NORGES MYALGISK ENCEFALOMYELITT FORENING

Living with ME

Strategies to reduce PEM and improve function

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NIH National Institutes of Health

CONFLICTS of INTEREST

Cardiopulmonary exercise test (CPET)

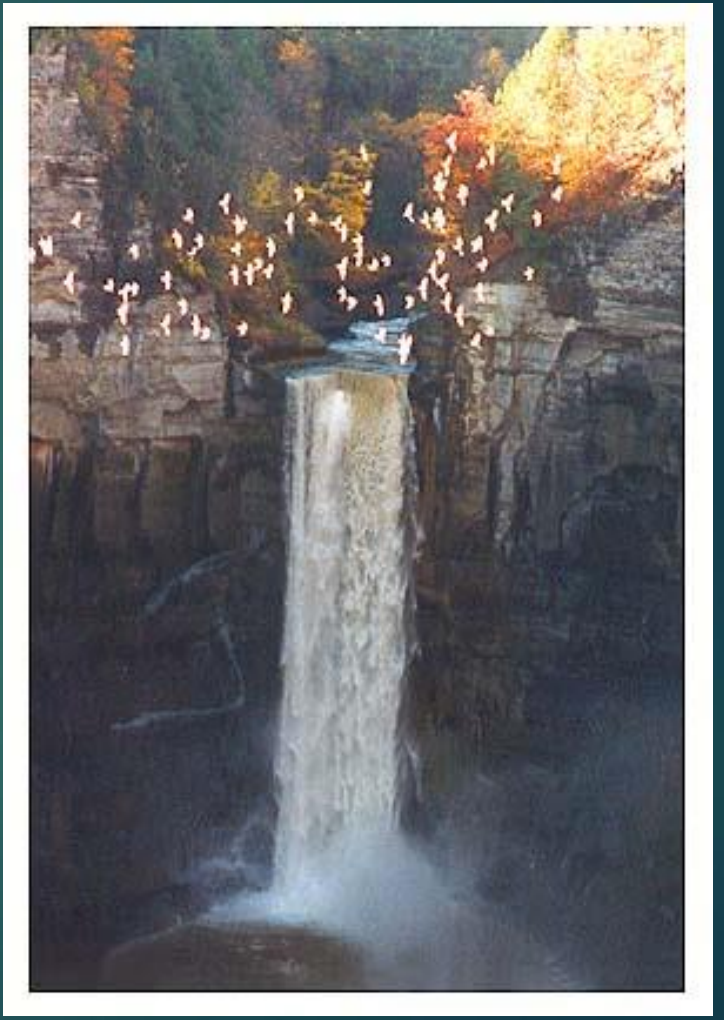
- research
- fee-based assessment for disability

BACKGROUND

- Few evidenced-based approaches to treat PEM
- Many anecdotal approaches to treat PEM – check the internet!
- Discussion of evidenced-based strategies known to be effective for some aspects of PEM
- *AND*
- Anecdotal strategies that have yet to be tested in ME/CFS but may be effective for symptoms of PEM

OUTLINE

- What is PEM?
- What exercise testing has taught us about PEM
- Strategies to reduce PEM
- How to balance activity and rest, improve or maintain function, and reduce PEM
- Individualizing your approach to living with ME/CFS



What is Post Exertional Malaise?

- **ME/CFS Canadian Consensus Definition:**

  "Physical or mental exertion often causes debilitating malaise and/or fatigue, generalized pain, deterioration of cognitive functions, and worsening of other symptoms that may occur immediately after activity or be delayed.

- **ME International Consensus Criteria**

  "Postexertional neuroimmune exhaustion is the hallmark feature. This cardinal feature is a pathological inability to produce sufficient energy on demand with prominent symptoms primarily in the neuroimmune regions"

- **IOM (NAM) Report**

  "Worsening of symptoms after physical, cognitive, or emotional effort"

APPENDIX 2 CANADIAN CLINICAL CRITERIA

It is recommended that this tick chart be used in the initial consultation to assist with a possible diagnosis of ME/CFS. (NB: Sections 1 to 6 must all be met as indicated below)

1) Post-Exertional Malaise and Fatigue:
(All criteria in this section must be met)
a) The patient must have a marked degree of new onset, unexplained, persistent, or recurrent physical and mental fatigue that substantially reduces activity level ..... ☐
b) Post-exertional fatigue, malaise and/or pain, and a delayed recovery period (more than 24 hours to recover) ..... ☐
c) Symptoms can be exacerbated by exertion or stress of any kind ..... ☐

2) Sleep Disorder:
(This criterion must be met)
Unrefreshing sleep or altered sleep pattern (including circadian rhythm disturbance) ..... ☐

3) Pain:
(This criterion must be met)
Arthralgia and/or myalgia without clinical evidence of inflammatory responses of joint swelling or redness, and/or significant headaches of new type, pattern, or severity..... ☐

4) Neurological/Cognitive Manifestations:
(Two or more of the following criteria must be met)
a) Impairment of concentration and short-term memory..... ☐
b) Difficulty with information processing, categorizing, and work retrieval, including intermittent dyslexia..... ☐
c) There may be an overload phenomena: information, cognitive, and sensory overload (e.g. photophobia and hypersensitivity to noise) and/or emotional overload which may lead to relapses and/or anxiety..... ☐
d) Perceptual/sensory disturbances ..... ☐
e) Disorientation or confusion ..... ☐
f) Ataxia..... ☐

5) Autonomic/Neuroendocrine/Immune Manifestations:
(At least one symptom in at least two of the following three categories must be met):

A) Autonomic Manifestations:
1) Orthostatic Intolerance (e.g. neurally mediated hypotension (NMH)) ..... ☐
2) Postural orthostatic tachycardia syndrome (POTS)..... ☐
3) Vertigo and/or light-headedness ..... ☐
4) Extreme pallor ..... ☐
5) Intestinal or bladder disturbances with or without irritable bowel syndrome (IBS) or bladder dysfunction ..... ☐
6) Palpitations with or without cardiac arrhythmia ..... ☐
7) Vasomotor instability..... ☐
8) Respiratory irregularities ..... ☐

B) Neuroendocrine Manifestations:
1) Loss of thermostatic stability..... ☐
2) Heat/cold intolerance ..... ☐
3) Anorexia or abnormal appetite, weight change ..... ☐
4) Hypoglycemia ..... ☐
5) Loss of adaptability and tolerance for stress, worsening of symptoms with stress and slow recovery, and emotional lability..... ☐

C) Immune Manifestations:
1) Tender lymph nodes ..... ☐
2) Recurrent sore throat ..... ☐
3) Flu-like symptoms and/or general malaise..... ☐
4) Development of new allergies or changes in status of old ones..... ☐
5) Hypersensitivity to medications and/or chemicals..... ☐

6) The illness persists for at least 6 months:
(This criterion must be met) ..... ☐

NB: ME/CFS usually has an acute onset, but onset

Canadian Clinical Criteria for diagnosis of ME/CFS

What have we learned about PEM from exercise testing?

What is a cardiopulmonary exercise test (CPET)?

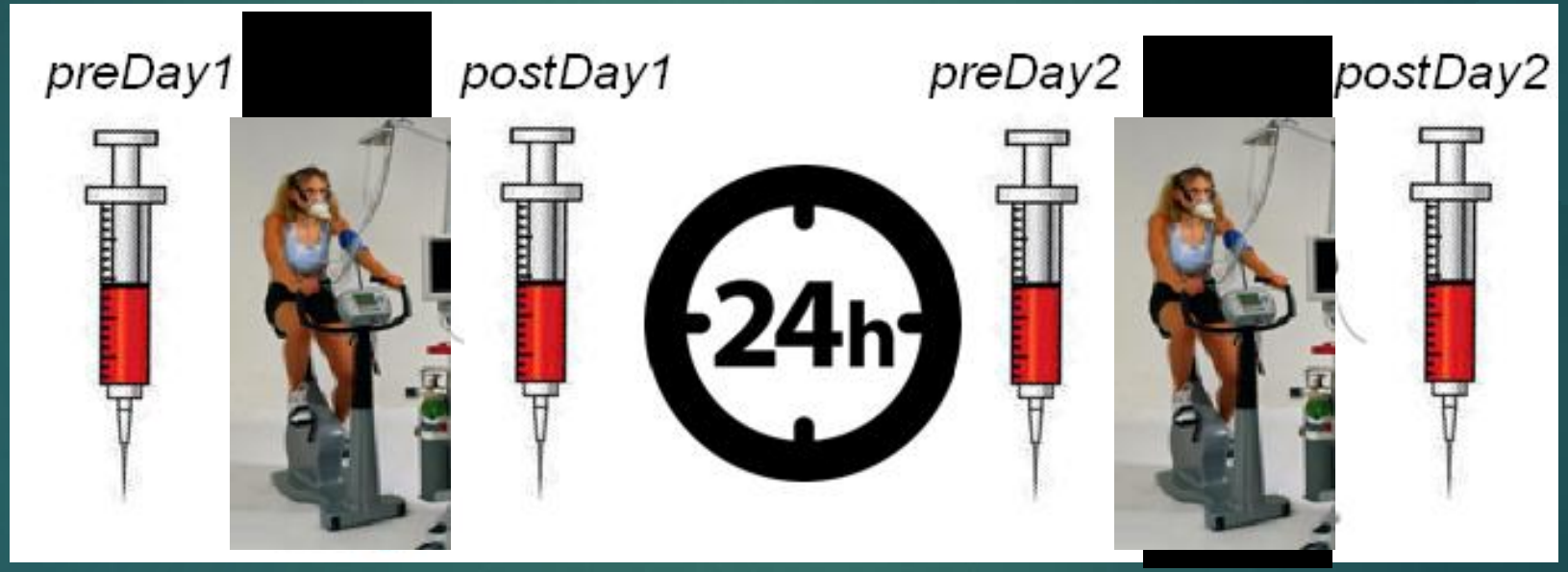
CPET measures effectiveness of heart, lungs & muscles to contribute to production of energy for work

Why do a 2-day CPET for ME/CFS?

1 CPET does not assess for post exertion symptom exacerbation or PEM

2-CPET protocol

post-exertional malaise



COMMON AND ABNORMAL EXERCISE TEST RESPONSES IN ME/CFS

low exertional oxygen consumption
low exertional heart rate
low exertional ventilation
low exertional blood pressure
cold extremities
lightheadedness
GI symptoms
thermodysregulation
cognitive dysfunction
exertion intolerance

AUTONOMIC DYSFUNCTION

Most ME/CFS symptoms due to:

- **INFLAMMATION**
- **IMPAIRED FLOW of BLOOD & LYMPH**
- **IMPAIRED VENTILATION**

Following approaches focus on these dysfunctions

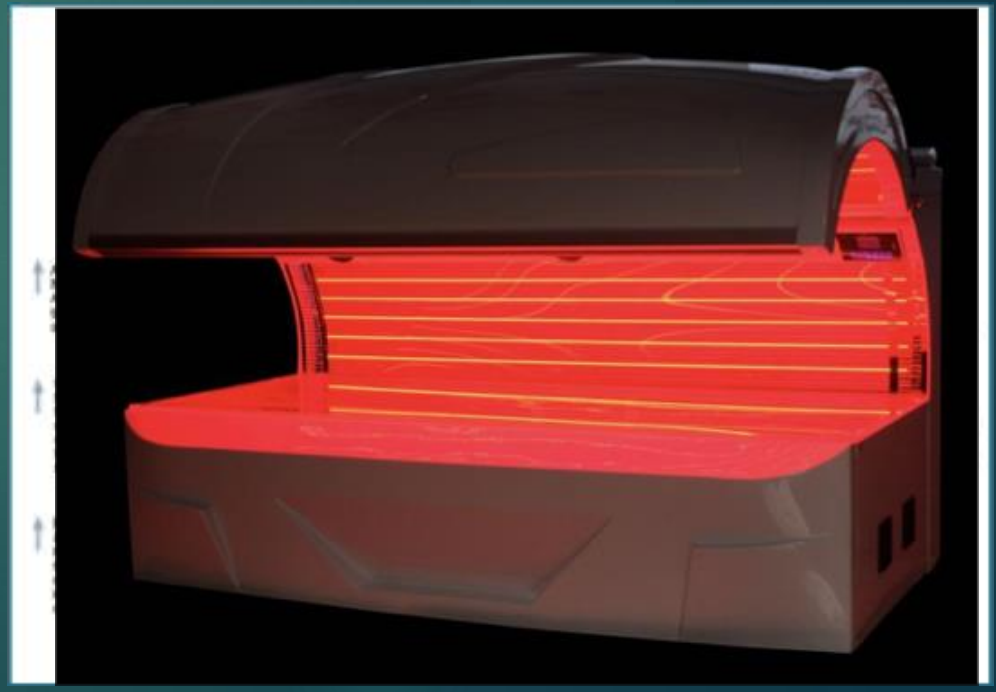
Strategies to reduce PEM

DRY BRUSHING

- **Evidence based treatment to detoxify, exfoliate, increase circulation, promote drainage and flow of lymph**
  - 5 minutes
  - 1-2 times per week, or per month if skin is sensitive
  - Stiff, natural bristle brush
- **May help to detoxify and reduce swollen lymph nodes by moving lymph**

RED LIGHT THERAPY – LLLT, NIR
(photobiomodulation)

- **Evidence based therapy to increase oxidative metabolism**
  - LLLT absorbed in mitochondrion –unsure of mechanisms on various signaling pathways
  - Photons dissociate inhibitory nitric oxide from enzyme (cytochrome c oxidase) in mitochondria, to increase e- transport, ATP production, more…
  - PRIMARY CLINICAL APPLICATIONS
    - **INJURY** - ↑ healing, remodeling, ↓ inflammation
    - **NERVES** - analgesia
    - **LYMPH NODES** - ↓ edema/inflammation
    - **TRIGGER POINTS** – ↓ tenderness, ↑ muscle relaxation
  - Recovery following activity



de Freitas & Hamblin, *IEEE J Sel Top Quantum Electron*. 2016 ; 22(3)

COMMON INFLAMMATORY FOODS

- **SUGAR/STARCH** - stimulates production of free fatty acids in liver, leading to production of pro-inflammatory substances. Contributes to muscle/joint pain, obesity, insulin resistance, ↑ gut permeability
  - **TYPES**: Sucrose (table sugar), HFCS, fructose, glucose (dextrose), corn syrup (glucose), maltose (glucose)
  - **MARKERS OF INFLAMMATION**: CRP, IL-6, IL-18, TNF-α, adiponection, more…
    - WHO recommends ≤ 10% of daily energy intake as free sugar (≤ 5% for added health benefits)
    - UK Scientific Advisory Committee on Nutrition ≤ 5%
    - US consumes 14.6%, down from 18.1% in 2008
  - **DRAINS MAGNESIUM**: at least 28 molecules of magnesium to metabolize 1 molecule of sugar
  - **HONEY** – still sugar (glucose+fructose), but also includes vitamins B & C and minerals with anti-inflammatory, anti-bacterial and anti-oxidant properties
  - **ARTIFICIAL SWEETENERS** ☠☠
- ***EVERTHING IN MODERATION***

www.ketoand.co

Della Corte, et al. (2018). *Nutrients, 10*(5)

COMMON INFLAMMATORY FOODS

- **GLUTEN** - protein found in grains
- Grains and starches containing gluten:
  - Wheat
  - Wheat germ
  - Rye
  - Barley
  - Bulgur
  - Couscous
  - Farina
  - Graham flour
  - Kamut Matzo
  - Semolina
  - Spelt
  - Triticale
- *MANY OTHER FOODS CONTAIN GLUTEN, SO READ LABELS*
- *NEED SUFFICIENT DIETARY FIBER*
- *CHECK B-VITAMIN LEVEL (MANY B_9 FORTIFIED FOODS HAVE GLUTEN)*
- *DIET & BRAIN FOG – food matters*
  - *https://www.drcourtneycraig.com/blog/ways-to-reduce-brain-fog*

SEED CYCLING

- Anecdotal naturopathic remedy to balance hormones, ease menopausal symptoms, boost fertility
- MAY:
  - Help to regulate menstrual cycle
  - Reduce acne
  - Treat PCOS, endometriosis
  - Reduce hot flashes, night sweats
- WHY?: phytoestrogens (flax) zinc (pumpkin seeds), polyphenol (sesame), Vitamin E (sunflower)
- HOW?:
  - DAY 1 to 13 of menstrual cycle – eat 1 Tablespoon (T) ground flax + 1 T pumpkin seeds daily to SUPPORT ESTROGEN
  - DAY 14 to 28 of menstrual cycle – eat 1 T sunflower seeds + 1 T sesame seeds daily to SUPPORT PROGESTERONE
- WHEN?: 3 to 4 months for hormone balance, date of ovulation may change
- ESTROGEN DOMINANT?
  - High estradiol (E2) linked to breast and prostate cancer
  - Flaxseed suppresses estradiol production, and supports higher ratio of the protective metabolite 2-hydroxy estrone

If male or post menopausal female – cycle seeds every two weeks

INTERMITTENT FASTING / FOOD TIMING

– eat according to your circadian rhythm

- **Objective is control of glucose & insulin**
  - **Fasting decreases insulin levels**
    - **Increased fat metabolism**
    - **Decreased overall calorie intake**
    - **"rests" lining of gut**
    - **Improved blood pressure regulation**
    - **Improved deep sleep**
  - **Fasting may help regulate circadian rhythm**
- **HOW?** ***Many approaches;*** **most manageable may be to consume all calories in 8 hour period (e.g., 10 am to 6 pm)**
- **NOT FOR ALL: Diabetics, eating disordered, pregnant or breast feeding should consult MD before I.F.**

(Gleason, 2019; Patterson & Sears, 2017)

COMPRESSION GARMENTS

- Developed by an engineer (Jobst) in 1950 to relieve symptoms of venous insufficiency (jobststockings.com)
- Evidence of Improved circulation & recovery time, reduced fatigue and muscle damage
  - 10-18 mmHg in most studies
  - 15-20 mmHg OTC (pantyhose, air travel)
  - 20-30 mmHg is medical grade I (swelling, sports, varicose veins, post surgery)
  - 30-40 mmHg is medical grade II (DVT, lymphedema)
  - Graduated compression
  - Shorts, tights, stockings, shirt, sleeve
  - CEP, Juzo, Mediven and Sigvaris.

Hill et al., *Brit J Sports Med*, 2013;0:1–7

Sodium/Electrolyte intake

Compared to healthy controls, pain in ME/CFS associated with:

- Low serum sodium
- Low serum essential amino acids
- Low urea
- High serum glucose
- High 24-h urine volume

- **Indicates methylation and acetylation defects**

- **Sodium supplementation often suggested to boost blood volume**
- **Electrolyte supplementation provides more balanced distribution of electrolytes**
  - **Coconut water**
  - **Homemade - no sugar, dyes**
    - https://wellnessmama.com/2575/natural-sports-drink/
  - **Electrolyte Caps/powders**

McGregor, NR et al. (2016). *Fatigue: Biomedicine, Health & Behavior*, 4(3):132-145.

SLEEP

- **Prevalence of sleep disruption is much higher in ME/CFS compared to general population**
  - **Unrefreshing sleep may be due to sleep apnea <u>not</u> ME/CFS**
  - **Sleep apnea increases in post-menopausal women**
  - **Wear pulse oximeter during night to see if pulse oxygen decreases while sleeping**
- **There's an App for that! *Zee Appnea***
  - **screening for risk of sleep apnea**
  - **requires standard earbuds with microphone**
- https://www.medgadget.com/2015/04/partner-risk-sleep-apnea-theres-app-interview.html

How to balance activity and rest, improve or maintain function, and reduce PEM

ACTIVITY MANAGEMENT FOR ME/CFS

- **KEY POINTS**
- Aerobic (endurance) energy production is very limited
- Graded exercise therapy (GET) WILL NOT fix it…so don't do it!
- "PUSH – CRASH" will worsen your illness…so don't do it!
- "WORK" or "EFFORT" is the combined influence of physical, cognitive and emotional stress…not just physical
- **GOAL:**
  - Do work without provoking PEM
  - Over time, do more work without provoking PEM
  - Progress is very slow, but can be made
  - ***Work the energy system that works…so must be short duration effort***

ACTIVITY MANAGEMENT FOR ME/CFS

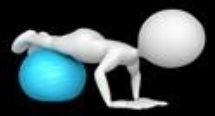
- **'FITT' principle for ME/CFS**
- **FREQUENCY - Most days of the week, but always depends on how you feel – start with 1 day**
- **INTENSITY –**
  - **10 bpm < HR@VAT**
  - **RPE ~ 11 (6-20 scale) or 3 (0-10 scale)**
- **TIME – keep 'Work' effort short, < 30 seconds**
  - **Followed by 4-6x rest period**
- **TYPE – Core stability**
  - **Lying, seated, or standing exercise?**
  - **Focus on correct spinal alignment**
- ***IS THIS WORKING FOR YOU?***
  - ***Keep a 'post-activity' journal***

Rating of Perceived Exertion
Borg RPE Scale

6		How you feel when lying in bed or sitting in a chare relaxed. Little or no effort
7	Very, very light	
8		
9	Very light	
10		
11	Fairly light	
12		Target range: How you should feel with exercise or activity
13	Somewhat hard	
14		
15	Hard	
16		
17	Very hard	How you felt with the hardest work you have ever done.
18		
19	Very, very hard	
20	Maximum exertion	Don't work this hard!

Understanding the Rating of Perceived Exertion (RPE) Scale






General Effort Level		% of 1-Repetition Maximum (1RM)	Additional Repetitions Possible
10	Maximal	100% 1RM	0 more reps
9	Near-Maximal	90% 1RM	1-2 more reps
8	Very Hard	80% 1RM	3 more reps
7	Hard	70% 1RM	4 more reps
6	Moderate-Hard	60% 1RM	5 more reps
5	Moderate	50% 1RM	6-7 more reps
4	Moderate	40% 1RM	8-10 more reps
3	Light-Moderate	30% 1RM	11-14 more reps
2	Light	20% 1RM	15-20 more reps
1	Very Light	10% 1RM	21-30 more reps
0	No Effort at all	0-10% 1RM	30+ more reps

@shakebotapp

1. The Rating of Perceived Exertion (RPE) scale is used to measure the intensity of your exercise. Our RPE scale runs from 0 – 10.
2. Can be used with many forms of exercise, including resistance, cardiovascular, & sport.
3. Session RPE can gauge the intensity of the entire session & Set RPE can gauge the intensity of each set of exercise.
4. Tracking RPE is a simple, easy way to monitor exercise stress & progression; it can decrease injury risk & improve training response.

Warm-up always begins with belly breathing

(thru your nose, 4 seconds in, 4-8 seconds out)

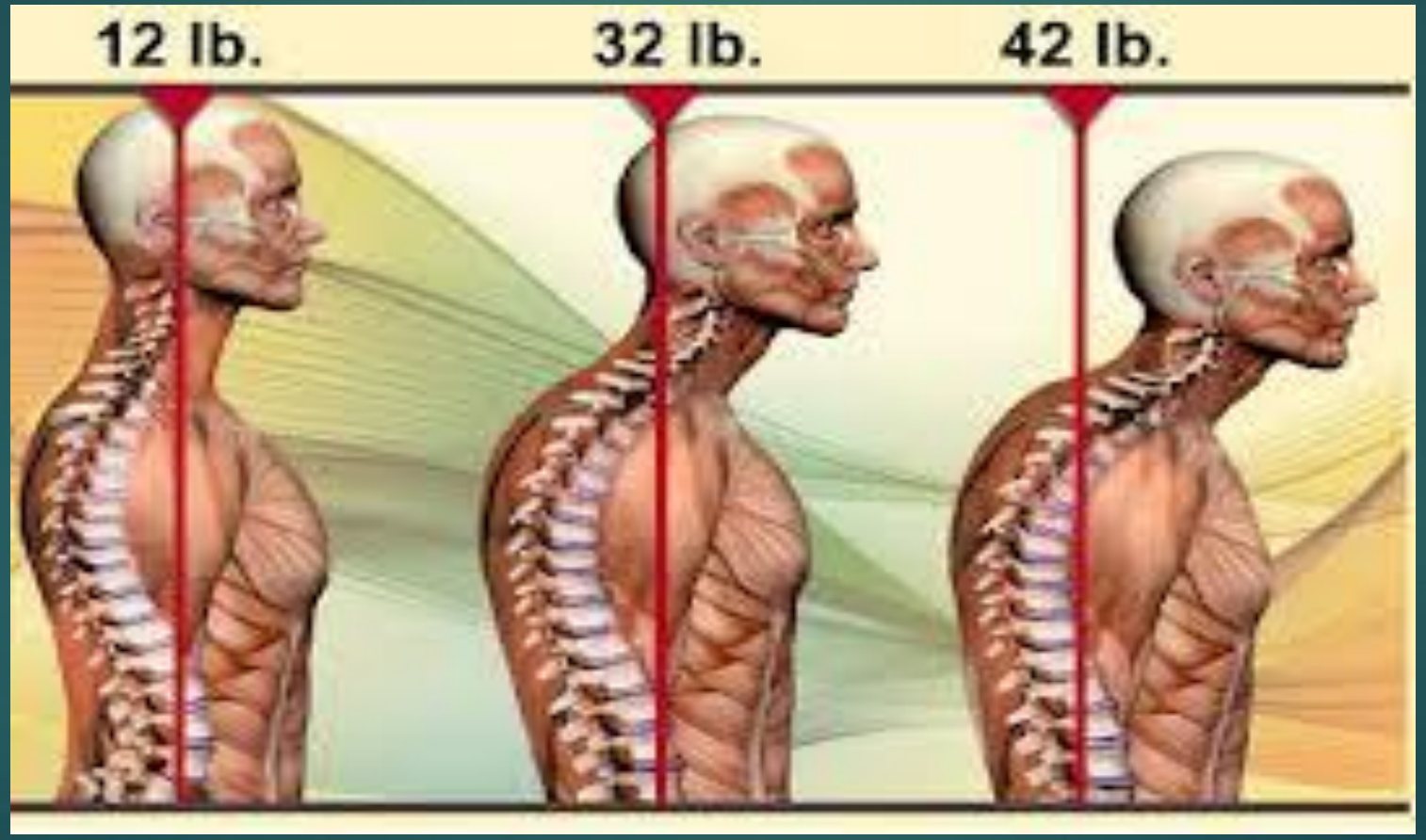
***HINT**: Also useful for pain, fatigue, anxiety, depression, healing, general rejuvenation*

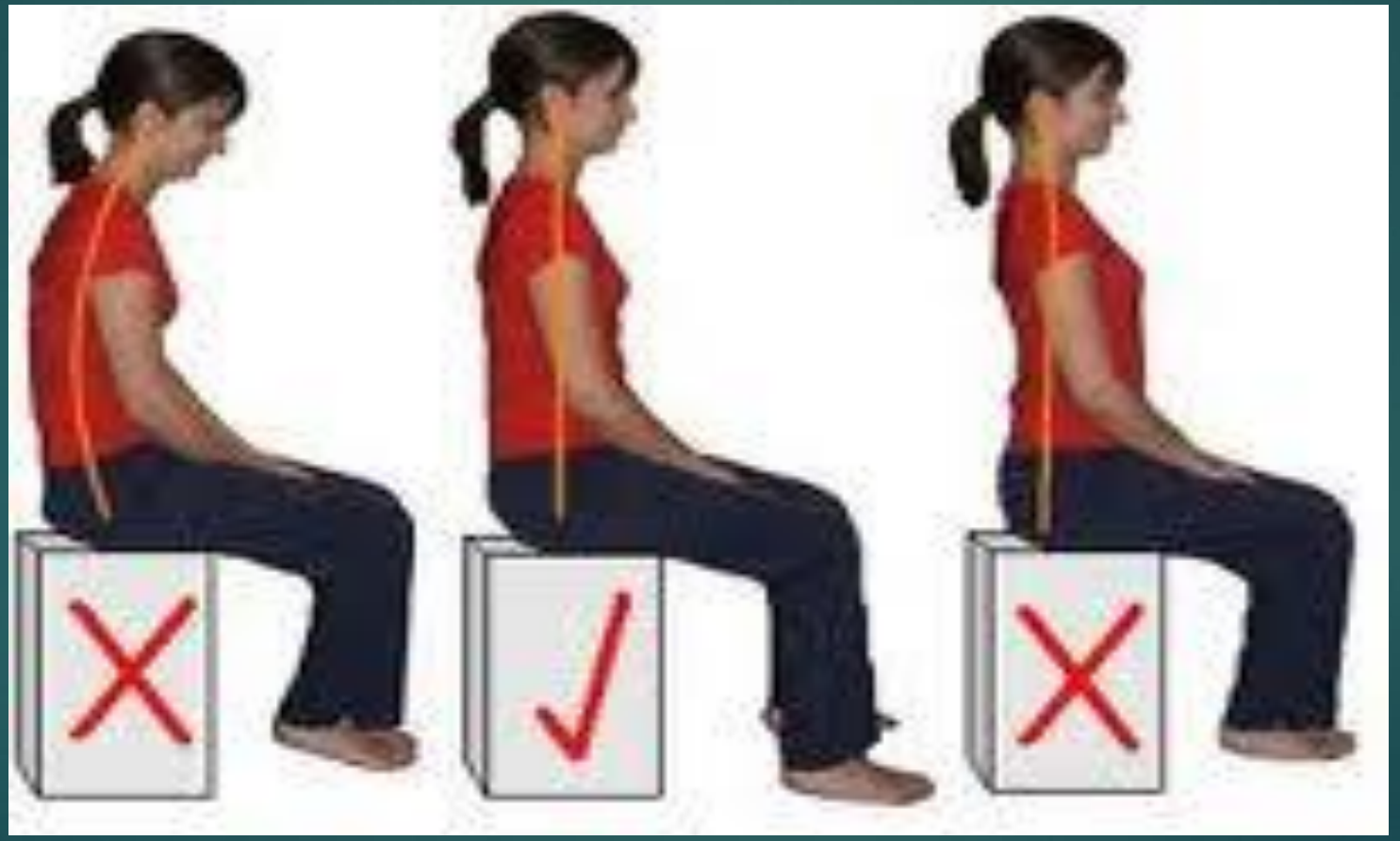
Diaphragmatic breathing

- Sit or lie comfortably – if lying on your back, bend your knees with feet flat on the floor, and rest arms on the floor at your sides.
- Place one hand on your upper chest to feel if your chest is still. If you are engaging your diaphragm properly, your chest should move very little, if at all.
- Place your other hand between the bottom of your ribcage and your navel to feel if your diaphragm is moving (it should be!).
- Through your nose, breath in slowly then breathe out slowly through pursed lips. Remember, your chest should be still.
- Don't force the exhalation, your belly should stay soft and supple.

Spinal alignment is KEY for good function AND energy conservation

The aging spine…or the weak spine

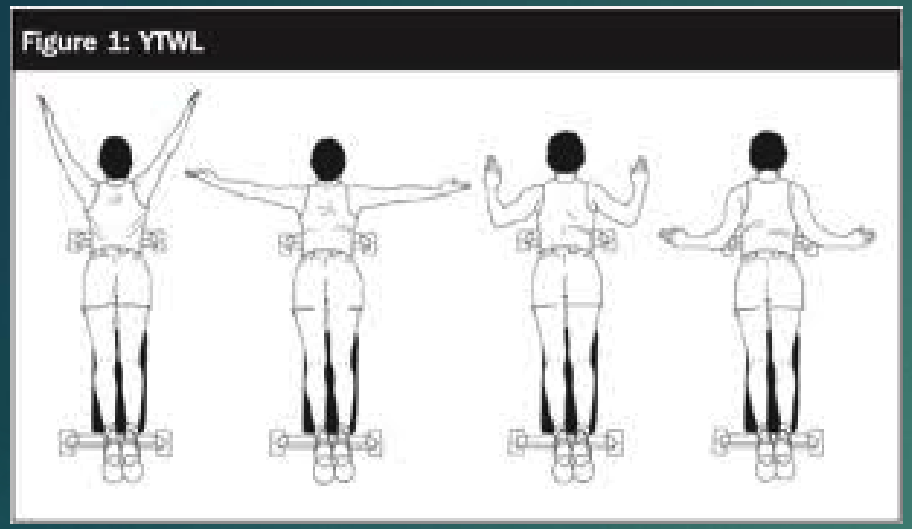


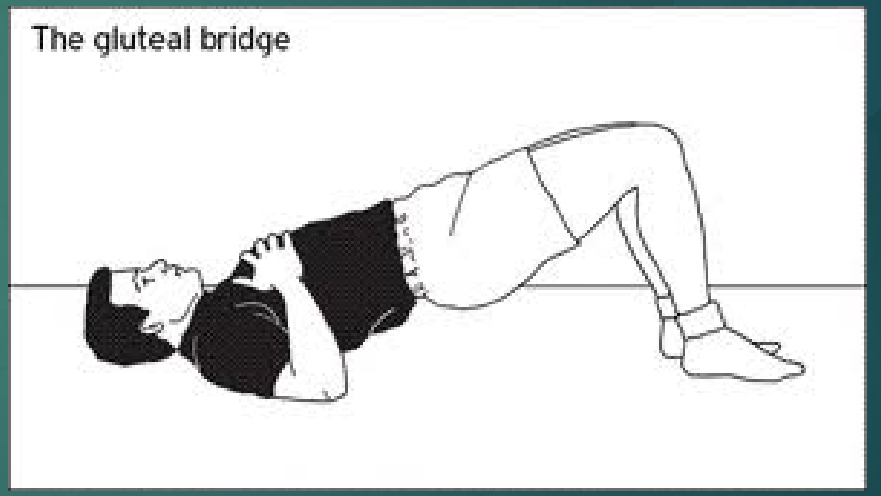


Core Training Principles

- **Quality vs. quantity**
  - Proper form
  - Attention to good balance
  - More reps / light or no resistance
  - Stop when fatigued or lose core stability
- Avoid exercises that cause or increase spine pain

A few Core Stability exercises





KEY POINTS

- Appropriate physical activity is movement from which you recover
- Physical activity needs to be restorative physically and mentally
- Match physical activity program to function
- Diaphragmatic breathing – focus on this; stay relaxed
- Make room for structured physical activity in place of another daily activity

ALWAYS think

Energy Conservation

Energy Conservation Approach

- Pacing – Live “circularly” not “linearly”
  - Rest breaks
- Body Position
  - Sit vs. stand
- Joint Protection
  - Assistive devices
- Activity Planning
  - Balance light and heavy tasks

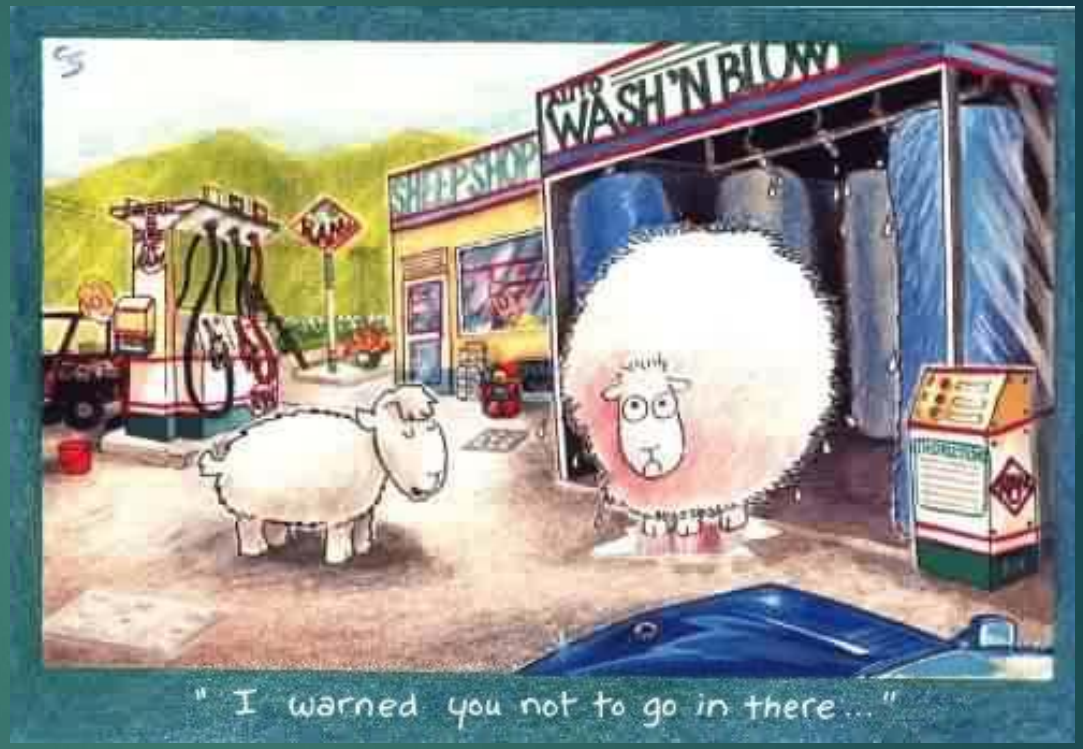
Top 10 Energy Saving Tips

1. **Learn to say "no" or "yes"**
   - **"*No*" to energy zappers**
   - **"*Yes*" to help when you need it**

2. **Prioritize**
   - **Plan what you most want to accomplish**
   - **Balance rest with activity**
   - **Sit or lie down whenever possible**

3. Simplify clothing and makeup choices

- “Wash and go" hairstyle or one that needs little extra care



- Wrinkle free clothing

4. Shower sitting down

- Shower chair or plastic outdoor chair

- Terrycloth robe

5. Use an answering machine

- Monitor incoming calls
- Talk when you wish to and are able

6. Take it with you

- **Use a basket / backpack**

  Phone, water, tissues, TV remote, paper/pen...

- **Take it from bed to chair or wherever you go**

7. Make bed while in it…or not at all

- It just takes a flip of the corner to finish making the bed

8. Cook Ahead

- When able, prepare foods for use in more than one meal - such as a roasted chicken or cooked beans.

- Plan simple, few-ingredients, one pan, or slow-cooker meals

9. Use a disabled parking placard

- Application from state Department of Motor Vehicles (check website)
- Signature from health care provider

10. Pack groceries smart

- Have perishable items packed separately
- Put them in the refrigerator or freezer right away
- Other groceries can wait to be unpacked
- Use grocery list to save time, energy
- Find a store that delivers

No more FLARES!

1. **Live <u>circularly</u> (exert, recover) not <u>linearly</u> (push, push, push, CRASH) for all ADLs**
2. **Understand activity limitations**
3. **Improve CORE stability**
4. **Structure physical activity to gradually improve physical function**
5. **Use energy conserving strategies always**

Individualizing your approach to living with ME/CFS

A short bit about genetics and epigenetics

- **Genetics: your DNA – your code doesn't change**

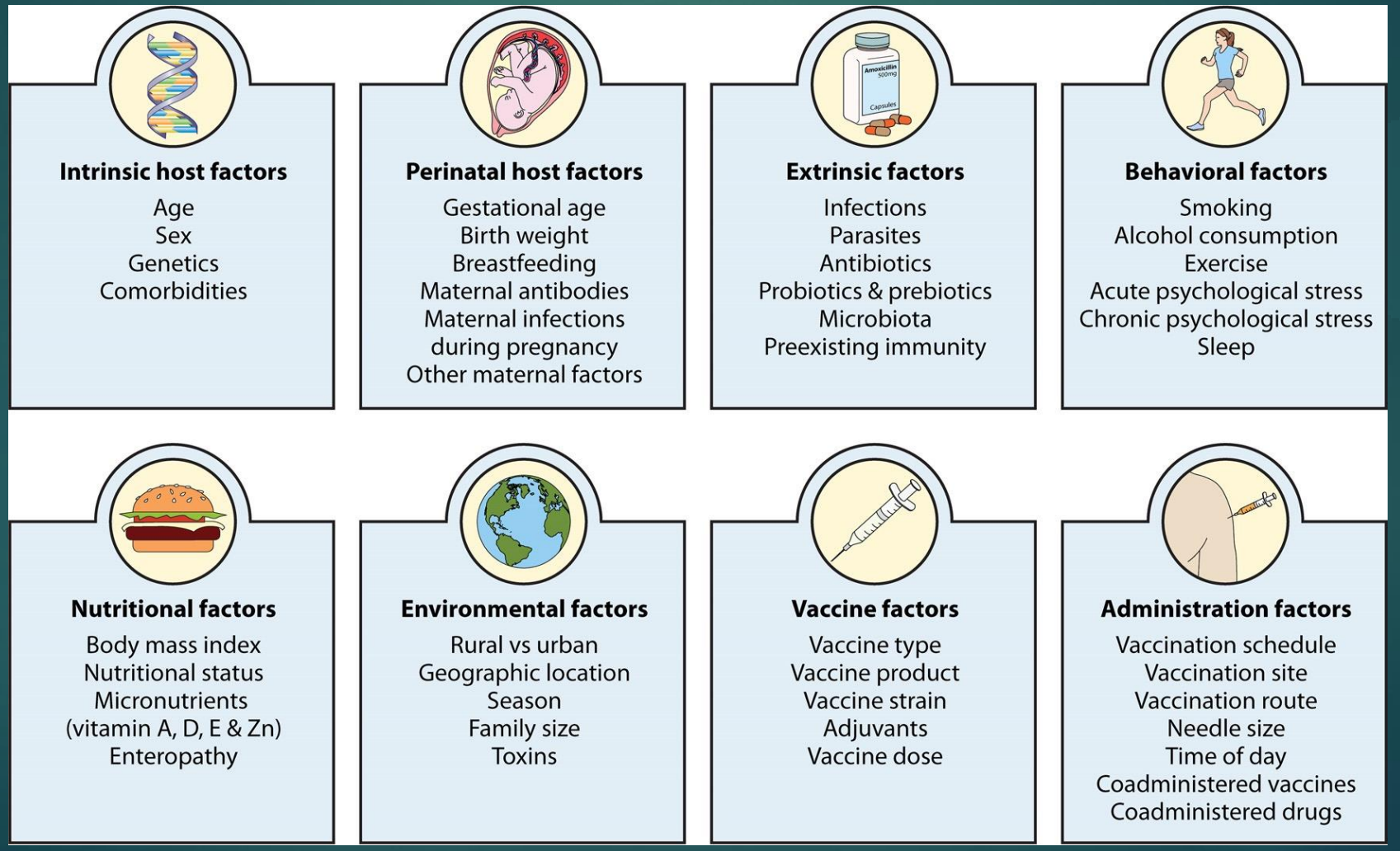
- **Epigenetics: the study of changes in organisms caused by modification of how genes express**
  - ***The variability of gene expression is heritable in humans***

Herrera, S. et al. *J Epigenetics*, vol. 13, 2018

Vandiedonck, C. *Clinical Genetics*, vol. 93, 2018

Factors that influence the immune response to vaccination

Zimmermann P, Curtis N. 2019. Factors that influence the immune response to vaccination. Clin Microbiol Rev 32:e00084-18. https://doi.org/10.1128/CMR.00084-18



Flu vaccine for ME/CFS/FM? *Hunter-Hopkins Center says…*

- **Due to reports of severe relapses following immunization, flu vaccinations are generally NOT recommended to persons with CFS or FM unless:**
  - **1. You have taken flu vaccinations in the past and tolerated them well,**

    OR
  - **2. You have a serious chronic illness (such as emphysema, diabetes, or heart disease) in addition to CFS/ME/ FM.**

  - **Not only do some patients relapse after flu vaccination, but many do not sero-convert (develop antibodies) to the vaccination. Thus you may suffer the discomfort of a "shot" plus the misery of a relapse, and not even develop immunity.**

An individualized approach to understanding your PEM triggers

TO BEGIN: *Activity Management*

Identify your exertional threshold

Live "circularly" not "linearly" (Pace)

Prioritize your energy expenditure

NEXT: *Biochemical support*

Prepare body/organs for detoxification with nutritional foundation for biochemical support

THEN: *Reduce known triggers*

Decrease microglial activation ("brain on fire", "tired and wired")

Identify and decrease:

- **environmental toxins**
- **behavioral stressors**
- **excito-toxic foods/substances**
- **others… (your "sickness" story)**

The Approach (con't.)

FOLLOWED BY: ***Probe for unknown triggers***

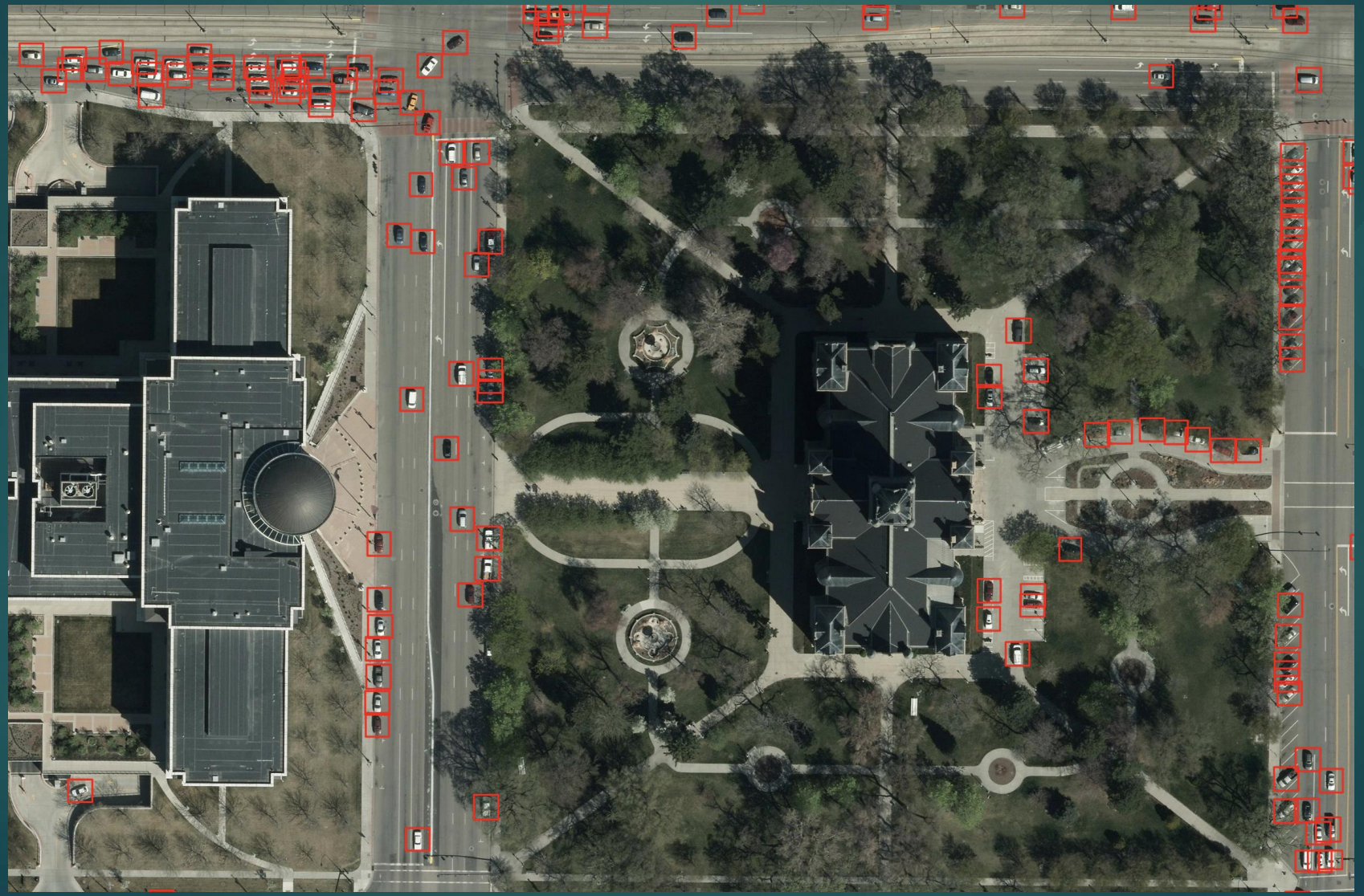
- **Study:**
  - **Urine – amino acids, toxic & essential elements**
  - **Blood –TSH, lipids, "Dutch +", CRP, homocysteine, CMP, CBC…**
  - **Stool – CSA for slow-growing factors due to gut dysfunction**
  - **Hair - metals**
  - **Saliva – reproductive & stress hormones**
  - **Genetics/epigenetics – 23&Me, Ancestry.com**

FINALLY: ***Detoxification***

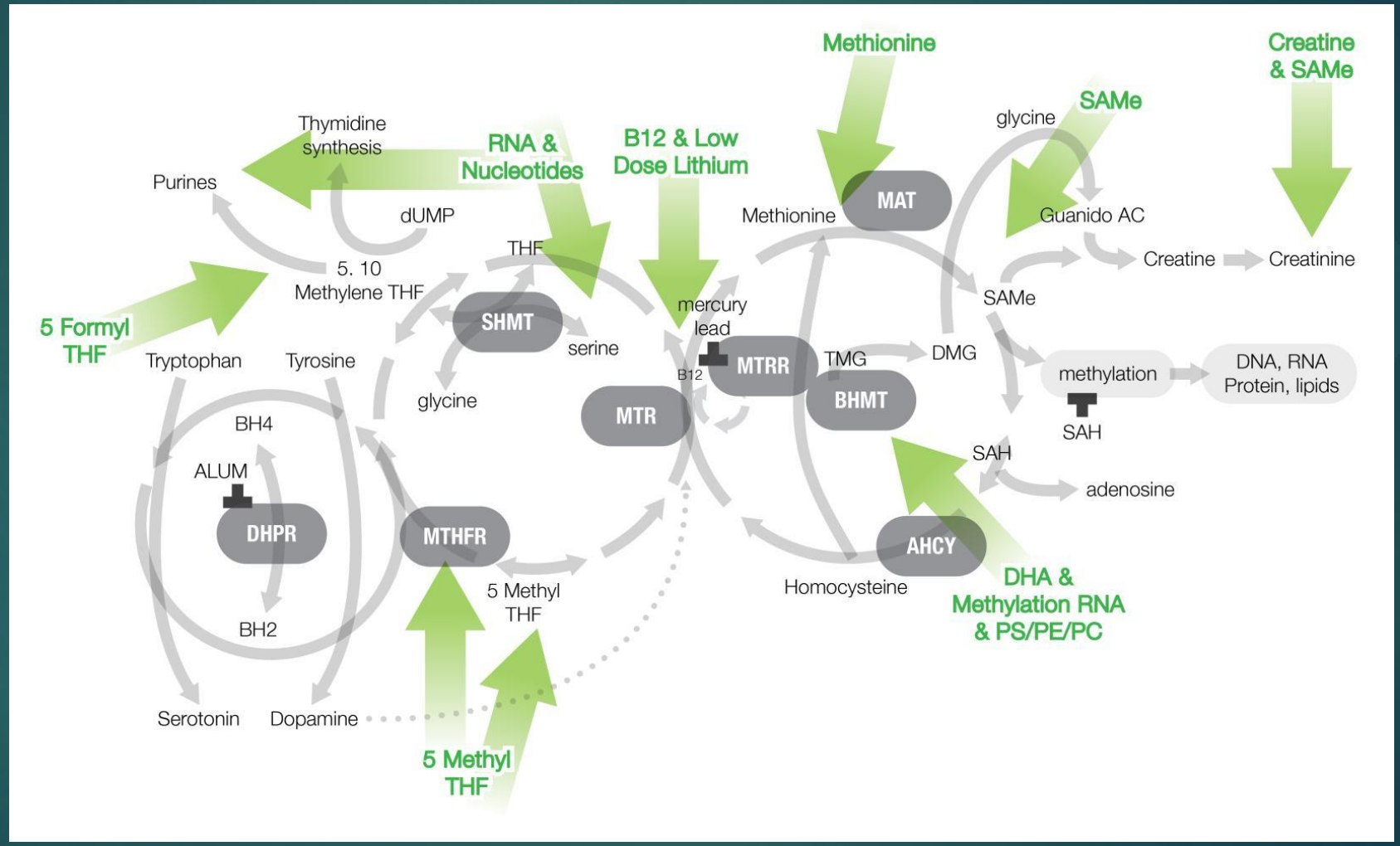
- **Mile 22 of your marathon – almost there!**
- **Use very personalized nutrition, supplement & symptom-specific approaches to address unknown triggers**
- **"Guess and check" every 3-4 weeks to re-assess levels**
- **Use and change strategies to manage detox symptoms**
- **Discouraging… but don't give up!**

Precision Analyticals, Inc. https://dutchtest.com

Unblock energy pathways

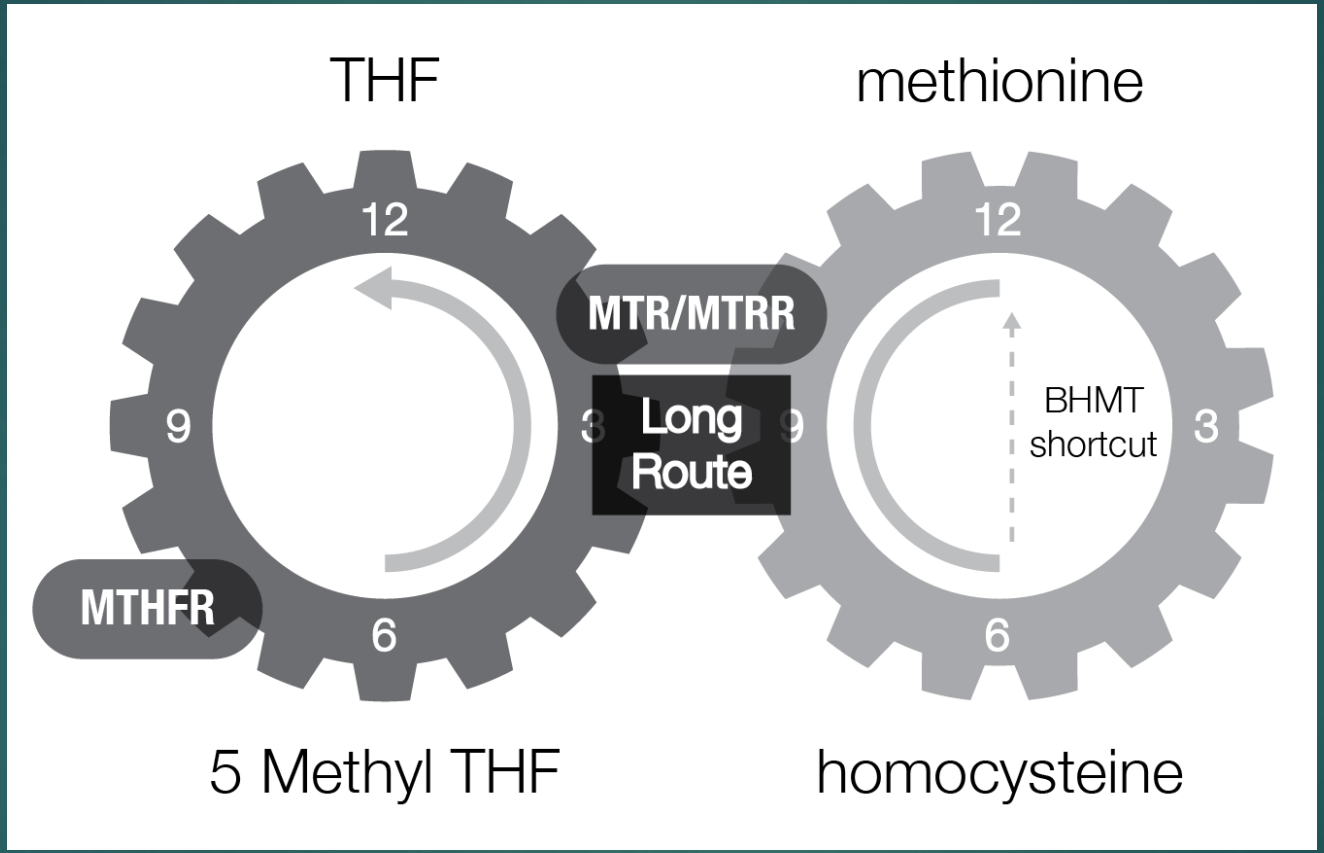


Methylation Pathway - "Methylation takes place over a billion times a second in the body. It is like one big dance, with biochemicals passing methyl groups from one partner to another." (The H Factor, Dr.James Brady and Patrick Holford).



From: Neurological Research Institute
Yasko, A., *Your simplified roadmap to health*

Long Route and Short Cut around the cycle:



From: Neurological Research Institute
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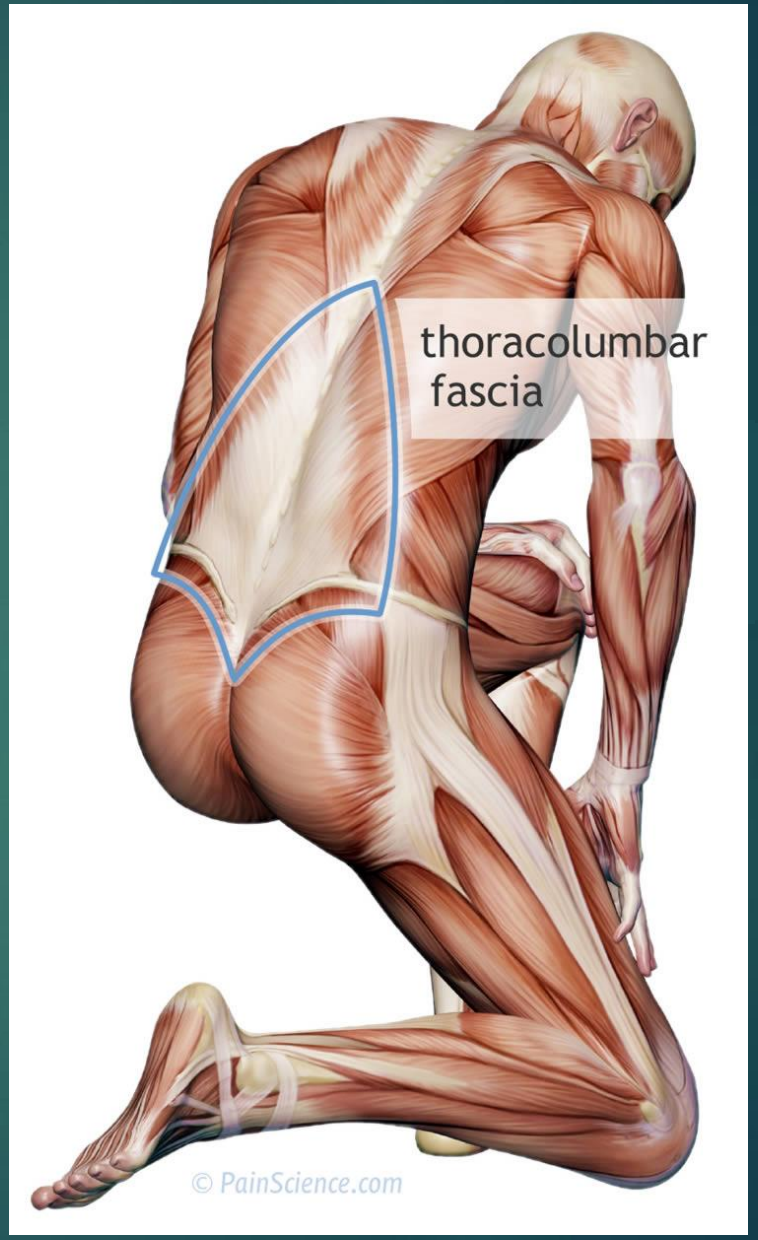
Stuff I didn't discuss

- Limbic system retraining (fight or flight)
- Massage
- Cranio-sacral work
- Dairy foods
- Excito-toxic foods
- tub soaks/pool therapy esp. for relapses and pain, Epson salt, hot water bottles
- Fascial scarring/adhesions



QUESTIONS?

Tusen takk

References

- de Freitas & Hamblin, *IEEE J Sel Top Quantum Electron*. 2016 ; 22(3): . doi:10.1109/JSTQE.2016.2561201
- Zimmermann P, Curtis N. 2019. Factors that influence the immune response to vaccination. Clin Microbiol Rev 32:e00084-18. https://doi.org/10.1128/CMR.00084-18
- Della Corte, K. W., Perrar, I., Penczynski, K. J., Schwingshackl, L., Herder, C., & Buyken, A. E. (2018). Effect of Dietary Sugar Intake on Biomarkers of Subclinical Inflammation: A Systematic Review and Meta-Analysis of Intervention Studies. *Nutrients*, *10*(5), 606. doi:10.3390/nu10050606
- https://www.medgadget.com/2015/04/partner-risk-sleep-apnea-theres-app-interview.html
- Hill et al., Compression garments and recovery from exercise-induced muscle damage: a meta-analysis, *Brit J Sports Med*, 2013;0:1–7
- https://www.drcourtneycraig.com/blog/ways-to-reduce-brain-fog
- https://www.healthrising.org/blog/2019/11/17/klimas-sleep-nutrition-cognition-orthostatic-intolerance-chronic-fatigue-syndrome/
- Patterson, R, and D. Sears. Metabolic Effects of Intermittent Fasting, *Annual Review of Nutrition* 2017 37:1, 371-393
- Precision Analyticals, Inc. https://dutchtest.com
- Yasko, A, *Your simplified roadmap to health (*Neurological Research Institute)
- Herrera, S. et al. (2018). Genome-epigenome interactions associated with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, J Epigenetics, (13);1174-1190. https://doi.org/10.1080/15592294.2018.1549769
- http://workwellfoundation.org/resources/#videolinks
- McGregor, NR et al. (2016). Widespread pain and altered renal function in ME/CFS patients, *Fatigue: Biomedicine, Health & Behavior.* 4(3):132-145 https://doi.org/10.1080/21641846.2016.1207400
- https://wellnessmama.com/2575/natural-sports-drink/
- Vandiedonck, C. (2017). Genetic association of molecular traits: A help to identify causative variants in complex diseases (Invited Review) *Clinical Genetics*, 93:52-532 2017

CENTRAL ILLUSTRATION: Determinants of the O_2 Transport and Utilization Chain Framed on the Fick Principle

Heart Failure

Signs and Symptoms

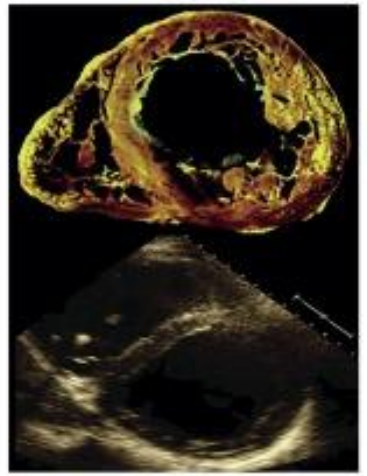
HFpEF

HFrEF

Exercise Intolerance
Dyspnea and Fatigue

Organ Systems and Pathways in O_2 Uptake Process
[Convection (Delivery), Release, Diffusion, and Use]

$VO2 = CO \times (CaO2 - CvO2)$



Pulmonary	Cardiac	Hematologic	Vascular	Mitochondrial
Ventilation/Gas Exchange	Stroke Volume Heart Rate	Hb Concentration Mediators of Release	Vasoregulation Capillary Network	Krebs Cycle-ATP Generation
O_2 Diffusion (Alveolar)	O_2 Delivery	O_2 Delivery and Release	O_2 Diffusion	O_2 Use (Extraction)

Guazzi, M. et al. J Am Coll Cardiol. 2017;70(13):1618-36.

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