

## OPEN BRIEF AAN DE MINISTER VAN VOLKSGEZONDHEID.

Aan Mevrouw de Minister  
Laurette Onkelinx  
Minister van Sociale zaken en Volksgezondheid  
Handelsstraat 76/80  
1040 Brussel

Brasschaat 30-10-2008

Mevrouw de Minister,

Het is nu duidelijk ook uit het rapport door de KCE (Chronisch Vermoeidheidssyndroom - CVS-: diagnose, behandeling en zorgorganisatie) dat de CVS Centra hebben gefaald in hun primaire missies. Het bleek zelfs onmogelijk om vanuit de ervaring van de CVS-referentiecentra gefundeerde wetenschappelijke richtlijnen op te stellen voor de diagnose en behandeling van CVS.

In de verslagen die nu voorliggen van uw Hoge Gezondheidsraad (nr 8338) en het KCE wordt niet vermeld dat de wetenschappelijk productie van de CVS centra die U financieel steunt verwaarloosbaar is: niet alleen werd geen enkel "landmark paper" gepubliceerd door deze CVS centra, zelfs het aantal gepubliceerde artikelen is bijzonder laag.

Niettegenstaande de royale financiering van deze Centra, zijn de klinische behandelresultaten van de CVS centra zo goed als onbestaande en is er ook geen wetenschappelijke output.

In voornoemde publicatie (nr 8338) maakt U dan aanbevelingen die feitelijk tegengesteld zijn aan de internationale state-of-the-art betreffende CVS. Zo beweert de Hoge Gezondheidsraad dat bepaalde biochemische testen vermeden moeten worden. Uw aanbeveling is om de biochemische markers van CVS vooral niet te meten (pagina 9), om patienten te behandelen met CBT (cognitieve gedragstherapie) en GET (graded exercise therapy) (pagina 11) en U vindt ook dat er geen aanwijzingen zijn om biochemische therapieën en voedingssupplementen te gebruiken (pagina 12).

Nochtans wordt in de internationale literatuur en de grote internationale CVS congressen aangetoond dat CVS een ziekte is die gepaard gaat met verschillende samenhangende biochemische en immunologische afwijkingen, die bevestigd werden door genenactiviteitsstudies.

1. Een overactief afweersysteem.
2. Persisterende ontstekingen.
3. Virale infecties bij een deel van de CVS patienten.
4. Dysfunktionele mitochondria (energiecentrales).

5. Verhoogde oxidatieve en nitrosatieve stress, resulterende in schade aan DNA, essentiële vetten, eiwitten, mitochondria, en rode bloedcellen.
6. Een verhoogde translocatie van gram-negatieve bacteria (leaky gut of lekke darm).

Er zijn verschillende publicaties in de Medline die tonen dat specifieke immunotherapieën en voedingssupplementen (die ook een biochemische en immunologisch werkingmechanisme hebben) wel nuttig zijn bij vermoeidheidstoestanden. Meer nog: zelfs “translational medicine“ experimenten hebben het nut aangetoond van specifieke voedingssupplementen bij vermoeidheid en spierpijnen. Om dit te verduidelijken heb ik een state-of-the-art review artikel toegevoegd, gebaseerd op de laatste publicaties ook van mijn hand. Het is verbazingwekkend te zien dat geen enkele van die studies ook maar vermeld wordt in het KCE verslag, noch in het verslag van de Hoge Gezondheidsraad. Uit dit en het volgende mag duidelijk worden dat U en uw instellingen die biochemische wetenschappelijke gegevens doelbewust negeren.

*Michael Maes. Inflammatory and oxidative & nitrosative stress (IO&NS) pathways underpinning chronic fatigue, somatization and psychosomatic symptoms. Invited Review: Current Opinion in Psychiatry, 2008.*

*Maes M, Mihaylova I, Leunis JC. Increased serum IgM antibodies directed against phosphatidyl inositol (Pi) in chronic fatigue syndrome (CFS) and major depression: evidence that an IgM-mediated immune response against Pi is one factor underpinning the comorbidity between both CFS and depression. Neuro Endocrinol Lett. 2007 Dec;28(6):861-7. PMID: 18063934 [PubMed - indexed for MEDLINE]*

*Maes M, Coucke F, Leunis JC. Normalization of the increased translocation of endotoxin from gram negative enterobacteria (leaky gut) is accompanied by a remission of chronic fatigue syndrome. Neuro Endocrinol Lett. 2007 Dec;28(6):739-44. PMID: 18063928 [PubMed - indexed for MEDLINE]*

*Maes M, Mihaylova I, Bosmans E. Not in the mind of neurasthenic lazybones but in the cell nucleus: patients with chronic fatigue syndrome have increased production of nuclear factor kappa beta. Neuro Endocrinol Lett. 2007 Aug;28(4):456-62. PMID: 17693979 [PubMed - indexed for MEDLINE]*

*Maes M, Mihaylova I, Kubera M, Bosmans E. Not in the mind but in the cell: increased production of cyclo-oxygenase-2 and inducible NO synthase in chronic fatigue syndrome. Neuro Endocrinol Lett. 2007 Aug;28(4):463-9. PMID: 17693978 [PubMed - indexed for MEDLINE]*

*Mihaylova I, DeRuyter M, Rummens JL, Bosmans E, Maes M. Decreased expression of CD69 in chronic fatigue syndrome in relation to inflammatory markers: evidence for a severe disorder in the early activation of T lymphocytes and natural killer cells. Neuro Endocrinol Lett. 2007 Aug;28(4):477-83. PMID: 17693977 [PubMed - indexed for MEDLINE]*

*Maes M, Mihaylova I, Leunis JC. Chronic fatigue syndrome is accompanied by an IgM-related immune response directed against neopeptides formed by oxidative or nitrosative damage to lipids and proteins. Neuro Endocrinol Lett. 2006 Oct;27(5):615-21. PMID: 17159817 [PubMed - indexed for MEDLINE]*

*Maes M, Mihaylova I, Leunis JC. Increased serum IgA and IgM against LPS of enterobacteria in chronic fatigue syndrome (CFS): indication for the involvement of gram-negative enterobacteria in the etiology of CFS and for the presence of an increased gut-intestinal permeability. J Affect Disord. 2007 Apr;99(1-3):237-40. Epub 2006 Sep 27. PMID: 17007934 [PubMed - indexed for MEDLINE]*

*Meeus M, Nijs J, McGregor N, Meeusen R, De Schutter G, Truijien S, Frémont M, Van Hoof E, De Meirleir K. Unravelling intracellular immune dysfunctions in chronic fatigue syndrome: interactions between protein kinase R activity, RNase L cleavage and elastase activity, and their clinical relevance. In Vivo. 2008 Jan-Feb;22(1):115-21. PMID: 18396793 [PubMed - indexed for MEDLINE]*

*Metzger K, Frémont M, Roelant C, De Meirleir K. Lower frequency of IL-17F sequence variant (His161Arg) in chronic fatigue syndrome patients. Biochem Biophys Res Commun. 2008 Nov 7;376(1):231-3. Epub 2008 Sep 5. PMID: 18774769 [PubMed - in process]*

Zowel in uw CVS centra als door huisartsen en door andere specialisten gebeuren voortdurend medische fouten omdat U de biochemische benaderingswijze hebt geelimineerd om plaats te maken voor de CBT benadering. Duizenden patiënten worden nog steeds door uw onthouding van publieke stellingname betreffende de biochemische oorzaken van CVS geormerkt als zijnde luiards, hypochonders, hysterica, en psychosomatische klagers ofschoon deze patiënten lijden aan ernstige, maar toch vaak te behandelen ziektebeelden. Nog steeds worden duizenden patiënten door uw onthouding van publieke stellingname betreffende de biochemische oorzaken van CVS langdurig behandeld met nonsens therapieën zoals CBT, magnesiumbaxters, rilatine, glucocorticoiden, botox behandelingen, herhaalde operaties, injecties, NSAIDs, psychoanalytische therapieën, morfine pompen, etc.

Uiteraard weerspiegelt zich dit ook in de door U benoemde instellingen, bijvoorbeeld de Werkgroep CVS van de Hoge Gezondheidsraad die is samengesteld uit mensen die internationaal weinig relevant zijn in het vakgebied. De Voorzitter van de commissie ervan heeft de laatste 8 jaar niets gepubliceerd over CVS.

Hierbij leg ik dan ook klacht neer tegen de wanpraktijken door de voornoemde CVS centra en andere geneesheren. Hierbij citeer ik enkele klachten van de tientallen die ik verzameld heb en die ik nu internationaal publiceer.

1. Specifieke klachten tegen het CVS Centrum, Universiteir Ziekenhuis, Antwerpen (UZA). Dit centrum onderzoekt een patient en schrijft magnesium voor, Lyrica en voornamelijk GET. Iets later wordt patient door mijn centrum onderzocht en wij vinden belangrijke afwijkingen in specifieke bloedanalysen:

- lage totaal carnitine en lage coenzyme Q10
- IgG3 deficiency
- verhoogde IgA
- hoge haptoglobine
- hoge orosomucoïd
- verhoogde CRP (C reactive protein)
- verhoogde peroxides
- serotonine antilichamen: positief
- IgM en IgA-gemedieerde immuunresponsen tegen LPS (de bacteriewand van gram negatieve bacteria)

Onze diagnose: Inflammatory Fatigue and Pain bij lage carnitine en CoQ10, inflammatie, oxidatie, autoimmunitet tegen serotonine en een verhoogde translocatie van gram negatieve enterobacteria en dus gut-derived-inflammation.

Een andere patient ging op raadpleging naar het CVS centrum UZA, interne geneeskunde in het kader van een follow up. Ze heeft in het centrum het volledige GET programma doorlopen en heeft zagezegd “goed inzicht” verworven in haar gezondheidsproblematiek. Er werd in dit centrum nog een omvangrijk maar helaas niet specifiek bloedonderzoek uitgevoerd.. Enkele dagen later komt patient in onze polikliniek en we kunnen de specifieke biochemische stoornissen van CVS vaststellen:

- T cell activatie
- lage acylcarnitine
- verhoogde C3 en C4 (complement factoren)
- verhoogde peroxides
- hoge interleukin-1
- verhoogde neopterine
- hoge tumor necrosis factor alpha

- serotonine antilichamen: positief
- gestoorde lactulose H2 test (SIBO)
- gestoorde fructose test

De diagnose luidt dus chronische vermoeidheid en depressie bij inductie van pro-inflammatoire cytokines en auto-immuniteit tegen serotonine en lichte oxidatie. Bovendien SIBO (small intestine bacterial overgrowth) en fructose intolerantie.

Dus het CVS centrum van het UZA stelt verkeerde diagnoses: - zij ontdekken niet de ontsteking die aanwezig is omdat zij te weinig specifieke testen gebruiken; - zij onderzoeken niet eens de gevolgen van oxidatieve stress hoewel nu bekend is dat dit een belangrijke rol speelt in de etiologie van CVS; - zij hebben niet de nodige en nuttige onderzoeken uitgevoerd, zoals bepaling van intracellulaire inflammatie, cytokines, T cell activatie, oxidatieve en nitrosatieve stress en verhoogde translocatie van gram-negatieve bacteria om de diagnose CVS te maken; - zij hebben niet eens een aanwezige depressie vastgesteld; - niettegenstaande patient lijdt aan gastro-intestinale symptomen (GIS) hebben ze deze toestand niet verder onderzocht en niet onderkent dat GIS stoornissen een rol spelen bij CVS.

Nog erger: gebaseerd op het niet onderkennen worden nutteloze therapieën uitgevoerd: - zij sturen patienten door voor CBT naar een psychiater; - zij stellen geen enkele therapie voor ter behandeling van de de GIS symptomen.

## 2. Klachten tegen het CVS Centrum, Katholieke Universiteit Leuven (KUL).

Een patient ging op de raadpleging interne geneeskunde KUL wegens aanslepende vermoeidheden dit bij mogelijke M. Crohn. Aan patiente werd door uw CVS centrum een behandeling met Rilatine voorgesteld, die gelukkig door de huisarts niet werd gevolgd. Het centrum kon geen biochemische afwijkingen vaststellen. Patient werd doorgestuurd naar de afdeling psychiatrie. De psychiaters beweren de diagnose CVS niet te kunnen stellen omdat het internistische onderzoek van het CVS centrum niet is afgerond. Zij melden erbij dat wanneer de internistische onderzoeken negatief zijn deze patient dient behandeld te worden met: geen medicatie; GET; en CBT.

Een week later liet patient zich onderzoeken in mijn polikliniek en wij vinden:

- zeer ernstige T cel activatie met toename CD38+, CD38CD4+, CD38+CD8+ en CD4+HLADR+ en CD8HLADR+ T cellen.
- verhoogde gammaglobines
- lage carnitines
- verhoogde IgG2
- positieve immuuncomplexen
- verhoogde IgG
- afwezige haptoglobine
- ANF =1/40
- lage CoQ10
- zeer hoge peroxides
- lage testosterone
- verhoogde interleukin-1
- verhoogde tumor necrosis factor alpha
- verhoogde neopterine
- serotonin antilichamen positief
- lactulose test: ernstig gestoord
- fructose test: ernstig gestoord
- verhoogde translocatie van LPS (de bacteriewand) van Hafnia Alvei (met immuunresponse)

- verhoogde IgM gemedieerde response tegen NO<sub>2</sub>-tyrosine, wijzend op een verhoogde damage door nitrosatieve stress

Onze diagnose: Inflammatory Fatigue and Pain met monocyttaire en Th1-like activatie, autoimmunitet (serotonin), oxidatieve stress en damage door nitrosatieve stress, verhoogde translocatie van gram negatieve bacteria en fructose intolerantie en mogelijk SIBO.

Dus uw CVS centrum stelt verkeerde diagnoses: - zij hebben geen ontsteking ontdekt omdat zij te weinig specifieke testen gebruiken; - zij hebben geen oxidatieve noch nitrosatieve stress ontdekt hoewel dit een belangrijke rol speelt in de etiologie van CVS; - niettegenstaande patient lijdt aan GIS symptomen en er vroeger sprake was van M. Crohn hebben zij deze toestand niet verder onderzocht en interne diagnoses gemist; - de internisten en psychiaters sturen patienten van het kastje naar de muur wat leidt tot een medische overconsumptie: de vraag is waarom de internisten patienten doorsturen naar de psychiaters als die toch geen diagnose kunnen stellen zolang de interne diagnose niet bekend is en waarom de psychiaters deze patienten ontvangen om te zeggen dat zij toch niets kunnen zeggen tenzij een gestandaardiseerd zinnetje dat de patient dient behandeld te worden met GET en CBT.

Nog erger: uw CVS centra passen verkeerde of geen therapieën toe

- zij behandelen met rilatine, een amfetamine-achtige stof, terwijl patienten lijden aan een ernstige ontstekingsziekte (van rilatine is aangetoond dat het bij jonge ratten oxidatieve beschadigingen teweegbrengt); - zij sturen patienten door voor CBT naar een psychiater; - zij stellen geen enkele therapie op ter behandeling van leaky gut die mede aan de oorzaak ligt van de ziekte.

Dus worden patienten, die eigenlijk ernstig ziek zijn, door uw nalatigheid onderworpen aan een ellenlange lijdensweg omdat ze verkeerd behandeld worden met:

1. GET - een training die ze meestal niet aankunnen en soms zelfs schadelijk is.
2. CBT - een psychologische therapie die de biochemische oorzaak van de CVS niet behandelt en die de patient stigmatiseert, namelijk "het zit tussen de oren".

Deze onethische aanpak leidt bovendien tot een overconsumptie in de gezondheidszorg.

Uw onthouding van publieke stellingname betreffende de biochemische oorzaken van CVS en uw publiekelijke afkeuring van biochemische testen en behandelingen bij CVS leiden niet enkel tot grote schade bij de tienduizenden patienten met CVS, maar ze zijn ook een vrijgeleide voor uw instellingen - zoals de commissies voor medische ethiek en de Orde der Geneesheren - om geneesheren en onderzoekers die zich bezig houden met de biochemische oorzaken van CVS te oormerken en te vervolgen.

Als voorbeeld: een ingediend project van mijn onderzoeksgroep betreffende de biochemische oorzaken van CVS werd ingediend bij de commissie voor medische ethiek van het KLINA, Brasschaat. Deze commissie valt ook onder uw bevoegdheid. Eerst dien ik te vermelden dat dit project mede tot stand gekomen was door een samenwerking met een tiental internationale Universiteiten / onderzoeksgroepen en dat ik zelf de meest gerefereerde Europese psychiater ben, wat een weerspiegeling is van de actuele belangrijkheid als onderzoeker. De psychiater die in uw commissie voor medische ethiek zetelt en dus meest zeggingskracht heeft over dit type voorstellen is Dr. J. Martens. Hij heeft nooit iets gepubliceerd. Maar binnen uw instellingen heeft hij de zeggingskracht om te beslissen over internationale programma's. De commissie voor medische ethiek van het KLINA heeft het ingediende project betreffende CVS (en depressie) irrelevant verklaard, heeft de onderzoekers (ikzelf en een tiental internationale top-groepen) inadequaar verklaard, heeft de instellingen waar het onderzoek

uitgevoerd wordt (een 4-tal top-laboratoria en onderzoekscentra in de wereld) inadequaar verklaard en uiteindelijk het project onethisch verklaard. Dus uw publiekelijke afkeur van biochemische testen en behandelingen voor CVS leiden ertoe dat uw instellingen internationaal onderzoek tegenwerken en aldus verbieden.

Uw publiekelijke afkeur van de biochemische testen en behandelingen bij CVS leiden bovendien tot ingrijpen door uw andere instelling, de Orde der Geneesheren. Ook zij tonen een onthouding van publieke stellingname betreffende de biochemische oorzaken van CVS hetgeen o.m. blijkt uit de afwezigheid op het internationaal symposium dd. 03.05.07 ondanks herhaalde uitnodiging daartoe vanwege Prof. Dr. M. Maes.

Bovendien seponeert deze instelling alle klachten die worden ingediend tegen de wanpraktijken aan de CVS centra en andere geneesheren bij de behandeling van CVS, waardoor U en de Orde der Geneesheren medische fouten op grote schaal toelaten en het lijden van de patienten laat voortduren. Nochtans plegen uw CVS centra - zoals hierboven uiteengezet - de volgende inbreuken op de medische codeleer:

Art. 34. Zowel voor het stellen van een diagnose als voor het instellen en voortzetten van de behandeling, verbindt de geneesheer er zich toe zijn patiënt zorgvuldig en gewetensvol de zorgen toe te dienen die stroken met de thans geldende wetenschappelijke kennis.

Art. 3. De uitoefening van de geneeskunde is een bij uitstek menslievende opdracht; de geneesheer waakt in alle omstandigheden over de gezondheid van de enkeling en van de gemeenschap.

Art. 4. Om zijn patiënt met de beste zorgen te kunnen omringen, moet de geneesheer zich op de hoogte houden van de vooruitgang van de geneeskundige wetenschap.

Art 35. De geneesheer mag zijn bevoegdheid niet overschrijden. Hij moet het advies inwinnen van confraters, onder meer van specialisten, hetzij op eigen initiatief, hetzij op verzoek van de patiënt, telkens wanneer dit binnen de diagnostische of therapeutische context nuttig of noodzakelijk blijkt.

Art. 37. De geneesheer zet zich in om elke vorm van afhankelijkheid te voorkomen. Hij wijst de patiënt onder meer op het verkeerd gebruik en het misbruik van substanties die tot afhankelijkheid kunnen leiden evenals op de risico's bij langdurig gebruik ervan.

Indien de behandeling van de patiënt een bekwaamheid vergt die de geneesheer onvoldoende bezit doet deze een beroep op een bevoegde collega of een bevoegd multidisciplinair team.

Deze instelling veroordeelt internationale specialisten op het gebied van de biochemische aanpak van CVS (en aanverwante ziekten zoals depressie en fibromyalgie) wegens niet kwaliteitsvolle geneeskunde. Meer nog: uw instellingen veroordelen nieuwe ontdekkingen en behandelingen die gepubliceerd zijn in internationale tijdschriften. De redenen van de veroordelingen uitgesproken door uw instelling zijn verbazingwekkend. a) Ik, de uitvinder van deze nieuwe oorzaak van CVS ("lekke darm" in de volksmond) wordt veroordeeld omdat ik de patienten zelf diagnosticeer en behandel voor lekke darm (zoals door mij als eerste gepubliceerd in internationale tijdschriften) terwijl U en uw Orde weten dat ik de patienten eigenlijk niet mag behandelen maar moet doorsturen naar de specialisten ter zake. Wie deze specialisten zijn mag Joost weten: immers zoals boven aangetoond wordt deze biochemische oorzaak van CVS niet erkent noch herkent door deze "specialisten". b) Blijkbaar is ook het gebruik van de test die mijn onderzoeksgroep heeft uitgevonden een strafbaar feit geworden. Namelijk uw Orde weet dat ik een andere test dien te gebruiken om aan te tonen wat wij uitgevonden hebben. c) Ook de biochemische testen die wij gebruiken en die we gepubliceerd hebben als state-of-the-art zijn nu strafbaar geworden. d) Ook de therapieen die we vaak met succes uitvoeren bij onze patienten en die gebaseerd zijn op wetenschappelijke literatuur en die gepubliceerd werden zijn nu strafbaar. Immers U en uw instelling weten dat noch het

gebruik van biochemische testen noch de biochemische behandelingen “in overeenstemming zijn met een kwaliteitsvolle geneeskunde, waarbij de menselijke naïviteit wordt misbruikt in een geest van mercantilisme en aanzet tot medische overconsumptie”.

Niettegenstaande het arrest 5-6-2008 Dr Thierry Hertoge dat de Orde der Geneesheren geen oordeel kan vellen over de wetenschappelijkheid van behandelingen worden de biochemische behandelwijzen van CVS toch door U veroordeeld. U onthoudt hierbij tien-duizenden patienten van een adequate diagnosestelling en behandeling waarbij U dictatoriaal uw wil aan het hele Belgische (bij generalisatie) bevolking wil opleggen dat enkel CBT en GET nuttig zijn. U bent hierbij verregaand onethisch omdat U en uw instelling inbreuken pleegt tegen art 36 van uw eigen codeleer, namelijk de geneesheer beschikt over de diagnostische en therapeutische vrijheid. Ook gaat U en uw Orde in tegen de geneeskundige codeleer dat de patiënt de genezing daar mag zoeken waar hij wil. Hier dient vermeld dat de patienten vrijwillig en in grote aantallen naar mijn centrum komen voor een “bloedcontrole i.v.m. tekorten en of overgevoeligheden die uw klassieke centra niet erkennen en een goede biochemische aanpak en behandeling omdat uw klassieke centra geen raad meer weten.”

Dus internationaal erkend onderzoek van wetenschappers en geneesheren die biochemisch werken en dus niet aan uw CVS centra zijn verbonden, wordt niet alleen niet financieel ondersteund, het wordt stilgezwegen, het wordt gericht tegengewerkt, om uiteindelijk te worden veroordeeld en vervolgd. We zijn hiermee in een gevaarlijke middeleeuwse toestand terechtgekomen waarbij U, de minister van volksgezondheid, onderzoek en succesvolle behandelmethoden verbiedt omdat ze niet in de GET - CBT strategie passen die u hebt gemaakt. Dit is een terugkeer naar Galileo Galilei.

Tijdens de onderzoeken van uw instelling, de Orde, zijn er voortdurend inbreuken op het Europees Verdrag Rechten van de Mens (EVRM), met intimidaties waarbij uw magistraten het recht van verdediging niet respecteren en waarbij uw magistraten en medische ordeleden doelbewust verkeerde informatie laten opschrijven en zelf schrijven in de verslagen waarbij uw Ordeleden dus valsheid in geschrifte plegen. Hierbij worden ook nieuwe overtredingen gefabriceerd. Een voorbeeld: de zogenaamde medische overconsumptie wordt ook bewezen geacht door uw Orde omdat mijn kliniek de patienten zou verplichten HIV testen te ondergaan, terwijl cijfers tonen dat mijn kliniek op 1442 bloedonderzoeken slechts 11 HIV testen heeft uitgevoerd enkel op vraag van de patient. Uw Orde pleegt bij haar werkwijze voortdurend inbreuken op de IVBPR art 14, nml 14.1, 14.2, 14.3 lid b, c, d, e, en g; en op de EVRM art 6, nml art 6.1, 6.2 en 6.3.

Bovendien, zijn de door U aangestelde kernleden van de Orde der Geneesheren notoire tegenstanders van de biochemische benadering van CVS. Een voorbeeld is P.Cosyns. Hij is de enige hoogleraar psychiatrie binnen de Orde te Antwerpen en ex-voorzitter van de Orde te Antwerpen, gewoon lid van de Orde te Antwerpen en plaatsvervangend lid binnen de Nationale Orde. Hij wordt veelvuldig gevraagd als expert bij CVS patienten. Dit palmares laat veronderstellen dat hij de deskundige en de meest prominente figuur is binnen de Orde zeker wanneer problemen voorkomen binnen het vakgebied psychiatrie en CVS.

Wanneer patienten met CVS naar hem gestuurd worden voor expertisen wordt een uitgebreide batterij psychologische testen gebruikt om het probleem te “psychologiseren”. De state-of-the-art biochemische testen om de ware oorzaak van CVS vast te stellen worden niet uitgevoerd.

Deze hoogleraar heeft zijn hele carrière inbreuken gepleegd tegen de good publication practice en heeft dus voortdurend intellectuele oneerlijkheid (“intellectual dishonesty”)

getoond. Volgens de COPE richtlijnen wordt “authorship” in wetenschappelijke artikelen duidelijk gedefinieerd: zie pagina 70, punt 3.1. (The award of authorship should balance intellectual contributions to the conception, design, analysis and writing of the study against the collection of data and other routine work. If there is no task that can reasonably be attributed to a particular individual, then that individual should not be credited with authorship). In de periode dat ik als assistent voor P.Cosyns werkzaam was en ook erna en ook ten opzichte van andere collega's, heeft P.Cosyns zichzelf opgedrongen als eerste auteur op artikelen waar hij geen enkele contributie heeft aan geleverd. Een voorbeeld:

*Cosyns P, Maes M, Vandewoude M, Stevens WJ, De Clerck LS, Schotte C. Impaired mitogen-induced lymphocyte responses and the hypothalamic-pituitary-adrenal axis in depressive disorders. J Affect Disord. 1989 Jan-Feb;16(1):41-8. PMID: 2521650 [PubMed - indexed for MEDLINE].* P.Cosyns heeft ook ge-eist dat zijn naam op iedere publicatie bijgezet zou worden zonder dat hij ook maar de minste participatie had gehad in dit type onderzoek waar hij ten andere niets van begrijpt. Voorbeelden zijn:

*Maes M, Vandewoude M, Schotte C, Cosyns P. Results of the 8 a.m. dexamethasone suppression test constitute a suitable tool for confirming the diagnosis of melancholia. A test unaffected by the variations in the bioavailability of dexamethasone. Neuropsychobiology. 1989;22(1):26-32. PMID: 2639285 [PubMed - indexed for MEDLINE]*

*Maes M, Vandewoude M, Maes L, Schotte C, Cosyns P. A revised interpretation of the TRH test results in female depressed patients. Part I: TSH responses. Effects of severity of illness, thyroid hormones, monoamines, age, sex hormonal, corticosteroid and nutritional state. J Affect Disord. 1989 Mar-Jun;16(2-3):203-13. PMID: 2522120 [PubMed - indexed for MEDLINE]*

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*Maes M, Maes L, Schotte C, Vandewoude M, Martin M, D'Hondt P, Blockx P, Scharpé S, Cosyns P. Clinical subtypes of unipolar depression: Part III. Quantitative differences in various biological markers between the cluster-analytically generated nonvital and vital depression classes. Psychiatry Res. 1990 Oct;34(1):59-75. PMID: 2176296 [PubMed - indexed for MEDLINE]* en nog enkele tientallen meer (zie medline).

P.Cosyns heeft dus onderzoek door wetenschappers uitgevoerd naar zich toe getrokken. P.Cosyns heeft dus zijn CV opgebouwd door het zich toe-eigenen van andermans werk nadat hij een politieke benoeming (loge) als hoogleraar had verworven, zonder een thesis gemaakt te hebben. Dit soort “onethische” mensen laat U dus beslissen over wat kwaliteitsvolle geneeskunde is en wat niet en gebruikt U als rechters om de nieuwe biochemische ontwikkelingen binnen het vakgebied psychiatrie (CVS e.a.) tegen te gaan.

Bovendien bestrijdt U en de leden van de Orde der Geneesheren mijn concurrentiële positie in het voordeel van uw CVS en universitaire centra en de actief-participerende leden van de Orde der Geneesheren.

Tot slot, zijn er vragen bij de grondwettelijkheid van alle instellingen en commissies die U mobiliseert om de biochemische benadering van CVS te fnuiken en onderzoekers en behandelaars die niet in uw kraam passen het zwijgen op te leggen. Immers KB78 (over de geneeskunst) en KB79 (de Orde der Geneesheren) werden in 1967 vervalst. U hebt zelf moeten toegeven in de commissie Volksgezondheid dat de versies van de KB's 78 en 79 die in ministerraad werden overlegd niet overeenstemmen met de versies zoals gepubliceerd in

het Belgisch Staatsblad en die thans nog steeds worden toegepast. U werd op de gevolgen gewezen van het gebruik van deze vervalste KB's door de heer Coveliers in de plenaire vergadering van de senaat van 23-10-2008. Dus éénieder die gebruik maakt van voormelde KB's, wetende dat ze het resultaat en voorwerp zijn van valsheid in openbare geschriften, stelt zich eveneens bloot aan strafrechtelijke vervolging.

In conclusie: ik leg klacht neer tegen U

1. Wegens uw onthouding van publieke stellingname betreffende de biochemische oorzaken van CVS;
2. Wegens uw publiekelijke afkeur van biochemische testen en behandelingen van CVS;
3. Wegens het feit dat U internationaal biochemisch onderzoek van Vlaamse onderzoekers op het gebied van CVS niet alleen verzwijgt, maar zelfs verbiedt waardoor U met voorbedachte rade de onderzoeksresultaten i.v.m. CVS manipuleert;
4. Omdat U de nieuwe ontdekkingen en succesvolle behandelingen die internationaal zijn gepubliceerd als niet kwaliteitsvol oormerkt en laat vervolgen om uiteindelijk te verbieden;
5. Omdat uw instellingen bij deze onrechtmatige vervolgingen valsheid in geschrifte plegen en inbreuken verrichten tegen de rechten van de verdediging en het EVRM en IVBPR;
6. Omdat U in al de instellingen voornamelijk mensen positioneert die weinig of geen kennis ter zake hebben en/of onethisch zijn;
7. Omdat U bij al deze onrechtmatige daden gebruik maakt van KBs die vervalst zijn, waarvoor U strafbaar bent.

Deze klachtenbrief wordt ook gestuurd naar de World Health Organization (WHO), de National Institute of Health, Bethesda, USA en de Europese Commissie. Ik zal de tekst ook publiceren in een internationaal tijdschrift zodat de internationale wetenschappelijke wereld op de hoogte wordt gebracht van de middeleeuwse toestand in dit koninkrijk.

Ik geef U twee weken om mij afdoende oplossingen te geven op al deze punten, bij gebreke waarvan ik U zal dagvaarden voor de daden hierboven vermeld.

Met bijzondere hoogachting,

Michael Maes, M.D., Ph.D.  
Olmenaar 9  
2610 Wilrijk  
[www.michaelmaes.com](http://www.michaelmaes.com)

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# Inflammatory and oxidative and nitrosative stress pathways underpinning chronic fatigue, somatization and psychosomatic symptoms

Michael Maes

From the Clinical Research Centre of mental Health (CRC-MH), Antwerp, Belgium

Correspondence to Prof Dr M. Maes, MD, PhD  
Director, M-Care4U Outpatient Clinics Olmenlaan 9,  
2610 Antwerp, Belgium  
Tel: +32 3 4809282; fax: +32 3 2889185;  
e-mail: www.michaelmaes.com, crc.mh@telenet.be

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## Purpose of review

The aim of this paper is to review recent findings on inflammatory and oxidative and nitrosative stress (IO&NS) pathways in chronic fatigue and somatization disorder.

## Recent findings

Activation of IO&NS pathways are the key phenomena underpinning chronic fatigue syndrome (CFS): intracellular inflammation, with an increased production of nuclear factor kappa beta (NF $\kappa$ β), cyclo-oxygenase-2 (COX-2) and inducible NO synthase (iNOS); and damage caused by O&NS to membrane fatty acids and functional proteins. These IO&NS pathways are induced by a number of trigger factors, for example psychological stress, strenuous exercise, viral infections and an increased translocation of LPS from gram-bacteria (leaky gut). The 'psychosomatic' symptoms experienced by CFS patients are caused by intracellular inflammation (aches and pain, muscular tension, fatigue, irritability, sadness, and the subjective feeling of infection); damage caused by O&NS (aches and pain, muscular tension and fatigue); and gut-derived inflammation (complaints of irritable bowel). Inflammatory pathways (monocytic activation) are also detected in somatizing disorder.

## Summary

'Functional' symptoms, as occurring in CFS and somatization, have a genuine organic cause, that is activation of peripheral and central IO&NS pathways and gut-derived inflammation. The development of new drugs, aimed at treating those disorders, should target these IO&NS pathways.

## Keywords

chronic fatigue syndrome, cytokines, inflammation, leaky gut, somatization

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## Introduction

Chronic fatigue syndrome (CFS) is a medically unexplained disease [1]. The diagnostic criteria were defined in 1988 and revised in 1994 [1]: the patient must have self-reported severe chronic fatigue lasting 6 months or longer with all other medical conditions being excluded; four or more of the following symptoms should be present: substantial impairment in short-term memory or concentration; sore throat; tender cervical and axillary lymph nodes; muscle pain; multijoint pain without swelling or redness; headache of new type; unrefreshing sleep; and postexertion malaise lasting more than 24 h. The symptoms must have persisted or recurred during 6 or more consecutive months of illness and must not have predated the fatigue. Other symptoms that frequently occur in CFS are muscular tensions, concentration difficulties, failing memory, irritability, sadness, sleep disturbances,

autonomic disturbances, irritable bowel, headache and subjective experience of infection [2].

Although the diagnostic criteria are well defined, many general practitioners and specialists still miss and dismiss the diagnosis. They consider that those patients experience somatizing, hypochondriasis or conversion symptoms (hysteria). Somatizing or somatiform disorder (Briquet's syndrome) occurs when a person has physical complaints referable to practically all organs in the body and which cannot be attributed to a medical illness or condition [3]. Hypochondriasis occurs when a patient is convinced that the physical complaints they suffer from are signs of a medical disorder [3]. Conversion (hysteria) occurs when a patient presents neurological symptoms without any objective neurological explanation for the symptoms [3]. Those psychiatric diagnoses are based on old and unscientific Freudian theories that intrapsychic

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conflicts, fear or other psychological difficulties may be converted into 'functional' physical complaints. In many countries, those patients are then referred to a psychiatrist or psychologist to undergo the mainstream treatment for those conditions, that is psychodynamic therapies or cognitive behavioral therapy. This means that patients with severe medical disorders are sometimes treated as having a mental illness with 'a nonsense treatment' that does not treat the underlying cause.

Martin *et al.* [4\*\*] described that there is a substantial overlap between CFS and somatizing disorder. Thus, 72% of the subjects with chronic fatigue fulfill the criterion for somatization syndrome. Lane *et al.* [5] found that CFS patients are more likely to suffer from somatization disorder and more often attribute their illness to a physical cause than fatigued controls. Many patients with CFS also experience 'functional' symptoms, which are not part of the diagnostic criteria of CFS. This substantial clinical overlap between chronic fatigue and somatization syndrome supports the hypothesis that both syndromes may be different manifestations of the same underlying processes [4\*\*]. In this paper we will review that chronic fatigue and somatization are manifestations of activated inflammatory and oxidative and nitrosative stress (IO&NS) pathways.

### Vegetative symptoms, depression and inflammation

The first inkling that inflammation may induce 'psychosomatic' symptoms came from research in depression [6,7], when it was found that there is a strong correlation between inflammation and the 'psychosomatic' symptoms of depression. In depression, there is a strong correlation between inflammation (as indicated by increased haptoglobin plasma levels) and the 'vegetative' symptoms of depression, for example anorexia or weight loss, sleep disorders (middle insomnia), psychomotor retardation and loss of interest [6,7]. Systemic inflammation causes a central neuroinflammation with increased levels of proinflammatory cytokines, which may remain elevated for several months [8\*]. In humans, cytokine-based immunotherapy may induce depression in up to 70% of all patients treated for cancer or hepatitis C [9]. An increased production of proinflammatory cytokines, such as interleukin-1 $\beta$  (IL-1 $\beta$ ), IL-6 and tumor necrosis factor- $\alpha$  (TNF $\alpha$ ), either peripherally or centrally may induce specific symptoms, labeled sickness behavior. The latter includes anorexia, soporific effects, disturbances of locomotor activity and exploration, and anhedonia [8\*]. As explained previously, there is a strong similarity between the vegetative symptoms of depression and inflammation-induced sickness behavior [6]. The above findings suggest that the inflammation in depression, which is characterized by increased levels of IL-1 $\beta$ , IL-6 and TNF $\alpha$ , may have caused the occurrence of the 'vegetative or psychosomatic symptoms' of depression [6]. Since these first papers published in the

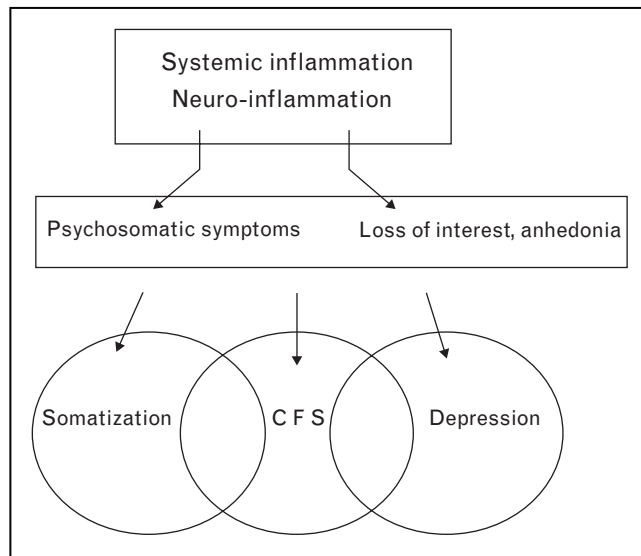
early nineties by Maes *et al.* more evidence has been reported that inflammatory responses may induce the vegetative symptoms of depression and anhedonia as well [7].

### Inflammation, chronic fatigue syndrome and somatization

In CFS, a low-grade inflammatory response has been observed. The findings comprise perturbations in proinflammatory cytokines; an acute phase response as indicated by increased serum  $\alpha$ -2 protein fractions and lowered serum zinc; an increased expression of activation markers; and reduced ex-vivo lymphoproliferative tests [10,11\*]. Cytokine-based immunotherapy (with IFN $\alpha$ ) in patients infected with the hepatitis-C virus (HCV) induces two overlapping syndromes fatigue and somatic symptoms, including pain, appearing early after starting treatment; and depressive symptoms, occurring some weeks later [12,13]. The degree of fatigue 1 week after starting cytokine treatment predicts the severity of depression [12]. The fatigue and the 'psychosomatic' symptoms are relatively refractory to antidepressants, whereas depression-specific symptoms respond well to serotonergic antidepressants [13]. In rats, immunologically induced fatigue by intraperitoneal injections of a synthetic double-stranded RNA, polyribinosinic:polyribocytidylic acid (poly I:C) induces profound fatigue, which is characterized by increased IFN $\alpha$  and serotonergic alterations in the brain [14]. Bull *et al.* [15\*] found that the 'low IL-6' synthesizing genotype together with the 'high transcription' serotonin transporter (5-HTT) genotype (LL) confer resistance to the development of cytokine-induced depression, but not to the development of cytokine-induced fatigue. These findings suggest that inflammatory pathways underpin both fatigue and depression, but that the latter is also related to disturbances in other systems, for example the serotonergic system.

The first paper showing that there is a connection between inflammation and somatization is published in 2001 [16]. These authors reported immune alterations in somatizing syndrome, that is monocytic activation and lowered activity of some T-lymphocytic functions. Monocytic activation is demonstrated by increased serum concentrations of the IL-1-receptor antagonist (IL-1RA). The same authors found that plasma L-tryptophan is lower in patients with somatoform symptoms, even when no depression was present [17]. Also these findings may point toward an acute phase or inflammatory response in somatoform disorders. Indeed, the catabolism of tryptophan is enhanced by proinflammatory cytokines, for example IFN $\gamma$  and IFN $\alpha$ , which induce indoleamine 2,3-dioxygenase (IDO), the enzyme that converts tryptophan into TRYCATs (tryptophan catabolites along the IDO pathway), for example kynurenine [18]. A case

**Figure 1** This figure shows that peripheral inflammation may induce a central neuroinflammation with increased levels of proinflammatory cytokines, which together may cause 'psychosomatic' and depressive symptoms and, consequently, clinical syndromes, for example, chronic fatigue syndrome (CFS), depression and somatiform disorder



report shows that IFN $\alpha$ -based immunotherapy in a 26-year-old female suffering from HCV infection causes somatization and that after discontinuation of IFN $\alpha$ -treatment, a gradual clinical stabilization could be obtained [19]. In a large group of HCV patients not receiving antiviral therapy significantly elevated depression, anxiety and somatization scores are found [20]. These results indicate that inflammation is accompanied by increased somatization and that infections and cytokine-induced inflammation increase somatization.

Figure 1 shows that inflammation may induce psychosomatic and depressive symptoms and, consequently, can induce clinical syndromes, for example CFS, depression and somatiform disorder.

#### **Oxidative and nitrosative stress and damage due to oxidative and nitrosative stress in chronic fatigue syndrome**

Following inflammatory stimuli, the production of oxygen radicals is increased with an increased production of H<sub>2</sub>O<sub>2</sub> (peroxides) and 2O<sub>2</sub><sup>-</sup> (superoxide). Likewise, there is evidence for increased oxidative stress in CFS: higher LDL thiobarbituric acid reactive substances (TBARS); increased isoprostane levels and oxidized low-density lipoproteins (LDL); and elevated protein carbonyl levels [21,22<sup>\*\*</sup>]. There are also reports that CFS is accompanied by a decreased antioxidant status, as indicated by lower serum levels of zinc, a strong antioxidant; and lowered

plasma levels of dehydroepiandrosterone-sulfate, a hormone with strong antioxidant properties [21,22<sup>\*\*</sup>].

There is now evidence for damage caused by oxidative stress in CFS. Thus, the serum IgM antibodies to fatty acids, that is oleic, palmitic, myristic acid and phosphatidyl-inositol (Pi) and azelaic acid and malondialdehyde (MDA), which are by-products of lipid peroxidation, are significantly greater in CFS patients than in normal controls [21]. This shows that CFS is characterized by an IgM-related immune response directed against disrupted lipid membrane components and by-products of lipid peroxidation, which are normally not detected by the immune system but due to oxidative damage have become immunogenic. In another study, statistically significant increases in MDA and methemoglobin (metHb), both indicating increased oxidative damage to the RBC membrane and hemoglobin; and 2,3-diphosphoglyceric acid (2,3-DPG) in the red blood cells of CFS patients are detected [23<sup>\*\*</sup>]. The membrane function of the RBC is regulated by 2,3-DPG, whereby increased 2,3-DPG may increase erythrocyte fragility [23<sup>\*\*</sup>]. The increased 2,3-DPG levels in CFS are regarded as a mechanism to compensate the reduced oxygen delivery to the tissues. Thus, the oxidative damage in CFS may have functional consequences: disorders in Pi may have biological effects by interfering with intracellular signaling processes, and the damage to membrane fatty acids may render the peroxydized membrane bilayer more rigid, thus inducing changes in different membrane (including receptor) functions.

The damage following oxidative stress is probably a causal factor in the muscle fatigue and pain and the postexertional malaise in CFS. The serum IgM levels directed against fatty acids, MDA and azelaic acid are significantly related to symptoms, such as aches and pain, muscular tension and fatigue [21]. Jammes *et al.* [24] report that in CFS the response to incremental exercise associates increased oxidative stress with marked alterations of muscle membrane excitability. Administration of *N*-acetyl-cysteine, a strong antioxidant that supports glutathione homeostasis, delays muscle fatigue in exercising humans (repetitive handgrip exercise) [25]. In hemodialysis and cancer patients, supplementation with carnitine reduces chronic inflammation and oxidative stress thereby reducing fatigue [26]. The presence of specific critical points in the muscle that are affected by free radicals points toward the possible role of skeletal muscle oxidative imbalance in the genesis of CFS [27<sup>\*</sup>]. Using classical projection methods, illness parameters in fatigue were identified as being related to basic cellular processes involved in cell signaling, ion transport and immune system function. The single most influential gene was sestrin 1 (SESN1) [28]. Sesn1 is a cysteine sulfinyl reductase that modulates peroxide signaling and

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antioxidant defenses, and reductions in its expression lower the antioxidant firewall against overoxidation [29].

Inflammation is also accompanied by nitrosative stress whereby nitrogen monoxide and peroxynitrite ( $\text{ONOO}^-$ ) are formed by activated neutrophils and monocytes. Nitration may cause chemical modifications of proteins with the formation of strongly immunogenic compounds, for example nitro-tyrosine [21]. CFS is accompanied by increased IgM antibody titers directed against nitrogen monoxide derivatives, such as nitro-tyrosine, nitro-phenyl-alanine, nitro-arginine, nitro-tryptophan and nitro-cysteine [21] and nitrogen monoxide-bovine serum albumin [30<sup>\*</sup>]. These findings show that CFS is characterized by an IgM-mediated immune response directed against proteins modified by nitrogen monoxide and peroxynitrite. This indicates that the natural structures of otherwise ubiquitous proteins are modified by nitrosative stress; this process is accompanied by the formation of neoepitopes (new epitopes) that eventually cause an IgM-mediated immune response [30<sup>\*</sup>].

##### **Intracellular inflammation in chronic fatigue syndrome**

One factor explaining IO&NS activation in CFS is the increased production of nuclear factor kappa beta ( $\text{NF}\kappa\beta$ ).  $\text{NF}\kappa\beta$  is the major upstream mechanism that regulates the IO&NS pathways [31<sup>\*\*</sup>]. Once activated  $\text{NF}\kappa\beta$  is translocated from the cytoplasm to the nucleus and binds DNA promoter sequences to induce the IO&NS pathways, for example the transcriptional activation of inflammatory mediators, such as IL-1 $\beta$ , IL-6, and TNF $\alpha$ ; and IO&NS mediators, such as cyclo-oxygenase-2 (COX-2) and inducible NO synthase (iNOS) [32]. COX-2 is a key enzyme that catalyzes the transformation of arachidonic acid to prostaglandins. The latter modulate pain, inflammation and smooth muscle contraction [32]. iNOS is localized in the macrophages and when stimulated it generates nitrogen monoxide. The latter is a major signaling molecule in neurons and in the immune system and is central to the immune responses by macrophages to invading microorganisms [32]. Nitrogen monoxide can combine with superoxide anions ( $\text{O}_2^-$ ) to form peroxynitrite ( $\text{ONOO}^-$ ), a toxic, oxidizing free radical that can cause nitration, DNA fragmentation and lipid oxidation [32].

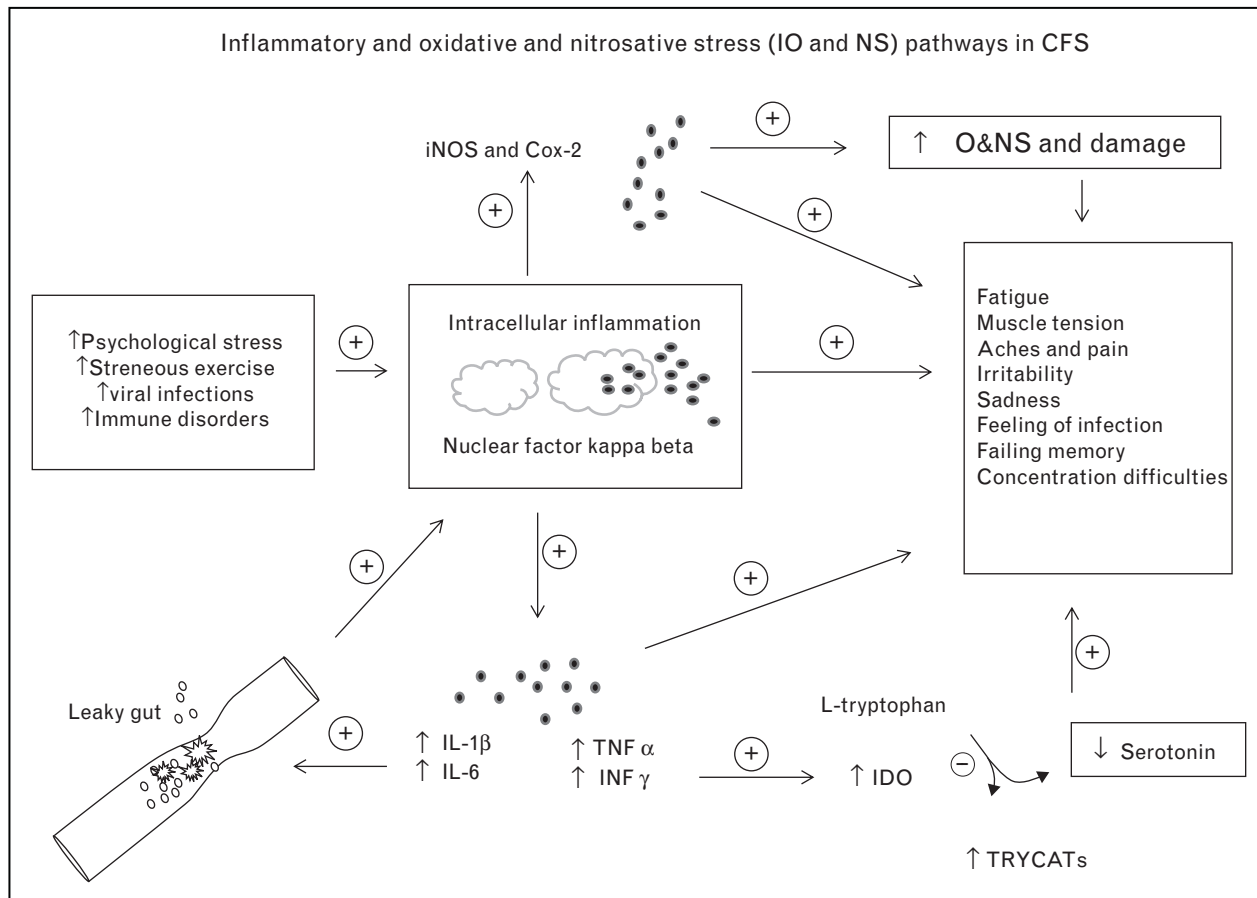
CFS is characterized by an increased production of  $\text{NF}\kappa\beta$  p50 in unstimulated, and in 10 ng/ml TNF- $\alpha$  (tumor necrosis factor alpha) and 50 ng/ml PMA (phorbolmyristate acetate) stimulated peripheral blood lymphocytes [31<sup>\*\*</sup>]. The increased production of  $\text{NF}\kappa\beta$  is significantly related to symptoms, such as aches and pain, muscular tension, fatigue, irritability, sadness and the subjective feeling of infection [31<sup>\*\*</sup>]. Using microarray, upregulated genes were found in CFS, comprising the  $\text{NF}\kappa\beta$  gene as well as other genes indicating hematological and

immunological disease, cancer, cell death, immune response and infection [33<sup>\*\*</sup>].

Also, the production of COX-2 and iNOS by peripheral blood lymphocytes is significantly higher in CFS patients than in normal controls [32]. The significant relationship between  $\text{NF}\kappa\beta$  and the production of COX-2 and iNOS, suggests that increased COX-2 and iNOS production are caused by an upregulated production of  $\text{NF}\kappa\beta$  [31<sup>\*\*</sup>]. The production of COX-2 and iNOS is significantly related to aches and pain, muscular tension, fatigue, concentration difficulties, failing memory, sadness and a subjective experience of infection [32]. The abovementioned shows that an intracellular inflammation is a key pathway in CFS; previous reports on IO&NS responses in CFS should be attributed to an increased production of  $\text{NF}\kappa\beta$ ; and the IO&NS pathways play a critical role in generating specific CFS symptoms [31<sup>\*\*</sup>,32]. This may be explained as these inflammatory mediators have specific effects. COX-2 is implicated in musculoskeletal pain. COX-2 inhibition alleviates muscle pain [34] and has a beneficial effect on muscle fatigue resistance [35]. iNOS is increased in the muscles of patients with fibromyalgia and is negatively correlated with total exercise time and reduced responses to aerobic exercise [36]. COX-2 overexpression may induce specific cognitive deficits, while COX-2 inhibition may alleviate cognitive defects [37,38]. In mdx mice (which lack the muscle protein dystrophin), IRFI-042, a strong antioxidant and lipid peroxidation inhibitor, blunts  $\text{NF}\kappa\beta$  DNA-binding and TNF $\alpha$  expression in muscles thereby increasing forelimb strength and decreasing fatigue [39]. Blockade of  $\text{NF}\kappa\beta$  by pyrrolidine dithiocarbamate decreases fatigue and increases muscle strength, which both are related to enhanced muscle regeneration [40]. The results suggest that the symptoms of CFS, such as fatigue, muscular tension, depressive symptoms, neurocognitive symptoms and the feeling of infection reflect a genuine IO&NS response in those patients.

##### **Trigger factors of chronic fatigue syndrome**

One of the diagnostic criteria for CFS is the presence of a severe chronic fatigue of longer than 6 months, whereas no other medical condition can explain the fatigue [1]. However, using the abovementioned IO&NS biomarkers a specific pathophysiology is found in all patients with CFS. This means that the CDC criterion 'no other medical condition may explain the chronic fatigue' is useless. Therefore, this CDC criterion should be deleted to meet the emerging view that CFS is a medical syndrome caused by a peripheral and central activation of IO&NS pathways, which are secondary to a number of trigger factors. The latter include psychological stress, sustained strenuous exercise, viral infections, bacterial infections and any other condition, which is accompanied by IO&NS, for example autoimmune disorders, cancers, radiation therapy, and so on. The abovementioned trigger

**Figure 2 The complex cause of chronic fatigue syndrome (CFS)**

Psychological stress, strenuous exercise, infections, leaky gut and other inflammatory disorders may trigger an increased production of nuclear factor  $\kappa\beta$  (NF $\kappa\beta$ ), which in turn may induce the inflammatory and oxidative and nitrosative stress (IO&NS) pathways, including cyclo-oxygenase-2 (COX-2) and inducible NO synthase (iNOS). Inflammation is accompanied by increased levels of proinflammatory cytokines, such as interleukin-1 $\beta$  (IL-1 $\beta$ ), IL-6, tumor necrosis factor- $\alpha$  (TNF $\alpha$ ), and interferon- $\gamma$  (IFN $\gamma$ ). O&NS may cause damage to membrane fatty acids and endogenous proteins. Increased IFN $\gamma$  may induce a decreased availability of tryptophan and thus lowered serotonin contents in the brain; and an increased production of some tryptophan catabolites along the IDO (indoleamine 2,3-dioxygenase (IDO) pathway (TRYCATs). All the above factors are known to induce the 'psychosomatic symptoms' occurring in CFS and somatization.

factors may activate NF $\kappa\beta$  [41], whereby NF $\kappa\beta$  functions as a 'smoke sensor' that detects the abovementioned threats and acts as a switch to turn inflammation and O&NS on and off [31<sup>••</sup>]. When the threats are severe or chronic and have caused IO&NS, 'psychosomatic' symptoms and chronic fatigue may emerge.

Figure 2 shows that the above trigger factors induce intracellular inflammation, which in turn induces the IO&NS pathways and consequently the symptoms of IO&NS, for example the psychosomatic symptoms listed. We now discuss some of these NF $\kappa\beta$  activators which induce IO&NS and which are known to be trigger factors for chronic fatigue [31<sup>••</sup>].

#### *Psychological stress and chronic fatigue*

Psychological stress in humans may induce the production of pro-inflammatory cytokines [42] and O&NS,

such as increased lipid peroxidation and oxidative/nitrosative DNA damage [43–46]. In the rat, forced swimming (a stress/depression model) increases the superoxide anion positive cells (and angiotensin II positive cells) in the cerebrum and cerebellum [47]. The O(2)(–) and angiotensin II responses to emotional stress may explain the stress-related increases in cardiovascular reactivity, which is a risk factor for hypertension and heart disease [48<sup>•</sup>]. iNOS inhibition in the rostral ventrolateral medulla significantly attenuates the autonomic responsivity to psychological stress via alterations in the redox state [49]. Recently it has been proposed that activation of NF $\kappa\beta$  evoked by psychosocial stress, may directly target various tissues and thus constitutes one link between external stress and the body [50]. Chronic unpredictable stress in rats can increase LPS-induced NF $\kappa\beta$  activation in the frontal cortex and the hippocampus [51]. In animal models, psychological stress also

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weakens glutathione antioxidant defenses [52<sup>••</sup>]. In patients suffering from chronic migraine, the effectiveness of biofeedback is related to muscular relaxation associated with decreased oxidative stress, as indicated by lower peroxide levels and increased superoxide dismutase [53]. Environmental stress is associated with more recurrences of infections and greater subsequent fatigue [54<sup>•</sup>,55]. These results show that psychological stress induces the IO&NS pathways and reduces antioxidant defenses and that treatments that inhibit IO&NS pathways have antistress effects.

### *Sustained strenuous exercise and chronic fatigue*

Increased levels of exercise throughout childhood and early adult life are associated with an increased risk to develop CFS. Subjects who later report CFS continued to exercise more frequently even after they began to experience early symptoms of fatigue [56]. Sustained strenuous exercise may generate IO&NS [57,58]. In muscles subjected to intense exercise an activation of NFκβ has been observed [59]. Thus, strenuous exercise may induce the IO&NS pathways and consequently the symptoms of chronic fatigue.

### *Viral infections and chronic fatigue*

In some patients with CFS, IgM serum antibodies to Epstein–Barr virus [60], human cytomegalovirus [61<sup>•</sup>], herpes VI virus [62], and human parvovirus B19 [63], are present. Therefore, some authors suggest that CFS may be due to a persistent viral infection [64]. In the latter study, up to 31% of CFS patients had significant titres of enteroviral IgM. Enterovirus VP1, RNA and noncytopathic viruses are significantly more detected in the stomach biopsy specimens of CFS patients, suggesting that some patients may have a chronic, disseminated form of enteroviral infection [65<sup>•</sup>]. There is also evidence that EBV viremia in CFS is associated with inflammation characterized by increased tryptophan degradation [66<sup>••</sup>]. As the serum concentrations of neopterin are positively correlated to enhanced tryptophan degradation, it can be concluded that those subjects suffer from IFNγ-induced activation of cell-mediated immunity. As explained under ‘Vegetative symptoms, depression and inflammation’ also in major depression and probably in somatization a similar mechanism occurs. This suggests that activation of IDO with decreased plasma tryptophan concentrations is related to depression, somatization and CFS following viral infections. Treatment of CFS patients with antiviral drugs (valacyclovir) for 6 months shows a significant efficacy in increasing energy indices, such as physical functional capacity, Holter monitoring, and multigated (radionuclide) MUGA rest/stress ventriculographic examination [67<sup>•</sup>].

### *Bacterial infections and chronic fatigue*

Also, gram-negative enterobacteria play a role in the cause of CFS [68,69,70<sup>••</sup>]. CFS is accompanied by

increased IgM and IgA responses to the lipopolysaccharide (LPS) of different enterobacteria, indicating that in CFS there is an increased translocation of LPS of gram-negative bacteria [69,70<sup>••</sup>]. This phenomenon most likely results from an increased gut permeability or leaky gut [68]. One of the key pathways that causes a loss of the epithelial barrier function is inflammation, that is increased levels of IFNγ and IL-6 [68]. This may cause the normally poorly invasive enterobacteria to exploit lipid raft-mediated transcytotic pathways to cross the intestinal epithelium, and these effects may precede cytokine-induced disruption of tight junctions [68]. Once LPS is translocated into the blood, a cascade of effects will be generated, that is increased NFκβ; induced COX-2 and iNOS; increased pro-inflammatory cytokines; damage caused by O&NS; and consequently symptoms of IO&NS, for example fatigue, muscle pain, postexertional malaise, depressive symptoms, neurocognitive symptoms, and the subjective feeling of infection. Treatment of leaky gut by means of specific antioxidants, which normalize the increased LPS translocation, is accompanied by a gradual remission of the CFS symptoms [69,70<sup>••</sup>].

## Conclusion

It is concluded that induction of intracellular IO&NS pathways is the key phenomenon underpinning CFS and psychosomatic symptoms. The IO&NS pathways are induced by a number of trigger factors, for example psychological stress, strenuous exercise, viral infections, an increased translocation of LPS from gram-bacteria and conditions characterized by IO&NS (some cancers, radiation therapy, autoimmune disorders, etc). These factors induce a cascade of events from an increased production of NFκβ, COX-2 and iNOS to inflammation and damage to membrane fatty acids and functional proteins caused by O&NS. Following stimulation of the IO&NS pathways, the symptom profiles of inflammation and O&NS appear, for example fatigue, muscle pain, postexertional malaise, depressive symptoms, neurocognitive symptoms and the subjective feeling of infection.

The above findings raise many questions which should be examined in future research: what other intracellular inflammatory pathways are involved in CFS and somatization; what IO&NS biomarkers can be used in the clinical practice; which are the mechanisms whereby external (psychosocial) and internal stressors activate the IO&NS pathways; can novel drug-targets be identified for the development of new anti-IO&NS drugs which can be used in the treatment of CFS and somatization; and what existing anti-IO&NS drugs or natural anti-inflammatory and antioxidative substances (NAIOSs) can be selected in clinical trials.

The view that intracellular molecular pathways underpin CFS and somatiform disorders in general calls for a powerful change in research methods, that is from epidemiological patient studies to a high throughput–high quality screening as made possible by the experimental medicine approach. Future research should focus on: functional genomics (DNA-chips to examine expression profiling); genotyping microarrays (SNP arrays to examine genetic predisposition); new animal models of CFS; transgenic mouse models with knock-outs or knock-in of IO&NS genes; novel ex-vivo and in-vitro models for CFS and somatiform disorders, for example brain slice, muscle and gut-mucosa culturing; and promoter-induction based indicator cell lines (brain, muscle and gut-specific) with promoter sequences of various IO&NS proteins.

### References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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**IO and NS pathways underpinning chronic fatigue, somatization and psychosomatic symptoms Maes 9**

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