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ARTICLE

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Thirty-eight years of stone meetings in Europe

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Abstract Of decisive importance for the many research groups all over Europe were the scientific symposia dealing with the theoretical foundations and clinical aspects of urinary stone disease. There were several sources from which today's European Urinary Stone meetings and the ''Eurolithiasis Society'' itself arose. It was a long way from Leeds in 1968 to Jena 1970, Bonn–Vienna in 1972 and to 11 European meetings from 1989 to 2005. Which developments in urinary stone disease research have been presented at our congresses during the past 40 years? The 1970s and 1980s are the years marked by efforts to measure the important lithogenic substances such as calcium, ionized calcium, uric acid, phosphate, oxalate with reliable methods. Hypercalciuria and specifically mild hyperoxaluria were the topics of numerous investigations in the 1970s, 1980s and 1990s. The calcium-loading test described by Pak has been discussed frequently since its application. It became apparent that oxalic acid is more important in urinary stone formation than hypercalciuria. Of importance were investigations done by Robertson and his colleagues on the influence of diet (in particular, an animal protein–rich diet) on urinary stone formation. Another emphasis of research was investigation of the crystallization process: supersaturation, crystal growth and aggregation are important steps in urinary stone formation. Of great importance in the formation of urinary stones are inhibitors (inhibitory activity): citrate, magnesium, pyrophosphate, macromolecules: GAGs, THP etc. and it became possible in the early 1970s to determine substances such as Tamm-Horsfall protein (THP) and GAGs. Much attention in the 1970s and 1980s was focused on urinary stone analysis (X-ray diffraction, infrared spectroscopy, polarization microscopy) and standardization of these methods. In the mid-1980s, a whole series of epidemiological studies were carried out, with data for the Federal Republic of Germany, East Germany, Czechoslovakia and Austria. The search for ''stone-removing'' medications, their description and clinical use was the subject of much clinical research and in vitro examinations. A definite advance occurred in the 1980s with the development of new instrumental technologies for the management of urinary stones such as shockwave (''Stoßwelle'') lithotripsy, percutaneous nephrolithotomy and ureterorenoscopy (" breakthrough innovations''). Since the 8th European Urolithiasis Symposium there have regularly been presentations pertaining to the topic of the molecular basis of inherited lithiasis. The last 10–15 years have shown an increasing turning toward the importance of cellular alterations and supersaturation and their relation to stone formation. In conclusion, I would like to note that it is of decisive importance for the research groups all over Europe to organize scientific symposia dealing with the theoretical foundations and clinical aspects of urinary stone disease under the protection of the European Urolithiasis Society.

Keywords Lithogenic substances · Stone formation · Percutaneous nephrolithotomy · Ureterorenoscopy · Extracorporeal shockwave lithotripsy · Eurolithiasis Society

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Basically, we must admit that a full understanding of the biomineralization processes involved in the pathogenesis of urinary stone disease in all its complexity still eludes our comprehension. Looking over the time span of the past 38 years, there have been many small advances in our understanding of the pathogenesis, diagnosis and therapy that have indeed brought us closer to a consensus.

A definite advance occurred in the 1980s with the development of new instrumental technologies for the management of urinary stones such as shockwave (''Stoßwelle'') lithotripsy, percutaneous nephrolithotomy and ureterorenoscopy.

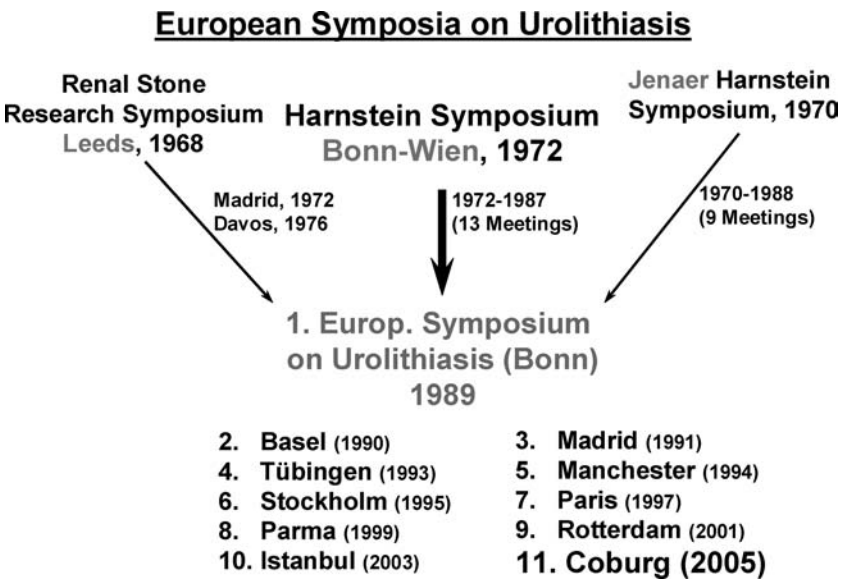

Fig. 1 Several sources from which today's European Urinary Stone meetings and the "Eurolithiasis Society" itself arose

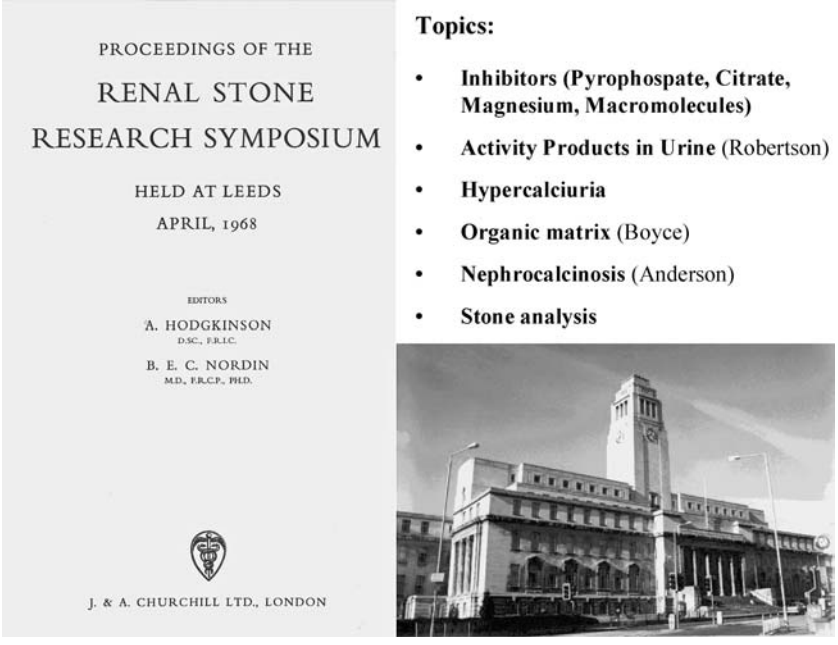

Fig. 2 Renal Stone Research Symposium, Leeds, 1968

Of decisive importance for the many research groups all over Europe especially were the scientific symposia dealing with the theoretical foundations and clinical aspects of urinary stone disease.

These meetings were organized and held for the first time in the late 1960s and early 1970s by the protagonists of urinary stone research. I would like to show the structural or developmental history, especially the important "germ cells" and "currents" that led finally toward the end of the last century to the founding of the "European Symposium on Urolithiasis" or rather the "Eurolithiasis Society."

There were several sources from which today's European Urinary Stone meetings and the "Eurolithiasis Society" itself arose (Fig. 1).

One of the formative events which for the first time brought researchers from different disciplines together at a Urolithiasis Symposium was the meeting held in Leeds in April 1968, hosted by Clark, Hodgkinson, Nordin and Williams (Fig. 2). Various themes were covered and this meeting remains, in my opinion, exemplary even for present-day gatherings. To mention just a few names of researchers, some of whom are still active and who participated in the years after Leeds in national and in Europe-oriented meetings: Robertson, Fleisch, Rose, Sutton, Krizek and Behrendt.

Subsequent symposia on Urolithiasis Research were held in Madrid in 1972 and in Davos in 1976 dealing with similar topics.

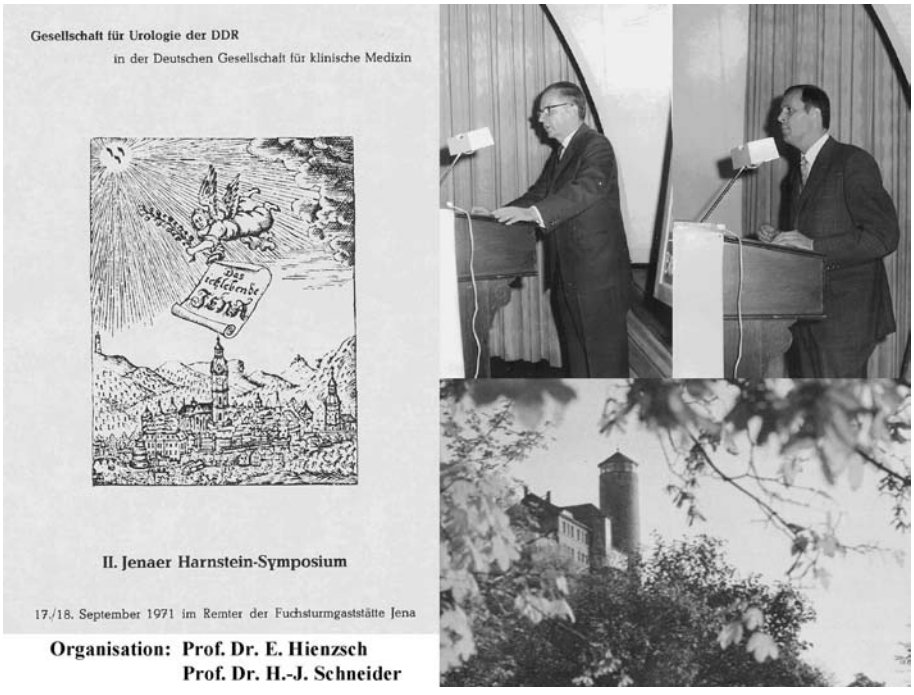

Fig. 3 Urinary stone symposia in Jena

Important later urinary stone symposia were those held in Jena. They were started in 1970 by Hienzsch and Schneider, and were carried out in 1–3 years intervals. The meetings were held in historical ''Fuchsturm'' (Fig. 3).

The major topics of these meetings corresponded to the international symposia, and the Bonn–Vienna Stone Symposium. The content of the Jena Symposium was decisively important for many questions. Reports of the proceedings and results were regularly published. Altogether, nine meetings took place between 1970 and 1988, including the one in 1974 in Marienbad. The one handicap of the Jena meetings was the restrictive political situation which permitted only very few western scientists to attend.

Continuing on the development overview of our European Urinary Stone meetings: An important recurring momentum for us ''stone researchers (''activists'') in the Federal Republic of Germany was the Bonn–Vienna Urinary Stone Symposium. The first one was in early summer 1972 hosted by Vahlensieck, and the second one by Vahlensieck and Gasser in November 1972 (Fig. 4). Participants at these first meetings came mostly from Germany.

Fig. 4 Bonn–Vienna Urinary Stone Symposium, 1972

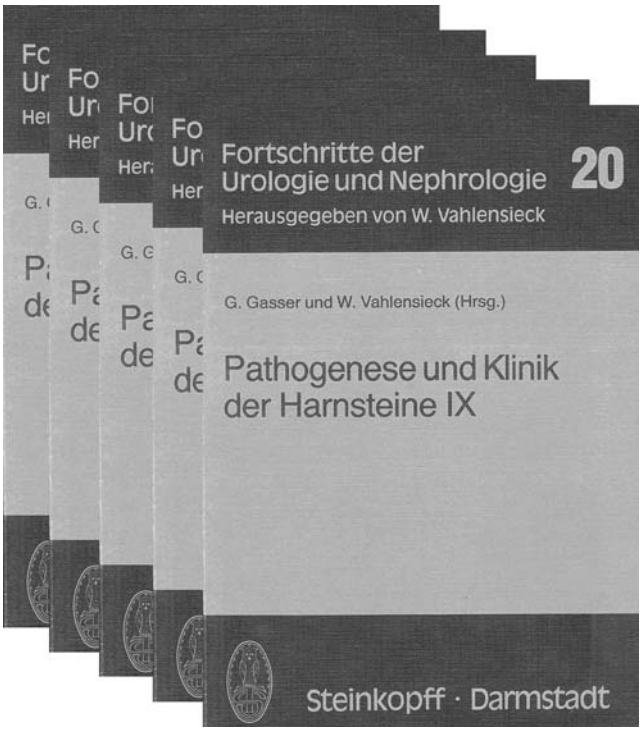

Fig. 5 Proceeding reports of Bonn–Vienna Meetings

Out of these meetings developed over the years, the 13 superb scientific symposia held until 1987 alternatively in Bonn and Vienna.

The reports of the proceedings were regularly published (Fig. 5).

It was from that podium that over the decades, urinary stone researchers, initially from Germany, then from the wider European area—Switzerland, Austria, Scandinavia, England and later also from North America presented their work.

The names of the members of the Advisory Board clearly show the opening toward Europe (Fig. 6).

These pictures show some of the European and American "activists" who participated in the Bonn–Vienna meeting (Fig. 7).

Contacts with Israel were also made. We held a meeting in 1980 in Tel Aviv together with Oded Sperling on "Uric acid Urolithiasis" (Fig. 8).

I would like to show synoptically the topics of the Bonn–Vienna Research Conferences:

- Epidemiology
- Pathogenesis
- Lithogenic substances and determination (standardization)
- Inhibitors
- Stone analysis
- Prophylaxis and metaphylaxis
- Operative and instrumental stone removal techniques

In 1989, after an increasingly Europeanization, or rather, internationalization of the meetings, Vahlensieck and Gasser provided the impetus to turn the Bonn–Vienna Urinary Stone Conference into a European Urolithiasis symposium. This is how Gasser, in his concluding remarks at the 13th Symposium in Vienna in 1987 put it:

"Ladies and Gentlemen! Though we have been more than satisfied with the results of our urinary stone symposia, we believe, nevertheless, that progress and changes in medicine and in other sciences ought to make likely the enlargement of our basis to European dimensions!"

And so came into being in May 1989 the first European Symposium, of course held in Königshof, Bonn. The idea was greeted with interest and approval by all involved (Fig. 9).

Out of this meeting developed over the years, ten scientific symposia, and the 11th in Coburg, June 2005. The map below shows the places in Europe where our meetings were held, usually at 2-year intervals, interrupted only by International Urinary Stone Symposia (Fig. 10).

At this point, I would like to mention that naturally, the individual hosts set the topics and emphasized their own special fields at the meetings. This proved to be an important aspect because in this way, international working groups got to know one another and were able

Fig. 6 Advisory Board of Urinary Stone Symposium Bonn–Vienna

Harnsteinsymposien Bonn – Wien

Organisation: G. Gasser, Wien
W. Vahlensieck, Bonn

Members of the Advisory Board

Prof. Dr. L. Andersson, Stockholm
Prof. Dr. K.H. Bichler, Tübingen
Prof. Dr. O. Bijvoet, Leiden
Prof. Dr. B.G. Danielson, Stockholm
Prof. Dr. Cifuentes Delatte, Madrid
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Prof. Dr. J. Pinter, Debrecen
Prof. Dr. A. Preisinger, Wien
Dr. W.G. Robertson, Leeds
Dr. G.A. Rose, London
Prof. Dr. G. Rutishauser, Basel
Prof. Dr. H.-J. Schneider, Jena
Prof. Dr. Dr. P.O. Schwille, Erlangen

Fig. 7 Bonn–Vienna Stone Symposium: participants from Europe and abroad

to engage in more intensive exchange of thoughts on the various topics.

The second meeting took place in Basle under the direction of Georg Rutishauser. As always when our Swiss colleagues hosted an event, the organization was perfect as was the hospitality.

The third meeting was held in Madrid, hosted by Rapado. Above and beyond the meeting, we all enjoyed the great cultural offerings of this city and used the opportunity to view the famous art collection at the Prado.

The fourth meeting took place in 1993 in Tübingen under the direction of Karl-Horst Bichler.

In addition to the standard themes, we had as a major topic the importance of the kidney tubule in the urinary stone pathogenesis. Fortunately, this topic had meanwhile reached broad attention in research. Thus, it was shown that urinary stone pathogenesis is better

Fig. 8 International Urolithiasis Symposium Bonn–Wien: Uric acid lithiasis, Tel-Aviv, December 10–11, 1980

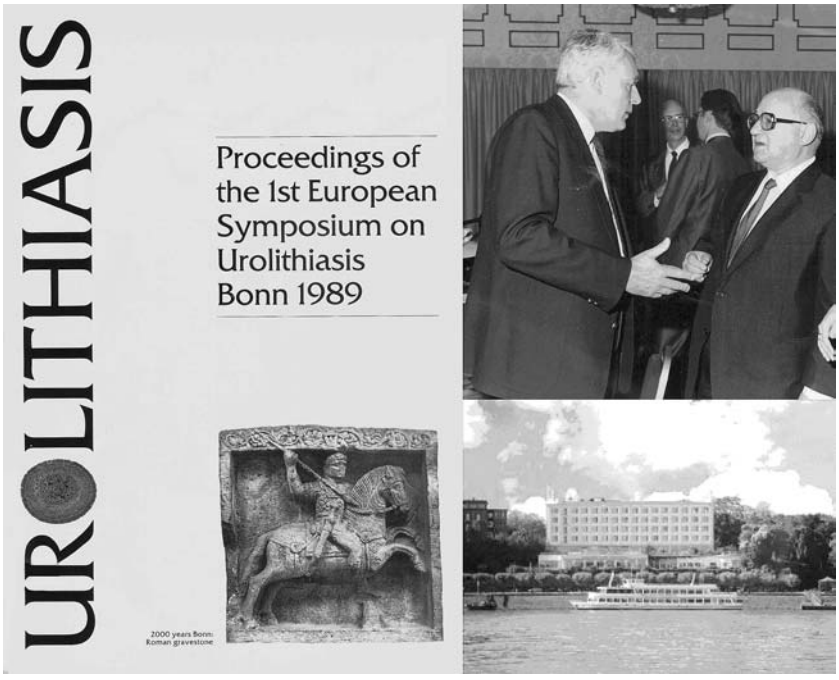

Fig. 9 First European Symposium in Bonn, 1989

understood as a coming-together of physiochemical processes and cellular alterations, and that we may perhaps are getting nearer to an understanding of biomineralization. This direction will also be addressed at this year's 11th meeting.

Next came the fifth symposium in April 1994 in Manchester hosted by Nagaraja Rao. In exemplary work sessions and roundtable discussions, important questions and issues of our mutual research problems were analysed. What I felt especially important: So

Fig. 10 Meeting places of the European Symposia on Urolithiasis (1989–2005)

much was questioned. In scientific discussions, controversial and "lateral thinking" approaches are crucial elements toward new insights and discoveries.

The well-organized sixth European meeting was held under direction of Hans-Göran Tiselius in June 1995 at the modern and spacious City Conference Centre in Stockholm. The main topics were risk factors, macromolecules, alkaline therapy of urolithiasis and prevention of recurrent calcium stone formation.

The seventh symposium took place in Paris under the direction of Paul Jungers. In this meeting, the primary hyperoxalurias and oxalate metabolism, hypercalciuria and bone disease were the important subjects discussed.

For the eighth meeting, we gathered in June 1999 in Parma, hosted by Loris Borghi and his colleagues. The main topics were risk factors, mild hyperoxaluria, hypercalciuria, medical and surgical managements, especially genetics and molecular biology.

The ninth meeting took place in September 2001 in Rotterdam under the direction of Dirk Jan Kok.

The emphasis of research topics concerned the questions of crystallization and macromolecules, cellular aspects, renal injury, disease of affluence and also genetic and molecular biology.

The tenth meeting was held in June 2003 in Istanbul. Here, Kemal Sarica hosted an excellent symposium with great organizational effort and Turkish hospitality. The main topics discussed were crystal–cell interaction, genetics, medical and surgical managements and paediatric urolithiasis.

Under the direction of Walter Strohmaier, the 11th symposium was held in Coburg. The main topics were epidemiology, pathophysiology, genetics, nutrition, diagnostic procedures, surgical management, metaphylaxis and economics. To enhance theoretical and practical knowledge, various instructional courses moderated by well-known experts were available at the symposium.

Which developments in urinary stone disease research have been presented at our congresses during the past 40 years?

Let me summarize some of the major topics and developmental stages of research on urolithiasis:

The 1970s and 1980s are the years marked by efforts to measure the important lithogenic substances such as calcium, ionized calcium, uric acid, phosphate, oxalate with reliable methods, especially oxalic acid by enzymatic or ion-chromatography and to standardize them [8]. Furthermore, it became possible in the early 1970s to determine substances such as Tamm–Horsfall protein (THP) quantitatively with the help of immunological methods and to identify the excretion by patients with various types of urinary stones [3, 4]. Also of interest were identification methods of other macromolecules, e.g. of GAGs and renal handling of risk factors involved in urinary stone formation.

Hypercalciuria and specifically mild hyperoxaluria were the topics of numerous investigations in the 1970s, 1980s and 1990s [22]. It became apparent that oxalic acid is more important in urinary stone formation than hypercalciuria.

Primary hyperparathyroidism was also the focus of research in the diagnosis and operative therapy. Especially identification of parathormone brought about progress in recognizing the disease.

The calcium-loading test described by PAK has been discussed frequently since its application at various clinics. Pathogenic understanding has been made easier by classification of absorptive, resorptive and renal-caused hypercalciuria [9, 12].

Of great importance in the formation of urinary stones are inhibitors, or rather, inhibitory activity. Among these modifiers of crystallization are citrate, magnesium, pyrophosphate, and of macromolecules: GAGs (AMPS), THP and substances described in the 1990s, osteopontin, osteocalcin and others [18]. During the 1980s, research showed the important inhibitory functions of GAGs. The relationship between urinary saturation and inhibitory activity has been called the primary risk factor. Among the secondary are calcium, oxalate, pH, citrate and GAGs.

Another emphasis of research was investigation of the crystallization process: Supersaturation, crystal growth and aggregation are important steps in urinary stone formation, and especially supersaturation is one of the key factors in the pathogenic chain of crystal- or stone formation [7, 10].

Of importance for the clinical but also for pathogenic understanding were investigations done by Robertson and his colleagues as to the influence of diet (in particular, an animal protein-rich diet) on urinary stone formation: the connection between prevalence of calcium stone and luxury or affluence (disease of affluence) and its influence on calcium, oxalate, urinary pH, uric acid and citrate excretion [17].

Table 1 Substances and medicaments for prophylaxis and metaphylaxis

Ca/CaOx	Orthophosphate	Cystine	MPG
	Diphosphonate (Fleisch)		Vit. C
	Magnesium		Alkalicitrate
	Cellulose phosphate		
	Dietary fibre preparation (Farnolith®)		
	Thiazide	Uric acid	Alkalicitrate
			Mineral water (allopurinol)
CaOx	Alkalicitrate	Infect ind. stones	Antibiotics
	Allopurinol (oxalo-uric syndrome)		L-Methionin (sulphate)
	Vit. B6, succinate		

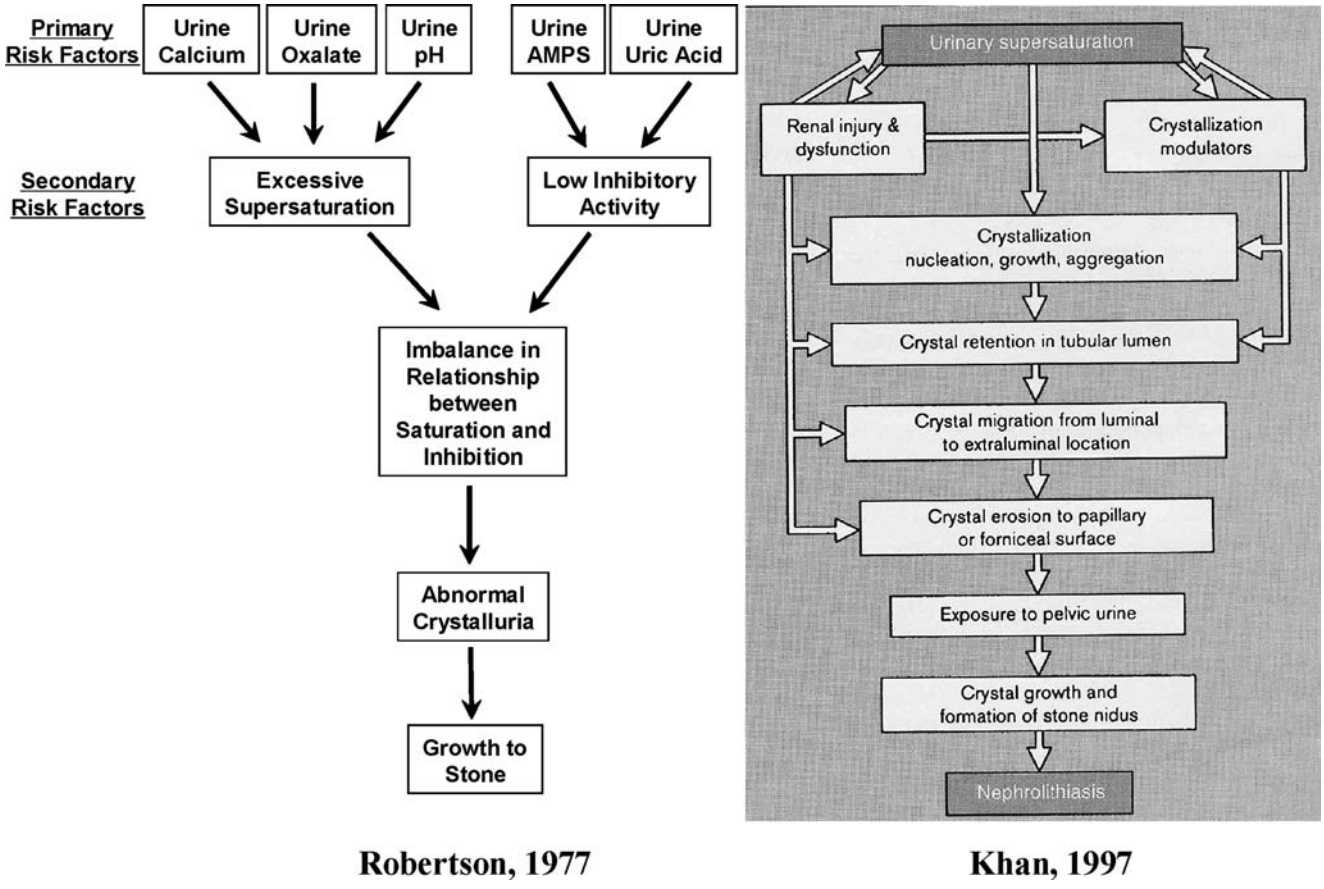

Fig. 11 Schemata of stone formation (pathogenesis) by Robertson and Khan [11, 16]

In the 1980s, there was a turn toward defining urinary stone formation potentials in order to recognize the interaction of lithogenic and inhibitory urinary substances. Robertson originally calculated calcium oxalate activity products by SUPERSAT in the late 1960s. Various quotients for lithogenic substances and litholytic substances were formulated by Tiselius and risk indices were described by Smith to calculate supersaturation by EQUIL Program and later by the Bonn Risk Index [14, 19, 21].

Much attention in the 1970s and 1980s was focused on urinary stone analysis (X-ray diffraction, infrared spectroscopy and polarization microscopy and standardization of these methods.)

In the mid-1980s, a whole series of epidemiological studies were carried out, among others by the Bonn group with data for the Federal Republic. Statistical investigations also provided information regarding East Germany, Czechoslovakia and Austria [23].

The efforts in the pre-ESWL era should also be mentioned regarding prophylaxis, respectively, metaphylaxis of urinary stone disease: Table 1 gives the different possibilities especially for hypercalciuria, CaOx stones, cystine-, uric acid- and infection-induced stones. Important substances are thiazides and alkaline citrates [5, 15].

The search for ''stone removing'' medications, their description and clinical use was the subject of much clinical research and in vitro examinations, mostly involving plant-based combination preparations.

The mid-1980s were marked by breakthrough innovations of ESWL and the instrumental endourological stone removal methods PNL and URS [1, 2, 6]. It had become possible to remove the urinary stones of a large number of patients with non-surgical methods, especially by using the low-invasive Shock wave (Stoßwelle).

The enormous developments in practical urology brought about a notable reduction in stone research, i.e. especially in pathogenesis and metaphylaxis. The opinion of a young, aggressive urologist in one of the meetings is typical for the then prevalent viewpoint: ''In the case of a recurrent stone disease, we use the ESWL once again. Metaphylaxis is not necessary, it is time-consuming and expensive.''

Gradually, during the 1990s, urologists began to recognize reality again. True, with modern methods, urinary stones could be removed better and more gently, but the danger of recurrent stone formation was not lessened.

Since the eighth symposium there have regularly been presentations pertaining to the topic of the molecular basis of inherited lithiasis [13]. Next to uncommon monogenic disorders, cystinuria and primary oxaluria, there is idiopathic CaOx lithiasis a polygenic disorder influenced by multiple genes with susceptibility at two or

more loci. Candidate genes may be responsible for excretion of calcium, oxalate and citrate. Polygenic systems interact with environmental factors to cause the onset of this disease.

Testing the genetic susceptibility of individuals to stone disorder could become a sought-after test, particularly for children in families who have members with recurrent disease.

While in previous decades research focus had definitely been on physicochemical methods, the last 10–15 years have shown an increasing turning toward the importance of cellular alterations and supersaturation and their relation to stone formation. Examinations of cell injuries in CaOx stone formation as well as in the development of nephrocalcinosis (phosphate stones) through various nephrotoxins have led to interesting pathogenic viewpoints [11, 20].

It is interesting to compare two schemata of the pathogenesis of urinary stone formation: One is from a 1977 description by Robertson, the other from 1997 by Khan (Fig. 11). Comparison of the two schemata shows the development of opinions in two decades. Together they indicate the connection between supersaturation and cellular alterations, and this synthesis gets closer to the phenomenon of biomineralization.

A still to be clarified problem is the importance of macromolecules (such as osteopontin, THP and others). Here, the final word–inhibitor or promoter or both under various conditions–has not been said. As I summarize the developmental trends during the past 40 years, I think that interestingly, what has come about is that we must focus our research on the connection between supersaturation and cellular alterations. Walter Strohmaier has given this thorough consideration in the 11th symposium program of this year. In this regard, for the future and with our patients in mind, I feel it is necessary to address the questions of uro- and/or nephroprotection.

In conclusion, I would like to note that it was and remains a lucky circumstance for our special field that out of the earlier, rather sporadic meetings over the course of time a firm organization: The ''European Urolithiasis Symposium'' was founded and built up as a platform for indispensable scientific exchange of ideas. We owe the early activists our sincere gratitude.

Lastly, I would like to thank Winfried Vahlensieck, Hans Joachim Schneider and Hans-Göran Tiselius for kindly lending me the historical photographs, and Dr. Weiss and Ruijun Shen for technical assistance.

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