Schizophrenia and Esophageal Cancer: Comments on Similarities in their Spatial Distributions

Harold D. Foster[1]

In the preceding publication, Templer and his colleagues (1990) demonstrated that, in both Italy and the United States, there are positive, statistically significant correlations between schizophrenia and esophageal cancer rates. Indeed, as these authors point out, esophageal cancer rate was the only one of their independent variables to significantly correlate with schizophrenia in both countries. Since the symptoms and consequences of these two diseases are so different, an initial reaction to such spatial similarities might be to dismiss them as coincidental, that is as mere statistical aberrations. The purpose of this paper is to provide evidence to the contrary, and to argue that this geographical parallelism probably reflects the key roles played by calcium and selenium deficiencies in the etiologies of both diseases.

Cancer of the Esophagus

Calcium

In 1986, this author published a geographical analysis of cancer mortality in the United States, for the period 1950 to 1967. A major part of this study involved a comparison of the distributions of mortality from 65 specific, or subgroups of cancers and malignant neoplasms as a whole with those of 219 environmental variables. Amongst the most interesting findings were strong negative Pearson correlations between the percentage of the surface area of a state covered by soils with a very high calcium content and mortality from cancer of the esophagus. This relationship occurred in both white males ($r = -0.48143$, $p = 0.0005$) and white females ($r = -0.56370$, $p = 0.0001$); supporting the hypothesis that where soils are calcium enriched, mortality from cancer of the esophagus is depressed (Foster, 1986).

In 1989, this relationship was further examined by Norie and Foster who established that, at the census division scale in Canada in males, there was a significant negative correlation between the calcium content of drinking water and mortality from cancer of the tongue, mouth and pharynx ($r = -0.16421$, $p = 0.0001$). This association could not be established in females ($r = -0.00360$, $p = 0.9227$), in whom the disease was rarer.

Whilst the evidence is, as yet, not so statistically sound, the author has been able to demonstrate that links between calcium deficiency and elevated esophageal cancer mortality appear to occur in England and Wales, France, Italy, the Soviet Union, Afghanistan and the People's Republic of China. In contrast, where drinking water and soils are very calcium enriched, as in Romania, mortality from cancer of the esophagus tends to be extremely low (Foster, 1986; 1989).

Selenium

The previously described analysis of cancer mortality at the state level (Foster, 1986) also implied a possible association between esophageal cancer death rates and soil selenium levels. To illustrate, in the United States, there appears to be a clear negative relationship between the percentage of a state covered by soils having a high selenium content and esophageal cancer mortality. To illustrate, in white males and females, the Pearson correlation coefficients were $r = -0.55505$, $p = 0.0001$ and $r = -0.21165$, $p = 0.1487$. In non-white men and women the relationships were $r = -0.60172$, $p = 0.0009$ and $r = -0.45663$, $p = 0.0167$ respectively.

1. Department of Geography, University of Victoria, P.O. Box 1700, Victoria, B.C. V8W 2Y2.

Conversely, soils containing very elevated mercury appeared to be linked to higher mortality from cancer of the esophagus. This may be because of the formation of insoluble mercury Selenide, which creates a sink for environmental selenium, rendering it unavailable for incorporation into the food chain.

Unfortunately, on a global scale, it is far more difficult to obtain accurate data on soil and water selenium levels than it is to collect information on environmental calcium. It has proved harder, therefore, to determine whether the hypothesized negative relationship between esophageal cancer mortality and elevated soil selenium levels is a worldwide phenomenon. Nevertheless, experimental and geographical evidence is rapidly accumulating to suggest that selenium may be protective against a wide variety of cancers, including that of the esophagus (Shamberger, 1970; Shamberger et al, 1973; Bogden et al, 1981; Schrauzer et al, 1986).

Trace and Bulk Elements in Combination

Correlations, in themselves, can never prove causal relationships. They do, however, suggest hypotheses that can then be tested using the scientific method. Fortunately, in the case of cancer of the esophagus, this step has already been taken. Global death rates from this type of cancer peak in parts of the People's Republic of China. Naturally, therefore, the Chinese are very interested in anything which might reduce this toll. Stone drugs, including "jiang-shi", which are selenium enriched calcium carbonate nodules taken from loess, have been repeatedly mentioned in traditional Chinese medical literature as being of value in the prevention and treatment of esophageal cancer. Researchers from the Chinese National Corporation of Traditional Herbal Medicine and from Jiangshui Hospital, Xingtai combined to field test this claim (Zhu and An, 1988). In 1974, a large number of "jiang-shi" concretions were dropped into the drinking water wells of a region of Xingtai, Hebei province which provided water for a population of some 90,000. In this area, mortality from esophageal cancer has decreased markedly since 1975. Of particular interest
was the decline experienced by five villages in Baian. Here five new wells were constructed, with either calcium carbonate nodules incorporated into the building materials, or containing large numbers of "jiang-shi" concretions. Prior to 1975, at least one death from esophageal cancer was recorded each year, in each one of these villages. Since this date, not a single case has been reported. This decline seems to strongly support the hypothesis that calcium and selenium deficiencies are a major cause of cancer of the esophagus.

Working Hypothesis: Cancer of the Esophagus

There are many possible reasons why a deficiency of calcium may be linked to cancer of the esophagus. It may simply be that hard, calcium enriched water tends to maintain an alkaline upper digestive tract, perhaps reducing the carcinogenic effects of tobacco, alcoholic drinks and other irritants. In addition, selenium which is thought to be protective against upper digestive tract cancers (Leonard et al, 1986) is more soluble in alkaline water. It is possible, therefore, that an alkaline diet simply increases selenium availability. However, there may be more involved than this, since animal experiments clearly show a significant association between calcium and the terminal differentiation of esophageal epithelial cells. Babcock and his colleagues (1983), for example, found it impossible to achieve the clonal growth and serial propagation of rat esophageal epithelial cells without reducing the calcium concentration of their serum-containing medium by a factor of ten. Calcium levels of 0.3mM or higher caused the cells to undergo terminal differentiation, making them of little value in the study of carcinogenesis. It seems obvious that, in rats, the level of serum calcium influences the development of esophageal epithelial cells. If a similar process occurs in humans then the lower esophageal cancer mortalities experienced in hard-water, calcium-enriched regions becomes more explicable.

It seems likely that cancer occurs in three major stages: decoupling, initiation and promotion. Calcium may have its greatest effect in the first phase, decoupling (Garland et al, 1988).

When extracellular fluid is low in calcium, cells begin to separate, that is they decouple. This is because calcium plays a key role in the transmission of information between cells. When communication breaks down, chaotic mitosis occurs, resulting in cell proliferations, known as hyperplasia, or if disorganized, dysplasia. Garland and his colleagues (1988) argue that this initial stage of carcinogenesis is most likely to take place when the dietary intake of calcium is depressed. Certainly, it seems logical to assume that esophageal epithelial cells that are constantly bathed in calcium-enriched hard water are less likely to undergo this process than those repeatedly exposed to acidic, calcium-deficient soft water.

The anticancer effect of selenium has been firmly established by a wide range of animal experiments. These have shown that protection appears to increase with dose until near toxic levels are reached. In addition, evidence suggests that selenium deficiency in animals enhances the deleterious effects of many carcinogens. Some 0.1 micrograms per gram of selenium in diet seems to provide significant protection (Ip and Sinha, 1981). Passwater (1980) has argued that the primary role of selenium is in glutathione peroxidase, which breaks down the epoxide formed from the reaction of carcinogens with aryl hydrocarbon hydroxylase. This is particularly significant since "the compounds that we call carcinogens are only the parent compounds or 'pro-carcinogens'. The 'active' carcinogens are the epoxides formed within our bodies" (Passwater, 1980).

Yet even if Passwater is correct, activity of the selenoenzyme glutathione peroxidase in human blood only increases until about serum levels of 100 nanograms per milligram are reached. Beyond this, no further rise occurs. This strongly suggests that elevated dietary selenium intake also provides protection against cancer in other ways that are, as yet, inadequately identified. Schrauzer (1978), for example, has suggested that selenium stimulates the immune response, protects the liver, maintains cellular respiration and is involved in the detoxification of environmental mutagens and carcinogens. Although the total picture is yet unclear, it seems highly likely that, in selenium-enriched environments, mortality from many digestive cancers, including that of the esophagus, is depressed.

Schizophrenia

Calcium

In 1988, this author attempted to discover what links, if any, existed between the prevalence of schizophrenia in the United States and environmental variables. A preliminary analysis was undertaken using the state geographic data bank developed to study possible causes of cancer and information on patients being treated for schizophrenia. Disease data was from 272 state and county mental hospitals for the year 1965 (Foster, 1988). It was found that there were relatively strong negative Pearson correlations between the prevalence of schizophrenia and both sunlight ($r = -0.57024$, $p = 0.0001$) and the percentage of the state covered by soils with a very high calcium content ($r = -0.45784$, $p = 0.0014$).

Selenium

This study also pinpointed a possible link between selenium deficiency and schizophrenia. Indeed, it was found that the prevalence of this illness, in United States state and country mental hospitals, in 1965, showed the strongest positive correlation with selenium deficient fodder crops ($r = 0.58497$, $p = 0.0001$). The disease, therefore, tended to be most prevalent in states where relatively little selenium was passing into the food chain (Foster, 1988).

Whether this is a global phenomenon is unclear. Certainly, Norway and Sweden are known to be very selenium deficient (Wester, 1974). In the eighteen country listing of schizophrenia prevalence rates provided by Templer and Veleber (1980), whilst rates were highest in Ireland at 7.1, Sweden ranked in second place at 5.8 and Norway third at 5.3 per 1,000 population. In contrast, the Japanese whose daily diet contains roughly three times as much selenium as that eaten by Scandinavians (National Research Council, 1983) have a schizophrenia prevalence of roughly half, that is 2.9 per 1,000 population.

Whilst the suggestion that selenium deficiency

may be involved in the etiology of schizophrenia appears new, evidence has been slowly accumulating to demonstrate that this trace element influences brain function. To illustrate, Tolonen and his colleagues (1987) have described a double-blind clinical trial conducted in an old people's home in Hartola, Finland, involving thirty elderly residents. The therapy group received 1,770 micrograms of selenium per day, together with 400 mg of vitamin E. The trial lasted for one year and resulted in statistically significant improvements in mental well-being in those participants receiving supplements. In addition, detailed psychological and neurological testing of children at all grade levels, in selenium deficient areas of the USSR, has demonstrated that a lack of this trace element was associated with retarded psychological development (Svistunova, 1987). Clearly, selenium is involved in brain function and perhaps in schizophrenia.

Working Hypothesis: Schizophrenia

There appears to be a growing body of evidence that suggests schizophrenia is perhaps related to disequilibrium in the manufacture or utilization of prostaglandins (Horrobin, 1979; Rudin et al, 1988). Prostaglandins are developed in the body from the essential fatty acids, linoleic and linolenic acids. Vincent (1970) has suggested that a dietary selenium deficiency results in the inability of the human body to manufacture several prostaglandin. Production of prostaglandin E_2 and A_2, for example, are both diminished. This appears to occur because a selenium containing enzyme is necessary in their manufacture, and perhaps for that of other prostaglandins (Passwater, 1980).

Christensen and his colleagues (1988) reported very strong statistical associations between the course and outcome of schizophrenia, in the eight national centres participating in the World Health Organization's international two-year follow-up study, and the amount of fat in their average national diets. Information about the latter was obtained from data published by the Food and Agriculture Organization of the United Nations. The reason for this association is obvious if Horrobin (1979) is correct and schizophrenics suffer from problems with the manufacture and metabolism of prostaglandins. Essential fatty acids are required for the absorption of sunlight to occur and for it to be stored in chemical bonds for future use by the brain (Erasmus, 1986). Saturated and monosa-turated fats such as those found in shortenings, margarine, butter, refined oils and many animal fats cannot substitute for the essential fatty acids in the process. "In fact they interfere with this function of the essential fatty acids when the diet contains excessive qualities of saturated and monosaturated fatty acids, as does the Western diet" (Erasmus, 1986). A diet high in total fat is likely to be rich in saturated and monosaturated fatty acids, which in turn may interfere with the use of linoleic and linolenic acid and hence the production of prostaglandins.

It is possible that these relationships between total fat in diet and prostaglandin production might also help to explain why schizophrenia appears less common in calcium enriched environments. It has been suggested, for example, that calcium may convert many fats and free bile in the digestive tract to insoluble soaps, so reducing their absorption (Garland et al, 1985). If this is the case then it is possible that a high calcium diet may help to offset the negative health impacts of large intakes of saturated fatty acids. Certainly animal studies have shown that a high fat diet is particularly deleterious if it is also lacking in selenium (Schwarz, 1954). Calcium, therefore, may assist the formation of prostaglandins by reducing the availability of saturated fatty acids.

Conclusions

It is always exciting to watch as the pieces of a jigsaw puzzle fall into place revealing the larger picture. While the preceding paper by Templer and his coworkers does not prove a common etiology for schizophrenia and cancer of the esophagus, it is one further piece of evidence which suggests it. This publication provides further data which supports the view that these two diseases are members of the deficiency branches of the family trees of both calcium and selenium.

It has already been demonstrated in the People's Republic of China that cancer of the esophagus can be prevented by increasing calcium and selenium levels in diet (Zhu and An, 1988). Perhaps, this may also be true of schizophrenia. In addition, the Chinese are beginning to treat esophageal cancer patients with these two elements. Clearly, this option ought to be available to schizophrenics.

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