



# *Too Hot, Too Cold, Too High, Too Low - Blame it on Dysautonomia!*

MitoAction Webcast

6-May, 2011

**Richard G. Boles, M.D.**

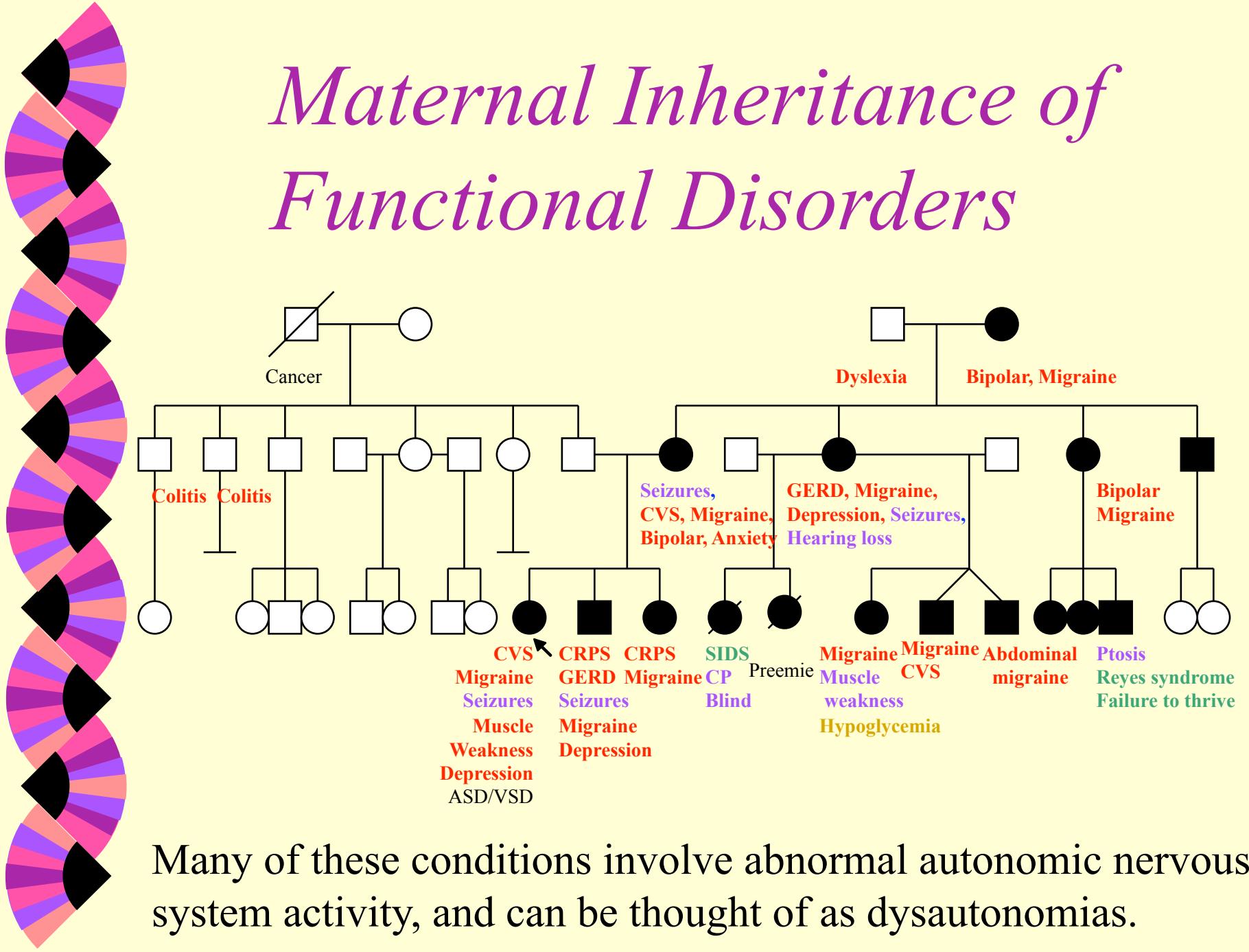
**Medical Genetics**

**Childrens Hospital Los Angeles**

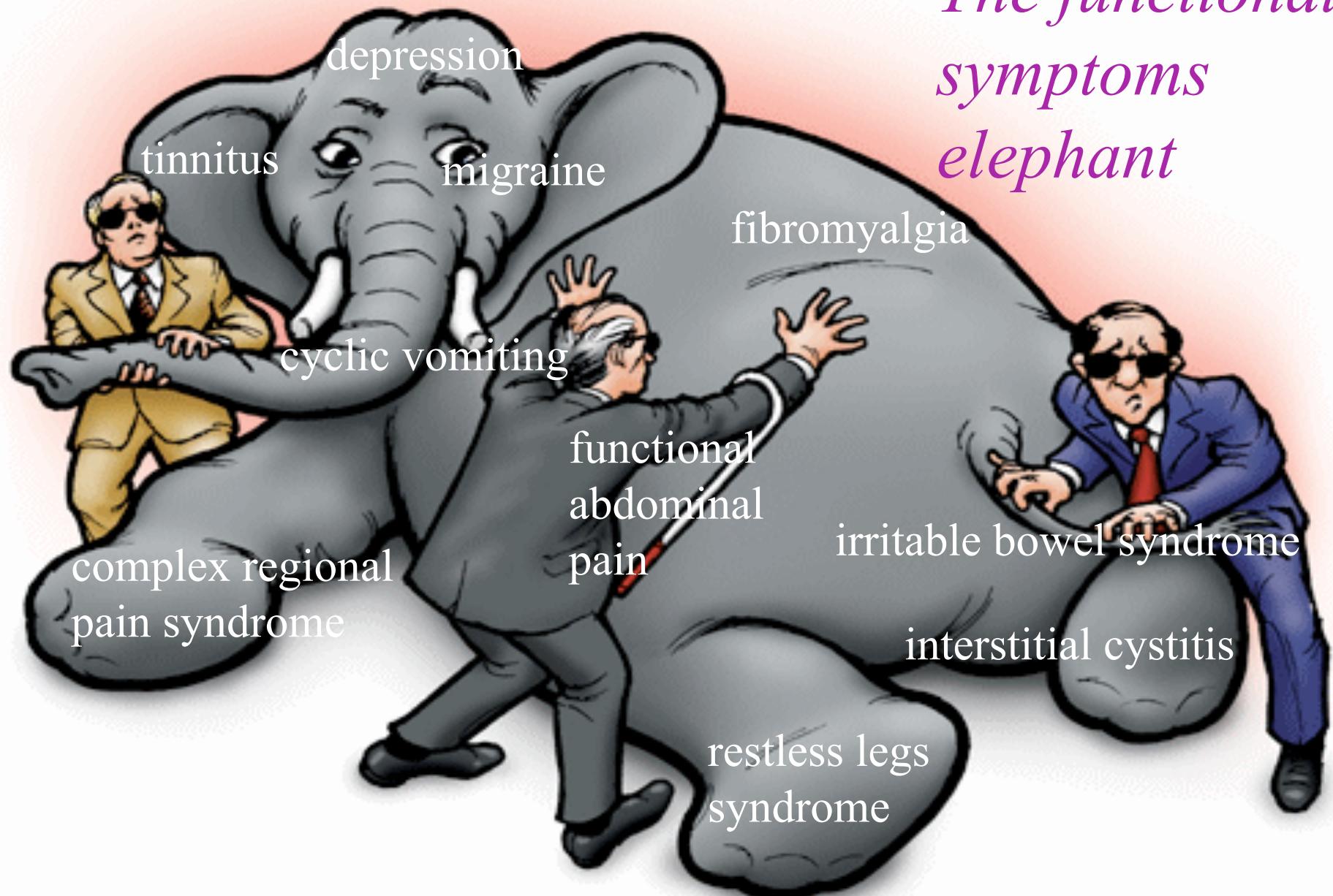
**Associate Professor of Pediatrics**

**Keck School of Medicine at USC**

# Maternal Inheritance of Functional Disorders



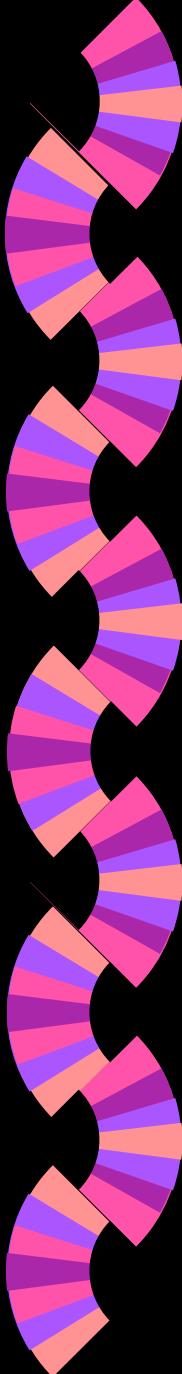
# *The functional symptoms elephant*



The elephant is lying down due to chronic fatigue



<http://newsfeed.time.com>



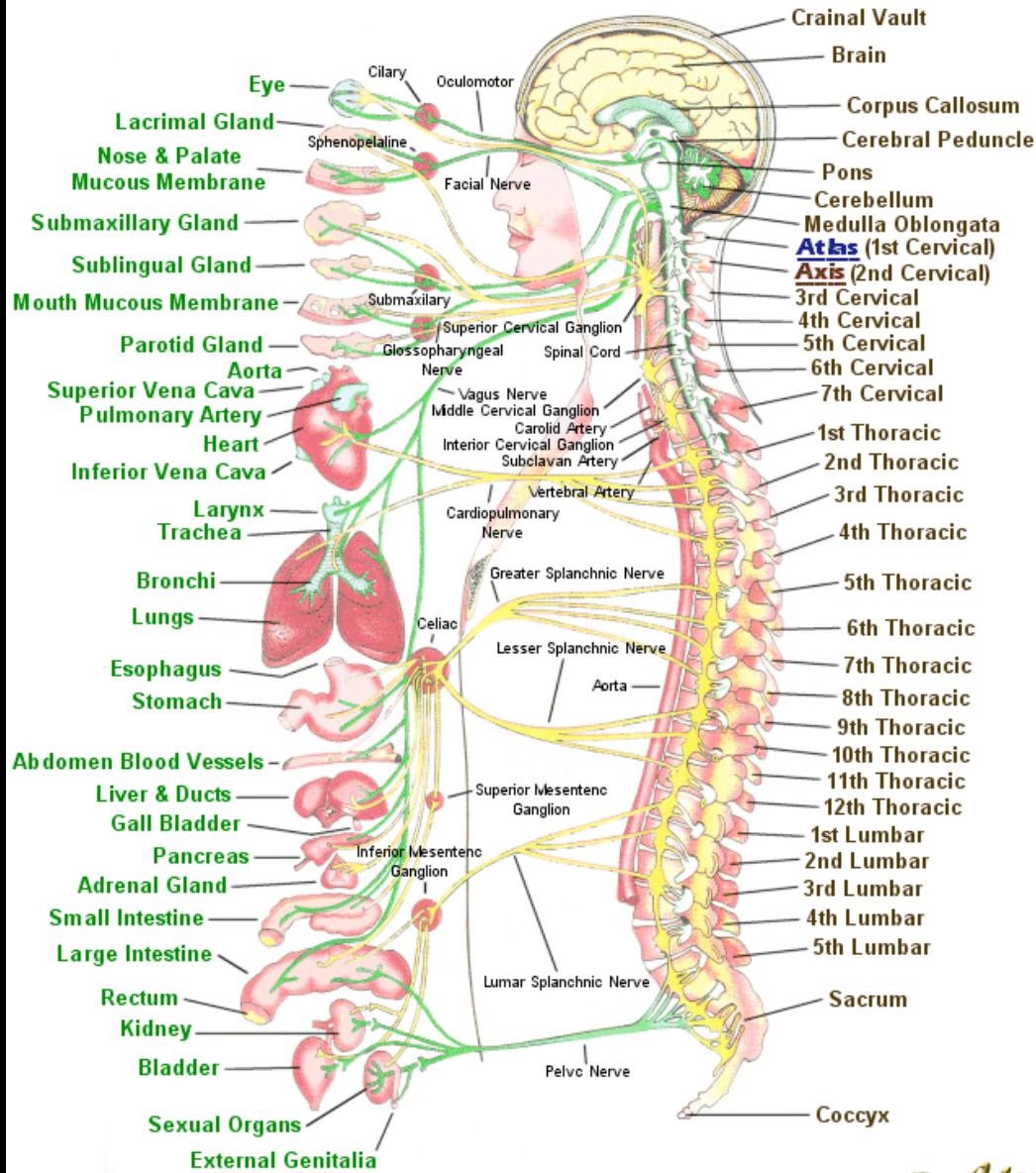
# *The Autonomic Nervous System Turns On and Off the “Fight or Flight” Response*

- ▶ Sympathetic Nervous System
  - On switch – tiger stalking
- ▶ Parasympathetic Nervous System
  - Off switch – tiger gone



# Autonomic Nervous System

Sympathetic - Yellow      Parasympathetic - Green

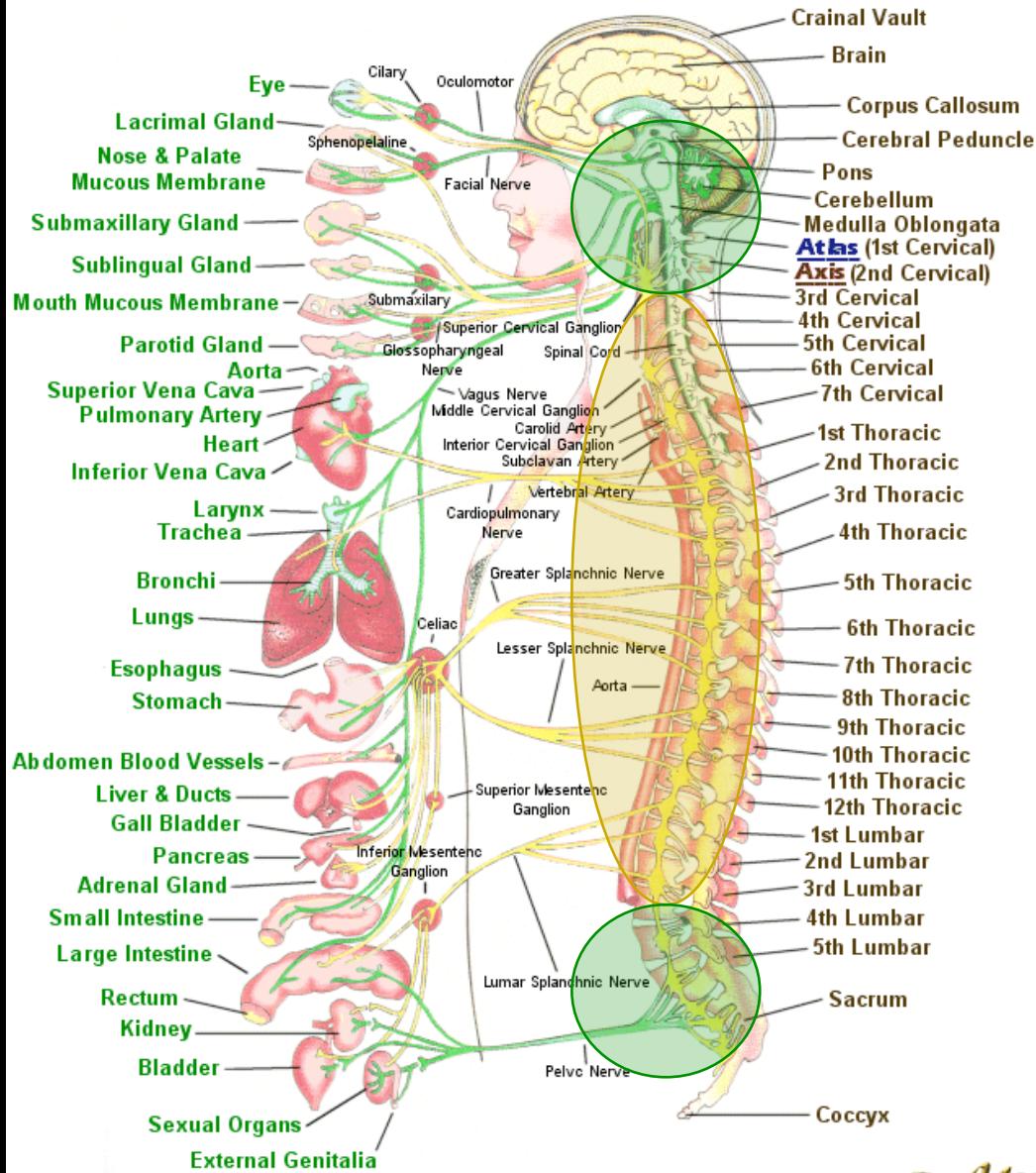


DrMac  
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# Autonomic Nervous System

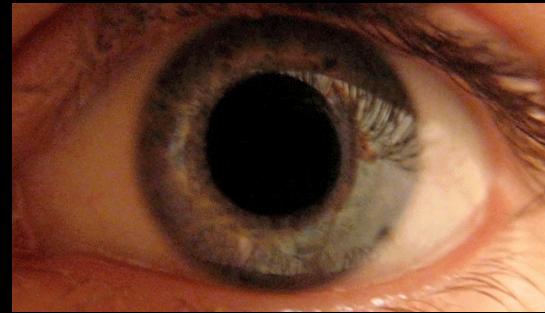
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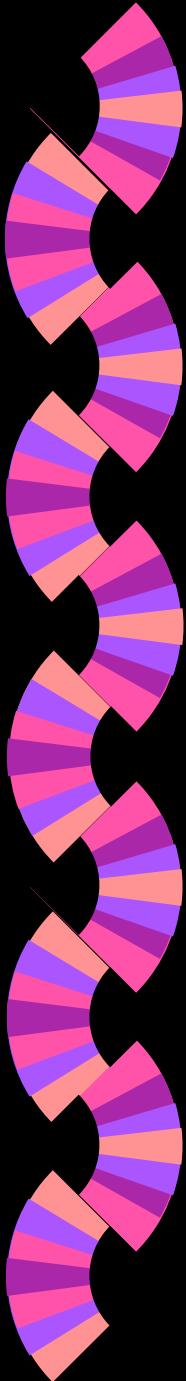
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# *Case Report*



- ▶ 15-year-old girl with cyclic vomiting syndrome, constipation and chronic fatigue
  - During vomiting episodes and viral infections she is unable to read.
    - Eye examinations are normal by two ophthalmologists.
    - The school is alleging psychiatric disease or malingering.
  - She is more comfortable wearing a hat, even indoors, and wears a hat to the clinic visit.

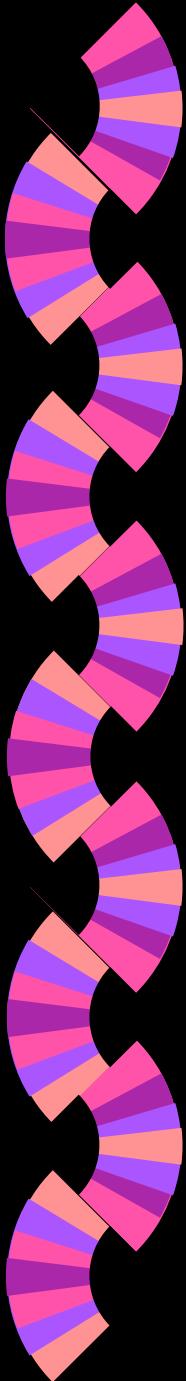


# *Autonomic Nervous System*

## *- The Eye*



- ▶ Sympathetic Nervous System
  - On switch – tiger stalking
    - Pupils dilate for better peripheral vision
    - Lens focuses on distance
- ▶ Parasympathetic Nervous System
  - Off switch – tiger gone
    - Pupils constrict to focus vision on central object
    - Lens focuses on near

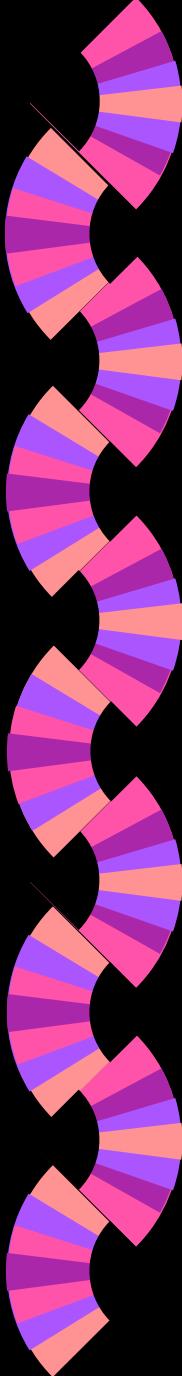


# *Autonomic Nervous System*

## *- The Eye*



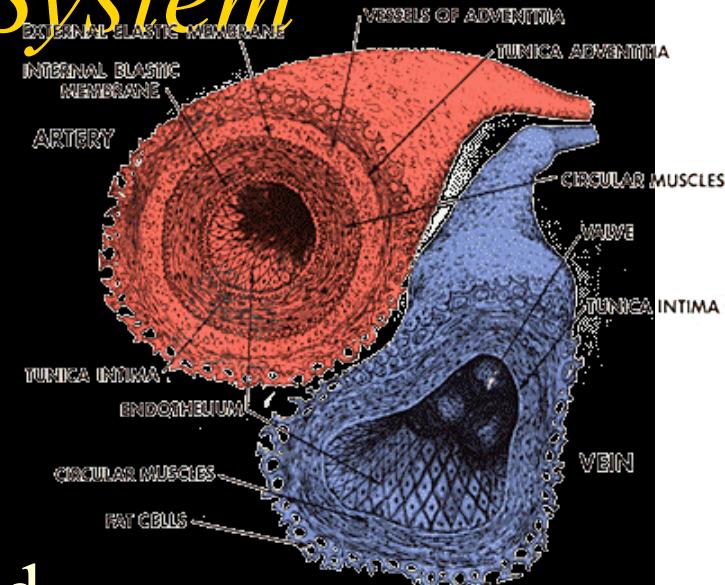
- ▶ Sympathetic Nervous System
  - On switch – tiger stalking
    - Pupils dilate for better peripheral vision causing photophobia; she is uncomfortable outdoors in the sunlight or under florescent lights. Wearing a hat is adaptive, so are sunglasses.
    - Lens focuses on distance making it difficult to read. The solution is reading glasses during illnesses.
- ▶ Parasympathetic Nervous System
  - Off switch – tiger gone
    - Pupils constrict to focus vision on central object
    - Lens focuses on near



# *Autonomic Nervous System*

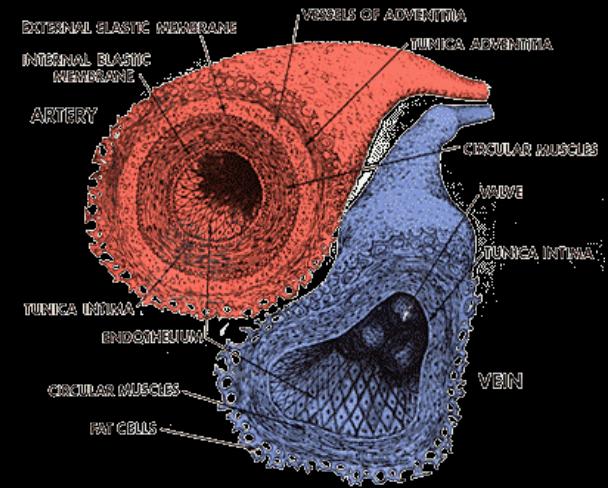
## *- Blood Vessels*

- ▶ Postural orthostatic tachycardia syndrome
- ▶ Color changes/rash: flushed, pallor, mottled, circles under eyes
- ▶ Heat and cold intolerance
- ▶ Pain syndromes
  - migraine/abdominal migraine
  - complex regional pain syndrome





# Case Report



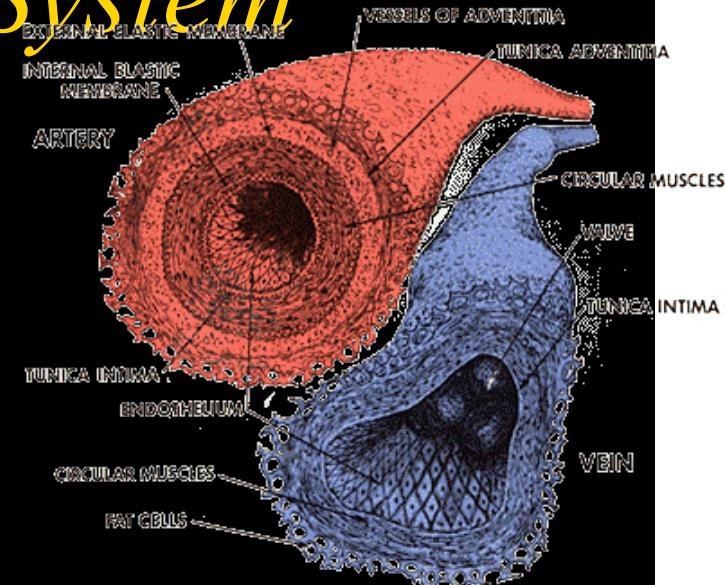
- ▶ 14-year-old boy with mild dysautonomic symptoms, including chronic pain syndromes. Sister and multiple matrilineal relatives have functional/dysautonomic-related symptoms/conditions
  - Presented with sudden episodes of loss of consciousness with pallor. Episodes are preceded by nausea and dizziness.



# *Autonomic Nervous System*

## *- Blood Vessels*

- ▶ Postural orthostatic tachycardia syndrome
  - Dizziness, blackouts
  - Often precipitated by standing up
  - More common in adolescents
  - First-line treatment is increased fluids and salt
  - Can be dramatic and appear as seizure
  - May require medication

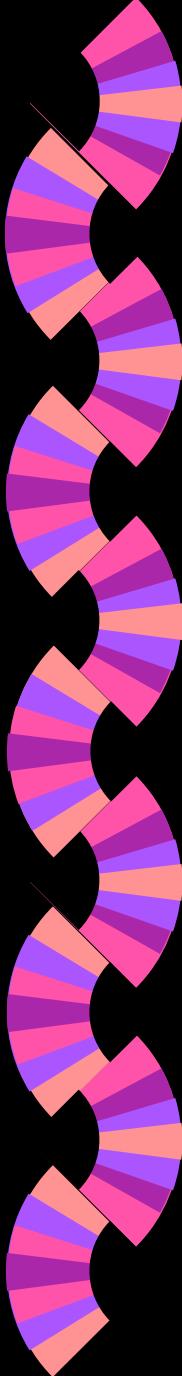




# *Complex Regional Pain Syndrome-I:*

Symptoms:  
alodynbia,  
painful,  
edematous,  
cold, purple,  
unable to stand  
or walk

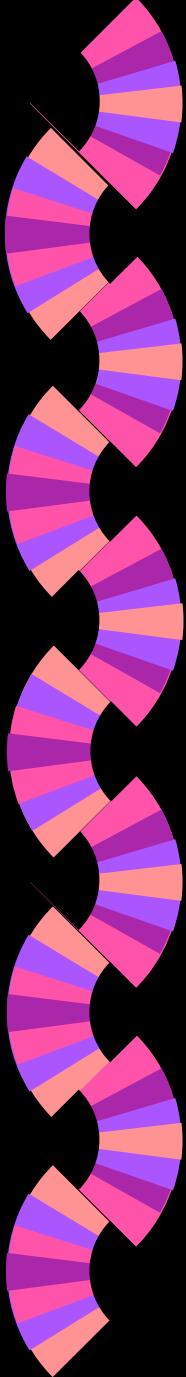




# *Complex Regional Pain Syndrome-I:*

Treatment:  
exercise/PT  
do not immobilize  
IVF D10+lytes  
amitriptyline  
coenzyme Q10



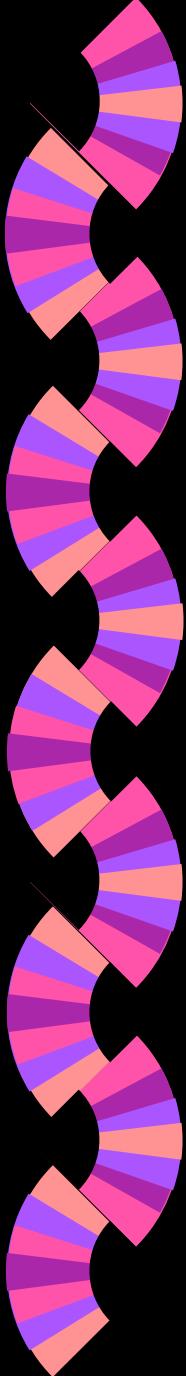


# *Autonomic Nervous System*

## *- The Heart*

- ▶ Fast (tachycardia) and slow (bradycardia) heart rates are very common in mito disease.
- ▶ In adults, heart attacks are not uncommon, but rare in children. Usually, there was a trigger (Imitrex, surgery) or no mito-care.
- ▶ Chest pain in mito kids is almost always GERD, and occasionally costochondritis.
- ▶ Syncope is usually due to dysautonomia.
- ▶ Cardiac birth defects are likely increased.





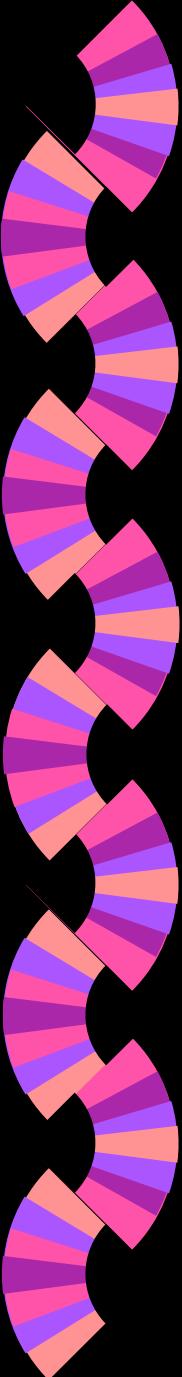
# *Autonomic Nervous System*

## *- Secretory Glands*

- ▶ Sweat glands
- ▶ Salivary glands
- ▶ Lacrimal (tear) glands
- ▶ Mammary (milk) glands
- ▶ Reproductive system glands
- ▶ Digestive system glands

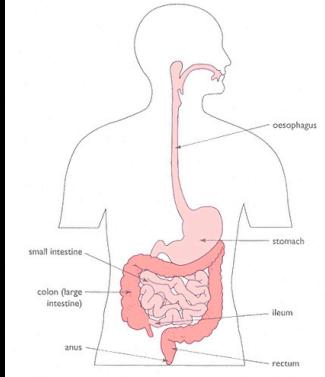


[www.buzzle.com](http://www.buzzle.com)

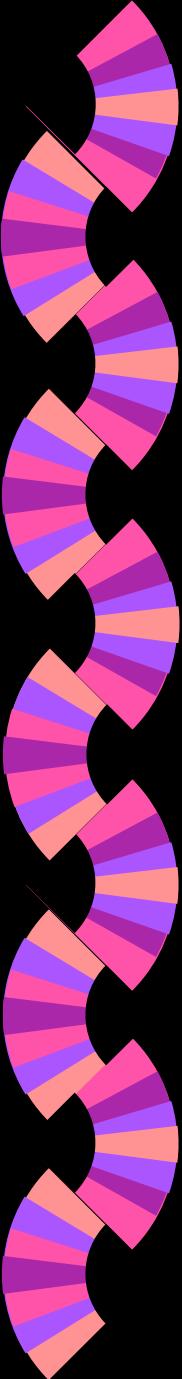


# *Autonomic Nervous System*

## *- The Gut*

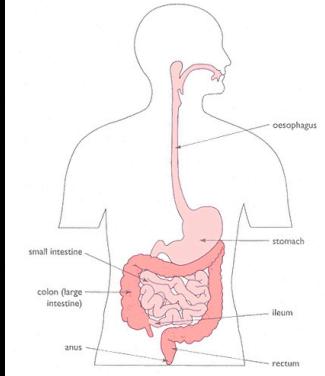


- Sympathetic Nervous System
  - On switch – tiger stalking
    - Blood flow increases to brain and muscle, for quick thinking and the power to act.
    - Blood flow decreases to the gut, this is no time for digestion.
- Parasympathetic Nervous System
  - Off switch – tiger gone
    - Blood flow increases to the gut allowing for digestion.



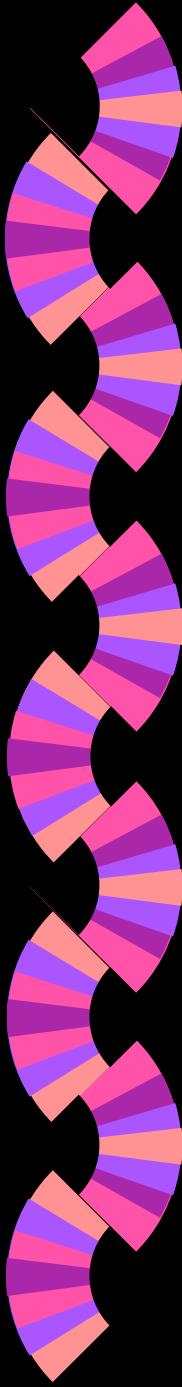
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## *- The Gut*



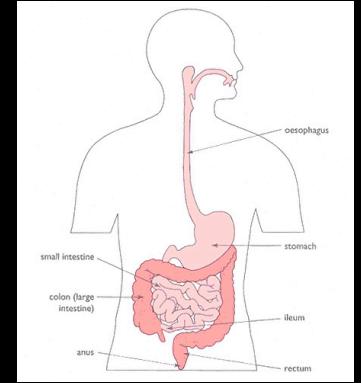
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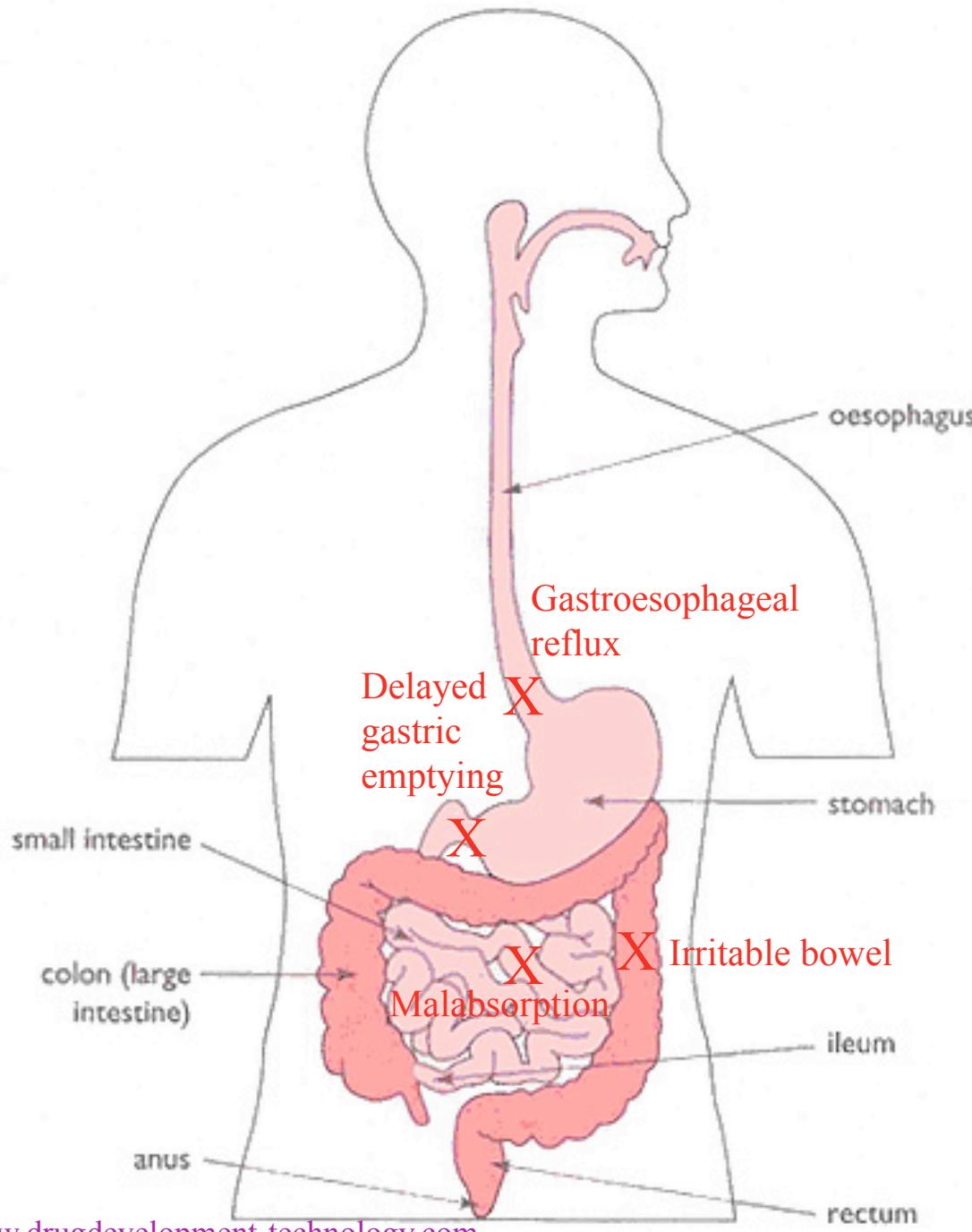
Thus, “indigestion” caused by decreased gut dysmotility is common in sympathetic-driven conditions precipitated in part by mitochondrial dysfunction.



# *Dysmotility = bad movement*

- ▶ Abnormal rate
  - Fast: dumping, diarrhea
  - Slow: bloating, constipation
- ▶ Direction
  - GERD
  - Vomiting
- ▶ Failure (very poor motility)
  - Pyloric stenosis
  - Malabsorption
  - Pseudoobstruction





## *Mito-dysmotility*

Often occurs at different levels in the same child

Intermittent

Very common in mito disease

Occurs in many different mito disorders

Another example of mito disease preferentially affecting the high-energy demand tissues of muscle and nerve:

The GI tract is composed of muscle, and synchronized by nerves.

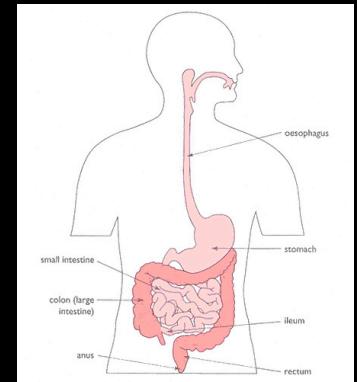


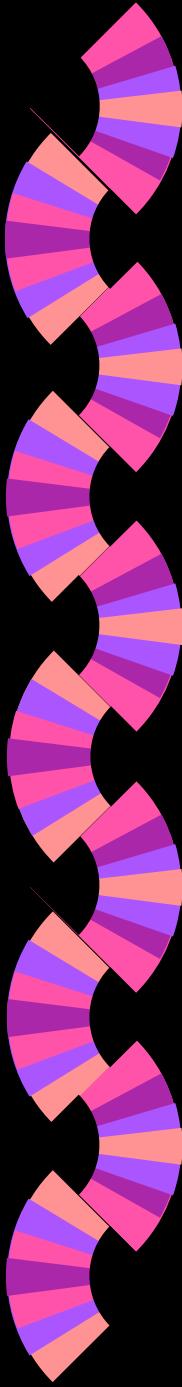
# *Level of Dysmotility: Esophagus*

## *Gastroesophageal Reflux Disease*

### **“GERD”**

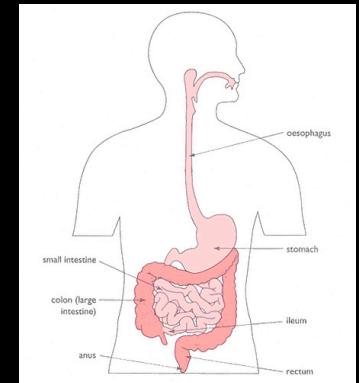
- ▶ High prevalence:
  - Very common in the general population.
  - Nearly universal in mito
- ▶ Clinical presentations: quite varied:
  - Heartburn, abdominal pain
  - Chronic nausea
  - Chronic sinusitis, “allergy”
  - Cough, “asthma”
  - Failure-to-thrive
  - Malaise, fatigue

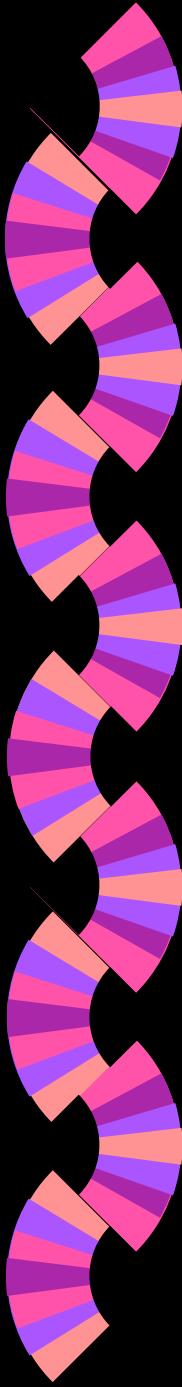




# *Level of Dysmotility: Esophagus Gastroesophageal Reflux Disease “GERD”*

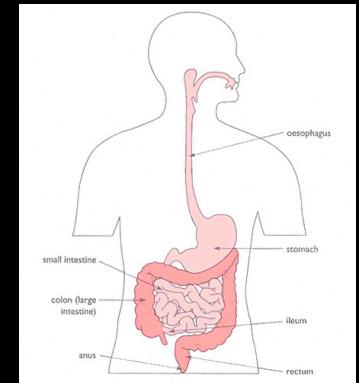
- ▶ Diagnosis:
  - Scans (nuclear medicine, upper GI)
  - Tubes (pH probe, endoscopy)
  - Response to empirical treatment
- ▶ Treatment:
  - Mechanical (angle bed)
  - Diet
    - thicken feeds
    - small, frequent meals/snacks
    - low-fat “heart-healthy diet”
  - Antacids
  - Acid blockers (Zantac)
  - Proton pump inhibitors (Prilosec OTC, Protonex, Aciphex, Nexium)
- ▶ Prognosis: Usually intermittent, worse in babies and elderly





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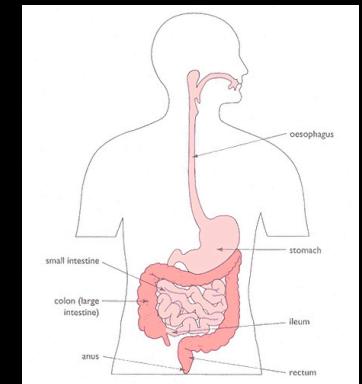
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# *Level of Dysmotility: Stomach Delayed Gastric Emptying*

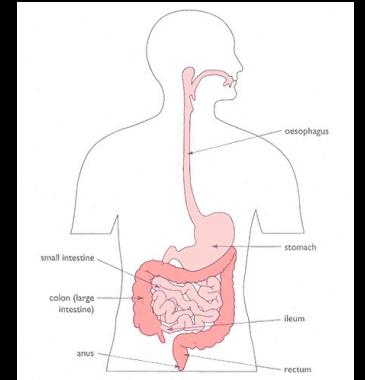
- ▶ Intermediate prevalence
- ▶ Causes
  - Stomach failure (gastroparesis)
  - Outlet obstruction (pyloric stenosis)
- ▶ Clinical presentations:
  - Abdominal pain
  - Bloating
  - Chronic nausea
  - Early satiety
  - Failure-to-thrive





# *Level of Dysmotility: Stomach Delayed Gastric Emptying*

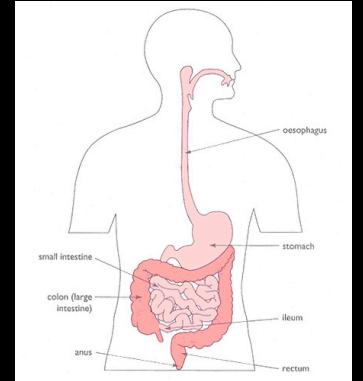
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  - Response to empirical treatment
- ▶ Treatment:
  - Diet
    - small, frequent meals/snacks
    - low-fat “heart-healthy diet”
    - liquid/pureed diet
  - Medications - prokinetic drugs (Reglan)
  - Surgery
    - pyloroplasty
    - bypass stomach (J-tube or G-J-tube)
- ▶ Prognosis: Intermittent or progressive





# *Level of Dysmotility: Stomach Delayed Gastric Emptying*

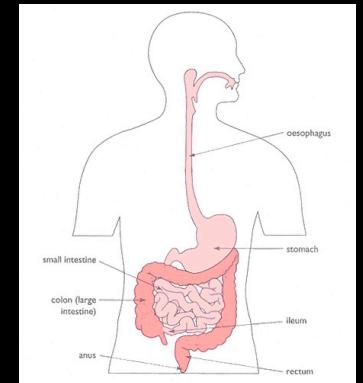
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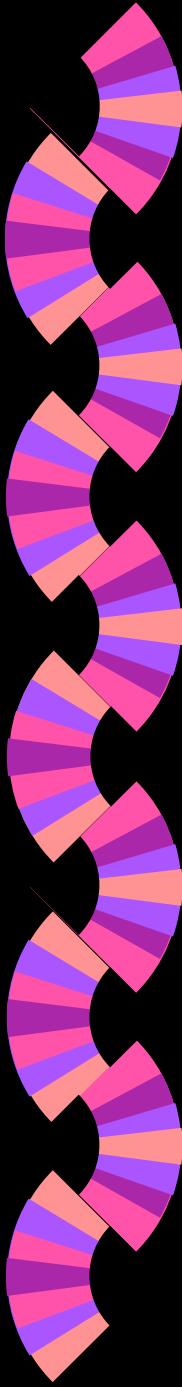




# *Level of Dysmotility: Small Intestine Malabsorption*

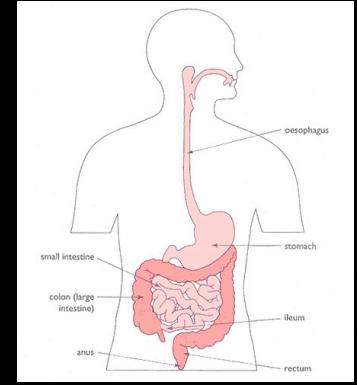
- ▶ Low prevalence
- ▶ Clinical presentations:
  - Diarrhea
  - Failure-to-thrive
  - Metabolic decompensation (fasting-invoked)

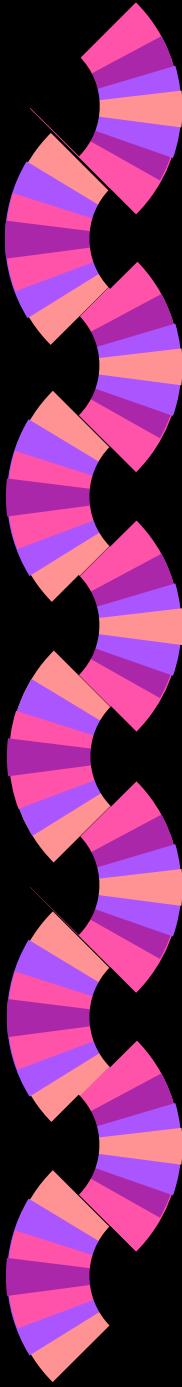




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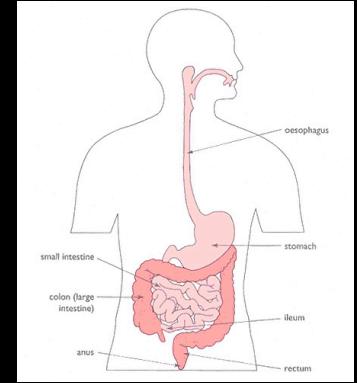
- ▶ Diagnosis:
  - Imaging (nuclear medicine, upper GI)
  - Tubes (pH probe, endoscopy, colonoscopy)
  - Capsule
  - Motility studies
- ▶ Treatment:
  - Diet
    - small, frequent meals/snacks
    - low-fat “heart-healthy diet”
    - liquid/pureed diet
    - elemental diet
  - Medications
    - antibiotics (small intestine bacterial overgrowth = SIBO)
    - probiotics
  - Parental nutrition (“TPN”)
- ▶ Prognosis: Often progressive, SIBO is treatable





# *Level of Dysmotility: Small Intestine Malabsorption*

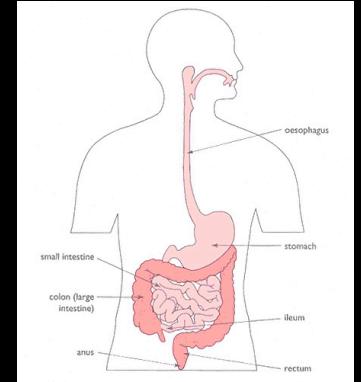
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# *Level of Dysmotility: Large Intestine Irritable Bowel*

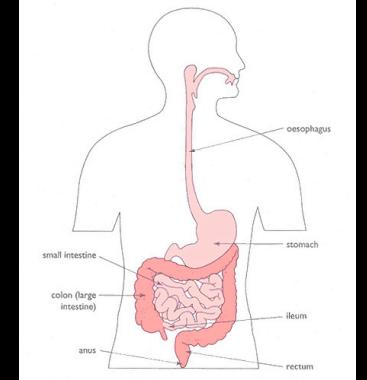
- ▶ High prevalence:
  - Very common in the general population.
  - Nearly universal in mito
- ▶ Clinical presentations:
  - Constipation
  - Diarrhea
  - Alternating constipation and diarrhea
  - Abdominal pain (usually relieved by BM)
  - Distension/bloating
  - Vomiting
  - Failure-to-thrive
  - Metabolic decompensation (fasting-invoked)

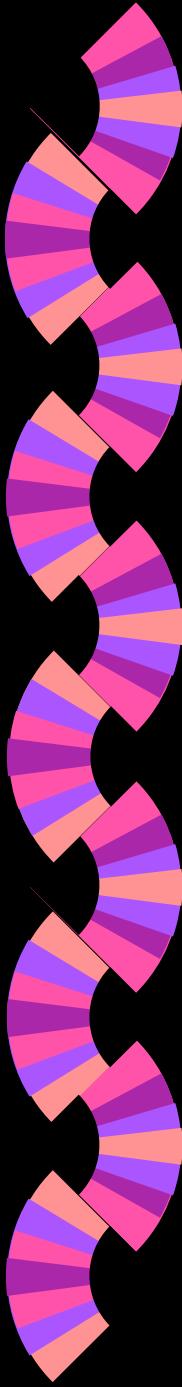




# *Level of Dysmotility: Large Intestine Irritable Bowel*

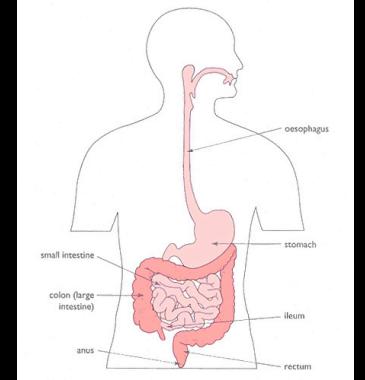
- ▶ Diagnosis:
  - Imaging (x-ray for stool)
  - Tubes (colonoscopy)
  - Motility studies
- ▶ Treatment:
  - Diet
    - low-fat “heart-healthy diet”
    - prune juice, etc.
  - Medications
    - Polyethylene glycol (MiraLax, GoLytely)
    - Milk of magnesia
    - Amitiza
  - Mechanical (enemas)
- ▶ Prognosis: Usually intermittent, serious cases can progress to pseudoobstruction





# *Level of Dysmotility: Large Intestine Irritable Bowel*

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## *Diagnosis*

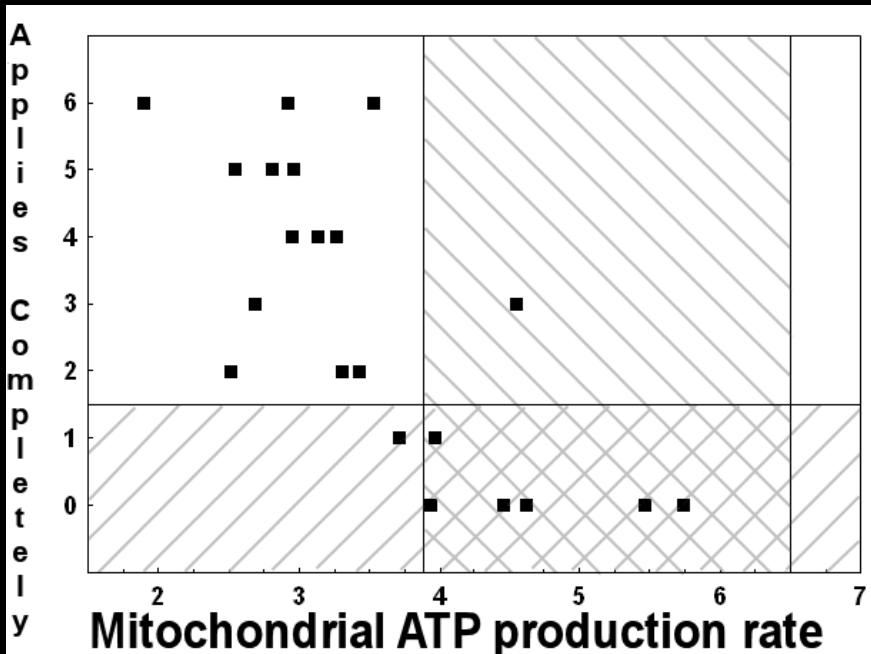
- ▶ Clinical – intermittent, multiple functional symptoms
- ▶ Increased symptoms with illness, fasting
- ▶ Maternal inheritance
- ▶ Urine organic acids, ketosis
- ▶ Other biochemical testing
- ▶ mtDNA sequencing
- ▶ Ruling out other possible diagnoses
- ▶ Response to mitochondrial-targeted therapies



# *Six Questions Predict Mitochondrial Function*

## *Gardner and Boles, Bio Psycho Soc Med 2008*

- "My heart sometimes beats hard or irregularly for no real reason." (*Somatic Anxiety*, item 34,  $p = 0.003$ ).
- "I often have aches in my shoulders and in the back of my neck." (*Muscular Tension*, item 4,  $p = 0.031$ ).
- "My body often feels stiff and tense." (*Muscular Tension*, item 33,  $p = 0.031$ ).
- "I think I must economize my energy." (*Psychasthenia*, item 40,  $p = 0.015$ ).
- "In order to get something done I have to spend more energy than most others." (*Psychasthenia*, item 53,  $p = 0.031$ ).
- "I feel easily pressured when I am urged to speed up." (*Psychasthenia*, item 93,  $p = 0.014$ ).

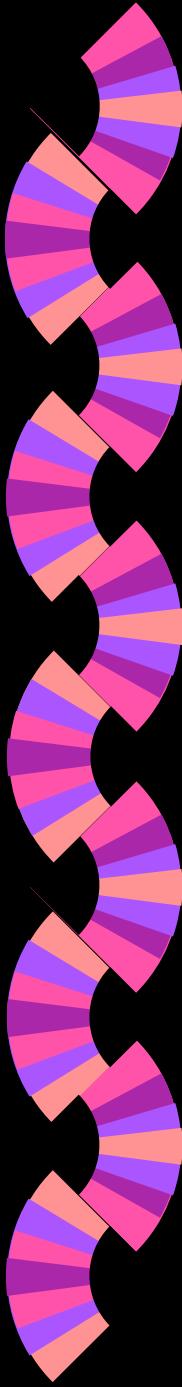


**13/14 subjects with ATP production rates below the normal range answered at least two of those six items as “Applies Completely”, compared to only 1/7 subjects with ATP production rates within our control range (chi-square P = 0.0003).**



## *Therapy: General Principles*

- ▶ Combine mitochondrial-directed treatment together with symptom-directed treatment.
- ▶ Mitochondrial-directed treatment is to:
  - Decrease energy demand
  - Increase energy supply



# *Therapy: Agents*

- ▶ Lifestyle Changes:
  - Fasting avoidance
    - “3+3 diet”
    - Special caution during viral illnesses, may need IV fluid
  - Hydration
  - Exercise in moderation
- ▶ Cofactors:
  - Co-enzyme Q10
  - L-carnitine
  - Riboflavin
  - Creatine
  - Antioxidants (vitamins C and E)
- ▶ Medications:
  - “Psychtropics” (amitriptyline)
  - PPIs (Prilosec)
  - PEG (Miralax)

