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# Functional and Structural Stress-Related Gastrointestinal Diseases: IBS and IBD

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Wood-2731

# BRAIN-GUT AXIS IN STRESS

## Ulcerative Colitis and Colon Cancer



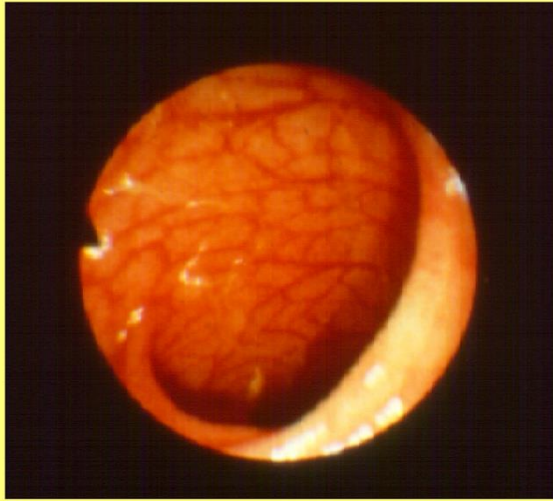
## Cotton-Top Tamarin

Model for Spontaneous Colitis  
and  
Colon Cancer

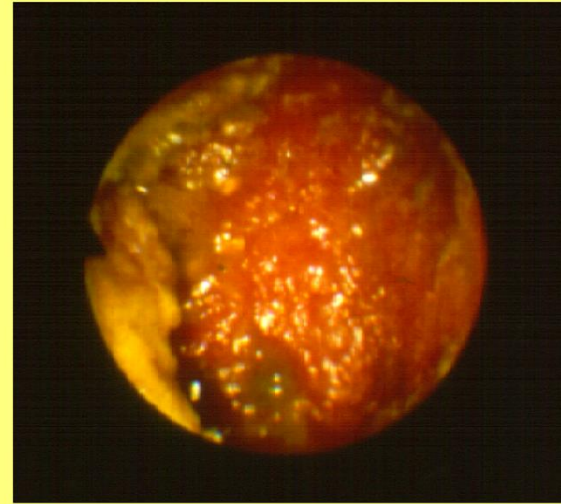


# BRAIN-GUT AXIS IN STRESS

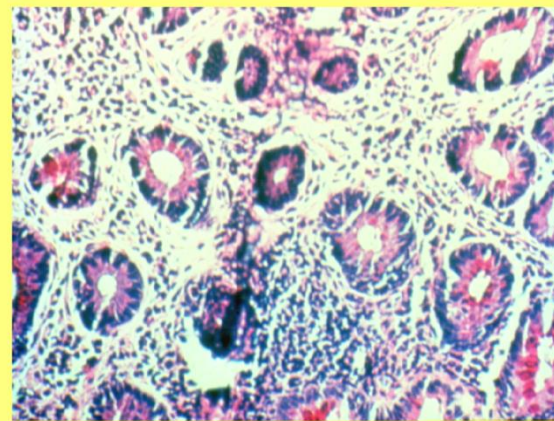
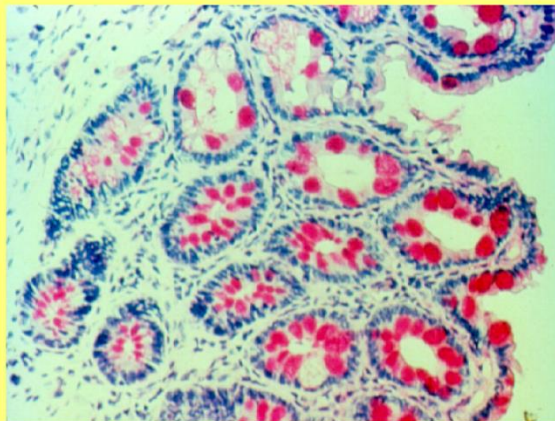
Colitis in cotton-top tamarins:



Normal

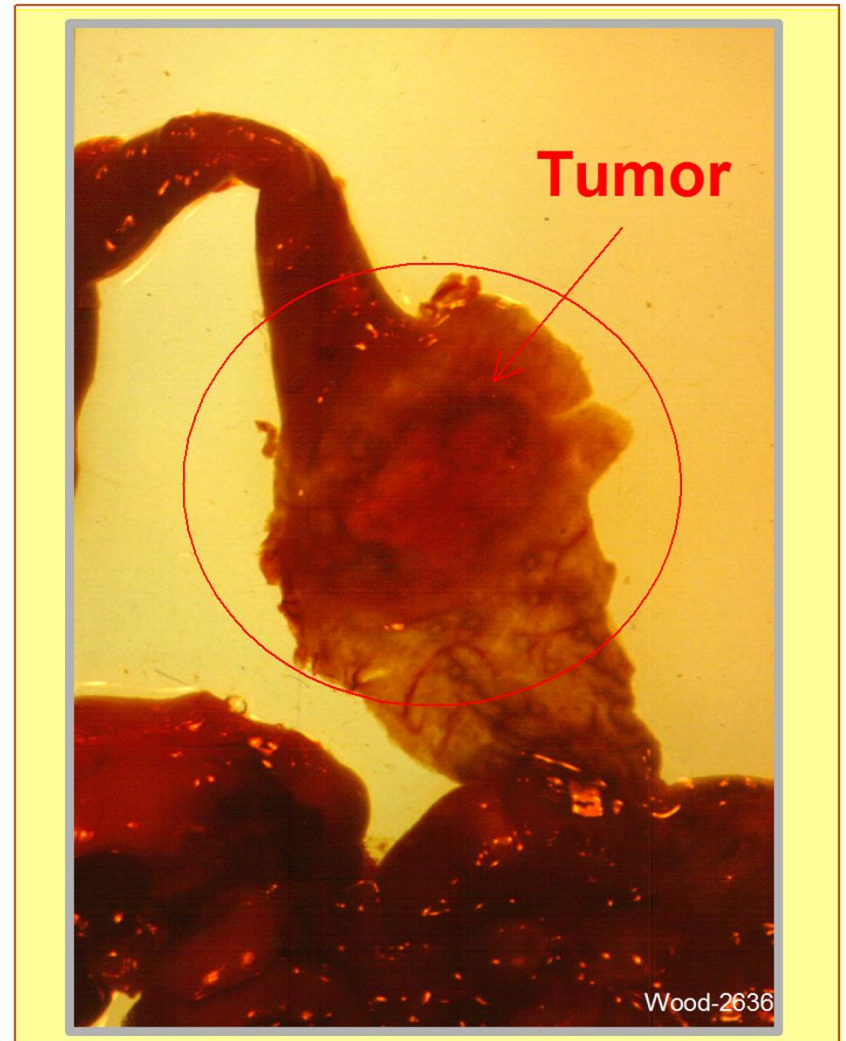
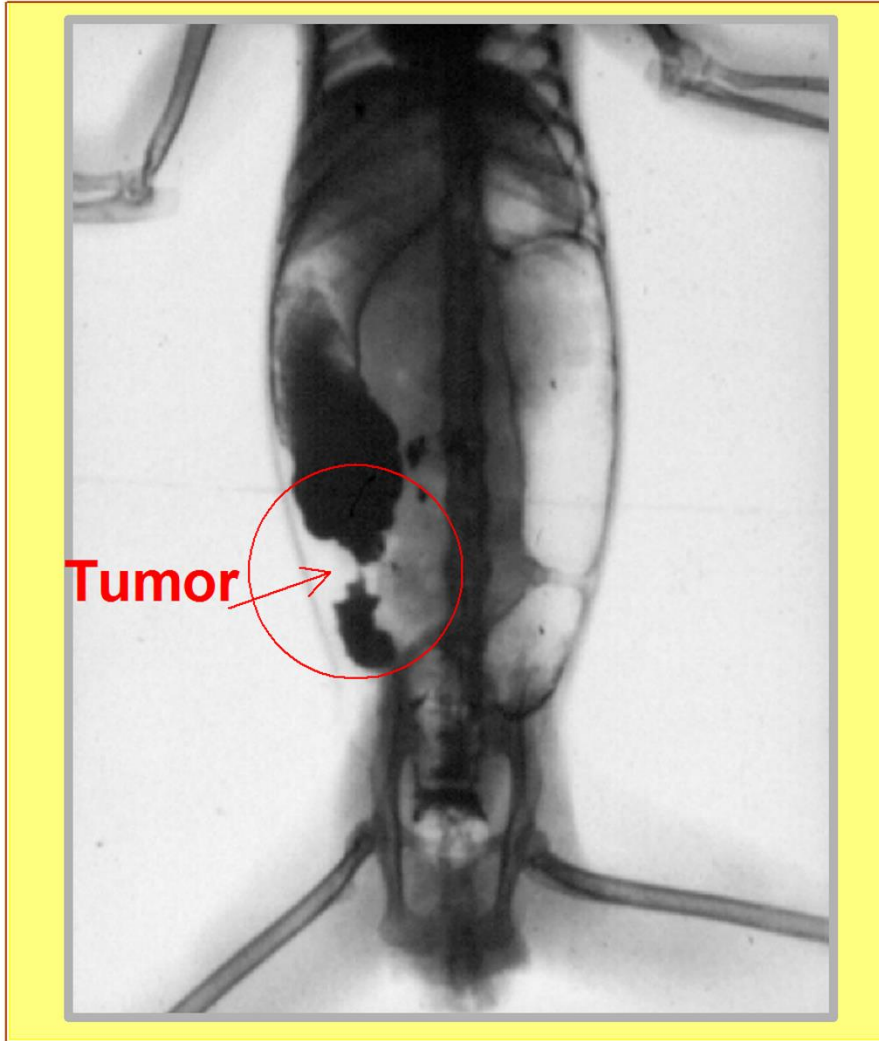


Idiopathic Colitis



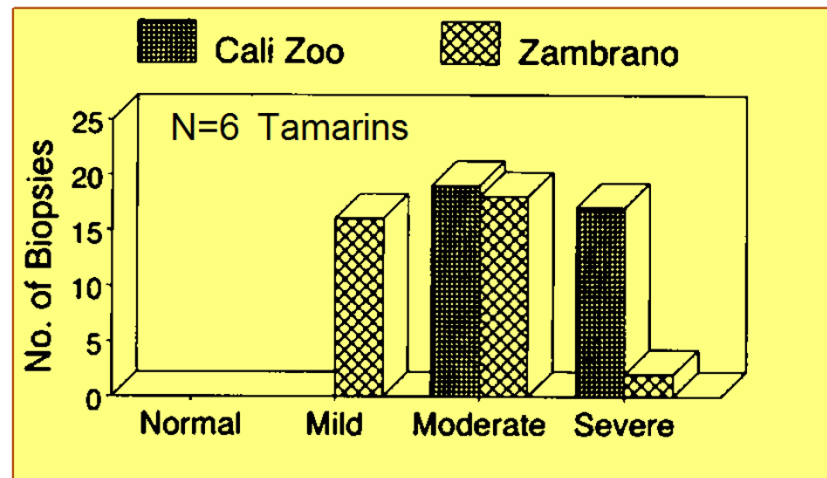
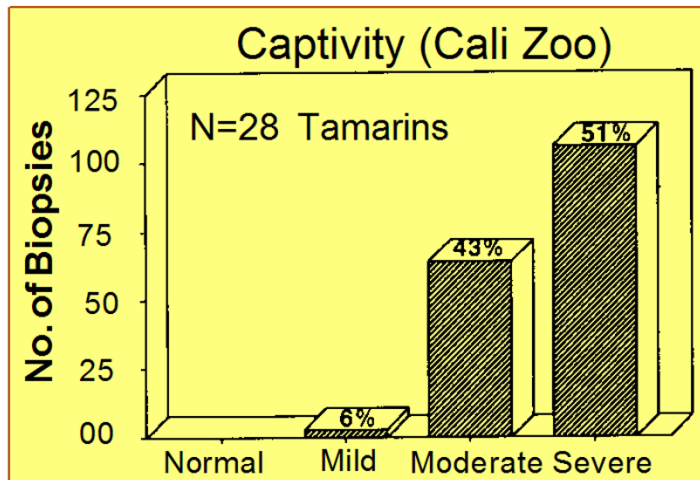
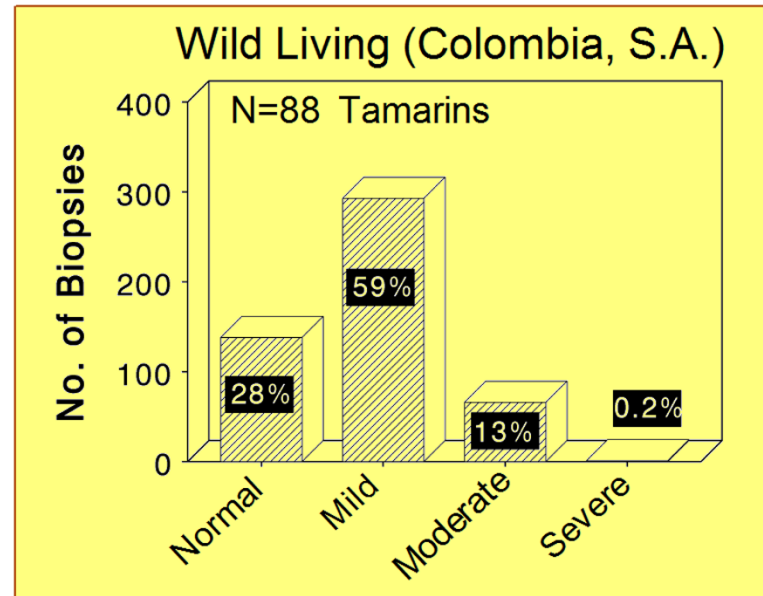
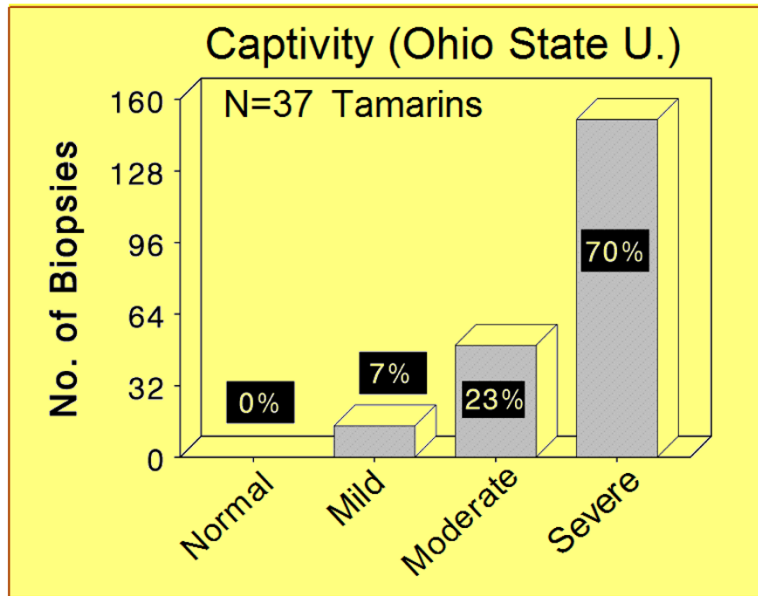
# BRAIN-GUT AXIS IN STRESS

Colon Cancer Associated with Colitis  
in the Cotton-Top Tamarin



# BRAIN-GUT AXIS IN STRESS

## Ulcerative Colitis in Cotton Top Tamarins



# STRESS AND INFLAMMATORY BOWEL DISEASE

Dig Dis Sci. 2000 Feb;45(2):385-93.

**Evidence that colitis is initiated by environmental stress and sustained by fecal factors in the cotton-top tamarin (*Saguinus oedipus*).**

Wood JD<sup>1</sup>, Peck OC, Tefend KS, Stonerook MJ, Caniano DA, Mutabagani KH, Lhoták S, Sharma HM.

# **INFLAMMATORY BOWEL DISEASE (Ulcerative Colitis and Crohn's Disease)**



**Owen C. Peck, M.D.**

# **INFLAMMATORY BOWEL DISEASE (Ulcerative Colitis and Crohn's Disease)**



**Edward Teller (1908 - 2003)**

**(Hungarian - American Theoretical Physicist)**



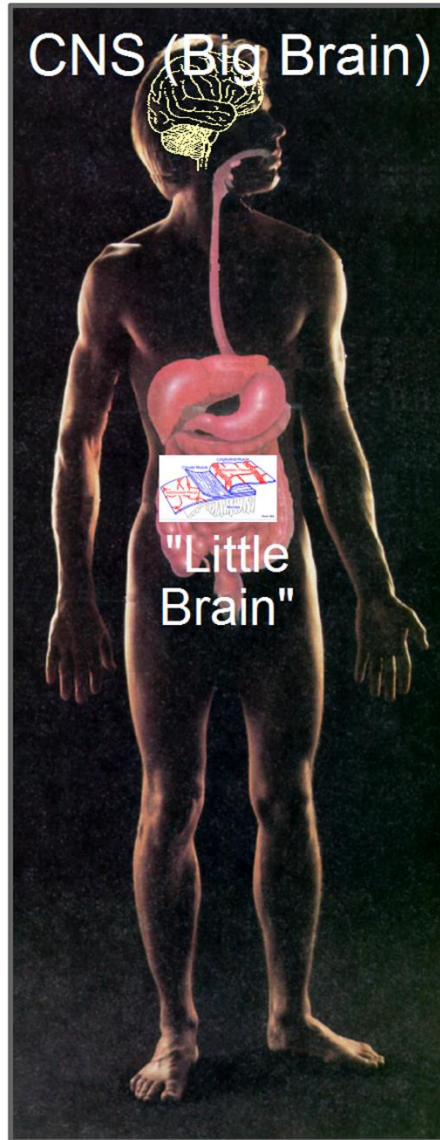
# ENTERIC NERVOUS SYSTEM (ENS) IS A BRAIN-IN-THE-GUT

## ENS (Little Brain)

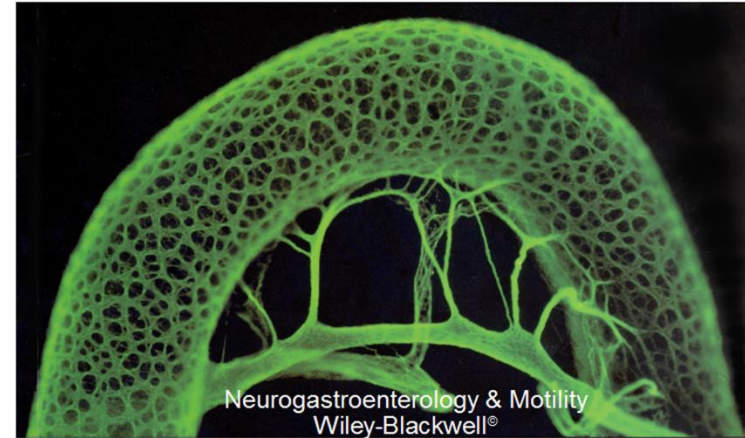
Integrated Neural Circuits

1. Program (App) Library
2. Feedback Control
3. Reflexes
4. Information Processing

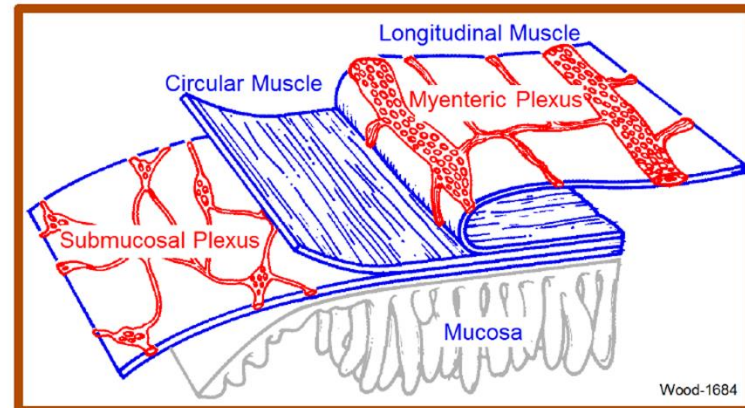
CNS (Big Brain)



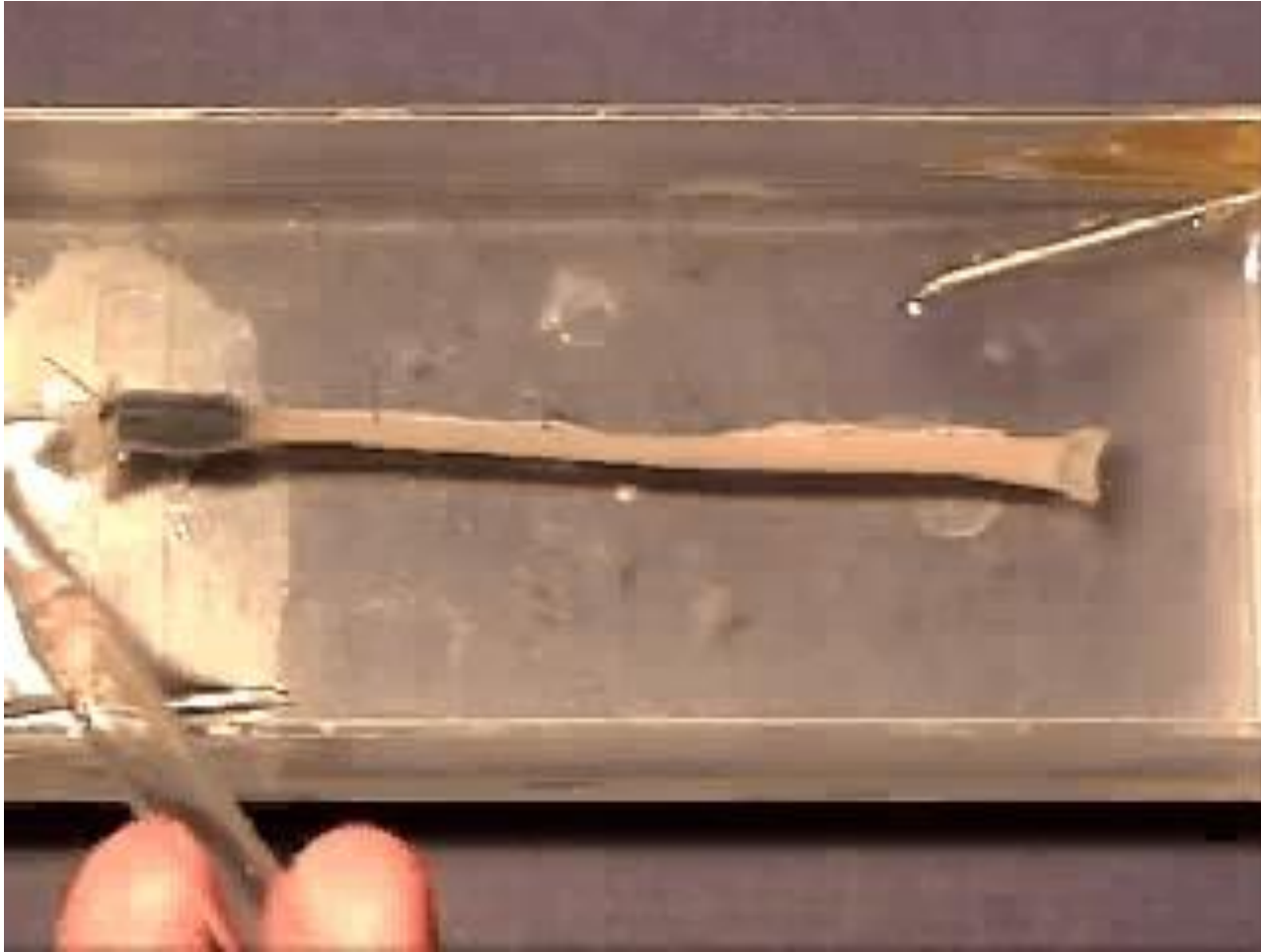
## Brain-In-The-Gut (100 Million Neurons)



## ENS (Little Brain)

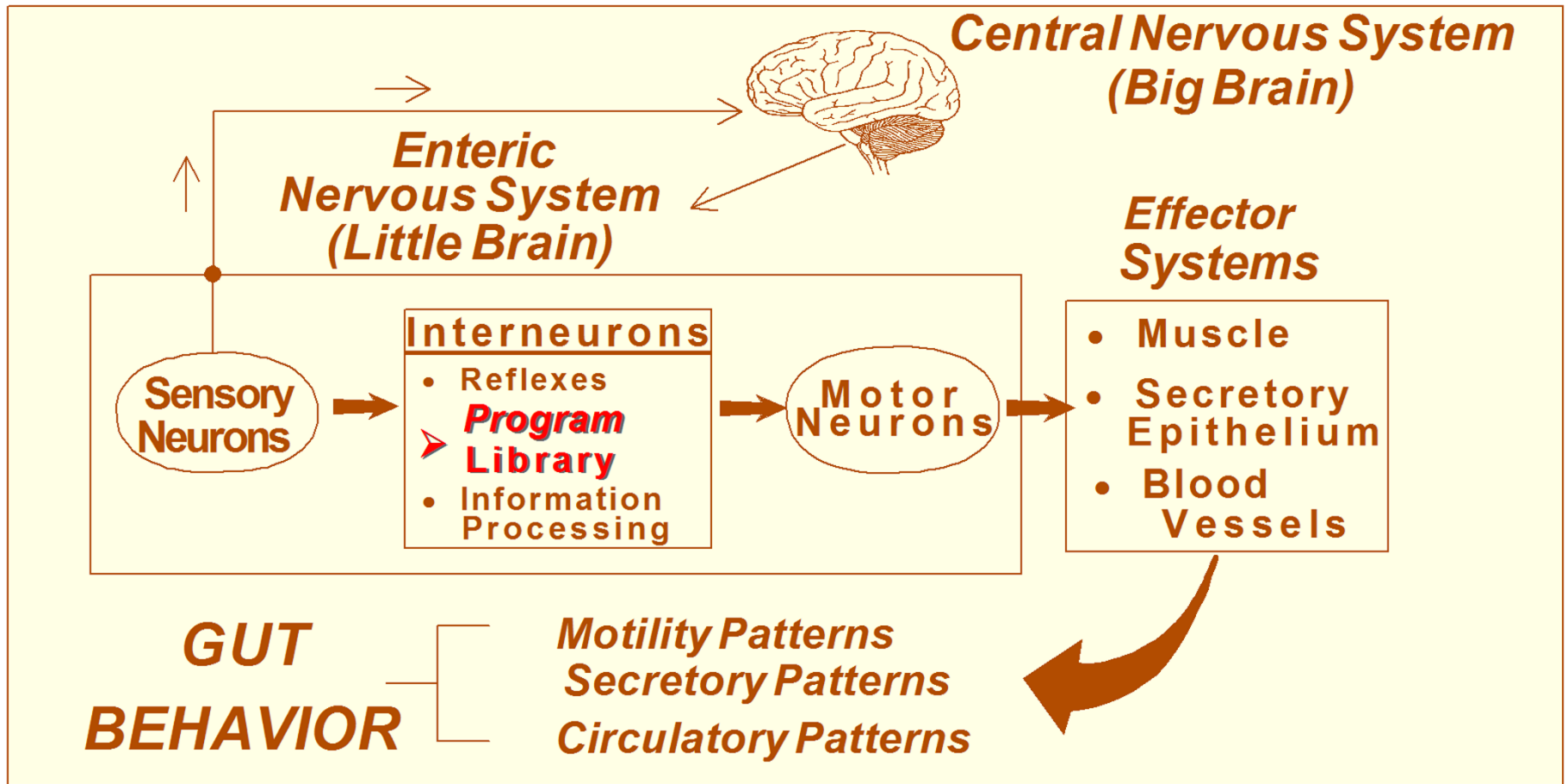


# GUINEA PIG LARGE INTESTINE



# ENTERIC NERVOUS SYSTEM

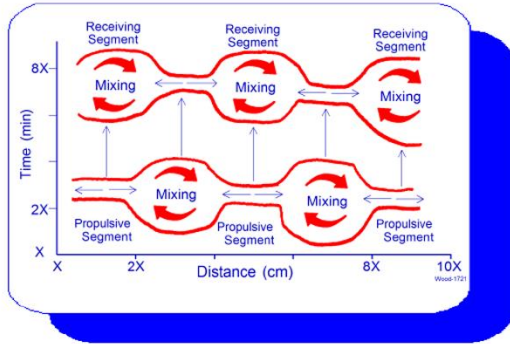
## HEURISTIC MODEL: THE BRAIN-IN-THE-GUT



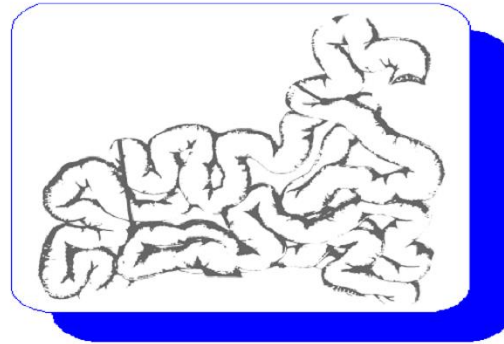
➤ Apps in the ENS library of programs determine gut behavior. Wood-2736

# ENTERIC NERVOUS SYSTEM APPS LIBRARY

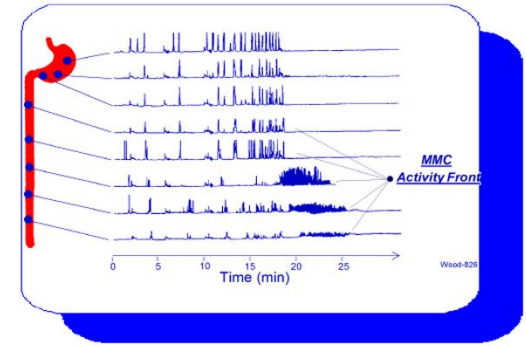
Analog Example: Apps Digital Software Smart Phones/Tablets



Postprandial App  
(Mixing Motility)



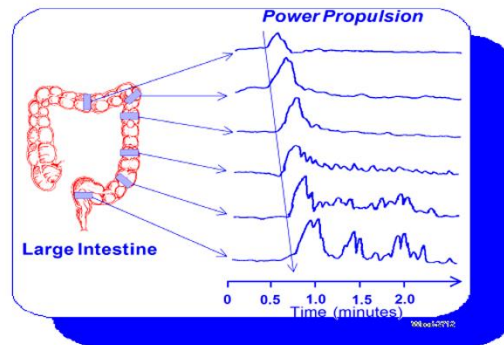
Physiologic Ileus App  
(Absence of Motility)



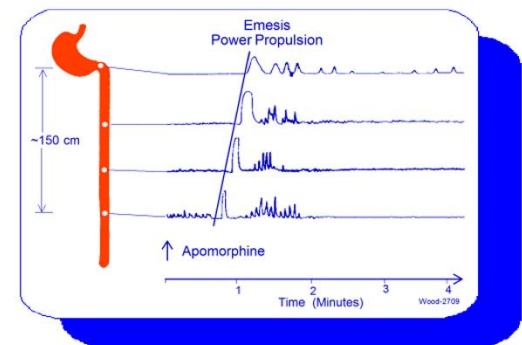
Interdigestive App  
(Migrating Motor Complex)



Haustral App  
(Colon)



Power Propulsion App  
Aboral Direction



Emesis App  
Power Propulsion  
Oral Direction



**CONVERSION  
POSTPRANDIAL APP (MIXING APP)  
TO  
EMESIS APP – POWER PROPULSION**



# PROGRAMMED DEFENSE APP

**"Running" of a *Defense App* Accounts for the Symptoms Cluster of:**  
**1) Abdominal Malaise, 2) Cramping Pain, 3) Fecal Urgency,**  
**4) Acute Watery Diarrhea.**

**Which are Common symptoms in:**

**1) Postprandial IBS**

**2) Food Allergies**

**3) Enteritis**

**a. Infectious**

**b. Radiation - Induced**

**4) Ulcerative Colitis**

**5) Microscopic Colitis**

**6) Crohn's Disease**

**7) Collagenous Colitis**

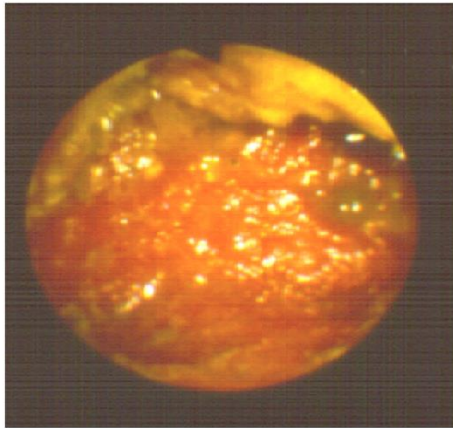
**8) Stress**

# ENTERIC NEUROGENIC PROGRAMMED DEFENSE

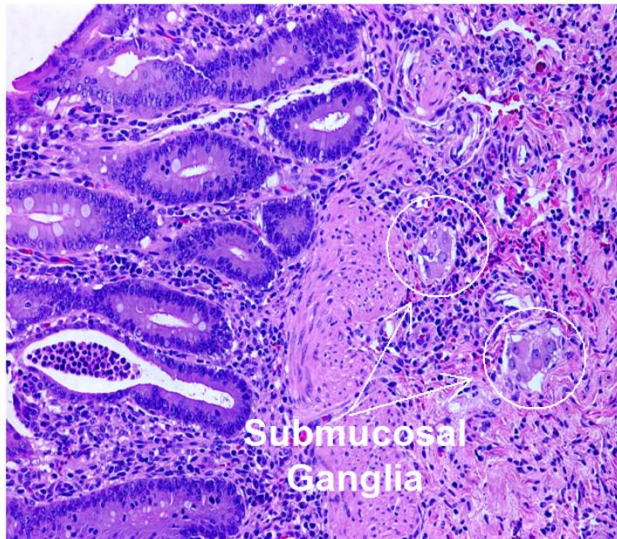
DEGRANULATION OF ENTERIC MAST CELLS  
"CALLS-UP" THE *DEFENSE APP*.

# INFLAMMATION: COLITIS

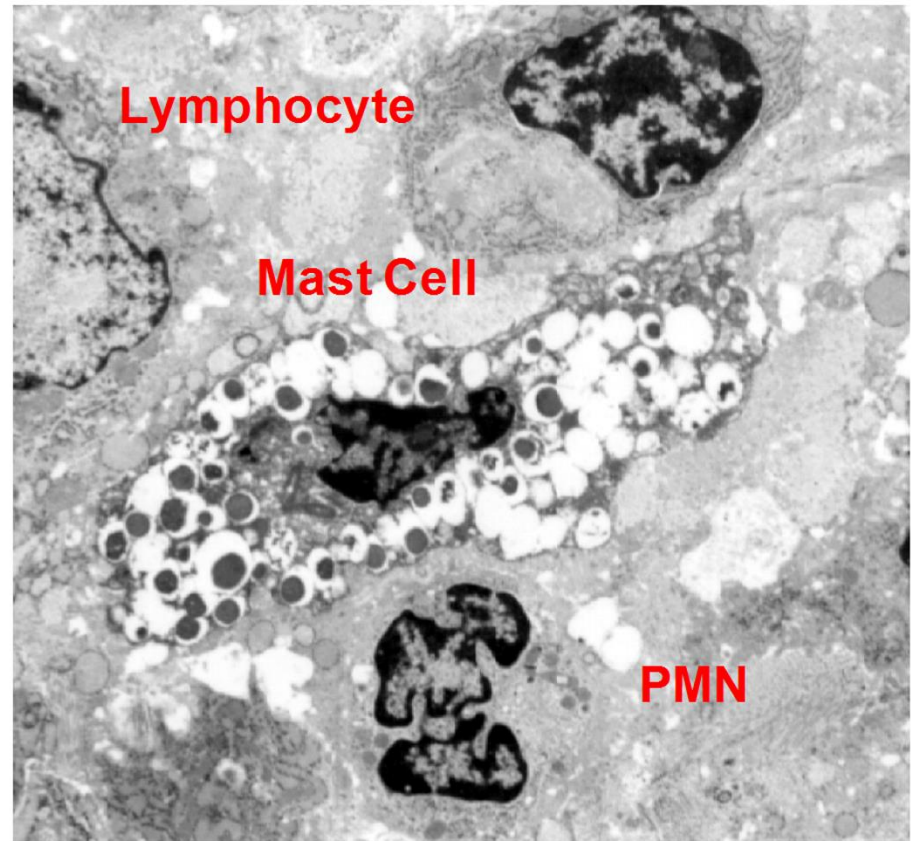
## Cotton-Top Tamarin Model Colitis & Colon Cancer



Endoscopic



Light Microscopic

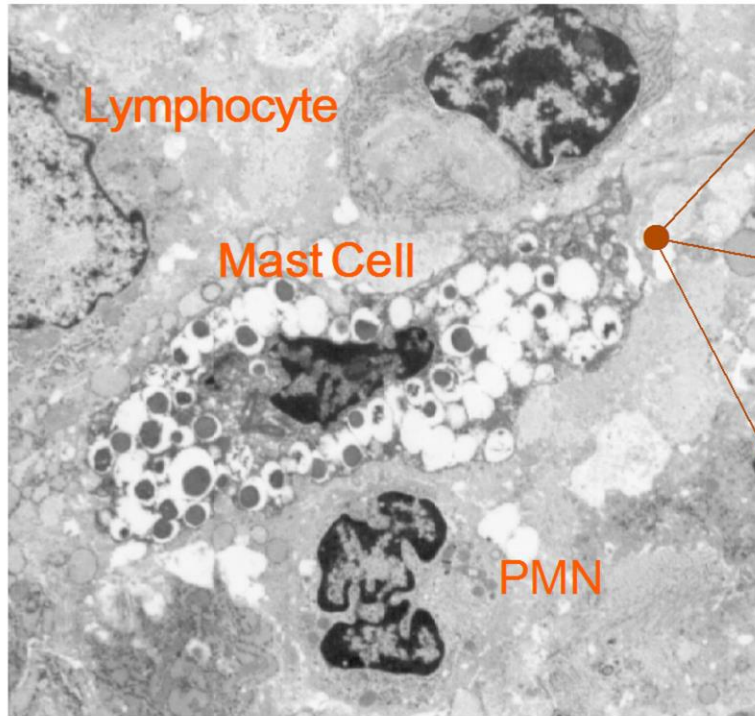


Electron Microscopic



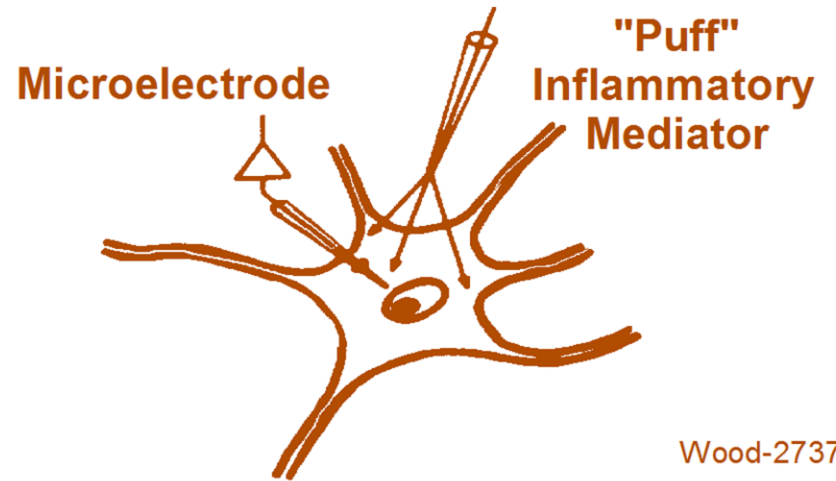
# MAST CELL SIGNALING:

## *Mast Cell Mediators Function as:*

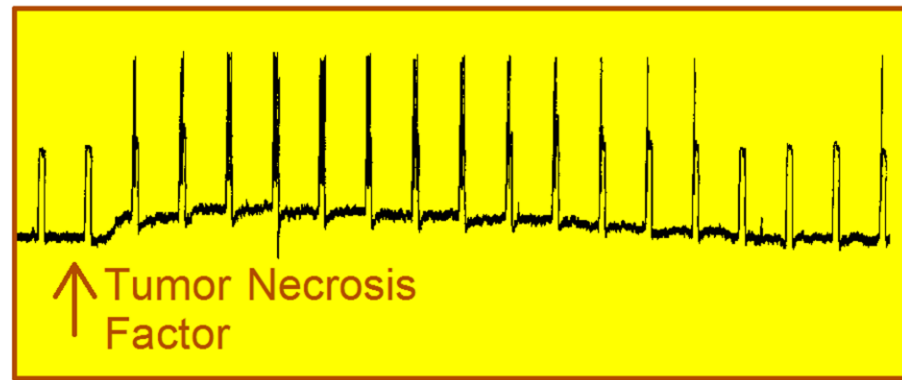


- Chemoattractant Factors for Immune/Inflammatory Cells
- Paracrine Signals to Enteric Nervous System (Brain-In-The-Gut)
- Paracrine Signals to Intramural Sympathetic Postganglionic Nerves

# INFLAMMATORY MEDIATORS EXCITE ENTERIC NEURONS

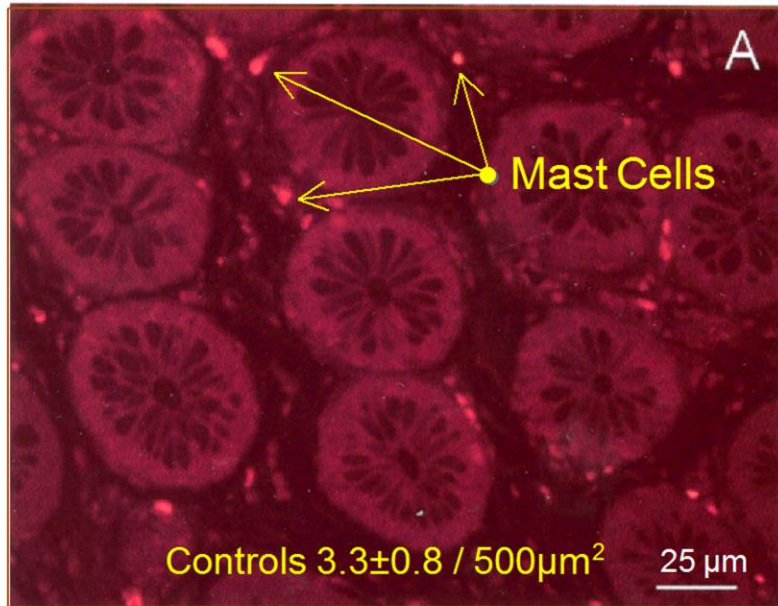


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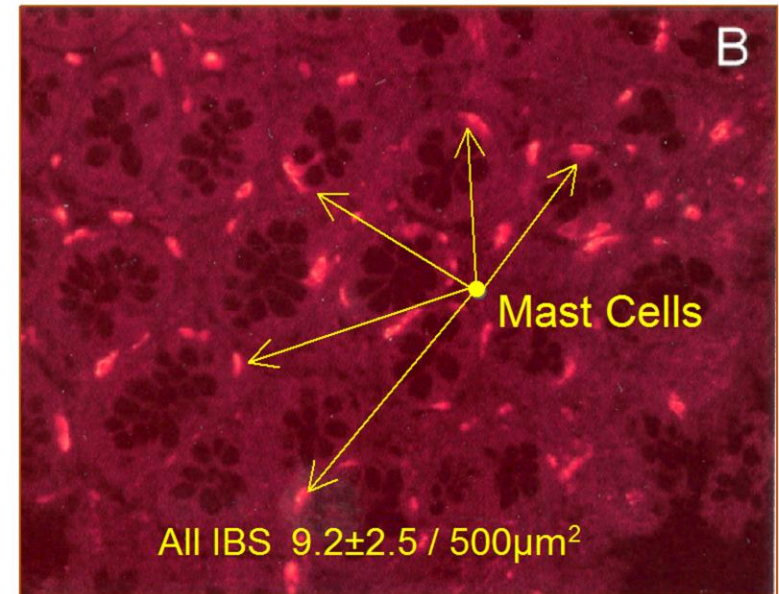


# MAST CELL NUMBERS ARE ELEVATED IN THE DIARRHEA-PREDOMINANT FORM OF IBS

Normal Colon  
Mucosal Biopsy



Irritable Bowel Syndrome  
Mucosal Biopsy



## Immunoreactivity for Mast Cell Tryptase

# ***PROGRAMMED DEFENSE APP:***

## **Case: Food Allergy**

**A 46-year-old medical school professor explains a personal need to be cautious while eating-out in New Orleans, USA because a trace of shrimp in any kind of meal triggers an allergic reaction including abdominal cramping, urgency and acute watery diarrhea.**

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# FOOD ALLERGY MODEL:

## Sensitization to milk



### Milk-Sensitized Guinea-pigs

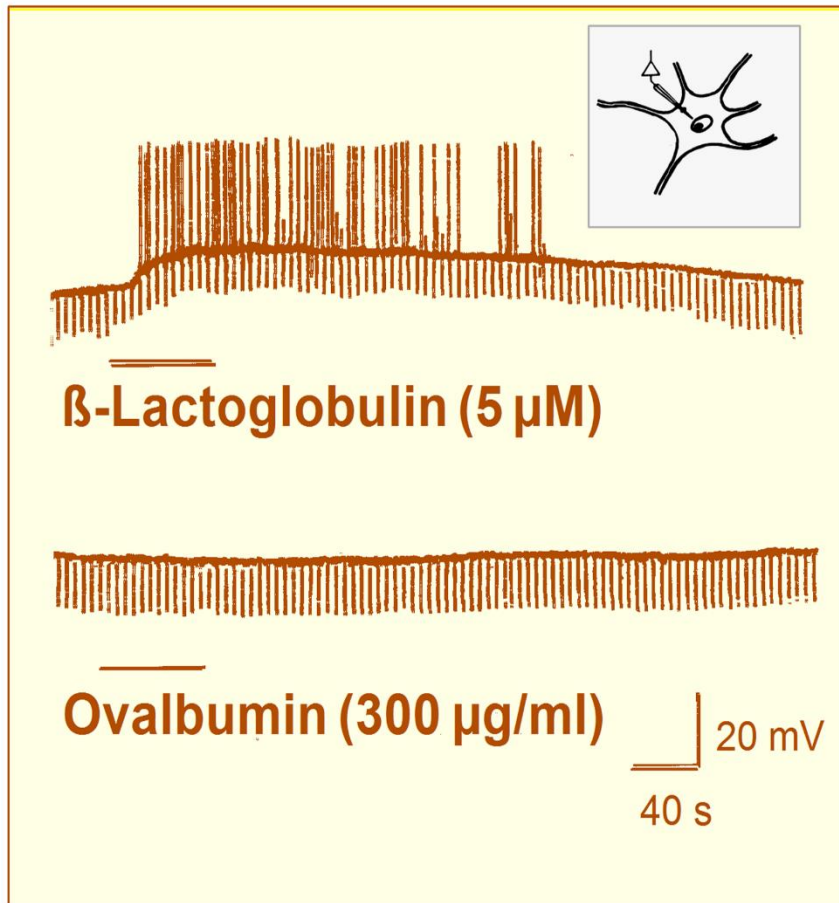
Drink cow's milk in place of H<sub>2</sub>O for 3 weeks.  
Tap H<sub>2</sub>O replaces milk for 1 to 3 days  
before sacrifice and set-up for  
electrophysiologic recording from  
enteric neurons.

### Non-Milk-Sensitized Guinea-pigs

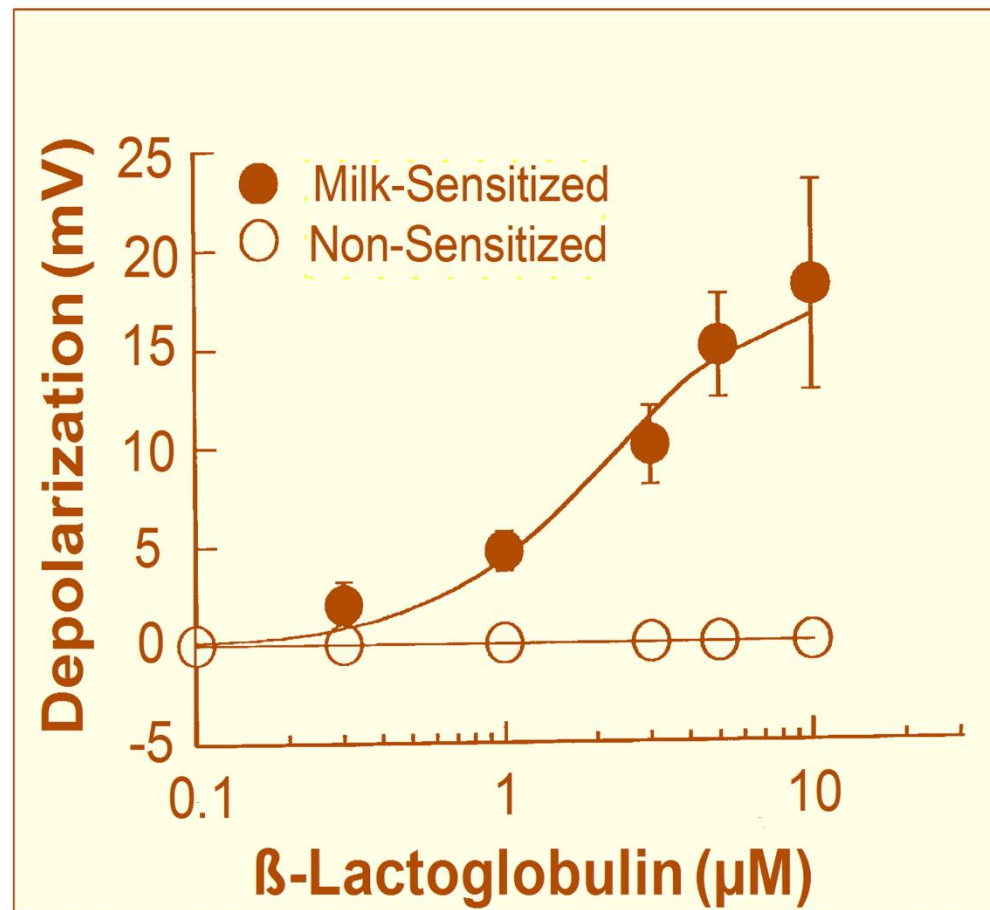
Drank tap H<sub>2</sub>O during 3-week period  
Never exposed to milk.

# ANTIGEN EXPOSURE IN MILK-SENSITIZED SMALL INTESTINE

## Neuronal Electrical Activity

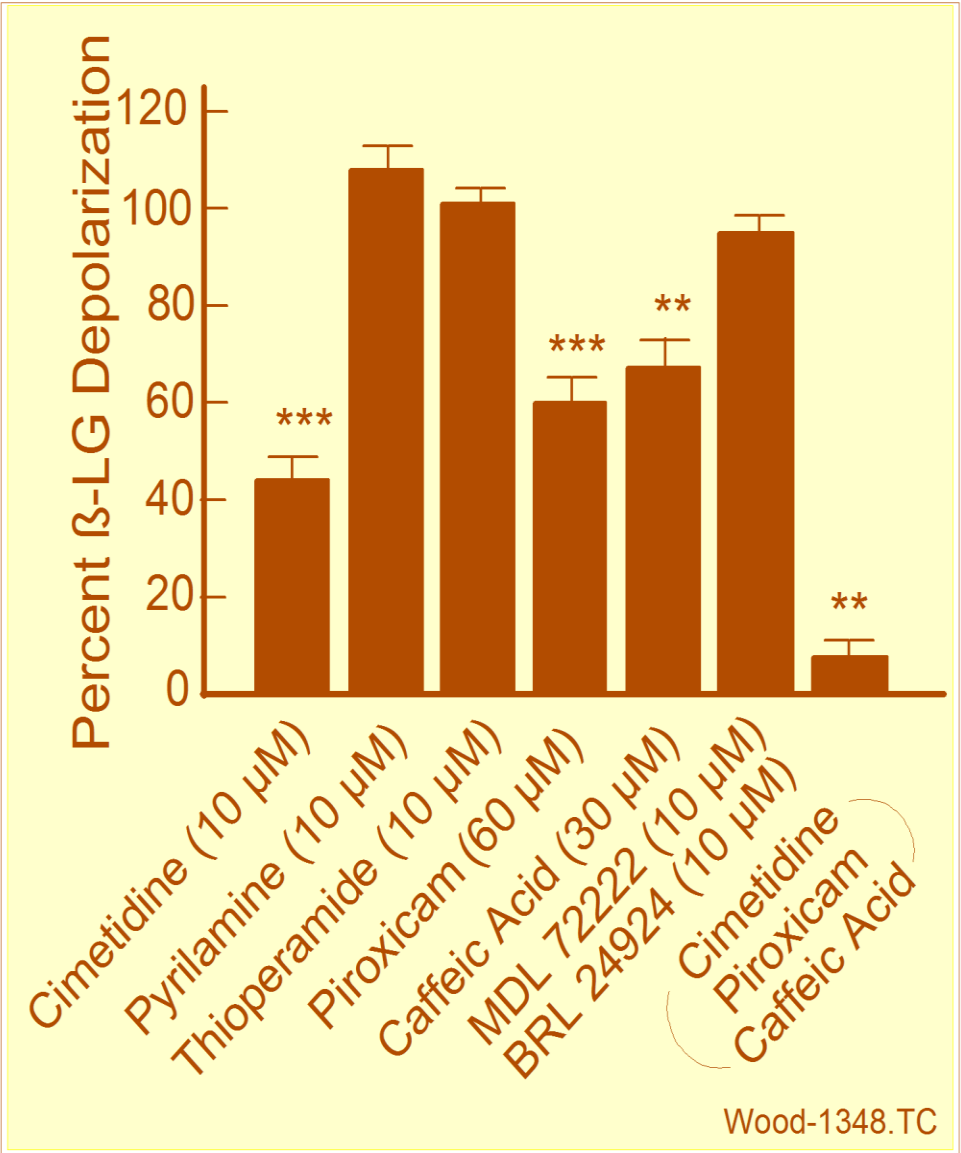
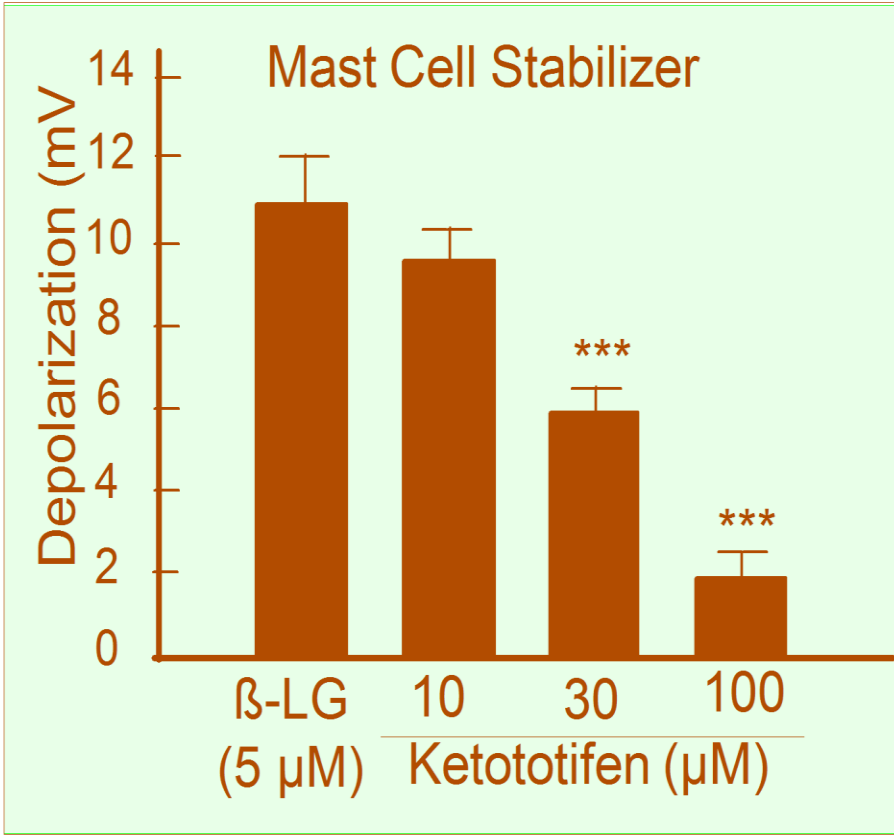


## Results



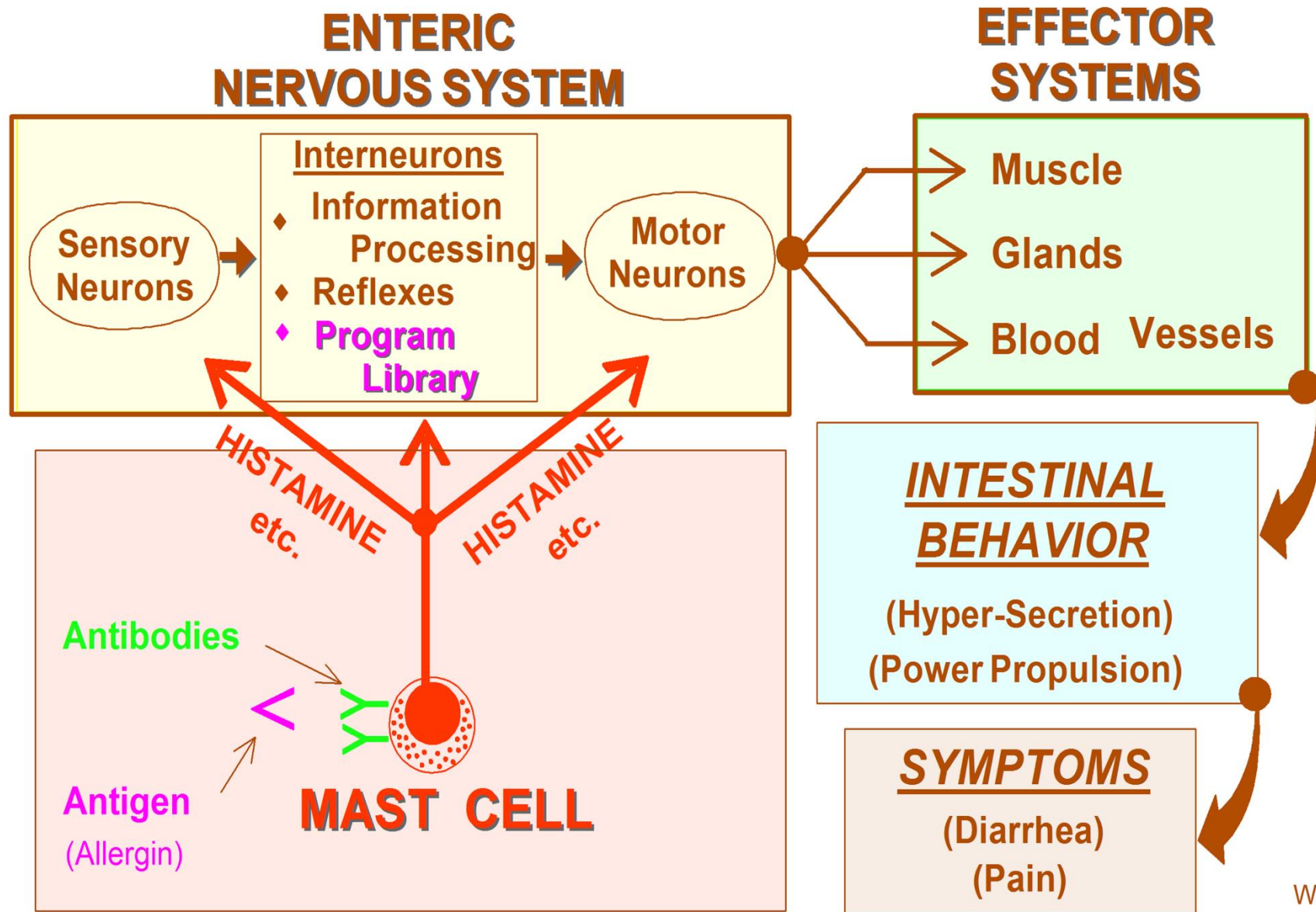
# PHARMACOLOGY:

## MILK-SENSITIZED GUINEA PIG SMALL INTESTINE



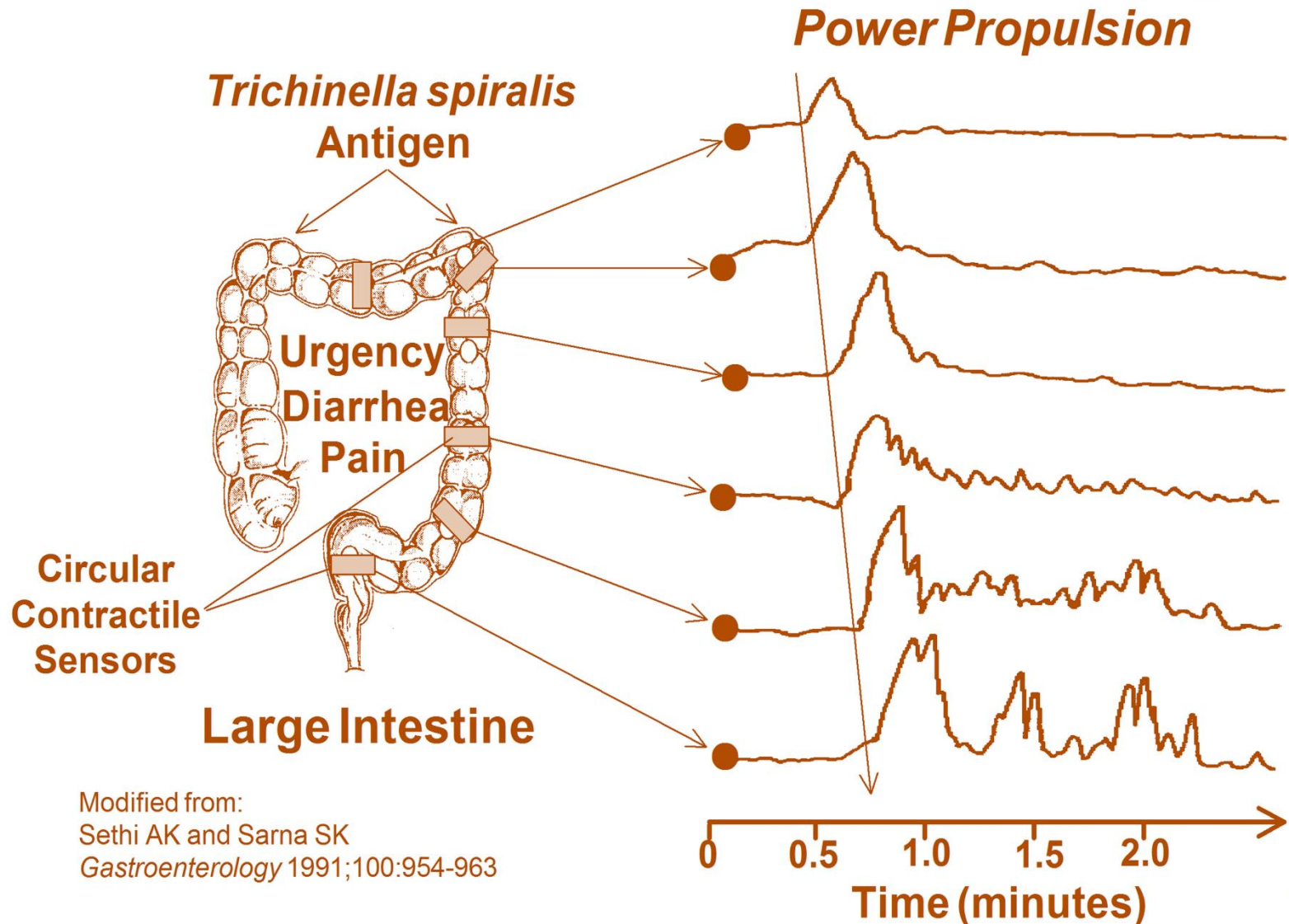
Liu et al. (2003) *Am. J. Physiol.* 284:G154-G164

# ENTERIC IMMUNO-NEURAL COMMUNICATION: FOOD ALLERGY



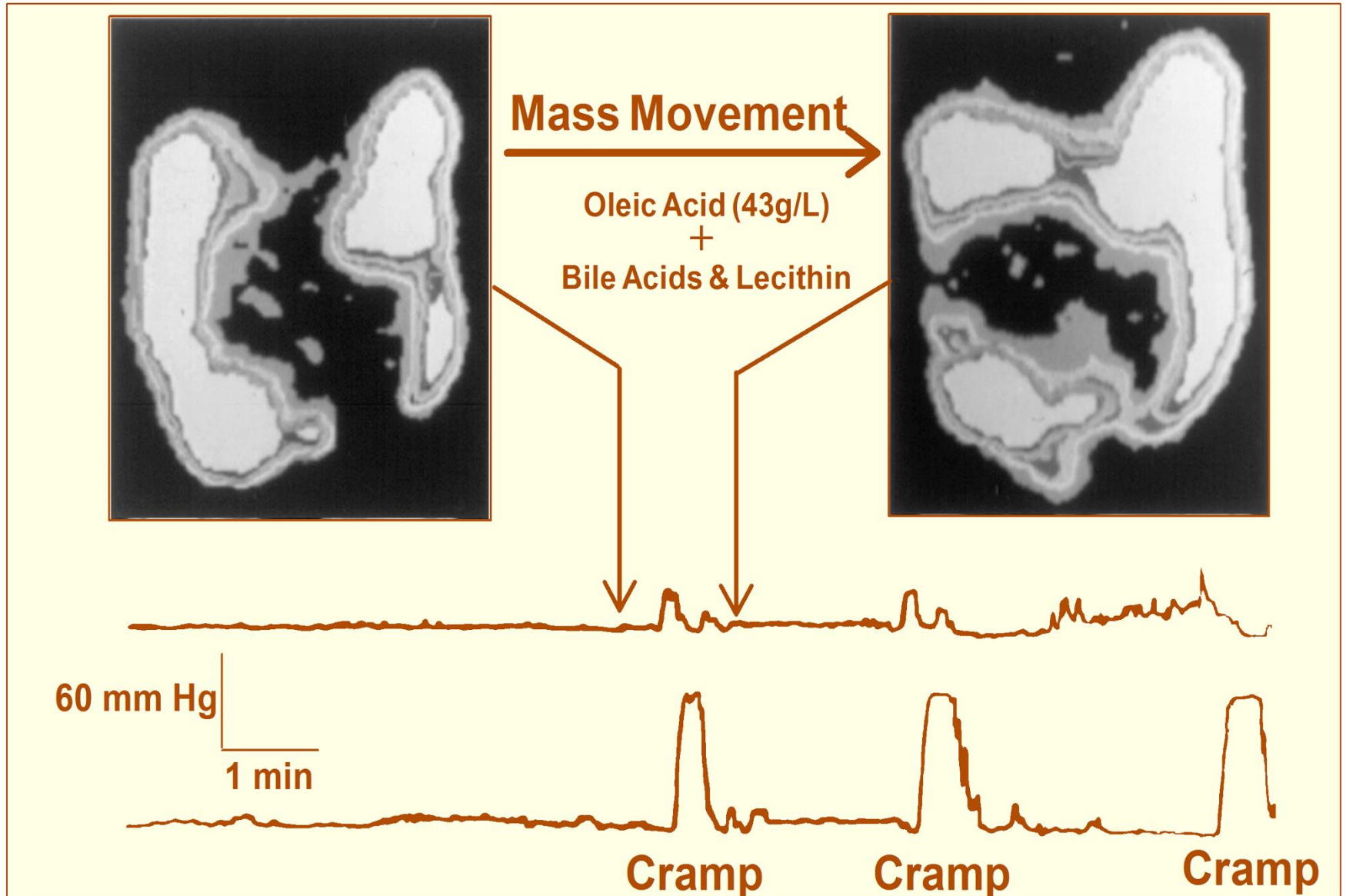


# ENTERIC IMMUNO-NEURAL COMMUNICATION: COMMON SYMPTOM: CRAMPING PAIN



Modified from:  
Sethi AK and Sarna SK  
*Gastroenterology* 1991;100:954-963

# FUNCTIONAL GI DISORDERS: Power Propulsion



## KEY POINTS:

- Ambient stressors are factors in IBD.
- The ENS is an independent brain-in-the-gut.
- "Apps" in an ENS library evoke specific gut behaviors.
- Mast cell signals "call-up" a specific defensive "app".
- Mast cell hyperplasia is a factor in IBS.

## STRESS HYPOTHESIS:

**Mast Cells → ENS → Defense**

## SYMPTOMS

- 
- ```
graph LR; A[Mast Cells → ENS → Defense] --> B[Accelerated Colonic Transit]; A --> C[Fecal Urgency]; A --> D[Diarrhea]; A --> E[Cramping Abdominal Pain];
```
- Accelerated Colonic Transit
  - Fecal Urgency
  - Diarrhea
  - Cramping Abdominal Pain

# Stress and the GI Tract

## The Ohio State University Brain-In-The-Gut Group 2006



## CRF Molecular Biology 2015



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## The Ohio State University Brain-In-The-Gut Group 2010

