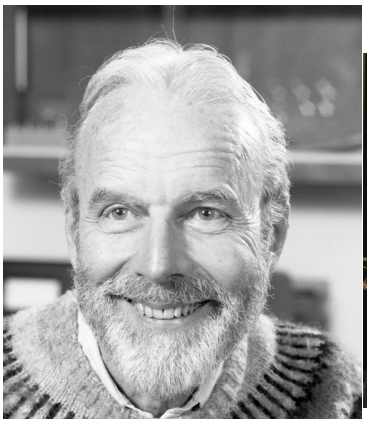
In Memoriam: Marvin A. Van Dilla 1919-2019


Marvin Van Dilla, a pioneer and inventor of early flow cytometry and sorting, and dear friend and colleague of many, many ISAC members, died on October 19, 2019 in Santa Fe, New Mexico, shortly after celebrating his 100th birthday. He was born June 18, 1919 in New York City.

Marv's early research interests were in thyroid metabolism. After radioiodine became available in the 1940's, it enabled monitoring of thyroid metabolism. Marv used an array of Geiger counters to measure radioiodine uptake in patients. After joining the Los Alamos Scientific Laboratory in 1955, he set up a very large and sensitive NaI spectrometer to do the same thing but with greatly reduced radioiodine doses (by a factor of about 1000) to minimize patient exposure. His prime research interest was in using highly sensitive detection techniques to study the uptake and metabolism of radio-nuclides in humans and animals. Early in the 1960's, Marv was joined by Mack Fulwyler. They expanded their research program to apply gamma ray spectroscopy to many biological and medical problems These studies occupied Marv for many years, and lead to significant advances in our understanding of radionuclide metabolism – their dangers and their diagnostic potential (1-25).

Not long after, their group leader, Wright Langham, asked Marv and Mack to help a pathologist, C.C. Lushbaugh, to extend the capability of the newly invented Coulter red blood cell counter to the measurement of red blood cell size distributions. The counter gave strange results when coupled to a pulse height analyzer to measure the volume distribution of cells. Marv made a careful study of the operating characteristics of the cell counter, which was designed to merely count the number of cells in a sample; he discovered that the volume distribution generated by the machine was entirely dependent on the way the counter was set up and operated. Marv's analysis then went on to establish the conditions that must be met for the cell counter to indeed provide accurate volume distributions. This got Marv and Mack into the field of high-speed detection of the properties of cells in aqueous suspension (26-29).
1/29/20Marv then went on to develop what came to be known as a "Flow Cytometer (FCM)", the name being proposed by the Los Alamos group (30-31). He recognized the potential for greatly increasing the usefulness of the device by attaching fluorescent molecules to

components of the cells (32,33), and by using light sources (UV lamps and later, lasers) to activate the fluorescent molecules and produce a light signal in proportion to the amount of the component. This led to the measurement of the DNA content of cells and then to the distribution of DNA among a population of cells (34). At the same time Paul Mullaney was working on a similar flow system to measure light scattering by cells. Other early contributors were Jim Coulter, Ted Trujillo and Phil Dean (30).

One of Marv's early projects was the high-resolution measurement of the DNA content of tissue culture cells, known to be highly aneuploid with a large number of "extra" chromosomes and translocations (34). This project developed a detailed analysis of DNA distribution, addressing questions relating to the coefficient of variation of the G1 peak. Specifically, what fraction was due to instrument variation versus DNA cell to cell variability.

Marv enrolled Phil Dean to analyze the DNA fluorescence distribution from cells in exponential growth. Could the data be analyzed to determine the number of cells in each phase of their life cycle? Using techniques developed for the analysis of radiation distributions, they developed a method for the analysis of DNA distributions.

At this time Mack Fulwyler suggested the possibility of developing a flow cell sorter to remove individual cells from a mixture of cells at a high rate; thousands of cells per second. He combined the Coulter counter concept with the principle of electrostatic deflection, as developed by Dick Sweet, of Varian Corporation, for ink jets in a high-speed oscillograph. He, Marv and the Los Alamos team produced a device that sorted cells based on their volume (29).

Later, sorting technology was enhanced by the use of fluorescent dyes to identify cells with components of interest and eventually dual laser excitation was used to sort cells on the basis of more than one component (35).

Marv transferred to the Lawrence Livermore National Laboratory in the summer of 1972, fresh from his pioneering work on flow cytometry (still called flow microfluorometry (31)) with Paul Mullaney at the Los Alamos National Laboratory. He joined Mort Mendelsohn, Brian Mayall and Bart Gledhill to create a biomedical sciences program dedicated to the idea that new cell measurement technologies could revolutionize understanding, detection and treatment of diseases caused by environmental insults. Understanding and quantifying radiation- and energy byproduct-induced cellular damage was at the heart of the mission assigned to Livermore by a succession of federal agencies including the Atomic Energy Commission, the Energy Research and Development Agency and eventually the Department of Energy. Marv took on the task of developing flow cytometry and fluorescence-activated cell sorting for these purposes (although it took some time for these terms to become standard jargon). Marv recruited an accomplished staff over the years: it included Don Peters, Phil Dean, Joe Gray, Dan Pinkel, Maria Pallavicini, Barb Trask, and Ger van Den Engh.

Marv's team, in collaboration with other biological, chemical and mathematical teams at Livermore and around the world, made pioneering contributions to several areas of analytical

cytology. These included: development of flow instrumentation and high-speed sorting (36-38); separation of sperm carrying X or Y chromosomes according to differences DNA content (39-43); bacterial classification (44); cell cycle analysis by assessment of BrdUrd incorporation and DNA content (45); fluorescence in situ hybridization FISH (46); and multiple advances in the flow analysis and separation of chromosomes (), leading to the preparation of chromosome specific libraries ().

The developments of Marv and his colleagues have had profound effects worldwide in our understanding of the biological effects of radio nuclides, and in the fields of animal husbandry, quantification of induced and spontaneous DNA damage, analysis of cell proliferation in cancer and other diseases, and in enabling the chromosome specific libraries which lead to the initiation of the human genome project. He was the initiator and visionary leader of so much that now is taken for granted in the discipline of cytometry.

Personal Memories

Scott Cram: Above all else, Marv was a dedicated supporter of his colleagues, so many of passionately committed to good science but always gave credit to those with whom he collaborated.

Phil Dean: I first met Marv when I was a First Lieutenant in the US Air Force. I had been assigned the task of developing a device to measure the radiation dose rate in the Van Allen Belt, needed for decisions about personnel traveling in space. I contacted Marv for possible help since the group he worked with at the Los Alamos Scientific Laboratory (LASL) was known to be very active in the measurement of radiation. Marv came to Los Alamos from the University of Utah where he had been working on the detection of radio-nuclides in animals, principally dogs [3]. Marv and LASL agreed to develop a detector for us, which eventually flew through the Van Allen Belt and provided the needed data.

When I was released from active duty in 1961, Marv asked me to accept employment with the Low Level Counting Section of the Health Research Group at LASL. He and I worked for some time on the measurement of radiation emanating from people, animals and the environment [1-25]. During this work I discovered that Marv was very careful about what he did and kept meticulous records in laboratory notebooks. He continued this practice for all the time I worked with him. He was active in the measurement of radioactivity in people, primarily from nuclear fallout due to the testing of nuclear weapons in the atmosphere, but also in the use of radio-nuclides in medicine. In this area Marv was involved in the development of the largest existing device to measure the radiation coming from people. I joined him in that effort, eventually taking over the program. An unusual sideline in that effort was measurement of lunar and intra-stellar radiation (16, 18, 24) and the radioactivity of meteorites (12); these interested Marv greatly, and resulted one year in our scouring the area West of Los Alamos for a meteorite that passed over the area one evening.

Joe Gray: Marv was always driven by the science and the potential societal benefits of this work and remained open to new ideas throughout his career. Indeed, after many years of research leadership and administration, his interests lead him to spend a sabbatical period learning biochemistry, and to return to being a bench scientist in that area. While doing all of this, Marv pursued and inspired others to pursue outside interests including hiking, skiing and photography. He cared deeply for others and he shared his passions about science and life with them freely.

Brian Mayall: Marv impressed me immediately with his curiosity. He was always asking questions in that laconic voice of his. Sometimes the questions would seem naïve; often they would be deep and penetrating. He would never allow one to get away with a superficial response. He was forever pushing the bounds of the possible. It was this restlessness and refusal to accept the status quo that made him such an important pioneer in so many aspects of modern cytometry. And he had an uncanny ability to recognize the strengths of others as he built his team at LLNL

My family and I also got to know Marv well at a personal level. Marv introduced us to backpacking in the Sierra Nevadas and to his classic collection of jazz recordings. His enthusiasm was contagious, but we could have survived without his out-of-tune whistling as he greeted the dawn!

J.Paul Robinson: I was privileged to run the Toronto ISAC meeting in 2006 and it was my honor to have been able to invite Marv van Dilla as the president's special guest to the congress. What an honor to meet this foundation of our field. Marv told me many stories about how they envisioned a technology that would be able to analyze any fluorochome and become a vital technology in the field of cytometry. Indeed Marv was absolutely right.

Marvin A. Van Dilla: Selected Publications

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