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Arsenic, Geographical Isolates, Environmental Epidemiology, and Arteriosclerosis

"Science is built of facts much as a house is built of bricks. But a collection of facts is no more science than a pile of bricks is a house." Henri Poincaré (1901)

The characterization of disease occurrence by the triad of **time, person, and place** has been the principal approach used by epidemiologists to develop and validate etiologic hypotheses.¹ For example, Garraway and Whisnant recently reported on the temporal decline in stroke incidence in Rochester, Minnesota.² They were able to relate that decline (time) with greater utilization of antihypertensive medications (person), thereby confirming the relationship between hypertension and cerebrovascular disease. Although this example illustrates the usefulness of "time, person, and place," the exemplar of this triad is provided by the geographical isolate.

What is a "geographical isolate"? A geographical isolate is a geographically defined population in which a markedly elevated incidence of a disease has been observed. As defined by Kurland, one of the pioneers in the use of geographical isolates, such a population may be "inbred, remote, isolated, or otherwise distinct. It is of interest because within it prevails a high incidence of a new or rare disease or an unusual prevalence of a well-known disease."³ Examples of geographical isolates include the New Guinea highlands and kuru (the investigation of which formed the basis of a Nobel Prize), Guam and amyotrophic lateral sclerosis, the Farøe Islands and multiple sclerosis, South Africa and mesothelioma, and Turkey and mesothelioma.⁴⁻⁸ In the case of kuru, the disease had not been observed prior to Gajdusek's studies in New Guinea in the 1950s. These studies led to the finding that kuru was caused by a slow virus spread through cannibalistic rituals.⁴ In contrast, amyotrophic lateral sclerosis had been well-recognized in the United States prior to the identification of a high-incidence focus of the disease in Guam in the late 1940s.⁵ Although it is not clear what the precise etiology of this disease is, the geographical isolate on Guam has been invaluable in clarifying the importance of environmental factors in the condition's natural history.

Few geographical isolates of cardiovascular conditions have been reported, an exception being the recent report of an elevation in the incidence of sudden death in Southeast Asian men.⁹ Perhaps this "dearth" results from the efforts of environmental epidemiologists being focused predominantly on cancer, pulmonary disease, and birth defects rather than on cardiovascular disease. Perhaps it results from the orientation of most cardiovascular epidemiologists toward preventive cardiology. Few cardiovascular epidemiologists deal with environmental epidemiology and vice versa. It may also be that such isolates have not been found because they do not exist, at least not in great numbers. A requisite for locating such isolates is the existence of comparison incidence rates in the general population.³ Such rates are not necessarily available for a number of cardiovascular conditions in the same manner that they are for various cancer sites or for birth defects.

The observation three decades ago by Wu et al.¹⁰ of the endemicity of blackfoot disease, a peripheral vascular condition, in an isolated section of Taiwan and of its association with an environmental exposure, arsenic in well water, provided the conditions for a remarkable report by Chen et al. in this issue of *Arteriosclerosis*.¹¹ The report relating arsenic exposure to a variety of cardiovascular conditions and to cancer of the bladder, skin, lung, and liver is noteworthy for several reasons. First, it is one of the few examples of a cardiovascular disease geographical isolate. Second, the approach taken by the investigators was a logical series of studies that examined the etiology of and natural history of blackfoot disease. Third, the studies reported by Chen et al. are elegantly simple. The investigators did not

have to "guesstimate" the effect of sampling biases because such effects were *by design* eliminated from the studies. The investigations were of high statistical power. The levels of arsenic in the water that the populations were exposed to were also simply stated. No doubt one could contest the definition of disease used by the investigators or the methods used for investigating dietary factors. However, the perfect epidemiologic study has not yet been conducted. It will likely never be conducted. It is for this reason that the simplicity of the Chen et al. report, which allows one to focus on the epidemiologic findings rather than only on the methods used, assigns a compelling nature to the investigators' conclusions. (Indeed, for this very reason, this report provides a model for students of environmental epidemiology to emulate.)

To focus on arsenic and not on the other contaminants in the well water, the investigators used a marker for arsenic exposure, i.e., keratosis and skin cancer, to examine the relationship between arsenic and blackfoot disease. In this manner, the researchers identified a dose-response relationship between consumption of the arsenic-laced artesian well-water and blackfoot disease. They were also able to relate the arsenic exposure (and blackfoot disease) to generalized arteriosclerosis, which was reflected in increased mortality from peripheral vascular and cardiovascular diseases in the population studied. Interestingly, no increase in cerebrovascular mortality was noted, with the authors suggesting that this finding reflects the relative impermeability of the blood-brain barrier to inorganic arsenic. On the other hand, it is not clear why the blood-brain barrier should enter into consideration, given that one is dealing with *cerebrovascular* disease. The associated cerebrovascular arteriosclerosis should occur well before the arsenic begins to interact with the blood-brain barrier. This distinction between generalized arteriosclerosis and cerebrovascular arteriosclerosis in relation to arsenic would be an area prime for future study. The authors also reported on the increased mortality from cancers of the lung, skin, liver, bladder, and kidney in the blackfoot disease population. They noted that the first two malignancies have been previously associated with arsenic exposure, which supports their conclusion of the relationship between arsenic and blackfoot disease.^{12,13} Also, liver cancer has been previously associated with arsenic exposure.^{14,15} Given the role of the kidney and the bladder in the excretion of arsenic from the body, it is perhaps not surprising that mortality from cancer of these sites was elevated.¹⁶ It is, however, the investigators' findings with regard to cancer that provide the basis for placing this report into perspective.

Of what importance are these findings? Chen et al. have provided further evidence of the relationship between arsenic and blackfoot disease. Yet, they have also provided much information on the natural history of atherosclerosis. In 1986, Ross published an updated version of his classic review of the development of atherosclerosis.¹⁷ He noted that there are two principal hypotheses for atherogenesis: 1) the "response-to-injury" hypothesis, in which an endothelial injury leads to intimal proliferation and a subsequent atherosclerotic lesion, and 2) the "monoclonal" hypothesis, in which each cell in an atherosclerotic lesion results from the proliferation of a single smooth muscle cell, i.e., a neoplastic process. Last year, Adams and his colleagues reported on a marked association (approximate relative risk of five) between past cytomegalovirus (CMV) infection and atherosclerosis.¹⁸ They speculated that this finding may represent a role for CMV in atherogenesis. Such a role could be the initiation of a neoplastic process that results in atherosclerotic lesions, i.e., the monoclonal hypothesis.¹⁹ Chen et al.'s report of the relationship between arsenic exposure, generalized arteriosclerosis, and cancer would seem to provide further support for the monoclonal hypothesis. Certainly if arsenic can initiate a neoplastic process in the lung, the skin, the kidney, the bladder, and the liver, why should it not be able to do so in a blood vessel? (It should be noted that the liver cancer histology associated with arsenic exposure is angiosarcoma.¹⁴) The next step in testing such a hypothesis would be a series of laboratory experiments to evaluate the atherogenic potential of arsenic and to study the lesions so produced. Unfortunately, arsenic has been one of the few human carcinogens (as determined by the International Agency for Research on Cancer) for which animal demonstration of such activity has been relatively unsuccessful.¹² Hence, much work may be needed to fully evaluate the role of arsenic in atherogenesis. Yet such research could provide much information about the validity of the monoclonal hypothesis if and when it is conducted. It would provide the "mortar" for the proper arraying of the factual "bricks" that define much of our current knowledge of atherogenesis.

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