Editorial

A Planetary Health Perspective for Kidney Disease

Stenvinkel P[1], Shiels PG[2], Painer J[3], Miranda JJ[4], Natterson-Horowitz B[5], Johnson RJ[6]

[1]Division of Renal Medicine, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Campus Flemingsberg, Stockholm, Sweden

[2]Wolfson Wohl Cancer Research Centre, Institute of Cancer Sciences, University of Glasgow, United Kingdom

[3]Research Institute of Wildlife Ecology, Department of Integrative Biology and Evolution at the University of Veterinary Medicine, Savoyenstreet 1, 1160 Vienna, Austria

[4] CRONICAS Centre of Excellence in Chronic Diseases, Universidad Peruana Cayetano Heredia, Lima, Peru

[5]Harvard University, Department of Human Evolutionary Biology, UCLA Division of Cardiology, Co-Director, Evolutionary Medicine Program at UCLA, California, USA

[6]Division of Renal Diseases, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA

Corresponding author:

Peter Stenvinkel, Prof

Dept of Renal Medicine M99

Karolinska University Hospital

141 86 Stockholm

Sweden

Peter.stenvinkel@ki.se

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Planet earth has been witness to at least five major mass extinctions (Ordovican, Denovian, Permian, Triassic-Jurassic and Cretaceous-tertiary) over the last 450 million years. Depressing evidence suggest that *Homo sapiens* (i.e." wise man") is responsible for the ongoing 6th major mass extinction, which has led to a multitude of urgent external environmental problems, such as global warming, deforestation, habitat loss, pollution and shortage of clean water. Global temperatures have risen 1°C since 1880 and continue to increase at an accelerated rate. Global temperature rise is currently responsible for extreme wheather conditions, such as heat waves, hurricanes, mega wild fires and droughts. The rapidity of temperature change has challenged our ability to adapt and respond, but international efforts are ongoing to reduce CO_2 emissions and slow this ever looming threat.

The kidney, more than any other organ, has a critical role in protecting the body from rising temperatures, through its ability to control water and electrolyte balance. Nephrologists should take a special interest in the effects of global warming on health and its potential to cause acute and chronic kidney injury, severe dehydration, and electrolyte disturbances. Special interest should be given to those with impaired kidney function who may have particular difficulty adapting to rapidly changing environmental conditions, a trait that could be more common or with worse outcomes among populations whose organ's capacity have not reached their full development potentials, mainly in low- and middle-income settings (1). This alone may include up to 10-15 % of the world population, with vulnerable groups including the aged and the 3.4 million people in the world who are on dialysis. It can estimated that with about 3 million hemodialysis patients on the planet, >230 billion liters of clean water are used and 1.3 billion tons of mostly plastic waste are generated every year. Thus, dialysis services and industry must urgently start efforts to advance sustainable kidney-treatment technologies that minimize water usage and generation of waste (2).

Climate change is also expected to have negative effects on the current epidemic of 'burden of lifestyle diseases', which comprise a diseasome of ageing, such as chronic kidney disease (CKD), type-2 diabetes, obesity, fatty liver disease, cardiovascular disease, cancer, depression, osteoporosis and Alzheimer's disease, with some of these conditions initiating at a younger chronological age during an individual's lifetime. It is likely that the current high incidence of 'burden of lifestyle diseases' represent a by-product of past genetic and functional adaptions to various climatic, dietary and pathogen selection pressures (3). Increasing heat may have multiple effects, including stimulating sedentary behaviour, driving intake of sugary beverages, and potentially by direct effects on inflammatory and oxidative pathways that facilitate development and progression of the diseasome of ageing, including the impairment of mitochondrial function and integrity, central to metabolic and kidney disease. As the uremic phenotype is characterized by persistent inflammation, tissue hypoxia and decreased mitochondrial biogenesis with oxidative stress, it is not surprising that impaired kidney function (i.e internal environmental problem) is a major risk factor and component of 'burden of lifestyle diseases' (4).

Epidemics of CKD are emerging in various regions of the world where the common denominator appears to be working under extreme heat conditions. While toxins may play a role in these outbreaks (5), the evidence that recurrent heat stress is playing a role is substantial (6). The stress on the local populations, both in terms of

availability for health care and resources, such as safe drinking water, adequate nutrition and exposure to novel pathogens, could be extreme. Furthermore, the effects of climate change may have dire effects on many regions of the world, and the lack of clean water, extreme weather conditions, such as hurricanes and increasing sea levels due to melting of glaciers in polar regions, may lead to massive migration of "environmental refugees", with subsequent increased risk of conflicts and epidemics, adding more pressing challenges for the global nephrology community. We have already seen that increases in intense weather events, such as hurricanes, owing to climate change have damaging effect on the provision of care to dialysis patients (7)

The effects of global warming, water shortage (6) and air pollution (8) on the risk of CKD is already evident. In 2015, the United Nations adopted an agenda for sustainable development that includes 17 sustainable development goals (SDGs) as the blueprint to transform our world into a better place by 2030 (**Figure 1**). The 17 SDGs are integrated, that is, they recognize that action in one area will affect outcomes in others. Thus, in order to accomplish these Goals, the expertize of the Renal Community should be used, not only for SDG #3 (Good Health and Well-being) but also across others, such as SDG #6 (Clean Water and Sanitation) and SDG #13 (Climate Action).

We advocate investigation of novel solutions to the challenges humans face via a study of nature's solutions. The broad diversity in biology contained within circa 8.7 million species that currently inhabit the planet is one of the most conspicuous aspects of life on earth. Indeed, since the time that animal life emerged on our planet about 650 million years ago, animals have survived (or not) based on whether their adaptations to the enviroment and environmental changes have been beneficial or not. Failure to evolve adaptations which aid survival has lead to species extinction. Unfortunately, nature has been framed inappropriately by humans, with overexploitation and destruction of ecosystems and animal habitats. It will take million of years for the planet to recuperate from the loss of mammal diversity that occur during the present-day biodiversity crisis (9). Instead of exploiting and consequently devastating natural environmental balance, the "wise man" should learn from ingenious natural solutions that have evolved over time and mimic them (i.e. biomimetics).

Innovation-based solutions found in nature have proven successful in a wide variety of fields, but medical science has been lagging behind on recognizing and uptaking such clues (10). As a biomimetic approach builds on evolution through natural selection for ideal solutions to conquer diseases and survival in extreme environments, it may be more cost effective and efficient than the current pharma drug discovery approach to tackle human health problems. Such an approach can complement current biological approaches that largely focuses on research in laboratory mice and rats. Indeed, it should be emphasized that nature is never careless and never cheats in its evolutionary "experiments".

There are many examples where we can learn from nature about mechanisms to escape one or several burden of lifestyle diseases that have bedeviled humans (4). For example, hibernating bears, despite months of anuria and decreased renal function during winter sleep, do not develop osteoporosis, inflammation, muscle wasting

and atherosclerosis (11). Hibernating bears also provide a reversible natural model of healthy obesity with favorable seasonal changes of insulin resistance (11). Another example is the giraffe, which is protected from kidney disease and stroke despite alarmingly high blood pressures (10). The superior longevity and resistance against cancer and vascular ageing in naked mole rats (exposed to chronic hypoxia in underground burrows) have immediate implications for several burden of life style diseases, including CKD (10). The links between fat mass accumulation and hydration status in species exposed to shortage of fresh water, such as camels and blue whales, provide clues of the existence of a survival pathway involving fructose metabolism that may have gone awry in modern society, due to a sedentary life style and over-consumption of calorie-dense nutrients (12). Other animals have evolved unique mechanisms for organ regeneration (such as sharks, lizards and spiders), rapid organ growth (Python snakes), rapid wound healing (non-human primates), cancer protection (elephants and naked mole rats), protection against the toxic effects of chronic alcohol consumption (Malaysian pen-tailed tree shrew), blood glucose control (Gila monster), protection against bacterial pathogen resistance (cockroaches), UV-ray protection (hippopotamus) and protection against renal hypoxia (Harbour seals) that could inspire us to find novel solutions for human diseases (11). To this date, the best example of a successful biomimetic application In Nephrology is the development of captopril (a biomimetic of a bradykinin-potentiating peptide) from the poisonous Brazilian viper (*Bothrops jararaca),* whose effects on blood pressure mechanisms mimick those of the snake's venom. Although venom from snakes is a natural pharmacopeia, <0.01% of the planets snake venom toxins have yet been identified and characterized (13).

The maladaptation of other species to the environment may also provide insights. For example, the susceptibility of CKD among felids provide valuable information on risk factors for deteriorating kidney health related to nutritional habits (intake of red meat) and dehydration (11). Some studies, based on this approach to look cross species, have led to insights into key underlying mechanisms of protection or injury. For example, at the basis of many of these diseases is the importance of mitochondrial integrity, and evidence suggests that loss of the cytoprotective Nuclear factor erythroid 2-related factor 2 (Nrf2) may represent a common pathway for many metabolic diseases, suggesting potential targets for therapy (4). Studies from the animal kingdom suggest that Nrf2 plays a role in protection against heat stress and dehydration (14), as well as air pollution mediated disease (15). Critically, the beneficial effects of Nrf2 agonism can be modulated by natural food stuffs (e.g. sulforophane, fisetin, quercetin, curcumin) offering a route to evidence based non-pharmacological interventions to improve health (4). It is ironic that as the evidence base rapidly grows for nutritional interventions in medicine using "*food as medicine*", global warming, pollution and environment loss threaten its development. Moreover, since about 35% of the medicines we use today have originated from nature, the development of future drugs is dependent on the preservation of nature. Thus, since Brazil presents the largest biodiversity in the world (> 50,000 species of higher plants) deforestation of Amazonas should be prevented also for health reasons.

The "*One Health*" approach (i.e. designing and implementing programmes, policies, legislation and research to achieve better outcomes in public health) has attracted recent interest. However, it has mainly focused on the understanding of disease transmission between humans and animals and food safety and has not addressed the

possibility to use biological biomimetics to find novel treatment strategies for burden of life style diseases. We therefore propose a "*Planetary health*" approach (i.e. the health of human civilisation is dependent on the state of the natural systems) that includes the focus on burden of lifestyle diseases in relation to animal and environmental health, and thus ensure the wellbeing of the whole planet (**Figure 2**). The "*Planetary Health*" approach could also be used for comparative studies of health in different human populations (i.e. developed vs underdeveloped regions, regions exposed to heat stress, water shortage and starving vs affluent regions) and relate this to studies on how different animals cope with heat stress, water shortage, pollution, prolonged periods of fasting, etc. Detailed studies of survival mechanisms in wild animals to identify insights for human diseases and impact of environmental cues requires multidiscipline collaboration including medical doctors, veterinarians, zoologists, climate researchers, ecologists, biologists, anthropologists and social scientists (11). A "*Biomimetic alliance for better health*" with collaborative research between different disciplines could contribute not only to better health and lower prevalence of burden of lifestyle diseases, such as CKD, but also a better and more sustainable environment. In so doing, this also supports the notion of a better "*Planetary Health*". The benefit of such an approach will be substantial.

Conflicts of interest: Peter Stenvinkel serves on a Scientific Advisory Board for REATA. Richard Johnson has equity in XORTX Therapeutics and Colorado Research Partners, LLC. Paul Shiels has equity options in Pathfinder Cell Therapy, is in receipt of research awards form 4D Pharma and Constant Pharma.

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Legend to Figure 1: The 2030 Agenda for Sustainable Development, adopted by all United Nations Member States in 2015, provides a shared blueprint for peace and prosperity for people and the planet, now and into the future. Sustainable Development Goal #3 commits the planet to reduce premature mortality due to burden of life style diseases by one-third.

Legend to Figure 2: Burden of life style diseases associated with inflammation, tissue hypoxia, mitochondrial dysfunction and oxidative stress are intimately linked to the health of animals and the environment. **A** Contained within adaptations that evolved in certain species during evolution to survive extreme environments, such as long cold winters, water shortage and hypoxic environments are survival strategies that could provide clues for human health. **B** Lack of clean water, pollution and heat stress cause human disease, i.e. climate medicine. **C** Lack of clean water, pollution and heat stress cause loss of animal and plant habitat. Habitat loss, illegal trade, natural selection and evolution affect animal health in both ways. Animals that have occupied niches and developed mechanisms to protect themselves against environmental cues such as lack of water, infections, oxygen deprivation and heat stress could provide valuable clues for protection from environmental changes.