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’. 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 century.

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’. 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’. 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 smallpox vaccine in 1796 did not lead to eradication of the disease until 1979, 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 ‘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 dollars’. 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 treatment. 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 promised.

Fifteen years later, continuing through today, 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 affluence. 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 expenditure. That conditions might improve can be inferred from 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 systems, restricting application of present uremia regimens to affluent nations.

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 replacement: design of semipermeable microcapsules as artificial cells. 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 adsorbent. 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...
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 deficiency\textsuperscript{20}, as well as living hepatocytes\textsuperscript{21} to control hyperbilirubinemia in the Gunn rat\textsuperscript{22}.

**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 kidney\textsuperscript{23}. As reviewed by Thompson\textsuperscript{24}, 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 charcoal\textsuperscript{25}, oxidized starch\textsuperscript{26}, locust bean gum (a mannose polymer derived from seeds of the ceratonia siliqua tree)\textsuperscript{27}, and microcrystalline carbon with an oxygen complex surface oxide\textsuperscript{28} 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 year\textsuperscript{29}. Not unexpectedly, Kolff had speculated on the value of extracting solutes via the gut as a substitute kidney\textsuperscript{30} both by lavage (dialysis) and by extraction using an oral sorbent\textsuperscript{31}. Sparks found that bowel fluid contained sufficient urea, creatinine, and uric acid to suggest that intestinal extraction might be clinically of value\textsuperscript{32} by means of ingestion of chemical ‘binders’ now termed sorbents\textsuperscript{33}, testing a combination of activated charcoal and oxidized starch.

Giordano\textsuperscript{34} in Naples, Italy evaluated the periodic acid oxidation product of starch, dialdehyde starch (oxystarch), as a nitrogen sorbent in clinical trials combined with charcoal\textsuperscript{35} 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 York\textsuperscript{36}. Oxystarch under physiologic conditions binds urea at a capacity of 178–277 mmoles/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 preserved\textsuperscript{37}. Miles et al. reported increased mean survival of 7/8ths nephrectomized, AST-120 treated rats to 104 days compared with 68 days in controls\textsuperscript{38}. 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 repletion\textsuperscript{39}. 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 Taipi, successfully introduced an oral kidney failure regimen consisting of hypertonic fluid containing mannitol 220 mMols/l administered at 240 ml every 5 min until a total of 7 l is reached\textsuperscript{40}.

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 session\textsuperscript{41}.
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 to 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 chemicals reactions when feeding urea and cellulose wastes to cattle who convert urea to essential amino acids utilizing ammonia, 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
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

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Figure 3. Linkage between annual per person income and
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United Kingdom
Russia
China
Haiti
Congo

Thousands of Dollars
60 50 40 30 20 10 0

600 500 400 300 200 100

ESRD Incidence Per Mil
0 10 20 30 40 50 60

ESRD RATE LINKED to INCOME
Per Person $/Yr

United States
363

33.8

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USRDS 2008

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New ESRD Per Million

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United States

Per Person $/Yr

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