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Birth and Development of Bologna Nephrology School with Vittorio Bonomini and Pietro Zucchelli

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Abstract

In the years 50th the Nephrology was born in Italy. Among the protagonists of those years, there were Vittorio Bonomini and Pietro Zucchelli. In Bologna, they created the school of Nephrology of great national and international importance that has generated so many distinguished pupils. In the 60s the author joined the school as a student and then as an assistant and he describes life at university at the time of one of the last barons: Domenico Campanacci. Moreover it is illustrated the adventurous birth and then the swirling development of hemodialysis and peritoneal dialysis under the guidance of Bonomini and Zucchelli.This story pays tribute to those two charismatic geniuses and masters of nephrology.

Keywords: *History of nephrology. History of dialysis. Artificial kidney. Peritoneal dialysis*

"We cannot know who we are or where we're going if we do not know where we came from. In the past, we can look for the elements of our identity and the prospects for the future. Pablo Neruda "

Nephrology was born in Italy as a specialty of medicine in the 50's through the work of young and passionate researchers in universities whose interest was focused on renal pathophysiology. They were all internists, but then nephrology was based on laboratory. The main interests were the renal clearance, the electrolyte metabolism and acid-base balance. In 1954 in Italy the word "Nephrology" began to circulate when publications of "Minerva Nephrologica" quarterly magazine were launched and then it was made official in 1957 when a group of university professors founded the Italian Society of Nephrology (SIN), from which only two members would have interests in prevailing in the field of physiology and clinical kidney disease: Gabriele Monasterio (1903-1972) in Pisa and Luigi Migone (1912-2002) in Parma. In the latter town, Migone would organize the 1st Congress of the SIN. In that time, at the Institute of Medical Pathology of the University of Bologna two young researchers Vittorio Bonomini and Pietro Zucchelli had created a section of Nephrology. The section was founded by Vittorio Bonomini in 1953. After graduation, he moved from Parma to Bologna following prof. Domenico Campanacci who had won the Chair of Medical Pathology. Here, at the request of the director who wanted each of his pupils to specialize in a field of internal medicine, Bonomini began to study renal pathophysiology. The kidneys were still semi-unknown organs. Tests for the study of renal function had been developed in the second half of the 40s. In Italy, the kidney tests were limited to urinalysis and azotemia. Great merit of Bonomini, the first sign of his genius, was to create a laboratory dedicated to the study of renal functions. In a few years, methods were developed for the dosage of inuline and creatinine with calculation of the clearance for the evaluation of glomerular filtrate and Sodium para-aminohippuric acid (PAI) which injected into the vein allowed to calculate the renal plasma and blood flow. These dosages allowed him to make his first publications (1-4). Then in 1957, the nephrology laboratory underwent a great and decisive development with the arrival of a new doctor who had just graduated: Pietro Zucchelli. He was fond of hydroelectrolyte metabolism and was fundamental in the development of a series of innovative tests: plasma and urinary electrolytes (Na,

K, Ca with Bekman flame photometer); Phosphates, Mg, Cl, uric acid, titratable acidity and NH3 urinary with colorimetric methods; bicarbonates with the Van Slyke method; osmolarity with Fiske osmometer. In Italy, very few laboratories were able to perform these tests. They were unknown in most hospitals and above all, very few were able to interpret the data and draw conclusions. With these exams, refined studies on the functionality of the renal tubules began, which together with the clearance data allowed a complete evaluation of renal functions. The team published a series of works of great importance on the hydroelectrolytic and acid-base renal metabolism (5-8) and on the effects of new diuretics (9-11). Unfortunately, all the works of those years have been published in italian magazines and therefore have not had a international resonance. Medical Pathology of Bologna had become a center of reference for Italian nephrology and Bonomini became an authoritative speaker in major national congresses.

In 1962 i came as a student at St. Orsola hospital in the Institute of Medical Pathology of Bologna University, which was directed by prof. Domenico Campanacci (1898-1986) (Fig.1). He had a charismatic personality, possessing what was then called the "clinical acumen" which in the pre-technological era was based on thorough anamnesis, refined semiotics and clinical experience. His lectures were beautiful and infused with historical quotes about ethic and morality where the clinic mixed with Latin. With an enlightened mind and ahead of his time, he created various specialized sections in the Istitute, including nephrology. The visit of Campanacci became a great educational gym because all the specialists participating in the discussion on the sick, with each making his own contribution on news of international literature. Campanacci listened to them all and then drew the conclusions, suggesting treatment and establishing prognosis with a lucidity and a formidable intuition. He distrusted technology but at the same time he accepted it because he feared that this would move away the doctor from the patient. For auscultation, he used a wooden stethoscope. He said, "My father, a doctor of the nineteenth century, touched the patients listening to the heart with the ear. I walk away from the palm using a stethoscope whereas you stray more using the fonendoscope." Observatio et ratio were his recommendations. For a student her visit was worth more than any book and was followed by 50 to 60 people including doctors and students. At that time in Bologna there were a lot of American students who certainly remembered his lessons. He died in 1986, but still his pupils gather to remember the master.

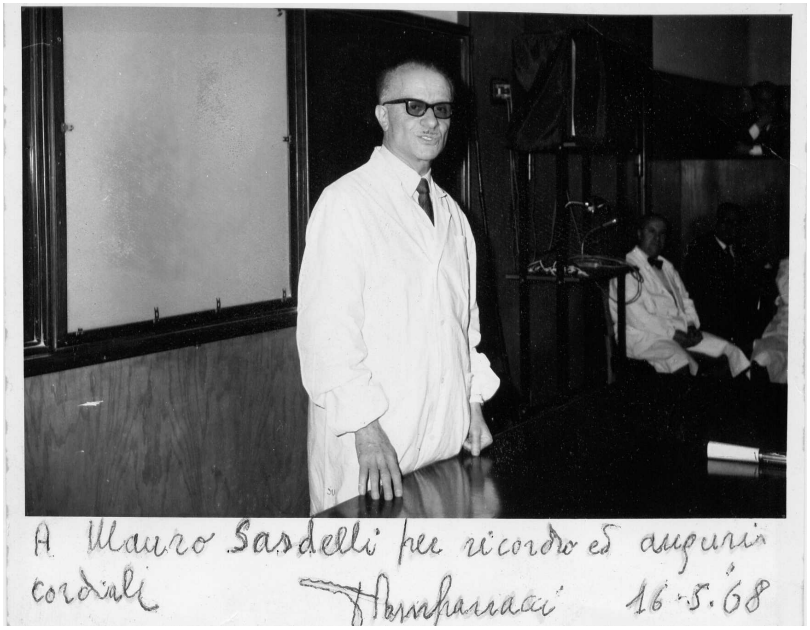

Fig 1. *Prof. Domenico Campanacci, Director of Medical Pathology at the University of Bologna from 1953 to 1968 (with photos dedicated to the undersigned)*

I had applied for cardiology, but I was assigned to nephrology section directed by Vittorio Bonomini (Fig.2). At that time, Bonomini's main interest was the study of renal biopsy. He had learned the technique of percutaneous biopsy in London in 1955 and in 1961 he published his experience more than 300 kidney biopsies, which was one of the most numerous series in Europe (12-13). His interest was in the study of primary or secondary interstitial nephritis (14-15). He performed the biopsy after creating pneumoperitoneum with his own hands with the needle of Vim Silverman-Franklin, reading the slides with a simple optical microscope. The reading was a kind of sacred ritual in which students could assist in silence, but were not allowed to participate in the microscopic view and the slides were jealously kept in a closet of which only Bonomini had the key.

Fig 2. ***60's.*** *Bonomini standing in the Laboratory of Nephrology of Medical Pathology at St.Orsola Hospital*

Fig 3. ***60's.*** *Zucchelli standing with Dalmastri and Fusaroli seen from behind sitting*

In thise section among structured doctors there was Pietro Zucchelli (Figure 3), the great expert on fluid and electrolyte metabolism. He oversaw the analysis laboratory with three other doctors including Giampaolo Dalmastri (1930-2001) who was also Bologna Football Club's doctor and Vittorio Mioli (1934-2002), who followed Bonomini like a shadow. That year, together with me, Maurizio Fusaroli, Alberto Albertazzi, Alba Evangelista came in as intern students. A year later, it was the arrival of Renata Caudarella and others who subsequently would live. At 8 am, we had to the ward to help doctors. Each of us were assigned to 4 patients. Our tasks were to draw blood, take the pressure and write the anamnesis (which had to be read to the doctors and then typed) and then be present at the doctor's visit. After the visit, we went to the lab to do the tests. There was a nurse who performed urine tests and preparing the sediment's slides that would then be read by the doctors. In the ward, various functional examinations were made: the creatinine clearance to assess the glomerular filtration rate (urine was collected with bladder catheter for an hour and a blood sample up to half an hour) and Clerance of PAI which was injected to assess Plasmatic and Blood Renal Flow and Tm; tests for the study of tubular functions: the concentration and dilution tests, the load of ammonium chloride, the test by Mannitol to evaluate Osmolar Clearance and the reabsorption of free water; the load of phosphate and calcium gluconate for the diagnosis of hyperparathyroidism; the glucose load to evaluate the Tm of glucose . In hypertensive patients, Zucchelli performed bilateral ureteral catheterization in a basement with a cystoscope that leaked water like a fountain, slipped two catheters in the ureters and then proceeded to separate urine collection which various electrolytes and osmolarity were assayed. The processing of data allowed to put the suspicion of renovascular hypertension for the indication to arteriography (16).

The group was led by the duo Bonomini-Zucchelli with a safe hand who demanded commitment and diligence from morning to night, six days out of seventh. We worked and studied at the Institute. There was a great desire to emerge and assert ourselves. The team was cohesive, enthusiastic and optimistic about a bright future. Frequent were the dinners organized by Bonomini that we could not miss and where he would totally transform himself, after plenty of alcohol consumption, by letting go of inhibition and rage, inciting transgression and revelry, making the owners of the restaurant' s hair stand on end and so profoundly taken aback by the distinguished professors uncivilized behavior to order us not to return to the restaurant. The work at the hospital was gratifying because we felt to be part of a high level team under the shadow of great director. Campanacci was honored and praised by family doctors and patients from all over Italy. Nobody felt exploited and almost all the doctors working full-time in Medical Pathology were volunteers, therefore unpaid. The director was the great father, all--powerful and magnanimous. Everyone knew that if they continued to work hard, they would at least secure a teaching qualification and then a director position in a hospital (at the time there wasn't a state selection, but the directors used to help their pupils). And for those few who had saints in heaven, the university career would open up.

In 1963, an event occurred that changed our history. An industrialist of Bologna whose son died for uremia, expressed his desire to donate to prof. Campanacci a device called "artificial kidney", which had been invented by Scribner in Seattle and built in USA by the Sweden company that used as a filter the Kiil plates. This model of the kidney was the first in Italy and in Europe there was only another one in Lion in France. Zucchelli went to Lion at prof. Traeger in order to learn how to use the machine. When he returned, in 1964, we began to perform dialysis. The kidney was composed of a large tub of 385 liters, a cooler, a pump for dialysis liquid and a heater for the blood (Fig. 4).

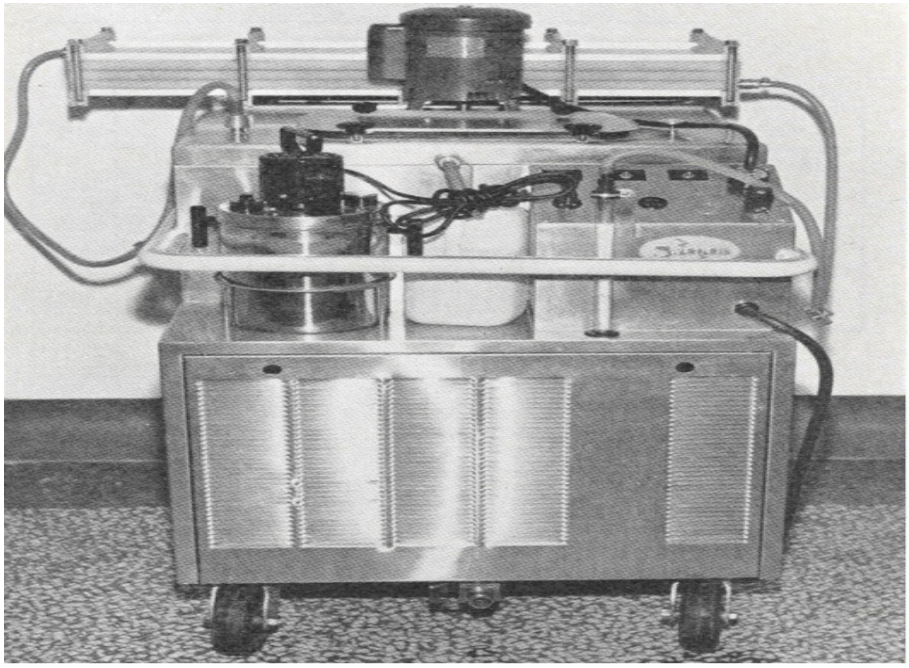

Fig 4. *The Scribner-Sweden Artificial Kidney with Kiil filter*

The dialysis fluid was prepared in the tub. Salts already prepared in special bags were added to tap water and mixed with the pump. After about half an hour, a sample of the bath was sent to the laboratory. The bath had to have a Na of 132 mEq / l- K 4- Ca 4,6- Mg 1,5- Cl 112- HCO3 30 and glucose was added up to an osmolality of 310 mOsm /l . Meanwhile the Kiil filter was prepared. It was composed of three plates of polypropylene which were part of two pairs of sheets of cellophane inside which the blood was circulating, while the dialysis liquid was passing in the opposite direction through the area between cellophane and plates. The plates were fastened to a metal grid, which was tightened with a torque wrench. Before starting the dialysis, it was necessary to pump air into the blood area and make sure with a pressure gauge that there were no leaks. Then proceed to wash the sheets of cellophane with physiological solution in order to eliminate the formalin in which they were conserved between one treatment and another. It was a test for formalin and if it was negative, the circuit is filled with a blood unit and treatment would be initiated. The water was not treated because it was thought to be cool enough to eliminate bacteria, but we still didn't know the importance of toxins and various contaminants contained in the tap water. The preparation lasted about an hour. At the end of the dialysis the filter was lowered from the venous side. The arterial line was detached and a bottle of physiological solution was drained to facilitate the return of blood and prevent air from entering the circuit. A certain amount of blood would stll remain inside.

The biggest problem was made up of the vascular access. The arteriovenous shunt was not initially considered by us because surgeons were not interested. At the beginning, the machine had not pump blood. The radial artery and a vein cannulated in the forearm were surgically externalized and this operation had to be repeated for each dialysis. Then the veno-venous catheterization of the femoral vein was performed percutaneously with Shaldon technique (17). The catheters were left to stay and coagulation was prevented by a perfusor capillary invented by Giovanetti in Pisa (18) which issues 1-2 drops per minute of a solution of heparin. The perfusors were uploaded every day and removed before dialysis. The circuit veno-venous involved the use of a peristaltic blood pump. The blood flow rate was 300-500 ml / min and the flow of the dialysis liquid of 2-3 l / min. The ultrafiltration was initially obtained by adding glucose to the dialysis bath, then with a clamp on the outflow pipe from the venous side. The bed did not have the weight scale and during dialysis we would try to weigh the patient making him get out of bed which was hard to achieve. At the beginning and every hour, heparin was injected from the arterial side by controlling the clotting time with manual method. The room where the dialysis was performed had a UV lamp over the entrance and the doctors were dressed in operating room complete with boots mask and gloves (Figure 5).

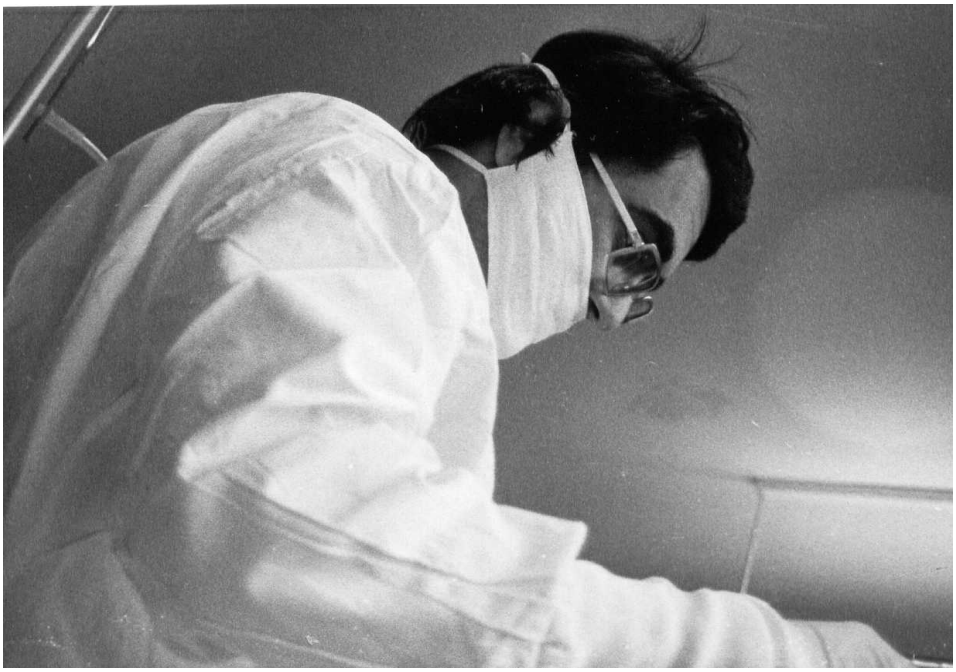

Fig 5. *The student Mauro Sasdelli during dialysis*

It was on a small lamp in her twilight that the patient was sedated at the beginning of the dialysis in order to be sound asleep during the treatment. There was not expected duration, but it was based on BUN. Every time we sent a blood sample to the laboratory and when the values were near to 50 mg%, the treatment was halted. It could last 12-24 hours. We students had to stay close to the patient's bedside and did shifts of 6-8 hours, day and night. We had an intercom and we communicated the progress of the patient with the doctors who were in the Laboratory. While dialysis performed, the blood pressure was extremely variable. Once the Systolic rose above 180 mmHg we injected a vial of reserpine (Serpasil) in the venous circuit. If it dropped below 90, we used vials of Etilnefrina (Effortil). For each session, we used at least a dozen of vials. There was also the fever with chills like seizures that we treated with injections of Diazepam. The risk was that the patient might rip the vascular catheters and as a result, at least until the patient calmed down, we had to lay him on the bed and hold it firmly. There wasn't a fixed rate of dialysis. The focus was on increasing BUN and symptoms. In a year four cases of acute renal failure and two of chronic renal failure were treated, all young people. The results were disastrous and all patients died so as to create doubt about the effectiveness of the technique (19). Finally, a young woman with anuria post-abortion began to urinate after some dialysis and we all toasted the event. The news spread among the staff of the Institute, which until then had looked upon us with pity and distrust getting all the credit. Finally, it was decided not to treat the chronic uremic, but only acute renal failure (20).

Without realizing it, we young students had participated to the birth of hemodialysis and we can say we have made our contribution to the development of this technique whose importance we couldn't fully grasp at the time. Then in the late 60's results improved markedly when in Italy the Dasco company built the centralized production of dialysis fluid with single pass monitors that had control over the positive pressure on the venous line, the flow of the liquid dialysis and the heater of the blood with temperature control. The water was purified with a softener and would then be sent to two tanks where the concentrate cans were poured with the acetate in place of the bicarbonate . The dialysis bath was then sent by a pump to the monitors that were initially four with relative Kiil filters. The section of dialysis of St. Orsola Hospital to treat chronic uremia was born.

In 1966-67 we all internal students got to graduate. My thesis was based on bilateral catheterization for the differential diagnosis of hypertension prepared with Zucchelli and discussed with Bonomini. The thesis was later published (21). I became a volunteer assistant and I worked in Medical Pathology, of course without taking any money. To earn some money, I made substitutions for family physicians. The beds

that I was responsible were not divided by specialties, thus I acquired a wealth of experience in general medicine. Along with me, Zucchelli, Fusaroli and Caudarella were mostly spending time at the clinic and in the Laboratory, while Bonomini with Mioli, Albertazzi, Evangelista and Sergio Stefoni pursued dialysis and biopsies. Besides the clinic visit and lab, we had to teach lessons and tutorials to students and participate in examinations. In addition, I was were on night and in Sunday duty. I would come on Saturday morning and leave on Monday at night.

In 1968 the group split: I and Fusaroli followed Zucchelli to Malpighi Hospital in Bologna, where we opened a new service of Nephrology and Dialysis. The others remained with Bonomini at St. Orsola hospital. We were placed in a Division of Urology which had a huge number of beds, led by prof. Francesco Corrado. It was one of the most important Italian urologists. The Division was located in a building in the hills of Bologna and beyond the hospital beds, it had the laboratory and radiology and nothing else. The service had six dialysis places with scale-beds and eight hospital beds. The dialysis system was the single pass of the Dasco with Kiil filters (Fig.6). The water was purified with the Culligan water softener. Patients performed one or two dialysis per week of 10-12 hours. The vascular access was veno-venous femoral catheterization that was repeated at each dialysis. Sometimes the filter congealing and we had to throw away all the blood. Mortality was consistently high for underdialysis and poor blood pressure control. Frequent complications were hemorrhagic gastritis and cardiovascular ones such as stroke, pulmonary edema and pericarditis with tamponade.

Since the dialysis centers were few and mostly found in northern Italy, the requests were so many we had to select patients. The elderly or those with various complications were not treated and unfortunately destined to certain death. In dialysis there was patients who had come from as far as south Italy and were forced to move to Bologna with families.

In 1968, we began to use the intermittent peritoneal dialysis in chronic uraemic with the method described by Maxwell (22). We filled the abdomen using a needle with about one liter of dialysis liquid, then we inserted in the under-umbilical region a rigid catheter by means of a three-quarters (23). The load was done with two liters contained in two glass bottles, which were then grounded and after thirty minutes of stay, it opened the infusion tube discharge. Each cycle lasted about one hour and dialysis about 12 hours. The rate was once or twice weekly and the catheter was repositioned to each dialysis. The technique was painful for the patient, the results were poor, the complications frequents and the survival low. We decided to use it in acute renal failure or chronic patients waiting for a free place in hemodialysis

Fig 6. *The dialysis room with Dasco monitors, scale-beds and Kiil filter*

Fig 7. *Mauro Sasdelli in dialysis at Malpighi Hospital. The patient has a shunt. You see the Dasco monitor and Kiil filter*

In addition to nephrological activity, we had the task of managing the medically operated patients and the laboratory analysis. We were internists lending a hand to urology, but behind us, we had the great school of Medical Pathology. Zucchelli was a very good clinical and was able to treat almost all medical illness. He practiced renal biopsies and read the slides. Rarely we were forced to resort to expert advice. In 1969 the urologists at Malpighi Hospital performed the shunts and after the fistulas allowing us to expand the dialysis (25) (Figure 7). Shunts were comfortable because they avoided the sting of the veins, but they had a huge flaw. They clotted easily and became the nightmare of doctors on duty. I wonder why they clotted mainly at night or on a Sunday and then we had to wash the venous line by injecting a heparinized solution and then vacuum it. We also used a Clot Screw which was a metal guide with a terminal part spring invented by Giovanetti (26). He had the defect that caused lesions of the vessel walls and if you exercised the power, the tube shunt could detach. In addition to clinical activity, Zucchelli forced us to the study of the scientific literature. We were assigned the papers that we had to read and we would then discuss in meetings that often took place in the evening at his house. By working in the same city, we lived a kind of competition with the Bonomini group who in 1969 would become director of the service of Nephrology at st. Orsola Hospital and in 1975 associate professor and finally Professor of Nephrology at University. Between Bonomini and Zucchelli there was an attempt to excel, to strive for greatness and supremacy but always in a fair fashion because they both admired and respected each other. The Bologna school of Bonomini and Zucchelli has germinated pupils who have occupied positions of prestige in Italian universities and hospitals. From Zucchelli group . I went as a Chief of Nephrology Division to Arezzo Hospital in Tuscany, Carmine Stallone to San Giovanni Rotondo, Maurizio Fusaroli to Ravenna, Leo Cagnoli to Rimini, Luigi Catizone to Ferrara, Alessandro Zuccalà to Imola, Antonio Santoro to Bologna (instead of Zucchelli) and finally Sonia Pasquali to Reggio Emilia. From the group of Bonomini, Vittorio Mioli came in Ancona (he died in 2002 and was replaced by Giovanni M. Frascà); Alberto Albertazzi as Professor of Nephrology first in Chieti (replaced by the son of Bonomini, Mario) and then to Modena; Sergio Stefoni as Professor of Nephrology in Bologna (instead of Bonomini); Alessandro Nanni Costa as director of National Tranplant Center; Carlo Felletti in Cesena, Andrea Buscaroli in Ravenna and Giovanni Mosconi in Forlì .

Bonomini died in 2008, Zucchelli in 2011. They chased each other for a lifetime. Bonomini would take a step forward and Zucchelli would catch up with him and often exceeded him, but by then the other had already taken another step forward. It kept on going like this

until the end. Bonomini finished first, but Zucchelli would follow suit. Both were presidents of the SIN: Bonomini in 1988-90 and Zucchelli in 1994-96. They organized two each national congresses of SIN: Bonomini in 1971 and 1991, Zucchelli in 1980 and 1998. In 1975 Bonomini organized the international congress of Nephroloy in Florence. Bonomini was extroverted, brilliant, creative, ambitious, with a great ability to relate to others, very politically in the sense that he could sell his ideas well and give prominence to his person and his work, sometimes even beyond there his merits, full of interests outside of medicine like hunting, clay pigeon shooting, the Bologna football team. Zucchelli was serious, often wary, despotic, commanded and wanted obedience. He had only one interest: the hospital and the Nephrology, the only hobby was fishing. Both of them demanded the same dedication from others to the work they were the first to give, even to the detriment of family life. They were excellent doctors and before nephrologists, they were internists. The patient was their interest in dealing with great humanity and cordiality. With the patient they had an equal relationship, they took charge of it and were always available, they were convincing and charismatic. They have published hundreds of papers, have been spoken at all most important conference of the world and in Italy they have spread a lot of pupils in the important hospital and university. Each of them has created his team and in turn they have carried out their careers with great commitment and professionalism followed in the footsteps of the great school of the St. Orsola-Malpighi. These are the memories of a period of my life that has been exceptional, stimulating, formative, under the guidance of charismatic personalities, true masters of medicine and life, who so much demanded, but they gave you so much.

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