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. 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. Yase 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. Furthermore, mercury poisoning, associated with a wide range of neurological symptoms, termed Minamata disease, also can cause “madness.” In addition, evidence suggests an etiologic role for aluminum in Alzheimer’s disease.

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. 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. Furthermore, Berry suggested that a defect in a hypothesized selenium transport enzyme selenoprotein P must accompany a deficiency in this trace element to cause schizophrenia.
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. 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. 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. 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

Hill argued that an association is more likely causal if it is consistent with "known facts" or "established truth". In 1990, Torrey and Bowler argued that there is an urban factor in schizophrenia. As a result, the illness became more common with the onset of the Industrial Revolution. 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. In addition, Trowell and Burkitt 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 caries, 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. Foster 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. These observations are compatible with reports of some schizophrenics appearing more likely to recover quickly in countries where diets emphasize vegetables, fish and seafood. 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.

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.\textsuperscript{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?” 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. Horrobin\textsuperscript{24} 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. 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.\textsuperscript{25} 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.\textsuperscript{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.\textsuperscript{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)\textsuperscript{29} to 12-hydroxy-5, 8, 11, 14 - eicosatetraenoic acid (12-HETE). 12-HPETE, therefore, accumulates in selenium deficient individuals.\textsuperscript{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.\textsuperscript{31} In addition, Schoene and co-workers\textsuperscript{32} argued that selenium deficiency, and hence decreased glutathione peroxidase activity, impairs platelet activation, thus permitting increased injury from inflammatory agents. Finally, Suttle and Jones\textsuperscript{33} 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,\textsuperscript{35} urban crowding and selenium deficiency might promote a viral etiology for schizophrenia, particularly if such a deficiency encouraged continued inflammation and brain damage.\textsuperscript{13}

While viral theories are reviewed elsewhere,\textsuperscript{34} recent research indicates links between selenium deficiency and enhanced virulence or evolution of several viruses. Beck et al\textsuperscript{35} 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 al. 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. 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.

The Temporal Relationship of the Association

Any suspected putative cause must precede, or at least be simultaneous with, its suspected effect(s). 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, for example, discovered elevated selenium in the hair of male but not female patients. In contrast, Alertsen and colleagues found no difference between the levels of selenium in the serum and blood of Norwegian schizophrenics and controls. Yet Buckman et al. 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.

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, Foster 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, Brown 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 X2). 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's 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. 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. Berry 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 al. 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. Rudin et al. discovered, however, that supplementing the diets of schizophrenics with essential fatty acids only worked when selenium levels were high. Vaddadi 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. 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 Torrey, 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. 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. 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, 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.

New Zealand also has severely deficient soil selenium levels. As a consequence, livestock supplementation started in 1960 and the addition of selenium to fertilizers in the late 1970s. 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. Interestingly, however, first admissions for schizophrenia to New Zealand hospitals have dropped since 1974, a decline that is considered a real decrease in incidence. 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 1986 and is currently believed to be only 34 micrograms. 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. In 1967, Kubota and co-workers 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.

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

Hill 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, numerous cancers, and to acute myocardial infarction. Beyond this, deficiency of this trace element may be involved in some forms of dementia and even in male infertility. 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.
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 northeast to southwest. 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. 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.

Svistunova 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.

**Celiac Disease**

Celiac disease is extremely common in Ireland, a country also known for its elevated schizophrenia prevalence. There is extensive evidence to show that celiac disease is greatly exacerbated by gluten in numerous grains. Dohan 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 disease and schizophrenia may not be coincidental. Schizophrenia is more common in celiacs than in the general population. Dohan and Perisic, et al, estimated the incidence of schizophrenia in adult celiac patients at approximately 37/1,000 cases, while Cooke and Holmes argued that it reached at least 10/1000 patients. These rates are comparable to total population (non-age corrected) rates reported by Torrey for high schizophrenia countries such as Ireland, Yugoslavia and urban areas of the United States. Furthermore Bender and Dohan provided case studies which suggested schizophrenic children suffered from an abnormally high incidence of celiac disease. Perisic, et al also reported that children of schizophrenics have increased risk of celiac disease. Another link between brain function and celiac disease was established by Dickey who reported that seizure frequency declines in many epileptics on gluten-free diets.

Templer and Veleber 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 clinically although some clinical trials were negative. 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. 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. 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 authors 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. Recent evidence suggests that mortality from esophageal cancer may be reduced by either increasing dietary antioxidant levels, including selenium, or by adding jianshi (calcium concretions) to drinking water. If both schizophrenia and esophageal cancer are associated with selenium deficiencies, their prevalences may peak together in the same regions. Indeed, Templin et al 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. In the United States, Mason et al 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 Bowler and Brown.

Multiple Sclerosis

Campbell, Crow and Lang first drew attention to the fact that multiple sclerosis (MS) was most common in regions where goiter was endemic. Stevens 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 argued that MS is related 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, Brown suggested that selenium deficiency might promote schizophrenia by interfering with viral immunity. Both schizophrenia and MS have been theorized to result from viral infections, and the overlap of MS and schizophrenia might result from reduced immunity from selenium deficiency to endemic, geographically-defined viruses. Although global MS rates correlate with Scandinavian populations which appear genetically at risk for MS 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. 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 occured
from excess selenium intake from medically unsupervised supplements sold in health food stores. Although one death was reported from medical administration of selenium to a child with cystic fibrosis, the dose (25 mcg) was equal to a child’s daily requirement and far below adult dietary requirements of 50-200 mcg which suggests that mortality from therapeutic levels of selenium may be related to individual patient factors. Selenium appears protective against most cancers but some isolated reports identified increased risk of some cancers, under certain conditions, with selenium supplementation. Finally, teratogenic risk from selenium is reported from a few animal studies. 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 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.

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