

# The Danish Perspective

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Denmark

# Thank you

- HPV-vaccine related disorders
- Worldwide problem
- Japan and Denmark in front ?
  - Simultaneously and independently
- Collaboration and communication essential
  - We need to know more – fast
  - We need to address this challenge from several countries
- Thank you for inviting me

# Denmark



- Population 5.627.235 (2014)
- 5 Regions
- The Danish welfare model
  - High taxation levels
  - Educational and health system free



# Denmark

Nov. 23, 2015



# The HPV-vaccine in Denmark

- qHPV vaccine Gardasil introduced 2006
- Part of Childhood Vaccination Program since 2009 (12 year old girls)
- Three vaccines → two vaccines August 2014
- Catch up program

# Why do we see these patients?

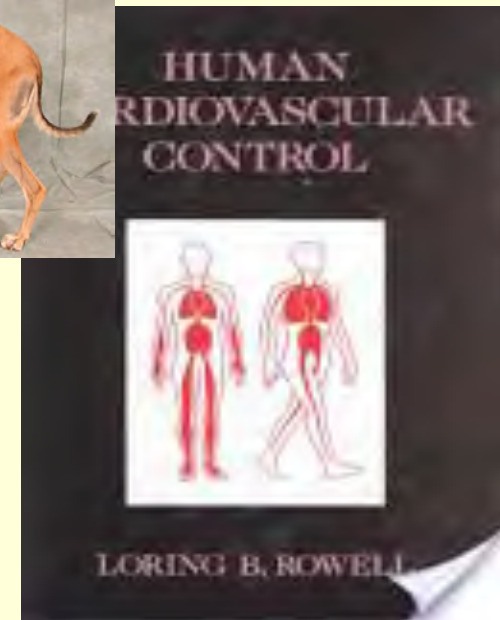
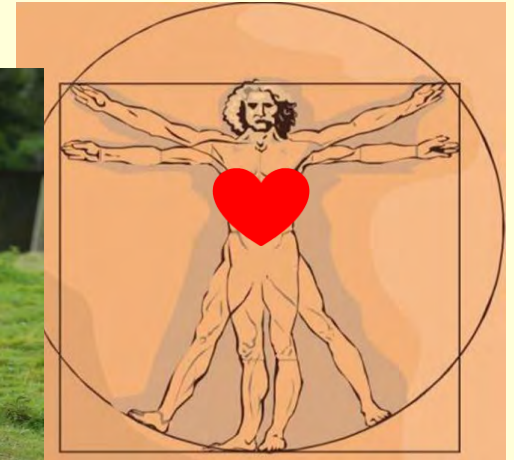


- Frederiksberg Hospital
- Syncope Unit
- Autonomic laboratory
- Research Center
- Already interested in ME and fibromyalgia

# The human challenge

Nov. 23, 2015

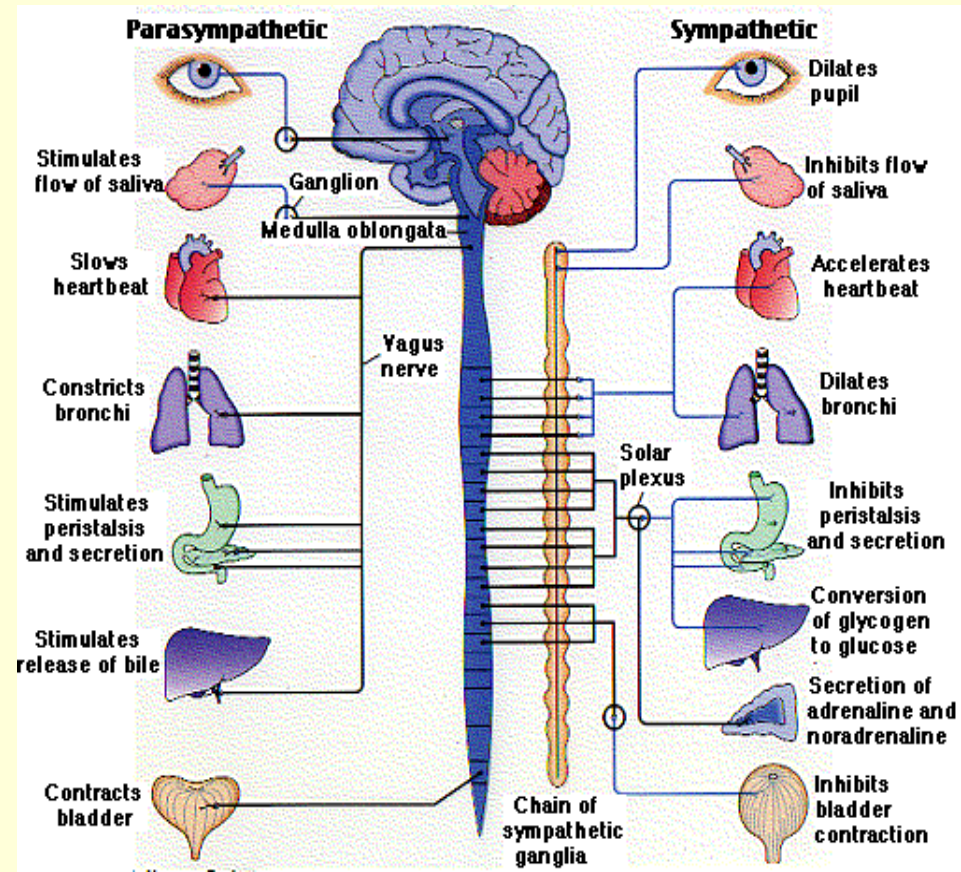
- Becoming upright
- Keeping upright
- "The circulatory adjustments to upright posture demands the full capabilities of the reflexes that governs cardiovascular function"
- Autonomic nervous system
- Cardiovascular system



*"When man's subhuman ancestors first dared to rise and walk upon their hind legs, they essayed a physiological experiment of no mean difficulty" W.R. Amberson 1943*

# The autonomic nervous system (ANS)

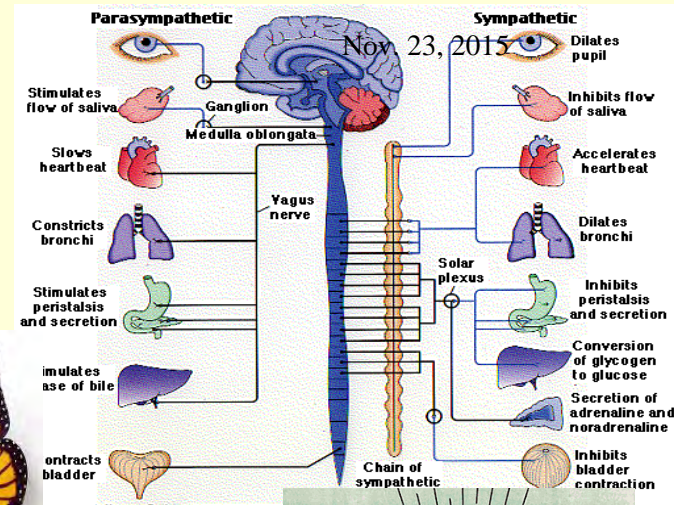
- Antagonistic but coordinated interplay SNS/PNS
- Remember the autonomic afferents
- 80% of vagal fibres are afferents
- ANS senses and responds to both intra- and extra somatic stimuli
- Homeostasis
- Fight and flight
- Reflexes – autonomic





# The patients we see

- Function and dysfunction of the autonomic nervous system
- Autonomic dysfunction –
  - many symptoms from many organs



- PSYCHE – SOMA
- Gut feelings.....

• "The circulatory adjustments to upright posture demand the full capabilities of the reflexes that govern cardiovascular function"



- Difficult overlap to psychosomatic illness, functional disorders
- Orthostatic intolerance

# POTS diagnosis

- Postural orthostatic tachycardia syndrome
- POTS central in Europe when discussing suspected HPV-vaccine side effects
- Orthostatic intolerance
- Heart rate increment  $\geq 30(40)$ bpm or to levels  $> 120$  bpm within 10 minutes of standing or HUT
- Absence of orthostatic hypotension (often instability of blood pressure)
- Absence of other overt causes of orthostatic tachycardia

# Suspected side effects to the HPV-vaccine

Nov. 23, 2015

- 2011 – first patients referred to our clinic for evaluation due to orthostatic intolerance suspected to be side effects to the HPV-vaccine
- 2013 – after having evaluated 6-7 patients we suspect a pattern in the symptoms described by this group of patients.
- November 2015 – evaluated 300 patients, 700 referred

# What have we done?

- Reported side effects
- Informed health authorities
- Disseminating activities
- Established network of clinicians and researchers
- Published three papers
- 5 regional "HPV-centers"



# Reporting side effects

- Healthcare professionals and medicine users/relatives can report side effects directly to the Danish Health and Medicines Authority
- Health care professionals obliged by law to report possible side effects if they can not be dismissed...

# Possible side effects

- 1.651.152 doses
- 543 serious adverse effects

HPV-vaccine	2009	2010	2011	2012	2013	2014	Til 30. juni 2015	Total
Antal indberetninger	288	66	43	95	514	192	387	1586
Antal alvorlige	25	7	9	18	186	96	202	543
Antal solgte doser	347.690	151.476	163.374	349.730	488.224	114.467 <sup>4</sup>	36.191	1.651.152

# 1st paper

VACCINE XXX (2015) XXX–XXX



Contents lists available at [ScienceDirect](#)

## Vaccine

journal homepage: [www.elsevier.com/locate/vaccine](http://www.elsevier.com/locate/vaccine)



Orthostatic intolerance and postural tachycardia syndrome as suspected adverse effects of vaccination against human papilloma virus

1 Louise S. Brinth, Kirsten Pors, Ann C. Theibel, Jesper Mehlsen\*

*Coordinating Research Centre, Frederiksberg Hospital, Nordre Fasanvej 57, 2000 Frederiksberg, Denmark*

# Patients referred with orthostatic intolerance as a possible side effect to Gardasil

Number of patients:	78 patients referred
	70 examined with HUT
	35 included in first publication
Age at HUT :	23,3 år (range: 13 – 39)
Age at symptom onset:	22,0 år (range: 12 – 39)
Height: 168 cm	Weight: 62,4 kg
BMI: 22,0 kg/m <sup>2</sup>	<19: 13%; 19-25: 74%
	26-30: 3%; >30: 10%
Level of activity before symptom onset:	Moderate: 29%; High: 71%
(IPAQ-SF)	(Elite:33%)



# Patients with orthostatic intolerance as a possible side-effect to Gardasil

- Time from vaccine to symptom-onset: 9 days (0-30)
- Time from symptom-onset to HUT: 1,9 år (0-5)
- Symptom onset after:
  - 1st vaccine: 24%
  - 2nd vaccine: 51%
  - 3rd vaccine: 25%
- Activities of daily living
  - 97 % seriously affected
  - 60% had quit school/work

# Symptoms

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- Orthostatic intolerance 100%
- POTS 60%
- Nausea 94 %
- Headache 82 %
- Fatigue 82 %
- Palpitations 77 %
- Cognitive dysfunction 77 %
- Skin changes 76 %
- Segmental dystonia 68 %
- Neuropathic pain 68 %
- Sleeping disorder 61 %
- Muscular weakness 61 %

# Symptoms

- Compass-31
    - +POTS: 52,7
    - POTS: 45,6
- (p=0,194)

(Healthy controls: 9,6

Patients with "autonomic failure": 39,2)

*Sletten DM et al. Mayo Clin Proc 2012  
December;87(12):1196-201.*

*Singer W et al. Neurology February 12, 2013; 80.  
37.001*

# 2nd paper

Dan Med J 62/4

April 2015

DANISH MEDICAL JOURNAL

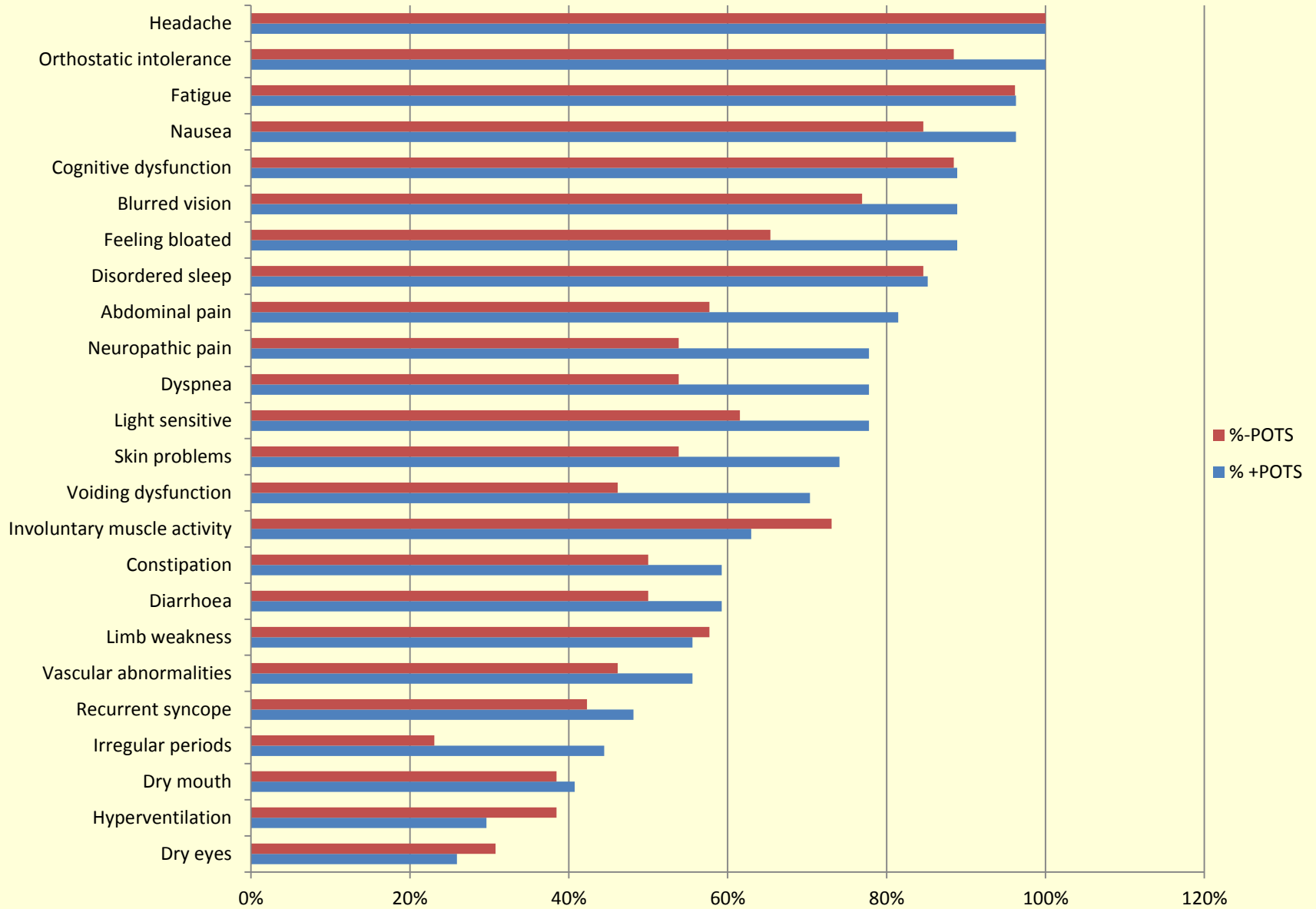
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## Suspected side effects to the quadrivalent human papilloma vaccine

Louise Brinth<sup>1,2</sup>, Ann Cathrine Theibel<sup>1,2</sup>, Kirsten Pors<sup>1</sup> & Jesper Mehlsen<sup>1,2</sup>

**Symptom or disease?**

**Is POTS a relevant diagnosis?**



# 3rd paper

## Is Chronic Fatigue Syndrome/Myalgic Encephalomyelitis a Relevant Diagnosis in Patients with Suspected Side Effects to Human Papilloma Virus Vaccine?

### Abstract

The quad valent human papilloma virus vaccine (Q-HPV-vaccine) was included into the Danish childhood vaccination program in 2009. During the past years possible side effects have been described in several countries encompassing a collection of symptoms consistent with pronounced autonomic dysfunction coupled with severe non-migraine-like headache, excessive fatigue, cognitive dysfunction, gastrointestinal discomfort and widespread pain of a neuropathic character.

The assessment of the prevalence and the possible pattern in symptoms suspected to be side effects has been hampered by a lack of consistency in the diagnostic criteria applied on seemingly similar symptom complexes. As fatigue and fatigability is a prominent symptom in many of the patients with suspected side effects to the vaccine, chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) could be suspected to be a suitable diagnosis.

We have performed a retrospective analysis on the applicability of the CFS/ME diagnosis in 39 patients referred to our Syncope Unit from May 2011 to April 2015 for clinical evaluation including a head-up tilt test. The patients were referred due to orthostatic intolerance and symptoms compatible with autonomic dysfunction occurring in a close temporal association to vaccination with the Q-HPV vaccine. We found that 34 (87%) and 35(90%) of the patients fulfilled the diagnostic criteria for CFS/ME regarding to the Canadian and the IOM (Institute of Medicine) criteria respectively and suggest that CFS/ME may be a suitable diagnosis for patients with severe and persistent suspected side effects to the Q-HPV vaccine.

### Research Article

Volume 1 Issue 1 - 2015

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# 3rd paper

- Primary finding: Most of the patients we see with suspected side effects to the HPV-vaccine fulfills the diagnostic criteria for ME

# Diagnostic mess....

- HANS
- POTS
- CRPS
- ME/CFS
- Fibromyalgia
- Psychogenic/"Functional disorder"
- MS
- ADEM
- PANDAS
- Anxiety/Depression
- Munchausen by proxy

**We need biomarkers!**



# What is going on in Denmark?

- An increasing number of ADR
- TV-documentary March 26th 2015
- "Danish Regions" promises to open 5 regional centres for patients with diffuse symptoms suspected to be side effects to the HPV-vaccine – plans to open late spring 2015

# What is going on in Denmark?

- ~ 2000 patients referred to 5 regional "HPV-centres"
- Health minister wants the five regional centers to offer same evaluation and treatment of the patients
- Health authorities will decide on and implement criterias for evaluation and treatment of patients in the 5 regions HPV-centers

# EMA (European Medicines Agency) and Danish risk assessment December 2014 concerning POTS/CRPS

- In the December review of Gardasil® safety, the possible connection between the HPV vaccine and POTS1 and CRPS2 was thoroughly assessed. The PRAC concluded that presently it is not possible to confirm or disprove that there is a causal relationship between Gardasil® vaccination and the occurrence of POTS and CRPS, respectively.
- Therefore, POTS and CRPS should be monitored closely in future reviews of Gardasil® safety, and a special initiative in the form of a new questionnaire has been launched to ensure appropriate follow-up on ADR reports that describe symptoms suggestive of POTS or CRPS.

# EMA

(European Medicines Agency)

- Press release 13/07/2015 : EMA to further clarify safety profile of human papillomavirus (HPV) vaccines
- In its review the PRAC will consider the latest scientific knowledge, including any research that could help clarify the frequency of CRPS and POTS following vaccination or identify any causal link. Based on this review, the Committee will decide whether to recommend any changes to product information to better inform patients and healthcare professionals. While the review is ongoing there is no change in recommendations for the use of the vaccine.
- Result: The PRAC concluded that the available evidence does not support that CRPS and POTS are caused by HPV vaccines. Therefore there is no reason to change the way the vaccines are used or amend the current product information

# What is going on in Denmark?

- EMA-conclusion adopted by health authorities
- 7.000.000 Danish Kroner ~123.600.000 JPY given to research in suspected side effects over next 3 years (government)

# What is going on in Denmark?

- Vaccination rates are decreasing
- EMA looking into CRPS and POTS as possible side effects
- Five "HPV-centres" in Denmark – patients referred with suspected side effects to the HPV-vaccine –so far more than 2000 patients referred
- Research needed – and planned and funded.....

# Research

- Pathophysiology?
  - Neuroinflammation?
  - Autoimmunity?
  - Small fiber neuropathy?
  - Psychosomatic?
  - Mitochondrial dysfunction?
  - Autonomic dysfunction?
  - Cellular depletion?
  - Toxic reaction?

# Research

- Pathophysiology?
  - Neuroinflammation?
  - Autoimmunity?
  - Small fiber neuropathy?
  - Psychosomatic?
  - Mitochondrial dysfunction?
  - Autonomic dysfunction
  - Cellular depletion?
  - Toxic reaction?

*What is the primary pathological problem?*

*Causal link to the HPV-vaccine?*

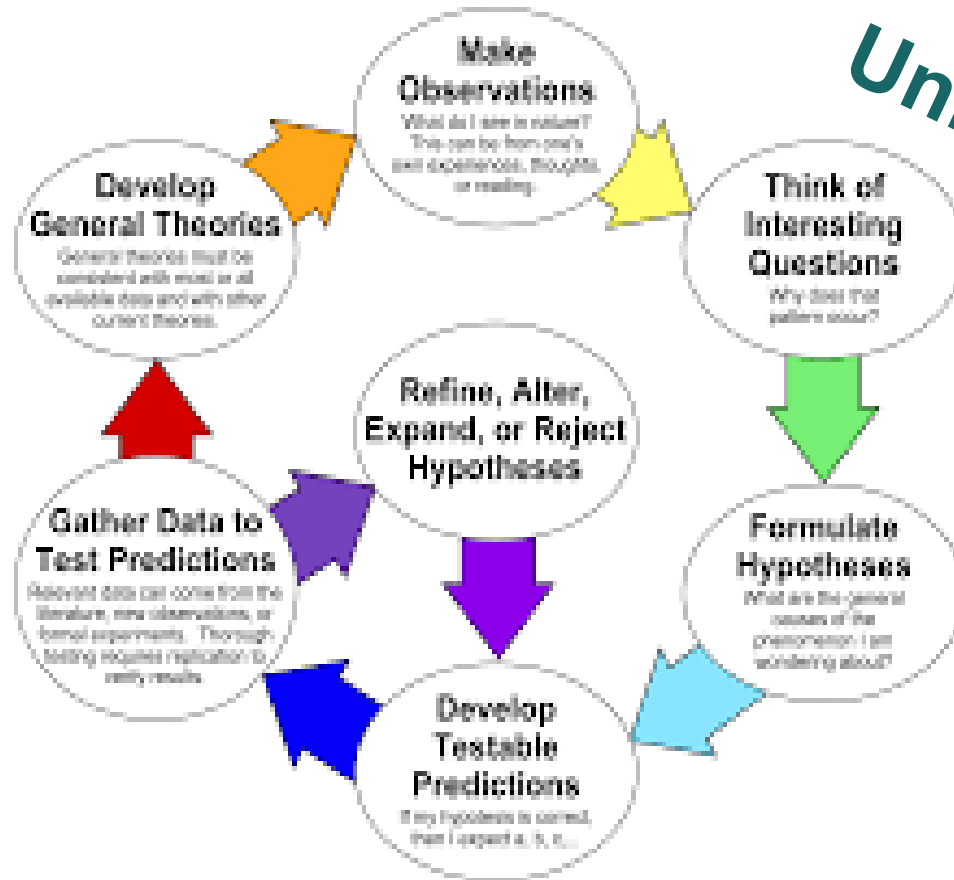


# Research

- 1. Case definition
- 2. Neuroinflammation
- 3. Small fiber disease
- 4. Narcolepsy
- 5. Autoimmunity
- 6. Mitochondrial dysfunction
- 7. Genetic susceptibility

# Research

## The Scientific Method as an Ongoing Process



**Unifying hypothesis?**

**Collaboration and communication**

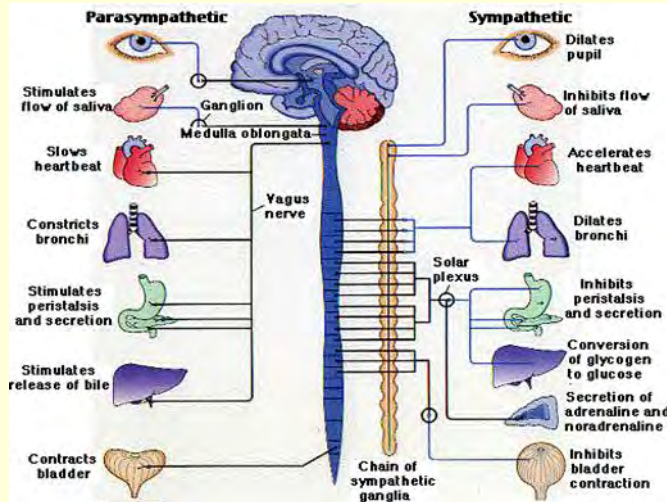
# Research

## The Scientific Method as an Ongoing Process



- Japan and Denmark
- Independently
- Simultaneously
- Same observations
- Same hypothesis
- Same conclusion?

# Conclusion



- Autonomic dysfunction ~ many and "diffuse" symptoms
- Central autonomic network
- Primary pathophysiological process?

*The central autonomic network (CAN) is an integral component of an internal regulation system through which the brain controls **visceromotor, neuroendocrine, pain, and behavioral responses** essential for survival. It includes the insular cortex, amygdala, hypothalamus, periaqueductal gray matter, parabrachial complex, nucleus of the tractus solitarius, and ventrolateral medulla.*

# Why is this so difficult?



- Vaccine side effect



- Psychosomatic disorder?

Status? Fibromyalgia? CRPS?  
ME/CFS? Functional disorder/Psychosomatic?  
POTS?

HANS  
Diagnosis?



Vaccine

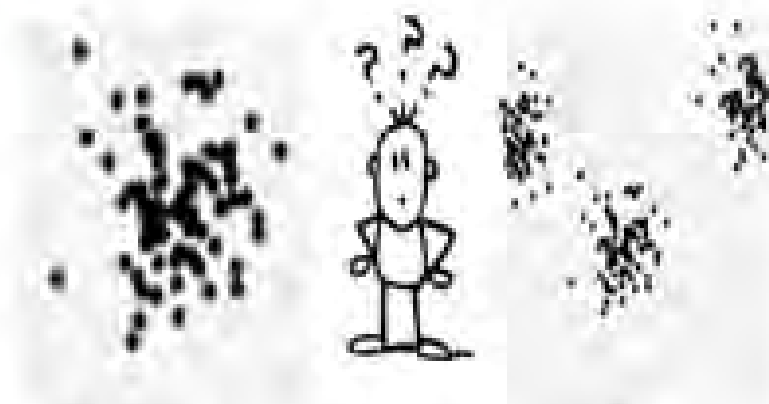


Symptoms

Psyche



Soma



One heterogeneous group?

Status? Fibromyalgia? CRPS?  
 ME/CFS? POTS? Functional disorder/ Psychosomatic?



HANS

Diagnosis?



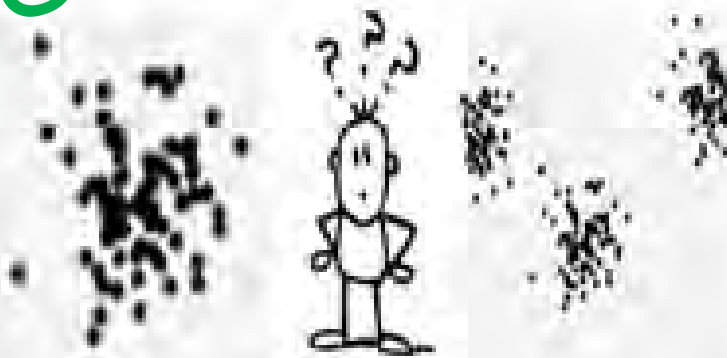
Vaccine

Symptoms

Psyche

Soma

**Shared reality!?**



One heterogeneous group?

