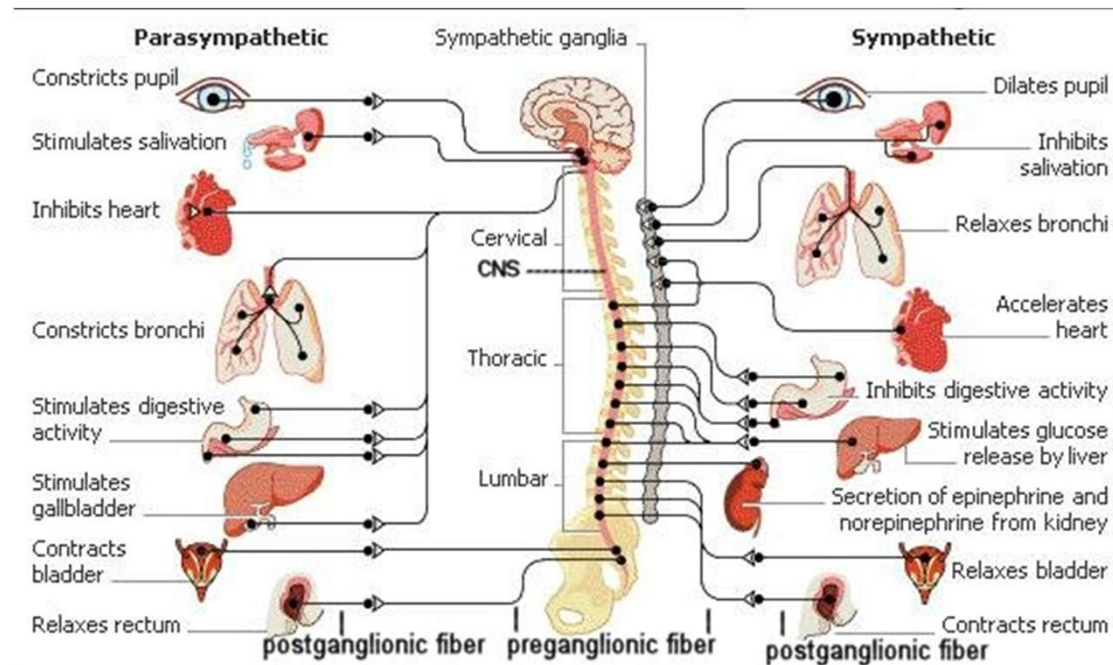
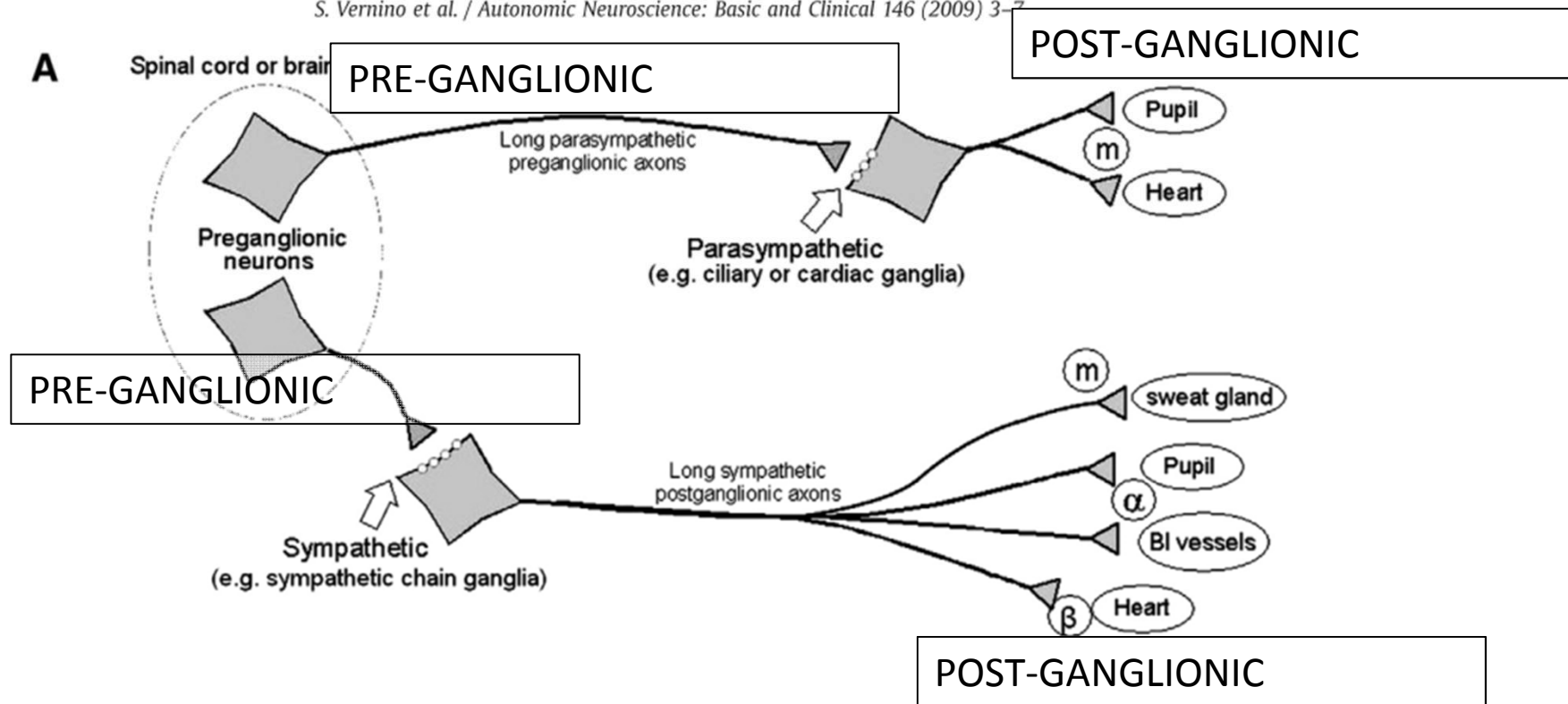


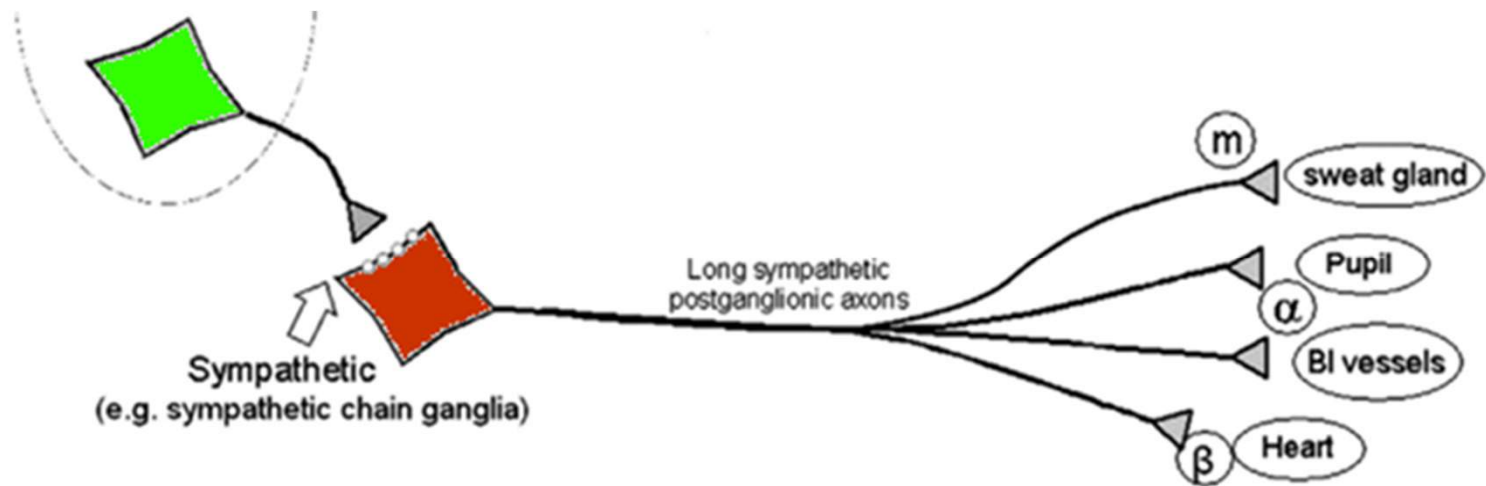
Autonomic Dysfunction



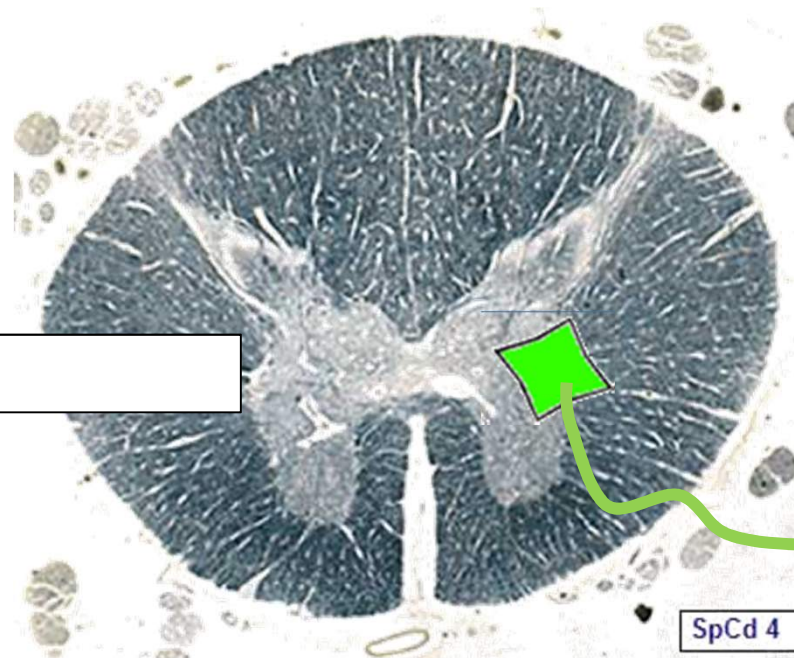
Unique anatomy

S. Vernino et al. / Autonomic Neuroscience: Basic and Clinical 146 (2009) 3–7



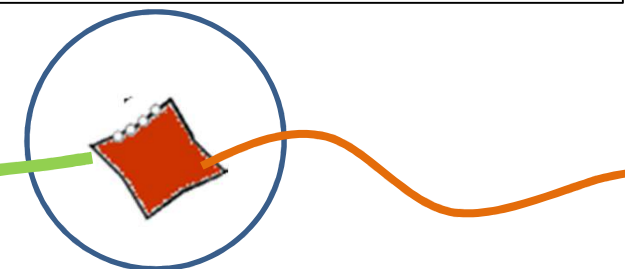


PRE-GANGLIONIC



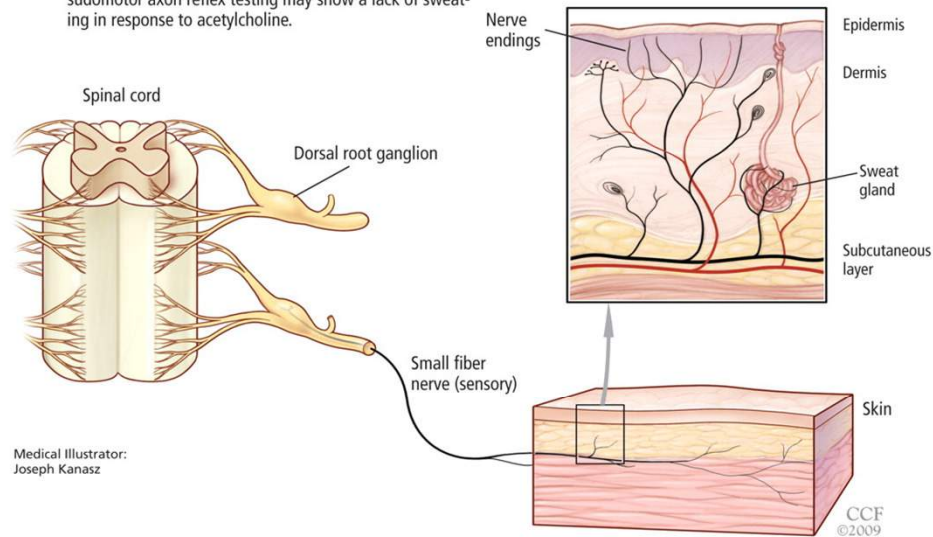
SpCd 4

POST-GANGLIONIC



■ Small fiber neuropathy affects sensory nerves

Small fiber neuropathy is a major cause of pain in the hands and feet, especially in the elderly. Diabetes mellitus is the most common identifiable cause, but there are many others. The affected nerve fibers are the small-diameter myelinated A-delta fibers and unmyelinated C fibers, which mediate pain, thermal sensation, and autonomic function. Large fibers that innervate muscles are not affected. Skin biopsy may show a paucity of nerve fibers. Quantitative sudomotor axon reflex testing may show a lack of sweating in response to acetylcholine.

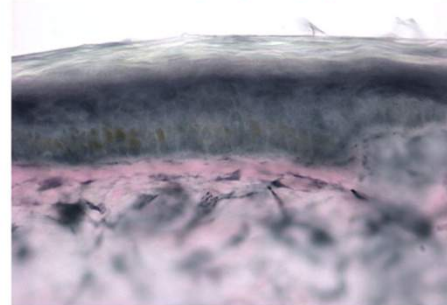


Normal skin biopsy



Normal innervation with small nerve fibers seen in the epidermis (arrows). Skin biopsy specimens with protein gene product 9.5 immunostaining.

Small fiber neuropathy biopsy



A specimen from a patient with small fiber neuropathy shows denervation with no small nerve fibers seen in the epidermis.

**TAVEE J , ZHOU L Cleveland Clinic Journal of Medicine
2009;76:297-305**

The Baroreflex

- Fall in BP when you stand/ responds to hypertension

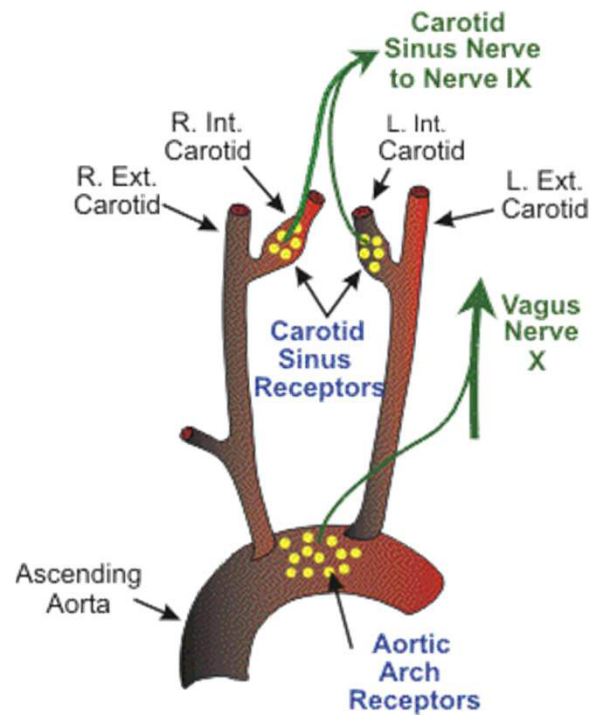
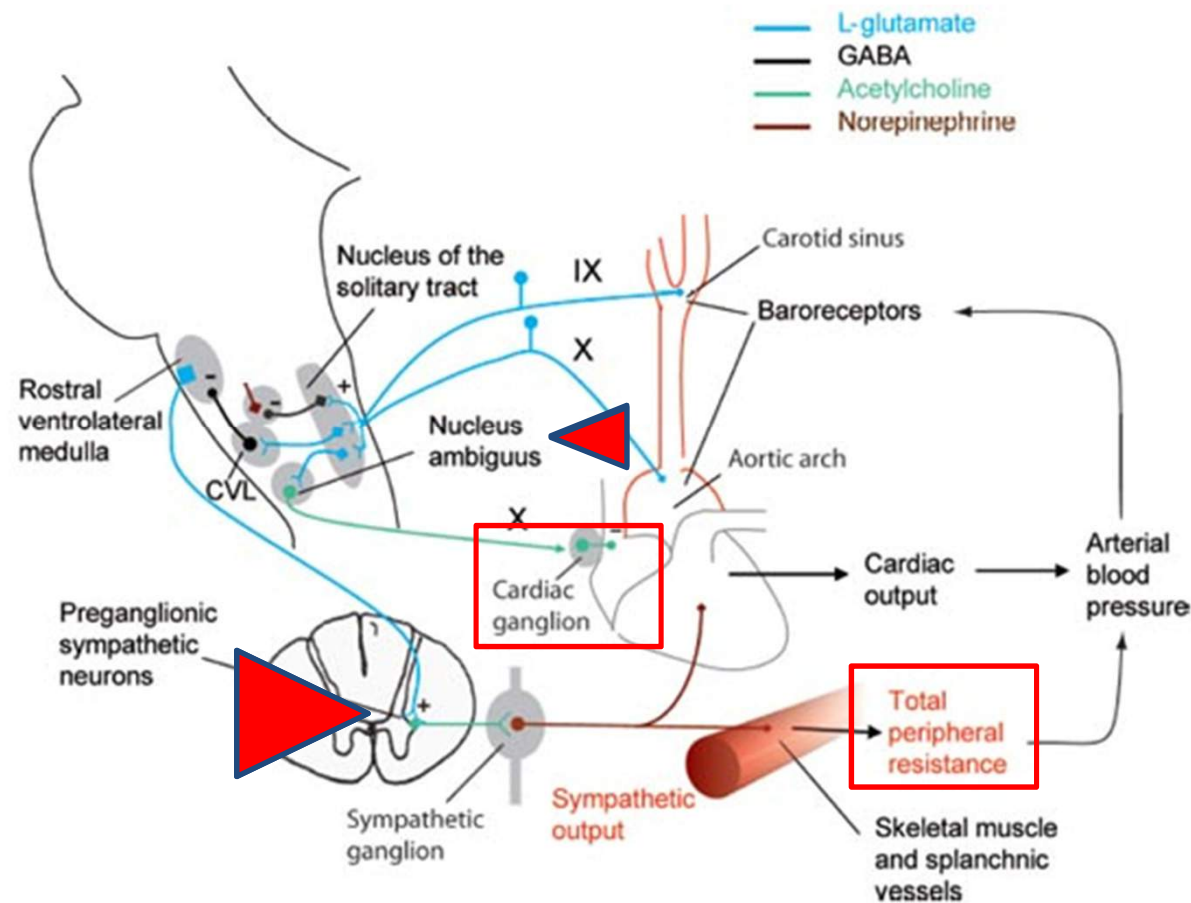


Figure 1. Location and innervation of arterial baroreceptors.

Critical CV reflex:

Continuous buffering of acute fluctuations of ABP in situations such as changes in posture, exercise, and emotion

:CO, TPR



Symptoms

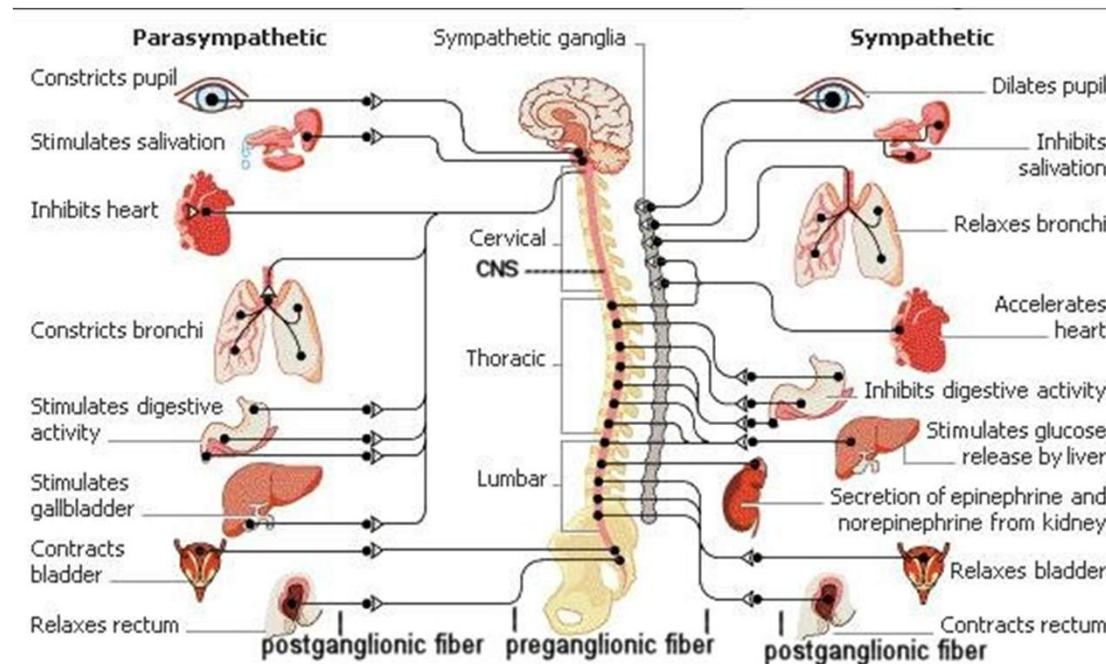
- Sympathetic
- Parasympathetic

-
- ```
graph TD; Sympathetic --> Enteric; Parasympathetic --> Enteric; Enteric --> Ileus; Enteric --> Colic[Abdominal colic]; Enteric --> Diarrhea; Enteric --> Constipation;
```
- Enteric
    - Ileus
    - Abdominal colic
    - Diarrhea
    - Constipation



# Transmitter

- Always Acetylcholine
- (except post-ganglionic sympathetic, NA)





# Sympathetic Failure

- Sympathetic adrenergic failure
  - Horner's
  - OH
  - Point & Shoot (ejaculatory failure)
- Sympathetic cholinergic failure
  - Abnormalities of sweating



# Parasympathetic Failure (think opposite of SLUD)

- **Failure** of the system results in
  - Hypotonic bladder/urinary retention
  - Secretomotor dysfunction (dry mouth, dry eyes)
  - Gastrointestinal dysfunction
- Erection failure (P & S)
- Poor pupillary light response(think Surgical 3<sup>rd</sup>)
- Tachycardia (think vagal lesion in GBS)



# Causes of Autonomic Dysfunction

- Central
- Peripheral
- Ganglionic
- DM DM DM DM DM DM DM DM DM DM DM DM DM
- Obviously, PD and things that look just like PD



# PD:Non-motor symptoms

- Autonomic dysfunction
- 40% have OH
- PD with OH: older, > dementia, > autonomic dysfunction.



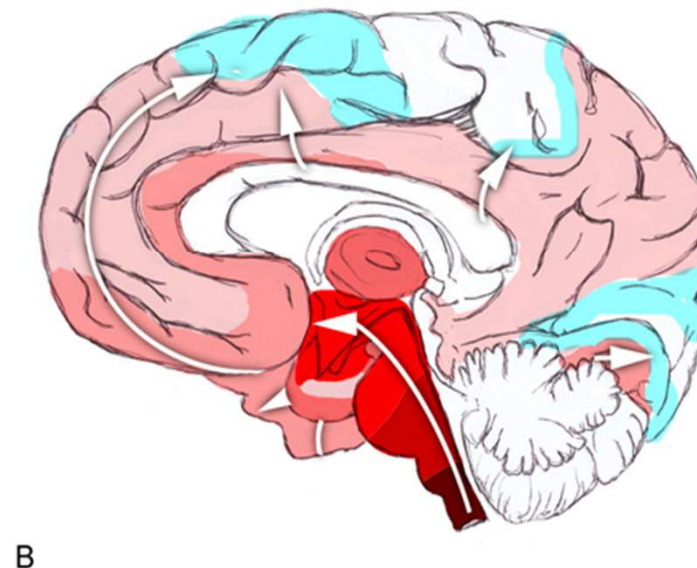
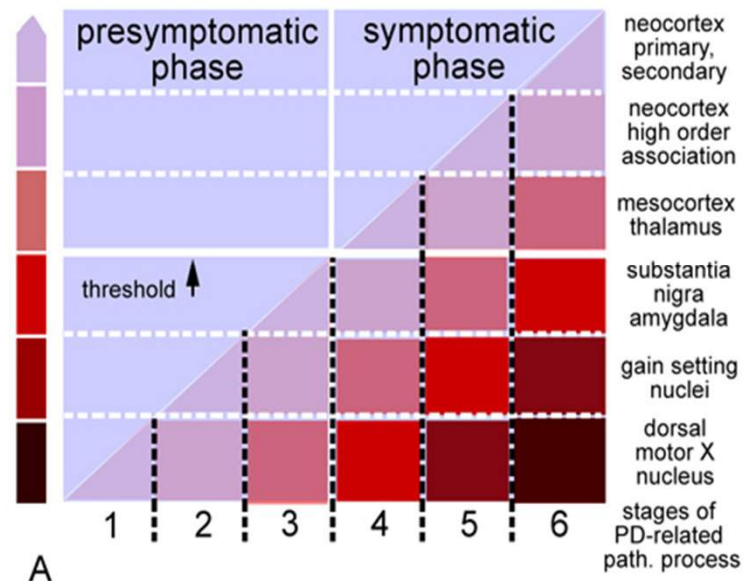
# PD:Non-motor symptoms

- Subgroup of patients with early-onset autonomic failure (largely bladder and GI motility)
- Involvement of:
  - Cardiovascular function
  - GI function
  - Urinary and sexual function
  - Thermoregulatory function and skin changes
  - Pupillary changes



# When does it start?

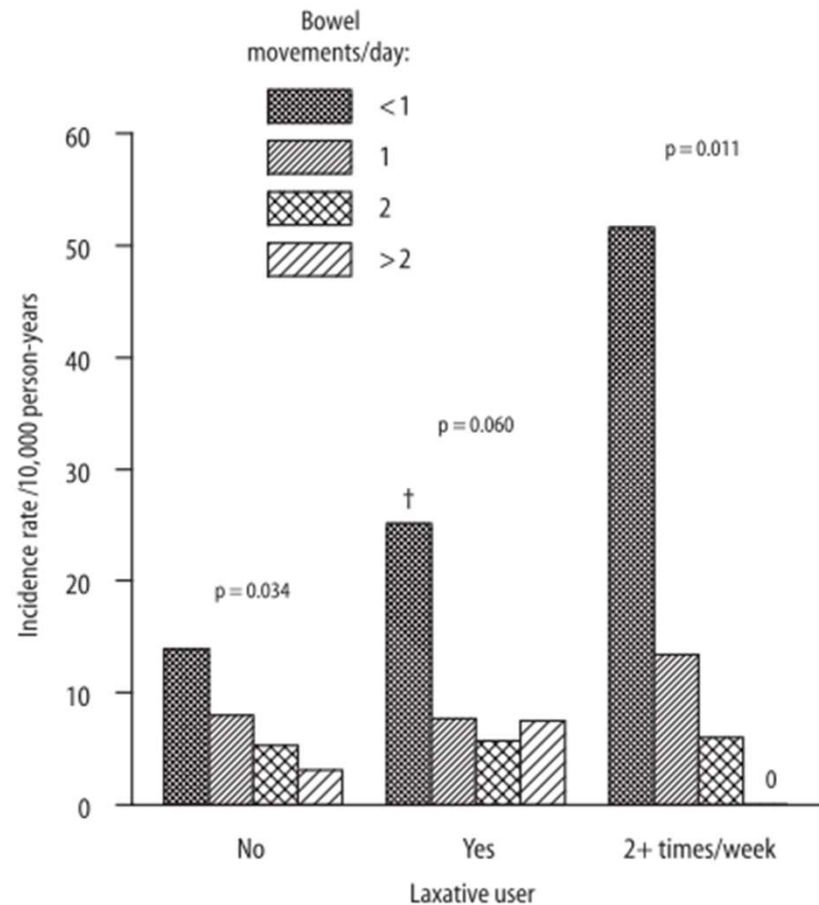
- 24 years of follow-up after data were first collected on bowel



those with  $>2/\text{day}$  ( $p = 0.005$ ). After adjustment for age, pack-years of cigarette smoking, coffee consumption, laxative use, jogging, and the intake of fruits, vegetables, and grains, men with  $<1$  bowel movement/day had a 2.7-fold excess risk of PD versus men with 1/day (95% CI: 1.3, 5.5;  $p = 0.007$ ). The risk of PD in men with  $<1$  bowel movement/day increased to a 4.1-fold excess when compared with men with 2/day (95% CI: 1.7, 9.6;  $p = 0.001$ ) and to a 4.5-fold excess versus men with  $>2/\text{day}$  (95% CI: 1.2, 16.9;  $p = 0.025$ ). **Conclusions:** Findings indicate that infrequent bowel movements are associated with an elevated risk of future PD. Further study is needed to determine whether constipation is part of early PD processes or is a marker of susceptibility or environmental factors that may cause PD.



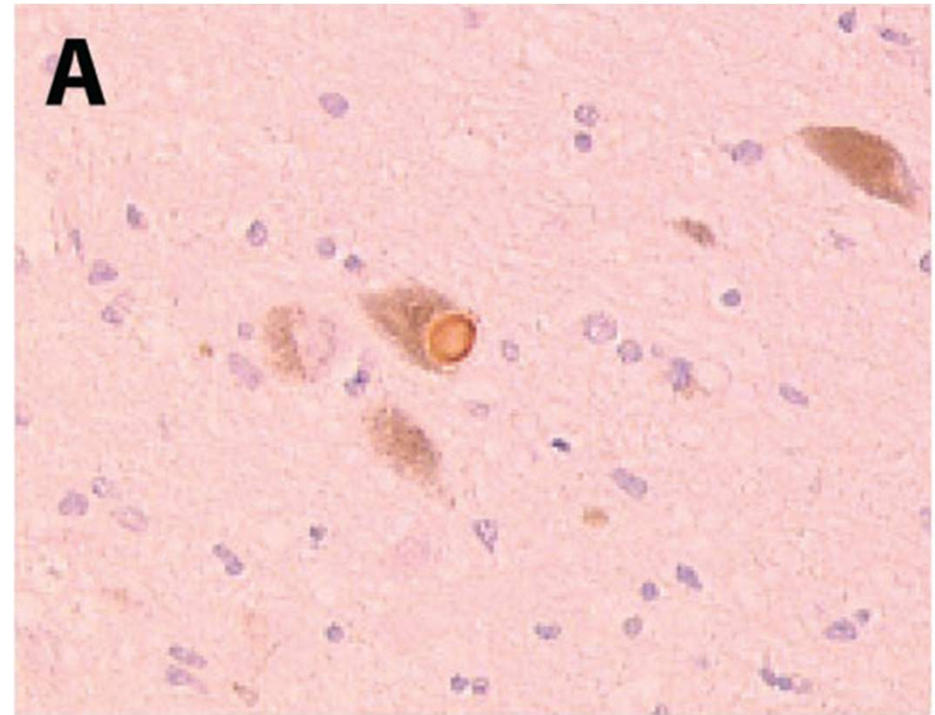
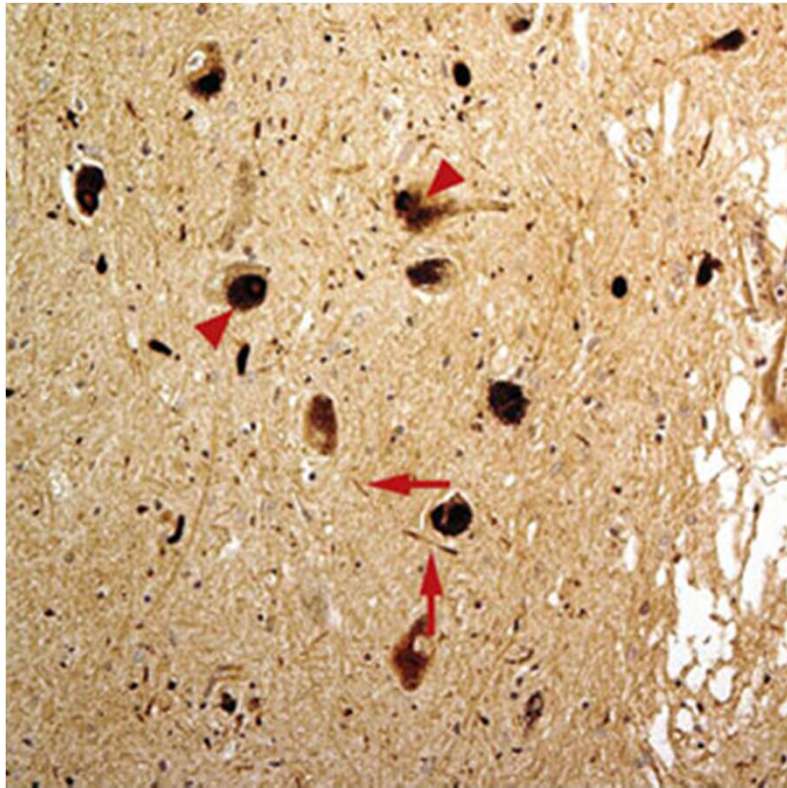
# Age adjusted incidence of PD



†Significant excess of PD vs. men with more frequent bowel movements ( $p=0.009$ ).



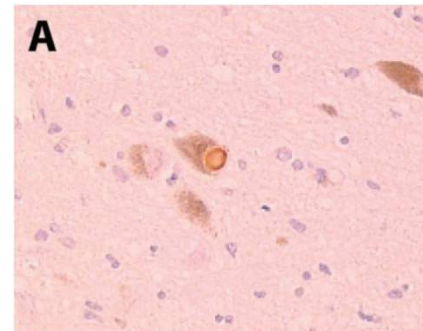
# $\alpha$ - synuclein staining LB





# PD and autonomic failure

- LBs in:
  - Hypothalamus, NTS, ventrolateral medulla
  - The sympathetic system (intermediolateral nucleus of thoracic cord and sympathetic ganglia)
  - Parasympathetic system (dorsal, vagal, and sacral parasympathetic nuclei)





# Autonomic Dysfunction

- Compare
  - PD
  - PD with Autonomic Failure
  - PAF
  - DLB
  - MSA



# Clinical phenotypes correlate with regional localisation of the Lewy body

- PD: brainstem distribution (peripheral)
- DLB: cortical distribution (brainstem distribution (peripheral))
- (Pure)Autonomic failure: autonomic pathways
- MSA: spares peripheral neurons, has no LB



# PAF Pure Autonomic Failure

- Bradbury-Eggleston
- Progressive sympathetic and parasympathetic failure.



# AUTONOMIC FAILURE WITH ORTHOSTATIC HYPOTENSION DUE TO INTERMEDIOLATERAL COLUMN DEGENERATION

*A Report of Two Cases with Autopsies*<sup>1</sup>

By R. H. JOHNSON, G. DE J. LEE, D. R. OPPENHEIMER, AND  
J. M. K. SPALDING

(From the Depts. of Neurology, Neuropathology and of the Regius Professor of  
Medicine, Radcliffe Infirmary, Oxford)

## *Clinical Findings*

| <i>History</i>                                  | <i>Case 1 (E. S.)</i>                |
|-------------------------------------------------|--------------------------------------|
| Sex . . . . .                                   | Male                                 |
| Age at death . . . . .                          | 66 yrs.                              |
| Duration of symptoms . . . . .                  | 4 yrs.                               |
| Fainting attacks when erect . . . . .           | +                                    |
| Consciousness regained when recumbent . . . . . | +                                    |
| Sweating . . . . .                              | —                                    |
| Impotence . . . . .                             | +                                    |
| Course . . . . .                                | Accidental death<br>from hypotension |

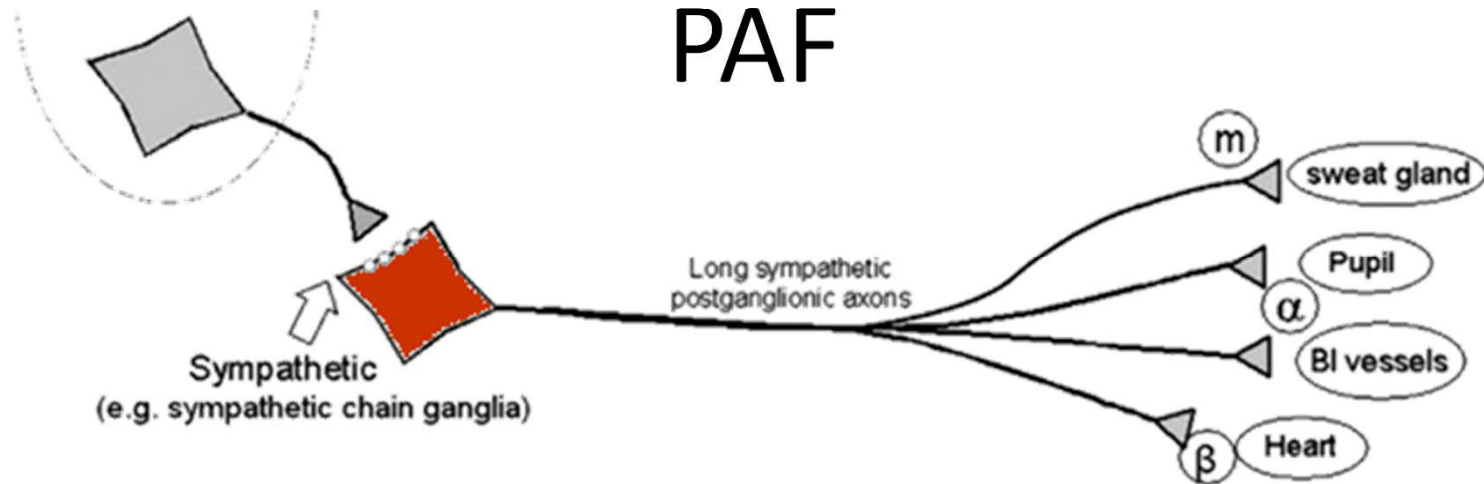


# PAF Pure Autonomic Failure

- Incapacitating postural hypotension with cardiovascular, gastrointestinal, urogenital, thermoregulatory, sudomotor, and pupillomotor dysfunction.
- In severe cases, unable to stand for more than a few seconds.



# PAF

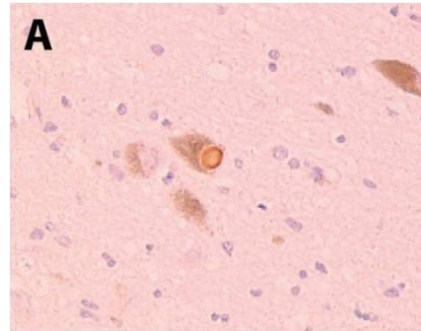


- Degeneration of sympathetic postganglionic neurons.
- Intermediolateral column cell loss

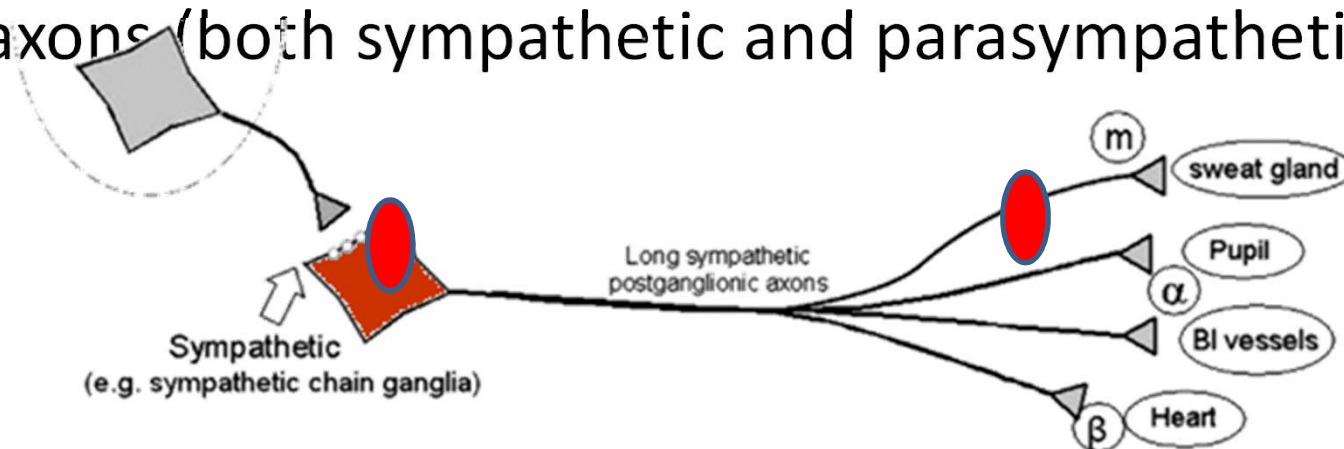




# PAF Pure Autonomic Failure



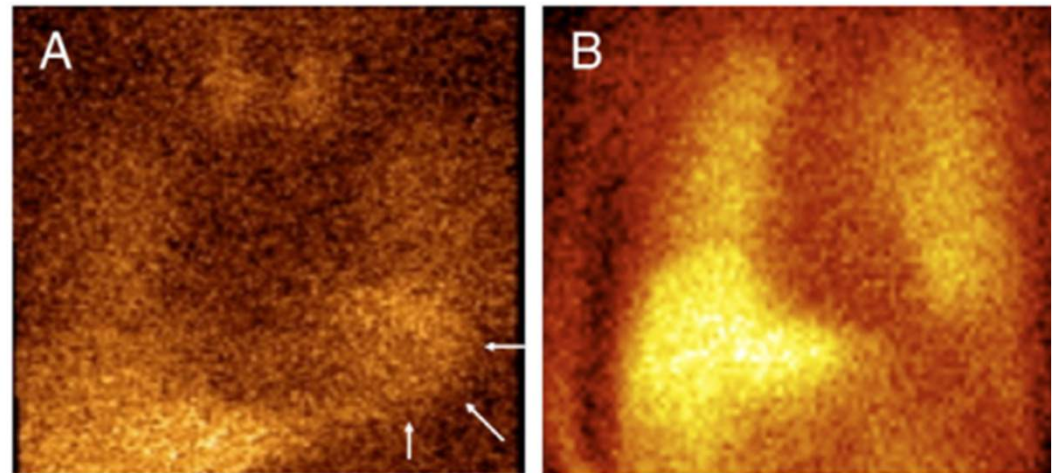
- Lewy bodies:
  - **Central**: substantia nigra, locus ceruleus, dorsal vagal nuclei and
  - **>> Peripheral**: LBs in sympathetic ganglia, parasympathetic ganglia and distal autonomic axons (both sympathetic and parasympathetic)





# PD, PAF, DLB

- Decreased myocardial concentration of radioactivity after injection of MIBG (sympathetic neural imaging agent)
- = postganglionic sympathetic neuron
- (Not seen in MSA)



**Fig. 2.** MIBG scintigraphy of a healthy person (A) in contrast to a PD patient (B). MIE accumulation as indicated by the arrows in (A) is not present in (B) (provided by Prof. Kotzerke, Dresden).



# PD, PAF, DLB

- EARLY: all can have AF
  - Patient underwent lumbar sympathectomy for management of peripheral vascular disease and three years later developed classical features of PD.....
  - Lewy bodies were seen in sympathetic ganglia

8. Stadlan E, Duvoisen R, Yahr M. The pathology of Parkinsonism. In: Fifth International Congress of Neuropathologists, 1965. Zurich: Excerpta Medica, 1965:569–571.



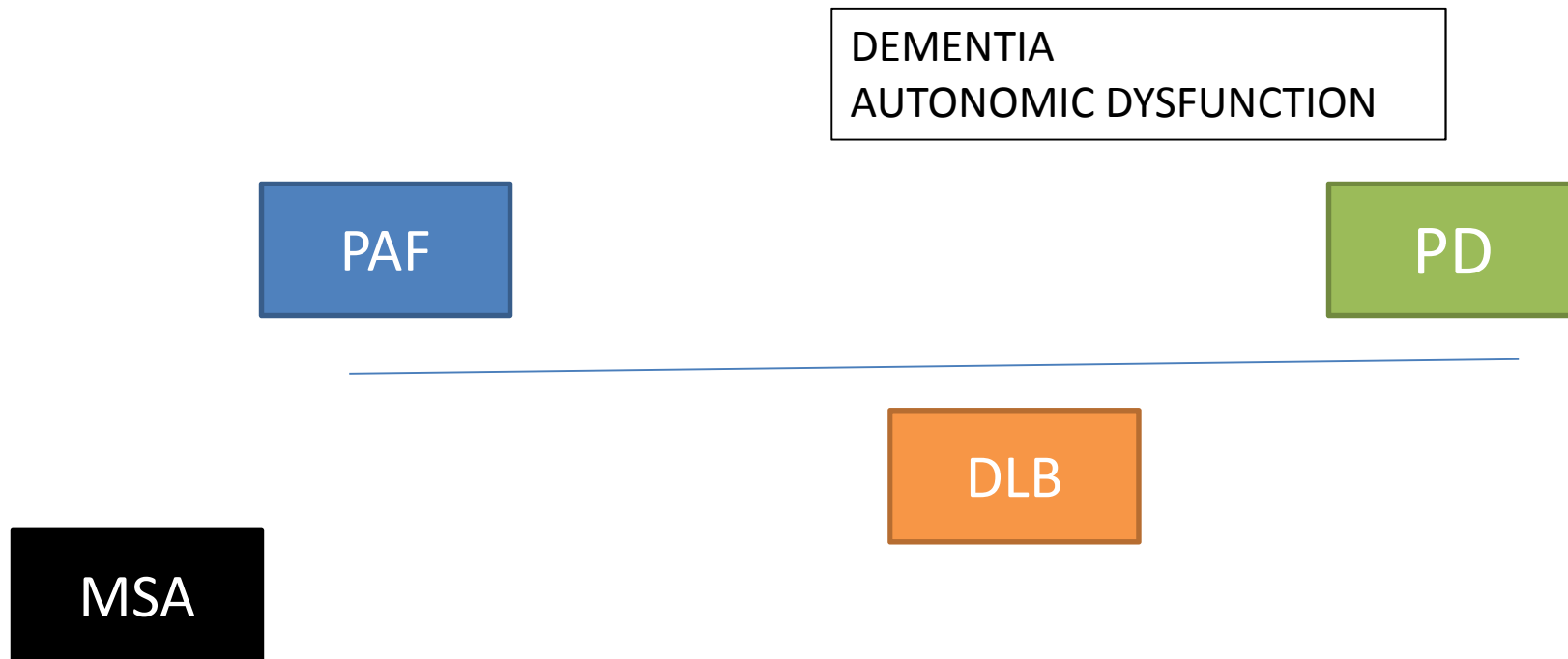
# DLB

- v: OH is common (cases presenting with AF)
- v: Cardiac noradrenergic denervation
- Lewy bodies:
  - intermediolateral columns of the spinal cord
  - Numerous in autonomic ganglia and sympathetic neurons



# PAF

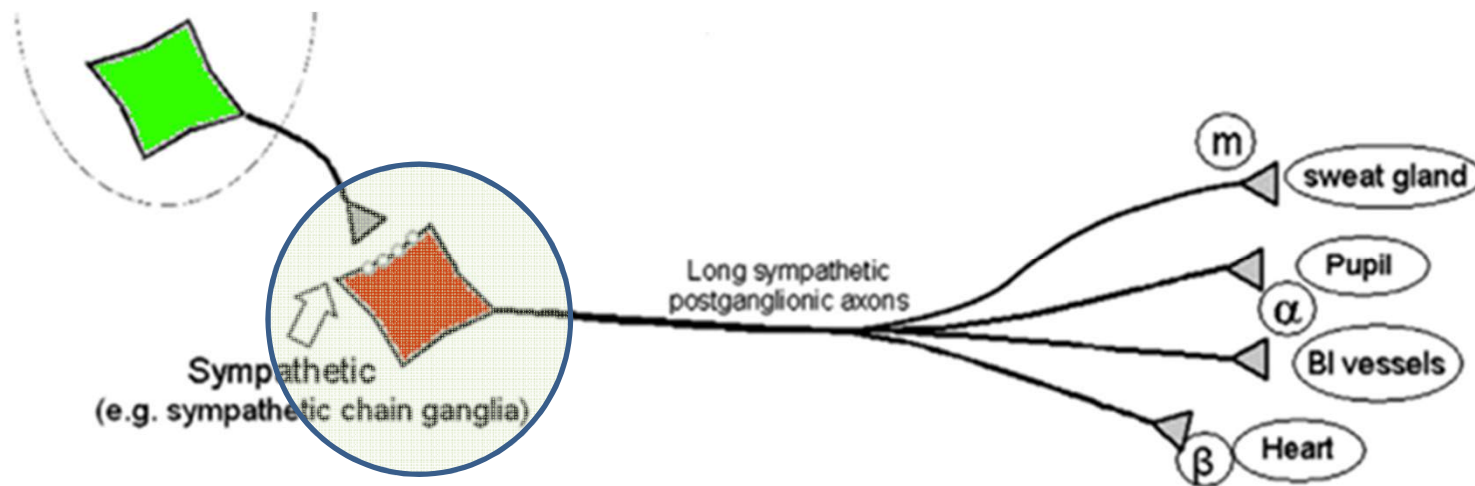
- Very slowly progressive
- Some will progress to clear-cut Parkinson's disease.





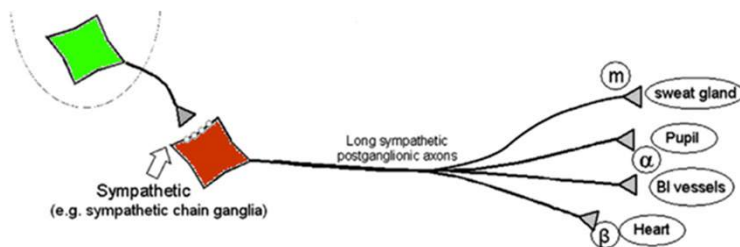
# PD PAF DLB vs **MSA**

- Post-ganglionic vs Pre-ganglionic





- Peripheral/postganglionic: PAF(and other Lewy body syndromes): low plasma noradrenaline (supine) (primary postganglionic involvement)
- Central/pre-ganglia: MSA: levels normal/elevated (sympathetic neurons not activated)



**TABLE 13** Diagnostic value of plasma norepinephrine in autonomic failure

- ▶ Plasma NE >99 pg/mL in PAF 18%
- ▶ Plasma NE <100 pg/mL in MSA 4%

NE norepinephrine  
PAF pure autonomic failure  
MSA multiple system atrophy



# MSA

- Shy Drager
- Striatonigral degeneration
- OPCA
- All one disease with different clinical expressions
  - MSA Multisystem Atrophy (P-, C-)



# PAF

**Table 1 Clinical and Pathological Differences between Alpha-Synucleinopathies**

|                   | DLB | PD  | PAF | MSA |
|-------------------|-----|-----|-----|-----|
| Autonomic failure | +/- | +/- | +++ | +++ |

DLB, dementia of Lewy bodies; PD, Parkinson's disease; PAF, pure autonomic failure; MSA, multiple system atrophy.



# “Synucleinopathies”

- PD
- DLB
- PAF
- MSA

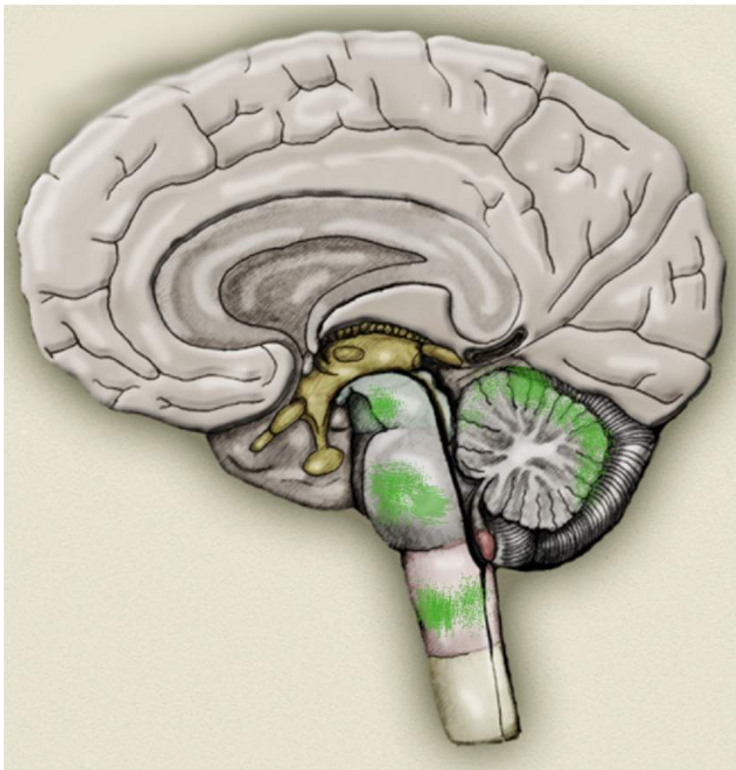


MSA: Where is the autonomic defect?

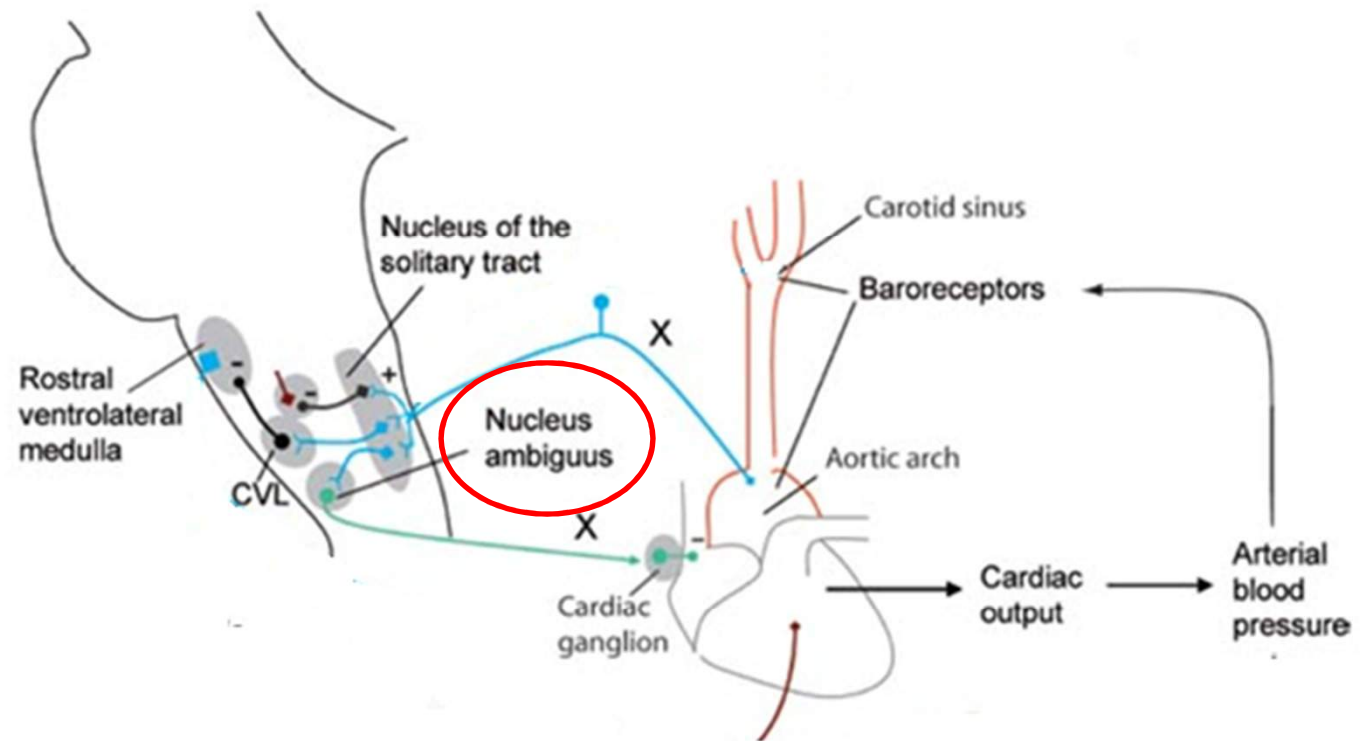


# MSA

- Sacral Parasympathetic outflow: Onuf's nucleus (sphinter EMG)



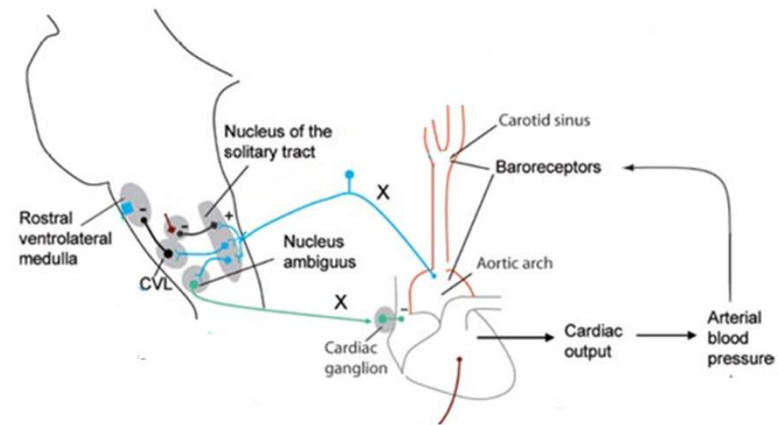
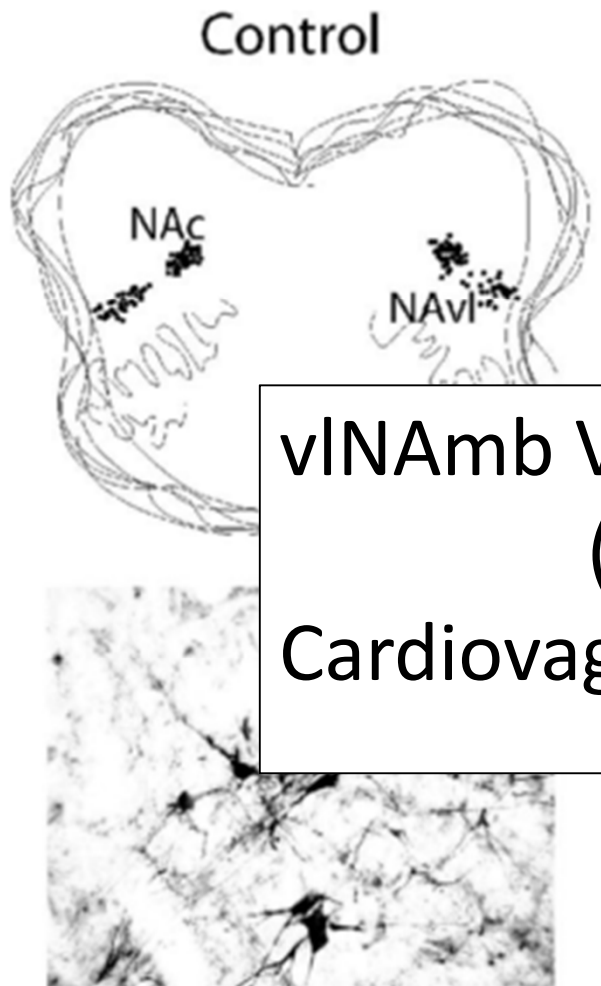






# N Ambiguus

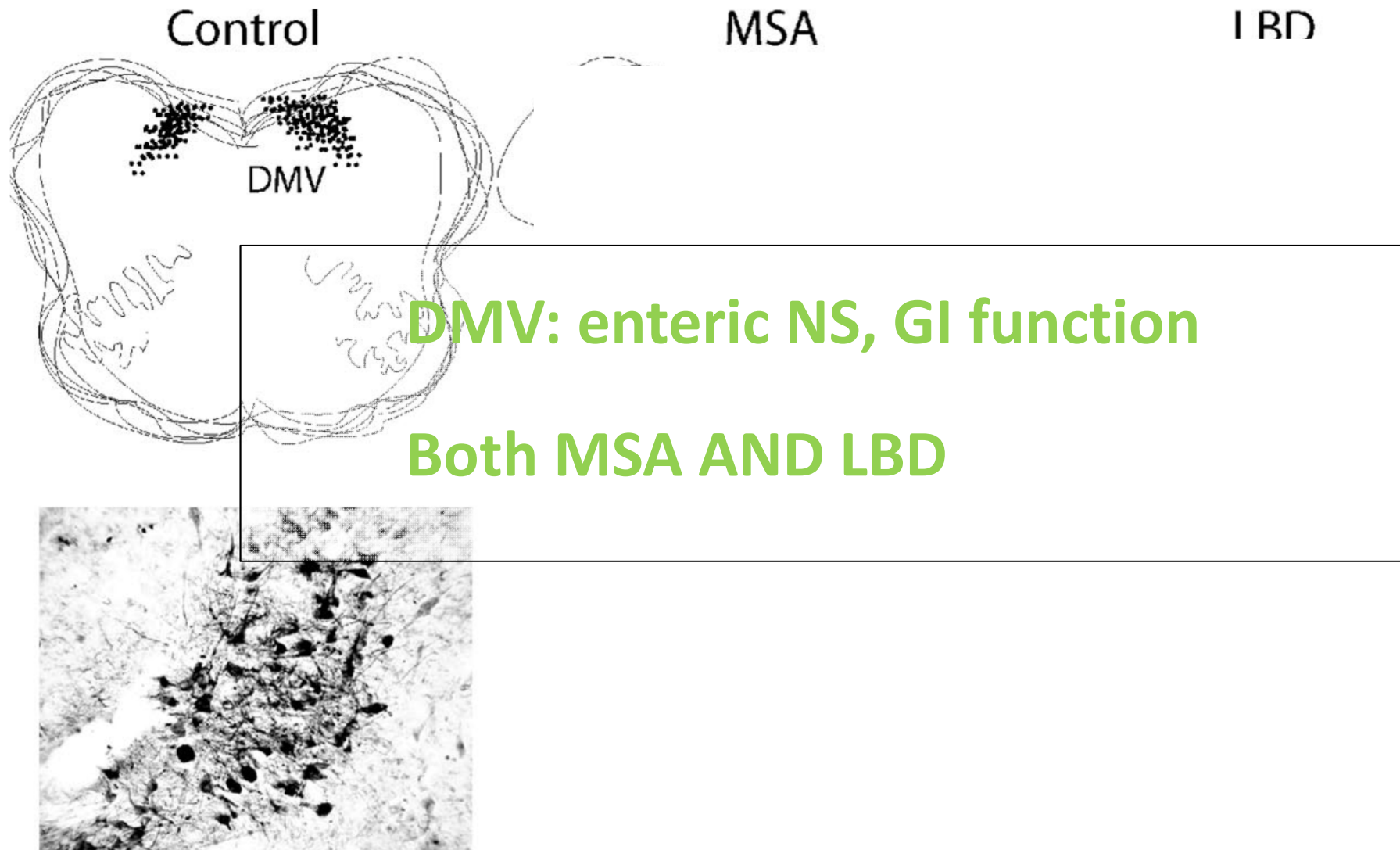
## Vagal preganglionic neuron





# Dorsal Vagal Nucleus

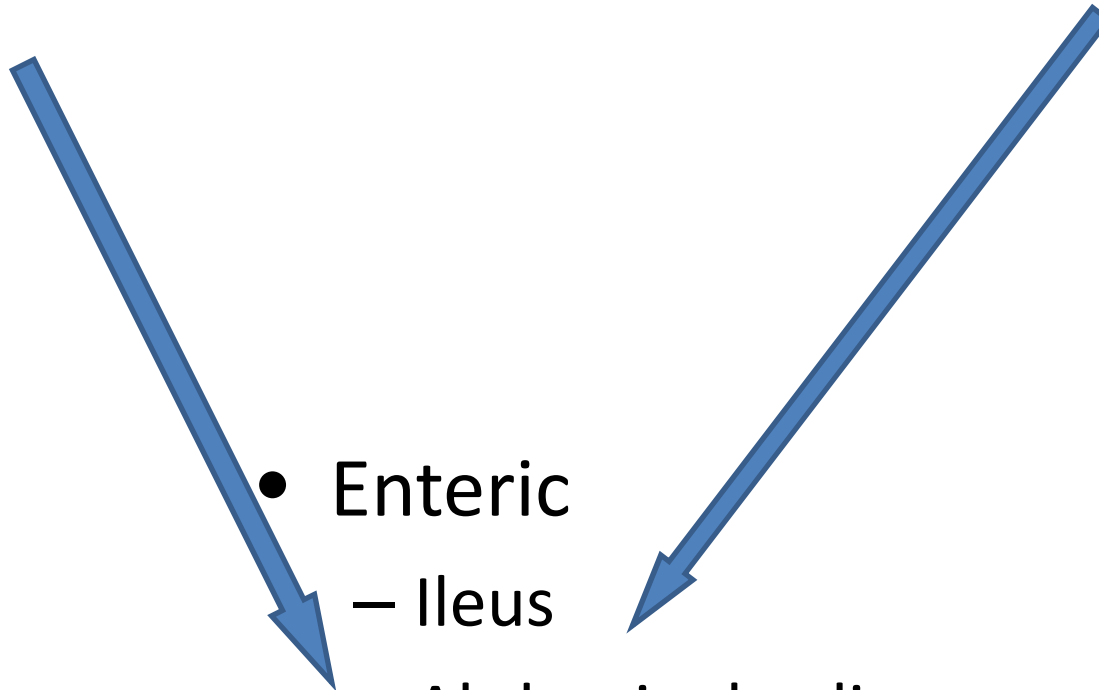
## Vagal preganglionic neuron





# PD and Constipation

- Sympathetic
- Parasympathetic



- Enteric
  - Ileus
  - Abdominal colic
  - Diarrhea
  - Constipation



## FEATURED ARTICLE

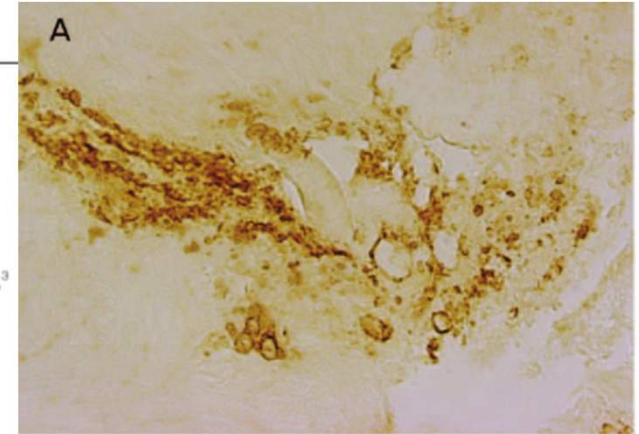
### Alpha-Synuclein in Colonic Submucosa in Early Untreated Parkinson's Disease

Kathleen M. Shannon, MD,<sup>1\*</sup> Ali Keshavarzian, MD,<sup>2</sup> Ece Mutlu, MD,<sup>2</sup> Hemraj B. Dodiya, MS,<sup>3</sup> Delia Daian,<sup>2</sup> Jean A. Jaglin, RN,<sup>1</sup> and Jeffrey H. Kordower, PhD<sup>3</sup>

<sup>1</sup>Departments of Neurological Sciences, Rush Medical College, Chicago, Illinois, USA

<sup>2</sup>Department of Gastroenterology and Nutrition, Rush Medical College, Chicago, Illinois, USA

<sup>3</sup>Center for Brain Repair, Rush Medical College, Chicago, Illinois, USA



- Ten subjects with early PD (7 men; median age, 58.5 years; median disease duration, 1.5 years) underwent unprepped flexible sigmoidoscopy with biopsy of the distal sigmoid colon.
- All showed  $\alpha$ -syn in colonic submucosa neurites

| No.            | Age        | Sex | Time since onset (y) | Time since diagnosis (mo) | Total UPDRS | HY stage | $\alpha$ SYN |
|----------------|------------|-----|----------------------|---------------------------|-------------|----------|--------------|
| 1              | 55         | M   | 4                    | 3                         | 28          | 2        | 1+           |
| 2              | 66         | M   | 1                    | 5                         | 27          | 2        | 1+           |
| 3              | 56         | F   | 1                    | 9                         | 15          | 1.5      | 2+           |
| 4              | 79         | M   | 1                    | 6                         | 20          | 2        | 4+           |
| 5              | 75         | M   | 4                    | 1                         | 28          | 2        | Inadequate   |
| 6              | 68         | F   | 0.5                  | 4                         | 24          | 2        | 4+           |
| 7              | 46         | F   | 2                    | 12                        | 16          | 1        | 4+           |
| 8              | 47         | M   | 8                    | 12                        | 18          | 2        | 4+           |
| 9              | 61         | M   | 1                    | 6                         | 18          | 2        | 4+           |
| 10             | 57         | M   | 2                    | 18                        | 28          | 2        | 3+           |
| Median (range) | 59 (46–79) |     | 1.5 (0.5–8)          | 7.5 (1–36)                | 22 (15–28)  | 2 (1–2)  |              |



# Causes of autonomic dysfunction

- Diabetes!



## **Disorders Resulting in/Associated with Autonomic Failure/dysfunction**

- Gastroparesis, nocturnal diarrhoea, erectile failure, and ultimately bowel and bladder dysfunction.
- Initial vagal neuropathy: brady
- With involvement of cardiac sympathetic fibers: tachy
- OH: efferent sympathetic vasomotor denervation, with ↓ vasoconstriction of splanchnic vascular bed.



## **Disorders Resulting in/Associated with Autonomic Failure/dysfunction**

- But note: AF does not = bowel & bladder
- Autonomic dysfunction is clearly a risk factor for mortality (including sudden death) in the diabetic population, may promote nephropathy.



## **Disorders Resulting in/Associated with Autonomic Failure/dysfunction**

- Diabetic autonomic neuropathy is associated with a generalised distal polyneuropathy,
- May also be associated just with impaired glucose tolerance.
- Treatment of diabetes may also induce a painful autonomic neuropathy
- Prevalence of Cardiovascular AN 20%, increasing up to 65%.



## **Disorders Resulting in/Associated with Autonomic Failure/dysfunction**

- Other peripheral neuropathy's
  - AIDP itself: tachy/brady, bowel & bladder, sweating and pupillomotor disturbances
  - variants of AIDP

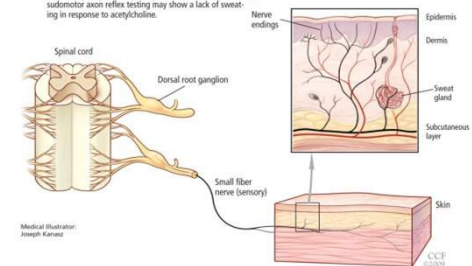


# Disorders Resulting in/Associated with Autonomic Failure/dysfunction

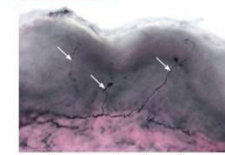
- Hereditary amyloidosis (Transthyretin gene mutations)
  - Autonomic involvement: peripheral neuropathy, S(M), small fibers
  - Present with distal S symptoms (numbness, pain etc), CTS
  - Sympathetic/Parasympathetic dysfunction (just like DM)
  - Dx: subcut fat pad aspiration/nerve biopsy
  - Not common in secondary amyloidosis

## ■ Small fiber neuropathy affects sensory nerves

Small fiber neuropathy is a major cause of pain in the hands and feet, especially in the elderly. Diabetes mellitus is the most common identifiable cause, but there are many others. The affected nerve fibers are the small-diameter myelinated A-delta fibers and unmyelinated C fibers, which mediate pain, thermal sensation, and autonomic function. Large fibers that innervate muscles are not affected. Skin biopsies may show a paucity of nerve fibers. Quantitative sudomotor axon reflex testing may show a lack of sweating in response to acetylcholine.

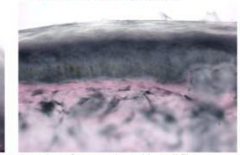


Normal skin biopsy



Normal innervation with small nerve fibers seen in the epidermis (arrows). Skin biopsy specimens with protein gene product 9.5 immunostaining.

Small fiber neuropathy biopsy



A specimen from a patient with small fiber neuropathy shows denervation with no small nerve fibers seen in the epidermis.



## **Disorders Resulting in/Associated with Autonomic Failure/dysfunction**

- Primary amyloidosis (most common form of Amyloid in developed world)
  - Plasma cell dyscrasia/monoclonal population: Ig light chain associated
  - Deposition of insoluble proteins in a beta-pleated sheet
  - 50 -70 years
  - Fatigue, LOW
  - P Neuropathy 20%
  - Hepatomegaly, proteinuria
  - autonomic involvement of the cardiovascular, gastrointestinal and urogenital systems.



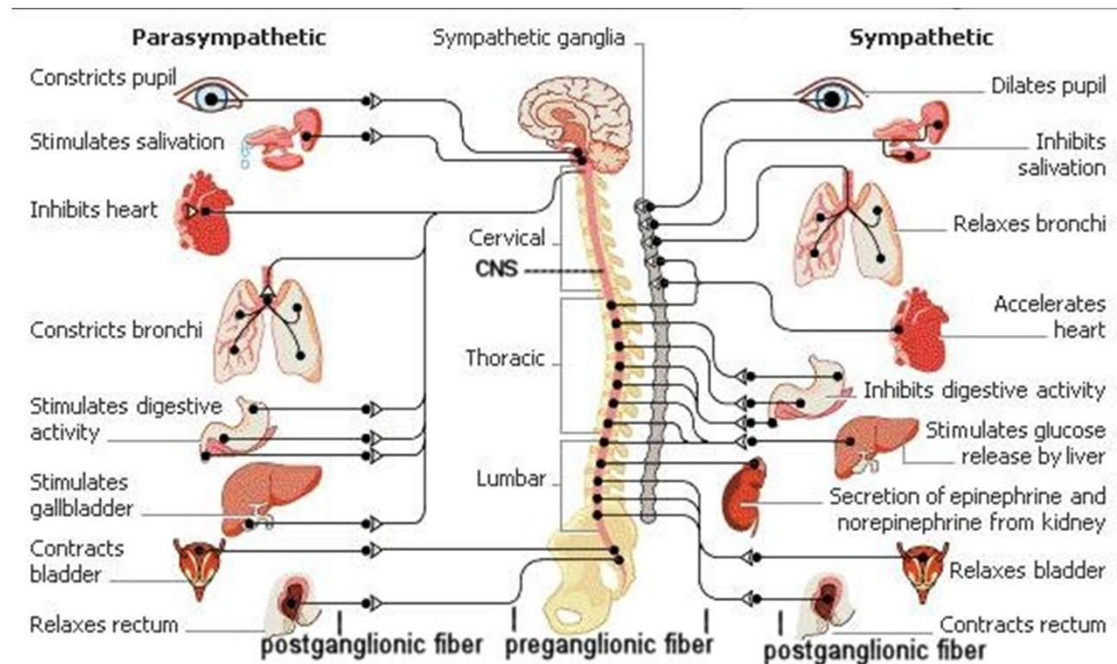
## **Disorders Resulting in/Associated with Autonomic Failure/dysfunction**

- Infectious diseases
  - acute pan-dysautonomia may occur: EBV
- Collagen-Vascular
  - Sjogren's



# Disorders Resulting in/Associated with Autonomic Failure/dysfunction

- Antibody mediated: **Ganglionic Acetylcholine Receptor Abs**
  - Autoimmune (some triggered by infections)
  - Paraneoplastic (small cell, thymoma)





# Typical patient

- More in women
- Young-middle aged
- Severe parasympathetic failure, that evolves within days 21-2 weeks (similar to GBS).
- Monophasic, slow, incomplete recovery.
- Clinical picture:
  - Orthostatic hypotension
  - Widespread anhidrosis
  - Dry mouth, dry eyes
  - Urinary retention
  - Impaired pupillary responses
  - Reduced heart rate variability

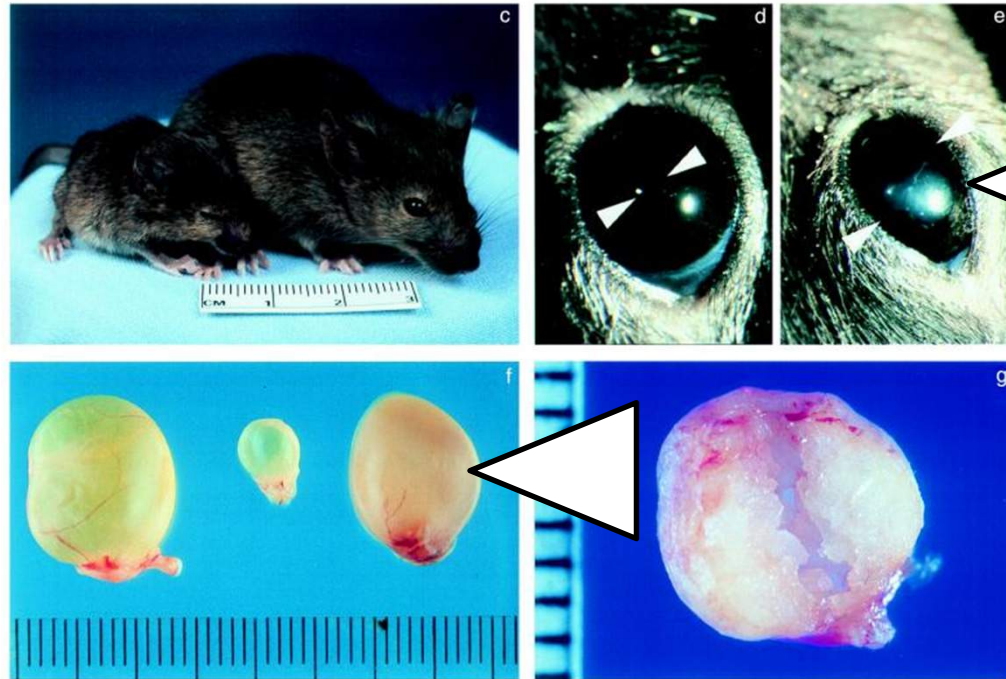
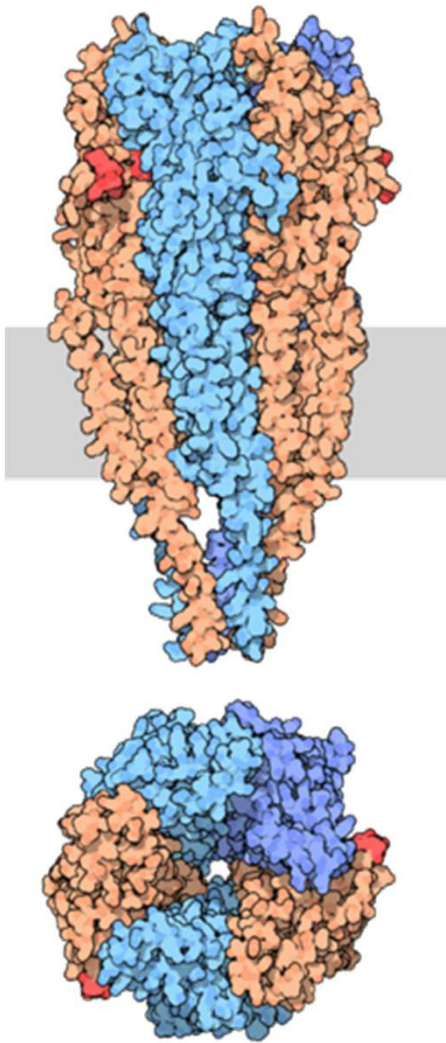


# Autoimmune autonomic ganglionopathy (AAG): Treatable!

- Constellation of
  - tonic pupils
  - Gastrointestinal dysmotility
  - Severe OH
- High levels of autoantibodies that bind to ganglionic AChR (RIA similar to that used to detect AChR abs in MG.)
- Specifically recognize the  $\alpha 3$  subunit of the ganglionic AChR



# Nicotinic ACh Receptor similar to muscle AChR





Lower antibody levels (0.05–0.20 nmol/L) may be seen:

- Limited forms of dysautonomia, including those with:
  - isolated gastrointestinal dysmotility
  - postural tachycardia syndrome.



- Some patients with AAG and positive antibody titer have a clinical course resembling a degenerative condition like PAF.



# Paraneoplastic Autonomic Failure

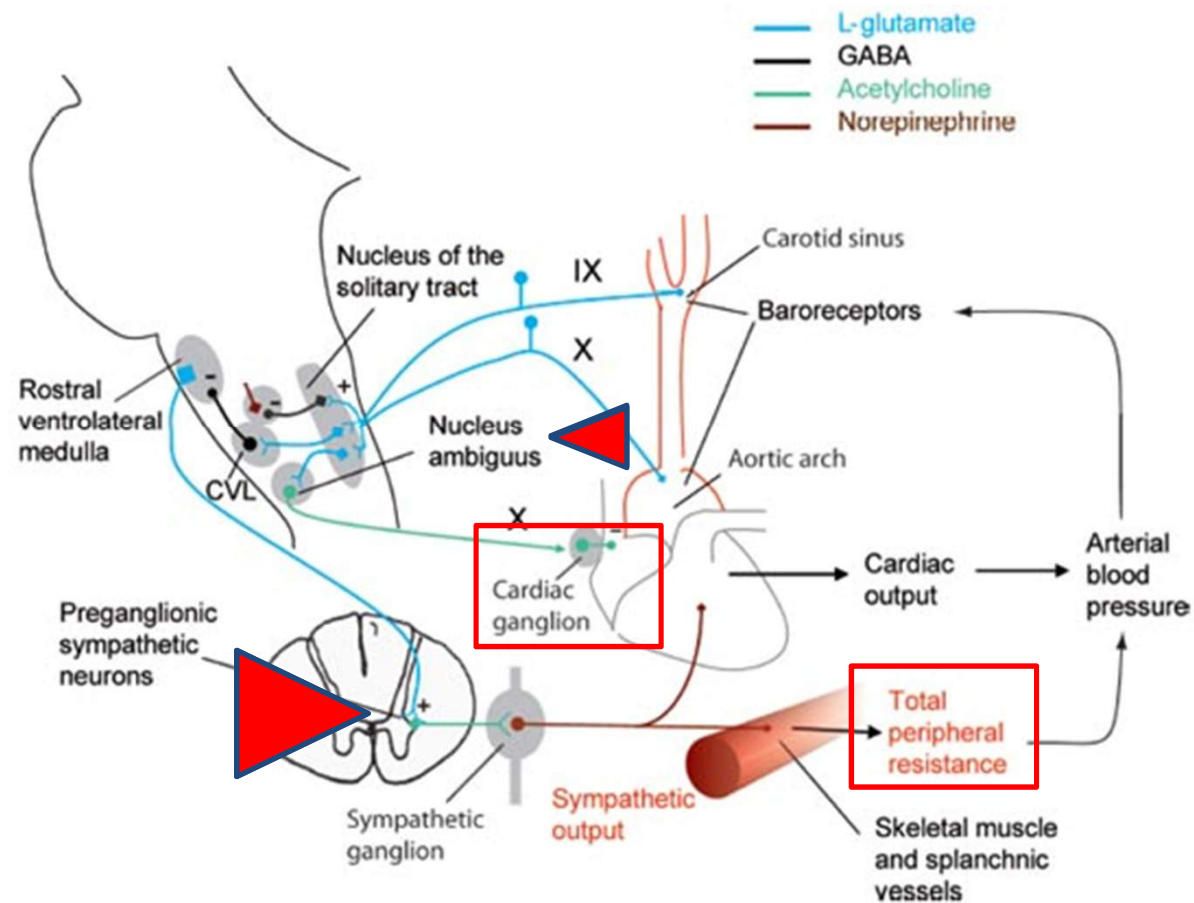
- Small and non-small-cell, GI, prostate, breast, bladder etc
- May be seen together with brainstem encephalitis and sensory neuronopathy.
- Anti-Hu, Purkinje cell, CRMP-5, P/Q Calcium channel



# Baroreflex failure



Critical CV reflex: continuous buffering of acute fluctuations of ABP in situations such as changes in posture, exercise, and emotion  
:CO, TPR





# Hypertensive crises and fluctuating hypertension

- Elevation of plasma norepinephrine to levels comparable to those encountered in pheochromocytoma

| <b>Table 2</b> Causes of baroreflex failure |                                                                                                         |
|---------------------------------------------|---------------------------------------------------------------------------------------------------------|
| Site of involvement                         | Example                                                                                                 |
| Carotid baroreceptor                        | Neck surgery (thyroid, larynx)<br>Carotid surgery (paraganglioma, endarterectomy)<br>Carotid dissection |
| Baroreceptor afferent                       | Neck radiation<br>Cranial neuropathy (e.g., Guillain-Barré syndrome)                                    |
| Central baroreflex pathways                 | Syringobulbia<br>Brainstem stroke affecting the nucleus of the solitary tract<br>Leigh syndrome         |



# Baroreflex Failure

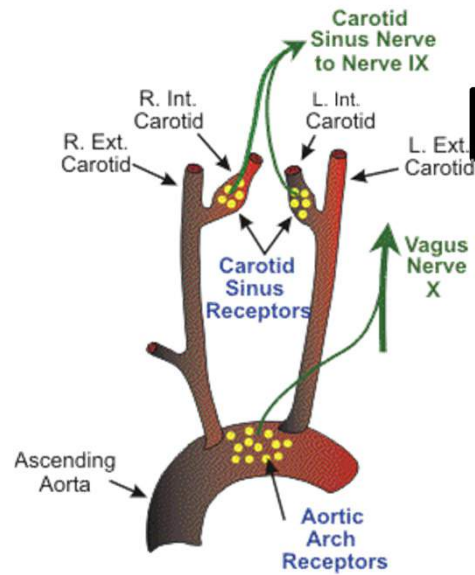
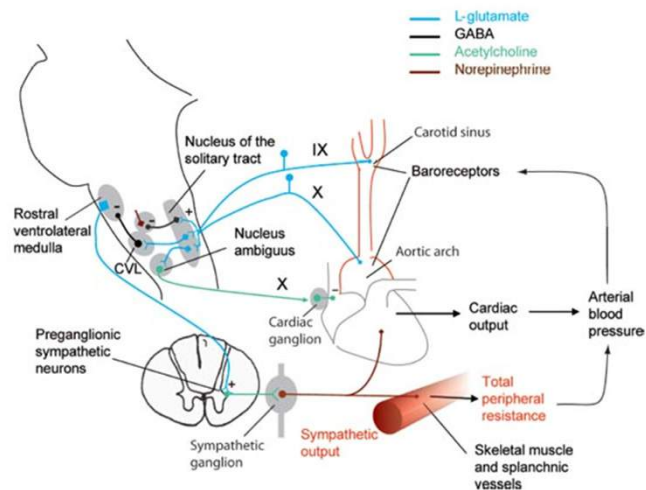


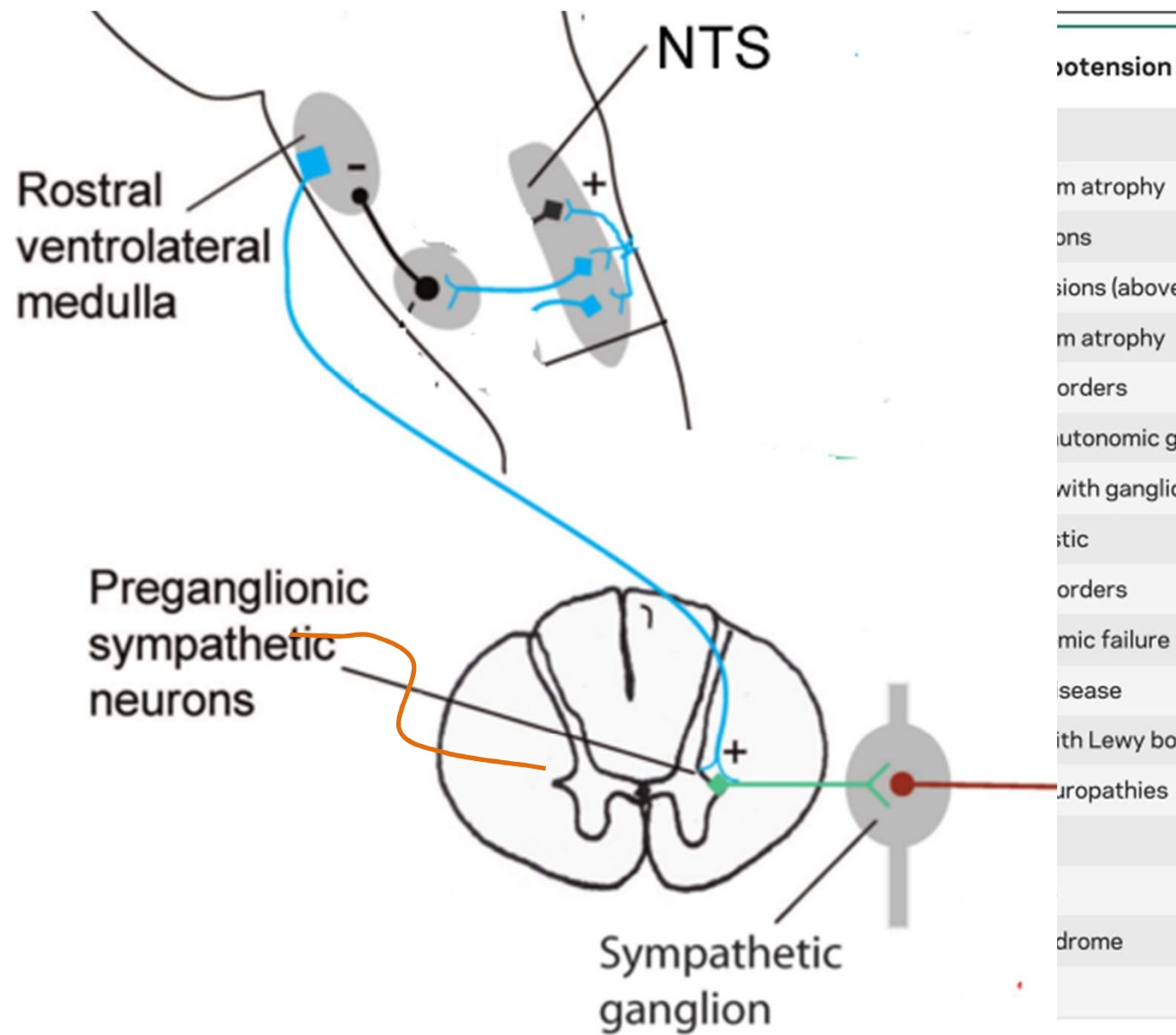
Figure 1. Location and innervation of arterial baroreceptors.

**Table 1** Differential features between baroreflex failure and autonomic failure

| Clinical feature                        | Baroreflex failure | Autonomic failure |
|-----------------------------------------|--------------------|-------------------|
| Supine hypertension                     | +/-                | ++                |
| Labile hypertension                     | +++                |                   |
| Orthostatic or postprandial hypotension | +/-                | +++               |
| Episodic tachycardia                    | ++                 | -                 |
| Orthostatic tachycardia                 | +/-                | -                 |
| Bradycardic episodes                    | ++                 | +/-               |







hypotension

muscle atrophy

neurons

lesions (above T5)

muscle atrophy

disorders

autonomic ganglionopathies

associated with ganglionic nAChR antibody

idiopathic

disorders

cardiac failure

disease

associated with Lewy bodies

neuropathies

syndrome



# Measure

- Lying, standing:
- 20/10 mm Hg
- May want to wait 3 minutes, hold arm horizontal

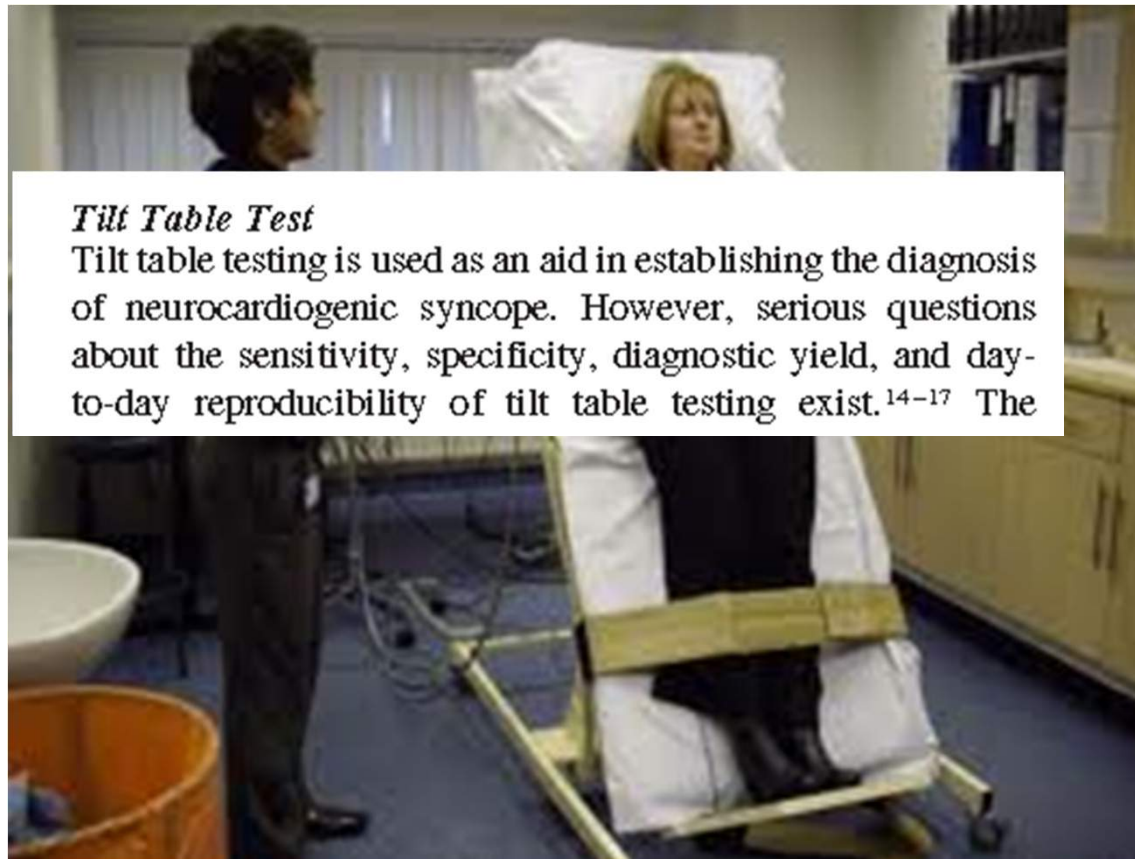


# Other features of autonomic failure

- Resting tachycardia (rare)
- Loss of sinus arrhythmia: ECG machine: six breaths per minute: 5 seconds in, 5 seconds out.
- Sweating



# Tilt table testing



## *Tilt Table Test*

Tilt table testing is used as an aid in establishing the diagnosis of neurocardiogenic syncope. However, serious questions about the sensitivity, specificity, diagnostic yield, and day-to-day reproducibility of tilt table testing exist.<sup>14-17</sup> The