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COMMENTARY

Kynurenine Pathway Pathologies: do Nicotinamide and Other Pathway Co-Factors have a Therapeutic Role in Reduction of Symptom Severity, Including Chronic Fatigue Syndrome (CFS) and Fibromyalgia (FM)

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Abstract: The definition of dual tryptophan pathways has increased the understanding of the mind-body, body-mind dichotomy. The serotonergic pathway highlights the primary (endogenous) psychiatric disorders. The up-regulation of the kynurenine pathway by physical illnesses can cause neuropathic and immunological disorders[1] associated with secondary neuropsychiatric symptoms.

Tryptophan and nicotinamide deficiencies fall within the protein energy malnutrition (PEM) spectrum. They can arise if the kynurenine pathway is stressed by primary or secondary inflammatory conditions and the consequent imbalance of available catabolic/anabolic substrates may adversely influence convalescent phase efficiency. The replacement of depleted or reduced NAD+ levels and other cofactors can perhaps improve the clinical management of these disorders.

Chronic fatigue syndrome (CFS) and fibromyalgia (FM) appear to meet the criteria of a tryptophan-kynurenine pathway disorder with potential neuroimmunological sequelae. Aspects of some of the putative precipitating factors have been previously outlined.[2,3] An analysis of the areas of metabolic dysfunction will focus on future directions for research and management.

Keywords: Vitamin B-12, nicotinamide, tryptophan, mental status, nutrition, chronic fatigue syndrome, fibromyalgia, neurology, psychiatry, pernicious anaemia

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The Mind-Body Dichotomy

Over the centuries, there has been intense speculation as to whether human physical dysfunction originated in the mind or arose from the body. Elements of this diagnostic uncertainty have prevailed to present times and are reflected in the opposing views of hysteria and somatoform disorders. Not all health workers accepted the validity of some of the psychiatric symptom inventory scales.

Solomon[4] listed several organic neurological lesions, such as glove and stocking neuropathies, which could be misdiagnosed as hysteria.[4] David and co-workers[5] attempted to initiate the debate that "the fruitless dichotomy of 'organic versus functional' should be replaced by a multi-factorial approach".[5] Other clinicians were concerned about the low discriminatory diagnostic value[6] and ambiguous or unclear items[7] in the Illness Behavior Questionnaire. This questionnaire was designed to validate abnormal illness behavior as a psychiatric diagnosis in those patients with "insufficient pathological change to explain the intensity of pain or degree of disability and suffering".[8] They were also perceived as suffering "unsolved medical problems" with social and economic disadvantages. These patients required further research with psychiatric constructs to address their somatization issues.[9]

Neuropharmacologists have studied the serotonergic pathway over 5 decades and produced numerous treatment options for psychiatric disorders. The function of the kynurenine pathway has been undervalued. It is upregulated by physical (organic) illnesses[1] which can be accompanied by transient secondary deliriums and dysphorias. Mental and physical illnesses sometimes coexist[10,11] or a dysphoria can herald an organic disorder.[12–14] It is a challenge for researchers to better understand the interactive balancing of the dual pathways under stress. This could bring clarity to the physiological interface of the mind-body dichotomy.

Protein Energy Malnutrition (PEM) Niacin and Cofactors

Historical background

The historical accounts of the discoveries of both the connection of pellagra with niacin and the existence of the state of PEM are interlinked.[15–17] 18th Century Spanish Conquistadores imported maize (corn) from Central America to Europe[15] and it was in 1735 that Casal, a Spanish physician, was the first to describe aspects of pellagra. The use of maize as a staple food then spread to many other countries, including Southern Africa and parts of India.

Pellagra reached epidemic proportions in parts of the Southern United States of America at the beginning of the 20th Century. Dr. Joseph Goldberger was challenged to prove that pellagra was not an infectious disease but rather that it was caused by a dietary deficiency. Subsequently, Elvehjem linked niacin to the prevention of pellagra in 1937.[15] The next phase of research focused on Kwashiorkor, the malnutrition of impoverished communities, usually in underdeveloped countries, which afflicts infants and children on restricted diets often with a high maize content. Biochemical analysis demonstrated that maize had low tryptophan content and its niacytin component lacked bioavailability. Interestingly, the South American Indians had fortuitously escaped pellagra due to their custom of presoaking their corn in alkaline lime water, prior to cooking tortillas.

Tryptophan and niacin

Tryptophan was discovered at the beginning of the 20th Century and was the first amino acid to be recognized as an essential component of the human diet.[15,17] It is a critical precursor in the synthesis of the serotonin neurotransmitter and the nicotinamide ring of coenzymes NAD and NADP.[1,17] Approximately 60 mg of tryptophan, subject to hormonal and other influence, can be converted into l mg of nicotinamide.[17] Dietary niacin is an additional source of nicotinamide.

Tryptophan contributes to the structural, neuroactive inflammatory, and immunomodulatory functions of the body.[1–3] Its importance in the function of the kynurenine pathway combined with the presence of an adequate supply of nicotinamide substrate is, however, only of recent interest.[1,18] Nicotinamide has numerous functions,[19,20] including its potential control over infections[21–26] and DNA repair.[27] Additionally, it can improve the management of some cancers[28–30] and CFS/FM[3,31] subject to the stage and phase of these conditions.

Deficiencies in both tryptophan and nicotinamide produce symptoms of pellagra and inadequate supplies of tryptophan can make the patient vulnerable to the development of PEM. Its levels are reduced

because of undernutrition,[17] malabsorption,[3,32] or any significant illness or injury which upregulates KP catabolism.[1]

Symptoms of pellagra or nicotinamide deficiency range from mild oral gum changes to severe weakness, paresthesias, dysphagia, glossitis, various mucosal and skin changes, and mental disturbances.[34] Hartnup's disease and carcinoid tumor are rare causes of this nutritional disorder.[3]

Alcoholism is an iatrogenic cause of pellagra in combination with a lack of other critical nutrients.[34–36] Similar abnormal urinary amino acid profiles have been identified in Pellagrins and HIV-AIDS patients with compromised availability of nicotinamide.[37,38] Pellagra is infrequently recognized as a secondary complication of chronic illnesses with a stressed kynurenine path.[1,39]

Protein energy malnutrition (PEM)

PEM is due primarily to an inadequate intake of essential proteins or to the ingestion of poor quality protein foods. Poverty, famines, dietary ignorance, alcoholism, and mental illness contribute to this etiological category.[17,34] Hypermetabolic response to severe acute or chronic illnesses and trauma can produce bodily protein substrate deficiencies.[17,40] These inflammatory conditions include infections (eg, HIV-AIDS), neoplasms, chronic renal failure, and burns in which secondary PEM can occur.

The daily homeostatic turnover of nutritional protein is regulated to achieve a zero nitrogen balance between intake and output. In circumstances of PEM "a sustained imbalance" occurs "between nutritional availability and nutrient requirements, resulting in a pathophysiological state in which intermediary metabolism, organ function, and body composition are variously altered".[40]

The degree of physiological impairment, consequent to the catabolism of somatic muscle mass, is proportionate to the severity of the underlying ailment.[40] The immune system is the most vulnerable of the body organ compartments to the adverse effects of PEM. Another example of compromise is the tardy structural repair of the gastric intestinal tract which aggravates any pre-existing propensity to malabsorption. Additionally, wound healing is less efficient and the manufacture of T4 and its conversion to T3 is reduced so that the patient's thyroid status can resemble the euthyroid sick syndrome.[40–42] The challenge of treatment is to contain the illness[43] and include nutritional strategies and relatively depleted anabolic agents in the therapeutic restoration of homeostasis.[40]

Reductions in the levels of other metabolic fuels occur concurrently with the previously described metabolic stresses.[17,40] The B group vitamins, especially B6, are important cofactors in several enzymes required for function of the tryptophan pathways.[17] Other micronutrients,[44] such as L-carnitine[31,45] and ribose,[31,46] have been trialed in various medical conditions. The optimistic results may, however, reflect a placebo component. Future research protocols are required to determine which cofactors are exhausted and require replacement to supply positive anabolic therapeutic support in acute and chronic illnesses with hypermetabolic states.

CFS/FM—the Metabolic Enigma

CFS/FM is a complex autoimmune spectrum disorder which is frequently familial.[2,3,41,47] The onset is either acute or insidious and has a variable and unpredictable course and outcome. Central nervous symptoms are prominent, patients are lethargic and suffer pain, sleep disturbances and dysphorias, and their powers of concentration and cognition are decreased while aspects of memory are impaired. Patients may complain of headaches and paresthesias and exhibit an ataxic gait. Food intolerances are amongst the various gastro-intestinal disturbances described. The physical response to infection can be atypical and protracted[2,3,48–50] and their hypothyroid state can present with an unusual pattern of T3 behavior.[40–42]

Tryptophan[32] and Vitamin B-12 deficiencies are associated with malabsorption and contribute to the causes of nutritional demyelinating disorders.[3] Both substances have juvenile forms of illnesses. If enzyme defects and other genetic irregularities are present, conditions such as Hartnup's disease and dysfunctions of homocyteine can also occur.[3,51–53] These genetic aberrations may not be expressed until adulthood when they are often misdiagnosed.

Evidence has accumulated that CFS/FM is in part a neuroinflammatory condition of the kynurenine pathway with CNS[3,41,54] and peripheral nerve involvement.[55]

Pernicious anaemia (PA) is an autoimmune disorder with defective B-12 metabolism. It is frequently

associated with hypothyroidism and PA can manifest either as a megaloblastic anaemia or as a neurological complication with or without the anemic component of Vitamin B-12 deficiency.[17,52,53,56] The subsequent peripheral neuropathy produced by the sub-acute combined degeneration of the spinal cord explains the paresthesias and sensory losses in the distal part of the limbs.[55] Occasionally PA presents as a psychiatric illness[10,57] or with autonomic nervous system involvement.[58,59]

Vitamin B-12 is a cofactor in the enzyme formation of methionine synthetase (methylmalonic CoA) and leucine aminomutase. Reduced levels of B-12 have a negative impact on certain aspects of tryptophan function.[17] The gastric achlor-hydria interferes with the gastrointestinal bacterial balance, which then creates a propensity to secondary infection.[32,60,61] Defective substrate production, such as NK and T cells[62] reduces effective KP immunological function. Vitiligo or depigmented white spots is a skin change associated with PA.[63]

Routine blood diagnostic tests are not always sufficiently robust to detect the earlier stages or atypical forms of PA. The measurement of methylmalonic acid (MMA) and homocysteine (HCY) levels are more sensitive indicators of an underlying PA.[53,64] Past use of these tests, ie, MMA and HCY blood levels, clarified the fact that a neuropsychiatric form of PA existed which could present in the absence of an haematological component[51,56] or that there could be an inverse correlation between the severity of the neurological damage and the PA megaloblastic anaemia.[56,58]

Carmel and colleagues had an interest in the genetic aberrations of PA.[51] This aspect of PA was utilized in a subsequent research project which enquired into the divergent behaviors of the neurological and haematological forms of PA.[56] They found:

> "Cobalamin therapy restored all metabolic changes to normal. The results indicate that changes in several metabolic pathways differ in patients with and without neurologic dysfunction. Cysteine levels were the most significant predictors of neurological dysfunction, but it is unclear if they are direct or indirect indicators of neurotoxicity."[56]

Regland et al[65] examined 12 females with CFS/FM. Their peripheral blood test results were generally normal, whereas tests of their cerebro-spinal fluid demonstrated elevated HCY levels and low B-12 levels. These correlated with the degree of patient fatigue. In his informal surveys, Lapp[66] noted that CFS patients returned positive HCY and MMA tests for PA when the routine blood tests for folate and B-12 were normal. In addition these patients appeared to respond to cyanocobalamin injections. Myhill[67] theorized that CFS/FM symptoms were due to oxidative stress which could be relieved with B-12 as it is a powerful nitric oxide scavenger. She was also of the opinion that neurological symptoms responded to B-12 therapy in the infrequent cases of subclinical PA. In recent decades, CFS/FM support group councilors have commented on the prevalence of client reports which made mention of family members who received B-12 injections. They also noted that some clients claimed that B-12 injections cleared their "brain fog".[67] It is a paradox that CFS/FM members are rarely diagnosed with clinical PA.

The above clinical patient research data provides good reason to extend the current investigative diagnostic parameters of CFS/FM patients.[47] Avitaminosis and mild PEM should be included in the assessment of gastrointestinal conditions. Genetic disorders of tryptophan and Vitamin B-12 status should be tested for, to exclude neurologic PA and other aberrations. Search for unexpected silent or chronic infections is required.[2,48–50] In conclusion, the presence of nutritional[3,31,68] and thyroid deficiencies and unsuspected infections offer a rational explanation as to the etiology of the patient's signs and symptoms, such as ataxia, pain, paresthesias, and dysphorias.[55]

Nutritional Status and Convalescence Outcome

The study of tryptophan/kynurenine ratio imbalance in chronic disorder has added explanatory detail to the catabolic use of protein in the urea-nitrogen cycle.[1,69] However, a consensus reviewer report[70] on adult starvation and disease related malnutrition, considered the varied definitions of malnutrition syndromes to be unsatisfactory. They proposed a simplified framework to incorporate the contemporary notion of the inflammatory response.[69] Their three recommended groups are:

1. Chronic starvation without inflammation;
2. "Chronic disease-related malnutrition" with lower levels of inflammation; and

3. "Acute disease or injury response" with severe inflammation.

PEM has been studied mainly in developing countries where malnutrition retards physical and mental development in childhood.[17,40] Neonates and infants have matured kynurenine pathways which can be activated by physical stressors[71,72] and therefore tryptophan deficiencies can become a contributor to PEM and its complications. The normal process of convalescence is disrupted when infections, such as malaria and measles, convert subclinical malnutrition into an overt Kwashiorkor within a latent interval of a couple of months.[17] Researchers have looked into nutritional treatments in both subclinical and illness phases of PEM.[73–75] High quality tryptophan food supplements can be useful[73] and anabolic support might produce better outcomes in acutely sick infants.[72] Children with PEM appear to possess an altered disposition in their utilization of medications, although some of the outcomes of their therapies remained inconclusive.[42] It has been observed that the efficacy of vaccinations is reduced[76] and their cytokine profile can be altered by PEM with inflammatory consequences.[77,78]

In adult illness situations, undernourished surgical patients are at increased risk of developing complications and hence experience a longer recovery period.[40,79] Aggressive preoperative nutritional support can reduce adverse perioperative events.[40] Additionally, adequate nutritional support may enhance the quality of life in patients undergoing radiotherapy even if their prospects of longevity are unchanged.[40] Chronic renal disease is another example of an impoverished nutritional state where acute or subclinical infections can readily complicate the primary condition of the patient.[80]

These above examples collectively demonstrate that in patient populations, pre-existing nutritional deficiencies from numerous different causes can distort and extend the convalescent phase of any acute injury or illness, or result in chronic morbidity.[3]

The question arises in neurasthenia, a post-infective phase of convalescence[81,82] whether it is an equivalent entity to the post-infection nutritional decline observed in Kwashiorkor. An increased understanding of the substrate requirements of activated metabolic pathways in health and disease should enable researchers to pinpoint compensatory anabolic support constituents with greater accuracy.

Conclusion

In illness and health, the body competes for essential metabolic substrates to achieve equilibrium. Significant substrate deficiencies can be created by the additional demands[1,17,40,69] imposed on the body by neoplastic cells,[83] micro-organisms (eg, gut saprophytes[84–86] and B-12 requirements of the blind loop syndrome),[53] undue physical exertion by the ill patient, and interference by metabolic activity of medications (eg, isoniazid).[16,17,40,53] The resultant upregulation of the tryptophan kynurenine pathway offers an explanatory model for an immunological connection between malnutrition and infection, and for the pathophysiological and neurological complications of severe trauma and illness, CFS/FM included.[1,2]

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References

1. Chen V, Guillemin GJ. Kynurenine pathway metabolites in human disease and healthy states. *Int J Tryptophan Res*. 2009;2:1–19.
2. Blankfield A. Kynurenine pathway hypothesis: the nature of the chronic fatigue syndrome (CFS) revisited. *Int J Tryptophan Res*. 2011;4: 47–8.
3. Blankfield A. A brief historic overview of Clinical Disorders associated with Tryptophan: The Relevance to Chronic Fatigue Syndrome (CFS) and Fibromyalgia (FM). *Int J Tryptophan Res*. 2012;5:27–32.
4. Solomon S. Clinical Neurology and Pathophysiology. In: Freedman AM, Kaplan HI, Sadock BJ, editors. *Comprehensive Textbook of Psychiatry*, 2nd ed. Baltimore Williams and Wilkens; 1975.
5. David AS, Wessely S, Pelosi AJ. Postviral Fatigue Syndrome: time for a new approach. *Brit Med J*. Mar 5, 1988;296(6623):696–9.
6. Singer A, Thompson S, Kraiuhin C, et al. An investigation of patients presenting with multiple physical complaints using the illness. Behaviour questionnaire. *Psychother Psychosom*. 1987;47(3–4):181–9.
7. Zonderman AB, Heft MW, Costa PT Jr. Does the illness behavior questionnaire measure abnormal illness behaviour? *Health Psychol*. 1985;4(5):425–36.
8. Pilowsky I. Abnormal illness behaviours and their treatments. *Med J Aust*. 1990;153:346–8.
9. Lipowski ZJ. Somatization: Medicines unsolved problem. *Psychosomatics*. 1987;28(6):294–7.
10. Kate N, Grover S, Agarwal M. Does B-12 deficiency lead to lack of treatment response to conventional antidepressants? *Psychiatry (Edgmont)*. 2010;7(11):42–4.
11. Deahl MP. Physical illness and depression: the effects of acute physical illness on the mental state of psychiatric inpatients. *Acta Psychiatrica Scand*. 1990;81(1):83–6.
12. Tripathi AK, Verma SP, Kimanshu. Acute psychosis: A presentation of cyanocobalamin deficiency megaloblastic anaemia. *Indian J Haematol Blood Transfus*. 2010;26(3):99–100.
13. Jenkins AP, Treasure J, Thompson RPH. Crohn's disease presenting as anorexia nervosa. *Brit Med J*. 1988;296(6623):699–700.
14. Hall RCW, Gardner ER, Stickney SK, LeCann AF, Popkin MK. Physical Illness Manifesting as psychiatric Disease II. Analysis of a state hospital inpatient population. *Arch Gen Psychiatry*. 1980;37(9):989–95.
15. Middleton J. Pellagra and the blues song 'Cornbread, meat and black molasses'. *JR Soc Med*. 2008;101(11):569–70.
16. Bender DA. Biochemistry of tryptophan in health and disease. *Molec Aspects Med*. 1982;6(2):101–97.
17. Bender DA. *Introduction to Nutrition and Metabolism*, 4th ed. Boca Raton: CRC Press; 2008.
18. Stone TW. Kynurenines in the CNS: from endogenous obscurity to therapeutic importance. *Prog Neurobiol*. 2001;64(2):185–218.
19. Houtkooper RH, Canto C, Wanders RJ, Auwerx J. The secret life of NAD+: An old metabolite controlling new metabolic signaling pathways. *Endocr Rev*. 2010;31(2):194–223.
20. Sauve AA. NAD+ and Vitamin B3: From metabolism to therapies. *J Pharmacol Exp Ther*. 2008;324(3):883–93.
21. Murray MG. Nicotinamide: An oral antimicrobial agent with activity against both mycobacterium tuberculosis and human immunodeficiency virus. *Clin Infect Dis*. 2003;36(4):453–60.
22. Braidy N, Grant R, Brew J, Adams S, Jayasena T, Guillemin GJ. Effects of kynurenine pathway metabolites on intracellular NAD+ synthesis and cell death in human primary astrocytes and neurons. *Int J Tryptophan Res*. 2009;2:63–9.
23. Braidy N, Guillemin GJ, Grant R. Effects of kynurenine pathway inhibition on NAD+ metabolism and cell viability in human primary astrocytes and neurons. *Int J Tryptophan Res*. 2011;4:29–37.
24. Bellac CL, Coimbra RS, Christen S, Leib SL. Inhibition of the kynurenine—NAD+ pathway leads to energy failure and exacerbates apoptosis in pneumococcal meningitis. *J Neuropathol Exp Neurol*. 2010;69(11):1096–104.
25. Murray MF, Langan M, MacGregor RR. Increased plasma tryptophan in HIV-infected patients treated with pharmacologic doses of nicotinamide. *Nutrition*. 2001;17(7–8):654–6.
26. Murray MF. Tryptophan depletion and HIV infection: a metabolic link to pathogenesis. *Lancet Infect Dis*. 2003;3(10):644–52.
27. Surjana D, Halliday GM, Damian DL. Role of nicotinamide in DNA damage, mutagenesis and DNA repair. *J Nucleic Acids*. 2010;2010:157591.
28. Kirkland JB. Niacin status and treatment-related leukemogenesis. *Mol Cancer Ther*. 2009;8(4):725–32.
29. Audrito V, Vaisitti T, Ross D, et al. Nicotinamide blocks proliferation and induces apoptosis of chronic lymphocytic leukemia cells through activation of the p53/miR-34a/SIRT 1. Tumour suppressor network. *Cancer Res*. 2011;71(13):4473–83.
30. Inculet RI, Norton JA, Nichoalds, Maher MM, White DE, Brennan MF. Water-soluble vitamins in cancer patients on parental nutrition: a prospective study. *J Parenter Enteral Nutr*. 1987;11(3):243–9.
31. Werbach MR. Nutritional strategies for treating chronic fatigue syndrome. *Altern Med Rev*. 2000;5(2):93–108.
32. Ledochowski M, Propst T, Fuchs D. The role of psychological and biological factors in post-infective gut dysfunction. *Gut*. 2000;46(1):140–1.
33. Monteiro AM, Coutinho H, Janz GJ, deLoureiro JA. Endemic pellagra in northern Portugal. *J Hygiene*. 2009;44(6):518–25.
34. Robertson EE. Organic disorders. In: Forrest A, Affleck J, Zealley A, editors. *Companion to Psychiatric Studies*, 2nd ed. Edinburgh, Churchill, Livingstone; 1978.
35. Vannucchi H, Moreno FS, Amarante AR, et al. Plasma amino acid patterns in alcoholic pellagra patients. *Alcohol Alcohol*. 1991;26(4):431–6.
36. Creeke PI, Dibari F, Cheung E, van den Briel T, Kyroussis E, Seal AJ. Whole blood NAD and NADP concentrations are not depressed in subjects with clinical pellagra. *J Nutr*. 2007;137(9):2013–7.
37. Hortin GL, Landt M, Powderly WG. Changes in plasma amino acid concentrations in response to HIV-1 infection. *Clin Chem*. 1994;40(5):785–9.
38. Trusswell AS, Hansen JK, Wannenburg P. Plasma tryptophan and other amino acids in pellagra. *Am J Clin Nutr*. 1968;21(11):1314–20.
39. Brown RR, Ozaki Y, Datta SP, Borden EC, Sondel PM, Malone DG. Implications of interferon-induced tryptophan catabolism in cancer, autoimmune diseases and AIDS. *Adv Exp Med Biol*. 1991;294:425–35.
40. Mason JB. Nutrition in Gastroenterology. In: Feldman M, Friedman LS, Brandt LH, editors. *Sleisenger and Fortran's Gastrointestinal and Liver disease; Pathophysiology, Diagnosis, Manage Merit*, 8th ed. Philadelphia: Saunders Elsevier; 2008.
41. Russell IJ, editor. The fibromyalgia syndrome: A Clinical Case Definition for Practitioners. *J Musculoskeletal Pain*. Haworth Medical Press. 2003;11(4).
42. Oshikoya KA, Senbanjo IO. Pathophysiological changes that affect drug disposition in protein-energy malnourished children. *Nutr Metab*. 2009;6:50–5.
43. Zangerle R, Widner B, Quirchmair G, Neurauter G, Sarcletti M, Fuchs D. Effective antiviral therapy reduces degradation of tryptophan in patients with HIV-1 infection. *Clin Immunol*. Sep 2002;104(3):242–7.
44. Dhaliwal W, Shawa T, Khanam M, et al. Intestinal antimicrobial gene-expression: Impact of micronutrients in malnourished adults during a randomized trial. *J Infect Dis*. 2010;202(6):971–8.
45. Rossini M, Di Munno O, Valentini G, et al. Double-blind, multicentre trial comparing acetyl L-carnitine with placebo in the treatment of fibromyalgia patients. *Clin Exp Rheumatol*. 2007;25(2):182–8.
46. Santaella ML, Font I, Didier OM. Comparison of oral nictotinamide adenine dinucleotide (NADH) versus conventional therapy for chronic fatigue syndrome. *Health Sci J*. 2004;23(2):89–93.
47. Torpy D. Chronic Fatigue Syndrome, Chap 33b. In: Adrenal Physiology and Diseases. http://www.endotext.org/adrenal/adrenal33b.
48. Nicolson GL, Gan R, Haier J. Multiple co-infections (Mycoplasma, Chlamydia, human herpes virus-6) in blood of chronic fatigue syndrome patients: association with signs and symptoms. *APMIS*. 2003;111(5):557–66.
49. Kerr JR, Barah F, Mattey DL, et al. Circulating tumor necrosis factor-alpha and interferon-gamma are detectable during acute and convalescent parvovirus B19 infection and are associated with prolonged and chronic fatigue. *J Gen Virol*. 2001;82(Pt 12):301–19.
50. Kerr JR, Gough J, Richards SCM, et al. Antibody to Parvovirus B19 nonstructural protein is associated with chronic arthralgia in patients with chronic fatigue syndrome/myalgic encephalitis [CFS/ME]. *J Gen Virol*. 2010;91(Pt 4):893–7.

51. Carmel R, Watkins D, Goodman SI, Rosenblatt DS. Hereditary defect of cobalamin metabolism (cblG mutation) presenting as a neurologic disorder in adulthood. *N Engl J Med*. 1988;318(26):1738–41.
52. Taghizadeh M. Megaloblastic Anemias. In: Harmening D, editor. *Clinical Hematology and Fundamentals of Hemostasis*, 5th ed. Philadelphia: FA Davis & Co; 2009.
53. Stopler S. Medical Nutrition Therapy for Anemia (Chap 34). In: Mahan LK, Escott-Stump S, editors. *Krause's Food, Nutrition and Diet Therapy*, 11th ed. Philadelphia: Saunders Elsevier; 2004.
54. Komaroff AL, Cho T. Role of infection and neurological dysfunction in chronic fatigue syndrome. *Semin Neurol*. 2011;31(3):325–37.
55. Caro XJ, Winter EF, Dumas AJ. A subset of fibromyalgia patients have findings suggestive of chronic inflammatory demyelinating polyneuropathy and appear to respond to IVIg. *Rheumatology*. 2008;47(2):208–11.
56. Carmel R, Melayk S, James SJ. Cobalamin deficiency with and without neurological abnormalities: differences in homocysteine and methionine metabolism. *Blood*. 2003;101(8):3302–8.
57. Lindenbaum J, Healton EB, Savage DG, et al. Neuropsychiatric disorders caused by cobalamin deficiency in the absence of anemia or macrocytosis. *N Engl J Med*. 1988;318(26):1720–8.
58. Savage DG, Lindenbaum J. Neurological complications of acquired cobalamin deficiency: clinical aspects. *Baillieres Clin Haematol*. 1995;8(3):657–78.
59. Toru S, Yokota T, Inaba A, et al. Autonomic dysfunction and orthostatic hypotention caused by vitamin B-12 deficiency. *J Neurol Neurosurg Psychiatry*. Jun 1999;66(6):804–5.
60. Fitzgerald P, Cassidy EM, Clarke G, et al. Tryptophan catabolism in females with irritable bowel syndrome: relationship to interferon-gamma, severity of symptoms and psychiatric co-morbidity. *Neurogastroenterol Motil*. 2008;20(12):1291–7.
61. Hashimoto T, Perlot T, Rehman A, et al. ACE 2 links amino acid malnutrition to microbial ecology and intestinal inflammation. *Letter Nature*. 2012;487(7408):477–81.
62. Tamura J, Kubota K, Murakami H, et al. Immunomodulation by vitamin B-12; augmentation of CD8+ T lymphocytes and natural killer (NK) cell activity in vitamin B-12-deficient patients by methyl B-12 treatment. *Clin Exp Immunol*. 1999;116(1):28–32.
63. Kannan R, Ng MJM. Cutaneous lesions and vitamin B-12 deficiency. An often-forgotten link. *Can Fam Physician*. 2008;54(4):529–32.
64. Carlson TH. Laboratory Data in Nutrition Assessment (Chap. 18). In: Mahan LK, Escott-Stumps, editors. *Krause's Food, Nutrition and Diet Therapy*, 11th ed. Philadelphia: Saunders Elsevier, 2004.
65. Regland B, Anderson M, Abrahamsson L, Bagby J, Dyrehag LE, Gottfries CG. Increased concentrations of homocysteine in the cerebrospinal fluid in patients with fibromyalgia and chronic fatigue syndrome. *Scand J Rheumatol*. 1997;26(4):301–7.
66. Lapp CW. Using vitamin B-12 for the management of chronic fatigue syndrome (CFS). Feb 25, 2000. http://www.ProHealth.com.
67. Myhill S. Diagnosing and treating chronic fatigue syndrome (CPS). 2009. Self-published. http://www.drmyhill.co.uk.
68. Markus CR, Oliver B, de Haan EH. Whey protein rich in alpha-lactalbumin increases the ratio of plasma tryptophan to the sum of the other large neutral amino acids and improves cognitive performance in stress-vulnerable subject. *Am J Clin Nutr*. 2002;75(6):1051–6.
69. Schrocksnadl K, Wirleitner B, Winkler C, Fuchs D. Monitoring tryptophan metabolism in chronic immune activation. *Clin Chim Acta*. 2006; 364(1–2):82–90.
70. Jensen GL, Mirtallo J, Compher C, et al. Adult starvation and disease-related malnutrition: a proposal for etiology-based diagnosis in the clinical practice setting from the International Consensus Guideline Committee. *Clinical Nutrition*. 2010;29(2):151–3.
71. Munoz-Hoyos A, Molina-Carballo A, Macias M. Comparison between tryptophan methoxyindole and kynurenine metabolic pathways in normal and preterm neonates and in neonates with acute fetal distress. *Eur J Endocrinol*. 1998;139(1):89–95.
72. de Betue CT, van Waardenburg DA, Deutz NE, et al. Increased protein-energy intake promotes anabolism in critically ill infants with viral bronchiolitis: a double-blind randomized controlled trial. *Arch Dis Child*. 2011;96(9):817–22.
73. Manary MJ, Yarasheski KE, Hart CA, Broadhead RL. Plasma urea appearance rate is lower when children with Kwashiorkor are fed egg-white-Tryptophan rather than milk protein. *J Nutr*. 2000;130(2):183–8.
74. Abassy AS, Zeitoun MM, Hassanein EA, et al. Studies on tryptophan metabolism in protein-calorie malnutrition. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1970;64(1):148–55.
75. Metwalli OM, Shukry AS, Ghali I, Shukry I, Ismail S, El-Bishlawi A. Studies of tryptophan metabolism in protein-energy malnutrition (PEM). *Gaz Egypt Paediatr Assoc*. 1977;26(1):57–66.
76. Iyer SS, Chatrow JH, Tan WG, et al. Protein energy malnutrition impairs homeostatic proliferation of memory CD8 T cells. *J Immunol*. 2012;188(1): 77–84.
77. Sauerwein RW, Mulder JA, Mulder L, et al. Inflammatory mediators in children with protein-energy malnutrition. *Am J Clin Nutr*. 1997;65(5):1534–9.
78. Thumham DI, Mburu ASW, Mwaniki DL, DeWagt A. Micronutrients in childhood and the influence of subclinical inflammation. *Proc Nutr Soc*. 2005;64(4):502–9.
79. Karl A, Staehler M, Bauer R, et al. Malnutrition and clinical outcome in urological patients. *Eur J Med Res*. 2011;16(10):469–72.
80. Utaka S, Avesani CM, Draibe SA, Kamimura MA, Andreoni S, Cuppari L. Inflammation is associated with increased energy expenditure in patients with chronic kidney disease. *Am J Clin Nutr*. 2005;82(4):801–5.
81. Greenberg DB. Neurasthenia in the 1890s: Chronic mononucleosis, chronic fatigue syndrome, and anxiety and depressive disorders. *Psychosomatics*. 1990;31(2):129–37.
82. Hickie I, Davenport T, Wakefield D, et al. Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study. *BMJ*. 2006;333(7568):575.
83. Dreizen S, McCredie KB, Keating MJ, Andersson B. Nutritional deficiencies in patients receiving cancer chemotherapy. *Postgrad Med*. 1990; 87(1):163–70.
84. Vella A, Farrugia G. D-Lactic acidosis: pathological consequence of saprophytism. *Mayo Clic Proc*. 1998;73(5):451–6.
85. Sheedy JR, Wettenhall REH, Scanlon D, et al. Increased D-lactic acid intestinal bacteria in patients with chronic fatigue syndrome. *In Vivo*. 2009;23(4):621–8.
86. Evengard B, Nord CE, Sullivan A. Patients with chronic fatigue syndrome have higher numbers of anaerobic bacteria in the intestine compared to healthy subjects. *Eur Soc Clin Microbiol Infect Dis*. 2007;17:S340.