Let us intelligently design a new kidney!

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As my colleagues and I finished teaching this year's courses in renal pathophysiology, I was struck again by how much our medical students love to think that the kidney is a perfectly designed organ. Like most of us, they are slaves to teleology, where the Panglossian view that we live in the best of all possible worlds reigns supreme. But thinking about the basic principles of design of the kidney is not only an excuse for idle ruminations; it is also an urgent issue for nephrology today, given the clear need for a well-designed artificial kidney that provides something better than hemodialysis.

The paramount reasons for metazoa to 'invent' the kidney were the control of the composition of the internal environment and the excretion of toxic wastes. So why filter 200 liters a day only to have to reabsorb 199 back at a tremendous energy cost? Close to 7% of the daily energy expenditure is 'wasted' on reabsorption of what had already been filtered. That is the same amount of energy that the brain, our other intelligent organ, expends. Two reasons are often given; one is that there are so many toxic wastes of diverse chemical composition that the best way to excrete them is to filter huge volumes of blood and selectively reabsorb most of the good things back, leaving the bad ones behind. This rationale, stated in Homer W Smith's classic book *From Fish to Philosopher*,[1] is merely based on common sense, always a dangerous thing in science. Common sense, after all, is simply the accumulated biases that we have developed through experience, and it affords merely a beginning analysis of a question rather than its proof. The other advantage that high filtration rates supposedly give (also mentioned by Smith) is the ability to excrete large volumes of dilute urine, which was necessary for survival in fishes living in fresh water and drinking massive quantities of it.

Because it is easy to dismiss the first issue first, let me state that the idea that waste products need to be excreted 'passively,' by being filtered and concentrated, is no longer tenable. I use 'passive' in the manner of a previous generation of physiologists — that is, transport of a material that does not require a specific carrier protein. Our modern gene-based view of transport across membranes shows that there are so many transport proteins that there are bound to be some for waste products. For one thing, waste products are produced inside cells by metabolism, and hence they have to cross the cell membrane to the blood; how would they do that without specific transport proteins? Such a transporter might easily be made to concentrate them in the urine. In fact, we already know that a number of gene families exist each of which contains a large cohort of molecules that are able to transport an astonishing array of substrates, such as inorganic or organic anions and cations, hydrophobic non-electrolytes, and hydrophilic compounds, and even compounds that have not been seen by the organism during its history, such as xenobiotics and drugs. A large number of these transport proteins are expressed by the kidney tubule. The idea that materials have to be transported passively is too 'twentieth century'; as I pointed out elsewhere, for any molecule that you can think of, there is a transport protein to ferry it across the membrane.[2] Hence this rationale for a large filtration capacity is no longer physiologically correct. All one needs is the disposition of these transporters across the apical or basolateral membrane of the kidney tubule, allowing whatever toxic material is present in the blood to be directly secreted into the urine.

In a similar vein, metazoa found other interesting solutions to these problems without resorting to the filtration/reabsorption model. Insect malpighian tubules are outgrowths of the intestine and are composed of two segments; the first (distal) segment is a blind loop that secretes a salty solution that flows into the proximal segment, where many of the salts are reabsorbed.[3] Insects eat plants, all of which have a large number of 'secondary metabolites,' which are organic compounds synthesized by the plants to defend them against foraging animals and include many toxic alkaloids and terpenes. But insects eat many times their body weight in leaves and do not seem to have a problem in secreting these toxic compounds in their malpighian tubules.

What about excreting large volumes of fluids? Again, malpighian tubules have an astonishing capacity to handle massive amounts of load; many blood-feeding insects can ingest ten times their weight in blood at one feeding. This stimulates a severe diuresis from the distal segment in which

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a large amount of salt and water is excreted without the need of filtration. This is clearly larger than our ability to excrete only 20 liters of dilute urine a day. Even among vertebrates, there are aglomerular fishes; hence they must be able to excrete large volumes of fluid just by secretion in a manner similar to that of insects. Hence the filtration reabsorption system does not appear to be a necessary development without which we would have perished.

Let us discuss how new designs appear in nature. François Jacob, in a little book full of insights, starts by comparing how an engineer and a tinkerer work.[4] An engineer starts by defining the problem, then develops new methods and new equipment to come up with a novel set of solutions (that could be patented!). Novelty is paramount; the less one uses older methods the better. The light bulb designer did not copy the candle; the jet engine is not related to the internal combustion one, nor was there any precedent for phonographs and tape recorders. A tinkerer, on the other hand, is somebody who works happily using pieces of string, metal plate, propellers, bicycle tires, mirrors — whatever is around in his garage — to make his machine. Charles Darwin himself had actually come up with this description in his book on the evolution of orchids.[5] Further, different engineers working on the same problem often come up with similar solutions, since they are pushing the limits of the technologically possible; it is difficult to distinguish between Boeing and Airbus planes. Intelligently designed kidneys would all look as alike as cars (Kolff's design of the artificial kidney hardly changed in 60 years). The evolutionary tinkerer, on the other hand, produced different types; vertebrate kidneys are quite different from insect kidneys: one filters and absorbs, the other secretes. Finally, Jacob states that engineers strive to achieve perfection (as far as the technology of their age allows). Evolutionary tinkering, on the other hand, results in many organs whose functions get superseded and hence are examples of bad design; think of the pronephros and mesonephros. At an even more drastic level, the extreme design failure — extinction — is fairly common; it is estimated that 500 million species have been eliminated since the beginning of life on earth.[6]

Perhaps the mammalian kidney's great triumph is to be able to excrete very dilute or very concentrated urine or urine with essentially no sodium. (However, I do not know of any studies in insect or worm kidneys that are relevant to these issues, and for all I know, these kidneys can also do that). My purpose here is to think about new designs for the kidney that can be used by patients, rather than by nomads roaming the desert. To think with a fresh perspective when designing a new kidney from scratch, we will need to stop emphasizing replication of the filtration/absorption kidney that has limited our imagination. We need to see how evolution has solved the problem that a kidney must solve for all organisms, not just vertebrates, which constitute a small, even trivial fraction of metazoa. Taking ideas from evolution, that is, bio-mimetic design, is always a good first step, since we could combine the roles of tinkerer and engineer. Insects and vertebrates have wings, and makers of flying machines have benefited from studying their aerodynamics. We need to look at worms and how they do what they do with only four cells per kidney, which simply secrete urine.[7] Let us engineer a new artificial kidney that does more than passively remove toxins by filtration. Insects and worms have had a longer history than we have, and yet their kidneys needed to do the same things ours do. So why not think about producing a secretory organ that can be exposed to the blood so that it can extract the bad humors from it as well as give it back the needed factors and hormones that our kidney does? Is this plausible? I think so, but perhaps the issue is one of quantity. How many billions of cells do we need to form this artificial kidney? Do we need to make thousands or millions of units in micro-capillaries? Or do we need to modify evolutionary design so that we can just grow a large sheet of cells? Then how do we collect the effluent and guide it to the outside? These are the principal design issues that need to be overcome. Although producing a whole kidney based on a new engineering design, even one taken from a different branch of the animal kingdom, is a tall order, even partial solutions that might merely be halfway measures would be a good beginning. It is heartening to see that attempts are being made to provide a new way of thinking about the kidney that goes beyond filtration and reabsorption (JASN 2006:16:46A (Abstract)).

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