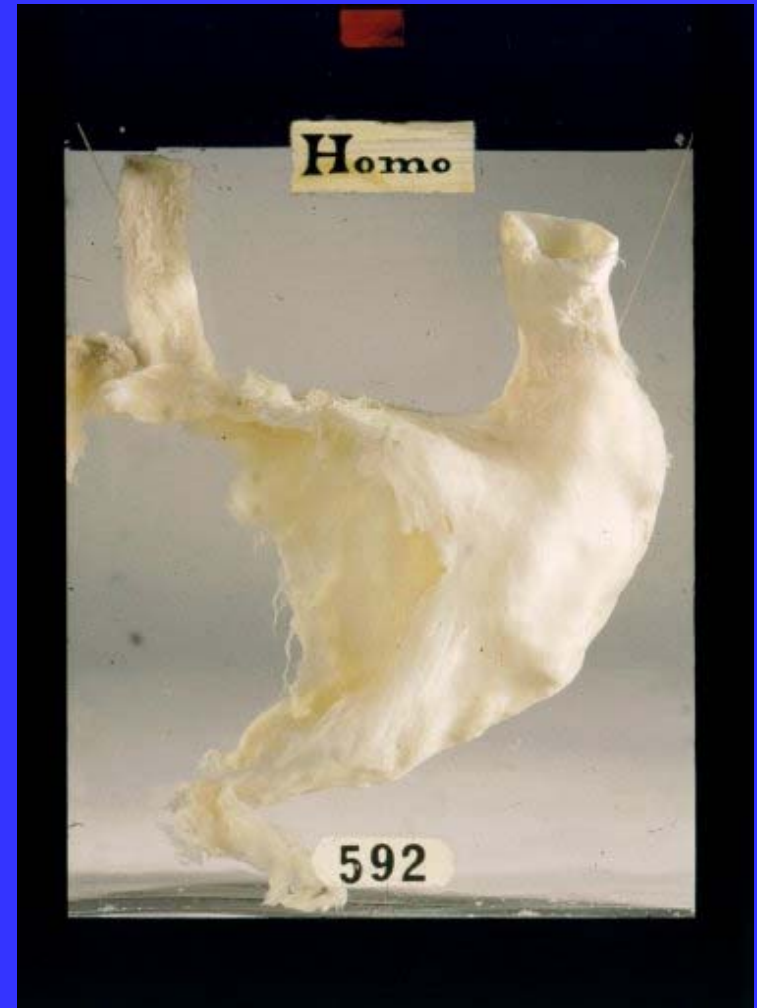


Gut Origin of Sepsis Hypothesis



Gut Barrier Function

John Hunter 1728-1793



Gut origin of sepsis hypothesis; ? evidence



10% hospitalised patients develop a nosocomial infection

E. coli most common pathogen

Wells 1996

Nosocomial infection and bacterial translocation

- 55 episodes of sepsis in 329 patients following coronary artery revascularisation
- 75% caused by gram negative enteric bacteria

Ford et al. Ann Thoracic Surg 1991: 52:514

Intestinal colonisation and bacterial translocation

Krause	1969	Ingested 180g live candida	Blood culture	Developed candidaemia
Wells	1984	Organ transplant	blood & faecal cultures	commonality of organisms
Tancrede	1985	Leukaemia	blood & faecal cultures	commonality of organisms
Marshall	1993	GI diseases	Naso-gastric aspirates and septic morbidity	Association between upper GI flora and sepsis
MacFie	1998	GI diseases	Naso-gastric aspirates and septic morbidity	Association between upper GI flora and sepsis

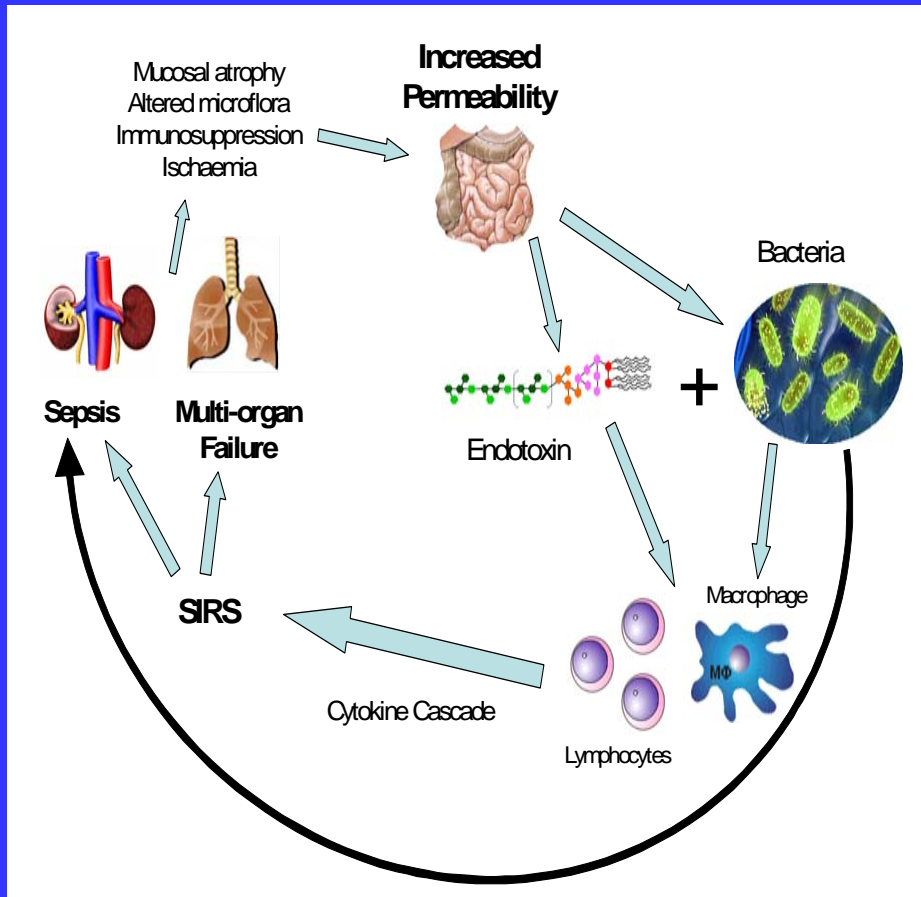
Bacterial Translocation : Humans

Direct evidence

Ambrose	1984	Crohn's	n=46	15/46	33%
		Controls	n=43	2/43	5%
Deitch	1989	Intest obst	n=17	10/17	59%
		Control Surgical	n=25	1/25	4%
Braithwaite	1993	Surgical	n=20	1/20	5%
Peitzman	1991	Trauma	n=25	0/25	0%
		GI disease	n=4	3/4	75%
Reed	1994	Trauma	n=16	13/16	81%
Sedman	1996	GI disease	n=267	27/267	10.4%

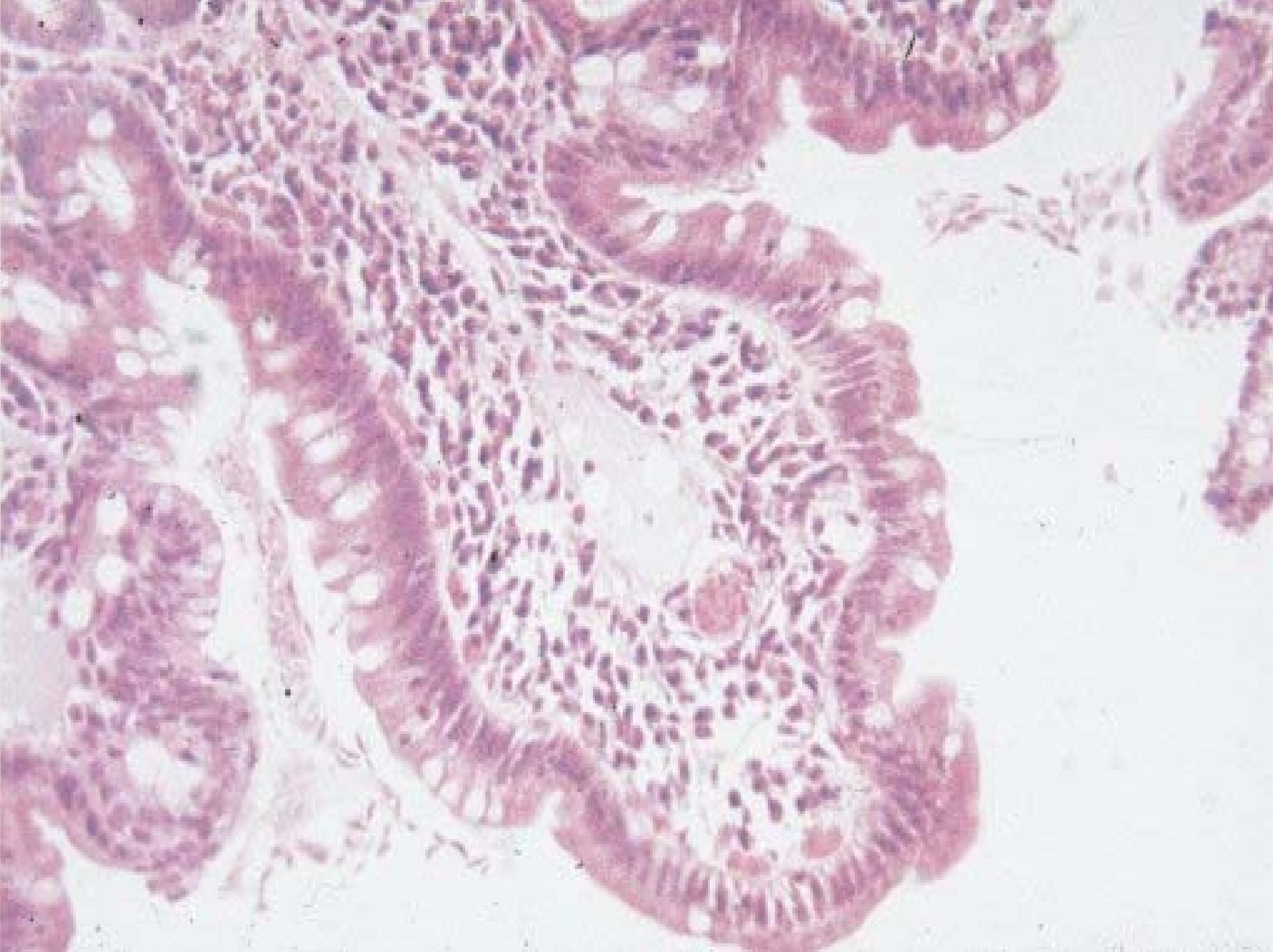
Gut Origin of Sepsis Hypothesis

Sca'bro studies

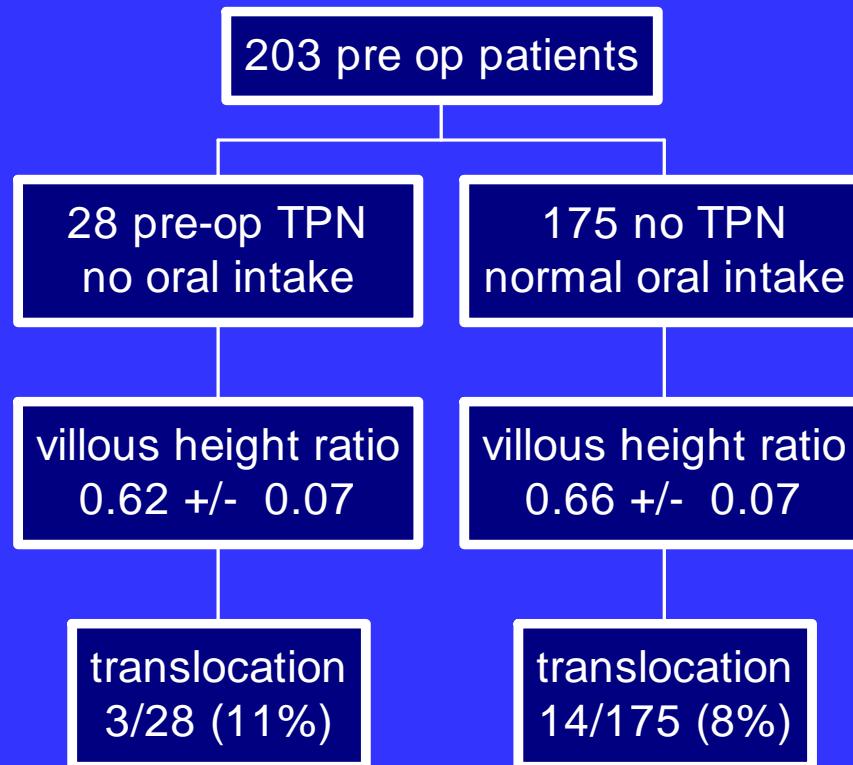


End Points:

- villus morphology
- intestinal permeability
- bacterial translocation
- septic morbidity



TPN, mucosal atrophy and bacterial translocation



TPN and mucosal atrophy in human subjects

Guedon et al 1986

No atrophy after 21 d of NPO

Rossi et al 1993

Atrophy after 9 months of NPO

Pironi et al 1994

Atrophy after 2-3 months of TPN

Sedman et al 1995

No atrophy with TPN vs EN after 10 days

Groos et al 1996

Atrophy after 7-12 weeks of TPN

TPN and mucosal atrophy

- “no changes in mucosal histology after 21 days TPN”

Greenburg et al 1981

Guedon et al 1986

- “the dramatic mucosal atrophy seen in animals on bowel rest and receiving TPN does not seem to occur in humans even after a few weeks of TPN”

Jeejeebhoy 1991

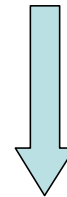
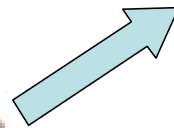
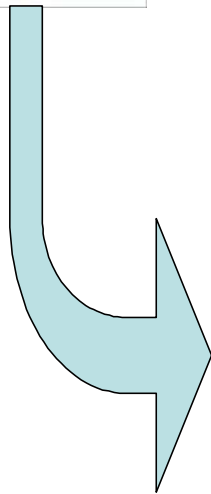
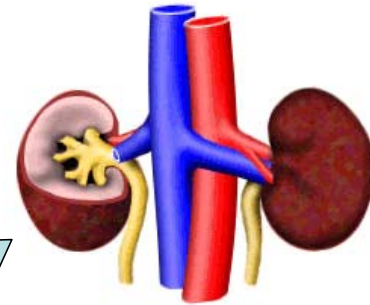
Mucosal atrophy and TPN

- no evidence to confirm that short-term TPN causes significant changes in villous morphology
- no evidence to confirm association between changes in villous morphology and bacterial translocation

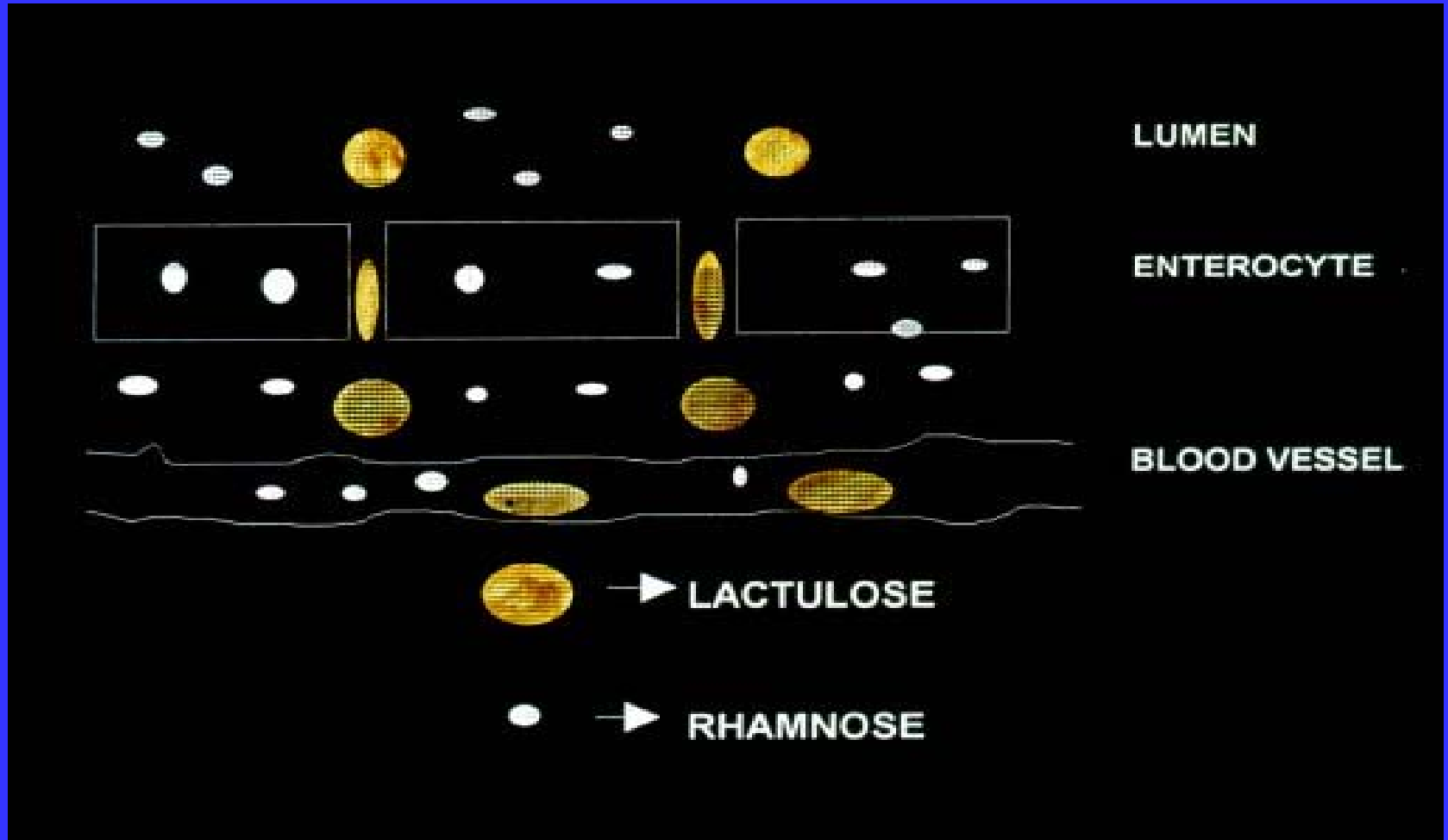
Intestinal Permeability Tests



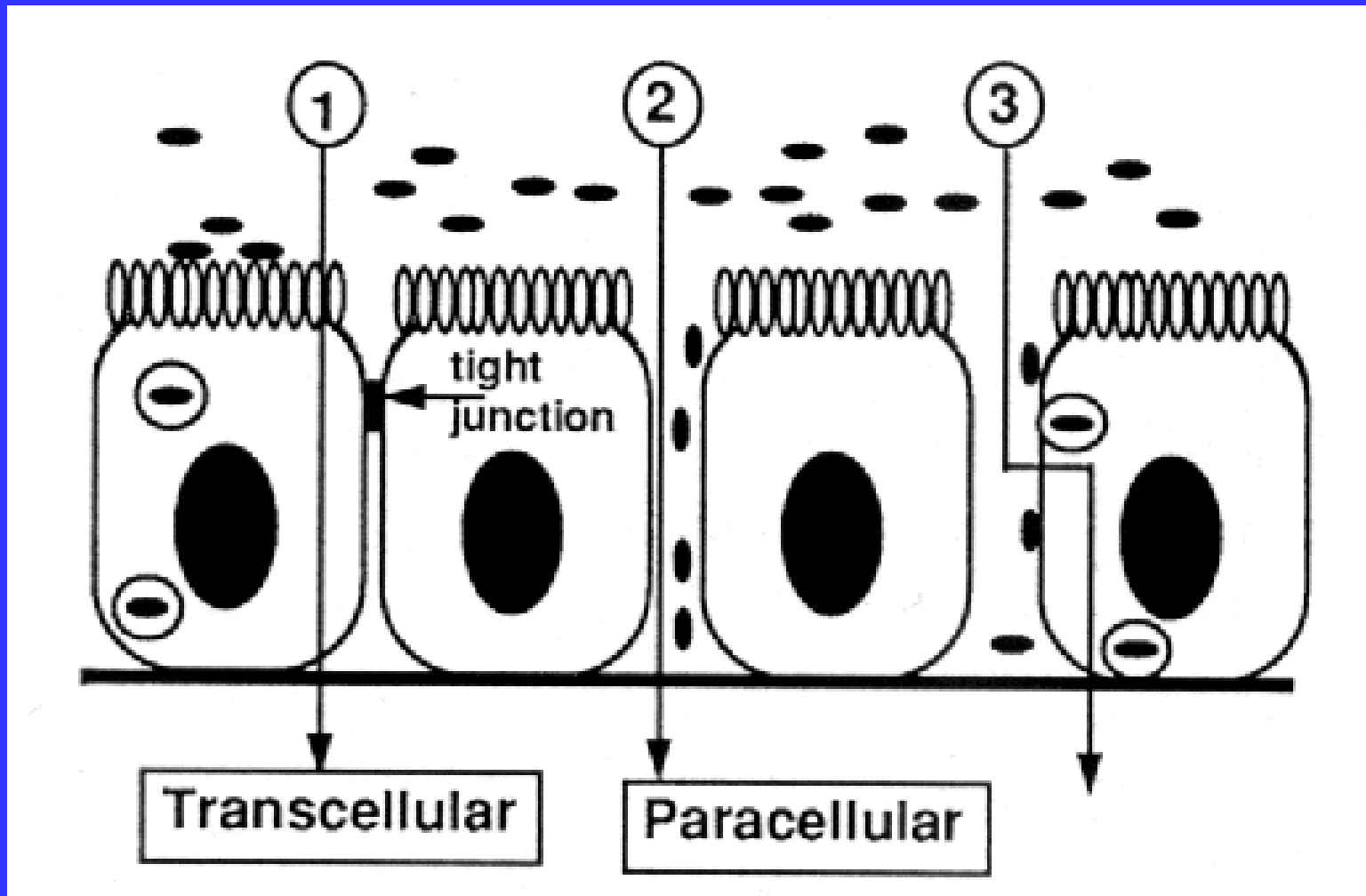
**Passive
Paracellular
Diffusion**



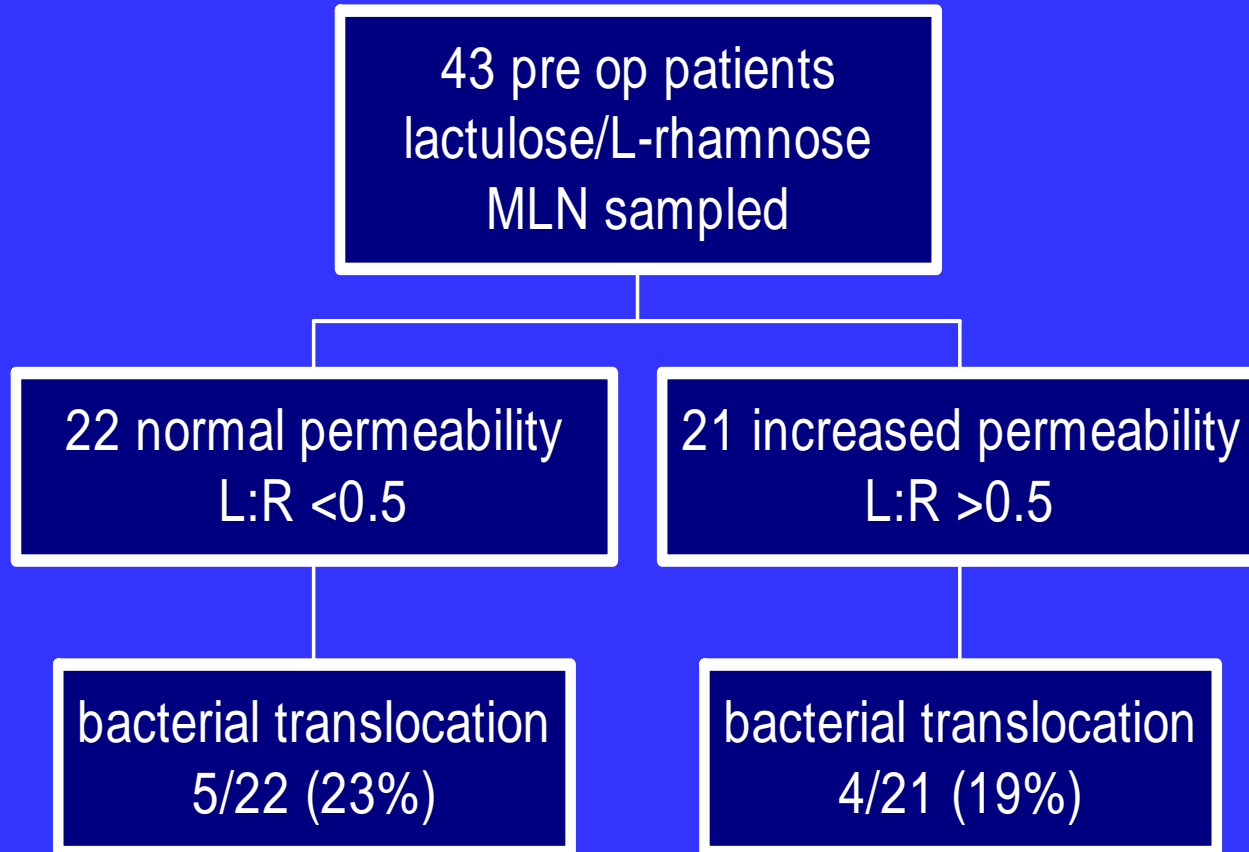
Gut barrier function: intestinal permeability



Gut barrier function: intestinal permeability

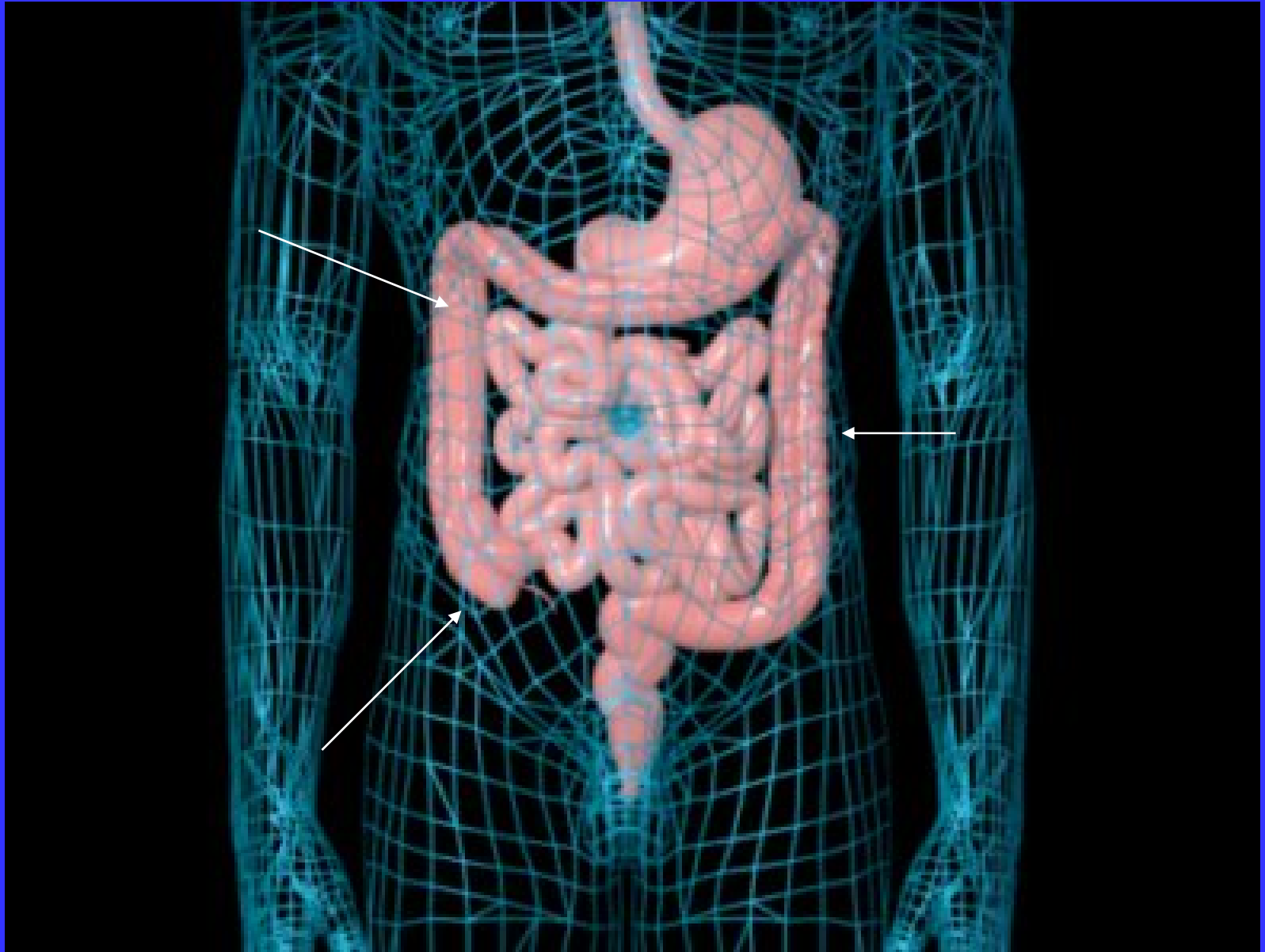


TPN and intestinal permeability



Intestinal barrier function and bacterial translocation

- Changes in intestinal barrier function assessed by measurements of villous morphology and intestinal permeability are not related to alterations in bacterial translocation
- Changes in villous morphology do not correspond with alterations in permeability



Sugar Test Probes

Established

- Lactulose + Rhamnose
Lactulose + Mannitol
 - Fermented in colon
 - Measures small intestinal permeability
 - Extensively studied since 1970's

New

- Sucralose
 - Stable throughout GI tract
 - Theoretically measures “whole-gut” permeability
 - Not established in humans

Triple Sugar Test

- Lactulose + Rhamnose + Sucralose
 - Overnight fast
 - Urine collected for 0-5 and 5-24 hours
 - 5-hr L/R ratio measure of SI permeability
 - 24-hr sucralose excretion theoretical measure of “whole-gut” permeability

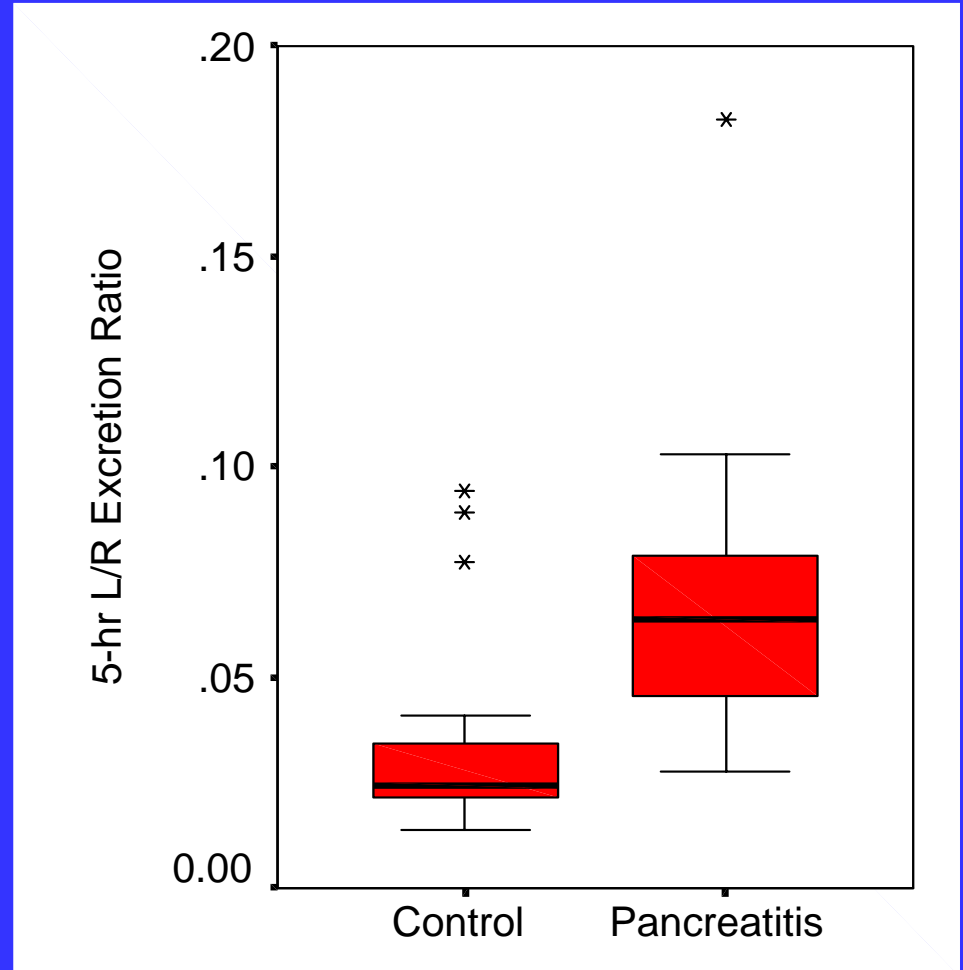
Acute Pancreatitis - Patients

- Control Subjects
 - 21 healthy volunteers (12 females)
 - Median age 46 (IQR 33-51)
- Pancreatitis
 - 9 patients (5 females) admitted with AP
 - Median age 51 (44-67)
 - 2 severe, 7 mild
 - Triple sugar test performed within 6 days of admission

Small Intestinal Permeability

Increase in 5-hr L/R
excretion ratio
($p=0.004$)

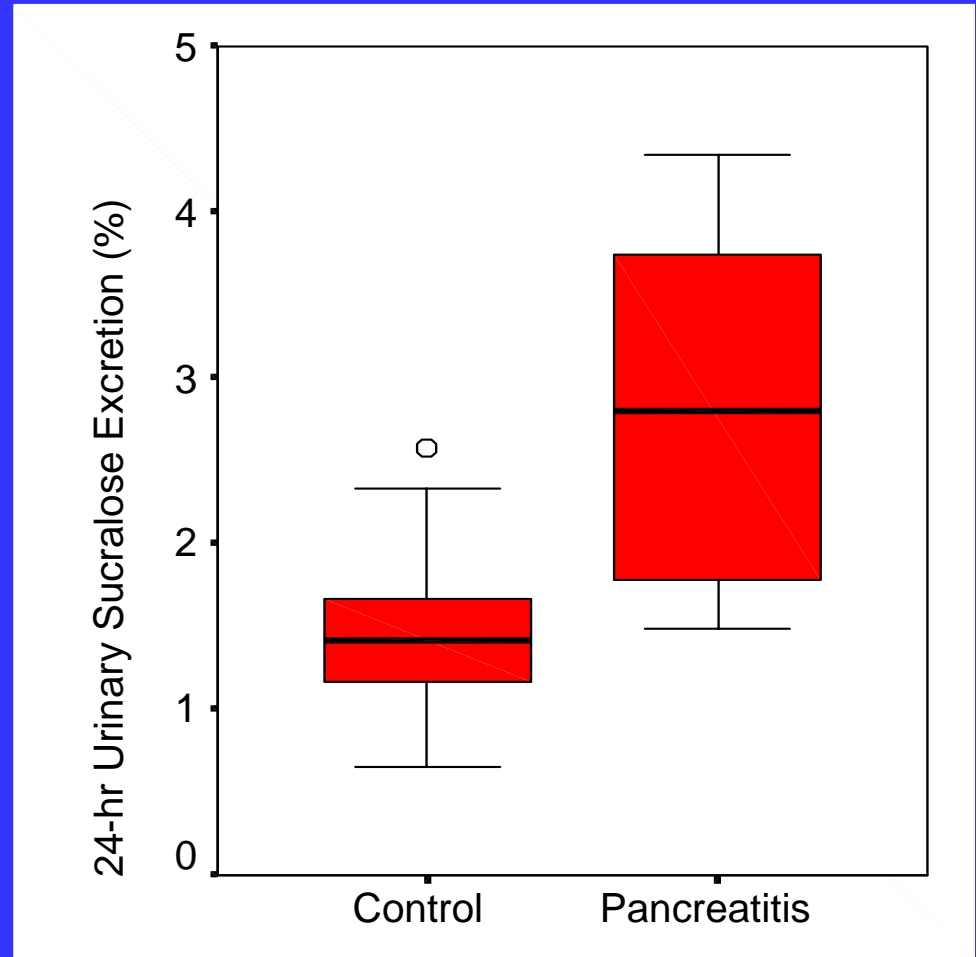
*Anderson A et al
BJS 2004; 91 (supp 1):44*



“Whole-Gut” Permeability

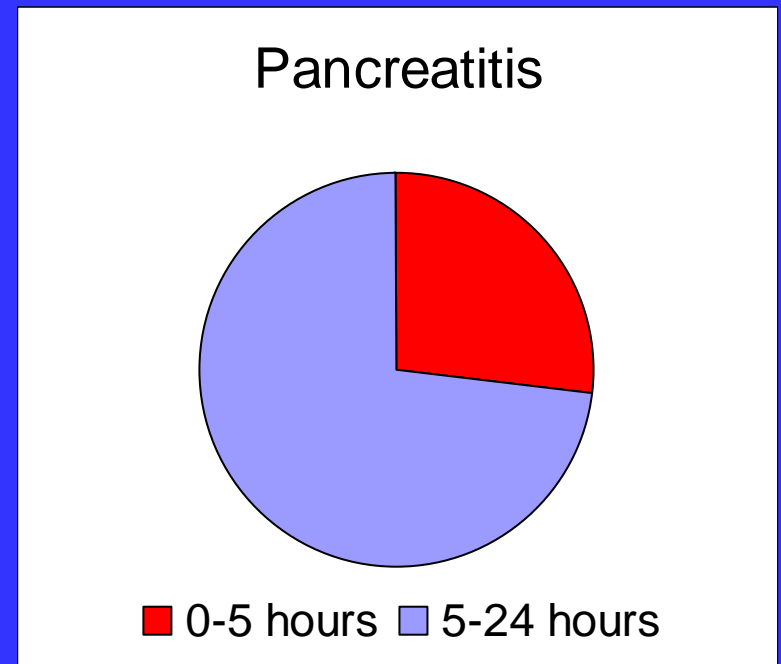
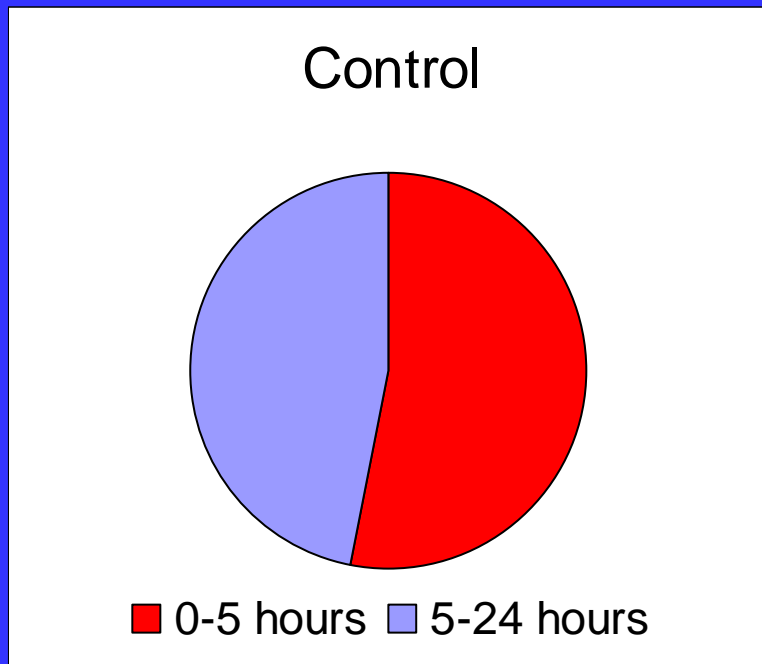
Increase in 24-hour
sucralose excretion
($p < 0.001$)

*Anderson A et al
BJS 2004; 91 (supp 1):44*



Timescale of Sucralose Excretion

Alteration in pattern of sucralose excretion
($p=0.049$)



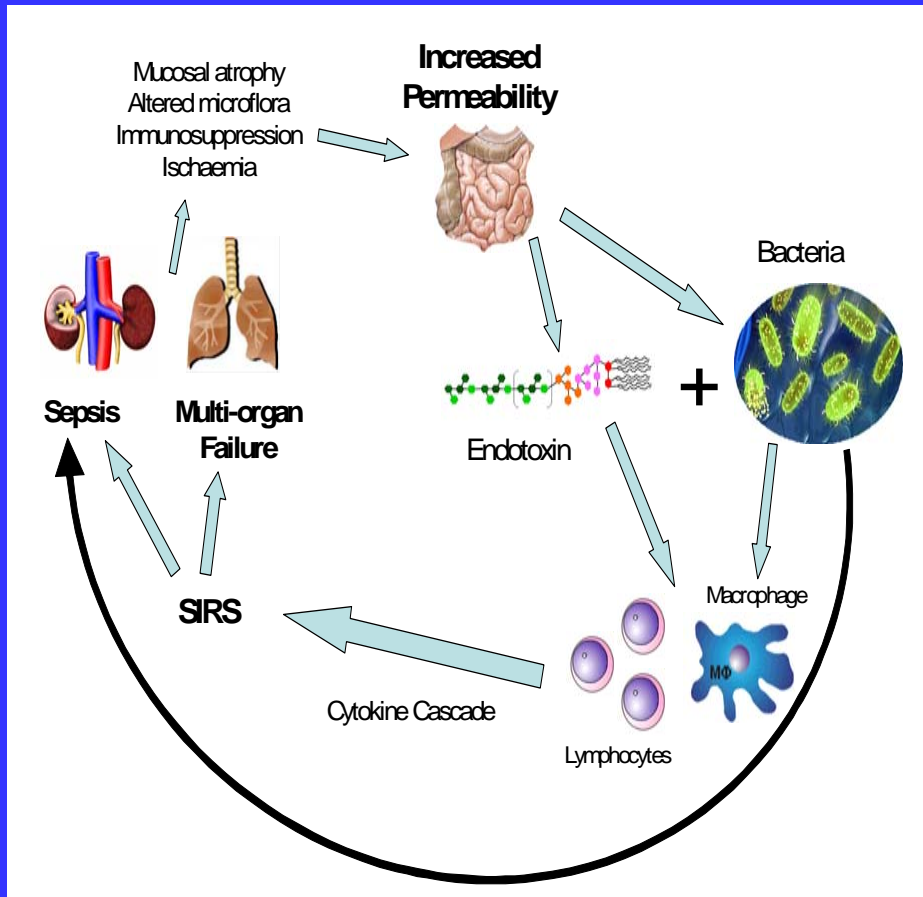
Gut barrier function: intestinal permeability

- *“dual sugar probe” methods of measuring intestinal permeability only assess small intestinal function*
- *The significance of changes of intestinal permeability remains unclear as regards barrier function*
- *“triple sugar test” allows assessment of colonic permeability*
- *Both small intestinal and colonic permeability are increased in pancreatitis*

*Anderson A et al
BJS 2004; 91 (supp 1):44*

Gut Origin of Sepsis Hypothesis

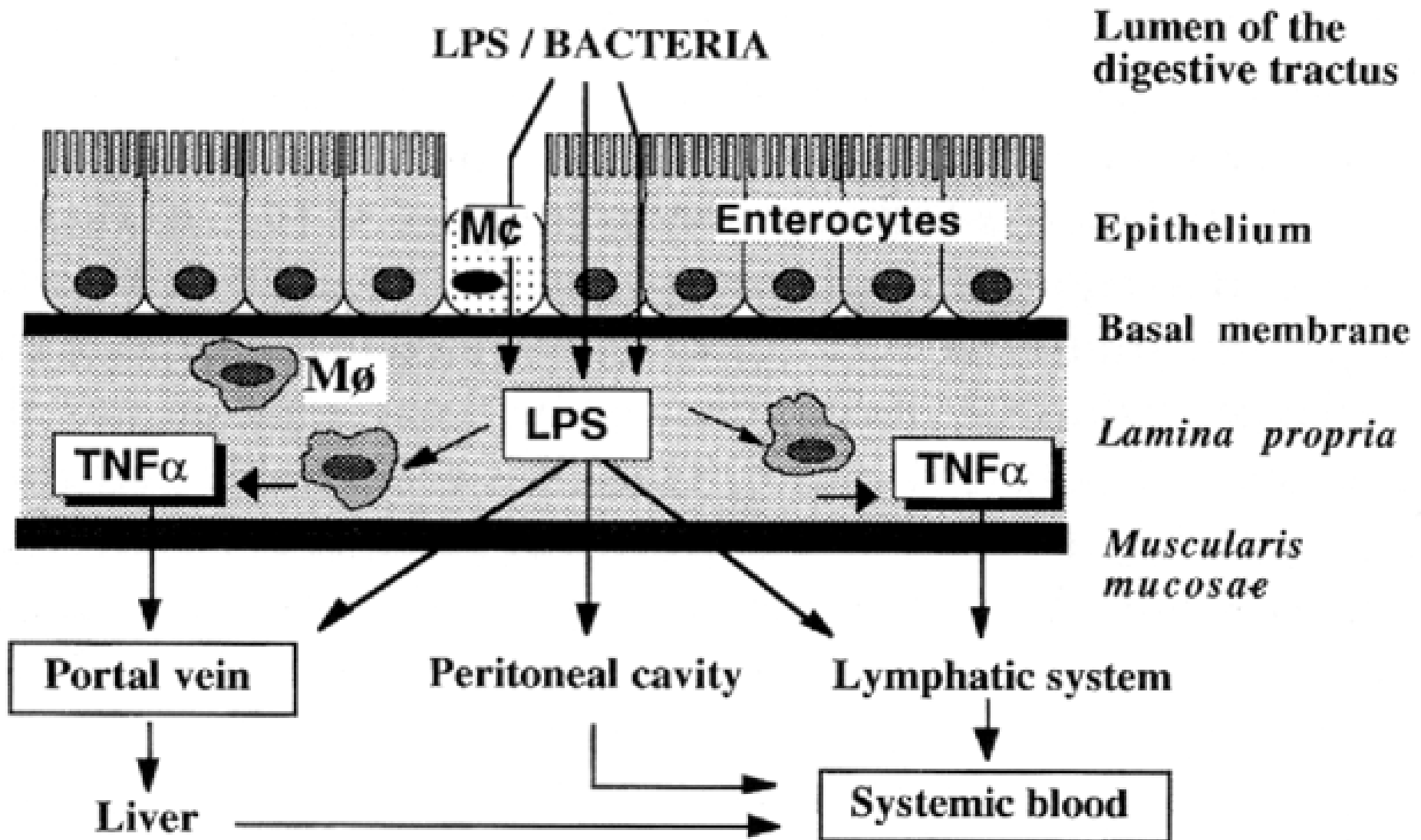
Sca'bro studies



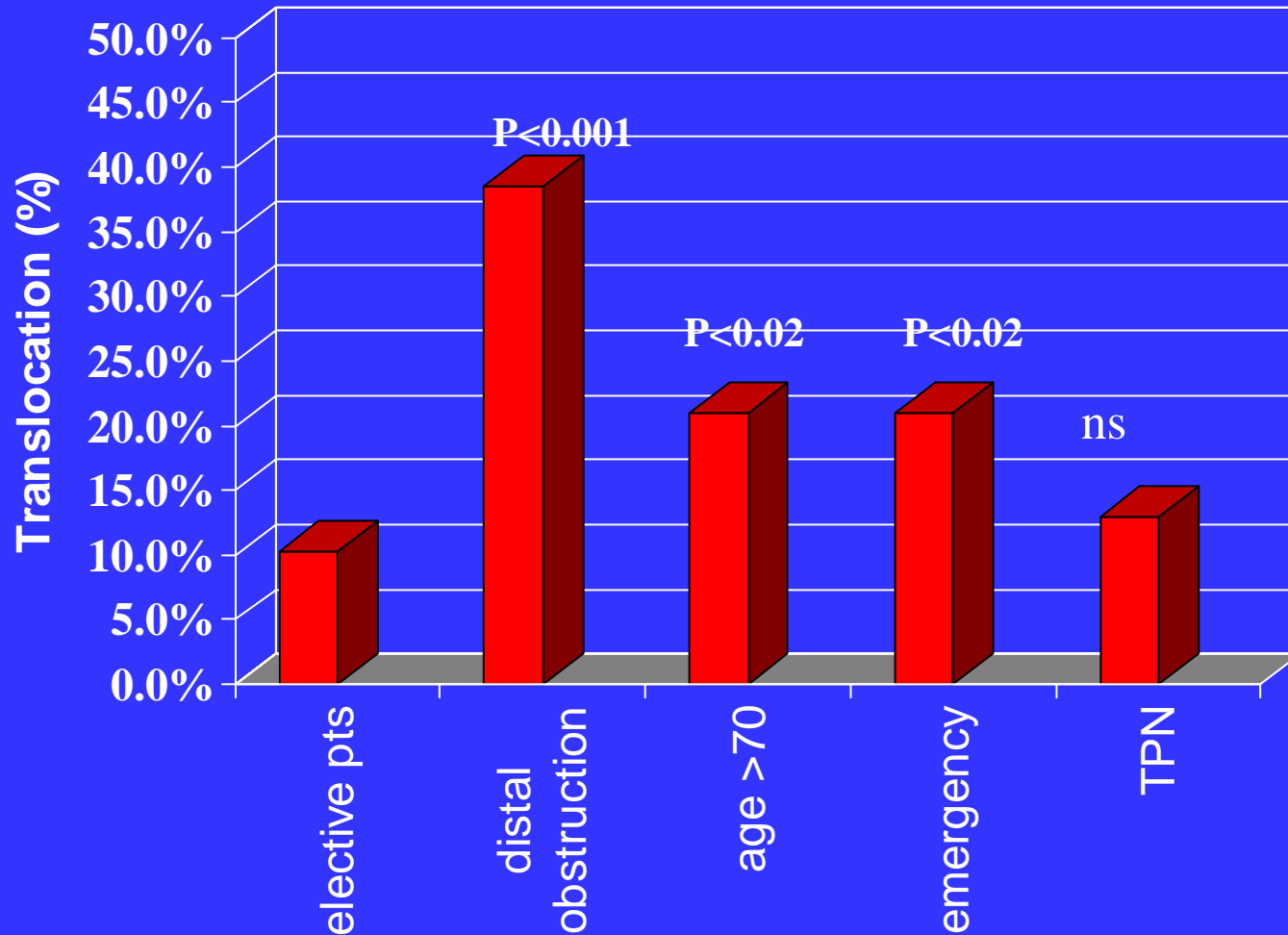
End Points:

- *villus morphology*
- *intestinal permeability*
- bacterial translocation
- septic morbidity

Pathways of translocation:



Clinical Associations with Translocation



Bacterial Translocation: Scarborough series

- 448 surgical patients
- mesenteric lymph node assays

- *overall prevalence 15.4%*

- *more common in patients: > 70yrs*

distal intestinal obstruction

urgent surgery

- *is associated with ↑ septic morbidity*

- *is associated with ↑ gastric microflora*

- *not increased by preoperative TPN*

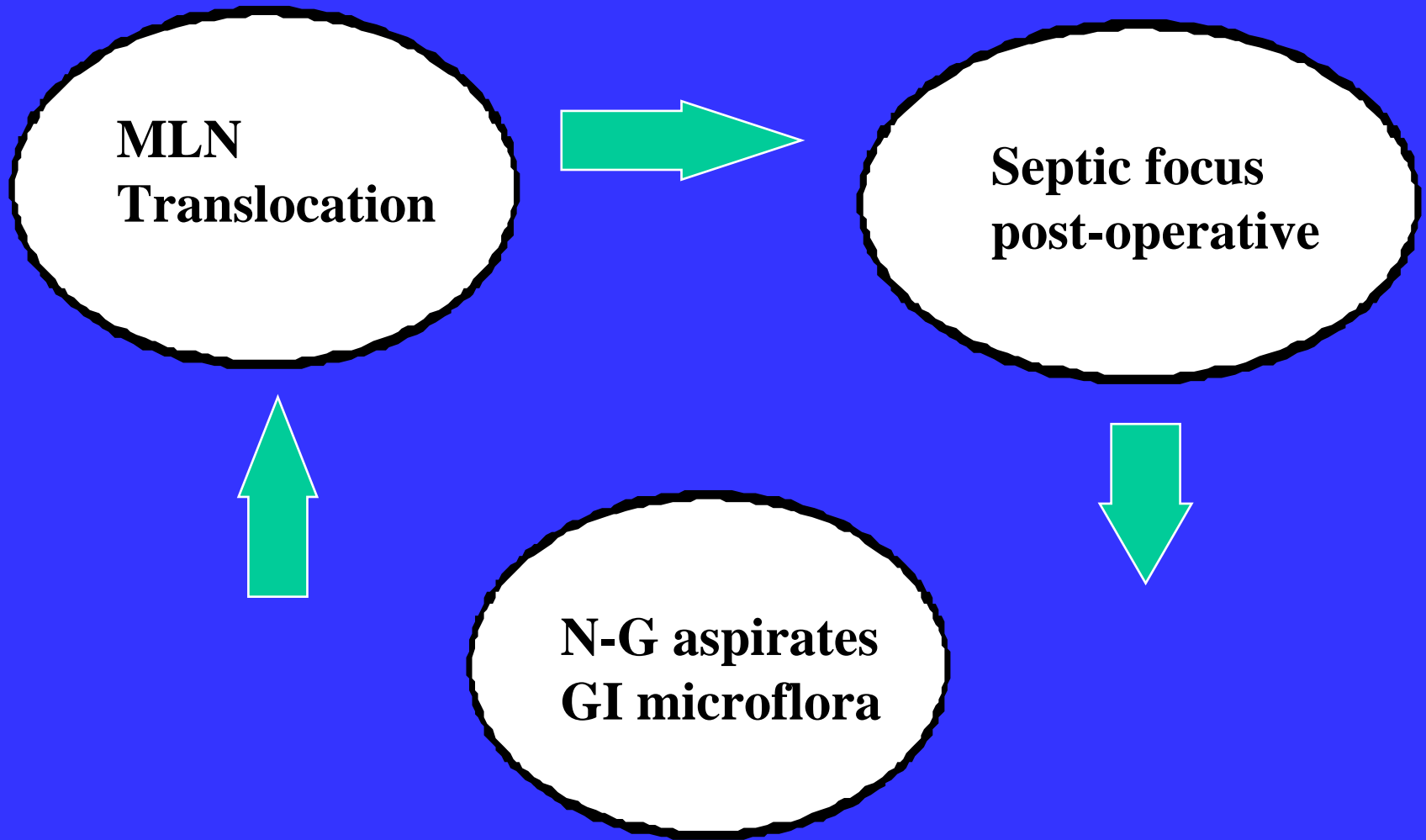
Gut origin of sepsis hypothesis: Scarborough series

279 surgical patients
upper GI microflora assessed from N-G aspirates

136 underwent laparotomy
bacterial translocation assessed from mesenteric
lymph nodes

50 patients had positive bacterial culture in
post-operative period

Associations between microflora



Translocation and septic morbidity

Septic Complications

Translocation

16/29

(55%)

No translocation

30/107

(28%)

p < 0.01

Translocation and GIT microflora

Nasogastric aspirate

Translocation

Sterile/monoculture

12/86 (14%)

Polyculture

17/50 (34%)

$p < 0.01$

Bacterial translocation, GI microflora and septic morbidity

Summary

- Only 30% N-G aspirates sterile
- Colonisation by multiple species is associated with a significant increase in septic morbidity and translocation
- Identical biotype in N-G aspirate and septic focus in 29%
- Identical biotype in N-G aspirate and MLN in 31%

Bacterial Translocation

- *does occur in humans*
- *is associated with septic morbidity*
- *similar organisms identified in mesenteric nodes and N-G aspirates*
- *colonisation of stomach associated with ↑ translocation and septic morbidity*

these data provide supportive evidence that the “gut origin of sepsis hypothesis” is correct

Pros and Cons of Gut Origin of Sepsis Hypothesis

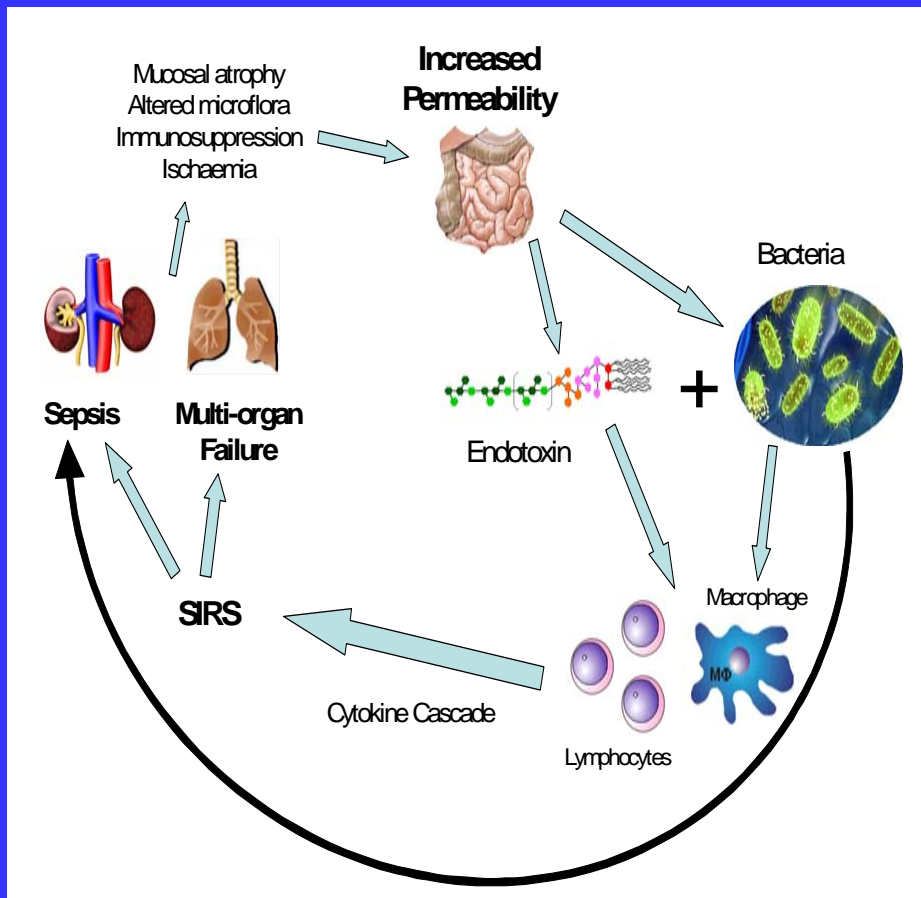
Pros:

- *Clinical studies of bacterial translocation*
- *Clinical studies showing association between GI microflora and septic morbidity*
- *Experimental studies*

Cons:

- *Failure to document bacteria or endotoxin in MLNs or portal blood in ALL pts with SIRS or MODS*
- *Failure of selective gut decontamination to show consistent benefit*
- *Failure to demonstrate consistent beneficial effect from “gut specific nutrients”*

Gut Origin of Sepsis Hypothesis



Consider:

- is not “simply” dependant on “bacterial translocation”
- the gut is itself the largest cytokine generating organ

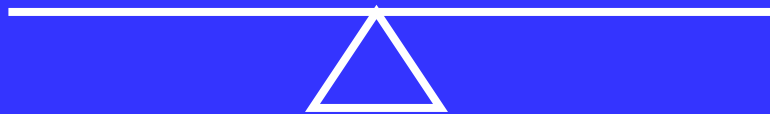
The balance between pro-and anti-inflammatory cytokines is important

**Pro-inflammatory
cytokines**

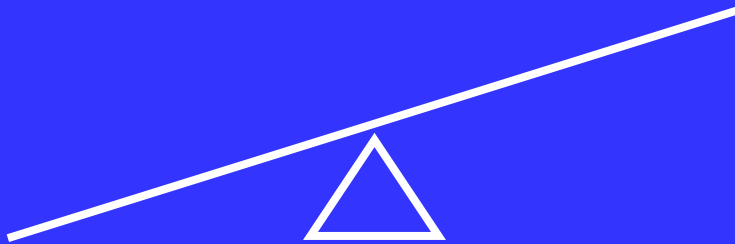
TNF, IL1, IL6, IL8

**Anti-inflammatory
cytokines**

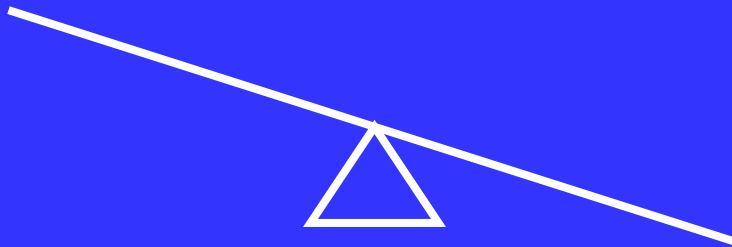
IL4, IL10 etc



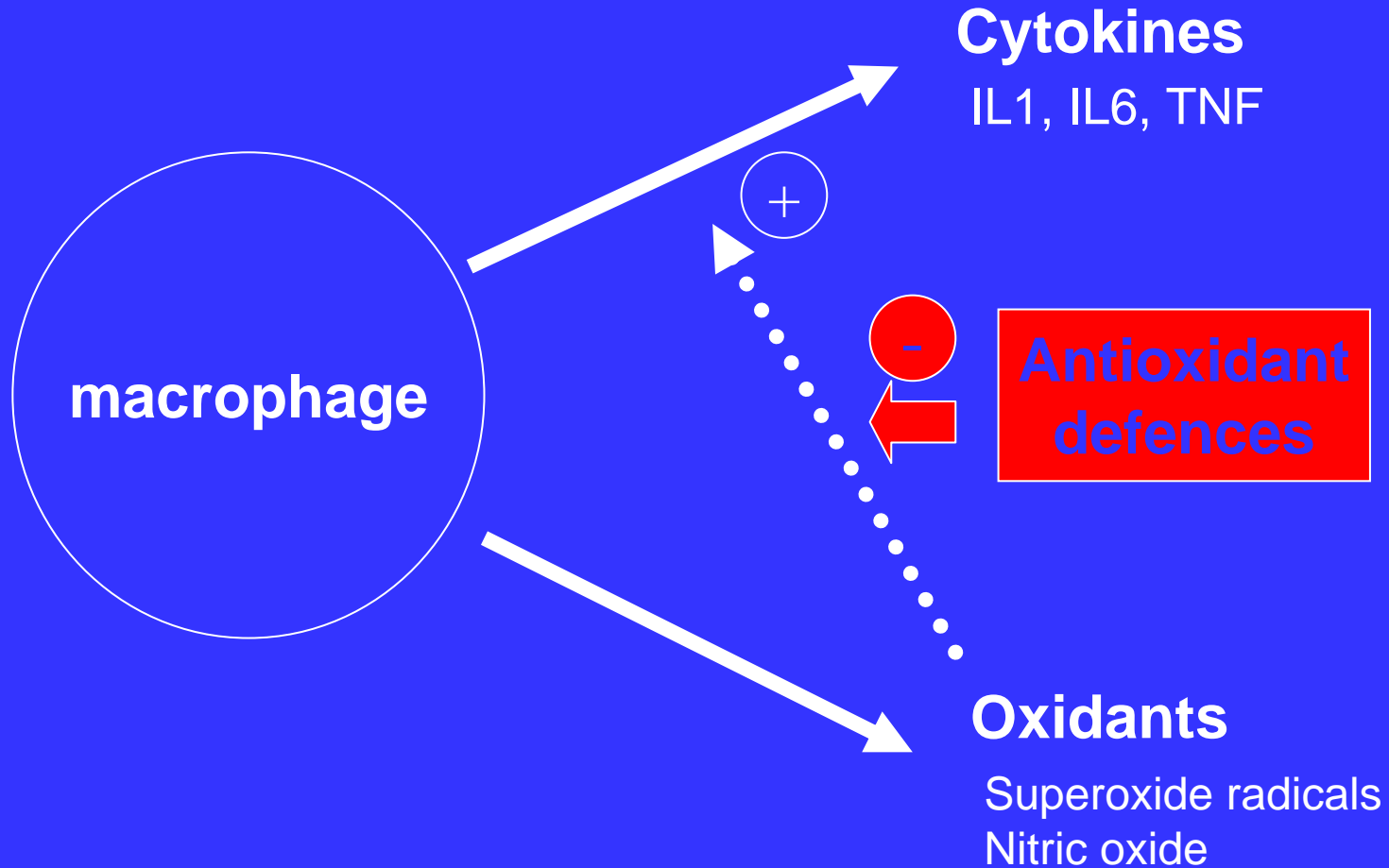
**Optimal
outcome**



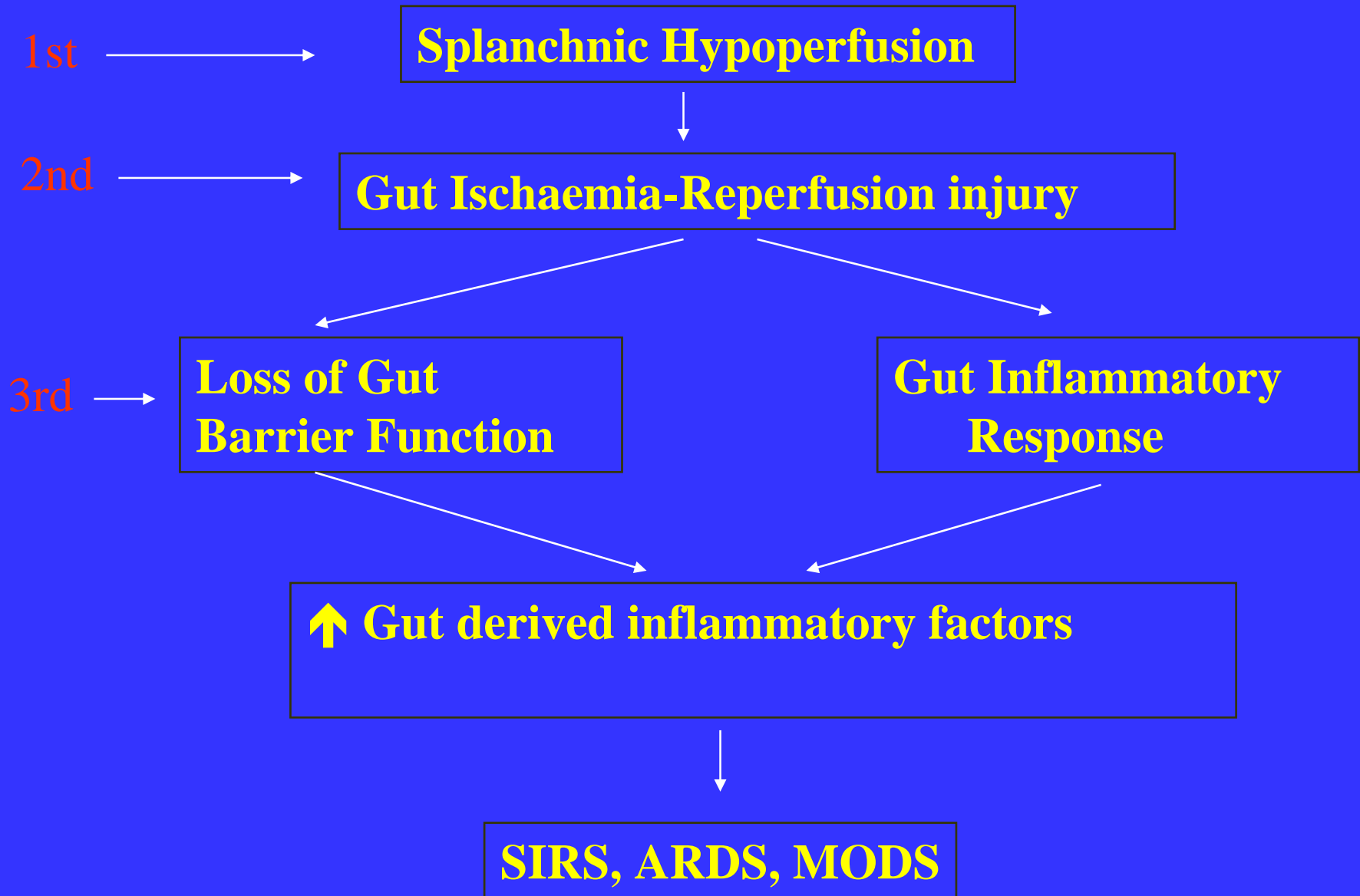
**Poor outcome,
increased
mortality**



Oxidant – antioxidant balance



“3 – Hit Model” (Deitch A. *Surgery* 2002,131:241)



ESPEN 2004

Starvation, Intestinal Permeability and Bacterial Translocation

Summary:

- *gut barrier function is difficult to measure*
- *inappropriate to use measures of starvation or intestinal permeability as surrogate measures bacterial translocation*
- *on balance, there is sufficient evidence to conclude that the “gut origin of sepsis hypothesis” is proven*

gut function (digestive and immunological) is bound to be a major determinant of clinical outcome

