Understanding Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and the theories behind our therapy approach.

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a multi-system illness that affects many different aspects of the body's physiology. Current research indicates dysregulation of several systems in the body and this may explain the wide range of symptoms that people experience.

the key pathology which underpins CFS is potentially best understood in computational terms as resulting from altered messages passing amongst homeostatic networks
(Clark et al 2019)

To understand this dysregulation, it is useful to firstly understand how healthy systems work and what symptoms can occur if each of these systems are not regulated. Then the interaction of the systems and how they impact upon each other, before considering how dysregulation can be applied to ME/CFS.

What are demands on the body and how does the body respond to demands?

Our body needs to respond immediately to the demands of life combining information from internal systems within the body and information from the external environment. The body responds dependant on the needs at the time - either active or restorative, that will help to maintain or return the body to a stable state. This state is referred to as homeostasis (Selye 1956). Homeostasis could be summarised as the body maintaining balance to provide ideal internal conditions for long term health and survival.

Demands are many and varied. There are internal demands that are part of everyday life such as hunger, thirst, physical activity, cognitive activity, processing emotions and sleep. There can be additional internal demands that occur including infection, inflammation, injury, and disease. The body also needs to respond to external demands including gravity, temperature change and pollution. Demands on the body can be increased by disruptions to daily patterns which affect circadian rhythms or our body clock, for example shift working, sleep disruption, lack of daylight exposure or changes in eating patterns.

The circadian clocks are present at both cellular and system control levels and are essential time-tracking systems in our bodies that anticipate regular environmental changes and adapt appropriately to the time of day. For example, coordinating the hormones we need to wake up in the morning and go to sleep at night. Disruption of these rhythms greatly influences health (Koch 2017).

Ultimately the body's response to demand, change or need is achieved by regulating various *dynamic* systems at a body-wide and cellular level. At a body-wide level three of the systems involved are the **Autonomic Nervous System** (neurological), the **Hypothalamic Pituitary Adrenal Axis** (neuroendocrine), and the **Immune System** which all work together to coordinate a response to change or demands. At a cellular level, the processes of **Metabolism** are involved.

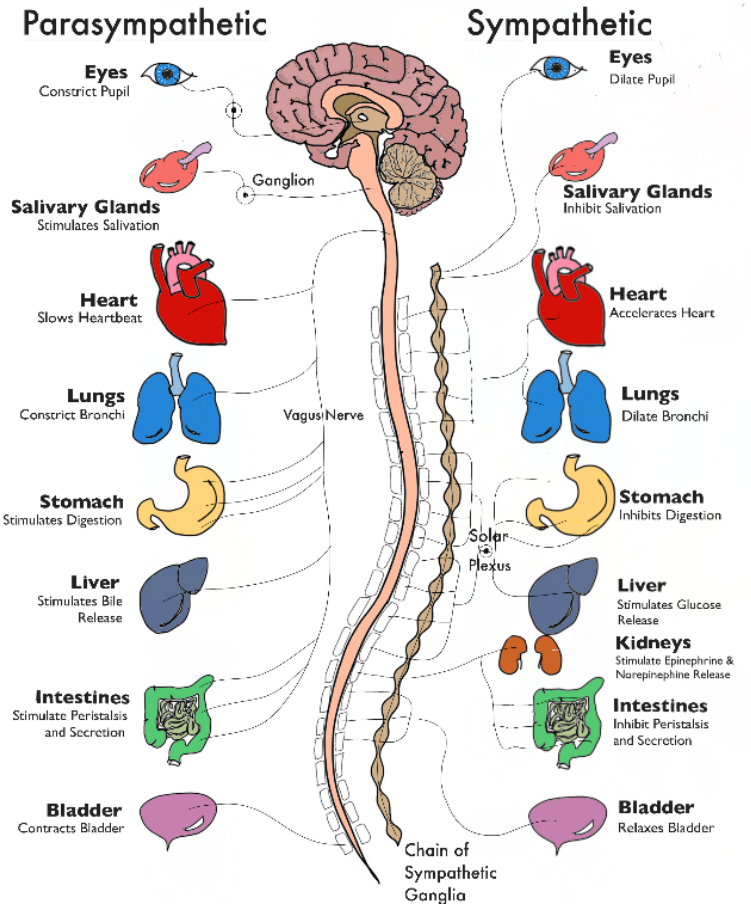
How do these systems work?

Autonomic Nervous System

The **Autonomic Nervous System** (ANS) is key in automatically and rapidly responding to demand, regulating many body processes including:

- Blood pressure
- Circulation
- Heart rate
- Breathing rate
- Body temperature
- Sweating
- Digestion including saliva and digestive enzyme production, and gut motility
- Metabolism including regulation of blood sugar
- Balance of water and electrolytes, including urination
- Sexual response
- Pupil response

The ANS has two main divisions, **sympathetic** and **parasympathetic** which have an opposite effect on different organs in the body. For example, increased sympathetic activity would increase heart rate and increased parasympathetic activity would decrease heart rate. Therefore, the ANS responds by changing body processes through the stimulating actions of the sympathetic division (turning up) or inhibiting processes through the parasympathetic division (turning down). Consequently, the sympathetic division is sometimes referred to as the 'fight and flight' response and the parasympathetic division is sometimes called the 'rest and digest' response. Both systems are active, but one will be more dominant depending on the situation and the needs of the body.



Autonomic Nervous System

The sympathetic division is needed for every-day activity, such as physical movement, and is also a basic survival response preparing the body for stressful or emergency situations. Therefore, its actions have been termed the fight and flight response due to its role as part of the evolutionary development of human beings. Bodily changes include

- Increasing heart rate and force of heart contraction
- Widening blood vessels (vasodilation)
- Widening airways
- Releasing stored energy
- Increasing blood flow to peripheral areas of the body
- Increased sweating
- Increasing conscious processing of sensory information
- Altering focus of thoughts onto more immediate survival needs
- Slowing body processes that are less important for immediate survival such as digestion and reproduction.
- Working with the somatic nervous system to stimulate skeletal muscle and send energy to fuel muscle contraction.

The parasympathetic division, or the rest and digest response, conserves and restores, and reverses the processes above to allow recovery with the following bodily changes:

- Slowing the heart rate
- Decreasing blood pressure
- Stimulating digestive and reproductive systems
- Using energy from digested food to restore and rebuild tissues
- Filtering out unnecessary sensory input and focussing on what is necessary
- Enabling logical cognitive processing.
- Focus of thoughts onto more long term and strategic needs.
- Supporting sleep.
- Working with the somatic nervous system to relax muscles and conserve energy.

This is a simplified explanation of the ANS as there can be complex changes occurring where both the sympathetic and parasympathetic divisions are active and exerting different effects on different organs at the same time.

There are differences in how the ANS responds to acute demand or stress on the body and how it responds to long-term excess demand. In repeated exposure to excessive demand there can be lasting adaptations in the body, for example in energy metabolism and immune response (Danese and McEwan, 2012).

Symptoms that can occur due to Autonomic System Dysregulation

There are many different conditions that can give rise to Autonomic System problems and there are different types of Autonomic System dysfunction which can generate different patterns of symptoms. These are some of the common symptom patterns seen:

Orthostatic intolerance – escalation in symptoms (often fatigue and pain) in response to being upright/standing still. Often described as a feeling of energy draining out. May be accompanied by a feeling of needing to fidget or move around, lean on something or sit or lie down. Can also impact when showering or bathing and result in significant escalation in fatigue in response to these activities.

Postural hypotension – some people can experience feeling faint or have vasovagal blackouts

Fatigue - different and more debilitating than the typical tiredness that everyone can experience

Muscle Pain – dysregulation in the circulatory changes during physical activity can contribute to the accumulation of lactic acid in muscles which can cause muscle achiness often likened to the feeling of having done a lot of exercise

Headaches – generalised headaches sometimes provoked by activity or upright position. Potentially some association with migraine type headaches

Palpitations – some people will experience a postural pattern whereby they feel their heart rate speed up in response to standing but there can also be random and unexplained episodes of palpitations

Breathing symptoms – altered breathing patterns while awake and during sleep can occur. Breathlessness provoked by minimal activity or occurring for no reason.

Gastrointestinal symptoms – problems related to gut motility such as nausea, reflux, feeling full with reduced appetite, diarrhoea and constipation. There can also be patterns related to the timing of eating with significant escalation in fatigue 20-30minutes after eating sometimes accompanied by sweating or a need to lie down or sleep.

Sensory changes – increased sensitivity to sensory input including light and sound, often provoking feelings of distress or anxiety. Problems regulating pupil size can contribute to light sensitivity along with difficulty focusing vision.

Temperature regulation – instability in regulating body temperature often swinging rapidly from too hot to too cold

Sweating – can be increased or decreased

Anxiety – a physiological sensation of anxiety in the body that wasn't provoked by having anxious thoughts or worries

Cognitive symptoms – changes in cerebral perfusion may contribute to the cognitive symptoms experienced including word finding difficulties, poor concentration and short-term memory problems

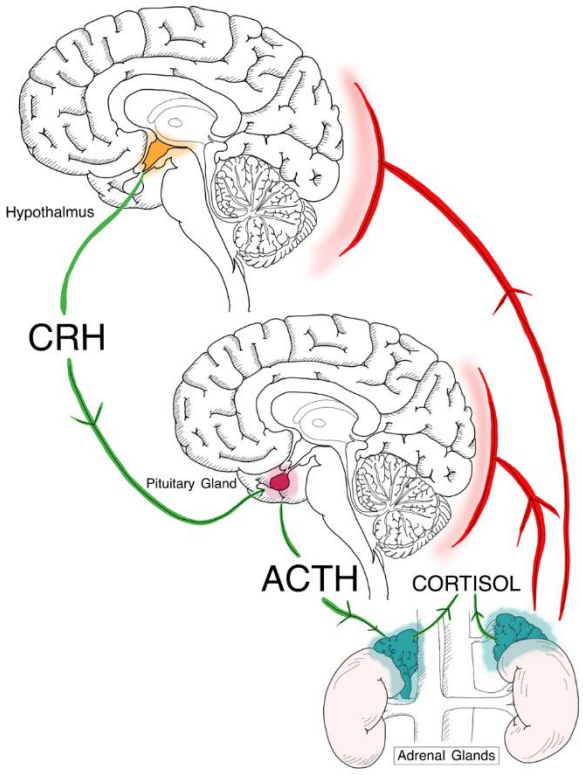
Hypersomnia – some types of autonomic dysregulation can lead to increased daytime sleepiness. Often occurs at the point of stopping physical activity or after eating a large meal

Sleep disturbance – inappropriate sympathetic activation during dreams can result in night time wakening

Hypothalamic-Pituitary-Adrenal Axis

The endocrine system is made up of many different glands throughout the body which release hormones that travel through the blood stream. They cause changes in many different body processes and help to regulate the activity of cells and organs.

The **Hypothalamic-Pituitary-Adrenal Axis** (HPA Axis), is one part of the Neuroendocrine system where parts of the nervous system and parts of the endocrine system operate together to regulate physiological processes in the body. It is another system which contributes to the body's response to demand and aims to maintain **homeostasis**. It tends to work more slowly and has a longer impact than the ANS response.



The Hypothalamus is a part of the brain which is responsible for regulating metabolic processes and the autonomic nervous system and it also has an important role in regulating circadian rhythms or 'the body clock'. It releases corticotropic releasing hormone (CRH) which acts on the pituitary gland.

The pituitary gland is a very small structure which sits at the base of the brain and releases several different hormones. The CRH from the hypothalamus stimulates the pituitary gland to make and release adrenocorticotropic hormone (ACTH) which then acts on the adrenal glands.

The adrenal glands are located above the kidneys and produce several different hormones including adrenaline, cortisol, and aldosterone. In response to ACTH from the pituitary gland, the adrenal glands release cortisol.

There is a feedback loop in this system which means the glands can detect the levels of circulating hormones and alter production levels in order to achieve or maintain homeostasis.

Factors which influence hypothalamic function include:

- Physical activity
- Illness
- Sleep/wake cycle
- Stress
- Levels of cortisol (from the adrenal glands)

The HPA axis is responsible for regulating many systems including:

- The metabolic system
- Cardiovascular system
- Immune system
- Reproductive system
- Central nervous system

Through its action on these systems, the HPA axis integrates physical and psychosocial factors which allow the body to adapt to its environment and the resources available in a way that optimises survival.

Symptoms that can occur due to HPA axis Dysregulation

Disrupted sleep cycle – changes in sleep patterns including insomnia and difficulty waking

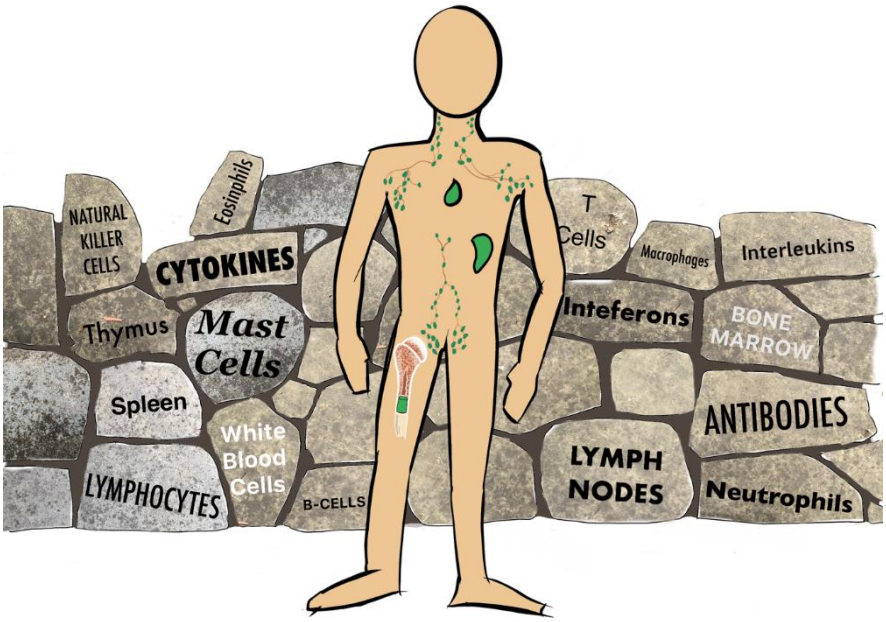
Body temperature changes – feeling cold all the time or experiencing hot flushes

Appetite – reduced appetite, nausea and weight changes

Mood – low mood/depression can be associated with altered cortisol patterns

Fatigue - often described as exhaustion

Immune System



The immune system is a network of structures, cells and processes whose primary role is to protect the body against attack. Parts of the immune system include the spleen, bone marrow, lymph nodes and thymus, white blood cells and antibodies and the complement system and lymphatic system.

The immune system also has roles to play in many other body processes including healing, growth, cancer prevention and reproduction.

The immune response is how the body recognises and defends itself against bacteria, viruses, and substances that appear foreign and harmful (antigens). There is an innate

system which responds immediately in a non-specific way and an adaptive system which can learn from previous antigen exposures and improve future immune responses.

The immune system is also involved in the normal responses to physical activity and exercise. The immune system creates small amounts of inflammation to improve muscle strength and improve metabolic processes. Therefore, it is normal to ache after exercise. Inflammation is also required for healing and repair.

The immune system influences many body processes by producing a wide variety of chemical messengers called Cytokines. Cytokines can trigger and promote inflammatory processes in the body and other cytokines can act to reduce inflammation. In a healthy person the immune system's reaction to infection includes the release of pro-inflammatory cytokines which then influence the cells around them and attract blood cells that attack the foreign substances. Many of the symptoms of infection such as fever, sore throat and tender lymph nodes are caused by the body's own immune responses. Once the infecting organism has been killed, it is important that the body is able to stop the inflammatory response otherwise damage will be caused to the tissues of the body.

Cytokines can travel throughout the body including into the brain where they can have direct effects on neurological processes. Immune system changes can influence mood, behaviour, and pain responses.

The immune system must, therefore, be able to respond rapidly, activating many complex systems, upregulating and downregulating activity as required and then stopping in order to allow recovery and restoration of homeostasis.

Symptoms that can occur due to Immune System Dysregulation

Malaise - a general whole-body fatigue and feeling of being unwell as if dealing with an infection

Tender Glands/sore throat– typically lymph nodes in the neck are affected but can be at other sites

Pain – some cytokines are released from pain neurons so increased pain sensitivity and allodynia can occur

Headaches – generalised headache associated with malaise

Cognitive fatigue – difficulty concentrating, reduced short term memory capacity

New sensitivities to medications, foods etc. – repeatable escalation in symptoms in response to specific triggers which resolves when the trigger is removed e.g. gluten/wheat sensitivity in the absence of coeliac disease

Mood – some cytokines can cross the blood-brain barrier and exert direct neurological effects which can result in symptoms of low mood

Metabolism

The chemical processes of metabolism in the body serve 3 main functions:

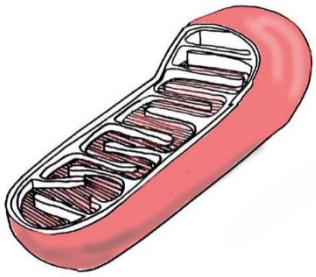
- The conversion of fuel into energy
- To make building blocks such as proteins, fats, and carbohydrates
- Elimination of waste

Metabolic reactions can be either anabolic i.e. 'building up' reactions or catabolic i.e. 'breaking down' processes. There are thousands of metabolic pathways in the body which occur at a cellular level and affect the body on a global level. These reactions must constantly adapt and regulate to maintain homeostasis.

When considering energy metabolism at a cellular level, one of the key metabolic pathways is the production of adenosine triphosphate (ATP). ATP is the chemical that the body makes in order to fuel many of the processes required to sustain life including muscle function, nerve function and chemical synthesis. ATP can be thought of as the chemical currency of energy. Most ATP production takes place within the mitochondria which are present in varying amounts in virtually all cells in the body.

Mitochondria

Aerobic Metabolism
Fuel + Oxygen = ATP



ATP can be made via 2 different metabolic routes- aerobic (with oxygen) and anaerobic (without oxygen).

Aerobic metabolism is where ATP is made using oxygen and fuel (e.g. glucose or fat). This is the most efficient way for mitochondria to make ATP. When the demand for energy is greater than the ATP available from aerobic metabolism, more ATP is made through anaerobic metabolism (i.e. without oxygen). Anaerobic metabolism is a less efficient process and creates lactic acid as a waste product which can accumulate in muscles and cause pain. The process of breaking down lactic acid requires more energy from ATP.

The anaerobic threshold refers to the point where ATP production has switched from aerobic to anaerobic and lactic acid is being produced at a higher rate than it is being used up resulting in an accumulation in cells.

Mitochondria constantly adapt and communicate with other structures to produce the appropriate amounts of ATP for the demands of the body. If the capacity of the aerobic process is reduced there will be an increase in anaerobic metabolism.

Symptoms that can occur due to Metabolic Dysregulation

Exercise intolerance – decreased ability to do physical activity due to fatigue with slow recovery after activity

Post-exertional malaise – worsening exercise intolerance 1-2days after increased activity due to changes in the anaerobic threshold

Muscle pain – increased utilisation of anaerobic pathways can result in lactic acid accumulation in muscles

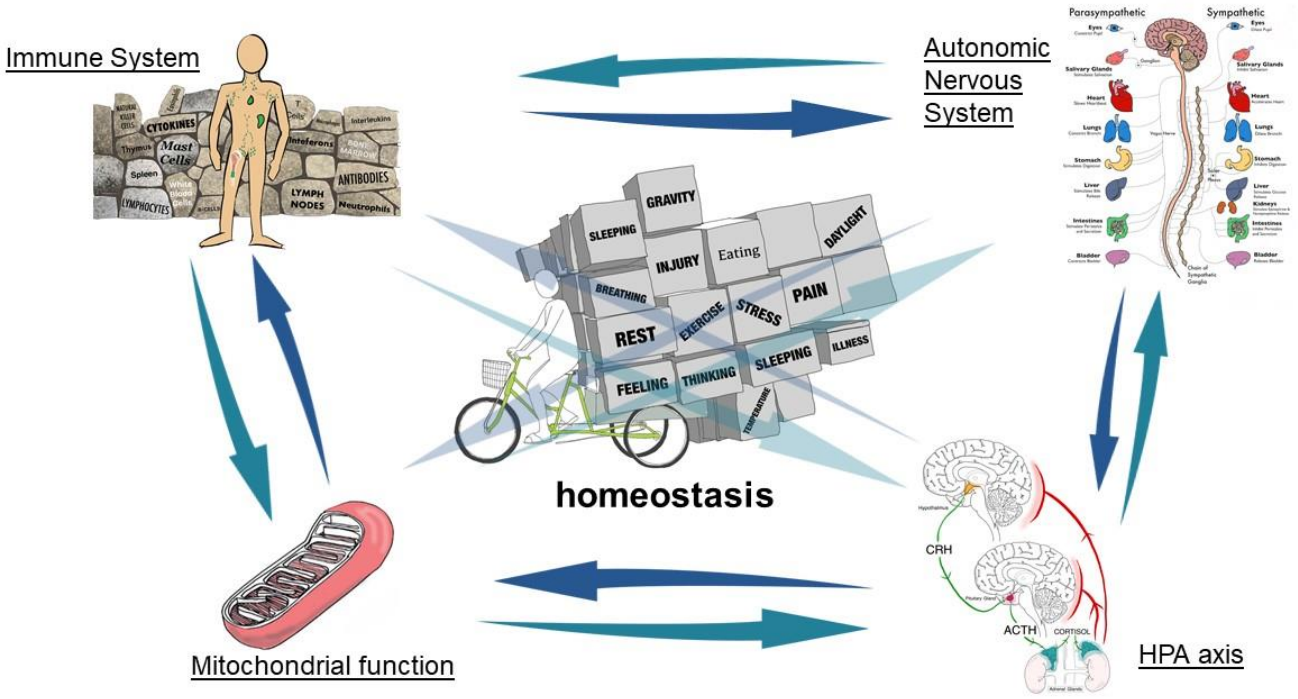
Medication sensitivities - possibility of disrupted enzyme pathways affecting drug metabolism

How do these systems interact with each other?

The autonomic nervous system innervates immune system structures such as the spleen, thymus, and lymph nodes. It can contribute to the up or down regulation of inflammatory responses in the immune system. Immune system cytokines can have a direct influence on the activity of sympathetic and parasympathetic nerves. The HPA axis is involved in regulating immune responses and cytokines involved in immune responses can influence HPA axis function. The Hypothalamus acts as the central control for the Autonomic Nervous System. Mitochondria have a key role to play in regulating immune system activity and during infections mitochondrial function alters. Changes in circulation responses directed by the autonomic nervous system can influence metabolic processes. So, all the dynamic systems are interconnected.

The nervous, endocrine, and immune systems continue to interact as part of the response to infection and this includes hypofunction (suppression) of the HPA axis, sometimes referred to as the sickness response or sickness behaviour. This triggers appropriate physiological and behavioural changes to infection or injury such as fatigue, pain, fever, reduced appetite, and increased anxiety, and activates the body's stress response, to allow it to prioritise fighting infection and recovery. This is also a protective action, limiting activity and exposure to potential threats when we are more vulnerable (Viamontes 2009).

What might go wrong in ME/CFS?



Although our understanding is still developing around the biological pathways for this illness, current information suggests multisystem involvement.

It has been described as the following:

Although no single dysfunction turned out to be a hallmark of the illness, our understanding of CFS has increased substantially. The onset of CFS is often sudden and precipitated by an infectious episode, but in some patients, onset is more insidious and can be preceded by negative, stressful life events. The latter may explain the malfunctioning of the short-term (autonomic nervous system) and long-term (hypothalamus–pituitary–adrenal axis) stress response systems. Indeed, patients with CFS have many autonomic manifestations, and the hypothalamus–pituitary–adrenal axis is characterised by mild hypocortisolism (Nijs et al, 2012).

Research evidence suggests a range of systems and responses that may be dysregulated or not responding in the expected way, such as:

- Repeated exposure to excessive demand can result in alteration of Autonomic System function and can lead to lasting adaptations in the body, for example in energy metabolism and immune response (Danese and McEwan, 2012).
- Sensitisation of the sympathetic nervous system or kindling (Jason et al 2009) – the SNS is more sensitive and reactive to triggers, the body can become stuck in a state of high sympathetic arousal, responding as if survival is threatened, even when resting or sleeping.
- Orthostatic Intolerance or difficulty regulating the body's response to gravity is seen as a key feature associated with ME/CFS (Garner and Baraniuk, 2019)
- Cerebral blood flow in ME/CFS patients is reduced during tilt testing even when BP and pulse readings are normal and correlates with symptoms of orthostatic intolerance (van Campen et al 2020)
- Different patterns of ANS dysregulation generate different patterns of symptoms and may account for some of the variation in severity of the illness (Slomko et al, 2020)
- HPA axis changes are evident in many people with ME/CFS however there is a lot of interindividual variation which suggests multifactorial causes and could indicate it is causal in some cases and a secondary consequence in others (Tomas 2013)
- For some people there may be ongoing hypofunction of the HPA axis with prolonged sickness response – the body continues to respond as if a virus/infection is present wanting to shut the body down (Van Houdenhove et al 2009)
- There may be variance in the expected level of cortisol which is associated with increased levels of fatigue (Torres-Harding et al, 2008)
- Disorganised circadian rhythms which can be linked to metabolic changes including how energy is used in cells (Lacourt 2018)
- Increased activation of the immune system such as elevation in the level of pro-inflammatory cytokines (Montoya et al 2017)
- Prolonged inflammatory response to exertion and slower recovery to baseline – for example in muscles (Van Oosterwijck, 2017)
- Alterations in anaerobic and aerobic threshold in muscles (Van Ness, 2003) – the type of energy production changes at a lower level of demand moving away from using oxygen.
- Abnormal recovery processes after physical activity leading to compromised oxygen delivery following the induction of post-exertional malaise (Keller 2014).

These biological changes may alter over time as it is thought there may be differences in new onset ME/CFS compared to someone who has had it longer term (Horning et al 2015).

The symptoms that occur in people with ME/CFS can be complex and involve multiple different systems and organs of the body. Exploring the patterns of symptoms can often give clues as to which systems may be dysregulated, however it is also important to recognise that similar symptoms can be generated from different systems and the symptom patterns can change through the course of the illness. Equally some people will have additional medical conditions or other body systems which become dysregulated which can also contribute to the symptom burden.

So, although there is no clearly understood pathway regarding the disorder, based on the evidence we have so far, a simple way to think about the illness may be:

Risk factors:

- In some people there may be a pre-existing vulnerability, such as possible genetic factors or increased activation of the immune system during its development (Morris 2019). Developmental changes occurring through childhood could be another vulnerability factor. Many patients were highly active before becoming unwell, often describing an inability to rest or relax prior to the illness and this may indicate a pre-existing highly responsive sympathetic nervous system (on mode) and poor responses in the parasympathetic nervous system (off mode). Some conditions including Hypermobility and Autism may also constitute an underlying vulnerability as they are now being recognised to have associations with Autonomic System Dysfunction.

Onset:

- In some cases, there is a clear trigger for the onset of symptoms, for example a viral infection or a major emotional event such as a bereavement.
- In other cases, chronic demands over time act as the trigger possibly by causing the body to enter an immune reaction or sickness response, with changes in the HPA Axis and Autonomic Nervous System.

Dysregulation:

- The illness may impact on the regulation of the autonomic nervous system, causing dysautonomia including orthostatic problems (our body's response to being upright against gravity)
- The body remains in a protective state and is highly reactive to any changes in internal and external demands, for example having an increased immune response to exertion (Post Exertional Malaise).
- In some people the nervous system remains in high sympathetic arousal and the parasympathetic responses are inhibited restricting the body's restorative functions, such as sleep, and making it hard to achieve and maintain homeostasis (HPA regulation).
- Mitochondrial function can be altered with disordered recovery after activity meaning there is a reduction in the anaerobic threshold following physical activity.

So, the dynamic systems in the body that are supposed to work together and regulate each other to keep us well or in homeostasis are now dysregulated and may work in opposition to each other. Many patients describe that their brain wants to go but the body wants to stop.

What can be done about dysregulation?

As these are complex systems that need to regularly adjust and change in response to demands and our world, it is difficult to find one factor that will correct dysregulation. However, we know factors that can aggravate dysregulation along with strategies that can improve stability and support homeostasis.

The approaches that can be helpful to therapy include:

- Regulation of the body clock and circadian rhythms, including sleep, light and eating patterns.
- Desensitisation of the sympathetic nervous system and increasing the parasympathetic response.
- Supporting orthostatic tolerance through fluid levels and management techniques.
- Matching energy availability and energy expenditure, understanding that there are different currencies for different types of activity, such as physical, cognitive, social and emotional. Working within the energy envelope, not pushing outside of it.
- Working aerobically within tolerance levels and reducing heart rate at rest and on exertion.
- Minimising immune activation and triggers for increased inflammation
- Balancing and managing overall demands and activity to remain within limits and allow recovery, reducing the impact of a boom and bust pattern on the HPA.
- Recovery time for restorative rest following exertion to allow return to baseline
- Ensuring diet is providing appropriate nutrients and supporting regulation of blood sugar levels.

Initially the focus is on consistency and regulating, to support stability before increasing the level of demand. This should be done gradually allowing development of tolerance and adaption prior to any further increases in demand, to enable the body to rebalance. This is the reason why the therapy approach we use works on different phases of stabilisation and then building tolerance. It is important that any strategies are implemented after a careful assessment of the individual's condition, and which aspects of dysregulation are most prominent and need to be addressed to support greater stability. Understanding how the body's physiology can be affected by this illness is an important starting point to any therapy programme.

Dr Sue Pemberton, PhD, MSc, BHSc, Dip COT MRCOT,
Therapy Director
Dr Vikki McKeever, MB BS MRCGP
General Practitioner with Special Interest in ME/CFS
Joseph Bradley, BSc OT, MRes, MRCOT
Clinical Specialist Occupational Therapist
Published 26/10/2020

References:

Cara Tomas, Julia Newton, Stuart Watson, "A Review of Hypothalamic-Pituitary-Adrenal Axis Function in Chronic Fatigue Syndrome", *International Scholarly Research Notices*, vol. 2013, Article ID 784520, 8 pages, 2013. https://doi.org/10.1155/2013/784520

Clark JE, Ng W-F, Rushton S, Watson S, Newton JL (2019) Network structure underpinning (dys)homeostasis in chronic fatigue syndrome; Preliminary findings. PLoS ONE 14(3): e0213724. https://doi.org/10.1371/journal.pone.0213724

Danese, A. and McEwen, B.S., 2012. Adverse childhood experiences, allostasis, allostatic load, and age-related disease. *Physiology & behavior*, 106(1), pp.29-39.

Garner, R., Baraniuk, J.N. Orthostatic intolerance in chronic fatigue syndrome. *J Transl* Med 17, 185 (2019) doi:10.1186/s12967-019-1935-y

Hornig, M. et al. Distinct plasma immune signatures in ME/CFS are present early in the course of illness. *Sci. Adv. 1*, e1400121 (2015)

Jason, L.A., Porter, N., Herrington, J., Sorenson, M., & Kubow, S. (2009) Kindling and Oxidative Stress as Contributors to Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *Journal of Behavioral and Neuroscience Research, 2009, Vo1. 7, 1-17*

Keller, B.A., Pryor, J.L. & Giloteaux, L. Inability of myalgic encephalomyelitis/chronic fatigue syndrome patients to reproduce VO_2peak indicates functional impairment. *J Transl Med* **12,** 104 (2014). https://doi.org/10.1186/1479-5876-12-104

Koch CK et al (2017) Interaction between circadian rhythms and stress, *Neurobiology of Stress*, available online 6 (2017) 57-67

Lacourt TE, Vichaya EG, Chiu GS, Dantzer R and Heijnen CJ (2018) The High Costs of Low-Grade Inflammation: Persistent Fatigue as a Consequence of Reduced Cellular-Energy Availability and Non-adaptive Energy Expenditure. *Front. Behav. Neurosci*. 12:78. doi: 10.3389/fnbeh.2018.00078

Montoya J. et al (2017) Cytokine signature associated with ME/CFS severity. *Proceedings of the National Academy of Sciences* Aug 2017, 114 (34) E7150-E7158; DOI: 10.1073/pnas.1710519114

Morris, G., Maes, M., Berk, M. *et al.* Myalgic encephalomyelitis or chronic fatigue syndrome: how could the illness develop? *Metab Brain Dis* **34,** 385–415 (2019) doi:10.1007/s11011-019-0388-6

Nijs, J., Meeus, M., Van Oosterwijck, J., Ickmans, K., Moorkens, G., Hans, G. and De Clerck, L.S. (2012), In the mind or in the brain? Scientific evidence for central sensitisation in chronic fatigue syndrome. *European Journal of Clinical Investigation*, 42: 203-212. doi:10.1111/j.1365-2362.2011.02575.x

Psychiatric Annals. 2009;39(12):985-996 https://doi.org/10.3928/00485718-20091124-04
Selye, H (1956) The Stress of Life, McGraw-Hill, New York,

Słomko, J.; Estévez-López, F.; Kujawski, S.; Zawadka-Kunikowska, M.; Tafil-Klawe, M.; Klawe, J.J.; Morten, K.J.; Szrajda, J.; Murovska, M.; Newton, J.L.; Zalewski, P., on behalf of the European Network on ME/CFS (EUROMENE); Autonomic Phenotypes in Chronic

Fatigue Syndrome (CFS) Are Associated with Illness Severity: A Cluster Analysis. *J. Clin. Med.* **2020**, *9*, 2531. https://www.mdpi.com/790174

Tomas, C., Newton, J. and Watson, S., (2013). A review of hypothalamic-pituitary-adrenal axis function in chronic fatigue syndrome. ISRN *neuroscience*, 2013. doi: 10.1155/2013/784520

Torres-Harding, S., Sorenson, M., Jason, L., Reynolds, N., Brown, M., Maher, K. and Fletcher, M.A. (2008), The Associations Between Basal Salivary Cortisol and Illness Symptomatology in Chronic Fatigue Syndrome. Journal of Applied Biobehavioral Research, 13: 157-180. doi:10.1111/j.1751-9861.2008.00033.x

van Campen CLMC, Verheugt FWA, Rowe PC, Visser FC. Cerebral blood flow is reduced in ME/CFS during head-up tilt testing even in the absence of hypotension or tachycardia: A quantitative, controlled study using Doppler echography. *Clin Neurophysiol Pract*. 2020;5:50-58. Published 2020 Feb 8. doi:10.1016/j.cnp.2020.01.003

Van Houdenhove, Van Den Eede & Luyten, (2009) Does hypothalamic-pituitary-adrenal axis hypofunction in Chronic Fatigue Syndrome reflect a crash in the stress system? *Medical Hypothesis* 72: 701-705

Van Oosterwijck, J., Marusic, U., De Wandele, I., Paul, L., Meeus, M., Moorkens, G., Lambrecht, L., et al. (2017). The role of autonomic function in exercise-induced endogenous analgesia : a case-control study in myalgic encephalomyelitis/chronic fatigue syndrome and healthy people. *PAIN PHYSICIAN*, 20(3), E389–E399.

VanNess, J.M., Snell, C.R., Strayer, D.R., Dempsey, L.I.N.E. and Stevens, S.R., (2003). Subclassifying chronic fatigue syndrome through exercise testing. *Medicine and science in sports and exercise*, 35(6), pp.908-913.

Viamontes (2009) The Sickness Response: An Adaptive Brain–Body Reaction to Medical Illness.