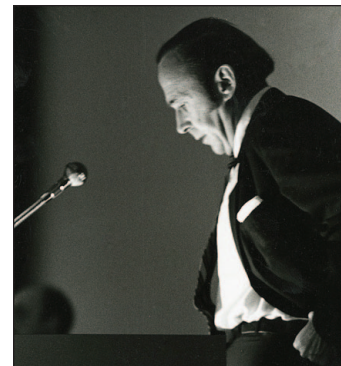

LEGENDS IN UROLOGY

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The invitation from *The Canadian Journal of Urology* (CJU) to contribute to “Legends of Urology” was a pleasant surprise as I never imagined becoming a “Legend”.

My luteinizing hormone-releasing hormone (LHRH) methods have been used for many years for prostate cancer. Extensive studies in prostatic oncology led the National Institutes of Health (NIH) to classify me as an “endocrine oncologist”. I was also recently elected a Fellow of the Inaugural Class of the American Association for Cancer Research Academy. Perhaps my involvement with the effects of new analogs of hypothalamic peptides on experimental benign prostatic hyperplasia (BPH) with my colleagues Drs. N. L. Block and F. G. Rick gave the CJU the idea to issue this invitation.

I was born in Poland and spent the war years in Romania, Italy, and France, eventually joining my father in England. I completed high school in Scotland and then studied chemistry in London.

As a child, I was exposed to many languages and became fluent in Latin, Romanian, Italian, French, Yiddish, and German. This facility allowed me to later acquire Spanish and Portuguese. Spanish was extremely useful in the 1960’s and 1970’s; many LHRH clinical trials were done in Latin America. Language ability facilitated collaborations and lectures in those countries. When I lectured in Paris in the 1960’s, then president, Charles de Gaulle, said that reimbursement for my travel and hotel required the lectures to be in French!!!

My medical research interest started in 1949; I joined Britain’s National Institute for Medical Research (NIMR). I worked with and was scientifically stimulated by various scientists several of whom later won Nobel prizes in Chemistry or Physiology and Medicine. They trained my hands and brain. I learned technical expertise on peptide chemistry, the philosophy of research, and a systematic approach to scientific investigations. These formative years (1950-1952) greatly influenced my later career. At NIMR I received my “baptism of fire” in medical research.

In 1952, I moved to Canada studying at McGill University. I learned endocrinology from Prof. D. L. Thomson and worked with Drs. M. Saffran and R. A. Cleghorn at the Allan Memorial Institute. Thus my academically formative years were spent in Canada.

At McGill we studied corticotropin (ACTH) and adrenal cortical steroids related to stress. That period heralded my beginning interest in the relationship between brain function and endocrine activity. In 1955 Murray Saffran and I demonstrated the presence of a corticotropin-releasing factor (CRF) in hypothalamic and neurohypophyseal tissue. It was the first experimental proof that hypothalamic hormones regulated pituitary function, as postulated by the great English physiologist Dr. G. W. Harris.

I received my doctorate at McGill University in 1957 and I am profoundly thankful to Canada for those 5 1/2 years that I spent in this great country. My co-discovery of hypothalamic hormones led to my move to Baylor University. My years at Baylor (1957-1962), as Assistant Professor of Physiology, were frustrating because of slow progress in isolation of CRF. We showed that CRF was a peptide and using my NIMR experience, facilitated purification and assays for several more hypothalamic hormones.

I became a U.S. citizen in 1962 and also Senior Research Fellow of the U.S. Public Health Service. Dr. Joe Meyer, Director of Research of the Veterans Administration (VA), organized a VA laboratory devoted to research on the hypothalamus. I established this laboratory in New Orleans in December 1962 and became Chief of the Endocrine

and Polypeptide Laboratories at New Orleans VA Hospital, Associate Professor of Medicine at Tulane University and Professor in 1966. In 1964 Dr. A. J. Kastin, from NIH, joined us to help in our clinical studies on hypothalamic hormones. In 1965, Dr. A. Arimura, an experienced Japanese physiologist and endocrinologist, also joined us and made great contributions.

I had been working intensively on thyrotropin-releasing hormone (TRH) with C. Y. Bowers and Tom Redding. We reported the first isolation of porcine TRH and determination of its structure. In 1969, we determined the structure and amino acid sequence with help from Drs. F. Enzmann and J. Bøler in K. Folkers laboratory in Austin, Texas. Knowing the structure of porcine TRH permitted its synthesis. For this I received the Endocrine Society Award and Van Meter Prize of the American Thyroid Association. We shared credit with Guillemin's group which had elucidated ovine TRH structure. Thus TRH became the first hypothalamic hormone to be structurally determined and synthesized. This settled forever the skepticism surrounding the interaction of hypothalamus and pituitary.

In 1965, Dr. C. Gual from Mexico City invited me to carry out clinical testing of hypothalamic hormones there. We demonstrated that preparations of natural TRH are active in humans. We then redoubled efforts on the structure and synthesis of LHRH. Subsequently, Drs. Gual, Kastin and I established that porcine LHRH unequivocally released LH and FSH in men and women. This dispelled our fears of a species specificity that had been found for growth hormone (GH). The realization that LHRH might be clinically useful encouraged us to continue the agonizing effort involved in its purification. Although I considered myself a neuroendocrinologist, not a biochemist, I personally did the isolations, as the effort required to obtain pure material from hypothalamic extract was so discouragingly enormous that only a person such as myself, with unshakable faith in hypothalamic hormones, would endure the many laborious steps of purification. I was able to isolate a small amount (800 µg) of LHRH from 160,000 pig brains, proved it to be a peptide, and passed it on to our structural chemists, Drs. H. Matsuo and Y. Baba. They were able to determine the complete structure of LHRH from this tiny amount. Thus we won the race to solve the structure of LHRH. After confirming the structure of LHRH by synthesis I presented it at the Endocrine Society meeting in San Francisco in 1971. It was one of the high points in my life to be able to report, for the first time, the solution to this paramount and supremely complex problem which had preoccupied me and the other experimental endocrinologists for so many years.

Many clinical studies with LHRH were done in Latin America. From 1972-1978, I developed agonistic and antagonistic analogs of LHRH (also called GnRH). Starting in 1972, several thousand analogs of LHRH were synthesized by various groups including ours in the search for better, long-acting, superactive analogs which could be used clinically and antagonistic analogs which would block LH and FSH release and were aimed at the development of new methods for birth control. Only later did the oncologic uses manifest themselves. In 1976 we established that the antagonists of LHRH could block ovulation in animals and with Drs. D. Gonzalez-Barcena and A. Zarate, in Mexico, we showed that these synthetic antagonists were active in humans.

In 1973, Brazeau and collaborators announced the isolation and structure of ovine somatostatin; we then isolated and synthesized the porcine form and showed it to be identical to the ovine peptide. Clinical work with synthetic somatostatin with Profs. R. Hall and G. M. Besser, in normal subjects and patients with neuroendocrine tumors, showed that somatostatin inhibits the release of GH, TSH, glucagon, insulin, and gastrin. Since somatostatin has a short half-life, we synthesized long-acting, more selective analogs of somatostatin, and demonstrated their antitumor activity in animals. Some of these analogs became practical clinical agents. Thus I became a pioneer in the development and application of somatostatin for oncological uses. I have been credited with influencing the field of oncology not only with LHRH analogs, but also somatostatin analogs, now being used for the treatment of acromegaly and endocrine tumors (e.g., carcinoids). Somatostatin analogs labeled with radionuclides, pioneered in Holland, are presently used for tumor localization and therapy.

My studies of the hypothalamus and its peptides have garnered the Charles Mickle Award of the University of Toronto; Gairdner Foundation International Award, Canada; Borden Award of American Medical Colleges; Lasker Basic Medical Research Award. In 1971, I became a member of the National Academy of Medicine of Mexico. In 1973 I was made Senior Medical Investigator of the Veterans Administration. Then, in 1977, for my work on the isolation, identification, synthesis, and clinical application of hypothalamic hormones, I received the Nobel Prize in medicine or physiology and in 1978 was elected to the U.S. National Academy of Sciences.

After 1978, my interest shifted to the application of hypothalamic hormones for cancer treatment. Grasping the therapeutic potential of hypothalamic hormones, I switched completely to cancer research and became an

“endocrine oncologist”. Many anticancer peptides have been developed in my laboratory and are in current use. The use of LHRH agonists for treatment of advanced prostate cancer is based on experimental work done by me and Tom Redding. We first showed that LHRH agonists inhibit the growth of prostate cancer in the Copenhagen rat model. I organized, with Dr. George Tolis in Montreal, the first clinical trial of LHRH agonists in patients with advanced androgen-sensitive prostate cancer. We demonstrated clinical efficacy of these. Development of sustained delivery systems in the form of microcapsules or implants, which release LHRH agonists over time, came next. These are now the preferred treatment of advanced prostate carcinoma. Previous primary endocrine treatments, based on the work of Charles Huggins (Nobel Prize in Medicine for 1966) included orchiectomy or estrogens. However, surgical castration is associated with undesirable psychological effects and estrogens have serious cardiovascular, hepatic and mammatropic side effects. My method is based on induction of androgen deprivation utilizing agonistic analogs of LHRH which down-regulate pituitary receptors for LHRH and block the release of LH, FSH, and sex steroids. This avoids castration and estrogenic side effects and is now the dominant treatment. I received the Health Memorial Award from the M.D. Anderson Cancer Center, Houston, Texas for development of these new methods of cancer therapy.

New, more recent LHRH (GnRH) antagonists (e.g., degarelix) induce an even more powerful inhibition of LH, FSH and testosterone than agonists and may offer even greater therapeutic advantages.

Recently my work has focused on new approaches with targeted therapy for various tumors. We showed that receptors for LHRH are present in many tumors including human prostatic, mammary, endometrial, ovarian, melanomas, colorectal, pancreatic, and bladder. Similar findings were made for somatostatin and bombesin receptors. Based on this demonstration of receptors for these neuropeptides in various tumors, I started, in 1995, the development of cytotoxic analogs of these neuropeptides which chemically combine a neuropeptide moiety with a cytotoxic one and can be targeted to peptide receptors on primary cancers or metastases. These hybrid molecules can produce tumor regression or eradication. Targeted chemotherapy of many cancers based on these cytotoxic peptide analogs should be more efficacious and less toxic than the currently used systemic chemotherapeutic regimens. Cytotoxic LHRH analog, AN-152 (AEZS-108), is a conjugate of LHRH agonist with doxorubicin and is now in clinical trials in men with castration-resistant prostate cancer.

After Hurricane Katrina devastated New Orleans and destroyed my lab I moved from New Orleans to the VA Hospital in Miami, Florida and I was appointed Professor of Pathology and of Medicine at the University of Miami.

About 30 years ago I realized that tumors express autocrine-paracrine growth factors and their receptors. We began to investigate the manipulation of this phenomenon. Tumoral growth hormone-releasing hormone (GHRH) was of particular interest. My reconstituted group developed new, greatly improved antagonists of GHRH which block tumoral receptors of this hormone which inhibit a wide variety of experimental cancers. Dr. Ferenc Rick demonstrated that antagonists of GHRH inhibit growth of androgen-independent prostate cancer through inactivation of ERK and Akt kinases. We found that cytotoxic LHRH analog, AN-152, (AEZS-108) and GHRH antagonists could be used concurrently in the management of castration resistant prostatic carcinoma.

Let me now mention a topic dear to the heart of all urologists. That is BPH. Clinical studies in men with BPH by D. Gonzalez-Barcena and A. Comaru-Schally indicated that treatment with an LHRH antagonist could produce long term prostatic shrinkage and symptom improvement. In their studies, cetrorelix significantly decreased prostatic volume and induced clinical improvement (International Prostate Symptom Score). After discontinuation of the drug patients showed persistently improved urinary symptoms and sexual function; prostatic volume remained diminished. Results suggested that cetrorelix could reduce serum testosterone and suppress growth factors. In delayed release formulation, there was dissociation between testosterone suppression and effects on BPH. Cetrorelix provided a rapid, symptomatic improvement of BPH, which was sustained for 6 months. A phase III study randomized to Cetrorelix versus placebo, however, showed no significant differences between study groups.

To develop an efficacious drug for treatment of BPH, my expert urologic collaborators, Drs. F. G. Rick and N. L. Block, and I investigated the influence of GHRH antagonists on testosterone-induced BPH in rats. After 6 treatment weeks, prostate weights were reduced and significant changes in gene expression of more than 80 genes, related to growth factors and inflammatory cytokines, occurred; also there were reductions in levels of IL-1 β , NF- κ B/p65, and cyclooxygenase-2 (COX-2). We concluded that GHRH antagonists can inhibit BPH through GHRH receptors.

We also evaluated our bombesin/gastrin-releasing peptide (BN/GRP) antagonist, RC-3940-II, on the viability and cell volume of BPH-1, human prostate epithelial cells in vitro and in BPH induced in rats in vivo. It inhibited BPH-1 cell proliferation and reduced volume in vitro and induced shrinkage in vivo. Thus, we believe that GRP antagonists may work in human BPH.

I hopefully have improved the treatment methods of hormone-dependent prostate cancer as pioneered by C. Huggins. Hormonal therapies that I developed or proposed are based on the peptide analogs of hypothalamic and other hormones and are not only reversible but are also relatively free of side effects, in contrast to other therapies. I am gratified that these discoveries have led to so many practical applications. It is my hope that the significance of these discoveries and their applications to oncology will increase even further in the future.

In conclusion, I have tried to list some possible contributions which I may have made to the international audience of urology. I am most grateful for the honor to describe my endeavors and to share them with the international audience of *The Canadian Journal of Urology*.

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