



Om Vård för Patienter med ME/CFS

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Birgitta Evengård

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CHRONIC EPSTEIN-BARR VIRUS INFECTION¹

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Oxford Criteria (UK)
(Sharpe et al 1990)

Chronic fatigue syndrome (CFS)

1. A syndrome characterized by fatigue as the principal symptom.
2. A syndrome of definite onset that is not life long.
3. The fatigue is severe, disabling, and affects physical and mental functioning.
4. The symptom of fatigue should have been present for a minimum of 6 months during which it was present for more than 50% of the time.
5. Other symptoms may be present, particularly myalgia, mood and sleep disturbance.
6. Certain patients should be excluded from the definition.

They include:

1. Patients with established medical conditions known to produce chronic fatigue (eg severe anaemia). Such patients should be excluded whether the medical condition is diagnosed at presentation or only subsequently. All patients should have a history and physical examination performed by a competent physician.
2. Patients with a current diagnosis of schizophrenia, manic depressive illness, substance abuse, eating disorder or proven organic brain disease. Other psychiatric disorders (including depressive illness, anxiety disorders, and hyperventilation syndrome) are not necessarily reasons for exclusion.

Post-infectious fatigue syndrome (PIFS)

This is a subtype of CFS which either follows an infection or is associated with a current infection (although whether such associated infection is of aetiological significance is a topic for research).

To meet research criteria for PIFS patients must:

- fulfil criteria for CFS as defined above and
- should also fulfil the following additional criteria:
 1. There is definite evidence of infection at onset or presentation (a patient's self-report is unlikely to be sufficiently reliable).
 2. The syndrome is present for a minimum of 6 months after onset of infection.
 3. The infection has been corroborated by laboratory evidence.

CDC Criteria
(Centers for Disease Control, USA)
(Fukuda et al 1994)

1. Clinically evaluated, unexplained, persistent or relapsing chronic fatigue that is of new or definite onset (has not been lifelong); is not the result of ongoing exertion; is not substantially relieved by rest; and results in substantial reduction in previous levels of occupational, educational, social, or personal activities; and
2. the concurrent occurrence of four or more of the following symptoms, all of which must have persisted or recurred during six or more consecutive months of illness and must not have predated the fatigue:
 - self-reported impairment in short-term memory or concentration severe enough to cause a substantial reduction in previous levels of occupational, educational, social or personal activities.
 - sore throat
 - tender cervical or axillary lymph nodes
 - muscle pain
 - headaches of a new type, pattern or severity
 - unrefreshing sleep
 - post-exertional malaise lasting more than twenty four hours
 - multijoint pain without joint swelling or redness

Australian Criteria
(Lloyd et al 1988)

1. Disabling and prolonged feelings of physical tiredness or fatigue, exacerbated by physical activity.
2. Present for at least 6 months.
3. Unexplained by an alternative diagnosis reached by history, laboratory, or physical examinations.
4. Accompanied by the new onset of neuropsychological symptoms including impaired short-term memory and concentration, decreased libido, and depressed mood. These symptoms usually have their onset at the same time as the physical fatigue, but are typically less severe, and less persistent than those seen in classic depressive illness.

Patients are excluded if:

1. They have a chronic medical condition that may result in fatigue.
2. There is a history of schizophrenia, other psychotic illnesses, or bipolar affective disorder.

In addition, drug or alcohol dependence makes CFS very unlikely.

Kanadensiska kriterierna

De kanadensiska kliniska kriterierna väljer patienter som har mer fysisk funktionell nedsättning, mer trötthet/svaghet, neurokognitiva och neurologiska symtom och hade fler variabler som skiljer dem från personer med psykiatriska sjukdomar än vad 1994 års kriterier gör.

CFS idag - epidemiologi

- Invalidiserande trötthet som ej förbättras av vila och där fysisk/mental aktivitet förvärrar symtomen
- Karakteriseras av ospecifika symtom som nedsättning av koncentrationsförmåga och minne, diffus muskelvärk, ny typ av huvudvärk, återkommande halsont, ömmande lymfkörtlar, icke-rekreerande sömn, lättare ledbesvär
- En sjukdom som 0,5-1% av svenska folket lider av, en million amerikaner och där studier visar att endast 20 % blivit diagnosticerade. 80% är kvinnor.
- \$9 miljarder i förlorad produktivitet i USA



All Databases	PubMed	Nucleotide	Protein
Search	PubMed	for "chronic fatigue syndrome"	Go Clear Save Search

- Från 1987 till 2007 har det publicerats mer än 3,500 vetenskapliga och medicinska artiklar om Kroniskt trötthetssyndrom.
 - Ämnen spänner från behandlingar till patogenes .
 - Publicerade av forskare och läkare från hela världen
 - USA, Japan, Australien, Nederländerna, Sverige, England, Italien, Spanien, Kanada, Korea, World Health Organization (WHO)

CFS Idag- Biologi

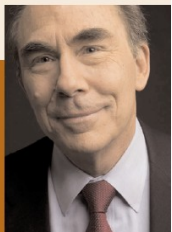
- Skiljer sig från depression
- Kronisk immunaktivering
- NK cell dysfunktion
- MRI skillnader I hjärnan
- Hjärnmetabolismen skiljer sig
- Neuroendokrina störningar
- Kognitiv försämring
- ANS påverkan
- Genom skillnader
- Infektiösa triggers och latent virus aktivering



Ten Discoveries about the Biology of CFS

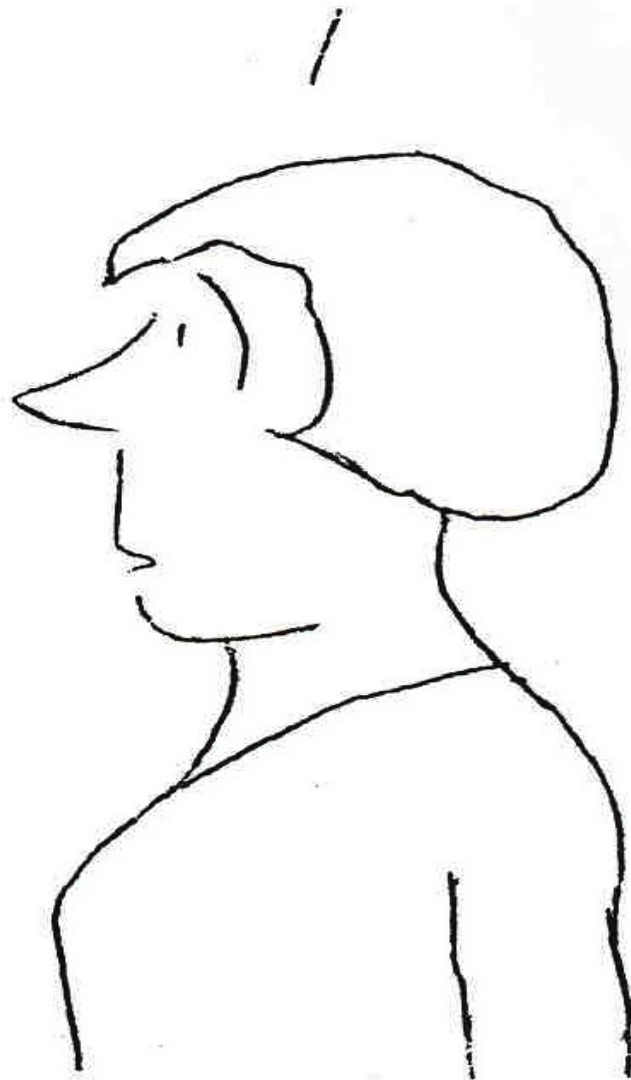
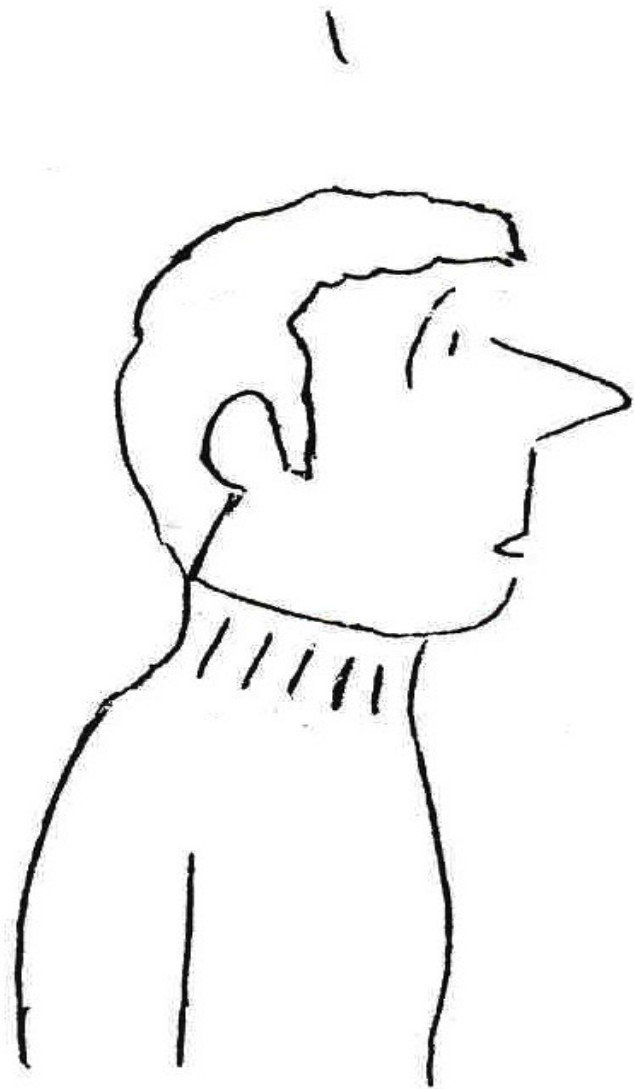
- 1** Chronic fatigue syndrome is not a form of depression, and many patients with CFS have no diagnosable psychiatric disorder. As with most chronic illnesses, some CFS patients become depressed because of the impact of the illness on their lives, but most studies find that the majority haven't experienced depression before the onset of illness.
- 2** There's a state of chronic, low-grade immune activation in CFS. There is evidence of activated T cells, activation of genes reflecting immune activation and increased levels of immune system chemicals called cytokines.
- 3** There's substantial evidence of poorly functioning natural killer (NK) cells—white blood cells important in fighting viral infections. Studies differ as to whether there may be increased numbers of NK cells in CFS patients.
- 4** Abnormalities in the white matter of the brain have been found in CFS patients using magnetic resonance imaging (MRI) scans. Typically, these are small (fraction of an inch) areas just below the cerebral cortex, the outermost area of the brain hemispheres. Differences in gray matter volume are also being observed.
- 5** Abnormalities in brain metabolism, as indicated by single photon emission computed tomography (SPECT) and positron emission tomography (PET), have been discovered. Other research suggests there's something wrong with energy metabolism and the oxidative electron transport chain in the mitochondria of CFS patients.
- 6** CFS patients experience abnormalities in multiple neuroendocrine systems in the brain, particularly depression of the hypothalamic-pituitary-adrenal (HPA) axis, but also the hypothalamic-prolactin axis and hypothalamic-growth hormone axis.
- 7** Cognitive impairment is common in CFS patients. The most frequently documented abnormalities are difficulty with information processing, memory and/or attention.
- 8** Abnormalities of the autonomic nervous system have been found by numerous independent researchers. These include a failure of the body to maintain blood pressure after a person stands up, abnormal responses of the heart rate to standing and unusual pooling of blood in the veins of the legs. Some studies also find low levels of blood volume.
- 9** CFS patients have disordered expression of genes that are important in energy metabolism. Energy comes from certain natural chemicals that are processed by enzymes inside each cell. These enzymes are controlled by specific genes. Other genomic research is revealing involvement of genes connected to HPA axis activity, the sympathetic nervous system and immune function.
- 10** There's evidence of more frequent latent active infection with various herpesviruses and enteroviruses. The herpesviruses include Epstein Barr, HHV-6 and cytomegalovirus. Other infectious agents, like bacterium that cause Lyme disease, Ross River virus and Q fever, can also trigger CFS.

The above summary of CFS research findings was provided by Anthony Komaroff, MD, a professor of medicine at Harvard Medical School, senior physician at Brigham and Women's Hospital in Boston and the editor-in chief of Harvard Health Publications. Dr. Komaroff has an ongoing research program on chronic fatigue syndrome and has published over 230 research articles and book chapters.



"Chronic Fatigue Syndrome— isn't
that all in your head?"

"It was, but then it spread
to the rest of my body."



Kroppsliga system som är påverkade vid KTS



Brain (command and control center with 100 billion neurons each linked to as many as 10,000 other neurons)

Endocrine system (glands that secrete helpful chemicals into the blood)

Cardiovascular system (the system that moves nutrients, gases and wastes to and from cells, helps stabilize body temperature and pH to maintain homeostasis)

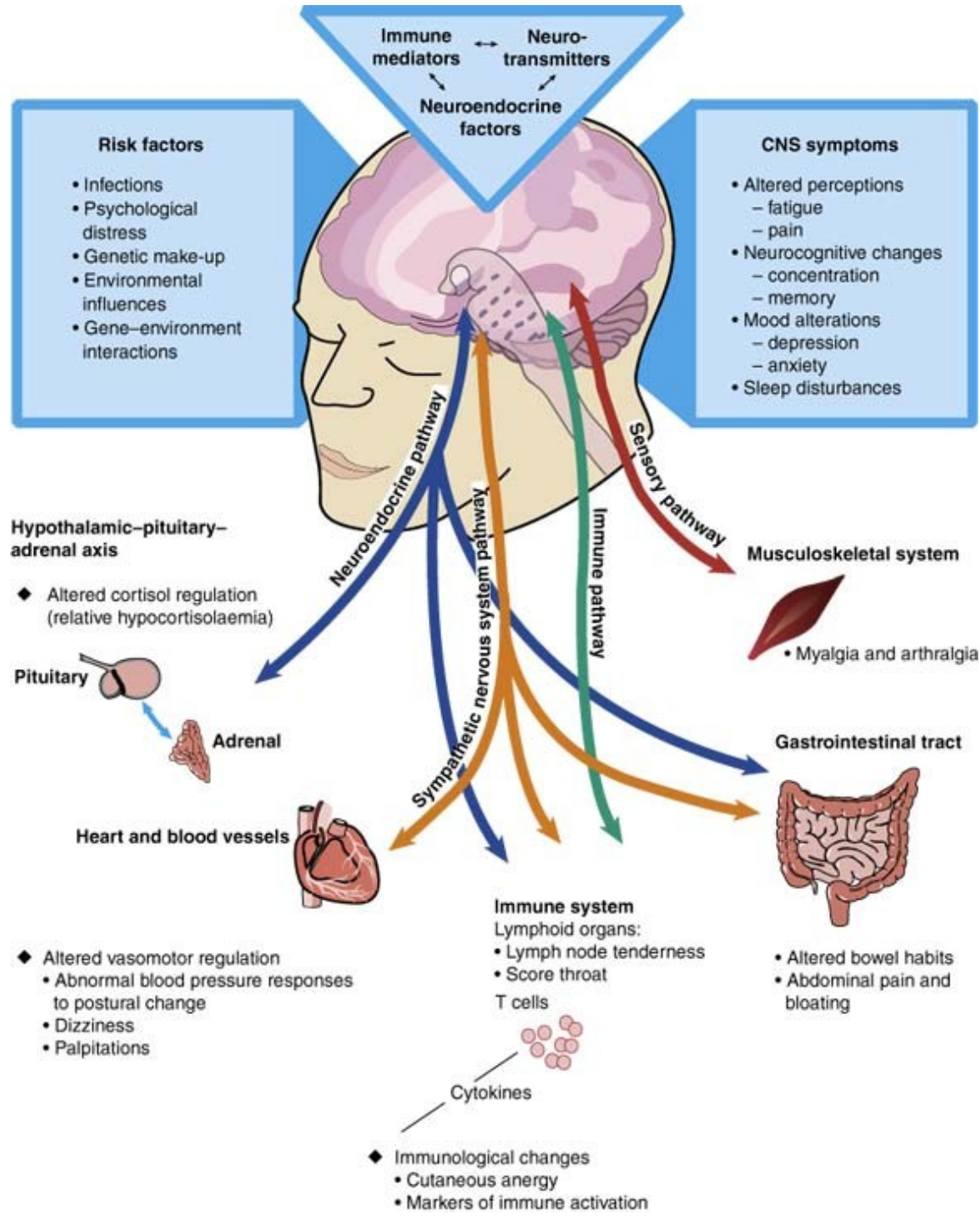
Musculoskeletal system (bones, joints, muscles and tendons)

Immune system (the defense system, helps maintain body homeostasis)

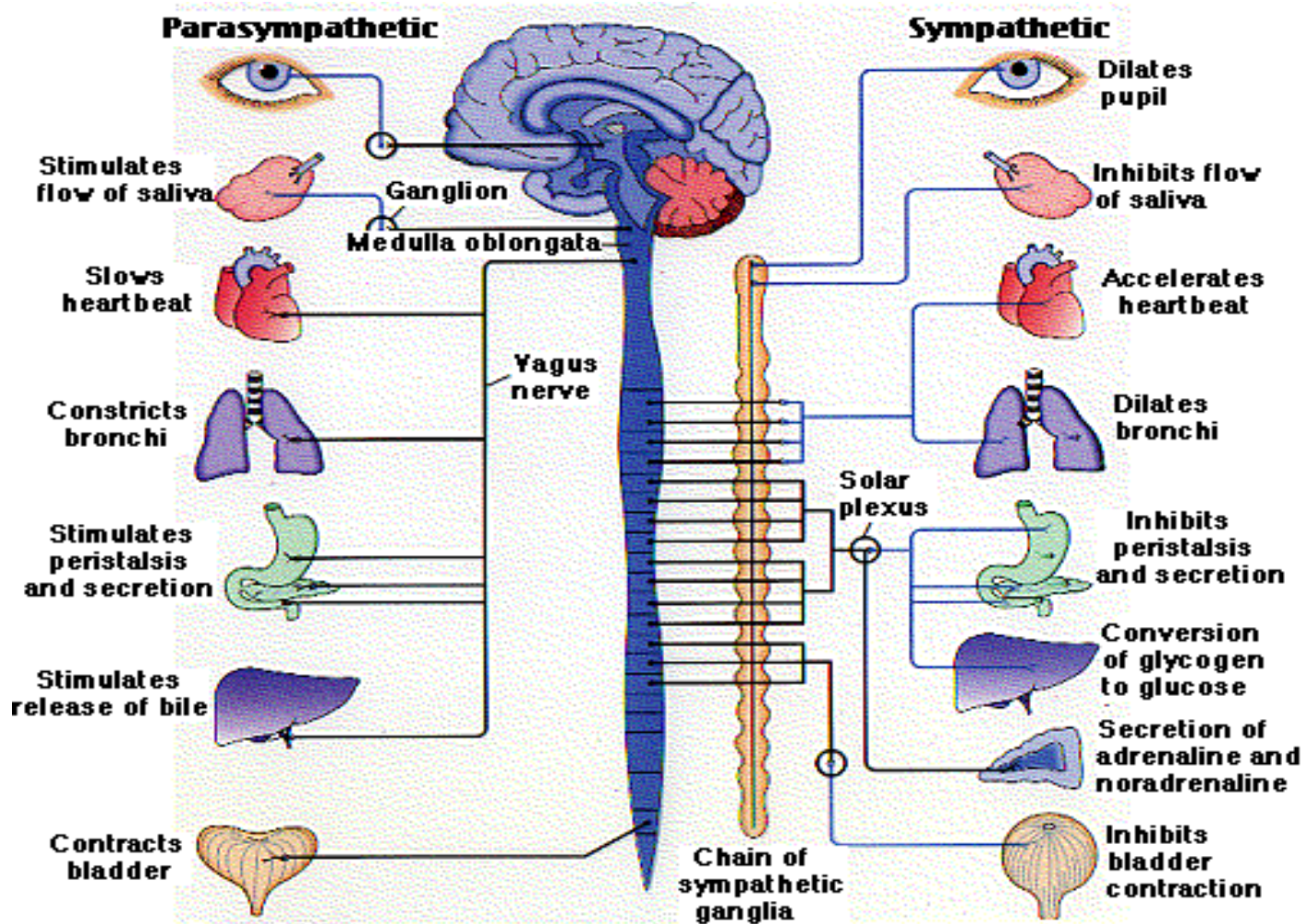
CHRONIC FATIGUE SYNDROME



KTS är ett komplext tillstånd som uppkommer från en kombinerad samverkan av gener, genomet, miljöfaktorer och riskbeteende.

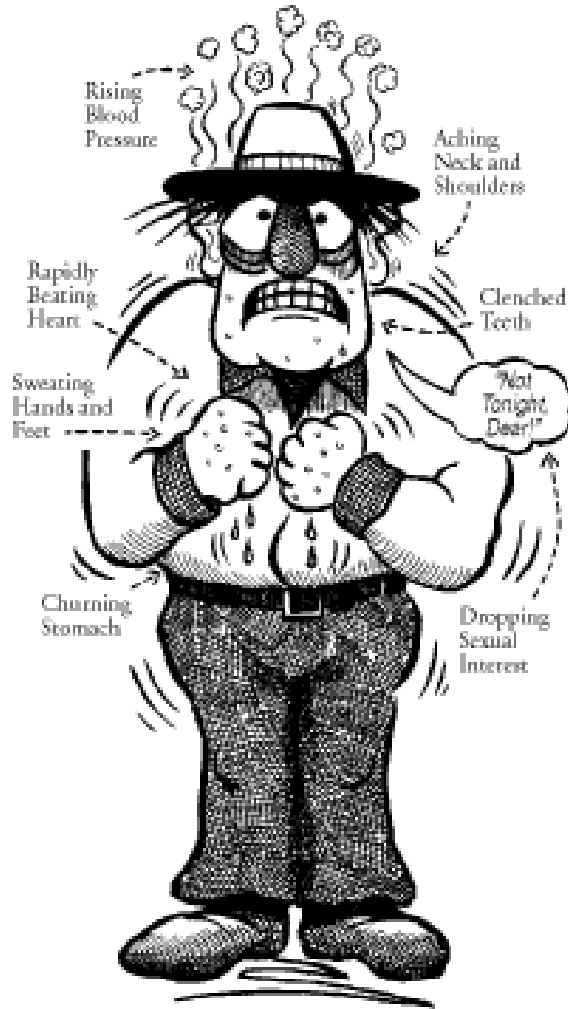


Autonomic Nervous System (ANS)



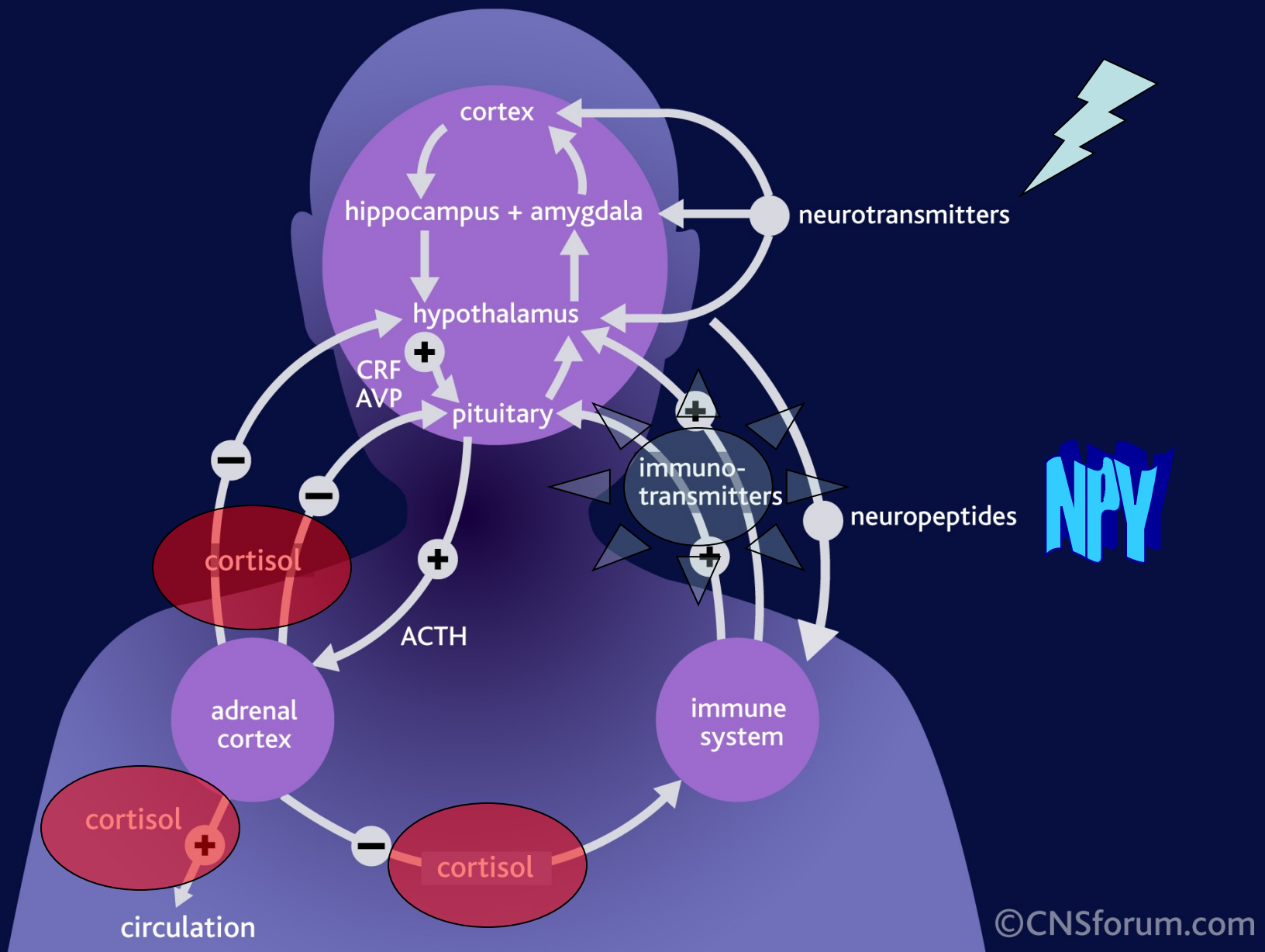
Nerves transmitting information from one cell to another (“telephone cable”); between the central nervous system (especially the hypothalamus and medulla oblongata) and internal organs such as the heart, lungs, guts and glands.

Neuroendokrina störningar

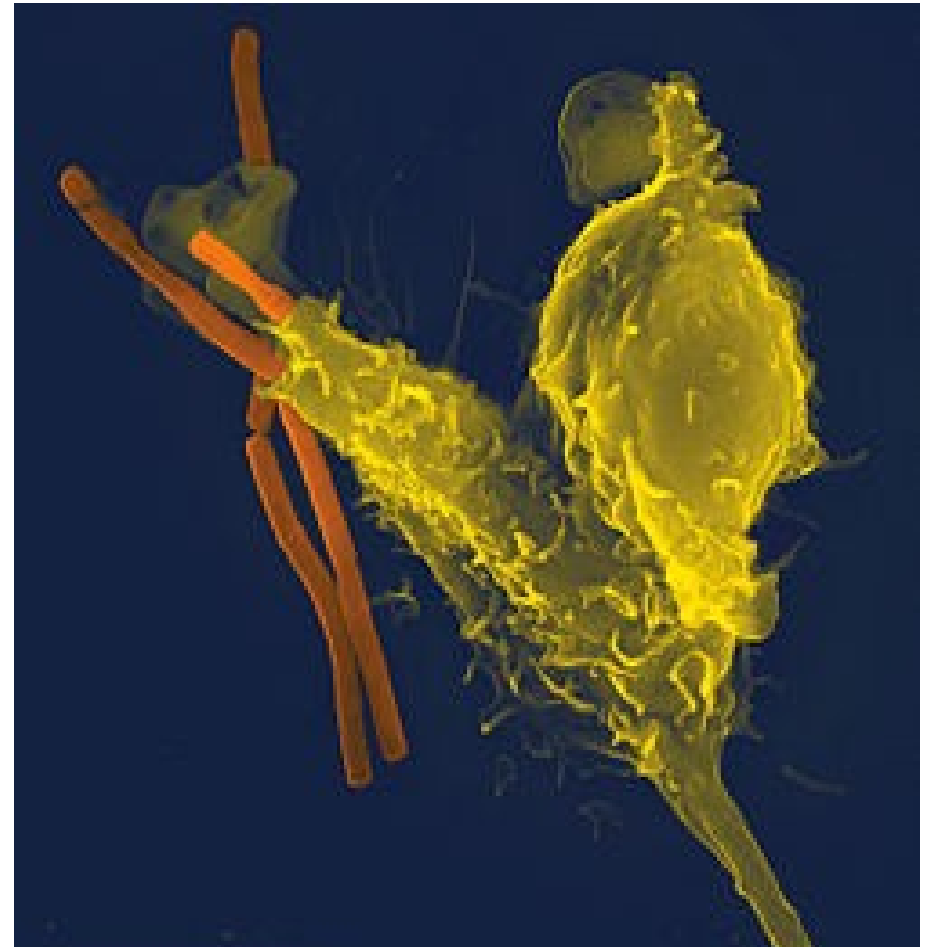
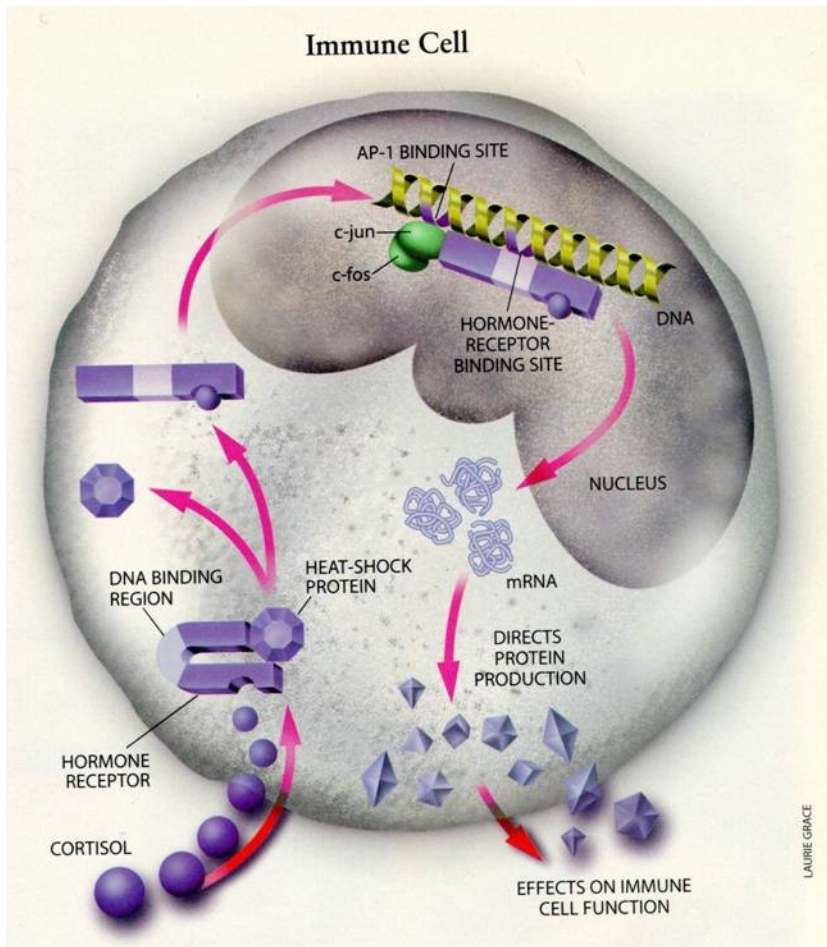


- HPA axeln kontrollerar reaktioner som svar på fysisk (infektion, trauma) och psykologisk (rädsla, känslor)
- Reglering av stress svaret hos patienter med KTS skiljer sig åt

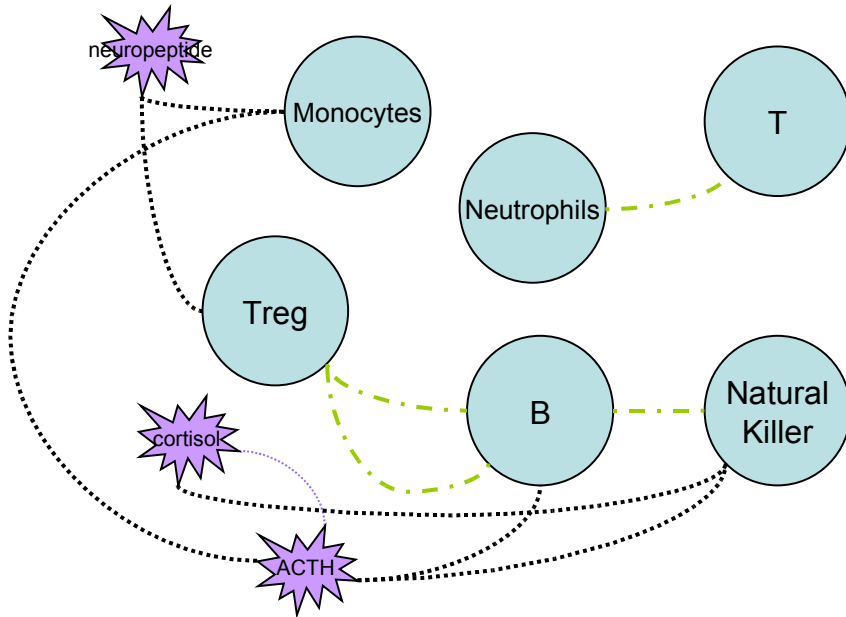
HPA Axeln: Störningar vid KTS



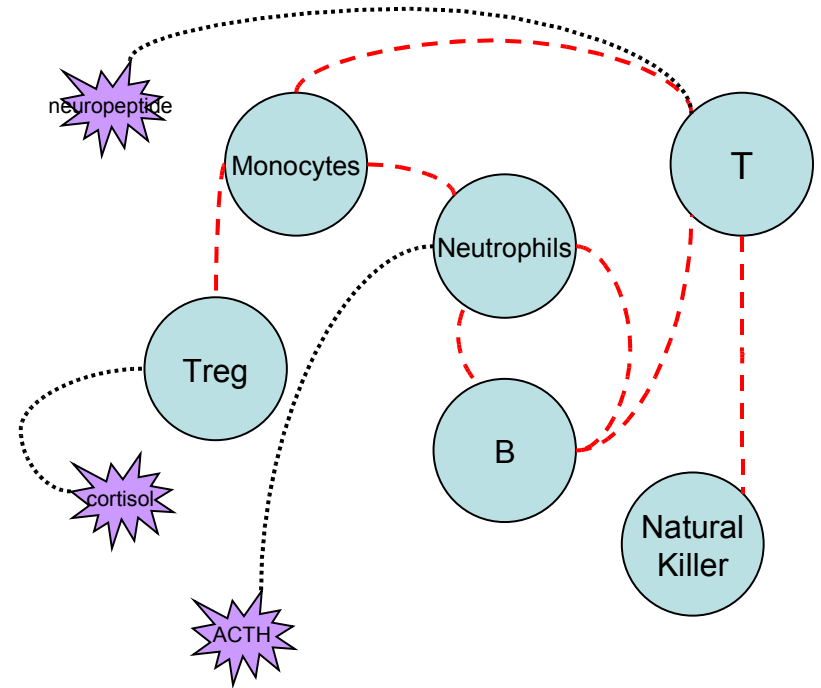
Immunsystemet



Immun dysfunktion

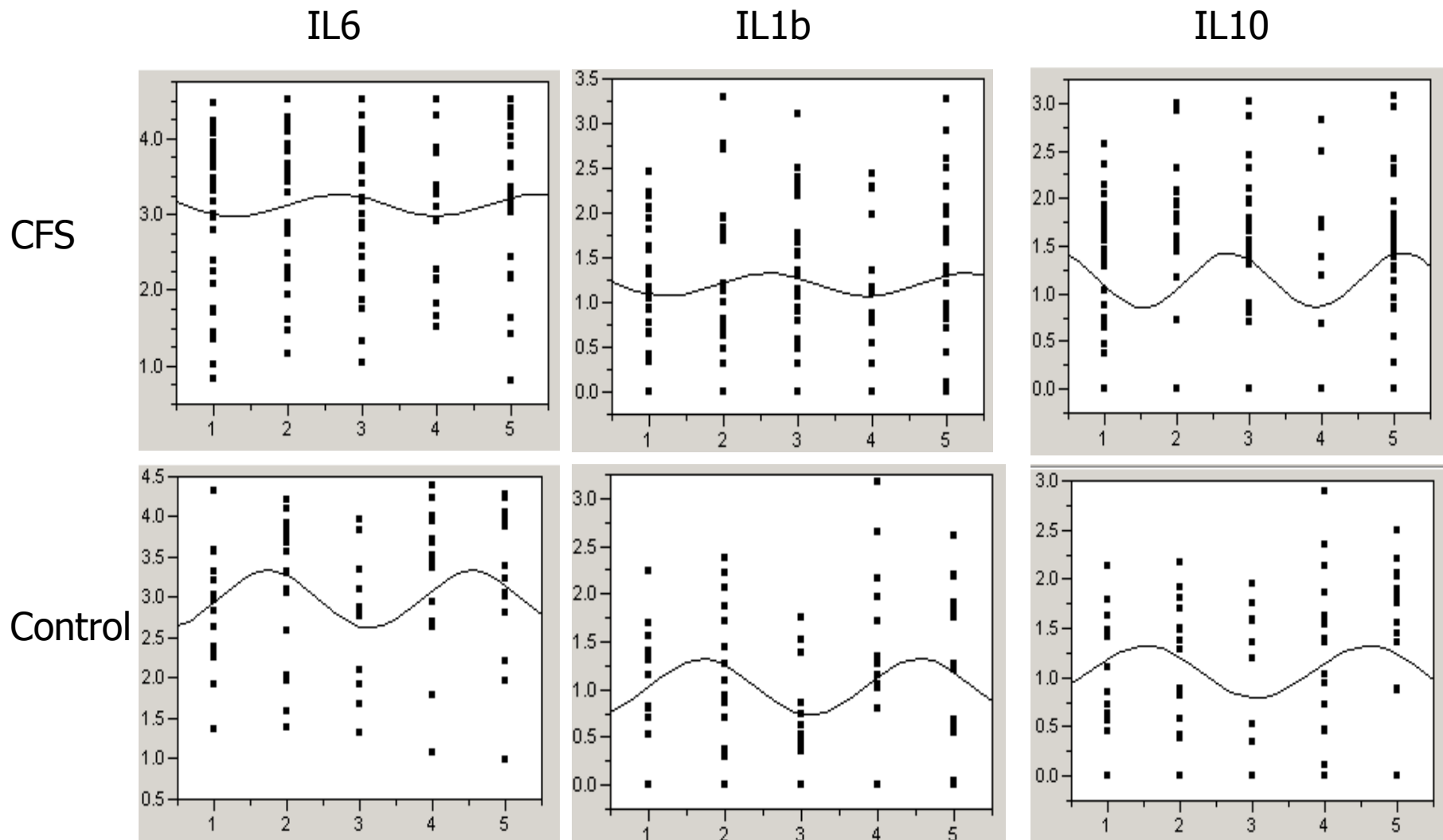


Immuncell Kommunikation hos friska



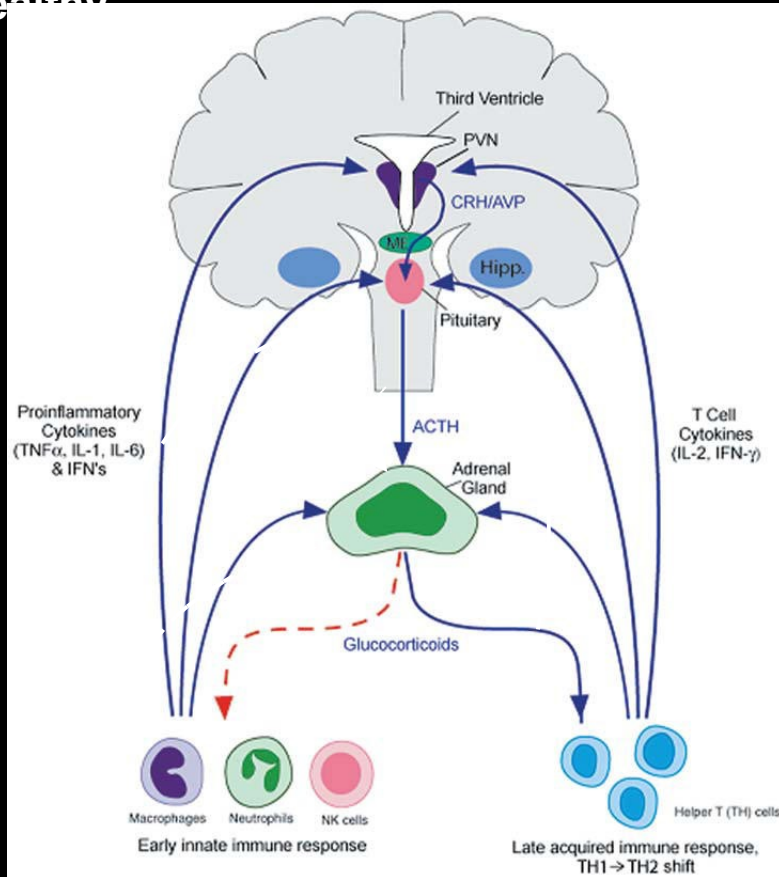
Immuncell Kommunikation hos patienter med KTS

Dynamiken av cytokiner vid KTS

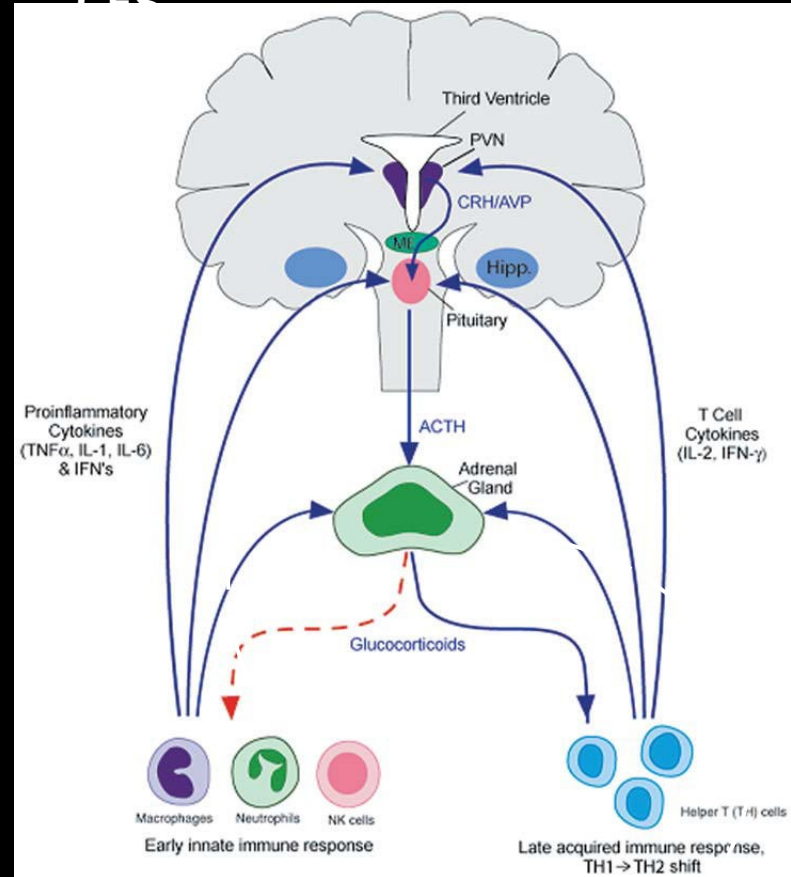


Blood Hjärn Kommunikation

Healthy



CES



KTS och Infektion

- Post-infektiös trötthet är en undergrupp till KTS som antingen följer en infektion eller är associerad med en aktuell eller reaktivering av en
- Mikroorganismer som man vet är associerade med eller triggas Postinfektiös trötthet eller KTS
 - Epstein Barr Virus
 - Coxiella burnetii (Q fever)
 - Dengue (Flavivirus)
 - Borrelia burgdorferi (Lyme Disease)
 - Ross River Virus (Alphavirus; epidemic polyarthritis)
 - Human herpes virus 6 (placebo kontrollerad Valcytetest)
 - Enteroviroser

Summering av vår nuvarande kunskap av biologin runt KTS

Flera kroppsliga system är engagerade vid KTS:

-Centrala nervsystemet, endokrina-, immun-, kardiovaskulära- .

– koordinerad kommunikation (eller misskommunikation mellan dessa olika system orsakar sjukdom

- Inte troligt att det är en gen eller en molekyl som orsakar KTS

– Personer blir sjuka på grund av predisponerande genetiska faktorer som kan påverkas av händelser och miljön under livet

– T.ex infektion, trauma, toxiska exponeringar, “stress”

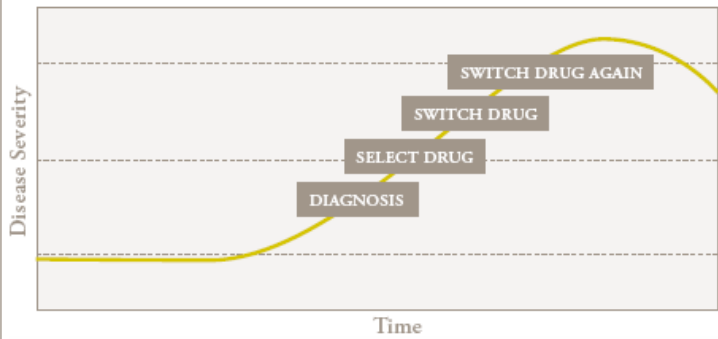
Behandling

- Individualiserad - och - Gemensam
- Medicinsk utredning, rätt utförd kognitiv beteende terapi ökar livskvalitén för en del av patienterna liksom sakta utökad grad av fysisk aktivitet.
- Komplementär medicin är en stor sak inom detta område; kostar mer än den vanliga vården

Information

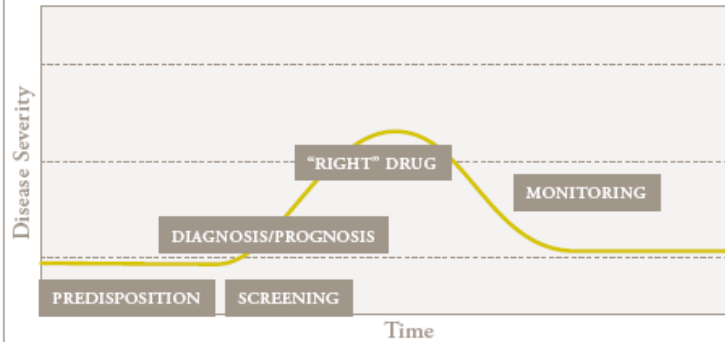
- www.iacfsme.org
- www.rme.nu

REACTIVE MEDICAL CARE



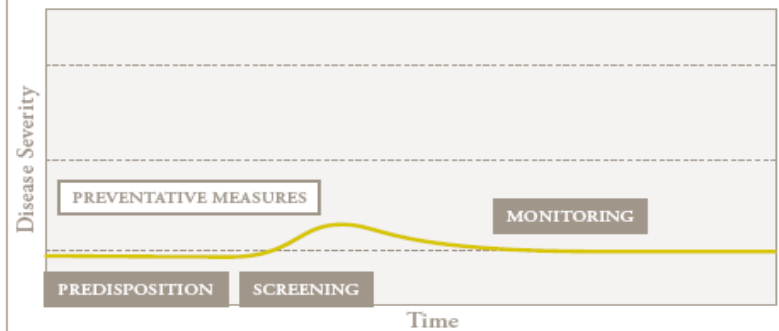
Diagnose Disease; Treat Symptoms;
Costly, Trial and Error Treatment

EFFICIENT MEDICAL CARE



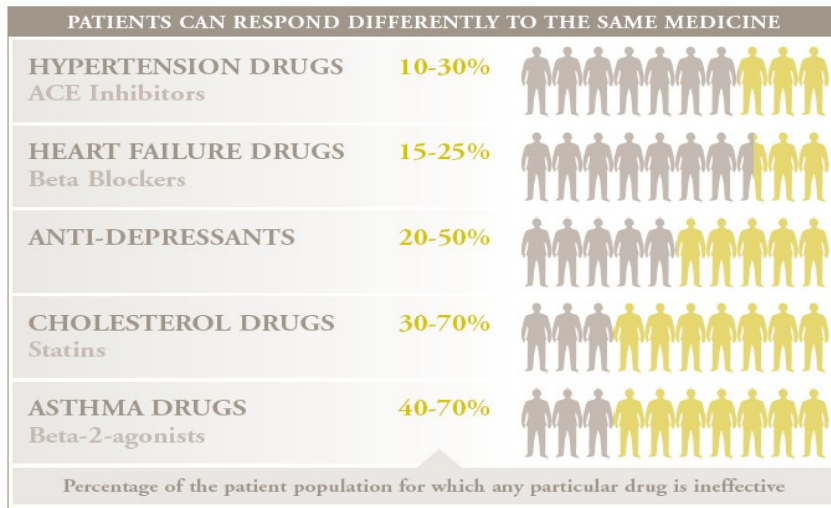
Health Management; Molecular Screening; Early Detection;
Rapid Effective Treatment; Improved Quality of Care

PREVENTIVE MEDICAL CARE



Predisposition Guides Prevention; Treat the Molecular Markers
vs. Symptoms and Disease; Healthcare Cost Reduction

Pharmacogenomics and CFS

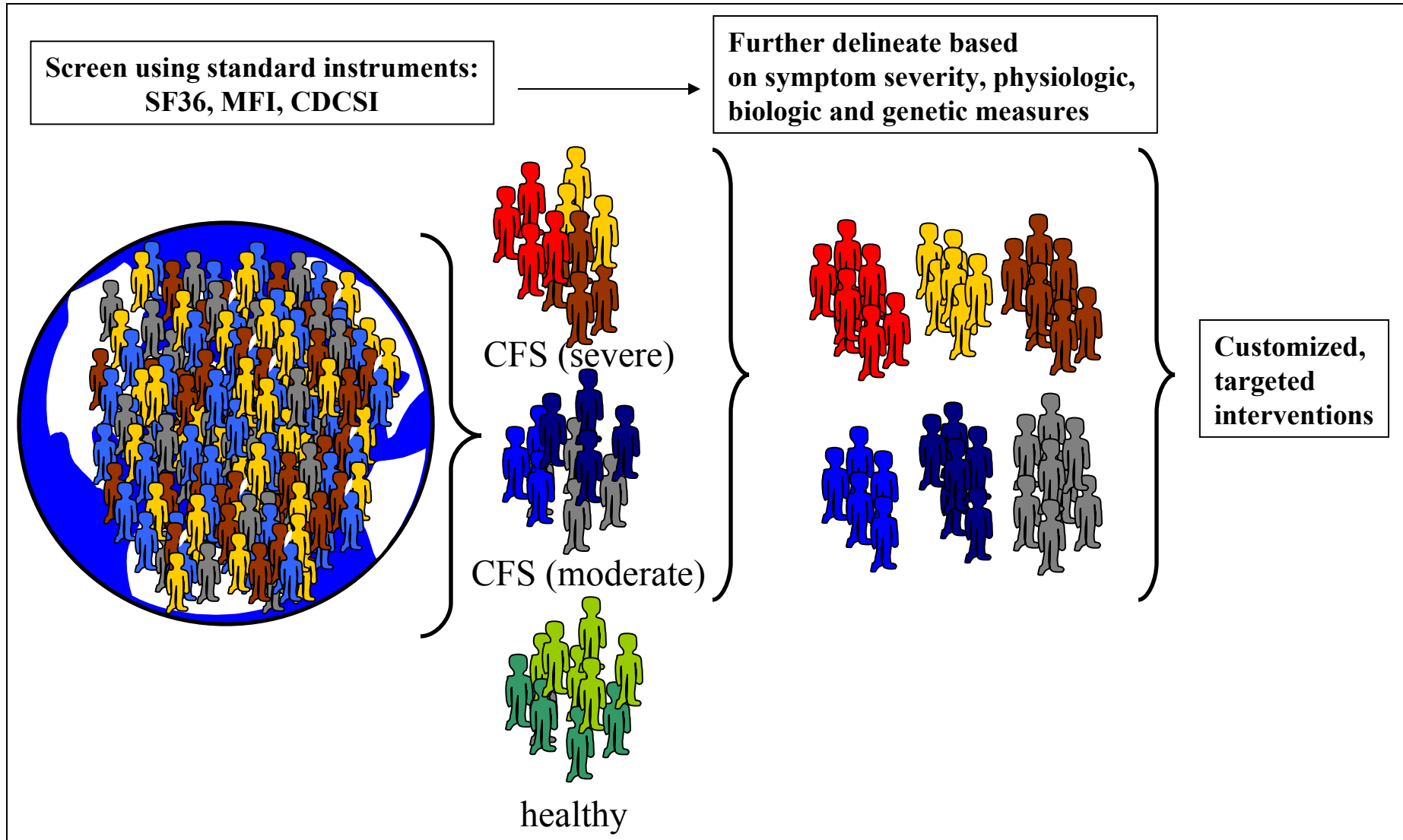


- Variable response to drugs administered for symptom relief

- Customization of therapy based on molecular profile



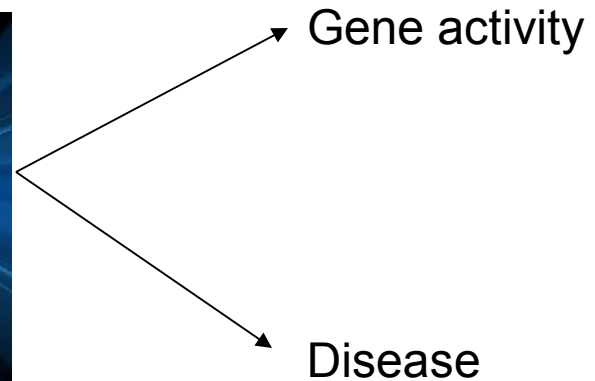
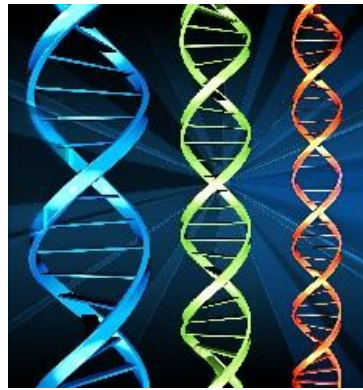
Delineation of CFS Subgroups and Implications for Intervention



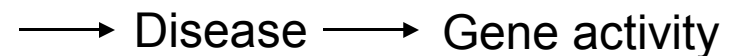
CFS is Different from Depression

- Causal models

- CFS fits an independent model

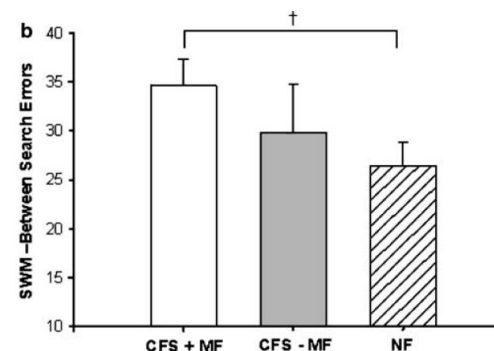
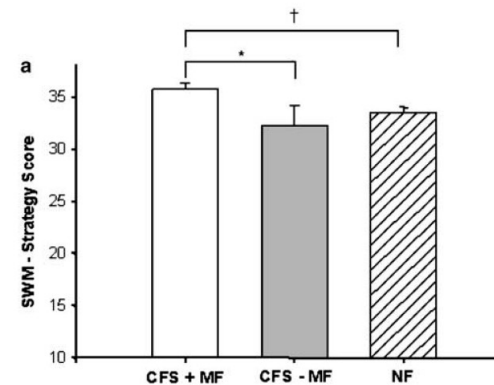
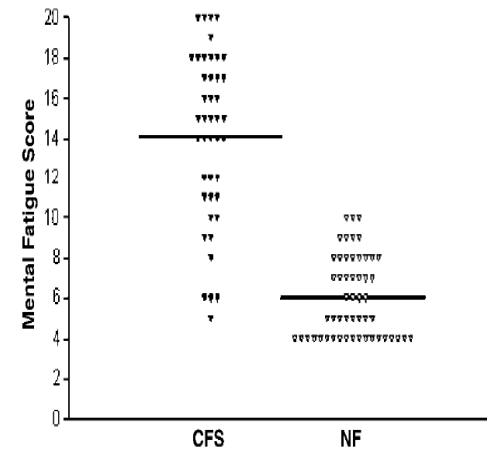


- Depression fits a reactive model

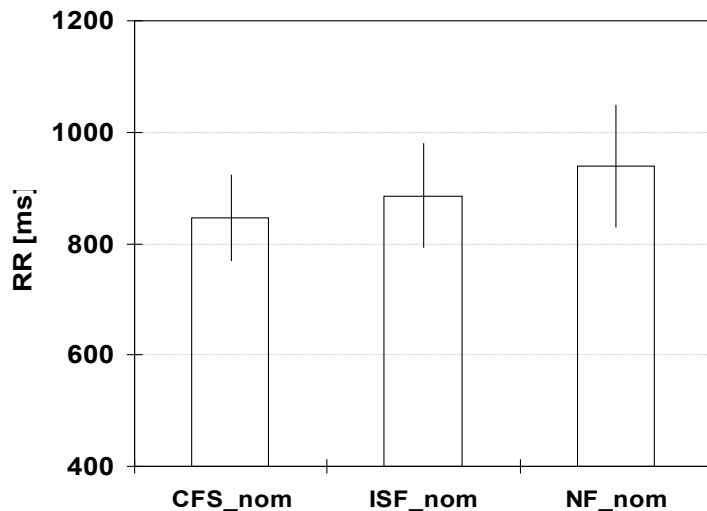
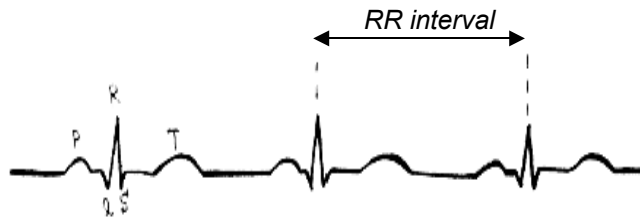


Cognitive Impairment

- The mental process of knowing, including aspects such as awareness, perception, reasoning, and judgment.
- Strong concordance between subjective complaints of mental fatigue and objective measurement of cognitive impairment in CFS patients.
 - working memory and sustained attention/vigilance
- Changes in neural circuits involving the frontal and parietal cortex as well as the thalamus and basal ganglia may constitute a primary pathway in the pathophysiology of mental fatigue and cognitive dysfunction in CFS.
- Specific to people with significant mental fatigue



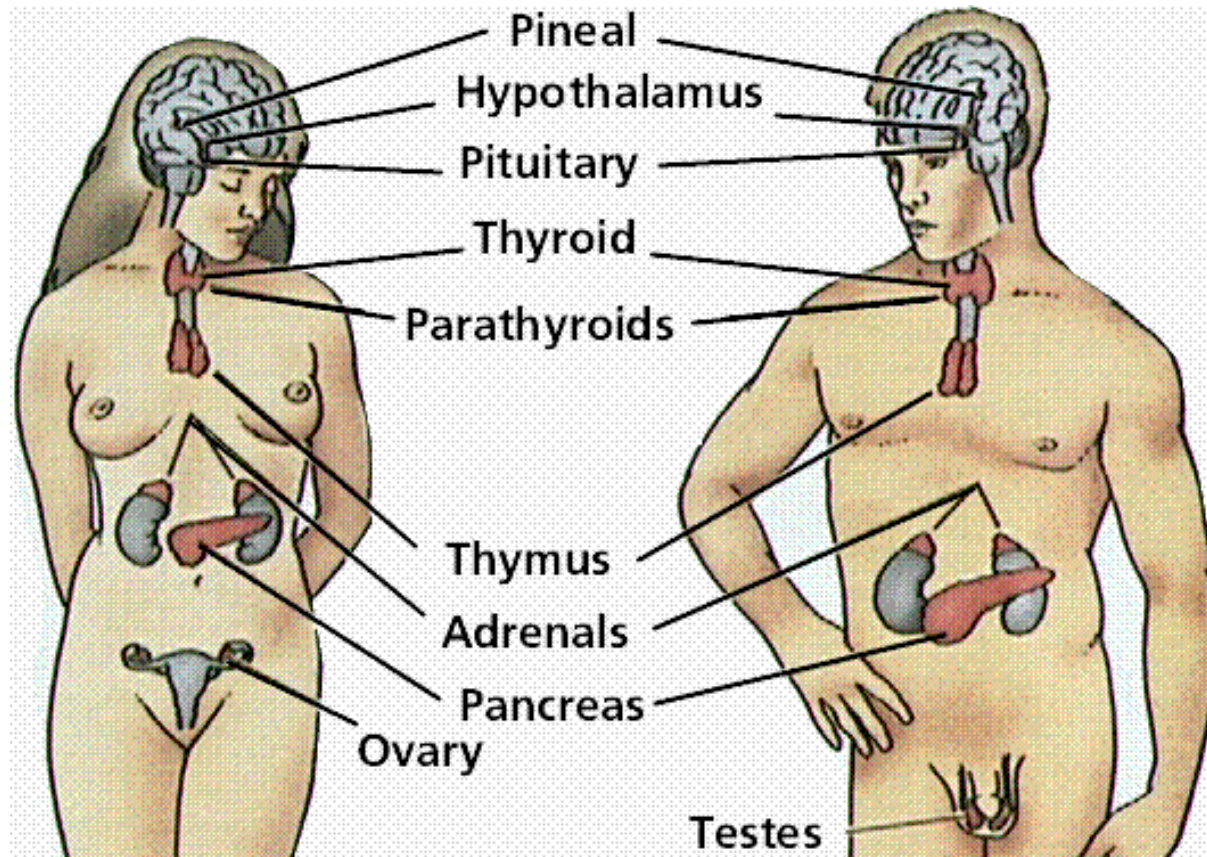
ANS Abnormalities



- Increased HR and reduced HRV in CFS during sleep coupled with higher norepinephrine levels and lower plasma aldosterone suggest sympathetic ANS predominance and neuroendocrine alterations
- CFS patients had greater increase in HR and greater drop in BP on standing compared to healthy individuals (Winkler AS 2004)
- Shorter mean RR interval (faster HR) in CFS pts vs normal sedentary controls at rest and during HUP (Yamamoto Y, 2002)
- Decreased vagal power in patients with CFS vs normal controls during exercise and rest (Cordero, 1996)
- Higher HR (shorter RR) in patients with FM compared with controls (Cohen H, 2000)
- Reduced HRV in ill Gulf War veterans compared to control veterans (Haley RW, 2004)
- Shorter RR interval and decreased HRV at rest and during HUT in CFS adolescents compared to normal controls (Stewart JM 2000)

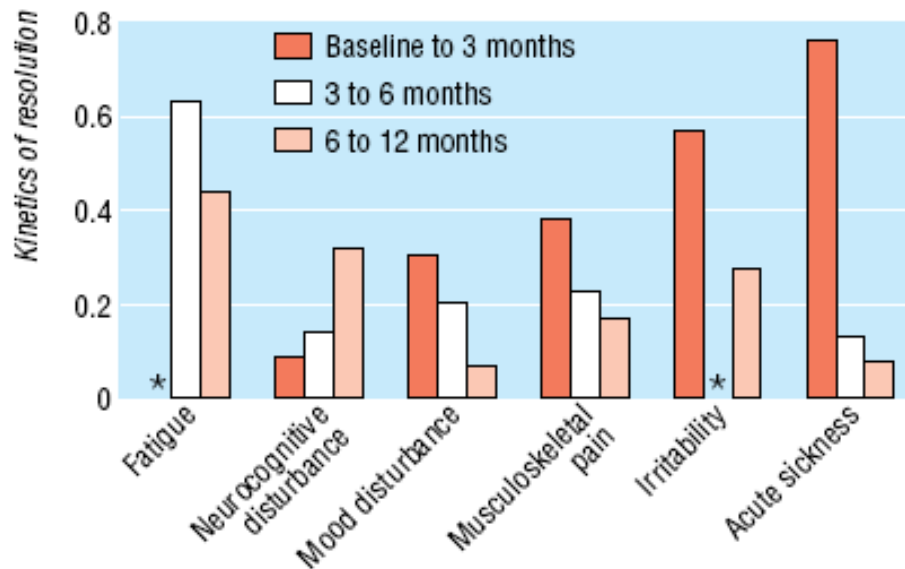
Neuroendocrine System

- This system can be thought of as the “broadcasting system” because its messenger chemical (for example, hormones) are secreted into the blood and reach the entire body
- The hypothalamic pituitary adrenal (HPA) axis - a major part of the neuroendocrine system that controls reactions to stress and regulates various body processes including digestion, the immune system, mood, sexuality and energy usage.



Infection and CFS

- What is it about the infection or the agent that can cause CFS?



What is already known on this topic

A post-infective fatigue syndrome that meets diagnostic criteria for chronic fatigue syndrome may follow Epstein-Barr virus infection but not common, minor viral infections

What this study adds

Post-infective fatigue syndrome represents a common and stereotyped outcome from several viral and non-viral infections

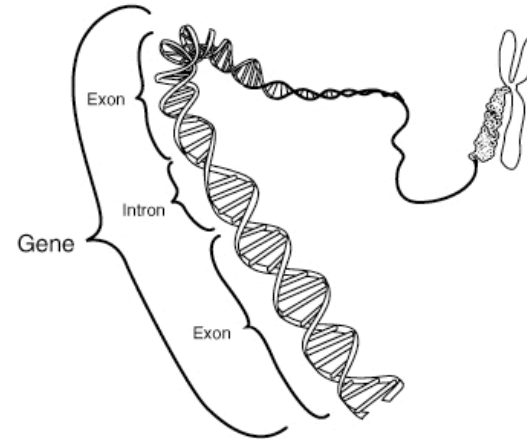
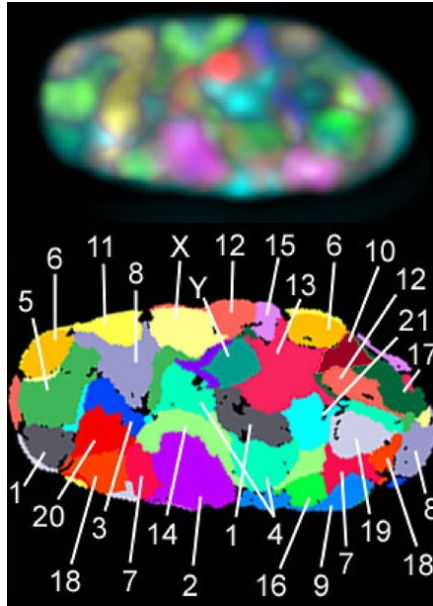
The key risk factor for post-infective fatigue syndrome is the severity of the acute illness and not age, sex, or psychological factors

Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study

Ian Hickie, Tracey Davenport, Denis Wakefield, Ute Vollmer-Conna, Barbara Cameron, Suzanne D Vernon, William C Reeves, Andrew Lloyd, for the Dubbo Infection Outcomes Study Group

BMJ. 2006 Sep 16;333(7568):575.

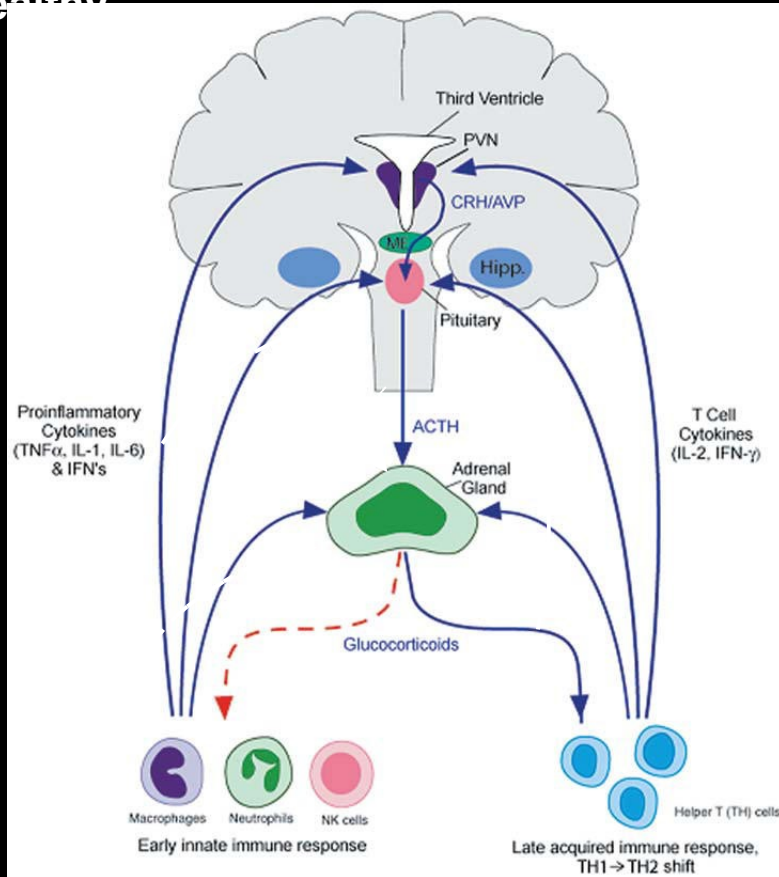
Gener och Genaktivitet



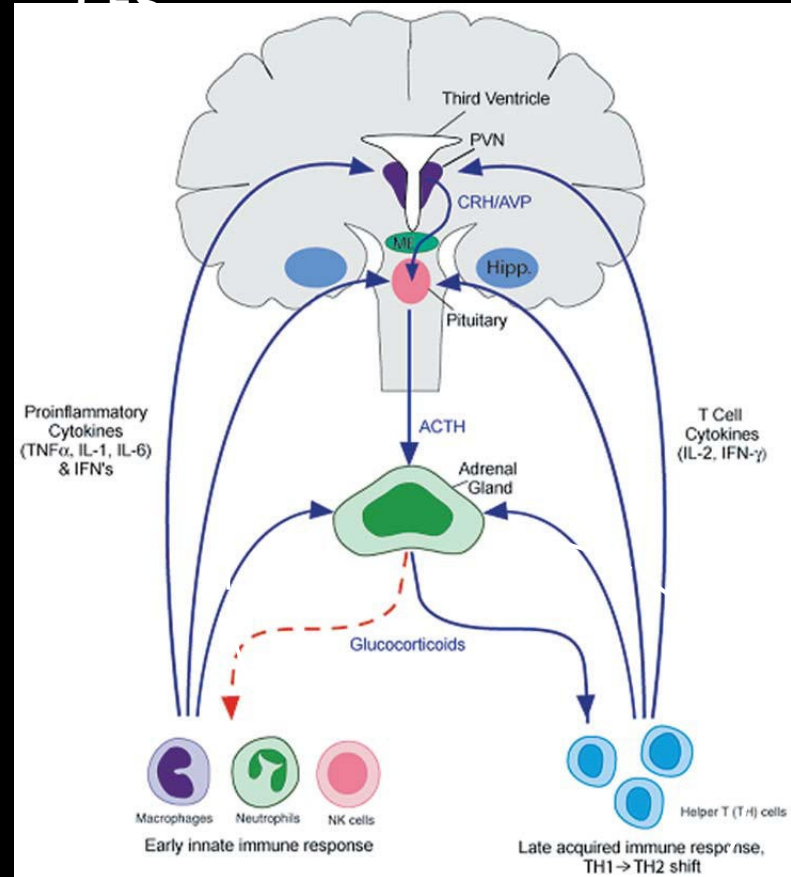
- Vår växt och utveckling och hur vi lever/mår kan ses som en effekt av hur våra gener interagerar med varandra och med omgivningen environment. Vi ärver våra gener.

Blood Brain Communication

Healthy



CES



Valcyte, HHV6 and EBV

- Valcyte (valganciclovir) is an antiviral. It was used in patients who were experiencing central nervous system dysfunction including long-standing fatigue and who appeared to have active infections with Human Herpesvirus-6 (HHV-6) and Epstein-Barr Virus (EBV)
 - Kogelnik et al, J Clin Virol. 2006 Dec;37 Suppl 1:S33-8.
- At least 75% of the patients improved after going of the 6 month treatment regimen.
 - (It is not clear if these are new infections or reactivations)

