

Carmelo Giordano (1930-2016): uremia therapy by low protein alimentation and sorbents

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ABSTRACT

Carmelo Giordano was born on August 23, 1930 in Naples and died there on May 12, 2016. He qualified MD in 1954 and then trained with Professor Magrassi and later Professor John Merrill in the USA. Returning to Naples he established a clinical research laboratory at the University Federico II which was funded for many years from the National Institute of Health in Bethesda. In 1969 he became a full Professor of Nephrology and established the postgraduate school of nephrology.

Giordano developed a worldwide reputation for his work on dietary management of uremia, recognised by the eponym “the Giordano-Giovannetti diet”. In this field he followed on from a galaxy of clinicians dating from antiquity and he worthily followed their high reputations.

He studied treatment of chronic renal failure (CRF) with low protein diets, essential amino acid diets/supplements and was the first to use ketoacids. The effect of these diets was assessed by nitrogen balance studies. He collaborated with other centres in this work including London and Stockholm.

Giordano’s other major interest and contribution to the conservative management of CRF was in the field of sorbents. He manufactured and studied, in patients and animals, the sorbent effects of oxidised starch-oxystarch and oxycellulose in removing, through the gut, significant amounts of nitrogenous waste. These studies raise the possibility of managing CRF using a combination of oral sorbent treatment and hemoperfusion. The latter is discussed in this paper as is dialysate regeneration and “portable” dialyzers.

KEYWORDS: Carmelo Giordano, Low Protein Diet, ketoacids in CKD, oxystarch, oxycellulose, cold carbon apparatus, portable artificial kidneys, wearable artificial kidneys

A Short Biography

Carmelo Giordano (Carmine, Luigi, Giuseppe Giordano) (Figure 1) was born in Naples on August 23, 1930 in the house of Raffaele and Anna Tirone. He received the MD *cum laude* in 1954, at the Faculty of Medicine of the University Federico II of Naples, the oldest state university of the world. He was fellow and assistant to Professor Flaviano Magrassi (1908-1974). From 1958 to 1960 he trained in nephrology with Professor John P. Merrill (1917-1984). At the Peter Bent Brigham Hospital of Harvard University where “no institution had done more for propagating dialysis in the United States”, he was viewed by some as “the father of nephrology as a discipline” (1). The relationship between Giordano and his mentor was extraordinary, both from the intellectual and the professional points of view. It was strengthened by the fact that Giordano during the first year in USA stayed in Merrill’s home. So, he had the privilege to learn directly from the maestro not only during the working hours at the university but also at home (2-8).

Figure 1



Carmelo Giordano (1930-2016).

On his return to Naples Giordano organized a clinical research laboratory at the Department of Medicine of the University Federico II, where he developed a program of low protein alimentation for patients with CKD, utilizing a grant from the National Institute of Health of The United States in Bethesda. The laboratory was subsequently financed with a series of 33 grants by the National Institutes of Health till 1985 (2-8). He also started hemodialysis for AKI by utilizing an artificial kidney (Brigham Merrill rotating drum) which was a personal gift to him by Mr. Olson, the manufacturer. Maintenance hemodialysis and peritoneal dialysis were started in 1966.

In 1961 Giordano was enrolled as assistant professor of medicine at the university Federico II in Naples where, in the years 1969-1985, he was Professor of Nephrology and chief of the renal unit. There he also established the postgraduate school of nephrology and the kidney transplantation program. In the years 1986-2002 he was Professor of Medicine at the Second University of Naples and physician in chief of the Division of Nephrology. After retirement he continued to attend congresses of medicine and nephrology and directed a successful renal unit in a private hospital until his death in 2016. In 2016 he participated in *Survival is Not Enough*, an event organized by the Italian Institute for Philosophical Studies on the occasion of World Kidney Day. In his welcome

address to the participants he underlined the need to increase the number of renal transplants because of the quality of life this treatment provides, its lower cost and the longer patient survival.

Details about his achievements in science and clinical medicine, the investigators he trained and promoted in the academy and hospitals, the papers and the books he published, the selective Capri Conferences on Uremia (1973-1980), the guest professors, his hobbies and his family have been described elsewhere (1-8). Historical reconstruction of Giordano's contributions to nephrology have been presented by De Santo at the Congress of the International Society of Nephrology in Milan (2010), at the meetings of the International Association for the History of Nephrology (IAHN) in Wloclawek (2017) and at the 58th ERA-EDTA Congress in Madrid (2017). Biagio di Iorio highlighted the Giordano-Giovannetti diet at the IAHN Congress in Olympia-Patras (2012). Giovambattista Capasso illustrated Giordano's achievements at the 2017 annual meeting of the Campania-Sicily branch of the Italian Society of Nephrology in Avellino.

Giordano's name is known worldwide for his contributions to uremia therapy by means of low protein diets and by sorbents (2-8). His name is linked to the eponym: the Giordano-Giovannetti Diet (9).

Prehistory of renal nutrition

We have already traced the timeline of the progress in the field (2-4). Herein we will expand on some of his forerunners listed in Table 1, compiled taking also advantage of a recent paper on history of uremia research (10). Forerunners are important in science. Only Archimedes did not have one thus he started everything on his own. Indeed John of Salisbury (*Methalogicon*, 1159 AC) recounts that his maestro Bernard of Chartres used to say that "we have seen further and farther since we stood on the shoulders of giants".

Table 1

Year	Scientist/Lifespan/Country	Discovery
After 168AC	Galen (129-c.130-c.200/c.216 AC) Pergamon and Rome.	<i>Excessive food intake causes cold and moist diseases.</i>
1591	Prospero Alpini (1563-1616), Republic of Venice.	<i>First description of Mediterranean diet.</i>
1614	Santorio Santorio (1561-1636), Republic of Venice.	<i>Balance between food and drink intake and excreta (urine, feces, and perspiration).</i>
1664	Jan Baptist van Helmont (1580-1644), Belgium.	<i>Urea a natural salt of the urine.</i>
1732	Herman Boerhaave (1668-1738), Holland.	<i>A native salt of urine that tastes different from sea salt. Resembles "sal ammoniac".</i>
1773	Hilaire Rouelle (1718-1779), France.	<i>Saponaceous extract of urine; high in nitrogen content, crystallizes into octahedral rather than cubic crystals of sea salt.</i>
1785	Claude-Louis Berthollet (1748-1822), France.	<i>Urea source of ammonia in urine.</i>
1798	William Cruickshank (d. 1810), UK.	<i>Urea crystallizes by addition of nitric acid; isolated the crystals in diabetic urine.</i>
1799-1908	Antoine Fourcroy (1755-1809), France.	<i>Urea crystallized, nitrogen content determined.</i>
1813	John Bostock (1773-1846), UK.	<i>First to realize the relationship between the diminution of urea in urine and its raising in blood.</i>

1814	William Prout (1785-1850), UK.	<i>Analyzed isolated pure urea crystals. Confirmed Bostock's findings.</i>
1821	Jean Louis Prévost (1790-1850), France.	<i>Extra-renal origin of urea. Elevated blood urea after bilateral removal of the kidneys.</i>
1828	Friedrich Wöhler (1800-1882), Germany.	<i>First to synthesize urea, an organic substance, from silver cyanate and ammonium chloride.</i>
1829	Robert Christison (1797-1882), UK.	<i>Urea increased in blood and reduced in Urine of patients with Bright's disease.</i>
1836	Richard Bright (1789-1858), UK.	<i>1st description of dropsy and proteinuria in end-stage kidney disease.</i>
1833	George Owen Rees (1813-1889), UK.	<i>Elevated blood urea in diabetic patients.</i>
1850	Thomas Graham (1805-1869), UK.	<i>Dialysis of urea across semi-permeable membranes.</i>
1850	Mariano Semmola (1831-1895), Kingdom of Naples.	<i>Effects of various protein intakes on albuminuria, urinary uremia and specific gravity in Bright's disease.</i>
1851	Friedrich T. Von Frerichs (1819-1885), Germany.	<i>Identified stages of Bright disease through urea concentration.</i>
1856	Antoine Bechamp (1826-1908), France.	<i>Urea product of protein oxidation.</i>
1856	Joseph Picard (1834-1896), France.	<i>Differential urea levels between renal artery and vein.</i>
1869	Lionel Smith Beale, USA.	<i>Low protein diet in renal disease would lower urea generation.</i>
1868	Adolph Fick (1829-1901), Germany.	<i>Calculated filtration rate from urea excretion.</i>
1883	Johan Kjeldhal (1849-1900), Denmark.	<i>Introduced an exact method for nitrogen measurement.</i>
1902	Hermann Strauss (1868-1944), Germany.	<i>Blood urea introduced in clinical medicine.</i>
1904	Fernand Widal (1862-1929).	<i>Relation of protein intake to blood urea in Bright's disease.</i>
1904	Nestor Gréhant (1838-1910), France.	<i>First simultaneous determination of urea in blood and urine.</i>
1910	Léon Ambard (1883-1962), France.	<i>Introduced the urea coefficient (blood to urine urea concentration ratio).</i>
1918	Franz Volhard (1872-1950), Germany.	<i>A vegetarian low protein diet may ameliorate uremic symptoms.</i>
1927	MacKay EM and MacKay LL, (USA).	<i>Gaussian distribution of blood urea concentration.</i>
1931	Newburgh LH, Johnston MW, USA.	<i>High nitrogen diets and renal injury. The dependence of the injury upon the nature of the nitrogenous substance.</i>
1932	Hans Krebs (1900-1981), UK.	<i>Urea (ornithine) cycle.</i>
1944	Walter Kempner (1903-1997), USA.	<i>Treatment of kidney disease and hypertensive vascular disease with a diet of 250-350 g of rice a day.</i>
1948	Thomas Addis (1881-1949), UK-USA.	<i>Protein restriction may be beneficial in uremia.</i>
1954	Theodore N Pullman, USA.	<i>Early studies the effects of various protein intakes on GFR.</i>
1955	John P Merrill (1917-1984), USA.	<i>Experience with AKI let him suggest for CKD a diet of 0.5-0.6 g/Kg of protein a day.</i>

Building a critical mass of data on urea excretion by the kidneys before Giordano. Modified from reference n. 10

Galen (c.129-c.130-c.200/216 AC Pergamon and Rome): Food and Diet (after 168 AC)

Excessive food intake is harmful. In Ian Johnston's translation and editing of Galen's *On Diseases and Symptoms* (11) one reads:

".. the excessive intake of what are to the animal the most useful and nourishing foods is a cause of cold diseases. However, many of the things eaten and drunk that are too cold in nature (VII.14K) are also causes of cold diseases. These, then, are the causes of dry diseases. All the opposites (are causes) of moist diseases: an abundance of foods that are moist in capacity, an excess of drinks, an altogether more luxurious way of life".

Prospero Alpini (1563-1616)

In 1591 the printing house of Franciscus De Franciscis in Venice published a book entitled *De Medicina Aegyptiorum Libri quatuor/Egyptian medicine, four books* (12). It was the *opera prima* of a young physician who later became professor of medicine, lecturer in simples and prefect of the Botanical Garden (the first worldwide) at the University of Padua (13). The book—an innovative output of a travelling physician (14)— reported on the personal experience of Alpini in Cairo from March 1581 to October 1584 as physician to Giorgio Emo, Consul of Venice. The book, dedicated to Antonio Morosini Senator of Venice, described for the first time the use of coffee, a popular drink in Cairo. Coffee was previously unknown in the western world. We have translated into English some passages related to various medical practices of Egyptian physicians. In Book I, Chapter X, Alpini describes Egyptian alimentation:

"They prepare their meals using milk and eat all dairy products. They eat very simple foods, many of them at lunch and dinner may eat a water melon or corn bread, which is utilized by everyone. They also use broth made of the roots of colocassia, of the bamnia fruit or barley corn or lentils or other legumes or with the green part of the sugar cane, or they feed themselves with grapes, figs, cucumbers and similar. As a beverage the Egyptian followers of Mohammed use Nile water which for its quality is to be preferred to all others".

In Book I, Chapter XI, Alpini reports on Egyptian longevity:

"Therefore I think that the main reason which grants long life to Egyptians is their sobriety and abstention from an abundance of meat (...), the water of the Nile. In fact in Europe by much eating and drinking excessive quantities of wine, inhabitants of Germany and Poland live less".

This is the first description of what in the twentieth century was defined as a Mediterranean diet. In Egypt they made use of corn bread, consumed great amounts of fresh or cooked vegetables including lentils and other legumes, and of fruits. They also used milk and dairy products, drank the Nile water or coffee prepared with the same water. Such a diet links to the longevity of the population giving a preventive role to abstention from meat and wine.

Mariano Semmola (1831-1895)

Semmola was born in Naples, studied at the University Federico II and obtained the MD in 1852. He studied in France under Claude Bernard, Trousseau and Rayer, and later was Professor of Pharmacology in Naples. He is credited with 28 national and international papers on Bright's disease.

As a medical student he illustrated at the Academy of Medicine and Surgery in Naples (on January 26, February 23 and April 22, 1850) seminal experiments on the effects of different protein intakes on: (i) urinary specific gravity, (ii) urinary urea excretion and (iii) albuminuria in patients with primary albuminuria receiving either a) a usual mixed diet, or b) a meat diet (600-700 g of boiled

meat), or c) a vegetable soup based on greens and bread, or d) a nitrogen-free diet based on fat, tomatoes and chestnuts. Urinary specific gravity was highest under the meat regimen, whereas albuminuria and urinary urea excretion were lowest under the nitrogen-free diet (15-17).

These studies were well received in France and were praised by Sigismund Jaccoud (1630-1930), François Henri Hallopeau (1842-1919), and Georges Dieulafoy (1839-1911). The studies were described at the Academy of Medicine in Paris and appeared in its Bulletin in 1892. That means that Semmola worked in the field for 42 years after 1850 (16).

Fernand Vidal and Adolphe Javal

These scientists made significant contributions to the patho-physiology of Bright's disease demonstrating that blood urea increased with the protein content of the diets, and that knowing the composition of the latter was a prerequisite to understanding the meaning of blood urea concentration. These studies were important for Léo Ambard during his studies on the urea-secretory constant (19, 20).

The history of low protein nutrition in CKD: The role of Carmelo Giordano

Coming back to the origins of the Giordano-Giovannetti diet, we now illustrate the experiments Giordano performed in the years 1961-1963 which shook the world of uremia specialists. His debut was unexpected, pregnant scientifically, and promised a new perspective for patients with chronic renal disease. Giordano's studies opened a new era and further results are still expected.

Giordano's first study (21) was a self-experimentation on one healthy subject (himself). He undertook a 4 period protocol (A,B,C,D) for a total of 53 days. In A he ingested a diet made from essential amino acids + 3 g of nitrogen (N) in the form of glycine. In Period B only 0.5 g of N as glycine supplemented the essential amino acids. In C essential amino acids were supplemented with 2 g of N as ammonium citrate. In D essential amino acids were supplemented with 2 g of N derived from urea. Nitrogen balance was positive and body weight remained constant throughout the experiment.

In the same year Giordano (22) reported on two patients with advanced renal failure treated with essential amino acids (a total of 2 g of N a day) along with 2500 calories. A significant reduction of blood urea concentration occurred during the treatment.

At the Second Congress of the International Society of Nephrology in 1963 in Prague, Giordano (23) reported studies on 23 CKD patients (Table 2) followed with a dietary protocol for 5 weeks. In week 1 and 5 they ate a low protein diet providing 3.8 g of N (23 g of proteins of high biological value (HBV) rich in energy (2,300-3,100 calories). In weeks 2,3 and 4 they consumed a diet containing 2.4 g of N (85% as L-essential amino acids) and providing a high energy supply. Blood urea was reduced by the amino acid diet which normalized N balance after 1 week. At this world convention there were no other presentations on low protein alimentation in renal disease.

Table 2

Patients No.	Creatinine mg/dl plasma	Follow up months
5	2.6-6.0	79
6	6.3-9.0	10
117	8 > 9.0	40
Total patients no. 23		236

Patients studied in reference no. 23

In September 1963 Giordano published a paper in the *Journal of Laboratory and Clinical Medicine* (24). He reported data on 8 CKD patients (eGFR 3-26 ml/min) seven of whom were hypertensive (Table 3). They received for 7 weeks a diet providing L-essential amino acids (2 g of N a day). The energy content provided 2,300 calories in women and 3,100 in men. Thereafter they were given a low protein diet providing 23 g of HBV proteins. Blood urea was reduced under amino acids, nitrogen balance started to be positive after 3 weeks.

Table 3

Persons	eGFR/MDRD)	Hypertension
Pat. 1	26	yes
Pat. 2	22	yes
Pat. 3	15	yes
Pat. 4	17	yes
Pat. 5	9	yes
Pat. 6	6	yes
Pat. 7	8	no
Pat. 8	3	yes

Patients participating in the studies described in reference no.24.

A series of seminal studies were presented by Giordano and his initial group of fellows at the 3rd Congress of the International Society of Nephrology in Washington 1966 (25). They reported on 221 patients followed for 60 months. The patients started with 0.3g/Kg of HBV proteins associated with 35 kcal/kg and were followed by assessing the nitrogen balance. When the N balance was negative, 2-3 g of proteins were added (in total 24 g for a 70 kg man). The study reported on more than 1000 days of N balance in 25 of the patients, given various dietary intakes (free intake, 8-11-g L-essential amino acids, and low protein diets providing 17-g, 20-g, 23-g and 25g. 85.7% per cent of the patients were in positive nitrogen balance with 25 g of proteins. This anticipated the evidence that with a 40g protein diet all CKD patients would receive an adequate amount of protein, as demonstrated in 1968 by Kopple et al (26). The study of Giordano et al (25) also disclosed a reduced phenylalanine to tyrosine ratio and a loss of 10-20 g of amino acids and peptides during a dialysis session of six hours.

Three studies documented for the first time the potential of ketoacids in the treatment of CKD. The first was a study on amino acids L and DL, the remaining two mark the origin of ketoacid therapy by using the ketoacids of phenylalanine and valine (27-29). The experiments were made in

collaboration with the group of Peter Richards at the St. Mary Hospital in London, where the ketoacids of phenylalanine and valine were administered and their effects evaluated by nitrogen balance studies and ^{15}N incorporation. Plasma albumin was broken down and their constituent amino acid were separated in Naples. Peter Fürst evaluated the ^{15}N enrichment of each amino acid at the Institute for Mass Spectrometry of the Karolinska Institute in Stockholm directed by Garnar Ryhage.

The concept began with a paper on the effects on nitrogen balance of D-isomers of essential amino acids in uremia (27). It was hypothesized that it was the ketoacid of the D-isomers of amino acids that would be utilized. Two papers were published in 1971 showing the feasibility of a low protein diet based on ketoanalogues (28, 29). Ketoacids of the essential amino acids valine and phenylalanine could be utilized in studies with nitrogen balance and ^{15}N incorporation. It was shown that phenylalanine and valine may be synthesized by healthy and uremic individuals. Walser et al. brought strong additional evidence to the importance of ketoacids (30) and nurtured the field for the subsequent 30 years. However, the initial enthusiasm of Giordano et al. for ketoacids diminished since anoxic infants on ketoacid formulations failed to achieve catch-up growth whereas with amino acid formulations they did (31). Thus a new reference pattern was proposed (32). In this way Giordano and his associates lost the advantage they had generated in 1964 (27) and it took many years for Giordano to acknowledge the importance of ketoacids (33).

Prehistory of sorbents

Athanasios Diamandopoulos, historian of nephrology, once wrote:

“nature uses various natural membranes to eliminate toxic substances. The membranes used for this purpose are those of the gastrointestinal system and of the skin. Humans tried to imitate nature... the beginnings of these practices can be dated to at least 4000 years ago. Herodotus described the practices of enemas among Egyptian who preserve good health by clystering themselves 2-3 times a month”. He also quotes Aetius Amidanus (6th Century AD) for treating acute renal failure with clysters made of “mallow, linseed oil, peeled barley, warm water, reed, camomille and dill”, a practice also suggested by Albucasis (10th century) and by Avicenna (11th century). On the other hand Hippocrates suggests to “purge to get rid of the rest from above and from below” (34).

Terra sigillata / sealed earth from the Island of Lemnos in Greece, packed together and bearing the head of Artemis should be considered as the first sorbent for medical use as reported by Dioscorides in *De Materia Medica* (40 BC).

Spyros Marketos, a founder and president of the Hippocratic Foundation of Kos, produced a seminal paper on purgatives, charcoal and artificial kidney (35). He says that Hippocrates in *Aphorisms* suggests “Bodies that are to be purged must be rendered fluent... If the matters purged be such as should be purged, the patient profits and bears up well. If not, the contrary”.

Therein one also learns that charcoal was a recognized drug in Ancient Egypt (36) and Pliny the Elder in *Naturalis Historia* (90 AD) described its virtues for “disease of the spleen, of the kidney abundant menstruation, poisonous serpents’ wounds”. Its use was supported by Thonery, a French pharmacist who used it in the course of self-experimentation by ingesting it along with strychnine before the Medical Academy of France (37). But it was Yatzidis who introduced carbon hemoperfusion for intoxication (38, 39).

Santorio Santorio (1561-1636) in *De statica medicina* (1514) started a medicine based on measurements by measuring food intake, drinks, urine, feces and calculating perspiration and by suggesting remedies capable to affect the quantity of excreta (40).

On the history of sorbents and the contribution of Carmelo Giordano in the years 1968-1984

A total of 31 papers (41-71) represent an incomplete list of the output of a strong, motivated team which included Carmelo Giordano, Renato Esposito (chief of the laboratory, Associate Professor of Nephrology, nutritionist, immunologist and expert in clinical chemistry), Ernesto Quarto (Associate Professor of Bioengineering, Giovanni Demma and Piero Bello (both doctors in Chemistry), Giacomino Randazzo (Full University Professor of Biochemistry), Miss Maria Pluvio (Dr in biology and medicine, nephrologist and Ph. D in Nephrological Sciences), Mrs Norina Lanzetti (physician, nephrologist and Ph. D in Nephrological Sciences), Mr. Tonino Ariano (laboratory technician).

Lavage of intestinal wastes

Lavage of intestinal wastes was reported by Kolff in *New Ways of Treating Uremia*" (20). Kolff created a double ended ileostomy in an isolated ileal loop with an intact blood supply in a 57 year old uremic man. As much as 0.48 g of urea/hour was removed by the patient who performed home intestinal dialysis assisted by his wife for two months until his death. Prolongation of life by intestinal dialysis has been accomplished in dogs (73) and man (74, 75). Clearances during isolated jejunal loop dialysis in uremic patients were reported by Schloerb (74) as 5 to 10 ml/min for creatinine and 3.2 to 5.0 ml/min for uric acid, values about one third and one eighth as efficient, respectively, as obtained with peritoneal dialysis and hemodialysis. Intestinal perfusates contain smaller but significant amounts of larger molecules including aldosterone and 17-oxyhydroxycorticosteroids.

By 1960, hemodialysis was made practical by the development of an external plastic arteriovenous shunt. A slowly increasing number of patients were sustained (albeit suboptimally) by periodic intestinal dialysis. Analyzing 15 cases in the literature plus five of their own, Clark et al. (75) reached the conclusion that intestinal dialysis "remains the best method of adjunctive management of progressive uremia." Thereafter, the improving success rate of maintenance hemodialysis diverted interest from the quest for nitrogenous waste extraction from the gut.

Removing urea from blood and/or intestinal tract and the birth of oxystarch and oxycellulose

Activated charcoals have a low sorption capacity for urea although they effectively remove other uremic toxic substances. To provide a urea-reactive adsorbent, a chemically modified oxystarch with albumin or gelatin was prepared. Elemental analysis and Fourier transform infrared (FT-IR) spectroscopic analysis demonstrated that the reaction of a small amount of protein (albumin or gelatin) with oxystarch had taken place possibly by chemical combination (41-46).

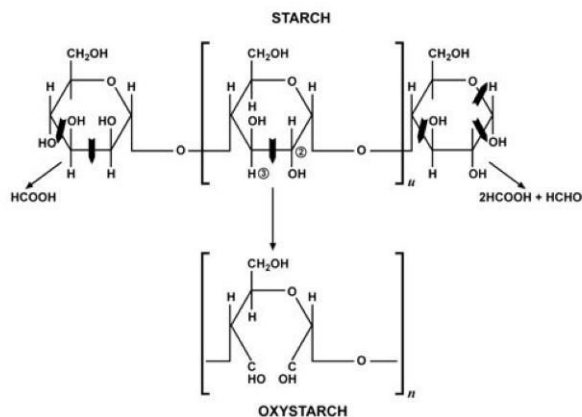
The influence of the dialdehyde content of the oxystarch on urea sorption, its sorption isotherm, and the adsorption rates were investigated. It was found that the swelling factor of oxystarch is closely related to the sorption activity under physiological conditions (pH 7.2-7.4 at 37° C). Adsorption studies showed that sorption capacity was increased by surface treatment and can reach 6-8.2 g urea/kg-dried adsorbent (initial urea concentration was 70 mg/dL). The oxystarch had 49.2% of glucose unit oxidized and was surface treated with albumin. These results suggested that the newly prepared surface-treated oxystarch would be utilized as an effective chemisorbent for urea removal under physiological conditions.

Sorbents in the Management of Uremia (60) documented easy transfer of urea from plasma into the intestinal lumen. The potential for treating renal failure by extraction of nitrogen waste from the gut became self-evident. Urea in the gut is degraded to ammonia by bowel bacteria to the extent that normal human feces contain no urea. In healthy volunteer subjects given an antibiotic cocktail, stool urea concentrations increase to blood levels while the fecal ammonia content

decreases. This supports the inference that urea in the bowel is biodegraded by luminal microorganisms. Estimates of the quantity of urea converted to ammonia in the gut have been computed by Man et al. (79), from 4 to 7 g/day in normal patients and from 17 to 50 g/day in uremic patients.

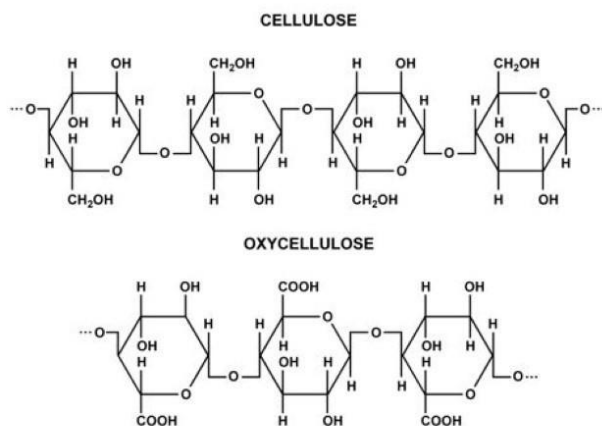
Promising additional data indicating that gastrointestinal sorbents can bind to and remove, in the feces, clinically important amounts of nitrogenous wastes were demonstrated by Giordano and associates (5, 41-46) using oxidized starch (oxystarch) and oxidized cellulose (oxycellulose) (Figure 2 and Figure 3).

Figure 2



Transforming starch into oxystarch.

Figure 3



Turning cellulose in to oxycellulose.

Corn starch or potato starch suspended in a solution of sodium periodate at 4°C for 24 hours slowly oxidizes to dialdehyde starch (oxystarch). Cellulose treated similarly, oxidizes to oxycellulose. At body pH and temperature, each repeat unit of oxystarch binds 1.5 to 1.9 moles of ammonia in vitro in an 0.3N ammonia solution; when present in excess, oxystarch will bind all the ammonia in a 0.3N solution. Oxystarch also adsorbs urea.

Oxystarch adsorbs aspartic acid in vitro, but it does not bind creatinine, uric acid, L-lysine or albumin. In weanling mice fed 2 per cent oxystarch in a casein diet, growth and development are normal. In rats fed 2 per cent oxystarch in a casein diet severe diarrhoea develops, whereas dogs tolerate as much as 5 per cent dietary oxystarch without apparent adverse effect. Explosive diarrhoea and a cholera-like fluid and electrolyte depletion syndrome occur in dogs fed more than

10 per cent of oxystarch in their diets. In uremic patients fed 20 to 35 g of oxystarch in divided doses stool volume increases by 200 to 600 ml/day and the frequency of bowel movements is increased, but frank diarrhoea does not develop. Giordano's initial trials of oxystarch manufactured in his laboratories (42-44) showed that uremic patients (creatinine clearances of 0.4 to 3.2 ml/min) tolerated divided doses of 20 g/day well for two months and that, in each case, there was a significant fall in the blood urea nitrogen level. Fecal nitrogen content increased to a mean of 1,450 mg/day (range 730 to 8,050 mg/day). Confirmation of increased stool nitrogen content during oxystarch treatment was provided by a double blind starch/oxystarch full balance study (76-80). In this study seven uremic patients (creatinine clearances of 6 to 30 ml/min) were fed 29 g of oxystarch or starch daily in four equal doses added to a diet containing 40 to 50 g of protein and 2 to 4 g of salt. Blood urea nitrogen levels fell 33 per cent during oxystarch treatment from a mean of 93.1 mg/ 100 ml to a mean of 62.1 mg/100ml. There was no significant change in serum creatinine, plasma amino acid, uric acid and plasma glucose levels during oxystarch ingestion. Oxystarch significantly increased fecal nitrogen from a control mean of 1.4 g/24 hours to 2.5 g/24 hours. A concomitant decrease in urinary nitrogen excretion, however, from a control mean of 7.6 g/24 hours to 5.5 g/24 hours during oxystarch treatment prevented development of negative nitrogen balance.

During minimal nitrogen ingestion, uremic patients fed oxystarch (28 g) daily have an increased fecal excretion of nitrogen and potassium, and a counterbalancing decrease in urinary nitrogen and potassium excretion (81). There was a significant increase in the fecal potassium content when oxystarch was ingested, ranging from 5 to 22 mEq/day, which was also counterbalanced by a decrease in urinary potassium excretion. To exclude the possibility that increased fecal nitrogen content noted during oxystarch treatment was due to direct binding of unabsorbed undigested dietary nitrogen rather than bound intestinal nitrogen, four uremic patients were fed oxystarch while ingesting a "no protein" diet (82). In these patients the increases in fecal nitrogen and potassium were similar to those in the previous group indicating that the origin of the extra fecal nitrogen was indeed nitrogenous waste. Will feeding oxystarch to uremic patients have clinical import? In urine-producing patients the counterbalancing decrease in urinary nitrogen excretion tends to detract from the benefit of increased fecal nitrogen content. What will be the effect on nitrogen balance in anuric patients?

Oxystarch in bilaterally nephrectomized rats

While awaiting completion of sorbent trials in functionally anephric (undergoing dialytic maintenance) patients, several helpful animal experiments have been completed. To date, chronically uremic animals in need of dialysis have not been sustained by sorbents alone. Gavage feeding of oxystarch alone or in combination with charcoal will prolong the life of anephric rats of three days to five days. Friedman et al. (81) investigated the mechanism of sorbent-induced life extension in bilaterally nephrectomized rats fed charcoal (1 g daily), oxystarch (1 g daily) or oxystarch plus charcoal (1 g of each daily). In sorbent-treated rats the increase in blood urea concentration was less than in untreated nephrectomized controls, but they also had lower serum potassium concentrations throughout their increased life span. Both actions of oxystarch, increased fecal excretion of nitrogen and potassium, were detectable in this in vivo model of fatal acute renal failure.

Charcoal as an oral sorbent and for hemoperfusion

The work of Yatzidis on charcoal (38, 39) is important. Administered in oral doses of 20 to 50 g daily, with or without sorbitol as a vehicle, Yatzidis (82) was also able to manage patients with

end-stage renal failure for 4 to 20 months without resorting to dialysis.

For completeness in this survey, the technique of direct exposure of blood to a sorbent, termed hemoperfusion, will be mentioned. During a single passage over granular activated charcoal, creatinine, uric acid, indican, phenols, guanidines and organic acids are nearly totally extracted from the blood. Only negligible quantities of urea, magnesium and phosphate are adsorbed on charcoal from blood. Each gram of powdered charcoal will in vitro bind simultaneously 9 mg of creatinine, 8 mg of uric acid, 1.75 mg of phenols, 1 mg of guanidines and 35 mg of urea.

Yatzidis (38, 39) devised a hemoperfusion device containing 200 g of activated charcoal in a siliconized glass cylinder 20 cm in length and 6 cm in diameter. Based on an experience of 20 humans undergoing hemoperfusion, Yatzidis estimated that 60 minutes of blood exposure to two or three 200 g charcoal columns had about the same extraction efficiency (for uremic patients) as a 4 to 6 hours hemodialysis. Hemoperfusion was advocated for the treatment of renal insufficiency, gouty arthritis, and intoxications with salicylates, barbiturates and glutethimide (82-84).

Charcoal microencapsulation

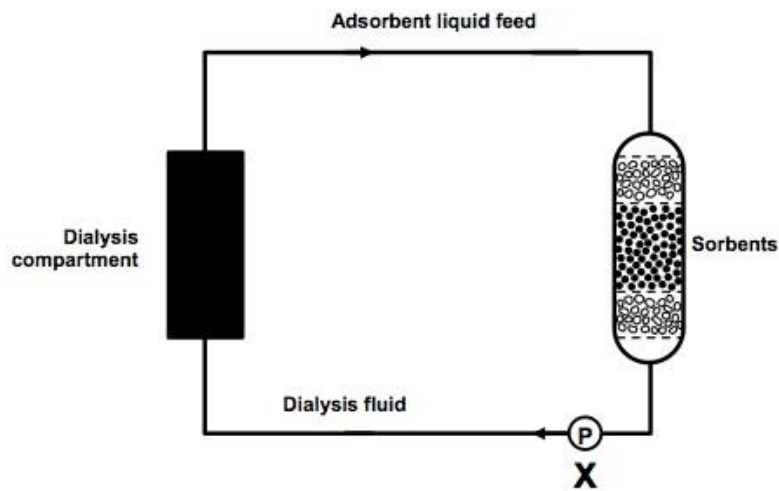
Chang et al. (85, 86) have systematically studied several approaches to microencapsulation of charcoal and they developed a blood-compatible albumin-complexed polymer. Chang's microencapsulated "kidney" contains 300 g of double coated charcoal granules 2 to 5 mm in diameter with a surface area of 2.25 m². This device achieves clearances in vitro, which are superior for middle molecules (MW 200 to 1,800), to hollow fiber, coil or parallel flow hemodialyzers. Periodic hemoperfusion as a sole treatment for uremia is inadequate because of the need to extract water and probably urea to maintain acceptable morbidity. Combination of hemoperfusion in series with ultrafiltration of blood for water removal might prove a workable therapy for uremic patients who ingest ammonia binding sorbents such as oxidized starch. The efficiency advantage (shorter treatments) of hemoperfusion over hemodialysis in renal failure is sufficiently attractive to consider sorbents in the management of uremia, coupling hemoperfusion with oral sorbent ingestion.

Dialysate regeneration

The field of closed circuit artificial kidneys was opened by Yatzidis (38, 39) who introduced carbon to remove uremia waste products. Gordon (87, 88) introduced the use of zirconium phosphate which adsorbs ammonium ions in presence of sodium and releases Na⁺ and H⁺. This allowed regeneration of dialysate through a sorbent cartridge.

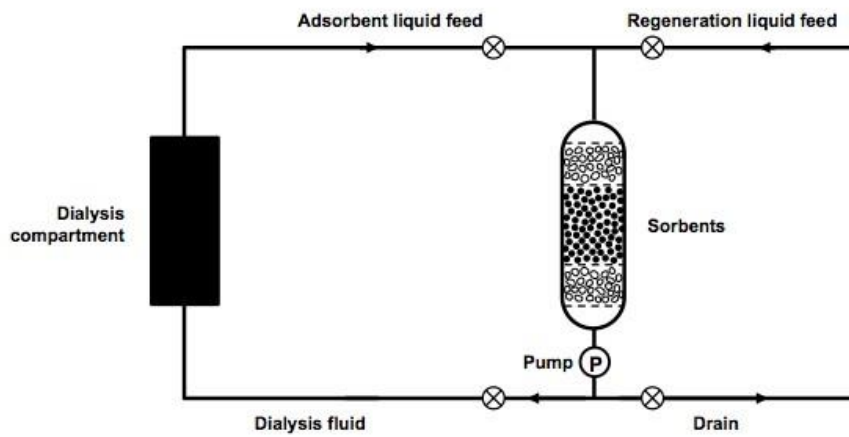
A remarkable reduction in dialysate volume to 1.5 liters was devised by Gordon and co-workers by the clever means of converting urea in dialysate to ammonium ion and carbonate by urease treatment. Ammonium ion is adsorbed by zirconium phosphate which also extracts calcium and magnesium necessitating continuous reinfusion of these ions. Zirconium oxide binds phosphate and fluoride while charcoal extracts uric acid, creatinine, guanidines, organic acid and phenols. The total weight of the sorbent cartridge is less than 2 kg. The importance of the Gordon (89) system is not only the size reduction, which makes a "travel-suitcase" artificial kidney practical, but it is also a clear demonstration of the value of sorbents in simplifying the therapy of uremia. Zirconium phosphate could also be used in association with charcoal, starch and oxystarch (48-58) by Giordano and his associates for portable artificial kidneys (Figure 4, Figure 5 and Figure 6).

Figure 4



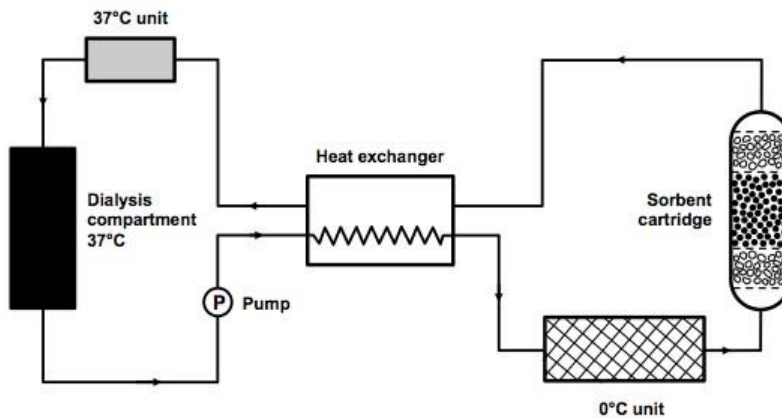
Sorbents for portable artificial kidneys (modified from reference no.60).

Figure 5



Sorbents for portable artificial kidneys (modified from reference no.60).

Figure 6



Sorbents for portable artificial kidneys (modified from reference no.60).

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