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Microcrystalline pathologies: Clinical issues and nanochemistry / *Pathologies microcristallines : questions cliniques et nanochimie*

Tribute to Paul Jungers (1932–2022)

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Originally from a modest family in Lorraine, he said that from a very young age he learned a culture of work and dignity.

“My vocation was inspired by the enthusiasm I had felt for Pasteur’s brilliant discoveries, during natural science classes in the final years of high school. I was fascinated by the logic that demonstrated the inanity of the theory of spontaneous generation, and by the discovery of the principles of immunity and their application to vaccination. I admired Pasteur’s willingness to devote his discoveries to the service of mankind and the courage it had required of him to take the risk of vaccinating, thereby defying all conventions and prohibitions... Pasteur represented for me a model of scientific requirement, and passion for caring, that corresponded to my aspirations; this confirmed my vocation to undertake medical studies.”

Having graduated Major of the PCB of Nancy, he is admitted as a scholarship holder to the Cité Universitaire and begins his medical studies in Paris.

“During my first two outpatient internships in the surgical departments of the Necker Hospital, I took advantage of the proximity of Professor Hamburger’s department to follow his wonderful weekly

visit, where his scientific and humanistic approach to medicine influenced me deeply.”

“It was my good fortune to be accepted as an intern from the outset, then as clinic head (1961–1970), and finally as an associate. I had the privilege of living through all the stages of the nephrology adventure, from the advent of medical resuscitation to the beginnings of acute renal failure treatment by the artificial kidney, chronic renal failure by periodic hemodialysis, and finally to the continuous improvements in the conservative treatment and prevention of chronic renal failure.”

During his 40 years at Necker Hospital, Paul Jungers developed an eclectic research programme. He published numerous books and books’ chapters and more than 300 publications in the most prestigious journals. His dynamism was contagious: it benefitted several generations of interns, clinic heads, doctors in the process of specialization, residents from all parts of the world, and doctors from associated dialysis centres: as soon as he spotted good will and expertise he initiated scientific collaborative work.

The common thread of this monumental labour? “To benefit patients without delay by applying cutting edge therapeutic advances as and when they are made.” Most studies have led to tangible therapeutic applications. Among the main therapeutic topics addressed are:

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- Hepatitis B. Paul Jungers described the epidemiology of hepatitis B incidence in patients and caregivers in haemodialysis units, and coordinated the national randomized trial of an Institut Pasteur vaccine. Colleagues had to be convinced of the need for a prospective randomised trial, which by definition puts half of the participating subjects at risk of contamination without treatment. The national ethics committee convened on this occasion validated the principle of the trial, attracting unanimous support. From 1981, vaccination enabled the gradual eradication of hepatitis B in dialysis and resuscitation units, and its prevention in the general population.

- Treatment of severe forms of lupus nephropathy. In an evaluation (led by JF Bach) in 32 patients, supplementation of corticosteroids with cyclophosphamide significantly improved the remission rate of severe forms of lupus nephropathy.

- Pregnancy in lupus patients. Epidemiological studies, conducted with Maxime Dougados, François Tron, Frédéric Lioté and Pascal Houillier, established the conditions necessary for favourable foetal and maternal pregnancy outcomes in women with lupus nephropathy. Collaboration with the Necker Hospital endocrinology department defined the principles of hormonal contraception so as to avoid exacerbation of the disease.

- Pregnancy issues in women with nephropathy. Pregnancy was not recommended at the time in women with kidney disease. Considering that the aspiration of motherhood is legitimate for any woman, and that this (in effect) prohibition was not based on rigorous proof, Paul Jungers undertook an epidemiological study, with the help of Pascal Houillier and Dominique Forget, in more than a thousand patients, pregnant or not, with kidney diseases of all types. This study established the optimal conditions of planned pregnancy leading to successful live birth without exacerbating maternal nephropathy. In addition, a case-control study of 360 women with different types of primary glomerulonephritis demonstrated that pregnancy by itself does not increase the risk of progression to renal failure when kidney function is initially normal or close to normal. These studies, the findings from which have been universally confirmed and adopted, have enabled many women to fulfil their desire for motherhood.

- Treatment of chronic uremia by keto-analogues. From 1982 the possibility of slowing the progression

of uremia by using a preparation of essential amino acids lacking their alpha-amino groups was investigated with Philippe Chauveau. This approach enabled a substantial delay in the initiation of replacement dialysis in many patients, an important objective at a time when the number of dialysis stations was still very inadequate. This nutritional approach, restrictive and difficult to comply with, was abandoned in France when sufficient dialysis stations became available, but was made available again a few years ago.

- Highlighting and contrasting the adverse consequences, in patients with chronic renal failure, of late initiation of dialysis management, with the benefits of early nephrological follow-up.

- Evaluation of the respective indications, for replacement dialysis or conservative treatment, and their consequences, in very elderly subjects with advanced renal failure.

- Highlighting, with Philippe Chauveau and Malik Touam, the atherogenic role of hyperhomocysteinemia in chronic renal failure, and the possibility of correcting it with oral folic acid (with the complementary benefit of enhancing erythropoiesis).

- Study of immune dysregulation induced by the uremic state, in particular highlighting the increase in the plasma level of pro-inflammatory cytokines (TNF α and IL-1 β) and advanced oxidation proteins products (AOPP) responsible for oxidative stress contributing to atherogenesis, with Béatrice Descamps-Latscha and Lucienne Chatenoud.

- Epidemiological demonstration of a threefold higher incidence of atherothrombotic accidents in dialysis and predialysed renal insufficiency, characterizing accelerated atheroma, and analysis of risk factors for atheroma in uremics, leading to the concept of the importance of cardioprotection in these patients, with NK Man, Ziad Massy, Thao Nguyen-Khoa and Gérard London.

- Comprehensive epidemiological survey on the incidence of end-stage renal failure treated with replacement dialysis in Ile de France in 1998, which served as a pilot study for the development of the national "REIN" programme (Epidemiology and Information in Nephrology Network).

- Complete revision, with Michel Daudon, of the concepts around the exploration and medical treatment of urolithiasis, both in its common and severe hereditary forms, and development of new practical

rules adopted since by the entire uro-nephrological community. Paul Jungers was very early interested in the concept that among the common chemical compounds of kidney stones, namely calcium oxalate, calcium phosphate or uric acid, crystalline phases within the same chemical species were more important to take into account to understand the cause of the stones. He was always eager to understand the precise causes of lithiasic pathologies to propose the most suitable treatment for each patient. With regard to calcium oxalate, which is the most common chemical species of kidney stones, Paul Jungers was quickly convinced of the clinical interest of distinguishing between crystalline species and pathology and in particular of the privileged links between whewellite and urinary oxalate on the one hand and weddellite and urinary calcium on the other. He was a strong advocate of the morpho-constitutional analysis of urinary calculi by physical methods at a time when chemical analysis was still very widespread. Very attentive to detect as early as possible the causes of lithiasis, especially from genetic origin, likely to have deleterious consequences on kidney function, he has greatly contributed to raising awareness in the urological community of the importance of exploring lithiasic patients very early from the first stone manifestation. Thanks to his unwavering commitment, practices have gradually evolved for the benefit of patients. Paul Jungers also understood early on that two calculi of the same crystalline composition could have very different structural characteristics, therefore different morphologies that signed in an even more specific way the pathology involved in the lithiasic process. This approach has proven to be particularly effective for the early diagnosis of genetic pathologies such as primary hyperoxaluria or distal tubular acidosis or acquired diseases such as Sjögren syndrome. This relationship between precise (non-dietary) cause and stone morphology was then extended to other clinical contexts such as inflammatory bowel diseases, bariatric surgery or chronic diarrhoea sometimes responsible for very active lithogenic processes that can impair kidney function.

Paul Jungers was also a remarkable, passionate and captivating teacher. His didactic works on lithiasis, Chronic Kidney Disease, and dialysis, regularly republished and updated, have trained and continue

to train generations of French-speaking nephrologists.

Respected and admired, but far from intimidating, Paul Jungers was very close to the nursing staff, as well as an empathetic clinician, truly listening to patients during his consultations and during hospitalizations. Ahead of his time, he understood the importance of comprehensive and not exclusively technical patient care for kidney disease.

“Starting from the principle that it is not only up to the patient to adapt to the treatment, but also for the treatment to adapt to the patient, it seemed essential to me to individually adapt therapeutic prescriptions to conditions of lifestyle and activity, family context, and patient age, and to pay the greatest attention to their morale and concerns. My greatest reward was to see many patients, who approached our consultation with reserved and anxious faces, leave with a smile, assured that all possible measures were implemented to delay the deadline for dialysis and allow them to lead as normal lives as possible.”

An accomplished researcher, teacher and physician, Paul Jungers was a role model for many. Those who had the chance to work alongside him loved this enthusiastic man, teeming with ideas, insightful, tenacious, and upright and demanding certainly, but also warm, attentive and available.

In 2012, Paul Jungers received with emotion the Jean Hamburger Medal of the Society of Nephrology. These words bring together the French and French-speaking nephrology family to pay tribute to him.

Our thoughts are with his widow, Mrs. Suzanne Jungers, his children Mr. and Mrs. Olivier Jungers, Mr. and Mrs. Pierre-Yves Jungers, and his grandchildren, Pierre, Victoire, Bryan, Lara, and Nicolas.

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