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A great contributor to the French urological science: Michel Daudon



Un grand contributeur à l'urologie française : Michel Daudon

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ABSTRACT

The 40 years of Michel Daudon's working life in the field of urolithiasis are difficult to sum up in a few lines. His knowledge, expertise and publications in the fields of biology, chemistry, nephrology, and eventually urology have contributed to make him a national and international recognized researcher in the understanding of the complex mechanisms of urolithogenesis. His great collaboration with the community of nephrologists, kidney physiologists, biologists, and urologists, seniors or in training, has widely contributed to improve modern and complete treatments of urolithiasis, which is at the origin of complicated urinary stones causing severe consequences on renal function and true public health problems. His hard working, his willingness, and the clarity of his presentations contributed to make him a national and international recognized lecturer in France and North Africa, where he created a network connecting laboratories with clinicians. Always looking forward in his scientific field, he has established links with approved research teams, making them interested in working on urolithiasis, even though research on urolithiasis disease seems to be less important than research on cancer.

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R É S U M É

La vie de travail de Michel Daudon ne peut se résumer en quelques lignes. Ses compétences en clinique, en biologie et en biochimie ont fait de lui un acteur reconnu sur le plan national et international dans la compréhension des mécanismes de la lithogénèse urinaire, source de calculs souvent complexes aux conséquences parfois graves. Il a largement contribué à la prise en charge moderne et complète de la lithiase urinaire, en permettant aux néphrologues cliniciens et physiologistes, aux biologistes, mais aussi aux urologues séniors et/ou en formation, de mieux cerner la complexité des calculs rénaux et leurs conséquences sur la fonction rénale ayant un impact en santé publique. Son travail incessant, sa disponibilité et la clarté de ses exposés ont contribué à le faire reconnaître comme un enseignant recherché par la communauté urologique aussi bien en France que dans les pays étrangers, notamment en Afrique du Nord, en créant des réseaux de collaboration entre laboratoires et cliniciens. Toujours en éveil scientifique, il a établi des liens avec des unités labellisées de recherche de haut niveau. Il a su les intéresser

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chercheurs à la lithiase urinaire, dont la genèse est au moins aussi complexe que la cancérogenèse, mais peut-être trop souvent considérée comme secondaire, bien qu'ayant des impacts de santé publique tout aussi importants, justifiant l'implication de ces structures de recherche.

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1. Introduction

Almost 250 referenced publications by Michel Daudon testify to the importance of his work. A survey of his 40 working years as a biologist specialized in the field of urolithiasis appears to be truly justified. But the risk was to be reductive, since his collaborative work with his research colleagues, biologists, clinicians and physicians, was intensive.

His knowledge in the fields of biology, biochemistry and physiology applied to medicine quickly attracted specialists involved in the treatment of various diseases, characterized by crystallization phenomena, such as nephrologists, rheumatologists, cardiologists, and obviously urologists, whose main area of interest was urolithiasis.

The first publication from Michel Daudon in 1978 focused on the spectrophotometric analysis of gallbladder stones [1] and did not foresee its forthcoming intellectual “crystallization” on urinary lithogenesis and lithogenic diseases. Two meetings directed Michel Daudon's researches on urolithiasis. The first one led him to work with R.-J. Reveillaud at the laboratory of biochemistry (CRISTAL Laboratory) in Saint-Cloud hospital, which was dedicated to urinary stone analysis. The second one allowed him to collaborate with P. Jungers, professor of nephrology at Necker hospital, in which he entered the laboratory headed by M. Lacour, after Reveillaud's death. Such meetings initiated his passion for research and led him to seek to understand the complex mechanisms of lithogenesis, particularly those of urinary stones, and the deepest mechanisms of nephron functioning [2]. Their collaborative studies on the epidemiology of urolithiasis and the risk factors of lithogenesis contributed to the analysis and understanding of various factors increasing the risk of recurrence of urolithiasis and their clinical and economic consequences on public health [3,4].

At the beginning of the 1980s, R.J. Reveillaud and M. Daudon developed the bases of a clinical-biological confrontation between the composition and the crystalline architecture of urinary stones, most often very heterogeneous, and their association with the various and complex mechanisms involved in their formation [5].

In collaboration with P. Jungers, they studied the factors of recurrence of oxalate stones in patients treated with piridoxylate [6].

Quickly, the members of the urolithiasis committee of the French urological association (CLAFU) understood the importance of Daudon's work in the field of stone analysis at the time when new techniques such as extracorporeal lithotripsy (ESWL), percutaneous nephrolithotomy (PCNL) and retrograde ureteroscopy were emerging.

In this article, we aim at describing this collaboration.

2. Collaborations with urologists

2.1. Clinical research

Clinical research was Daudon's main topic.

2.1.1. The CLAFU

He was involved in clinical research right from the start of the CLAFU in 1994 and continues to help the urologists in their research themes and in the setup of recommendations and clinical guidelines [7]. The objectives of the committee remains to make the urologists sensitive to the systematic realization of efficient metabolic patient's assessment, coupled with the physical analysis of the stones expelled after the first renal colic and that of the fragments extracted by the modern techniques of treatment. Many other themes were addressed by the committee, due to M. Daudon's diligence and that of P. Jungers, M. Normand and J.-P. Haymann as contributing nephrologists. So, he brought his experience in various fields, such as ESWL, in which from 1989 he could foresee the importance of the frequency of the shock waves on the quality of fragmentation as well as that of the nature of the stones [8,9]. He helped the urologists to take an interest in the correlations between stone composition and lithogenic diseases [10], and between lithogenesis and different aspects of metabolism. He focused on various mechanisms related to phosphate, calcium oxalate [11], uric acid, metabolic syndrome, diabetes, pregnancy and infection [12–16].

But one of the most important contributions of M. Daudon for the urologists was to make them aware of the importance of stones collection after removal, intended for physical analysis that replaced the obsolete chemical analysis. Stone analysis with infrared spectrophotometry (SPIR) corrected many diagnostic errors previously related to the discriminative inadequacy of chemical analysis. The highlighting of the type Ic calcium oxalate monohydrated stone allowed early recognition and treatment of primary hyperoxaluria, a serious lithogenic disease affecting children and adults [17–19], in which crystalluria is a simple and reliable tool [20]. Likewise, the diffusion of the SPIR diagnosis of 2,8-dihydroxyadenin stones, related to adenine phosphoribosyl transferase deficiency, allowed many biologists taught by M. Daudon to perform an early diagnosis of such a disease [21]. Its genetic identification should facilitate preventive measures and adapted treatment (allopurinol) of this serious and recurrent disease affecting adults and children and requiring sometimes kidney transplantation [22–29].

2.1.2. Cystinuria

Daudon proposed and coordinated with the CLAFU a national survey on cystinuria. This collaborative work,

assembling urologists, nephrologists and biologists, listed more than 600 patients in an exhaustive study, whose results are in press [30]. This retrospective study, focusing on a rare disease, whose treatment remains difficult, is one of the most important ones in the literature. It supplements numerous collaborative publications on clinical and fundamental research that demonstrated the pathogen mutation of a part of the *Slc3a1* in an animal model, similar to the human case [31–35].

2.1.3. Endoprosthesis encrustations

The collaborative work with urologists allowed Daudon to study a diversity of encrustations in various biomaterials constituting endoprostheses, either in non-lithiasic patients with bladder indwelling catheters or in lithiasic patients with “double-J” stents after stone treatment [36]. He demonstrated that hydrogel-coated stents displayed faster encrustation than others, requiring special surveillance and frequent replacement [36–40]. Other researches were performed with cardiologists and vascular surgeons on bio-prosthesis and aortic valves [41,42].

2.1.4. Prevention of stone recurrence

Prevention of stone recurrence is a common objective of urologists and nephrologists. Daudon always focused his work on the role of the inhibitors and promoters of lithogenesis. [43].

Three peculiar aspects can be reported:

- drinking waters are one of the most important preventive tools against stone recurrence, by the means of the dissolution of crystals. Likewise, Daudon collaborated with urologists to evaluate the influence of different sorts of water and that of diuresis on stone recurrence [44,45]. Nevertheless, this subject remains controversial;
- Randall’s plaque currently displays a resurgence of interest as a cause of stone recurrence. Its role as a factor of nucleation of calcium carbonate amorphous phosphate (PACC) and calcium phosphate was addressed in numerous collaborative studies associating physicians, nephrologists and urologists under Daudon’s coordination [46–50];
- urolithiasis and infection have a strong and complex relation, which was widely studied by Daudon. He collaborated with physicians and urologists to assess infection stones due to urea splitting microorganisms, responsible for phosphate ammoniac magnesium (struvite) and carbapatite stones. Using spectrometry and neutronic diffraction, Daudon demonstrated that only carbapatite displayed bacterial imprints, since its crystals were smaller than those of struvite [51].

Urolithiasis in VIH-infected patients receiving antiviral agents (indinavir, ritonavir, atazanavir, darunavir, efavirenz, foscarnet) was an important theme of research for Daudon [52–54]. This work joined other researches on the relation between urolithiasis and various drugs (flumequin, amoxicillin, fluoroquinolones, oxolinic acid, piridoxilate) [55,56].

2.1.5. Correlation between CT scan and stone analysis

The results of stone treatments, particularly ESWL, are correlated with stone composition. Many works have been done by urologists and radiologists, in association with Daudon, who studied the composition of stone fragments and compared pretreatment stone density (HU) with the main component highlighted by SPIR analysis [57–59]. The comparison of stone density measurements obtained with various CT scan devices, however, did not allow the prediction of various sorts of urinary stones identified by SPIR analysis [60].

2.1.6. The French conference on urology

The collaboration between Daudon and the urologists was also materialized by an important contribution to the annual report of the French conference on urology in 2007, in which Daudon addressed various themes, such as epidemiology, lithogenesis, and its relation with the metabolic syndrome [61–63].

2.2. Teaching

Daudon contributed to spread the results of his clinical and fundamental researches toward nephrologists, biologists and urologists, with whom he continues to collaborate.

2.2.1. Teaching at the French College of Urology (*enseignement du collège d’urologie* [ECU])

Daudon is an active member of the different meetings organized by the French College of Urology (*Collège français des urologues* [CFU]), intended for young urologists in training, under the responsibility of the French Association of Urology (AFU). Likewise, he taught the trainees in the fields of lithogenesis, epidemiology, and stone classification based on SPIR analysis, correlations between stone composition and lithogenic diseases [64].

2.2.2. Workshops on urology (*SUC*)

Daudon was also involved in the medical continuing education intended for certified urologists. During the workshops (*séminaire d’urologie continue* [SUC]), he instructed them on the recent advances in stone analysis by the means of SPIR instead of chemical analysis, and contributed to a better management of urolithiasis. He focused on the absolute need for stone collection after treatment for SPIR analysis [10] and on the importance for urologists:

- of the knowledge of the guidelines about metabolic evaluation, recommended from the moment of the first clinical manifestation of urolithiasis, with the aim of reducing the recurrence risk [7];
- of the collection of stone fragments for SPIR analysis [65];
- of PCNL, which could be performed bilaterally and safely during the same procedure under certain conditions [66];
- of giving special consideration to VIH-infected patients due to the risk of upper urinary tract obstruction by drug-induced stones [67];

- of the removal of various sorts of stones present in the prostate during transurethral operations [68].

2.2.3. The university diploma on urolithiasis

This diploma was created 15 years ago by Daudon and remains attractive. It favors meetings between biologists, nephrologists and urologists from Europe and North Africa. All aspects of urolithiasis are covered during workshops in which numerous exchanges and brainstorming meetings are included. Young urologists are more and more frequently present and this aspect testifies to their increasing interest in lithogenesis and consequently to the exhaustive insight into urolithiasis they have got, allowing a better management of the disease, including recurrence prevention.

2.2.4. Clinical and biological confrontations on urolithiasis at Necker hospital

The increasing links between urologists, nephrologists, and biologists led to create such annual meetings 20 years ago, which were intended for a better understanding of urolithiasis and to favor exchanges on lithogenesis, preventive, and therapeutic measures. This collaborative work was extended to the radiologists and the physicians involved in fundamental research, such as D. Bazin. Consequently, young urologists could develop master research projects such as microscopic studies of stones by means of synchrotrons [69], electronic microscopic studies of Randall's plaques and the role of heavy elements such as zinc and strontium in calcic lithogenesis and selenium in cystine lithogenesis [70].

2.2.5. Contribution to educational materials in urology

Daudon contributed to many textbooks and articles dedicated to urolithiasis. He aimed to help all physicians, including nephrologists and urologists certified or in training, to improve their knowledge in the field of urolithiasis and understand the complex lithogenic mechanisms so that they could:

- adapt their handling of urolithiasis, which is a public health problem;
- reduce the recurrence risk, which can be cost-effective for the healthcare system [71].

Two editions of collaborative books were published, associating nephrologists with biologists and urologists. They presented an exhaustive and updated survey on urolithiasis, including the recent advances, as an expression of Daudon's willingness in the transmission of validated knowledge [72,73].

3. Conclusions

The importance of Daudon's work in the field of urolithiasis is a trump card for the community of urologists who were lucky to meet him. His contribution to a better understanding of lithogenesis, his emphasis on systematic physical analysis of stone fragments after urologic

treatment may hopefully point to a reduction of the stone recurrence rate, which remains at a high level although technical progress.

The future must be imagined. Daudon is an unrelenting worker and the urologists hope they will rely on his successor, whose task will be hard.

Indeed, urolithiasis, the core of our job, found in M. Daudon its cornerstone: his original work must resist to the shock waves of the passage of time...

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