Nutritional Impact on Environmental Toxicology
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A Personal Note

After attending a symposium in Beijing in October 2007 to celebrate the 25th Anniversary of Sino-US Collaborations on the Nutritional Intervention of Esophageal Cancer in Linxian, I spent four weeks visiting different universities and institutions in six provinces in China. I appreciated the remarkable economic and scientific developments made in recent years. I also experienced the problem of environmental pollution for four weeks. As I was walking along the West Lake, I could not see a clear blue sky and green mountains anymore. This is very unpleasant and the health effects of environmental pollution could be detrimental. I began to think about how to use the experience that we have gained from cancer prevention studies during the past 25-30 years to alleviate the damage caused by environmental pollutants. I have discussed this issue with many scientists inside and outside of China. I would especially like to thank Professor Zuo-Feng Zhang of UCLA and Professor Jim Zhang of UMDNJ-School of Public Health, who both provided me with a substantial amount of information. Because I am just a beginner in this field, the following can be considered as a study note or a rough draft of some of my ideas. I would like to share these ideas with scientists who are interested and hope this will eventually benefit the society at large. Please feel free to contact me about your thoughts or suggestions.

Environmental pollution is a worldwide problem. The situation is most serious in areas undergoing rapid economic growth. For example, in China, the rapid economic development has created massive environmental pollution problems, even as it has improved the standard of living for many citizens.

The emerging pollution problem in China

According to the report on the "Cost of Pollution in China" published by the World Bank in 2007, the increased energy use, especially coal use, contributed to an alarming increase in the emission of SO$_2$ and soot. Of the 341 cities surveyed in 2007, 74%, 17%, and 9% of the cities had SO$_2$ levels of $<60$ μg/m$^3$, 60-100 μg/m$^3$, and $>100$ μg/m$^3$, respectively; and 47%, 39%, and 14% of the cities had PM$_{10}$ levels of $<100$ μg/m$^3$, 100-150 μg/m$^3$, and $>150$ μg/m$^3$, respectively. China's cities rank among the most polluted in the world. Water pollution is also a serious problem. In the period of 2001-2005, about 54% of the 7 main rivers in China contained water that was unsafe for human consumption. Approximately 90% of the sections of rivers around urban areas were seriously polluted. Many of the most polluted rivers have been devoid of fish for many years. People in many areas, especially those in Northern China, bear the double burden of air and water pollution.

Regression analysis of environmental monitoring data and population mortality data for over 30 Chinese cities suggest that urban air pollution causes significant public health impacts.
These health problems include reduced lung functions, respiratory symptoms, chronic bronchitis, cardiovascular and cerebrovascular diseases, hospitalization, premature death, and work and school absenteeism. The involvement of SO$_2$, O$_3$, NOx, and CO in these diseases has been suggested and PM$_{10}$ may be a useful index for air quality. The biological effects of particulate matter are beginning to be understood at the molecular levels. A recent paper reported the occurrence of germ-line mutations, DNA damage, and global hypermethylation in mice exposed to particulate air pollution in an urban/industrial location in Ontario, Canada. The possible epigenetic changes caused by pollution is an important new area for research.

Biological pollutants in water can cause infections such as hepatitis A or E, diarrhea, dysentery, typhoid fever, and cholera. Chemical pollutants, including inorganic substances such as arsenic, nitrites, mercury, and lead as well as organic compounds such as benzene, phenols, and other aromatic compounds can cause cancer and other diseases.

**A nutritional approach for reducing environmental toxicity**

The fundamental solution to the pollution problem is to take effective measures for pollution reduction and environment protection. Public awareness and government policies are the key. It is important for the general public to be aware of the seriousness of the problem and to strongly advocate the central and local governments to enforce stricter environmental protection laws. In the meantime, it is also important to develop preventive measures that can reduce the harmful effects caused by exposure to environmental pollutants.

In this abstract, I propose a nutritional approach for the alleviation of environmental toxicity. The rationale is that many of the pollutants, including particulate matters, can cause oxidative stress and DNA damage. Nutrients such as vitamins E and C are well recognized for their physiological antioxidative functions. Selenium is important for the function of antioxidative enzymes such as glutathione peroxidase. Riboflavin, which is not generally considered an antioxidant, is the coenzyme of glutathione reductase, which keeps a key bio-defense molecule, glutathione, at the reduced state. Even marginal inadequacy in these nutrients, without overt signs of vitamins deficiencies, is expected to make individuals more susceptible to environmental assaults. Similarly, dietary antioxidants such as carotenoids and polyphenols compounds may also play a role in protecting against antioxidative stress. Low nutritional status in selenium and vitamin E is not uncommon in China, and it has been associated with the high incidence of esophageal and other cancers. My working hypothesis is that supplementation of antioxidative nutrients to individuals or populations with low nutritional status in these nutrients will increase their defense against oxidative stress and thus reduce damage caused by pollutants. Before this hypothesis can be translated into a practical approach, carefully designed studies in animals and humans are needed.

**Proposed studies, agents, and biomarkers**

The proposed hypothesis can be tested in animal models and human subjects. In animals studies, it is important to use a low vitamin E and selenium diet to mimic humans with inadequate intake of these nutrients. For example, an AIN93M based diet with vitamin E content lowered from 89 IU to 46 IU per kg diet (which meets the nutritional requirement) and with selenium lowered from 0.15 ppm to 0.06 ppm in the diet could be used. This is the selenium level from the constituents in the diet (no selenium added in the salt mixture), and should produce a marginal adequate situation. As for exposure, the approach of the Ontario study...
using ambient vs. HEPA filtered air may be used. Another possibility is to house the mice in animal rooms: one in a room receiving ambient air and another room receiving filtered (cleared) air. The experimental period could be a few or several weeks. As for endpoints, oxidative stress and inflammatory markers in the blood and lung are important. Genotoxic markers are also important, and it could be from simple assays, such as sperm counts, to more sophisticated assays, such as germ-line epigenetic changes.

In human studies, a 2-step approach could be used. In the first step, inhabitants in a polluted area (e.g. Datong of Shanxi or Handan of Hebei) will be analyzed for oxidative stress and inflammatory markers as well as blood levels of selenium and fat soluble nutrients. We have an HPLC method that can simultaneously determine levels of $\alpha$-tocopherol ($\alpha$-T), $\gamma$-T, $\delta$-T, $\beta$-carotene, $\alpha$-carotene, lycopene, lutein, zeaxanthin, chryptoxyanthin, and retinol in one run using 0.2 mL of plasma or serum. It would be ideal, if we could observe an inverse correlation between tocopherol/selenium levels and oxidative stress/inflammatory biomarkers. Even if we cannot see such a clear correlation, this study will provide a baseline for an intervention study. In the proposed intervention study, individuals with low nutritional status of vitamin E (tocopherols) and selenium will be recruited and divided into two groups: Group A will receive supplements of tocopherols and selenium and Group B will receive placebo. The levels of supplementation could be 2-3 times the RDA levels. The U.S. RDA level for selenium is 55 $\mu$g/day and for vitamin E is 15 mg/day. The most practical approach is to supplement with selenium-enriched yeast and a tocopherol mixture that is rich in $\gamma$-T. This tocopherol mixture is a by-product of soybean oil manufacturing, representing the ratio of tocopherols in our diet, and should be rather inexpensive. Recent studies have suggested that $\gamma$-T has stronger antioxidative, anti-inflammatory, and anti-cancer activities than $\alpha$-T. $\gamma$-T is effective in trapping reactive nitrogen species, but $\delta$-T is not. As for the period of intervention, a month may be sufficient.

Biomarker analysis will depend on the expertise of the research group. The peripheral blood Comet and micronucleus assays are commonly used methods and should be useful. A recent publication demonstrated that an increased micronucleus in peripheral lymphocytes can predict the risk of cancer in humans. Plasma levels of 8-isoprostane (for oxidative stress), fibrinogen, and inflammatory cytokines can also be measured by ELISA. Specific assays for pulmonary inflammation and oxidative stress (exhaled nitric oxide as well as 8-isoprostane and nitrite & nitrate in exhaled breath condensates), endothelial functions (vascular NO production, von Willebrand Factor), and platelet functions (soluble CD62P, SCD40L, platelet aggregation) could also be measured [This information is from an ongoing study carried out by Dr. Junfeng (Jim) Zhang of UMDNJ-School of Public Health and EOSHI, and collaborators].

Additional considerations

The above is just an example for the proposed nutritional intervention approach. Many other preventive agents could also be considered. For example, tea consumption has been shown to reduce oxidative damage and to be associated with lower cancer risks. Administration of olive oil high in phenolic compounds to human subjects has been shown to decrease oxidative stress parameters.

The key to the success of the proposed experiments is the ability to measure reliably biomarkers that reflect changes caused by environmental pollutants. Based on the available
information from the literature, some of the above proposed biomarkers should be able to reflect changes in inhabitants in heavily polluted cities such as Datong or Handan. With improvement and refinement of biomarker analysis, we hope the proposed hypothesis can be successful tested in cities such as Beijing, Tianjin, Nanjing, and Shanghai. If results in support of the hypothesis could be obtained, then the impact of the proposed nutritional intervention approach to public health would be tremendous.

References