

# **What causes CFS/ME ?**

**Is it all in the Gut ?**

**Research on Extremely Disabled ME Patients Reveals the True Nature of the Disorder**

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# **Myalgic encephalomyelitis: A highly prevalent debilitating disease**

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- **Persistent, debilitating fatigue associated with numerous physical and neurocognitive symptoms**

Disease severity can range from moderate to extremely severe: patients bedridden for years, totally caregiver dependent

- **Prevalence estimates: 0,3 to 0,6%; one million patients in the USA, two million patients in Europe**

This may just be the tip of the iceberg

- **High socio-economic cost**

Cost to the society estimated as approximately \$16 billion in the USA, €20 billion in Europe

## **Norwegian study: design, parameters tested**

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- **Norwegian study focused on a group of extremely disabled patients**

Purpose of the study: investigate clinical dysfunctions in totally bedridden patients (Karnofski score 20-30) compared to moderately ill patients (Karnofski 60-70), contact controls and non-contact controls

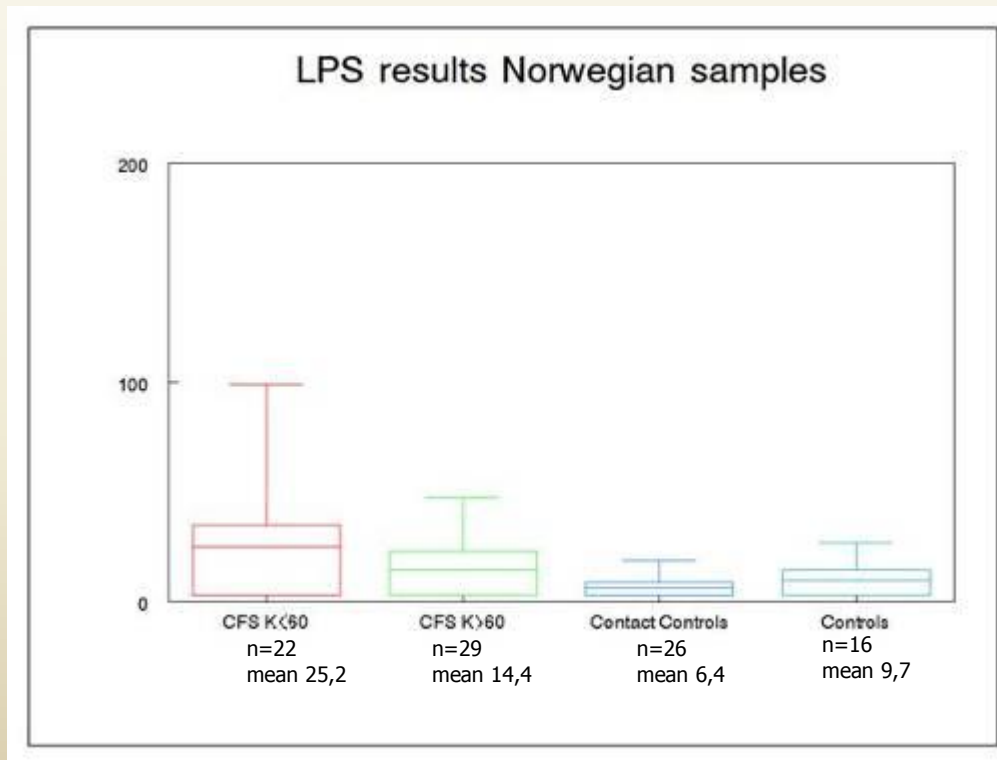
- **Parameters tested included immune function parameters, viruses, intestinal dysfunction markers**

- HHV-6, EBV antibodies: no differences between the groups
- Bornavirus: few positive patients, no more than controls
- HHV-6, EBV PCR: a few positive patients. Not always correlated with antibody titers

# Intestinal dysfunction marker, LPS, was significantly different between the groups

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- Plasma LPS is more elevated in patients with low Karnofski score



# High levels of plasma LPS are indicative of increased intestinal permeability in ME patients

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- **LPS is a strong activator of the immune system. Presence of LPS in the bloodstream suggests a hyperpermeable gut, which is consistent with the numerous intestinal symptoms seen in most ME patients**

Nausea  
Poor appetite  
Gastric reflux

Abdominal pain  
Abnormal bowel motility  
Bloating

- **Most likely explanation of gut permeability: alteration of the intestinal microbial flora**

## Alterations of intestinal microflora in ME patients (aerobes)

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- *Enterococcus* and *Streptococcus* species are strongly over-represented in ME patients :

Organisms	Control	ME patients	<i>p</i> -value
<i>E.coli</i>	$1.0 \times 10^8$	$4.26 \times 10^7$	$p=0.98$
<i>Enterococcus</i> spp.	$5.0 \times 10^6$	$3.5 \times 10^7$	<b><math>p&lt;0.001</math></b>
<i>Streptococcus</i> spp.	$8.9 \times 10^4$	$9.8 \times 10^7$	<b><math>p&lt;0.001</math></b>

## Alterations of intestinal microflora in ME patients (anaerobes)

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- Among anaerobic bacteria, *Prevotella* is the most consistently overgrown bacteria :

Organisms	Control	ME patients	<i>p</i> -value
<i>Bacteroides</i> spp.	3.2 x 10 <sup>11</sup>	1.6 x 10 <sup>11</sup>	<i>p</i> =0.39
<i>Prevotella</i> spp.	1.0 X 10 <sup>8</sup>	9.0 x 10 <sup>9</sup>	<b><i>p</i>&lt; 0.001</b>
<i>Bifidobacterium</i> spp.	6.0 x 10 <sup>8</sup>	5.5 x 10 <sup>9</sup>	<b><i>p</i>=0.001</b>
<i>Lactobacillus</i> spp.	2.7 x 10 <sup>7</sup>	1.8 x 10 <sup>8</sup>	<b><i>p</i>=0.002</b>

## Alterations of intestinal microflora in ME patients : ratios anaerobes/aerobes and Gm(-)/Gm(+)

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- Gm(-)/Gm(+) ratio are very significantly altered :

<b>Organisms</b>	<b>Control</b>	<b>Patients</b>	<b><i>p</i> value</b>
<b>Anaerobes / Aerobes</b>	13210.62	11295.19	<b>= 0.08</b>
<b>Gm(-) / Gm(+) ratio</b>	16114.79	658.96	<b>&lt;0.001</b>



# Bacterial overgrowth correlates with symptom severity

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- *Enterococcus* spp. counts correlate with symptom expression :

Symptoms	r and <i>p</i> -values
Headache	r=.17, <i>p</i> <0.01
Arm pain	r=.20, <i>p</i> <0.003
Shoulder pain	r=.15, <i>p</i> <0.04
Myalgia	r=.20, <i>p</i> <0.003
Palpitations	r=.16, <i>p</i> <0.02
Sleep disturbance	r=.20, <i>p</i> <0.004

# Bacterial overgrowth correlates with symptom severity

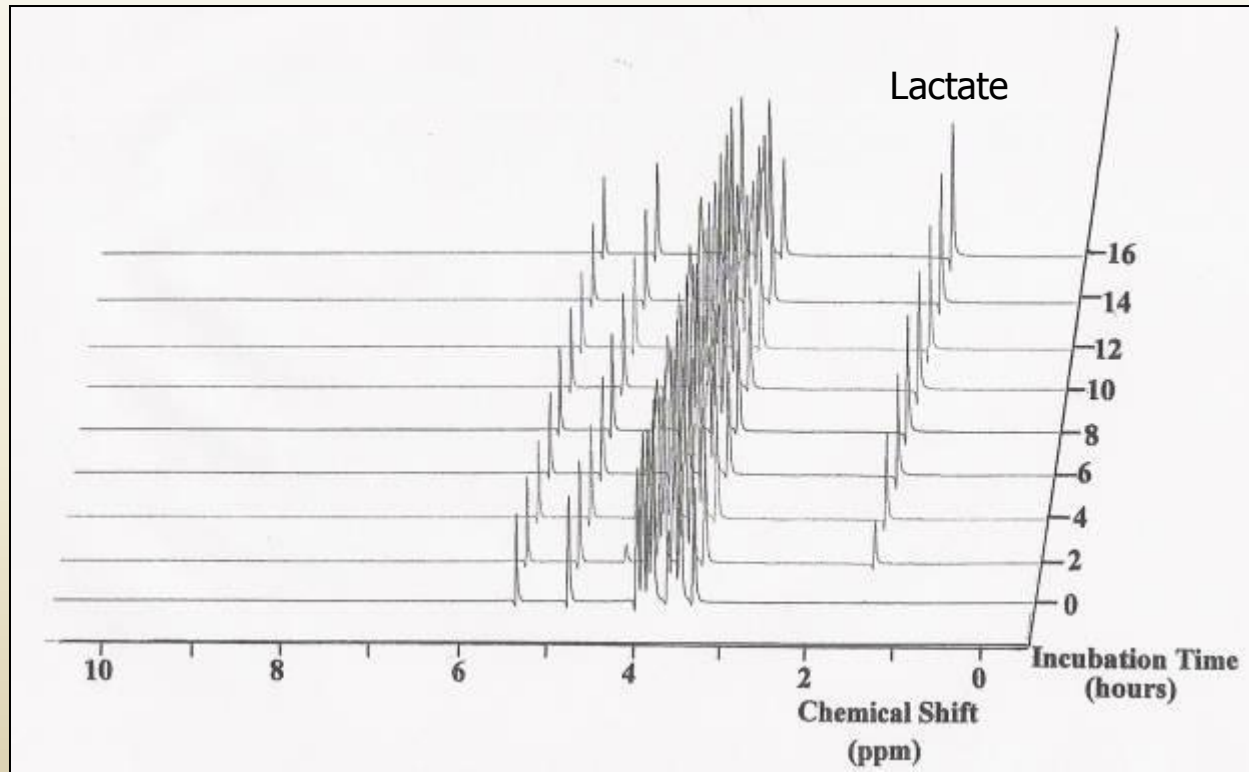
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- *Streptococcus* spp. counts correlate with symptom expression :

Symptoms	r and <i>p</i> -values
Post Exertional fatigue	r=.15, <i>p</i> <0.03
Photophobia	r=.14, <i>p</i> <0.04
Mind going blank	r=.17, <i>p</i> <0.01
Cervical gland lymphodynia	r=.14 <i>p</i> <0.04
Palpitations	r=.15, <i>p</i> <0.03
Dizziness/Faintness	r=.14, <i>p</i> <0.05

# Overgrown bacteria produce lactic acid

- NMR metabolic profiles of *Enterococcus faecalis*



# Increased production of lactic acid (Lactic Acidosis) could contribute to symptoms

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- “Lactic acid” bacteria counts correlate with symptom expression :

Symptoms	r, <i>p</i> -values
Mental fatigue	r=.18, <i>p</i> <0.009
Photophobia	r=.18, <i>p</i> <0.008
Urinary frequency	r=.16, <i>p</i> <0.03
Urinary urgency	r=.14, <i>p</i> <0.04
Palpitations	r=.15, <i>p</i> <0.03
Dizziness/Faintness	r=.13, <i>p</i> <0.05

# Another potential toxin produced by bacteria is hydrogen sulfide (H<sub>2</sub>S)

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- **Hydrogen sulfide (H<sub>2</sub>S) has important physiological functions...**

H<sub>2</sub>S is produced by the cells and is an important gaseous signal molecule, involved in regulation of blood pressure, neurotransmission, muscle relaxation and regulation of inflammation

- **...but exogeneous exposure can be extremely toxic**

In excess, H<sub>2</sub>S acts as a mitochondrial poison. It can directly inhibit enzymes involved in the cellular production of energy. H<sub>2</sub>S also interferes with oxygen transport by blocking hemoglobin in the red blood cells. H<sub>2</sub>S is a potent neurotoxin

***Enterococcus, Streptococcus, Prevotella* are strong H<sub>2</sub>S producers**

# A marker associated with H<sub>2</sub>S production can be measured with a simple urine test

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1. Collect urine



2. Open tube containing test reagent



3. Add a few drops of urine to the test reagent



4. Mix by shaking gently.  
Wait for two minutes



5. Observe color changes. Dark color = positive sample



Negative or  
Pre-ME

Moderate  
disease


Severe  
disease

# Heavy metal exposure is another contributing factor to the disease

- Patients often present intoxication with mercury, nickel or other metals

**MICRO TRACE MINERALS GmbH** environmental & clinical laboratory

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 USA, P.O. Box 4812, Boulder, Co 80306-4812      Telefax: +49 (0) 9151 2306      <http://www.microtrace.de>  
 service@microtrace.de

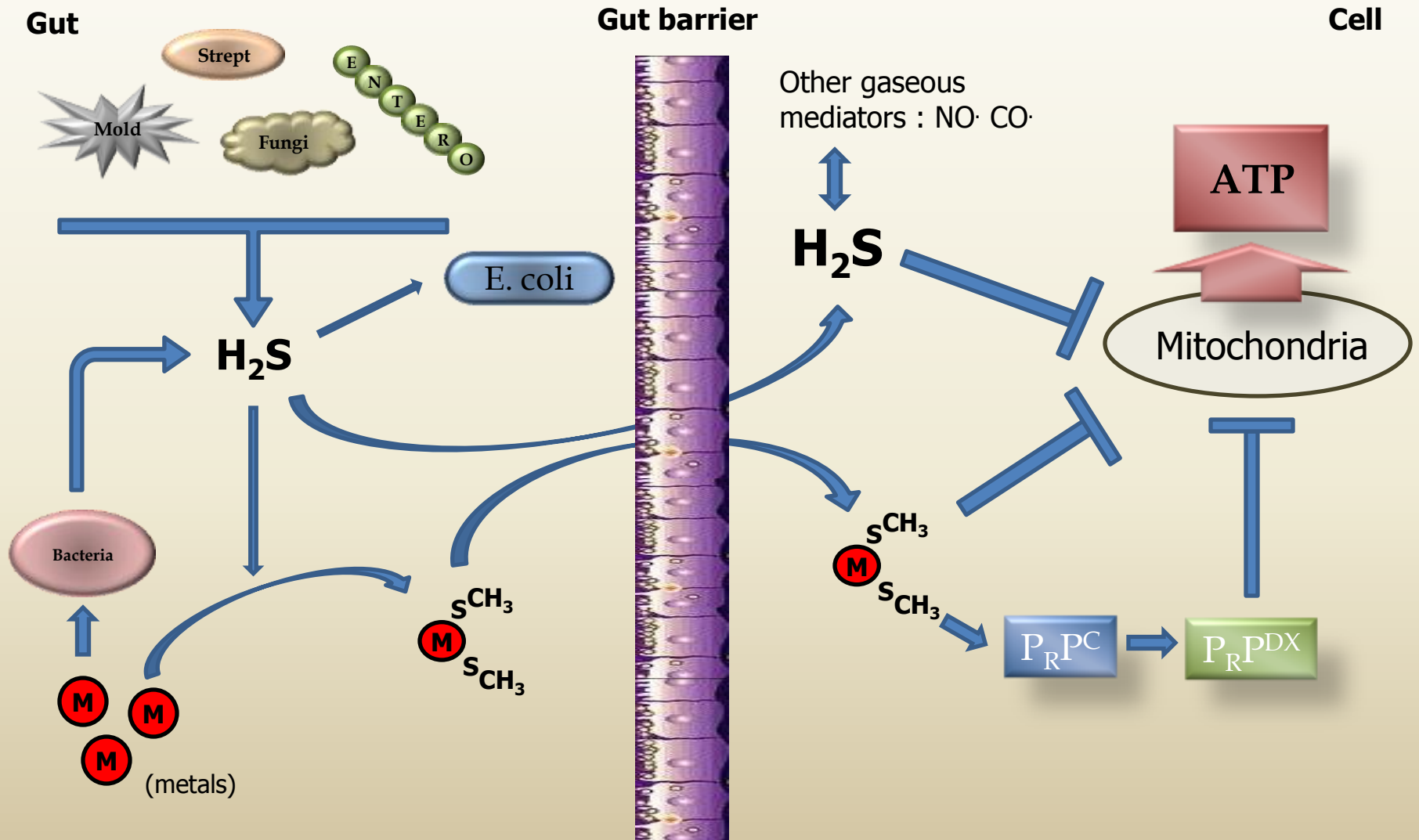


MINERAL ANALYSIS		Urine		Lab Number
				UR92853
Doctor	Prof. Dr. K. De Meirick			
Patient Name				
Clinical Information	Dosis: 250mg. Sul. DMPS+150ml NaCl 0.3% 2hr			
Test Date	20. Mai. 09	D.O.B.	31.12.1987	Sex:  r  Creatinine (µg/l): 0.3
Essential Macro- & Trace Elements (mg/g creatinine)		Low	Acceptable Range	High
Acceptable Range Test Value				
Calcium	55,00 – 245,00	137,05	*****	
Magnesium	12,00 – 150,00	89,75	*****	
Zinc	0,07 – 7,00	3,64	*****	
Essential Trace Elements (µg/g Creatinine)		Low	Acceptable Range	High
Acceptable Range Test Value				
Chromium	0,10 – 3,50	0,00	Low	<
Cobalt	< 5,00	0,97	*****	
Copper	1,45 – 60,00	651,86	High	*****
Iron	2,00 – 95,00	12,34	*****	
Manganese	< 4,50	2,95	*****	
Molybdenum	9,70 – 100,00	13,03	*****	
Selenium	12,00 – 90,00	10,24	Low	*****
Vanadium	< 70,00	0,24	*****	
Potentially Toxic Elements in mg/g Creatinine		Low	Acceptable Range	High
Acceptable Range Test Value				
Aluminium	< 125,00	19,75	*****	
Arsenic	< 15,00	7,67	*****	
Barium	< 8,22	1,04	*****	
Beryllium	< 1,20	0,94	*****	
Cadmium	< 1,50	0,13	<	
Lead	< 5,00	4,88	*****	
Mercury	< 1,00	16,56	High	*****
Nickel	< 3,00	27,69	High	*****
Silver	< 1,40	1,47	High	*****
Tin	< 5,00	3,23	*****	

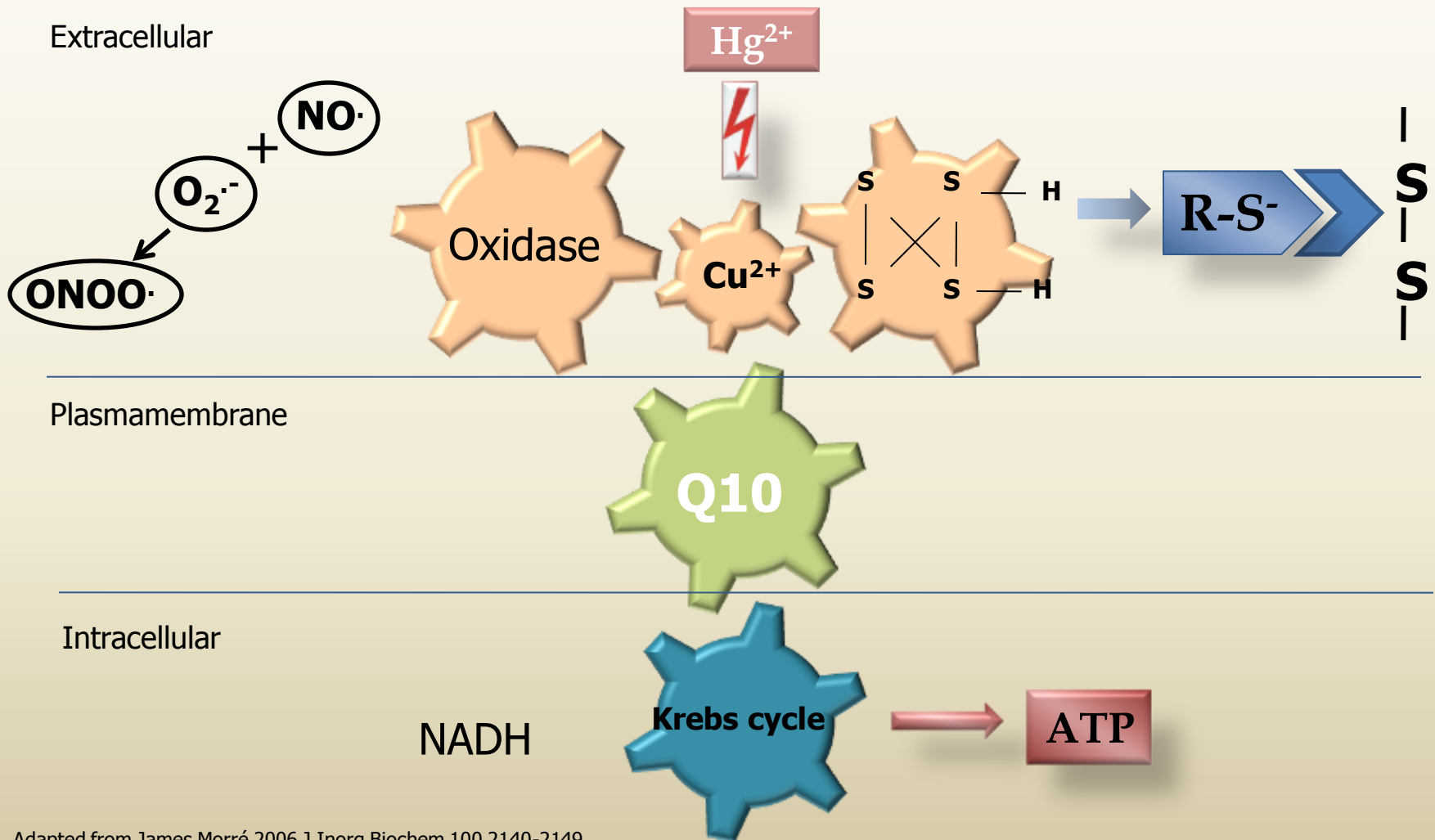
\* The 95percentile Ranges represent baseline urine values and are calculated on the creatinine value. The utilized range is 0.3 to 3.0 g/L creatinine (WHO 2005). For chelator-specific information see attachments.

Accreditation: DIN EN ISO 17025; Quality control: Dr. Rautland PhD; Validation: Dr. E. Blumrock-Brosch PhD

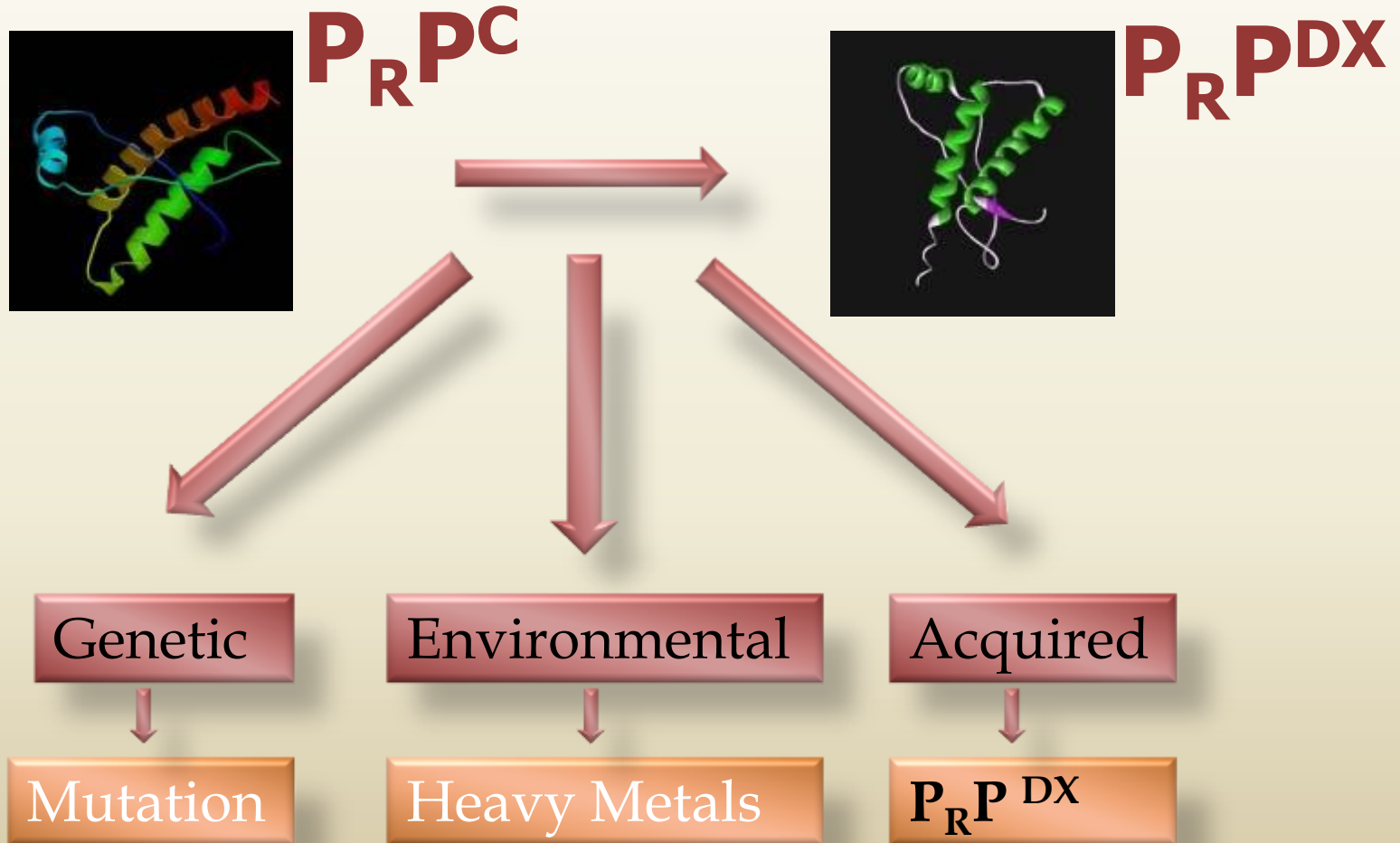
# H<sub>2</sub>S and heavy metals have cumulative effects, causing reduction of ATP production



# Heavy metals interfere directly with energy production



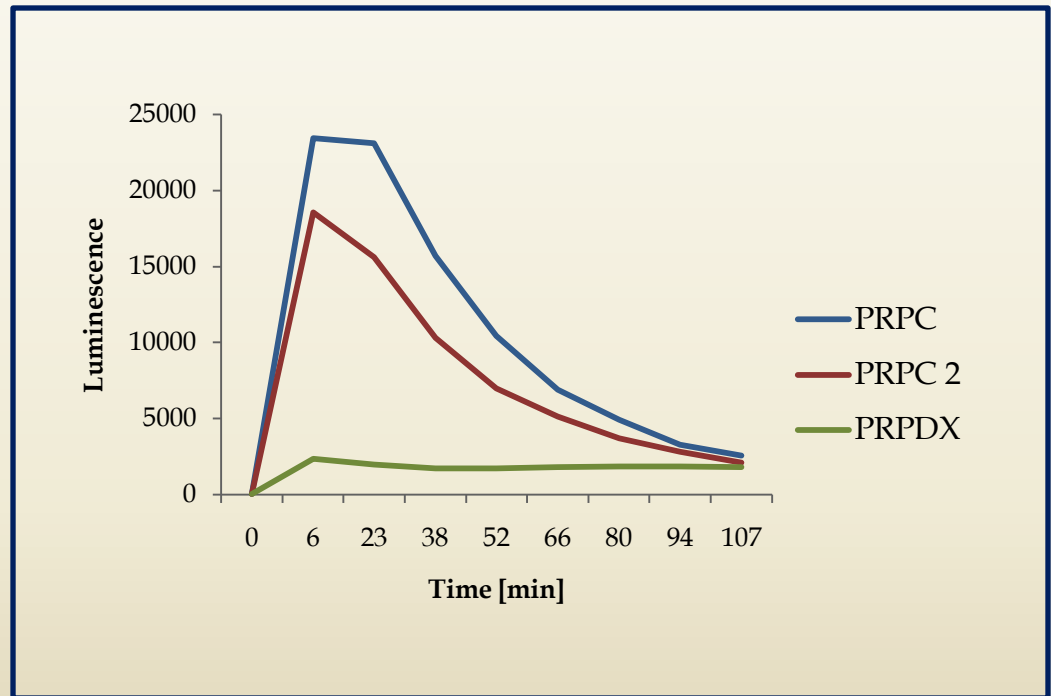
# Genetic and environmental factors contribute to aberrant protein conformation



# Abnormal protein conformation assay

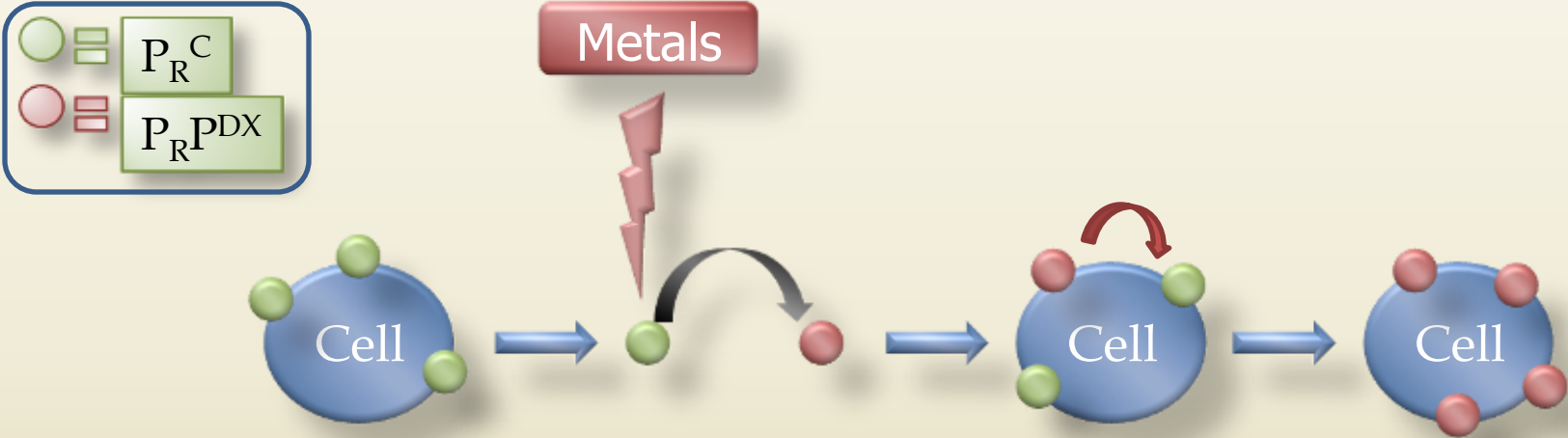
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- **Aberrant luminescence response indicates abnormal conformation**



# Abnormal conformation can be transmitted from one cell to another

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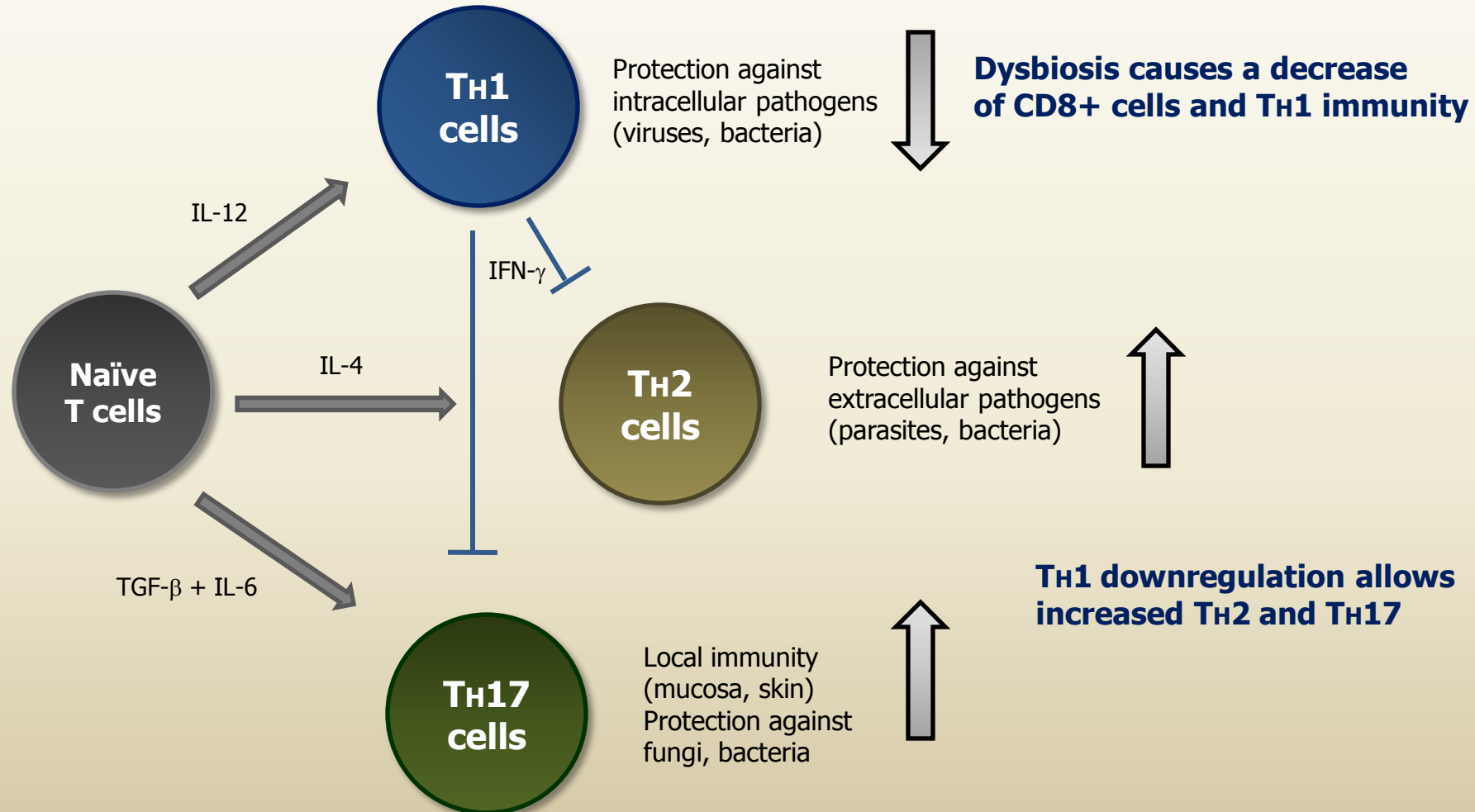


# Disease severity in ME is associated with different physiological dysfunctions

	<b>I</b> <b>"Pre-ME"</b>	<b>II</b> <b>Moderate disease</b>	<b>III</b> <b>Severe disease</b>
<b>Dysfunctions</b>	Abnormal faecal test, high H <sub>2</sub> S	Abnormal faecal test, high H <sub>2</sub> S, exposure to heavy metals	Abnormal faecal test, high H <sub>2</sub> S, exposure to heavy metals that has caused aberrant protein conformation (APD)
<b>Symptoms</b>	No fatigue, possible gastro-intestinal symptoms. Low VO <sub>2</sub> , slow recovery. May be asymptomatic	Fatigue, gastro-intestinal symptoms	Strong fatigue, multiple symptoms
<b>Treatment</b>	Restore the gut: probiotics	Restore the gut: probiotics, enterocoated antibiotics. Metal chelation, Zinc supplementation	Difficult. Gut restoration, metal chelation. Treatment of associated dysfunctions (opportunistic infections). Treatment of APD is still experimental

Increasing immune dysregulations (depressed T and NK cells, Th17 activation, opportunistic infections...)

# Immune alterations resulting from intestinal dysfunction



# Consequences of altered immunity

- **TH1 decrease favors the development of opportunistic viral infections**

HHV-6, Epstein-Barr, parvovirus B19, enteroviruses are found in ME patients. Gastro-intestinal mucosa is a major site of infection

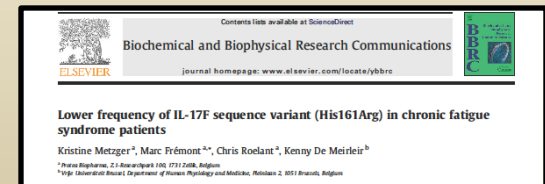


- **TH2 increase favors the development of allergies**

- **TH17 increase promotes inflammation, autoimmunity, blood-brain barrier disruption**

## Genetic background plays a role in T<sub>H</sub>17 upregulation

Polymorphisms of IL-17F, IL-6, TLR4, TGF- $\beta$  genes are associated with ME and other intestinal diseases (Crohn's disease, UC, IBS)



# The case of the XMRV virus

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- **XMRV is an infectious gamma retrovirus**
  - “Xenotropic murine leukemia virus-related virus”
  - Causes mild immuno-suppression
  - First isolated in patients suffering from a form of prostate cancer associated with a defective RNase L
- **An association between XMRV infection and CFS has been reported**
  - In a recent report, found in the blood cells of 67% of CFS patients (68/101) vs. 3.7% of controls (8/218)
  - more research needed to know whether XMRV is a causal factor in the pathogenesis of CFS or reactivates as a consequence of depressed immunity in already sick people
  - Like for other retroviruses, co-infections with other viruses (HHV-6) may be an important issue

# Patient evaluation

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- **Urine test for marker associated with H<sub>2</sub>S production**
- **Intestinal microflora evaluation**
- **Heavy metals analysis**
- **Presence of proteins with abnormal conformation**
- **Assays evaluating subsequent immune dysfunctions (immune dysregulations, opportunistic infections...)**

# CONCLUSIONS

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- **Gastro-intestinal dysfunctions play a central role in the pathogenesis of ME**
- **Dysbiosis detrimental effect mediated by increased production of H<sub>2</sub>S**
- **Immune dysfunctions and opportunistic infections arise as a consequence of pre-existing intestinal problems**

Once established, infections will contribute to the maintenance/aggravation of the disease

# Acknowledgements

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- **Henry Butt at the Bio21 Institute, University of Melbourne**



- **Marian Dix Lemle, Independent Researcher, Washington DC**

*Med Hypotheses. 2009 Jan;72(1):108-9. Epub 2008 Sep 16. Hypothesis: chronic fatigue syndrome is caused by dysregulation of hydrogen sulfide metabolism. Lemle MD.*