



NATIONAL VETERINARY LABORATORY

P.O. Box 239, 1Tice Road
Franklin Lakes, NJ 07417
877-NVL-LABS (877-685-5227)
www.natvetlab.com

NEWSLETTER

Honoring People Who Made a Difference: 2011 was a Year of Great Loss[©]

Evelyn E. Zuckerman, Editor

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In This Issue:

The winter 2011 issue of the NVL Newsletter will reflect on the loss of 2 great men, a dear friend and an outstanding scientist, both who made a great contribution to me and society.

By William D. Hardy, Jr., V.M.D.

The Year:

2011 began with a bang- as I wrote in an earlier Newsletter, after presenting a *Bartonella* paper at the 1st International One Health Congress in Melbourne, Australia; we were trapped in New Zealand by a major earthquake in February and were evacuated by the Royal Air Force. In May I took my long time friend and scuba diving buddy, Herman Gross and his wonderful wife Gertrude, to dinner for his 94th birthday. A month later Herman passed away. In August William Jarrett, the discoverer of the Feline Leukemia Virus (see Fall 2011 Newsletter) died, and in October Lloyd J Old, M.D. my scientific mentor at Memorial Sloan Kettering Cancer Center, passed away.

Herman Gross:

Everyone has someone in her or his life who is both a character and dear friend. I met Herman Gross on my first dive trip to the South Pacific when, at 37,000 feet, he had me paged me on the American Airline flight. He identified himself to me and said he was on my dive trip and I immediately knew I liked this person. We dove together on 22 more trips, several with the Society for Aquatic Veterinary Medicine, to almost every ocean and sea. Herman was a reckless scuba diver but he grew on everyone who met him. As dive buddies we would jump into the water together but rarely see each other again due to our passionate picture taking.

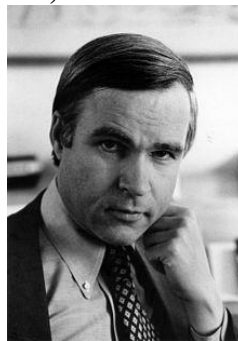


Herman Gross- Aldabra Atoll, Indian Ocean

Herman was a Harvard educated lawyer, at the top of his class, who became a successful business man and a philanthropist. He was

generous to his friends with his time and with his resources.

Lloyd J. Old, M.D.:



Lloyd J. Old, M.D., circa 1974

Lloyd J. Old was born in San Francisco on September 23, 1933. He attended public schools in Burlingame, California, a town south of the San Francisco. Although Dr. Old would eventually go into science, his first aspiration was to be a violinist. He became concertmaster of his high school orchestra and, following graduation in 1951, went to Paris to study violin with European masters. After a year in France, he returned to the United States to attend the University of California at Berkeley, where he trained and played with the Griller String Quartet, Berkeley's resident ensemble. At Berkeley, Dr. Old's fascination for science grew. While continuing to perform as a musician, he simultaneously began pre-med studies. He graduated Phi Beta Kappa, with a degree in biology, in three years and then attended medical school at the University of California, San Francisco. Courtesy: Cancer Research Institute.

I, as a new graduate from the University of Pennsylvania, School of Veterinary Medicine, did a 1 year internship at the Henry Bergh Memorial Hospital of the ASPCA in NYC, a mere 24 blocks from the Memorial Sloan Kettering Cancer Center (MSKCC). Realizing that I would like to study the recently discovered feline leukemia virus (FeLV), I sought the advice of Dean Robert Marshak at Penn, who had been conducting research on the bovine leukemia virus. I asked if I could come back to Penn for a research Post-Doctoral Fellowship. He said he would be happy to have me back but, to my ever lasting appreciation, suggested I do my fellowship with Dr. Lloyd J. Old at MSKCC and then return to Penn. He indicated the training with

Dr. Old would be the best available and arranged a meeting with him for me. To my great fortune, Dr. Old was looking for a young scientist and thus I had was fortunate to study under Dr. Old and I remained with him for 5 years after my fellowship. He then assisted me in obtaining my own autonomous laboratory, The Laboratory of Veterinary Oncology. I remained at Sloan Kettering for 24 years with a close association with Dr. Old.

Dr. Old was a giant in cancer biology with an emphasis on tumor immunology where he was essentially the father of the field. As an MD, he had a deep love of all animals and although his research entailed the use of mice, rats and rabbits, he saw to it that they were maintained in the most comfortable and humane environments. He was instrumental, along with the Cancer Research Institute (CRI) founder Helen Coley Nauts, in the establishment of the Donaldson-Atwood Cancer Clinic at the Animal Medical Center (AMC) in New York City. This unit was initially staffed with 3 veterinary oncologists and headed by the late Dr. Greg MacEwen. Dr. Old and Mrs. Nauts, through the CRI, obtained funding support for this endeavor which has helped countless pet animals with cancer. This was a formative period in veterinary medicine and with the encouragement of Dr. Old, the unit trained many veterinarians in clinical oncology and lead to the establishment of the Veterinary Cancer Society by myself, Dr. McEwen and others. The Donaldson-Atwood Cancer Clinic is still in operation today at the AMC. In 1973, Dr. Old recommended, to the director of MSKCC, that I be allowed to establish a private testing laboratory, the National Veterinary Laboratory, to provide FeLV testing while I maintained my appointment at MSKCC. Without his advocacy this laboratory would not exist and FeLV testing may not have been introduced.



Dr. Old and with Cancer Research Institute founder Helen Coley Nauts, circa 1978.

Under Dr. Old's guidance, and funding and support from Mrs. Nauts at the CRI and the Leukemia Society of America, we began our studies into the biology of the feline leukemia virus (FeLV) and soon developed a diagnostic blood test for the virus. Using this test we studied pet cats from the ASPCA and the AMC and soon discovered that the virus was transmitted contagiously (horizontally) between cats.^{1,2} This discovery was in direct opposition to the prevalent dogma that this type of virus, retrovirus, was only transmitted vertically (genetically) as was found in mice and chickens at that time. We suffered much scientific doubt from the scientific community but Dr. Old steadfastly defended our observations which turned out to be correct.



Dr. Hardy (left) and Dr. Old (right) in 1973 celebrating the publication of the FeLV horizontal transmission paper in the journal Nature.

At this time, Dr. Old's own early research efforts were directed at understanding the immune system's role in cancer. His group had been studying the cell surface and viral expressed antigens on murine leukemia cells. They discovered mammalian leukemia viruses shared a major viral common antigen named gs-3.³ My research integrated with Dr. Old's group and we quickly showed that this antigen was also present in the feline leukemia virus. (FeLV).⁴

Dr. Old asked us to test immunotherapeutic agents in naturally occurring cancers of pet animals, cats and dogs. He knew that carefully controlled studies in mice and rats had to be verified in animals with naturally occurring cancers. We tested laetrile, a compound extracted from almond pits that had a checkered history in medicine and we rigorously evaluated the compound and found it was ineffective. We then showed that the new drug L-asparaginase worked effectively in lymphosarcoma of dogs which hastened its approval for use in humans. At the same time Dr. Old had me studying human tumors in a search for a human cancer virus.

Throughout all these wonderful years, Dr. Old seemed to know more about my daily experiments and data that I did. I later learned that he would read my notebooks and experimental sheets each night to keep current. At the time, he did the same for the more than 10 research scientists in his laboratory. Each morning when I would eagerly enter the lab to develop my overnight experiment he seemed to know the results before I did. He never criticized any experiment but did steer and guide us all in the correct directions. His laboratory meetings were exciting and stimulating and we always left with new ideas.

Dr. Old was shy and did not like to present the data from his laboratory at meetings and would ask his associates to make the presentations.

There is no better development tool than preparing to present your research data and conclusions and then being challenged at an international meeting by world class scientists. On our return he would "de-brief" us by asking what type of questions and criticisms we received and who asked them.

Dr. Old was scientific director of the CRI for 40 years from 1971 until 2011, held the William E. Snee Chair of Cancer Immunology at Memorial Sloan-Kettering Cancer Center, where he was director of the NY Branch of the Ludwig Institute for Cancer Research. He made noteworthy contributions to veterinary medicine by helping to establish the first multi-disciplined animal cancer unit at the Animal Medical Center, by being a co-investigator for the first FeLV diagnostic test, a collaborator in the immunological studies of immunity to FeLV which laid the groundwork for the FeLV vaccines, and a collaborator in our discovery of the *kit* oncogene from a feline fibrosarcoma which has led to both diagnostic reagents and therapeutics for cancers.

Father of Cancer Immunology:

Dr. Old is credited with developing the field of cancer immunology. The following is a list of his, and his collaborator's seminal discoveries which are relevant to veterinary and human medicine. This list is reproduced verbatim or with few changes from Wikipedia, the free encyclopedia.

1. Introduced Bacille Calmette-Guérin (BCG), the tuberculosis vaccine, into experimental cancer research to stimulate non-specific resistance to tumor growth. BCG was FDA-approved in 1991 and is now widely used as a first line treatment for superficial bladder cancer (1959).⁵
2. Discovered the first linkage between the major histocompatibility complex (MHC) and disease—mouse leukemia—opening the way for the recognition of the importance of the MHC in the immune response (1964).⁶
3. In collaboration with Edward A. Boyse, M.D., he identified the first cell surface markers, or antigens, that could distinguish different functional subsets of immune cells. They first coined TL (for "thymus-leukemia" antigen in mice), this discovery led directly to the wide use of cell surface markers to distinguish and classify normal and malignant cells. This is now known as the "cluster of differentiation," or CD, system in humans, with the most recognized being CD8 to identify "killer" T cells, which Dr. Old discovered as Ly-B in mice, and CD4 to distinguish "helper" T cells, which has become widely known because of the role of CD4 T cells in the development and classification of HIV/AIDS. CD8 cells, often referred to as "killer" T cells, are one of the major cells of the adaptive immune response, and are capable of directly killing dangerous or foreign cells (1964-1968). This research laid the groundwork for identifying the molecular markers on the surfaces of cells that has revolutionized immunology and medicine as it is practiced today.^{7,8} Evelyn Zuckerman, the NVL Newsletter editor, was a research technician for Dr. Boyse for some of these important studies.

4. Discovery of the association between Epstein-Barr Virus (EBV) and nasopharyngeal cancer (1966).⁹

5. Discovery of tumor necrosis factor (TNF), a key immune signaling molecule (cytokine) that, in addition to its promise for the treatment of cancer and other diseases, has provided a powerful research tool in biomedicine (nearly 88,000 articles published as of May 25, 2011) (1975).^{10,11}

6. Identification (independently, along with two other groups) of the p53 protein, the gene for which is mutated in ~ 50% of cancers (1979).¹²

7. Studied the cell surface of human cancers using monoclonal antibodies, with the identification of an array of cell surface antigens as targets for antibody-based therapies of human cancer. Of the monoclonal antibodies developed in Dr. Old's laboratory, thirteen have been licensed and seven are in clinical trials.

Dr. Hardy's Reflection:

Dr. Old was truly a scientific giant interested only in the pursuit of knowledge and the training of future scientists. He did this by quiet devoted scientific example and demonstration. He sought and obtained millions of dollars of grant and private funding for support of hundreds of scientists. I feel his collective cancer immunology contributions should have been recognized with a Noble Prize. I am proud to say that he was my mentor and my friend.

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