



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

MitoAction Webcast

6-May, 2011

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

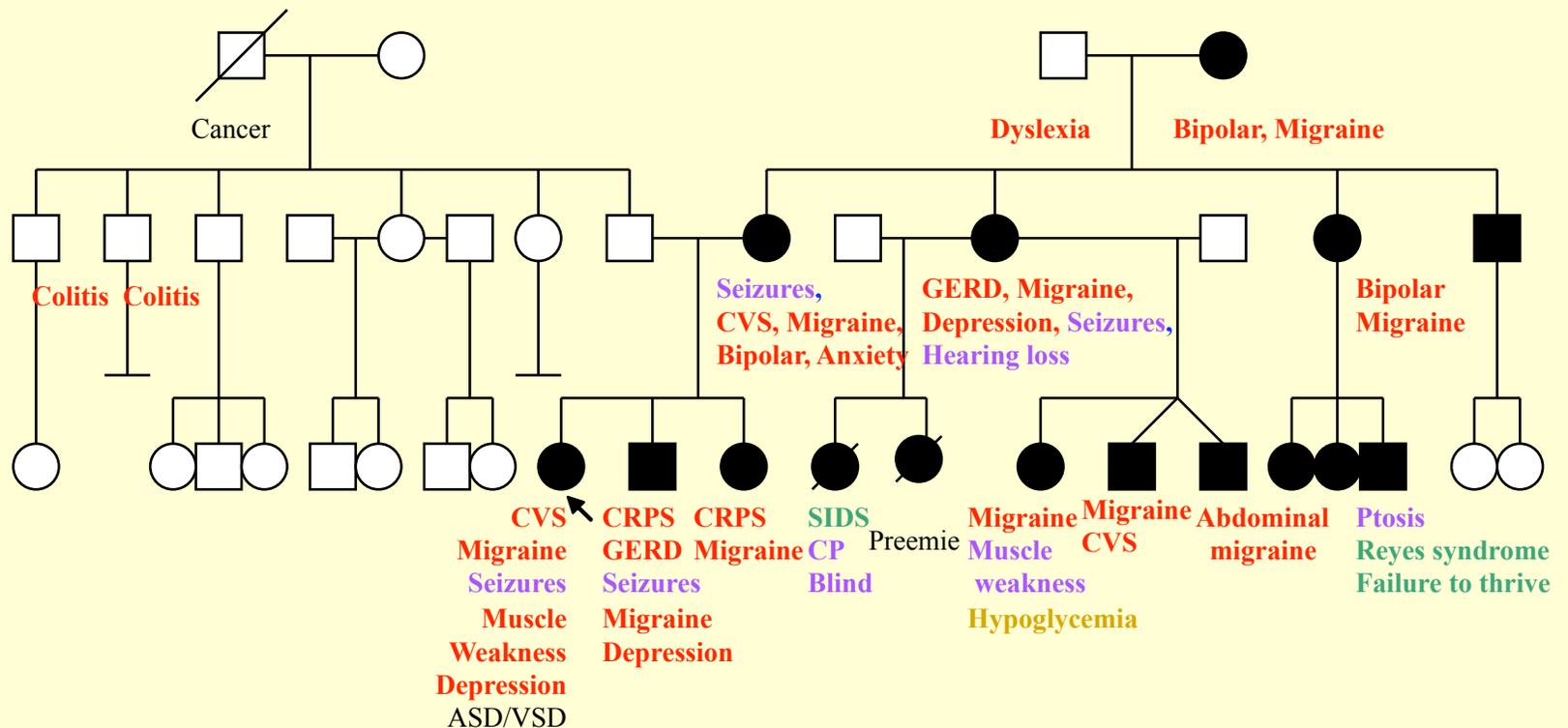
**Medical Genetics**

**Childrens Hospital Los Angeles**

**Associate Professor of Pediatrics**

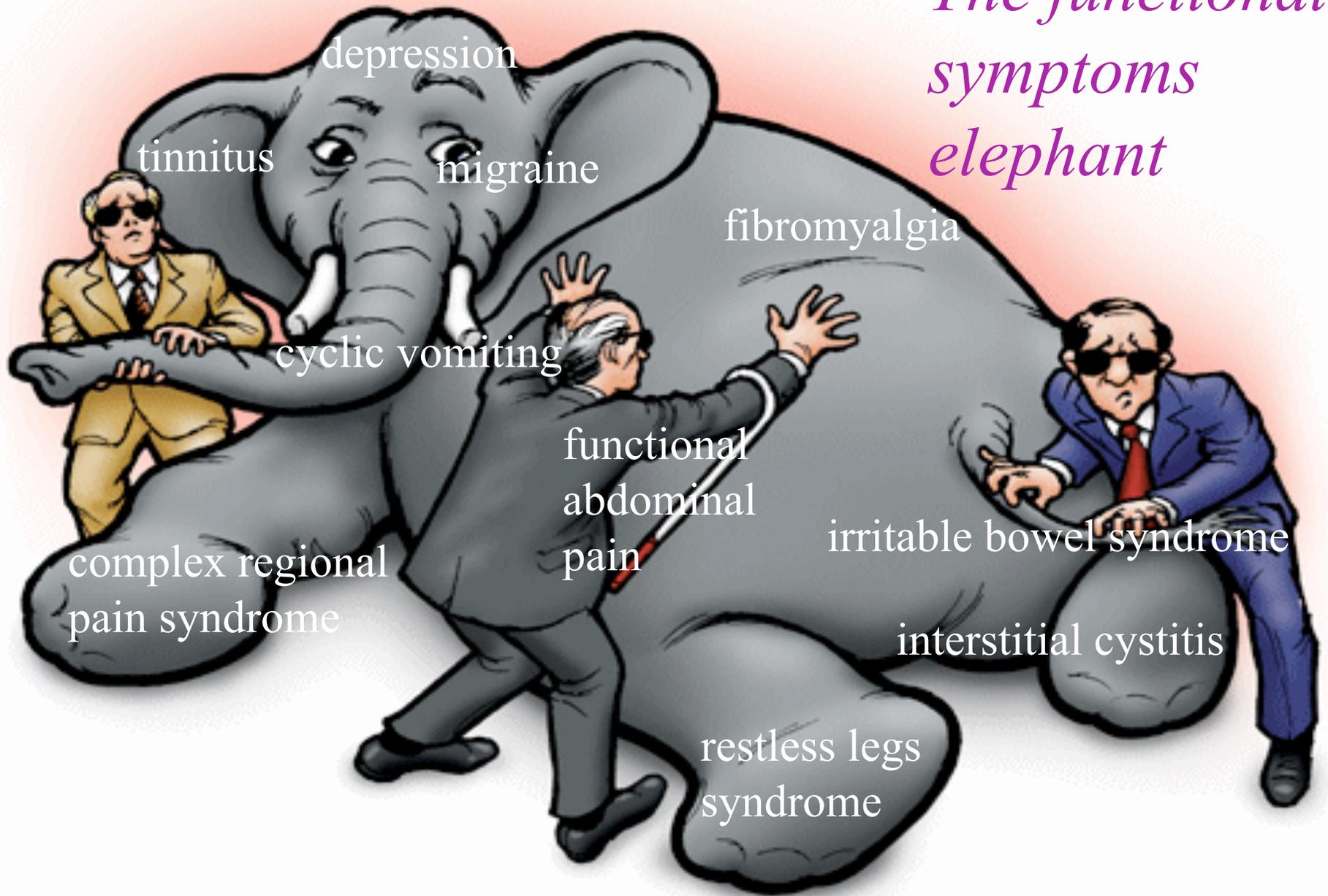
**Keck School of Medicine at USC**

# Maternal Inheritance of Functional Disorders



Many of these conditions involve abnormal autonomic nervous system activity, and can be thought of as dysautonomias.

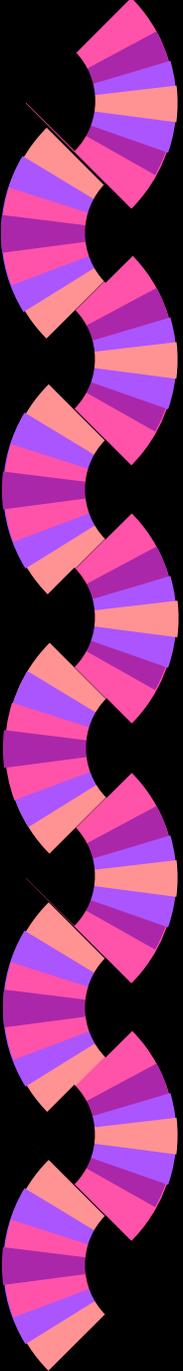
# *The functional symptoms elephant*



*The elephant is lying down due to chronic fatigue*

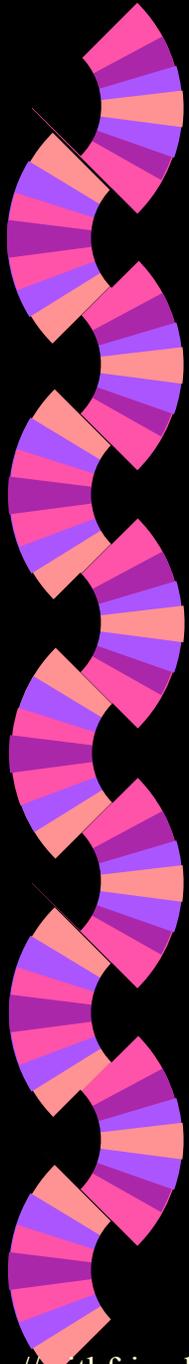


<http://newsfeed.time.com>



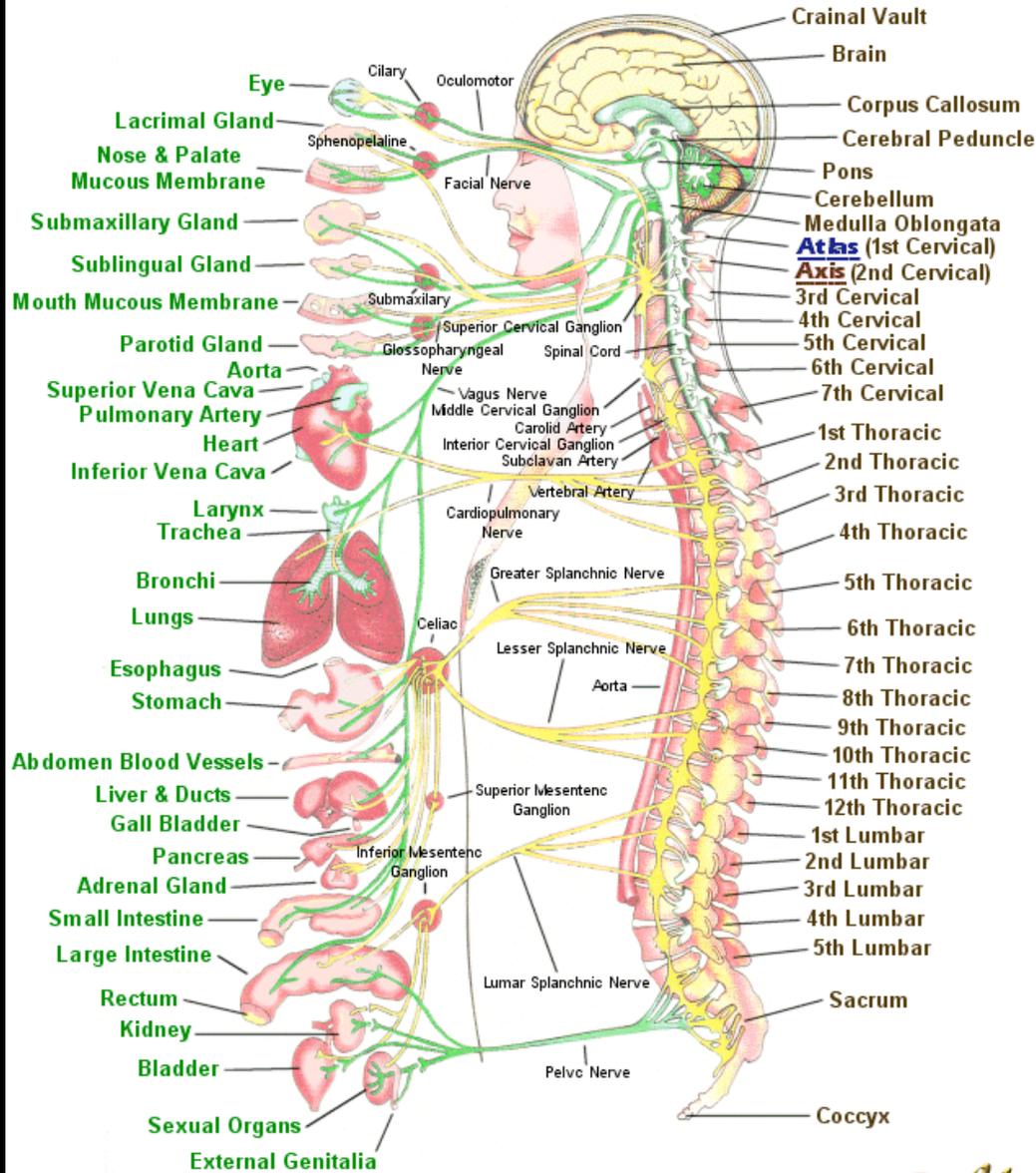
# *The Autonomic Nervous System Turns On and Off the “Fight or Flight” Response*

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

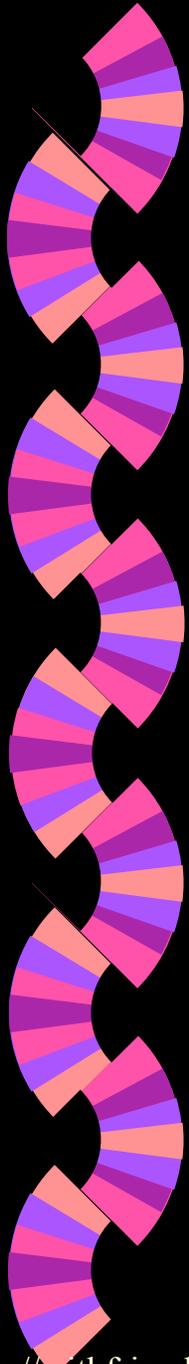


# Autonomic Nervous System

Sympathetic - Yellow      Parasympathetic - Green

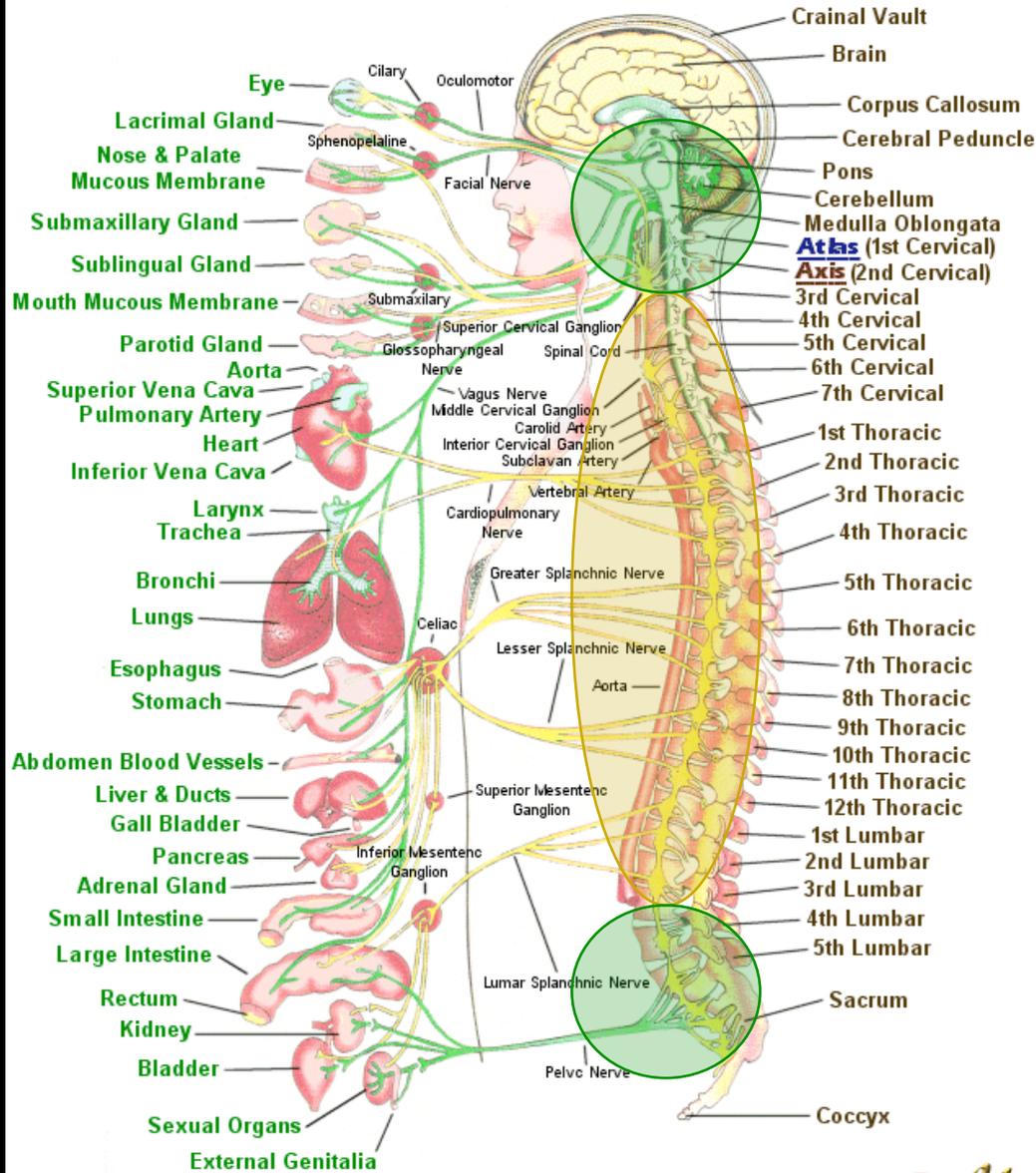


*DrMae* DC.COM



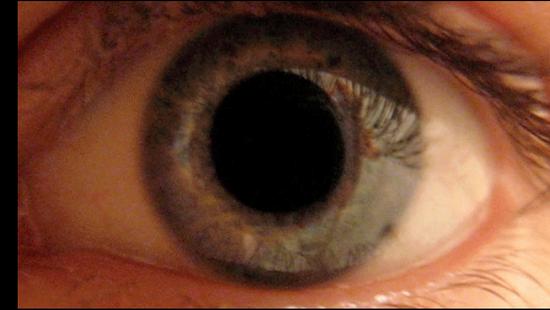
# Autonomic Nervous System

Sympathetic - Yellow      Parasympathetic - Green



DrMae<sup>DC.com</sup>

# *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.

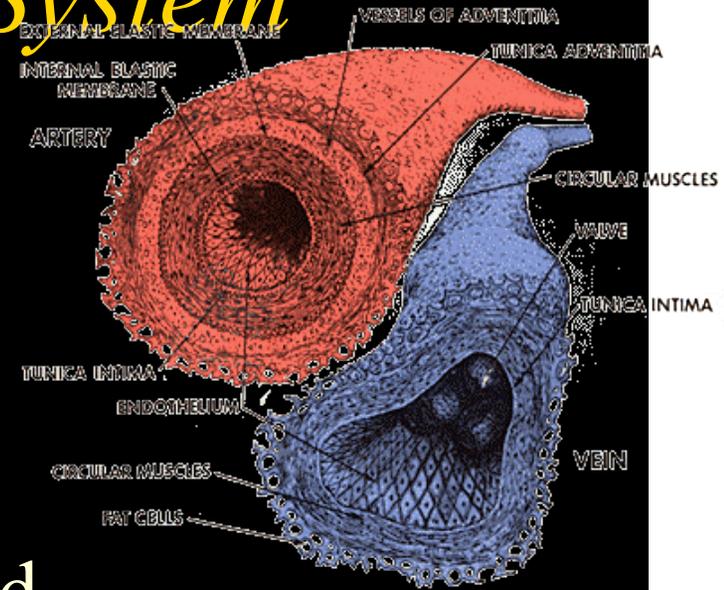
### ▶ Parasympathetic Nervous System

- Off switch – tiger gone
  - Pupils constrict to focus vision on central object
  - Lens focuses on near

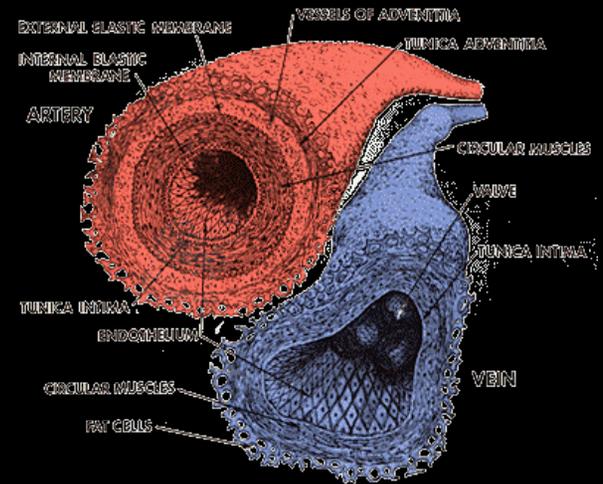
# *Autonomic Nervous System*

## *- 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



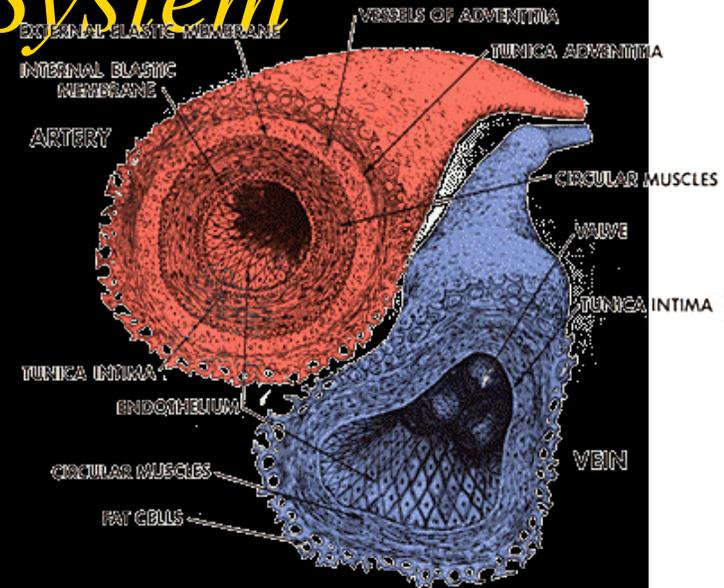
- 14-year-old boy with mild dysautonomic symptoms, including chronic pain syndromes. Sister and multiple matrilineal relatives have functional/dysautonomic-related symptoms/conditions
  - Presented with sudden episodes of loss of consciousness with pallor. Episodes are preceded by nausea and dizziness.

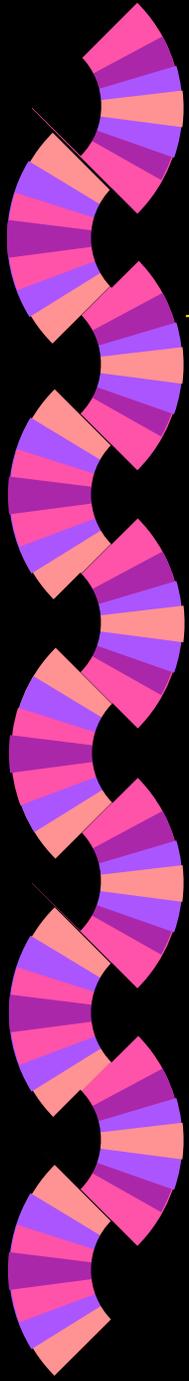
# *Autonomic Nervous System*

## *- Blood Vessels*

### • Postural orthostatic tachycardia syndrome

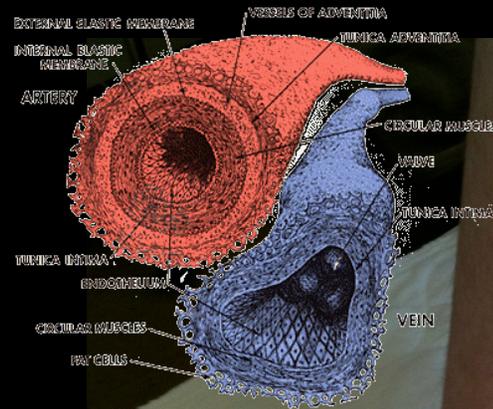
- Dizziness, blackouts
- Often precipitated by standing up
- More common in adolescents
- First-line treatment is increased fluids and salt
- Can be dramatic and appear as seizure
- May require medication

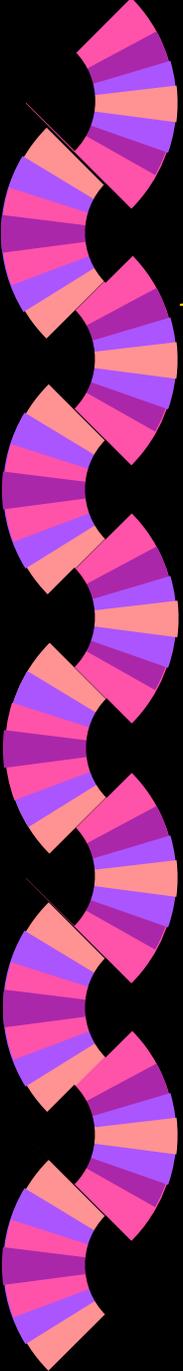




# *Complex Regional Pain Syndrome-I:*

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





# *Complex Regional Pain Syndrome-I:*

Treatment:

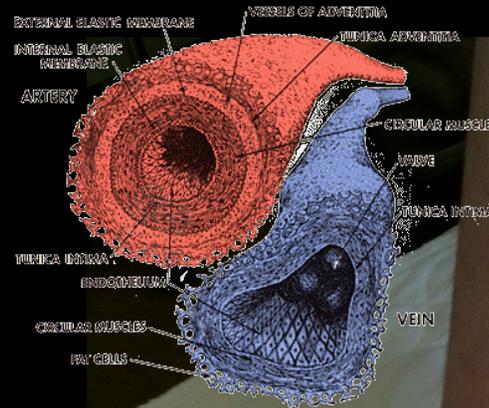
exercise/PT

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*

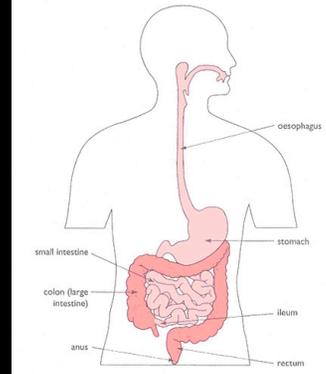
- ▶ Sweat glands
- ▶ Salivary glands
- ▶ Lacrimal (tear) glands
- ▶ Mammary (milk) glands
- ▶ Reproductive system glands
- ▶ Digestive system glands



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

# *Autonomic Nervous System*

## *- The Gut*



### ▶ Sympathetic Nervous System

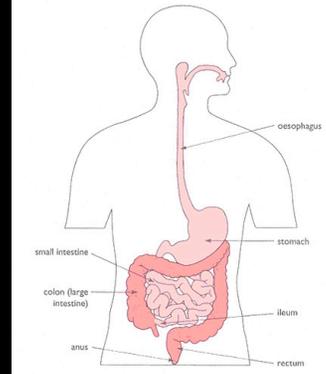
- On switch – tiger stalking
  - Blood flow increases to brain and muscle, for quick thinking and the power to act.
  - Blood flow decreases to the gut, this is no time for digestion.

### ▶ Parasympathetic Nervous System

- Off switch – tiger gone
  - Blood flow increases to the gut allowing for digestion.

# *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.

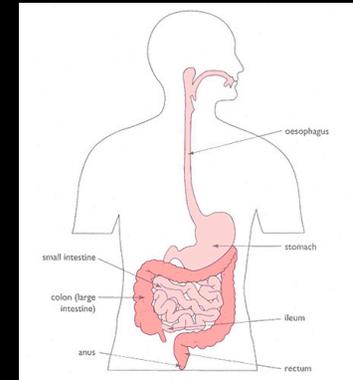
### ▶ Parasympathetic Nervous System

- Off switch – tiger gone
  - Blood flow increases to the gut allowing for digestion.

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

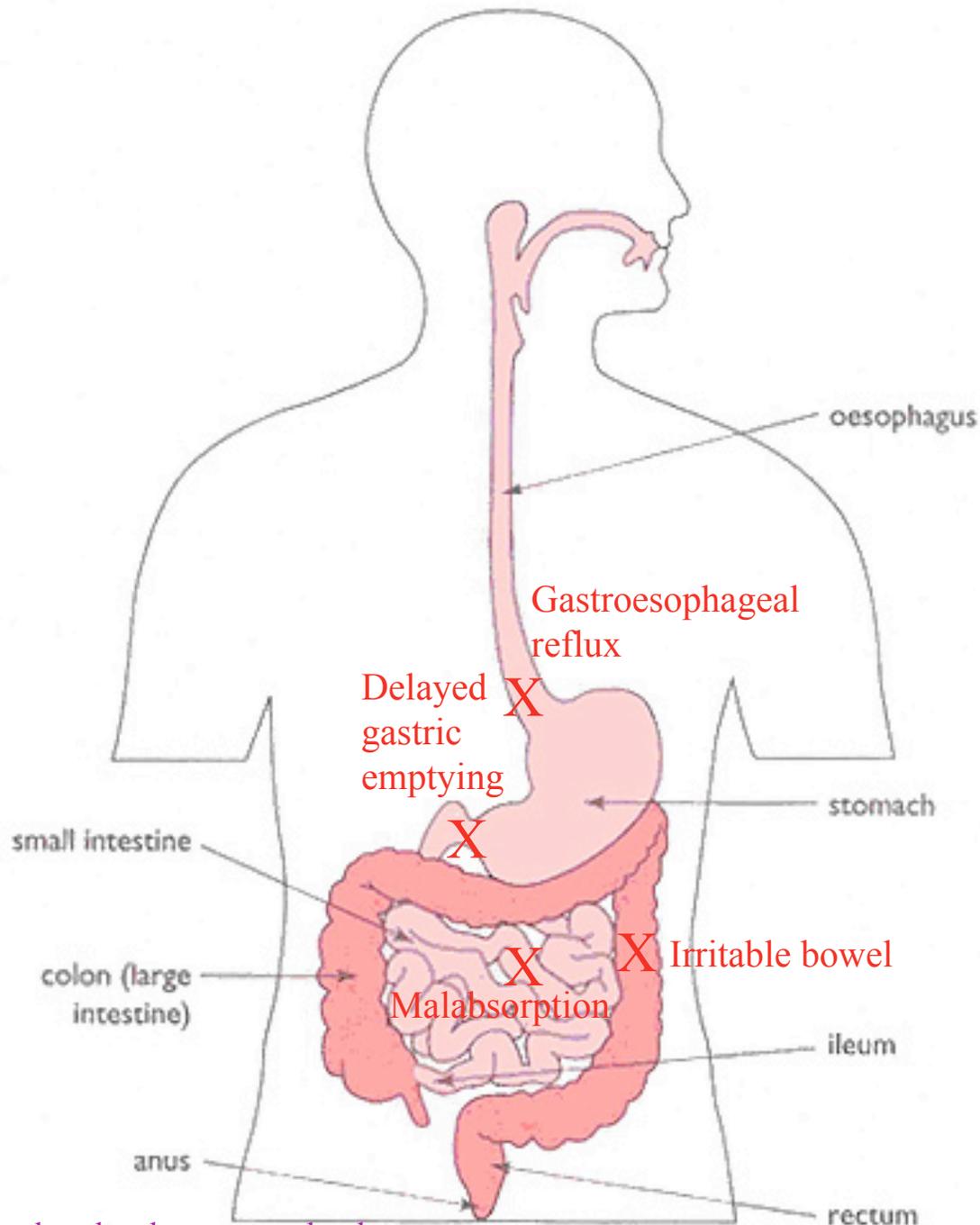
Intermittent

Very common in mito disease

Occurs in many different mito disorders

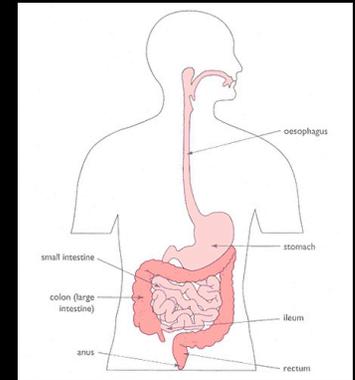
Another example of mito disease preferentially affecting the high-energy demand tissues of muscle and nerve:

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”*

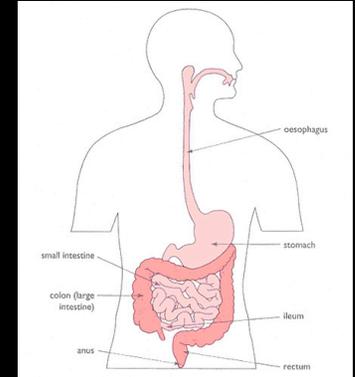
## • Diagnosis:

- 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



# *Level of Dysmotility: Esophagus*

## *Gastroesophageal Reflux Disease*

### *“GERD”*

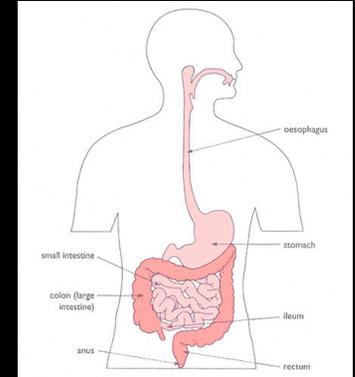
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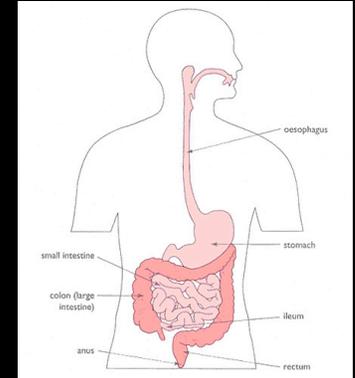
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# *Level of Dysmotility: Stomach Delayed Gastric Emptying*

- 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*

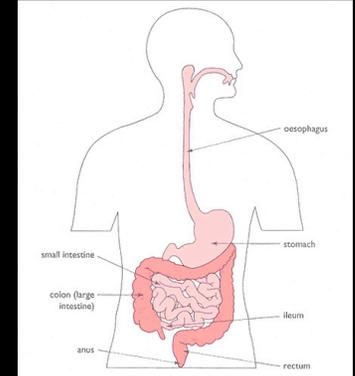
## ◆ Diagnosis:

- Imaging (nuclear medicine, upper GI)
- Tubes (pH probe, endoscopy)
- 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*

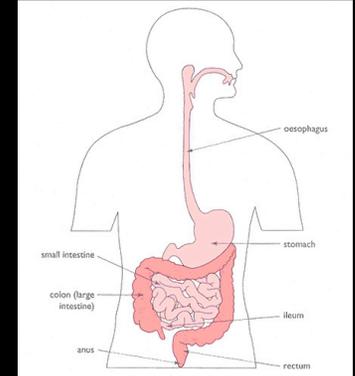
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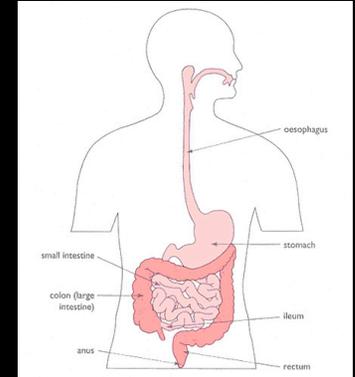
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## ◆ Prognosis: Intermittent or progressive



# *Level of Dysmotility: Small Intestine Malabsorption*

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



# *Level of Dysmotility: Small Intestine Malabsorption*

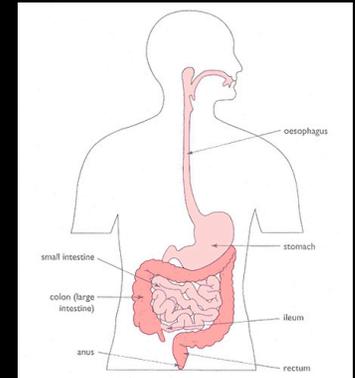
## • Diagnosis:

- Imaging (nuclear medicine, upper GI)
- Tubes (pH probe, endoscopy, colonoscopy)
- Capsule
- Motility studies

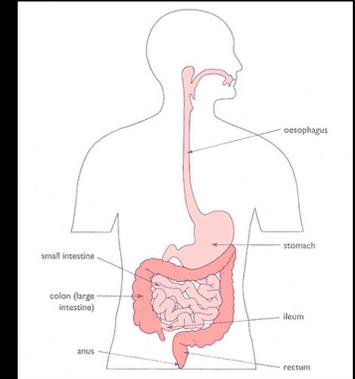
## • Treatment:

- 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*



## ◆ Diagnosis:

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- Tubes (pH probe, endoscopy, colonoscopy)
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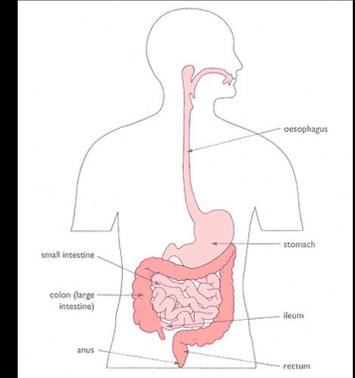
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## ◆ Prognosis: Often progressive, SIBO is treatable

# *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*

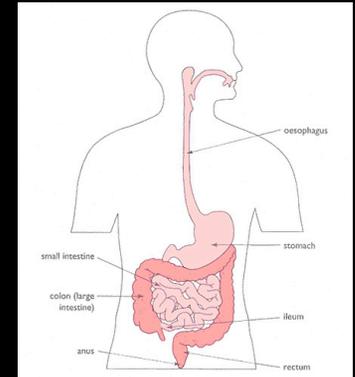
## • Diagnosis:

- 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*

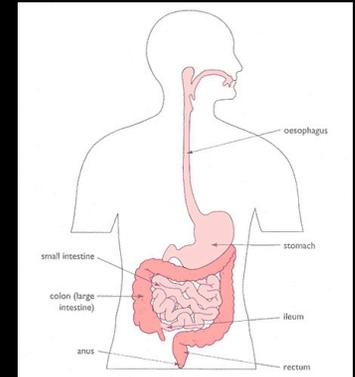
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## *Diagnosis*

- 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*).

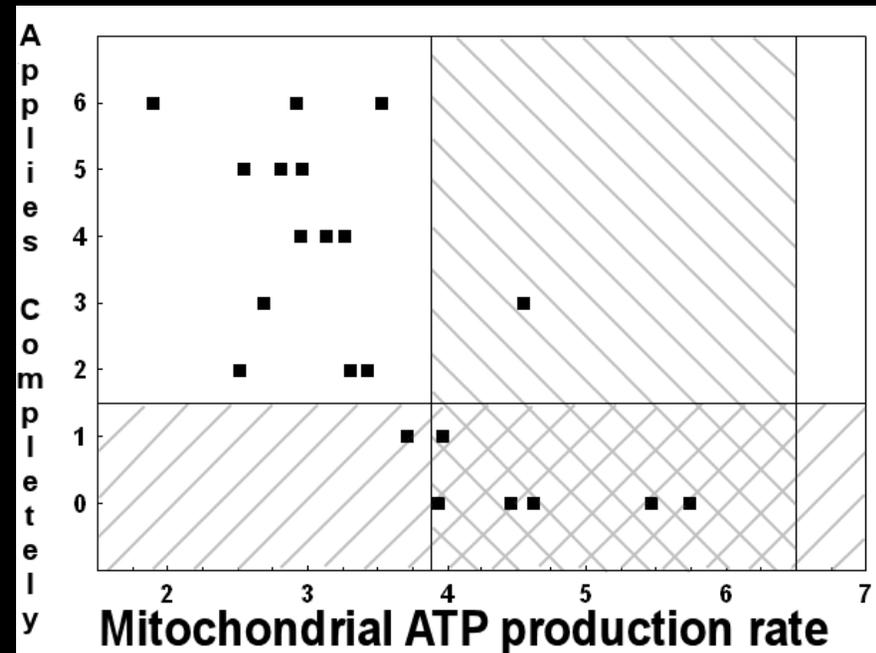
•“I often have aches in my shoulders and in the back of my neck.” (*Muscular Tension, item 4, p = 0.031*).

•“My body often feels stiff and tense.” (*Muscular Tension, item 33, p = 0.031*).

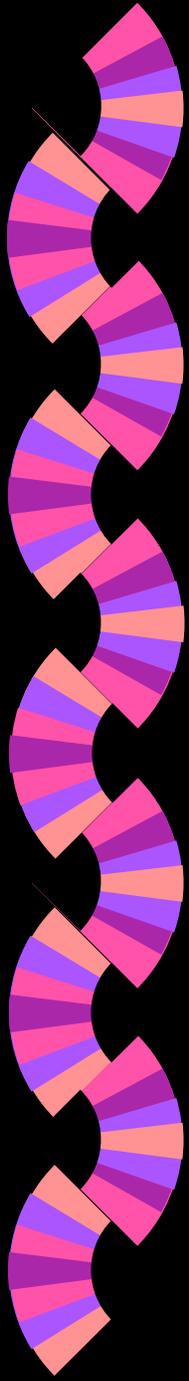
•“I think I must economize my energy.” (*Psychasthenia, item 40, p = 0.015*).

•“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*).

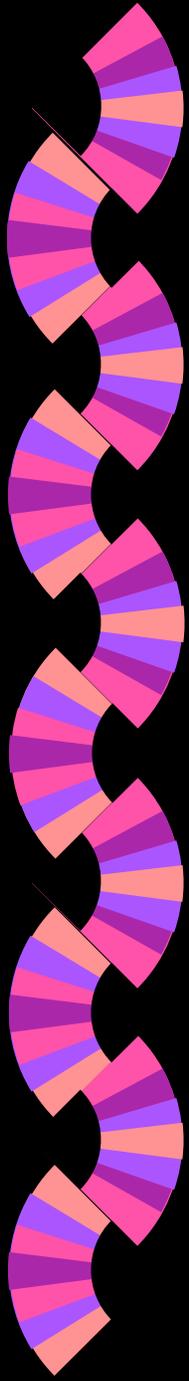


**13/14 subjects with ATP production rates below the normal range answered at least two of those six items as “Applies Completely”, compared to only 1/7 subjects with ATP production rates within our control range (chi-square P = 0.0003).**



## *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:

- “Psychotropics” (amitriptyline)
- PPIs (Prilosec)
- PEG (Miralax)

