## JOSEPH MEITES, Ph.D. THE CAREER OF A PIONEER IN NEUROENDOCRINOLOGY RESEARCH By Mable E. Meites

#### Background

Joseph Meites had many experiences which shaped his life and the subsequent development of a seminal career in a new field of neuroendocrinology research. This presentation of his career will attempt to show the importance of his life experiences along with a summary of the areas of his research. Most of the scientific data is taken from his applications for or the renewal of grants.

Joe was born in Kishinev, Russia on December 22, 1913. He arrived with his parents, in St. Joseph, Missouri in mid December 1920. His maternal grandparents had left Russia in 1913 as they were victims of many pogroms. They went to St. Joseph as relatives had already settled there. His parents left Russia because of pogroms, economic hardships, and to keep his father from being inducted into the Russian army. He was six years old and immediately entered grade school. He spoke only Yiddish. His family stressed the importance of education. Fortunately, St. Joseph had an excellent school system. He graduated from grade school in 1928, high school in 1932, and Junior College in St. Joseph in 1934. While in Junior College the yearbook had a photo of Joseph (known hereafter as Joe) with the caption *"Name some line in which 'the Professor' is not a success if you can. From radio to debate he has attained the highest honors, including the National Honor* Society." He was involved in extracurricular activities including building radios, international relations, history, arts and literature, music appreciation, track, and ROTC.

His family became interested in the Zionist movement as it had become clear by the 1930s, that Hitler was trying to exterminate the Jews in Germany, and anti-semitism was widespread in America. About 1934, Joe worked on a farm during the summer as he was thinking of going to Palestine to live and help settle the land. Some of the Meites family who lived in Russia had gone to Palestine to live and settled in Kibbutz Dalyia. Going to Palestine meant participating in the Kibbutz movement, which was focused largely on agriculture. Joe thought he should learn about agriculture before going. After Junior College, Joe hitch hiked to New York where he worked in a mothball factory for about a year and was able to save some money to enter the University of Missouri in 1935. He received the B.S. degree in agriculture at the University of Missouri in 1938, and the Masters degree in biochemistry in 1940.

In Chapter 18 of Pioneers in Neuroendocrinology, Vol. II, 1978, Joe described his entry into endocrinology as accidental.

"While still an undergraduate at the University of Missouri (1937) I became a part-time technician in the laboratory of the late Professor C. W. Turner, and after a year became one of his graduate students. Turner received his training in genetics but also developed an early interest in endocrinology while at the University of Wisconsin. In the 1920's he became a professor in the Dairy Science Department at the University of Missouri where he soon became immersed in work on endocrine regulation of mammary growth and lactation (milk production). His research attracted many graduate students and postdoctoral fellows. Turner not only was an enthusiastic and dedicated investigator

but also was a kind and generous man, and a good spirit of camaraderie prevailed in the laboratory. The atmosphere was stimulating and there was a general belief in hard work and long hours. Everyone had a maximum of freedom to pursue his own ideas, and Turner always was prepared to give good advice and encouragement. Over the years he developed some pet theories which he held onto tenaciously even when challenged by his students and others, but he never took offense and conceded the right of everyone to his/her opinions. He retained his scholarly interests to the end of his life in 1975 and probably contributed more than anyone else to the foundations of modern lactational physiology.

I took my first course in endocrinology in 1937, while still an undergraduate student, and was taught, at that time, that the endocrine and nervous systems were separate and for the most part operated independently of each other to control body functions. The endocrine system was described as being a collection of glands including the pituitary, thyroid, adrenal, pancreas, ovary and testes. The functions of the endocrine system was thought to be the regulation of body energy levels, reproduction, growth and development, internal balance of body systems (homeostasis), mood and responses to surroundings such as stress and injury. If disorders of the glands occurred, various diseases or abnormalities occur, including but not limited to diabetes and growth and development.

These glands produce hormones which are chemical substances that affect and control the activity of another part of the body. They serve as messengers and are transmitted through the blood stream. Most hormones are proteins, others are steroids. It was vaguely appreciated that there was some kind of connection between the pituitary and brain, as evident from the action of the milking stimulus on lactation, the effect of coitus in evoking ovulation in the rabbit, the stimulating effect of light on reproductive processes in birds and mammals, etc. However there was little understanding of the mechanisms involved. I had become interested as a graduate student in the control of prolactin secretion and lactation, and had studied the effects of different hormones on these processes. Prolactin is a peptide hormone associated with lactation.

The focus of my research was to determine which hormones were released by which gland, what pathways they took to reach and affect other parts of the body, and what the function was of each. Since the research was being done at the Dairy Science Department at the University of Missouri there was great interest in milk production and why diseases and abnormalities occurred in the mammary glands. Dairying was an important industry in Missouri as there were many dairy farms in the state. At that time most women nursed their babies and they and their physicians wanted to be informed about disorders of the endocrines and mammary glands. The University was affectionally called 'Moo U'.

For the master's degree I chose to study the question of why lactation (milk secretion) was not initiated during pregnancy, but was initiated at about the time of parturition. The research centered largely on the changes in prolactin secretion during pregnancy and at parturition, the effects of estrogen and progesterone on prolactin secretion and lactation, and the combined actions of estrogen, progesterone and prolactin on the mammary gland. In a series of experiments in ovariectomized and male rabbits, I found that injections of estradiol and progesterone in combination stimulated mammary growth but prevented prolactin from initiating lactation. This showed that the two steroids interfered with the peripheral lactational action of prolactin on the mammary gland.

I concluded that lactation was not initiated during gestation primarily because (a) the predominance of progesterone over estrogen secretion during pregnancy resulted in stimulation of mammary lobulo-alveolar growth, and prevented prolactin and glucocorticoids from initiating lactation; (b) near the end of pregnancy, progesterone and estrogen secretion fell, and prolactin and ACTH-glucocorticoids rose markedly, permitting the onset of lactation. On the whole, this theory of lactation was held, although some aspects remained to be clarified. In women, both pituitary and placental prolactin rise during gestation, but the high progesterone and estrogen secretion prevent prolactin from initiating copious lactation until about the time of parturition, when the progesterone and estrogen secretion show a marked decline. I received the Masters Degree in 1940.

For the Ph.D. degree I developed a theory to explain the onset of lactation of parturition based on the interactions during pregnancy among estrogen, progesterone, and prolactin (Meites and Turner, 1942). Aside from estrogen and to a lesser extent testosterone, none of the other hormones, including oxytocin and vasopressin, appeared to be capable of stimulating prolactin secretion. By 1942 I had published nineteen research papers which appeared in several major scientific journals. I also had received the Junior Sigma XI award. I was about to complete the Ph.D. degree when I was inducted into the U. S. Army."

#### The Army and Sanitary Corps Years (1942-1946)

According to his army records, Joe was inducted into the U. S. Army as a private, in October 1942. He was not eligible for combat duty because he had very little vision in one eye. In January 1943 Pvt. Meites married his college sweetheart, Mable Rumburg. While receiving his basic training in Salina, Kansas, he applied for either Officers Candidate School or a direct commission in the newly created Sanitary Corps. He wanted to be in a branch of service that would enable him to contribute his skills in a field commensurate with his background. The Sanitary Corps was made up of scientific medical specialists, including sanitary engineers, bacteriologists, biochemists, physiologists, entomologists, and other scientific personnel.

In June 1943, he received a Direct Commission in the U. S. Sanitary Corps as a Second Lieutenant and was assigned to an Army Hospital laboratory in Springfield, Missouri. In August 1943, he was assigned to the laboratory of an army hospital in a Chemical Warfare training camp in Alabama. This was his first exposure to soldiers in training with chemicals. The soldiers were involved in testing chemicals and protective clothing used in warfare. He was involved in treating soldiers who were moderately to severely injured by the chemicals. Since he spoke a little German, he was assigned to a group of German prisoners who had been brought to the U.S. and placed on a work detail. He found they believed Hitler's propaganda and did what they were told to do without questioning anything.

In June 1944 he was transferred to Ft. McClallan and was assigned to the 106th General Hospital. This hospital was sent to Wimbourne, Southern England. He soon was promoted to First Lieutenant and became Assistant Chief of Laboratory Services. Later he was promoted to Chief of Laboratory Services. Some other British and American Army hospitals and some air bases were located in the same area. They were about ten miles from the English Channel and received the deceased and wounded soldiers from the Battle of the Bulge and the European theatre. He saw many young and severely wounded soldiers. He also saw thousands of deceased soldiers as one of his assignments was to help with autopsies. He said this was one war he believed was necessary, but it was very difficult emotionally to witness so much horror.

One soldier needed a blood transfusion immediately. Joe had the same blood type and volunteered to be the donor. There was no time for cross matching. The soldier lived and Joe said he would never forget the look of gratitude on the young soldier's face. He obtained passes to go to London and saw how the British were having to live underground or any way they could, and how they survived the V-2 bombs. He got to know some airmen who flew their missions, knowing full well that they were endangering their lives but they knew that was their job. I saw Joe cry twice. First, when we visited the American Cemetery at Normandy in the 1970's and saw the crosses row on row. He actually had known some of them. Second, when we visited his brother Isidor's grave in St. Joseph, Missouri. His beloved brother had made the death march on Corregador and died there. He cared very deeply about all of them as they had sacrificed their lives for all of us. He felt that Isidor was a tremendous sacrifice to society, as he was considered by the family and the school teachers to have a brilliant mind and personality and a person who could make outstanding contributions to society. He graduated summa cum laude from the University of Missouri with a master's degree in organic chemistry.

After being in hospital laboratory work for a while, Joe wrote his wife, Mable:

"I have found that working in the hospital laboratory made me realize more than ever how well suited I am for research work. I loved to search for the new and miss my work at the University of Missouri. I am proud of the work I was able to accomplish while there and I am anxious to do more creative work. I want to do something worthwhile."

In May 1945, the war in Europe ended and Joe's assignment was to organize a school for the hospital personnel to prepare them to go to Japan as a part of the occupation force of Japan. The Japanese had not yet surrendered. In August 1945, many troops were returned to the USA for additional training. He was on the Queen Elizabeth enroute to the USA when the atom bomb was dropped on Hiroshima. The more than 16,000 troops on the Queen concluded that they probably would not be sent to Japan. Instead, Joe was assigned to three different hospital laboratories in the USA in one year to assist with clean up and laboratory closings. He was discharged in August, 1946. He then returned to the University of Missouri and completed the Ph.D. degree in 1947.

## The Michigan State University Years (1947-1984)

Joe obtained the position of Assistant Professor in the Department of Physiology and Pharmacology at Michigan State College, East Lansing, Michigan in September, 1947. The Physiology and Pharmacology Department was in the College of Veterinary Medicine located in Giltner Hall. His "office and laboratory" was located in the basement. He shared a room with two other new faculty. The room was a narrow corridor with one or two sinks, some cabinets, and the faculty sat on stools. The first few years were devoted to developing and teaching new courses, finding graduate students, finding grant money, and doing some research.

A brief look at the history of Michigan Agricultural College and East Lansing gives some perspective for understanding our starting point. According to internet historians (<u>http://www.answerbag.com/q\_view/273144</u>),

"the Michigan State Legislature, in 1855, passed Act 130 which provided for the establishment of the Agricultural College of the State of Michigan. The post office address was Agricultural College, Michigan. The settlement of East Lansing began in 1847 and was an important junction of two major native American trails, the Okemah Road, and the Park Lake Trail. By 1850 the Lansing and Howell Plank Road Company was established to connect a toll road to Detroit. Howell Plank Rd (now Grand River Avenue) cut through present East Lansing. It was a toll road, completed in 1853, and included seven toll houses between Lansing and Howell, Michigan. East Lansing was not incorporated until 1907. Hence, the reason for the post office address of the college.

Twenty two sections (677 acres) of Salt Spring Lands was appropriated for the support and maintenance of the college and \$40,000 to carry the college through its first two years. The Agricultural College of the State of Michigan was officially opened in 1857. It is considered the prototype of land grant colleges created by the Morrill Act of 1862. For the first four decades, the students and faculty lived mainly on the college campus. A street car line was built in the 1890s to connect Lansing and the campus.

By 1887 Professors William J. Beal and Rolla C. Carpenter created Collegeville, along what is now Harrison, Center, and Beal streets. However the first residents were "teamsters and laborers". In 1898, the College Delta subdivision (now Delta Street) had the support of the college itself which provided utilities.

After John Hannah became president, he was able to purchase about 5,000 additional acres of land to the south of the old campus. "One hundred years after its founding, the Michigan Senate Judiciary Committee suspended the rules on a motion by Sen. Harry Hittle (R-E. Lansing) to allow the Michigan State College name to be changed to Michigan State University of Agricultural and Applied Sciences. The University of Michigan opposed the name change on the grounds that the similarity of names would lead to confusion. The bill was approved by a vote of 88 to 14. The name was shortened as of January 1, 1964 to Michigan State University." The last four digits of the main telephone line for the college still are 1855 and a street MAC Avenue stands for Michigan Agricultural College.

By 1947, 100 years after the Agriculture College of the State of Michigan was authorized, the student population was about 5,000. After two world wars, one severe depression, and several drops in the economy, President John Hannah was forward looking, wanted to expand, enroll more students, and become a university. This gave many returning World War II veterans, who received the benefit of the GI Bill and sought to prepare themselves for the future, a rare opportunity to develop new areas of study and be involved, from the very beginning, in the growth and development of a college.

We arrived in East Lansing in September 1947. We found housing to be a scarce commodity. Arrangements had been made for us to stay briefly in a room at the Student Activities Center instead of a hotel. We then moved into a barracks apartment on Chestnut Street (on campus). The college had acquired a number of army barracks, which had been divided into small apartments. Our apartment consisted of one room which contained a small kitchen, a living room, and a small bathroom. It was heated by a large kerosene stove. We found a second hand couch that converted into a very hard bed. Some months later we moved into one of the brick apartments which was an improvement. There were no buses nearby so we bought a 1936 Chevrolet, the stick-shift variety. I used the car for my social work job. After several insurance claims, AAA insurance notified us that they were canceling our policy because we had too many claims for road service, for flat tires. The culprit was nails left on our parking area by the contractors who converted the barracks into apartments. Another scarce item was telephones. Fortunately, at that time, MAC had a very good support system of volunteers, provided by faculty wives. They not only welcomed us, but helped us find resources and get acquainted. They were known as the Faculty Folk Club, but renamed MSU Community Club. Still another scarce item was salaries. The Beginning salary for Joe, with a Ph.D., was \$4,000 per year. For my social work position, the salary was \$2,000 per year, with a master's degree.

In 1949, Joe was diagnosed with uveitis in both eyes. After unsuccessful treatment in East Lansing, he sought treatment at the University Hospital in Ann Arbor. After the examination by an opthalmologist, he was told there was no further treatment and he should find another kind of work that did not require vision. This was most alarming and frightening, as it threatened loss of vision and his whole career. From his research work, he knew that the use of ACTH was being considered for treatment of some diseases and he researched the possibility of trying it to treat his eye condition. He found that some opthalmologists at Henry Ford Hospital in Detroit were using ACTH on an experimental basis. He arranged for treatment which required two weeks of hospitalization so his reactions to the drug could be monitored. Happily, the ACTH cleared the eyes, his vision was saved, and his career continued.

Joe found the laboratory space was limited and few graduate students had come to the department. Scientific articles published with Joe's name during 1949 to mid 1950s indicate that he did research by collaborating with colleagues within the department as well as with faculty in animal and poultry sciences and veterinary medicine.

Some of his research attracted the attention of the news media as they began publishing articles about scientific work at Michigan Agricultural College (MAC). In May, 1950 a Newsweek article, entitled "Milk Without Motherhood" reflected some of Joe's research work. It read:

"The modern dairy cow, a machine which permits human beings to eat grass, is a tribute to the science of animal breeding. Several Milleniums of effort have transformed her from a wild animal into an unnaturally bountiful milk machine. But, in recent times endocrinologists have dreamed of an even more highly specialized cow, her milk production raised to new heights by the judicious use of hormones. They would like to start lactation at a much earlier age and maintain it continuously throughout life without wasteful interruptions for breeding and calving. They even plan to turn sterile heifers into prolific milk producers.

Experiments along this line have been going on since the mid '30s, (in the Turner Laboratory in Missouri) but little success has been reported. Sterile cows treated with diethylstilbestrol, a synthetic chemical similar to some female sex hormones, have given fair amounts of milk. British researchers have found that animals so treated seemed to develop brittle bones and must be confined to stalls where they can be constantly guarded against injury. Also these chemicals keeps the cows in such feverish heat that they injure themselves and other animals with violent love play.

This week the outlook for artificially stimulated milk production suddenly became much brighter. Three Michigan Agricultural College scientists revealed that two sterile Guernsey heifers, aged 2 and 4 years, are now yielding a daily 25 pounds of milk apiece. This production level would be 'quite normal' for a Guernsey which has had its first calf.

The work started last December when Michigan Agricultural College (know as MAC) bought the apparently useless animals for \$325, about the price they would bring as beef. They were turned over to Drs. Joseph Meites and E.P. Reineke of the physiology and pharmacology department and Dr. C.F. Huffman of the dairy department, who named them Josephine One and Josephine Two (after Meites). Under the fawn and white mottled skin of the cows they inserted tablets of both chemicals. As the chemicals

were slowly absorbed into the blood stream, the cows' immature udders began to develop. After 100 days the undissolved remnant of the hormones was removed, and milk began to flow.

The Michigan researchers explain that they are aiming, in effect, at "pregnancy without conception". The implanted hormones copy roughly the hormone content of the blood of a naturally pregnant cow. Removing the hormone supply after 100 days stimulates the drop in blood hormones which occur at birth.

Meites, Reineke, and Huffman agree unanimously that their technique could stand some improvements. There may be a more effective ratio between the two hormones. They would like to be able to administer the chemicals orally, thus making it possible for a farmer to treat his cows without the aid of a veterinarian. On the other hand, cost seems to be no problem, with hormones selling for less than \$10 per pregnancy.

What would hormones do for a normal cow? Looking far into the future, Meites saw the endocrinologist's vision: It should be possible to keep a normal animal in lactation indefinitely. But where would the little cows come from?" Joe thought the College obtained a patent on this procedure. The procedure was dropped after a few years as the milk production of these heifers was not sufficient to be profitable.

In February, 1951 the Michigan State News reported that *Meites and Wolterink were initiating the use of radioactivity to enhance the accuracy of their research. The article read: "While news of atomic explosions fill the front pages of almost every newspaper, Michigan State College carries on research with the peaceful use of an atomic byproduct, radio-active isotopes.* 

Radio-active materials are being used in graduate studies whenever possible. There is a great psychological fear of radio activity, said Prof Wolterink. In many ways this impedes scientific progress. The sooner the public learns that radio activity is not a magic thing but a useful tool, the more rapid will be the progress of science. In the department of physiology, work with radio-active isotopes has two divisions. One is concerned with mineral metabolism and uses radio-active calcium and cobalt. The other works with hormones, especially those associated with the thyroid gland.

One of the projects deals with mineral metabolism and the effect of calcium injections on bone growth.... Another project deals with radio-active cobalt and its effect on growth of the body and the effect on the blood cells. The scientists were studying how fast the body consumes cobalt and what effect thyroxine and the sex hormones have on the intake and loss.

A synthesized radio-active hormone, thyroxine, was developed and is being used to study the effect of this hormone on the bodies of rats and chickens. The part that phosphorous plays in the development of the mammary gland was being studied. They found it was possible to take a picture of the gland with dental film which enabled them to trace the growth of the gland and of cancer growth."

In May, 1953 the Lansing State Journal had an article entitled:

"Vitamins Given With Cortisone. Professor Joseph Meites says he has found a possible answer to some of the harmful side effects of taking cortisone and ACTH. These manufactured hormones, gifts of science to victims of arthritis or rheumatism still have their drawbacks. Some of their most serious limitations are that they tear down muscle tissue and step up the loss of body protein, causing acute weakness. Cortisone is a synthetic version of what the adrenal glands secrete - ACTH, an extract of the pituitary gland, stimulates the adrenals to produce more natural hormone than normally.

Dr. Meites has found that giving the rodent vitamins B-12 and/or an antibiotic along with the cortisone keeps animals healthy. Rats given cortisone without the vitamins or antibiotics appear sickly and scrawny and do not live long. Meites also found that rats also need Vitamin B-1 (thiamine) and B-6 (pyridoxine) in larger amounts..."

In the meantime, Joe introduced courses in endocrinology for students and incorporated both teaching and research. He began to acquire graduate students who either worked toward the master's degree and/or wanted to obtain the Ph.D. degree. As time progressed he also had postdoctoral students.

In 1953 Joe was promoted to full professor, and we had bought a small house off campus. In 1955 he was eligible to take a sabbatical leave. He received a Weizmann Institute of Science Fellowship (postdoctoral) in Rehovot, Israel and spent a year doing research with ergot drugs. Ergot is an alkaloid derived from the grain fungus Claviceps purpurea. His research was to determine if ergot drugs could be used for treating cancer. Ergot drugs were known to have potential for hastening labor and preventing postpartum hemorrhaging. He was invited to remain at the Weizmann Institute. However, after comparing his experience there and at MSU, he realized that Michigan State offered more opportunity for him to pursue his interests and goals. He already had established the first endocrinology laboratory at MSU, had received grant funding, and had several graduate students. He clearly had a vision as to what he wanted to do which was teaching and research. Later, he had many offers to be the department head at different universities and to work in commercial pharmacological firms, but he declined.

Upon his return to Michigan State University, in September, 1956, Joe and his students continued to pursue questions about the initiation of lactation and other topics. According to a grant proposal, he and his students were among the first to show that tranquilizing drugs such as reserpine and chloropromazine could initiate lactation in rats and rabbits. Other drugs found to initiate lactation included morphine and serotonin. Both subsequently were shown to release prolactin, whereas LSD (ergot derivative) and iproniazid (monoamine oxidase inhibitor) were found to depress lactation. Joe summarized his research work to fall within about four areas, including; a) Environmental Influences on Pituitary Function; b) Role of Hypothalamus in Control of Anterior Pituitary Function; c) Relationship Between the Hypothalamus and Development of Growth and Mammary (Breast) and Pituitary Tumors; and d) The Neuroendocrinology of Aging. His grant proposals summarize the work of the Meites laboratory as follows:

## **Environmental Influences on Pituitary Function**

"Joe and his students began, in the 1960s, to use different stress techniques to determine whether they influenced pituitary function. The use of food restriction resulted in a reduction in pituitary and blood growth hormone, which was the opposite of that found in food restriction in human subjects. Caloric restriction was shown to result in a reduction in serum luteinizing hormone, follicle stimulating hormone, prolactin and thyroid stimulating hormone, as well as in serum growth hormone. They concluded that the effects of caloric restrictions on the pituitary were exerted by the hypothalamus and not the pituitary itself. In 1967, the Meites laboratory gave half food intake portions, and estrous cycling ceased in two weeks.

In the 1980s, the Meites laboratory conducted experiments to determine the relationship between nutrition in the development, growth and progression of carcinogen-induced mammary tumors in rats. The results demonstrated that the inhibitory effects of underfeeding on carcinogen-induced mammary tumorigenesis results from a hormonal deficiency at the time of tumor initiation and can be counteracted by elevations in circulating estrogen and prolactin levels.

Subsequent studies were conducted to determine the role of estrogen and prolactin during the critical period on subsequent hormone dependency of carcinogen-induced mammary tumors. Results showed that the rats, made deficient in estrogen and prolactin at the time of carcinogen administration, developed fewer tumors, but the majority of tumors that did develop were not dependent on these hormones for subsequent growth. These findings demonstrate that the hormonal milieu in rats at the time of carcinogen exposure determines not only tumor incidence, but also subsequent hormonal dependency.

In 1984-87, experiments were conducted to determine the role of endogenous opioid peptides in pituitary luteinizing hormone secretory responses to acute and chronic stress and nutrient restriction. They found that within a brief interval following acute exposure to ether, plasma luteinizing hormone levels were elevated compared to controls and that pretreatment with the exogenous opiate, morphine, prevented this stimulatory response. Prolonged etherization significantly depressed the circulating luteinizing hormone, whereas naltrexone, a specific opiate antagonist, reversed the decline. Immobilizing rats for several hours resulted in significant increase in leutenizing hormone release. These studies provided novel evidence for endogenous opioid involvement in the effects of acute and chronic stress, as well as nutrient deficiency on Luteinizing hormone release in rats.

A study investigated the impact of opiate receptor blockade on suppression of pituitary thyrotropin secretion by acute and chronic stress. The findings demonstrated that opiate/receptor interaction is required for inhibition of pituitary thyrotropin secretion during both acute and chronic stress. A study on the counteraction of morphine on stress-induced inhibition of growth hormone release in the rat aimed to study the influence of morphine on pituitary growth hormone secretion during stress. These findings, taken together with evidence for overall enhancement of central opioid neurotransmission during stress, suggested that stress-induced reductions in growth hormone release reflect an overriding inhibitory influence of an independent nonopioid mechanism. The ability of this exogenous opioid administration to counteract this inhibitory signal further supports the view that stress and the opiates may influence growth hormone release via separate mechanisms.

If rats were placed under constant light, they developed ovaries with large cystic follicles and came into constant estrus, despite continued reduced food intake. If the rats were given constant light together with epinephrine-in-oil, they not only developed follicles but ovulated and developed corpora lutea. It was also shown that hypophysectomized female rats with a pituitary graft underneath the kidney capsule, could be induced to develop follicles and show estrogen stimulation of the uterus, when placed under constant light. The grafted pituitary also increased in size and showed differentiation of cell types. This suggested that constant light induced release of luteinizing releasing hormone into the systemic circulation which acted on the grafted pituitary. It was shown by the Meites laboratory that placing female rats under constant light resulted in reduced release of luteinizing hormone release hormone by the hypothalamus, and it decreased norepinephrine and increased serptonin turnover. These effects on the hypothalamic biogenic amines are believed to be primarily responsible for the constant estrous condition in rats produced by continuous light. It also was shown that rats under continuous illumination and in constant estrus, could be induced to cycle by administration of L-dopa and PCPA, to increase catecholamines and to reduce serotonin activity in the hypothalamus.

The Meites laboratory showed that stress-induced prolactin release and inhibition of thyroid stimulating hormone release, were associated with an increase in serotonin turnover in the hypothalamus. Serotonin itself can increase prolactin and decrease thyroid stimulating hormone release in rats. It is of interest that stress also has been shown to increase hypothalamic opiate activity, and opiates can increase hypothalamic serotonin activity. Opiates also increase prolactin and reduce thyroid stimulating hormone release. Thus there appears to be a relationship between stress, endogenous opiates, serotonin and pituitary hormone function.

Rats placed in warm temperatures were found to have lower serum thyroid stimulating hormone and growth hormone, but higher serum prolactin values, whereas, cold temperatures raised serum Thyroid Stimulating Hormone, lowered serum prolactin, and had no effect on serum Growth Hormone levels. Old rats, in contrast to young rats, responded to cold temperatures with smaller elevations in serum thyroid stimulating hormone and thyroxine than young rats. Meites reported that we now know that the nervous system and the endocrine systems are highly integrated. They function closely together and profoundly influence each other. His laboratory was exploring whether the environmental factors, internal and external, influence the brain to produce or not to produce nerve hormones."

An article in Chicago Today, dated September 10, 1969, stated that Meites reported at a meeting of the International Society for Neurochemistry, in Milan, Italy that

"...light gets into your eyes and can effect body chemistry and sexual behavior. The light passes into the eye, reaches the optic lobe, then influences the brain by causing neuro hormones to be secreted from the brain. Secretions of neuohormones from the lower brain follow tiny blood vessels that reach into the pituitary gland. This action triggers the release of such elements as gonadotropins, which are dumped into the blood stream and affect sex glands. Scientists are beginning to measure the vital importance that light rays, absorbed by the eye, have on human well being, and probably human behavior and illness."

## Role of the Hypothalamus in Control of Anterior Pituitary Function.

Joe credited the English anatomist, Dr. Geoffrey Harris, for creating a beginning foundation for neurendocrinology by showing that portal vessels rather than nerves connect the hypothalamus to the pituitary by postulating the existence of chemical control by the brain. In the 1950s, when Dr. Harris announced the chemotransmitter hypotheses, the Meites laboratory was already beginning studies in this area. Applications for grants indicate that "Meites believed that Neuroendocrinology is the study of interactions between the nervous system and the endocrine system. This concept arose from the recognition that the secretion of hormones from the pituitary gland is closely controlled by the brain, especially by the hypothalmus. The glands of the neuroendocrine system had been found to include the hypothalmus, anterior and posterior pituitary, pineal body, thyroid and parathyroids, thymus, adrenal, kidney, pancreas, ovary and testis.

The nervous system also had been found to be organized into two parts: the central nervous system which consists of the brain and spinal cord, and the peripheral nervous system which connects the central nervous system to the rest of the body. These glands secrete hormones which are chemical substances that guide such processes as body energy levels, reproduction, growth and development, internal balance of body systems (homeostasis) and responses to surroundings, stress and injury.

According to the internet (<u>http://www.hormone.org/endo</u>), "neuroendocrine research was also concerned with endocrine system diseases and disorders that happen when one or more of the endocrine systems are not working well. Hormones may be released in amounts that are too great or too small for the body to work normally. These irregularities are also called hormone imbalance. There may not be enough receptors, or binding sites, for the hormones so that they can direct the work that needs to be done."

Joe renamed his laboratory, as he had become known as the Center for the Study of **Neuroendocrinology** instead of just Endocrinology. His grant proposal said that the Meites laboratory

"was among the first to prepare the hypothalmic extracts from the brain of animals to determine whether they could induce the release or inhibit release of anterior pituitary hormones. They were the first to report the existence of a prolactin releasing factor in 1960, of a prolactin release inhibiting factor, in 1961, of a growth hormone releasing factor in 1962-1963, and of a follicle stimulating hormone releasing factor in 1964. We also developed bioassay procedures for each of these factors, and showed that their activity in the hypothalamus was altered in response to many external and internal environmental stimuli. We also were among the first to demonstrate that brain biogenic amines (dopamine, norepinephrine, serotonin) and other neuro-transmitters could influence secretion of anterior pituitary hormones, by interacting with the Hypothalamic Releasing Factors. In a friendly and extensive debate with Dr. John Folley and his collaborators in England over whether oxytocin could induce prolactin release, Meites and his students proved that oxytocin does not release prolactin from the pituitary as claimed by Folley et al. This was confirmed by radio-aminoassays."

A colleague, Dr. Richard Gala, of Wayne State University, wrote that "at this point the Meites laboratory was a scientific community to be reckoned with. While many investigators went from step 1 to step 2 in elucidating a problem, Meites had the intuitive ability to eliminate steps 2 and 3 and go right to step 4, thus allowing him to be the first to report a new observation and develop a new concept. This ability combined with his love of learning and his love and concern for the people that worked with him contributed to making him a great and wonderful man." Colleagues began to refer to him as Mr. Prolactin and to credit him with being the father of prolactin.

Joe wrote an article for Science, dated 11 November, 1977 in which he described

"A bitter race occurred between Drs. Schally, Guilleman, McCann and others to identify the chemical base of the hypothalamic hormones discovered by the Meites Laboratory. Subsequently, several of these hypothalamic (hormones) were isolated and chemically identified by Drs. Schally of New Orleans and Guillemin of San Diego. These were highly competitive researchers who wanted to be the first to solve the chemical base of these hormones as they recognized it would be a breakthrough to bring them fame. These two men received the Nobel Prize in Physiology in 1977, along with Rosalyn Yalow who developed the radioaminoassay procedure which made the discovery possible." In short, the Meites laboratory did the basic research which laid the foundation for this prize. Some in the scientific community believe the Meites laboratory should have been included in the Nobel Prize.

Meites further wrote in <u>Science</u> that: "Geoffrey Wingfield Harris, an English anatomist who died in 1971, developed a theory that the hypothalamic portion of the brain controlled pituitary function. It is doubtful that any two discoveries in the last 40 years or more have had as great an impact on basic and clinical endocrinology as the development of radioamunoassays, and the discovery that the hypothalamic region of the brain secretes hormones that control the secretion of hormones by the anterior pituitary gland. Since the brain is the seat of the intellect, it opens the doors toward the understanding of the mind and may have such medical benefits as new contraceptives and the control of diabetes."

I accompanied Joe on as many trips to scientific conferences as my vacation time permitted. I often wondered whether we were in the USA, Europe, India, or elsewhere, why we ended the day and into the night, sitting at cafes with one or more scientists while they talked shop. Dr. Harris was among them. I found the reason was they were learning from each other. Joe wrote that he "felt deeply indebted to Geoffrey Harris. I looked up to Harris as a teacher who inspired many of our first efforts in neuroendocrinology, and as a friend. Because of my early interest in the control of prolactin and other pituitary hormones, I was highly stimulated by Harris's article in Physiological Reviews in 1948. Harris's 1955 book, neural Control of the Pituitary Gland became a virtual Bible of Neuroendocrinology in our laboratory." Shortly after Harris died, in 1971, Joe and others organized the first International Neuroendocrinology Society and Joe was elected its first president.

# Relationship Between the Hypothalamus and Development and Growth of Mammary (Breast) and Pituitary Tumors.

Joe was a systems physiologist and used a systems approach to the study of the relation of the neuroendocrine system to mammary tumors. A grant application stated:

"In the 1960's we were the first to report that placement of lesions in discrete areas of the hypothalamus could alter the incidence and growth of spontaneous and carcinogeninduced mammary cancers in rats. Thus placement of lesions in the median eminence was shown to hasten development and increase the number of spontaneous mammary tumors (mainly benign fibroadenomas), but to inhibit development of carcinogen-induced mammary adenocarcinomas. Reserpine administration or grafting of extra pituitaries underneath the kidney capsule also hastened development of spontaneous mammary tumors, whereas L-dopa administration prevented development of these tumors. Placement of median eminence lesions in rats with mammary tumors, evoked a rapid increase in growth of these tumors, but this growth increment could not be maintained if the rats were ovariectomized. Thus the ovaries, as well as the pituitary, appear to be essential for mammary tumor growth in rats. Numerous central acting drugs were tested in rats with mammary tumors. L-dopa, ergot drugs and monoamine oxidase inhibitors (iproniazed, pargyline) were demonstrated to inhibit mammary tumor growth, whereas reserpine, phenathiazines, haloperidol, sulpiride, and serotonin agonists were found to stimulate mammary tumor growth. The first reports that L-dopa and ergot drugs could inhibit growth of carcinogen-induced mammary cancers came from our laboratory. Subsequent trials with these drugs in human patients with breast cancer showed only a very limited degree of success, perhaps due to the fact that these drugs do not reduce and may actually increase Growth Hormone secretion in humans.

A co-relation between prolactin receptors and mammary cancer responsiveness to prolactin was first demonstrated in collaboration with Friesen and Kelly. The Meites laboratory also reported on the mechanisms by which large doses of estrogen inhibited growth of existing mammary cancers in rats. It was shown that when large doses of estrogen were administered that inhibited mammary cancer growth, serum prolactin was increased but the number of specific prolactin receptors in the mammary tumor tissue was significantly decreased. Thus, even if prolactin in the serum was high, it could not act on the tumor tissue to stimulate growth. We also reported that the mechanism by which postpartum lactation results in regression of mammary cancer size in rats is due to increased adrenal cortical activity. When postpartum lactating rats were adrenalectomized, the mammary cancers showed the same continuous growth as in non-lactating control rats.

We showed that when normal female rats were grafted with a pituitary underneath the kidney capsule, and implanted monthly with diethylstibesterol pellets subcutaneously, pituitary tumors arose both in situ site and in the kidney graft. However, the pituitary tumors were more numerous and larger in the in situ than in the kidney site. This demonstrated that pituitary tumors could be produced by a direct action of estrogen on the grafted pituitary, and that the in situ pituitary, perhaps aided by increased pituitary releasing factor secretion from the hypothalamus, responded even better to estrogen administration. We were the first to report that a variety of ergot drugs could evoke a rapid reduction in serum prolactin and tumor size in rats carrying a Furth pituitary tumor graft that secreted enormous amounts of prolactin and growth hormone. It was subsequently confirmed by clinical investigators that ergot drugs (bromocryrptine and lergotrile) could rapidly reduce serum prolactin levels in human patients with prolactin secreting adenomas or microadenomas, and more recently it was demonstrated that prolonged treatment with bromoergocryptine could induce regression in size of such pituitary tumors.

The Meites laboratory used numerous central acting drugs to test for treatment of mammary tumors. L-Dopa, ergot drugs and monoamine oxidase inhibitors (iproniazid, pargyline) were demonstrated to inhibit mammary tumor growth, whereas reserpine, phenathiazines, halopedol, sulpiride, and serotonin agonists were found to stimulate mammory tumor growth. His laboratory was the first to report that L-Dopa and ergot drugs could inhibit growth of carcinogen-induced mammary cancers. Subsequent trials with these drugs in human patients with breast cancer showed only a very limited degree of success, perhaps due to the fact that these drugs do not reduce and may actually increase growth hormone secretion in humans." An article in the Michigan State News, March 7, 1973, states that

"Meites and students reported that the purpose of their research was to try to find what causes mammary cancer and to develop drug treatments that will hopefully prevent cancer. Drugs that MSU scientists have developed and experimented with, including Meites and Barnett Rosenberg, biophysicist, are currently being tested on human cancer in the United States, England and Canada in hopes that a cure may soon be found. One effect of the cancer research is the training of young scientists who expect to make greater strides in the coming years in the treatment of physical problems that have plagued mankind for centuries."

An Article in the MSU News-Bulletin, October 20, 1977, states that

"the Meites laboratory was the first to demonstrate convincingly that the brain controlled the release of pituitary hormones and these hormones were casually linked to cancers in other parts of the body. They found that the normal release of pituitary hormones is controlled by the "hypothalamus". In 1966, Meites demonstrated that electrical lesions in certain parts of the brain, particularly in the hypothalamus could influence the growth and development of some cancers."

#### The Neuroendocrinology of Aging

Meites summarized his laboratory's research on the neuroendocrinoloy of aging in grant proposals as follows:

"The Meites laboratory began work on the relation of the hypothalamus to pituitary function about 1955, and on the relation of hypothalamic-pituitary system to aging processes about 1965.

The Meites laboratory questioned whether the aging process was inevitable, whether it is possible to have its cause fully understood, and whether it might be altered and/or reversed. Although there is wide agreement that aging should be considered a disease subject to eventual control and cure, there is almost no agreement on its cause. Some of the theories for the cause of death include: 1) Aging and therefore natural death is prompted by a breakdown in the body's immunological system; 2) Aging is caused by intracellular developments which cause the body to self-destruct; 3) aging is caused by changes in body chemistry like kidney degeneration and arteriosclerosis; 4) Aging is caused by a death hormone produced by the pituitary gland. The focus of their research was to determine cause as well as determine if people could live healthier lives."

According to the American Federation of Aging Research,

"Research on aging and the aging process leads the way to a greater understanding of all age-related diseases. It has the potential to improve public health to a far greater extent than science that examines only one disease at a time. Research on aging also provides the hope and the promise for everyone to live healthier, longer lives less susceptible to disease and disability. It may be the least expensive path to preventing and curing many diseases of aging. Studying aging requires two complementary approaches: studying the underlying mechanisms of aging and how they regulate the processes in our body." The Meites laboratory focused its research on the functioning of the neuroendocrine system during the aging process.

"The first aging process we investigated, using older rats as a model, was the decline in reproductive functions. The approach we used, was three fold: first, to measure by bioassay and radioimmunoassays the changes that occur in hypothalamic, pituitary and gonadal hormones of aging female and male rats; second, to determine whether any such changes found are related to loss of estrous cycles in aging female rats and to a possible decline in testosterone secretion and spermatogenesis in aging male rats; third, to investigate whether it is possible by neuroendocrine intervention to reinitiate estrous cycles in old female rats that had ceased to cycle, and to increase testosterone secretion in aging male rats.

Aging male rats were found to show a decrease in testosterone secretion, increased body weight, and reduced sexual activity, although they were capable of sexual activity well into old age.

Insofar as hormone secretion is concerned, we found that both old female and old male rats showed a reduced capacity to secrete pituitary luteinizing hormone and prolactin, when compared with young or mature rats of either sex. In the young and mature female rats, there is a cyclic increase in luteinizing hormone, follicular secreting hormone, prolactin, estrogen and progesterone during every 4-5 day estrous cycle, but no such changes were seen in the old female rats. Also, when old female or male rats were castrated and compared with young castrated rats, the rise in luteinizing and follicular secreting hormone in old rats was significantly less than in the young rats. This, as well as other tests of the capacity of old rats to secrete gonadotropic hormones, pointed to a defect in the hypothalamic mechanisms that regulate gonadotropin and prolactin secretion.

The neuroendocrine approach has demonstrated that the major cause for the reproductive decline lies in changes that occur in neurotransmitter functions in the hypothalamus and perhaps elsewhere in the brain. These changes are characterized by a decrease in hpothalamic catecholamine activity, which normally stimulate gonadotropic function by the pituitary, but inhibit prolactin secretion and by an increase in seretonin activity which normally inhibits gonadotropin function and stimulates prolactin release. We have shown that estrous cycles can be renewed in old female rats by administering drugs that increase hypothalamic catecholamines, thereby correcting the deficiency in these neurotramsmitters. This gives rise to questions as to whether other functioning can be reversed.

We also have found that direct electrical stimulation of the hypothalamus can induce ovulation in old female rats. Some of the treatments of old female rats have resulted in pregnancies. The studies in rats are believed to serve as a model and to provide basic information on the causes of the reproductive decline with aging in human subjects."

According to an article "Remembrances: Neuroendocrinology and Aging. A Perspective", by Joseph Meites, published in <u>Endocrinology</u>, 1992,

"Other changes reported in the hypothalamus with age include loss of neurons in specific nuclei, a decrease in hormone receptors, an increase in hydogren peroxide and hydoroxyl radicals resulting from catabolism of catecholamines, a reduction in tyrosine hydroxylase, the rate-limiting enzymes for synthesis of catecholamines, and an increase in monoamine oxidase, the major enzyme responsible for catabolism of monoamines. These changes may largely account for the decline in hypothalamic catecholamines with age.

In addition to the dysfunctions that develop in hypothalamus with age, there is evidence that other components of the neuroendocrine system develop faults. The pituitary of old rats has been reported to be less responsive to stimulation by gonadotropin releasing hormones, growth hormone releasing hormones, thyrotopin releasing hormones, and corticotropin (ACTH) releasing factor than the pituitary of young rats. Similarly, the pituitary of elderly human subjects was observed to be less responsive to stimulation growth releasing hormones and growth hormone releasing hormones than the pituitary of young individuals. There also is some evidence that target gland responses to pituitary hormones, and body tissue responses to target gland hormones may decrease with age. Some of these have been found to be associated with a decrease in receptors or to postreceptor changes in cells. These decreases in response of endocrine and nonendocrine tissues to hormones are believed to be of secondary importance to the faults that develop in the hypothalamus with age.

Significant declines also occur in the immune system with age. Since the neuroendocrine and immune systems function coordinately as a bidirectional network, and both systems exhibit a functional decline with age, it is important to determine the relation of each system to the decline of the other.

In the late 1980's, the Meites laboratory became interested in the thymus-pituitary axis and its changes during aging in rats. They found that a number of thymic preparations of bovine origin were active with the secretion of some pituitary and peripheral hormones when intravenously injected in rats. In most cases the endocrine responses that these thymic preparations elicited in the animals were inhibitory. Invariably, the responses of young rats were stronger than those of old rats. This suggested that during aging the pituitary gland became progressively desensitized to thymic signals.

It is doubtful that any single theory of the causes of aging can explain all aspects of the aging phenomenon. It is clear however that the neuroendocrine approach, although relatively recent in origin, has already provided some valuable knowledge and insights into the causes of the aging declines in body functions, and has suggested methods of intervention that may inhibit or reverse aging processes and perhaps lengthen the life span."

A partial record of publications and activities: It has been reported that the Meites laboratory had more than 500 articles published. A complete record is not available. Joe left a list of over 400. The ISI web 0 Knowledge lists the articles by the times cited. While the citations were numerous, it is significant that the Science Citation Index lists about fifty, out of 360, that were cited more than 100 times each. These are considered Scientific Classics. Joe had 55 chapters in books. Joe was editor or co-editor of 5 books. He and his students presented a significant number of papers at scientific meetings.

## **Curriculum Vitae**

According to Joe's curriculum vitae, he participated in many professional activities, in addition to research and teaching. These activities were related to the field of neuroendocrinology, including, but not limited to serving as a member of the Endocrinology Study Section, Na-

tional Institute of Health (NIH), from 1966-1970; on the National Pituitary Agency, NIH from 1969 to 1976; on the Subcommittee on Use of Hormones in Domestic Animals; National Academy of Sciences-National Research Council from 1960; was chairman of the International Congress of Physiological Scientists (IUPS) 1971-1980); Commission on Neuroendocrinology from 1977 to 1980; Council, International Brain Organization, 1977 to 1980; Chairman, American Physiological Society "Specialty meetings on Neurotransmitters and Endocrine Function", 1979; Program Committee, American Physiological Society, 1975 to 1980; Chairman, Neuroendocrine Discussion Group, Federation of American Biological Societies, 1978, Officer 1977 to 1984; Chairman, Symposium on "Brain Opioid Peptides and Endocrine Functions"; Functions of American Biological Societies, 1979; First President of the International Society of Neuroendocrinology, 1972 to 1976; Member, Committee on anti-Fertility Drugs, NICHD, 1971-1972; invited to numerous national and international meetings, and served on organizing committees of many of these; invited to present seminars and talks to many universities, including nine of the "Big Ten" universities. He was a recipient of grants-in-aid from NIH, American Cancer Society, National Research Council, Michigan Cancer Foundation, drug firms, and Nutrition Foundations. He was a member of the editorial Boards of the publications of Neuroendocrinology, 1967-1979, Cancer Research, 1972 to 1979; Psychoneuroendocrinology, 1975 to 1977; Endocrinology, 1953 to 1956, 1966-1974, Comparative and General Endocrinology, 1968-1971; Endokrinologie, 1975-1977; Proceedings, Society for Experimental Biology and Medicine, 1975-1980; Pepides, 1979-1984; Neurobiology of Aging, 1979-1984. He was a Referee for the American Journal of Physiology, Science, Journal of the National Cancer Institute, Journal of Endocrinology and Journal of Reproductive Biology."

## Honors

Joe received the following awards at the University of Missouri. He received the Sigma XI award, 1938 and Commendation was received from Sanitary Corps, Regional Hospitals, 1946. Later Junior and Senior Sigma XI Awards, 1953 and 1967 from Michigan State University; the Weizmann Institute of Science, Israel Fellowship award (Postdoctoral), 1955-1956; elected vice President and President, Michigan Section, Society of Experimental Biology and Medicine; 1959-1960; Distinguished Faculty Award, Michigan State University, 1970; The Carl Hartman Award, Society for the Study of Reproduction, 1970; was Visiting Professor, Cairo University, Cairo, Egypt, 1980; Visiting Professor, Kansas State University, 1978; Traveling Fellow of the Clinical Research Institute, Montreal Canada, 1977; Visiting Professor, University of Florida, Gainesville, FI. 1978; presented the W. E. Peterson Memorial Lecture, University of Minnesota, 1973; received the Robert H. Williams Distinguished Leadership Award of the Endocrine Society, 1981; presented the Geoffrey Harris Memorial Lecture, Cambridge University, England, 1981; Professor Emeritus, 1984; Visiting Professor, University of Tokyo, Japan, 1984; Visiting Professor, introducing neuroendocrinology to medical schools in Shenyang, Harbin, Beijing, X'ian, Suzhou, Shanghi and Guangzhou, Republic of China, 1984; Nominated for National Academy of Science, 1980 and 1983; participated in International conferences in Jerusalem, Israel, 1995, and Bregenz, Austria, 1996 and 1997. He continued to serve on editorial boards and referee scientific articles until about 1998; The National Endocrine Society honored him with an elegant Executive office chair in 1981.

When Joe officially retired in 1984, funding was begun for an endowed scholarship for students in the physiology department, under the name "*The Joseph and Mable Meites Scholarship Fund*". Income from the fund enables the department to hold scientific seminars annually. They are known as the *Joseph and Mable Meites Lectureship Series*. After Joe passed away in 2005, The *Meites Seminar Room* was opened in Giltner Hall, the building where he did

all of his teaching and research. The furniture, books and memorabilia from his home office were donated by his wife, Mable.

# Some Reflections on a Research Career

In Chapter 18, Pioneers in Neuroendocrinology, Vol. II, 1978, Joe wrote:

"Scientific research is not without its problems and frustrations, but there also are many compensations. Among the greatest satisfactions for me has been the opportunity to be associated with many young, bright, and motivated graduate students and postdoctoral fellows, and, outside of my laboratory, with many outstanding scientific colleagues throughout the world. A total of 13 graduate students have received their M.S. degree, 37 Ph.D. degrees, and 31 Postdoctoral Fellows have come to my laboratory for additional training. These associations almost always resulted in reciprocal benefits since I have received much from my students. Without their skills, hard work, and insights into problems, most of whatever we shared and accomplished in neuroendocrinology would not have been possible. I have followed their careers after they left my laboratory with great interest and have taken pride in their accomplishments. I always enjoy the opportunities to get together with them at scientific and other meetings and to exchange personal and scientific notes. We have remained good friends.

Another great personal pleasure has been the opportunity to meet and to make friends with scientific colleagues throughout the world. From them I have received much stimulation, encouragement, understanding, unfailing kindness, and hospitality which would be difficult to ever repay in full. Their approval or criticism of our work have provided a strong motivation for our research. All the men and women I have known in the field of neuroendocrinology have been and remain strong personalities, as befits those who enter untrodden paths. They all have displayed highly individual styles in their approach to their research and in their personal lives outside of the laboratory. Sometimes there have been sharp disagreements, but I do not believe I have ever permitted an honest difference of opinion to interfere with my admiration, respect, and friendly feeling from my scientific colleagues. I consider the international scientific fraternity (and sorority) to be one of the marvels of the world.

Like others, I feel deeply indebted to Geoffrey Harris in many ways. I looked up to him as a teacher who inspired many of our first efforts in neuroendocrinology, and as a friend. Because of my early interest in the control of prolactin and other pituitary hormones, I was highly stimulated by his article in Physiological Reviews in 1948. I consider myself particularly fortunate to have spent many hours with him at the last meeting at which I saw him, the International Congress of Physiological Sciences in Munich in 1971, since he died a few months later. At the Congress, he participated with enthusiasm in the formation of the new International Society of Neuroendocrinology, and undoubtedly would have been its first president had he survived. He was a warm and sensitive human being, and the recognized leader of neuroendocrinology. All of us will continue to miss his presence.

Among the highlights of my career was the period in 1965-1970 when I served on the Endocrinology Study Section of the National Institutes of Health (NIH). Although it was mostly a great deal of hard work, I greatly enjoyed the opportunity of working with the many distinguished colleagues on the committee. Morris Graf did an extraordinarily fine job as executive secretary, and ran its affairs with aplomb and efficiency. I was proud of the work of the Study Section, which dealt fairly and conscientiously with the numerous applications for grants they reviewed. Most of my own financial support for our work in neuroendocrinology has come from NIH, for which I am very grateful. I also have received funding from the Michigan Agricultural Experiment Station, from the American Cancer Society, the Michigan Cancer Foundation, the National Research Council, the Upjohn Company, Eli Lilly Co., and other sources. For many years I operated on a relatively modest budget in a small laboratory, but was fortunate enough to be able to increase funding just at the time we were entering our most productive phase of neuroendocrine research.

I have had the privilege of working on some of the early studies on hypothalamic releasing factors and applying neuroendocrine approaches to the solution of basic problems in reproduction, lactation, mammary and pituitary tumors, nutrition, aging, and environmental stimuli. There is no question in my mind that the period from the early 1950s onward, when my major focus has been on neuroendocrinology, has been the most exciting, fruitful, and enjoyable of my career. The exhilaration of having been able to participate in the development of a new branch of science will remain with me to the end."

# **Reflections of Joe's Colleagues**

Excerpts from Joe's 1980 evaluation, made by his department chairman, Harvey Sparks, M.D., reads: "Your contributions to the department are of the highest caliber. You provide a model of research excellence and productivity which inspires the rest of us. Your commitment to the Department, both in terms of teaching and research represent an exceptionally strong, positive force. Your courses in endocrinology and neuroendocrinology and the physiology of aging have inaugurated a new area of teaching for the Department. Your teaching of graduate students and postdoctoral fellows sets a high example for the rest of us to follow. Your activities on various departmental and university committees, along with your local, state and international contributions have been numerous and of high quality."

Many colleagues, worldwide, were invited to attend Joe's retirement symposium in 1984. Excerpts from their letters of response are summarized as follows: Your scientific life has been so full that if you look back you will find only reasons for satisfaction. You have contributed more than anybody else to the birth and development of neuroendocrinology. You have been active with excellent programs and papers, you have trained a lot of scientists who have made beautiful independent careers. They, in turn, have trained many more scientists who continue to contribute new knowledge. Moreover you have created friendships around the world. All of us have benefitted from your friendship, guidance and suggestions. The international reputation which MSU has gained in physiological science is in large part due both to your exemplary research standard of excellence which you have displayed for so many years, and to the institutional prestige which your presence on campus has lent to the university. Your integrity and adherence to scientific principles allowed us to share ideas with confidence that your advice and criticism offered had only one goal - to advance the pursuit of knowledge. You are considered one of the greatest scientists of our time.

## **Reflections of the Wife of Joe Meites**

There were plenty of bumps in the road along the way, and we made our share of mistakes. Being a part of a worldwide scientific community has brought opportunities and experiences beyond my wildest dreams. To mention a few: travel to many different countries brought an awakening about other peoples and cultures, their history, religion, art, architecture, music, how they lived, and their unfailing hospitality and friendship. These things do not come from textbooks.

When Joe and I were dating I did not have a clue as to where a scientific career could lead. At the time, the1930s, the great depression had rendered many people hopeless. Also, anti-semitism was so widespread that Jewish youth had difficulty gaining entrance to opportunities. Yet, President Franklin Roosevelt had the foresight to provide governmental funding to universities so they could hire students who could work and go to college at the same time. Both of us benefitted from that National Youth Administration (NYA) funding. This brought hope and a strong segment of the young people to colleges who were then more ready to assume their responsibilities and be productive citizens. After Joe was inducted in the U.S. Army, there were so many uncertainties about the future that it was difficult to know what to do. Fortunately we made some right choices and benefitted personally and professionally, including but not limited to taking a chance on marriage and completing our formal education.

I could not have been more fortunate than to have a husband like Joe Meites. We always have been happy that his younger brother, Isidor, introduced us. I discovered that Joe was bright and a very modest, highly motivated and competitive person who passionately loved life and learning, had a phenomenal memory, and loved what he was doing. He welcomed everyone with a smile and usually had a twinkle in his eyes. I believe he was very fortunate to have found work in Dr. Turner's laboratory as he emulated this wonderful mentor. His experience as an officer in the Sanitary Corps and as the Chief of Laboratory Services in the 106th General Hospital gave him a depth of leadership knowledge that was beneficial throughout his life. I remember that I was a bit jealous of his very close relationships with some of his Sanitary Corps colleagues. However, I realized that a special relationship was developed among soldiers. They were in dangerous places and positions far from home and learned to bond and look after each other during the World War II years. I was grateful to them when I understood. I believe these experiences contributed to Joe's development, attitudes and behavior toward others. Joe respected and supported my desire to obtain a graduate degree and become a professional medical social worker. He always inspired his students and me to be the best person we could be. His ability to love was genuine and definite. He always wanted us to be together and encouraged me to travel with him as my vacation time permitted. This broadened our acquaintance with his colleagues in that their wives often accompanied them and we became good friends.

We welcomed Joe's students as a part of our family and many considered us their second parents. Our swimming pool and lawn picnics were popular and gave us an opportunity to really feel close to each other. Some of the students were married and had children, and we were happy to assume the grandparent role. They were bright, caring and very responsive to being in a comfortable relationship away from home. They were most considerate of both of us and great fun to be with. When we were at scientific conferences the students not only enjoyed meeting each other but included us. When a meal was involved, the students would manage to collect all the students attending and find a table where we could all sit and have an enjoyable time together. Some of the students have retired and/or passed away but we have continued to keep in touch and visit those remaining. It has been fascinating and rewarding to watch their growth and development professionally and as good human beings. They are scattered around the world and have made significant contributions to new knowledge through their research and training of many other scientists. When Joe was ill they formed an email and telephone network which not only kept each of them informed but brought comfort to us. There is no greater reward. Joe passed away January 31, 2005.

#### **Reflections of Students of Joseph Meites**

When Joe retired in 1984, one of his postdoctoral fellows had prepared two volumes of photos and letters from as many students as he could find. The two volumes were presented to Joe at the retirement dinner party. These volumes tell a story of about 80 young, bright and hardworking students who also admitted that they were a bit wild at times but who found the excitement of developing the new field of neuroendocrinology, and of producing new knowledge exciting and rewarding. It also reflects the excitement of being a part of the growth and development of the students themselves, and of the great responsibility of the teacher to provide an atmosphere which promotes learning and prepares the student for the future. Both Joe and I have always appreciated Michigan State University for providing an opportunity for him to pursue his love of research and especially for the opportunity to be among the early scientists to develop the field of Neuroendocrinology.

I find it impossible to end this memoir without giving full credit and appreciation to his students for the tremendous contributions they made. It would have been impossible without them. Joe firmly believed that the responsibility of a university is to teach students who could attain undergraduate and graduate degrees and continue to provide the basis for advancing their field of study which, hopefully, would benefit society. I have chosen to share their reflections by summarizing, from their letters and comments, their reflections of their experiences and by adding a list of all the students that I could find along with the title of their theses or dissertation. The titles should reflect some of their major contributions. If I missed anyone, I apologize.

Most of the reflections of students are so similar that the following summary attempts to capture the essence for all of them. All of Joe's research students were at the graduate and postdoctoral level. Those who took his courses in neuroendocrinology and aging could have been at other levels. Most graduate students sought opportunities to find a laboratory where they could pursue their scientific interests. Others entered as laboratory assistants and became so interested in pursuing a scientific career that they became graduate students in his laboratory. Some students were being mentored by other professors but collaborated with Joe's students.

One of the hallmarks of Joe's teaching was to go to the laboratory where they kept the coffee pot and have a cup of coffee. He would be joined by the students and discussions of their goals and research would informally ensue. One student wrote: "I began looking for a laboratory where I could undertake postdoctoral studies. My goal was to learn more about the neuroendocrinology of the developmental process of aging. I had visited two prestigious laboratories previously and was nervous when I arrived. But, the moment I walked into your laboratory and found you sitting on the couch drinking your morning cup of coffee, and talking with several graduate students and postdoctoral fellows, I was immediately at ease. I found myself surrounded by some of the brightest young scientists in the field. After an interview with you, I had the feeling that this is where I want to be. You always seemed to be there to listen, to direct, and to mold. You never insisted on, but always suggested, possible approaches to problems." Two students wrote: "I will never forget how excited I was when I had to defend my thesis. When I discovered that I forgot my coat, you loaned me your coat." Others wrote that "few people had as much influence on their lives because of Joe's inspiration and instillation of the work ethic and in regard to training, professional development, and career." They appreciated that he taught a lot outside of the areas of science and by example. They found that in addition to their academic training, he gave them an appreciation of different cultures by bringing together students of many different backgrounds and nationalities. Students felt that Joe made them feel at ease, like a part of a team working toward accomplishing something important. They

were impressed with his high standard of expectation and performance, and no one worked harder than he did. He was a positive example to everyone, and no one was more trusted and respected. Some mentioned that Joe recommended that they be opportunists whether in research, teaching, or administration, if they wished to succeed, because opportunities do not come very often and they should seize upon them. Students felt that the years spent in the laboratory were the most exciting and enjoyable years in biomedical research that they had ever had. All of the students included me and reminded us about how many people's lives both of us had touched during our lifetime, and how many people love and admire us.

Joe's 90th birthday was December 22, 2003. One of Joe's Postdoctoral Fellows organized a birthday party in October, 2003 and kept it a secret from Joe. As many students as could be found were invited. Joe thought just the two of us were invited to dinner. When we arrived at Kellogg Center, Joe and I were asked to walk toward another room. As we approached the room, the faces of former students were crowding into the doorway. They had come from Japan, Israel, India, Hong Kong and ten different states. When Joe saw the students he stopped in disbelief, and asked "am I hallucinating?" The evening could be called a culmination of the lives and scientific legacy of Joe and his students.

These accolades were humbling and sometimes embarrassing as we knew we had made mistakes, had not always measured up, but we had tried to learn how to improve, along with the students. They created an atmosphere of expectations from us which kept us challenged and on our toes. Measuring up to their expectations kept us in a learning mode and motivated us to be the best examples we could be.

The names of graduate students who completed the degree requirements along with the title of their thesis or dissertation will be found on the following pages. The names of postdoc-toral fellows are listed along with the title of only one of their publications. There were a number of students who collaborated with Joe and his students but had different mentors.

## MASTERS THESES OF STUDENTS OF PROFESSOR JOSEPH MEITES, Ph.D. Michigan State University, East Lansing, MI.

- Aylesworth, Charles, Effects of Variable Fat Diets on Development of DMBA Induced Mammary Tumors and Serum Prolactin Levels. M.S., 1979
- Baker, William P., A Study of the Interactions of Vitamin B 12 and Deaxycoritisone Acetate in Unilaterally Nephrectomized Rats, M.S. 1953
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