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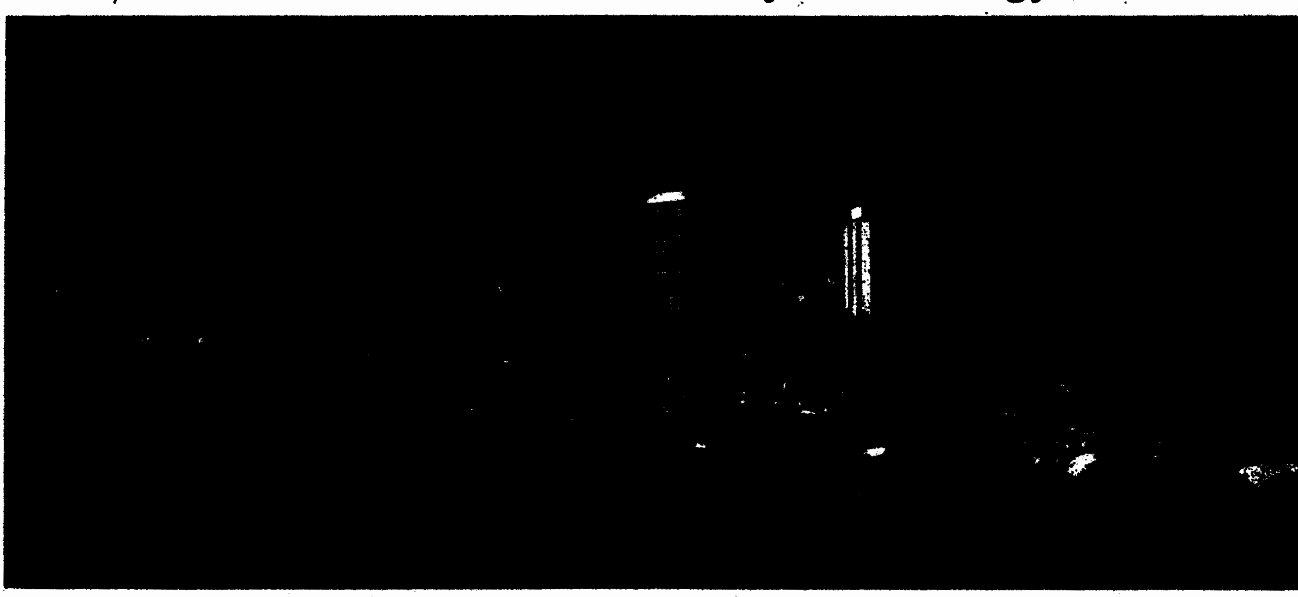

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Geological factors in the emergence of infectious disease

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ABSTRACT: GEOLOGICAL FACTORS IN THE EMERGENCE OF INFECTIOUS DISEASE

Many of the determinants of human morbidity from emerging infectious diseases can be construed—either directly or indirectly—as relating to environmental change. Little attention has been paid to the infections associated with *geological* processes, arguably because 'medical geology' has only recently become an established and legitimate field of study. This paper focuses specifically on infections, and their associated pathologies, directly or indirectly influenced by geological conditions. Specific diseases occur in relation to the nature of their geogenic 'driver' at three major levels of environmental change: that is, *local*, *regional* and *global*. The paper reviews the pathological mechanisms of pulmonary tuberculosis secondary to silicosis, and geological factors impacting on the transmission of coccidioidomycosis and Lyme disease. Further examples discussed include the close relationship between water-borne infections and geological processes and formations, and the disease potential from long-range dispersal of pathogens (such as in dust storms). We contend that the geosphere is an under-recognised factor affecting the emergence and pathological profiles of infectious diseases.

INTRODUCTION

The emergence and re-emergence of infectious diseases over the last couple of decades pose a significant public health problem and have triggered widespread concern among health professionals and communities. Globally, we confront a formidable range of actual and potential pathogenic threats, including mosquito-borne diseases, such as dengue and malaria, and ever-growing numbers of zoonotic organisms, such as those originating in primates (eg HIV; monkeypox), birds (eg West Nile virus; avian influenza) and rodents (eg hantaviruses and arenaviruses) (eg Gubler 2002; Mouchet, 1997).

Many of the determinants of human morbidity from these emerging diseases can be construed—either directly or indirectly—as relating to environmental change. Factors leading to emergence have been well described, and include ecosystem injury from urbanisation, bioinvasion, climate change, and changing patterns of travel and trade (Aron, 2001). A specific example is large-scale dam construction, which has been linked to numerous adverse effects, including epidemics of malaria, schistosomiasis, and other parasitic infections, such as onchocerciasis and trypanosomiasis (Parent, 1997).

Although pathogen emergence have been linked to numerous 'drivers' (ie any factors that change an aspect of an ecosystem), less attention has been paid to the infections associated with *geogenic* processes, arguably because 'medical geology' has only recently become an established and legitimate field of study (Mullick, 2002; Skinner, 2003; Selinus *et al.* in press). Since the formation of the Earth 4.5 billion years ago, geological environments have been changing constantly under the influence of natural physical processes such as volcanism, erosion, and geothermal or seismic events. Life, including microorganisms, evolved to adapt to such changing environments, and it is therefore not surprising to find infectious pathogens responding to natural or anthropogenic disturbances in novel and unexpected ways.

This paper focuses specifically on infections directly or indirectly influenced by geological conditions. We contend that the geosphere is an under-recognised factor affecting the relationship between changing environments and the emergence and re-emergence of infectious diseases. Using the comprehensive framework provided by the Millennium Ecosystem Assessment (2003), specific diseases are discussed in relation to the nature of their geogenic 'driver' at three major levels of environmental change: that is, *local*, *regional* and *global*.

1. LOCAL GEOLOGICAL FACTORS

Localized natural processes may facilitate geogenic infections, such as through geothermal processes. The use of thermal pools for bathing, particularly where immersion of the head occurs, is a well-established risk factor for often fatal form of primary amoebic meningitis (usually caused by *Naegleria fowleri*; Visvesvara, 1999). More commonly, however, disease transmission occurs with anthropogenic interventions. With the advent of agriculture millennia ago, and later mining, the first non-natural changes to geological environments took place. These anthropogenic disturbances were at first highly localized because of limited human technology, but have nevertheless been significant enough in some cases to lead to changes in infectious disease patterns.

Eisler (2003) has summarised the numerous health problems of gold miners who worked underground in many continents: Australia, North America, South America, and Africa. Infections formed a large component of the burden of disease, including increased frequency of pulmonary tuberculosis; increased frequency of insect-borne diseases, such as malaria and dengue fever; and increased prevalence of certain bacterial and viral diseases. In a number of situations, the infection is not specifically related to geogenic exposure: for example, HIV rates are elevated in miners but secondary to particular lifestyle factors. Epidemics often relate to the arrival of large numbers of non-immune workers, such as occurred with skin diseases such as yaws in Africa (Hackett, 1984) and with malaria and Ross River virus outbreaks during gas field development in Papua New Guinea (Hii, 1997).

However, mining activity can act to increase disease transmission. A recent study in the Burdwan district, West Bengal, examined the relative densities of a disease vector, *Culex quinquefasciatus*, infection rates, microfilariae-density and microfilaraemic persons in the colliery versus non-colliery areas (Adhikari, 1995). All these indicators were significantly higher in colliery areas, in turn accounting for an elevated prevalence of filariasis. Fungal infections such as sporotrichosis—a skin and lymphatic infection—which affected 3 000 miners in the Transvaal in the 1940s, has been traced to sources such as mine timbers, which served as a reservoir of the fungus (Quintal, 2000). However, other analyses indicate that mine soils may carry and transit a range of fungi, including sporotrichosis and others such as paracoccidioidomycosis, histoplasmosis and *Nattrassia mangiferae* (a cause of onychomycosis and superficial skin infections) (Rodrigues, 1996; Gugnani, 1989).

Pulmonary tuberculosis (TB) is one of the major diseases that have been linked to local anthropogenic geologic change. Some occupational groups, and arguably communities generally, are at increased risk of TB because of their exposure to silica (quartz) dusts. Silicotics have significantly increased standardised mortality rates from tuberculosis (TB) and silicotuberculosis (Goldsmith, 1995).

The possible mechanisms by which silicosis predisposes to immunologic impairment and tuberculosis are described in Ding (2002). Exposure has been shown to increase the risk of TB in a range of contexts, with risk estimates ranging from a doubling of risk of TB in South African Gold miners (Kleinschmidt, 1997) to a nine-fold risk among silicotic patients in Hong Kong (Chang, 2001). A recent paper reviewing the health of Indian miners also reported that pulmonary tuberculosis was an important complication, seen in up to 50% of patients of silicosis in some populations (Jindal, 2001). Patients with silicotuberculosis or other forms of infection often have significant expectoration, hemoptysis, fever, and rapid progression to respiratory failure. The infection risk may also be elevated in the absence of concurrent pulmonary pathology (ibid.). The risk remained elevated even after the exposure to silica dust has ceased, a finding that supports a call for longer-term health surveillance of local populations exposed to short-term geological hazards such as volcanic eruptions (Weinstein, 2002).

In some situations, water-borne infections have a close relationship to geological processes and formations. Unique conditions—such as subsurface geological formations—may therefore create unexpected risks in terms of pathogen transmission. Recent work has focused on relationships between microbial survival and hydrogeological parameters, including the fate and transport of microbes in groundwater/aquifer media. Microbial movement and viability is affected by flow velocity, aquifer grain size, porosity, solid organic carbon content, temperature, pH, and other chemical characteristics of water and mineral composition of the aquifers. A 1998 outbreak in Texas attributed to *Cryptosporidium* was associated with chlorinated wells located in limestone (Barwick, 2000). Because *Cryptosporidium* is resistant to many water disinfecting agents, the parasite must be physically removed by filtration. However, in the Texas outbreak, limestone and fractured bedrock failed to provide adequate natural filtration (Robertson, 1997).

In another localized outbreak, Norwalk virus gastroenteritis affected 900 people in an Arizona resort. The infection was traced back to a contaminated well, which remained contaminated even after prolonged pumping. It was eventually determined that effluent from the resort's sewage treatment facility was seeping through fractures in the subsurface rock—with minimal filtration—into the deep well used for water supplies (Lawson, 1991). The geological implications of such findings in securing effective sanitation and safe water supplies will clearly grow in importance with the advancing rate of human impingement on geological systems.

Geological compounds and infectious agents may even act as co-carcinogens. A possible interaction between asbestos and the SV(simian virus)-40 virus in the development of mesothelioma has been suggested in recent studies. Cristaudo (2002) argues that SV-40, which was probably transmitted by the inadvertent administration of contaminated poliovaccines to millions of people in Europe and the United States between 1955 and 1963, appears to be the best candidate as a cofactor with asbestos in the development of human mesothelioma.

2. REGIONAL GEOLOGICAL FACTORS

Many geological structures and processes may be considered at a regional scale, including predominant soil types, excesses or deficiencies of trace elements, and the predominance of a particular geological formation. As human populations have expanded and technology improved, anthropogenic changes to the geological environment have also expanded, many operating at a regional scale. All these factors, both natural and/or artificial, may in turn impact upon infectious disease patterns and susceptibilities in human populations.

Analysis of bacteria and fungi in sand- and dust-storms have identified a wide range of airborne pathogens, including *Aspergillus*, *Actinomyces*, *Pseudomonas*, and *Staphylococcus* species, suggesting that sandstorm dust is a prolific source of organisms linked to human illness (Kwaasi, 1998).

Among the best characterized of dust-associated infections result from the spores of the dimorphic fungus *Coccidioides immitis*, which grows in topsoil. In the past few decades, the incidence of coccidioidomycosis has shown a marked increase in semiarid regions of the Western Hemisphere, particularly California (Centers for Disease Control, 1994). Approximately 60% of infected persons are asymptomatic; the remainder can develop a spectrum of manifestations that range from mild to moderate influenza-like illness to pneumonia to disseminated disease, including meningitis.

Soil conditions are a major determinant of the distribution and abundance of this environmental hazard: soil nature, temperature and moisture content combine to permit an accumulation in the soil of viable spores. Where such conditions are prevalent, the disease is endemic (and enzootic), and outbreaks among non-immune, non-resident people entering such an area are common. It is also well-established that cases are common after dust storms (Pappagianis, 1978; Flynn, 1979; Williams 1979). More recently, an association with earthquakes has been identified, in which masses of spore-laden dust become airborne with seismic shock waves. Schneider (1997) reported a 1994 outbreak of 203 coccidioidomycosis cases (including 3 fatalities), peaking 2 weeks after an earthquake in California. The majority of cases (56%) and the highest attack rates (114 per 100 000 population) occurred in the town of Simi Valley. Environmental data indicated that large dust clouds, generated by landslides following the earthquake and strong aftershocks in the Santa Susana Mountains north of Simi Valley, were dispersed into nearby valleys by northeast winds. A case-control study in the community indicated that physically being in a dust cloud (odds ratio, 3.0; 95% CI, 1.6-5.4; $P<0.001$) and time spent in a dust cloud ($P<0.001$) significantly increased the risk for being diagnosed with acute coccidioidomycosis.

Geological attributes may also act indirectly on infectious disease transmission, such as through the effect of soil types and mineral constituents on distributions of disease vectors and reservoirs. An example is the association between soils and the distribution of the black-legged tick, *Ixodes scapularis*, the vector of Lyme disease, human granulocytic ehrlichiosis, babesiosis, and other pathogens (Bunnell, 2003). Environmental data and geographic information system (GIS) modelling in Wisconsin and Illinois indicated that soil type and land cover are very important determinants of clustering of ticks in the environment, even when the host population is adequate (Guerra, 2002). With regard to soil cover, tick presence was positively associated with alfisol-type soils of sandy or loam-sand textures overlying sedimentary rock, while absence was associated with acidic soils of low fertility and a clay soil texture, and Precambrian bedrock. Similar relationships between soil qualities and the disease vector *Ixodes ricinus* were found in Scandinavia (Jensen, 2000).

In some circumstances, levels of heavy metals, and the toxic reactions they produce in the human body, may increase likelihood of pathogen transmission. For example, there is some evidence of an interrelationship between arsenic and hepatitis B infection. In Taiwanese villages in which chronic arsenosis is hyperendemic, hepatitis B surface antigen chronic carrier status with liver dysfunction appears to have significant role in the development of arsenic-induced skin cancer (Hsueh, 1995). Despite its use as an antimicrobial in the era before antibiotics, arsenic may also have the capacity to raise the risk of infection given its association with the development of diabetes mellitus, extensive skin changes (e.g. keratoses) and peripheral vascular disease (Taeng, 1996). However, these pathways remain relatively speculative and have yet to be confirmed in large scale studies.

3. GLOBAL GEOLOGICAL FACTORS

In the last few decades, there has been a growing awareness that some environmental changes occur on a scale that affects global ecologies: atmospheric, hydrogeological, and food production systems worldwide have been transformed in ways that sometimes leads to the emergence of human infectious disease.

By the processes of deforestation and water abstraction for irrigation, areas with moist rich soils can be changed into dry, dusty plains subject to severe wind erosion. In its extreme form, this process is referred to as desertification, and can result in vast areas (eg much of northern Africa and China) that act as sources for globally dispersed dusts. Anthropogenic influences (such as from farming and irrigation) have contributed to dust formation by enhancing the process of desertification, with losses of over 10 million hectares (~29 million acres) of farmland per year (Griffin, 2001). Estimates suggest that annual volumes of over 1 billion tons are transported from the main African deserts alone (Moulin, 2001).

The respiratory impact of North African dust on Caribbean and South American ecosystems is well established, as is the morbidity associated with atmospherically dispersed dust in High Asia (Derbyshire 2003). Surprisingly, the microbiology and infectious disease risk associate with massive atmospheric soil and dust transportation has not been studied in any detail. This paucity of research is surprising given the potential risks of long-range microbial dispersal. As Griffin (2001) notes, if storm-blown African locusts can survive transoceanic transport and arriving in the Caribbean, 'then so can the much more versatile, tolerant and adaptive microbes'.

This warning is substantiated both by laboratory findings (which indicate a tenfold increase in normal microbial fall-out during dust events) and by recent outbreaks of foot and mouth disease in stock (thought to be spread internationally by airborne viruses; Donaldson, 2002). Although no outbreaks of human disease have yet been attributed to the intercontinental airborne transportation of pathogens, this is perhaps only a matter of time: globally, desertification continues to alter the geological environments that will make such infectious disease outbreaks a realistic possibility.

5. CONCLUSION

In this paper we have highlighted how changes to the geosphere can impact on human disease burdens, looking specifically at infectious diseases. These processes may occur in conjunction with infection-promoting disruptions in the hydrosphere (cf. the emergence of waterborne cryptosporidiosis), the atmosphere (cf. climate change and the re-emergence of vectorborne disease), and biosphere (cf commerce and travel -related dispersal of pests and pathogens) (Sutherst, 2004).

This pattern of emerging infectious diseases associated with ecosystem disruptions is referred to as the 'third epidemiological transition'. The first epidemiological transition occurred with the advent of agriculture and cities, and its accompanying change in disease burden from famine to contagious (crowd) disease; the second with the industrialisation and the advent of the cardiovascular diseases and cancers of affluence; and the third, underway at present, with the disruption of global ecosystems (McMichael, 1993). As Mouchet (1997) notes, the need for and almost aggressive utilisation of new areas and resources may have serious epidemiological consequences.

The geogenic processes described above clearly form a major component in understanding this third disease transition. As Sutherst (2004) notes, to understand the dynamics of infectious disease we must account for factors impacting on ecosystems, including geological processes, ranging from local disturbances—such as mining—to changes playing out on a global scale. The natural time-scale of geospheric events may also be distrupted by humans: unlike more gradual geological processes, anthropogenic interventions often cause dramatic changes in much shorter time frames, often within the period of a single human generation.

In summary, the process of adapting to and remediating the health effects from ecosystem disruption requires an intimate understanding of the relationship between human health and ecological health. Geological environments are integral to most of Earth's ecosystems, and should be considered explicitly in our understanding and evaluations of how environmental processes impact on health. In this review, we hope that we have reinforced the need for research in medical geology in order, ultimately, to decrease global disease burdens.

REFERENCES

Adhikari P, Haldar JP. Prevalence of bancroftian filariasis in Burdwan district, West Bengal: II. Vector and microfilariae density in colliery and non-colliery areas. *Journal of Communicable Diseases* 1995; 27 (3):181-5.

Aron JL, Patz J. *Ecosystem Change and Public Health: a Global Perspective*. John Hopkins University Press, Baltimore, 2001.

Barwick, RS; Levy, DA; Craun GF *et al.* Surveillance for Waterborne-Disease Outbreaks: United States, 1997—1998. *MMWR* 2000; 49 (SS04):1-35.

Bunnell JE, Price SD, Das A. *et al.* Geographic information systems and spatial analysis of adult Ixodes scapularis (Acari: Ixodidae) in the Middle Atlantic region of the U.S.A. *Journal of Medical Entomology* 2003; 40 (4):570-6.

Centers for Disease Control and Prevention. Coccidioidomycosis following the Northridge earthquake—California, 1994. *JAMA* 1994; 271 (22):1735.

Chang KC, Leung CC, Tam CM. Tuberculosis risk factors in a silicotic cohort in Hong Kong. *International Journal of Tuberculosis & Lung Disease* 2001; 5 (2):177-84.

Cristaudo A, Foddis R, Bigdeli L *et al.* SV40: a possible co-carcinogen of asbestos in the pathogenesis of mesothelioma? *Medicina del Lavoro* 2002; 93 (6):499-506.

Derbyshire, E. 'Natural dust and pneumoconiosis in High Asia.' In: Skinner, H.C.W. and Berger, A.R. (eds.) *Geology and Health: closing the gap*, Oxford University Press, New York 2003.

Ding M, Chen F, Shi X *et al.* Diseases caused by silica: mechanisms of injury and disease development. *International Immunopharmacology* 2002; 2 (2-3):173-82.

Eisler R. Health risks of gold miners: a synoptic review. *Environmental Geochemistry & Health* 2003; 25 (3):325-45.

Finkelman RB, Belkin HE, Zheng B. Health impacts of domestic coal use in China. *Proc Nat Acad Sci;* 1999; 96: 3427-3431.

Flynn NM, Hoeprich PD, Kawachi MM, *et al.* An unusual outbreak of windborne coccidioidomycosis. *N Engl J Med* 1979; 301;358-361.

Goldsmith, DF; Beaumont, JJ; Morrin LA, Schenker, MB. Respiratory cancer and other chronic disease mortality among silicotics in California. *American Journal of Industrial Medicine* 1995; 28 (4): 459-467.

Griffin DW, Kellogg CA, Shinn EA. Dust in the wind: Long range transport of dust in the atmosphere and its implications for global public and ecosystem health. *Global Change & Human Health* 2001; 2: 20-33.

Gubler DJ. The global emergence/resurgence of arboviral diseases as public health problems. *Archives of Medical Research* 2002; 33: 330-342.

Guerra MA, Walker E, Jones C *et al.* Predicting the Risk of Lyme Disease: Habitat Suitability for *Ixodes scapularis* in the North Central United States. *Emerging Infectious Diseases*, 2002; 8: 289-297.

Gugnani HC, Oyeka CA. Foot infections due to Hendersonula toruloidea and Scytalidium hyalinum in coal miners. *Journal of Medical & Veterinary Mycology* 1989; 27 (3):167-79.

Hackett CJ. On the epidemiology of yaws in African miners (1942). *Transactions of the Royal Society of Tropical Medicine & Hygiene* 1984; 78 (4):536-8.

Jensen PM, Hansen H, Frandsen F. Spatial risk assessment for Lyme borreliosis in Denmark. *Scandinavian Journal of Infectious Diseases* 2000; 32 (5):545-50.

Jindal SK, Aggarwal AN, Gupta D. Dust-induced interstitial lung disease in the tropics.*Current Opinion in Pulmonary Medicine* 2001; 7 (5):272-7.

Guerra M, Walker E, Jones C. *et al.* Predicting the risk of Lyme disease: habitat suitability for Ixodes scapularis in the north central United States. *Emerging Infectious Diseases* 2002; 8 (3):289-97

Hill J, Dyke T, Dagoro H, Sanders RC. Health impact assessments of malaria and Ross River virus infection in the Southern Highlands Province of Papua New Guinea. *Papua New Guinea Medical Journal* 1997; 40 (1):14-25

Hsueh YM, Cheng, GS, Wu MM *et al.* Multiple risk factors associated with arsenic-induced skin cancer: Effects of chronic liver disease and malnutritional status. *British Journal of Cancer* 1995; 71 (1): 109-114.
Kleinschmidt I Churchyard G. Variation in incidences of tuberculosis in subgroups of South African gold miners. *Occupational & Environmental Medicine* 1997; 54 (9):636-41.
Kwaasi AA, Parhar RS, al-Mohanna FA, *et al.* Aeroallergens and viable microbes in sandstorm dust. Potential triggers of allergic and nonallergic respiratory ailments. *Allergy* 1998; 53 (3):255-65
Lawson HW, Braun MM, Glass RI. *et al.* Waterborne outbreak of Norwalk virus gastroenteritis at a southwest US resort: role of geological formations in contamination of well water. *Lancet* 1991; 337 (8751):1200-4.
McMichael AJ. *Planetary Overload: Global Environmental Change and The Health of the Human Species.* Cambridge University Press, Cambridge, U.K, 1993.
Millennium Ecosystem Assessment. Ecosystems *and human well-being : a framework for assessment.* World Resources Institute 2003, Washington.
Mouchet J, Carnevale P. Impact of changes in the environment on vector-transmitted diseases. *Sante* 1997; 7 (4):263-9.
Moulin C, Lambert CE, Dulac F, Dayan U. Control of atmospheric export of dust from North Africa by the North Atlantic Oscillation. *Nature* 1997; 387:691-694.
Mullick T, Eto K. Medical geology: an emerging specialty. (Symposium 19: Environmental pathology) Histopathology 2002; 41 (S2): 320-340.
Pappagianis D, Einstein H. Tempest from Tehachapi takes toll or Coccidioides conveyed aloft and afar. West J Med 1978;129:527-530.
Parent G, Ouedraogo A, Zagre NM, *et al.* Large dams, health and nutrition in Africa: beyond the controversy. Sante 1997; 7 (6):417-22.
Robertson JB, Edberg SC. Natural protection of spring and well drinking water against surface microbial contamination. I. Hydrogeological parameters. Critical Reviews in Microbiology 1997; 23 (2):143-78.
Rodrigues MT, de Resende MA. Epidemiologic skin test survey of sensitivity to paracoccidioidin, histoplasmin and sporotrichin among gold mine workers of Morro Velho Mining, Brazil. Mycopathologia 1996; 135 (2):89-98.
Quintal D.Sporotrichosis infection on mines of the Witwatersrand. Journal of Cutaneous Medicine & Surgery 2000; 4 (1):51-4.
Schneider E, Hajjeh RA, Spiegel RA *et al.* A coccidioidomycosis outbreak following the Northridge, Calif, earthquake. JAMA 1997; 277 (11):904-8.
Selinus O (Ed); Medical Geology, Academic Press, UK, 2004.
Skinner, HCW, Berger, AR (eds) Geology and Health: closing the gap, Oxford University Press, New York, 2003.
Sutherst RW.Global change and human vulnerability to vector-borne diseases. Clinical Microbiology Reviews 2004; 17 (1):136-73.
Tseng CH, Chong CK, Chen CJ, Tai TY. Dose response relationship between peripheral vascular disease and ingested inorganic arsenic among residents in blackfoot disease endemic villages in Taiwan. Atherosclerosis 1996; 120: 125-33.
Visvesvara GS, Martinez AJ. *Protozoa: free-living amebae.* In: Infectious Diseases, Vol. 2. D Armstrong and S Cohen (eds). London: Mosby, 1999.
Williams PL, Sable DL, Mendez P, Smyth LT. Symptomatic coccidioidomycosis following a severe natural dust storm. An outbreak at the Naval Air Station, Lemoore, Calif. *Chest* 1979; 76 (5):566-70.

Long-term arsenic expoeure and ischemic heart disease

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ABSTRACT

Human beings can be exposed to arsenic from a variety of environmental and occupational sources. Arsenic is atherogenic and has been suggested to be the most possible cause of an endemic peripheral arterial disease known as 'blackfoot disease (BFD)' along the southwestern coast of Taiwan. According to an early epidemiologic study, patients with BFD suffered from a high mortality rate (4.84 per 100 patient-years) and the causes of death were mostly attributed to cardiovascular diseases (44%). Later epidemiologic studies carried out in the BFD villages demonstrated that the excess mortality of cardiovascular diseases was associated with the arsenic content in the well water. The relative risks for mortality from ischemic heart disease (IHD) were 1.0, 2.5, 4.0 and 6.5, respectively, for those with cumulative arsenic exposure (CAE) of 0, 0.1-9.9, 10.0-19.9 and = 20.0 mg/l-years. A recent study evaluating the association between arsenic exposure and IHD in the residents of the BFD villages clearly showed that IHD was associated with CAE in a dose-response pattern. For those with CAE of 0, 0.1-14.9 and ≥15 mg/l-years, the prevalence rates of IHD were 5.2%, 10.9% and 24.1%, respectively ($p < 0.001$); and the adjusted odds ratios (95% confidence intervals) were 1.00, 1.60 (0.48–5.34), and 3.60 (1.11–11.65), respectively. In conclusions, long-term arsenic exposure as demonstrated from epidemiologic studies in Taiwan is associated with increased risk of IHD and cardiovascular mortality. The mechanism of arsenic-induced atherosclerosis requires further investigation.

INTRODUCTION

An extensive pathologic study done in early 1960s demonstrated that 30% of the BFD patients had histologic lesions compatible with thromboangiitis obliterans and 70% showed changes of arteriosclerosis obliterans (Yeh and How, 1963). Since atherosclerosis is a systemic disease, which might not only involve the lower extremities, it is rationale to look into the problem of IHD, which represents atherosclerotic involvement of the coronary arteries. In this paper, the author briefly reviewed the association between arsenic exposure and IHD from epidemiologic studies carried out in Taiwan.

ARSENIC EXPOSURE AND CARDIOVASCULAR MORTALITY

The annual death rate of BFD patients was relatively high and has been estimated to be 4.84 per 100 patient-years after