

# Selenium and Health: Insights from the People's Republic of China

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## Selenium Deficiency Diseases

### Keshan Disease and Kaschin-Beck Disease

It was discovered, in 1957, that selenium was an essential trace element for both rats and chickens (Schwarz and Foltz, 1957; Schwarz et al, 1957). Soon afterwards, research workers began to identify a wide range of livestock diseases that were also linked to dietary deficiencies of this element. These included white muscle disease in lambs and calves (Muth et al, 1958; Hartley and Grant, 1961). Since the Chinese often suffered losses from this cause they were quick to give sodium Selenite to livestock which were at risk. Initial experiments were conducted at the Huai-Shu-Zhuang farm in Shaanxi Province with extremely encouraging results (Yang, 1987). Soon afterwards, it was recognized that Keshan disease, a cardiomyopathy of unknown cause, was also very common amongst farmers in regions where white muscle disease was endemic in livestock. Both diseases displayed striking similarities in clinical symptoms and pathologic changes; leading to the suggestion that Keshan disease in humans might also be due to selenium deficiency. This hypothesis was further supported by the discovery of comparable histopathologic changes in heart tissue in both diseases (Li et al, 1982). It was quickly recognized that Kaschin-Beck disease, which is characterized by necrosis of cartilage and dystrophy of skeleton muscles, was also very common amongst inhabitants of selenium deficient regions, especially those where both white muscle disease and Keshan disease were endemic (Hou and Zhu, 1982). As a consequence of these insights, the Chinese began a series of selenium supplementation programs, undertaken by organizations such as the Keshan Disease Research Group of

the Chinese Academy of Medical Sciences and the Institute of Antidemic Diseases, Gansu Province (Yang, 1987). Results were very promising, suggesting that, although selenium deficiency is not the sole cause, it is significant in the etiology of both Keshan and Kaschin-Beck diseases.

As a consequence of these successes, the Chinese have developed a major interest in selenium and its roles in animal and human health. Perhaps for this reason they have played gracious hosts to two international conferences at which the significance of selenium has been discussed in great detail. This article seeks to describe some of the major research findings presented at either the *Third International Symposium on Selenium in Biology and Medicine* or at the *International Symposium on Environmental Life Elements and Health*. Both of these meetings were held in Beijing. Proceedings of the former were published in 1987, while the latter took place as recently as November 1988. It was attended by this author with the support of a B.C. Scholars to China Travel Grant.

As Mertz (1987) has pointed out, selenium seems unique amongst the essential elements in the way in which its deficiencies are manifested. The consequences of pure, uncomplicated deficiency in mammals are largely metabolic and biochemical. As a consequence, clinical signs tend to be light, develop slowly or appear only in the second generation of animals exposed to the lack of this element. This also seems to be true of selenium deficient children (Lombeck et al, 1978). However, it is the interaction of some additional insult with the selenium-deficient status that ultimately results in acute, life-threatening symptoms and perhaps even death (Mertz, 1987). Several interacting variables have been identified. They include vitamin E deficiency, excessive food intake

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(especially of polyunsaturated fats), various heavy metals, carcinogens and xenobiotics. Even so, as Mertz emphasizes this list is incomplete since none of these known factors seem to account for the high incidence of fatal Keshan disease amongst selenium-deficient children in China, while equally selenium deficient children, with phenylketonuria, in the Federal Republic of Germany, do not develop this disease.

It seems that most essential trace elements are subject to antagonistic interactions that can aggravate the significance of any deficiency. However, in the case of selenium, certain interactions appear to completely alter the nature of the deficiency itself. Severely selenium-deficient rats often show no pathological signs until the second generation, yet if they are also lacking in vitamin E they die from liver necrosis in a few weeks (Schwarz, 1951). Even more interestingly, if they are force fed with fat they die within hours (Schwarz, 1954).

Keshan disease and Kaschin-Beck disease are widespread in the selenium deficient regions of China, yet do not occur in Finland or New Zealand, despite the fact that selenium intake in these countries is also very depressed. It would appear, therefore, that both diseases also involve at least one other trigger mechanism. The Chinese are very aware of this possibility and are actively searching for additional interacting factors. Numerous suggestions have been made, these include deficiencies of vitamin E, methionine, molybdenum and zinc and excesses of protein, copper, cadmium, manganese, iron, strontium and barium (Yang, 1987; Li, 1988; Li et al, 1988). However, despite an enormous body of ongoing Chinese research, no typical animal models of either Kaschin-Beck disease or Keshan disease have been successfully produced in the laboratory. The search for additional trigger mechanisms continues, despite the fact that there is universal agreement that both illnesses involve selenium-deficiency. However, it is very interesting to note that the intravenous injection of large doses of vitamin C has been beneficial in treating cardiogenic shock of acute Keshan disease. Indeed it appears that vitamin C can increase glutathione peroxidase activity in the rat heart and may play a similar role in humans (Li

and Yang, 1987). This suggests that selenium and vitamin C may be synergistic.

### Cancer

The anticancer effect of selenium has been firmly established by numerous animal experiments. These have shown that protection increases with dose until near toxic levels are reached. In addition, evidence suggests that selenium deficiency in animals enhances many carcinogens. About 0.1 micrograms per gram of selenium in diet seems to provide significant protection (IpandSinha, 1981). Yet 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 selenium intake may provide protection against cancer in ways that are as yet unidentified. However, as Mertz (1987) points out, this conclusion is very difficult to reconcile with the enhancing effect of selenium deficiency on carcinogenesis. Possibly selenium influences the process several significant ways.

Certainly there is a great deal of geographical and epidemiological evidence to suggest that cancer mortality tends to be depressed where environmental selenium levels are high (Shamberger and Frost, 1969). This author has argued that with the exception of selenium which is generally protective, other trace and bulk elements, including calcium, magnesium, phosphorus, sodium, strontium, potassium and iodine, appear associated with both high mortality from some specific cancers and reduced death rates from others (Foster, 1986). Antagonists of these elements, including mercury and barium also seem to influence cancer mortality rates. For these reasons, the geographical distributions of specific cancers often show obvious spatial correlations with bedrock geology, which is of course the ultimate source of many of these elements.

Cancer is a major health problem in China, with some 700,000 deaths each year. Indeed in Shanghai, which has the highest accumulated mortality of cancer in China, between 20 and 25 percent of the city's population can be expected to eventually

die of cancer. This may be the highest rate in the world (Fang, 1988). Naturally, therefore, the Chinese are involved in research which seeks to reduce this death rate. Stone drugs, including "jiang-shi", which are selenium enriched calcium carbonate nodules taken from loess deposits, have been repeatedly mentioned in traditional Chinese medical literature as being useful in the prevention and treatment of esophageal cancer. For this reason, 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, large numbers of "jiang-shi" concretions were dropped into the drinking water wells of an area of Xingtai, Hebei province having a population of nearly 90,000. In this area the mortality from cancer of the esophagus has decreased markedly since 1975. This decline was particularly significant in five villages in Baian. Here five new wells were constructed, either using calcium carbonate nodules as building material, or containing large numbers of these "jiangshi" concretions. Prior to 1975, at least one death from esophageal cancer was reported each year, in each one of these villages. Since this date, not a single case has been recorded. This decline appears to strongly support the hypothesis that calcium and selenium deficiencies are the major cause of cancer of the esophagus. As a consequence, powdered "jiang-shi" and selenium are now being used to treat esophageal cancer patients. The results show promise (Zhu and An, 1988). Indeed, the Chinese are sufficiently convinced that selenium is protective against at least some cancers that they permitted The Zhou Kou Area's First Pharmaceutical Factory of Henan Province to sell supplements containing this and other trace elements to delegates at the *International Symposium on Environmental Life Elements and Health*. Advertising for this company was also carried on the back cover of the *Conference Abstracts*, a publication sponsored by the Chinese Academy of Sciences and the National Natural Science Foundation of China.

The Chinese are also beginning to measure levels of selenium and other trace elements in

hair as an aid to predicting who will develop cancer. To illustrate, there is a high incidence of lung cancer in workers at the Yunnan tin mine, possibly because of elevated levels of the selenium antagonist arsenic in the ore. Xu and his colleagues (1987) have, however, been able to predict with 86 percent accuracy which miners are likely to be suffering from the initial stages of lung cancer by measuring hair levels of selenium, zinc, cadmium, chromium, copper, lead, arsenic and tin. Similarly, Zhang and his co-workers (1987) have been able to show that the mean selenium content of the hair of controls is far higher than that of fifty-four patients with cancer of the digestive tract. To illustrate, the mean selenium hair levels in patients with cancer of the esophagus, stomach and intestines were 0.39, 0.42 and 0.43 micrograms per gram respectively. This compared with 0.74 micrograms per gram in fifty healthy controls. Of course, whether the illness was precipitated by the deficiency could be debated. However, significantly lower serum selenium levels have also been found in breast cancer patients and indeed in a 110 patient sample of individuals with a variety of carcinomas (Lewko and McConnell, 1987). Indeed, patients with particularly low serum selenium exhibited higher incidences of metastases, multiple primary tumors, recurrence and decreased survival time when compared to those cancer patients who had relatively higher serum selenium levels. In addition, the Chinese have also noted depressed selenium levels in the hair of patients suffering from Wilson's disease, coronary heart disease and cerebral blood vessel disease. Levels in these patients were 0.28, 0.39 and 0.56 respectively, compared with healthy controls with a mean selenium hair concentration of 0.72 micrograms per gram (Huang, et al, 1988).

### Liver Cirrhosis

Certain individuals appear to have difficulty in either absorbing or utilizing selenium effectively. These include chronic alcoholics (Aaseth et al, 1980) and patients who have undergone intestinal bypass surgery. In both cases, fatty degeneration and liver cirrhosis may occur. While it is not certain that this is due to selenium

deficiency, Schwarz (1954) reported that vitamin E, selenium and cystine can protect animals against dietary necrotic liver degeneration. There seems little doubt that intestinal bypass surgery does lower selenium in serum to about 75 percent of normal. Aaseth and his colleagues (1987) also noted that the glutathione concentrations in the red blood cells of bypass patients was as low as 54 percent of the mean control value. In addition, other nutrient deficiencies including vitamins A and E, zinc and copper were discovered. These may also play a role in the development of fatty degeneration and/or liver cirrhosis in intestinal bypass patients.

### **Chronic Rheumatoid Arthritis**

There is also some evidence to suggest that chronic rheumatoid arthritis is related to selenium deficiency. Kondo (1987) describes a four-month trial in which seven patients, who had suffered severe joint pain for over four years, were given 350 micrograms of selenium daily, together with 400 IU of vitamin E. In addition they received doses of 50 million allogeneic lymphocytes three times, at 4 to 6 week intervals. These had been isolated from the blood of healthy young donors.

After the four month trial, rheumatoid factor titers dropped significantly and became normal in 4 out of 7 cases. In these individuals all joint pains completely disappeared. The condition of the three remaining patients improved markedly, as illustrated by diminished pain and improved joint mobility. Selenium and vitamin E supplementation in the form of selenium yeast was continued after the trial ended, for a further five months. During that period, rheumatoid factor titers remained normal in the four patients in remission and normalized in a fifth individual. Other patients reported only slightly transient episodes of joint pain. This trial appears to support the work of Spallholz (1980) who has reported strong stimulation of immunological responses by selenium and vitamin E in several animal experiments.

### **Mental Illness and Diseases of the Brain**

Selenium deficiency may also play a significant role in mental illness and in diseases of the brain.

The current author, for example, presented tentative data which indicated that a lack of selenium might be involved in schizophrenia (Foster, 1988). In addition, Tolonen and his colleagues (1987) described a double-blind clinical trial conducted in an old people's home in Hartola, Finland, involving thirty elderly residents. Half of these received supplements of sodium Selenite and organic selenium (roughly equivalent to 1,770 micrograms of pure selenium per day) together with 400 mg of vitamin E. The remainder of the group were given placebos. At the beginning of the study the mean age of the verum group was 76.8 (range 58-90) and that of the control group 76.2 (range 50-92). The trial lasted for one year. At the start of the study, and at two monthly intervals, the Sandoz Clinical Assessment Geriatric (SCAG) scale was used to measure any changes in mental well-being. Statistically significant improvements were observed in the therapy group compared with those patients taking placebos in the following variables: anxiety, depression, fatigue, hostility, anorexia, mental alertness, self-care, emotional lability, motivation, initiative and interest in the environment. Indeed, after only two months, such changes were so marked that nurses were able to predict with 80 percent accuracy those patients receiving selenium and vitamin E supplements. Despite the high doses involved, the treatment had no side effects. It seems possible that the supplementary intake of antioxidants inhibits lipid peroxidation and accumulation of lipofuscin, thus slowing down the aging process (Yunice and Hsu, 1987).

The Chinese have also been using selenium in the treatment of epilepsy (Cheng, 1988). They claim to be able to alleviate symptoms in a variety of types of this disease including that due to brain tumors, brain injury, infection or parasites. In contrast, selenium has been found to be of no value in treating hereditary epilepsy.

### **Psychological Development**

Kaschin-Beck disease also occurs in the USSR where it is termed Urov disease. Researchers there have been carrying out

detailed psychological and neurological testing of children at all grade levels in endemic areas (Svistunova, 1987). These tests have been repeated with control groups of similar children living in provinces where Kaschin-Beck disease is not endemic. Results suggest that all children in endemic provinces have retarded psychological development, even those that show no signs of the illness. Impairment is greatest, however, in those suffering from Kaschin-Beck disease. Although these results do not prove that selenium deficiency in children causes retarded psychological development, since some other as yet unrecognized trigger mechanism may be involved, they are highly suggestive that this element is required for psychological development. These results from the USSR are particularly interesting since Marlowe and colleagues (1986) and Ely and his co-workers (1981) both reported increased levels of selenium in the hair of the children with learning disabilities.

### **Selenium Excess Diseases**

#### **Loss of Hair, Nails and Other Disorders**

Although deficiency is the most serious problem with selenium in China, there are a few areas where intoxication can be significant. Perhaps the worst of these is Enshi County, Hubei Province in South China. Selenium intoxication occurs in Enshi for several reasons. Very high levels of the element are derived from a local coal, one sample of which contained as much as 8.2 percent selenium (Yang, 1987). Unfortunately, in the early 1960s the local farmers began to use lime and plant ash as fertilizers, increasing soil pH which in turn resulted in greater selenium uptake by plants. Furthermore, a drought forced villagers to subsist largely on highly seleniferous maize and vegetables. One maize sample, for example, contained 44 ppm selenium. In a seriously affected village, newcomers became sick within three to four days, presumably because they were eating roughly 38 mg of selenium daily. Naturally, exceptionally high selenium levels became obvious in hair, blood and urine. Villagers tended to lose their hair and nails. Indeed skin lesions, abnormalities of the nervous system, disturbances of

the digestive tract and possibly tooth decay also appeared as symptoms of pronounced human selenium intoxication (Yang, 1987). It was also found that there was a slight, but significant reduction in hemoglobin levels in residents of the chronic selenosis area. No differences were found in the SGPT (serum glutamate-pyruvate transferase [alanine amino transferase] activities). However, although most of the elderly in this region had experienced hair and nail loss, no evidence can be found to indicate a negative impact on life expectancy. Whether this suggests an adaptive mechanism in humans exposed to long periods of excessive selenium intake is unclear.

### **Selenium Inventories**

Several countrywide inventories of elements, that are thought to play significant roles in animal and/or human health, are currently underway in the People's Republic of China. These include national surveys of zinc and molybdenum in soils (Zhu and Liu, 1988; Liu and Zhu, 1988) and of fluorine in drinking water (Chen, 1988). A series of attempts are also being made to establish the geographical distribution of selenium. One of the most fundamental of these inventories is that underway at the Institute of Geography, Academia Sinica, Beijing (Xia and Tan, 1988). This involves the collection and analysis of rock samples from around the country. The data so far developed indicates that, on average, selenium levels are lowest in limestones (0.028 ppm), schists (0.031 ppm) and tuffs (0.032 ppm). In contrast, they tend to be more elevated in slates (0.131 ppm), claystones (0.118 ppm) and olivine rich ultrabasic rocks (0.108 ppm). It has been found that the selenium content of Chinese sedimentary rocks tends to be low (0.047 ppm), with that of both mesomorphic (0.070 ppm) and igneous rocks (0.067 ppm) being relatively higher. Selenium also seems to increase as igneous rocks become more basic.

Naturally, the Chinese are interested in whether these differences in the selenium content of bedrock are reflected in the food chain. To this end between 1980 and 1982, 29 collaborating institutions collected 11,467 food and forage samples from 1,103

counties in 28 provinces (Liu et al, 1987). Each of these was analyzed for its selenium content. Several significant discoveries followed from this inventory. It was established, for example, that if the conventional 0.05 ppm content of dry matter was used as a standard, more than 70 percent of the sampled counties were selenium deficient. Seven provinces, Heilongjiang, Jilin, Inner Mongolia, Qinghai, Shaanxi, Sichuan and Tibet were particularly selenium deficient. For example, in Heilongjiang, not one of the 69 counties surveyed produced foodstuffs that contained more than 0.05 ppm selenium. Indeed, 93 percent of the counties from this province yielded foodstuffs having less than 0.02 ppm selenium, that is they were extremely deficient in this element.

In an effort to determine the selenium status of China's livestock, a total of 4,547 liver samples were also obtained from adult pigs slaughtered in 129 abattoirs located in 26 provinces (Zhai et al, 1987). The mean selenium level in swine livers throughout China was found to be  $0.67 \pm 0.47$  ppm (dry matter). This is much lower than the selenium level in pigs found elsewhere, which Lindberg (1968) claimed to average  $1.82 \pm 0.16$  ppm. This again tends to confirm that much of China is selenium deficient. However, exceptions clearly occur, the selenium content of swine livers in Ziyang county, Shaanxi Province having a mean level of  $3.30 \pm 1.21$  ppm. Serious selenium intoxication of both animals and people has been reported from this region.

At least two computer data bases have also been established in the People's Republic of China to attempt to analyze possible links between selenium status and disease. One of these, operated by the Xi'an Institute of Technology (Lu, et al, 1988) tends to focus on livestock, especially cows, horses, and sheep. The other, located at the Research Center for Environmental Sciences, Academia Sinica, Beijing (Bai and Zhang, 1988) contains selenium information from 28 provinces, together with data on the distribution of Keshan and Kaschin-Beck diseases, cancer, heart disease and other possible selenium-related illnesses in humans. This

system, which is managed using DATATRIEVE and operates on a VAX-11/780 computer has permitted correlations to be drawn between selenium levels in human hair and longevity. A linear relationship has been discovered, with a correlation co-efficient of 0.71. This strongly suggests that, in China, life expectancy is positively related to selenium intake. This is a very significant finding since it is clear from the inventories already described that much of the country is selenium deficient.

In addition to these major selenium inventories, the Chinese are preparing to issue a national atlas of endemic disease. Although this is not yet available, at least one regional publication, an *Atlas of Endemic Disease and Natural Environment in Jilin Province* appeared in 1984. This atlas emphasizes diseases which are related to the geochemical environment, such as endemic goitre, cretinism, fluorosis, Kaschin-Beck disease and Keshan disease. As well as showing their distribution patterns, it also includes detailed spatial information on the trace and bulk elements which are thought to be involved in their etiology. This volume, and the forthcoming national atlas, are evidence of cooperation between medical organizations, such as the First and Second Institutes for Endemic Disease Control and Research of Jilin Province and geographical institutions. In the case of the Jilin regional atlas, environmental data was provided by the Changchun Institute of Geography, the Chinese Academy of Sciences and Team One of Hydrogeology of Jilin Province. Unfortunately there is less evidence of such interdisciplinary cooperation in North America. To mark the holding of the *International Symposium on Environmental Life Elements and Health* the Library and Information Section of the Changchun Institute of Geography (1988) also produced the *Bibliographical Contents About Regional Environment and Human Body's Health in China*. This volume, published in English, contains the titles of over one thousand articles and books on endemic disease in China. Each is accompanied by several key words which give the publication's flavour.

### Increasing Selenium in the Food Chain

Given the number of diseases that appear related to selenium deficiency, it is not surprising that there is widespread interest in attempts to increase the levels of this element in the food chain. However, this may be more difficult to achieve than was anticipated, largely because selenium can enter plants as a wide variety of complex compounds, many of which are not bioavailable to humans. It is important, therefore, to establish which foods will supply the most readily available forms of selenium. Much of this research involves measuring the restoration of glutathione peroxidase activity in selenium-depleted animals. This technique is better than merely determining selenium levels in tissues, because this selenoenzyme represents selenium which is biologically active (Levander, 1987). This functional criterion of bioavailability is especially important for selenium because it is unclear whether all the many different compounds of the element, that naturally occur in foods, can be metabolized to biologically active selenium, even where they are effectively absorbed.

Selenium depleted rats have been used in this way to test the bioavailability of selenium in a wide range of foodstuffs. It has been established, for example, that selenium is readily available from whole wheat bread, Brazil nuts, beef kidney and Baltic Herring. In contrast, it has a low availability from oysters, tuna and mushrooms. Indeed only 4 percent of that existing in mushrooms appears bioavailable (Chansler et al, 1983). These three foods may have a capacity of accumulate heavy metals, which may account for the low availability of their associated selenium. However, it is also possible that they contain unusual chemical forms of the element that are not available to animals (Levander, 1987).

While these animal experiments are instructive, it is obviously necessary to conduct placebo-controlled double-blind studies. This approach has been used in Finland where the bioavailability of selenium in humans was assessed using three criteria: the measurement of short-term changes in platelet glutathione peroxidase activity and blood serum level to estimate

immediate availability; the measurement of medium-term plasma selenium levels to estimate tissue retention; and the assessment of long-term platelet glutathione peroxidase activity, after supplements were withdrawn. This latter test allows estimates to be made of the convertibility of the retained selenium to biologically active selenium. Sodium Selenite supplements, selenium-rich yeast and selenium-rich wheat were each tested in this manner. Interestingly, each source induced a different pattern of response in these three measures of bioavailability. As had occurred in animal studies, however, selenium-rich wheat was highly positive in all three criteria, suggesting that this is also the source most readily utilized by humans (Levander, et al, 1983; Levander, 1987).

The Chinese are beginning to attack endemic diseases by deliberately modifying the environment. The addition of selenium-enriched calcium carbonate nodules to wells, in an effort to reduce the incidence of cancer of the esophagus in Xingtai, Hebei has already been described (Zhu and An, 1988). Similarly, efforts have been made to reduce the incidence of Kaschin-Beck disease by adding selenium to fertilizers (Chen, et al, 1988). This experiment was conducted in Bin county, on the loess plateau, where the disease was very common amongst the inhabitants of seven villages. The fertilizer used consisted of 12 percent nitrogen, 10 percent phosphorous and 0.05 percent selenium. Approximately 150-200 kilograms per hectare of this fertilizer were applied in the autumn of 1986. This resulted in the addition of roughly 2000 grams per hectare of sodium Selenite to the soil, which was then planted with wheat. Prior to fertilization in this manner wheat crops contained some 6.6 ppb selenium. In contrast in 1987, levels had risen to 79 ppb selenium, dropping to 48.4 ppb in 1988. That is, the fertilizer had increased selenium levels in the wheat crop some 7 to 12 times. As a consequence, daily selenium dietary intake in the local area increased from 3.2-6.7 micrograms to 21.2 micrograms. Levels in children's hair rose from 82.3 ppb to 294 ppb (Chen et al, 1988).

The health benefits of this experiment were obvious. All children between 3 and

15 years old were X-rayed in the villages taking part and in a similarly affected control group of settlements. In the area receiving additional selenium, 11.56 percent of the children had recovered from Kaschin-Beck disease, and a further 32.78 percent showed improvement. In the control group, nobody had completely recovered and only 8.15 percent of the children showed any improvement. There was no deterioration and no new cases in the experimental group; whilst 13.50 percent of the controls had deteriorated and 1.52 percent new cases had emerged.

Various other experiments are underway in the People's Republic of China in attempts to monitor the impact of adding selenium to the environment. In the district of Kalaqinqi, Inner Mongolia, for example, members of the Institute of Applied Ecology, Academia Sinica, Shenyang (Ju, et al, 1988) have been spraying sodium Selenite onto crops for some ten years. Although this area is naturally very selenium deficient and, as a result, has a high incidence of Keshan disease, it has been possible to produce grain crops that provide sufficient selenium to meet World Health Organization standards (40-150 micrograms per day). It has been found that the selenium content of the hair of individuals eating sprayed crops has roughly doubled.

In Youngshov county, Shaanxi province, researchers have been experimenting with the addition of both sodium Selenite and fly ash (which is high in selenium) to soils. Both were found capable of significantly increasing the levels of this element in wheat, an important finding because this region has a very high incidence of Kaschin-Beck disease (Wang et al, 1988).

There are, of course, more direct ways of providing selenium than adding it to fertilizer, or spraying it on growing crops. To illustrate, research workers at the Institute for Endemic Disease Control in Henan Province, Zhengzhou have been feeding leghorn fowl a variety of diets designed to produce selenium enriched eggs. Fifteen selenium-deficient children, from an area where Kaschin-Beck disease was endemic, were then fed one egg, the mean selenium content of which was about 70 micrograms, each day for 45 days. As a consequence, selenium levels in blood

increased from 21.48 ppb to 55.61 ppb and in hair from 85.18 ppb to 203.80 ppb. It seems clear that the addition of selenium to chicken feed could be used to significantly alter the selenium status of individuals living in deficient regions (Wang, 1988).

Similar experiments have been conducted by research workers at the Institute for Prevention and Cure of Endemic Disease of Chengde Prefecture, Hebei Province (Guo et al, 1988). Some 150 Kaschin-Beck disease patients, aged between 3 and 13 years old, have been treated daily with one of three selenium compounds; either selenium-enriched yeast, organic selenium oxalic acid, or inorganic sodium Selenite. After six months their recovery rates were found to be 66.67 percent, 58.02 percent and 40.84 percent respectively.

A variety of other methods are being used to increase the bioavailability of selenium in deficient areas. To illustrate, Keshan disease is extremely prevalent in Lianshan Prefecture in Sichuan Province (Cheng and Qian, 1988). From 1984 to 1986 selenium fortified salt was supplied to a population of 1,050,000. Four neighbouring counties, where Keshan disease is also prevalent, were used as controls. In the experimental area, latent Keshan disease in children declined by 66.8 percent between 1983 and 1986, as indicated by abnormal ECG readings. In contrast, it rose by 33.3 percent in the control counties. It became clear that not only was selenium-fortified salt protective against Keshan disease in children, but that this protection increased steadily the longer the salt was used.

A further successful experiment with selenite-supplemented salt was conducted in Linyou county, Shaanxi province from September 1980 through July 1981. Forty-six children suffering from Kaschin-Beck disease were repeatedly given salt containing sodium Selenite. Eighty-nine further children were used as controls. X-ray monitoring showed that some 79.17 percent of the experimental group improved, while only 17.14 percent of the controls did so. No additional cases developed in those children eating selenium-fortified salt, whilst two new cases of Kaschin-Beck disease were discovered amongst controls.



In addition, research workers from the Gansu Institute for Prevention and Treatment of Endemic Disease have been using yearly intramuscular injections of seleno-diacetic acid. It was found that this method was highly effective, cheap, convenient and had low toxicity. It is recommended by them for use to combat Kaschin-Beck disease (Li et al, 1988). It might, of course, be used in treating other selenium deficiency diseases, including senility.

Zhi and Tan (1988) have described an interesting case of accidental selenium supplementation which appears to have reduced the incidence of Keshan disease in the village of Donggua. This happens to be the site of a major phosphate fertilizer manufacturing plant which is causing extensive air pollution. Its pollutants include large quantities of selenium, iodine and fluorine. Although Keshan disease is endemic in the region, this heart disease only occurs in 0.02 percent of the population of Donggua. The level is 4 to 8 times higher than this, however, in neighbouring villages, suggesting a beneficial role for air pollution in Donggua.

### **The Need for Increasing Selenium Elsewhere**

Chinese research into methods of deliberately enhancing selenium food chain levels is particularly pertinent because evidence is accumulating that, over large areas of the globe, plant uptake of this element is in decline (Frost, 1987). Several reasons are cited to account for this, the most significant of which seems to be the burning of fossil fuels. The use of coal and oil adds large quantities of sulphur to the atmosphere which eventually reaches the soil as acid rain. Unfortunately, as soil sulphur levels rise, plant uptake of selenium declines. In addition, sulphate and nitrate ions in acid rain also lower soil pH, once again decreasing selenium uptake by vegetation. Insoluble metal selenides such as those of lead and mercury, also created during this process, may perhaps become a sink for environmental selenium. The use of sulphur rich fertilizers by agriculture compounds these problems, although liming increases the availability of selenium to crops (Frost, 1987). As a result of these processes, which appear to be combining to reduce the entry of selenium into

the food chain, it is not surprising that physicians are reporting that many selenium deficiency diseases appear to be increasing. Given the nature of our technological society, this decline in health seems likely to continue unless steps are taken to emulate the Chinese and artificially enhance the selenium cycle in agricultural areas.

### **Selenium's Dose-Response Curve**

Since selenium is an essential nutrient, protection of human health depends on recognition of the range within which intake is nutritionally adequate, yet not associated with adverse toxic effects. However there are other good reasons for linking the toxicological evaluation of selenium with nutritional considerations (Parizek, 1987). Selenium deficiency, for example, makes animals more sensitive to various chemicals, including paraquat and diquat (Cagen and Gibson, 1977; Burke et al, 1980). Elevated selenium can also mitigate the adverse effect of numerous chemical carcinogens and protect against the toxicity of arsenic, cadmium, mercury and thallium (Griffin and Lane, 1981; Whanger, 1981; Parizek, 1987).

The situation is further complicated by the fact that other nutritional interactions can modify the levels at which signs of selenium toxicity, or deficiency appear. The amount of selenium required by animals to prevent deficiency, for example, clearly depends on vitamin E status (National Academy of Sciences, 1976). In addition, it has been found that certain nutrients in diet, such as some cyanogenic glycosides found in animal meal can modify selenium's toxicity (Palmer et al, 1980). Similarly, interactions with arsenic can also prove protective (Levander, 1977). There is also evidence of a further complication in developing a dose-response curve for selenium. Animal studies suggest that it may be possible to adapt to high selenium intake (Ermakov and Kovalskij, 1968). If this occurs in humans, then it would be of great significance in evaluating the health risks associated with living in seleniferous regions.

Despite the obvious complexity, the Chinese experience with both selenium

deficiency and toxicity diseases allows some comments to be made about this element's dose-response curve. From observations in Enshi County it appears that a daily adult intake of between 1.08 to 38 mg of selenium induces intoxication. However, the duration of such an intake seems to be a very important consideration. Although a diet containing 1.08 mg a day was toxic, it was tolerated for more than two years and only seemed to result in diseased nails. This dosage is only 1/56 of the daily intake of 1.0 mg/kg body weight that Smith and Lillie (1940) considered toxic. Indeed, there is some Chinese evidence to suggest sensitive individuals may find even 750 micrograms per day mildly intoxicating (Yang et al, 1983). It is suggested that in China an intake of between 40 to 200 micrograms does not lend to obvious health problems. However, when diet yields less than 11 micrograms of selenium per day, Kaschin-Beck disease and Keshan disease are endemic (Yang, 1987). Research elsewhere suggests that mental impairment in the elderly may be obvious at levels which are higher than this (Tolonen et al, 1987).

### Conclusions

Western society should perhaps draw several lessons from the Chinese experience with selenium. Clearly, there is a wide range of illnesses that are associated with deficiencies of this element. Fortunately, many of these can be prevented by the addition of selenium to the environment through sprays and fertilizers. In addition, protection may be provided by increasing selenium in the food chain through the use of selenium enhanced animal feeds, or more directly by adding this element to table salt. Alternatively, selenium supplements or injections can be taken. Although the need for such practices varies geographically and, no doubt from individual to individual, this research areas seems to carry with in enormous potential for reducing suffering. It is also apparent that many of these diseases are not due solely to selenium deficiency. That is they are not first order selenium diseases (Foster, 1987). Keshan disease and Kaschin-Beck diseases, for example, appear to require other additional deficiencies or triggers before they develop. Nevertheless, the evidence presented here indicates that they can be

prevented, and often cured, by removing selenium deficiency alone. This will be critically significant if it proves to be a general characteristic of endemic disease. Clearly, it is far easier to identify, and rectify, one deficiency or excess than it is to establish every antagonistic and synergistic dietary relationship.

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