

Post-Infectious Irritable Bowel Syndrome

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WDHD 2011

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Why are we here today?

- World Digestive Health Day
 - Sponsored throughout the world by the World Gastroenterology Organisation
(www.worldgastroenterology.org)
 - To highlight digestive disorders
 - GI complaints the most common reason for seeing a doctor
 - Among the most common causes of loss of time from school, work
 - Several important common chronic diseases:
 - Irritable bowel, coeliac disease, colitis, hepatitis, cirrhosis, gall stones, diverticulitis, reflux.
 - The most common cancers world wide:
 - Colon, stomach, oesophagus, pancreas, liver, gall bladder

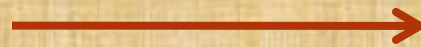


WDHD | Enteric Infections: Prevention & Management

World Digestive Health Day | May 29, 2011



Enteric Infections



IBS

Is there a link?

IBS in the “Real” World!

Community survey of over 40,000 adults in eight European countries:

- Overall prevalence: 11.5% (6.2%–12%)
- 9.6% had symptoms at the actual time of the survey
- But, 2.8% had been formally diagnosed as IBS
- Symptoms:
 - Abdominal pain: 88%
 - Bloating: 80%
 - Trapped wind: 66%
 - Tiredness: 60%
 - Constipation: 53%
 - Diarrhea: 59%
 - Heartburn: 47%

IBS; the Clinical Challenges

- No blood test
- No scan or X-ray
- No 'scope or physiological test
 - That is diagnostic!
 - So how do you make the diagnosis?
 - Symptoms that are present and absent
 - Negative tests

Definition

Two Approaches

- By exclusion
- Definitive; based on symptoms
 - Rome I, II, III
 - Manning
 - Kruis symptoms + some tests

IBS: a simpler definition?

“IBS is defined by **abdominal discomfort**
associated with **altered bowel habits.**”

ACG position statement, 2002



The American College of Gastroenterology
Digestive Disease Specialists Committed to Quality Patient Care



Infection and IBS

- Post-amoebiasis IBS

Palmer 1946, Davis, 1949, Stewart, 1950



THE IRRITABLE COLON SYNDROME
*A Study of the Clinical Features, Predisposing Causes, and
Prognosis in 130 Cases*
BY NAZIR A. CHAUDHARY AND S. C.
TRUELOVE
(From the Nuffield Department of Clinical
Medicine, Radcliffe Infirmary,
Oxford)

**Quarterly Journal of Medicine, New Series
XXXI, No. 133, July 1963.**

- **Demographics**

“The condition was seen twice as commonly in women as in men”

- **Symptoms**

“Pain of colonic origin was present in 106/130”

“The bowel habit was variable, sometimes being normal, but sometimes associated with periodic constipation or diarrhoea, or with both these symptoms alternating”

“In more than half of the patients the act of defaecation was followed by temporary relief of pain”

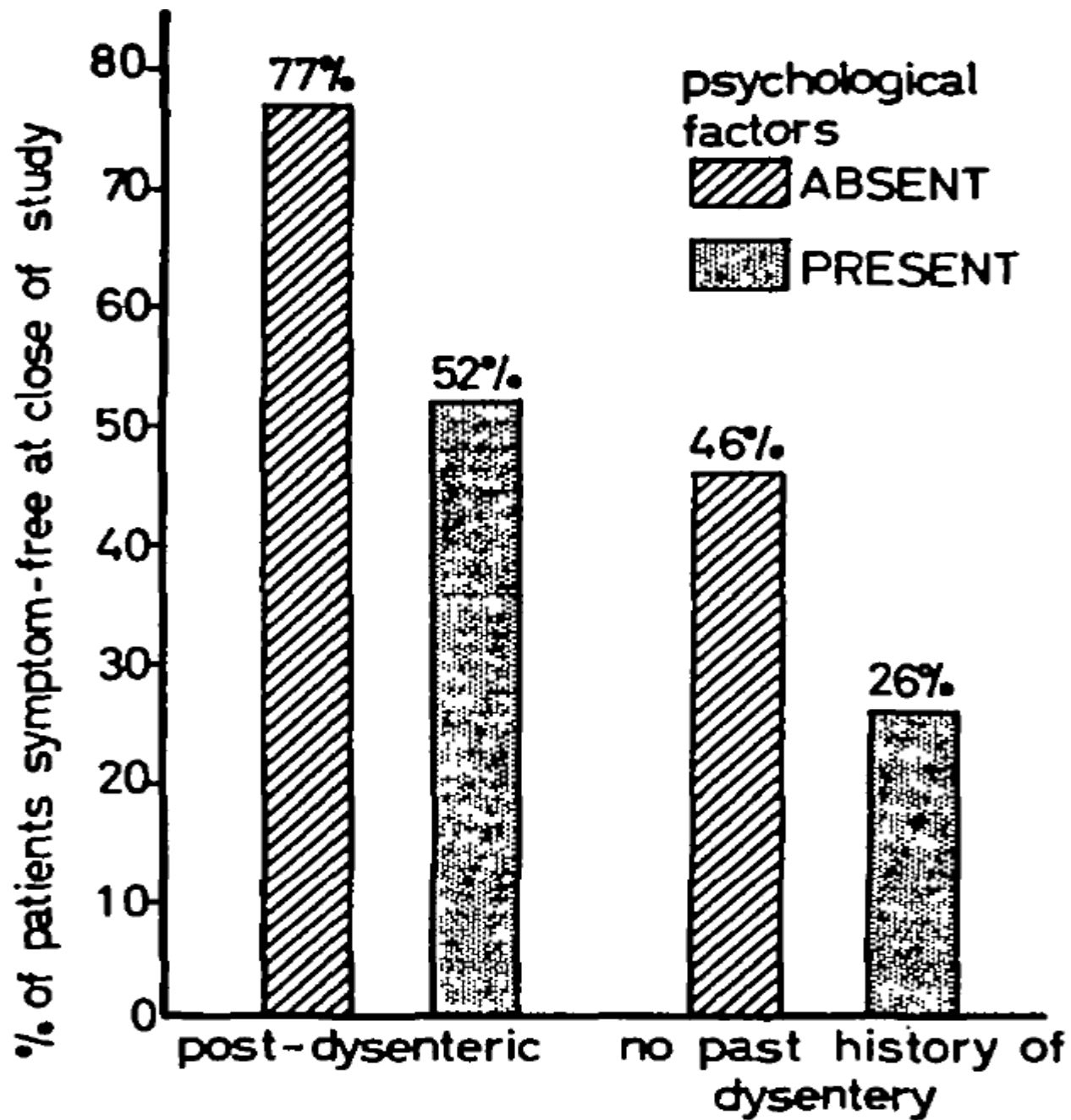
“The majority complained of one or more general symptoms: a sense of fatigue, loss of mental concentration, depression, and anxiety”

- **PI-IBS**

“In 34 patients the symptoms dated from an attack of infective dysentery, either proven or strongly presumptive”

- **Prognosis**

“Approximately one-third became symptom-free. A small number of patients were symptom-free but still receiving regular treatment, the large majority continued to have mild symptoms, some still receiving treatment”



Chaudhary and
Truelove 1963

Infection and IBS

- Post bacterial gastroenteritis

McKendrick and Read, 1994

Neal et al, 1997 (7%)

Gwee et al, 1996 (22/75)

Garcia Rodriguez, 1999 (RR for IBS at 12 months X 12)

Ilnyckyj et al, 1999 (9.5% post travellers diarrhoea)

Li et al, 2006 (OR 2.9, following shigella)

Borgaonkar et al, 2006 (community incidence - 3.7%)

Post-Infectious IBS

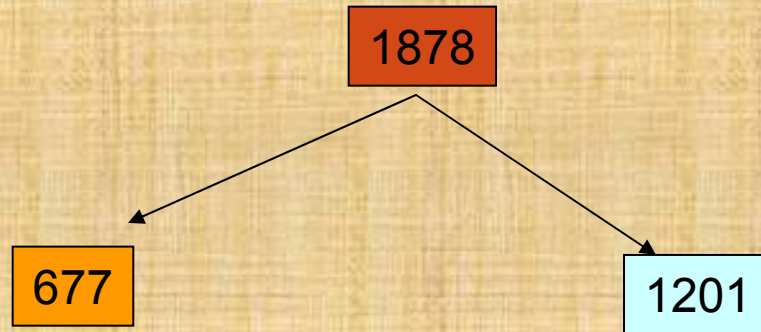
- Overall, 10-14% incidence following confirmed bacterial gastroenteritis

Dunlop et al, 2003

Mearin et al, 2005

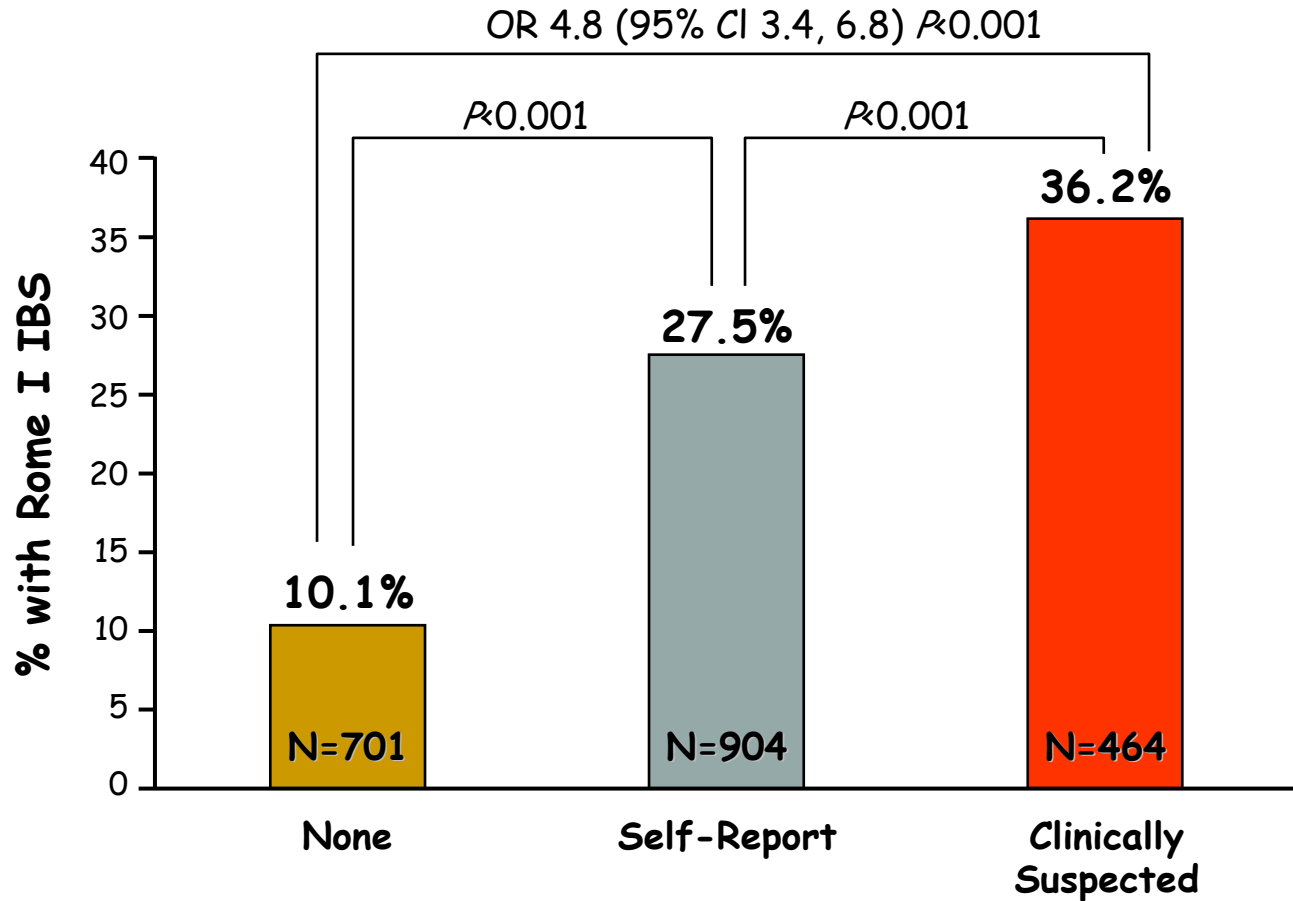
- Risk factors
 - Female
 - Severe illness
 - Pre-morbid psyche
 - depression
 - *Persistent inflammation in the gut wall*

The Catalan Experience!



At 12 months	Pre-Exposure	Exposed	Non-Exposed
FD	5.2%	2.7-2.8%	3.8%
IBS	7.8%	3.1-2.9%	2.5%

Walkerton, Ontario



Risk Factors

Gender	PI-IBS	No PI-IBS	Adjusted RR
M	6	153	1
F	17	171	3.39 (1.2-9.8)
Duration (d)			
0-7	2	104	1
8-14	7	123	2.94 (0.6-15)
15-21	7	44	6.46 (1.3-34)
> 22	7	38	11.37(2.2-58)

PI-IBS; a Global Issue!

- Beijing, China. 295 patients post bacillary dysentery (shigellosis)
- Followed at 1-2 years
 - FBD – 22.4%
 - IBS (Rome II) – 8.1%
- Associations:
 - Prolonged diarrhoea

Long-term Outcome: does PI-IBS go away?

- Sweden
- Likelihood of symptomatic bowel problem, like IBS, following a defined episode of gastroenteritis
 - 3 months: 12%
 - 5 years: 9%

Tornblom et al, 2007

- Similar results from the UK

Other issues

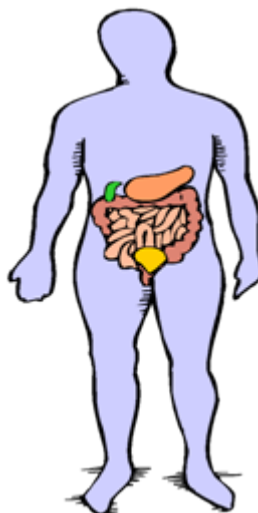
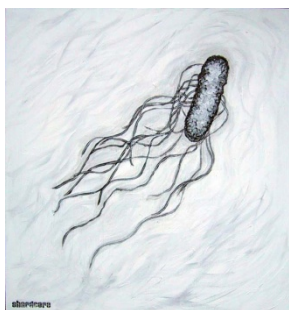
- Most of the outbreaks have involved:
 - Salmonella
 - Shigella
 - Campylobacter
 - Multiple organisms
 - No identified organism
- But there have been reports of IBS following infections with:
 - Giardia
 - Amoeba
 - Viruses

CSGNA Outbreak - Norovirus

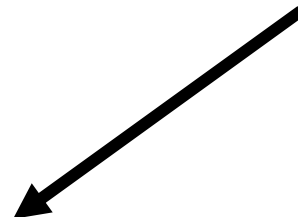
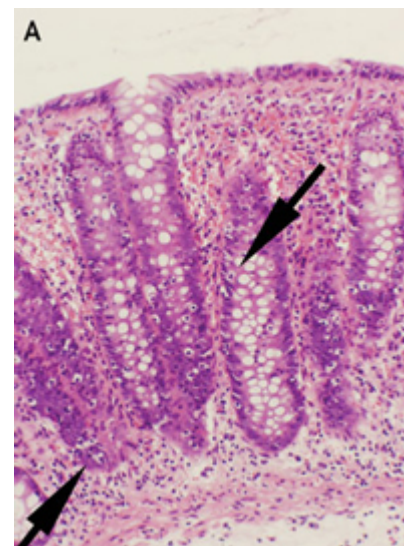
Time (mo)	Exposed	Un-exposed	OR
3	23.6	3.4	6.9
6	12.5	10.3	NS
12	15.1	7.8	NS
24	19.5	8.3	NS

Lessons from PI-IBS

Disturbed Flora



Inflammatory Response

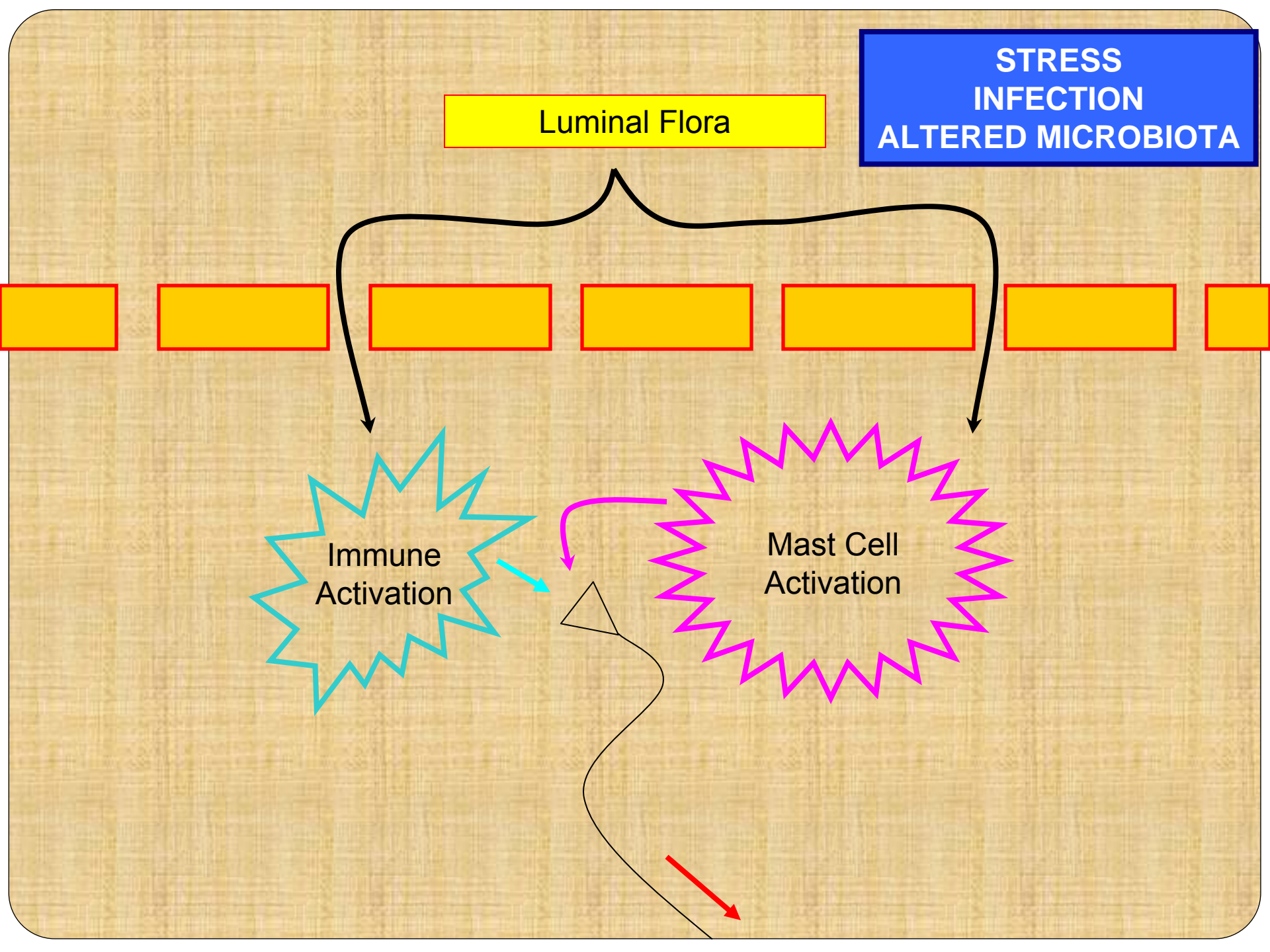


Susceptible Host

Gut Muscle
and Nerve
Dysfunction

SYMPTOMS



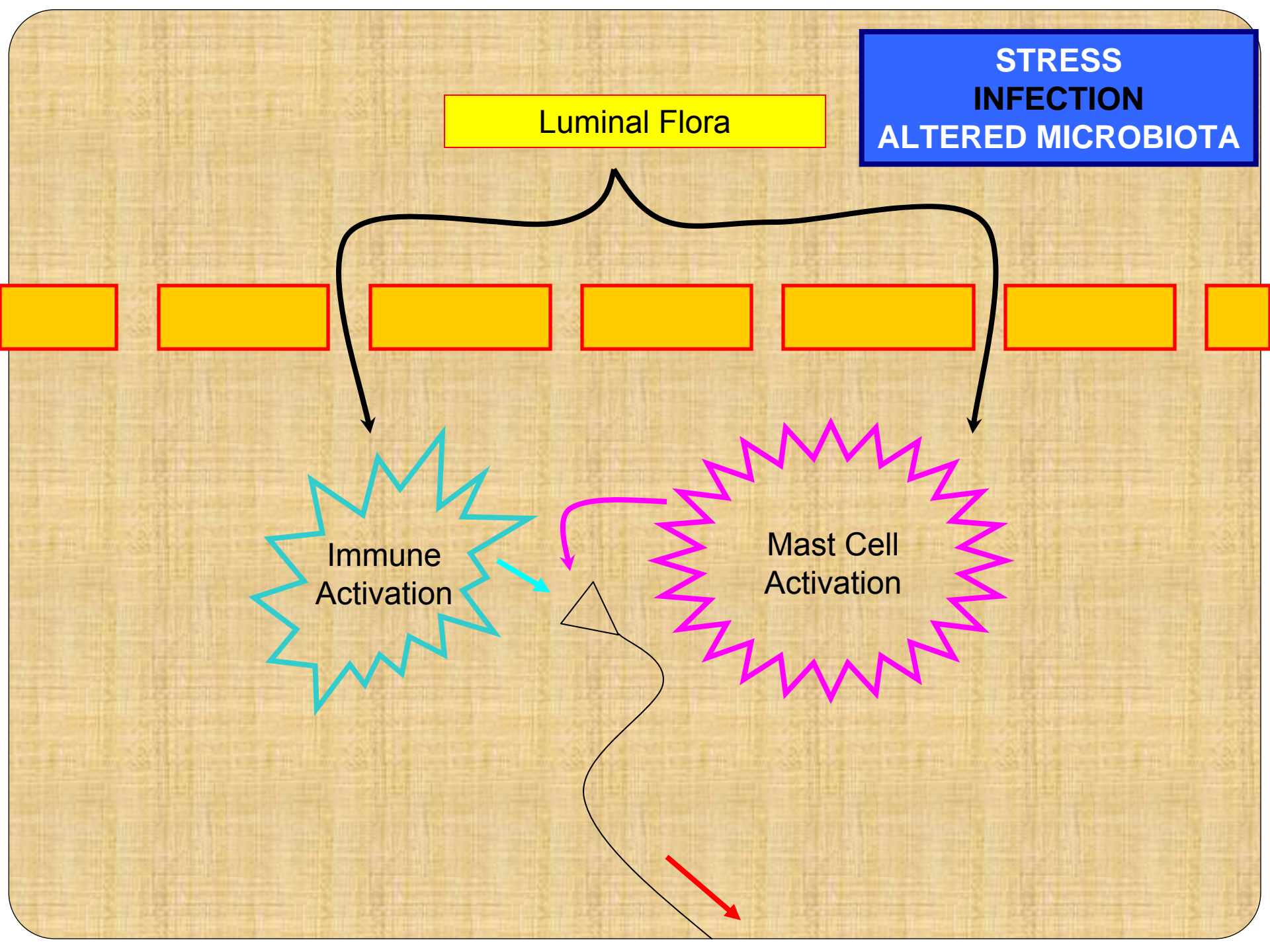


Luminal Flora

STRESS
INFECTION
ALTERED MICROBIOTA

Immune
Activation

Mast Cell
Activation



Luminal Flora

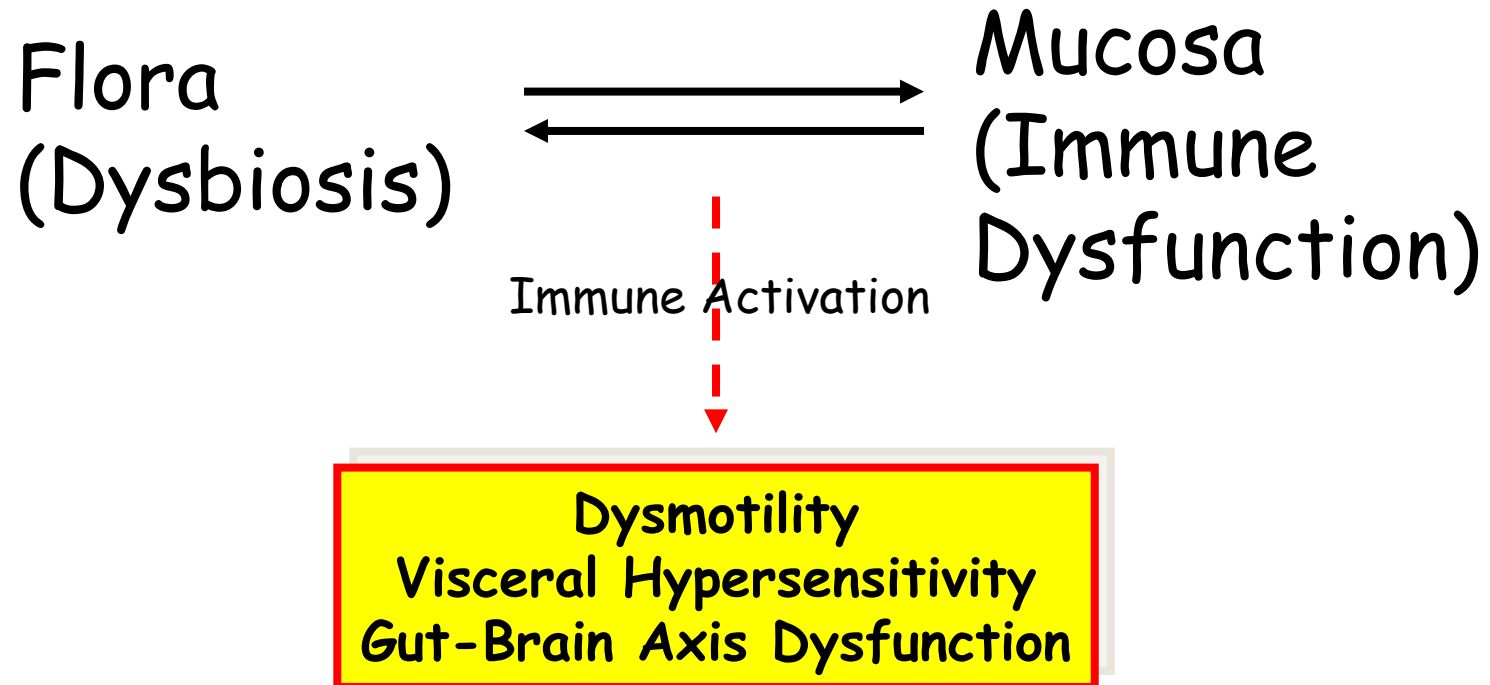
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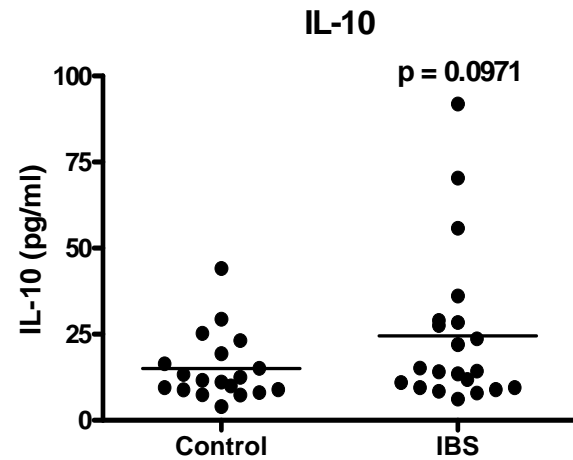
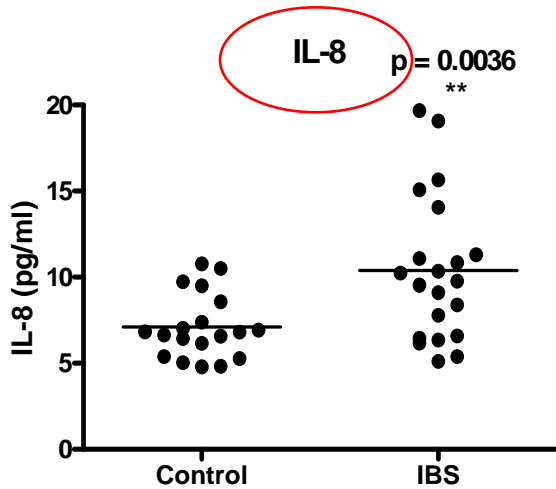
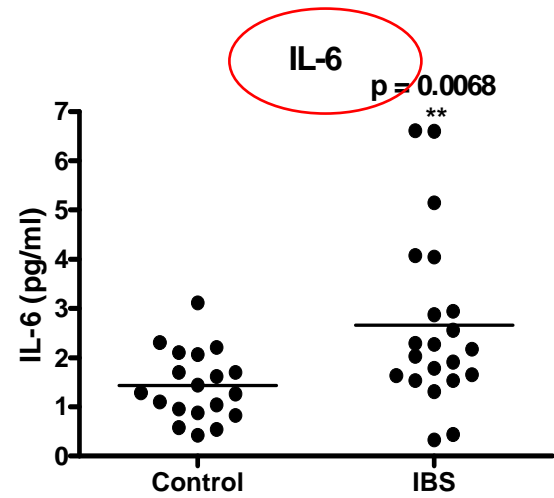
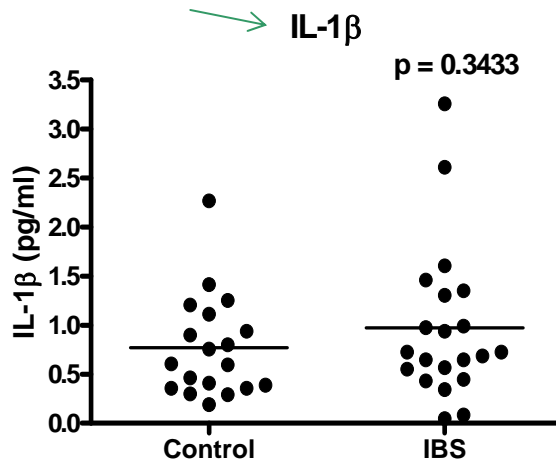
But how about the rest of IBS?



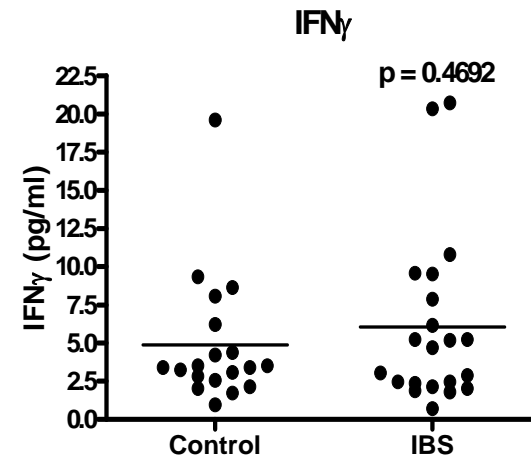
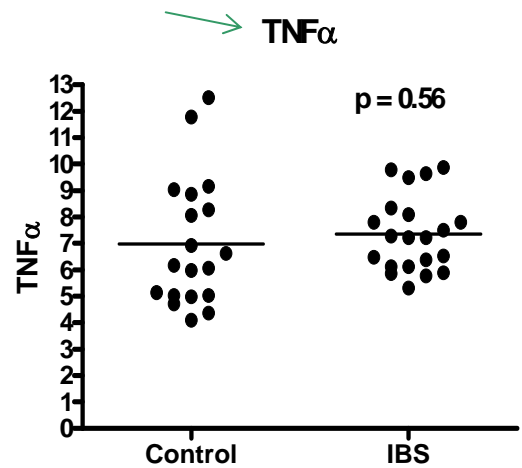
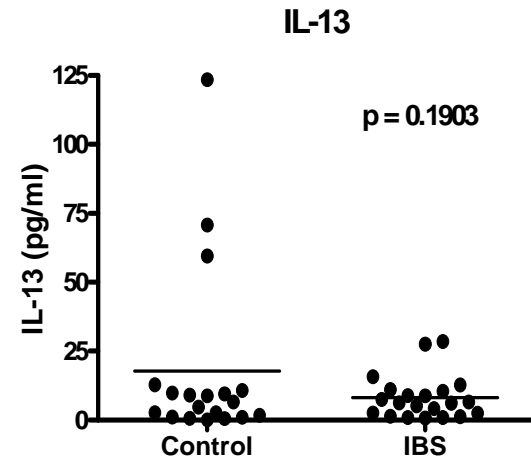
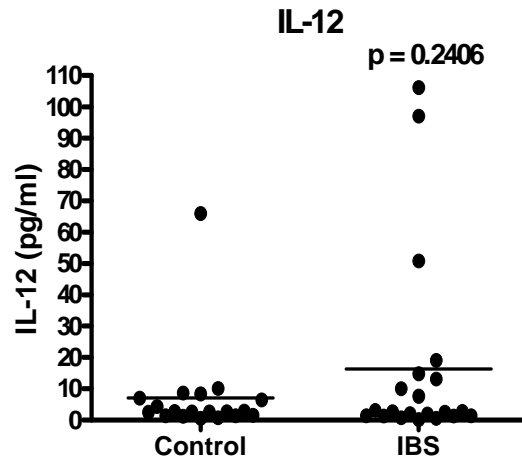
What is the evidence?

- Subtle changes in the blood indicating immune activation
- Subtle change in the mucosa indicating an altered immune response
- Subtle changes in the bacteria in the colon

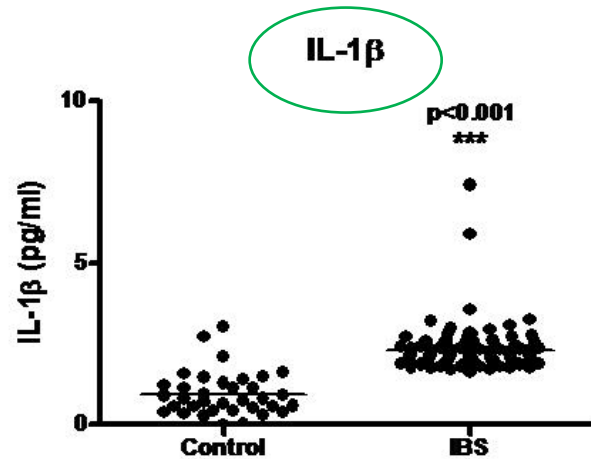
“Pure” IBS



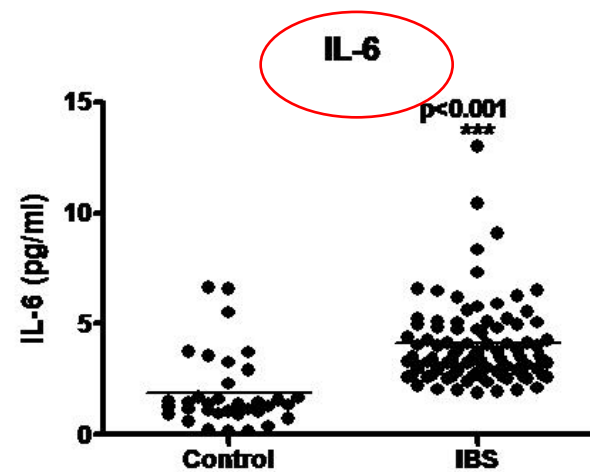
“Pure” IBS



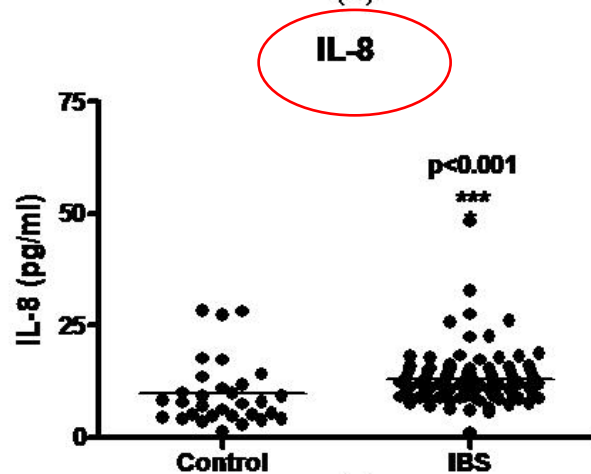
Extra-Intestinal Features of IBS (CFS, Fibromyalgia, PMS)



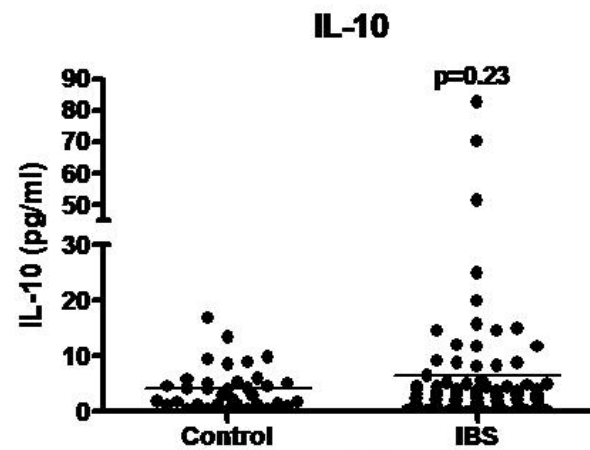
(a)



(b)

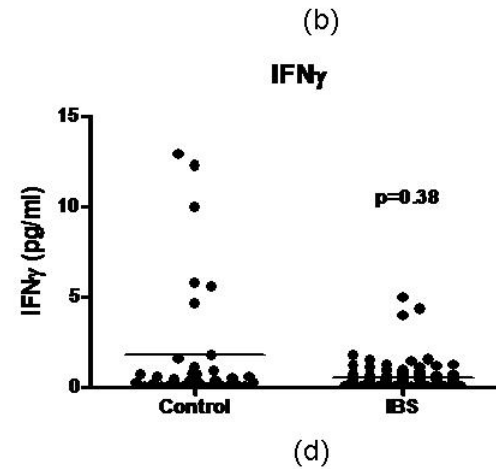
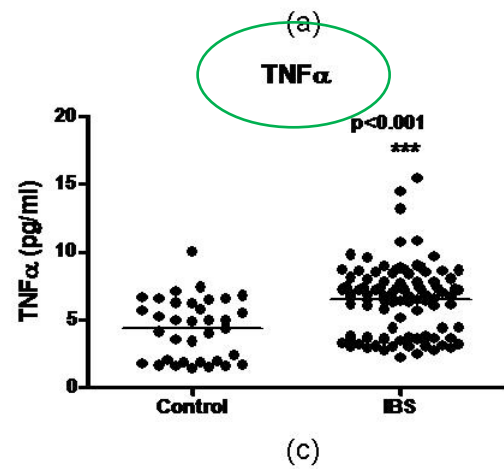
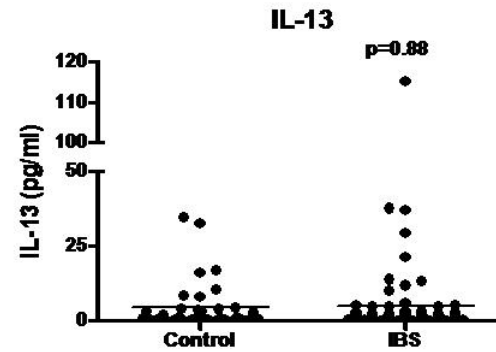
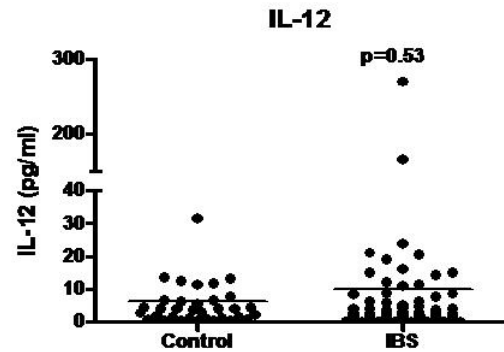


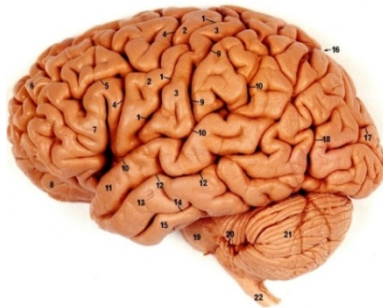
(c)



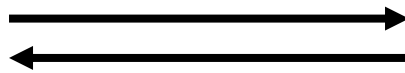
(d)

Extra-Intestinal Features of IBS (CFS, Fibromyalgia, PMS)





Flora
(Dysbiosis)



Mucosa
(Immune
Dysfunction)

Immune Activation



IL6, IL8

Dysmotility
Visceral Hypersensitivity
Gut-Brain Axis Dysfunction

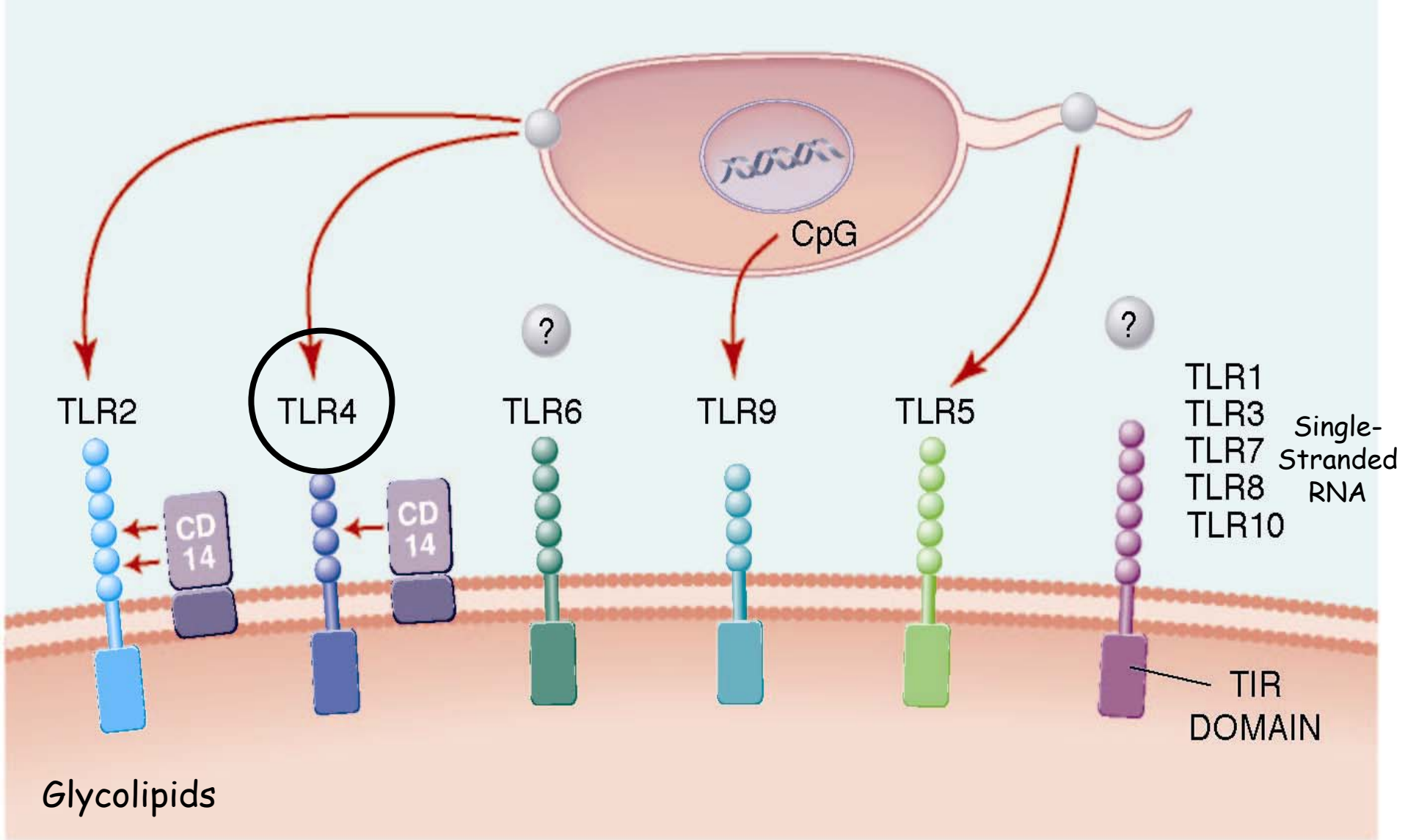


IL1 β , TNF α

Beyond the Gut?

What is the evidence?

- Subtle changes in the blood indicating immune activation
- Subtle change in the mucosa indicating an altered immune response
- Subtle changes in the bacteria in the colon
- BUT DO THESE MEAN ANYTHING?



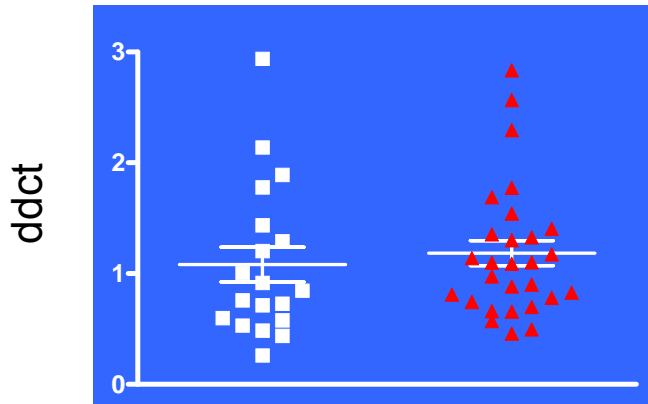
Glycolipids

LPS
Heat shock Proteins

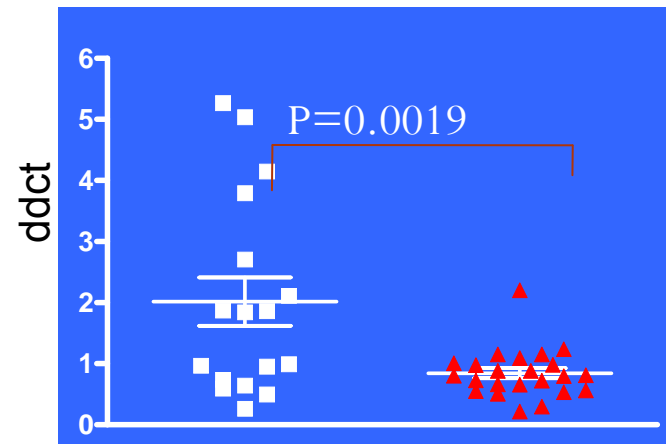
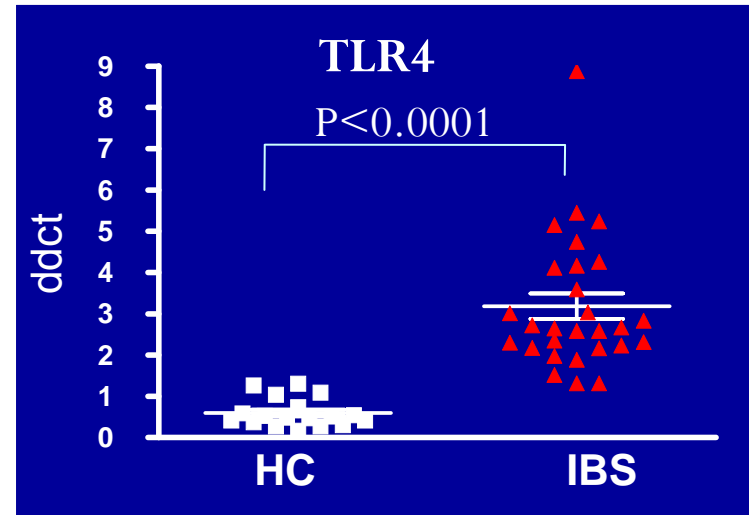
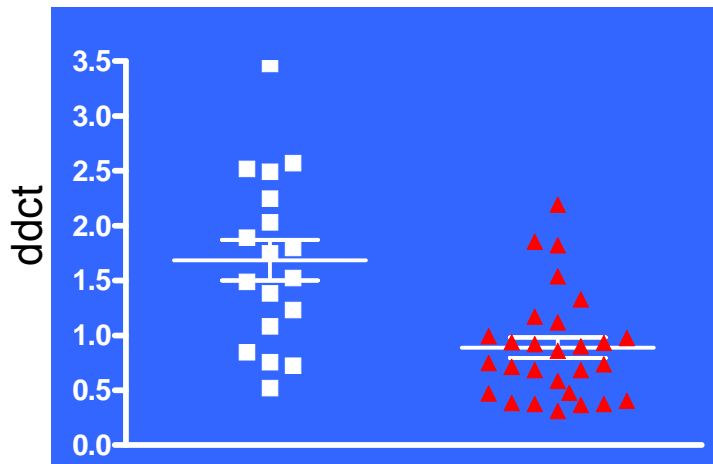
Flagellin
Shanghai Science & Medicine 2003

Toll-Like Receptors in IBS

TLR3

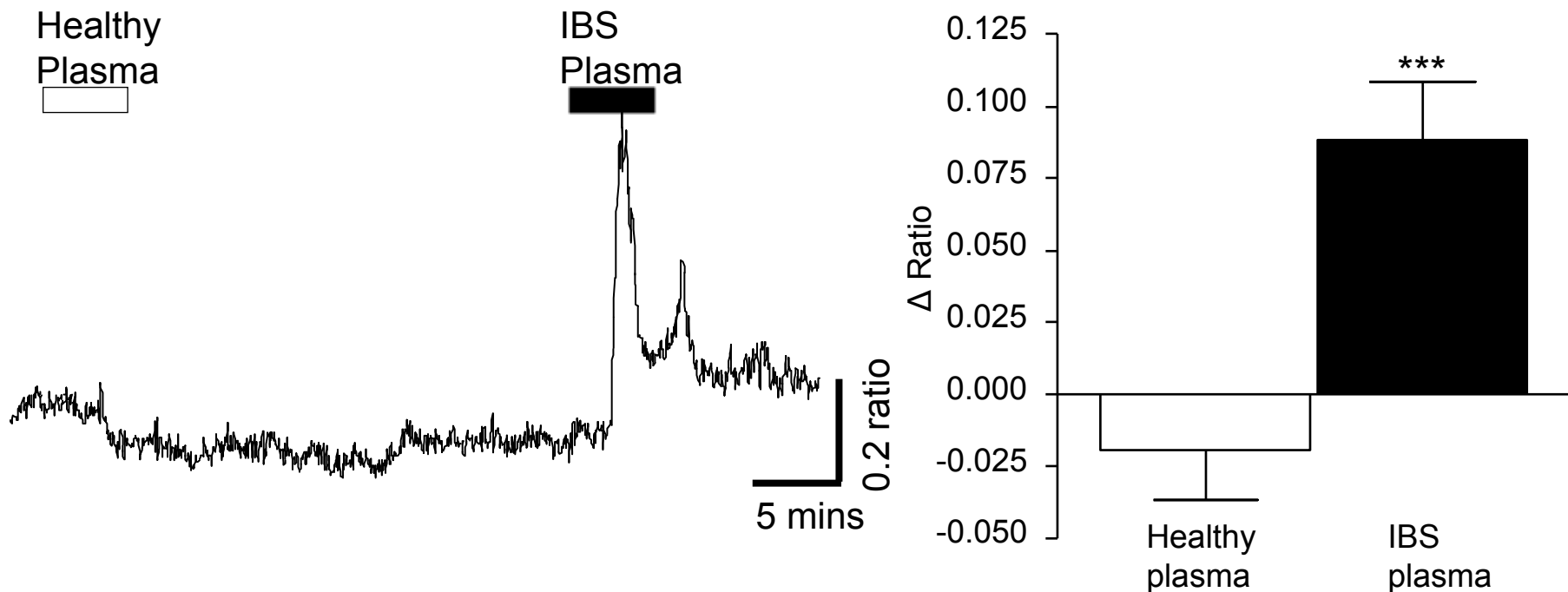


TLR7



TLR8

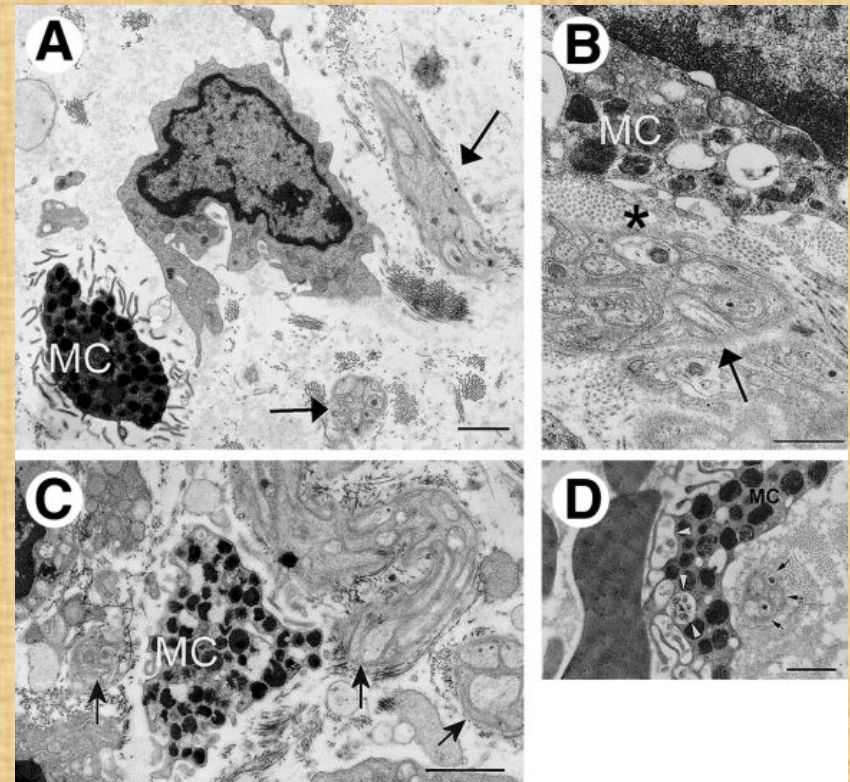
Plasma from IBS activates rat sub-mucosal neurons.



Calcium influx in naïve SD sub-mucosal neurons evoked by IBS (diluted 1:250 in Krebs) but not healthy plasma (n=24 neurons, p<0.001)

Evidence of Inflammation in IBS

- Increased mast cells
- Close relationship between mast cells and sensory nerves in the gut
- Immune Activation
- Changes in genes which produce immune molecules
- Genetic predisposition to a changes immune response



Summary

- Progress
 - Post-Infectious IBS is a real entity
 - Its development is associated with persistent inflammation and immune activation
 - Research in IBS, in general, has identified similar changes in immunity and also shown changes in the gut bacteria

Summary

- Promise
 - New diagnostic tests
 - New treatments:
 - Probiotics,
 - Prebiotics,
 - Antibiotics,
 - Anti-inflammatory

Summary

- Questions:
 - Is all IBS post-infectious?
 - Why do so few develop IBS post-infection?
 - What are the other triggers for immune activation in IBS?

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Enterprise Ireland
Higher Education Authority



Thank you for all your support!