Parasitosis, dopaminergic modulation and metabolic disturbances in schizophrenia: evolution of a hypothesis

Tamas Treuer, Ferenc Martenyi & Jamie Karagianis

Neuroscience Research, Area Medical Center Vienna, Eli Lilly Regional GmbH, Vienna, Austria

Correspondence to: Tamas Treuer, MD., PhD.
Neuroscience Research, Area Medical Center Vienna, Eli Lilly Regional GmbH
Kölblgasse 8-10, A-1030 Vienna, Austria
PHONE: +36 304752080
FAX: +36 13285103
EMAIL: treuert@lilly.com

Submitted: August 24, 2007 *Accepted: September 20, 2007*

Key words: **schizophrenia; parasitosis; dopamine; metabolic disturbances**

Neuroendocrinol Lett 2007; **28**(5):535–540 **PMID:** 17984933 NEL280507A29

Abstract

Recent meta-analyses have provided a comprehensive overview of studies investigating *Toxoplasma gondii* antibodies in schizophrenic patients, thus attempting to clarify the potential role these infections might play in causing schizophrenia. Issues for further research have been suggested. Associations and theories that may enrich the current level of knowledge with regard to this significant subject deserve attention. Anti-parasitic agents as well as antipsychotics are effective in treating parasitosis. Both classes of drugs have been shown to exert dopaminergic activity. Parasites and human organisms have a long history of mutual contact. The effect of parasitosis on the host and the host's response to infection are undoubtedly the product of a long evolutionary process. The neurochemical background of delusions of parasitosis is potentially similar to ancient evolutionary traces of altered neurotransmission and neuropeptide gene expression caused by parasites; these include fungal and viral infections. This is very unique in medicine if a class of drugs is effective in the treatment of an illness but also cures the delusion of the same disorder as well. Furthermore, metabolic disturbances such as hyperglycemia and insulin resistance were reported several decades before the antipsychotic era. Toxoplasmosis may also be linked to insulin resistance. Schizophrenia research can benefit from understanding this evolutionary link. New chemical entities that are liable to alter neurochemical changes related to the brain's perception of the risk of predation secondary to parasites may result in new approaches for the treatment of psychosis. These findings suggest that further research is needed to clarify this evolutionary link between parasite infection and delusions of parasitosis. We believe this model may well open up new avenues of research in the discovery of drugs to counteract schizophrenia.

REVIEW

INTRODUCTION

In their recent editorial meta-analysis, Torrey & Yolken provided a comprehensive overview of studies investigating Toxoplasma gondii antibodies in schizophrenic patients, thus attempting to clarify the potential role these infections might play in causing schizophrenia, and suggested avenues for further research (Torrey & Yolken, 2006; Torrey *et al*., 2007; Zhu *et al*., 2007). Toxoplasmosis, a latent and asymptomatic phenomenon, is one of the most common human infections. Potential mechanisms by which T. gondii may affect human behavior include its effect on dopamine and testosterone (Flegr, 2007); the higher level of testosterone could be responsible for at least some of the toxoplasmosis-associated shifts in human and animal behavior. (Hodkova *et al*., 2007). Several studies have demonstrated the direct anti-parasitic effect of antipsychotics. Medications used to treat schizophrenia and bipolar disorders have the ability to inhibit the in vitro replication of parasites such as Toxoplasma gondii (Jones-Brando *et al*., 2003; Weisman *et al*., 2006; Henry *et al*., 2006). It is interesting to note that some anti-parasitic agents also have a dopaminergic effect, such as chloroquine (Amabeoku, 1994), which is patented for the treatment of Parkinson's disease (Nelson, 2002).

UNANSWERED QUESTIONS

Is it a mere coincidence that anti-parasitic agents as well as antipsychotics are effective in treating parasitosis and that both types of drugs were clearly shown to exert dopaminergic activity? Particularly atypical antipsychotics are effective in the treatment of the *delusion of parasitosis*; this effect is attributed to their unique dopamine-antagonist profile (Freudenmann *et al*., 2007; Meehan *et al*., 2006). This is very unique in medicine if a class of drugs is effective in the treatment of an illness but also treats the delusion of the same disorder as well. Delusion of parasitosis is a monosymptomatic persecutive psychosis, a type of psychopathology relatively distinct from the remainder of the personality. A patient who suffers from a delusion of parasitosis firmly believes that he/she is infected by parasites. Delusional parasitosis was first studied systematically by the Swedish psychiatrist Karl-Axel Ekbom in 1938 (Ekbom, 2003). The patients have no obvious cognitive impairment or abnormal organic factors. Huber and colleagues hypothesized that an impaired striatal dopamine transporter may serve as an etiologic condition for delusional parasitosis (Huber *et al*., 2007).

Anti-parasitic agents appear to have reciprocal effects. When administered to treat the infection and eliminate the parasites, they notify the brain internally of the presence of an infection. Thus, they potentially worsen the fears or accompanying delusions in respect of parasites. Some antipsychotics merely act on the delusion of parasitosis. Anti-parasitic drugs, on the other hand, may be effective in the treatment of delusions as well (Haydu *et al*., 1965; Holden *et al*., 1968; Traficante *et al*., 1977), although some studies have reported ambiguous results in this regard (Desta *et al*. 2002). In addition to this some antipsychotics have been known to possess good antiviral properties. Clozapine was found effective in the presence of HIV infection (Jones-Brando *et al*., 1997). In this study, two clozapine metabolites demonstrated antiviral activity inhibiting of virus-induced cytopathic effect, suggesting that antiviral agents may prove to be effective adjuncts in the treatment of schizophrenia. Conversely, the broad-spectrum psychotropic effect of anti-fungal drugs, such as the functional glucocorticoid antagonist ketoconazole, has also raised considerable interest (Wolkowitz *et al*., 1999, Marco *et al*., 2002).

It has been known for decades that neuropeptide genes are preferentially affected during parasitosis (Hoek *et al*., 1997). Parasites do, indeed, cause a differential gene expression pattern, particularly affecting neuropeptide precursors encoding genes that are involved in the regulation of vital physiological and behavioral processes. This is possibly due to decreased striatal dopamine transporter functioning of the D2/D3 receptor in the ventral striatal regions as suggested by Hoek *et al*. Changes in expression were observed in many cases between 1.5 and 5 hour post infection, suggesting that alterations in gene expression are a direct effect of parasitosis. The direct regulation of neuropeptide gene expression is a strategy to induce physiological and behavioral changes in the host by the parasite. The evolutionary advantage of such alteration in neurodulation is to victimize the intermediate host (i.e. human) for a predator (primary host), in favour of completing the parasite's lifecycle. Parasites and human beings have a long history of mutual contact. The effect of parasitosis on the host and the host's response to infection are undoubtedly the product of a long evolutionary process (Anderson and May 1982, Barnard and Behnke 1990). Studies demonstrated that, while T. gondii appears to alter the rats' perception of the risk of predation, turning their innate aversion into a 'suicidal' predator attraction, anti-psychotic drugs were shown to be as effective as anti-T. gondii drugs in preventing such behavioral alterations (Webster *et al*., 2006). A recent study provided strong arguments in favor of the behavioral manipulation hypothesis (Vyas *et al*., 2007). Other correlations have been found between latent Toxoplasma infections and various behavior characteristics, increased risk-taking behavior, slower reactions, feelings of insecurity and self-doubt, and neuroticism. This proved to be a very successful evolutionary survival strategy for T. gondii: in fact, Toxoplasma gondii is the only known existing species of its genus. Is it possible that the inner perception of the image and/or delusion of parasitosis creates similar neurochemical changes as a real parasite infection in the brain does?

METABOLIC DISTURBANCES IN SCHIZOPHRENIA BEFORE THE ANTIPSYCHOTIC ERA

Evidence of metabolic disturbances and insulin resistance in schizophrenia was reported several decades before the antipsychotic era (Meduna *et al*., 1942; Braceland *et al*., 1945, Redlich, 1903; Singer & Clark, 1917; Appel & Farr, 1929; Menninger, 1935; Freeman, 1936). Based on these early findings, which nearly sank into oblivion after the introduction of antipsychotics, Dr Meduna's group drew the following conclusion in 1942: "*...The disturbance found in schizophrenia indicates the presence of an anti-insulin substance in the blood of schizophrenic patients..This disturbance or the failure of the organism to adjust this disturbance may be one of the etiologic factors in schizophrenia...*" (Meduna *et al*., 1942). Even earlier, Julius Schuster refered to Moravcsik and Miskolczy and hypothesized glucose abnormalities in schizophrenia (Schuster, 1923). Several decades later, hyperinsulinemia and hyperglycemia associated with insulin resistance were found to potentially contribute to the pathogenesis of tardive dyskinesia, as reported by Schultz (1999): "*... There are many layers of complexity among the interactions of dopamine, insulin, and glucose in the context of neuroleptic treatment...*". Gillman and Sandyk (1986) first suggested that chronic neuroleptic administration is associated with increased activity of pancreatic insulin and elevated fasting blood sugar levels. Franzen and Nilsson (1968) measured glucose and insulin values following insulin coma and reported that insulin resistance was greater in psychotic than nonpsychotic patients. The influence of insulin on intracellular protozoon Toxoplasma gondii replication was also investigated. It was found that insulin had a dose-responsive mitogenic effect on intracellular T. gondii replication (Zhu *et al*., 2006). Hypothalamopituitary function is known to be disturbed in children with congenital toxoplasmosis; this phenomenon may well be responsible for endocrinological disturbances such as precocious puberty (Setian *et al*., 2002). Serum levels of insulin-like growth factors and their binding proteins were found to be reduced in patients with toxoplasmosis (Nedic *et al*., 2003); the authors investigated the insulin-like growth factor (IGF) system in patients with toxoplasmosis and confirmed that IGFs may influence glucose metabolism. An imbalance in circulating IGF/IGFBP might affect the glucose/insulin response. In addition, insulin has a dose-responsive mitogenic effect on intracellular T. gondii replication (Zhu *et al*., 2006). These findings are strongly suggestive that Toxoplasma infection may result in insulin resistance. But why does Toxoplasma gondii require a host organism with high serum glucose levels? It possibly serves as a successful survival strategy to gain energy from the host. This statement is currently speculative in nature but future research may well confirm its validity.

ANOTHER OBSCURE LINK: FEVER THERAPY IN SCHIZOPHRENIA AND PARASITOSIS

Psychopharmacological treatments for schizophrenia were initially used to induce fever as well. The patient remained rational for a few days, as long as the fever lasted. Psychotic patients were known to became more lucid during high fever or critical illness (Naudascher, 1923) Injections of sulfur in oil also caused pyrexia (Groce, 1932). They were quite painful, but in some cases produced brief partial remissions (Lehman & Ban, 1997). Interestingly sulfates are also used in cases of parasitosis, including delusional parasitosis (Aw *et al*., 2004). Pyretotherapy – the treatment of a disorder by inducing fever – was used to treat psychosis at the turn of the 19th century, but fell into disuse after the introduction of convulsive methods. A case of a schizoaffective disorder and a review of old and recent literature on fever and psychosis were reported recently (Sani *et al*., 2007). The first of the very few Nobel Prize winners in psychiatry is Wagner-Jauregg, who was awarded the prize for developing fever therapy for psychosis secondary to neurosyphilis. As these methods of treatment were not very effective, in 1917 Jauregg attempted inoculation of malaria parasites. This approach proved effective in cases of dementia paralytica (also known as general paresis of the insane). Fever therapy and changes in body temperature were also known to improve parasitic infections. However, linking the success of fever therapy in schizophrenia with parasite infections remains speculative in nature.

LINKS TO CURRENT THEORIES OF SCHIZOPHRENIA

The importance of glucose abnormalities and related metabolic disturbances in schizophrenia has received considerable attention after the introduction of atypical antipsychotics. However, the historical findings mentioned above indicate that these disturbances were observed well before the antipsychotic era. Their role and consequences in the etiopathogenesis of schizophrenia need further clarification.

Significant attention has been devoted to food metabolism in the presence of schizophrenia. Plausible hypotheses have been postulated in this regard. In a recent report Elman *et al*. summarized the potential associations between food intake and reward mechanisms in patients with schizophrenia (Elman *et al*., 2006a). The authors hypothesized that patients with schizophrenia may have a predilection for excessive consumption of fast food, owing to a functionally impaired neural substrate consisting of homeostatic and reward mechanisms. Recent findings in basic neuroendocrinology research may explain these complex mechanisms. Diano *et al*. found that a hormone produced in the stomach directly stimulates the

higher brain functions of spatial learning and memory development (Diano *et al*., 2006). The study showed that the hormone ghrelin, previously associated with growth hormone release and appetite, has a direct, rapid and powerful influence on the hippocampus, a higher brain region critical for learning and memory. Peripheral ghrelin is able to enter the hippocampus and bind to local neurons, thus promoting alterations in connections between nerve cells in mice and rats. However, further empirical research is needed to verify these theories and their consequences in the pathogenesis and treatment of this complex disorder. In addition to this, hunger is probably one of the drivers of cognitive development through hormonal regulation. Patterns of these endocrine regulatory circuits of energy intake are probably the result of ancient survival strategies of a species or even an individual. There is probably enough scientific evidence to hypothesize a neuroendocrinological background of an old German proverb: "Ein voller Bauch studiert nicht gern" "Full stomach is not very keen on learning" (Treuer & Karagianis, 2006). An extension of the neurodevelopmental theory of schizophrenia may be used to explain the disturbed metabolism observed in these patients: the schizophrenic brain is unable to handle environmental and developmental challenges at the onset of the disorder while the schizophrenic gastrointestinal tract – which is derived from the same neural crest tissue – affects the ingestion of food. A fixed neurogastric lesion in early life might interact with certain normal maturational events that occur much later, especially upon encountering a toxic food environment. The adapted responses of the hormonal and neurotransmittal regulatory circuits at this age may also play a role. The gastrointestinal tract contains the same hormones and neurotransmitters that mediate reward and homeostatic processes in the brain. Concentrations of these substances in the gastrointestinal tract are similar to, or even in excess of, those in the brain (Gershon, 1998). In other words, the pathology of schizophrenic metabolism is not the direct result of the location or existence of a neurodevelopmental lesion, but is more likely due to the interaction between the suspected lesion and the normal course of development in the affected portion of the gastrointestinal tract (Elman *et al*., 2006b). This parallels the pathogenesis of the mental symptoms of schizophrenia, analogous to the difficulties resulting from wiring and uploaded software.

If Toxoplasma infection plays any role in the etiopathogenesis of schizophrenia then it could easily be linked to its direct impact on the glucose homeostasis regardless of the effect of medications.

CHALLENGES OF FUTURE RESEARCH – AN EVOLUTIONARY LINK

Professor Torrey suggested that if a causal relationship is to be established between toxoplasmosis and schizophrenia, it will most likely be established by treatment trials, specifically by demonstrating that medications suppressing *T. gondii* infections improve the clinical symptoms of schizophrenia (Torrey & Yolken, 2007). This experiment would be similar to the observations made in children affected by the PANDAS syndrome. PANDAS is an abbreviation for Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections. The term is used to describe children who are believed to have developed obsessive-compulsive disorder (OCD) and/or tic disorders such as the Tourette syndrome following a Group-A beta-hemolytic streptococcal infection. However, studies with PANDAS children have shown that antibiotic treatment is not consistently effective in reducing the infection rate or the severity of obsessive-compulsive and/or tic symptoms in these children. Once the damage has occurred, corrective treatment against the infective agent is not always beneficial. The working hypothesis for the pathophysiology of PANDAS states that, after a Group-A beta-hemolytic streptococcal infection, the susceptible host produces antibodies that cross-react with the cellular components of the basal ganglia, particularly in the caudate nucleus and the putamen. The obsessions, compulsions, tics, and other neuropsychiatric symptoms seen in these children are postulated to arise from an interaction of these antibodies with neurons of the basal ganglia (Snider & Swedo, 2004). However, the validity of PANDAS will continue to be questioned (Murphy *et al*., 2006).

Immune disturbances related to schizophrenia also deserve attention. Schizophrenia has been associated with several immune-system related abnormalities. These include abnormal monocytic cell products such as the IL-1 and IL-1 receptor antagonist (Katila *et al*. 1994, Maes *et al*. 1996), increased plasma levels of IL-6 (Shintani *et al*. 1991), and a significantly increased expression of tumor necrosis factor (TNF-2) A allele (Boin *et al*. 2001). However, the response to clozapine was associated with the presence of the TNF-alpha A allele (Zai *et al*. 2006). Treatment with clozapine appears to normalize blood TNF levels (Monteleone *et al*., 1997) in schizophrenia.

Thirty percent to 65% of all persons worldwide are infected with Toxoplasmosis and it is known to induce behavioral changes and an increase of dopamine in mice (Jackson & Hutchison, 1989; Skallova *et al*., 2005). It may well have been 100% prior to the awareness of hygiene in modern times. Owing to the long history of contact between parasites and humans, the neurochemical background of persecutory delusions is potentially similar to ancient evolutionary traces of altered neurotransmission and neuropeptide gene expression secondary to parasites, including fungal and viral infections. The effectiveness of antipsychotics in treating persecutory delusions may be due to their ability to alter the brain's perception of the risk of predation. Similar correlations may be found with regard to the antipsychotic effect of anti-viral and anti-fungal agents in the treatment of delusions. Schizophrenia research may benefit from understanding this

evolutionary link. New chemical entities that alter the neurochemical changes related to the brain's perception of the risk of predation secondary to parasites may well lead to new approaches in the treatment of psychosis.

CONCLUSION

Further research is needed to clarify this evolutionary link between parasite infections, delusions of parasitosis and metabolic disturbances in schizophrenia. We believe this model may well open up new avenues for understanding the complex etiology of schizophrenia and for the discovery of drugs to treat schizophrenia. The neurodevelopmental theory of schizophrenia and the subjects' general susceptibility to internal or external stressors with regard to the development of psychosis fit well with this model.

ACKNOWLEDGMENTS

The authors are employees of Eli Lilly & Company.

REFERENCES

1 Amabeoku GJ (1994). Some behavioural effects of chloroquine in rats suggesting dopaminergic activation. *Indian J Med Res.* **99**: 87–94.
2 Appel KE, Farr CB (1929). The blood sugar reaction to insulin in psychoses. *Arch Neurol Psychiatry* **21**: 145–148.
3 Anderson RM, May RM (1982). *Population Biology of Infectious Diseases*. Berlin: Springer-Verlag.
4 Aw DC, Thong JY, Chan HL (2004). Delusional parasitosis: case series of 8 patients and review of the literature. *Ann Acad Med Singap.* ***33****: 89–94.*
5 Barnard CJ, Behnke JM. (1990). *Parasitism and Host Behaviour.* London: Taylor and Francis.
6 Braceland FJ, Meduna LJ, Vaichulis JA (1945). Delayed action of insulin in schizophrenia. *Am J Psychiatry*. **102**: 108 –110.
7 Boin F, Zanardini R, Pioli R, Altamura CA, Maes M, Gennarelli M (2001). Association between -G308A tumor necrosis factor alpha gene polymorphism and schizophrenia. *Mol Psychiatry*. **6**: 79–82.
8 Croce G (1932). Pyretotherapy of schizophrenia in initial stages by injections of sulphur. *Schizofrenie*. **1**: 31–40.
9 Desta M, Tadesse A, Gebre N, Barci BM, Torrey EF, Knable MB (2002). Controlled trial of hydroxychloroquine in schizophrenia. *J Clin Psychopharmacol*. **22**: 507–510.
10 Diano S, Farr SA, Benoit SC, McNay EC, da Silva I, Horvath B, *et al.* (2006). Ghrelin controls hippocampal spine synapse density and memory performance. *Nature Neurosciences*. **9**: 381–388.
11 Ekbom KA (2003). The pre-senile delusion of infestation, *Hist Psychiatr*. **14**: 229–256.
12 Elman I, Borsook D, Lukas SE (2006a). Food intake and reward mechanisms in patients with schizophrenia: implications for metabolic disturbances and treatment with second-generation antipsychotic agents. *Neuropsychopharmacology*. **31**: 1–30.
13 Elman I, Borsook D, Lukas SE (2006b): Is there such thing as a schizophrenic stomach? *Neuropsychopharmacology*. **31**: 2328.
14 Flegr J (2007). Effects of toxoplasma on human behavior. *Schizophr Bull*. **33**: 757–760.
15 Franzen G, Nilsson L (1968). A study of blood sugar response to insulin injection in schizophrenia. *Acta Psychiatr Scand*. **44**: 24–26.
16 Freeman H (1946). Resistance to insulin in mentally disturbed soldiers. *Arch Neurol Psychiatry.* **56**: 74 –78.
17 Freudenmann RW, Schonfeldt-Lecuona C, Lepping P (2007). Primary delusional parasitosis treated with olanzapine. *Int Psychogeriatr*. **5**: 1–9.
18 Gershon M (1998). *The Second Brain*. Harper & Collins, New York, NY.
19 Gillman MA, Sandyk R (1986): Tardive dyskinesia and glucose metabolism (letter). *Arch Gen Psychiatry.* **43**: 192–193.
20 Haydu GG, Dhrymiotis A, Korenyi C, Goldschmidt L (1965). Effects of methionine and hydroxychloroquine in schizophrenia. *Am J Psychiatry*. **122**: 560–564.
21 Henry M, Alibert S, Orlandi-Pradines E, Bogreau H, Fusai T, Rogier C, *et al.* (2006). Chloroquine resistance reversal agents as promising antimalarial drugs. *Curr Drug Targets*. **7**: 935–948.
22 Hoek RM, van Kesteren RE, Smit AB, de Jong-Brink M, Geraerts WP (1997). Altered gene expression in the host brain caused by a trematode parasite: neuropeptide genes are preferentially affected during parasitosis. *Proc Natl Acad Sci*. **94**:14072–14076.
23 Hodkova H, Kolbekova P, Skallova A, Lindova J, Flegr J (2007). Higher perceived dominance in Toxoplasma infected men--a new evidence for role of increased level of testosterone in toxoplasmosis-associated changes in human behavior. *Neuro Endocrinol Lett*. **28**:110–4.
24 Holden JM, Itil TM, Keskiner A (1968). The effects of metronidazole on schizophrenic psychopathology. *J Clin Pharmacol J New Drugs*. **8**: 333–341.
25 Huber M, Kirchler E, Karner M, Pycha R (2007). Delusional parasitosis and the dopamine transporter. A new insight of etiology? *Med Hypotheses*. **68**: 1351–1358.
26 Jackson MH, Hutchison WM (1989). The prevalence and source of Toxoplasma infection in the environment. *Adv Parasitol.* **28**: 55–105.
27 Jones-Brando L, Torrey EF, Yolken R (2003). Drugs used in the treatment of schizophrenia and bipolar disorder inhibit the replication of Toxoplasma gondii. *Schizophr Re.* **62**: 237–244.
28 Jones-Brando LV, Buthod JL, Holland LE, Yolken RH, Torrey EF (1997). Metabolites of the antipsychotic agent clozapine inhibit the replication of human immunodeficiency virus type 1. *Schizophr Res.* **25**: 63–70.
29 Julius Schuster (1923). *Zur Entdeckung der Insulintherapie bei akuten Geistkrankheiten, insbesondere Schizophrenie.* Budapest, Druckerei der Pester Lloyd-Gesellschaft.
30 Katila H, Appelberg B, Hurme M, Rimon R (1994). Plasma levels of interleukin-1B and interleukin-6 in schizophrenia, other psychoses, and affective disorders. *Schizophr Res*. **12**: 29–34.
31 Lehmann HE, Ban TA (1997).The history of the psychopharmacology of schizophrenia. *Can J Psychiatry*. **42**: 152–162.
32 Maes M, Bosmans E, Ranjan R, Vandoolaeghe E, Meltzer HY, De Ley M, *et al.* (1996). Lower plasma CC16, a natural-inflammatory protein, and increased plasma interleukin-1 receptor antagonist in schizophrenia: effects of antipsychotic drugs. *Schizophr Res*. **21**: 39–50.
33 Marco EJ, Wolkowitz OM, Vinogradov S, Poole JH, Lichtmacher J, Reus VI (2002). Double-blind antiglucocorticoid treatment in schizophrenia and schizoaffective disorder: a pilot study. *World J Biol Psychiatry*. **3**: 156–161.
34 Meduna, L, Gerty F, Urse V (1942). Biochemical disturbances in mental disorders. *Arch Neurol Psychiatry*. **44**: 38–52.
35 Meduna L (1937): *Die Konvulsionstheapie der Schizophrenie.* Carl Marhold Verlag, Halle.
36 Meehan WJ, Badreshia S, Mackley CL (2006). Successful treatment of delusions of parasitosis with olanzapine. *Arch Dermatol*. **142**: 352–355.
37 Monteleone P,Fabrazzo M, Tortorella A, Maj M.: Plasma levels of interleukin-6 and tumor necrosis factor alpha in chronic schizophrenia: effects of clozapine treatment. *Psychiatry Res*. 1997; **71**(1): 11–17.
38 Murphy TK, Sajid MW, Goodman WK (2006). Immunology of obsessive-compulsive disorder. *Psychiatr Clin North Am*. **29**: 445–469.
39 Nelson J (2002). Chloroquine derivatives for the treatment of Parkinson's disease. Patent description. 2002.09.07. available online http://www.freepatentsonline.com/6417177.html, Accessed at 13 :00pm CET, 12 of August, 2007.
40 Menninger WC (1935). The inter-relationship of mental disorders and diabetes mellitus. *J Ment Sci.* **81**: 332–357.
41 Naudascher G (1923). Psychoses guéries sous l'influence d'une maladie intercurrente. *Ann Med Psychol.* **81**: 400–404.

42 Nedic O, Nikolic AJ, Baricevic I, Jovanovic B, Ilic N (2003). Insulin-like growth factors and their binding proteins in the circulation of patients with echinococcosis, trichinellosis and toxoplasmosis. *Clin Chim Acta*. **335**: 83–88.
43 Redlich E (1903). Zur Frage der beziehungen zwischen diabetes mellitus und Psychosen. *Wien Med Wochenschrift*. **53**: 1041–1046.
44 Sani G, Manfredi G, Pacchiarotti I, Caltagirone SS, Mancinelli I, Koukopoulos AE, *et al.* (2007). A case of resolution of an acute psychotic episode after high fever. *CNS Spectr*. **12**: 447–450.
45 Schultz SK, Arndt S, Ho BC, Oliver SE, Andreasen NC (1999). Impaired Glucose Tolerance and Abnormal Movements in Patients With Schizophrenia. *Am J Psychiatry*. **156**: 640–642.
46 Schuster, Julius (1937). *Zur Entdeckung der Insulinschocktherapie bei akuten Geistkrankheiten, insbesondere bei der Schizophrenie.* Pester Lloyd-Gesellschaft, Budapest.
47 Setian N, Andrade RS, Kuperman H, Manna TD, Dichtchekenian V, Damiani D (2002). Precocious puberty: an endocrine manifestation in congenital toxoplasmosis. *J Pediatr Endocrinol Metab*. **15**: 1487–1490.
48 Singer HD, Clark SN (1917). Psychoses associated with diabetes mellitus. *J Nerv Mental Disease*. **46**: 421–428.
49 Skallova A, Novotna M, Kolbekova P, Gasova Z, Vesely V, Sechovska M, Flegr J (2005). Decreased level of novelty seeking in blood donors infected with Toxoplasma. *Neuro Endocrinol Lett*. **26**: 480–486.
50 Shintani F, Kanba S, Maruo N, Nakaki T, Nibuya M, Suzuki E, *et al.* (1991). Serum interleukin-6 in schizophrenic patients. *Life Sci*. **49**: 661–664.
51 Snider LA, Swedo SE (2004). PANDAS: current status and directions for research. *Mol Psychiatry*. **9:** 900–907.
52 Torrey EF, Yolken RH (2003). Toxoplasma gondii and schizophrenia. *Emerg Infect Dis*. **9**: 1375–1380.
53 Torrey EF, Yolken RH (2007). Schizophrenia and Toxoplasmosis. *Schizophrenia Bulletin*. **33**: 727–728.
54 Torrey EF, Bartko JJ, Lun ZR, Yolken RH (2007). Antibodies to *Toxoplasma gondii* in patients with schizophrenia: a meta-analysis. *Schizophrenia Bulletin*. **33**: 729–736
55 Traficante LJ, Hine B, Gershon S, Sakalis G (1977). Chloroquine potentiation of thioridazine effects in rats and drug-resistant schizophrenic patients: a preliminary report. *Commun Psychopharmacol*. **1***:* 407–419.
56 Treuer T, Karagianis J (2006). Is hunger a driver of the cognitive development? *Neuropsychopharmacology*. **31**: 2326–2327.
57 Vyas A, Kim S, Giacomini N, Boothroyd JC, Sapolsky RM (2007). Behavioral changes induced by Toxoplasma infection of rodents are highly specific to aversion of cat odors. *Proc Natl Acad Sci*. **104**: 6442–6447.
58 Webster JP, Lamberton PH, Donnelly CA, Torrey EF (2006). Parasites as causative agents of human affective disorders? The impact of anti-psychotic, mood-stabilizer and anti-parasite medication on Toxoplasma gondii's ability to alter host behaviour. *Proc Biol Sci*. **273**: 1023–30.
59 Weisman JL, Liou AP, Shelat AA, Cohen FE, Guy RK, DeRisi JL (2006). Searching for new antimalarial therapeutics amongst known drugs. *Chem Biol Drug Des*. **67**: 409–416.
60 Wolkowitz OM, Reus VI,Chan T, Manfredi F,Raum W, Johnson R, *et al.* (1999). Antiglucocorticoid treatment of depression: double-blind ketoconazole. *Biol Psychiatry*. **45**: 1070–1074.
61 Zai G, Muller DJ, Volavka J, Czobor P, Lieberman JA, Meltzer HY, *et al.* (2006). Family and case-control association study of the tumor necrosis factor-alpha (TNF-alpha) gene with schizophrenia and response to antipsychotic medication. *Psychopharmacology (Berl)*. **188**: 171–182.
62 Zhu S, Guo MF, Feng QC, Fan JM, Zhang LX (2007). Epidemiological evidences from China assume that psychiatric-related diseases may be associated with Toxoplasma gondii infection. *Neuro Endocrinol Lett*. **28**:115–20.
63 Zhu S, Lai DH, Li SQ, Lun ZR (2006). Stimulative effects of insulin on Toxoplasma gondii replication in 3T3-L1 cells. *Cell Biol Int*. **30**: 149–153.