Changsheng Li

Selenium Deficiency and Endemic Heart Failure in China: A Case Study of Biogeochemistry for Human Health

A PECULIAR DISEASE

In 1937, a terrible disease of heart failure was reported in some rural areas in Heilongjiang, a far northeastern province of China. Women and children were its primary victims. The disease frequently occurred without warning and led to the death of a large number of people. The major symptom of the disease was myocardial necrosis, which led to acute hypoxia, vomiting, and finally death in several hours. Preliminary investigations were conducted in the late 1930s and 1940s but biotic infecting agents could not be identified. The peculiar disease was then named after the county, Keshan, where the first cases of death from the disease were reported. Since then, Keshan disease was found in another 12 provinces across China between the 1940s–60s. About eight million people lived in the affected areas in the country during that period of time, and thousands of people died of Keshan disease every year. The disease was so severe that a special government office was established to coordinate the nationwide efforts against the disease in the 1950s.

In the 1950s and 60s, large-scale epidemiological investigations were launched in the provinces affected by Keshan disease, including Heilongjiang, Jilin, Liaoning, Hebei, Shandong, Henan, Inner Mongolia, Shanxi, Shaanxi, Gansu, Sichuan, Yunnan, and Tibet.

A variety of biotic or abiotic factors, such as indoor carbon monoxides, nitrite in drinking water, parasites, fungi or bacteria in the local diet, etc., were considered during the investigations. The campaigns did not prove any of the factors related to the incidence of Keshan disease with convincing evidence. However, the nationwide investigations demonstrated that Keshan disease occurred within a geographic belt stretching from the northeast to the southwest of China. In some places, the affected and unaffected areas had clear boundaries. It was not uncommon to see two adjacent villages differing in disease status substantially and constantly for decades. Through the field investigations, the possibility that Keshan disease was an infectious one was excluded. The striking spatial distribution of Keshan disease implied that there could be some geographic or geological factors causing the disease. In fact, the local villagers whose families had lived in the affected areas for generations insisted that the disease was caused by the local "soil and water." A number of medical researchers started looking in a new direction, the geochemical environment. In 1966, Dr. Haijiang Cai, one of the pioneer medical researchers studying Keshan disease in China, declared "We must team up with the geologists who are interested in the medical issues."

THE WUYUR RIVER WATERSHED PROTOTYPE

In the winter of 1967, a group of eight young scientists from the Institute of Geochemistry, Chinese Academy of Sciences, were organized to respond to the call of the medical researchers. Realizing that the major challenge for the Keshan disease study was how to explain the peculiar spatial distribution of the disease, the new team oriented their focus on the geochemical patterns of the areas affected by Keshan disease. To implement their research strategy, the team selected Keshan County in Heilongjiang Province, the origin of Keshan disease, as their first study area. By teaming up with the local medical doctors, this group conducted a thorough field survey by literally walking across the entire county in 1968. They visited almost all the villages in the county, obtaining information on the incidence of Keshan disease as well the local environmental conditions. Soil and drinking water samples were collected from each of the villages for chemical analysis. The investigation resulted in a map of multiyear cumulative deaths from Keshan disease, with the chemical composition of the drinking water and soils at the village level described for the county. The map demonstrated an interesting pattern of Keshan disease in its geographic distribution in the county. The villages heavily affected by Keshan disease were mostly located in the central part of the county with hilly terrain; in contrast, the villages located along the river valleys along the northern or southern edge of the county had few cases reported during the previous decades. Field investigations indicated the topographic and soil conditions in the central part of the county were favorable for leaching, a geochemical process leading to a loss of dissolved salts or elements from the soils. The observation was supported by the results from the chemical analysis of the soil and water samples. The mineral contents in the drinking water samples collected from the affected villages were significantly lower than those from the unaffected villages. A hypothesis emerged from the investigations that Keshan disease could be caused by a deficit of a chemical or chemicals that are essential for human health and exist in soluble or leachable forms in the soils (1).

To test the hypothesis, the field investigation was expended from Keshan County to the Wuyur River watershed in 1969–1970, within which Keshan County was located. Wuyur River is an interior river with a length of about 300 km. The river begins in Beian County in the foothills of the Xiao-Xinganling Mountains; flows to the southwest across Kedong, Keshan, Yian, Fuyu, and Lindian counties; and finally ends in the low-lying plains in Durbat County (Fig. 1). As an interior river, the Wuyur River doesn't have a coastal outlet; this implied to the researchers that the chemical elements could be transported only within the watershed. If some elements were lost in the soils of the upper stream, they should accumulate in the soils downstream. The Wuyur River watershed provided an ideal domain to test the hypothesis of the relationship between Keshan disease and geochemical leaching. If the areas affected by Keshan disease were characterized with losses of certain soluble elements, it would be very interesting to find out the incidence of Keshan disease in the areas where these elements were deposited downstream.

To complement the investigation of the Wuyur River watershed, the research team was enhanced by involving more medical researchers from the Harbin Medical University, the Institutes of Endemic Diseases of Heilongjiang, and the Institute of Labor and Food Health in the Chinese Academy of Medical Sciences. During the coupled epidemiological and geochemical survey, historical incidence data for Keshan disease were collected and verified at the commune (a cluster of villages)

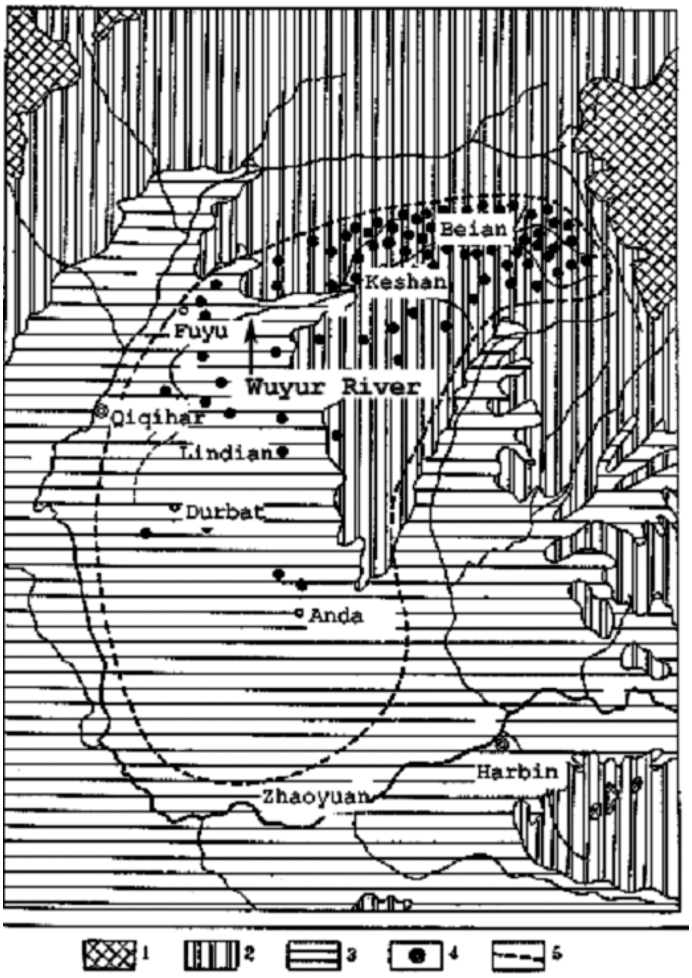

Figure 1. The spatial distribution of Keshan disease is closely related to the geographic conditions in the watershed of the Wuyur River. (Legends: 1. Xiao-Xinganling Mountain, 2. Hilly terrain, 3. Plains, 4. Keshan disease-affected communes, 5. Boundary of Wuyur River watershed) (3).

scale for the entire watershed; meanwhile soil and water samples were collected and analyzed for potassium, sodium, calcium, magnesium, chloride, sulfate, carbonate, bicarbonate, nitrate, nitrite, fluoride, and some trace elements. Results from the survey clearly indicated that the incidence of Keshan disease gradually decreased downstream in the Wuyur River basin (Figure 1); meanwhile the contents of most of the cations and anions in the drinking water increased downstream. For example, in the upstream counties, such as Keshan, Beian, Dedu, and Fuyu, dozens of villagers had died of Keshan disease every year during the previous 15 y. In contrast, in the downstream counties, such as Durbat, Zhaodong, Zhaoyuan, and Anda, no deaths from Keshan disease had been reported during the previous decades. In drinking water, the total mineral contents ranged between 350–680 mg L^{-1} for Keshan and Fuyu counties and 750–950 mg L^{-1} for Durbat and Zhaoyuan (1, 2). The 2-y watershed investigation confirmed the relationship between Keshan disease and the geochemical environment.

ESTABLISHMENT OF A BIOGEOCHEMICAL MODEL

The peculiar distribution of Keshan disease had long been a mystery puzzling the researchers. For example, in Heilongjiang, Keshan disease was reported in dozens of counties, which spread across the entire province without any clear pattern (Fig. 2). Could the hypothesis emerging from the Wuyur River investigation be used to explain the spatial distribution of Keshan disease in the province? The Wuyur River survey indicated that there were four main environmental factors, namely, climate, topography, vegetation and soil texture, controlling the leaching intensity of the soluble cations or anions in the soils. For example, the upstream areas (e.g., Keshan, Fuyu, etc.) of the Wuyur River watershed were characterized by relatively high precipitation with hilly topography that led to high leaching rates. In contrast, the downstream areas such as Durbat or Zhaoyuan had flat land with low precipitation and high evaporation rates that led to the accumulation of the soluble salts in the soils. In fact, soil salinization was observed in a broad area downstream where Keshan disease had never been reported during the previous 200 y. If Keshan disease was induced by deficiency of certain chemical elements, the correlation of the disease with the environmental factors, which controlled the element leaching intensity, should be identified based on their spatial patterns at the provincial scale. A mathematical model was established to quantify the leaching intensity driven by the four environmental factors (i.e., climate, topography, vegetation, and soil) for the entire Heilongjiang Province. At first, each of the environmental factors was divided into several grades based on its impact on the leaching process. For example, climate was divided into nine grades based on the precipitation/evaporation ratio. Areas with higher precipitation/evaporation rates had a stronger leaching effect, so they were assigned a higher grade number. The same principle was applied to topography, vegetation type and soil texture to produce their grades. Since the grades of all four environmental factors were defined based on the same principle, i.e., their impact on leaching, the grade numbers for the four factors could be summed up to produce a single number to represent the collective effect of the factors on leaching intensity. This single number was called the leaching index (LI). A database was constructed to hold the information on climate, topography, vegetation, and soil for Heilongjiang. The entire Heilongjiang Province was divided into about 1000 grid cells. By overlapping the gridded map with the maps of climate, topography, vegetation, and soil, the researchers obtained the specific climate, topography, vegetation, and soil conditions for each of the grid cells for the entire Heilongjiang Province. A LI value was calculated for each cell based on the specific climate, topography, vegetation, and soil grades in the

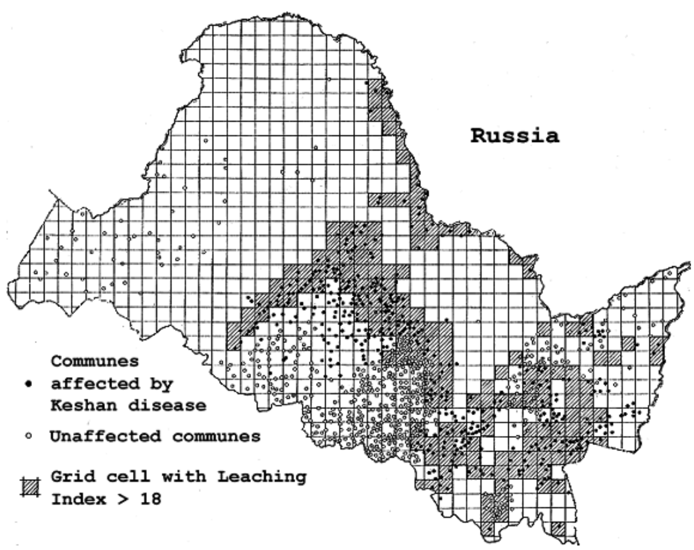

Figure 2. The grid cells with the modeled leaching index (LI) values higher than 18 covered most of the communes affected by Keshan disease in Heilongjiang Province. The spatial coincidence between Keshan disease and LI values indicated that Keshan disease could be related to deficiency of some chemical elements, which were lost from the soils through leaching (3).

cell. The calculations across the 1000 grid cells resulted in a map of leaching intensity (LI) for Heilongjiang Province. On this map, the LI values provided a semiquantitative expression indicating the leaching intensity of the soluble elements across the entire domain.

The LI map was validated against a multiyear observational dataset from 19 local hydrological stations across the province. Observed leaching intensity was calculated for each subhydrological unit based on the unit area and the measured fluxes of minerals (i.e., potassium, sodium, calcium, magnesium, chloride, sulfate, carbonate, bicarbonate, nitrate and nitrite). Meanwhile, a mean LI value for each subhydrological unit was calculated by averaging the modeled LI values for the grid cells included in the subhydrological unit. When the observed leaching fluxes and modeled LI were compared, the two factors demonstrated a significant correlation (3).

To link the LI map with Keshan disease, a threshold value of LI, 18, was selected arbitrarily. By highlighting the grid cells with LI values higher than 18, an irregular pattern was outlined on the map. The pattern was amazingly consistent with the pattern of Keshan disease (Fig. 2) (3).

The success in reproducing the spatial distribution of Keshan disease in Heilongjiang was regarded by medical researchers as a breakthrough for understanding the endemic nature of Keshan disease (4). The biogeochemical modeling practice enhanced the hypothesis of deficiency of essential elements for Keshan disease and then attracted more research focusing on the geochemical causes.

FOCUSING IN ON SELENIUM

During the field investigations in Heilongjiang Province in 1968–1970, the interdisciplinary team visited several horse farms. It was found that all the horse farms located in the areas affected by Keshan disease suffered from an animal disease, known as white muscle disease. At that time, white muscle disease had been recognized as a myopathy of livestock due to deficiency of a trace element, selenium (Se), and supplements of Se to the livestock effectively prevented the disease (5, 6). Given the understanding that soil Se mainly existed in the forms of selenate or selenite, two highly soluble salts, and hence could be easily leached from the soils, water samples were collected from the affected and unaffected villages in Keshan County for chemical analysis. The results indicated that Se contents in the samples from the affected areas were lower than those from the unaffected areas (<0.2 *vs.* >0.5 μg L^{-1}) (7). Based on the preliminary observations that *i)* Keshan disease mainly occurred in the areas with strong leaching effect; *ii)* Se could be leached from soils easily; and *iii)* white muscle disease existed with Keshan disease in the affected areas, Se deficiency emerged as the most likely cause of Keshan disease. When this idea was presented in a workshop held in Shangzhi County in Heilongjiang in 1971, Se received great attention, especially from a group of nutritionists from the Chinese Academy of Medical Sciences. Prevention experiments were almost immediately launched to test the hypothesis in the same year.

The spatial relationship between Keshan disease and livestock white muscle disease was observed not only in Heilongjiang but also in Shaanxi, Gansu, Sichuan, and other provinces during the same time period. In the 1970s and even the early 1980s, a wide range of geoscientists and medical researchers were involved in quantifying Se contents in soil, water, food, human hair, urine, and blood samples collected from the areas affected by Keshan disease and adjacent areas. Results from the analytical tests indicated that the spatial distribution of Se was basically consistent with that of Keshan disease. Along the belt from the northeast to the southwest of China where Keshan disease was reported, Se contents in the soils ranged from 0.03 to 0.10 mg kg^{-1}. In contrast, in the southeastern or northwestern part of China where there was no Keshan disease reported, the soil Se contents were usually higher than 0.12 mg kg^{-1} (8). The Se contents in food were also significantly different between the affected and unaffected areas. For example, Se contents were 0.005 ± 0.003, 0.007 ± 0.003, and 0.010 ± 0.008 mg kg^{-1} in samples of corn, rice and soybeans, respectively, from the affected areas, and 0.036 ± 0.056, 0.035 ± 0.027, and 0.069 ± 0.076 mg kg^{-1} in corn, rice, and soybeans, respectively, from the unaffected areas in China (9).

Preventive experiments supplementing Se in the diet were conducted in most of the provinces affected by Keshan disease in the 1970s and 1980s. Selenium-containing tablets or supplements were adopted to directly increase Se doses in the diets, or Se fertilizer was applied to the soil to increase the Se content in the food (10). The decade-long preventative campaign finally eliminated Keshan disease nationwide in China.

DISCUSSION

Keshan disease was a special phenomenon occurring under specific natural and social conditions in China. Until very recently, most Chinese farmers were bound to their local land, which was almost the only source of food and drinking water to the local residents. If there was anything abnormal with the geochemical conditions in the land, e.g., deficiency of essential elements or accumulation of toxic chemicals, the villagers had little chance to escape (11). As a human health problem, Keshan disease had complex features influenced by seasonality, gender, age, etc. Deficiency of Se was an important, but not the only, factor affecting the incidence of Keshan disease. Now we have learned that Se is an essential element in glutathione peroxidase (GSH-Px), which plays an important role in antioxidant defense (12). In human diets, the range of Se content between deficiency (<40 μg a day) and toxicity (>400 μg a day) is narrow. A small dosage of supplement can protect people from the disease. Along with the drastic changes in the entire socioeconomic structure of China in the 1980s and 1990s, the contemporary transportation systems of food reaching even the very remote corners of the country have fundamentally eliminated the local deficiency of Se in the diet.

Keshan disease is becoming a historic term. However, reviewing the processes of the Chinese researchers during the Keshan disease studies can teach us something. That is that interdisciplinary approaches, such as medical geology, could play a crucial role in human health-related environmental problems (13). The human beings on this planet are faced by a series of unprecedented changes in the environment at local, regional, and global scales. Every species is in a hurry to adjust itself for adaptation. New problems related to human health are arising due to pollution, climate change, or biological or chemical weapons. The concepts and methodologies developed in geosciences, specifically in biogeochemistry, could be directly applied to a wide range of environmental issues by linking spatial or temporal patterns displayed by these problems to biogeochemistry, which determines the abundance, coupling, and cycling of various chemical compounds or elements in the environment that control people's health and life (14, 15). I hope the story of Keshan disease reported in this paper will draw more young scientists to interdisciplinary studies.

References and Notes

1. Li, C., Cai, Y., Hong, Y., Cheng, H., Liang, Q., Yu, Z., Xie, C., Zhu, Y. et al. 1972. Relationship between potable water quality and Keshan Disease, Keshan Disease Research Group, *Geochemica, 1*, 265–273 (In Chinese).

2. Li, C., Cai, Y., Hong, Y., Cheng, H., Liang, Q., Yu, Z., Xie, C., Zhu, Y. et al. 1972. Geochemical characterization of the regions affected by Keshan Disease and Kaschin-Beck Disease in China, Keshan Disease Research Group, *Geochemica, 1*, 12–22 (In Chinese).
3. Li, C. and Yu, Z. 1973. Establishment of an environmental model for Heilongjiang Province and its application for the study of Keshan disease. In: *Environmental Geology and Health*. Institute of Geochemistry, Chinese Academy of Sciences (ed). Science Press, Beijing, Volume 1, pp. 9–26 (In Chinese).
4. Su, Y. and Yu, W. 1973. Studies on soil- and water-relevant causes of Keshan disease. In: *Environmental Geology and Health*. Institute of Geochemistry, Chinese Academy of Sciences (ed). Science Press, Beijing, Volume 1, pp. 27–43 (In Chinese).
5. Muth, O.H., Oldfield, J.E., Remmert, L.F. and Schubert, J.R. 1958. Effects of selenium and vitamin E on white muscle disease. *Science 128*, 1090.
6. Muth, O.H. 1963. White muscle disease, a selenium-responsive myopathy. *J. Am. Vet. Med. Assoc. 142*, 272–277.
7. Committee for Atlas of Endemic Diseases and Environment. 1989. *Atlas of Endemic Diseases and Environment*. Science Press, Beijing, p. 74.
8. Chinese Environmental Science Press. 1994. *The Atlas of Soil Environmental Background Value in the People's Republic of China*. National Environmental Protection Agency, National Education Committee (ed). Chinese Academy of Sciences, Beijing, pp. 74–75 (In Chinese).
9. Chen, X.S., Yin, S.A., Xue, K.N., Pu, J.H. and Chen, J.S. 1989. Selenium, In: *Trace Elements and Health*. Chen, Q. and Lu, G. (eds). Peking University Press, pp. 166–181 (In Chinese).
10. Tan, J. and Hou, S. 1989. Environmental selenium and health problems in China, In: *Environmental Selenium and Health*. Tan, J., Li, R., Hou, S., Zhu, W., Zheng, D. and Zhu, Z. (eds). People Health Press, Beijing, pp. 219–234.
11. Li, C. and Liu, D. 1978. Environmental geology and human health. In: *Proceedings of the First Environmental Science Symposium of Academia Sinica,* Committee for Environmental Science of Academia Sinica (ed). Science Press, Beijing. (In Chinese).
12. Rotruck, J.T., Pope, A.L., Ganther, H.E., Swanson, A.B., Hafeman, D.G. and Hoekstra, W.G. 1973. Selenium: biochemical role as a component of glutathione peroxidase. *Science 179*, 588–590.
13. Li, C. and Jackson, M.L. 1985, Selenium affects heart death rates in China and USA. In: *Trace Substances in Environmental Health, XIX*. Hemphill, D.D. (ed) University of Missouri, Columbia, MO.
14. Li, C., Aber, J., Stange, F., Butterbach-Bahl, K. and Papen, H. 2000, A process-oriented model of N_2O and NO emissions from forest soils: 1, model development, *J. Geophys. Res. 105*, 4369–4384.
15. Li, C. 2001. Biogeochemical concepts and methodologies: Development of the DNDC model. *Quat. Sci. 21*, 89–99 (In Chinese with English abstract).

Changsheng Li, Institute for the Study of Earth, Oceans, and Space, University of New Hampshire, Durham, New Hampshire 03824, USA.
Changsheng.li@unh.edu