We thank Dr. Klatsky (1) for his interest in our paper (2) and his discussion of the outbreak of cases of heart failure during the episode of arsenic-contaminated beer poisoning in Manchester in 1900 (3, 4). This study was not included in our systematic review of arsenic and cardiovascular disease (5) because it lacked a comparison group. While we identified this outbreak and other papers using the electronic database OLDMEDLINE and the manual review of references, most of these early reports were case series. Indeed, of the studies on arsenic and cardiovascular disease published before 1950 that we identified, only the study by Bradford Hill and Faning in 1948 (6) fulfilled all the inclusion criteria for our systematic review.

Since none of the studies included in our review investigated the link of arsenic with heart failure, we focused the discussion on the association of arsenic with arteriosclerotic cardiovascular outcomes, such as coronary heart disease or peripheral arterial disease. Motivated by Dr. Klatsky’s highlight of the Manchester arsenic-beer episode, we discuss herein additional case series of heart failure or cardiomyopathy in which arsenic has been implicated. In addition to the Manchester outbreak, heart failure had been reported in a smaller arsenic-beer episode in Halifax in 1902 (7), in a heavy drinker patient receiving weekly injections of arsenic for therapeutic use in 1946 (8), and in a French vintner poisoned by arsenic in 1968 (9). Cardiomegaly was also described in eight of 10 autopsies conducted among children and young adults exposed to arsenic in drinking water in Antofagasta, Chile (10). In Región Lagunera, Mexico, maleolar edema was common, in particular among subjects with cutaneous signs of arsenic poisoning (11, 12). In Antofagasta, Chile, and in Región Lagunera, Mexico, study participants were characterized by severe malnutrition in addition to high-chronic arsenic exposure in drinking water. Finally, in a small study in Rome, Italy, the concentration of arsenic in endomyocardial tissue obtained through cardiac catheterization biopsy was 213 times higher in 13 subjects with idiopathic dilated cardiomyopathy compared with 14 controls with normal left ventricle (13). The source of arsenic exposure was not identified, and arsenic accumulation was interpreted to be a consequence of cardiomyopathy progression (13). We could not identify any reference to the association of arsenic exposure with heart failure in populations chronically exposed to high arsenic in drinking water from Taiwan (14), China (15), or Argentina (16), populations that have been extensively studied for other health outcomes.

The mechanisms through which arsenic may induce heart failure or cardiomyopathy are unknown, and the role of malnutrition, alcohol exposure, or concomitant exposure to other toxicants in the episodes of arsenic-related cardiomyopathy described above is unclear. In a mouse model, arsenic trioxide induced cardiomyopathy, myocardial apoptosis, and functional changes in intraventricular pressure during ventricular contraction (17). Arsenic trioxide is currently used in the treatment of certain types of leukemia (18). Although we found reports of electrocardiographic abnormalities and arrhythmias in patients treated with arsenic trioxide (18–20), we could not identify reports of heart failure or cardiomyopathy in these patients.

Available case series provide detailed clinical and pathologic descriptions, but their ability to establish the role of arsenic in heart failure population-wide is very limited. These studies, however, indicate that heart failure and cardiomyopathy should be included as outcomes in epidemiologic and mechanistic studies of arsenic and cardiovascular disease.

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