Carmelo Giordano (1930-2016): a giant in Nephrology

cap.15 Carmelo Giordano (1930-2016)

Natale G. De Santo[1], Carlo De Pascale[2], Ernesto Quarto[3], Malcolm E. Phillips[4], Biagio Di Iorio[5]

[1]Department of Medicine, Università degli Studi della Campania Luigi Vanvitelli, Naples, Italy
[2] Retired Physician in Chief, Renal Unit Cotugno Hospital, Naples, Italy
[3]Retired Professor of Bioengineering, University Federico II, Naples , Italy
[4]Retired Nephrologist and Medical Director of Charing Cross and Hammersmith Hospitals Trust London, UK
[5]Division of Nephrology, Solofra General Hospital, Avellino, Italy


Natale Gaspare De Santo

Abstract
Carmelo Giordano (Carmine, Louis, Joseph Giordano) was born in Naples on August 23, 1930 in the house of Rafael and Anna Tirone He received the MD cum laude in 1954. He was Fellow and assistant to Professor Flaviano Magrassi and studied nephrology at the Peter Bent Brigham Hospital, University of Harvard in Boston, under the guidance of John P. Merrill (1958-1960). He was nominated Professor of Nephrology at the University Federico II, Naples in 1975 and Professor of Medicine at the Second University of Naples (1986-2002). The National Institutes of Health of the United States in Bethesda financed his research for more than 20 years. He started low protein alimentation (Giordano-Giovannetti diet according to Geoffrey M. Berlyne) with or without addition of amino acids and ketoacids and devised formula diets for CKD infants and children. He demonstrated that 85% of CKD patients receiving a 25 g protein diet were in positive nitrogen balance. Later he introduced the concept of energy load from dialysate in CAPD and the assessment of amino acid losses during hemodialysis and peritoneal dialysis. He also researched the minimum protein requirement under CAPD regimens. He synthesized, with Professor Renato Esposito, oxystarch and oycellulose and introduced the use of carbon at low temperature and its regeneration at 90 ˚C. He introduced wearable and portable artificial kidneys. He died in Naples on May 12, 2016.

Key words: Carmelo Giordano, low protein diets, amino acids, ketoacids, nitrogen balance, sorbents, oxystarch, oxycellulose, carbon, peritoneal dialysis belt, wearable and portable artificial kidneys

Abstract italiano
Carmelo Giordano nacque il 23 agosto l 1930 a Napoli dove è deceduto il 12 maggio 2016. Conseguì la laurea in medicina e chirurgia nel 1954, e fu allievo e successivamente assistente del Professore Flaviano Magrassi. Imparò la nefrologia all'Ospedale Peter Bent Brigham dell'Università di Harvard in Boston (USA) sotto la guida di John P. Merrill. Giordano divenne Professore di Nefrologia nel 1975 all'Università Federico II e Professore di Medicina alla Seconda Università di Napoli (1986-2002). I suoi studi furono finanziati dagli Istituti Nazionali di Medicina degli Stati Uniti di Bethesda. Giordano introdusse il concetto di diete a basso contenuto di azoto con e senza amino acidi e/o chetoacidi (dieta Giordano-Giovannetti secondo la definizione di Geoffrey M. Berlyne). Egli dimostrò che 85% dei pazienti con malattia renale cronica trattati con diete di 25g di proteine erano in bilancio di azoto positivo. In tempi successivi evidenziò il concetto di apporto energetico dal dializzato nella CAPD e misurò le perdite di aminoacidi in emodialisi e CAPD e l'apporto minimo di proteine per pazienti in CAPD. Egli sintetizzò insieme al Prof. Renato Esposito ossiamido ed ossicellulosa, inoltre usò il carbone a bassa temperatura e lo rigenerò indefinitamente a 90 gradi costruendo reni artificiali indossabili e portabili.

Parole chiave: Carmelo Giordano, diete a basso contenuto di proteine, amino acidi, chetoacidi, bilancio azotato, sorbenti, ossiamido, ossicellulosa, carbone, cintura per dialisi peritoneale, reni artificiali indossabili e portabili

GIORDANO'S LIFE

Carmelo Giordano (Carmine Louis, Joseph Giordano) (Figure 1) was born in the house of Rafael and Anna Tirone in Naples on August 23 1930 (Figure 2).

Figure 1

Figure 2

His father held the title of Baron. He was baptized on the 28 September in the Catholic Parish of the Holy Cross and Saint Rita (Figures 3 and 4).

Figure 3

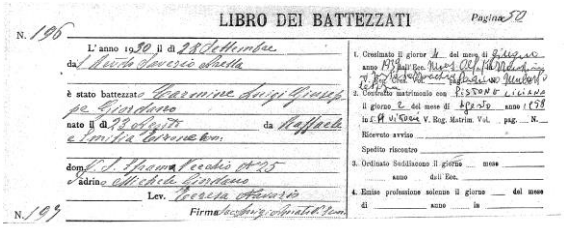
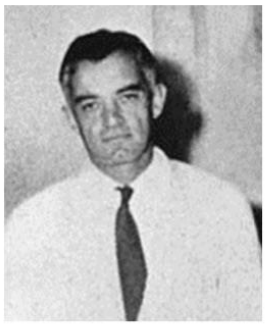
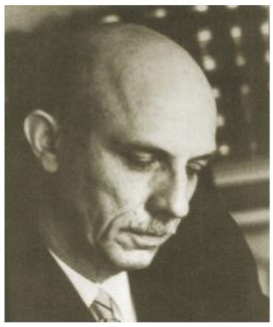


Figure 4



John Putnam Merrill (1917 – 1984)



Flaviano Magrassi (1908 – 1974)

Figure 5

Giordano attended primary, junior high and grammar schools in Naples. In the same city he studied medicine at the feet of Professor Flaviano Magrassi (Figure 5), at the University Federico II, and in 1954 he obtained the MD *cum laude*. During the fourth medical course he had joined the Institute of Medical Pathology directed by Professor Flaviano Magrassi, an expert in infectious diseases and leukaemia, originating in the famous Roman School of Cesari Frugoni. Magrassi, a forerunner of medical specialists in the university, had just arrived in Naples from Sassari in Sardinia. He attracted many talented young students who prepared their Ph.D theses with him and later achieved chairs in many specialties. After obtaining the MD Giordano started a laboratory for the assessment of renal function (mainly devoted to clearance studies) in various human models of renal and vascular disease.

In 1958 Giordano moved to Boston (MA, USA) and remained there for the next 3 years (Table 1).

Year	*Role and functions*
1955-1957	Voluntary Fellow Institute of Medical Pathology
1958	On August 2, married Liliana Pistone (4 children were born: Dario, Diego, Mauro and Laura)
1958-1960	Investigator Peter Bent Brigham Hospital of the University of Harvard, Boston USA
1961-1963	Extraordinary assistant of the Institute of Medical Pathology
1964-1971	Ordinary assistant of the Institute of Medical Pathology
1971-1975	Ordinary assistant at the institute of Clinical Medicine
1969-1985	Professor of Nephrology (yearly renewable by the Faculty of Medicine)
1975	Professor of Nephrology (after the National Contest)
1975-1978	Extraordinary Professor of Nephrology
1983-1986	Director of the Institute of Internal Medicine and Nephrology
1978-1985	Full Professor of Nephrology
1984-1986	Dean for Curricula Faculty of Medicine
1985-1986	Full Professor of Medical Pathology
1987- 2002	Full Professor of Internal Medicine
1975-2002	Director of the Postgraduate School of Nephrology
1987-2002	Director Department of Clinical and Experimental Medicine

Table 1 – Roles and functions (research, clinical duties and teaching) at the University Federico II in Naples, at the Second University of Naples (Italy) and at the University of Harvard in USA.

There he studied clinical nephrology, dialysis and transplantation at the feet of Prof. John Putnam Merrill (Figure 5) the "father of nephrology as a discipline" (Prof. Murray Epstein, Nobel prize in medicine in 1991), at the Peter Bent Brigham Hospital of the Harvard Medical School ("no Institution has done more for propagation of dialysis in the United States"- again Professor Epstein).

He had been able to contact Professor Merrill while the Harvard professor was travelling to conferences throughout Italy. Merrill was very impressed by the talents of the young Italian physician and even offered him hospitality at his home (1958). This resulted in a daily scientific exchange with the man who, in association with Professor Joseph E. Murray, had made the first successful renal transplant between identical twins: the brothers Herrick, namely Richard (the recipient) and Ronald (the donor). So Giordano was at the right time in the most prestigious place in the forefront of modern nephrology. There he learned and practiced at the same time dialysis and transplantation from top investigators.

Upon his return to Naples (1961) he developed a laboratory devoted to nutrition in renal disease, which was located in 3 large rooms on the 3rd floor of the Institute of Medical Pathology. Available equipment included a flame photometer, an osmometer, a spectrophotometer, laboratory centrifuges and one ultracentrifuge, a Warburg apparatus, equipment for acid base measurement in blood and urine, an amino acid analyser and Kjeldhal apparatus for measuring nitrogen in urine and faeces. However the most important piece of equipment was a Kolff-Brigham artificial kidney, which had been donated to Giordano by Mr. Edward Olson, its manufacturer. The artificial kidney was located in a special room (called room no. 6) on the fourth floor of the institute where dialysis for acute renal failure was performed. Dialysis for ESRD was started in 1966.

In 1959 Giordano applied a project for nutrition of patient with chronicc kidney disease to the National Institutes of Health of the United States of America. He was financed. He received grants and a contract for projects on nutrition, sorbents and peritoneal dialysis for the next 21 years (1959-1980).

At the University of Naples Federico II Giordano (Table 1) was ordinary assistant (1964-1971), and then Professor of Nephrology-after the national examination in 1975- until 1986. He was invited to

take up the chair in Medicine and Nephrology at the Catholic University in Rome but he declined. Thus he was made full Professor of Medicine in Naples in the years 1986-2002. He was Dean for C*urricula* and founded the postgraduate school of nephrology. He was a member of the board of professors for the Ph. D. Program In Nephrological Science (1980-2002). He was one of the 10 founders of the Italian Society of Nephrology over which he subsequently presided. He was also a founder of the Italian Society of Artificial Organs, a founder of the International Paediatric Nephrology Association, International Society of Artificial Organs and the International Society of Peritoneal Dialysis. In addition he was instrumental in starting academic paediatric nephrology in Italy.

With Wichtig Editore he set up the *International Journal of Artificial Organs*, the *International Journal of Pediatric Nephrology* (later changed by Karger AG into Child *Nephrology and Urology)*, and *Giornale Italiano di Nefrologia*. There were problems in breaking the collaboration with the group of *Minerva Nefrologica*. However, as pointed out in the letter to the readers, this was just the act of independence of the Italian Society of Nephrology as confirmed by the nomination of Prof. Giuseppe Piccoli as Editor in Chief to express continuity with the work of the previous editorial staff.

Fellows and Collaborators

His first fellow was Dr Renato Esposito, a talented investigator with a great interest in clinical chemistry. Giordano also attracted two medical students working on their theses (Natale G. De Santo and Carlo de Pascale) who were the first to be tutored by Giordano for the MD. The initial group also included Mr. Antonio Ariano (laboratory technician), Ada Crescenzi (Ph.D in chemistry), Maria Pluvio and Lia Poderico (nutritionists). An incomplete list of collaborators is given in Table 2.

(i) Fellows

- **Renato Esposito**, (expert in renal nutrition, **s**orbents, tissue typing, member of the transplant team, Associate Professor of Nutrition and chief of unit for nutrition of surgical patients
- **Natale Gaspare De Santo**, physiologist, space physiologist, nephrologist, expert in peritoneal dialysis, member of the transplant team, full Professor of Pediatric Nephrology and full Professor of Nephrology
- **Carlo de Pascale**, nephrologist, expert in nitrogen balance, amino acid analysis and peritoneal dialysis, Chief of Nephrology of the Cotugno Hospital for Infectious Diseases in Naples.
- **Giuseppe Capodicasa**, nephrologist, expert in renal transplantation, vascular access, hemodialysis, and hemoperfusion, Associate Professor of Nephrology (*Deceased*)
- **Domenico Cirillo**, Expert in renal transplantation, vascular access, hemodialysis and renal pathology, Associate Professor of Nephrology
- **Nicola Perna**, cardiologist, nephrologist, forerumner of cardionephrology. Associate Professor of Nephrology
- **Daria Acone**, nephrologist, expert in hypertension and hemodialysis University Investigator
- **Vincenzo Calderaro**, nephrologist, expert in peritoneal dialysis and ultrasonography, renal pharmacologist. University Investigator (*Deceased*)
- **Ferdinando Cocco**, virologist, nephrologist, expert in renal transplantation. University Investigator, Chief Renal Division at Nocera and Nola Hospitals
- **Ugo Cocco**, diabetologist, endocrinologist. University Assistant
- **Francesco Saverio Di Maio**, nephrologist, expert in hypertension and hemodialysis. University investigator
- **Sonia Garzoni**, nephrologist, expert in hypertension and hemodialysis, **U**niversity **I**nvestigator
- **Mario Landolfi**, nephrologist, expert in tissue typing, member of the transplant team, **U**niversity Investigator (*Deceased*).
- **Norina Lanzetti**, nephrologist, expert in sorbents. University Investigator
- **Massimo Manzo**, expert in vascular access, tissue typing and hemodialysis, member of the transplant team University Investigator
- **Anna Papa**, nephrologist, expert in peritoneal dialysis. University Investigator. (*Deceased*)
- **Teresa Troiano Rattazzi**, (expert in nutrition), subsequently in Brooklyn with E.A. Friedman and in Seattle

with B. Scribner. Director of a dialysis unit. (*Deceased*)
- **Sabino Rinaldi**, nephrologist, expert in amino acid analysis.University Investigator. (*Deceased*)
- **Antonio Saggese**, nephrologist, immunologist, member of the transplant team. University Investigator
- **Pietro Castellino**, nephrologist, expert in protein related kidney hyperfiltration. Full Professor of Medicine, University of Catania
- **Maria Pluvio**, biologist, nutritionist, nephrologist, Ph.D in nephrology, University Technician. (*Deceased*)
- **Paolino Raiola**, nephrologist, expert in hemodialysis. Clinical Assistant in Nephrology of the Campania Region
- **Amalia Poderico**, nutritionist, chief nurse
- **Antonio Ariano**, expert in biochemical analyses for nitrogen balances, Laboratory technician (*deceased)*

(ii) *Group on Sorbents*
- **Renato Esposito**, Coordinator
- **Giacomino Randazzo**, Advisor, Full Professor of Biochemistry Faculty of Science
- **Giovanni Demma**, Doctor in Chemistry, investigator Faculty of Agriculture
- **C. Rufolo**, Doctor in Chemistry
- **Piero Bello**, Doctor in Chemistry, high school professor
- **Ernest Quarto**, Engineer, University Professor of Mathematics. Professor of Medical Engineering
- **Norina Lanzetti**
- **Maria Pluvio**
- **Antonio Ariano**
- **Mario Landolfi**
- **Massimo Manzo**
- **Antonio Saggese**

(iii) Group for physiology, peritoneal dialysis, pediatric nephrology, epidemiology of renal disease and space research
- **Natale G De Santo**, Coordinator
- **Giovambattista Capasso**, physiologist, expert in acid-base and electrolytes and peritoneal dialysis. Full Professor of Nephrology University of Campania Luigi Vanvitelli, Scientific Director Biogem at Ariano Irpino (AV)
- **Massimo Cirillo**, nephrologist, internist, epidemiologist, expert in hypertension, biostatician. Associate Professor and **C**hief of Nephrology at the University of Salerno
- **Pietro Anastasio**, nephrologist, pediatric nephrologist, urologist, expert **in** GFR assessment and hemodialysis. University Investigator
- **Rosa Maria Pollastro**, nephrologist, expert **in** glomerular disease and renal pathology, Ph.D in Space Physiology. University **I**nvestigator
- **Alessandra Perna**, nephrologist, Ph.D in nephrological sciences, expert in homocysteine. Associate Professor University of Campania Luigi Vanvitelli
- **Biagio Di Iorio**, nephrologist, Ph.D in Nephrological Sciences, uremia specialist, Professor Postgraduate School of Nephrology at the Second University of Naples. Chief of Nephrology Solofra Hospital
- **Daniela Molino**, nephrologist, Ph.D in Nephrological Scienes, expert in coagulation. Pediatric Nephrologist Santobono Hospital Naples
- **Francesca Nuzzi**, nephrologist, Ph.D. in Nephrological Sciences, expert in renal pathology. Pediatric Nephrologist of Santobono Hospital Naples
- **Teresa Cicchetti**, nephrologist, expert in peritoneal dialysis. Chief of Nephrology at the General Hospital at Rossano Hospital
- **Raffaele Senatore**, nephrologist, expert in peritoneal dialysis. Former Chief of Nephrology at the General Hospital at Cariati Hospital
- **Maria Damiano**, nephrologist, expert in peritoneal dialysis. Anesthesiologist San Carlo Hospital Potenza

- **Table 2. Giordano's collaborators**

Table 3 lists some of Giordano's achievements in science. Table 4 lists his active membership in various societies, and the congresses that he organized personally.

(i) Honors
- Doctor Honoris causa of the Polish Academy of Sciences

- Golden Kidney Award from the European Society of Pediatric Nephrology
- Domenico Cotugno Award from the University of Bari
- President and Hon President of the Italian Society for Artificial Organs
- President of the Italian College of University Professors of Nephrology
- Hon. member of the German Society of Nutrition

(ii) Lectures

Polish Academy of Sciences, Nephrological Societies of Italy, Sweden, Brazil, Argentina, Japan, Czechoslovakia, Singapore, EDTA (1975, 1985), International Society of Nephrology, International Society of Artificial Organs, European Society of Nutritionists

(iii) Editorial boards

Minerva Medica, Nephron, Clinical Nephrology, Kidney International, Giornale Italiano di Nefrologia (founder), International Journal of Artificial Organs (founder), Artificial Organs International Journal of Pediatric Nephrology (founder), Diabetic Nephropathy, Diabetes Complications, Medizin und Ernhaung, Peritoneal Dialysis Bulletin

(iv) Funding

He received 50 scholarships among them 33 research grants and contracts from the National Institutes of Health Bethesda. He was also supported from the National Research Council of Italy, Regione Campania, Italian Ministry of Health

Table 3 – Gordano's achievements

(i) Scientific Societies

- International Society of Nephrology (A founder in Geneva)
- European Dialysis and Transplant Association (Councillor)
- European Society for Paediatric Nephrology (President)
- International Society for Pediatric Nephrology (Founder)
- International Society for Peritoneal Dialysis (Founder and President of the Venice congress)
- International Society for Artificial Organs (Founder)
- Italian Society of Nephrology (Founder and President)
- Società Italo-Americana di Nefrologia (Secretary)

(ii) Congresses (as organizer)

- The Second Italian Congress of Peritoneal Dialysis
- The Italian Congress of Nephrology
- The Capri Conferences on Uremia in 1974, 1977, and 1980
- The Sorrento International Workshop on Artificial Organs in 1980
- The Venice Congress of the International Society for Peritoneal Dialysis

Table 4. Scientific societies and congresses

INVESTIGATORS ON SABBATICAL

Various creative clinical scientists worked during sabbaticals at the nephrology department directed by Carmelo Giordano (Table 5).

(i) Visiting scientists from abroad and from Italy

- Kazimierz Backzyk, 2nd Medical Clinic, University of Poznan, Poland
- Otto Busato, Professor of Nephrology, University of Porto Alegre, Brazil
- Malcolm Phillips, Consultant Nephrologist at Charing Cross Hospital, Medical Director Charing Cross and Hammersmith Hospitals Trust in London
- Alejandro Trevino Becerra, Chief Division of Nephrology, Mexico City, DF, Mexico

- Francisco Gonzales, Professor of Medicine, Louisiana State University, USA
- Shaul Massry, Professor of Medicine, Keck School of Medicine, Los Angeles
- Domenico di Landro, Assistant in Nephrology at the Polyclinic **T**eaching Hospital in Padua. Chief of Nephrology at Cannizzaro Hospital in Catania for studies on sorbents
- Gianfranco Romagnoli, assistant in nephrology at the Polyclinic Teaching Hospital in Padua, Chief of the same, for studies on sorbents

(il) Most productive collaborations

- Peter Richards, St Mary's Hospital London, for ketoacids
- Peter Fürst, St. Eriks Sjukhus, Stockholm, for nitrogen incorporation into proteins
- Garnar Ryhage, Director Institute for Mass Spectrometry, Karolinska Institute, Stockholm, for studies on nitrogen utilization in healthy and uremic men
- Staley M. Levenson, Albert Einstein College of Medicine, New York, for nitrogen incorporation in germ-free rats
- Jules Traeger, University of Lyon, France for renal transplantation
- Herve Betuel, Immunologist, University of Lyon, for renal transplantation and for genetic studies
- Jean-Michel Dubernard, University of Lyon, for Renal transplantation
- Eli A**.** Friedman, State University of New York, for amino acid losses in hemodialysis and for sorbents
- Ciro Balestrieri, Full Professor of Medical Chemistry, at both medical faculties in Naples, for studies on nitrogen balance and amino acid synthesis and degradation
- Domenico Cittadini, Associate Professor of Medical Chemistry at both medical faculties in Naples, for studies on nitrogen balance and amino acid synthesis and degradation

Table 5. Visiting Scientists and most productive collaborations

The first was Prof. Kazimierz Backzyk, later Professor of Nephrology at the Medical University of Poznan (Poland). He arrived in Naples at a time when Eastern Europe began to separate from the West with the construction of the Berlin wall.

Dr. Malcolm Phillips came to Naples from London as a Welcome Trust Research Fellow for 2 years (1970-1972). His fellowship was arranged between Professors Hugh de Wardener and Carmelo Giordano. He studied amino acid losses on dialysis, the effects of essential amino acid supplements in hemodialysis patients and the utilisation of keto-acids in healthy and uremic subjects. Later, when back in London, Dr. Phillips was, for varying periods General Manager of the Charing Cross Hospital and Medical Director of the Charing Cross and Hammersmith Hospitals Trust.

Prof. Otto Busato came from the Department of Nephrology at the University of Porto Alegre, Brazil, to work on nutrition and peritoneal dialysis. Also Prof. Alejandro Trevino Becerra came with the same goal and subsequently was anchored long term to the topic. Francisco Gonzalez, Professor of Medicine and Chief of Nephrology at Louisiana State University in New Orleans, during his stay attracted many young investigators to study acid-base balance in HD and PD and focused his research on pharmacological means to augment peritoneal dialysis clearances.

The collaboration with Professors Ciro Balestrieri and Domenico Cittadini of the Department of Biological Chemistry at the University of Naples was long-lasting and produced outstanding results.

Drs. Gianfranco Romagnoli and Domenico Di Landro came from the Hospital of the University of Padua to learn about sorbent therapy.

The list of visiting scientists includes, among many others, Professors Jan Brod, Jan Roguski, Thadeus Orlowski, Geoffrey M. Berlyne, Karl Julius Ullrich, Shaul Massry, Klaus Hierholzer, Jules Traeger, Gerhard Malnic and Willem Kolff who was attracted by the use of sorbents for wearable kidneys from Professor Renato Esposito and wrote on this experience in *Dialysis and*

Transplantation.

GIORDANO'S HOBBIES

Giordano had many interests. He enjoyed to play with words and look into their etymology, a reflection of his days at the grammar school (in Italian Liceo Classico). He was interested in soccer and had season tickets for the home matches of the Naples Soccer Club at the time of the great player Armando Maradona.

He also enjoyed driving Porsche cars, and sailing. He had a boat constructed in Finland (*Black Swan)*, described in the *Treccani Lexicon*-where photos of Giordano and his crew appear- for its outstanding technical characteristics. He participated in many national and international races and developed an international reputation. Once, with a crew made of young investigators and professors including the famous Professor of Modern History, Giuseppe Galasso (a member of Accademia dei Lincei-Linx) who was responsible of the *fiocco* (jib), Giordano made third place in the Giraglia Cup. For those not experts the jib is a triangular sail placed in the ship's bow and the Giraglia Cup is a race starting in St. Tropez, France, passes through the Îles d'Hyères off the French coast near Toulon, then around Giraglia, and finishes in Genoa, Italy, a total of 243 nautical miles.

Giordano also loved to cook simple Neapolitan dishes and from time to time he prepared, late in the evening, spicy spaghetti for his colleagues and guests.

He aspired to perfection in work and used to say "we shall do without mistakes". This imposed a strong work ethic and mental concentration in his collaborators.

The University Federico II: a university with two medical faculties

In Naples**,** for reasons difficult to explain in a few words**,** there were two medical faculties at the University Federico II. There was competition between the two schools (normal healthy university life) but there were also frictions, which surpassed the politically correct and affected the academic life of fellows. In 2014 there was finally peace, but it was too late. The wounds had healed with ugly scars.

Publishing or perish

Giordano had a great interest in teaching medical students and fellows**.** He was convinced that the best way to teach was through writing books. A complete list is given in Table 6. The frontispiece is depicted in Figures 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17. The first book (Figure 6) was the nicely printed *Nefrologia*. The outline was that of a U.K. manual, being fresh, modern and easy to read. It included dietary treatment for acute and chronic renal failure

(i) For medical students and fellows

1. Giordano C. *Nefrologia*. Idelson, Napoli, 1963, pp VIII+ 290+IV (Figure 6)
2. Giordano C. *La nutrizione nelle malattie renali*, Edizioni Minerva Medica, Torino, 1964, pp. IV+70+IV (Figure 7)
3. Giordano C*. Fisiopatologia dell'apparato urinario*. In Magrassi F, Ed, *Trattato di Fisiopatologia Medica*. Società Editrice Universo, Roma 1966, pp. 1241-1390 (Figure 8)
4. Giordano C. *Nefrologia*. Idelson, Napoli,1979; pp XV+325+II (Figure 9)
5. Giordano C. *Sorbents and their clinical applications*. Academic Press, New York, 1980 (Figure 10)

6. Giordano C. *Nefrologia*. In Zanussi C, Ed, Medicina Interna. UTET, Torino, 1986 pp XV+372+IV (Figure 11)
7. De Santo NG, Capasso G, Giordano C. *Alterazioni del ricambio Idroelettrolitico*. USES, Firenze,1988. pp. VII+271+IV (Figure 12)

(ii) Conference Proceedings

8. Giordano C, Friedman EA. Uremia. *Pathobiology of patients treated for 10 years or more*. Wichtig Editore, Milan 1981, pp X+311+IV (Figure 13)
9. Giordano C and De Santo NG. *Dialisi Peritoneale*. Atti II Congresso Nazionale di Dialisi Peritoneale, Capri 1983, Wichtig Editore Milan, 1984 (Figure 14)
10. Giordano C, De Santo NG. *Nefrologia, Dialisi Trapianto*. Atti XXVII Congresso SIN, Napoli 23-25 maggio 1986; pp. XV+447+IV (Figure 15)
11. Friedman EA, Beyer M, De Santo NG, Giordano C. *Prevention of Progressive Uremia*. Vol I and II. Field and Wood, New York, 1989. Vol I pp XIV+ 179 +IV, Vol II XVIII+ 229 pp+ II (Figure 16)
12. Avram MM, Giordano C, Eds, De Santo NG, Mittman N, Bazzato G, Co-eds. *Ambulatory Peritoneal Dialysis*. Plenum, New York, 1990, pp.XVI+349+IV (Figure 17)

Table 6. Giordano's books

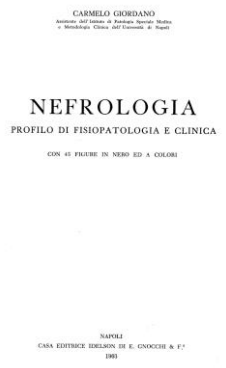


Figure 6

Figure 7

Figure 8

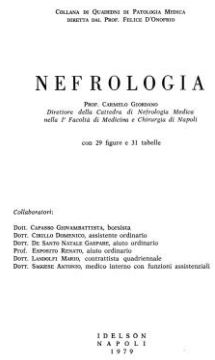


Figure 9

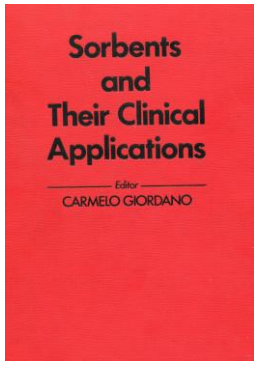


Figure 10

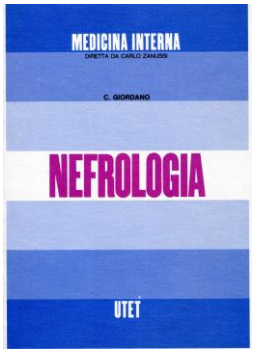


Figure 11

Figure 12

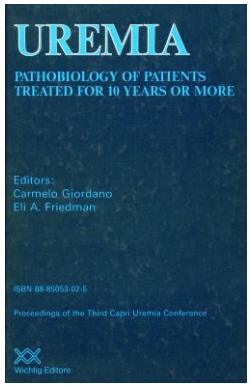


Figure 13

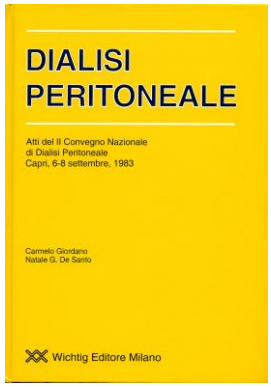


Figure 14

Figure 15

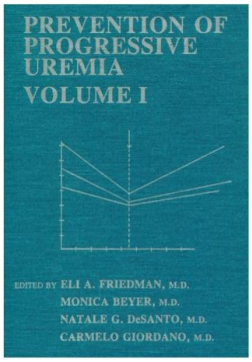


Figure 16

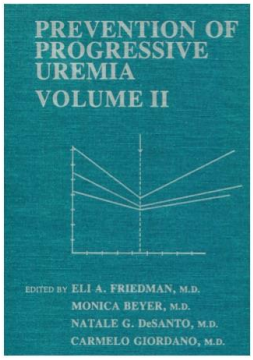


Figure 17

The second book was a concise monograph on nutrition in renal disease (Figure 7), the first of its kind worldwide**.** It could be easily read by students and by practitioners. Giordano put great emphasis on electrolytes and acid base balance (Figures 8 and 12).

His most important book was *Sorbents and their clinical applications* (Figure 10), which opened the field to the use of sorbents in the clinical setting. It was the work of a renowned specialist in the field.

For many years Giordano laid great store in participating in congresses, including the Annual Contractors' Conference in Bethesda, the Congress of the EDTA and of the International Society of Nephrology, the Italian Society of Nephrology, Giornate Nefrologiche of the Saint Carlo Hospital in Milan, as well as those relating to artificial organs work. Many outstanding data are contained in the proceedings of those congresses.

NUTRITION IN CHRONIC KIDNEY DISEASE

Diets in CKD

In 1959 Giordano applied to the National Institutes of Health of the United States in Bethesda for funding for a project devoted to nutrition in kidney disease. He proposed the use of low protein diets in the form a) essential amino acids and b) as proteins of high biological value, both rich in energy. The project was financed and was the first of a series of grants (1959-1980). Giordano's first study with L-essential amino acids was a classical example of self-experimentation. For 53 days Giordano ingested L-Essential amino acids in a quantity classically defined by Rose. The basic formulation was supplemented either with 3 g of nitrogen (N) derived from glycine (period A), or 0.5 g of N derived from glycine (period B), or 2 g of N in the form of ammonium citrate (period C) or 2 g of N in the form of urea (period D). Nitrogen balance was calculated by daily analysis of urine and fecal nitrogen. The study was published in the *Bollettino della Società Italiana di Biologia Sperimentale* (1).

The subsequent experiment (2) with amino acids (2 g of N/day) was carried out in two patients with very low GFR's and this produced positivity of nitrogen balance.

The third crucial experiment was performed in one healthy person (C. Giordano himself) and in 8 patients with eGFRs of 9-26 ml/min (Table 7).

Persons	*eGFR/MDRD)*	*Hypertension*
Healthy	120	no
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

Financed by National Heart Institute Grants H-5773 (C1- C2), HE-05773-03

Table 7. Studies on low protein nutrition

These subjects received L- essential amino acids (2g N/ day - period A) followed by a diet (period B) containing 23 g of protein of high biological value. The energy intake was high in both periods. In that paper (3) there are data on the effects of a synthetic diet containing essential amino acids (17.7g/ 2g of N), 2300 calories in women, 3100 in man-followed by a low protein diet (3.8g/N, 68 % from milk, 23g of protein in total). The paper published in J Lab Clin Med was cited 401 times. A typical experiment in 1 subject is depicted in Figure 18.

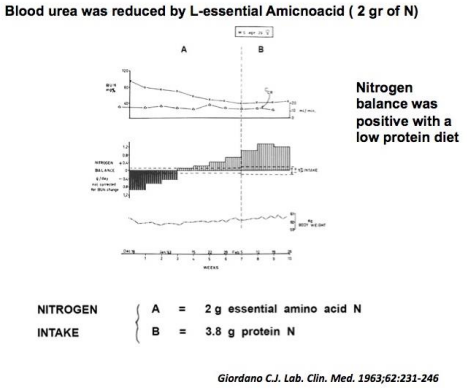


Figure 18

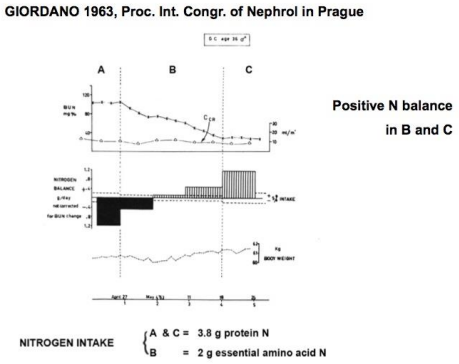


Figure 19

At the second congress of the International Society of Nephrology in Prague in 1963 Giordano presented unique work on low protein alimentation. This consisted of data in 23 patients with chronic kidney disease (plasma creatinine 2.6 to 9.0 mg/dl) treated for a total of 236 months. The patients underwent a dietary schedule for 5 weeks: in weeks 1 and 5 they ate a low protein diet (23g day in the form of protein of high biological value) and in weeks 2-4 a diet providing 2 g of N/day as L-essential amino acids (4). A typical experiment in 1 subject is depicted in Figure 19.

In 1964 Giovannetti and Maggiore published data on CKD patients with GFRs of 3-6 ml/min who received a protein poor diet (N 1.0-1.5 g/day) for 10-15 days followed for 2 weeks by a low nitrogen intake (1.74 g/day) as L- essential amino acids and then (indefinitely) by a restricted protein intake (2.2 g of N/day) in the form of egg protein, or egg albumen. Amino acids promoted a positive nitrogen balance, which was maintained under the low protein regime (5).

In the same year Giordano published the aforementioned book on *La Dieta nelle Malattie Renali/ Nutrition in Renal Disease,* in which he suggested the use of L-essential amino acids for 2-3 weeks followed by a low protein diet with natural foods providing 23 g of protein/day (6). Additional data from the groups in Naples and Pisa were published in *Minerva Nefrologica* in 1965 (7, 8). This was the genesis of the Giordano-Giovannetti Diet, as said first by Geoffrey M. Berlyne (9, 10, 11, 12, 13). The pioneering nature of this work has been described elsewhere (14, 15, 16).

At the III Congress of Nephrology in Washington Giordano, De Pascale, Esposito and De Santo (14) presented data in 25 CKD patients kept on diets providing up to 25g proteins a day. It was shown that 85% of patients achieved a positive nitrogen balance when the diet provided 25g of protein/day (Table 8). Many other studies (17, 18, 19, 20, 21, 22, 23) confirming the feasibility and

the usability of low protein diets were published in the years 1967 and 1968. Kopple at that time was ready to prescribe a 40g protein diet (20). Of course this diet was easy to take since 0.6g/kg is, according to nutritionists, a normal intake in adults.

At the Scottsdale Conference on Nutritional Aspects of Uremia (23) Giordano was applauded as is apparent from the proceedings, published in the *American Journal of Clinical Nutrition, which* contained favorable comments by very eminent scientists (Table 9).

Tab 8. Nitrogen Balance (reference no. 20)

Case no.	Nitrogen free diet	Ess. amino acid diet 8–11 g	Low protein 17	20	23	25
1			— .600	+ .415		
2			— .403	+ .195		
3			— .407	—1.597		
4	—1.337	+ .606	— .750	— .320		+1.200
5	—2.482	+ .100				+ .900
6	—3.662	+ .368	— .540		— 778	
7		— .931	— .605	— 854	— 070	+ .292
8		+ .306				+ .935
9	—1.962	—1.416				—1.210
10					+ .052	
11			— .891	.879	— .379	
12			— .650	— .318	+ .550	+ .972
13			+ .095	+ .450	+ .780	+1.000
14			—1.682	—1.105		+ .240
15		— .800		+ 309	+ .171	+ .756
16		— .048	— .240			
17		— .537	+ .096		+ .450	+ .432
18			—1.000			
19		+ .092				
20			—4.073			
21		+ .069		— .230		+ .865
22		+ .405	— .184	+ .461		+1.210
23			—1.691		— .870	— .905
24		+ .125	— .430	+ .628	+ .890	+ .775
25		— .204	+ .129			
percentage of positivity		57%	16%	46%	60%	85%

Lewis E. p.350. "Giordano had previously presented evidence to support the concept that urea nitrogen can be utilized for protein anabolism in attaining positive nitrogen balance when the diet **is** adequate calorically". "Our special thanks to Dr. Carmelo Giordano who came from afar to make an important contribution".

*Hemmett L and Holt JR, p..375 "*We did not have the wit which Dr. Giordano had to apply this to uremia problem. I was very impressed when his paper came to my attention and I would like to congratulate him for making this use of it".

Swendseid M. p. 382. "It is quite possible that in chronic renal failure the optimal amino acid requirements are different than in health. The innovating experiments of Giordano are indications in this direction"

Ginn EA, Frost A, Lacy WF, p.385. "Our effort was based on the possibility of treating uremic subjects with a diet that permitted the use of endogenous urea for protein synthesis as was earlier suggested by Giordano and after by Giovannetti and Maggiore".

Berylne G, Gaan D, Ginks WR, p. 547. "We have put over 100 patients suffering from chronic renal failure on the Manchester modification of the Giordano-Giovannetti diet".

Kopple JD et al, p. 560. "This conclusion was buttressed by the demonstration of marked decrease in SUN, intact or only slightly negative nitrogen balance and possibly endogenous urea for protein synthesis".

*Gulyassi P*F et al, p. 565. "Rigid reduction of protein intake can produce considerable clinical improvement in patients with moderately or far advanced uremia"

Salteri P and Pittaluga L, p. 590. "Dietetic products, treatment of Chronic Uremia, and the Giordano Giovannetti-Diet.

Lonergan ET and Lange K, p. 595. "In the last 10 years a diet developed by Giordano and Giovannetti and later modified by Berlyne"

Table 9. Some comments on Giordano's work as it emerged at the Scottsdale Conference on the Nutritional Aspects of Uremia (Am J Clin Nutr 1958; 21 pp. 640-642).

Studies on ketoacids

Giordano had many doubts on the long-term usability of ketoacid analogs in CKD. However he worked hard on this topic. The first experiments dated back to 1968. At that time there was uncertainty about the possibility of utilizing D amino acids for protein synthesis in man (24). An experiment was devised on a young patient with chronic glomerulonephritis who underwent various amino acid regimens (Table 10). The diet provided 5 DL-essential amino acids and 3 L-essential amino acids (Period A), 8 L-Essential amino acids (Period B), 8 L-Essential amino acids with urea (Period C). In period D 8 L-essential amino acids + urea where given in association with paromomycin to sterilize the gut. Nitrogen balance was positive in periods A, C and D, negative in B (Figure 20). The experiment demonstrated that the α-amino nitrogen of D amino acids was fully utilized indicating that nitrogen balance was enhanced by the extra nitrogen of D-isomers.

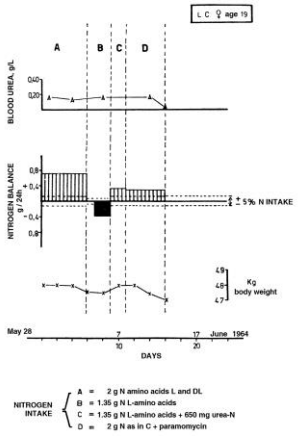


Figure 20

In 1970 experiments were carried out at St Mary Hospital in London study in nitrogen balance and ^{15}N incorporation in patients receiving the keto analogs of valine and phenylalanine in health and CKD. Nitrogen balance rapidly became negative when either or both phenylalanine and valine were withdrawn from the diet of healthy persons and patients with chronic renal failure. Replacement of these essential amino acids by their α-ketoacid analogs ameliorated or normalized nitrogen balance (25). Data on N incorporation went in the same direction as nitrogen balance pointing to the possibility of substituting amino acids with their keto analogues (26). However, with time, the enthusiasm for this was cooled by data, which showed absence of catch-up growth in infants switched from an amino acid to a ketoacid diet (27). In that study 6 children with GFRs of 0.9 -3 ml/min and two babies (GFRs of 22 and 15 ml/min) were fed either with a formula diet (28) according to the data of Holt and Snyderman (diet D) or according to the uremia reference pattern (29) of Giordano, De Santo and Pluvio (diet C). Both formulae (27) were made either with amino acids or amino acid + 4 ketoacid analogs and a hydroxyacid: alfa-keto-isocraproic acid, L-ketoβmethylvaleric acid, alfa-ketoisovaleric acid, phenylpyruvic acid, αhydroxy-γmethylbutiric acid as keto analogues of L-leucine, L-isoleucine, L-valine, L-phenylalanine, and as the hydroxyacid of L-methionine, respectively.

In children taking formula C diets (amino acids) nitrogen balance was +0.54±018g whereas with the formula C (keto analogues) it averaged +0.14±0.16g (Table 10). In infants formula C (amino) and fomula D (amino) provided growth superior to formula C (keto) and formula D (keto) diets, as indicated in Table 11.

However the results of the studies data of Professor Mackensie Walser on ketoacids were more and more convincing and were confirmed in other laboratories. Thus on the occasion of the plenary lecture at the Athens Congress of the International Society of Nephrology Giordano, while acknowledging the impossibility for nutrition to compete with dialysis and transplantation, made the point that appropriate alimentation should be used very early in the course of chronic kidney disease. He was finally able to bring opinions together from available studies on the use of ketoacids and supported their use as one modality of nutrition in chronic kidney disease (30).

6 children with GFR of 0.3-3.0 ml/min and 2 babies (GFT of 22 and 15 ml/min) were nourished either with a formula diet according to Holt and Snyderman (Diet D) or According to the uremia reference pattern of Giordano De Santo and Pluvio (Diet C).Both formulas were made either by amino acids or amino acids + 4 ketoacid analogs and 1-hydroxyacid

α-ketoisocaproic acid	**L-Leucine**
α-ketoβmethylvaleric acid	**L-Isoleucine**
α-ketoisovleric acid	**L-Valine**
Phenylpyruvic acid	**L-Phenylalanine**
A-hydroxy-γ-methylbutiric acid	**Hydroxyacid of L-Methionine**

NITROGEN BALANCE **+0.54±0.18 g/day** **FORMULA C, AMINO ACIDS**
+0.14±0.16 g/day* **FORMULA D, KETO ACIDS**
***p<0.005 vs Formula C**

Giordano C, De Santo NG, Di Toro R, Pluvio M, Perrone, Kidney Int 1978; 13:S83-86 (27).

Table 10 – Amino acid and keto acid in uremic children and infants

FORMULA*		DAILY GROWTH (g)	
		Pat 7	Pat 8
Control Similac		13.3	10
Formula C	amino	25.3	38.6
Formula C	keto	10	8.3
Formula C	amino	40	25
Formula D	amino	50	31.5
Formula D	keto	30	30

Table 11 - Growth in infants on various amino acid and keto acid formulations. Growth was superior with amino acid diets (Modified from reference n. 36).

Further studies on nitrogen metabolism in health and uremia

Plasma aminograms from uremic patients showed, for the first time, an impaired tyrosine to phenylalanine ratio, an increase in 3- methylhistidine and a depression of the histidine to methylhistidine ratio. Loss of free amino acids and small peptides was 15-20 g per each hemodialysis session (31).

Labeled molecular nitrogen was administered subcutaneously in a CKD patient (creatinine clearance 7.5 ml/min). Labeled nitrogen was subsequently found in amino acids of plasma albumin, indicating that molecular nitrogen is not an inert gas in humans (32).

In another study the energy load from dialysate (800 cal/day) in CAPD patients was described (Figure 21). The patients were undergoing 2 liters exchanges five times a day (33). Nitrogen balance studies were performed for the first time in CAPD patients and it was demonstrated that a protein intake of 1 g/kg/day was sufficient (Figure 22) to keep a neutral or positive nitrogen balance (34).

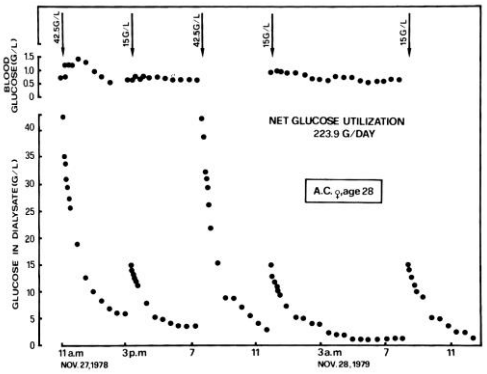


Figure 21

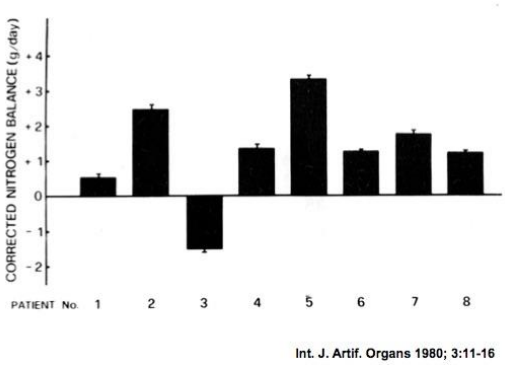


Figure 22

Giordano was also first to describe (i) amino acid losses in CAPD in children, (ii) the protein requirements of children on CAPD, (iii) the energy load of children on CAPD. In addition he showed that nitrogen balance of diabetic patients on CAPD was maintained by prescribing a diet containing 1.3 g/kg of protein per day (35).

Although dialysis and transplantation (a procedure available to a minority of patients) are vital treatments they are expensive. Giordano continuously searched for improvements in renal nutrition. Even one year of dietary treatment would spare relevant resources. This interest was not lessened by the negative results of the very publicized MDRD study (14, 15)

Giordano's last thoughts of low protein alimentation

The last time Carmelo Giordano participated in a scientific meeting (*Survival is not Enough* no.10, Naples March 10, 2016 at the Italian Institute for Philosophical Studies) he declared his interest in promoting transplantation because of the quality of life it offered (36). However he declared himself very pleased by the paper of Denis Fouque and William E Mitch which stated: "In the history of medical sciences fewer topics have been the focus of so many clinical trials, reviews, speculation, and discussions than the question of what constitutes an optimal protein intake for patients with kidney disease... But probably we are reaching a consensus" (37).

He felt that this tenet was strongly supported by: (*i*) the studies of Massimo Cirillo et al. in middle aged subjects of the Gubbio Population Study (the whole population of that city in central Italy) showing that higher protein intake is associated cross-sectionally with higher GFR but longitudinally with greater GFR decline over time (38); (*ii)* data of Bruno Cianciaruso et al (39); (*iii*) data of Vincenzo Bellizzi et al. (40), (*iv*) a report on the costs of CKD therapy in the Campania Region co-authored by many authorities and coordinated by Giorgio Liguori (41), and (*v*) by data of Vincenzo Bellizzi and Biagio Di Iorio et al. (42) as well as (*vi*) by the data of Di Iorio's team on the effects of very low protein diets on Fibroblast Growth Factor 23 (43) and on indoxyl sulphate (44).

Studies on sorbents in uremia

Giordano was interested in the use of sorbents in uremia, having developed the idea that the intestine could be used as a third kidney, and having been fascinated by Professor Yatzidis and his studies on carbon. He imprinted this enthusiasm in Professor Renato Esposito, nephrologist and expert in clinical chemistry, Professor of Nutrition and Immunologist (Table 2). He was chief of the laboratory for the development of sorbents (Table 2) which included doctors in chemistry (Pietro Bello, Giovanni Demma, C. Rufolo), a mathematician, bioengineer and associate professor (Ernesto Quarto), a full university Professor of Biochemistry (Giacomino Randazzo), a Ph. D and nephrologist (Norina Lanzetti), a doctor in biological science, Ph.D and nephrologist (Maria Pluvio), a technician (Antonio Ariano) and Carmelo Giordano. We provide here a synopsis of their major achievements (45-75).

Oxystarch

Oxystarch -binding urea and nitrogenous substances- was obtained by oxidizing potato or maize starch (Figure 23). Oxystarch reacts with urea in a manner proportional to the concentration. The isotherm of oxystarch is given in Figure 24. At urea concentrations typical of uremia the reaction yields interesting results at low and neutral pH values. Oxystarch was developed in 1968 and data was published in *Bollettino Società Italiana di Biologia Sperimentale* (45). Oxystarch administered to uremic patients caused increased fecal nitrogen excretion (Figure 25) along with decreased blood urea nitrogen. In a patients treated by peritoneal dialysis (Figure 26) increased fecal nitrogen and reduced blood urea nitrogen were observed and dialysis was postponed by 3 weeks. In a patient on HD oxystarch allowed a prolongation of the interdialytic interval (Figure 27). The data were confirmed by different groups and were shown to be dependent on the fecal mass and the quality of foods. Sorbents bind urea in the stomach and ammonia in the colon. It was shown that the amount of oxystarch could be increased in order to obtain up to 4 g. of nitrogen in feces, which is equivalent to the quantity of urea generated by a protein intake of 24g/day (46, 47, 48, 61, 53, 54).

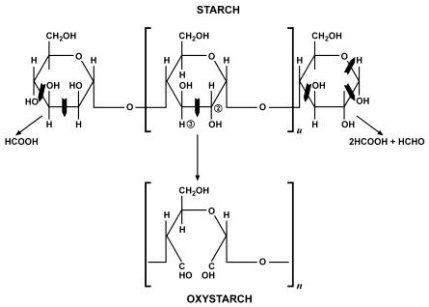


Figure 23

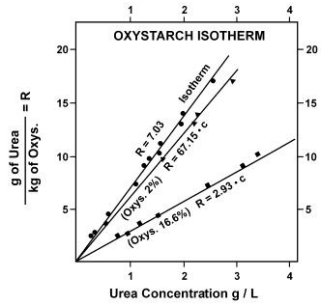


Figure 24

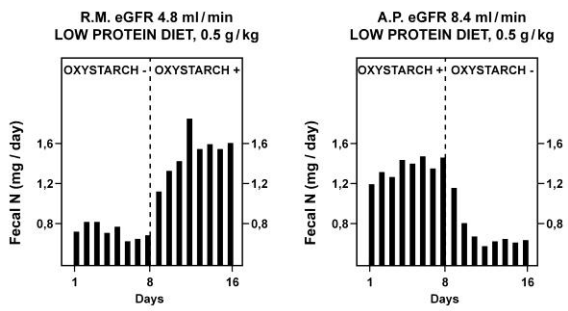


Figure 25

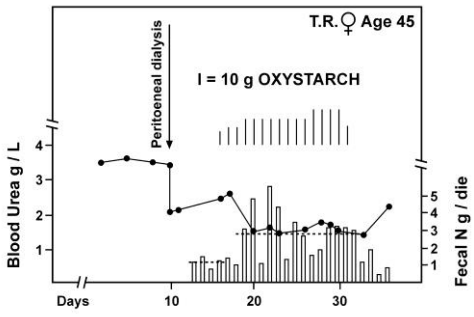


Figure 26

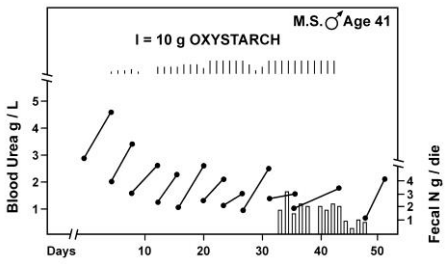


Figure 27

Oxycellulose

Oxycellulose-binding urea and nitrogenous toxins-was obtained by treating wood cellulose with hot acids, cellubiase and cellulase (Figure 28). It reacted with urea at blood concentrations typical of uremia (Figure 29). The reactivity was pH dependent and higher at pH 1 than at pH 7.4 (Figure 30) and is maximal at pH 1 (Figure 31). Oxycellulose could be administered orally (49, 50, 53, 54).

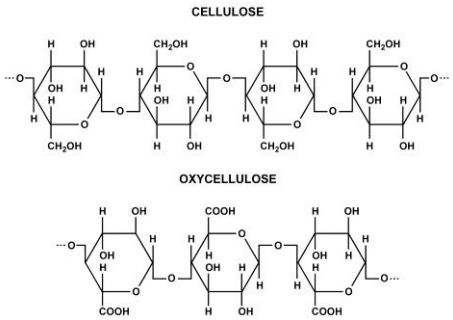


Figure 28

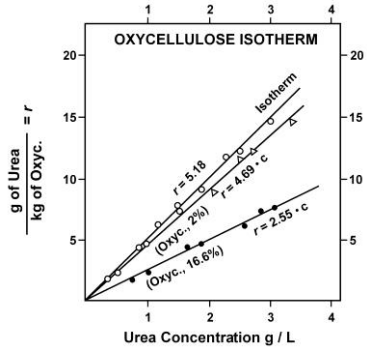


Figure 29

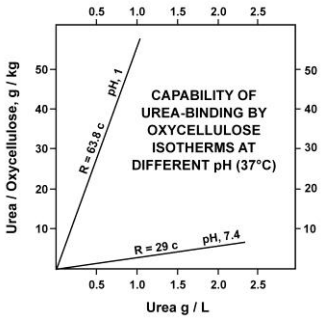


Figure 30

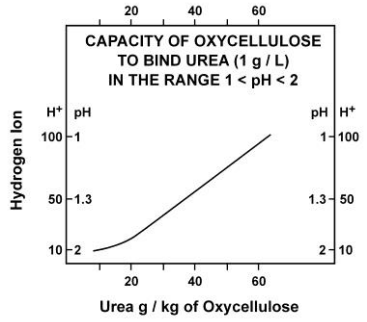


Figure 31

Carbon reactivity with urea between 1 and 90 ˚C

The group on sorbents studied carbon reactivity towards urea (Figure 32) and introduced the use of carbon at 0˚C to bind urea and nitrogenous waste products (Figure 33). They also introduced the concept that working between 1˚C (maximal adsorption) and 90˚C (complete desorption they could indefinitely regenerate carbon (Figure 34), as described in references nos. 54,56, 60.

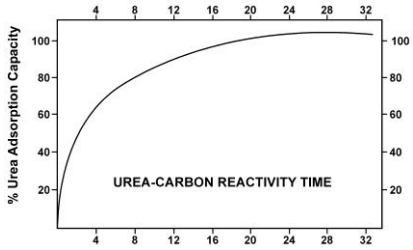


Figure 32

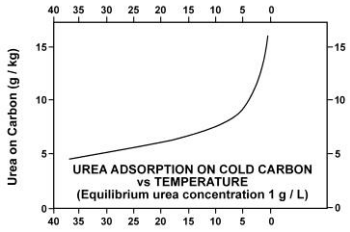


Figure 33

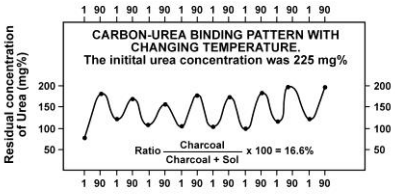


Figure 34

Studies on a carbon based portable artificial kidney

The study allowed the construction of a cold carbon apparatus (35). Carbon is very active at 0˚C so it can be used to regenerate dialysis fluid in a closed circuit. With this approach catabolic products are adsorbed onto cold carbon without interfering with electrolytes which are not adsorbed on carbon. Carbon can also be treated to avoid adsorption of useful metabolites. Adsorption and desorption of solutes is an independent operation for each solute, thus the strategy resembles a natural process. Therefore a portable artificial kidney was envisaged using only a few liters of tap water with low expenditure of energy (around 100 watts) by recovery of energy via a thermal exchanger (52, 54, 59, 60, 61, 62, 63).

A combination of sorbents for portable and wearable artificial kidneys

A portable as well as a wearable kidney were also built by combining, resins, carbon, oxycellulose, oxystarch and 2 liters of dialysis fluid (Figure 35) continually regenerated (55, 56, 61, 62, 63**)**.

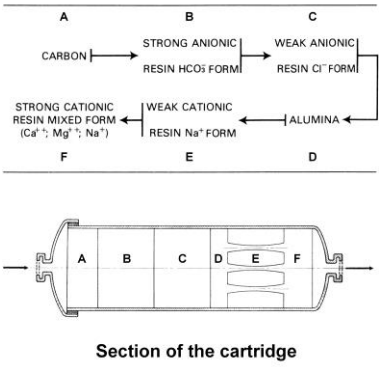


Figure 35

A peritoneal dialysis belt

The group on sorbents finally proposed a peritoneal dialysis belt by using a cartridge containing oxycellulose, active carbon and ion exchange resins. It could work without sorbents for urea as oxystarch and oxycellulose could be given orally. Thus the peritoneal dialysis belt was devised to remove urea and non-urea toxins and to restore fluid and electrolyte balance (Figure 37). The belt was assembled using a strong cation exchange resin in H^+ form, oxycellulose and a weak cationic resin in Na^+ form. The first resin acidified the fluid to pH so that oxycellulose was able to react maximally, the second resin would reconstitute the pH and the electrolytes (62, 63).

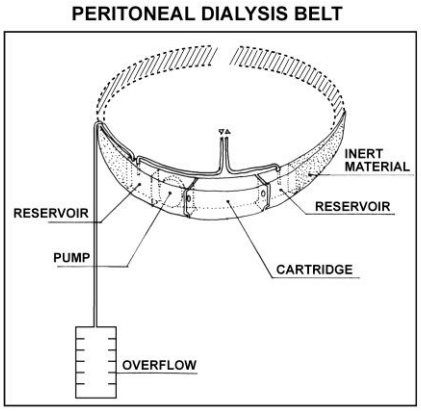


Figure 36

Sorbents and their clinical applications

The group gained international reputation. Their place in academic medicine is indicated by an incomplete list of papers (ref. from 45 up to 75), published in the years 1968-1984 and the details of congresses to which they were invited. Pim Kolff came to visit Renato Esposito and Carmelo Giordano and their group and worked with them. He wrote in *Dialysis and Transplantation* of his cultural experience in Naples. Finally in 1980 a provocative book-mentioned before-was edited by Carmelo Giordano (64) on *Sorbents and their clinical application* (Figure 10 and Table 6) and this included a broad view of future applications. The book, dedicated to Arthur Gordon, was published even in Russian. It hosted papers from thirty illustrious specialists including Renato Esposito (66, 68), Carmelo Giordano(66, 68), Pietro Bello (67), Ernesto Quarto (65), Thomas Ming Swi Chang, Eli A. Friedman, R.E. Sparks, William J Asher, Kenji Maedaand Roger Williams.

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Correspondence:
Natale Gaspare De Santo
MD, Emeritus, Chair of Nephrology
Via Pansini 5, Pad 17, 80131, Naples, Italy;
E-mail: nataleg.desanto@unicampania.it
Phone: +393484117376