

Orthomolecular Treatment For Schizophrenia: A Review (Part Two)

Raymond J. Pataracchia, B.Sc., N.D.¹

Introduction

This two-part review on schizophrenia describes various segments of the schizophrenic population that fall into subgroups of distinct biochemical imbalance. To recap, these subgroups include essential fatty acid deficiency, inadequate nutrition, dysglycemia, food intolerance, digestive compromise, malabsorption, under-methylation, vitamin B₃ deficiency, B₆ deficiency, vitamin C deficiency, zinc deficiency, heavy metal toxicity, brain hypothyroidism, and hypoadrenia. Complementary alternative medicine (CAM) has a key role in the treatment of schizophrenia. In Part Two of this review, we discuss heavy metal toxicity, B₆ deficiency, zinc deficiency, brain hypothyroidism, and hypoadrenia.

Heavy Metal Toxicity in Schizophrenia

Most heavy metals are free radicals that induce oxidative stress (lipid peroxidation) and have an affinity for brain tissue.^{1,2} Free radical-mediated neurotoxicity and oxidative stress are implicated as a causative factor in schizophrenia.^{3,4} These free-radicals have the ability to compromise and/or destroy brain tissue and, in so doing, decrease the availability of viable brain tissue. Note that other mechanisms of brain tissue compromise are involved in schizophrenia, so the added burden of toxic metals is to be avoided.

Elevated heavy metal levels are associated with schizophrenic pathology.⁴⁻⁸ It is not uncommon to see toxic levels of copper, lead, mercury, aluminum, arsenic and cadmium in schizophrenics. We find some of the most advanced schizophrenic cases having three or more heavy metals.

Heavy metal toxicity is also associated with ADHD, anxiety, OCD, depression, bipolar disorder and dementia.

Heavy metals are excreted by using the body's metal-removing protein, metallothionein.^{2,9} In the process of ridding the body of heavy metals, this protein loses zinc.¹⁰ Zinc loss in schizophrenia in turn compromises the ability to transcribe proteins and make neurotransmitters. Investigators recognize compromised brain protein transcription pathways in schizophrenia.^{3,11} Zinc deficiency is associated with schizophrenia and other psychiatric pathologies including mood dysfunction and dementia.⁹

Lead disrupts mental function.¹² Toxic lead levels are associated with psychosis.¹³ Lead toxicity is also associated with behaviour disturbance, mood disorder, learning disabilities, insomnia, immune compromise, brain damage and delayed infant development. Lead has been found to disrupt the carriage of thyroid hormone (T4) into the brain.^{14,15} If you are a city dweller, you are exposed to lead and the risk of lead toxicity rises with age. With widespread pesticide use, lead accumulates in the food chain. Lead is found in paints, print colour, glass, batteries, rust protectants, alloys and old water pipes and bathtubs.¹⁶

Mercury is toxic and has no therapeutic use; in fact, it disrupts dopamine and norepinephrine metabolism.¹⁷ It is not uncommon to find elevated mercury in patients with schizophrenia. Mercury is found in fluorescent lights, vaccines, thermometers, and fish, animals, and plants exposed to toxic environments. Dental fillings contain on average about 40% mercury which has the potential to leach with electrolytic decay. Mercury

1. Naturopathic Medical Research Clinic, 20 Eglinton Avenue East, Suite#441, Toronto, Ontario, Canada, M4P 1A9.

often causes headaches, nervous irritability, memory decline, depression, rapid fatigue, nausea, stomach aches and allergic susceptibilities.¹⁶ Mercury has a strong affinity for the brain but also sequesters in the liver, kidney, and spleen.

Aluminum can be toxic in patients with schizophrenia, mood disorders, Alzheimer's Disease and digestive system pathologies. Aluminum disrupts enzyme function and is well-documented to disrupt cognition, learning and memory. Environmental sources of aluminum include aluminum cookware (especially from heating and deglazing with an acid such as vinegar or wine), drinking boxes, processed cheese, deodorants, and drinking water (aluminum is more soluble in our acidic magnesium deficient drinking water).¹⁸

In excessive concentrations, copper has a toxic effect and, in schizophrenia, contributes to excess catecholamine oxidation, the end products of which are unstable toxic hallucinogens.^{6,19} We have found copper toxicity to be the most common heavy metal pattern in schizophrenia. It is also associated with ADHD, autism, depression, anxiety, bipolar disorder and paranoia. With copper toxicity we see clinical zinc deficiency.²⁰ Copper is abundant in food and water as it is found in soil, pesticides and animal feed. Since World War II we have been exposed to greater levels of copper due to copper piping in modern homes and the widespread use of birth control pills (estrogen based). Estrogen dominance is associated with higher circulating copper levels and copper is thought to transfer via placenta from generation to generation.²⁰ Other copper sources include copper tea pots, copper sulfate treated Jacuzzis or swimming pools, drinking water, dental fillings, prenatal vitamins, and copper IUD's. Neuroleptics, antibiotics, antacids, cortisone, Tagamet, Zantac, and diuretics often encourage copper dominant biochemistry.

The liver produces the copper regulating proteins metallothionein and ceruloplasmin and, with low thyroid function, their hepatic protein synthesis is diminished. The body attempts to remove excess copper by excreting it out of the liver via gall bladder excretion to the bowel. Vitamin B₃, vitamin C, and zinc are helpful clinically because of their physiological antagonism to copper.

Schizophrenics relapse when thyroid function is low.²¹ Poor thyroid function encourages heavy metal retention. Conversely, heavy metals seem to play a major role in blocking peripheral enzyme conversion of T4 to T3.²²⁻²⁵ Heavy metal removal involves mobilizing and eliminating the metal and this is often best done after thyroid function has been optimized. The organs involved in the elimination of the metal tend to function more efficiently when thyroid metabolism is intact. It is also essential to avoid environmental exposures to heavy metals.

Zinc and B₆ Deficiency in Schizophrenia

Zinc and iron are the most concentrated metals in the human brain. Zinc is important to several biochemical pathways as over 200 enzymes are zinc dependant. Zinc deficiency is very common in schizophrenia.⁷⁻⁹ Insufficient levels of zinc are also associated with depression, dementia, mental retardation, learning disability, lethargy and apathy.²⁶ Zinc is essential for the synthesis of serotonin and melatonin.²⁰ It is crucial to brain development because it plays a major role in protein synthesis.^{20,26} In the brain, zinc lowers excitability by moderating NMDA receptor release of excitatory glutamate. Zinc is involved in the synthesis of inhibitory GABA by the modulation of glutamate decarboxylase activity. Among the zinc-dependant proteins are metallothionein which is essential for heavy metal regulation and zinc bioavailability. The

synthesis of Zn-thionein and CuZnSOD are essential in preventing oxidative damage.²⁰ Zinc protects against fatty-acid peroxidation which destroys neuron structure and function. Zinc is involved in neuronal plasma membrane structure and functioning and, may play a key role in blood-brain-barrier integrity.²⁷ Zinc is involved in storing biogenic amines in synaptic vesicles and, in axonal transport. The biogenic amine histamine regulates nucleus accumbens activity, which is responsible for filtering sensory information and communicating with the amygdala, ventral tegmentum, and hypothalamus. In the limbic system, zinc is involved in the metabolism of emotional regulation. In the hypophysis and hypothalamus, zinc is involved in hormonal metabolism.

Vitamin B₆ (pyridoxine) is involved in the decarboxylation of tyrosine, tryptophan, and histadine into the neurotransmitters norepinephrine, serotonin, and histamine respectively.²⁸ B₆ deficiencies are associated with schizophrenia, depression and behaviour disorders. It is a cofactor in homocysteine re-methylation.²⁹ B₆ has been found useful in memory acquisition, with just a 20mg dose.³⁰ It has demonstrated usefulness in controlling neuroleptic-induced akathisia and drug-induced movement disorders.³¹⁻³³ B₆ is essential for the synthesis of antioxidants such as metallothionein, glutathione, and CoQ₁₀ which help prevent neuronal oxidative stress. B₆ (and zinc) are involved in the synthesis of glutamic acid decarboxylase (GAD) which blocks excitotoxicity with eventual secondary oxidative damage. B₆ is also essential for glutathione peroxidase and glutathione reductase which are helpful in preventing mitochondrial decay.

The major neurotransmitters of the brain are derived from protein building-blocks and precisely assembled according to messenger RNA (mRNA) transcription of neuronal DNA templates. Brain tissue samples of schizophrenics have been as-

essed with high-dimensional biology and found to be compromised in basic mRNA transcription and protein synthesis.³ These perturbations influence an array of neuronal changes in the schizophrenic brain among which are neurotransmitter synthesis and mitochondrial functioning. Oxidative stress can cause these perturbations and the ensuing changes in neuronal structure and function may be integral in understanding schizophrenic pathophysiology.

It is interesting to note here that zinc and vitamin B₆ together are needed by the body as co-factors for neurotransmitter synthesis; zinc is needed for transcription and B₆ is needed for transamination. Previous investigators have described B₆ and zinc depletion in the context of pyrolluria. In this metabolic syndrome, B₆ and zinc interact with 2,4-dimethyl-3-ethylpyrrole and are readily excreted.³⁴⁻⁴²

Hypoadrenia in Schizophrenia

Thyroid and adrenal function are compromised in many schizophrenics.^{21,43} The thyroid and adrenal are pivotal endocrine glands. Many symptoms common to adrenal dysfunction are seen in thyroid dysfunction and vice versa. The adrenal works in concert with the thyroid gland and often both glands need to be supported together.^{44,45}

Hypothalamic-Pituitary-Adrenal axis dysregulation is integrally associated with schizophrenia.^{21,43} The adrenal glands are involved in stress response, sugar metabolism, electrolyte balance, peripheral epinephrine synthesis, blood pressure regulation, and sex hormone metabolism. Many schizophrenics who are heavy coffee drinkers have low adrenal function. Low adrenal symptoms include sluggishness on waking, stress intolerance, lack of enjoyment, post-traumatic stress, addiction, dizziness, low blood pressure, fluctuant body temperature, insomnia at 4am, immune compromise, hypoglycemia,

dermatitis, PMS, phobia and poor libido. Schizophrenics can be warm at times and at other times cold with trouble adapting to daily temperature extremes. Fluctuant body temperatures and heat intolerance are a sign of low adrenal function which often accompanies low thyroid function.⁴⁶ Adrenal symptoms are a good indicator of adrenal status. In some cases, saliva testing is useful to assess the adrenal hormones DHEA and cortisol. Cortisol is part of the stress response but elevated cortisol disturbs mental function. Cortisol levels are commonly elevated in schizophrenics and depressives.^{47,48} Adaptogens and supplements can be used effectively to support adrenal function without elevating cortisol.

Hypothyroidism in Schizophrenia

Active thyroid hormones are responsible for enabling cells, at the DNA level, to maintain their metabolic rate. Thyroid hormones also maintain oxygen availability in the brain and elsewhere. With healthy thyroid hormone function, our cells produce energy and complete their tasks efficiently. When tissue cells including neurons have energy, they work efficiently. When thyroid function is low, cells remain in a state of hypofunction. Hypofunctioning cells work slowly and produce minimal energy. Consequently, fewer enzymatic reactions occur, cells don't give off heat and core body temperature decreases. Intolerance to cold is a typical complaint in low thyroid function.²¹ When body temperature is insufficient, enzymatic reactions do not occur as readily, yet these reactions are needed throughout the body for, among other things, neurotransmitter synthesis. It is not uncommon to have schizophrenics report that they feel warm despite having low average body temperature.

Low thyroid symptoms are seen often in psychosis.^{21,49-51} In treatment-refractory depression, psychiatric 'thyroid augmen-

tation' treatment is frequently applied.^{52,53} The most obvious low thyroid symptoms include impaired cognition, easy weight gain, fatigue, pain, headache, irritability, anxiety, panic, PMS, depression, poor memory, poor concentration, insomnia, constipation, indigestion, hair loss, high cholesterol and frequent infection.^{21,52,54,55} The digestive tract of a low thyroid patient has poor motility and slow stool transit which results in constipation and inefficient nutrient absorption.⁵⁶ In low thyroid patients, core body temperatures are often so low that digestive enzymes do not reach their reaction threshold. Patients with varied non-specific complaints often have low thyroid function.

Classic hypothyroidism, occurring in a small percentage of schizophrenics, is a problem with the inability to produce adequate thyroid hormone. In classic "conventional" hypothyroidism, blood tests show low output of thyroid hormone T4 with elevated thyroid stimulating hormone (TSH) levels. Immune involvement as in Hashimoto's thyroiditis is usually seen in 80% of classic hypothyroid cases. Othman et al. assessed a sample of 249 chronic schizophrenics and reported a prevalence of thyroid antibodies in 20% of cases.⁵⁷ Many blood thyroid imbalances are found to correlate with the degree of symptom presentation, as for example, in acute psychotic episodes.⁵⁸

The reliance on thyroid blood tests in schizophrenia leads practitioners astray because a large portion of schizophrenics are euthyroid with "normal" blood test measures but, paradoxically, have a low core body temperature and low thyroid symptoms (fatigue, psychosis, depression, etc). There is no accepted diagnostic agreement on this physiological state, however Wilson's Temperature Syndrome (WTS) has emerged as a condition that meets this criteria. WTS factors in the possibility of inefficient peripheral conversion of T4 to active T3 despite

having adequate circulating thyroid hormone T4.^{52,53,59} In classic hypothyroidism and WTS, we can implement desiccated thyroid, sustained release T3 (T3-SR) and botanical medicine.

Brain Hypothyroidism

The brain is highly dependent on thyroid hormone for the regulation of dopamine, norepinephrine, and serotonin pathways.^{50,60,61} Brain hypothyroidism has been described by Hatterer et al. as a state that occurs when systemic T4 does not readily cross into the brain.⁶² Active thyroid hormone T3 is synthesized in the brain by brain type II 5'-deiodinase conversion of T4 to T3.^{53,63} Brain neurons therefore depend on a ready supply of T4. The choroid plexus of the brain produces transthyretin (TTR), a transport protein that binds T4 and transports it across the blood-cerebral spinal fluid barrier to the brain.⁶³ Transthyretin is significantly downregulated in the cerebral spinal fluid (CSF) of schizophrenics versus healthy controls.⁶⁴ This suggests that schizophrenics lack adequate amounts of T4 in the brain. Without adequate T4, brain cells remain hypo-metabolic and this may, among other things, reduce neurotransmitter synthesis and disrupt the regulation of dopamine, norepinephrine, and serotonin.

Huang et al. suggest that low CSF transthyretin may prove useful as a biomarker for early diagnosis of schizophrenia.⁶⁵ Also of interest is the fact that lead has been linked to the reduction of CSF transthyretin in humans.^{14,15} Reduced CSF transthyretin is also seen in depression and suicidal propensity.^{66,67} Many schizophrenics and depressives relapse when thyroid function drops.²¹

Peripheral blood thyroid levels can be normal in the context of brain hypothyroidism. T4 to T3 conversion by brain type II 5'-deiodinase can be inhibited by cortisol.^{68,69} This is important because

cortisol levels are commonly elevated in schizophrenics, especially during stress. Cortisol is an adrenal stress hormone and, during stressful periods, we tend to conserve energy by shutting down thyroid hormone production.

Anti-thyroidal Adrenochrome

Adrenochrome is a quinone and many molecules in this class are anti-thyroidal. In schizophrenia, a ready supply of oxidized adrenaline may account for thyroid compromise. Adrenochrome has the ability to induce oxidative stress and functional changes in thyroid tissue and peripheral metabolism.⁷⁰⁻⁷⁸ It is not known to what degree adrenochrome damages the thyroid gland. Skoliarova suggests that functional changes can be inferred from the structural "deterioration" of the thyroid and hypophysis of chronic schizophrenics autopsied 20 minutes to five hours post-mortem.⁷⁹

Thyroid Treatment

There are some remarkable studies reporting the outstanding efficacy of thyroid therapy in acute and chronic schizophrenia. A study by Danziger reported in 1958, showed that 100 days of optimally dosed desiccated thyroid or thyroxine with B-complex lead to the full recovery of 54 (45%) of 80 schizophrenics.⁸⁰ Twenty of the 80 patients were given thyroid therapy alone while 60 of the 80 patients were given thyroid plus shock (ECT) therapy. Fifteen (75%) of the 20 patients given thyroid therapy recovered fully and, 39 (65%) of the 60 patients given thyroid therapy plus ECT recovered fully. Of the 15; two were sick for 60 or more months, two were sick 24-59.9 months, three were sick 12-23.9 months, two were sick 12-23.9 months, and six were sick less than 6 months. Of the 39; six were sick for 60 or more months, five were sick 24-59.9 months, five were sick 12-23.9 months, six were sick 12-23.9 months, and 17 were

sick less than six months. After discharge, the incidence of relapse was very small with a maintenance treatment that kept the basal metabolic rate (BMR) in check. Full recovery was defined appropriately; that is, being “symptom-free, returning to a former place in society/occupation and accepted as well by family, friends and co-workers.” The prognosis of the 80 patients at the onset of the study was “generally unpromising” as they were treatment refractory to ECT, psychoanalysis, and psychotherapy (all were neuroleptic naïve).

Many of the 80 schizophrenic patients reported by Danziger required high doses of desiccated thyroid (128–1280 mg) or racemic thyroxine (1–9 mg). Of the 54 patients that recovered with thyroid therapy or thyroid plus ECT, only four required 640 mg or more of desiccated thyroid and, only two required up to 4mg of thyroxine. Such doses were probably required to combat adrenochrome’s anti-thyroid effects and, to make up for the lack of T4 transport from the CSF to the brain (“brain hypothyroidism”). Hoskins and others report on the tolerance of schizophrenics for even higher doses of desiccated thyroid than those used by Danziger.^{81,82} To enable good treatment outcome, the BMR is raised to a level that likely improves the function and production of respiratory enzymes in the cerebrum.⁸³ In Danziger’s study, first-episode cases had the best response however, one third of the chronic cases (five plus years post-onset) experienced full recovery as well.

A double-blind efficacy study reported by Lochner et al. in 1963 used T3 (L-triiodothyronine) treatment in a six-week trial on 30 chronic male schizophrenics eight plus years post-onset.⁸⁴ Typical tranquilizers prescribed at the time were discontinued in a wash-out period several weeks prior to treatment. Patients were included if they tolerated withdrawal

without exhibiting aggressive behaviour. 15 subjects were randomly assigned to the thyroid group and another 15 subjects to the placebo control group. Red blood cell uptake of I¹³¹-T3 was normal for all subjects at baseline; they were euthyroid according to blood tests. The treatment group received 50 mcg of T3 b.i.d. for one week, then 100 mcg b.i.d. (200 mcg per day) for six weeks.

In this short treatment period, seven of the 15 patients treated with T3 responded very well. They had improved motor activity, work performance, spontaneity, sociability and logical/relevant thinking. Some reported they were “more lively” and could “think better.” Mood improved and they showed interest in their environment. They showed improvements in executive functioning; some voiced “plans for the future” and wanted to visit relatives, return to work and resume family relationships outside of the hospital. Five of the 15 patients had some worsening. Two of these five patients were responsive and cooperative with generally better mood but, exhibited hallucinations and delusions that had been repressed and were tense, restless, and loquacious. Another two of these five patients became non-conversive and tense with masked facies and motor retardation. The last of these five patients became incoherent, irritable, and explosive with increased hallucinations, delusions, and activity. The remaining three of the 15 experienced no change. All schizophrenics returned to their previous state shortly after discontinuation of treatment. Lochner’s study was reproduced by Scheuing and Flach with the same cohort and, a consensus of results was determined.⁸⁵ The results with T3 are impressive when you consider the short treatment duration, the chronicity of the cohort and, the failure to implement optimal dosing strategy. Doses of 200 mcg of T3 may have been too high for those

patients that aggravated in the given six-week time-frame of the study. Conversely, 200 mcg may not have been a high enough dose for those schizophrenics that did not respond. To this author's knowledge, the use of T3 in first-episode schizophrenia has not been fully investigated.

Hoffer also reports on 12 schizophrenic patients treated on nicotinic acid and optimally dosed desiccated thyroid.⁷¹ Of the 11 patients that completed the treatment, nine had benefited. Six of the nine were moving toward rapid recovery and had very much improved. The remaining three were improving consistent with increasing doses of desiccated thyroid. The average maintenance dose of desiccated thyroid was 300 mg per day.

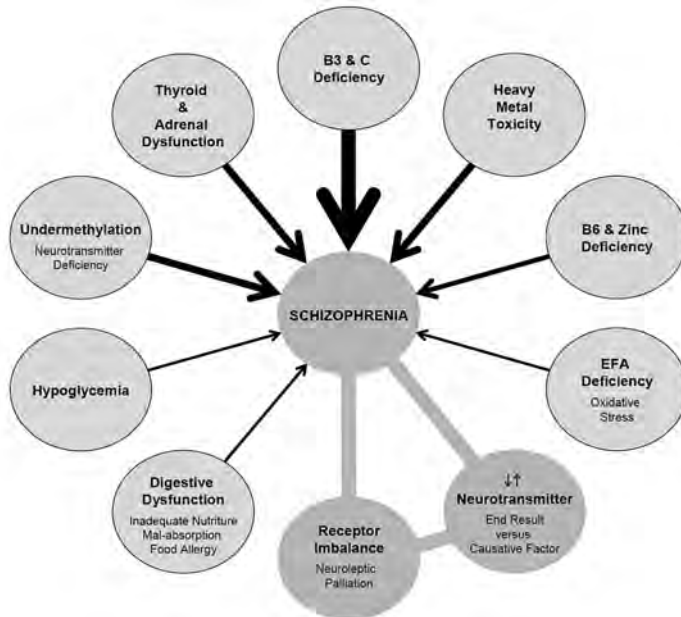
As adrenochrome reducing nutrients, vitamin B₃ and C play a key role in reducing the oxidative stress on the thyroid

gland. This thyroid link may explain in part, why vitamin B₃ and C yield such good success in treatment. As a final note on thyroid function, blood testing can help rule out the hyper-functioning state typical of Grave's Disease.⁵⁸ Grave's, in its active phase, is a state of thyroid hyperfunction and botanicals are very useful in calming thyroid function and preventing surgery and irradiation. In low thyroid states, botanical interventions are very useful to help support and restore the thyroid gland and peripheral conversion.

Overview

Figure 1 (below) is a schematic of the key causative factors of schizophrenia. Modern research continually confirms that these factors are important to schizophrenic pathophysiology. This is why, in

Figure 1. Schizophrenia: Summary of Causative Factors.



support of Dr. Hoffer's original work, we now see down-regulated niacin receptors in the anterior cingulate cortex of schizophrenics.⁸⁶ The list of assessments and treatments described herein are not exhaustive but represent the core considerations of optimal complementary treatment for schizophrenia. Orthomolecular treatment can be implemented safely as an adjunct to conventional psychiatric therapy. Schizophrenics treated with orthomolecular medicine experience positive changes. Response is based on the degree of severity and the duration of illness. We see schizophrenics who have been sick for a year or two who start responding within weeks. Schizophrenics sick over five years are less responsive initially but, improve with long term care. The pathological deterioration of brain tissue in schizophrenia should impel us to use orthomolecular treatment to keep oxidative stress at bay. The necessity of early screening and early intervention is important for both orthomolecular and conventional psychiatric treatment. In first-episode cases, a cocktail of desiccated thyroid (or T3-SR), vitamin B₃, and vitamin C may be the best early detection-intervention program ever developed. Complementary treatments for schizophrenia have been in the workings since the 1930s. A large outcome study is needed to compare the efficacy of orthomolecular treatment versus psychiatric medication. Orthomolecular treatment should play a key role in mainstream mental health care and schizophrenic patients/families constantly express their desire to see that happen.^{87,88} Conventional mental health costs are exorbitant in comparison to orthomolecular treatment costs and the potential for improved quality of life should empower practitioners to be steadfast in addressing core underlying biochemistry.⁸⁹

References

1. Kelly G: Peripheral Metabolism of Thyroid Hormones: A Review. *Altern Med Rev*, 2000; 5(4): 306-333.
2. Aschner M, Cherian MG, Klaassen CD, et al: Metallothioneins in brain--the role in physiology and pathology. *Toxicol Appl Pharmacol*, 1997; 142(2): 229-242.
3. Prabakaran S, Swatton JE, Ryan MM, Torrey EF, et al: Mitochondrial dysfunction in schizophrenia: evidence for compromised brain metabolism and oxidative stress. *Molec Psychiat*, 2004; 9(7): 684-697, 643.
4. Yao JK, Reddy RD, van Kammen DP: Oxidative damage and schizophrenia: an overview of the evidence and its therapeutic implications. *CNS Drugs*, 2001; 15(4): 287-310.
5. Kunert HJ, Norra C, Hoff P: Theories of delusional disorders. An update and review. *Psychopathology*, 2007; 40(3): 191-202.
6. Wolf TL, Kotun J, Meador-Woodruff JH: Plasma copper, iron, ceruloplasmin and ferroxidase activity in schizophrenia. *Schizophr Res*, 2006; 86(1-3): 167-171.
7. Stanley PC, Wakwe VC: Toxic trace metals in the mentally ill patients. *Niger Postgrad Med J*, 2002; 9(4): 199-204.
8. Wallwork JC: Zinc and the central nervous system. *Prog Food Nutr Sci*, 1987; 11(2): 203-247.
9. Ebadi M, Iversen PL, Hao R, et al: Expression and regulation of brain metallothionein. *Neurochem Int*, 1995; 27(1): 1-22.
10. Chimienti F, Jourdan E, Favier A, et al: Zinc resistance impairs sensitivity to oxidative stress in HeLa cells: protection through metallothioneins expression. *Free Radic Biol Med*, 2001; 31(10): 1179-1190.
11. Aschner M: The functional significance of brain metallothioneins. *FASEB J*, 1996; 10(10): 1129-1136.
12. Goyer RA: Nutrition and metal toxicity. *Am J Clin Nutr*, 1995; 61(3 Suppl): 646S-650S.
13. Bahiga LM, Kotb NA, El-Dessoukey EA: Neurological syndromes produced by some toxic metals encountered industrially or environmentally. *Z Ernährungswiss*, 1978; 17(2): 84-88.
14. Zheng W, Lu YM, Lu GY, et al: Transthyretin, thyroxine, and retinol-binding protein in human cerebrospinal fluid: effect of lead exposure. *Toxicol Sci*, 2001; 61(1): 107-114.
15. Zheng W, Blaner WS, Zhao Q: Inhibition by lead of production and secretion of transthyretin in the choroid plexus: its relation to thyroxine transport at blood-CSF barrier. *Toxicol Appl Pharmacol*, 1999; 155(1): 24-31.

Orthomolecular Treatment For Schizophrenia: A Review (Part Two)

16. Wenzel KG, Pataracchia RJ: *The Earth's Gift to Medicine: Minerals in Health and Disease*. Alton, Ontario. KOS Publishing. 2005.
17. Rajanna B; Hobson M: Influence of mercury on uptake of [3H]dopamine and [3H]norepinephrine by rat brain synaptosomes. *Toxicol Lett*, 1985; 27(1-3): 7-14.
18. Foster HD: *What Really Causes Alzheimer's Disease?* 2004. (PDF at <http://www.hdfoster.com>)
19. Rigobello MP, Scutari G, Boscolo R, et al: Oxidation of adrenaline and its derivatives by S-nitrosoglutathione. *Nitric Oxide*, 2001; 5(1): 39-46.
20. Johnson S: Micronutrient accumulation and depletion in schizophrenia, epilepsy, autism and Parkinson's disease? *Med Hypoth*, 2001; 56(5): 641-645.
21. Heinrich TW, Grahm G: Hypothyroidism Presenting as Psychosis: Myxedema Madness Revisited. *Prim Care Companion J Clin Psychiat*, 2003; 5(6): 260-266.
22. Gupta P, Kar A: Cadmium induced thyroid dysfunction in chicken: hepatic type I iodothyronine 5'-monodeiodinase activity and role of lipid peroxidation. *Comp Biochem Physiol C Pharmacol Toxicol Endocrinol*, 1999; 123(1): 39-44.
23. Gupta P, Kar A: Role of ascorbic acid in cadmium-induced thyroid dysfunction and lipid peroxidation. *J Appl Toxicol*, 1998; 18(5): 317-320.
24. Chaurasia SS, Kar A: Protective effects of vitamin E against lead-induced deterioration of membrane associated type-I iodothyronine 5'-monodeiodinase (5'D-I) activity in male mice. *Toxicology*, 1997; 124(3): 203-209.
25. Barregård L, Lindstedt G, Schütz A, et al: Endocrine function in mercury exposed chloralkali workers. *Occup Environ Med*, 1994; 51(8): 536-540.
26. Pfeiffer CC, Braverman ER: Zinc, the brain and behaviour. *Biol Psychiat*, 1982; 17(4): 513-532.
27. Noseworthy MD, Bray TM: Zinc deficiency exacerbates loss in blood-brain barrier integrity induced by hyperoxia measured by dynamic MRI. *Proc Soc Exp Biol Med*, 2000; 223(2): 175-182.
28. Marz RB: *Medical Nutrition from Marz*. Portland, OR. Omni-Press. 1997.
29. Levine J, Stahl Z, Sela BA, et al: Homocysteine-reducing strategies improve symptoms in chronic schizophrenic patients with hyperhomocysteinemia. *Biol Psychiat*, 2006; 60 (3): 265-269.
30. Deijen JB, van der Beek EJ, Orlebeke JF, et al: Vitamin B₆ supplementation in elderly men: effects on mood, memory, performance and mental effort. *Psychopharmacology (Berl)*, 1992; 109(4): 489-496.
31. Lerner V, Bergman J, Statsenko N, et al: Vitamin B₆ treatment in acute neuroleptic-induced akathisia: a randomized, double-blind, placebo-controlled study. *J Clin Psychiat*, 2004; 65(11): 1550-1554.
32. Lerner V, Kaptan A, Miodownik C, et al: Vitamin B₆ in treatment of tardive dyskinesia: a preliminary case series study. *Clin Neuropharmacol*, 1999; 22(4): 241-243.
33. Sandyk R, Pardeshi R: Pyridoxine improves drug-induced parkinsonism and psychosis in a schizophrenic patient. *Int J Neurosci*, 1990; 52(3-4): 225-232.
34. Wenzel KG: *Orthomolecular Treatment for Mental Health: The Roles of Hypoglycemia, Pyrroluria and Histamine Disturbances*. 2000 Apr. Nutritional Medicine Today 29th Annual Conference. Vancouver, BC.
35. Jackson JA, Riordan HD, Neathery S, et al: Case from the Center: Urinary Pyrrole in Health and Disease. *J Orthomol Med*, 1997; 12(2): 96-98.
36. Edelman E: *Natural Healing for Schizophrenia: A Compendium of Nutritional Methods*. Eugene, OR. Borage Books. 1996.
37. Hoffer A: Schizophrenia: an evolutionary defense against severe stress. *J Orthomol Med*, 1994; 9(4): 205-221.
38. Pfeiffer CC: *Mental and Elemental Nutrients*. New Canaan, CN. Keats Publishing. 1975.
39. Sohler A, Holsztyńska E, Pfeiffer CC: A Rapid Screening Test for Pyrroluria; Useful in Distinguishing a Schizophrenic Subpopulation. *Orthomol Psychiat*, 1974; 3: 273-279.
40. Pfeiffer CC, Iliev V: Pyrroluria, urinary mauve factor, causes double deficiency of B₆ and zinc in schizophrenics. *Fed Proc*, 1973; 32: 276.
41. Sohler A, Beck R, Noval JJ: Mauve factor re-identified as 2,4-dimethyl-3-ethylpyrrole and its sedative effect on the CNS. *Nature*, 1970; 228(278): 1318-1320.
42. McGinnis WR, Audhya T, Walsh WJ, et al: Discerning the mauve factor, part 1. *Altern Ther*, 2008(Mar/Apr); 14(2): 40-50.
43. Mello AA, Mello MF, Carpenter LL, et al: Update on stress and depression: the role of the hypothalamic-pituitary-adrenal (HPA) axis. *Rev Bras Psiquiatr*, 2003; 25(4): 231-238.
44. Abdullatif HD, Ashraf AP: Reversible subclinical hypothyroidism in the presence of adrenal insufficiency. *Endocr Pract*, 2006; 12(5): 572.
45. Candrina R, Giustina G: Addison's disease and

- corticosteroid-reversible hypothyroidism. *J Endocrinol Invest*, 1987; 10(5): 523-526.
46. Michel V, Peinnequin A, Alonso A, et al: Decreased heat tolerance is associated with hypothalamo-pituitary-adrenocortical axis impairment. *Neurosci*, 2007; 147(2): 522-531.
 47. Ritsner M, Maayan R, Gibel A, et al: Elevation of the cortisol/dehydroepiandrosterone ratio in schizophrenia patients. *Eur Neuropsychopharmacol*, 2004; 14(4): 267-273.
 48. Swigar ME, Kolakowska T, Quinlan DM: Plasma cortisol levels in depression and other psychiatric disorders: a study of newly admitted psychiatric patients. *Psychol Med*, 1979; 9(3): 449-455.
 49. Contreras F, Menchon JM, Urretavizcaya M, et al: Hormonal differences between psychotic and non-psychotic melancholic depression. *J Affect Disord*, 2007; 100(1-3): 65-73.
 50. Bauer M, London ED, Silverman DH, et al: Thyroid, brain and mood modulation in affective disorder: insights from molecular research and functional brain imaging. *Pharmacopsychiat*, 2003; 36 Suppl 3: S215-S221.
 51. McGaffee J, Barnes MA, Lippmann S: Psychiatric presentations of hypothyroidism. *Am Fam Physician*, 1981; 23(5): 129-133.
 52. Jackson IM: The thyroid axis and depression. *Thyroid*, 1998; 8(10): 951-956.
 53. Oppenheimer JH, Braverman LE, Toft A, et al: A therapeutic controversy. Thyroid hormone treatment: when and what? *J Clin Endocrinol Metab*, 1995; 80(10): 2873-2883.
 54. Westphal SA: Unusual presentations of hypothyroidism. *Am J Med Sci*, 1997; 314(5): 333-337.
 55. Heitman B, Irizarry A: Hypothyroidism: common complaints, perplexing diagnosis. *Nurse Pract*, 1995; 20(3): 54-60.
 56. Shafer RB, Prentiss RA, Bond JH: Gastrointestinal transit in thyroid disease. *Gastroenterol*, 1984; 86(5 Pt 1): 852-855.
 57. Othman SS, Kadir KA, Hassan J, et al: High prevalence of thyroid function test abnormalities in chronic schizophrenia. Australian and NZ *J Psychiat*, 1994; 28: 620-624.
 58. Roca RP, Blackman MR, Ackerley SM, et al: Thyroid hormone elevations during acute psychiatric illness: relationship to severity and distinction from hyperthyroidism. *Endocrine Res*, 1990; 16(4): 415-447.
 59. Lum SM, Nicoloff JT, Spencer CA, et al: Peripheral tissue mechanism for maintenance of serum triiodothyronine values in a thyroxine-deficient state in man. *J Clin Invest*, 1984; 73(2): 570-575.
 60. Haddow JE, Palomaki GE, Allan WC, et al: Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med*, 1999; 341(8): 549-555.
 61. Brouwer A, Morse DC, Lans MC, et al: Interactions of persistent environmental organohalogens with the thyroid hormone system: mechanisms and possible consequences for animal and human health. *Toxicol Ind Health*, 1998; 14(1-2): 59-84.
 62. Hatterer JA, Herbert J, Hidaka C, et al: CSF transthyretin in patients with depression. *Am J Psychiat*, 1993; 150(5): 813-815.
 63. Schreiber G: The evolutionary and integrative roles of transthyretin in thyroid hormone homeostasis. *J Endocrinol*, 2002; 175(1): 61-73.
 64. Wan C, Yang Y, Li H, et al: Dysregulation of retinoid transporters expression in body fluids of schizophrenia patients. *J Proteome Res*, 2006; 5(11): 3213-3216.
 65. Huang JT, Leweke FM, Oxley D, et al: Disease biomarkers in cerebrospinal fluid of patients with first-onset psychosis. *PLoS Med*, 2006; 3(11): e428.
 66. Sullivan GM, Mann JJ, Oquendo MA, et al: Low cerebrospinal fluid transthyretin levels in depression: correlations with suicidal ideation and low serotonin function. *Biol Psychiat*, 2006; 60(5): 500-506.
 67. Sullivan GM, Hatterer JA, Herbert J, et al: Low levels of transthyretin in the CSF of depressed patients. *Am J Psychiat*, 1999; 156(5): 710-715.
 68. Hidal JT, Kaplan MM: Inhibition of thyroxine 5'-deiodination type II in cultured human placental cells by cortisol, insulin, 3',5'-cyclic adenosine monophosphate, and butyrate. *Metabolism*, 1988; 37(7): 664-668.
 69. Visser TJ, Leonard JL, Kaplan MM, et al: Kinetic evidence suggesting two mechanisms for iodothyronine 5'-deiodination in rat cerebral cortex. *Proc Natl Acad Sci, USA*, 1982; 79(16): 5080-5084.
 70. Foster HD: *What Really Causes Schizophrenia?* 2003. (pdf at <http://www.hdfoster.com>)
 71. Hoffer A: Thyroid and schizophrenia. *J Orthomol Med*, 2001; 16(4): 205-212.
 72. Langer P, Földes O: Effect of adrenaline on biliary excretion of triiodothyronines in rats mediated by alpha 1-adrenoceptors and related to the inhibition of 5'-monodeiodination in liver. *J Endocrinol Invest*, 1988(Jul-Aug); 11(7): 471-476.
 73. Nauman A, Kamin'ski T, Herbaczyn'ska-Cedro K: *In vivo* and *in vitro* effects of adrenaline

Orthomolecular Treatment For Schizophrenia: A Review (Part Two)

- on conversion of thyroxine to triiodothyronine and to reverse-triiodothyronine in dog liver and heart. *Eur J Clin Invest*, 1980(Jun); 10(3): 189-192.
74. Ceremuzyn 'ski L, Herbaczyn 'ska-Cedro K, Broniszewska-Ardelt B, et al: Evidence for the detrimental effect of adrenaline infused to healthy dogs in doses imitating spontaneous secretion after coronary occlusion. *Cardiovasc Res*, 1978(Mar); 12(3): 179-189.
75. Maayan ML, Ingbar SH: Effects of epinephrine on iodine and intermediary metabolism in isolated thyroid cells. *Endocrinology*, 1970(Sept); 87(3): 588-595.
76. Hoffer A, Osmond H: *The Hallucinogens*. Academic Press, New York, 1967.
77. Hupka S, Dumont JE: *In vitro* effect of adrenaline and other amines on glucose metabolism in sheep thyroid, heart, liver, kidney and testicular slices. *Biochem Pharmacol*, 1963 (Sep); 12: 1023-1035.
78. Pastan I, Herring B, Johnson P, et al: Studies on the mechanism by which epinephrine stimulates glucose oxidation in the thyroid. *J Biol Chem*, 1962; 237(2): 287-290.
79. Skoliarova NA: Morphology of the endocrine system in schizophrenia according to early autopsy findings (the hypophyseal-thyroid system). *Zh Nevropatol Psikhiatr Im S S Kor-sakova*, 1975; 75(7): 1045-53. (abstract only)
80. Danziger L: Thyroid therapy of schizophrenia. *Dis Nerv Syst*, 1958; 19(9): 373-378.
81. Hoskins RG, Sleeper FH: The thyroid factor in dementia Praecox. *Am J Psychiat*, 1930: 87: 411-432.
82. Hoskins RG, Walsh A: Oxygen consumption ("Basal Metabolic rate") in schizophrenia: II. Distribution in 214 cases. *AMA Arch Neurol Psychiat*, 1932; 28: 1346-1364.
83. Danziger L, Kindwall JA: Thyroid therapy in some mental disorders. *Dis Nerv Syst*, 1953; 14(1): 3-13.
84. Lochner KH, Scheuing MR, Flach FF: The effect of L-triiodothyronine on chronic schizophrenic patients. *Acta Psychiatr Scand*, 1963; 39: 413-26.
85. Scheuing MR, Flach FF: The effect of L-triiodothyronine on chronic schizophrenic patients. *Am J Psychiat*, 1964(Dec); 121: 594-595.
86. Miller CL, Dulay JR: The high-affinity niacin receptor HM74A is decreased in the anterior cingulate cortex of individuals with schizophrenia. *Brain Res Bull*, 2008; doi:10.1016/j.brainresbull.2008.03.015. (in press)
87. Zammit S, Lewis S, Gunnell D, et al: Schizophrenia and neural tube defects: comparisons from an epidemiological perspective. *Schizophr Bull*, 2007 Jul; 33(4): 853-858.
88. Regland B: Schizophrenia and single-carbon metabolism. *Prog Neuropsychopharmacol Biol Psychiatry*, 2005 Sep; 29(7): 1124-1132.
89. Rössler W, Salize HJ, van Os J, et al: Size of burden of schizophrenia and psychotic disorders. *Eur Neuropsychopharmacol*, 2005; 15(4): 399-409.