

Assessing Human Health-Correlation of Autoimmune Diseases with Chemically Suppressed Acute Infections of Patient's Past Medical History

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Abstract: This is an effort to present to the medical profession, a new concept for evaluating the level of health of an individual, through the theory of Professor George Vithoulkas.

The theory of Levels of Health has proven to be a valuable aid to clinicians as it enables them not only to evaluate the patient's health status, but also to adapt the course of individual treatment. This is achieved by assessing the body's response, to therapy of any kind. When coupled with the 'Continuum of unified theory of diseases', disease and treatment are better understood and provide a reference standard for clinicians.

The application of the concepts of Psychoneuroimmunology (PNI) and those correlating the suppression of acute diseases with simultaneous emergence of chronic conditions opens up new horizons in understanding the human body's nature in this respect. The treatment of acute diseases can lead in two opposite directions: it can either bring about a cure or, on the contrary, cause a gradual degeneration of the body's PNI defense.

With regard to 'symptoms,' their reduction or the disappearance following a treatment, is either because the body does not need them anymore, having reached a higher level of health or, that it cannot maintain them anymore, as its health has been degraded due to the treatment.

The ideal treatment should not simply eliminate the symptoms while the overall health deteriorates. Instead, it must aim at enhancing the action of the immune system in its own direction by strengthening the symptoms generated by it. This way the immune system becomes stronger after getting rid of the disease and the overall health becomes better.

Keywords: Past history, fever, acute infections, autoimmunity, suppression, drugs, Immune system, Prognosis, Levels of Health, Continuum of diseases, Psychoneuroimmunology.

Keymessage: Autoimmunity has to be correlated with chemically suppressed acute infection of the past medical history, in order to understand and treat patients' immunological profile as a whole entity. Protective immune mechanisms must be supported instead of suppressed to make the organism better in health.

BACKGROUND

The levels of health theory was originally presented in the book the "Science of Homeopathy" and recently in a more complete form in "The Levels of Health" [1, 2]. Initially, the classification of the patients' health level was conceived and created in order to understand and explain the different reactions that patients experienced following the administration of a homeopathic remedy. But, it soon became clear that this theory could explain responses to all therapies, including the conventional one.

According to this theory, patients may be classified into different levels of health, from the highest to the lowest. The criteria used for this classification are the

immune responses of the body to different disease agents and treatments (Table 1). Between the uppermost level - the healthiest state and the lowest - the most degenerated near death state, lie all the intermediate levels. We may observe in the table that as we go down the levels, the diseases get more complicated and the response to treatment, more difficult. The infectious agents become more virulent as we go down the levels; from streptococcus and staphylococcus infection to proteus to bacillus pyocyaneus and to fungi [3, 4].

It has been observed that sometimes, after an acute disease, a chronic condition emerges. Such a reaction is usually attributed to the infection itself or to the side effects of the medication [5-9]. Also after the emergence of a chronic condition, the organism stops developing acute febrile infections, that were regular in the past [2]. This change may mean that the immune system is compromised and does not have the

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Table 1: Levels of Health According to Homeopathic Theory by Prof. G. Vithoulkas: (Group A to group D, from higher to lower levels of health)

Group A Levels 1-3	Homeopathic potency up to 50m	All diseases - but mostly functional disturbances curable by homeopathy, symptoms lead to clear homeopathic remedy infrequent infections, mostly typical bacterial childhood diseases in the uppermost level therapeutic homeopathic aggravation may not appear. very seldom acute diseases. in the lower levels 2&3, mild therapeutic homeopathic aggravation may appear. occasional acute diseases. in the uppermost level strong health, usually no repetition of the homeopathic remedy or other remedy will be needed in the lower levels 2-3 more homeopathic remedies in the appropriate order will be needed, in order to have the maximum result. in the lower levels - 2&3, acute diseases appear more frequently
Group B Levels 4-6	Homeopathic potency 10m-1m	As we go down the levels, we have the appearance of more frequent and severe acute conditions (e.g. pneumonia) bacterial infections more resistant to antibiotics more severe homeopathic aggravation more homeopathic remedies, one after another, will be needed in the lower level, acute diseases recurrent, after treating with chemical drugs, the level of health goes down. in the lower levels 5-6, therapeutic homeopathic aggravation can last a long time
Group C Levels 7-9	Homeopathic potency 200 ch	More severe chronic degenerative diseases (e.g. crohn disease, ulcerative colitis) in the upper level, less acute diseases, less severe, subside easily in the lower level, no appearance of acute conditions in the upper level, very severe initial therapeutic homeopathic aggravation in the upper level, homeopathic therapeutic aggravation can be severe - requiring conventional medical intervention 4-5 homeopathic remedies, in the appropriate order will be needed, before realising the positive effects. a wrong homeopathic remedy can confuse the case. in the lower level 9, homeopathic aggravation may mean that the remedy was wrong
Group D Levels 10-12	homeopathic potency 30CH-12CH repeatedly	Most severe chronic diseases, effecting immune and cns several homeopathic remedies will be needed in sequence before an acute disease appears. no acute infections at all no initial aggravation. if homeopathic aggravation appears, then the remedy was definitely wrong. in the lower level, cases incurable by homeopathy, only palliation is possible

potential to initiate and complete a necessary acute inflammatory process.

So, who is healthier? A child presenting recurrent febrile tonsillitis or a child which has developed asthma or Crohn's disease, after tonsillectomy, but who does not develop any more febrile infections? [10] On what basis should we decide whether our therapeutic interventions led the organism to a higher, or to a lower level of health?

The human body fights as a whole in order to maintain homeostasis, It has become evident through

the study of Psychoneuroimmunology that the body has a mechanism to establish specific memory of immunological reactions to a random disease agent, that has previously been encountered and fought against [11, 12]. It is programmed to react as an integrated system to recruit the necessary inflammatory processes - including high fever - to achieve this. According to this theory, the body's inability to develop high fever during an epidemic or even worse, the inability to develop any acute febrile disease during the running of a chronic condition, is definitely a negative prognostic factor for the overall health condition.

Cure Vs Treatment

All physicians agree that the ideal outcome of a treatment is cure; this means that no further treatment is needed, for a specific disease.

In the absence of the ideal, the treatment must result in an improved state of health - which must be apparent on evaluating the present community health status. The situation we see in the world today is quite the opposite. In reality, statistics show that the percentage of the population diagnosed with chronic and degenerative diseases, especially at young age, is dramatically increasing [13-17]. This trend should be of concern to the medical community.

Treated Disease but not Cured Predisposition

Such a shift in the population health status should make us analyze every time we prescribe a treatment, whether it has the potential to cure the patient or to just eliminate the symptoms of the disease.

For instance, consider the treatment of a child with acute suppurative otitis media. If within a few days of treatment, the clinical signs and symptoms disappeared, we assume that the otitis has been cured. If after two months, the same child returns with another incidence of the same, we have two ways to explain the reappearance of this second episode: it is a random occurrence, or we had never really cured it in the first place [18].

Let us assume we further repeated the treatment and the signs and symptoms disappeared again. After six months, the child presents with his first asthma attack. Can we consider the asthma attack as a random occurrence as well? Or, should we think that we had never cured the child and the immune system has now become weaker - since a more serious chronic inflammation has manifested? [19]. If, after our constant efforts to chemically treat the asthma, the same child develops a psychotic behavior a year later, we could again either consider the appearance of this third, even more serious condition, as a random occurrence or, realize that we never cured the child. We now have to deal with an even more compromised immune system.

The inference is that the immune system was not allowed to successfully complete the inflammatory course by raising a high fever in the first place and therefore established a state of a persistent ineffectual inflammatory condition manifesting as asthma with

acute exacerbations. The activated chronic condition is in keeping with the hereditary predisposition that the organism carries. This means that the inflammatory process, representing both the disease and immune system status is actually a continuous process from birth to the point of consideration in time [20-22].

Correlation between the Patient's Present Complaint and his Past Medical History

Studies correlating acute diseases and chronic, like autoimmune disorders, have provided useful data about the potential protection of the body by the former, against the latter [23-31]. Furthermore, since the associations between eczema, allergic rhinitis and asthma are documented in the scientific literature [32, 33] the next logical step is the study of other such correlations. We also need to study body's reaction to therapeutic interventions in the acute and chronic diseases.

In the practice scenario, the pediatric dermatologist may have been satisfied with the outcome of the treatment with corticosteroids in neurodermatitis earlier in his patient's life. But he may never be informed that this same child, subsequently develops allergic asthma. Therefore, this child's allergic predisposition was never actually eradicated.

Theory of "Levels of Health" and the "Continuum of a Unified Theory of Diseases"

In the above example the infantile eczema seems to have disappeared following the use of topical corticosteroids. However, the important question is, whether the overall organism is healthier than before.

Medicine needs a unified theory to evaluate the patient's overall health in the long run, focusing beyond the specific diseases appearing at the time the patient is seeking medical help. This theory has been provided in the article: "The continuum of a unified theory of diseases", by G. Vithoukas and S. Carlino [34]. A significance of this theory, is in the explanation of the complex issues of health and disease, in two ways: first, by treating the patient as a cohesive Psycho - neuro - immunological entity and second, by evaluating the incidences in his entire medical history; by analyzing the patient's present disease in the light of his medical history and all past treatments. Although this theory has been developed for Homeopathy, it is relevant to and can be applied to all faculties of medicine [35-40].

SALIENT FEATURES OF THE THEORY

1. Immuno - Sufficiency to Raise Fever

The ability to raise a high fever requires the proper functioning of the immune system, so that the hypothalamus is capable of responding to the PGE2 being released. In order for this to happen, the body should readily be able to produce cytokines, interleukin-1, interleukin-6, TNF-alpha: all endogenous pyrogens, in response to the LBP-LPS complex [41-44]. This is a protective mechanism through which the immune system learns to fight pathogens successfully.

2. Effect of Suppression of Acute Inflammations

The aggressive suppression of fever leads to increased infection episodes and higher mortality rates, compared to a milder treatment of fever [45, 46]. Suppressing fever even in cases of septic shock has been seriously questioned. Studies conducted with ICU patients have shown that the survival rate in such patients is increased when they are allowed to develop high fever [47]. These evidences have led researchers to approach parents, pharmacists, and physicians about the appropriate management of fevers [48-51]. According to the "Levels of Health" theory, the frequency of infections increases because of the lowering of a person's health.

3. Activation of Chronic Inflammatory Process - Activation of Autoimmune Diseases

Eventually the patient reaches a point when he starts presenting frequent relapses of an acute infection. This means that the body is in a state where it cannot take adequate advantage of the stimulus from a pathogen to mount an efficient inflammatory response required to develop PNI memory. Any therapeutic intervention at this crucial point can alter and determine the body's subsequent immunological evolution, its overall future health. All aggressive treatments (antipyretic, anti-inflammatory antibiotic etc), can suppress the symptoms and further compromise the immune system [52-55].

When, for instance, a child presents with tonsillitis for the fifth time within a year, the first question is whether the child was ever left to maintain a single episode with a high fever to achieve its immunological target. On the contrary, in such cases, exactly the opposite has often occurred. The body now reaches a state where it is unable to develop acute infections anymore due to its compromised immune system [20,

56-59] This "immunological silence" – of not developing a high fever - can last from a few months to a few years until the patient eventually develops a chronic disease. This silence in many cases indicates the beginning of a chronic degenerative disease, when the immune system shifts from acute inflammatory responses to sub acute persistent inflammation and eventually chronic [60].

We have been witnessing an epidemic rise in the prevalence of multiple sclerosis (MS), a demyelinating disease, in the young population [61]. It is the major cause of non-traumatic disability in young adults [62]. On inquiring the detailed history, we note that they often have long periods of no infections or high fever. We often hear them saying: "Everyone in my family got sick except me", appearing to be 'healthy'. However, these previously "robust" people, in the prime of their life, developed a degenerative autoimmune disease. It is common in such chronic degenerative diseases that patients report to have not developed any acute febrile infection for many years [2].

4. Re Emergence of Acute Inflammation during Treatment of Chronic Disease

During the course of treating a chronic condition, the re-emergence of an acute inflammatory condition, with high fever, is a positive prognostic factor. It indicates that the organism has gone back to the original condition of having acute episodes before the onset of chronic disease. This was our experience when we treated patients with severe migraine at the Headache Clinic of the "G.Genimatas" Public hospital in Athens, Greece [63]. It is also our repeated experience that autistic children do not easily develop acute infections, nor do they often raise high fever. But, improved conditions could be observed, when these children eventually developed an infection, after months or even years of treatment. We have heard their parents emphasize that their children improved during febrile episodes [64, 65]. Parents of autistic children, report in the online portals that their child's situation ameliorated after febrile infections. In recent years, many researchers are addressing this phenomenon akin to fever therapy of the old [65-67]. The US National Institute of Health is currently funding a study, researching the mechanism behind the improvement of the autism-related symptoms, during febrile infections [68].

5. Initial Enhancement of 'Symptoms'

With the correct homeopathic remedy in any given condition and if the disease is curable, there will be

enhancement of symptoms that the immune system has generated in response to the pathogenic stimulus. This is followed by cure of the disease in question and improvement of the health in general [2].

DISCUSSION

Treating Diseases by Suppressing the Symptoms - is it Right?

We must understand that symptoms don't constitute indications of disease. Symptoms are indications of the body's fight against a pathogenic stimulus. An organism without symptoms is either completely healthy, or dead. In every stage between these two extremes, the human body develops symptoms in its effort to combat disease agents, physical or mental.

The healthier an organism is, the more complete will be its reaction against a pathogenic stimulus. This complete reaction will result in an overall PNI response of the body [69-72].

For example, a child with fever will have poor appetite, will be thirsty and ask for small sips of water; his face will be hot but his hands and feet will be cold - which is a sign of peripheral vasoconstriction and central vasodilation. All these symptoms are manifested by the immune system as a reaction to the pathogen in order to achieve homeostasis [69]. Therefore therapy should assist this response and enhance the symptoms rather than suppressing them.

Such a process is followed in homeopathic treatment which results in initial aggravation of the symptoms; subsequently, the body's homeostasis will be restored, a PNI memory will develop and finally, the overall level of health will improve.

The initial aggravation of symptoms is a good sign and an indication that the body is truly moving in right direction under the effect of the treatment [73].

The Necessity of Linking Different Efficient Studies, with a Unified Theory

Medical universities have not taught the importance of a patient's health history with relevance to his present condition; that there is a "continuum" in the PNI of an organism from birth to the present. As a consequence, we classify more than half of the diseases as of 'unknown etiology'.

But several published studies support the 'Levels of Health' and 'Continuum' theories. However these

theories do not have a common theoretical background leading to the lack of conceptual connection between the process of diseases and cure. It may be necessary to initiate a research that will document the evidence to such a 'Unified Medical Theory.'

SUGGESTED FUTURE RESEARCH

- a. A retrospective, multi - centre study may be designed to establish whether or not, acute diseases' treatment is related to the development of chronic diseases later on. For example, if recurrent expression of allergic predisposition on the skin was left untreated prevented the appearance of severe asthma later on when compared to the ones treated with topical steroids.
- b. Establishment of an updating and reporting information system for physicians, via electronic messages from their respective Medical Association can help formulate a definitive inference regarding the fate of suppressing acute diseases. For instance, a dermatologist could receive, periodically, text messages reporting the health of the patients, with acne, he treated with retinoids. These reports would inform him that, some of those patients subsequently developed depression or even suicidal tendencies, while acne remained well controlled; meaning suppression but not cure of the neuro - hormonal basis of acne [74-76] and worsening of health.

Thus long term effects of medical interventions may be provided to the Medical Community.

CONCLUSION

The understanding of human organism as a whole is required to comprehend its response to disease stimuli and to promote health. The application of 'Levels of Health' theory and the 'Continuum' theory gives a sound basis for evaluating health and treatment in the light of new concepts evolving in medical science such as that of psychoneuroimmunology. If we are to make progress in medicine today, we must establish studies that follow a person's health from the beginning and record the pathogenic and therapeutic influences and then arrive at a bigger picture that can dictate the treatment strategies of future.

ROLES

Dr Spiros Kivellou drafted the original article and poster, the article was edited and poster was presented

in the conference by Dr Seema Mahesh. The guidance for the whole project and the theories presented are that of Prof George Vithoulkas

CONFLICT OF INTEREST

None.

ABBREVIATIONS

PNI	= Psychoneuroimmunology
TNF alpha	= Tumor Necrosis Factor Alpha
PGE2	= Prostaglandin E2
LBS	= Lipopolysaccharide binding protein
LPS	= Lipopolysaccharide
ICU	= Intensive Care Unit

REFERENCES

- Vithoulkas G. The science of homeopathy. Athens: A.S.O.H.M. 1978.
- Vithoulkas G, Woensel E. Levels of health. Alonissos, Greece: International Academy of Classical Homeopathy 2010.
- Casadevall A, Pirofski LA. Host-pathogen interactions: redefining the basic concepts of virulence and pathogenicity. *Infection and Immunity* 1999; 67(8): 3703-13.
- Hart PD, Russell E, Remington JS. The compromised host and infection. II. Deep fungal infection. *The Journal of Infectious Diseases* 1969; 120(2): 169-91. <https://doi.org/10.1093/infdis/120.2.169>
- Ghadirian P, Dadgostar B, Azani R, Maisonneuve P. A case-control study of the association between socio-demographic, lifestyle and medical history factors and multiple sclerosis. *Canadian Journal of Public Health* 2001; 92(4): 281.
- Hofstra AH, Li-Muller SM, Uetrecht JP. Metabolism of isoniazid by activated leukocytes. Possible role in drug-induced lupus. *Drug Metabolism and Disposition* 1992; 20(2): 205-10.
- Kim SW, Grant JE, Kim SI, Swanson TA, Bernstein GA, Jaszcz WB, Williams KA, Schlievert PM. A possible association of recurrent streptococcal infections and acute onset of obsessive-compulsive disorder. *The Journal of Neuropsychiatry and Clinical Neurosciences* 2004; 16(3): 252-60. <https://doi.org/10.1176/jnp.16.3.252>
- Kivity S, Agmon-Levin N, Blank M, Shoenfeld Y. Infections and autoimmunity—friends or foes? *Trends in Immunology* 2009; 30(8): 409-14.
- Molina V, Shoenfeld Y. Infection, vaccines and other environmental triggers of autoimmunity. *Autoimmunity* 2005; 38(3): 235-45. <https://doi.org/10.1080/08916930500050277>
- Koutroubakis IE, Vlachonikolis IG, Kapsoritakis A, Spanoudakis S, Roussomoustakaki M, Mouzas IA, Kouroumalis EA, Manousos ON. Appendectomy, tonsillectomy, and risk of inflammatory bowel disease. *Diseases of the Colon & Rectum* 1999; 42(2): 225-30. <https://doi.org/10.1007/BF02237133>
- Ziemssen T, Kern S. Psychoneuroimmunology—cross-talk between the immune and nervous systems. *Journal of Neurology* 2007; 254: 118-11.
- Maier SF, Watkins LR, Fleshner M. Psychoneuroimmunology: The interface between behavior, brain, and immunity. *American Psychologist* 1994; 49(12): 1004. <https://doi.org/10.1037/0003-066X.49.12.1004>
- Autoimmune Info - American Autoimmune Related Diseases Association [Internet]. AARDA. 2017 [cited 5 June 2017]. Available from: <https://www.aarda.org>
- Cooke A. Infection and autoimmunity. *Blood Cells, Molecules, and Diseases* 2009; 42(2): 105-7. <https://doi.org/10.1016/j.bcmd.2008.10.004>
- Lerner A, Jeremias P, Matthias T. The world incidence and prevalence of autoimmune diseases is increasing. *International Journal of Celiac Disease* 2015; 3(4): 151-5. <https://doi.org/10.12691/ijcd-3-4-8>
- Lipman TH, Katz LE, Ratcliffe SJ, Murphy KM, Aguilar A, Rezvani I, Howe CJ, Fadia S, Suarez E. Increasing incidence of type 1 diabetes in youth. *Diabetes Care* 2013; 36(6): 1597-603. <https://doi.org/10.2337/dc12-0767>
- Malaty HM, Fan X, Opekun AR, Thibodeaux C, Ferry GD. Rising incidence of inflammatory bowel disease among children: a 12-year study. *Journal of Pediatric Gastroenterology and Nutrition* 2010; 50(1): 27-31. <https://doi.org/10.1097/MPG.0b013e3181b99baa>
- Casselbrant ML, Mandel EM, Doyle WJ. Information on comorbidities collected by history is useful for assigning Otitis Media risk to children. *International Journal of Pediatric Otorhinolaryngology* 2016; 85: 136-40. <https://doi.org/10.1016/j.ijporl.2016.03.040>
- MacIntyre EA, Heinrich J. Otitis media in infancy and the development of asthma and atopic disease. *Current Allergy and Asthma Reports* 2012; 12(6): 547-50. <https://doi.org/10.1007/s11882-012-0308-x>
- Maté-Jimenez J, Correa-Estañ JA, Perez-Miranda M, Gomez-Cedenilla A, Pajares JM, Moreno-Otero R. Tonsillectomy and inflammatory bowel disease location. *European Journal of Gastroenterology & Hepatology* 1996; 8(12): 1185-888. <https://doi.org/10.1097/00042737-199612000-00010>
- Schlehofer B, Blettner M, Preston-Martin S, Niehoff D, Wahrendorf J, Arslan A, Ahlbom A, Choi WN, Giles GG, Howe GR, Little J. Role of medical history in brain tumour development. Results from the international adult brain tumour study. *International Journal of Cancer* 1999; 82(2): 155-60. [https://doi.org/10.1002/\(SICI\)1097-0215\(19990719\)82:2<155::AID-IJC1>3.0.CO;2-P](https://doi.org/10.1002/(SICI)1097-0215(19990719)82:2<155::AID-IJC1>3.0.CO;2-P)
- Haroon E, Raison CL, Miller AH. Psychoneuroimmunology meets neuropsychopharmacology: translational implications of the impact of inflammation on behavior. *Neuropsychopharmacology* 2012; 37(1): 137-62. <https://doi.org/10.1038/npp.2011.205>
- Ahmed R, Gray D. Immunological memory and protective immunity: understanding their relation. *Science* 1996; 272(5258): 54. <https://doi.org/10.1126/science.272.5258.54>
- Bach JF. Infections and autoimmune diseases. *Journal of Autoimmunity* 2005; 25: 74-80. <https://doi.org/10.1016/j.jaut.2005.09.024>
- Bach JF. The effect of infections on susceptibility to autoimmune and allergic diseases. *New England Journal of Medicine* 2002; 347(12): 911-20. <https://doi.org/10.1056/NEJMra020100>
- Bach JF. Six questions about the hygiene hypothesis. *Cellular Immunology* 2005; 233(2): 158-61. <https://doi.org/10.1016/j.cellimm.2005.04.006>

- [27] Cahoon EK, Inskip PD, Gridley G, Brenner AV. Immune-related conditions and subsequent risk of brain cancer in a cohort of 4.5 million male US veterans. *British Journal of Cancer* 2014; 110(7): 1825-33. <https://doi.org/10.1038/bjc.2014.97>
- [28] Cooke A, Zacccone P, Raine T, Phillips JM, Dunne DW. Infection and autoimmunity: are we winning the war, only to lose the peace? *Trends in Parasitology* 2004; 20(7): 316-21.
- [29] Gaisford W, Cooke A. Can infections protect against autoimmunity? *Current Opinion in Rheumatology* 2009; 21(4): 391-6.
- [30] Okada H, Kuhn C, Feillet H, Bach JF. The 'hygiene hypothesis' for autoimmune and allergic diseases: an update. *Clinical & Experimental Immunology* 2010; 160(1): 1-9. <https://doi.org/10.1111/j.1365-2249.2010.04139.x>
- [31] van der Kleij D, Yazdanbakhsh M. Control of inflammatory diseases by pathogens: lipids and the immune system. *European Journal of Immunology* 2003; 33(11): 2953-63. <https://doi.org/10.1002/eji.200324340>
- [32] Burgess JA, Lowe AJ, Matheson MC, Varigos G, Abramson MJ, Dharmage SC. Does eczema lead to asthma? *Journal of Asthma* 2009; 46(5): 429-36.
- [33] Spergel JM. From atopic dermatitis to asthma: the atopic march. *Annals of Allergy, Asthma & Immunology* 2010; 105(2): 99-106. <https://doi.org/10.1016/j.anai.2009.10.002>
- [34] Vithoulkas G, Carlino S. The "continuum" of a unified theory of diseases. *Med Sci Monit* 2010; 16(2): 15.
- [35] O'connor TG, Moynihan JA, Caserta MT. Annual research review: the neuroinflammation hypothesis for stress and psychopathology in children—developmental psychoneuroimmunology. *Journal of Child Psychology and Psychiatry* 2014; 55(6): 615-31. <https://doi.org/10.1111/jcpp.12187>
- [36] Root-Bernstein R, Fairweather D. Complexities in the relationship between infection and autoimmunity. *Current Allergy and Asthma Reports* 2014; 14(1): 407. <https://doi.org/10.1007/s11882-013-0407-3>
- [37] Sampson TR, Mazmanian SK. Control of brain development, function, and behavior by the microbiome. *Cell Host & Microbe* 2015; 17(5): 565-76. <https://doi.org/10.1016/j.chom.2015.04.011>
- [38] Solomon GF. Psychoneuroimmunology: interactions between central nervous system and immune system. *Journal of Neuroscience Research* 1987; 18(1): 1-9. <https://doi.org/10.1002/jnr.490180103>
- [39] Sperner-Unterweger B. Biological hypotheses of schizophrenia: possible influences of immunology and endocrinology. *Fortschritte der Neurologie-Psychiatrie* 2005; 73: S38-43.
- [40] Sperner-Unterweger B. Immunological aetiology of major psychiatric disorders. *Drugs* 2005; 65(11): 1493-520. <https://doi.org/10.2165/00003495-200565110-00004>
- [41] Riedel W, Maulik G. Fever: an integrated response of the central nervous system to oxidative stress. *Molecular and Cellular Biochemistry* 1999; 196(1): 125-32. <https://doi.org/10.1023/A:1006936111474>
- [42] Smith RS. The immune system is a key factor in the etiology of psychosocial disease. *Medical Hypotheses* 1991; 34(1): 49-57. [https://doi.org/10.1016/0306-9877\(91\)90064-6](https://doi.org/10.1016/0306-9877(91)90064-6)
- [43] Stefferl A, Hopkins SJ, Rothwell NJ, Luheshi GN. The role of TNF- α in fever: opposing actions of human and murine TNF- α and interactions with IL- β in the rat. *British Journal of Pharmacology* 1996; 118(8): 1919-24. <https://doi.org/10.1111/j.1476-5381.1996.tb15625.x>
- [44] Sternberg EM, Chrousos GP, Wilder RL, Gold PW. The stress response and the regulation of inflammatory disease. *Annals of Internal Medicine* 1992; 117(10): 854-66. <https://doi.org/10.7326/0003-4819-117-10-854>
- [45] Schulman CI, Namias N, Doherty J, Manning RJ, Li P, Elhaddad A, Lasko D, Amortegui J, Dy CJ, Dlugasch L, Baracco G. The effect of antipyretic therapy upon outcomes in critically ill patients: a randomized, prospective study. *Surgical Infections* 2005; 6(4): 369-75. <https://doi.org/10.1089/sur.2005.6.369>
- [46] Ackerman Z, Flugelman MY, Wax Y, Shouval D, Levy M. Hepatitis during measles in young adults: possible role of antipyretic drugs. *Hepatology* 1989; 10(2): 203-6. <https://doi.org/10.1002/hep.1840100214>
- [47] Su F, Nguyen ND, Wang Z, Cai Y, Rogiers P, Vincent JL. Fever control in septic shock: beneficial or harmful? *Shock* 2005; 23(6): 516-20.
- [48] de Bont EG, Brand PL, Dinant GJ, van Well GT, Cals J. Risks and benefits of paracetamol in children with fever. *Nederlands Tijdschrift Voor Geneeskunde* 2013; 158(2): A6636. <https://doi.org/10.1093/fampra/cmz029>
- [49] de Bont EG, Peetoom KK, Moser A, Francis NA, Dinant GJ, Cals JW. Childhood fever: a qualitative study on GPs' experiences during out-of-hours care. *Family Practice* 2015; 32(4): 449-55.
- [50] Kelly M, McCarthy S, O'Sullivan R, Shiely F, Larkin P, Brenner M, Sahn LJ. Drivers for inappropriate fever management in children: a systematic review. *International Journal of Clinical Pharmacy* 2016; 38(4): 761-70. <https://doi.org/10.1007/s11096-016-0333-2>
- [51] Knoebel EE, Narang AS, Ey JL. Fever: to treat or not to treat. *Clinical Pediatrics* 2002; 41(1): 9-16. <https://doi.org/10.1177/000992280204100104>
- [52] Bailey LC, Forrest CB, Zhang P, Richards TM, Livshits A, DeRusso PA. Association of antibiotics in infancy with early childhood obesity. *JAMA Pediatrics* 2014; 168(11): 1063-9. <https://doi.org/10.1001/jamapediatrics.2014.1539>
- [53] Jernberg C, Löfmark S, Edlund C, Jansson JK. Long-term impacts of antibiotic exposure on the human intestinal microbiota. *Microbiology* 2010; 156(1): 3216. <https://doi.org/10.1099/mic.0.040618-0>
- [54] Smith TW, Girolami UD, Hickey WF. Neuropathology of immunosuppression. *Brain Pathology* 1992; 2(3): 183-94. <https://doi.org/10.1111/j.1750-3639.1992.tb00691.x>
- [55] Zandman-Goddard G, Shoenfeld Y. HIV and autoimmunity. *Autoimmunity Reviews* 2002; 1(6): 329-37. [https://doi.org/10.1016/S1568-9972\(02\)00086-1](https://doi.org/10.1016/S1568-9972(02)00086-1)
- [56] Earn DJ, Andrews PW, Bolker BM. Population-level effects of suppressing fever. In *Proc. R. Soc. B* 2014 Mar 7 (Vol. 281, No. 1778, p. 20132570). The Royal Society.
- [57] Gündüz Ö. Immunomodulation with antibiotics. immunomodulatory and immunosuppressive drugs in dermatology 2016; 19.
- [58] Lee WM. Hepatitis B virus infection. *New England Journal of Medicine* 1997; 337(24): 1733-45. <https://doi.org/10.1056/NEJM199712113372406>
- [59] Torres AR. Is fever suppression involved in the etiology of autism and neurodevelopmental disorders? *BMC Pediatrics* 2003; 3(1): 9.
- [60] Koenig W, Sund M, Fröhlich M, Fischer HG, Löwel H, Döring A, Hutchinson WL, Pepys MB. C-reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men. *Circulation* 1999; 99(2): 237-42. <https://doi.org/10.1161/01.CIR.99.2.237>
- [61] Alonso A, Hernán MA. Temporal trends in the incidence of multiple sclerosis A systematic review. *Neurology* 2008; 71(2): 129-35. <https://doi.org/10.1212/01.wnl.0000316802.35974.34>

- [62] World Health Organization (WHO). Atlas. Multiple sclerosis resources in the world, 2008. World Health Organization 2008.
- [63] Kivellos S, Skifti S, Vithoulikas G. EHMTI-0396. Reappearance of high fever on migraine patients, after individualized homeopathic treatment, is a valuable prognostic factor. *The Journal of Headache and Pain* 2014; 15(1): M7.
- [64] 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(6): e1386-92.
- [65] Megremi AS. Is fever a predictive factor in the autism spectrum disorders? *Medical Hypotheses* 2013; 80(4): 391-8.
- [66] Cann SH, Van Netten JP, Van Netten C. Dr William Coley and tumour regression: a place in history or in the future. *Postgraduate Medical Journal* 2003; 79(938): 672-80.
- [67] Mehler MF, Purpura DP. Autism, fever, epigenetics and the locus coeruleus. *Brain Research Reviews* 2009; 59(2): 388-92.
<https://doi.org/10.1016/j.brainresrev.2008.11.001>
- [68] NIH funds study on why fever sometimes eases autism symptoms [Internet]. *Autism Speaks*. 2017 [cited 6 June 2017]. Available from: <https://www.autismspeaks.org/science/science-news/nih-funds-study-exploring-why-fever-sometimes-eases-autism-symptoms>.
- [69] Chrousos GP, Gold PW. The concepts of stress and stress system disorders: overview of physical and behavioral homeostasis. *JAMA* 1992; 267(9): 1244-52.
<https://doi.org/10.1001/jama.1992.0348009002034>
- [70] Duff GW, Durum SK. Fever and immunoregulation: hyperthermia, interleukins 1 and 2, and T-cell proliferation. *The Yale Journal of Biology and Medicine* 1982; 55(5-6): 437.
- [71] Kiecolt-Glaser JK, McGuire L, Robles TF, Glaser R. Emotions, morbidity, and mortality: new perspectives from psychoneuroimmunology. *Annual Review of Psychology*. 2002; 53(1): 83-107.
<https://doi.org/10.1146/annurev.psych.53.100901.135217>
- [72] Kiecolt-Glaser JK, McGuire L, Robles TF, Glaser R. Psychoneuroimmunology: psychological influences on immune function and health. *Journal of Consulting and Clinical Psychology* 2002; 70(3): 537.
<https://doi.org/10.1037/0022-006X.70.3.537>
- [73] Stub T, Salamonsen A, Alraek T. Is it possible to distinguish homeopathic aggravation from adverse effects? A qualitative study. *Forschende Komplementärmedizin/Research in Complementary Medicine* 2012; 19(1): 13-9.
<https://doi.org/10.1159/000335827>
- [74] Barak Y, Wohl Y, Greenberg Y, Dayan YB, Friedman T, Shoal G, Knobler HY. Affective psychosis following Accutane (isotretinoin) treatment. *International Clinical Psychopharmacology* 2005; 20(1): 39-41.
<https://doi.org/10.1097/00004850-200501000-00008>
- [75] Bravard P, Krug M, Rzeznick JC. Isotretinoïne et depression: soyons vigilants. *Les Nouvelles Dermatologiques* 1993; 12(4): 233-54.
- [76] Bremner JD, Shearer K, McCaffery P. Retinoic acid and affective disorders: the evidence for an association. *The Journal of Clinical Psychiatry* 2012; 73(1): 37.
<https://doi.org/10.4088/JCP.10r05993>

Received on 01-11-2017

Accepted on 30-11-2017

Published on 31-12-2017

DOI: <https://doi.org/10.12970/2310-9874.2017.05.06>© 2017 Kivellos *et al.*; Licensee Synergy Publishers.

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