mortality between facilities, and could also facilitate comparisons for other outcomes, including hospitalizations and costs. In the current environment of exceedingly high costs of ESRD care and nationwide efforts to control costs and maximize quality and outcomes in patients with chronic diseases, there is likely to be increasing interest in comparing facilities and even individual physicians on the basis of costs, quality, and outcomes of maintenance dialysis treatment. Accurate accounting for patient comorbidity—using tools such as the index developed by Liu *et al.*[7]—will be an essential component of these efforts.

DISCLOSURE
The author declared no competing interests.

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Hydrogen: another gas with therapeutic potential

James F. George[1,2] and Anupam Agarwal[2,3]

Cardinal and colleagues describe the use of molecular hydrogen, the most abundant molecule in the universe, as a treatment for chronic allograft nephropathy (CAN) in a rat model of kidney transplantation. They demonstrate that the addition of hydrogen to the drinking water results in a decrease in the severity of CAN and increased graft survival, and they provide evidence that the mechanism of action could be due to a reduction in reactive oxygen species.

Kidney International (2010) **77,** 85–87. doi:10.1038/ki.2009.432

The list of therapeutic gases continues to grow. Previous studies have reported on the beneficial effects of gases such as nitric oxide (NO), carbon monoxide (CO), and, more recently, hydrogen sulfide (H_2S) in animal models of many diseases.[1–3] Inhaled NO is already in clinical use for the treatment of hypoxic respiratory failure and pulmonary hypertension, particularly in neonates, and additional uses of NO are being investigated in other settings of lung and cardiac diseases.[4] Convincing preclinical data have prompted the initiation of clinical trials involving the use of inhaled CO for delayed graft function in kidney transplant recipients and H_2S (using sodium sulfide) in patients undergoing coronary artery bypass surgery and in patients with impaired renal function (http://www.clinicaltrials.gov). Cardinal and colleagues[5] (this issue) now describe the use of yet another promising gaseous molecule, hydrogen (H_2), as a treatment for chronic allograft nephropathy (CAN) in a rat model of kidney transplantation. They nicely demonstrate that rat kidney allograft recipients fed water containing dissolved H_2 exhibited better graft survival, reduced incidence of CAN, lower levels of reactive oxygen species (ROS), and reduced activation of proinflammatory secretory and signaling pathways. CAN (also called interstitial fibrosis and tubular atrophy of unknown etiology (IF/TA)) remains one of the most vexing clinical entities for the renal transplant physician because it is remarkably recalcitrant to current treatment modalities and is a major cause of long-term graft loss.[6] Therefore, potential new approaches to the treatment of CAN such as the one described by Cardinal and colleagues[5] are of great interest.

Hydrogen is the first element in the periodic table and constitutes at least 90% of the observable universe.

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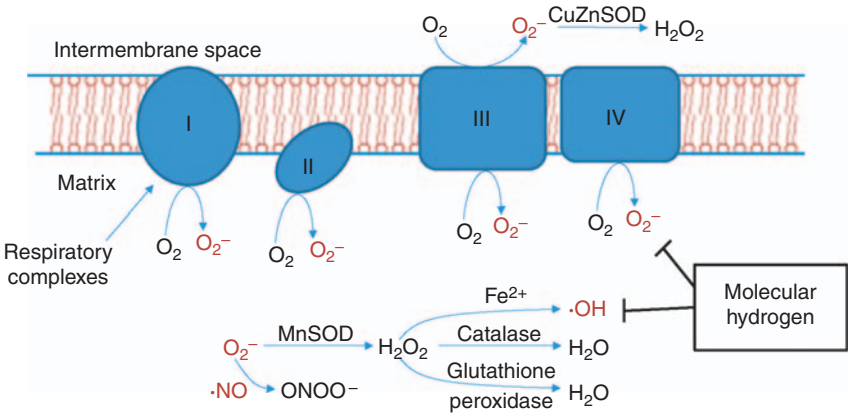

Figure 1 | A schematic of reactive oxygen species generation in the mitochondria. Oxygen radicals are colored red. The potential sites for the neutralizing antioxidant effects of molecular hydrogen are shown. SOD-super oxide dismutase.

Robert Boyle (1671) was the first to produce hydrogen when he dissolved iron in diluted hydrochloric acid. This observation occurred long before it was actually discovered as a distinct gas in 1766 by Henry Cavendish, who originally called it 'inflammable air'; it was later named hydrogen (Greek *hydro*, 'water,' and *genes*, 'forming') by Lavoisier, the father of modern chemistry. On earth, free hydrogen is comparatively rare. The majority of hydrogen found on earth is in water and organic compounds. It is highly reactive in the presence of specific catalysts and/or heat. One of the more spectacular examples of its reactivity was shown in 1937 when the zeppelin *Hindenburg*, using hydrogen for lift, ignited and was destroyed in less than a minute in the ensuing conflagration. Therefore, the use of hydrogen as a therapeutic agent is not intuitively obvious. However, recent data have shown that hydrogen can behave as an antioxidant in biological systems because of its ability to reduce ROS.[7] ROS or free radicals, such as the superoxide anion (O_2^-), are generated through the leak of electrons to molecular oxygen in the mitochondria during the production of adenosine triphosphate by oxidative phosphorylation (Figure 1). In the normal state, mitochondria generate 2–3 nmol of superoxide anion per minute per milligram of protein,[8] resulting in the generation of the superoxide radical, hydrogen peroxide, and the highly toxic hydroxyl radical. These ROS can be safely reduced to water by superoxide dismutase, catalase, and glutathione peroxidase (Figure 1). During ischemia–reperfusion injury, which inevitably occurs during organ transplantation, the balance between the generation of ROS and the mechanisms to detoxify them can be upset, resulting in the accumulation of ROS in the tissues, where they quickly react with lipids, proteins, and nucleic acids, causing disordered cellular functions.

The paper by Cardinal and colleagues[5] is based on the premise that oxidative stress, resulting from ischemia–reperfusion, is a common pathway of injury in the setting of transplantation and is therefore a significant contributor to the development of CAN. These findings are an extension of the elegant work of Ohsawa and colleagues, who were the first to demonstrate that inhalation of hydrogen gas was an effective antioxidant strategy in cultured neuronal cells and in a model of ischemia–reperfusion in the brain *in vivo*.[7] These authors also showed that hydrogen gas was capable of rapidly diffusing through membrane compartments, gaining ready access to the cytosol, mitochondria, and nucleus and reducing hydroxyl radicals (·OH; the strongest of oxidant species in living cells) but did not appear to compromise essential homeostatic mechanisms dependent on ROS.[7] Cardinal and colleagues[5] show that the administration of water containing dissolved hydrogen results in (1) a sustained increase in the levels of hydrogen in the kidney and serum, without any accumulation over time; (2) improved kidney allograft function over a 60-day follow-up period; (3) a decrease in several markers of inflammation, including graft-infiltrating cells, proinflammatory cytokines, and mitogen-activated protein kinase activation; and (4) decreased levels of lipid peroxides and peroxynitrite in the tissues.

A variety of other gases, such as NO, CO, and H_2S, are considered poisonous in large amounts but, in smaller concentrations, have antioxidant properties or are involved in physiological functions. Given previous data, the interpretation that the beneficial effects of H_2 in a kidney transplant model are a result of antioxidant properties of the element is reasonable and likely. However, this may not be the sole explanation, and other as-yet undefined mechanisms may be involved. The presence of basal levels of H_2 indicates one or more endogenous sources, suggesting that it plays a physiological role. Precedent for this possibility can be easily found in other gas-generating systems. CO, which is endogenously generated during the degradation of heme by the heme oxygenase enzyme system,[9] was previously thought of exclusively as a toxic gas. It is now understood that CO, which also has beneficial effects in inflammation and oxidative stress, plays a physiological role and participates in several signaling pathways known to modulate inflammation.[2] In fact, several clinical trials using inhaled CO are ongoing, including one in kidney transplant recipients. NO has attracted the most attention because of its involvement in cardiovascular biology, blood pressure regulation, and kidney and vascular function. NO is generated from arginine by nitric oxide synthases and has a number of molecular targets, including guanylate cyclase (which CO also targets) and phosphodiesterases.[1] Therefore, given the increasing number of systems in which H_2 is being shown to mediate beneficial effects, and likely, in the future, deleterious ones as well, it is probable that involvement of H_2 in signaling pathways or other physiological functions will be found. The molecular gases, H_2, NO, and H_2S are much simpler in structure than many of the drugs in use today. Our knowledge of them will continue to expand, providing an exciting potential for an entirely new class of drugs in the treatment of kidney diseases and end-stage organ failure.

DISCLOSURE

The authors declared no competing interests.

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