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INVITED COMMENTARY

Hydrogen-supplemented drinking water, just soda or an elixir of life?*

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Since its dramatic beginnings, the transplantation of organs has become standard treatment for many manifestations of end-stage organ failure. Undoubtedly, while many aspects of this complex have been continuously evolving and our understanding of key principles involved in ensuring long-term graft function has significantly increased, there has been only one real milestone discovery in clinical immunosuppression. Since the discovery of Cyclosporine in 1969, the realization of its immunosuppressive effects in 1972, and its first recorded clinical use by Calne *et al.* [1] in 1978, no comparable breakthrough has been achieved. Indeed, Cyclosporine remains to be of the most widely used drugs in immunosuppressive therapy after organ transplantation today. Many alternative or adjuvant drugs have been discovered, some of them have even been successfully introduced into clinical use, many different treatment concepts have been analyzed, some of them as exciting as the induction of immunological tolerance. Unfortunately, most of these work only in rodents and cannot be transferred into real life. And thus, when it comes down to the clinical effect, well, there is almost none. One look at the Registry of the International Society for Heart and Lung Transplantation reveals very nicely, that long-term survival after heart transplantation, conditional on survival for 1 year, which is an excellent way to analyze the effectiveness of long-term immunosuppression, did not improve over time. On the contrary, for the era of 1982–1991, it was significantly better than for the era of 1991–2001 (13.9 vs. 13.2 years, $P = 0.0002$) There was no significant difference between 1991 and 2001 and 2002 and 6/2009 [2] One might argue that this is a too simplistic approach and that is probably true; it does show, however, that no major breakthrough has been made in the last 40 years.

In this issue of *Transplant International*, Kentaro and his colleagues [3] from Pittsburgh, USA, present yet

another animal experiment analyzing the effect of hydrogen supplementation of drinking water on graft survival after cardiac transplantation and the reduction of intimal hyperplasia in aortic transplants using a well-established allogeneic rat model. I say yet another, because that was my first reaction upon reading the title of the manuscript. After reading the manuscript, however, I changed my opinion. First, this is truly a simple and novel idea, second, their model, although it is another rodent one, very elegantly demonstrates the effects. The main point is, however, the simplicity of the approach and the translational potential of the idea, as the effects of hydrogen supplementation will, in all likelihood not be species specific and thus can be translated into everyday clinical practice almost immediately.

The authors base their hypothesis on the studies by Huang *et al.* and Ohsawa *et al.* [4,5], who first demonstrated antioxidant, anti-inflammatory, antiapoptotic, and cytoprotective effects of hydrogen. Other groups have shown that molecular hydrogen can be delivered via oral uptake successfully and that it has a variety of ''anti-inflammatory'' effects when delivered via this route [6–10]. They go on to combine the above two in their model, transplanting Lewis rat hearts and aortic segments into Brown Norway recipients. Among the standard readouts including graft survival and histopathology, they analyze hydrogen concentration in the recipients' blood, myeloperoxidase activity as a marker of immunological activation, malondialdehyde levels as a marker of oxidative stress, cytokine and chemokine expression, and more. They are able to demonstrate clearly that hydrogen seems to significantly reduce the inflammatory response and more specific immunological activation of the recipients with its detrimental downstream effects on graft survival and observe an impressive increase in graft survival, accompanied by a clear reduction of intimal hyperplasia.

They speculate on the specific effects, but as this is likely to be the result of an extremely basic, conserved underlying mechanism, it will, in all likelihood, not be species specific. Of course, further studies will be necessary to elucidate the mechanisms involved. But from a clinical perspective, one is reminded of the difference between mathematicians and engineers. One does not have to completely understand everything to make it work. And thus and quite rightly, the authors suggest that this could easily be implemented into everyday clinical practice.

Now do not get me wrong, I do not suggest that we are witnessing the dawn of a new era in organ transplantation and it remains to be seen whether supplementation of drinking water will have any clinical effect. If so, however, it would be a surprisingly loud ''bang for the buck''. And furthermore, it was refreshing to see an idea that originated slightly out of the usual box being put to the test, successfully.

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