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# LEGENDS IN UROLOGY

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I was extremely honored to receive an invitation from The Canadian Journal of Urology to contribute to this series, “Legends in Urology.” At first, I felt compelled to decline the invitation. I do not feel like a legend, and, since the term “legends” also refers to something that happened many years ago, I cannot identify with this notion, since I am still actively pursuing what I consider to be an extremely rewarding career. I also feel slightly embarrassed to join the group of distinguished urological scientists who have already contributed to this section. Like my predecessors, however, I am motivated by the possibility that the description of my professional life may stimulate my younger colleagues to take on the endeavor of attempting an academic career in our wonderful discipline of urology.

Looking back, I feel very strongly that my achievements, if any are likely to endure, are due to excellent teachers, favorable circumstances, and excellent people around me who were perhaps propelled by my own enthusiasm and who helped to follow the lines of ideas that were often developed in multidisciplinary, cooperative efforts.

I have recently turned 71. My old friend, Professor Louis Denis of Antwerp, Belgium, gave an inspiring talk during a scientific symposium, which was organized by my former residents and PhD students on the occasion of my 70th birthday. Professor Denis has kindly sent me a copy of his slides, which I will use in the following description of my life in urology, and which takes away some of the embarrassment of speaking about myself.

## **My teachers**

I went to medical school and started my urological training in Germany under the guidance of Professor Dr. C. E. Alken, an inspiring but dominant Nestor of German urology in his time. He yielded to my request, after only 3 months, to continue my training in urology in the United States. I chose to study at UCLA under the chairmanship of Willard Goodwin. My boat trip from Rotterdam to New York and my subsequent drive across the United States in a VW Beetle was my first and unforgettable encounter with that country.

At UCLA I soon became good friends with Dr. Elmer Belt, who had developed his own approach to radical perineal prostatectomy. Working with him and getting closely acquainted with this extremely kind and at the same time determined person enriched my view on life and urology. The fact that he personally taught me how to do a radical perineal prostatectomy and allowed me to review his data has been a crucial step in determining my clinical interest.

Dr. Patrick Walsh, who was a resident in urology at the same time at UCLA, became a very good friend. This friendship has lasted and has been extremely rewarding and stimulating over the years. Dr. Ruben Gittes gave me an opportunity to be his first research fellow in San Diego. My work there at the Institute of Biology in Muir College not only led to the basis for my German qualification for academic teaching (Habilitation) — based on my work about “endocrinological and morphological studies of prostate tumors in vitro” — but also resulted in a lifelong interest in experimental aspects of prostate cancer, especially in experimental models that allow the study of the endocrine dependence of this disease. Dr. Gordon Sato, my mentor, taught me probably the most important lesson I learned during my training period: he exerted zero control on my presence and on the progress of my work and in this way helped me to learn that I could work and produce without someone supervising me and pushing me to work.

Without the exposure to my teachers, I would not have been able to identify the goals that have subsequently motivated my ambitions and my further professional development. In brief, this ambition was to provide patient care and education at a top level and to contribute to research mainly in the field of oncological urology.

### **The EORTC years (1979-1987)**

During my time at the European Organization of Research and Treatment of Cancer (EORTC), I served as secretary to Professor Louis Denis and then followed in his footsteps to become the chairman of the genitourinary group. Important trials were designed and executed with great enthusiasm by an international study group. These included studies that focused on my personal interest: prostate cancer. For example, an important study that compares radiotherapy to radiotherapy plus 3 years of endocrine treatment, the Bolla study, was designed and started during this period. Another study protocol, headed by Professor Denis, investigated the role of maximal androgen blockade in metastatic disease.

During this period, the debate about maximal androgen blockade had a transatlantic but also a strong personal dimension. Professor Ferdinand Labrie was and still is convinced that maximum antigen blockade is the best treatment for prostate cancer if endocrine treatment is indicated. Looking at the same data, I remain unconvinced of his views, in line with our publication in *Lancet* in 2002. Probably the loudest and longest-lasting applause I ever received was at the 1979 SIU congress in Montreal where I presented to a large audience the arguments against the use of maximal androgen blockade and stated that I had no conflict of interest due to industrial support to announce.

### **Professional activities**

During my career, many professional activities opened up. I had an opportunity to help to establish the European Board of Urology and, as Education Chair, to start an educational program in Eastern Europe soon after the fall of the iron curtain. This also included the establishment of the European Board Examination in Urology, which was first held in 1994 at the time of the European Urology Congress in Genoa, Italy.

After successful completion of a cooperative research project on biological markers within the Biomed II program of the European Union, the director of the life sciences program suggested attempting to establish an identifiable cancer program in the fifth framework program of the EU. This was achieved with the help of top European clinical and experimental scientists, members of the European Commission, and the European Parliament, in the framework of the European Cancer Research Initiative (ECRI). A budget of 435 million euro was established, which was spent on cancer research during the following 5-year period.

### **Research**

Without the stimulating influence of my teachers and without the help of many research associates who actually executed the research work, nothing would have been achieved. The original work conducted in Dr. Sato's laboratory showing that differentiated functions could be preserved in cell culture resulted in the development of research models first in cell culture and then in xenotransplants of human prostate cancer tissue into nude mice. Dr. Kenichiro Okada of Japan, working with me at the University of Würzburg a few years later, was the first person who showed that human prostate cancer tissue could be transplanted successfully into nude mice. His findings are documented in two papers published in 1976. This work stimulated the later establishment of 13 permanent nude mouse lines with prostate cancer and several tissue culture lines. It is rewarding for me to see that these lines, which are an indirect result of my fellowship at UCSD, are still used as model systems for research and commercial purposes within the department of urology here at Erasmus MC in Rotterdam and in other centers around the world. Applications include the study of dietary supplements that may in future be useful for prevention of prostate cancer. The ability to measure PSA and tumor volume in the same animals has turned out to be an important research tool.

An example of international and institutional cooperation in clinical research, the "Dutch-Japanese case control study of diet and prostate cancer," not only resulted in a better understanding of dietary effects and male hormone levels but also established a very close relationship between Kyoto University and the Academic Hospital and Faculty of Medicine here in Rotterdam.

### **The ERSPC**

In 1992, again, in close cooperation with Professor Denis, the first pilot studies of what is now called the European Randomized Study of Screening for Prostate Cancer (ERSPC) were performed in Belgium and in The Netherlands.

These efforts resulted in a research consortium of eight European countries and the randomization of about 267,000 men aged 55 to 74 years to a group that received screening for prostate cancer or to a control group in which screening was not offered. The study is powered to be able to show a 25% difference in prostate cancer mortality between the two randomized groups if it exists. The study has resulted in more than 300 peer reviewed publications that can be reviewed on the ERSPC website at [www.erspc.org](http://www.erspc.org).

The study findings have increasingly contributed to a better understanding of early diagnosis of prostate cancer. This study would not have been possible without the inspiring help of many colleagues especially Dr. Monique Roobol, the coordinator of the Rotterdam section. It is very difficult to summarize even the most important information that has come from this cooperative study. Just to mention one recent achievement, the study provided evidence that it is not necessary to biopsy men who have a PSA value  $\leq 3.0$  ng/ml. Data suggest that biopsy can be safely delayed until PSA progression above this value occurs.

Researchers from many disciplines work together within ERSPC; they have backgrounds in urology, pathology, public health, laboratory medicine, and social medicine (quality of life). Without my experience obtained during my work for the EORTC GU group with research minded colleagues, statisticians and epidemiologists, it would not have been possible to develop the broad vision and capabilities needed to establish a study as large as ERSPC. I am grateful to Dr. Richard Sylvester and Dr. Laurence Collette of the datacenter of ERSPC for the many lessons I received under their guidance.

#### **“Words of wisdom”**

This term was coined by Professor Francesco Montorsi, Editor-in-Chief of European Urology, to indicate a journal section that I suggested to be created and then had the privilege of editing. “You should give up drinking only water and have a little wine for the sake of your digestion and the frequent bouts of illness that you have,” attributed to St. Paul, was one example of “Words of Wisdom.” I never needed to be encouraged to exchange water for wine, and it is nice to see that St. Paul shared this view.

#### **Honors**

I have been honored in many ways and most of these honors came as a surprise to me. The biggest surprise was my promotion to knighthood in the Netherlands in the rank of a Commander in the Order of the Dutch Lion in 2002. I must state, however, that despite my age, I still do not feel like a sleeping lion as depicted in one of Professor Deni’s slides. I hope very much to remain healthy enough to see the end of the ERSPC study and the introduction of screening for prostate cancer based on solid, first-line scientific evidence. This will include the application of one of the biggest achievements of ERSPC so far: the possibility to identify potentially indolent, overdiagnosed cancers with a high degree of certainty. Without this, introduction of national screening programs, at least in Europe, are difficult to imagine.

#### **Music**

Music has always been very important in my life. I still practice cello every day and play chamber music regularly with a pianist and in a string quartet. Why do I do this while I am constantly short of time? I am not sure. It is the pleasure of playing music and a deep emotional involvement or possibly an emotional compensation that I could never completely understand. In the cello, as a Dutch poet puts it, lives a secret hidden sound which the player searches for and which he recognizes as he finds it. This sound reminds one of a forest and the colors of the autumn and of the wood of which the instrument is made. I still try to discover the secrets of the sound of the cello.

#### **My family**

Last but not least, I am grateful to my family who have facilitated an extremely intense professional life by being ready to live with a husband and father who was driven by a deep, all-encompassing interest in clinical, educational, and research aspects of urology.

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