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Reminiscence in the Field of Reproductive Physiology and Endocrinology

by

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Professor Leonard has had a long and illustrious career starting in the 1920's. He has taught thousands of undergraduate students in introductory zoology (both semesters and sometimes in summer school) plus hundreds of graduate students in endocrinology. At the same time he has nurtured many graduate students and prepared them to become leading endocrinologists in the U.S.A. Dr. Sam Leonard's career has spanned the time when most of what we know today in reproductive physiology and endocrinology was being pioneered. His own research program has been at the forefront of research. Several current research projects supported by the National Institute of Health center on problems and leads initially uncovered by Dr. Leonard.

Would he choose the same career again? He surely would! Dr. Sam's love of students and enthusiastic search for the truth has made his productive life a toil of joy and an inspiration to all that know him.

RHFoote

Reminiscences in the field of reproductive physiology

Samuel L. Leonard
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For some time, my colleagues at Cornell University, namely Doctors Ari Van Tienhoven, Robert Foote and Willian Hansel have been urging me to record in some way what it was like in the days of research in Endocrinology and reproductive physiology when I was a young graduate student and shortly thereafter. They wanted to know something of the personality of those scientists who were in the forefront in research in these fields and something on the state of knowledge in which these scientists worked. In general, I would say that the decade between 1925-1935 was most exciting although others might not agree. My own introduction to serious studies began in 1927 as an entering graduate student at Wisconsin. It was an exciting time because so many distinctly new discoveries were made in this decade. Many of the basic facts of reproductive endocrinology and physiology which are accepted to-day were newsworthy at that time. I use the word "newsworthy" guardedly because the word "sex" and anything suggesting the subject was taboo in popular print as the Victorian era was still present. However, once there was published in one of the Madison, Wisconsin's newspaper in 1928 a note stating that Prof. Hisaw discovered how to relax the "public" ligaments!.

It must be bourne in mind, I worked closely only with two of the many people active in research in this field and only certain points of possible interest can be called forth at this time. I hope I am not in error in my over-all recollections.

How I came to study reproductive physiology

A few words on this subject is put in writing, more for my children and grandchildren in case some day they might be interested. While an undergraduate at Rutgers University, Dr. Thurlow C. Nelson did most to stimulate me to be a biologist. His major interest was in invertebrate zoology with a side interest in parasitology. When in my senior year, he suggested a problem to investigate a peculiar 3-flagellated Euglena that lives in the intestine of Rana clamitans tadpoles as a commensal. When metamorphosis occurs, the Euglena disappears from the gut. I found that as the tadpole became larger and the skin thicker, less light gets through the body wall and the chloroplasts in the Euglena lose their color. Then, when I gave thyroid powder to speed up metamorphosis, the Euglena disappeared quickly which I presume is due to the changes in the secretory nature of the intestine. Tadpoles eat plants, frogs eat meat. It was at least exciting to witness the tail disappear and little legs appear and these effects of a hormone impressed me. Upon graduation, Dr. Nelson who had received his Ph.D. from Wisconsin recommended that I go there to study parasitology.

Not long after starting to teach as a lab. assistant and to study, my interest in parasitology waned precipitously, not because of any personality quirks in the professor but possibly by the type of research he was pursuing and the presentation of the subject. Meanwhile, Dr. Charles K. Weickert, who I knew previously at Rutgers, was studying under Dr. Frederick Hisaw in the same department. He urged me to change my major interest to reproductive physiology under Hisaw. This I did with no trouble and thus entered this field of research.

I would like to mention some of the graduate students who majored under Dr. Hisaw during the four years I was at Wisconsin and who continued to be active in the fields of endocrinology and reproduction: Charles K. Weickert, Roland K. Meyer, Roy 0. Greep, Robert Kroc and Roy Hertz.

A brief statement on each of the above as to their contribution to the field is in order.

Charles K. Weichert did research on deciduomata, delayed implantation and mammary gland development and became Dean at the University of Cincinnati.

Roland K. Meyer continued in Hisaw's position when the latter moved to Harvard. He not only published many papers in all phases of the subject but trained numerous other scientists in the Hisaw tradition.

Roy 0. Greep not only published countless research papers in endocrinology but also edited many books in the field, and is an active international leader in the profession. He also founded a special laboratory for the study of reproduction at Harvard.

Robert Kroc continued work on relaxing and thyroid hormones and is now director of the Kroc Foundation in California supported by his brother, Ray Kroc, founder of the MacDonald's Food Chain.

Roy Hertz followed up his Ph.D. with an M.D. and published excellent fundamental work in Clinical Endocrinology.

Concerning the state of knowledge, in general, on the endocrine glands about 1927-1928.

Adrenaline - was well known and chemically determined.

Thyroxin. Its general effects on metabolism was well known, but the

formulation was discovered in 1926 by Harrington in England. Incidentally, in 1927, on his way to visit Kendall's laboratory in Minnesota, Harrington stopped over at Madison to give a lecture on his work. I remember the very large audience that came to hear him and how thrilled We all were to hear of his brilliant work.

There was an anecdote in regards the thyroid gland – it may have been just scientific gossip, but it is a story. It was told about Dr. A.J. Carlson, a famous physiologist at the University of Chicago Medical Schoo] who was well known as a great "doubter". He was very critical and hard on those who did slip-shod work. He would say you must "show me" to his students. It is said he doubted the reported metabolic effects of ingested thyroid gland. So he obtained some fresh thyroid glands from one of Chicago's slaughter houses, cooked and ate them. The results, it was said, to be almost catastrophic as one might expect. Carlson was a great teacher and among his students was Dr. A.C. Ivy the discoverer of cholecystokinin. Once, long ago, I presented a paper before the Cornell Veterinary Society meetings here and found that Dr. Carlson was to be in the audience. Knowing of his reputation as a hard critic, it was with fear and trembling, more than usual, that I got up to speak. Talking to him afterwards, he was most kind but stated very firmly that "I talked too fast." I felt I got off lucky!

Before I came to Cornell, I attended a scientific meeting in which the function of the adrenal cortical hormone was being discussed and A.J. Carlson was presiding. A very controversial point came up over which the speaker and a doubter in the audience became quite belligerent, a scene I cannot forget. Unfortunately, I cannot recall

the participants for sure. A.J. Carlson quickly cooled the situation by saying words to the effect "let us have more sympathin in action and less adrenaline flowing and the differences will be reconciled." It saved the day and everyone had a good laugh.

Once in the late thirties, I had the pleasure of meeting Dr. J.F. Gudernatsch, a kindly white haired handsome man. In 1912, he fed thyroid gland tissue to frog tadpoles and observed for the first time accelerated metamorphosis. He also had fed thymus gland tissue to tadpoles and observed a delayed metamorphosis which he attributed to a specific thymus hormone. By his own admission in talking with him, he acknowledged he should have used other control tissue which also acts like the thymus. To-day it is well known that the thyroid gland in meat eating tadpoles is called upon to handle the specific dynamic effects of the high protein diet and the thyroid is unable to respond to produce enough extra hormone to induce metamorphosis on schedule.

Insulin was isolated in 1922. I was in high school at the time but I remember the banner headlines in newspapers of that event. At that time, diabetes was feared almost as much as cancer is to-day; in my family, sweets were limited in our diet for fear of becoming diabetic. Juvenile diabetes was and still is the one most greatly feared. One day in my class in Endocrinology about 1957-58, a student (Dr. Esther McCandless) came up to speak to me at the close of the lecture and said "I can now belong to the 25-year club." She was implying that she was born with diabetes and at the time insulin had just become available and she had taken insulin every day of her life.

Parathyroid - The association of this gland with bone diseases was known at the turn of the century but not until 1924-25 were the first active extracts prepared by Drs. Hanson and Collip. I knew Dr. Collip and met him on several occasions at meetings. He contributed to the refining processes of insulin and made fundamental discoveries on the pituitary hormones.

Gastro-intestinal hormones - Secretin was well known having been discovered in 1902. Cholecystokinin was discovered by A.C. Ivy in 1928 who was at the University of Chicago at the time.

Adrenal cortex - During the late 1920's and early 1930's there were many controversial discussions as to whether or not the adrenal cortex was essential to life. For some species such as the dog, cat and man there was no doubt but the controversy was with the rat. Arguments centered around surgical procedures and completeness of the operation and then strain differences were considered. Sprague-Dawley strain of rats died, Long-Evans strain lived. The resolution came about in finding that the Long-Evans rats frequently had accessory cortical tissue. Steven Martin, one of Hisaw's graduate students, took some of Sprague-Dawley rats to New York and met in Dr. Smith's laboratory where Fritz Agate, one of Smith's graduate students and Martin operated on both strains of rats. Thus it was not a difference in surgical procedures and I was there when it happened. I remember Fritz Agate had just been married and he postponed his honeymoon, all for the cause of science! Subsequently, Dr. Robert Loeb in Clinical Medicine at Columbia about 1932-33 found that high salt diet prevented death in adrenalectomized rats. Looking back on it, it could have been that the diets fed rats from different laboratories contained differing

amounts of NaCl and this factor prolonged the controversy.

Pineal body. It's function as an endocrine organ not known.

Posterior lobe of the Pituitary. "Pituitrin" an extract of the posterior lobe was known prior to 1927, namely for its oxytocic effect in parturition. It's biological effects as vasopressor and anti-diuretic action were also known. It was not until 1928 that Oliver Kamm at Parke Davis Co. separated "Pitocin" and "Pitressin" from the posterior lobe. Provided doses of these hormones were large enough, over-lapping effects could be demonstrated which was disconcerting. It was much later that Vincent DuVigneaud synthesized and formulated these hormones.

Intermediate lobe of the pituitary. The control of the melanocytes in the integument of many of the lower vertebrates, particularly Amphibia was well known in the 1920's. The term "intermedin" was used. However, I found this term in the index of Van Dyke's book on the pituitary gland in the 1936 edition which was the definite work on the subject at that time yet not once does it appear in the text! (Gonadal and Pituitary hormones - see later)

My four years at Wisconsin with Dr. Hisaw.

First, a few words about Dr. Hisaw as I came to know him in the 4 years I studied in his laboratory and listened to the stories of his early life. He was born August 23, 1891 in the southwest corner of Missouri on a farm and his early schooling was obtained in a one-room school house. The teacher was boarded around among the neighboring families and when his time came to be with the Hisaw family he urged the older son to prepare for college. After a year at a prep-school, he entered the University of Missouri at Columbia. Apparently he had a rough time of it the first year and had to plea for another chance to stay in college. The authorities agreed and 25 years later awarded him an Honorary Doctor's degree for his achievements.

Hisaw would tell us stories of his early life, reminiscent of those of Mark Twain's style particularly about the people, both black and white and their simple life in the community. He told us about some of the escapades he and his brother got into. For example, one day he and his brother gathered discarded empty nitroglycerine cans, the contents of which were used in mining operations. By setting up the can so that the residual fluid would flow into a corner, and placing the can on a tree stump, they would stand off and shoot for the corner with a rifle. He said the results were devastating.

Hisaw loved to tell earthy jokes, always having a point to clarify some problem under more serious discussion or to characterize the people where he grew up and their way of life. Some I remembered and passed on to later generations of graduate students. He spent a great deal

of time with his graduate students, his office was always open to them without going through a secretary first. In fact, there was one secretary for 9 members of the department including the chairman. His fund of ideas always surprised us and he could improve on any that we brought to him. He welcomed the graduate students to express their ideas and problems of research. Having no more than 3 or 4 graduate students at one time, he could do that but later, I learned, he had to wall himself off somewhat as academic life became more complicated. He smoked a pipe, — those that do, know it requires constant re-lighting. He would borrow a box of matches from us and absent-mindedly pocket them. One day, we made him empty his pockets and we recovered 10 boxes. He looked chagrined.

Hisaw encouraged his students to work together on projects, those he instigated and those we thought up. He gave us carte blanc to go off on our own to try things, such as repeating experiments of others as a way of learning. There were no courses in reproductive physiology or endocrinology and in the major course in physiology in the Medical School which we all took, these subjects were barely touched on. We all helped each other where more than one pair of hands were needed. There were no technicians nor much research money for that matter by to-day's standards. Except for surgical instruments, practically everything that could be, was made in the lab. We did obtain our first pH meter in 1929 and it was very temperamental as I recall. About this time, Hisaw was able to hire Dr. Harry Fevold, an organic chemist as part of the permanent Zoology staff and he had to help with chemical problems related to those of other members of the Department as well.

One of the first problems I participated in with other graduate

students was to determine the amount of the female sex hormone that was in normal and pregnant cow urine. (Note - the female sex hormone was the term for the first ovarian hormone and the only one at the time which we now call estrogen. It is fortuitous that the acronym F.S.H. was not coined or it would have confused us later with pituitary F.S.H.). The experiment required 24-hour samples. It happened that urine collections were made in late winter and the cow barn was very cold. Separate buckets and jars stood behind each cow and when she arched her back we had to run to position the bucket so as not to lose a drop. Since several cows were being studied at the same time, we had to keep on our toes. We soon discovered that we could periodically rub the cow's escutcheon and if she was near her time to urinate, we were in better control of the situation in obtaining complete samples.

As I mentioned above, Hisaw's graduate students worked together, discussed problems with each other and taught each other. In particular, I would like to mention Roland K. Meyer who had begun his studies a year previous to my joining the group. He taught me how to make vaginal smears, perform castration in rats and many other procedures. We were not too proficient in handling rats and learned together as a result of trying to repeat an experiment reported by others. It was the one on the induction of pseudopregnancy by mechanical stimulation of the rat cerivx when she was in estrus. Anyone trying to tie a rat to an operating board knows it can be frustrating, more so if one does not know how to handle them properly as it was with us. An easy way out was to anesthetize them first, which we did, before tying them to the operating board. The results

of stimulation were all negative. Repeatedly, we obtained the same negative results. Going over the published protocols again, we noted nothing was said of using an anesthetic. With gloves on at first and then without gloves, we tied the rats to the board along with some blood from our fingers. This time we were successful in inducing pseudopregnancy and wrote up the results for publication - "Effect of anesthesia on induction of pseudopregnancy" in 1929. This happens to be one of the earliest bits of evidence for the union of neural and endocrine activities which has blossomed much later in time.

Hisaw received his Ph.D. from Wisconsin in 1924. His thesis was on the sex dimorphism in the pelvis of the pocket gopher. Later, he investigated the sex dimorphism in the guinea pig pelvis and observed the loosening of the ligaments in the pubic symphysis that occurs during pregnancy. That the presence of corpora lutea was associated with pregnancy was well known, so he tried to loosen the ligaments and relax the pubic bones in non-pregnant, virgin females by hormonal means. Using the blood serum of pregnant guinea pigs, rabbits and sows, he found that these substances would give relaxation only if given when the virgin guinea pigs were in heat. The principle that corpus luteum hormones require pretreatment of the animal with estrogen for the former to produce an effect was thus first established.

Hisaw then began experiments to extract the hormone that caused this relaxation from pig ovaries. Oscar Mayer's slaughter house was located in Madison so he had easy access to the raw materials. Now it so happened that pig ovaries as they came off the hog disassembly line were saved and sold at the price of $20 a lb., fresh weight. The high

cost, I believe, was determined by the makers of Lydea Pinkhams Compound or the like which contained an ovarian extract but of what kind, I do not know. However, these preparations contained about 30% alcohol and I feel sure that that amount would be sufficient to alleviate many female troubles, real or imaginary. Hisaw would tell of a man in his home territory who would buy bottles of this preparation, for his own use claiming he had "female" troubles for years. I often wondered if this was a community where the people voted "dry" and drank "wet" as I do know this still happens in certain counties in the west, even Kentucky.

With limited research money, Hisaw made an arrangement with Oscar Mayer Co. for his students to go to the meat "cooling" room and there snip from the ovaries only those corpora lutea which were deep purplish red in color and which were most likely to come from recently ovulated follicles or pregnant sows. The cost of the corpora lutea was still $20 a lb. and the remainder of the ovaries was sold to someone else. I doubt if the L. Pinkham Co. ever knew the difference. Those of us doing the collecting wore overcoats at all times of the year; our hands would be so cold we could hardly hold the scissors to snip out the tissue after half an hour in the cold room.

Hisaw then looked for another test organ for the relaxing hormone and investigated the changes which occur in the vaginal epithelium of pregnant rats during the latter part of pregnancy. What happens is that a stratified columnar cell epithelium appears in which the cells become filled with mucus. After many experiments in which castrated female rats were given estrogen followed by relaxin for several days, no conclusive results were obtained. Later, the solution

of the problem was made by Willard Allen and R.K. Meyer where they showed that very small doses of estrogen given for a week or more are all that is needed to produce vaginal mucification in a castrated female rat. It should be pointed out now that the preparation of the relaxing hormone involved an initial acid alcohol extraction and the final product was in aqueous solution.

Meanwhile, the work of George W. Corner on the morphology of the rabbit uterus during the estrous cycle came to to my attention. In 1929, Corner and Allen reported that a fat soluble extract of corpora lutea produced changes in immature rabbits uteri similar to those of early pregnancy and pseudopregnancy but not all rabbits responded. Hisaw and I extracted corpora lutea with acetone and this extract in oil confirmed the work of Corner and Allen in 1930. In addition, we showed that it is necessary for the rabbit uterus to have been stimulated first by an estrogen in order for this corpus luteum hormone to produce it's characteristic effect. Corner and Allen reported the same observation simultaneously with ours. Thus the "one-two" effect of those ovarian hormones, first shown by Hisaw for relaxin held true for the second luteal hormone which we now recognize as progestin (progesterone).

In 1930, Hisaw, Fevold and Meyer, employing the same fat soluble corpus luteum preparation used on the rabbits, were able to produce the first pre-menstrual endometrium in a castrated monkey after first priming her with estrogen. This same year Dr. R.K. Meyer, who was a research assistant to Hisaw left to work in Dr. Corner's laboratory and I inherited his position. A routine job while Hisaw's assistant,

was to inject the monkeys for his studies on menstruation. One Sunday, I was invited to a formal gathering so I dressed up accordingly but first, on my way to the affair, I had to make a 4 PM injection in the monkeys. In a hurry, I did not put on a lab. coat. The monkeys disliked being caught, of course and literally flew around the inside of their cage. For some reason on this particular day, their bowels were very loose and not in good control. As they "boiled" around in their cage, I became their target. I had to return to my room, bathe and put on a complete change of clothes. From that time on, I never had a desire to work with rhesus monkeys. Besides that one experience, occasionally I had to chase and help capture the monkeys in the laboratory when they got loose. One time, on a cold day in winter, a monkey escaped the lab, diving head first through a large pane of glass and onto the campus. A precipitous chase without proper clothing resulted in my catching cold without catching the monkey. A few days later it was captured in the bedroom of a students rooming house and in the best of health.

Research on the Pituitary

During the period of 1927-31, many exciting things were happening in the field of reproductive physiology and related endocrinology. The names that I mention below are but a very few of many others at home and abroad who published stimulating works. Edgar Allen and Edward Doisy had prepared estrogenic extracts from many sources and in 1929 Edward Doisy isolated and crystallized theelin or estrone. Ascheim and Zondek had earlier discovered estrogenic substances in

the urine of pregnant women and later, gonadotropic hormones named Prolan A and B. The first; from menopausal women with predominant F.S.H. effects and Prolan B from pregnant women with predominant L.H. effects, now called H.C.G.. Dr. Philip E. Smith had published a masterpiece entitled "Hypophysectomy and replacement therapy in the rat" in 1930 but preliminary results of this study appeared as early as 1927. Incidently, in the course in Physiology that I took in the. Medical School in 1929, it was taught that death invariably and quickly followed hypophysectomy. Dr. Carl Moore and his group at Chicago were reporting on male reproductive physiology and had made extracts containing male hormone activity from testes and male urine. Dr. Domm, at Chicago, along with his colleagues were contributing much new information on bird reproductive physiology. Dr. Sydney Asdell made outstanding contributions to the subject in domestic as well as laboratory animals. Dr. Philip Smith and Dr. Earl Engle made implants of rat pituitaries into immature female rats to induce precocious ovarian development with ovulation and corpus luteum formation in 1927. Dr. Herbert Evans and others were characterizing growth hormone from the pituitary.

Beginning in 1929, Hisaw and his students initiated investigations on the gonadotropic hormones and their relation to the gonadal hormones. They found that chronic treatment of immature female rats for many weeks with estrogens inhibited the normal growth of the ovaries and they remained in an infantile state. It was also shown that the pituitary glands of estrogen treated rats had a much reduced capacity to induce ovarian enlargement when implanted into immature females and thus was reported for the first time what is now called the "feed-back

phenomenon". With the help of Harry Fevold, Hisaw entered into a study of the separation of the follicle stimulating and luteinizing hormones of the pituitary. The results were encouragingly successful and were reported at the A.A.A.S. meetings in 1930. Hisaw gave me the privilege of the presentation and I can still remember how frightened I was at this, my first experience. Friendly competition on the separation of the different hormonal components of the pituitary was very great and at that time, some laboratories believed there was only a single gonadotrophic hormone. My own thesis work was on the nature of the rabbit ovulating hormone and after finding that menopause urine very rich in F.S.H. and pregnancy urine, both, induced ovulation, there was a small lingering doubt about F.S.H. and L.H. being separate entities. However, the widely different doses of these urinary hormones needed for ovulation in terms of their morphological effects on immature rat ovaries led me to think of an ovulating hormone present in both urines. Now this is resolved; L.H. is the ovulation hormone or else F.S.H. and L.H. in purest formes have over-lapping qualitatively similar activity much like that known for pure oxytocin and vasopressin.

The time at College of Physicians and Surgeons, Columbia

In the spring of 1931, my graduate work was coming to a close. The depression was in high gear and only one possible job offer appeared. Hisaw suggested applying for a National Research Council Fellowship financed by the Rockefeller Foundation. This I did and Dr. Philip Smith accepted me. My interests were more with the

pituitary gland by now. However, I did not relish living in New York City. I was born in New Jersey, spent the first 17 years of my life within sight of the City and had worked there for 2 summers plus almost a year before I went to Rutgers. I never liked New York and even then remarked I would not live in New York even if rent was free! So I came to "eat" my words and lived there for two years. Fortunately, I had only one block to go to the laboratory and that is where I spent most all my waking hours.

Dr. Smith was most gracious to me, the facilities he offered were excellent, there was no restraints on what 1 wanted to do and he was most kind and helpful in every way. He was a tall slender man, very quiet, very soft spoken and had a wry sense of humor. He was so entirely different from the outgoing personality of Hisaw who loved to talk and joke with one that at first I had misgivings of my choice for post-graduate work. Later, I found out that at the time of my arrival at Smith's laboratory, he was to do his stint of teaching and devoted little or no time for research or other activities. As soon as that was over, he was a different person. He never spoke ill of any man although I heard from other sources that he had good reason to while he was teaching in California years before. He liked to work with his hands and designed and made all the essential instruments when he devised the method of removing the pituitary gland from rats and later from rabbits. He had a tremor in his hands and they would shake some until he arrived at the crucial time of drilling through the skull, then they would become steady to finish to operation. The last time I saw him, he was building a cement patio for his summer home in Maine.

Philip Smith never spoke of his early life and it wasn't till many years later that I learned about that. He was born in South Dakota in 1884, graduated from Pomona College, California and came to Cornell in 1909 to do graduate work in Entomology. He switched to Anatomy under the late Dr. Kingsbury in Stimson Hall, received a M.S. degree in 1910 and a Ph.D. in 1912. His work was on the development of the nervous system of the salamander but later concentrated on the pituitary, first in Amphibia and later in Mammals. He taught for many years at the medical school in Berkeley, California, moved to Stanford University for a short period, then came to Columbia in 1927. He was greatly honored in this country and abroad for his outstanding work. I do not know how many published papers he produced but I do not believe they were exceedingly great. The quality and innovations of work that he did has been as great as anyone has ever done in this field. From Smith, I learned not only surgical techniques but many priceless bits of knowledge that helped me in later years.

To digress, I would like to mention how surprised I was at the teaching load of members of the Anatomy department in the Medical School. Smith taught Histology, but he was one of several who gave the lectures. Each staff member gave about the same number plus some attendance at laboratory sections, all in one semester. That was it. The load for Professors' teaching in Biology Departments in undergraduate colleges was and is never like that. Even in those days of little or no research grants, the Medical Schools seemed to have sufficient funds. Also it was more rare to see the professorial staff return to the lab in the evening compared to what at least, it used to be in

undergraduate colleges that I have been familiar with. The distances from home to the laboratory in a big city may have had something to do with that.

There were others in the endocrine field in the Anatomy department during my fellowship period. Dr. Earl Engle was a close associate of Dr. Smith and he worked on problems of the pituitary. Engle had a personality which was more like Hisaw's, outwardly enthusiastic, jovial, story-teller and spoke with a booming voice – the antithesis of Smith. Together they produced many good papers. Dr. Aura Severinghaus worked on the cytology of the pituitary and thyroid glands and produced classic papers. Dr. Ray Zwemer in the department studied the adrenal cortex.

There were some Ph.D. candidates in Anatomy while I was there. The best known is Moses Chiam Shelesnyak who studied under the direction of Dr. Engle. His work on deciduomata formation and the effect of hormones and pharmacological drugs on the uterus are well known. The other graduate students either followed other lines of work later or were the women who did not continue scientific pursuits. There was one young lady, Smith's student, who developed the technique of thyroidectomizing a new born rat, using a block of ice as the anesthetic. Her name was Theodora Salmon and she continued her career as a full time teacher at Hunter College. Another post-doctoral fellow besides myself was Dr. Joseph Schochaert from Louvaine, Belgium who pioneered studies on the gonadotropic and thyrotropic hormone effects on ducks. His laboratory space nearby emitted much quacking to be sure.

Acquaintances in Science of Years Ago

I will try to make a few remarks about some of the great, active investigators of years ago that I had chance to meet and whose works were read and discussed by all in the field of reproduction and related endocrinology. There were many others whose excellent papers lie buried in the literature. Their contributions, however, have formed the basis of what we accept to-day and have built on in the advancement to the present level of knowledge. Several scientists came to visit Dr. Smith while I was at Columbia, to observe him operate, Once there was a Japanese visitor who, after observing the operation, came to my office to talk. He could speak no English but did speak German with a different accent. My German was worse than awful and besides, I always had a difficult time even reading it. (German was not taught during World War I when I was in high school and wanted to study it). Attempts to converse with this Japanese was a fiasco and with much smiling and bowing he departed to my relief. I secretly believed Smith had a bad time in conversing with him too and foisted him on me!

Bernard Zondek. He, with Dr. Aschheim, discovered sex hormones in urine from women and developed the first pregnancy test. For years, it was called the Aschheim-Zondek test for pregnancy - using immature mice or rats as test animals. (In 1929, it was Maurice Friedman from the University of Pennsylvania who introduced the rabbit ovulation test.) Zondek visited Smith while I was at Columbia, and after observing Smith operate he was heard to say "Ach! that was "gutt", very "gutt" and when Zondek says it's "gutt", it must be "gutt". He was a short stocky man and impressed me as being

rather over-bearing in the then typical Teutonic fashion of German scientists.

Harvey Cushing. He was a great brain surgeon of his time and Cushing's syndrome, resulting from a basophil adenoma of the pituitary, was described by him. He came to Columbia from Harvard to remove a brain tumor from a graduate student in the department of physiological chemistry. During his visit, the Anatomy and Surgical groups had a dinner for him and I was invited. Somehow or other I was seated next to him. Although I was at a loss as to how to be socially graceful at such an occasion, it turned out my worries were for naught. We discussed the current problems about the pituitary gland, he inquired about my work at Wisconsin and Columbia and in a fatherly way, encouraged me to continue on my research.

George W. Corner. While I was at Wisconsin, he visited the campus to lecture on anatomical illustrations in relation to art forms and the changes in accuracy which took place over the years. I visited his laboratory while he was at the University of Rochester and subsequently at meetings. He is a quiet soft spoken man, with tempered enthusiasm, very brilliant and knowledgeable in the History of Medicine as well as anatomy. Willard Allen who worked with him in preparing progestin was a medical student who took time off to do the chemical work in isolating the hormone. Willard Allen later taught and did research in clinical endocrinology. Both are still alive as I write this.

Carl Hartman. I heard him present a paper at the New York Academy of Medicine on the time of ovulation in Primates. On the podium, he laid a strip of red ribbon on each end of the lectern representing

two menstrual periods. Then he reached in his pocket, took out a child's marble representing the ovum and placed it mid-way between the ribbons saying "this is when ovulation occurs." He was entirely uninhibited in what he said and wrote and did a great deal to break down the Victorian treatment of scientifically related sex subjects. He was very physically active, outwardly enthusiastic, rather short in stature, moved in quick jerky movements and so much like the rhesus monkeys with which he worked that an unnamed scientist once said to me "I think Hartman is getting to be like his research subjects in his actions." If Hartman ever heard that I am sure he would have thought that a big joke.

Carl Moore. It was he, at the University of Chicago, that contributed much basic information on male reproductive physiology. He was a large, strikingly handsome man with a booming voice and in speaking reminded me of a top-notch auctioneer in his persuasive manner. One time at a science meeting, he was demonstrating the electric-ejaculation test in guinea pigs before a group of 15-20 people including a few women. Hisaw was standing next to me and after Moore recovered a mass of coagulated ejaculate in his hand, he looked over to Hisaw and said "Think you could do as good as that, Doc." As I recall, Hisaw didn't appreciate that very much. Moore told the following story in my presence.

It seems that Moore was at some meeting in Europe in the early '30's and had an encounter with one Alexander Lipshutz. Now Lipshutz had written a book on reproduction in the early 20's and at that time the question of sex antagonism in development was much discussed and

presented in his book. In spite of Moore's conclusive evidence in settling that problem, Lipshutz would not accept it and they got into a heated argument. This reached the point where Lipshutz challenged Moore to a duel, in good old German fashion. (Once when I attended a physiology congress in Italy, someone pointed out Lipshutz to me. He stood about 5 foot 4 inches, with a large low hanging beard and was very austere looking.) Moore stood at least 6 ft. 2 inches and was very well built like a foot-ball player. Moore agreed to the duel but since the choice of weapons was his, he said "let it be cream puffs at twenty paces in the morning." From all account the hostility cooled and all was well.

Herbert M. Evans. He probably has his name on more papers and on more diverse biological subjects than any scientist of whom I am aware. He was an extremely brilliant man, writing on such subjects as the History of Medicine, anatomy, endocrinology, vitamins, and nutrition, reproductive physiology and even to a paper in engineering I have been told. He made a striking appearance and spoke with a commanding voice with great authority. If one met him as an acquaintance, he would flatter your ears off in a most graciously charming manner. I do know first hand that several scientists who worked for or with him were very unhappy in his laboratory with unpleasant experiences but my simple personal encounters with him were always pleasant, discounting the accompanying flattery.

Oscar Riddle. He was most certainly a dedicated scientist, working most of his life at Cold Spring Harbor on Long Island, at the Carnegie Institute. He is known for his publications on prolactin in relation to the pigeon crop gland development and also general hormonal affects

in birds. His work so occupied his life, he told me one time, that he did not have time to get married but that when he retired at 65 years of age, he would quit all research then get married. This he did and lived for 20 more years enjoying life. One of his idiosyncrasies was chain-smoking de-nicotinized cigarettes. In a friendly way, he scolded me for not using them in place of regular cigarettes, then gave me a pack to try. This I did and vowed I would as soon smoked corn silk.

Henry Van Dyke. He contributed very much to the field of endocrinology but throughout his varied career I do not know if he trained any graduate students. He was trained as a physician but spent his time teaching pharmacology or doing research. He was primarily a pharmacologist as this subject as a separate discipline became more recognized during his life time. His books on the pituitary, published in 1936 and updated in 1939 are entitled "The Physiology and Pharmacology of the Pituitary Body". They are classical and certainly worth having to-day for historical interest. Van Dyke wrote the first one while teaching at the Peking Medical College and the second while director of hormone research at the Squibb Institute in New Brunswick, N.J. I first knew him when he was teaching at the University of Chicago and doing research on the purification of growth hormone. He gave me some which he had named "phyone" and which I used in my thesis research. Later, when Japan started their military conquest of China, he and his family moved to New Brunswick.

There we became close friends, even owning jointly a parcel of land with cabins at Cape May, bordering on Delaware Bay. We were fishing pardners and had many good scientific discussions especially

when the fish were not biting. He introduced me to statistical analyses of research data, which was not in general use prior to this period. Simple descriptive presentation of experimental endocrine research is not sufficient anymore. He chain-smoked cigarettes which I believe partly contributed to his early death. He loved to gamble and once I did win a bet from him, on September 1, 1939, when England declared war on Germany when the Balkan states were invaded. He bet England would not declare war. Van Dyke enlisted as an associate, Roy 0. Greep and together they advanced our knowledge of the gonadotropic hormones greatly.

Later, he moved to New York to the Columbia Medical School where he was chairman of pharmacology. It is interesting to note that he did most of the pharmacological testing on the posterior lobe hormones as they were synthesized and prepared by Vincent Du Vigneaud at the Cornell Medical School. Van Dyke was to retire just a short while before I did and I had planned to visit him to go fishing again. I have always felt life cheated me out of an anticipated pleasure.

Raphael Kurzrok. I first met him while I was at Columbia and he was professor of obstetrics and gynecology. He permitted me to attend his gynecological clinics where I saw first hand how estrogenic hormones were being used in cases of menopausal symptoms and how tests for sterility were made. Later, he went into private practice but kept up with clinical research. We published several papers jointly on research on hyaluronidase as related to fertility. He wrote a first class book on human reproduction about 1940 and his interest in sterility led him to be among the first to use artificial insemination in women. His studies for his Ph.D. while at Columbia (he had an M.D.

already) included the effects of extracts of semen on uterine contractions in women. He has been considered by some to be the discoverer of prostaglandins without knowing them by this name.

One interesting paper he wrote in the Am. J. Obst. and Gynecol. 15, 546, 1928 on sterility in some Jewish women is given to illustrate his sharp mind. Hebrew laws forbade coitus at some specific time after menstruation, assuming a 28 day cycle. Two women patients with an unusual 3-week-cycle were found to be past the time of ovulation and fertile period when the Hebraic law permitted coitus. By breaking the law by having coitus prior to the prescribed time, at Kurzrok's suggestion, pregnancy ensued. I also have a great personal regard for him, — he attended my wife in child-bearing so that I have two children where another physician at another time failed.

Sydney Asdell. I always considered him among the great contributors to reproductive physiology along with others who were stimulating me with their publications while I was a graduate student. I do not recall meeting him before I came to be his colleague on the Cornell faculty. Most of you know him personally as a quiet sincere person with a great breadth of knowledge and a willingness to help with ones problems — a great teacher too. His honors came rather belatedly, but deservedly so even if in the sunset of his life. It is no secret that when I applied for my post-doctoral fellowship in 1931, Dr. Asdell at Cornell and Dr. Edgar Allen at Yale were the other two I listed along with Dr. Smith, to continue my studies. It was only that my thesis work on the pituitary led me to continue along these lines with Dr. Smith.

Below is listed some of the older generation who I knew, recognized and met at various meetings but had no extended contacts. Their names may be recognized if one reads the literature from about 1925 to 1935 and later.

A.S. Parkes. I met in Sir Henry Dale's laboratory in England and when he was a visitor at the home of Dr. Asdell. He was most noteworthy among the English contributors to reproductive physiology.

J. Benoit. I believe his home base was in France and I met him when I was at Union College; he visited Cornell briefly. His contributions were on bird endocrinology.

Lucien Brouha. From France. He visited Hisaw's lab. when I was there and was interested in ovarian physiology.

L.V. Domm. From Chicago. He studied hormonal effects in birds, particularly feather coloration and development.

T. Bissonnett. From Trinity College, and noted for his work on the free-martin and effects of light on bird reproduction.

William Young. From Brown University, and who investigated male reproduction.

Emil Witschi. From Iowa State University, was a very astute scholar, and worked on amphibian reproduction and feather coloration in birds.

George Wislocki. From Harvard Medical School. He worked on many anatomical aspects of reproduction, ovulation and hormonal control of deer antler growth.

Maurice Friedman. U. of Pennsylvania. He was first to develop a pregnancy test based on ovulation in rabbits.

W.W. Swingle. Princeton is where he taught, after leaving Iowa State. He studied amphibian metamorphosis and produced the first albeit crude adrenal cortical extract that saved the life of a young man with Addison's disease. The parents of the young man built and furnished two summer homes on a lake in New Hampshire as a show of gratitude. Both houses were completely furnished - even to the dishes plus 2 boats each. One house was for Swingle, the other for his graduate students and guests. My wife and I visited them as their guests.

In closing, I hope I have fulfilled the mission that Drs. Robert Foote, William Hansel and Ari Van Tienhoven have urged upon me. My own contributions have been very modest but I am proud of those that I have had the good fortune to teach and to pass on to such men as Bob Foote, Bill Hansel and others, basic information in this field and to know that in my lifetime, they have contributed so much more to our understanding of this subject. Moreover, all of my colleagues here have also trained another generation of young people who will continue on as it has been in the past.

Recommended for Historical Interest.

Sex and Internal Secretions - Edgar Allen, Pub. by Williams and Wilkins, Baltimore, Md. 1932.

Sex and Internal Secretions - Edgar Allen, Charles Danforth and Edward Doisy, Pub. by William and Wilkins, 1939.

The Physiology and Pharmacology of the Pituitary Body, H.B. VanDyke, Pub. U. of Chicago Press, 1936 and in 1939.