Review

Positive Effect of Fever on Symptoms of Autism

Helen V. Ratajczak, PhD;*[1] Robert B. Sothern, PhD[2]

[1] *Edmond Enterprises, Danbury, CT*
[2] *College of Biological Sciences, University of Minnesota, St. Paul, MN*

Autism is no longer considered incurable. Numerous reports have documented cures of autism, especially in young children. In addition, transient improvement in symptoms of ASD has been reported during natural fever in response to infection, suggesting the potential use of fever as a therapy leading to a cure. Fever has proven to be very effective in treatment of human disorders. In the past, fever in response to malaria was successfully used to cure >84% of individuals with the terminal condition dementia paralytica. Malariotherapy has also been used to treat human immunodeficiency virus. Pertinent to autism, recent approaches to alleviate symptoms using heat alone include Sulforaphane (a phytochemical derived from a number of cruciferous vegetables, including broccoli), which has a fever-like effect, and the use of hot water baths to increase body temperature. However, these two means of producing heat do not include the involvement of the immune response, which provides antibodies, inflammatory cytokines, and other means of alleviating the symptoms of autism. It is suggested that trials of various means of producing fever be conducted in populations of individuals with autism. Of note, it is essential that the cause(s) of any induced fever can be cured. Herpes might be considered as a cause of fever that would be effective in alleviating symptoms of autism. A naturally-occurring infection in humans, herpes has been reported to be cured. Overall, the literature to date suggests that purposeful induction of fever is a promising approach in the search for an alleviation and/or cure of ASD.

[N A J Med Sci. 2016;9(4):167-171. **DOI:** *10.7156/najms.2016.0904167]*

Key Words: *autism spectrum disorder, fever, neuroinflammation*

INTRODUCTION

Scientists have recently determined that autism is a "dynamic encephalopathy" because it changes.[1] The most dramatic changes reported are those that document cures.[2-7] These reports include groups of individuals that had autism diagnosed at a young age who later no longer showed any significant symptoms of autism as they aged. In contrast, transient changes in autism have been reported in which improvement of symptoms of autism spectrum disorder (ASD) have occurred in response to infectious fever.[8-10]

This review focuses on the role of fever in the progression of autism and how fever might bring relief to autistic individuals.

AUTISM SPECTRUM DISORDER IS A DYNAMIC ENCEPHALOPATHY

Lord et al.[2] reported patterns of developmental trajectories in toddlers with autism. Seventy-eight children (18 - 36 months) were tested every 2 months for 1.5 years using standardized assessments of ASD. The results demonstrated variability in early trajectories and support the need for early identification. Very few children under 24 months of age received any ASD-targeted interventions, and none more than an hour a week. After 24 months, the amount of treatment generally increased and included: non-categorical preschool/toddler classes, home-based weekly non-categorical early childhood sessions, individual speech therapy, and/or a few hours of home-based applied behavior analysis. With these interventions, nearly one-third of the children who had a diagnosis of ASD showed steady improvements in social-affect and increases in the slope of acquisition of verbal skills up to the end of the study (around age 36 months).

In a later report, Fein et al[3] found optimal outcome (i.e., losing all symptoms of ASD in addition to the diagnosis, and functioning within the non-autistic range of social interaction and communication) in about a third of 112 subjects. Participants ranged from 8.1 years to 21.75 years in age. The authors cite 2 other manuscripts from their group that also reported that some children with an original diagnosis of autism at a young age (around 2 years) and who received (mostly behavioral) intervention lost the diagnosis by the age of 4 years: Sutera et al[4] report that the clearest distinguishing factor for those children who lost the diagnosis was motor skills at age 2. Helt et al[5] state that predictors of recovery include relatively high intelligence, receptive language, verbal and motor imitation, and motor development, but not overall symptom severity. Unfavorable signs include

Received: 09/20/2016; Revised: 10/19/2016; Accepted: 10/22/2016
***Corresponding Author:** 94C Miry Brook Road, Danbury, CT 06810. Tel: 203-778-6826. (Email: hratajcz@comcast.net)

presence of seizures, mental retardation and genetic syndromes.

A prospective study of toddlers with ASD compared cognitive, social, and communication skills of 89 children at an average age of 21.5 months and after reassessment ~2 years later at an average of 46.9 months of age.[6] Stability of ASD diagnosis was high (100%), with diagnosis of autism stable in 74% of cases, compared to 83% in PDD-NOS (Pervasive Development Disorders - Not Otherwise Specified) and 81% in non-ASD groups. In contrast, worsening of social disability symptoms resulting in autism diagnosis was noted in 17% of toddlers initially diagnosed with PDD-NOS and in 19% of toddlers with initial diagnosis of non-ASD disorder, while marked improvement was noted in approximately one-fourth of children initially diagnosed with ASD, warranting re-diagnosis to PDD-NOS. These results suggest particular relevance of the assessment of verbal and nonverbal communication skills to define subtypes with ASD for children in the second year of life. It was also noted that consideration of cognitive, social, and communication skills at the same time increases the accuracy of diagnostic classification and prediction of outcome. The investigators emphasized the importance of early identification of ASD so that appropriate interventions and therapies can be implemented. Cures have been documented to be long lasting. A more recent similar report found that some children diagnosed with autism as toddlers had no symptoms two decades later.[7] These reports of alleviation from ASD symptoms indicate that these cures were permanent. The individuals who were deemed free of ASD symptoms participated in therapy throughout their recovery.

EFFECTS OF FEVER

An example of autism as a dynamic encephalopathy is the improvement of symptoms when an autistic individual has an infectious fever, as has been reported. Curran et al.[8] carried out a prospective study of 30 children between the ages of 2-18 years with ASD during and after experiencing a fever. Children with genetic disorders were excluded from the study. Parental responses to the Aberrant Behavior Checklist were collected during fever (body temperature $\geq$ 100.4ºF) and after the child was without symptoms and fever for 7 days. Control data was gathered from parents of 30 afebrile children with ASD matched for age, gender, and language skills. Autistic children were more likely to show fewer aberrant behaviors (irritability, hyperactivity, stereotypy, inappropriate speech) during fever than children with a diagnosis of PDD-NOS or Asperger's. Time-by-group interactions from the repeated measures analysis of variance were significant for all measures (irritability, P = 0.016; lethargy, P = 0.002; hyperactivity, P = 0.001; stereotypy, P = 0.006; inappropriate speech, P = 0.003). Stratified analyses of fever group patients showed no marked differences in the mean patterns of aforementioned aberrant behaviors among patients with higher ($\geq$ 102.0ºF) and lower fevers (100.4-102.0ºF), suggesting that lowering of aberrant behavior during fever did not depend on the degree of the fever. Similar findings were seen between subject groups with higher and lower lethargy, suggesting that reduction of aberrant behavior during fever also did not depend on the amount of lethargy measured at that time. The lowering of symptoms in the autistic children who had fever, however, was transient, with symptoms recurring after the fever was gone. The authors reported that anecdotal reports suggest that effects that are stimulated by fever are not evoked by high ambient heat associated with a sauna, hot summer weather, or physical activity. Their data suggested that the effects from fever persisted in both less sick patients and those with severe illness. They concluded that the effects of fever were not solely the byproduct of general effects of sickness on behavior, but possibly included underlying biological mechanisms involving immunologic and neurobiologic pathways, intracellular signaling and synaptic plasticity.

A workshop report from SFARI (Simons Foundation Autism Research Initiative) held on April 1, 2010 summarized several reports pertinent to our discussion.[9] The neural link between fever and behavior could be a result of fever's effect on noradrenergic neurons in the locus coeruleus (LC) in the brain.[10] Mehler and Purpura[10] proposed that febrigenesis and the changes associated with fever in autism depend on selective normalization of key components of a functionally impaired locus coeruleus-noradrenergic (LC-NA) system. Fever temporarily restores the modulatory functions of the LC-NA system specification and neural network use and modulation linked to the core behavioral features of autism. The association of fever with alleviation of autistic symptoms suggests the potential intentional use of fever as a therapy. The fact that the LC is in the brain[10] and lymphatics have recently been discovered in the brain[11] proposes a possible role of the association between the LC and lymphatics in causing autism, in addition to possibly curing autism. Ghanizadeh[12] questioned if fever and neuroinflammation play a role in the neurobiology of autism and concluded that this is most probably true by altering glutamate levels in the brain, and thereby having an impact on the symptoms of autism. The role of neuroinflammation in ASD is currently being investigated.[13] Extending that approach to the intentional use of fever to cure autism would be an important next step.

EFFECTS OF HEAT ALONE ON ASD SYMPTOMS

A study questioning the effect of heat alone on the symptoms of autism was conducted by Ferretti et al.,[14] who investigated the effect of heat (102ºF) compared to the control condition (98ºF) in a water therapy pool. The study included fifteen children (5 - 17 years old): ten children with ASD and history of fever and five children with ASD without history of fever as controls. Children with ASD and history of fever response received two treatment conditions. First, to ensure the safety of the approach, the 5 control subjects without a history of fever completed the hyperthermia condition and suffered no ill effects. The 10 subjects with ASD and a history of fever response then completed the hyperthermia condition and control condition at the water therapy pool. Improvements in social cognition and repetitive/restrictive behaviors were observed in children at the high temperature using parent and

rater assessments. Side effects (redness, nausea) were minimal and were the same as those in a hot tub. The results showed improvement of socialization and repetitive and restricted behaviors during the hyperthermia condition, and that it was safe to increase children's temperatures into the fever range. The temperature increase caused significant improvement on both clinician ratings and parent ratings (both blinded to the temperature of the pool). Each child's fever response history was correlated with the improvements observed at the elevated temperature. Improvements were similar to those observed during febrile exposure: increased cooperation, communication, and social reciprocity, and decreased hyperactivity and inappropriate vocalizations. The authors stated that this was the first study exploring direct effects of temperature on ASD symptoms. They found that those with a history of marked fever response had the most observable behavior changes (which were similar to those observed by parents during at home febrile episodes). Such a means of increasing the temperature of the body would not elicit the body's response to infection, which includes an immune response (production of antibody and a cell-mediated response) and production of inflammatory cytokines, such as Interleukin-1 and tumor necrosis factor.[15] The advantage of use of infection in causing a therapeutic fever has not yet been demonstrated.

SOME PHYSIOLOGIC ABNORMALITES OF ASD

The majority of studies on issues of ASD have involved very few subjects. This has contributed to conflicting reports in autistic individuals. For example, increased cerebral blood flow has been documented in subjects with ASD,[16] and, in contrast, general hypoperfusion of the brain has been reported by others.[17] Reynall and Harris[18] present an explanation associating autism with a decrease of gamma amino butyric acid causing increased production of glutamate, triggering release of vasodilators and increased blood flow. Although the idea that fever may decrease autism symptoms by improving brain blood flow is still is question,[12] fever, of course, is associated with an elevation of body temperature and the increased production of pro-inflammatory immune cytokines. Fever may reduce some symptoms of autism because it has been shown to reduce blood glutamate levels.[12] This increase in glutamate in the blood[19] and brain[19,20] of individuals with autism has been reported, and the increased glutamate has been suggested to contribute to the pathophysiology of autism.[21,22]

Regarding the positive effect of lowering the symptoms of autism by infectious fever described above, it should be noted that the fevers were of short duration. When the fever subsided, the autistic symptoms returned to their pre-fever level. The infection causes an immune response, which could play a significant role in providing increased health by restoration of homeostasis. Certainly there is a communication between the immune and nervous systems.[23] For example, Herbert describes the contribution of the environment and environmentally vulnerable physiology to ASD.[24]

Immune and autoimmune considerations of ASD have been described by Gesundheit et al.[25] Furthermore, Shen et al. reported that altered plasma levels of chemokines in autism are associated with social behaviors,[26] and Filiano et al.[27] described the unexpected role of interferon gamma in regulating neuronal connectivity and social behavior.

MALARIOTHERAPY AND FEVER

It has been known since ancient times that Hippocrates used malaria fever to produce a calming effect on epileptic people.[28] Most prominent in citations from the past is Julius Wagner-Jauregg, a Nobel prize winner of 1927, who described the therapeutic value of malaria inoculation and resultant fever in the treatment of neurosyphilis, also known as dementia paralytica, considered an incurable disease.[29,30] A history of the use of fever to cure the progressive paralysis caused by a syphilitic brain disease was given in the Nobel lecture by Julius Wagner-Jauregg.[29] At the time of the award of the Nobel prize, Wagner-Jauregg stated the use of fever (from malaria) was currently used in all the countries of Europe, and in North and South America, South Africa, the Dutch East Indies, and Japan. In his experience, 84.8% of his patients obtained a full remission and 12.1% a partial remission after malariotherapy, and that only 1 in 38 had to be committed to an asylum. The treatment was performed in the hospital with monitoring of patients' vital signs and laboratory tests. A strain of tertian malaria (i.e., causing a fever every other day) was given by injection. This strain was very sensitive to quinine, which cured the malaria completely and permanently. When tertian malaria was acquired naturally, the patients remained carriers of the plasmodium, and the paralysis would recur. Therefore, the patients were kept under mosquito-proof netting during the duration of the treatment. The malaria was cured with quinine sulfate. After penicillin was discovered and proved to cure syphilis, the use of malaria treatment was discontinued.[28,30] However, other means of producing a fever were tried, including introduction into the patient of a parasitic disease, injection of a foreign protein, injections of sulphur, administration of diathermy or radiotherapy, placing the patient in an electromagnetic field, simple immersion of the individual in a hot bath, or placing the patient in a heat cabinet.[28]

More recently, Freitas et al[30] described historic and recent uses of the curative effect of fevers following treatment with malaria. Malariotherapy has been used to treat human immunodeficiency virus in China, syphilis, mental disease, as well as Lyme disease. Recent research in mouse models of autism has used fever induced by lipopolysaccharide.[31]

SULFORAPHANE AND FEVER

Sulforaphane, a phytochemical derived from a number of cruciferous vegetables, most notably broccoli sprouts, has metabolic effects that in some ways resemble that of fever.[32] It has potent activity in upregulating genes that control mechanisms involved in oxidative stress and inflammation,[33] which are mechanisms involved in autism.[1]

Singh et al[32,33] described the fever-like effect of Sulforaphane and its intracellular effects in addition to results of their clinical trial of Sulforaphane in young adults with autism. Using Sulforaphane as a treatment of autism, Singh et al.[32] demonstrated that Sulforaphane, administered by daily oral doses (50-150 umol) for eighteen weeks, followed by four weeks without treatment, substantially improved behavior of 29 young men with moderate to severe ASD. The autism was assessed by the Aberrant Behavior Checklist, Social Responsiveness Scale, and Clinical Global Impression Improvement Scale. Participants receiving Sulforaphane, vs. closely matched placebo controls, showed improvement in social interaction, abnormal behavior, and verbal communication. After discontinuation of treatment, total scores on all scales rose toward pretreatment level. In a more recent report, Singh and Zimmerman[33] describe the fever-like effect of Sulforaphane and intracellular effects in addition to results of a clinical trial of Sulforaphane in young adults with autism. Liu et al[34] described several ASD-associated basic physiological pathways that can be regulated by the small molecule phytochemical Sulforaphane and suggested how biomarkers could guide novel treatment strategies to correct these biochemical abnormalilties in order to improve core and associated symptoms of ASD.

NORMAL BODY TEMPERATURE AND FEVER

The "normal" functioning of the body's many processes are rhythmic. Humans, like all other organisms that inhabit Earth, have a rhythmic order underlying life.[35] Actually, change and not constancy is the norm of life and the rhythmic timing of change makes predictability a reality. This applies to body temperature[36] and virtually every other body function in humans, that rises and falls every 24 hours in relation to the daily light and dark spans with a so-called circadian/24h/diurnal rhythm.[37] Body temperature (oral or rectal) typically is lowest upon arising and highest in late activity (late afternoon or early evening).

Many if not all disease symptoms also express predictable peaks/troughs throughout the day/night in relation to one's sleep/wake schedule.[38] This includes certain aspects of fever, including acute onset of bacterial infection more prevalent in the morning (~06:00-10:00h) and of viral infection in the afternoon/evening (~16:00-22:00h).[39] Of interest, fever of children infected with plasmodium falciparum malaria parasite is ~3.5-fold more frequent at 18:00h than 06:00h[40] and fever onset in neutropenia is 5.5-fold more frequent at ~21:30h than 09:00h.[41]

Thus, for diagnostic and treatment purposes in order to possibly better affect underlying mechanisms and thereby more effectively alleviate symptoms, time of day, or more correctly, stage of rhythm, should to be taken into account when attempting to induce fever in ASD.

SUMMARY

While autism was once considered to be an incurable disorder, this is no longer the case, with many documentations of cures. In addition, the finding that fever alleviates symptoms of autism is promising. Some approaches that might be beneficial include using lipopolysaccharide-induced fevers, as has been tested in mouse models.[31] In addition, Sulforaphane has been documented to produce fever-like effects, and shows promise as a productive treatment of autism.[33]

It is critically important, if fever treatment of autism is used, that the cause of fever can be cured. As noted above, Wagner-Jauregg used a strain of malaria that could be cured by quinine. Because it has been documented that autohemotherapy cures herpes infections,[42] the use of herpes in the induction of fever to treat autism should be considered. The literature to date suggests that purposeful induction of a fever that can be cured warrants further investigation in ASD and related disorders in an attempt to alleviate symptoms and/or cure afflicted individuals.

DECLARATION OF INTEREST

The authors report no conflicts of interest and alone are responsible for the content and writing of this article. This review has been funded by Edmond Enterprises, LLC, of which Dr. H.V. Ratajczak is the sole member.

CONFLICT OF INTEREST

None.

REFERENCES

1. Herbert M, Weintraub K. The Autism Revolution: Whole-Body Strategies for Making Life All It Can Be. Ballantine Books, New York, NY 2012; 320.
2. Lord C, Luyster R, Guthrie W, Pickles A. Patterns of developmental trajectories in toddlers with autism spectrum disorder. J Consult Clin Psychol. 2012; 80:477-489.
3. Fein D, Barton M, Eigsti I-M, et al. Optimal outcome in individuals with a history of autism. J Child Psychol Psychiat. 2013;54:195-205.
4. Sutera S, Panday J, Esser EL, et al. Predictors of optimal outcome in toddlers diagnosed with Autism Spectrum Disorders. J Autism Dev Disord. 2007;37:98-107.
5. Helt M, Kelley E, Kinsbourne M, Pandey J, et al. Can children with autism recover? If so, how? Neuropsychol Rev. 2008;18:339-66.
6. Chawarska K, Klin A, Paul R, Macari S, Volkmar F. A prospective study of toddlers with ASD: short-term diagnostic and cognitive outcomes. J Child Psychol Psychiat. 2009;50:1235-1245.
7. Anderson DK, Liang JW, Lord C. Predicting young adult outcome among more or less cognitively able individuals with autism spectrum disorders. J Child Psychol Psychiat. 2014;55:485-494.
8. Curran LK, Newschaffer CJ, Lee LC, Crawford SO, Johnston MV, Zimmerman AW. Behaviors associated with fever in children with autism spectrum disorders. Pediatrics. 2007;120:e1386-1392.
9. Moorman D. Workshop report: Fever and autism._SFARI. 1 April 2010.
10. Mehler MF, Purpura DP. Autism, fever, epigenetics and the locus coeruleus. Brain Res Rev. 2009;59:388-392.
11. Louveau A, Smirnov I, Keyes TJ, et al. Structural and functional features of central nervous system lymphatics. Nature. 2015;523(7560):337-341.
12. Ghanizadeh A. Could fever and neuroinflammation play a role in the neurobiology of autism? A subject worthy of more research. Int J Hyperthermia. 2011;27;737-738.
13. Young AMH, Chakrabarti B, Roberts D, Lai M-C, Suckling J, Baron-Cohen S. From molecules to neural morphology: understanding neuroinflammation in autism spectrum condition. Mol Autism. 2016;7:1-8.
14. Ferretti CJ, Taylor BP, Noone R, Racine E, Kirsch J, Hollander E. Hyperthermia and the improvement of ASD symptoms. Eur Neuropsychopharmacol. 2016;26:890-891.

15. Walker BAM, Fantone JC. The inflammatory response. In: Immunology and Inflammation. Sigal LH and Ron Y, eds. McGraw-Hill Inc. New York 1994, 359-386.
16. Manouilenko I, Pagani M, Stone-Elander S, et al. Autistic traits, ADHD symptoms, neurological soft signs and regional cerebral blood flow in adults with autism spectrum disorders. Res Autism Spectr Disord. 2013;7:566-578.
17. Gupta SK, Ratnam RB. Cerebral perfusion abnormalities in children with autism and mental retardation: A segmental quantitative SPECT study. Indian Pediat. 46:161-164.
18. Reynell C, Harris JJ. The BOLD signal and neurovascular coupling in autism. Develop Cog Neurosc. 2013;6:72-79.
19. Shinohe A, Hashimoto K, Nakamura K, et al. Increased serum levels of glutamate in adult patients with autism. Prog Neuro-Psychopharmacol Biol Psychiat. 2006;30:1472-1477.
20. Ghanizadeh A. Increased glutamate and homocysteine and decreased glutamine levels in autism: A review and strategies for future studies of amino acids in autism. Dis Markers. 2013;35:281-286.
21. Tebartz van Elst L, Maier S, Fangmeier T, et al. Disturbed cingulate glutamate metabolism in adults with high-functioning autism spectrum disorder: evidence in support of the excitatory/inhibitory imbalance hypothesis. Mol Psychiatry. 2014 19:1314-1325.
22. Abu Shmais GA, Al-Ayadhi LY, Al-Dbass AM, El-Ansary AK. Mechanism of nitrogen metabolism-related parameters and enzyme activities in the pathophysiology of autism. J Neurodevel Disord. 2012;4:1-11.
23. Ziemssen T, Kern S. Psychoneuroimmunology – Cross-talk between the immune and nervous systems. J Neurol. 2007;254(S2):II8-11.
24. Herbert MR. Contributions of the environment and environmentally vulnerable physiology to autism spectrum disorders. Curr Opin Neurol. 2010;23:1-8.
25. Gesundheit B, Rosenzweig JP, Naor D, et al. Immunological and autoimmune considerations of autism spectrum disorders. J Autoimmun. 2013;44:1-7.
26. Shen Y, Ou J, Liu M, et al. Altered plasma levels of chemokines in autism and their association with social behaviors. Psychiatry Res. 2016;244:300-305.
27. Filano AJ, Xu Y, Tustison NJ, et al. Unexpected role of interferon-γ in regulating neuronal connectivity and social behavior. Nature. 2016; 535:425-429.
28 Karamanou M, Liappas I, Antoniou Ch, Androutsos G, Lykouras E. Julius Wagner-Jauregg (1857-1940): Introducing fever therapy in the treatment of neurosyphilis. Psychiatriki. 2013;24:208-212.
29. Julius Wagner-Jauregg. The treatment of dementia paralytica by malaria inoculation. Nobel Lectures. Physiology or Medicine 1922-1941. Elsevier Publishing Co., Amsterdam, 1965.
30. Freitas DRC, Santos JB, Castro CN. Healing with malaria: a brief historical review of malariotherapy for neurosyphilis, mental disorders and other infectious diseases. Rev Soc Bras Med Trop. 2014;47:260-261.
31. Zhong J, Amina S, Liang M, et al. Cyclic ADP-Ribose and heat regulate oxytocin release via CD38 and TRPM2 in the hypothalamus during social or psychological stress in mice. Front Neurosci. 2016;10:304.
32. Singh K, Connors SL, Macklin EA, et al. Sulforaphane treatment of autism spectrum disorder (ASD). PNAS. 2014;111(43):15550-15555.
33. Singh K, Zimmerman AW. Sulforaphane treatment of young men with autism spectrum disorder. CNS Neurol Disord Drug Targets. 2016;15:597-601.
34. Liu H, Talalay P, Fahey JW. Biomarker-guided strategy for treatment of autism spectrum disorder (ASD). CNS Neurol Disord Drug Targets. 2016;15:602-613.
35 Koukkari WL, Sothern RB. Introducing Biological Rhythms. A primer on the temporal organization of life, with implications for health, society, reproduction and the natural environment. New York: Springer, 2006, 655.
36. Simpson HW, Gruen W, Halberg E, et al. Human thermometry in health and disease: the chronobiologist's perspective. In: Chronobiotechnology and Chronobiological Engineering. NATO ASI Series. Scheving LE, Halberg F, Ehret CF, eds. Dordrecht: Martinus Mijhoff Publ, 1987. 141-188.
37. Sothern RB. Chapter 11: Clinical Medicine. In: Koukkari WL, Sothern RB, eds. Introducing Biological Rhythms. New York: Springer, 2006, 426-525.
38. Smolensky MH, Portaluppi F, Manfredini R, et al. Diurnal and twenty-four hour patterning of human diseases: acute and chronic common and uncommon medical conditions. Sleep Med Rev. 2015;21:12-22.
39. Hejl Z. Daily, lunar, yearly and menstrual cycle and bacterial or viral infections in man. J Interdiscipl Cycle Res. 1977;8:250e8.
40. Lell B, Brandts CH, Graninger W, Kremsner PG. The circadian rhythm of body temperature is preserved during malarial fever. Wien Klin Wochenschr. 2000;112(23):1014-1015.
41. Maher J, Browne P, Daly L, McCann SR, Daily PA. A circadian distribution to febrile episodes in neutropenic patients. Support Care Cancer. 1993;(1:98-100.
42. Olwin JH, Ratajczak HV, House RV. Successful treatment of herpetic infections by autohemotherapy. J Altern Complem Med. 1997;2:155-158.