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EDITORIAL

Can the bowel substitute for the kidney in advanced renal failure?

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ABSTRACT

This Editorial provides a brief commentary exploring the possibilities of the bowel acting as a substitute for kidney function in chronic kidney disease/end stage renal disease. Three concepts

are highlighted as potential means by which bowel function can serve as an alternative to renal filtration: oral sorbents, diarrhea therapy and bacterial-enzyme nitrogen recycling within the gut.

Willem Johan ('Pim') Kolff, who died a day before his 98th birthday on February 11, 2009, opened our current era of life extension via vital organ replacement when he invented the first practical artificial kidney in 1943. Acceptance of Kolff's vision of a bionic future, however, was highly limited. As recounted by Kolff, 'When in 1929, I told the Chef de Clinic at the University of Groningen, the Netherlands, that I was going to work on an artificial kidney, his reaction was not only disbelief but he actually became angry'¹. Working in a semi-secret, isolated laboratory, under the German occupation of the Netherlands in World War 2, Kolff tested prototypes of his artificial kidney though 15 consecutive patient deaths, between 1943 and 1945, until his 16th 'hemodialysis' treated patient survived, changing our world. Kolff brought his device to the United States and, in a newly established Department of Artificial Organs at the Cleveland Clinic, turned his attention to fabricating a substitute artificial heart. In 1990, *Life* magazine designated Kolff as one of the 100 most important Americans of the 20th century².

Typical of the majority of artificial organ enthusiasts, convened at the 1964 founding meeting of the European Dialysis and Transplant Association (EDTA), Kolff enthusiastically predicted in a talk entitled 'To Live Without Heart and Kidneys', that: 'The symbol of life, the site of love, and the habitat of the soul, the human heart, will be replaced by a

mechanical pump'³. After guiding medicine through the transformation of irreversible kidney failure from an absolute death sentence to a reason to seek treatment with one of several varieties of artificial kidneys, Kolff expressed the view that medical practice was 'just around the corner from implantable self-sensing insulin pumps, artificial livers, and an implantable kidney'⁴. A growing number of artificial organ visionaries predicted that the 'doctor's office' would soon be converted into a repair shop offering spare part replacement.

Absent from the early proceedings of newly established American and European societies devoted to reporting and discussing advances in the new field of 'Artificial Organs' was any consideration of the magnitude of the cost of treating all who might benefit from treatment with devices replacing vital organ function. American mass production – the basis for winning history's greatest war – followed by remarkable cost reduction for individual treatment with penicillin, and other wonder drugs, inhibited worry over any prohibitive expense of broad application of dialysis or artificial hearts. Industrialized nations, it was thought, should be able to extend renal replacement therapy, as its cost plummeted, to less wealthy nations making death in uremia a rarity.

Sadly, what actually happened throughout the world tells a different story. Just as the availability of a small-pox vaccine in 1796 did not lead to eradication of the disease until 1979⁵, having the means to avert death in

kidney failure has until this day been ineffectual for the large majority of those afflicted with the disease. Illustrating the point, the EDTA, in 1980, analyzed 14,084 incident patients with end-stage renal disease (ESRD) in 32 European countries, noting that 'there was a strong linkage between the rate per million population treated for ESRD in 35 countries and the per capita gross national product in dollars⁶. Affluent nations treated ESRD care at a rate in excess of 200 per million (Japan, US, Switzerland), while poor nations were unable to treat more than 50 per million (South Africa, German Democratic Republic, Greece) (Figure 1). Criticism of health care systems' delivery of care for kidney failure included the United Kingdom, a democracy with socialized medicine ranking near the bottom, meaning that the majority of British uremic patients died without treatment⁷. Japan, by contrast, a nation devastated by war, permitted dialysis as a private practice business, topped the list. There was minimal hope that the world might treat kidney failure at the rate that enthusiasts promised⁸.

Fifteen years later⁹, continuing through today¹⁰, the stark reality that despite the existence of a means for its prevention, death without ESRD therapy is the unavoidable fate for most so afflicted. Death in ESRD like overall mortality is an inverse correlate of each nation's affluence¹¹. In a cross-national examination of overall mortality in 25 developed countries, the key correlate of total death rate was each country's gross national product (GNP) and not the number of medical doctors, nurses, midwives, or hospital beds; nor was any association detected between total deaths and alcohol or tobacco consumption or military expenditure¹². That conditions might improve can be inferred from

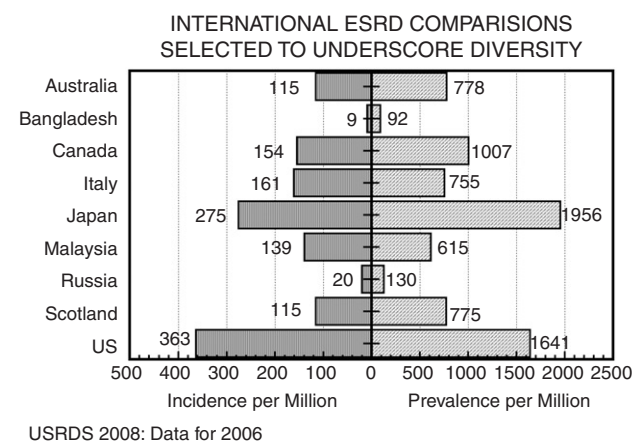


Figure 1. Selected national rates of incidence and prevalence of ESRD therapy as reported in the 2008 report of the United States Renal Data System¹⁰; the United States and Japan have the highest rates while Bangladesh illustrates the almost total absence of uremia therapy

events after the collapse of Communism, in Eastern Europe, when dialysis treatment rates tripled¹³ as a rise in GNP increased provision of health care¹⁴. It follows that current regimens of ESRD treatment, for the foreseeable future, cannot be supported by the majority of underfunded national health care systems¹⁵, restricting application of present uremia regimens to affluent nations¹⁶.

Given our current global recession, the objective for clinical nephrologists concerned with reducing death in kidney failure is to reduce the cost of treatment for ESRD (a year of hemodialysis requires \$40,000 to \$80,000 depending on country, Figure 2) by taking advantage of high technology. We have done this repeatedly in the past. As an example, the first quartz watches were priced above \$3,000 when introduced; in 2009 they can be purchased for less than 50 cents. One direction of active investigation is the production of engineered cells programmed to replace failed pancreases, livers, kidneys and lungs.

Concepts of substitute kidneys and livers are regularly reported. Chang, over fifty years ago, suggested an additional option for organ replacement¹⁷: design of semipermeable microcapsules as artificial cells¹⁸. Artificial cells use ultrathin polymer membrane envelopes, either as spherical membranes containing solutions or suspensions, or as a membrane coating on individual solid granules of adsorbent¹⁹. Because of their large surface to volume relationship (e.g. 2.5 m² surface area in 10 ml of 20 m diameter or 300 ml of 2–5 mm diameter microcapsules) and their ultrathin

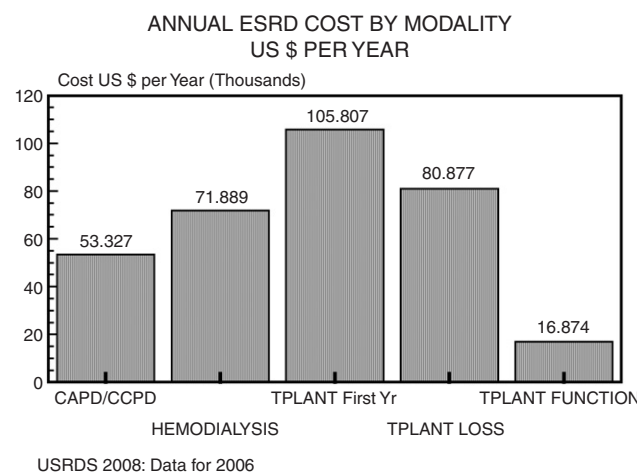


Figure 2. The United States Renal Data System 2008 report¹⁰ illustrates how the annual cost of renal replacement therapy is linked to the therapeutic modality chosen, overall expenses in the first transplant year amounted to over \$100,000 while each year of hemodialysis had Medicare reimbursement of \$71,889; the range of overall application of ESRD therapy is sharply different in affluent versus developing countries as shown in Figure 3

membranes (for example, less than 0.05 micron) artificial cells transport permeant molecules at incredibly rapid rates. Multiple reports recount the value of oral microencapsulation to replace enzymes in genetic deficiency²⁰, as well as living hepatocytes²¹ to control hyperbilirubinemia in the Gunn rat²².

Bowel as a kidney: oral sorbents

Another means of substituting for absent kidney function traces back through the beginnings of medicine indicating that employing the intestine may act as a substitute kidney²³. As reviewed by Thompson²⁴, Dioscorides' *Materia Medica* in 40 BC advocated administration of terra sigillata, a sacred earth found on the Greek island of Lemnos, for multiple disorders including diseases of the kidney. Pliny in 100 AD prescribed this 'esteemed medicine' as an oral sorbent 'against complaints of the spleen and kidneys, copious menstruation, also poisons and wounds caused by serpents'. Although terra sigillata is forgotten, other oral sorbents including charcoal²⁵, oxidized starch²⁶, locust bean gum (a mannose polymer derived from seeds of the ceratonia siliqua tree)²⁷, and microcrystalline carbon with an oxygen complex surface oxide²⁸ have each been reported in the 20th century as beneficial in the uremic syndrome by promoting nitrogenous waste extraction.

By 1960, several investigators documented the potential for nitrogen waste extraction from the human bowel. Schloerb, a surgeon at the Mayo Clinic, isolated a loop of ileum and by repeated perfusions with a lactated saline solution was able to prolong the life of otherwise fatally ill young individuals with chronic uremia for more than a year²⁹. Not unexpectedly, Kolff had speculated on the value of extracting solutes via the gut as a substitute kidney³⁰ both by lavage (dialysis) and by extraction using an oral sorbent³¹. Sparks found that bowel fluid contained sufficient urea, creatinine, and uric acid to suggest that intestinal extraction might be clinically of value³² by means of ingestion of chemical 'binders' now termed sorbents³³, testing a combination of activated charcoal and oxidized starch.

Giordano³⁴ in Naples, Italy evaluated the periodic acid oxidation product of starch, dialdehyde starch (oxystarch), as a nitrogen sorbent in clinical trials combined with charcoal³⁵ reporting evidence that the bowel might indeed be a useful focus of efforts to remove nitrogenous wastes in uremia, a conclusion confirmed in Brooklyn, New York³⁶. Oxystarch under physiologic conditions binds urea at a capacity of

178–277 mmol/mole of oxystarch aldehyde. Giordano's team maintained patients in advanced uremia using oxystarch at a dose of 30 to 40 g/day for over two years maintaining a constant blood urea nitrogen concentration while the serum creatinine gradually rose until the need for dialysis was inescapable.

More recently, AST-120, an oral sorbent comprised of particles of porous carbon with a diameter of 0.2 to 0.4 mm has attracted attention as a means of prolonging the interval until dialytic therapy is mandated. Preliminary studies in Sprague Dawley rats subjected to 4/5th nephrectomy and then treated with AST-120 1 g/day noted delay in onset of glomerular sclerosis while renal function is preserved³⁷. Miles *et al.* reported increased mean survival of 7/8ths nephrectomized, AST-120 treated rats to 104 days compared with 68 days in controls³⁸. Clinical trials, thus far limited to Japan, of AST-120 in a dose of 3.2 to 7.2 g/day to 27 patients with renal insufficiency prolonged the interval between an azotemic patient's serum creatinine level reaching 6 mg/dl to the start of maintenance hemodialysis from a mean of 5.0 months in controls to a mean of 14.3 months while improving the severity of anemia. There have been no prospective, double-blind, alternate case evaluations of AST-120 in uremia. In Japan, in 2004, thousands of patients with progressive renal insufficiency are being treated with AST 120; Phase 2 studies are in progress in the US.

Diarrhea therapy

During the 1947 Egyptian cholera epidemic Captain Robert Allan Phillips (1906-1976) devised highly efficacious methods for intravenous fluid repletion³⁹. Subsequently, at the United States Naval Medical Research Unit (NAMRU)-2 in Taipei, Phillips designed a glucose-based oral cholera rehydration therapy to replace the then standard intravenous regimen. Recognizing that as a consequence of profound and sustained diarrhea, those afflicted with cholera evinced a sharp decrease in their plasma levels of nitrogen-containing wastes (urea, creatinine, uric acid), Phillips grasped the potential utility of induced diarrhea as a means of treating renal failure. Subsequently, Young *et al.* in Taipei, successfully introduced an oral kidney failure regimen consisting of hyperosmotic fluid containing mannitol 220 mMol/l administered at 240 ml every 5 min until a total of 7 l is reached⁴⁰.

Diarrhea induced a urea clearance of 27.8 ml/min while bowel creatinine clearance reached 7.4 ml/min. Per three hour treatment session, a mean of 4931 mg of nonprotein nitrogen was removed, of which 3373 mg was urea nitrogen, during each diarrhea session⁴¹.

Bowel extraction of nitrogen during induced diarrhea is proportional to its initial level in plasma. Absent any dialysis program, Chinese uremic patients (creatinine clearance of 2–10 ml/min) were treated in Taipei with thrice weekly induced diarrhea lasting 3–7 hr for up to two years effecting symptomatic improvement with good tolerance of the regimen. All had improved appetite and reduced pruritus. When 17 uremic patients practiced diarrhea therapy at home on a thrice weekly 3 hr schedule for a mean of 6.8 months with a range of 1.3 to 16 months, a limit was reached when endogenous creatinine clearance fell to 1–2 ml/min when 'nausea and vomiting gradually reappeared and signs of fluid retention set in'. No objective, controlled, randomized prospective studies of diarrhea therapy have been reported, though the concept is appealing, yet proof of efficacy is lacking. Especially noteworthy is the low cost of components of the diarrhea regimen which at the time of reporting was less than \$3.00 per treatment, present costs would be about \$9.00 per treatment.

Bacterial enzyme nitrogen recycling within the gut

Probiotic bacteria are commonly defined as live microorganisms, which, when administered in adequate amounts, confer a health benefit to the host. Elsewhere in this issue, a preliminary prospective double-blind trial of administration of programmed probiotic bacteria in patients with chronic kidney disease is reported. Underlying this approach to reducing the cost and extending availability of uremia therapy are several reports by veterinarians. Ruminant animals utilize cellulose and urea for nutrition because of bacterial metabolism within their intestines⁴² surviving weeks to months following bilateral nephrectomy in sheep⁴³, and cows⁴⁴. Farmers depend on rumen-based chemical reactions when feeding urea and cellulose wastes to cattle who convert urea to essential amino acids using cellulose as an energy source. Dairy cows live for six generations, calve, and produce normal milk on a protein-free diet⁴⁵. Rumen microbial enzymes 'learn' to utilize urea and ammonium salts as sole sources of nitrogen permitting protein synthesis. After protein synthesis within the ruminant animal's gut, digestion and metabolism of protein following absorption are similar to that in non-ruminant animals.

Attempting to emulate ruminant physiology, Setälä, in Helsinki, administered enzymes extracted from cow feces to uremic patients basing the logic of his treatments on the hypothesis that bacterial enzymes utilize ammonia, potassium, phosphorus, and other

nitrogenous wastes to cleave 'vasoconstrictory peptides in the intestines'⁴⁶. Setälä treated 10 uremic patients and 10 normal controls, with specifically extracted enzymes from cultured (immobilized or free) 'pre-adapted' 'apathogenic' soil microorganisms 'trained' to convert urea, creatinine, uric acid, guanidino derivatives, and other nonprotein nitrogen compounds (NPN) to amino acids utilizing ammonia, potassium, phosphorus, and other nitrogenous wastes. Azotemia and hypertension decreased significantly during treatment but then increased again after the regimen was discontinued⁴⁷.

Based on the Setälä concept, Prakash and Chang continuously reduced blood urea levels in azotemic rats by instilling semipermeable microencapsulated genetically engineered live cells containing living urease-producing *Escherichia coli* DH5⁴⁸. Previously, these workers demonstrated that genetically engineered *E. coli* DH5 contain the urease gene from *K. aerogens* that metabolizes urea without production of ammonia. Pursuing this approach, bacteria engineered to catabolize unexcreted nitrogenous wastes within the intestine – termed probiotic bacteria – after testing in azotemic rats and miniature pigs, are now being fed to patients with CKD in a multicenter clinical trial⁴⁹.

Conducted in an outpatient nephrology clinic in Scarborough, Ontario, Canada, 13 outpatients with CKD Stage 3 or 4 first 3-month treatment period, were randomly assigned to group A or B and provided capsules containing either placebo or a probiotic formulation (90 billion CFU/day, 15 billion/gel cap, 2 caps × 3/day). In the second phase of the study, Groups A and B switched treatment for 3 months. Variables monitored included blood urea nitrogen (BUN), serum creatinine, phosphorus, and uric acid as well as responses to a self-administered quality of life questionnaire. Symptomatic complaints attributed to CKD decreased during administration of probiotic bacteria. From this preliminary trial, it appears feasible to expand study of probiotic formulations as adjunctive health supplements to help stabilize and maintain quality of life in CKD stage 3 and 4 patients. Expanded clinical trials of gut-based probiotic bacteria to determine their value as a component of renoprotection in progressive CKD may assist in sustaining life quality.

An intragut bacterial enzyme-based treatment for uremia in 2009 perspective is neither novel nor an overly optimistic expression of science fiction. Absent Chang's or other fresh directions in uremia research, our inability to improve the lot of most people with failing kidneys will persist far into this century resulting in tens of thousands of deaths forced by socioeconomic realities (Figure 3). Redefining artificial organs to encompass hybrid devices, smart cells, and even

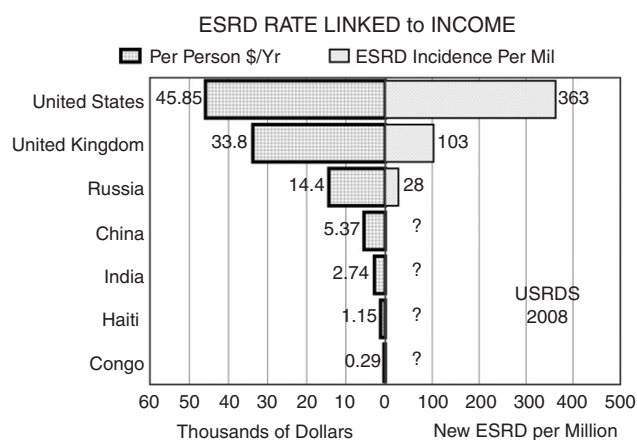


Figure 3. Linkage between annual per person income and incident ESRD treatment rate is depicted for several nations compared with the United States¹⁰; broadly applying any therapy requiring thousands of dollars per year is beyond the budget of both nations with a population of over one billion (China, India) and limited industrialization (Congo, Haiti)

fractional products of engineered cells and bacteria is a practical necessity and a pragmatic reality.

Transparency

Declaration of funding

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Declaration of financial/other relationships

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