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Tribute

Hotchkiss and MacLeod: An Historical Perspective

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This is an affectionate tribute to Dr Robert S. Hotchkiss and Dr John MacLeod, master teachers and giants in the field of male infertility. They were my remarkable mentors, whose work has probably touched and influenced every male-infertility investigator and every infertile male patient of the present generation. I would like to tell you about them and their close and warm relationship to one another.

Dr Robert Hotchkiss (Figure 1), a true pioneer in the field of male infertility and an inspiring teacher, was Director of the Department of Urology at New York University (NYU) Medical Center and at Bellevue Hospital when I started my urology training there in July 1951. Impressed by his enthusiasm, I decided to learn as much as I could about this young specialty of aiding couples to have children. My guide, the only one available at the time, was Dr Hotchkiss' textbook *Fertility in Men*, which had been published in 1944 (Hotchkiss, 1944).

Dr John MacLeod (Figure 2) was an authority on the human sperm cell and an avid explorer of the reproductive physiology of males at the New York Hospital–Cornell Medical Center.

MacLeod's Early Years

John MacLeod was born in Edinburgh, Scotland, in 1905 and was the oldest of 4 children. His father, Alexander, was a printer. John left school in 1917 at the age of 12 years to bring more money into the household. He began work, initially cleaning and delivering fish and then delivering hats part-time as a messenger. Seeking better employment, he searched newspaper ads and saw an advertisement for a "lab boy" in the physiology department at the University of Edinburgh. He told his current employers he was going to apply for this full-time job. The hatters were prominent people in Edinburgh, and they helped him get an interview and secure the job (Swan, 1981).

The University of Edinburgh had an outstanding department of physiology, and young John MacLeod was one of 6 boys assigned to keep the laboratory clean and set up laboratory experiments for the large first-year class of students (approximately 400 individuals) at the medical school. He was soon promoted to laboratory assistant, and his additional duties included teaching students how to smoke a kymograph drum and how to dissect a frog muscle-nerve preparation. When John was 16 years old, he was appointed to a position in which he assisted members of the faculty in their research. At that time, he first came into contact with Dr Edward Ponder, a physiologist whose specialty was the kinetics of red blood cell hemolysis. Dr Ponder later played a very important role in MacLeod's life.

At 17 years of age, MacLeod was made chief laboratory assistant to the chairman of the department, 70-year-old Sir Edward Sharpey-Schafer, and he prepared and participated in all of Sir Sharpey-Schaefer's research experiments and lectures. John was impressed by what seemed to him as the wonderful life of a scientist, and with this profession as his goal, he knew that he must acquire a formal education. He was permitted to attend evening lectures at a prep school for the University of Edinburgh, as well as all of the lectures given by members of the department. However, he realized that it was going to take more time and more money than he had, to qualify for a college degree.

During 1925 and 1926, there was a great influx of medical students from the United States, most of whom were Jewish. These students came to Edinburgh to study because they had been unable to gain admission into American medical schools because of their religious background. MacLeod recalled that he was most impressed with these American boys. John became friends with them, and during the next few years, he

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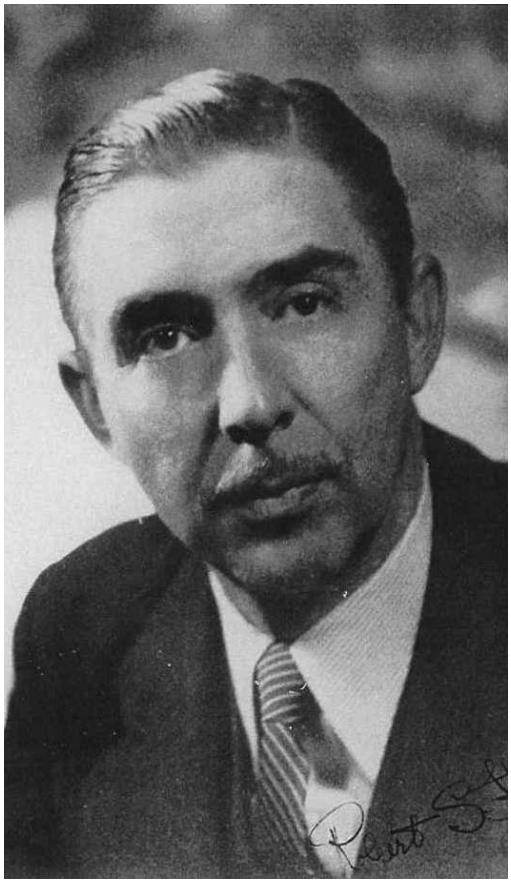

Figure 1. Robert Hotchkiss, MD.

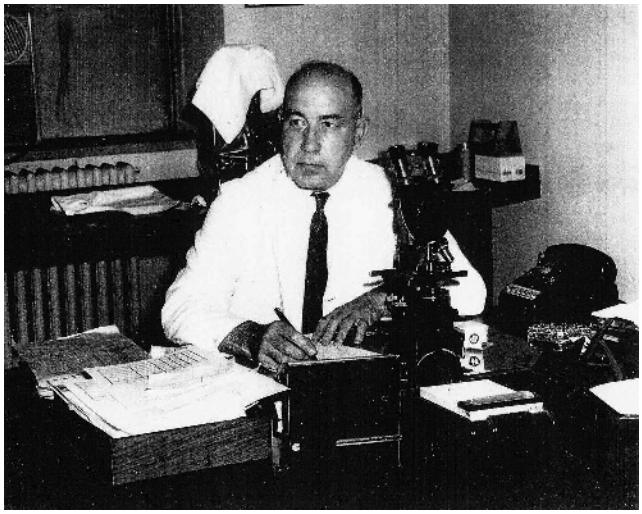

Figure 2. John MacLeod, PhD.

became thoroughly Americanized and began to think about coming to America, although he never lost his fine Scotch burr nor his taste for his favorite fine Scotch whiskey (The Glenlivet Single Malt).

His chance to come to America came in 1927 at the age of 22 years, when Dr Edward Ponder was appointed professor of biology at NYU. Dr Ponder invited John MacLeod to come with him to NYU and arranged for travel expenses, for a salaried job as his research assistant, and for a scholarship to NYU, which would enable MacLeod to get his bachelor's degree. John's first job at NYU was to study photographs of hemolyzing red blood cells, measuring their diameters with a micrometer. Gradually, he came to participate in Ponder's research, and his name and Ponder's appeared on a series of papers on the kinetics of hemolysis. Subsequently, with Ponder's encouragement, MacLeod became interested in the dynamics of white blood cells, which had a great deal more metabolic activity than red blood cells. He received a bachelor's degree from NYU in 1934 at the age of 29 years (Figure 3).

He had majored in English and biology, and when he graduated with honors in English, he received an offer to stay on as an assistant in the English department but decided to remain in science. At about that time, Dr Ponder was appointed director of the Laboratories at Cold Spring Harbor Research Center, located in a rustic setting on the north shore of Long Island, and invited MacLeod to join him. MacLeod was offered his own laboratory at Cold Spring Harbor, to pursue his interest in the metabolism of the white blood cell. He was pleased to go to Cold Spring Harbor Laboratory with Ponder, because of the presence there of a young secretary named Catherine Brown, referred to as "Kit." John had first met her in 1929 on a brief trip to Cold Spring Harbor with Ponder. He and Kit were married after John's graduation from NYU in 1934. Their daughter, Joan, was born the next year at Cold Spring Harbor. He earned a master's degree at NYU, which required traveling into the city 2 days per week, but he found it impossible to qualify for a PhD while at Cold Spring Harbor.

During the summer of 1937, while participating in a symposium at Cold Spring Harbor, he received an offer from Dr Joseph C. Hinsey, the head of the department of physiology of Cornell Medical College, to come to Cornell, work in Hinsey's department, and earn his PhD. At that same meeting, he met Dr Cornelius Rhodes, who was head of Rockefeller Hospital and was studying blood diseases. Rhodes was interested in the work John was doing on the metabolism of the white blood cell and offered him a position at Rockefeller Hospital with an annual salary of $2400 and the additional opportunity of taking as much time from work as necessary to earn his PhD degree at Cornell Medical College. John MacLeod left Cold Spring Harbor for Rockefeller Hospital and Cornell Medical College in 1938.

Figure 3. John MacLeod, 29 years of age, on the day he graduated from New York University.

Hotchkiss' Early Years

Robert Sherman Hotchkiss' ancestors arrived in America on the Mayflower in 1620. He was born on July 7, 1903, in Jamestown, New York. He had a relatively privileged childhood and was the younger son of Dr and Mrs Walter Hotchkiss. His father was an eye, ear, and nose specialist.

Robert Hotchkiss received his BS degree in 1925 and his MD degree in 1928 (both from the University of Michigan) and was elected to membership in Alpha Omega Alpha during his junior year of medical school. Upon graduation, he was appointed as an intern at the Royal Victoria Hospital in Montreal. The following year, he joined the house staff at Bellevue Hospital, and after completing an internship of 18 months on the medical and surgical services, he was appointed as resident in urology on the Bellevue Hospital Cornell Division.

He completed a chief residency in urology in l932 at the age of 29 years and was appointed to the attending staff at New York Hospital as an assistant urologist in the outpatient department. Dr Howard Jeck, who later became director of the department of urology at the Bellevue Hospital Cornell Division, was then the chief of the urology outpatient department at New York Hospital.

All of this was taking place at a time when the importance of the role of the male in infertility was first being acknowledged. In 1929, Macomber and Sanders published their article "The Spermatozoa Count" (Macomber and Sanders, 1929). The authors described a technique that, in all its essentials, closely resembles methods in use today, and involved use of blood-counting pipettes, diluting fluid, and use of the hemocytometer. They concluded that, whereas pregnancy could occur with sperm counts of less than 60 million sperm/mL, higher counts were more favorable to fertility. An interesting sidelight of the Macomber and Sanders article was their description of the restoration of fertility in a man with bilateral varicoceles who underwent surgery.

Hotchkiss developed an interest in male infertility. At the same time, Dr William Carey, a gynecologist at Cornell, had been studying sperm migration in post-coital tests. They collaborated in their research. Hotchkiss' first published paper, concerning staining procedures for the evaluation of sperm morphology, and with Carey as senior author, appeared in 1934 (Cary and Hotchkiss, 1934).

Margaret Sanger, a pioneer advocate of family planning in America, whose credo was "every child a wanted child," was a wealthy lady and was interested in funding a project concerned with the investigation of childless couples. In 1938, she made a novel proposal to Dr Jeck to establish a Male Sterility Clinic in the Outpatient Department at New York Hospital. Dr Jeck endorsed her proposal and assigned Dr Hotchkiss, the "low man on the totem pole," to direct the newly funded Male Sterility Clinic. Henricus Stander, director of the department of obstetrics and gynecology, gave support to the venture. Paul Reznikoff provided laboratory space in the department of medicine, and Ephraim Schorr was an advisor who supervised endocrinologic diagnosis and treatment.

Hotchkiss, with the research grant received from Margaret Sanger, went to Dr Joseph Hinsey, head of the physiology department at Cornell Medical College, with the request that Hinsey recommend someone from the physiology department to work under the grant to study the biologic behavior of human spermatozoa. Hinsey, who had lured John MacLeod to Cornell, promptly recommended MacLeod, who accepted the assignment with enthusiasm. He applied the experience he had already gained in studying the metabolism of blood cells to study the unique metabolism of the human sperm cell. MacLeod did not fully realize, when

he started, that he was going to encounter one of the most unusual cells of all. The unique metabolism of human spermatozoa would provide him with a lifetime of research.

The Middle Years

There began a close collaboration between Hotchkiss, the clinician, and MacLeod, the researcher, which continued for 2 decades. Their close, warm friendship lasted the rest of their lives.

In the course of his research, which was funded by Margaret Sanger through Dr Hotchkiss, MacLeod discovered that, unlike sperm of nonhuman species, human sperm have an anaerobic metabolism. The role of oxygen in human sperm metabolism is an extremely minor one. Unlike the behavior of other mammalian cells, high oxygen tensions are toxic to human sperm. MacLeod discovered that, in the presence of oxygen, human sperm produce hydrogen peroxide, which destroys their own motility.

The MacLeods' son, Ian, was born in 1940, a year before John MacLeod received his PhD in physiology from Cornell. His thesis, "The Metabolism of Human Spermatozoa," was summarized in the *American Journal of Physiology* (MacLeod, 1941).

MacLeod's Financial Support

Meanwhile, at Cornell, the money to support MacLeod's work came from Cornelius Vanderbilt (Sonny) Whitney, who sat on the Boards of Governors and Trustees at New York Hospital and Cornell Medical College. It was customary during the dinner hour at the combined monthly Board meetings for Dr Hinsey to select one of his faculty to present an informal discussion for these laymen on the work with which he was involved. When John MacLeod was selected in early 1942, he captivated his wealthy lay audience by telling them about his sperm studies on infertile men. MacLeod recalled that his financial support had its beginning with a phone call from Sonny Whitney's race-horse farm manager in Kentucky. He passed on the request that MacLeod come to Kentucky to examine Sonny Whitney's stallion, Boojum, who had been very productive in terms of his racing performance but was completely unsuccessful as a stud. At that same congenial dinner, another trustee, John Hay (Jock) Whitney, told MacLeod that he was also interested in his work because he, too, owned an apparently sterile horse, Twenty Grand, who had won the Kentucky Derby and the Triple Crown.

John MacLeod went down to Kentucky and saw Boojum at Sonny Whitney's stable and then saw Twenty Grand at Jock Whitney's stable next door. As MacLeod described it, there he was, never having seen a thoroughbred in his life, invited to Kentucky to try to determine what was wrong with these 2 splendid race horses.

It so happened that, as a result of his metabolism research, MacLeod was interested in the B-complex vitamins. In fact, he had suggested giving B-complex vitamins to infertile men, which had some beneficial results. So he put B-complex vitamin supplements into Boojum's feed, and Boojum impregnated 4 mares during the subsequent breeding season. Unfortunately, Twenty Grand had another problem, with a genetic sperm-tail defect that could not be corrected.

MacLeod recalled that, although his trip to Kentucky was hardly worthwhile for Twenty Grand, it was certainly valuable to himself and to Cornell: Sonny Whitney liberally supported MacLeod's human research for the next 14 years.

It is a remarkable coincidence that Robert Sherman Hotchkiss, Cornelius Vanderbilt Whitney, and John Hay Whitney could all trace their ancestry back to Governor William Crawford, who arrived at Plymouth Rock on the Mayflower in 1620.

Testicular Biopsy

Charles Charny published the first article on testicular biopsy in 1940, in which he acknowledged that Hotchkiss had been the first to use this technique in humans to differentiate cases of azoospermia due to obstruction of the ductal system from cases in which lack of sperm was due to absent or incomplete spermatogenesis (Charny, 1940). The use of testicular biopsy was gradually extended to include cases of oligospermia, and information was gathered about types of disturbances in sperm maturation in oligospermic men. Testicular biopsy also became an important research tool studying testicular effects of hormonal manipulations, toxic substances, stress, and radiation exposure.

World War II

World War II came. Early in 1942, at 39 years of age, Dr Hotchkiss was commissioned a lieutenant commander in the United States Navy and saw duty in the Pacific Theatre as senior medical officer aboard the *USS Monrovia*, which transported troops and evacuated casualties (Figure 4). The *Monrovia* was docked at Leyte in The Philippines when the Japanese surrendered there in August 1945. Hotchkiss retired from the Navy with the rank of commander in 1946. His book *Fertility in Men* was published in 1944 while he was still in the Navy, and it subsequently went through 4 printings (Hotchkiss, 1944).

Figure 4. "Doc Hotch" at Leyte, the Philippines, August 1945.

After World War II

On returning to civilian life, Hotchkiss succeeded Dr Howard Jeck as the director of urology in the Cornell Division at Bellevue Hospital. He served in that capacity until 1948, when he was appointed professor and chairman of the department of urology at NYU School of Medicine, succeeding Dr Meredith Campbell.

In 1945, only 4 years after receiving his PhD from Cornell, MacLeod was the first recipient of the prestigious Lasker Award presented by The Planned Parenthood Federation of America for his pioneering research on the metabolism of human spermatozoa. At that same ceremony, Dr Hotchkiss was honored for his book *Fertility in Men*, which had been published by JB Lippincott Company as a companion volume to *Fertility in Women*, by the gynecologist Dr Samuel Siegler (Siegler, 1944).

The Modern Era in the Study of Male Infertility

There was close collaboration between Hotchkiss, the clinician, who examined many hundreds of men involved in infertile marriages, and MacLeod, the researcher, who

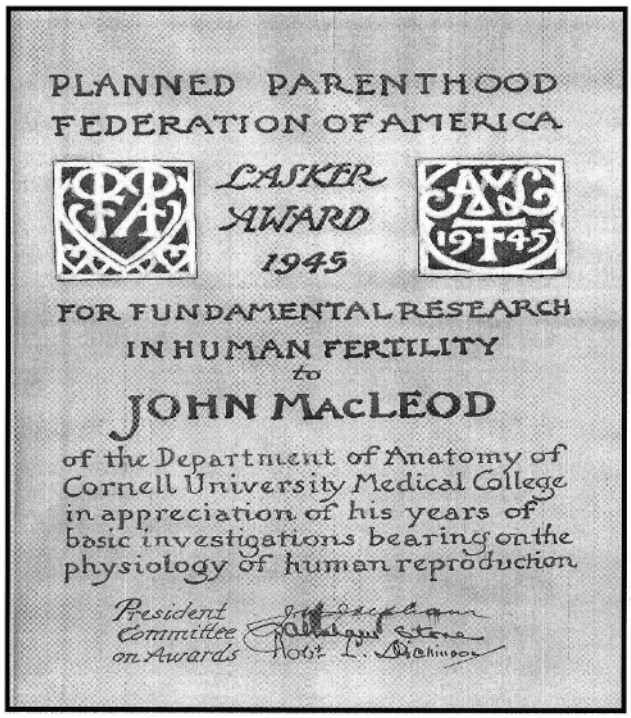

Figure 5. MacLeod's Lasker Award, 1945.

studied the semen specimens these men submitted for analysis. Similar studies were done on semen from a large number of men whose wives were pregnant. The data from both groups were subjected to rigorous statistical analyses. The validity of semen analysis as an accurate indicator of the state of spermatogenesis in the experimental animal was also investigated.

These combined approaches confirmed the opinion that a competently performed semen analysis (which involved appraisal of semen volume, sperm cell count, and concentration; the percentage and grade of motility; and differential morphologic characteristics) was a reliable tool in laboratory research. These studies also gave relevant evidence about the probability of conception for men.

MacLeod was convinced that the then existing standards for appraising the quality of human sperm in terms of potential fertility were too high. He decided to investigate the clinical accuracy of semen analyses for predicting conception (MacLeod, 1950, 1951). He soon realized that his data were huge and required the expertise of a biostatistician. He was fortunate in securing the full-time services of Ruth Z. Gold. She spent the next 7 years with MacLeod, meticulously analyzing his data. Together they published a series of 8 papers reporting on various aspects of semen quality as related to specific case histories of patients, thus providing standards which have received international recognition for their validity (MacLeod and Gold, 1951a, 1951b, 1952, 1953a, 1953b, 1955, 1956, 1957).

My Papers With Hotchkiss

My own early research on seminal coagulation before subsequent liquefaction and on the residual viscosity of human semen in relation to fertility led to my discovery that the seminal fluid of 6 of my patients with bilateral congenital absence of the vasa failed to coagulate because of the concomitant absence of the seminal vesicles (Amelar, 1962). This could be diagnosed with a simple seminal test for fructose, even before confirming the anatomical diagnosis by physically examining the patients. In the same article, I also described 2 effective methods for liquefying highly viscous semen specimens to enhance sperm motility.

Following the publication of this paper, I collaborated with Dr Hotchkiss in performing scrotal exploration and testicle biopsy studies in 10 fructose-negative, azoospermic patients, documenting bilaterally normal testicular biopsies coexisting with bilateral congenital absence of the scrotal vasa and distal epididymides (Amelar and Hotchkiss, 1963).

In 1965, I reported with Dr Hotchkiss on a study of 522 split-ejaculate semen specimens from husbands in infertile marriages, concluding that there are significant differences between the first and second portions of the human seminal ejaculate with regard to viscosity, sperm concentration, sperm motility, and sperm morphology and that, compared with the total ejaculate, these differences can be profound (Amelar and Hotchkiss, 1965). This information is applicable to the treatment of the infertile male, particularly if his semen volume is high.

MacLeod's Further Research

MacLeod conducted research, which was funded generously by Cornelius Vanderbilt Whitney, on various factors that might influence the production and behavior of sperm, such as heat and febrile illness, infections, allergies, and various environmental and developmental toxins. This led to the need for better methods to study the morphologic characteristics of sperm cells, and accordingly, he adapted the Papanicalou staining technique to the study of sperm morphologic characteristics.

His interest in the toxic effects of substances on the testes led to research on certain drugs, the bis-(dichloroacetyl)diamines, which were initially found to be effective amoebicides and later found to be toxic to the testes of animals and humans (MacLeod, 1961). A group of 60 state prisoners volunteered to participate in studies involving both semen analyses and testicular biopsies. MacLeod obtained complete inhibition of spermatogenesis and found that the profound effects were completely reversible within several months. This raised the hopes of scientists working in the area of population control that this drug would prove to be an effective birth control pill for men, but such hopes were dashed when it was found that nonprisoners became severely ill if they drank alcoholic beverages (ie, an Antibus-like effect). Nevertheless, this study led to continuing efforts to develop a pill that can completely suppress male fertility with no untoward adverse effects.

One of MacLeod's major contributions to the field of human seminal cytology was his classification of human sperm cells into 6 major categories; in the past, researchers had enumerated as many as 60 different morphologic types of human spermatozoa. McLeod's simplified classification enabled researchers throughout the world to standardize and compare their findings with mutual comprehension (MacLeod, 1962). He identified immature cells of the germinal line from the testes appearing in the ejaculate as recognizable sperm precursors and determined that this was a finding of clinical significance. This led to his description of the "stress pattern" (MacLeod, 1965) and its identification in patients who had adrenal cortical hyperfunction, as well as in patients with varicocele (MacLeod, 1965).

MacLeod most enjoyed the clinical aspects of his work, and in 1964, he had the opportunity to collaborate with Dr Bronson Ray, the head of neurosurgery at Cornell Medical Center. Dr Ray used hypophysectomy for the management of severe diabetic retinopathy, and the patients became sterile as a result of the removal of the pituitary gland. Dr MacLeod recognized the opportunity to perform clinical research on a new drug called Pergonal, a type of human follicle-stimulating hormone derived from the urine of menopausal women. He demonstrated that, when human spermatogenesis was abolished after removal of the pituitary gland, he could restore spermatogenesis completely with injections of Pergonal after the patient had been primed with luteinizing hormone in the form of human chorionic gonadotropin (MacLeod et al, 1966). This pioneering work by MacLeod has been confirmed daily in our now effective management of infertility in the hypogonadotropic male.

Infertility Due to Varicocele

MacLeod's attention to detail and his interest in the clinical problems of patients enabled him to make a striking correlation between infertility due to varicocele and its associated characteristic semen abnormalities: a combination of poor sperm motility and poor sperm morphology with a high percentage of tapering and primitive forms in the ejaculate (ie, the "stress pattern"). He subsequently urged urologists to recognize the role of varicocele and the benefits of correcting this condition in the treatment of the infertile male.

In 1965, I attended a meeting, arranged by Dr MacLeod, with a group of urologists from NYU (Drs

Jordan Brown, Lawrence Dubin, Adrian Zorgniotti, Hotchkiss, and Amelar) who were interested in male infertility. At a conference table in the Faculty Club at Cornell Medical College, Dr MacLeod proposed a co-operative study with urologists, in which he would do the studies on seminal cytologic characteristics before and after varicocele correction. A protocol was established for that study, again emphasizing MacLeod's strict research standards.

Dr MacLeod's Retirements

At the age of 67 years, McLeod retired from the anatomy department at the Cornell University College of Medicine in 1972, but he remained at the Medical Center, setting up a consultation laboratory for male infertility in the department of obstetrics and gynecology. He continued his studies as emeritus professor of cell biology and anatomy, and he retired again in 1977.

Then, in collaboration with a statistician, Dr Ying Wang, Dr MacLeod published his final article, which was a scholarly review comparing the 15 000 semen analyses he had personally performed between 1966 and 1977 with semen analyses he had performed between 1951 and 1956 (MacLeod and Wang, 1979). In an assessment of semen quality over the years, McLeod and Wang concluded that there had been no significant deterioration in sperm counts and that the observations on normal and abnormal parameters of semen quality made 30 years earlier by MacLeod were still valid.

John MacLeod died in New York Hospital of colon cancer on January 24, 1984, at the age of 79 years. His life and work may serve as an inspiration to young scientists, who might be persuaded that success is possible despite adversities and lack of funds—that achievements are possible if there is perseverance.

Dr Hotchkiss' Retirement

Dr Hotchkiss served with distinction as director of the department of urology at NYU Medical Center and Bellevue Hospital from 1948 until his retirement in 1974. On that occasion, in a moving address to the faculty and friends and current and former residents and staff at his retirement dinner, he said "....Lucky, very lucky, am I to have so many cherished friends. This, in addition to the marvelous experience of the past years, is not given to all. The interrelationships between the attending and the house staffs, generate a unique association that has few, if any counterparts in human rapport. Within it are elements of intimacy and exchange that sometimes approach a father-son attachment which does not lessen with the passage of time. There is an enormous satisfaction to observe the progressive development of an individual culminating in the ultimate major accomplishments which qualify him to become the senior resident and then to occupy a position of distinction in his post-residency years. The experience of working together often obscures the traditional hierarchy of a student-teacher convention. From these fresh young minds, unburdened with orthodoxy, spring novel ideas which the faculty, in its infinite wisdom, regard as either good or bad. These exchanges, nevertheless, often instruct those who profess to teach and thus provide a stimulating climate for mutual advancement. ..."

Following his retirement, he was able to spend more time at home with family and friends. In 1989, he died of pneumonia at the age of 86 years.

Closing Thoughts

In closing this essay, I would like to reflect on the occasion of my receiving the Distinguished Andrologist Award from The American Society of Andrology in 1999. It was an honor to be selected by the Society to follow in the giant footsteps of my mentors, Dr Robert S. Hotchkiss and Dr John MacLeod, who received this award in 1978 and 1980, respectively.

Acknowledgments

My information concerning Dr MacLeod's early years comes from a published interview I found in the New York Hospital Archives that Dr Roy Swan (deceased) had conducted with him (Swan, 1981). At the time of the interview, Dr Swan was the Joseph C. Hinsey Professor of Anatomy at the Cornell University College of Medicine. I am most indebted to Dr MacLeod's son, Ian, and to Dr Hotchkiss' son, Sherman, for being generously giving of their time and hospitality in providing me with rich family stories and loaning me precious records and photographs. I have enjoyed my meetings with both of them.

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