Autobiography

I was born in Wilno, Poland on November 30, 1926, being of Polish, Austro-Hungarian, French and Swedish ancestry. My father, a professional soldier trained in the military academies of Vienna, Austria and St. Cyr, France, had to leave his family when the Second World War broke out to fight with the Allied Forces. My life and outlook were influenced by the harsh childhood which I spent in the Nazi-occupied Eastern Europe, but I was fortunate to survive the holocaust while living among the Jewish-Polish Community in Roumania. I used to speak Polish, Roumanian, Yiddish, Italian and some German and Russian, but I have almost completely forgotten them, and my French in which I used to excel is also now far from fluent. In 1945, I moved via Italy and France to England and Scotland. In spite of post-war economic and nutritional austerity, the United Kingdom seemed like a paradise to me because of the respect for human rights. Since that time, I have always had a profound friendship for the British. I received my high school diploma in Scotland in 1946 and afterwards studied chemistry in London. I adored English and Scottish association football and I even tried out as an inside forward for some English and Scottish football clubs, but since I could not devote enough time to training I never made regular First Division teams. However, since 1946 I have always stayed in excellent physical shape by swimming daily and practicing other sports. "Mens sana in corpore sano" has always truly been my motto. In England I also developed a great liking for classical music, especially Beethoven, Brahms and Liszt.

My interest in medical research started at the age of 23, when I joined the National Institute of Medical Research (NIMR, MRC) Mill Hill, London, England. I was fortunate to work with and be exposed to the stimulating influences of such scientists as Dr. D. F. Elliott, Sir Charles Harington, Dr. R.R. Porter, Dr. A.J.P. Martin, Dr. R. Pitt-Rivers, Dr. J. Gross, Dr. T. S. Work, Dr. H. Fraenkel-Conrat, and Dr. W. Cornforth, several of whom later won Nobel Prizes for chemistry or physiology and medicine. Although my position was very junior at Mill Hill, my work was appreciated and this was a source of tremendous satisfaction for me, inasmuch as this recognition came from scientists of such caliber. I learned much in those 2 1/2 years, not only technical expertise but also the philosophy of research and a systematic approach to scientific investigations. These years of instruction (1950-1952) were decisive in providing inspiration, training, and laboratory discipline and profoundly influenced the course of my career. In fact, it was at NIMR, Mill Hill where I endured my "baptism of fire" in medical research and became addicted to it. In May, 1952, I moved to Montreal, Canada where I was given the opportunity to work and study at McGill University. There I learned endocrinology from the brilliant lectures by Professor D. L. Thomson and from my work with Dr. M. Saffran in the laboratory of experimental therapeutics of the Allan Memorial Institute of Psychiatry headed by Dr. R. A. Cleghorn. The work at this laboratory was devoted to ACTH and adrenal cortical steroids. That period marked the beginning of my interest in the relationship between brain function and endocrine activity, and it was there in 1954 that

my involvement in the hypothalamic field began.

In 1955, using *in vitro* systems, Dr. M. Saffran and I demonstrated the presence of corticotropin releasing factor (CRF) in hypothalamic and neurohypophysial tissue. This was the first experimental proof of the existence of hypothalamic hormones regulating pituitary function postulated with prophetic insight by Dr. G. W. Harris. I obtained my doctorate at McGill University in May, 1957, and in September of the same year I was able to secure a position which enabled me to continue my work on CRF at Baylor University College of Medicine in Houston, Texas, where I was associated with Dr. R. Guillemin. My years in Houston (1957-1962) where I was Assistant Professor of Physiology and a Senior Research Fellow of the U.S. Public Health Service were discouraging and frustrating because of problems with the isolation of CRF. Our failure to obtain enough CRF to determine its structure tended to cast doubt on the initial findings. We encountered much skepticism, but I remained unshaken in my confidence in the correctness of the observations on CRF and in the postulation of other hypothalamic hormones regulating anterior pituitary function.

In 1961 I spent about one month at the Institute of Biochemistry in Uppsala with Dr. J. Porath where I gained useful experience in the use of Sephadex and column electrophoresis. I also visited Dr. V. Mutt and the late Professor E. Jorpes in Stockholm, in connection with our collaboration on gastrointestinal hormones, and I was encouraged that they and other astute scientists had confidence in our work and the foresight to appreciate the possible scientific and medical importance of hypothalamic hormones.

I was grateful for the opportunities I was given in the United States, for which I felt a complete allegiance, and in 1962 became a naturalized citizen. When Dr. Joe Meyer, then head of the Veterans Administration (VA) basic research, offered in June, 1962, to set up a VA laboratory devoted to research on the hypothalamus and make me its chief, I accepted since this gave me a clear opportunity to be in complete command of such an effort. The support of a number of individuals, including Dr. E. H. Bresler, then Associate Chief of Staff for Research of the New Orleans VA Hospital, Dr. C. Y. Bowers and Dr. G. Burch of the Department of Medicine of Tulane University School of Medicine, and Dr. W. Locke of the Ochsner Foundation Hospital, was instrumental in helping me establish the laboratory in New Orleans. In December of 1962, I was appointed Chief of the Endocrine and Polypeptide Laboratories at the VA Hospital in New Orleans and Associate Professor of Medicine at Tulane University, and, in 1966, Professor. The earliest members of our 1962 VA-Tulane team were T. W. Redding, W. H. Carter, and M. Tanaka. They have stayed with me all these years, and without their devoted help we could not have resolved the many problems associated with our work on TRH in 1969, LH-RH in 1971, and porcine somatostatin in 1975. Working in a clinical environment, I became more aware of the need for better diagnosis and treatment of patients than I had been before. It occurred to me early that problems with infertility on the one hand and the necessity for population control on the other would make a breakthrough in the control of reproduction particularly desirable from the standpoint of society, and therefore I became especially interested in reproductive endocrinology. To broaden our knowledge of reproductive processes at the brain level, we studied the

central effects of contraceptive steroids and clomiphene. In some of the early studies on LH-RH, before its isolation, we collaborated with one of the pioneers of the hypothalamus and the man I always admired deeply, Professor C. H. (Tom) Sawyer and also with Drs. J. Hilliard, D. Holtkamp, A. Parlow and W. F. White.

It was my good fortune that in 1964 Dr. A. J. Kastin and in 1965 Dr. A. Arimura came to join our laboratory. Dr. Abba Kastin was mainly interested in continuing his work on control of release of MSH and in helping us in clinical work on hypothalamic hormones. He quickly became my best friend and a most efficient collaborator. Dr. Akira Arimura was an experienced physiologist and endocrinologist. Because of his great knowledge, enthusiasm and very hard work, he made great contributions in all phases of our program, and also broadened it with many independent ideas, especially in immunology. Other excellent collaborators at that time included Drs. I. Ishida, A. Kuroshima, T. Saito, and S. Sawano from Japan, and Dr. E. E. Muller from Italy.

All during the period since 1962, I had been hard at work on TRH with Cy Bowers and Tom Redding. In 1966, we reported for the first time the isolation of porcine TRH and determined that it contained three amino acids (glutamic acid, histidine, and proline) in equimolar ratio, but did not take full advantage of this original early finding, as we were preoccupied with parallel studies on reproduction and growth hormone-releasing hormone (GH-RH). However, when R. Burgus and R. Guillemin announced at the 1969 Tucson, Arizona, conference that they also found the same three amino acids in ovine TRH, I realized that we had the right substance. The same year I established the correct amino acid sequence of porcine TRH with Dr. R. M. G. Nair in New Orleans. Subsequently, with help from Drs. F. Enzmann and J. Bøler working in K. Folkers laboratory in Austin, Texas, we were able to determine the structure of porcine TRH and synthesize it. We have shared the credit with R. Burgus, W. Vale and R. Guillemin, who elucidated the structure of ovine TRH at about the same time.

The identification of TRH removed the skepticism surrounding the work on the hypothalamus and I realized that many workers would now be attracted to the field. We therefore redoubled our efforts on LH-RH.

In 1965, in Mexico City, I met Dr. C. Gual of the National Institute of Nutrition who invited me to collaborate with him in the clinical testing of hypothalamic hormones in Mexico. We took advantage of this invitation and in 1968 demonstrated, with Cy Bowers, that preparations of natural TRH are active in humans. Subsequently, again in collaboration with Carlos Gual, Abba Kastin and I established that highly purified porcine LH-RH unequivocally released LH and FSH in men and women under a variety of conditions. It was clear that LH-RH might be useful clinically and this encouraged us to continue the agonizing effort involved in the isolation of this hormone. Although I consider myself an endocrinologist or neuroendocrinologist, with considerable interest in clinical endocrine research and not a biochemist, I personally carried out the isolation work on TRH, LH-RH, somatostatin, and other hormones. Only a person such as myself with strong faith in the presence of these materials would have the patience to go through the many fastidious steps of the isolation procedure, since the effort required in isolating

exceedingly small quantities of gradually purer and purer materials from a crude hypothalamic exctract is so enormous. I was able to isolate a small amount (800 μg) of LH-RH from 160,000 hypothalami and proved it to be a polypeptide. This tiny amount of material was passed to our chemists, Dr. H. Matsuo and Dr. Y. Baba, with suggestions for a structural approach. Since I did not think that amounts of LH-RH on hand would be enough to complete our structural work, I decided to isolate additional amounts of LH-RH. Drs. Matsuo and Baba worked hard and efficiently, and we were able to determine the complete structure of LH-RH with the 800 μg material. After confirming the structure by synthesis, we were in a position to present our findings at the Endocrine Society meeting in San Francisco, California, in June 1971. It was one of the high points in my life to be able to report for the first time the solution to the problem which had preoccupied me and others for so long.

Physiological and subsequently immunological studies with natural and synthetic LH-RH in our laboratory by Drs. A. Arimura, L. Debeljuk, J. Reeves and M. Saito, and with others demonstrated that LH-RH was indeed the physiological hormone. With the synthetic LH-RH readily available, Dr. Kastin and I continued to carry out a variety of clinical studies in Mexico in association with Dr. Gual and later with Drs. A. Zarate and D. Gonzalez-Barcena. I also did parallel clinical tests with Dr. J. Zanartu in Chile and in Argentina with Drs. L. Schwarzstein, N. Aparicio, and the late R. Mancini.

The importance of analogs, particularly with respect to the possibility of developing a new birth control method was uppermost in my mind. I was very fortunate in being able to induce Dr. D. H. Coy, a superb peptide chemist and his wife Esther, also a researcher, to join our laboratory in 1972. More than 300 analogs of LH-RH were synthesized by the Coys with the help of Drs. Y. Hirotsu, K. Nikolics and J. Seprödi in our laboratory between 1972 and 1977. We were particularly interested in stimulatory long-acting superactive analogs for clinical use and in inhibitory analogs which would block LH and FSH release. We were joined in this important work by researchers from many countries. The work of Drs. J. Vilchez from Venezuela, A. de la Cruz from Peru, E. Pedroza from Colombia, and N. Nishi from Japan established in 1976 that the antagonists of LH-RH can indeed completely block ovulation in animals. Very recently with Dr. D. Gonzalez-Barcena in Mexico we showed that these analogs are also active in humans. This of course raises the possibility that such analogs could eventually form the basis of a new birth control method. However, much work is still needed to make my dream of being able to control reproduction at the central level come true.

In 1971, immediately after solving the LH-RH problem, I decided to reinforce our attacks on PIF and GH-RF next, but six years of hard work with Dr. A. Arimura and Drs. J. Sandow from Germany, A. Dupont from Canada and J. Takahara from Japan resulted only in a demonstration that hypothalamic catecholamines and gamma-amino butyric acid (GABA) may be involved in the control of release of prolactin, but did not yet lead to the development of any clinical agents. In our preoccupation with PIF and GH-RH, we did not work on factors inhibiting growth hormone release but after P. Brazeau and collaborators in 1973 announced the isolation and structure of ovine somatostatin, we purified this hormone from porcine hypothalami, determined its structure and synthesized

it. We also carried out much physiological and immunological work (some in collaboration with Dr. F. Labrie in Quebec, Canada), as well as clinical work which convinced us of its importance. Particularly important was the establishment of a radioimmunoassay for somatostatin by Dr. Arimura. The clinical work on somatostatin was carried out mainly in England. Brilliant clinicians Professor R. Hall from the Royal Victoria Infirmary in Newcastle-upon-Tyne and Professor G. M. Besser of St. Bartholomew's Hospital in London were our leaders of two clinical teams which also included excellent collaborators such as Drs. A. Gomez-Pan, D. Evered, C. Mortimer, S. R. Bloom, and others. These clinical studies in England (based in part on some of our suggestions) showed that somatostatin inhibits the release of GH, TSH, glucagon, insulin, and gastrin. Basic studies carried out in England in collaboration Dr. A. Gomez-Pan and in Poland with Professor S. Konturek showed that somatostatin also inhibits gastric acid and pepsin secretion, and the release of duodenal hormones, secretin and cholecystokinin. Since the immunological work of Dr. Arimura showed the presence of somatostatin in the pancreas, stomach and intestine, we then suggested that this substance may be involved in the control of secretion not only of the pituitary, but also of the pancreas, stomach and duodenum. Since somatostatin has multiple short-lived effects, Drs. D. H. Coy and C. Meyers are achieving considerable success in the synthesis of long-acting and selective analogs of somatostatin, some of which could be more practical clinical agents.

Also among our present projects is the isolation of all the compounds with PIF activity, of PRH, GH-RH, CRF, and other hypothalamic substances. In addition to authoring or co-authoring many publications, I take satisfaction from the fact that I helped Dr. W. Locke write a book for clinical endocrinologists.

Since much work with hypothalamic hormones and their analogs is being carried out in Latin America and Spain, my ability to communicate in Spanish and Portuguese has aided me greatly, and resulted in the formation of many beautiful friendships. However, the greatest reward for learning Spanish and Portuguese came when, in 1974, in the course of my work in Brazil I met a very charming endocrinologist, Ana Maria de Medeiros-Comaru (M.D.). Our friendship soon deepened into love and led to our marriage.

I have had the satisfaction that my work in the hypothalamus was honored by top U.S., Canadian and Spanish awards: Van Meter Prize of the American Thyroid Association; Ayerst-Squibb Award of the U.S. Endocrine Society; William S. Middleton Award, the highest award of the VA; Charles Mickle Award of the University of Toronto; Gairdner Foundation International Award, Canada; Edward T. Tyler Award; Borden Award of the Association of American Medical Colleges; Albert Lasker Basic Medical Research Award, and the Laude Award, Spain. In 1973 I was made a Senior Medical Investigator by the Veterans Administration, an honor reserved for only a few. When I learned about my Nobel Prize, I was too grateful and too moved to be overcome with joy, but that came a few hours later when my friends from all over the world began to phone or wire. However, I do not feel that these prizes will have an adverse effect on my future productivity. I am still as keen as ever to make new discoveries and useful contributions to endocrinology.

From *Les Prix Nobel. The Nobel Prizes 1977*, Editor Wilhelm Odelberg, [Nobel Foundation], Stockholm, 1978

Addendum, April 2005

In the years 1972-1978, I developed agonistic analogs of LH-RH (also called GnRH) and in 1981 was the first to show that they inhibit growth of prostate cancer in rats. On this basis, I organized with Dr. George Tolis the first clinical trial with LH-RH agonists in patients with advanced prostate cancer in 1982. This trial demonstrated the clinical efficacy of LH-RH agonists in palliative treatment of androgen-dependent prostate cancer. I then helped develop sustained delivery systems (microcapsules) for agonists of LH-RH and participated in evaluations of their efficacy. Sustained delivery systems of various LH-RH agonists (microcapsules or implants) now provide the preferred method for the treatment of advanced prostate carcinoma. Previous primary endocrine treatment modalities for advanced adenocarcinoma of the prostate based on the work of Charles Huggins (Nobel Prize in Medicine for 1966), used since the 1930s, included orchiectomy or administration of estrogens (DBS). However, surgical castration (bilateral orchiectomy) is associated with psychological impact and estrogens such as DES have serious cardiovascular, hepatic and mammotropic side effects. Treatment with LH-RH agonists is as effective as orchiectomy and offers the advantage of avoiding castration. The therapy with agonists of LH-RH is presently the preferred method of treatment for men with advanced prostate cancer and in about 70% of cases, LH-RH agonists are selected for primary treatment.

I helped Prof. R. Hall and Prof. M. Besser in the first clinical evaluations of somatostatin in normal subjects and patients with neuroendocrine tumors in England and I was profoundly influenced by its effects. Based on this experience, I became one of the pioneers in the development of analogs of somatostatin for oncological uses and demonstrated their antitumor activity in animal models of various tumors. I have been credited with influencing the thinking in the field of oncological applications of somatostatin. Analogs of somatostatin are used now for treatment of acromegaly and endocrine tumors, including carcinoid tumors. The fact that few relevant clinical benefits have been obtained in patients with pancreatic, colorectal, prostatic, breast and other cancers treated with somatostatin analogs is due to a low expression of SST receptor subtypes 2 and 5 in these malignancies that preferentially bind octapeptide somatostatin analogs. However, the expression of these subtypes should be high enough to permit therapy with targeted cytotoxic somatostatin analogs synthesized by my group or

somatostatin analogs labeled with various radionuclides developed in the meantime in Europe. Radiolabelled somatostatin analogs pioneered in Holland are now extensively used for tumor localization. Among my other major accomplishments is the development of antagonistic analogs of LH-RH, the demonstration of their antitumor activity in experimental cancer models and with my associates of clinical efficacy of these antagonists in patients with prostate cancer, endometriosis and leiomyomas. My late wife Ana Maria Comaru-Schally also showed that antagonists of LH-RH could be used as a therapy for benign prostatic hyperplasia (BPH).

My group demonstrated that the receptors for LH-RH, somatostatin and bombesin are present in various tumors, including human prostatic, mammary, endometrial and ovarian cancers. Based on this demonstration of receptors for peptides in various tumors, I started in 1995 the development of modern cytotoxic analogs of LH-RH, bombesin and somatostatin, which can be targeted to peptide receptors on various primary cancers and their metastases. We demonstrated in experimental models of human cancers that these hybrids produce tumor regression or eradication. Because the receptors for these peptides are present on many cancers, targeted chemotherapy based on cytotoxic analogs of these peptides should be more efficacious and less toxic than the currently used systemic chemotherapeutic regimens and might permit dose escalation. My group also developed bombesin antagonists aimed at decreasing EGF receptor levels in tumors and growth hormone-releasing hormone (GH-RH) antagonists, which suppress IGF-I and -II levels and block tumoral receptors for GH-RH and showed that they inhibit a variety of experimental cancers, including androgen-independent prostate cancers, estrogen independent breast cancers, ductal pancreatic cancers, colorectal cancers, lung cancers and brain tumors. My associates and I also demonstrated that GH-RH, which we found in mammary, ovarian, endometrial lung cancers and other tumors, is probably an autocrine growth factor. Our work suggests that cytotoxic somatostatin analog AN-238, cytotoxic LH-RH analogs AN-152 or AN-207 and GH-RH antagonists could be used in the management of patients with advanced prostatic carcinoma who relapsed androgen ablation. Cytotoxic LH-RH analogs or GH-RH antagonists might also be considered for improvement of primary hormonal therapy for prostate cancer.

In September 2004, my wife Ana Maria Comaru-Schally, M.D., F.A.C.P. died suddenly from thyroid cancer. I was profoundly hurt by the unexpected passing of my wife after 28 years of wonderful marriage, which was preceded by 2 years of an exciting and emotional romance. She was an ideal wife, companion, collaborator and my best friend. She will be sorely missed by me and many friends in various countries. Her death was the hardest blow and the biggest tragedy in my life. I am seeking consolation and comfort by continuing my work in cancer research. I believe that this is what she would want me to do.

In conclusion, since receiving the Nobel Prize, I developed the preferred method for treatment of advanced prostate cancer based on LH-RH agonists. My group synthesized several new classes of antitumor peptides such as LH-RH antagonists, somatostatin analogs, bombesin/GRP antagonists, GH-RH antagonists and targeted cytotoxic analogs of LH-RH, bombesin and somatostatin. I then proposed, and with my associates

experimentally demonstrated, the efficacy of new approaches to therapy of prostatic, mammary, ovarian, endometrial, renal, pancreatic, colorectal, gastric and lung cancer (SCLC and non-SCLC), osteosarcomas, melanomas, non-Hodgkin's lymphomas and brain tumors based on these antitumor peptides.

I have been credited with extending the concepts of hormone-dependent tumors beyond the pioneering work of the great Charles Huggins. Hormonal therapies that I proposed are based on the peptide analogs of hypothalamic and other hormones and are relatively free of side effects, in contrast to radiation and chemotherapy. I am gratified that my discoveries have led to many practical clinical applications that are widely used and highly effective. It is my hope that the significance of these discoveries and their applications to oncology will increase in the future.

I now have over 2200 publications, more than 1200 of which were published after I received the Nobel Prize.