NEWSLETTER

NIEHS Center, University of California, Berkeley

Spring 1998

International Environmental Health Research

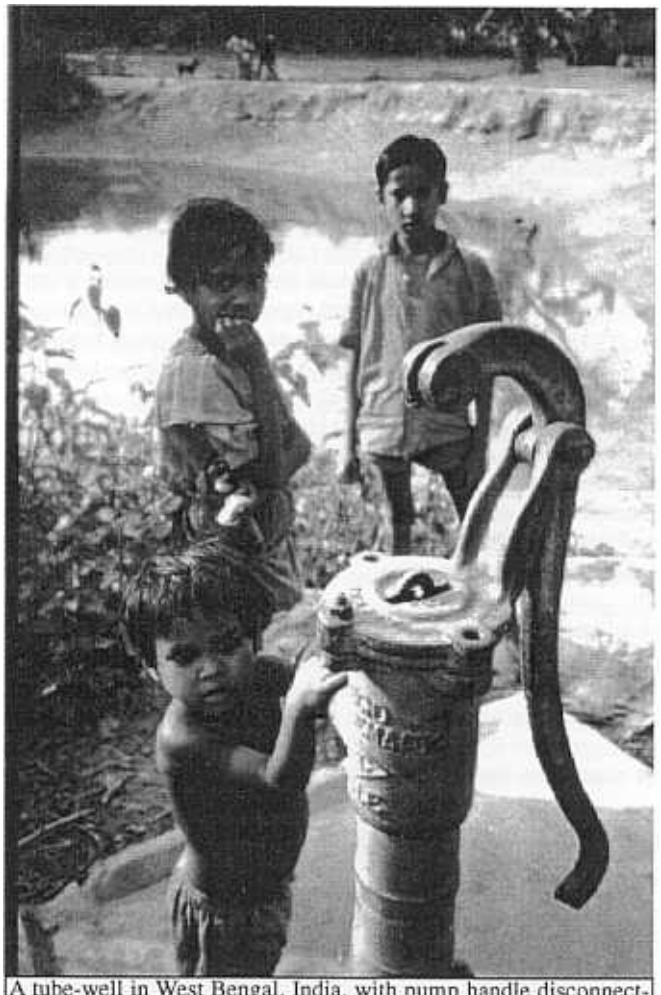
(Allan Smith, Mary Lou Biggs & Craig Steinmaus)

In this issue, we focus on international environmental health studies being conducted by some of our Center members. The countries involved include Argentina, Chile, China, and India. One aim of these studies is to provide information to developing countries with major environmental health problems. Another aim is to generate information on environmental health issues relevant to the United States. At first glance, this latter aim may seem surprising, and one may be tempted to ask why issues originating in the United States should be studied abroad rather than here?

A basic principle of epidemiology helps to answer this question. In general, causal associations between toxic chemicals and health problems are easier to identify in populations with high exposures. For example, if one did not know that smoking causes lung cancer, then studying cancer rates in heavy smokers would be wise as a start. A study of heavy smokers would be more likely to show an effect than a study of people exposed only to low levels of second-hand tobacco smoke. If one found a strong association between heavy smokers and lung cancer, then a hypothesis that people exposed to second hand smoke were at risk for cancer would be more plausible and worthy of further examination. Besides causal associations, susceptibility factors and dose-response relationships are also more clearly identified in populations in which at least some people are very heavily exposed. Therefore, as a general principle, epidemiological studies concerning environmental exposures should begin with those most highly exposed.

For certain environmental health problems, studies in other countries offer opportunities to study populations with significantly higher exposures than those found in the United States. Once an international study indicates that an environmental chemical may cause health problems, governmental agencies in the United States will be better able to assess the need for low dose studies domestically. Indeed, these agencies may be able to use the data from international studies to make regulatory decisions in the U.S., without the need for large, expensive low-dose studies. Thus, international studies offer the opportunity to advance scientific knowledge and to be of direct public health benefit both here and abroad.

These principles have led Center members to conduct environmental health studies in different parts of the world. In this issue we will describe several studies concerning naturally occurring inorganic arsenic in drinking water in Chile, Argentina, and India, and two studies in China, one concerning benzene exposure, and the other a parasitic disease called Schistosomiasis, which has been linked to an increased risk of bladder cancer.



A tube-well in West Bengal, India, with pump handle disconnected because of high arsenic water concentrations. Many thousands of adults, as well as children by the ages of 5-10, show skin lesion signs of arsenic poisoning throughout West Bengal and Bangladesh. (See "On the Other Side of the World", page 3.)

International Arsenic Research Program

(Allan Smith, Mary Lou Biggs & Craig Steinmaus)

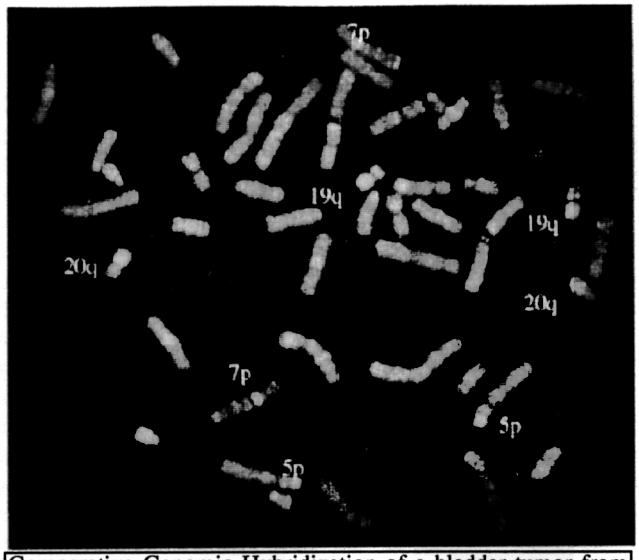
Center member Professor Allan Smith first became interested in the effects of naturally occurring arsenic in drinking water after being asked by the California Department of Health Services to consider potential cancer risks surrounding the current U.S. arsenic drinking water standard of 50μg per liter. At the time, it was well known that arsenic in drinking water could cause pigmentation of the skin, small raised keratotic lesions on the palms and soles, as well as skin can-

cer. However, based on studies from Taiwan, it was becoming increasingly apparent that arsenic could also cause fatal cancers such as bladder and lung cancer. A linear risk extrapolation from Taiwan to U.S. drinking water levels raised the possibility that consuming water containing 50µg arsenic/L (the drinking U.S. water standard) might result in 1 of 100 persons dying from arsenic caused cancer.

To confirm the Taiwan results, Dr. Smith and his research team searched for other highly exposed populations. This first led to Argentina, where the people of the Province of Cordoba were found to have high rates of skin diseases caused by drinking water from arsenic contaminated wells. The research team subsequently found increased mortality rates of both bladder and lung cancer in the region, especially in the most highly exposed areas where arsenic levels averaged close to 200µg/L.

Even more striking were the results from a second mortality investigation, this one in a remote desert area in northern Chile, where use of drinking water with arsenic levels as high as 1000µg/L began in the 1950s. The research team found bladder cancer mortality rates seven times higher than the rest of Chile, and lung cancer mortality rates also markedly above national levels. As in the Argentina study, smoking could be ruled out as an explanation since the rates of other pulmonary diseases in this region were normal. The research team reached the conclusion that naturally occurring arsenic in drinking water in Northern Chile, had been a more important cause of mortality than cigarette smoking.

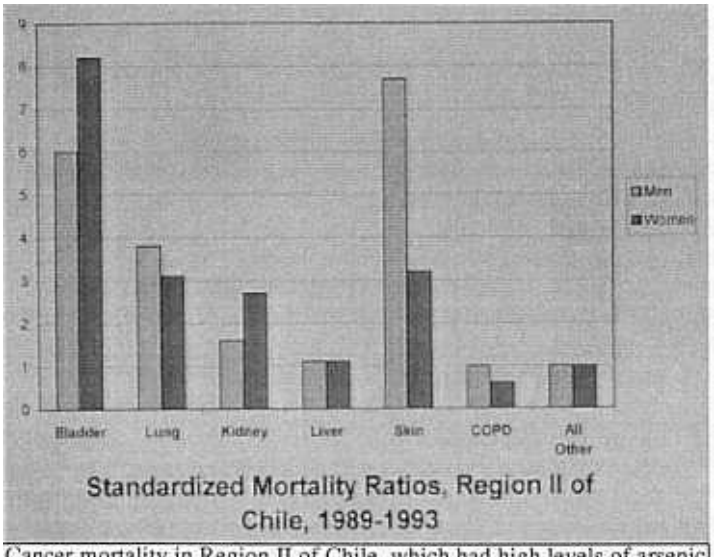
Additional studies by the research team investigated dose-response and susceptibility issues and the potential effects of arsenic at levels found in the United States. One set of studies investigated the role of methylation, which is thought to be the body's natural mechanism to protect itself from arsenic. It had been suggested that at low doses of arsenic the body has sufficient capacity to fully methylate and thereby inactivate all the inorganic arsenic it encounters. However, analysis of urine samples from studies in Nevada and Chile by collaborator Professor David Kalman from the NIEHS Center at the University of Washington suggested otherwise. Inorganic arsenic was present in urine even at low levels of arsenic intake in drinking water, implying incomplete methylation and no assurance of protection even at low exposures.



Comparative Genomic Hybridization of a bladder tumor from the arsenic study in Argentina showing varioous changes, e.g., deletions in chromosome 7p, identified in bright green.

A parallel set of studies, done in collaboration with Center Member and Superfund Program Director, Professor Martyn Smith, involved collecting bladder cells from people drinking arsenic-contaminated water in Nevada and Chile. The results provided evidence that those with high levels of arsenic in their water have an increased proportion of bladder cells with genetic damage. Furthermore, these changes were detected in study participants with arsenic levels equivalent to those commonly found in people in the United States. Additionally, when 40 of the highly exposed households in the Chile study were supplied with low-arsenic water (less than 50 µg/L) for a period of two months, there was a decrease in the number of people showing damage to bladder cells.

Currently, Dr. Allan Smith and his research team are involved in a number of other studies of arsenic health effects. In collaboration with local scientists, they are conducting a study of bladder cancer patients and healthy individuals in arsenic-exposed areas of Argentina and Chile. Researcher Mary Lou Biggs is supervising the fieldwork, which consists of interviews, collection of biological specimens, and determination of arsenic levels in drinking water sources. Additionally, post-doctoral fellow Dr. Lee Moore, in collaboration with Dr. Fred Waldman of the University of California, San Francisco, School of Medicine, is examining genetic changes in tumors from these bladder cancer patients in order determine the mechanism by which arsenic causes cancer. Dr. John Weincke, also at UCSF, is analyzing DNA from normal tissue of participants to see if certain genes can influence susceptibility to arsenic-caused cancer.

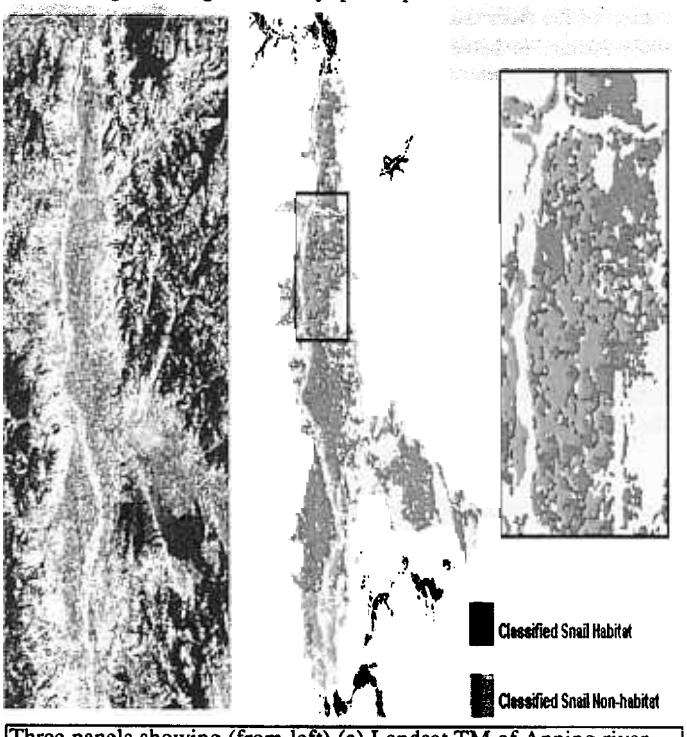


Cancer mortality in Region II of Chile, which had high levels of arsenic in drinking water, compared to the rest of the country, showing 6- to 8-fold increases in bladder cancer mortality, as well as increases in lung, kidney and skin cancer mortality. The lack of increase in deaths from chronic obstructive pulmonary disease (COPD), was part of the evidence that smoking was not involved in the increased cancer risks.

On the Other Side of the World
(Allan Smith

Dr. Smith and his research team have joined international efforts to address a major arsenic catastrophe which has unfolded in West Bengal, India and neighboring Bangladesh. It is estimated that over a million people in this region are drinking water naturally contaminated with arsenic. In order to better understand the effects of arsenic on this population, a research team in India, led by Dr. Guha Mazumder, conducted a survey of over 7,000 persons in one of the arsenic-exposed areas of West Bengal. The Berkeley research group assisted in analyzing findings which showed arsenic-caused skin lesions over a wide range of arsenic water levels from more than 1,000µg/L to less than 100µg/L. In a follow-up study just commencing, Dr. Smith's group along with Dr. Mazumder's team and Dr. David Kalman of the University of Washington will examine people with skin lesions occurring at relatively low levels of arsenic. In addition to investigating dose-response relationships, the researchers will also examine the role of nutrition in mitigating the adverse effects of arsenic.

Dr. Smith and the arsenic research team have recently begun a new drinking water study in the United States. The study area includes Kings County in central California and six counties in Nevada. Previous investigations have identified these two areas as having large populations exposed to drinking water with levels of naturally occurring arsenic of 90 to 100µg/L. This study is significant in that it examines the hypothesis that bladder cancer is caused by the ingestion of arsenic at levels lower than previously studied. The study team, led by Dr. Craig Steinmaus will interview approximately 200 bladder cancer patients identified from local cancer registries, and 400 matched controls selected from the general population by random digit dialing. All study participants will be interviewed about their residential histories, typical fluid consumption, and other potential causative or confounding factors such as smoking history and diet. Residential and fluid data will be linked to historical arsenic measurements from private wells and community water sources to obtain arsenic exposure patterns. Cases and controls will be compared with respect to their exposures to arsenic as well as other potential causative or confounding factors. Results from this study can potentially have a significant impact on the decision making process regarding the United States drinking water standard for arsenic.



Three panels showing (from left) (a) Landsat TM of Anning river valley, (b) classification of habitat using Isodata and maximum likelihood algorithms, and (c) enlargement of valley floor showing mixed habitat.

Selected Publications:

Hopenhayn-Rich C, Biggs ML, Kalman DA, Moore LE, Smith AH. Arsenic methylation patterns before and after changing from higher to lower concentrations of arsenic in drinking water. Environ. Health Perspect., 104 (11):1200-1207,1996.

Moore LE, Smith AH, Hopenhayn-Rich C, Biggs ML, Kalman DA, Smith MT. Decrease in bladder cell micronucleus prevalence after intervention to lower the concentration of arsenic in drinking water. Cancer Epidemiol., Biomarkers, and Prev., 6(12):1051-6, 1997.
Smith AH, Goycolea M, Haque R, Biggs ML. Marked increase in bladder and lung cancer mortality in a region of Northern Chile due to arsenic in drinking water. Am. J. Epidemiol. In press.

Guha Mazumder DN, Haque R, Gosh N, De BK, Santra A, Chakraborty D, Smith AH. Arsenic levels in drinking water and the prevalence of skins lesions in West Bengal, India. Intl. J. Epidemiol. In press.

Satellite Surveillance of Snails in China May Reduce Human Cancer Risk!
(Robert Spear)

Investigators within the Center have long been interested in the relationship between cancer induction and chronic inflammatory conditions that appear to significantly increase an individual's susceptibility to cancer. Various parasitic diseases, common in the developing world, lead to chronic inflammation, and some, like schistosomiasis are known to be associated with increased risk of bladder cancer. Schistosomiasis is a disease in which different forms of the parasite cycle between mammals and snails that live in or near fresh water. In the most common form of the disease in Asia, people (or cattle, pigs, etc.), become infected when the parasite penetrates the intact skin and eventually develops into a small worm which seeks a mate within the host. If successful, the happy couple set up housekeeping in the peripheral vasculature around the liver of people or animals. Copious numbers of eggs are excreted by the female worm, and it is these eggs which are responsible for chronic inflammation.

Center investigator Dr. Robert Spear is collaborating with Professor Peng Gong of the College of Natural Resources at Berkeley and colleagues in the Sichuan Institute of Parasitic Disease on studies aimed at developing more effective surveillance and control methods for schistosomiasis japonica in China, particularly, in view of the construction of the Three Gorges Dam which has the potential of expanding the geographical distribution of the disease along the Yangtze. The dam