

Schizophrenia: An Update of the Selenium Deficiency Hypothesis*

James S. Brown, Jr., M.D.¹ and Harold D. Foster, Ph.D.²

Abstract

The nine Bradford Hill criteria are used to further assess the possibility that selenium deficiency may be a risk factor in schizophrenia. This hypothesis appears compatible with the known link between industrialization and schizophrenia since air pollution increases soil acidity, reducing selenium's bioavailability. Several feasible biological mechanisms for a selenium deficiency-schizophrenia association are also identified, including prostaglandin imbalances, viral mutation and excess 12-HPETE production. Evidence of a strong negative correlation between activity of the selenoenzyme glutathione peroxidase and schizophrenic brain atrophy is also reviewed. Nine surveys, conducted between 1880 and 1963 indicate a continuing negative relationship between selenium levels in fodder crops and United States schizophrenia prevalence. Such variations in the prevalence of schizophrenia in state and county mental hospitals suggest a selenium related relative risk of 1.77:1. International similarities in the spatial distributions of schizophrenia and celiac disease, cancer of the esophagus and multiple sclerosis (all of which appear to involve selenium inadequacy as either a cause or an effect) further support a role for selenium deficiency in schizophrenia. It is concluded that the available evidence warrants the careful testing of selenium supplementation in the prevention and possible treatment of schizophrenia.

Introduction

Brain development and/or function is adversely affected by various trace element imbalances and by exposure to

heavy metals and other environmental toxins. To illustrate, fetal and infant deficiencies of iodine and selenium are both capable of causing severe mental retardation.^{1,2} Similarly, "manganic madness" (locura mangánica), common in miners in northern Chile, is the result of manganese poisoning. Typically, its onset is marked by nervousness, irritability, compulsions, hallucinations, and violent outbursts.³ Yase⁴ reported that an excess of Guamanian amyotrophic lateral sclerosis and Parkinsonism with dementia also occurs in manganese miners. Interestingly, many U.S. criminals, convicted of violent felonies, have abnormally elevated levels of hair manganese.⁵ Furthermore, mercury poisoning, associated with a wide range of neurological symptoms, termed Minamata disease, also can cause "madness."⁶ In addition, evidence suggests an etiologic role for aluminum in Alzheimer's disease.⁷⁻⁹

Finally, the role of general dietary deprivation in causing schizophrenia is supported by the increased risk of schizophrenia in persons born during the Dutch Hunger Winter in World War II.¹⁰ Given the diversity of such known links between brain development and function and exogenous variables, it would not be surprising if trace element deficiencies or excesses, or heavy metal toxicities played a role in the etiology of schizophrenia. Indeed, both authors independently presented evidence that suggests selenium deficiency may be involved in this psychiatric illness.¹¹⁻¹³ Furthermore, Berry¹⁴ suggested that a defect in a hypothesized selenium transport enzyme selenoprotein P must accompany a deficiency in this trace element to cause schizophrenia.

1. Medical Director, Community Mental Health Clinic, U.S. Military Academy, Bldg. 606, West Point, New York, USA 10996

2. Professor, Department of Geography, University of Victoria, P.O. Box 3050, Victoria, British Columbia, Canada V8W 3P5

* Disclaimer: The opinions expressed in this article are solely those of the author(s) and do not represent the opinions of the U.S. Military Academy, the U.S. Army, the U.S. Department of Defense or the U.S. Government.

Testing the Hypothesis: The Bradford Hill Criteria

Geographers and epidemiologists are well aware of the difficulties implicit in generalizing from the regional to the personal scale.^{15,16} In addition, statistical aberrations can sometimes produce spurious relationships between disease distributions and the environment, which tend to imply causal links where none exist. To address these difficulties, a set of principles, often referred to as the Bradford Hill criteria after their originator, were developed to rigorously test suspected cause and effect relationships.^{15,16} These principles are similar to those used by the U.S. Surgeon General's expert committee, set up to determine whether a causal relationship existed between lung cancer and smoking.⁹ In the remainder of this discussion these nine criteria are used to update our previous theory that selenium deficiency plays a role in schizophrenia's etiology.

Coherence

Hill¹⁵ argued that an association is more likely causal if it is consistent with "known facts" or "established truth". In 1990, Torrey and Bowler¹⁷ argued that there is an urban factor in schizophrenia. As a result, the illness became more common with the onset of the Industrial Revolution.¹⁸ This hypothesis is not necessarily in conflict with the belief that dietary selenium deficiency plays a role in the etiology of schizophrenia. Air pollution associated with industrialization raises the acidity of rainfall, which causes a decline in selenium bioavailability by reducing its solubility and hence its entry into the food chain.¹⁹ In addition, Trowell and Burkitt²⁰ showed that dietary changes associated with urbanization and "civilization" are linked to an enormous number of diseases which either first emerge, or increase in prevalence, in a predictable order as Western diet and lifestyle are adopted. These include constipation, appendicitis, diverticular disease, haemorrhoids, dental car-

ries, renal stones, hyperuricaemia and gout, thyrotoxicosis, pernicious anaemia, and various cancers, including those of the colon, lung and breast. These authors suspected, but could not prove, that irritable bowel syndrome, ulcerative colitis, Crohn's disease, hiatal hernia, and some autoimmune diseases also were promoted by Western diet and lifestyle. Even this extensive list may be incomplete. Foster¹² has argued that multiple sclerosis, Alzheimer's disease, schizophrenia and diabetes mellitus (type II) should be included. Specifically, he suggested that less consumption of essential fatty acids and more of saturated fats, which typically accompanies "civilization", plays a major role in the etiology of schizophrenia.

There may be a link between the need for selenium and the consumption of certain types of fat. It was demonstrated, for example, that selenium deficient rats may show no pathological signs or symptoms until the second generation. Yet, the superimposition of vitamin E deficiency leads to death from liver necrosis within a few weeks and force feeding such animals with fat causes death in a few hours.²¹ These observations are compatible with reports of some schizophrenics appearing more likely to recover quickly in countries where diets emphasize vegetables, fish and seafood.²²

Such diets provide high intakes of essential fatty acids, but relatively little saturated fat and are, therefore, conducive to the manufacture of certain prostaglandins. Conversely, diets high in saturated fats increase the body's demand for selenium, but do not contain the raw materials needed for such prostaglandin production.²³

Biological Plausibility

Biological plausibility is an important criterion for the establishment of cause and effect relationships. It is necessary to know, for example, whether a postulated association makes biological sense; that is, whether it is possible to elaborate the bio-

chemical and biological links between the suspected causal variable(s) and the illness.^{15,16} In the postulated association under discussion, the question to be answered must be “is it possible to identify biological mechanisms by which a deficiency of selenium might cause the psychiatric symptoms seen in schizophrenia?”²⁹ Indeed, several mechanisms linking schizophrenia to selenium deficiency appear feasible.

To illustrate, past theories of schizophrenia suggested that the biological defect in schizophrenia may be related to an excess of dopamine activity, to the production of an abnormal opioid, or excessive levels of a normal opioid, or to hypersensitivity to wheat proteins. It has been hypothesized further that the illness might be linked to an allergic phenomenon, to an inability to metabolize zinc effectively, or to pineal deficiency. Horrobin²⁴ proposed that such hypotheses are not mutually exclusive, but may simply be different dimensions of the same problem. He further suggested that the ultimate common path in schizophrenia is a failure of the formation and action of prostaglandins, particularly those of Series Prostaglandins are short-lived, hormone-like compounds (fat soluble lipids) which regulate cellular activities on a moment to moment basis. They are formed as the result of the controlled oxidation of highly unsaturated fatty acids. Some 30 distinct prostaglandins are known, each with a specific function in the human body, being involved, for example, in the regulation of heart beat, blood flow and the action of the immune system.²³ They also occur in the brain in large quantities. Experimental research demonstrated that selenium status has a significant impact on the production and activity of several prostaglandins.²⁵⁻²⁷ If so, the postulated selenium deficiency-schizophrenia relationship is biologically plausible.

There are, however, other feasible biological mechanisms for such an association. To illustrate, glutathione peroxidase is a

selenoenzyme that detoxifies free radicals, which may themselves be important in the pathogenesis of schizophrenia.²⁸ Alternatively, glutathione peroxidase is involved in the arachidonic acid cascade. Selenium supplementation in humans has been shown to allow the reduction of the lipoxygenase-derived 12-hydroperoxy-5, 8, 11, 14 - eicosatetraenoic acid (12-HPETE)²⁹ to 12-hydroxy-5, 8, 11, 14 - eicosatetraenoic acid (12-HETE). 12-HPETE, therefore, accumulates in selenium deficient individuals.³⁰ This may be highly significant since the arachidonic acid cascade, including 12-HPETE and 12-HETE, is being investigated for its role in modulating N-methyl-D-aspartate-sensitive glutamate receptors, which are thought to be involved in certain neurodegenerative diseases.³¹ In addition, Schoene and co-workers³² argued that selenium deficiency, and hence decreased glutathione peroxidase activity, impairs platelet activation, thus permitting increased injury from inflammatory agents. Finally, Suttle and Jones³³ showed that in selenium-deficient ruminants, inadequate glutathione peroxidase is associated with immune cell dysfunction. Even if such a dysfunction does not directly result in reduced resistance to infection,³³ urban crowding and selenium deficiency might promote a viral etiology for schizophrenia, particularly if such a deficiency encouraged continued inflammation and brain damage.¹³

While viral theories are reviewed elsewhere,³⁴ recent research indicates links between selenium deficiency and enhanced virulence or evolution of several viruses. Beck et al³⁵ demonstrated that while Coxsackie B3 virus was harmless in mice fed normal diets, it quickly produced serious heart damage in selenium deficient rodents. Viruses from affected mice could then cause heart damage even in mice on diets containing adequate selenium. Sequence analysis of the viral genome revealed that mutation to a more virulent form was driven by selenium deficiency.

Levander et al³⁶ postulated a similar process for Keshan disease, a human cardiomyopathy in China's selenium deficient regions. Like schizophrenia, this disease shows seasonality which is thought to reflect fluctuations in viral exposure. Many new strains of influenza also appear to originate in selenium depleted areas of China.³⁷ Further evidence suggests that both HIV and Ebola Zaire virus, which appear to cause selenium deficiency, may have evolved in Zaire in areas of extreme shortage of this trace element.^{37,38}

The Temporal Relationship of the Association

Any suspected putative cause must precede, or at least be simultaneous with, its suspected effect(s).¹⁶ Obviously, cause cannot follow effect. This principle of temporality implies that if the selenium deficiency hypothesis is correct, schizophrenics should display abnormal levels of this trace element and its associated derivatives before, or at least during, their illness. It is unknown whether schizophrenics display selenium deficiency prior to diagnosis. Indeed, whether schizophrenics, themselves, are selenium deficient is still under debate. Tada and co-workers,³⁹ for example, discovered elevated selenium in the hair of male but not female patients. In contrast, Alertsen and colleagues⁴⁰ found no difference between the levels of selenium in the serum and blood of Norwegian schizophrenics and controls. Yet Buckman et al⁴¹ measured the activity of the seleno-enzyme glutathione peroxidase in blood samples for a population of chronic schizophrenics and compared it with that of a control group of age and sex matched non-schizophrenic mental patients. They found a strong negative correlation, in schizophrenics, between glutathione peroxidase activity in both isolated platelets and erythrocytes and computed tomography scan measures of brain atrophy and increased ventricle-brain ratios. These relationships were not found in the control

group and seemed to suggest a unique relationship between glutathione peroxidase and hence selenium, and the mechanism of tissue damage that is found in the brains of some schizophrenics.⁴¹

Dose-Response Relationship

A dose-response relationship is a strong indication of cause and effect. As exposure to a suspected causal variable rises, its deleterious effects are expected to increase. If selenium deficiency is involved in schizophrenia's etiology, it is anticipated that this illness would be more common in environments which are very deficient in this trace element. Conversely, this psychiatric disorder would be rare in individuals living in selenium enriched regions.

In 1988, Foster¹¹ used Pearson correlation coefficients to compare spatial variations in the prevalence of schizophrenia, in 1965, in U.S. state and county mental hospitals with 219 environmental variables. The strongest positive correlation was with selenium deficiency in fodder crops, indicative of a low entry of this trace element into the local food chain ($r=0.58$, $p<0.0001$). Subsequently, Brown¹³ conducted a more detailed survey of the possible selenium-schizophrenia relationship. In it he used two-by-two contingency tables to compare prevalence data from nine U.S. schizophrenia surveys, conducted between 1880 and 1963, with selenium deficiency in crops. This study provided further evidence of a significant correlation between low selenium-high schizophrenia states ($p<0.0001$; Yates corrected χ^2). This research also demonstrated a significant correlation for States that reported high, or very high, schizophrenia rates in at least five of the nine surveys ($p<0.0002$). Indeed, there was a significant correlation ($p<0.0001$) between not only the 1880 survey, but also the 1963 survey and low selenium states. Brown's¹³ analyses, therefore, suggested a possible dose-response relationship between selenium deficiency and schizophrenia.

Experimental Support

It is rarely possible, for ethical reasons, to conduct strictly controlled experiments on humans in an effort to establish causal relationships. Usually, one must rely on animal models, quasi-experimental or simply observational studies.¹⁵ However, in the case of schizophrenia, some experimental support for an etiologic role for selenium is found in reports of various, although controversial, treatments of schizophrenia.

To illustrate, studies of niacin as a medication for schizophrenia produced mixed results, although some patients appear to benefit from its use.^{42,43} Berry¹⁴ hypothesized that the apparent benefits of niacin supplementation may result from niacin's action to decrease selenium methylation thus prolonging this essential trace element's action in the body.

Rudin et al⁴⁴ also reported some success in the treatment of schizophrenia with flax seed oil, although they point out the amount taken is critical. Overdosing can make the condition worse. Flax seed oil contains high levels of alpha-linolenic acid which is necessary for prostaglandin production.²³ Rudin et al⁴⁴ discovered, however, that supplementing the diets of schizophrenics with essential fatty acids only worked when selenium levels were high. Vaddadi⁴⁵ reported that a combination of penicillin and evening primrose oil had a dramatic positive effect on some schizophrenic patients. Evening primrose is one of the rare plants that contains significant quantities of gamma linoleic acid, the first biochemical step in the creation of the Series I family of prostaglandins.

Consistency of the Association

The consistency principle stresses the need for repetition, arguing that an association between a postulated cause and its effect is more likely true if it is observed in a variety of places, populations and circumstances.¹⁶ If the selenium deficiency hypothesis is correct, one would expect particularly low schizophrenia rates in countries

and states that had either vigorous selenium supplementation programs, or in which soil selenium levels were naturally elevated. In addition, one might expect less schizophrenia in ethnic or social groups with diets enriched in selenium.

According to Torrey⁴⁶ the highest international schizophrenia prevalence rates are in Finland, at 15.1 per 1000 population. This country appears to have the highest consistently reported prevalence in Europe.^{47,48} Interestingly, selenium intake in Finland was naturally so low that, starting in 1969, its national government mandated the addition of this trace element to fertilizers and animal feed.⁴⁹ If selenium deficiency plays a causal role in schizophrenia, one would expect a decline in its prevalence to have followed supplementation. This appears to have occurred. Lehtinen and co-workers,⁴⁸ for example, reported that schizophrenia prevalence in Finland peaked in the 50 to 54 year age group and then diminished with declining age. However, a similar decline was reported in countries, such as Denmark, that have low soil selenium levels, but no aggressive selenium supplementation programmes.⁵⁰

New Zealand also has severely deficient soil selenium levels.⁵¹ As a consequence, livestock supplementation started in 1960⁵² and the addition of selenium to fertilizers in the late 1970s.⁵³ New Zealand's schizophrenia prevalence rates, prior to 1970, are unknown, so that pre- and post-supplementation rates cannot be compared. However, New Zealand's current lifetime prevalence for this psychiatric illness is only 0.4 percent, which is as low as the lowest morbid risk rates in Europe.^{47,54} Interestingly, however, first admissions for schizophrenia to New Zealand hospitals have dropped since 1974, a decline that is considered a real decrease in incidence.⁵⁵ As previously mentioned, similar declines are recorded in some countries not engaged in selenium supplementation. It should be noted, however, that the post war period saw great increases in the export of North America wheat, the

consumption of wheat which, in itself, enhanced dietary selenium intake in many nations. In 1978, for example, the average daily selenium intake in the United Kingdom was 60 micrograms. However, trade barriers, a reflection of developing European unity, subsequently increased the use of locally grown wheat. As a consequence, average daily selenium intake in the United Kingdom fell to 43 micrograms by 1986⁵⁶ and is currently believed to be only 34 micrograms.⁵⁷ Similar declines in selenium intake, associated with less consumption of North American wheat, have probably occurred throughout much of the rest of Europe. Whether they will ultimately be associated with an increase in schizophrenia prevalence in those countries not mandating selenium supplementation in agriculture remains to be seen.

Strength of Association

Causality is more likely if the magnitude of the relationship between suspected cause and effect is high. A very large relative risk of, say, 8:1 is suggestive that any association is unlikely due to chance alone.¹⁵ In 1967, Kubota and co-workers⁵⁸ provided data on the selenium content of U.S. fodder crops, those containing <0.1 mg Se/kg being considered deficient. Except the states of Maine and Arizona (for which 1965 schizophrenia prevalence data is unavailable) 12 contiguous states produced very selenium deficient fodder crops, while in 16 others, crops were almost entirely above this minimum selenium level. Schizophrenia prevalence, based on patient counts in state and county mental hospitals, also is available for 1965.^{11,12,59}

A comparison of these two data sets indicated that in the 12 selenium deficient states, mental hospital based schizophrenia prevalence varied from a high of 0.278 per 1,000 population in New York to a low of 0.093 in West Virginia. The mean prevalence for these 12 states was 0.154 per 1,000 inhabitants. In contrast, in the 16 states growing fodder crops containing

adequate or high levels of selenium, schizophrenia prevalence varied from a high of 0.127 in North Dakota to a low of 0.034 per 1,000 persons in Iowa. The mean schizophrenia prevalence in 16 states was calculated at 0.087 per 1,000 population. A comparison of the prevalence means for these two groups of states produces a relative risk of 1.77:1, which is consistent with an etiologic role for selenium deficiency in schizophrenia. Clearly, schizophrenia is more common in regions of the USA where the level of selenium entering the local food chain is reduced.

The Specificity of the Association

Hill¹⁵ originally suggested that specificity of association might be considered a criterion for causality. A particular exposure should result in one specific disease. However since trace elements, such as selenium, play a diversity of biochemical roles, it is unrealistic to expect that a deficiency will be associated with only one disorder. To illustrate, selenium inadequacy is linked to Keshan and Kaschin-Beck diseases,⁶⁰ numerous cancers,⁶¹ and to acute myocardial infarction.⁶² Beyond this, deficiency of this trace element may be involved in some forms of dementia⁶³ and even in male infertility.⁶⁴ There is, therefore, no possible specificity of association between any of these diseases or disorders and selenium deficiency, nor can there be any such relationship between selenium and schizophrenia.

Analogue

If dietary selenium insufficiency were the sole cause of schizophrenia, the spatial distribution pattern of this illness would closely mirror those of other selenium deficiency disorders. Furthermore, selenium would be the only trace element showing such spatial disease associations. If the etiology of schizophrenia involved one or more additional exogenous variables, spatial similarities with other selenium deficiency diseases would be less apparent.⁶⁵

Clearly, there is more involved in the etiology of schizophrenia than just selenium inadequacy. Evidence suggests, however, that insights into the etiology of schizophrenia may come from studies of the geographies of other diseases that appear to involve selenium deficiency. This literature will now be reviewed.

Kaschin-Beck and Keshan Disease

Kaschin-Beck disease, an osteoarthropathy and Keshan disease, a cardiomyopathy are both endemic to a belt of very low selenium soils, crossing China from north-east to southwest.² Although their etiologies are not yet fully understood, both diseases clearly involve selenium deficiencies, since they can be prevented by the addition of this trace element to the foodchain.^{2,60} There is no evidence that either disease is associated with psychiatric symptoms. However, this would not be surprising if the etiology of schizophrenia also involved excess saturated fat consumption since, in these endemic areas, the Chinese diet is largely vegetarian. Svistunova⁶⁶ found that, in the former USSR, children living in regions with endemic Kaschin-Beck disease, display impaired psychological development, even when they show no overt symptoms of Kaschin-Beck. In China, individuals with the most severe form of Kaschin-Beck disease (grade III) are cretinoid and suffer from extreme mental retardation.²

Celiac Disease

Celiac disease is extremely common in Ireland,^{67,68} a country also known for its elevated schizophrenia prevalence.⁴⁶ There is extensive evidence to show that celiac disease is greatly exacerbated by gluten in numerous grains.^{69,70} Dohan^{71,72} found significant correlations between the drop in hospital admissions of newly diagnosed schizophrenic patients and reduced wheat and rye consumption in many countries as a consequence of World War II. Such parallels between celiac dis-

ease and schizophrenia may not be coincidental. Schizophrenia is more common in celiacs than in the general population.⁷³ Dohan⁷² and Perisic, et al,⁷⁴ estimated the incidence of schizophrenia in adult celiac patients at approximately 37/1,000 cases, while Cooke and Holmes⁷⁵ argued that it reached at least 10/1000 patients. These rates are comparable to total population (non-age corrected) rates reported by Torrey⁴⁶ for high schizophrenia countries such as Ireland, Yugoslavia and urban areas of the United States. Furthermore Bender⁷⁶ and Dohan^{77,78} provided case studies which suggested schizophrenic children suffered from an abnormally high incidence of celiac disease. Perisic, et al⁷⁴ also reported that children of schizophrenics have increased risk of celiac disease. Another link between brain function and celiac disease was established by Dickey⁷⁹ who reported that seizure frequency declines in many epileptics on gluten-free diets.

Templer and Veleber⁸⁰ established a positive correlation between wheat consumption and the world-wide prevalence of schizophrenia. This link may be causal, since patients on gluten-free diets often improve clinically⁸¹ although some clinical trails were negative.⁸² Gluten is the component of wheat which produces opioids in the gut. These may be absorbed into the bloodstream and, under certain conditions, can interfere with the actions of the Series I prostaglandins.²⁴ Gluten intolerance appears to be the major cause of celiac disease, which results in the malabsorption of vitamins A and E, and various trace elements. Several studies show, for example, that celiacs are typically selenium deficient.⁸³⁻⁸⁵ In addition, celiac disease is associated with the malabsorption of fats. It is possible, therefore, that because of a genetic intolerance to gluten, many schizophrenics have difficulty absorbing essential fatty acids, while also failing to adequately absorb antioxidants, including selenium, needed to protect these essential nutrients.

Cancer of the Esophagus

In 1986, one of the authors⁸⁶ examined the spatial patterns of mortality, in the United States, from 65 specific cancers, or subgroups of cancers and malignant neoplasms as a whole. Among the most interesting findings were strongly significant negative Pearson correlations between esophageal cancer mortality in the United States and soil levels of calcium and selenium. Esophageal cancer was least common where soil selenium and calcium were elevated. This relationship appears to be global.^{12,87} Recent evidence suggests that mortality from esophageal cancer may be reduced by either increasing dietary antioxidant levels, including selenium,⁸⁸ or by adding jianshi (calcium concretions) to drinking water.^{12,89} If both schizophrenia and esophageal cancer are associated with selenium deficiencies, their prevalences may peak together in the same regions. Indeed, Templer et al⁹⁰ found positive, statistically significant correlations between schizophrenia and esophageal cancer prevalence rates in both Italy and the United States. Esophageal cancer was the only independent variable to correlate significantly with schizophrenia in both countries.^{90,91} In the United States, Mason et al⁹² reported the highest rates of esophageal cancer in the east and west coast and Great Lakes states. This trend, more notable for males than females, parallels the well-known, stable geographic distribution of schizophrenia described by Torrey and Bowler¹⁷ and Brown.¹³

Multiple Sclerosis

Campbell, Crow and Lang⁹³ first drew attention to the fact that multiple sclerosis (MS) was most common in regions where goiter was endemic. Stevens⁹⁴ suggested that similarities in geographic distribution and other epidemiologic characteristics between MS and schizophrenia implied a common cause. Both authors presented separate explanations of these findings Foster^{12,95} argued that MS is re-

lated to childhood consumption of milk from iodine deficient cows. Such milk contains abnormally low levels of vitamin A, which plays a key role in protecting essential fatty acids from free radical damage. The situation is exacerbated if the cows are selenium deficient since this trace element also protects linoleic and linolenic acids. Some similarity between the spatial patterns of schizophrenia and MS might, therefore, be expected; although there is no evidence of a role for iodine in schizophrenia. Based on selenium's hypothesized role in humoral immune responses in animals,⁹⁶ Brown¹³ suggested that selenium deficiency might promote schizophrenia by interfering with viral immunity. Both schizophrenia and MS have been theorized to result from viral infections,^{34,97} and the overlap of MS and schizophrenia might result from reduced immunity from selenium deficiency to endemic, geographically-defined viruses.⁹⁸ Although global MS rates correlate with Scandinavian populations which appear genetically at risk for MS⁹⁹ vulnerability to central nervous system viruses can have genetic components.

Consequences

The hypothesis that schizophrenia is associated with selenium deficiency appears to meet several of the cause and effect criteria established by Bradford Hill.¹⁵ However, conclusive proof is lacking because of missing or limited data for the dose-responsive relationship and strength of association. Given the hypothesis' coherence, biological plausibility, temporal relationship of association, experimental support, consistency and analogue evidence, enough data exists to pursue it further. Since selenium is an essential trace element that appears protective against many diseases, clinical trials would appear to carry little risk. However, testable dietary hypotheses must be cautiously generated to validate, or refute, the postulated association between selenium inadequacy and schizophrenia. Deaths have occurred

from excess selenium intake from medically unsupervised supplements sold in health food stores.¹⁰⁰ Although one death was reported from medical administration of selenium to a child with cystic fibrosis,¹⁰¹ the dose (25 mcg) was equal to a child's daily requirement¹⁰² and far below adult dietary requirements of 50-200 mcg⁵¹ which suggests that mortality from therapeutic levels of selenium may be related to individual patient factors. Selenium appears protective against most cancers^{61,103} but some isolated reports identified increased risk of some cancers, under certain conditions, with selenium supplementation.¹⁰⁴ Finally, teratogenic risk from selenium is reported from a few animal studies.⁵¹ Therefore, careful patient screening and monitoring before and during selenium therapy would be necessary. Interpretation of the results of dietary supplementation with selenium might be difficult and possibly require lengthy follow-up observations. There is ample evidence suggesting that a pre- or perinatal injury increases the risk of developing schizophrenia^{105,106} but no evidence supports the notion that adult supplementation of a missing nutrient during infancy of a person predisposed to schizophrenia will fully reverse the adult manifestation of this particular illness. However, progression of the disease, if occurring at a later age, may be interrupted.

References

1. Hetzel BS: *The story of iodine deficiency: an international challenge in nutrition*. Oxford: Oxford University Press. 1989.
2. Editorial Board: *The atlas of endemic diseases and their environments in the People's Republic of China*. Beijing: Science Press. 1989.
3. Donaldson J: The physiopathologic significance of manganese in brain: its relation to schizophrenia and neurodegenerative disorders. *Neurotoxicol*, 1987; 8: 451-462.
4. Yase Y: The pathogenesis of Amyotrophic lateral sclerosis. *Lancet*, 1972; 2: 292-295.
5. Walker M: Excessive tissue manganese as a cause of antisocial behaviour. *Townsend Letter for Doctors*, 1994; 137: 1328-1334.
6. Ellis D: *Environments at risk: case histories of impact assessment*. Berlin: Springer-Verlag. 1989.
7. Flaten TD: Geographical associations between aluminium in drinking water and death rates with dementia (including Alzheimer's disease), Parkinson's disease and amyotrophic lateral sclerosis in Norway. *Environ Geochem Health*, 1990; 12(1-2): 152-167.
8. Martyn CN, Osmond C, Edwardson JA: Geographical relation between Alzheimer's disease and aluminum in drinking water. *Lancet*, 1989; 334: 59-62.
9. Houeland T: Aluminum and Alzheimer's disease: is there a causal connection? *Environ Geochem Health*, 1990; 12(1-2): 173-177.
10. Susser ES, Lin SP: Schizophrenia after prenatal exposure to the Dutch Hunger Winter of 1944-1945. *Arch Gen Psychiat*, 1992; 49: 983-988.
11. Foster HD: The geography of schizophrenia: possible links with selenium and calcium deficiencies, inadequate exposure to sunlight and industrialization. *J Orthomolecular Med*, 1988; 3(3): 135-140.
12. Foster HD: *Health, Disease and the Environment*. London: Belhaven Press, 1992.
13. Brown JS: Role of selenium and other trace elements in the geography of schizophrenia. *Schizophrenia Bulletin*, 1994; 20(2): 387-398.
14. Berry T: A selenium transport protein model of a sub-type of schizophrenia. *Med Hypoth*, 1994; 43: 409-414.
15. Hill AB: The environment and disease: association or causation? *Proc Roy Soc Med*, 1965; 58: 295-300.
16. Jones K, Moon G: *Health, Disease and Society: an Introduction to Medical Geography*. London: Routledge and Kegan Paul. 1987.
17. Torrey EF, Bowler A: Geographical distribution of insanity in America: evidence for an urban factor. *Schizophrenia Bulletin*, 1990; 16: 591-604.
18. Torrey EF: *Schizophrenia and Civilization*. New York: Jason Aronson. 1980.
19. Frost DV: Why the level of selenium in the food chain appears to be decreasing. In: Combs GF Jr, Spallholz JE, Levander OA, Oldfield JE (eds). *Selenium in Biology and Medicine* Part A. New York: Van Nostrand Reinhold. 1987: 534-547.
20. Trowell HC, Burkitt DP (eds): *Western Diseases: their emergence and prevention*. Cambridge, Mass.: Harvard University Press. 1981.
21. Mertz W: Selenium from a distance. In: Combs GF Jr, Spallholz JE, Levander OA, Oldfield JE (eds). *Selenium in Biology and Medicine* Part A. New York: Van Nostrand Reinhold. 1987: 3-8.
22. Christensen O, Christensen E: Fat consumption and schizophrenia. *Acta Psychiat Scand*,

- 1988; 78(5): 587-591.
23. Erasmus U: *Fats and Oils: the complete guide to fats and oils and health and nutrition*. Vancouver: Alive Books. 1986.
 24. Horrobin DF: Schizophrenia: Reconciliation of the dopamine, prostaglandins, and opioid concepts and the role of the pineal. *Lancet*, 1979; 529-531.
 25. Hong Y, Li CH, Burgess JR, et al: The role of selenium-dependent and selenium-independent glutathione peroxidases in the formation of prostaglandins F2 alpha. *J Biol Chem*, 1989; 264(23): 13793-13800.
 26. Fujita T, Nakatani E, Funaiishi N, et al: Potent inhibition of prostaglandin inactivation in rabbit gastric antral mucosal slices by selenium ions invitro. *J Pharm Pharmacol*, 1990; 42(9): 655-657.
 27. Hampel G, Reinke M, Hren J: Prostaglandin synthesis is increased in selenium supplemented human mesangial cells despite suppression of phospholipase A2 activity. *Life Sci*, 1991; 49(12): 881-888.
 28. Lohr JB: Oxygen radicals and psychiatric illness: some speculations. *Arch Gen Psychiat*, 1991; 48: 1097-1106.
 29. Van der Torre HW, Veenstra J, Van de Pol H, et al: Effects of selenium supplementation on platelet function as assessed by platelet aggregation and glutathione peroxidase activity. In: Wendel A (ed). *Selenium in Biology and Medicine*. New York: Springer Verlag. 1989: 219-222.
 30. Bryant RW, Simon TC, Bailey JM: Hydroperoxy fatty acid formation in selenium deficient rat platelets: coupling of glutathione peroxidase to the lipoxygenase pathway. *Biochem Biophys Res Comm*, 1983; 117: 183-189.
 31. Marangos PJ, Lal H (eds): *Emerging Strategies in Neuroprotection*. Boston, MA: Birkhauser. 1992.
 32. Schoene NW, Morris VC, Levander OA: Altered arachidonic acid metabolism in platelets and aortas from selenium deficient rats. *Nutr Res*, 1986; 6: 75-83.
 33. Suttle NE, Jones DG: Recent developments in trace element metabolism and function: trace elements, disease resistance and immune responsiveness in ruminants. *J Nutr*, 1989; 119: 1055-1061.
 34. Yolken RH, Torrey EF: Viruses, schizophrenia and bipolar disorder. *Clin Microbiol Rev*, 1995; 8: 131-145.
 35. Beck ME, Shi Q, Morriss VC, et al: Rapid genomic evolution of non-viral Coxsackievirus B3 in selenium-deficient mice results in selection of identical virulent isolates. *Nature Med*, 1995; 1(5): 433-436.
 36. Levander OA, Ager AL Jr, Beck MA: Vitamin E and Selenium: contrasting and interacting nutritional determinants of host resistance to parasitic and viral infections. *Proc Nutr Soc*, 1995; 54: 475-487.
 37. Oldfield JE: The China connection. *Bulletin of the Selenium-Tellurium Development Association*, September, 1995: 2-3.
 38. Taylor EW, Ramanathan CS: Theoretical evidence that the Ebola Virus Zaire strain may be selenium-dependent: a factor in pathogenesis and viral outbreaks: *J Orthomolecular Med*, 1995; 10(3): 131-138.
 39. Tada K, Nogami Y, Nagashima M, et al: Trace elements in the hair of schizophrenics. *Biol Psychiat*, 1986; 21: 325-328.
 40. Alertsen AR, Aukrust A, Skaug OE: Selenium concentration in blood and serum from patients with mental diseases. *Acta Psychiat Scand*, 1986; 74: 217-219.
 41. Buckman TD, Kling AS, Eiduson S, et al: Glutathione peroxidase and CT scan abnormalities in schizophrenia. *Biol Psychiat*, 1987; 22(11): 1349-1356.
 42. Osmond H, Hoffer A: massive niacin treatment in schizophrenia: Review of a nine-year study. *Lancet*, 1962; 1: 316-320.
 43. Ban TA: Nicotinic acid in the treatment of schizophrenias: practical and theoretical considerations. *Neuropsychobiol*, 1975; 1: 133-145.
 44. Rudin DO, Felix C (with Schraeder C): *The Omega-3 Phenomenon*. New York: Avon Books. 1987.
 45. Vaddadi KS: *Prostaglandins Medicine*, 2: 22. Cited by Horrobin DF, op. cit. 530.
 46. Torrey EF: Prevalence studies in schizophrenia. *Brit J Psychiat*, 1987; 150: 598-608.
 47. Jablensky A: Epidemiology of schizophrenia: a European perspective. *Schizophrenia Bulletin*, 1986; 12: 52-73.
 48. Lehtinen V, Joukamaa M, Lahtela J, et al: Prevalence of mental disorders among adults in Finland: basic results from the mini Finland health survey. *Acta Psychiat Scand*, 1990; 81: 418-425.
 49. Alftan G, Aro A, Hittunen JK: Supplementation of a population with selenium: reasons for action and initial experience. In: Wendel A (ed). *Selenium in Biology and Medicine*. New York, NY: Springer Verlag. 1989: 210-213.
 50. Jorgensen PM, Mortensen PB: Incidence and other aspects of the epidemiology of schizophrenia in Denmark, 1971-1987. *Brit J Psychiat*, 1992; 161: 489-495.

51. Gissel-Nielsen G, Gupta UC, Lamand M, et al: Selenium in soils and plants and its importance in livestock and human nutrition. In: Brady NC (ed). *Advances in Agronomy* 37. Orlando, Florida: Academic Press. 1984: 398-460.
52. O'Hara: Personal communication with Brown JS Jr. 1992.
53. Watkinson JH: Prevention of deficiency in grazing animals by annual topdressing of pasture with sodium selenate. *NZ Vet J*, 1983; 31: 78-85.
54. Wells JE, Bushnell JA, Hornblow AR, et al: Christchurch psychiatric epidemiology study: Part 1. Methodology and lifetime prevalence for specific psychiatric disorders. *Aust & NZ J Psychiat*, 1989; 23: 315-326.
55. Joyce PR: Changing trends in first admissions and re-admission for mania and schizophrenia in New Zealand, 1974 to 1984. *Aust & NZ J Psychiat*, 1987; 21: 82-86.
56. Barclay MNI, Macpherson A: Selenium content of wheat flour used in the UK. *J Sci Food and Agricul*, 1986; 37(7): 1133-1138.
57. Anon: New Survey reveals massive drop in selenium consumption. *Nutr Ther Today*, 1995; 5(2): 1.
58. Kubota J, Allaway WH, Carter DL, et al: Selenium in crops in the United States in relation to selenium-responsive diseases in animals. *J Agricul Food Chem*, 1967; 15: 448-453.
59. US Department of Health, Education and Welfare, Public Health Service, National Institute of Mental Health, Survey and Reports Section, Biometry Branch: Patients in Mental Institutions 1965 *Part II: State and County Mental Hospitals*, PHSP No. 1597. Chevy Chase, Maryland. 1967.
60. Tan J, Li R, Zhu W: Medical geography. In: Geographical Society of China (ed). *Recent development of geographical science in China*. Beijing: Science Press. 1990: 259-279.
61. Berkel J, Bako G: Selenium and cancer: Overview and data from Alberta. *Western Geographical Series*, 1992; 27: 71-88.
62. Kok FJ, Hofman A, Witteman JCM, et al: Decreased selenium level in acute myocardial infarction. *JAMA*, 1989; 261(8): 1161-1164.
63. Tolonen M, Hulme M, Sarna S: Vitamin E and selenium supplementation in geriatric patients: a double-blind clinical trial. In: Combs GF Jr, Spallholz JE, Levander OA, Oldfield JE (eds). *Selenium in Biology and Medicine* Part B. New York: Van Nostrand Reinhold. 1987:
64. Krsnjavi H: Selenium and fertility in men. *Trace Ele Med*, 1992; 9(2): 107-108.
65. Foster HD: Disease family trees: the possible roles of iodine in goitre, cretinism, multiple sclerosis, amyotrophic lateral sclerosis, Alzheimer's and Parkinson's diseases and cancers of the thyroid, nervous system and skin. *Med Hypoth*, 1987; 24: 249-263.
66. Svistunova TB: Biogeochemical influences on the psychological development of school-children (in Kaschin-Beck areas). *International Symposium on Environmental Life Elements and Health Abstracts*. Beijing: Science Press. 1988: 283.
67. O'Reilly D, Murphy J, McLaughlin J, et al.: The prevalence of coeliac disease and cystic fibrosis in Ireland, Scotland, England and Wales. *Int J Epidemiol*, 1974; 3(3): 247-251.
68. McCarthy CF: Coeliac disease: its Irish dimensions. *Irish J Med Sci*, 1975; 144(1): 1-13.
69. Dohan FC, Harper EH, Clark MH, et al: Is schizophrenia rare if grain is rare? *Biol Psychiat*, 1984; 19(3): 305-399.
70. Cole SG, Kagnoff MF: Celiac disease. *Ann. Rev. Nutr.*, 1985; 5: 241-266.
71. Dohan FC: Wheat "consumption" and hospital admissions for schizophrenics during World War II. A preliminary report. *American J Clin Nutr*, 1966; 18(1): 7-10.
72. Dohan FC: Cereals and schizophrenia. Data and hypotheses. *Acta Psychiat Scand*, 1966; 42: 125-152.
73. Pfeiffer CC: Schizophrenia and wheat gluten enteropathy. *Biol Psychiat*, 1984; 19(3): 279-80.
74. Perisic VN, Lopacic Z, Kokai G: Celiac disease and schizophrenia: family occurrence. *J Pediat Gastr Nutr*, 1990; 11: 279-287.
75. Cook WT, Holmes GKT: Neurological and psychiatric complications. In: *Coeliac Disease*, 1st Edition. Edinburgh: Churchill Livingstone. 1984: 195-213.
76. Bender L: Childhood schizophrenia. *Psychiat Quart*, 1953; 27: 3-81.
77. Dohan FC: Coeliac disease and schizophrenia. *Lancet*, 1970; I: 897-898.
78. Dohan FC: Coeliac disease and schizophrenia. *BritMed J*, 1973; 3(870): 51-52.
79. Dickey W: Epilepsy, cerebral calcifications, and coeliac disease. *Lancet*, 1994; 1585-1586.
80. Templar D, Veleber DM: Schizophrenia prevalence: wheat, milk and temperature. *J Orthomolecular Psychiat*, 1980; 9(4): 284-286.
81. Singh MM, Kay SR: Wheat gluten as a pathogenic factor in schizophrenia. *Science*, 1976; 191: 401-402.
82. Lorenz K: Cereal allergies and intolerances.

- In: Tu AT (ed). Food Poisoning: *Handbook of Natural Toxins* 7. New York: Marcel Dekker. 1992: 373-398.
83. Hinks LJ, Inwards KD, Lloyd B, et al.: Body content of selenium in coeliac disease. *British Med J, Clin Res Ed.*, 1984; 288(6434): 1862-1863.
 84. Collins BJ, Bell PM, McMaster D, et al.: Selenium in coeliac disease. *Brit Med J, Clin Res Ed.*, 1984; 289(6442): 439.
 85. Cortigiani L, Nutini P, Caiulo VA, et al.: Selenium in celiac disease. *Minerva Pediatrica*, 1989; 41(11): 539-542 [Italian].
 86. Foster HD: Reducing cancer mortality: A geographical perspective. *Western Geographical Series* 23. Victoria: Department of Geography, University of Victoria. 1986.
 87. Norie IH, Foster HD: Water quality and cancer of the digestive tract: Canadian experience. *J Orthomolecular Med*, 1989; 4(2): 59-69.
 88. Blot WJ, Li JY, Taylor PR, et al.: Nutrition intervention trials in Linxian, China: Supplementation with specific vitamin/mineral combinations, cancer incidence and disease-specific mortality in the general population. *J Nat Cancer Inst*, 1993; 85: 1483-1492.
 89. Yu W, Foster HD: Reducing the incidence of cancer of the esophagus: field evidence of the efficacy of jiangshi, a traditional Chinese stone drug. *J Orthomolecular Med*, 1991; 6(2): 57-63.
 90. Templer DI, Hughey BB, Chalgujian H, et al.: Multiple sclerosis, schizophrenia, temperature and latitude. *J Orthomolecular Med*, 1990; 5(3): 125-128.
 91. Foster HD: Schizophrenia and esophageal cancer: Comments on similarities in their spatial distributions. *J Orthomolecular Med*, 1990; 5(3): 129-134.
 92. Mason TJ, McKay FW, Hoover R, et al.: *Atlas of Cancer Mortality for US Counties: 1950-1969*. DHEW Publication No (NIH) 75-780. US Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, Maryland. 1975.
 93. Campbell AMG, Crow RS, Lang DW: Goitre and disseminated sclerosis. *Brit Med J*, 1960; 1: 200-201.
 94. Stevens JR: Schizophrenia and multiple sclerosis. *Schizophrenia Bulletin*, 1988; 14: 231-241.
 95. Foster HD: Reducing the incidence of multiple sclerosis. *Environments*, 1988; 19(3): 14-34.
 96. Spallholz JE: Selenium: What role in immunity and immune cytotoxicity. In: Spallholz JE, Martin JL, Ganther HE (eds). *Selenium in Biology and Medicine*. Westport: Avi Publishing. 1981: 103-117.
 97. Johnson RT: The virology of demyelinating diseases. *Ann. Neurol*, 1994; 36: S54-S60.
 98. Brown JS Jr: Geographic correlation of schizophrenia to ticks and tick-borne encephalitis. *Schizophrenia Bulletin*, 1994; 20: 755-775.
 99. Poser CM: The epidemiology of multiple sclerosis: a general overview. *Ann. Neurol* 1994; 36(S2): S180-S193.
 100. FDA: Drug Bulletin, 1984; 14: 19.
 101. Snodgrass W, Rumach FBH, Sullivan JB Jr, et al.: Selenium: Childhood poisoning and cystic fibrosis. *Clin Toxicol*, 1981; 18(2): 211-220.
 102. Van Campen DR: Trace elements in human nutrition. In: Mortvedt JJ, Cox FR, Shuman LM, Welch RM (eds). *Micronutrients in Agriculture* 2nd edition. Madison, Wisconsin: *Soil Sci Soc Am, Inc.* 1991: 663-701.
 103. Schrauzer GN: Selenium and cancer: Historical developments and perspectives. In: Spallholz JE, Martin JL, Ganther HE (eds). *Selenium in Biology and Medicine*. Westport: Avi Publishing. 1981: 98-102.
 104. Birt DF, Pour PM, Pelling JC: The influence of dietary selenium on colon, pancreas, and skin tumorigenesis. In: Wendel A (ed). *Selenium in Biology and Medicine*. Berlin: Springer-Verlag. 1989: 297-304.
 105. McNeil TF, Blennow G, Lundberg L: Congenital malformations and structural development anomalies in groups at high risk for psychosis. *Am J Psychiat*, 1992; 149: 57-61.
 106. McNeil TF, Cantor-Graae E, Nordstrom LG, et al.: Head circumference in "preschizophrenic" and control neonates. *Brit J Psychiat* 1993; 162: 517-523.

Keywords: Infection Hypothesis, Schizophrenia.

1. Introduction. Since the first part of the 20th century, largely following advances in molecular biology methods, mental health researchers have attempted to identify microorganisms that might be involved in the pathophysiology of mental illness, specifically schizophrenia. Many microorganisms have been implicated (Table 1) including viruses, bacteria, and at least one protozoan [5-7]. This paper identifies, reviews, analyzes, and quantifies the research on the infection hypothesis of schizophrenia. A systematic review was performed. The results and conclusions are discussed in the framework of the neuro

Schizophrenia is a chronic, severe, and disabling psychosis, which is an impairment of thinking in which the interpretation of reality is abnormal. Psychosis is a symptom of a disordered brain. Approximately 1 percent of the population worldwide develops schizophrenia during their lifetime. Although schizophrenia affects men and women with equal frequency, the disorder often appears earlier in men, usually in the late teens or early twenties, than in women, who are generally affected in the twenties to early thirties. People with schizophrenia often suffer symptoms such as hearing internal voices. Schizophrenia can be tricky to diagnose, because its symptoms sometimes masquerade as other diseases. Learn more about all the facets of schizophrenia here.

The duration of the prodromal phase can vary, and in some people may last over 2 years. Early symptoms can be difficult to detect because they can mirror the typical behavior of an anxious teenager or young adult. Since the comparison is most statistically significant for low selenium, the selenium theory of schizophrenia is evaluated by the principles of environmental epidemiology. Although this examination finds the theory deficient, CONTINUE READING.

Schizophrenia : an update of the selenium deficiency hypothesis. J. S. Brown, H. Foster. Medicine. Selenium deficiency occurs when an organism lacks the required levels of selenium, a critical nutrient in many species. Deficiency, although relatively rare in healthy well-nourished individuals, can have significant negative results, affecting the health of the heart and the nervous system; contributing to depression, anxiety, and dementia; and interfering with reproduction and gestation.