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INVITED EXPERIENCE AND HISTORY

Introduction of Dr. Andrew V Schally

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I first met Dr. Andrew V Schally (PhD, MDhc (Multi), DSc, Distinguished Medical Research Scientist, U.S. Department of Veterans Affairs Professor of Pathology and Department of Medicine, Miller School of Medicine, University of Miami, Miami, Florida, USA) many years ago, probably around the beginning of the 1990's in one of his visits to Mexico City (Figure 1). He has many friends in my country since some of the investigations that led to the development of the LHRH agonists were made in a couple of Mexican hospitals in collaboration with some outstanding Mexican physicians that I will mention later. In that time, I was the head of the Department of Urology of the Mexican National Cancer Institute and our Director, Dr. Jaime de la Garza, invited him for a meeting. I was surprised by his humbleness, intelligence and easy going personality, in spite of being a Nobel Prize scientist.

If we look a little back into his history, we will find out the reason both for his personality and his Nobel Prize achievement.

He was born in Poland and spent the war years in Romania, Italy, and France, eventually joining his father in England. He completed high school in Scotland and then studied chemistry in London. As a child, he was exposed to many languages and became fluent in Latin, Romanian, Italian, French, Yiddish, and German. This facility allowed him to acquire later Spanish and Portuguese. Spanish was extremely useful in the 1960's and 1970's; many LHRH clinical trials were done in Mexico and other countries of Latin America. Language ability facilitated collaborations and lectures in those countries.

His medical research interest started in 1949, when he joined Britain's National

Institute for Medical Research (NIMR). He worked with and was scientifically stimulated by various scientists – several of whom later won Nobel prizes in Chemistry or Physiology and Medicine. Working with them he learned technical expertise in peptide chemistry, the philosophy of research, and a systematic approach to scientific investigations. In 1952, he moved to Canada studying at McGill University, where he learned endocrinology at the Allan Memorial Institute. Thus, his academically formative years were spent in Canada. At McGill, they studied corticotropin (ACTH) and adrenal cortical steroids related to stress. That period heralded his beginning interest in the relationship between brain function and endocrine activity. In 1955, Murray Saffran and Dr. Schally 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. GW Harris.

He received his doctorate at McGill University in 1957. His co-discovery of hypothalamic hormones led him to move to Baylor University. He became a U.S. citizen in 1962 and also Senior Research Fellow of the U.S. Public Health Service. He established a VA laboratory devoted to research on the hypothalamus 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 1969, together with other scientists from Japan and other countries he determined the structure and amino acid sequence of porcine TRH which permitted its synthesis. For this, he received the Endocrine Society Award and Van Meter

Prize of the American Thyroid Association. 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. Carlos Gual from Mexico City invited him to carry out clinical testing of hypothalamic hormones there. They demonstrated that preparations of natural TRH are active in humans. They then redoubled efforts on the structure and synthesis of LHRH. Subsequently, Drs. Gual, Kastin and Schally established that porcine LHRH unequivocally released LH and FSH in men and women. This dispelled their fears of a species specificity that had been found for growth hormone (GH). The realization that LHRH might be clinically useful encouraged them to continue the agonizing effort involved in its purification.

Although he considered himself a neuroendocrinologist, not a biochemist, he 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 himself, with unshakable faith in hypothalamic hormones, would endure the many laborious steps of purification. He isolated a small amount (800 µg) of LHRH from 160 000 pig brains, proved it to be a peptide, and passed it on to their structural chemists, Drs. H Matsuo and Y Baba. They were able to determine the complete structure of LHRH from this tiny amount. Thus, they won the race to solve the structure of LHRH. After confirming the structure of LHRH by synthesis, Dr. Schally presented it at the Endocrine Society meeting in San Francisco in 1971. It was one of the high points in his life to be able to report, for the first time, the solution to this paramount and supremely complex problem which had preoccupied him and the other experimental endocrinologists for so many years.



Figure 1: Dr. Mendoza (right) and Dr. Schally (left) at the International Prostate Forum hosted by the American Urological Association Annual Meeting in 2014. Photo by Dr John Davis.

Many clinical studies with LHRH were done in Latin America. From 1972 to 1978, he developed agonistic and antagonistic analogs of LHRH (also called GnRH). Starting in 1972, several thousand analogs of LHRH were synthesized by various groups including theirs 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, they established that the antagonists of LHRH could block ovulation in animals and with Drs. D Gonzalez-Barcena and A Zarate, in Mexico, they showed that these synthetic antagonists were active in humans. Later on, he became a pioneer in the development and application of somatostatin for oncological uses. He has 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).

His 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, he became a member of the National Academy of Medicine of Mexico. In 1973, he was made Senior Medical Investigator of the Veterans Administration. Then, in 1977, for his work on the isolation, identification, synthesis, and clinical application of hypothalamic hormones, he received the Nobel Prize in medicine or physiology and in 1978 was elected to the U.S. National Academy of Sciences. After 1978, his interest shifted to the application of hypothalamic hormones for cancer treatment. Grasping the therapeutic potential of hypothalamic hormones, he switched completely to cancer research and became an "endocrine oncologist". Many anticancer peptides have been developed in his laboratory and are in current use.

The use of LHRH agonists for treatment of advanced prostate cancer is based on experimental work done by him and Tom Redding. They first showed that LHRH agonists inhibit the growth of prostate cancer in the Copenhagen rat model. He organized, with Dr. George Tolis in Montreal, the first clinical trial of LHRH agonists in patients with advanced androgen-sensitive prostate cancer. They 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. He received the Health Memorial Award from the M.D. Anderson Cancer Center, Houston, Texas for the 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, his work has focused on new approaches with targeted therapy for various

tumors. He 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, he 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 his lab so he moved from New Orleans to the VA Hospital in Miami, Florida where he was appointed Professor of Pathology and of Medicine at the University of Miami.

In summary, Dr. Schally has improved the treatment methods of hormone-dependent prostate cancer as pioneered by C Huggins. The hormonal therapies that he developed or proposed are based on the peptide analogs of hypothalamic and other hormones that he discovered and synthesized. These discoveries have led to many practical applications. Currently, he continues working on other applications of his discoveries to oncology, and particularly in urologic oncology. Recently *The Canadian Journal of Urology* in the section of Legends in Urology published his autobiography where I obtained most of this information.