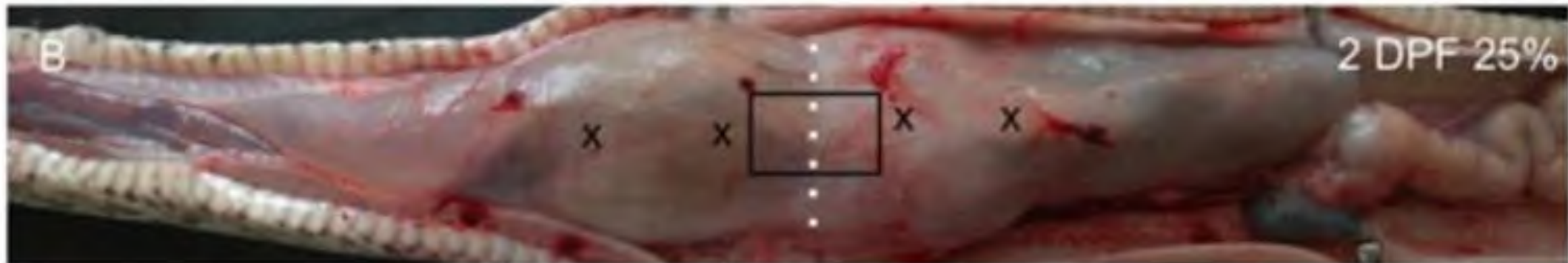
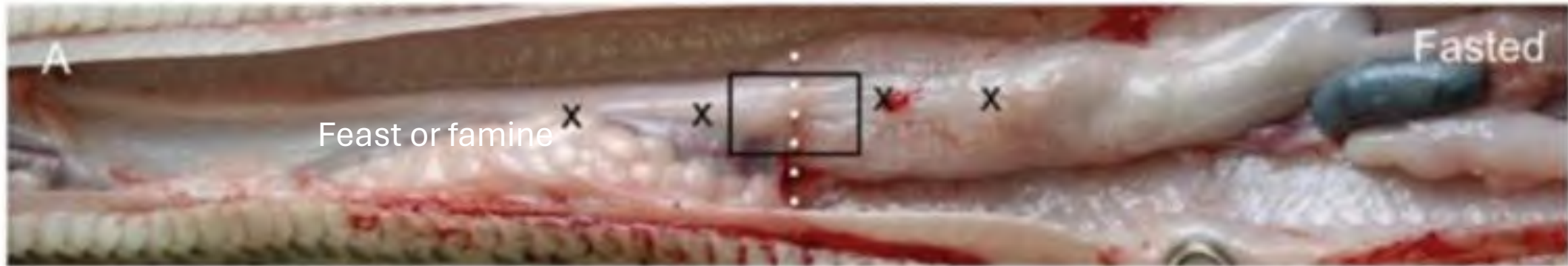
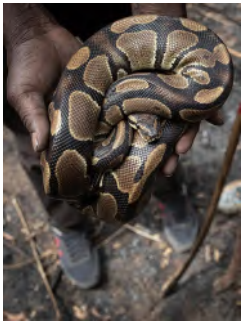


Lessons in Neurogastroenterology from rare disorders

Arun Chaudhury

“Stop and Go”



Stephen Secor

Swallow in this position?

Franz Ingelfinger



Saga of nerve & muscle

Skeletal Muscle

Squeeze
Squirt "IN"

S
M
O
O
T
H

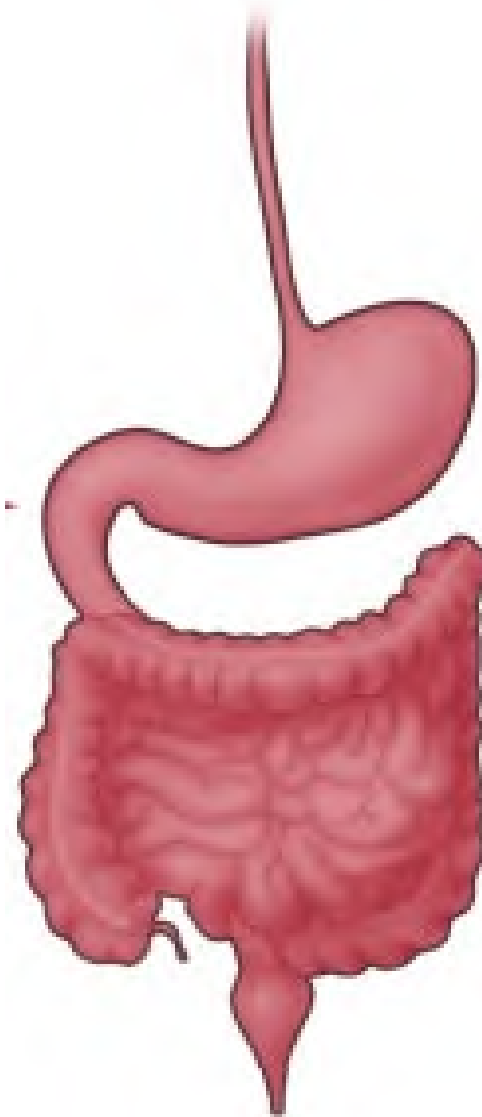
M
U
S
C
L
E

A
C
C
O
M
M
O
D
A
T
E

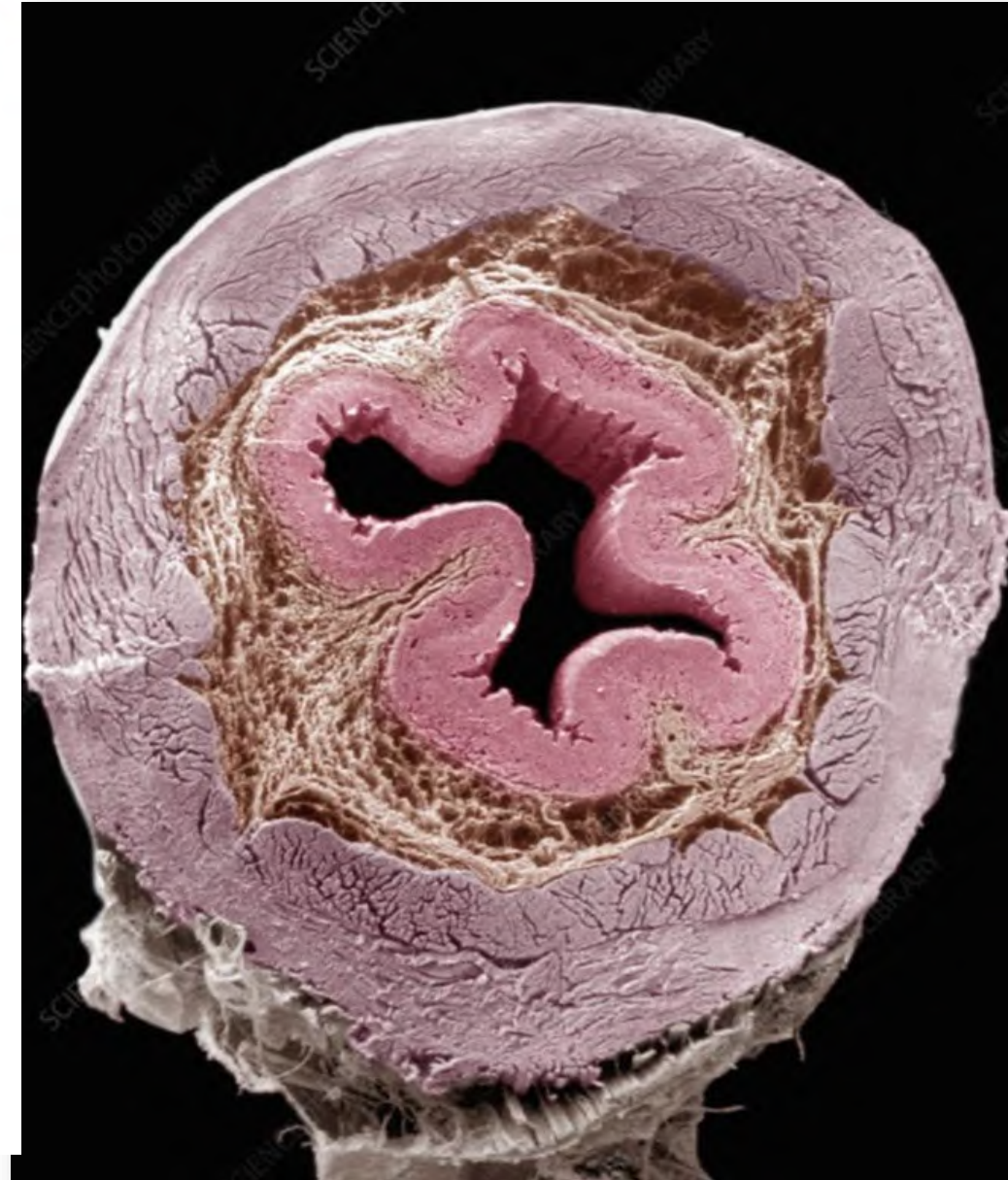
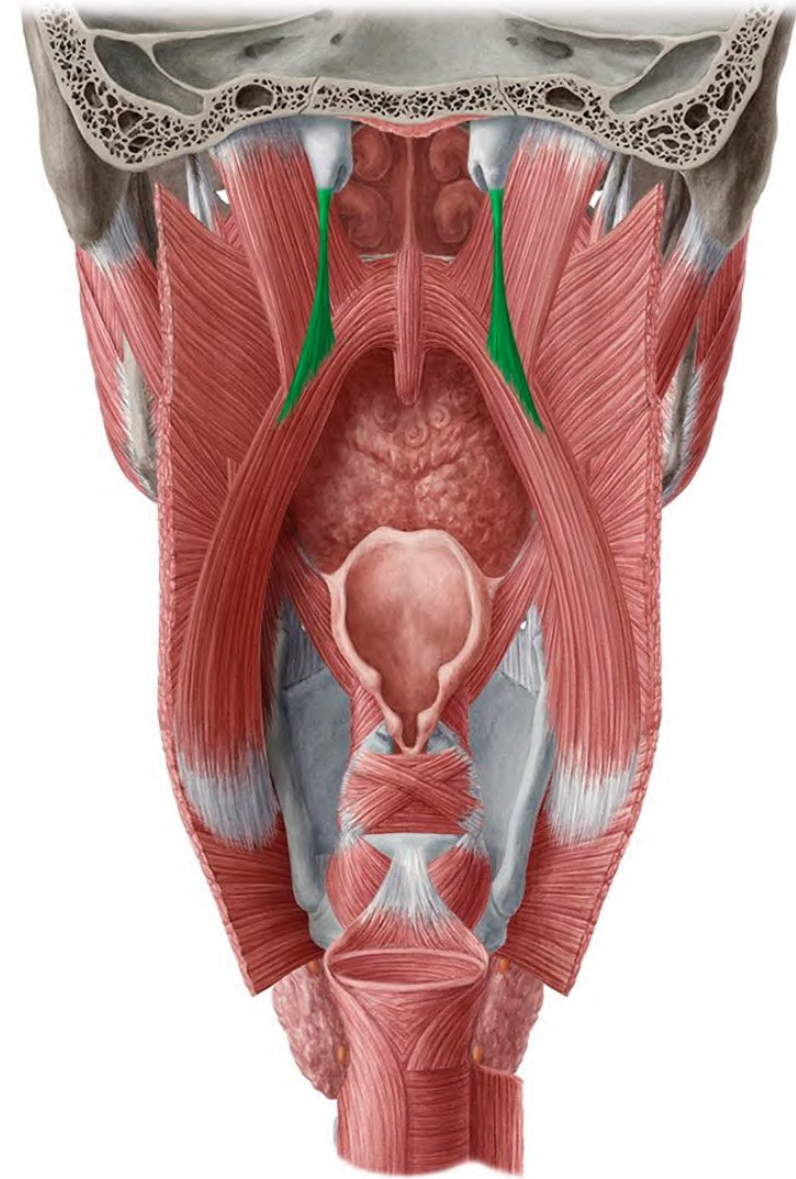
30Hz

Skeletal Muscle

Squeeze
Squirt "OUT"



Esophagus: Plump muscular tube



Upper esophagus & dysphagia

UMN

ALS
Polio
SMA
GBS
Stroke
Neurosarcoid



Gunther von Hagen

NSkMJ disorder

MG
Lambert Eaton

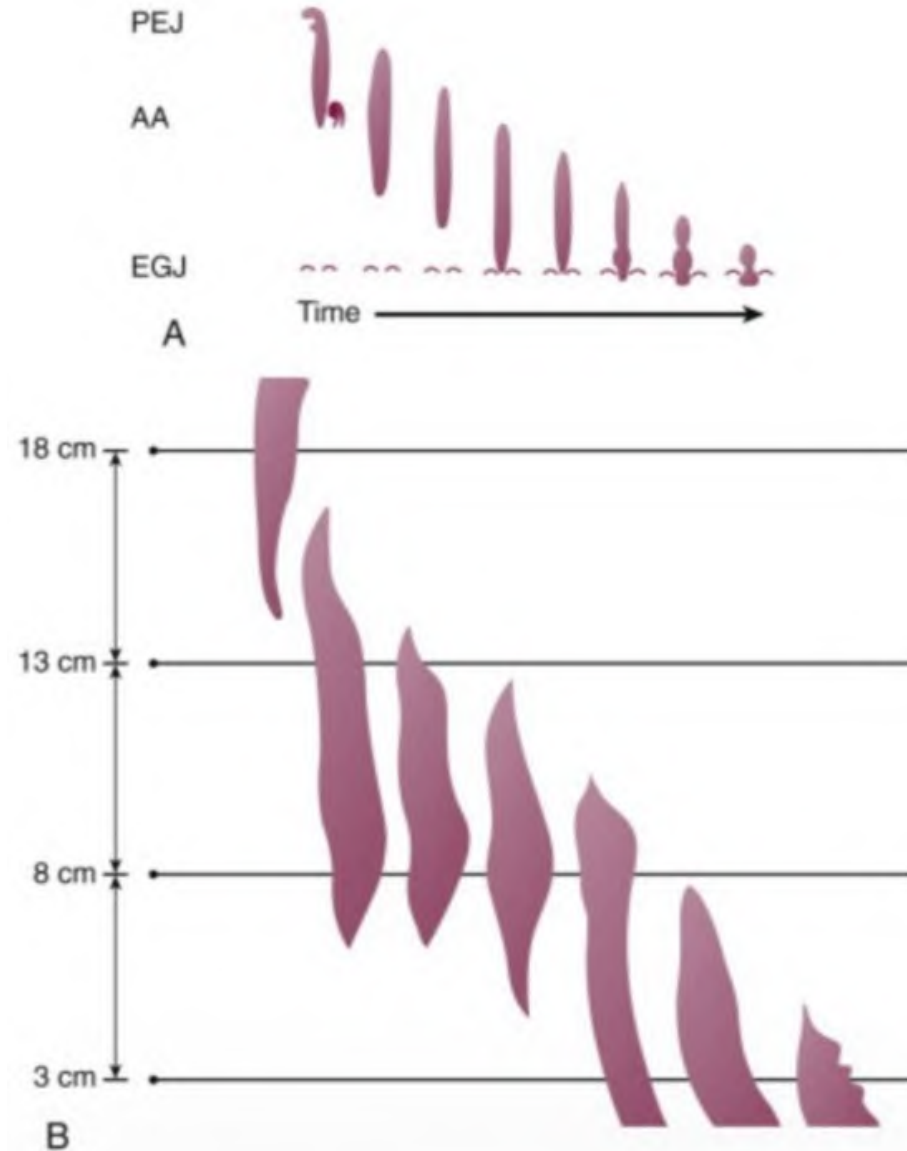


Skeletal Myopathy

DM
Polymyositis
MCTD
Myotonic dystrophy
Oculopharyngeal dystrophy
Duchenne
Pompe
Mitochondriopathy

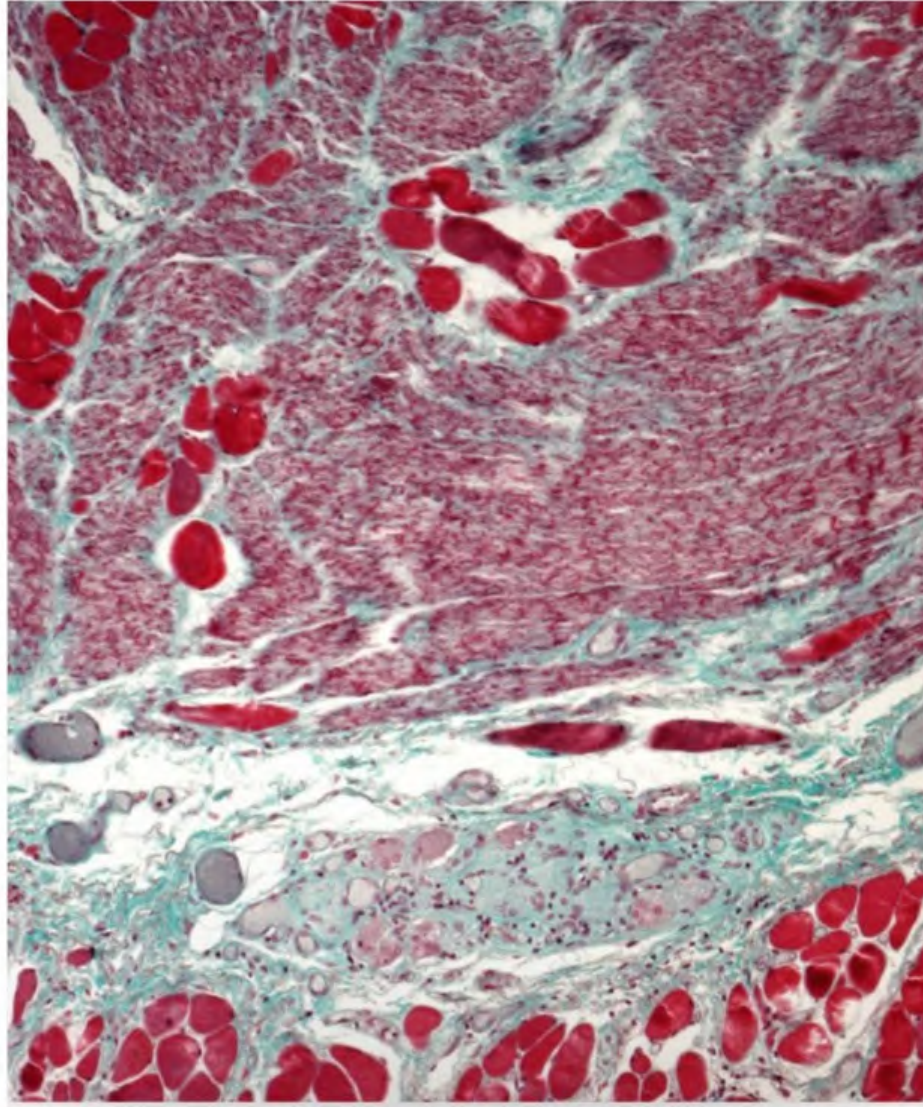
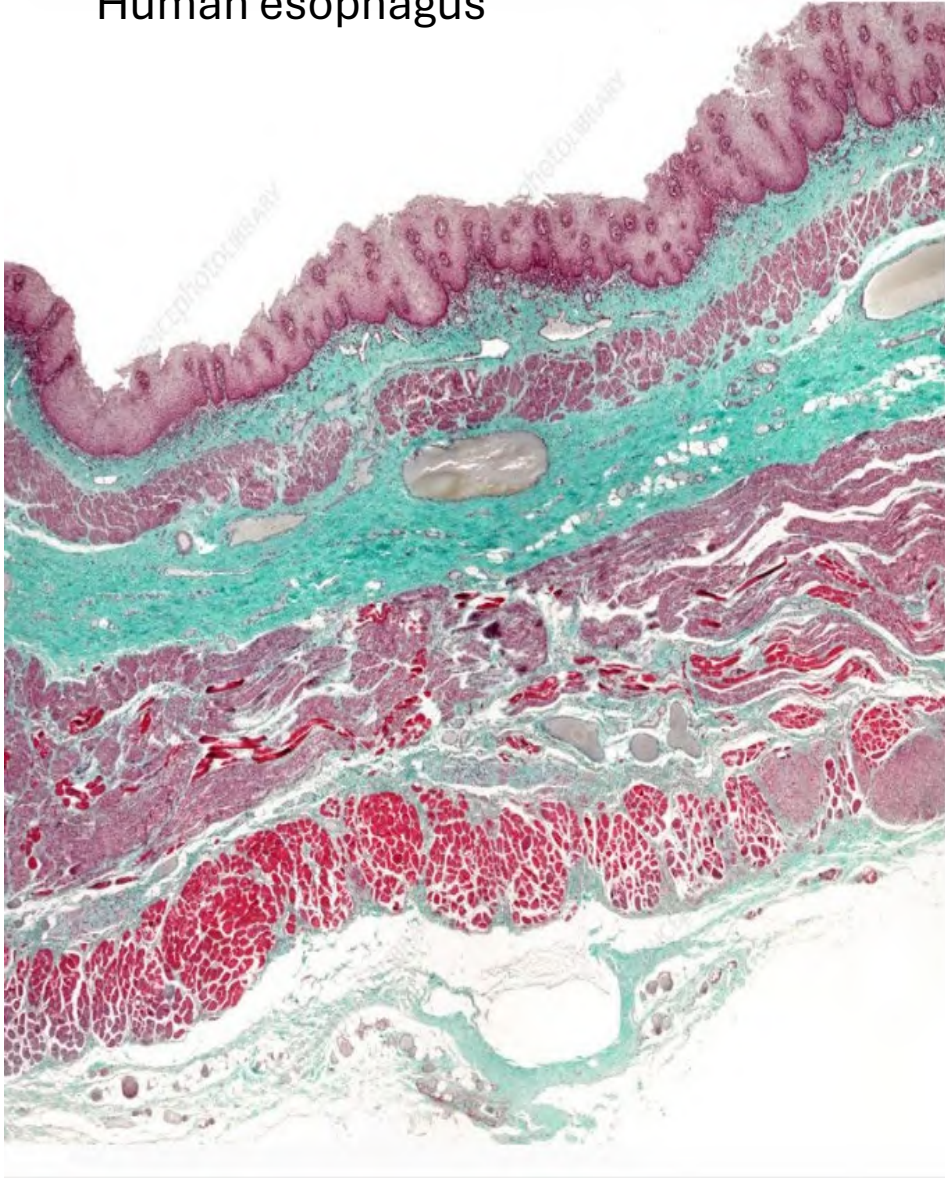
Esophagus relaxes to accommodate

Latency gradient

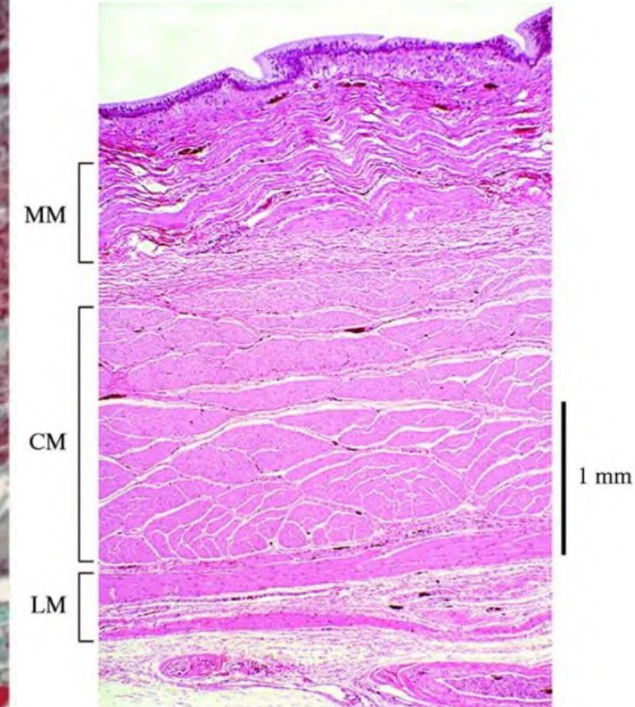


A rich “sandwich”

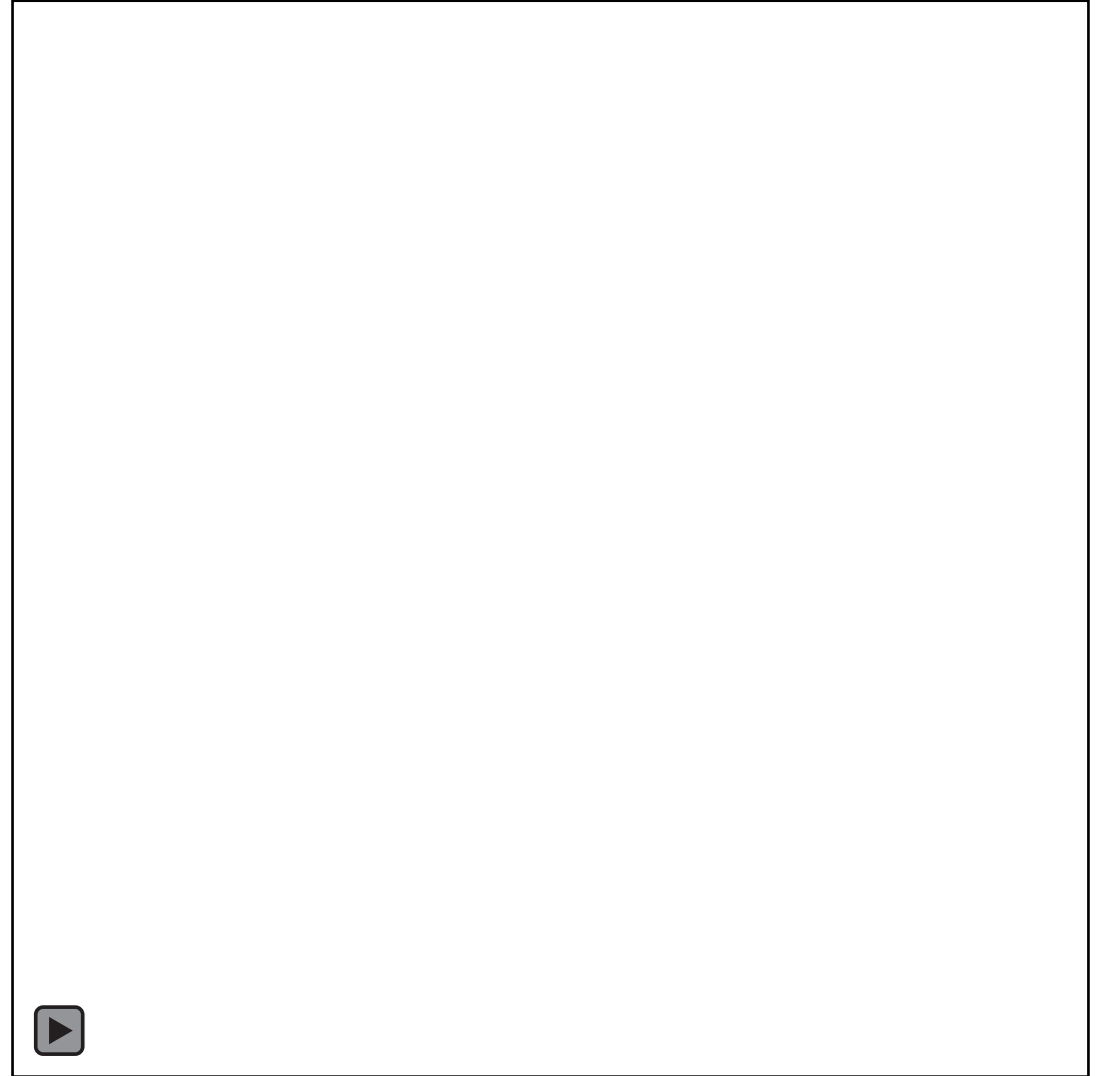
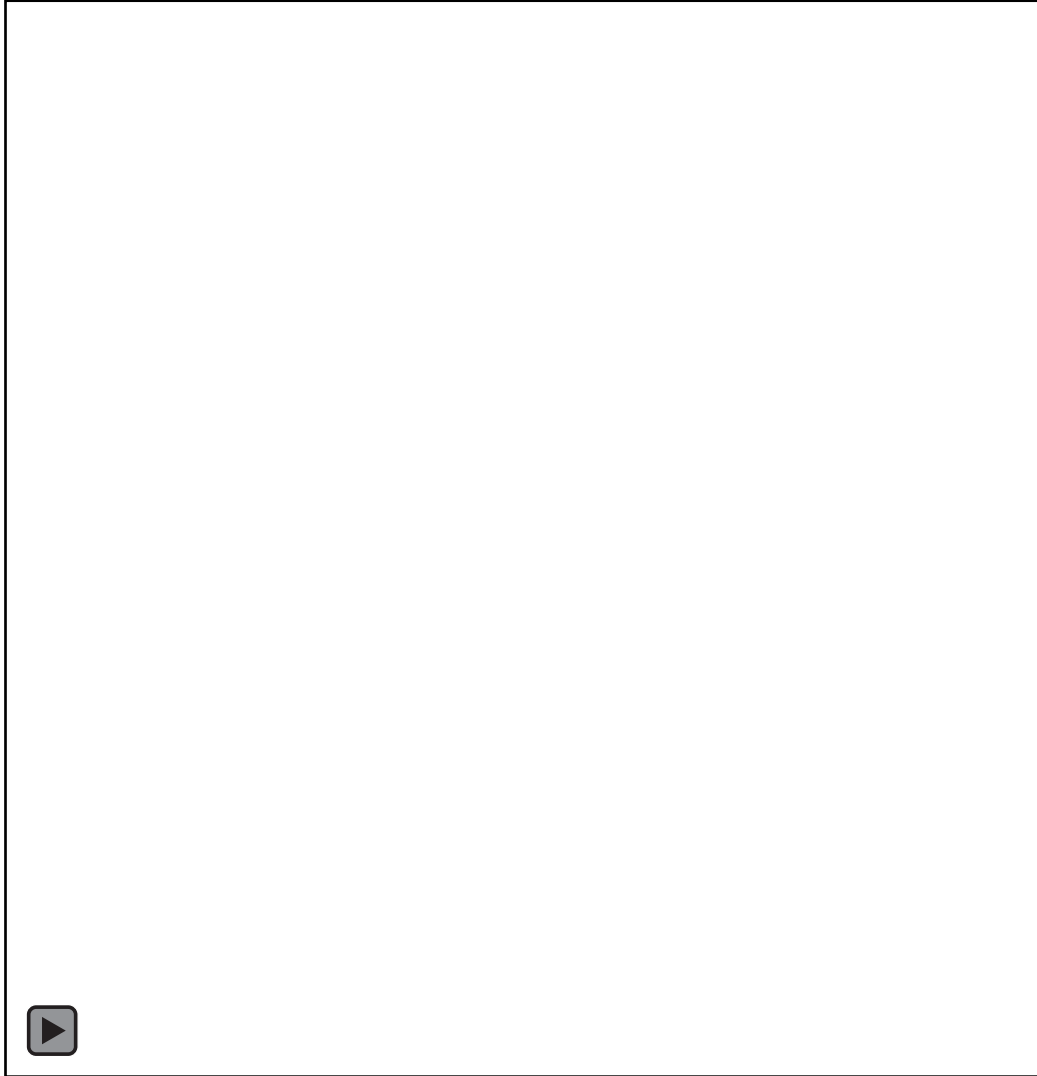
Human esophagus



Crocodile esophagus

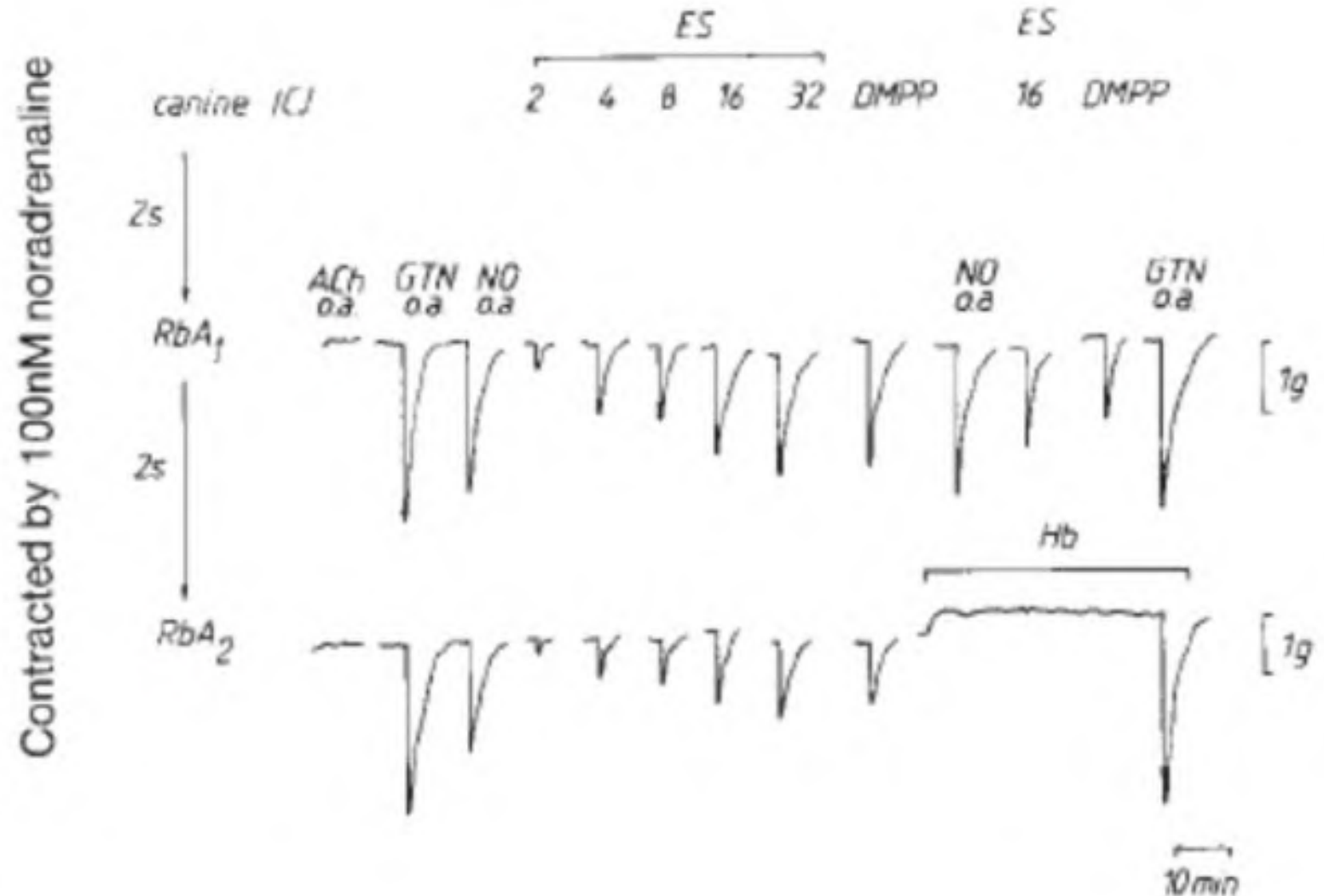


The symphonic orchestrator: Enteric Nervous System



Preliminary evidence of nitric oxide as a gut smooth muscle relaxant

Superfusion assay
John Vane



Bult et al 1990

Nitroergic Neuro-Smooth Muscle Junctions



L-arginine

Neuronal nitric oxide
synthase (nNOS)

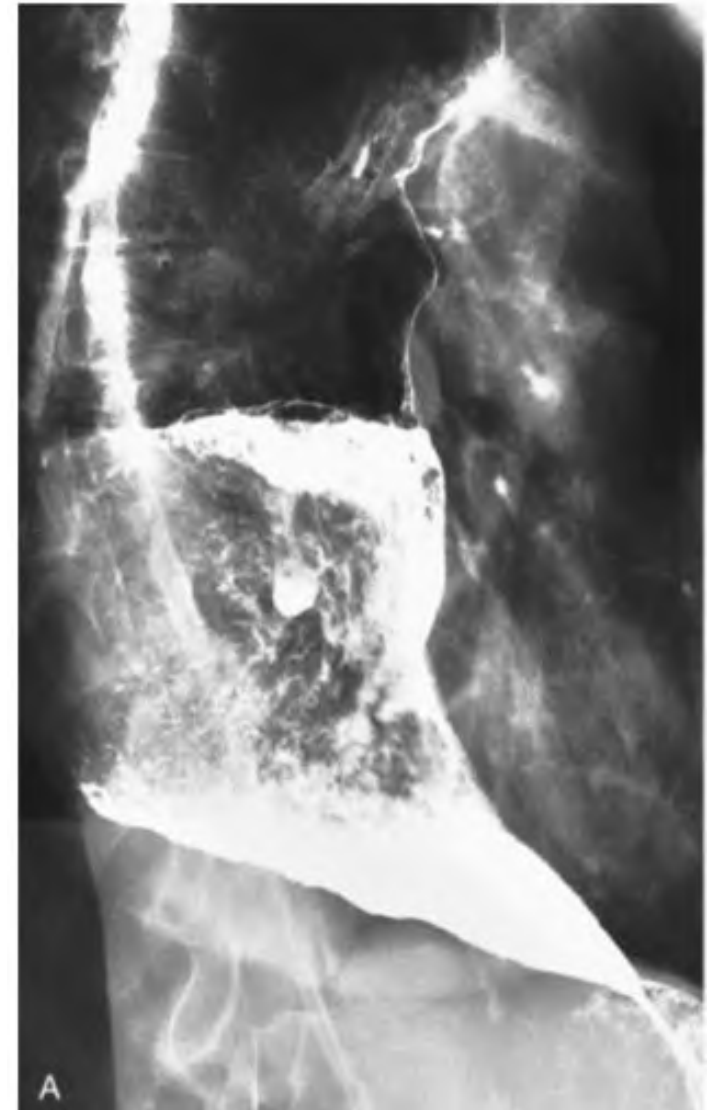
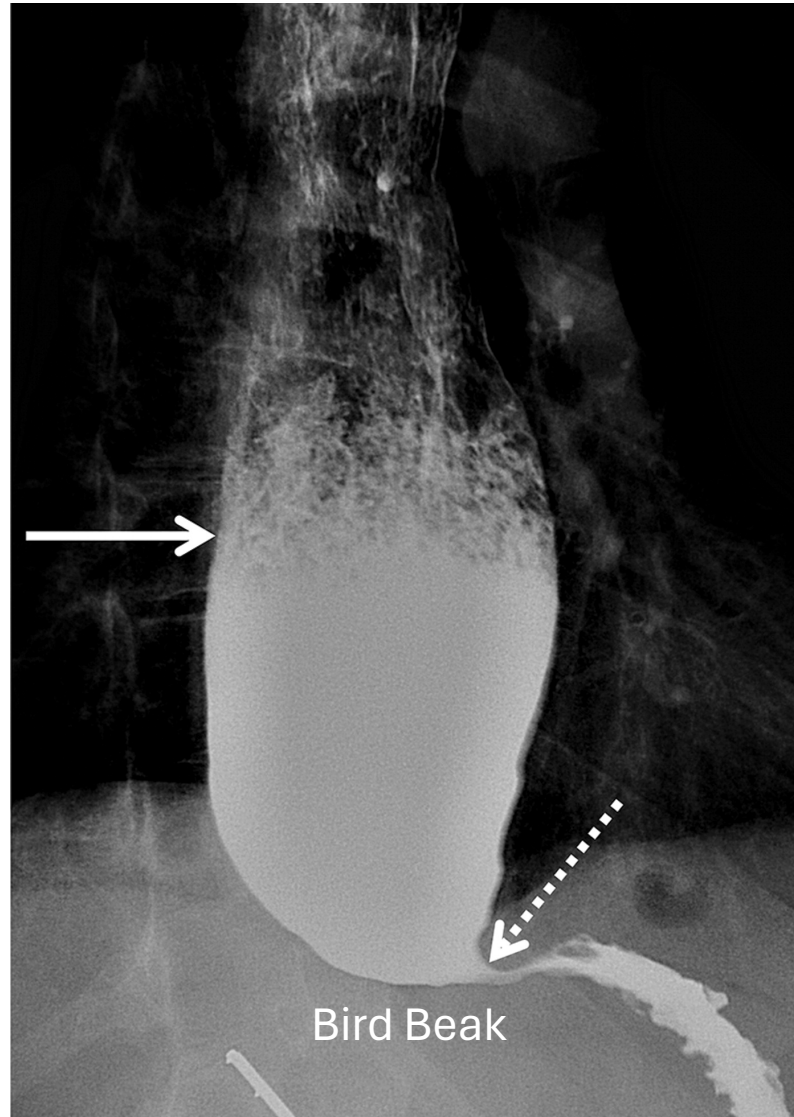
L-citrulline

NO

Chaudhury et al 2014

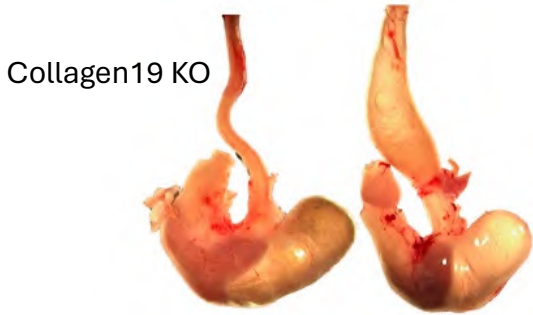
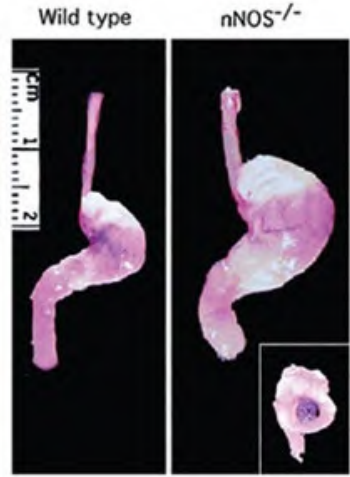
Αχαλασία

Failure to relax

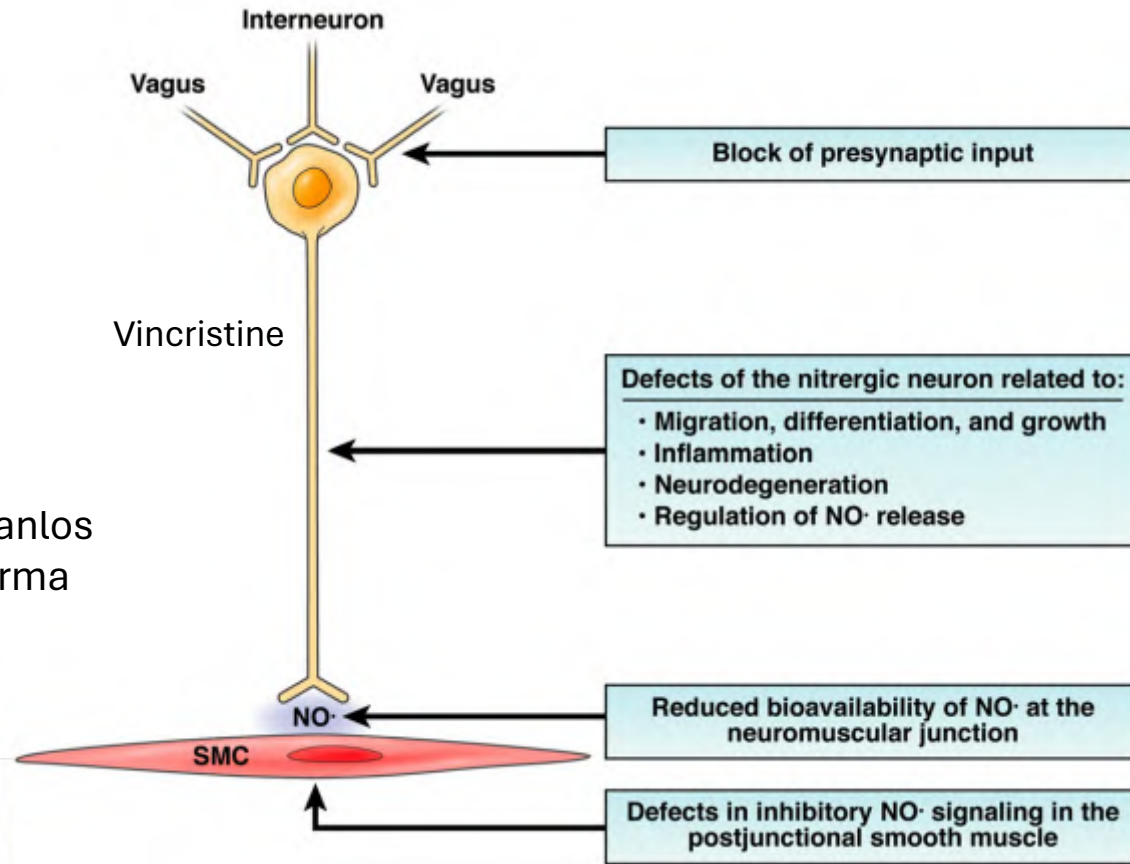


Nehra et al 2022

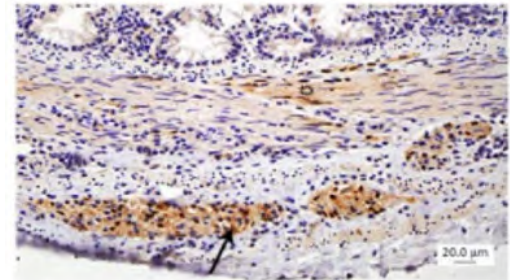
Prejunctional, junctional & postjunctional defects in nitrenergic neurotransmission



Crouzon
Ehlers-Danlos
Scleroderma

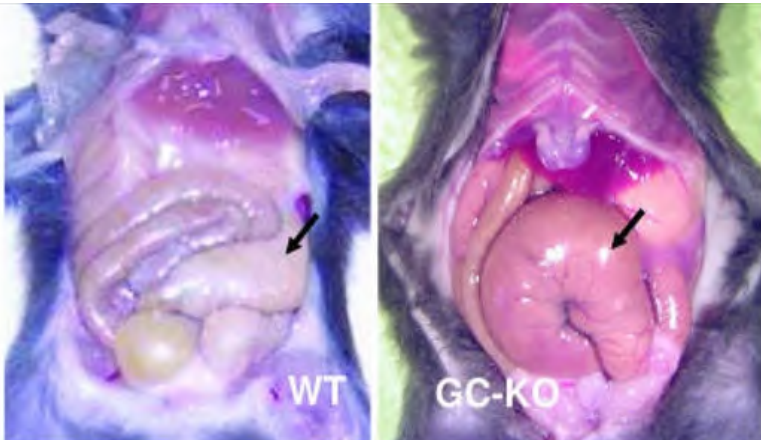


Proventricular dilation disease



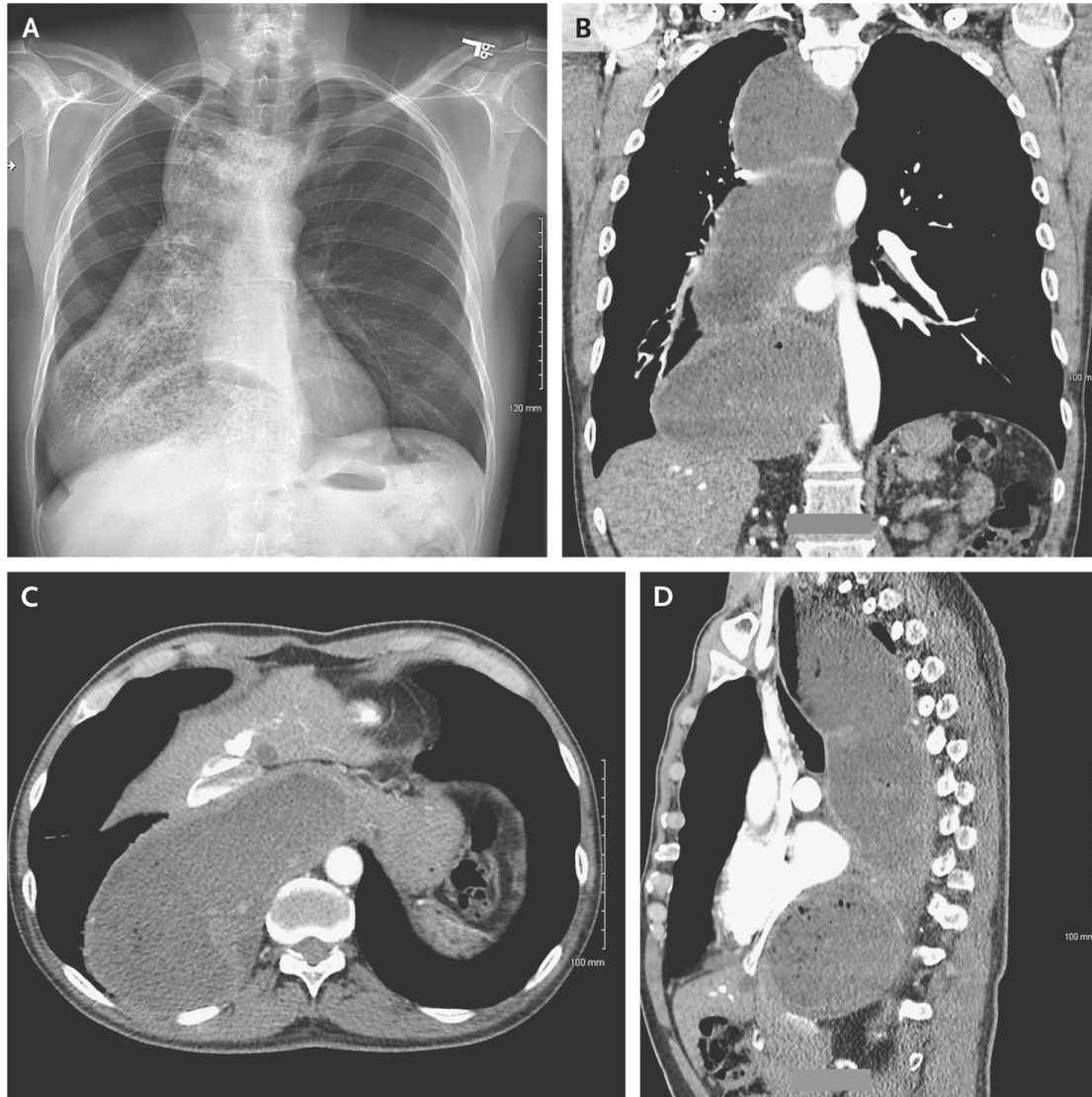
- HSV
- VZV
- West Nile virus
- Borna virus
- Zika
- Leprosy
- Measles
- Chagas disease
- Giardia
- CVID
- Anti CTLA4

Chaudhury 2016, 2013
Goyal and Chaudhury 2010
Huang et al 1996
Sumiyoshi et al 2001
Friebe et al 2007

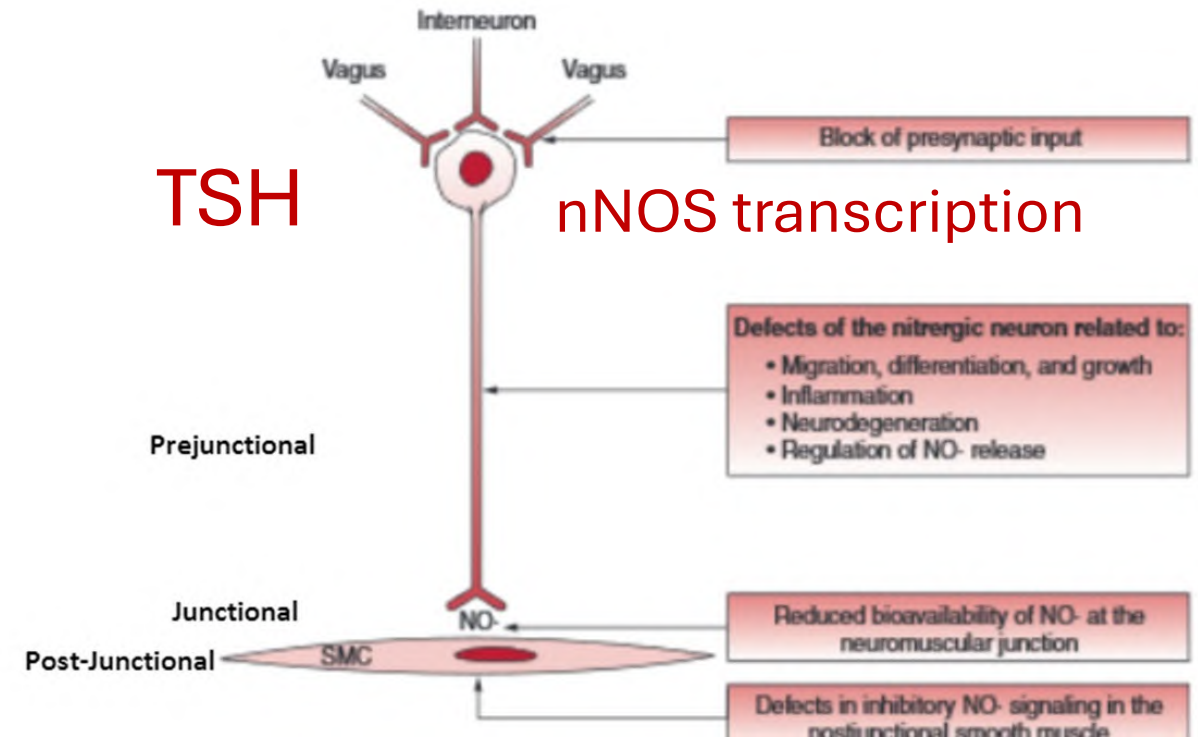


Hypothyroidism & Achalasia

63-year-old man with h/o hypothyroidism presented with a 10-year h/o dysphagia to solid foods and liquids. He had worsening of symptoms for 6 months, with an associated weight loss of 27 kg.



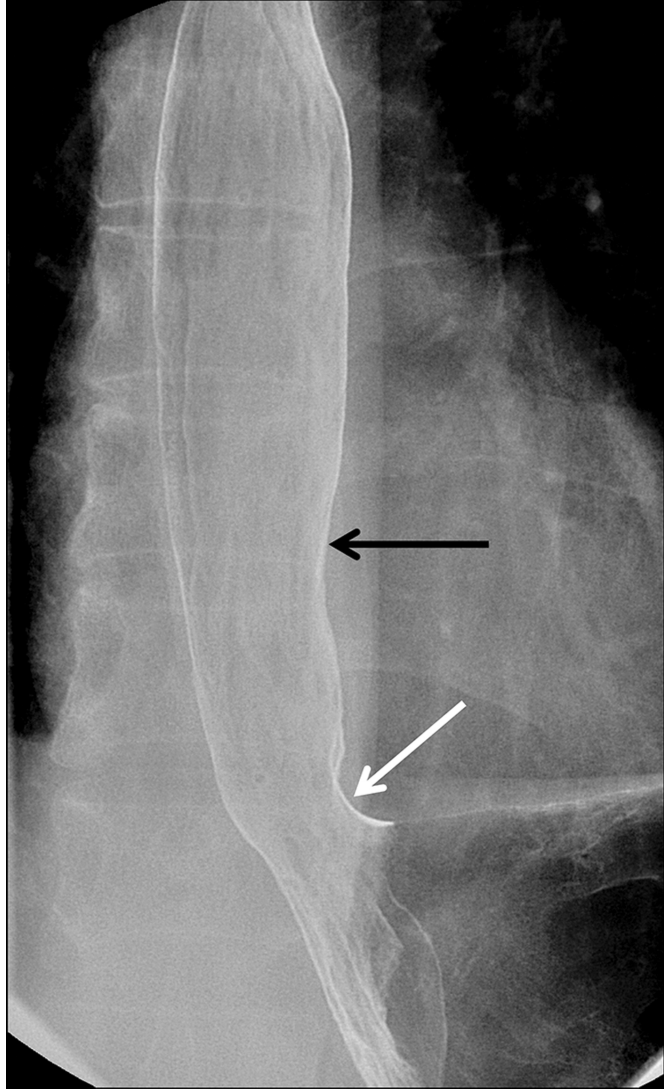
Okwara et.al., 2017 NEJM



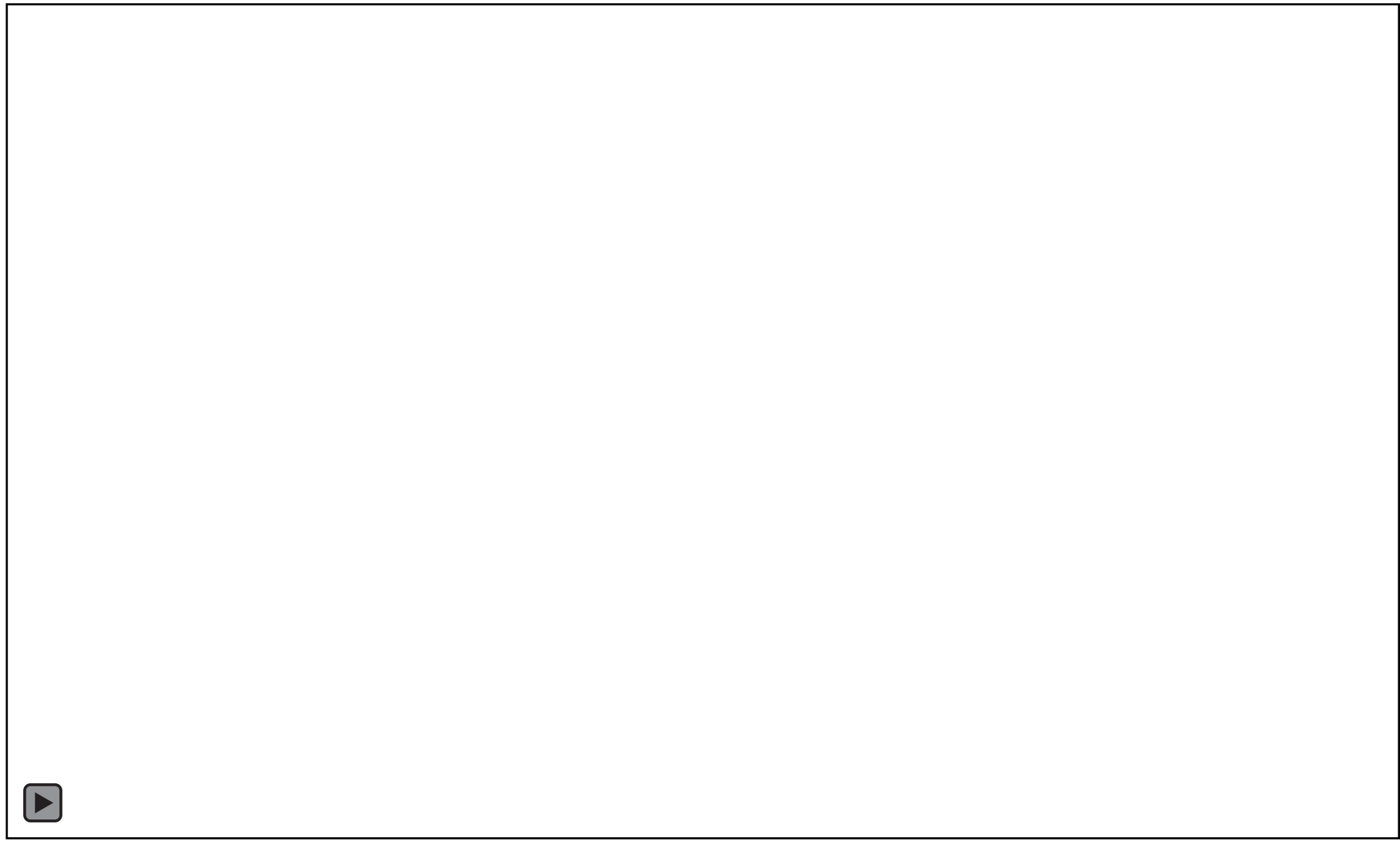
Ronald Evans

Chaudhury & Mashimo 2013

Esophageal Dysmotility in Scleroderma

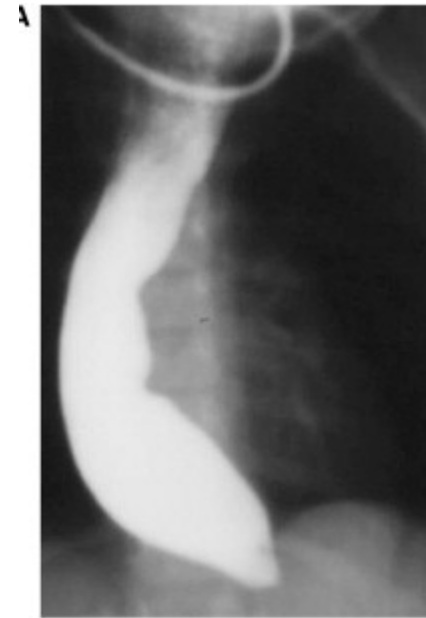
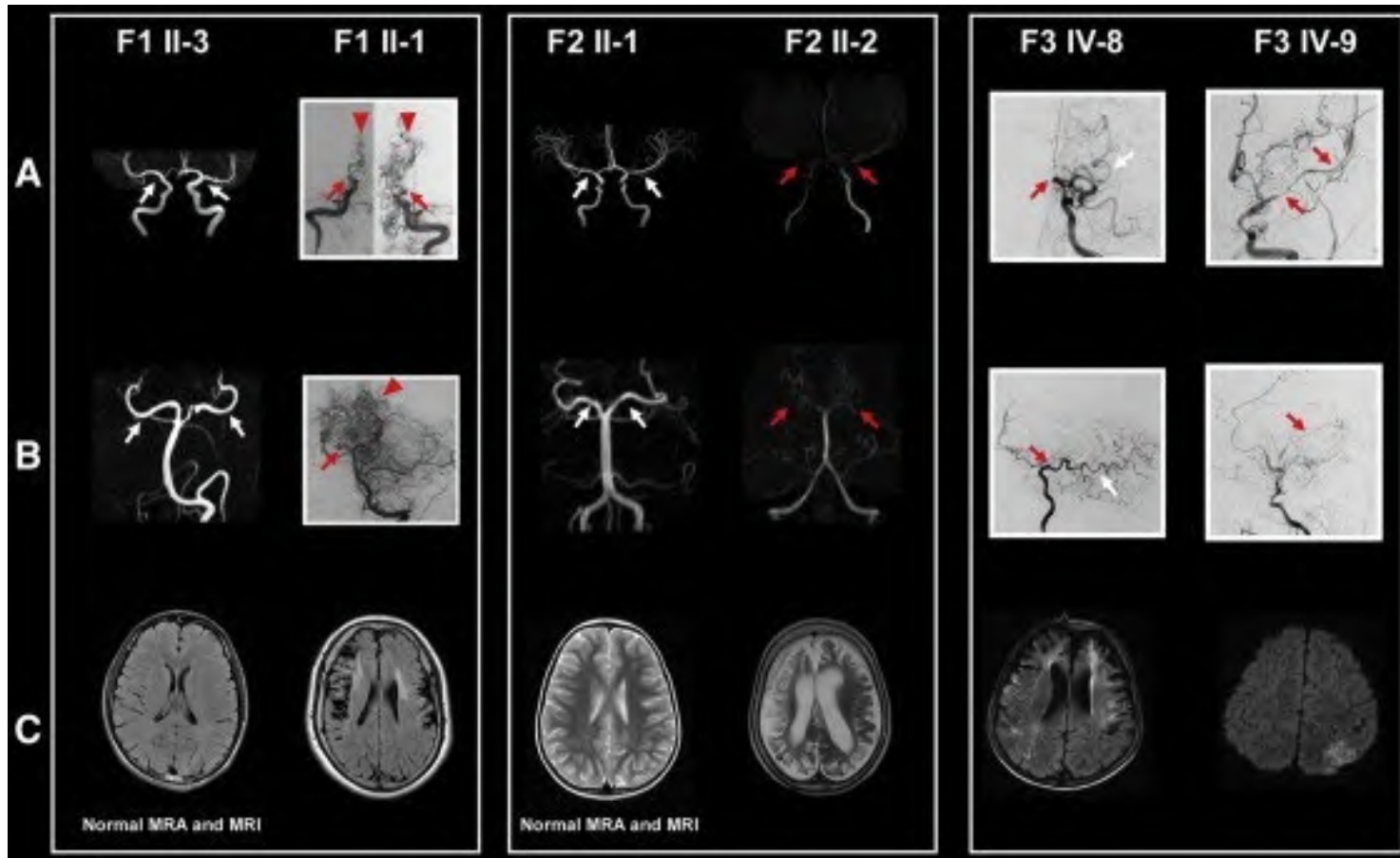


Impaired TLESR



Moyamoya & Achalasia

G cyclase

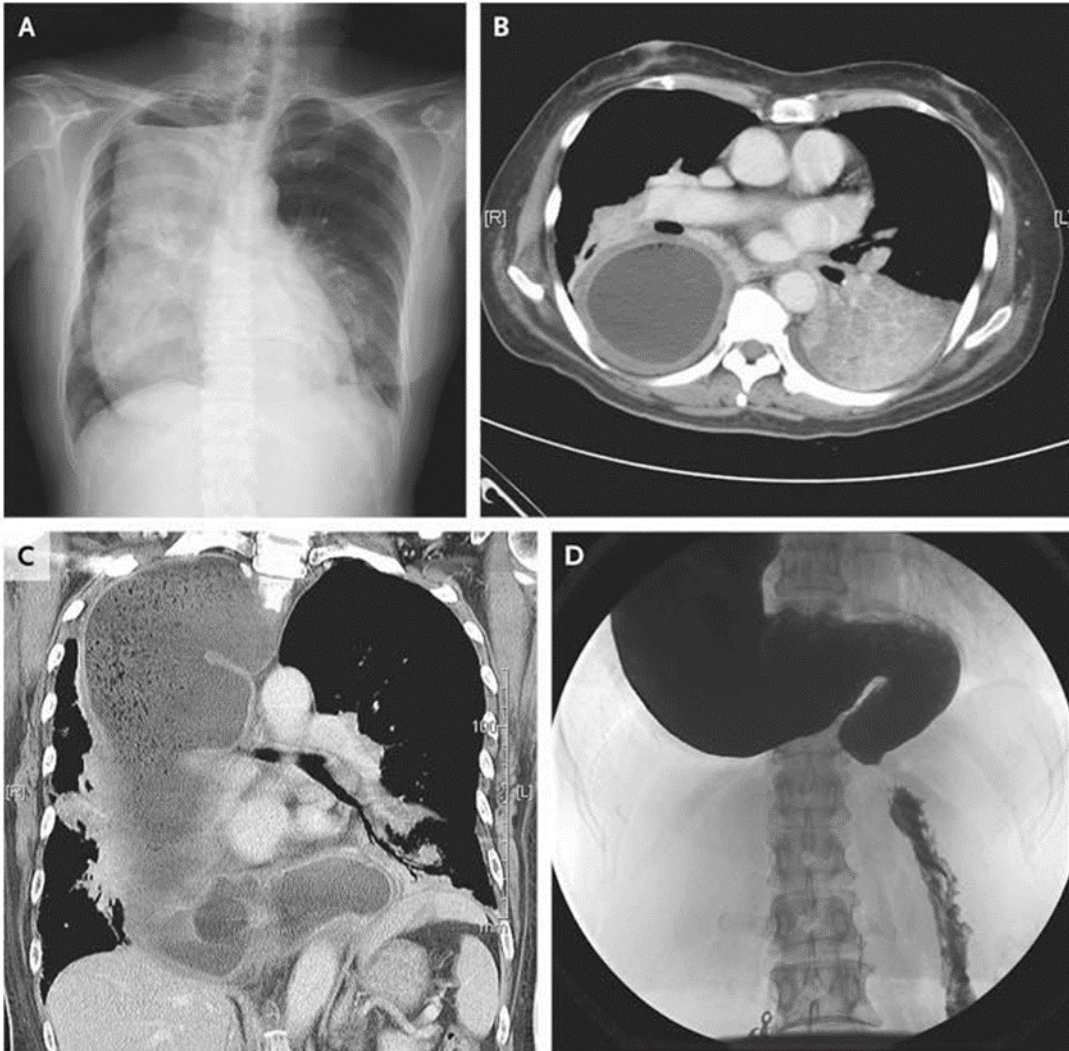


Genetic defects associated with achalasia

Site of defect/pathophysiology gene ^a	Function of gene product (Change)	Neuropathology of myenteric neurons	Achalasia/loss of nitroergic inhibition	Abnormality beyond esophagus	Human counterpart
Nitroergic neurons					
Commitment, migration, differentiation and growth					
Ascl1/Mash1	TF (D)	Absent	+ (?)	-	?
Arhgef1/Lsc	GEF (D)	Reduced	+ (M)	-	?
Spry2	Inh. RTK (D)	IND	? (Dil)	+	?
Nf1	Inh. Ras sig (D)	GNM	+	+	NF-1
Ret	RTK (I)	GNM	+	+	MEN B
Inflammatory loss of neurons					
Rassf1	Cycle arrest (D)	Inflamm. & reduced	+	-	?
Aaas	NPC (D)		+	-	AAA-S
Neurodegeneration					
Atxn7	CAG repeats (I)	Nuc. Incl.	+	+	ADCA
Snca	Inh. NTR (I)	Lewy body	+		PD-LB
nNOSα regulation					
Nos1	Source of NO (D)	Normal	+ (M)	+	?
Dlg4/PSD95	NTR (D)	Normal (?)	+	?	?
Neuromuscular junction					
Disorganized junction					
Col19a1	ECM, NTR (D)	Normal (?)	+ (M)	?	?
Postjunctional					
Loss of NO- signaling in the smooth muscles					
Gucy1b3	NO Receptor (D)	Normal	+ (?)	+	?
Prkg1/CGK1	cGMP target (D)	Normal	?	+	?
Mrvi/Irag	Inh. IP3 (D)	Normal	?	+	?



Achalasia may present late

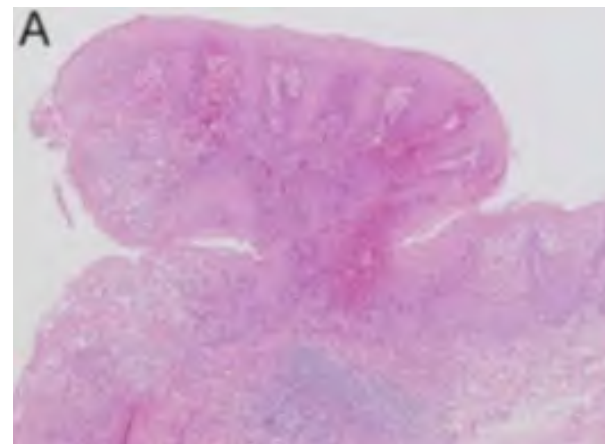


68-year-old woman with fever and dull pleuritic pain in left chest wall. Chest radiography revealed a large mass with an air-fluid level in the right hemithorax (Panel A) and a suggestion of pneumonia in the left lower lobe. CT w co revealed severely dilated esophagus containing food, consolidation in the left lower lobe, and compressed right lung (Panels B and C). She had difficulty in swallowing food since her 20s and had adapted by eating semiliquid diet for the past four decades.

Halitosis

Middle aged male with dysphagia

HPV Esophageal papillomatosis
Goltz syndrome
Focal dermal hypoplasia
PORCN

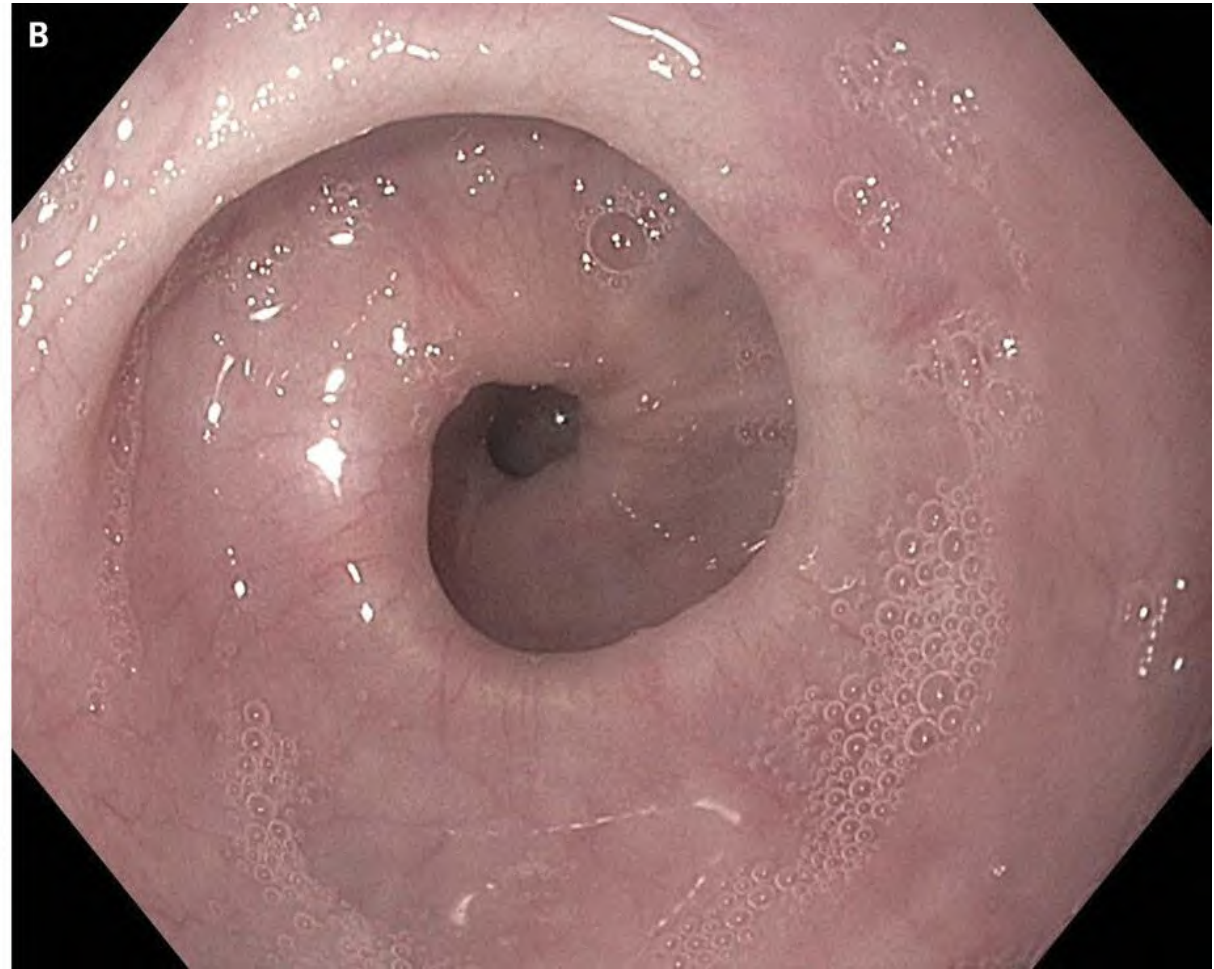


*Li et al 2023, Orphanet
Journal of Rare Diseases*

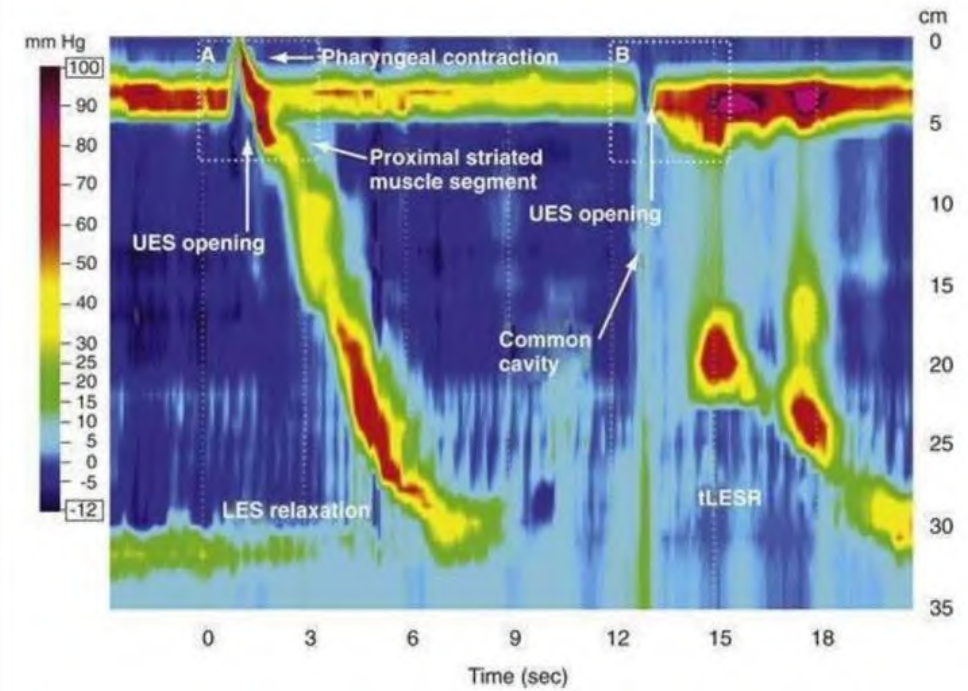
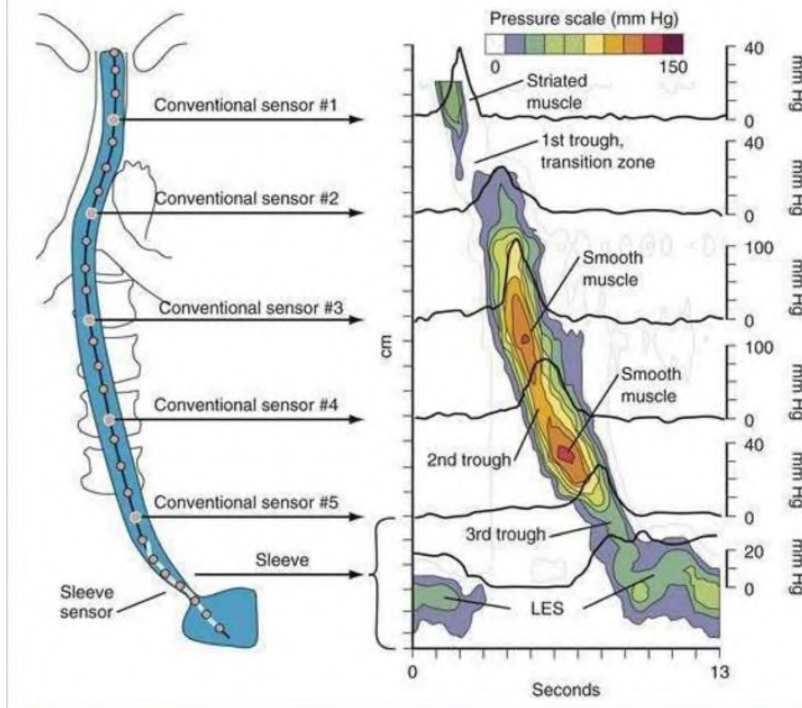
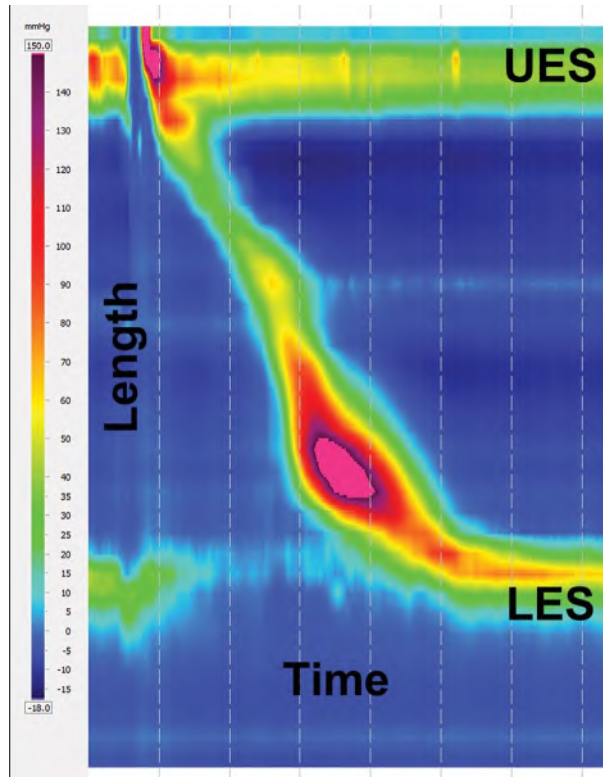
Diffuse esophageal spasm



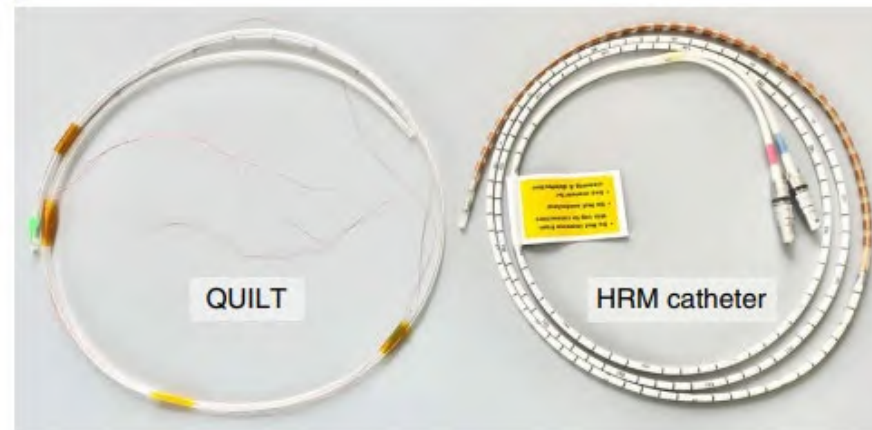
Corkscrew esophagus



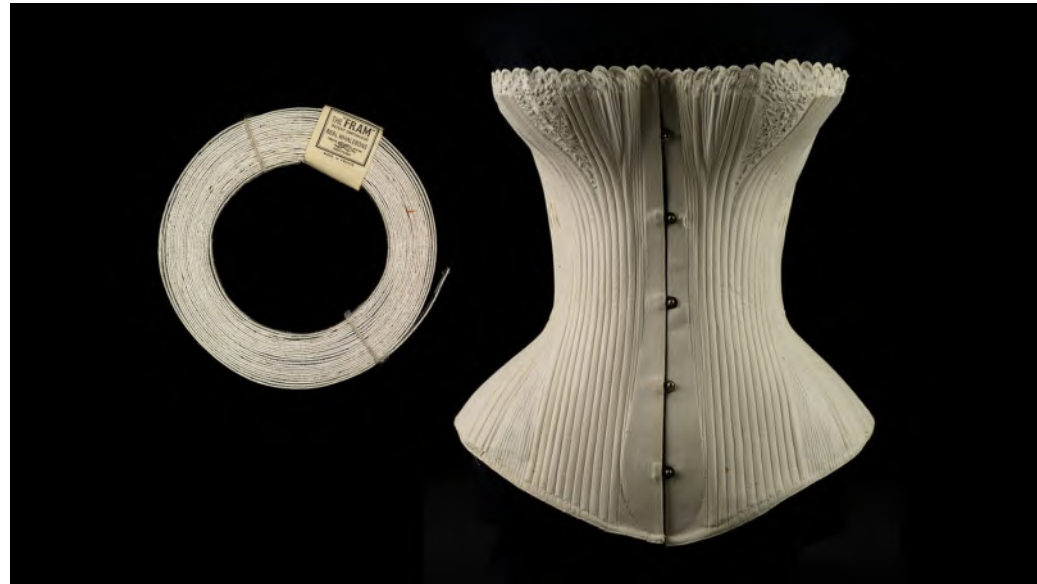
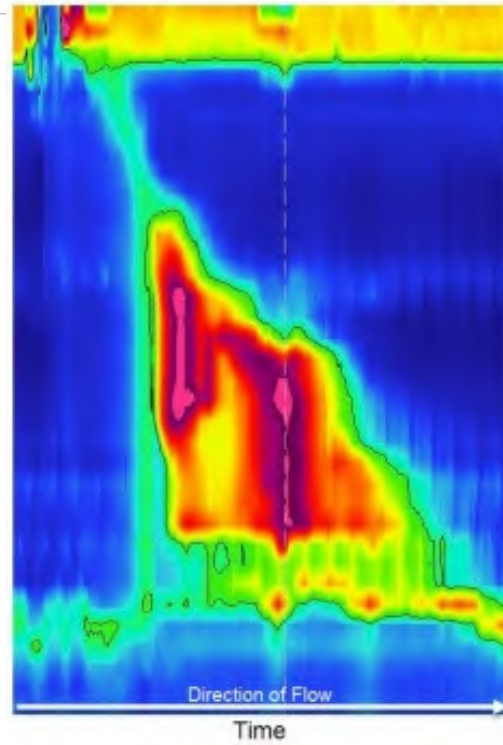
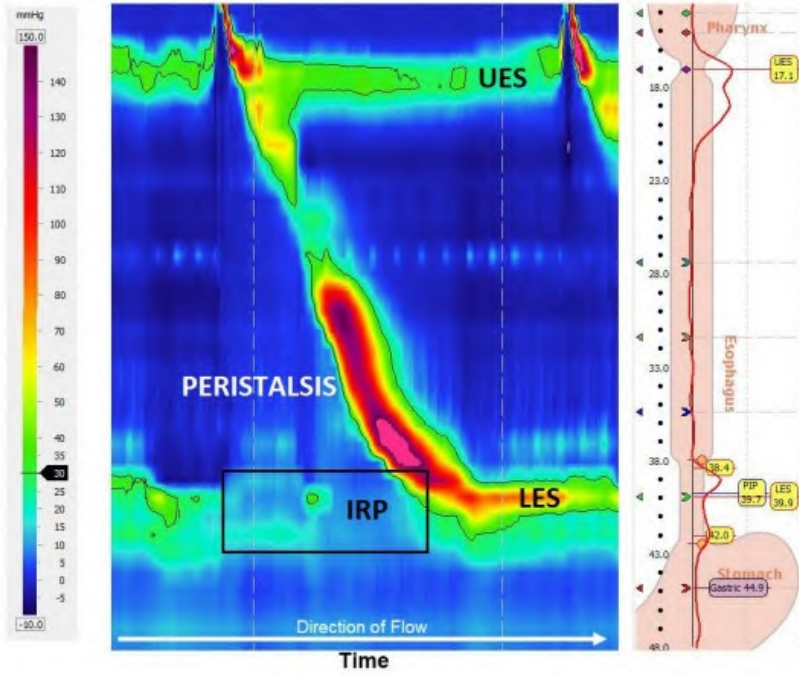
Definitive diagnosis by Manometry



Quipu



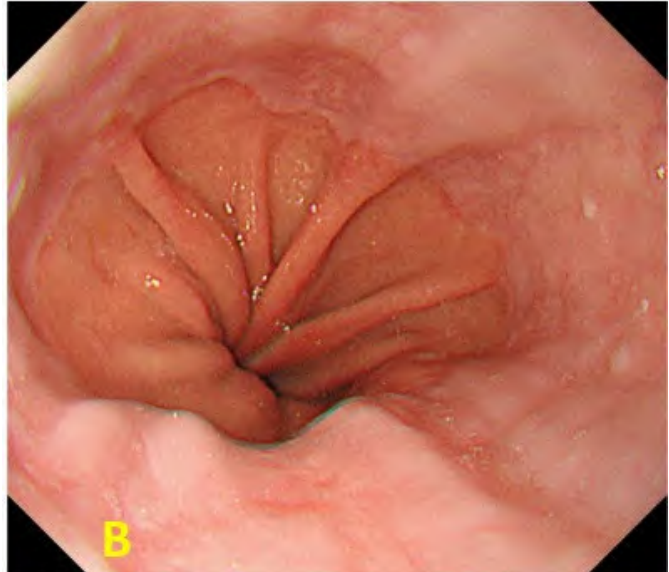
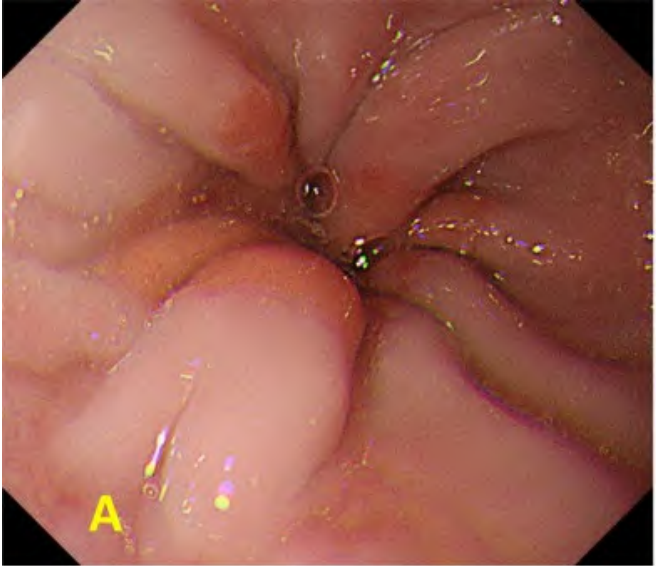
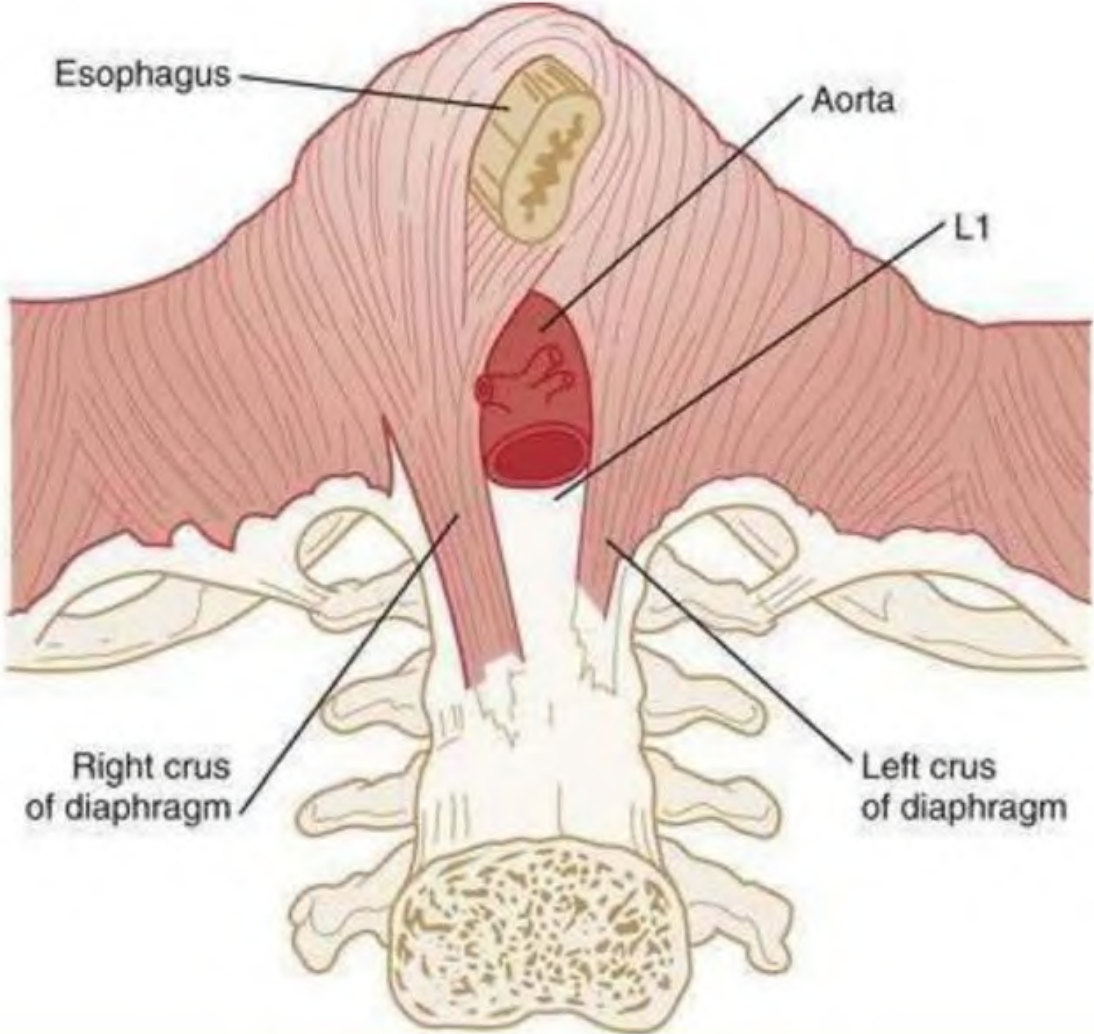
HRM in Achalasia



Bouginae
Botulinum
POEM

Esophagogastric junction outflow obstruction

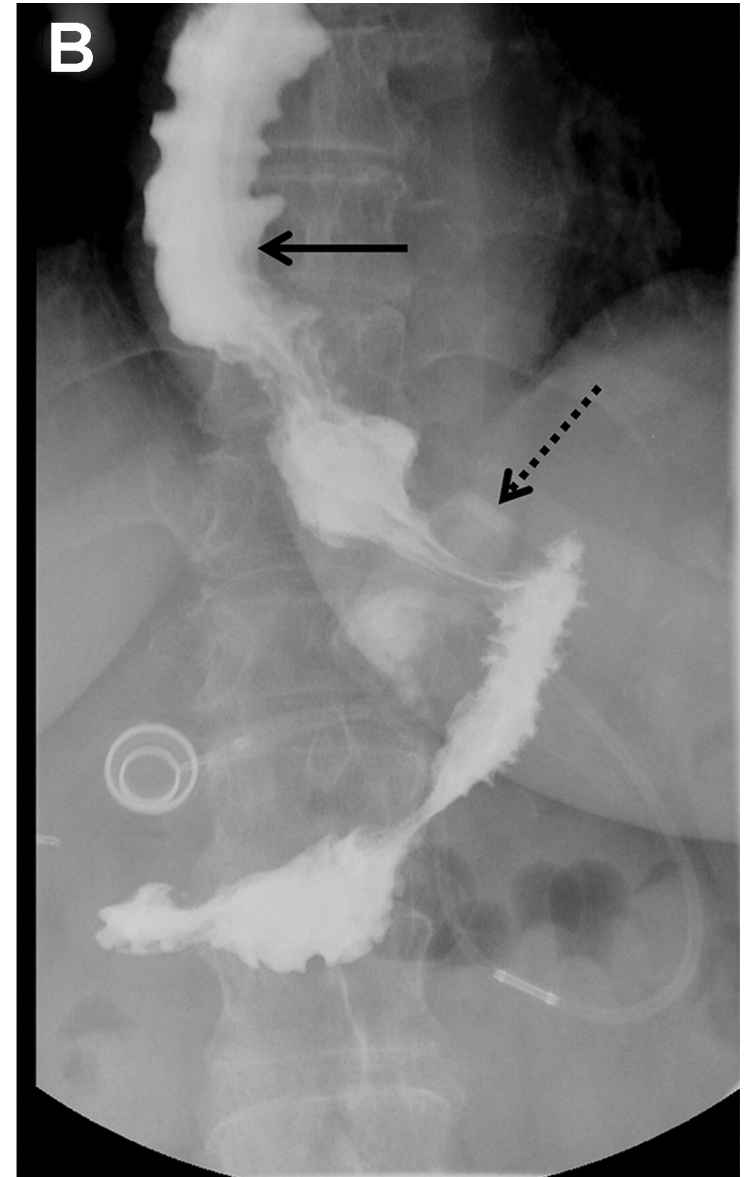
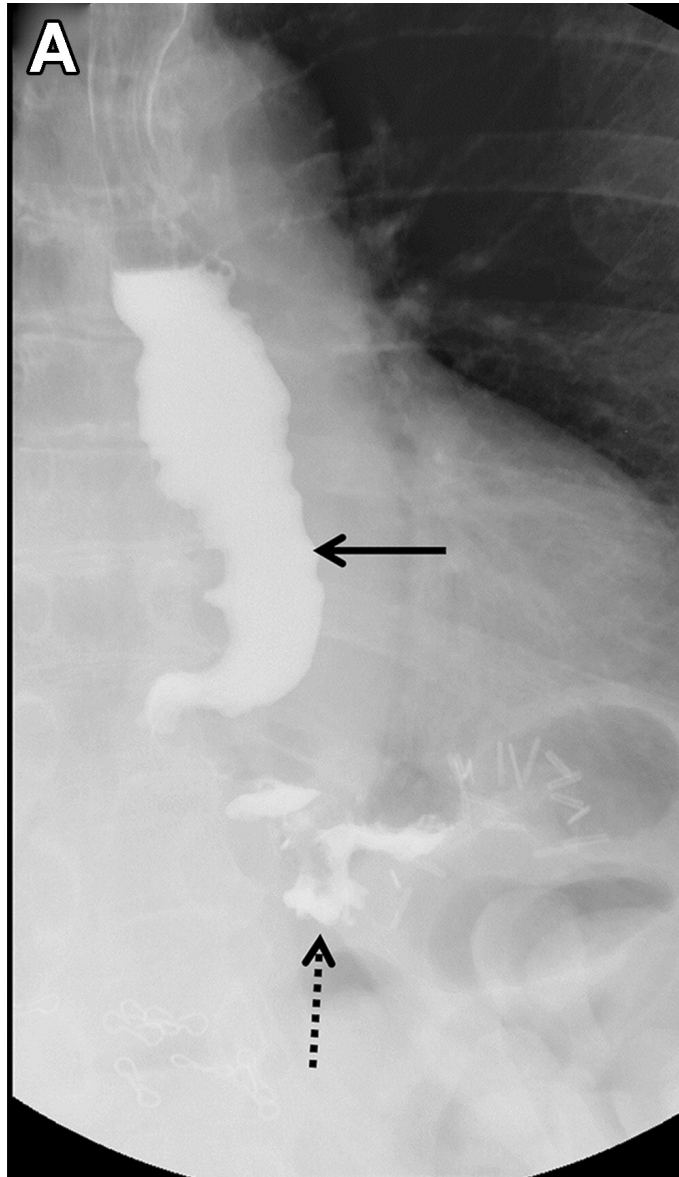
Opioid



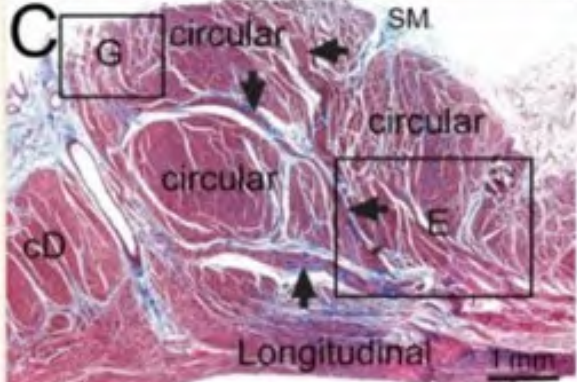
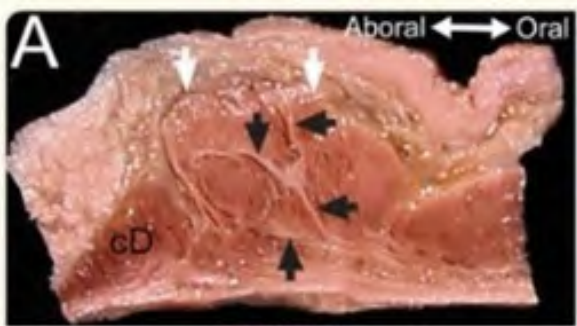
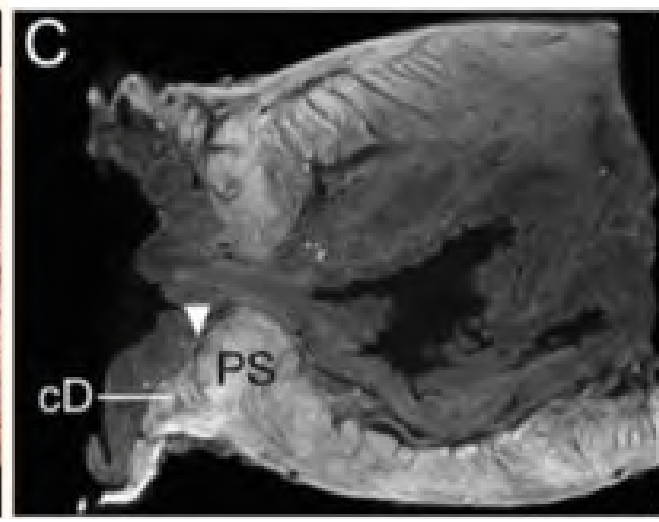
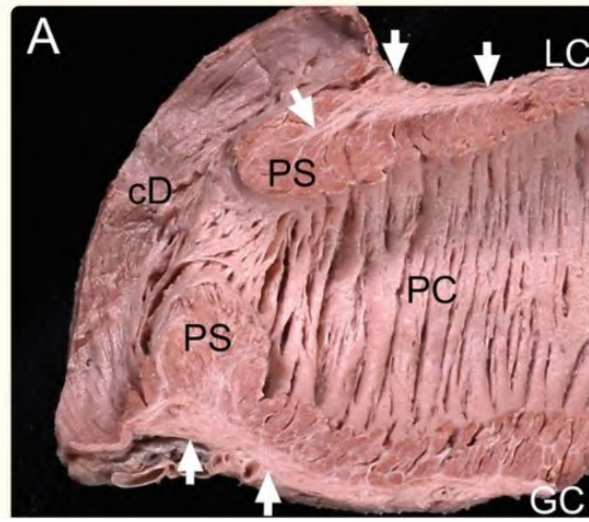
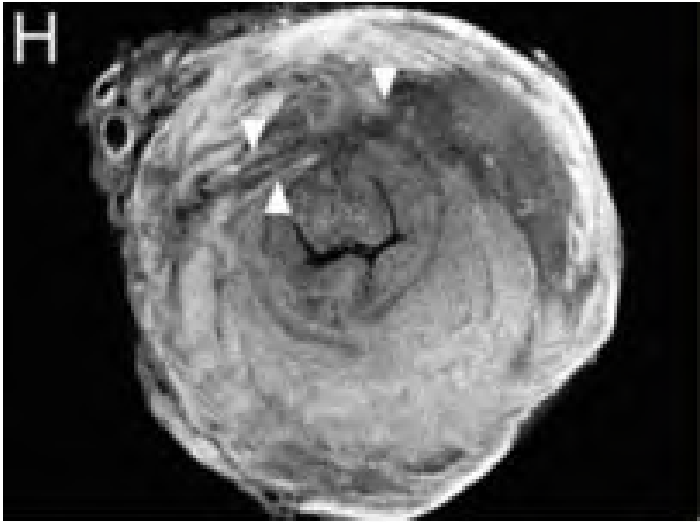
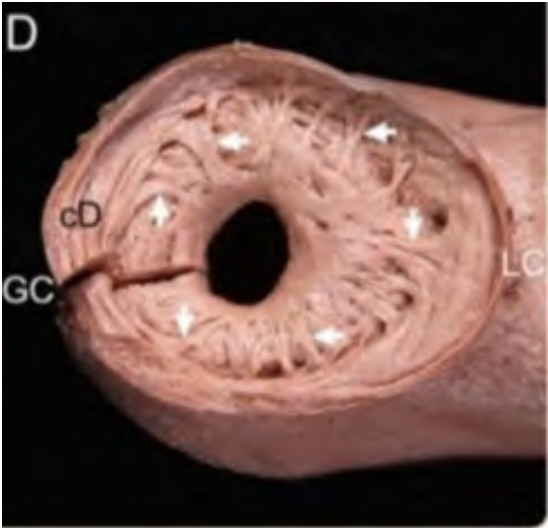
POSED

Post-obesity surgery
esophageal dysfunction

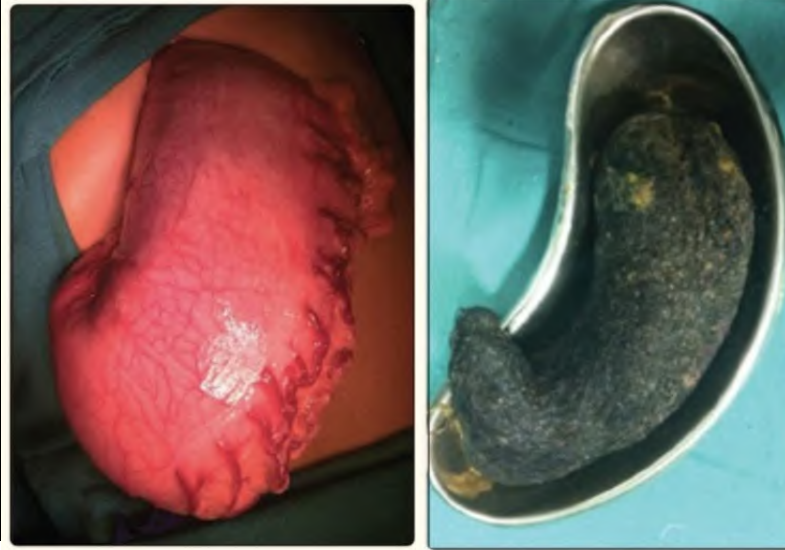
Stasis & Arthritis



Same story with Pyloric Sphincter



Gastroparesis



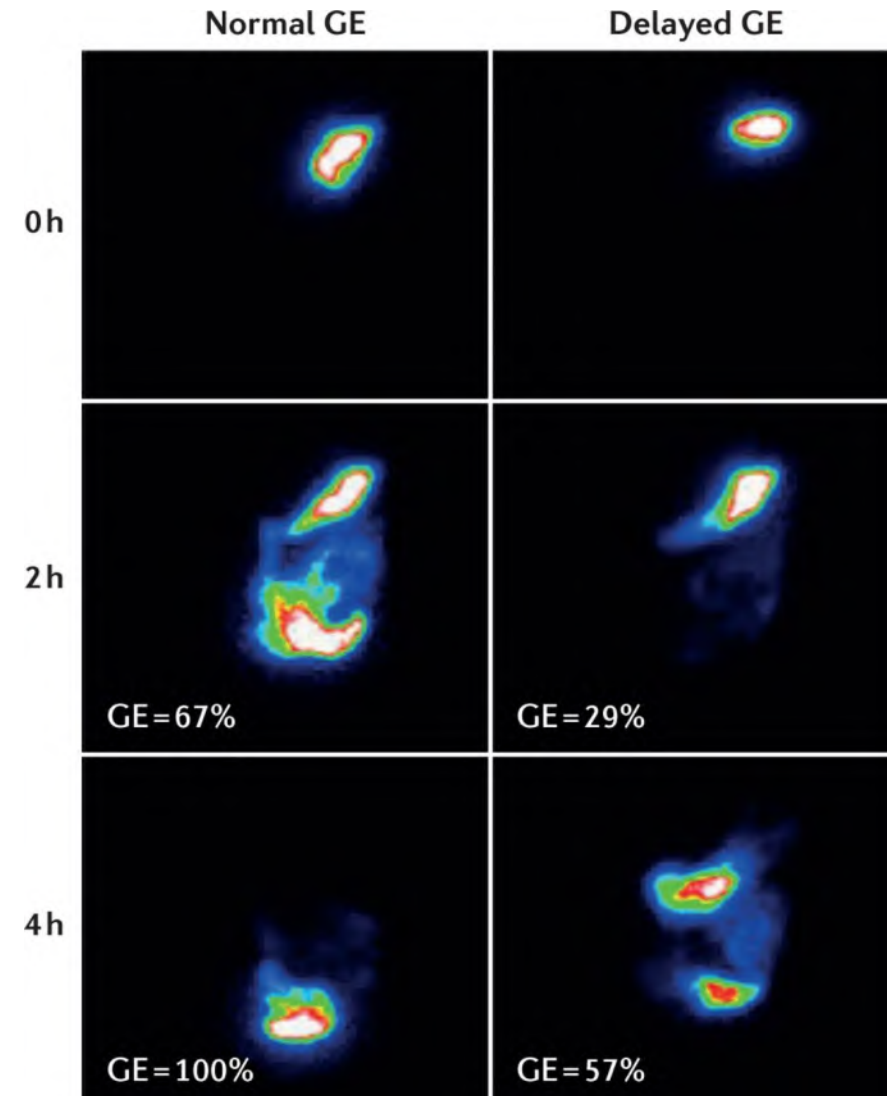
Rapunzel syndrome

Diabetes Mellitus
Idiopathic
Parkinson disease (On-Off)
Functional dyspepsia
Rumination
Paraneoplastic
GLP1 agonist
Medications

Bloating and Pain

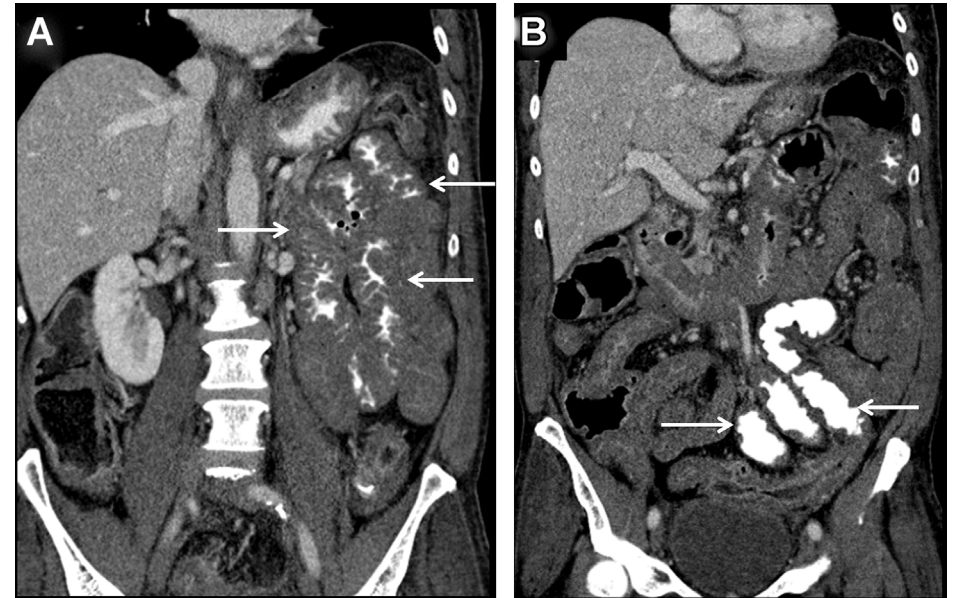
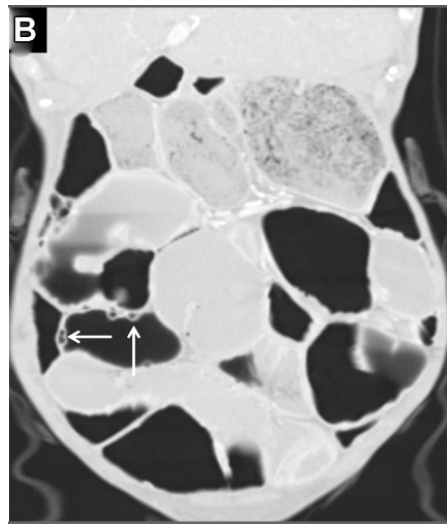
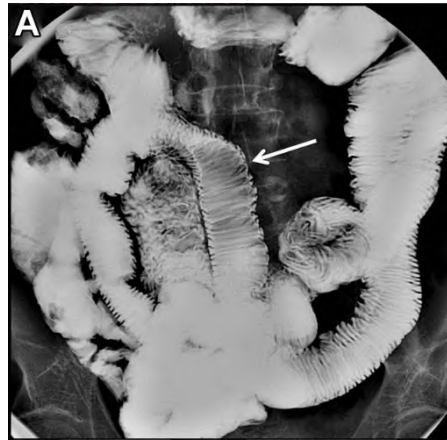
Srinivas Maddur

Scintigraphy



Keller et al 2018

Chronic Intestinal Pseudo-obstruction (CIPO)



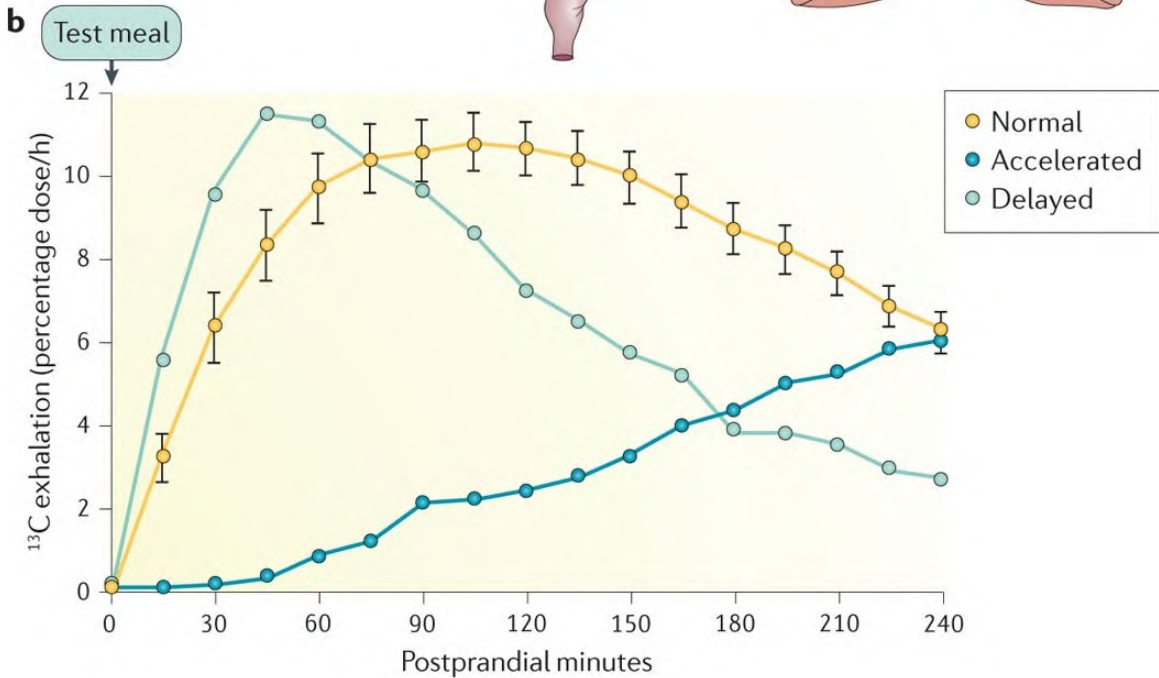
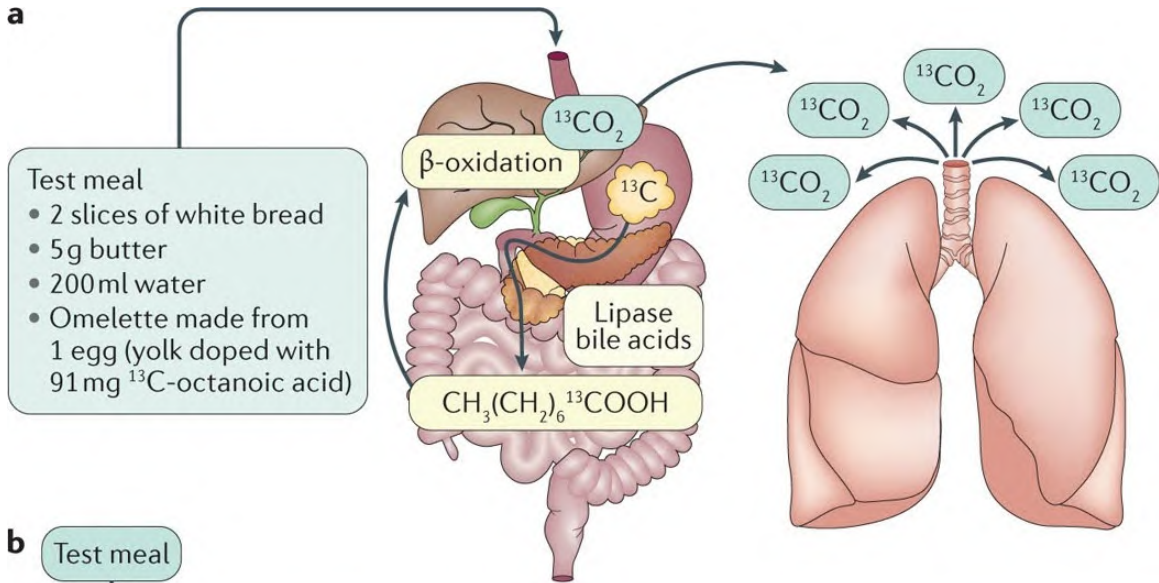
Amyloidosis

- Hypokalemia
- Visceral myopathy
- MNGIE
- Opioid
- ? IBS

Scleroderma & small intestine



Braverman 2003

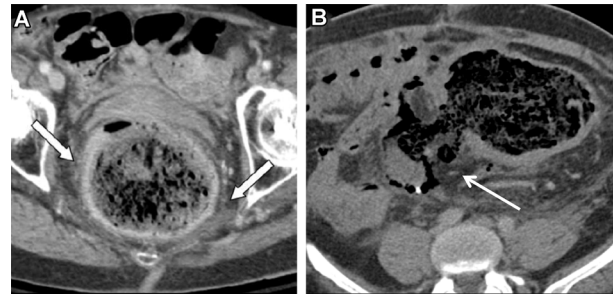


Keller et.al. 2018

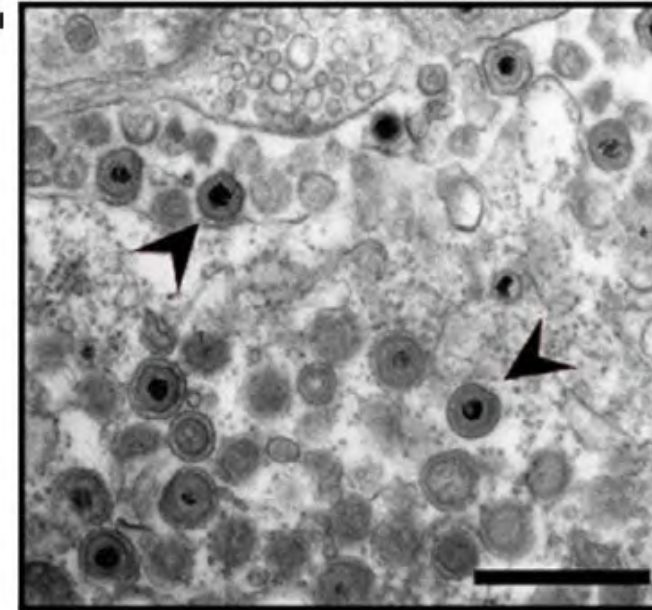
Delayed Colonic Transit & Constipation



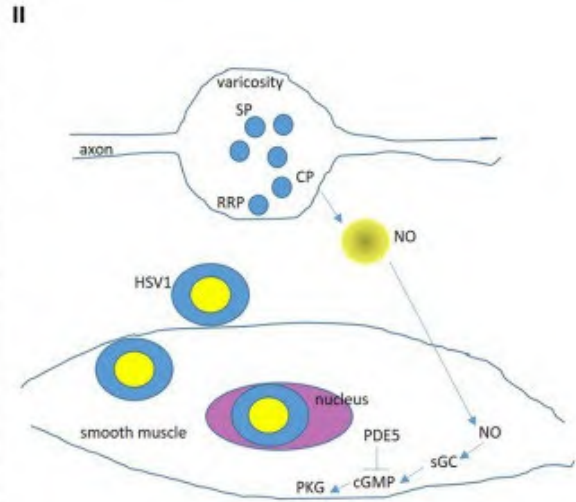
Opioid induced



Stercoral colitis



HSV Myopathy



Stimulant Laxative
Naloxegol
Naldemedine

MSM

LGBTQ+ health

Chaudhury et al 2017

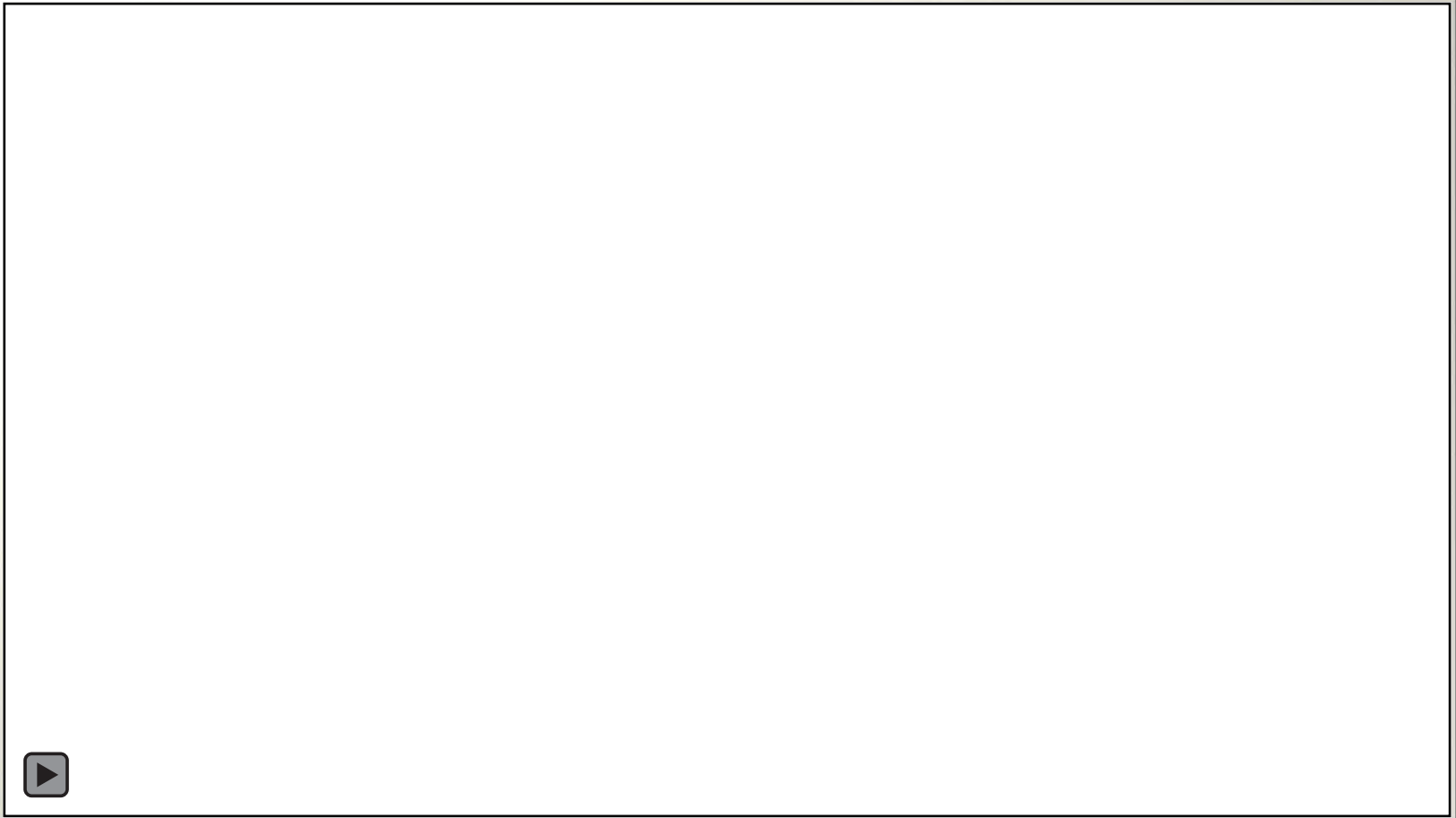


Chagasic colon @Mutter Museum

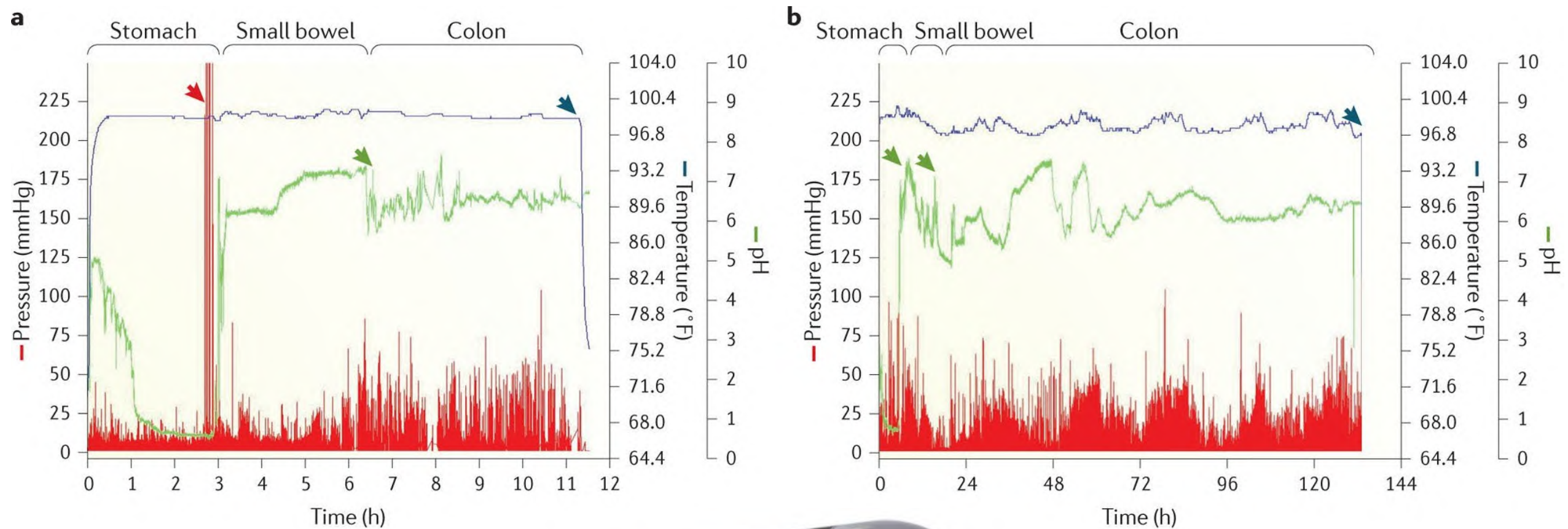
Pelvic Floor dysfunction



Coin invertogram



Deficits in transit can panoramically involve the whole GI tract



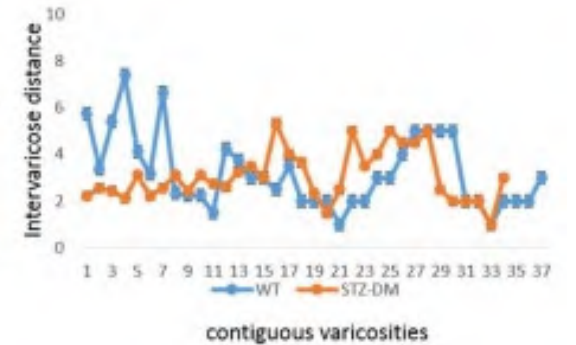
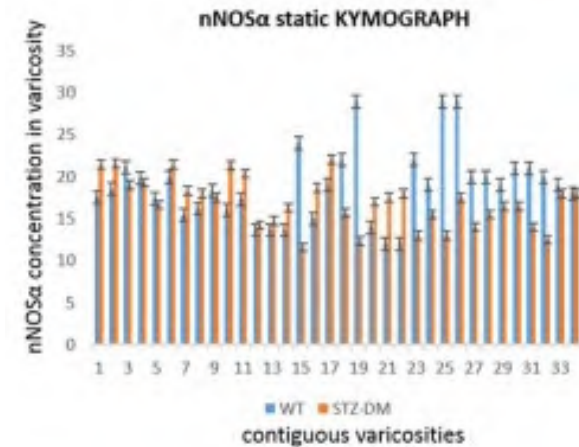
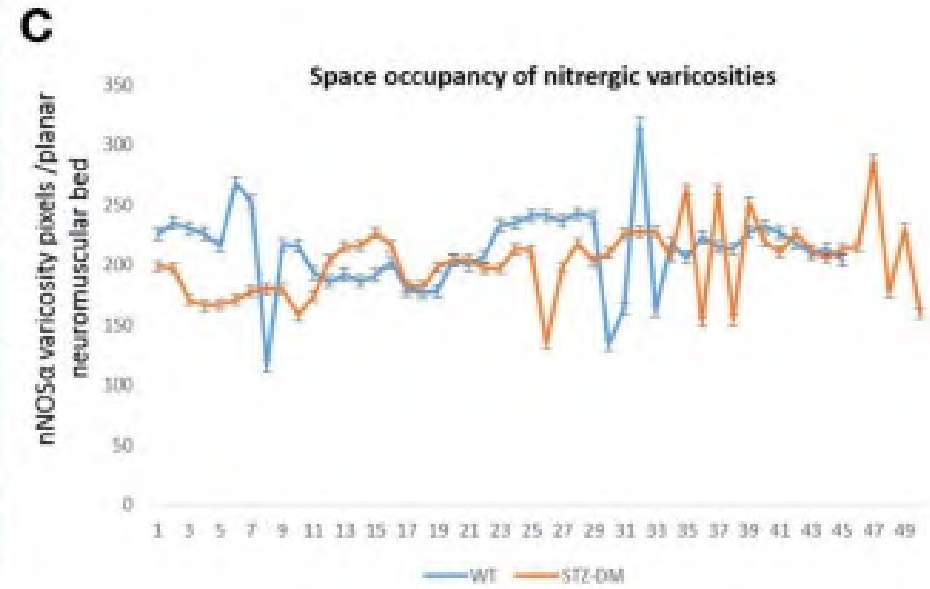
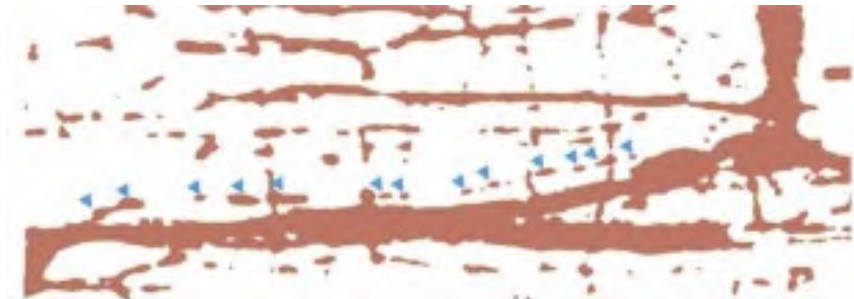
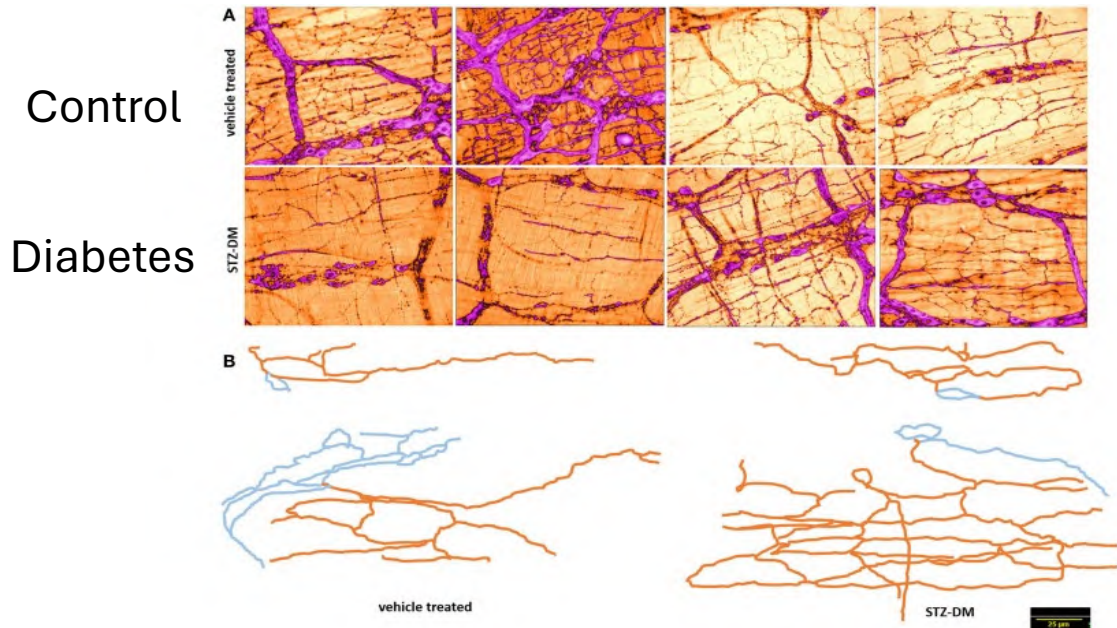
Chaudhury, 2015
Shteyer et al 2015



Keller et.al. 2018

Further details of pathophysiology: Insights into rational management

Histopathology of nitrenergic deficit is often equivocal



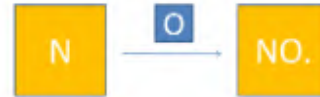
nNOS catalysis is very complex

Pas de deux

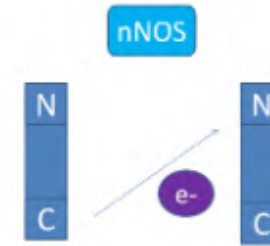
Dimer

Bioelectronics of Nitric Oxide (NO) synthesis

Synthesis of NO

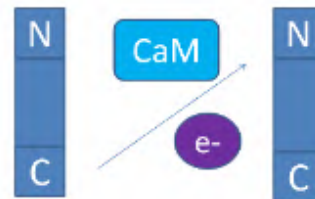


Catalytic synthesis of NO



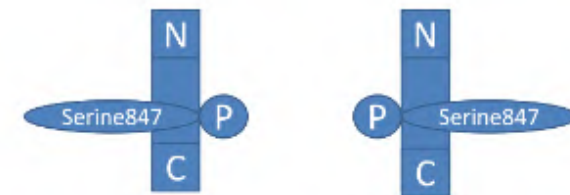
Looking at Neutrophils

Facilitation of electron transfer



Active nNOS

Inhibition of electron transfer



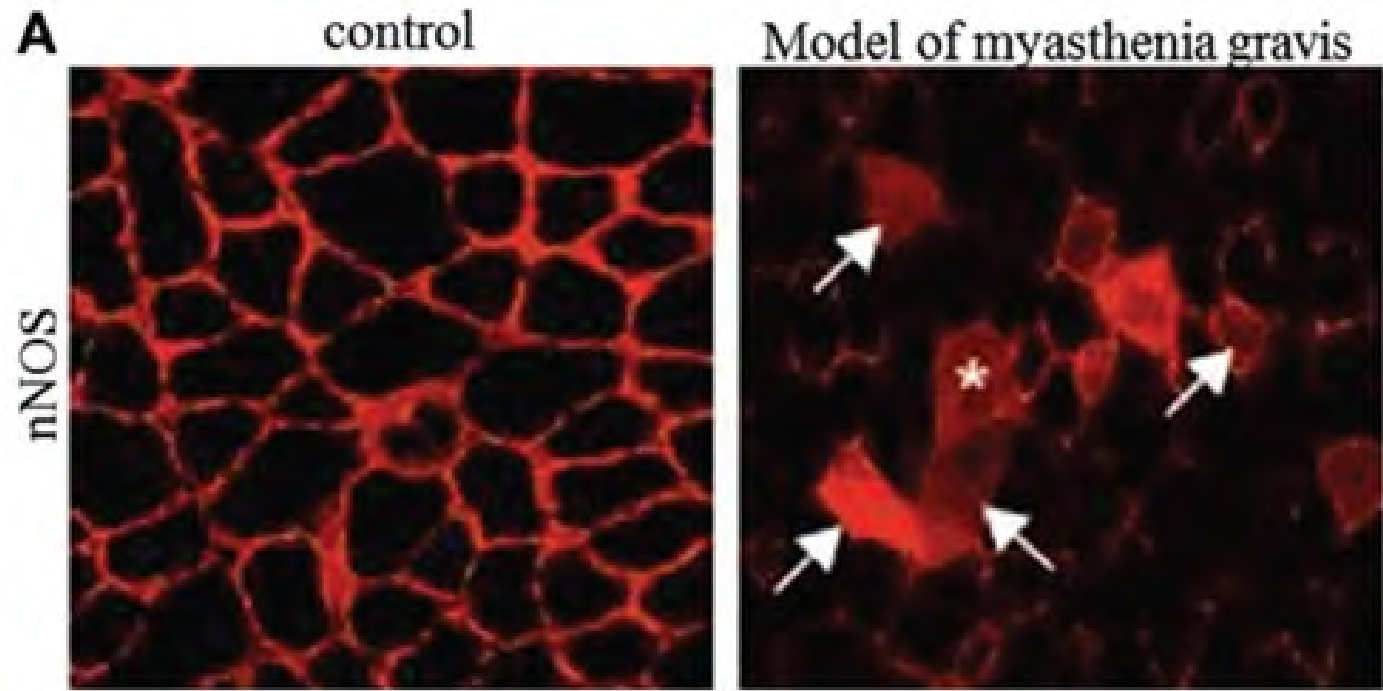
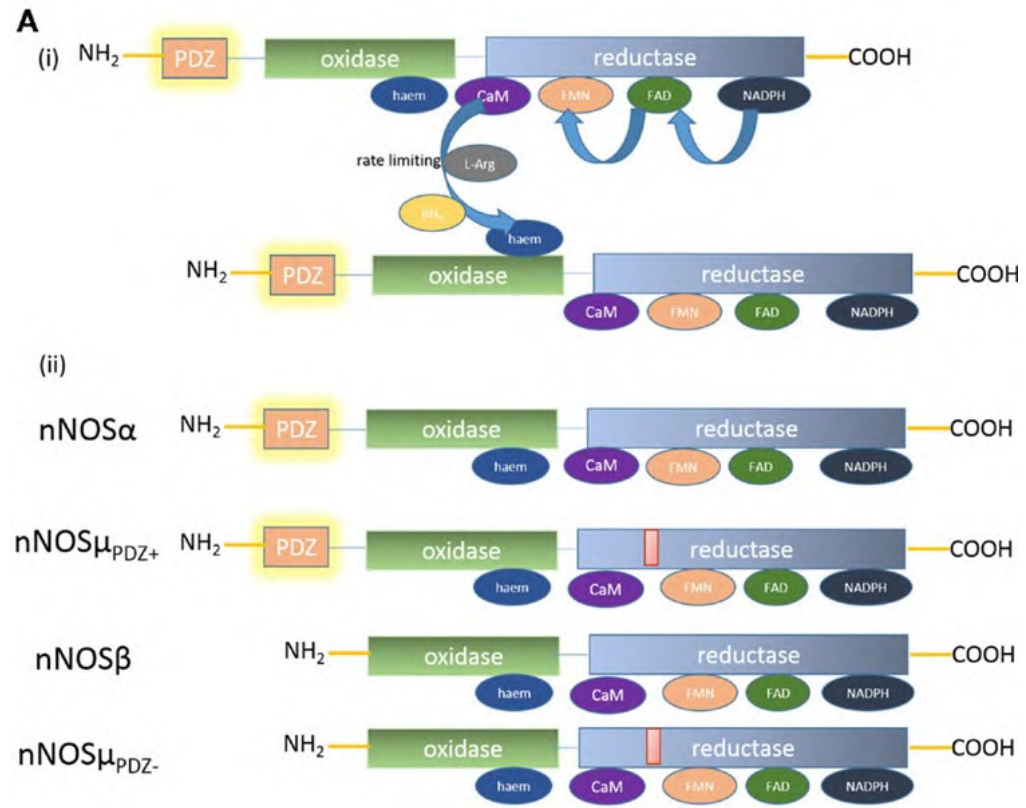
Inactive nNOS

Sexual dimorphism

Non-vesicular transmitter follows Sherringtonian laws of neurotransmission

Chaudhury et al 2008, 2009

Membrane attached nNOS is active



Skeletal muscle biopsy as surrogate for diagnosing nitroergic defect of enteric synaptosomes

nNOS transported to membrane of nerve terminals by Myosin Va

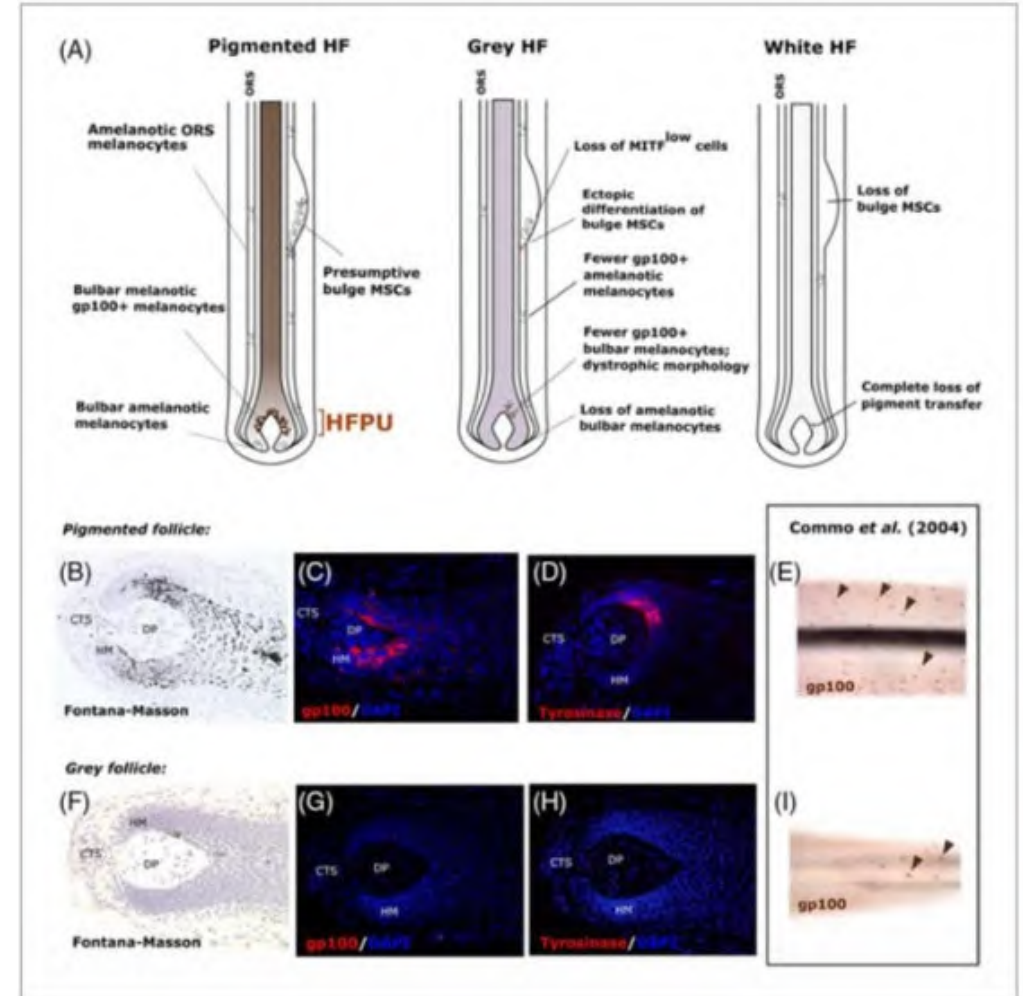
'Dilute'

by Myosin Va

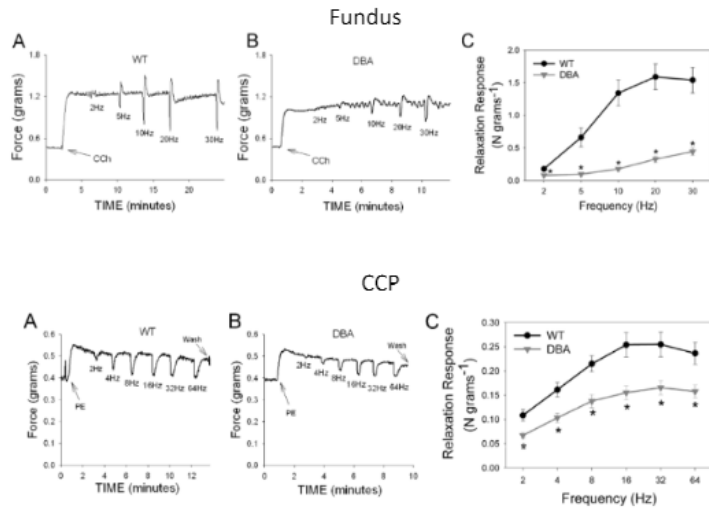
O'Sullivan et al 2021



Canities



Loss of relaxation in penile cavernosa & gastric fundus of DBA/2J mice

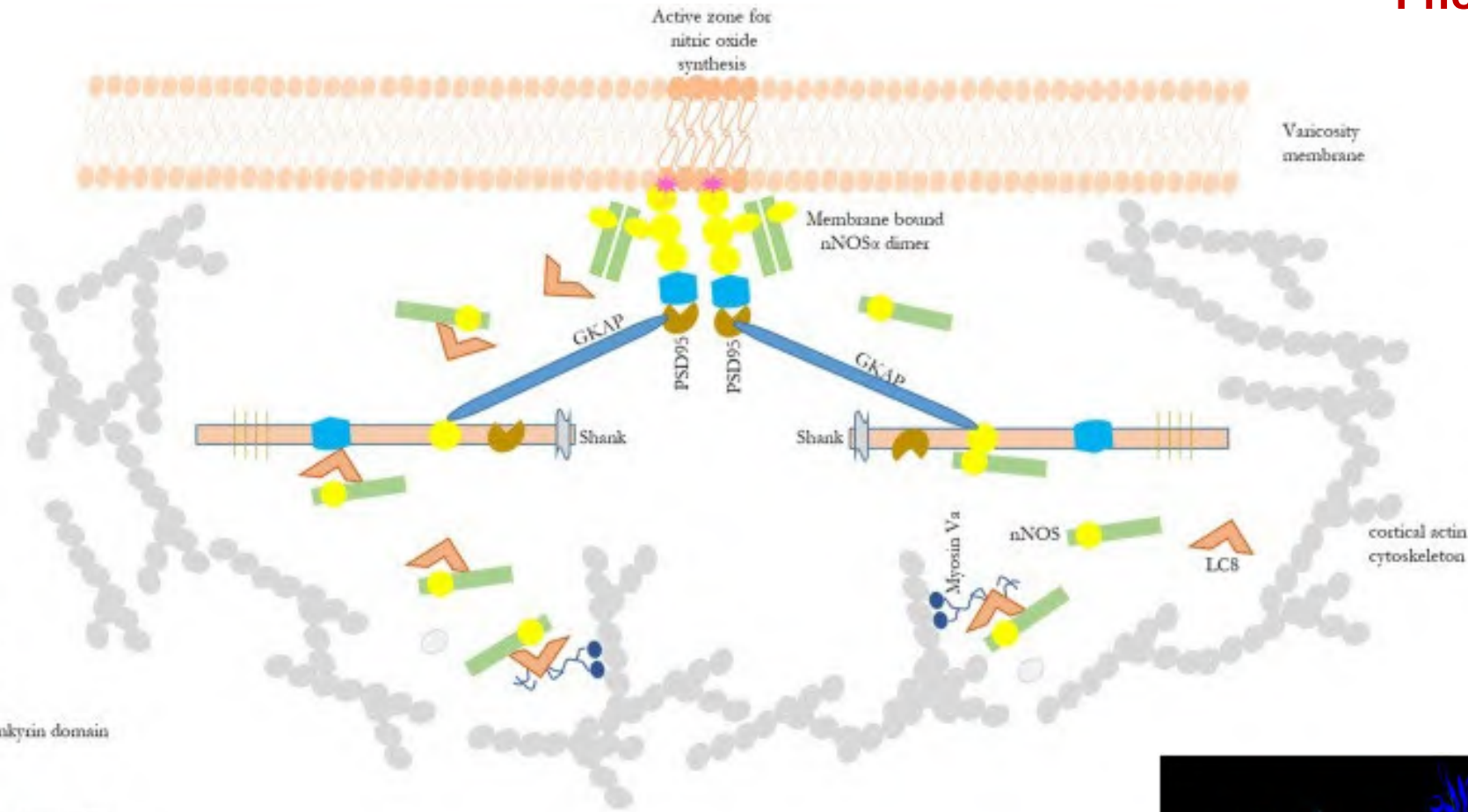


Chaudhury et al, 2011, 2011, 2014, 2024

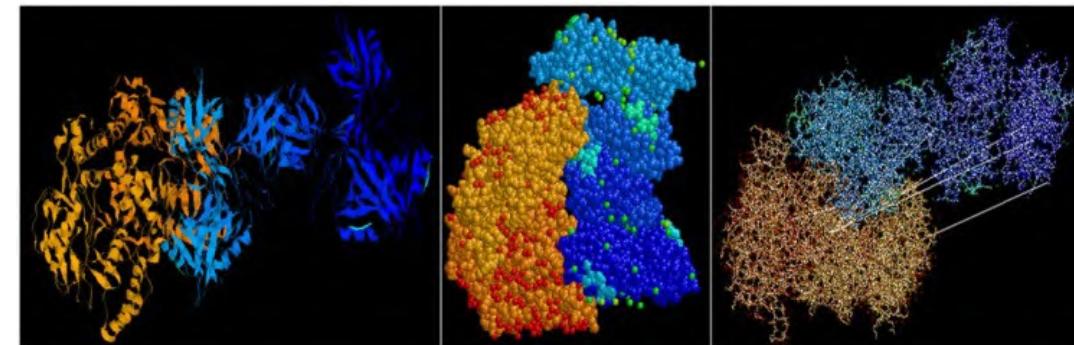
Story at cortical cytoskeleton gets even more complex

Phelan-McDermid syndrome

SHANKopathy
Cyclical vomiting
Encopresis



nNOS-shank3



Molecular handoffs in nitergic neurotransmission

Arun Chaudhury*

Department of Surgery, Brigham and Women's Hospital, Harvard Medical School and VA Boston Healthcare System, Boston, MA, USA

Mechanotherapy & Ethnopharmacology

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Rectal stimulation to relieve constipation in infants: is it safe?

Kalyanbrata Mandal

Department of Paediatrics, Calcutta Medical College,
Kolkata, West Bengal, India



Abhishek Roy

Department of Paediatrics, RG Kar Medical College,
Kolkata, West Bengal, India

ORIGINAL RESEARCH—CLINICAL | VOLUME 3, ISSUE 3, P402-409,
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Brian Weiner   • Chris Forsmark • Vikas Khular • ...

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DOI: <https://doi.org/10.1016/j.gastha.2023.12.013> •

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Efficacy and safety of elobixibat in hemodialysis patients with chronic constipation: a retrospective study

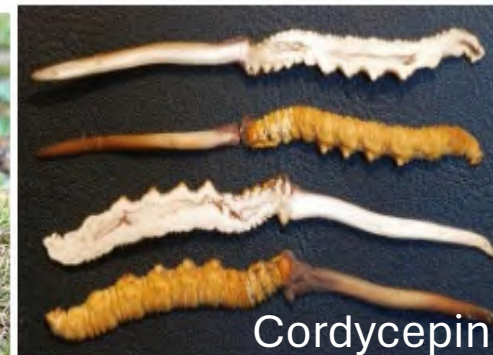
[Takefumi Shono](#)  & [Hiroyuki Hyakutake](#)

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Yartsa gunbu



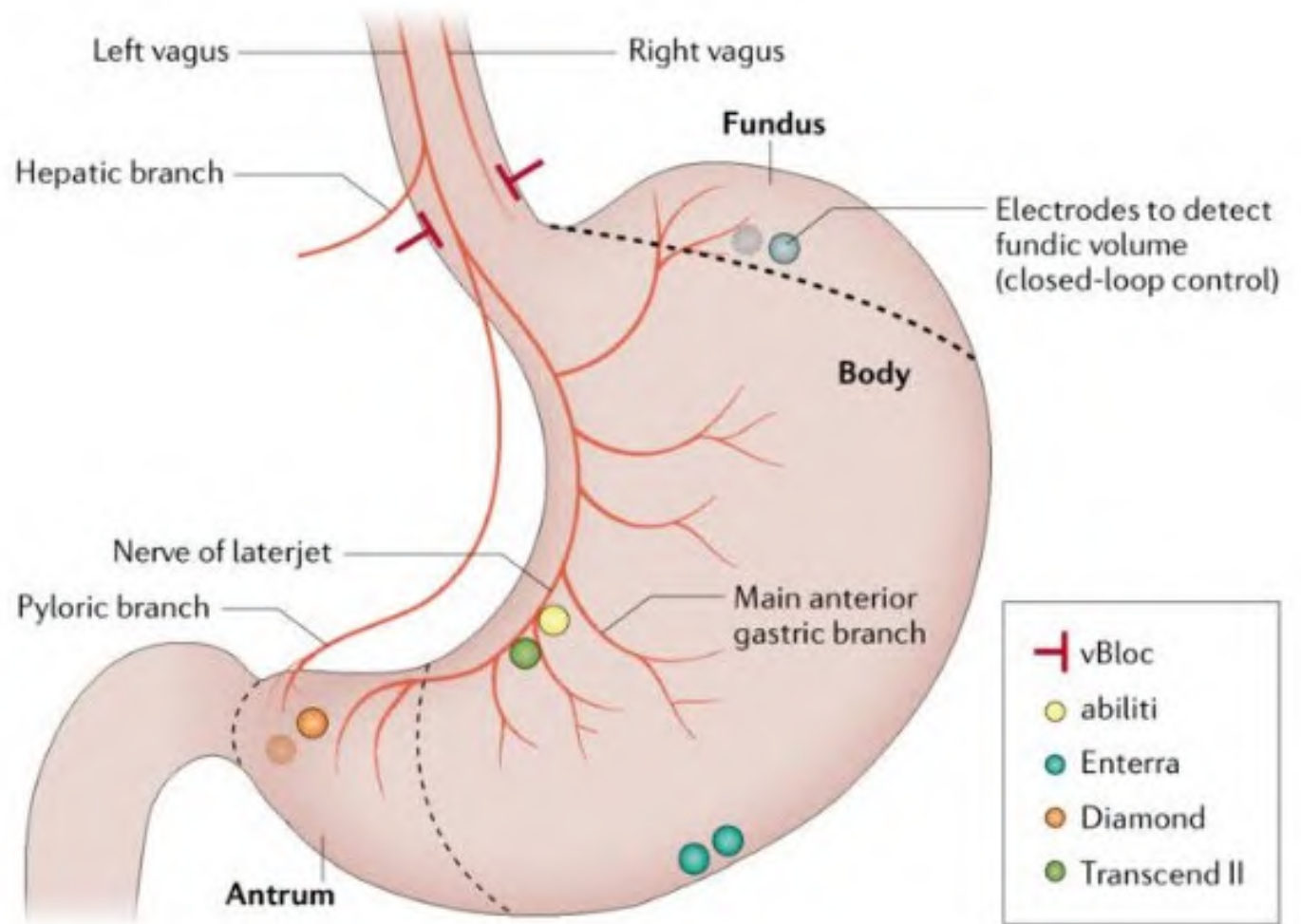
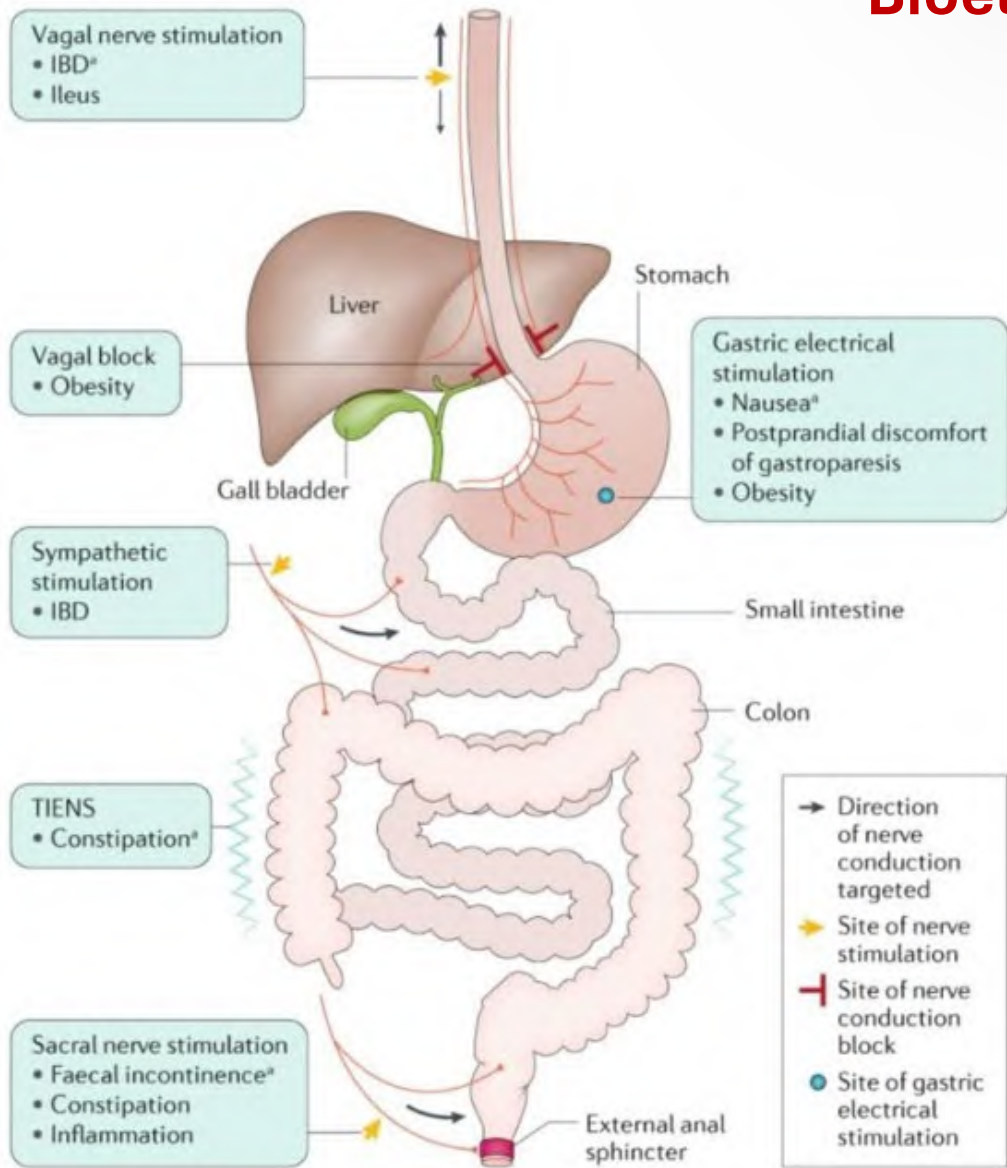
Cordycepin

Lessons from sex medicine

Chaudhury 2019

Electroceuticals

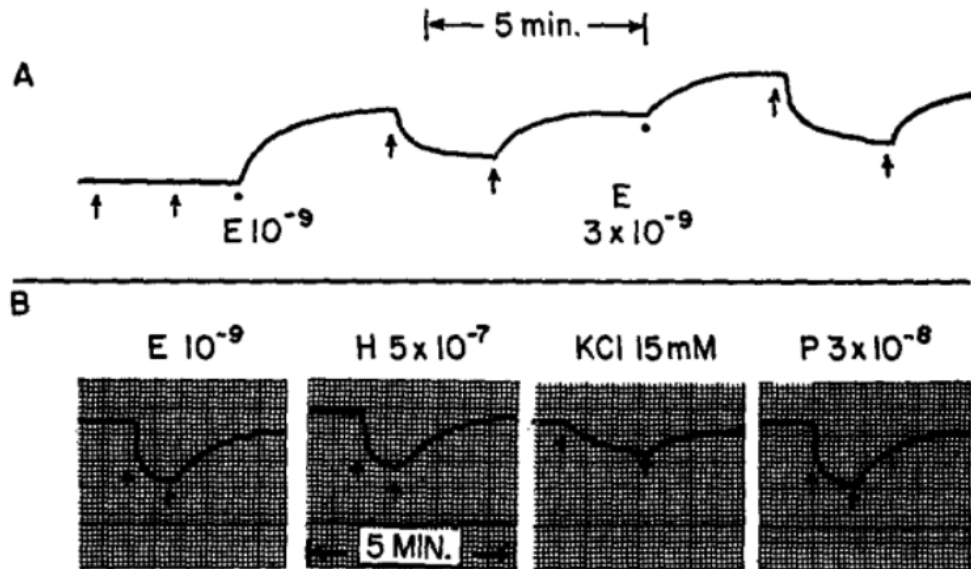
Bioelectronic medicine



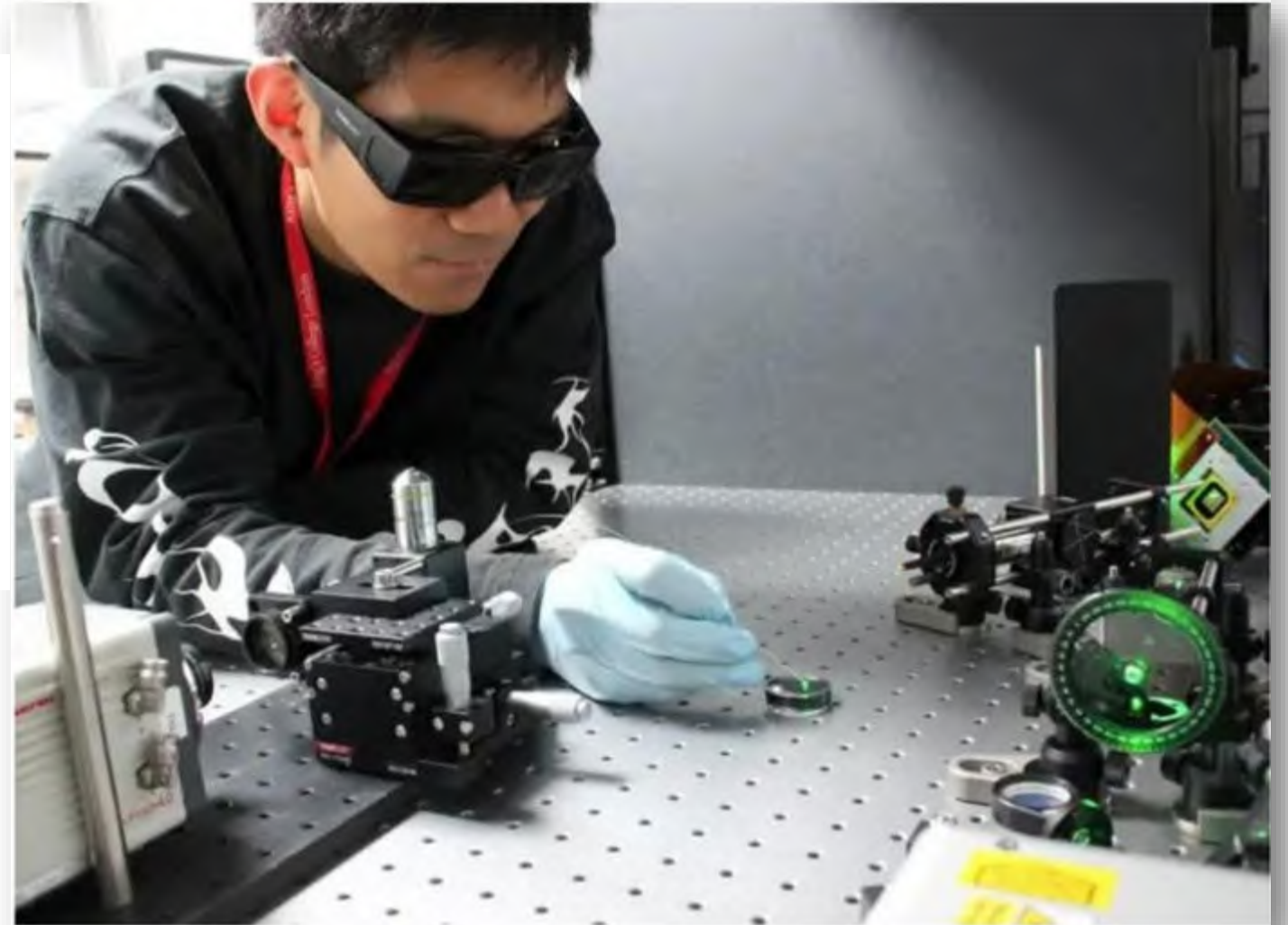
Can light do the trick?

de novo NO

Listening to light: Photoacoustic imaging

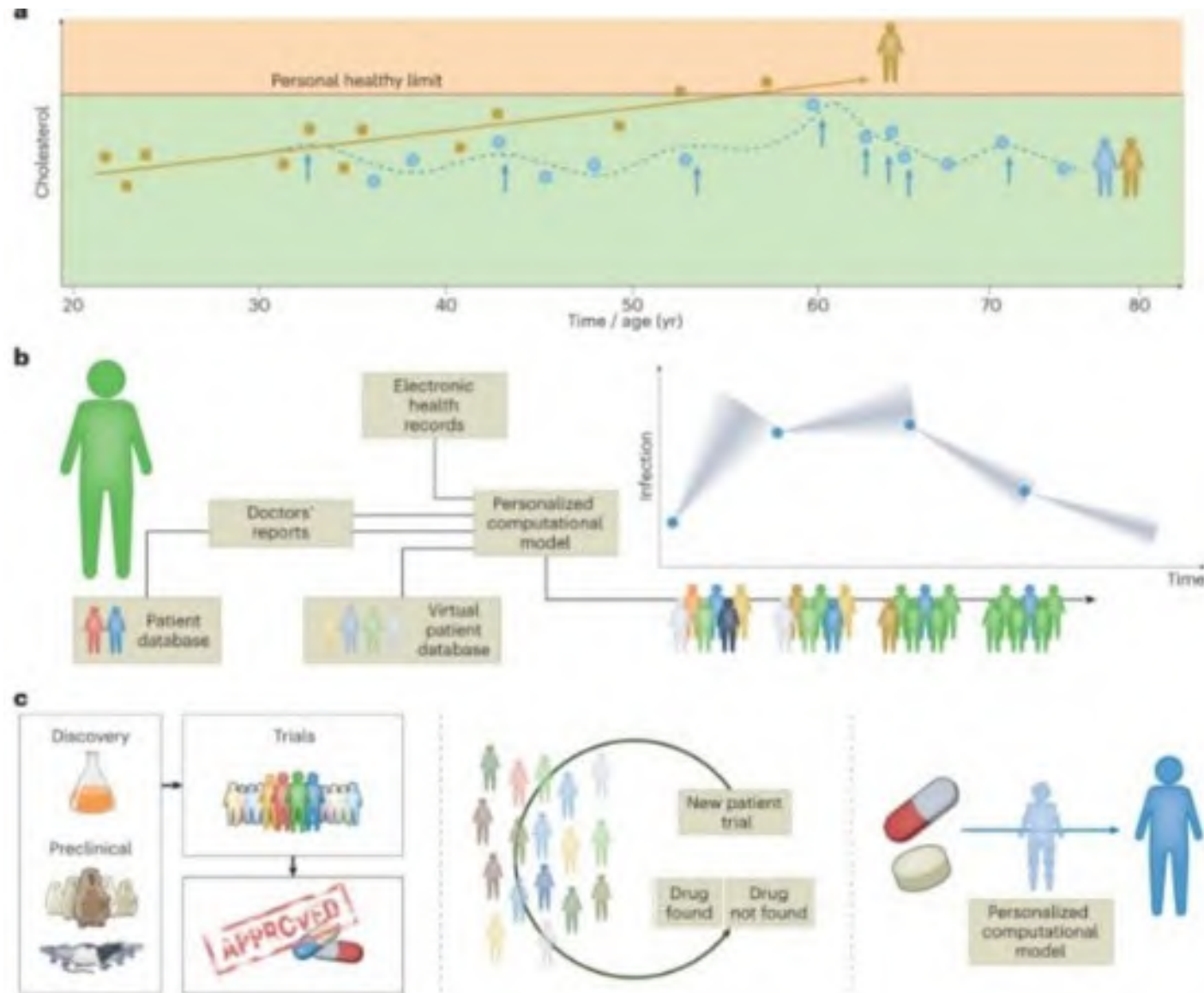


Furchgott et al, 1961



Chaudhury 2024; patent worthy

Digital Twin in NeuroGastroenterology



Careful history
Thorough physical
examination

[Turk J Gastroenterol.](#) 2021 Apr; 32(4): 336–348.

Published online 2021 Apr 1.

doi: [10.5152/tjg.2021.20514](https://doi.org/10.5152/tjg.2021.20514)

PMCID: PMC8975340 | PMID: [34231480](https://pubmed.ncbi.nlm.nih.gov/34231480/)

Patients with Specific Gastrointestinal
Motility Disorders are Commonly
Diagnosed as Functional GI Disorders in
the Early Stage by Community Physicians
due to Lack of Awareness

[Uday C. Ghoshal](#), [Bhavesh Bhut](#), and [Asha Misra](#)



What is the basis for multisystem involvement?

- 2 siblings from Ecuador, 11 and 14 yrs old
- Seizure disorders, pervasive neurodevelopmental disorder
- Achalasia
- Tuberculosis and recurrent fungal infections

WES showed nonsense mutation in NOS1 : (NOS1:NM_001204218:exon12:c.2027delG:p.G676fs).



Mind-body connection



Parcopresis

Seeing is believing



Collaborators

*Most Gratefully,
My Patients
Wasique Mirza
Connor Dougherty
Amit Munshi Sharma
Sreehari Cherukuri
Melad Kamel
Kishore Kumar*

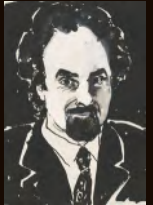
*Crawling on the
shoulder of giants*



Raj Goyal



Hemant Thatte



Geoff Burnstock



Srinivas Maddur



Jacqueline Zanoni



Renata
Pereira



Sayan Biswas



Bishnupriya Rout



Thank You

NIH DiaComp
Wellcome





? Questions

GIM Foundation

