Role of Selenium and Other Trace Elements in the Geography of Schizophrenia

by James S. Brown, Jr.

Abstract

Medical geology is the application of trace element geography to epidemiology. This approach is used to compare the geographic distribution of selenium and other trace elements in soil and food with that of high schizophrenia rates in the United States and other countries. 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, research questions are generated to test the theory further and to investigate the causes of schizophrenia.


... diet is the mother of diseases, let the father be what he will; and from this alone melancholy and frequent other maladies arise.
—Fernelius [Burton 1927, p. 189]


The confirmation of an environmental cause for a disease must demonstrate strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experimental evidence, and analogy (Underwood 1971; National Research Council 1991). These nine conditions must be met to avoid errors that arise when multiple trace elements are involved and when soil concentrations of elements are assumed to be passed on to living organisms through the food chain. These issues are extensively reviewed elsewhere (Cannon and Hopps 1971; Hopps and Cannon 1972; Freedman 1975) and will not be reviewed here. If these requirements are not met, erroneous conclusions can result in unfounded or fraudulent therapies, such as unique diets and healing crystals. Medical geology is valued for generating testable hypotheses based on geologic and clinical observations.

Psychiatric Applications of Medical Geology

Geologic investigations are rare in the psychiatric literature. Perhaps this rarity reflects a lack of known...
geographic epidemiology of mental illnesses. Most of the studies in the literature are summarized below.

Manganese. The neuropsychiatric illness “manganic madness” (locura mangánica) is caused by manganese poisoning. Mena et al. (1967) described the disease in manganese miners in villages of northern Chile; the typical onset consists of nervousness, irritability, compulsions, hallucinations, and violent outbursts. Donaldson (1987) based a manganese hypothesis of schizophrenia and neurodegenerative disorders on clinical similarities between manganic madness and schizophrenia. The theory’s weakness is its lack of consistency and specificity. For example, Donaldson correlates the “Groote Eylandt Syndrome” in northern Australia, where manganese outcrops are extensive, with the high rates of amyotrophic lateral sclerosis (ALS) in Guam. He theorizes that both diseases result from manganese toxicity. ALS in Guam has since been attributed to excitotoxins from the cycad plant, a dietary mainstay in Guam (Zor- umski and Olney 1992). Moreover, manganese excess in soils of the United States is limited in its geographic extent (Schlichting and Sparrow 1988) and therefore difficult to correlate with the more distinct geography of schizophrenia.

Lithium. In his article on the treatment of mania with lithium, Cade (1949) speculated that lithium in certain British well waters was responsible for the waters’ "special virtue in the treatment of mental illness” (p. 350). In 1885, waters in Mineral Wells, Texas, established the same reputation, when lithium-bearing water from a local well "cured" travelers of "hysterical mania.” By 1920 this well, named the "Crazy Well,” (Mineral Wells Index 1929; Webb 1952) was the center of a large health resort with hundreds of wells, a bottling plant, and thousands of annual visitors seeking to be healed by "Crazy Water.” One Texas county applied for a permit for a sanatorium on the basis of the belief that local waters produced psychiatric cures (Fowler 1991). Forty years later, Dawson et al. (1970) reported that the high lithium concentration in Texas drinking water led to low rates of psychiatric admissions from certain counties. The debate ended after Pokorny et al. (1972) demonstrated that this association lacked control for diagnosis, population differences, and distance to mental hospitals. Furthermore, a broader study of "affective psychoses” in U.S. cities near lithium deposits found no relationship between psychiatric admissions and proximity to the deposits (Steinberg and Rosin 1970).

Aluminum. After aluminum was found in neuritic plaques in the brains of Alzheimer’s disease patients, environmental exposure to aluminum was theorized to have a role in the disease’s etiology. Martyn et al. (1989) positively correlated aluminum levels in drinking water with Alzheimer’s disease rates in Britain. Neri and Hewitt (1991) made the same finding in Ontario, Canada. The issue remains controversial, since the aluminum in the neuritic plaques might have resulted from contamination of specimens (Landsberg et al. 1992). If so, correlations of environmental aluminum with Alzheimer’s disease would require reexamination.

Geography of Schizophrenia

The cause of the well-known geographic variability of schizophrenia in the United States has not been established. Torrey and Bowler (1990) reviewed this geographic distribution and demonstrated its stability over time. They concluded that "urban factors” might account for the findings. However, while the "social drift hypothesis” appears to explain the presence of persons with schizophrenia in poor areas of large cities, Torrey and Bowler argue that most States with a high prevalence of schizophrenia are not likely targets of migration (e.g., New Jersey and Wisconsin).

Urban factors associated with high schizophrenia rates include “industrialization,” which Torrey and Bowler credited Foster (1988) for previously correlating with schizophrenia. They failed to mention that Foster’s highest correlation coefficient (0.58) for high rates of schizophrenia was for low-selenium crops rather than urbanization. Foster speculated that low selenium levels might result in reduced prostaglandin synthesis previously described as abnormal in schizophrenia patients.

Association Between Selenium Deficiency and Schizophrenia

Strength. The extent of selenium deficiency in crops in the United States (figure 1) is well known (Oldfield 1974) because large numbers of livestock are at risk for white muscle disease, a fatal selenium-deficiency disease (Kubota et al. 1967). In the 1970s, selenium supplementation of livestock feed in the United States started to prevent this disease. The distribution of low selenium levels shown in
figure 1 has been reproduced in studies of selenium in human milk (Shearer and Hadjimarkos 1975) and blood (Allaway et al. 1968). Comparing the distribution of low-selenium areas with that of schizophrenia can test the strength of the association.

Torrey and Bowler (1990) provided maps of prevalence rates of schizophrenia for 1880, 1890, 1903, 1910, 1923, 1933, 1943, 1953, and 1963. They placed States in categories corresponding to very low, low, average, high, and very high rates of schizophrenia. The question is which year's map to compare with selenium distribution. The 1880 map is unique in that patients were assigned to their home States. Since the diet in 1880 likely represented consumption of local food, this map would allow for better correlation between prevalence and diet during the patients' developmental years. The 1963 map, however, has the advantage that schizophrenia was better defined in 1963 than in 1880, although food could be obtained from distant locations.

For this study, Torrey and Bowler's maps were used. The maps were examined to determine which States reported in the high or very high categories in at least seven of the nine years (table 1). These would be States where schizophrenia rates have been above average in the clear majority of surveys since 1880. Eleven States meet this requirement (figure 2). Only one, New York, reported very high prevalence in all nine surveys. New Jersey reported high or very high prevalence in all nine surveys. Six states had high or very high rates in eight of the nine surveys, and three more had such rates in seven of the nine surveys. Table 1 shows three more States that had high or very high prevalence in at least five (more than half) of the nine surveys. Figure 3 shows the 14 States with high or very high rates in more than half the surveys.

The data suggest that the 11 States shown in figure 2 represent high-risk areas for schizophrenia despite changing definitions of schizophrenia over the past century. Eight States (including Massachusetts) had rates at least as high in 1963 as in 1880; three had lower rates in 1963 than in 1880, but two of those decreased only between 1953 and 1963 after consistently high or very high rates until 1963. Massachusetts was not included in the surveys after 1943 but was in the highest category in all prior surveys.

Two-by-two contingency tables reveal a significant correlation between low-selenium States in figure 1 and high-schizophrenia States in figure 2 ($p < 0.001$; Yates corrected $\chi^2$). There is even a significant correlation for States that reported high or very high schizophrenia rates in at least five of the nine surveys (figure 3) ($p < 0.002$). In fact, there is a significant correlation ($p < 0.0001$) between not only the 1880 survey but also the 1963 survey and the low-selenium States in figure 1.

Cowgill (1975) found that 77.5 percent of the low-selenium areas were urban but only 67.8 percent of the high-selenium areas were urban. One might speculate that the association of schizophrenia with urban areas is due not to urban factors but to the fact that the cities are located in and surrounded by low-selenium areas.

One way to directly test the association between low selenium levels and schizophrenia is to
Table 1. States with elevated rates of schizophrenia

<table>
<thead>
<tr>
<th>Group</th>
<th>States</th>
<th>Year of survey and schizophrenia rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>New York</td>
<td>++ ++ ++ ++ ++ ++ ++ ++ ++ ++ ++ ++ ++</td>
</tr>
<tr>
<td>II</td>
<td>New Jersey</td>
<td>+ + ++ + + + + + + + + + + + + + + + +</td>
</tr>
<tr>
<td>III</td>
<td>California</td>
<td>++ ++ ++ ++ ++ ++ ++ ++ ++ ++ ++ av</td>
</tr>
<tr>
<td></td>
<td>Connecticut</td>
<td>++ ++ ++ ++ ++ ++ ++ ++ ++ ++ ++ ++</td>
</tr>
<tr>
<td></td>
<td>New Hampshire</td>
<td>++ ++ ++ ++ ++ ++ ++ ++ ++ ++ ++ ++</td>
</tr>
<tr>
<td></td>
<td>Oregon</td>
<td>+ + ++ ++ ++ ++ ++ ++ ++ ++ ++ ++ ++</td>
</tr>
<tr>
<td></td>
<td>Rhode Island</td>
<td>++ ++ ++ ++ ++ ++ ++ ++ ++ ++ ++ ++</td>
</tr>
<tr>
<td></td>
<td>Wisconsin</td>
<td>++ ++ ++ ++ ++ ++ ++ ++ ++ ++ ++ ++</td>
</tr>
<tr>
<td>IV</td>
<td>Illinois</td>
<td>av + + + ++ ++ ++ ++ ++ ++ ++ ++ ++</td>
</tr>
<tr>
<td></td>
<td>Massachusetts</td>
<td>++ ++ ++ ++ ++ ++ ++ ++ ++ ++ ++ ++ ?</td>
</tr>
<tr>
<td></td>
<td>Vermont</td>
<td>++ ++ ++ ++ ++ ++ ++ ++ ++ ++ ++ ++</td>
</tr>
<tr>
<td>V</td>
<td>Michigan</td>
<td>av + + ++ ++ ++ ++ ++ ++ ++ ++ ++ ++</td>
</tr>
<tr>
<td>VI</td>
<td>Minnesota</td>
<td>av + + ++ ++ ++ ++ ++ ++ ++ ++ ++ ++</td>
</tr>
<tr>
<td></td>
<td>Washington</td>
<td>av + + ++ ++ ++ ++ ++ ++ ++ ++ ++ ++</td>
</tr>
</tbody>
</table>

Note.—Adapted from Torrey and Bowler (1990). Rates: ++ = very high; + = high, av = average, − = low; --- = very low, ? = unknown. Group I: States ranked very high in all nine surveys; Group II: States ranked high or very high in all nine surveys; Group III. States ranked high or very high in eight of nine surveys; Group IV: States ranked high or very high in seven of nine surveys; Group V: States ranked high or very high in six of nine surveys, Group VI: States ranked high or very high in five of nine surveys.

Figure 2. Shaded States are those with high or very high rates of schizophrenia in at least seven of nine surveys (adapted from Torrey and Bowler 1990)

Measure selenium in schizophrenia patients. Two such investigations failed to find reduced selenium levels in schizophrenia patients. Tada et al. (1986) found elevated levels of selenium in the hair of male, but not female, patients. Alertsen et al. (1986) found that serum and blood selenium levels in a group of Norwegians with schizophrenia was no different from those in normal subjects. However, if schizophrenia results from a prenatal or childhood exposure, the significance of selenium studies in adults with schizophrenia is questionable. Furthermore, since the relationship between hair and total body selenium levels is unknown, and since selenium measurement is technically difficult, there is significant uncertainty in interpreting hair analysis (Cheng et al. 1990).
Figure 3. Shaded States are those with high or very high rates of schizophrenia in at least five of nine surveys (adapted from Torrey and Bowler 1990)

Consistency. One can assess the consistency of the association by comparing the rates of schizophrenia in high- and low-selenium countries. Maps of selenium levels in cereal crops in European countries are available (Gissel-Nielsen et al. 1984; Adriano 1986). Sweden, Norway, and Finland have less soil selenium than other European countries (Adriano 1986).

The Finnish selenium level is so low that, starting in 1969, the population required selenium supplementation through additives to fertilizers and animal feeds (Alfthan et al. 1989). If the theory is correct, one should find high schizophrenia rates in Finland that have decreased following supplementation. The theory is supported by the high point prevalence in Finland of 13 to 15 per 1,000. This is the highest consistently reported point prevalence in Europe (Jablensky 1986; Lehtinen et al. 1990). Furthermore, Lehtinen et al. (1990) found that schizophrenia prevalence in Finland was highest in the 50-54 age group and diminished with decreasing age. However, such supporting evidence is nonspecific, since prevalence has also decreased in countries such as Denmark that have low soil selenium levels but no extensive selenium supplementation (Jorgensen and Mortensen 1992).

Oster and Prellwitz (1989) reported that West Germany had lower soil selenium levels than Finland. Comparable schizophrenia indices are not available for West Germany and Finland. However, the incidence of schizophrenia in West Germany was twice that in Norway, where incidence rates are a "reasonable estimate of schizophrenia in European populations" (Jablensky 1986). Since Norwegian blood levels of selenium are above average despite low levels in crops (Meltzer et al. 1989), this finding appears to support the association of low blood selenium levels with high schizophrenia rates. However, West German blood levels of selenium are unknown and could also be higher than the reported soil selenium levels would suggest.

New Zealand has severely deficient soil selenium (Gissel-Nielsen et al. 1984). Livestock supplementation started in 1960 (P.J. O'Hara, New Zealand Ministry of Agriculture and Fisheries, personal communication, 1992) and was followed by fertilizer supplementation in the late 1970s (Watkinson 1983). Schizophrenia rates before 1970 are not available, and pre- and post-supplementation rates cannot be compared. However, New Zealand's current lifetime prevalence of schizophrenia is 0.4 percent, which is as low as the lowest morbid risk rates in Europe (Jablensky 1986; Wells et al. 1989).

Joyce (1987) found that first admissions for schizophrenia have been dropping since 1974 but attributed this finding to an actual decrease in the incidence of schizophrenia rather than a nosologic change. Although the hypothesis is not supported by the low incidence of schizophrenia in a low-selenium country, it is supported by the decreasing incidence of schizophrenia in postsupplementation years. Unfortunately, this argument provides no consistent support for the same reason discussed above for Finland: Schizophrenia diminished during this time in nonsupplemented countries. The consistency of the selenium theory cannot be clearly demonstrated.

Specificity and Analog. For the theory to be supported, selenium deficiency should be associated
with diseases that are associated with schizophrenia. Furthermore, selenium should be the only trace element with this association.

Kaschin-Beck and Keshan disease. Two selenium-deficiency diseases are thought to occur in humans: Kaschin-Beck disease, an osteoarthropathy (Sokoloff 1987), and Keshan disease, a cardiomyopathy (Laryea et al. 1989). Neither is associated with psychiatric symptoms, but both are known only in endemic areas of China and are not found in areas of even more profound selenium deficiency (Sokoloff 1987; Laryea et al. 1989), so additional factors seem to be involved. However, a comparison of rates of schizophrenia, Kaschin-Beck disease, and Keshan disease in selenium-deficient provinces in China would test the specificity of the association between low selenium levels and schizophrenia.

Multiple sclerosis (MS). Because of similarities in geographic distribution and other epidemiologic characteristics between MS and schizophrenia, Stevens (1988) suggested that these two diseases belong to a similar class of disorders sharing an infectious or immunologic cause. For example, the northern areas of the United States that have high schizophrenia rates also have high MS rates (Templer et al. 1985). If these diseases are related and if the selenium theory is correct, then selenium deficiency should be found in association with high MS rates. Such a theory was proposed by Schalin (1980), who found low soil selenium levels in high-MS regions (Hasanen et al. 1986). Another theory concerning the geographic distribution of MS proposed that high soil molybdenum levels were responsible for high MS rates in New Zealand, Finland, and parts of the United States (Layton and Sutherland 1975). This theory's fundamental assumption was not supported by Welch et al. (1991), who found high molybdenum levels only in the Western United States, not in the Northern States where MS risk is highest.

Other diseases. Low selenium levels are also correlated with the geography of low birthrates (Cowgill 1975) and high rates of dental caries (Ludwig and Bibby 1969). Low birth weight, obstetrical complications, and skeletal abnormalities are associated with schizophrenia (Fish et al. 1992), but geographic distribution of dental caries and birthrates in schizophrenia patients have not been investigated.

Other trace elements. Various trace elements may be involved in schizophrenia, and some—such as zinc, iron, chromium, and strontium—are associated with the geography of MS in Finland (Hasanen et al. 1986). Low zinc and high copper levels were reported in the serum of schizophrenia patients (Srinivasan 1984; Lohr 1991). Others found abnormalities in manganese (Srinivasan 1984), magnesium (Tada et al. 1986), nickel (Nielsen 1977), and iron (Lohr 1991). Do other trace element distributions share selenium's strong, statistically significant geographic correlation with schizophrenia?

In the 1970s, the United States Geological Survey (USGS) published elemental composition maps of "surficial material" in the United States (Shacklette et al. 1971a, 1971b, 1973, 1974). These maps of 35 elements were based on 863 sample sites spaced at 50-mile intervals throughout the United States (Kubota 1978). The elements included those of neuro-psychiatric significance: copper, zinc, aluminum, lithium, selenium, lead, mercury, manganese, nickel, and others. It is tempting to use such information for medical geology; however, soil profiles are not significant unless they are reflected in vegetation and ultimately in the human body. The USGS selenium map exemplifies this problem: It shows low soil selenium levels in some areas of high-selenium crops. The presence of selenium-accumulator plants in areas with low soil selenium is responsible for this contradiction (Kubota et al. 1967). Such confounding factors render these maps unusable for this study.

Trace element distribution in the surface waters of the United States can be compared with schizophrenia rates as well. In 1968 the Federal Water Pollution Control Administration published mean values for 19 trace metals for the 15 major river basins in the United States (Kopp and Kroner 1968), but these values do not reflect water supplies that would be consumed by most urban residents. Durfor and Becker (1962) published trace element concentrations found in the water supplies of the 100 largest U.S. cities, but this information of Durfor and Becker has limited applicability to this study because the 100 largest cities are located in only 38 States. However, the water quality of the largest cities in high-schizophrenia States can be compared with that of the largest cities in low-schizophrenia States. Arithmetic means were calculated for beta activity, aluminum, barium, chromium, lithium, nickel, lead, rubidium, and strontium for high- and low-schizophrenia States. Means for aluminum, barium, chromium, lead, rubidium, and strontium were un-
expectedly higher in the low-schizophrenia States. The mean for lithium was also higher in the low-schizophrenia States, and those for nickel and beta activity were higher in the high-schizophrenia States. Beta activity represented emission of beta particles from naturally occurring strontium and contamination from nuclear weapon testing and nuclear power plants. If no connection is demonstrated with levels in human blood, this data cannot be used. The reason why lithium is different from other elements in having higher mean levels in low-schizophrenia States is unknown.

There are studies of trace element distributions in vegetation or human blood. Kubota (1968) mapped cobalt deficiency in forage and soils of the United States. Low cobalt levels are limited to areas in New England, northern Michigan, Iowa, and Florida. This distribution does not significantly correlate with high-schizophrenia areas. Berger (1962) investigated deficiencies of boron, copper, iron, manganese, molybdenum, and zinc in crops. Two-by-two tables comparing States low in boron, iron, manganese, or zinc with high-schizophrenia States revealed no significant correlation. The correlation between high-schizophrenia States and those whose crops were low in molybdenum (figure 4) or copper (figure 5) was significant ($p < 0.02$). However, human blood levels of molybdenum and copper demonstrate no geographic pattern (Kubota et al. 1968). Similar studies of vanadium, cadmium, and lead in human blood from blood donors in the United States found no geographic pattern (Allaway et al. 1968; Kubota et al. 1968). Although serum zinc levels in human blood decrease from north to

**Figure 4.** Shaded States are those with molybdenum deficiency in crops (adapted from Berger 1962)

**Figure 5.** Shaded States are those with copper deficiency in crops (adapted from Berger 1962)
south in the Eastern United States (Kubota et al. 1968), this finding is contrary to zinc deficiency theories of schizophrenia, since schizophrenia rates also decrease from North to South.

Other maps showing the distribution of surface and groundwater hardness, treated and untreated (Angino 1978), and metal ion precipitation (Lazrus et al. 1970) show no visual correlation with schizophrenia rates. Finally, geologic sources of radioactivity (Cannon 1978) show no visual correlation with schizophrenia rates. Low selenium levels thus appear to be more specifically correlated with schizophrenia than are other trace element deficiencies or excesses.

**Biological Gradient.** The highest schizophrenia rates should be found in the lowest selenium areas. In the United States the lowest selenium States are Florida, Oregon, and Washington. The remaining low-selenium States are generally equal in their selenium levels. Since Florida, Oregon, and Washington do not have the highest schizophrenia rates, a biological gradient of the association is not established.

Schizophrenia is most common in eastern and northern Finland (Lehtinen et al. 1990). Biological gradient could be further tested if the distribution of selenium in Finland were known.

**Plausibility and Coherence.** The association of low selenium levels with high rates of schizophrenia is plausible and coherent with several biological facts about schizophrenia. First, glutathione peroxidase is a selenoprotein that detoxifies free radicals, which are theorized to be important in the pathogenesis of schizophrenia (Lohr 1991). Second, glutathione peroxidase is involved in the arachidonic acid cascade. Selenium supplementation in humans allows the reduction of the lipoxygenase-derived 12-hydroperoxy-5, 8, 11, 14-eicosatetraenoic acid (12-HPETE) to 12-hydroxy-5, 8, 11, 14-eicosatetraenoic acid (12-HETE) (van der Torre et al. 1989). 12-HPETE thus accumulates in selenium deficiency (Bryant et al. 1983). The arachidonic acid cascade, including 12-HPETE and 12-HETE, is under investigation for its role in modulating N-methyl-D-aspartate-sensitive glutamate receptors, which are implicated in neurodegenerative diseases (Mangos and Lal 1992). Furthermore, Schoene et al. (1986) suggested that selenium deficiency impairs platelet activation by decreasing the activity of glutathione peroxidase, thus allowing increased injury from inflammatory agents. Third, Lohr (1991) reported a negative correlation between glutathione peroxidase activity and brain activity in schizophrenia. Finally, Suttle and Jones (1989) reported that deficient glutathione peroxidase is associated with immune cell dysfunction in selenium-deficient ruminants. Although this dysfunction may not directly result in reduced resistance to infection (Suttle and Jones 1989), the coexistence of urban crowding and selenium deficiency might promote a viral etiology of schizophrenia, especially if the deficiency further promotes continued inflammation and brain damage.

**Temporality.** The requirement of temporality stipulates that (1) the exposure to a causative agent must occur within a reasonable interval before the development of the symptoms and (2) the time between exposure and symptoms must be consistent with known characteristics of the disease (National Research Council 1991). Schizophrenia appears to be a disease that presents years after exposure to the causative agent or agents. It can only be speculated how long, at what age, and under what circumstances an individual would need to be exposed to a selenium-deficient diet to develop schizophrenia. For example, could schizophrenia result from a viral infection followed by years of a selenium-deficient diet?

**Experimental Evidence.** The theory has not been tested by experiment. One possible test is to identify infants with and without obstetric or viral complications. A prospective comparison of the schizophrenia rates and dietary intake of selenium by these infants would test the hypothesis.

**Conclusion**

This examination does not fully support the selenium theory of schizophrenia. Some proof is lacking because of missing or limited data for consistency, biological gradient, temporality, and experimental evidence (see table 2). Given Table 2. Criteria for confirmation of the selenium theory

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Support for theory</th>
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<tr>
<td>Strength</td>
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<tr>
<td>Consistency</td>
<td>Mixed</td>
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<tr>
<td>Specificity and analogy</td>
<td>Yes</td>
</tr>
<tr>
<td>Biological gradient</td>
<td>No</td>
</tr>
<tr>
<td>Plausibility and coherence</td>
<td>Yes</td>
</tr>
<tr>
<td>Temporality</td>
<td>No data</td>
</tr>
<tr>
<td>Experimental evidence</td>
<td>No data</td>
</tr>
</tbody>
</table>
the theory's strength of association, specificity, and biological plausibility, enough evidence exists to pursue the heuristic value of the theory. Testable hypotheses can be generated to experimentally validate or refute the association of low selenium with high schizophrenia rates.

The opinions expressed in this article are solely those of the author and do not represent the opinions of Walter Reed Army Medical Center, the U.S. Army, or the United States Government.

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