Floyd Dunn and His Contributions

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There were a few years in the 1960s when Floyd Dunn almost single-handedly managed to keep biomedical ultrasound alive.

Floyd Dunn (**Figure 1**) has been recognized time and time again as a pioneer and one of the most significant scientific leaders internationally to elucidate the mechanisms by which ultrasound interacts with biological materials. For nearly five decades, his full efforts were devoted to the subject; he maintained a steady flow of productive research; he built one of the largest organizations devoted to the field; and he encouraged the development of the field nationally and internationally, behind the scenes and through leadership and participation in many different organizations. He was involved in the first major blossoming of biomedical ultrasound in the 1950s. In the 1960s, there were a few years when he almost single-handedly managed to keep the field alive. No single scientist is more responsible for this success than Floyd Dunn.

Figure 1. *Floyd Dunn on the occasion of accepting the 1998 Gold Medal from the Acoustical Society of America.*

Getting to Illinois

Floyd was born in Kansas City, Missouri, on April 14, 1924. He was a child of the Great Depression. Floyd's father barely pieced together a living as a watchmaker. His family did not have the money to send him to a university, which would probably have been the University of Missouri or the University of Kansas. In his second year at Kansas City Junior College, Floyd joined the Navy, but the Navy discovered that Floyd was completely colorblind and discharged him the same month he joined (March 1943). That June, Floyd enlisted in the Army where he served for three years on active duty and in the reserves for an additional three years. Not long after he returned from the European theater as a veteran of the Battle of the Bulge, Floyd applied and was accepted into the Department of Electrical Engineering at the University of Illinois; his junior college physics teacher had received his physics degree from Illinois and continually claimed (according to Floyd) that the University of Illinois had the very best Department of Electrical Engineering in the country. Floyd thought that his junior college record and the GI Bill (Serviceman's Readjustment Act of 1944) were what got him accepted at Illinois.

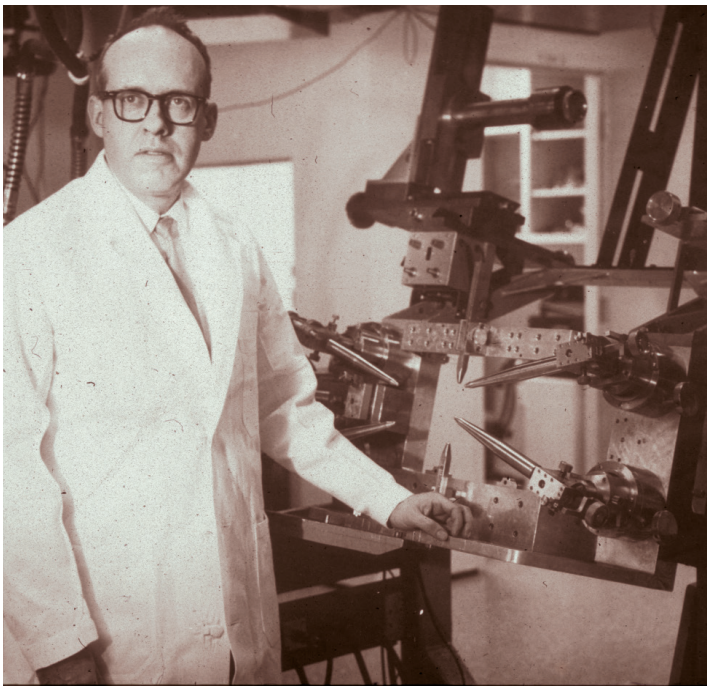

Figure 2. *Bill Fry with a novel stereotaxic apparatus that was designed and built by him, his brother Frank Fry, and coworkers to support the head of animals of varying sizes and used for precise neurosonic surgery applications.*

Floyd arrived at the University of Illinois in the fall of 1946 as an undergraduate student in electrical engineering. That was the same year that William J. "Bill" Fry (Figure 2) arrived on campus and founded the Bioacoustics Research Laboratory (BRL). Bill's younger brother Francis J. "Frank" Fry arrived a month or two later. The Fry brothers, and particularly Bill, would have a significant impact on Floyd's lifelong and amazing career. But Floyd and the Fry brothers would not get together until about three years later.

Floyd graduated in December 1949 with a BS in electrical engineering and then considered staying at Illinois for graduate studies. Someone, he forgot who, mentioned to Floyd that there was this guy Bill Fry doing some interesting stuff and that he was a little bit kooky, but everybody thought that he was an outstanding scientist. Floyd sought out Bill Fry to discuss the possibility of graduate school and financial support. Floyd connected well with Bill Fry when Bill queried him about his skill in mathematics. Floyd had taken the required math courses (through differential equations) and had continued to take a math course every semester, probably four or so courses beyond differential equations. Floyd indicated that Bill thought that was kind of curious and interesting, so he was hired as a research assistant.

Independence and Resourcefulness

There was an element of independence and self-sufficiency that marked the beginning of the BRL. This attitude ran strong with the Fry brothers and likely had a major impact on Floyd when he joined the BRL in 1949. For example, consider the early physical setting of the laboratory. Back in 1946 when the Fry brothers came to Illinois, there was little space for the new priority of research. At that time, the entire Department of Electrical Engineering was cramped into a small, antiquated building, the Electrical Engineering Research Laboratory (EERL). But when the Fry brothers arrived, they had been assigned small offices. Needing laboratory space, they set up their offices in a steam tunnel that ran under the Boneyard (a waterway that traverses the engineering campus and drains much of the cities of Urbana and Champaign) and used their assigned offices in the EERL for laboratories.

In the three years between when the Fry brothers arrived and Floyd joined the BRL, the Frys had developed ultrasound-based projects that were focused on the central nervous system. Pursuing the ultrasound biology research required equipment, supplies, laboratory space, and animals. As the animal colony developed, complaints arose about mice in the candy machine in the Department of Electrical Engineering (shortly thereafter found to be field mice, not lab mice). Also, there were challenges with using newspaper advertising to acquire cats. By about 1949-1950, the Fry brothers had some important successes that would also influence and benefit Floyd.

Funding Challenges and Successes

When Floyd joined the BRL, he became fully integrated with much of what the Fry brothers were doing. However, some of these projects that had been assigned to Floyd had to be dropped because their funding had ceased. This experience indicated to Floyd that there was not a lot of money available to conduct his bioacoustics research, but Bill Fry seemed to be pretty good at getting money anyway. To put those times in perspective: equipment to create, detect, quantify, and analyze ultrasound had to be constructed from scratch because many of the materials used today were not available and the funding agencies of today were in their early stages or did not yet exist. The Office of Naval Research was created in 1946 and the National Science Foundation in 1950. The long-standing (from the 1930s) National Institute of Health (note the singular *Institute*) at that time did not have an external research effort, supporting largely in-house research. In the later part of the 1940s, the name was changed to the

National Institutes of Health (note the plural *Institutes*) and slowly an extramural research program of grants evolved. Funding was mostly from the military (Navy Bureau of Ships, Office of Naval Research, and Air Force Aero Medical Laboratory) and the money focused largely on transducer developments.

Another problem for which Bill Fry successfully obtained funding significantly benefitted Floyd because it provided him with the experience and importance of carefully characterizing and calibrating acoustic fields in water. The skills acquired with this project were front and center in Floyd's future academic career as he successfully pursued groundbreaking tissue-based ultrasonic exposure and dose research. The research involved the development of a sonar transducer for the Navy that would have a continuously varying resonant frequency (Fry et al., 1951, 1955; Hall and Fry, 1951; Welkowitz and Fry, 1954; Dunn et al., 1956). This was a completely new and challenging problem and, if successful, was viewed by the Navy as a capability for potentially avoiding sonar detection. A column of mercury was intimately coupled to the transducer such that the transducer's resonance frequency changed continuously with the column's length; the mercury column effectively increased the thickness of the transducer crystal. Floyd assembled the 100 individual piezoelectric elements and was responsible for then measuring the shape of the sound field as a function of frequency (charactering it) and calibrating the relationship between the input voltage and the transmitted sound pressure level. A cubic foot of enormously expensive, triply distilled mercury was required to provide an effective bond with the piezoelectric elements. To avoid this expense, Floyd purchased less expensive, newly mined mercury ore and designed and constructed a still to process the metal.

Floyd meticulously acquired calibrated data from the variable-frequency transducer using a World War II signal generator and power amplifier as well as Navy-provided sonar detectors. The analyses showed that the frequency varied by a factor of 2 (22-44 kHz), as was required by the original design. However, the Navy wanted to verify the findings and required that the transducer be tested using sophisticated Navy instrumentation at a Navy facility in Connecticut called Dodge Pond. A university truck was outfitted to safely transport the transducer, and it took Floyd and Frank three to four days to drive the truck to Dodge Pond for the testing that required about a week. The observations from the Dodge Pond measurements were essentially the same as the measurements at Illinois.

Curiosity, Imagination, and a Movie

Floyd had to have inherited curiosity and imagination from his BRL experiences that fed him for a lifetime. From colleagues and students, Floyd demanded curiosity, critical thinking, imagination, thoughtfulness, and creative problem solving—not much different from how Floyd described those early BRL days when he was closely involved with a significant medical ultrasound research project. In 1955, a movie was produced in the BRL titled *Neuro Sonic Surgery*. This movie captured the details of a large project that a couple of years later led successfully to human neurosonic surgery (O'Brien and Dunn, 2015). Floyd was the movie's technical director. The movie largely documented Floyd's laboratory interactions as a graduate student with the Fry brothers' major project and showed how significantly Floyd was involved in and contributed to the work, including (1) developing a precision motion-controlled positioning system to guide the focused ultrasound beam to generate complex geometric tissue lesions; (2) calibrating the ultrasound field using newly developed measurement techniques (no national or international measurement standards existed then); (3) estimating the ultrasonic intensity delivered in vivo at the focus to generate spatially precise tissue lesions; and (4) conducting a wide range of carefully controlled ultrasound tissue biophysical experiments to either temporarily or permanently alter tissue.

Determining Thresholds: Functional Outcome

Floyd's PhD thesis (Dunn, 1956) represented a seminal study that yielded ultrasonic intensity relationships from a functional in vivo end point rather than from a histological (tissue structure) end point. At the time when Floyd was working on his thesis, the neurosonic surgery studies were also being conducted and were able to demonstrate precise and reproducible lesions in brain tissue for which histology was used for the lesion outcome measure. This, in itself, did not help to identify the mechanism responsible for the lesion. The ultrasonic mechanisms being mentioned frequently at that time were thermal and cavitation, and when theory and/or experiment appeared to rule out these two mechanisms, the literature often mentioned a nonthermal, mechanical mechanism (because sound is a mechanically propagated wave). It was viewed as essential then that the physical mechanism of the action of high-intensity ultrasound on tissue be understood so that its full medical potential could be realized. To this end, Floyd chose for his thesis and follow-up research an ideal subject: day-old mice.

Because mice within 24 hours of birth are essentially poikilothermic, that is, able to function without ill effects over a wide range of body temperatures (including down to almost 0°C), they are well suited for testing a thermal mechanism. Accordingly, Floyd comprehensively investigated the ultrasound-induced functional outcome of hind limb motor paralysis in these animals. For these experiments, ultrasound was focused in the region of the third lumbar vertebra of the anesthetized day-old mouse. If the spinal cord was damaged in that region, then hind limb paralysis resulted and was easily detected.

Figure 3 shows the 50% threshold of paralysis, that is, one-half of the mice were paralyzed for the specific exposure time-intensity values that defined the centerline. The exposure conditions were such that, for each animal, a single ultrasonic pulse of known duration and intensity was incident on the mouse's spinal cord. For the experiment shown in **Figure 3**, the ultrasonic frequency of the single pulse was 982 kHz and the animal's temperature was 10°C. **Figure 3** compares the reciprocal of the ultrasonic pulse duration (t^{-1}) with the square root of the ultrasonic intensity [there are a few listed ultrasonic intensity values along the x-axis; note that the square root of 121 W/cm^2 is 11 (W/cm^2)^{½}]. Reciprocal time is along the left y-axis and time is along the right y-axis. The ***solid diagonal lines*** that almost track the 50% threshold diagonal centerline are the 10% (above the centerline) and 90% (below the centerline) paralysis thresholds. The ***solid vertical*** and ***solid dashed horizontal lines*** provide visual guidance to the axes. Thermocouples were imbedded in the spinal cord to measure temperature; the ***open circles*** denote temperature increases of the indicated time-intensity coordinate.

Plotting the mouse paralysis data on a graph that related the pulse duration reciprocal (t^{-1}) with the square root of intensity ($I^{½}$) yielded a straight line for the 50% threshold. The slope of the straight line [$(t^{-1})/(I^{½}) = 1/(I^{½}\ t)$] was an early indicator for an important ultrasonic dosage quantity, $I\ t^{½}$ (Dunn et al., 1975), noting that the square root of $I\ t^{½}$ is $I^{½}\ t$, the denominator of the threshold slope term.

Floyd then expanded the mouse paralysis studies to include body temperatures of 2°C, 10°C, and 20°C (Dunn, 1958) and then later expanded to the normal body temperature of 37°C (discussed in **Determining Thresholds: Functional and Structural Outcomes**). The mouse spinal cords were also evaluated histologically, which led to an interesting observation: the lesions appeared histologically about 10-15 minutes after the loss of function occurred and the paralysis occurred almost immediately after the ultrasonic exposure, thus strongly suggesting that the histologically observed changes were associated with secondary processes of tissue damage. The care with which the experiments were conducted (later verified with repeatability) showed that cavitation and thermal processes were not the principal mechanisms of action and that there was insufficient information to define a dose quantity. Later, however, these early studies would provide the foundation for significant dose-effect observations because of the care and detail with which the experiments were performed.

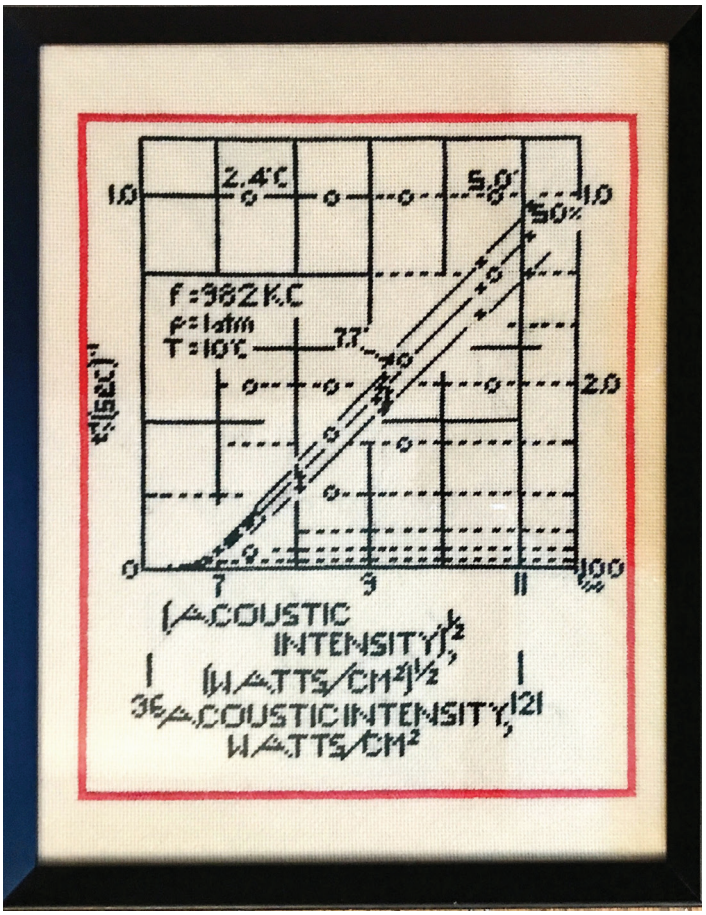

Figure 3. *"Floyd Dunn 1956 Thesis Graph" by Elsa Dunn, 1977. Needlepoint in wool and acrylic fibers. See text for explanation of the data shown. See Dunn, 1956, Figure 13; 1958, Figure 4.*

Determining Thresholds: Functional and Structural Outcomes

These ultrasonically induced functional outcomes originally observed by Floyd were further investigated by a host of graduate students and colleagues for decades to come, as were the earlier Fry brothers' histological (structural) outcomes from the brain lesion project. Both structure and

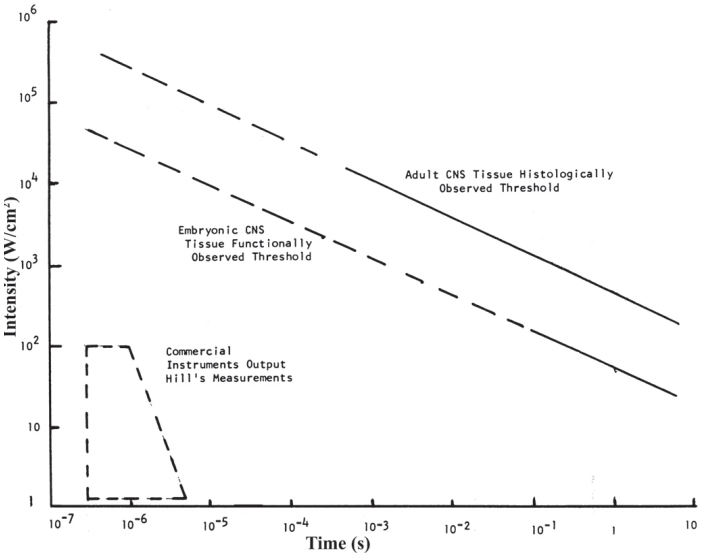

Figure 4. *Comparison of threshold curves for mammalian central nervous system (CNS) tissue with output of some commercially available ultrasonic diagnostic systems. From Fry and Dunn (1973).*

function were extensively evaluated using the same exposure condition, namely, for each animal, a single ultrasonic pulse of known duration and intensity was utilized. The common exposure condition allowed for a direct comparison between the two relatively large datasets.

Floyd compared the brain structural and spinal cord functional threshold outcomes graphically (**Figure 4**) on a log-log plot of intensity on the *y*-axis and exposure time (pulse duration) on the *x*-axis (Fry et al., 1970; Dunn and Fry, 1971; Fry and Dunn, 1973). The ***solid lines*** represent the 50% threshold observations from measurements and the ***dashed lines*** represent extrapolations to shorter pulse durations. The extrapolations are valuable for comparing the experimental data thresholds to pulse durations typically used with diagnostic ultrasound imaging systems, namely, around 1 microsecond (10^{-6} s). The functional data here represent the day-old mouse paralysis outcomes when the animal was at 37°C. Floyd observed that the threshold magnitudes (intensities) of embryonic (day-old mouse) functional outcomes were about a factor of eight less than the adult structural outcomes, suggesting that the embryonic tissue might be more easily damaged by ultrasound than adult tissue. The commercial diagnostic ultrasound imaging system peak intensity levels (**Figure 4**, ***dashed-line box***) were much lower in magnitude than the extrapolated magnitude values, suggesting a significant margin of safety. Also, even if one were to consider today's commercial diagnostic ultrasound system outputs, their peak intensity levels might be closer to 1,000 W/cm^2 in **Figure 4** and still represent a significant margin of safety.

A supportive aspect for the structural threshold line in **Figure 4** is that additional threshold data, acquired at the University of Rochester, fit well on the line. The additional data consisted of structural lesions of rabbit liver, kidney, and testes (Frizzell et al., 1977). Furthermore, the slopes of both the structural and functional threshold lines were very nearly −½, meaning that the lines could be described mathematically by $I\,t^{½}$ = a constant where the constant would be different for the two lines (Dunn et al., 1975). This mathematical expression is strongly related to the paralysis slope term [1/($I^{½}\,t$)] mentioned in **Determining Thresholds: Functional Outcome** and pointed out Floyd's continued quest for quantitative dose concepts.

A significant aspect of these studies was the determination of ultrasonic thresholds of exposure for irreversible functional and structural changes. It should be noted that the key ultrasonic characteristic varied in the experiments was intensity, which represents tissue *exposure* to ultrasound but provides no quantitative information about how much ultrasonic energy is actually *absorbed* by tissue. Accordingly, Floyd initiated the quest for an absorbed dose quantity (Dunn, 1962; Johnston and Dunn, 1976). Floyd was the first to quantify in vivo the temperature dependence of the ultrasonic absorption (a measure of the amount of ultrasonic energy that is converted to heat), showing that in vivo tissue exhibits absorption behavior considerably different from that of in vitro preparations. This discovery had a marked influence on ultrasonic hyperthermia (controlled ultrasonic tissue heating) and on the quest for an ultrasonic dose quantity. Thus, utilizing the irreversible mammalian structural data, an "energy absorbed per unit volume of lesion" quantity was developed that suggested a direction for a universal dose quantity. This dose quantity showed that there was no difference between gray and white matter brain lesion thresholds, whereas there was such a difference when the exposure quantity "intensity" was used.

From this work, Floyd was able to provide descriptions of the threshold regions in terms of the physical mechanisms of interaction. These threshold regions became a de facto worldwide standard for separating bioeffects from the lack of bioeffects, from which government and standard-setting bodies established safety criteria. Almost two decades later, when the United States Food and Drug Administration (FDA) adopted regulatory guidelines for diagnostic ultrasound equipment, it used a biophysical dose quantity "thermal index" that was, to a large extent, based on Floyd's earlier observations. Furthermore, the widespread use of

diagnostic ultrasound (virtually every pregnant woman has her fetus evaluated ultrasonically) could not have occurred without these assurances of "lack of effect."

Ultrasonic Toxicity

Finally, and in keeping with the scholarly theme of ultrasonic safety, Floyd's studies of ultrasound toxicity dealt largely with mammalian reproductive organs because these organs had an ample opportunity to become ultrasonically exposed during routine therapy and diagnostic clinical procedures. The mammalian testis was shown to respond considerably differently to ultrasound exposures than to ionizing radiation exposures (O'Brien et al., 1979; Bailey et al., 1981; Carnes et al., 1991). Also, studies with the mammalian ovary (Bailey et al., 1983, 1984) showed that the different ovarian phases manifested different ultrasonic responses. Both organ systems were evaluated extensively, and these studies have, to date, been reassuring as to the safety of diagnostic ultrasound. Floyd's seminal work on reproductive tissues is doubly important (and reassuring) because of the potential concern of ultrasonically induced genetic effects (Carnes et al., 1995).

Elsa and Crazy Thoughts

It is not possible to write about Floyd Dunn without including his wife Elsa. Floyd and Elsa (**Figure 5**) were introduced in 1946 shortly after Floyd returned from the European theater. According to Floyd and Elsa's daughter Andi and son Roo, "Aunt Minnie, who seated them together at a family wedding, had exclaimed, 'They are both crazy. Maybe they will talk to each other.' Aunt Minnie was right, and the conversation continued for more than 64 years." Floyd and Elsa were married on June 11, 1950, after Floyd became an electrical engineering graduate student. Elsa passed on December 26, 2014. Floyd passed 29 days later on January 24, 2015.

Floyd and Elsa both greatly enjoyed their travels. Floyd was a visiting professor in the Department of Microbiology at University College, Cardiff, Wales; a visiting senior scientist at the Institute of Cancer Research (University of London), Sutton, Surrey, UK; a visiting professor at the University of Nanjing, Nanjing, China; and a visiting professor at Tohoku University, Sendai, Japan.

Public Service and Awards

Floyd Dunn served important leadership roles in the Acoustical Society of America (ASA) as vice president (1981-1982) and president (1982-1983). Floyd also served for almost five decades as an associate editor on *The Journal of the Acoustical Society of America* (*JASA*), starting in 1968 and serving for many years following his 1995 retirement from the University of Illinois when he and Elsa moved to Tucson, AZ. As a *JASA* Associate Editor, Floyd was responsible for the field of bioacoustics, for which he maintained high standards and made *JASA* an essential repository of research findings in this area.

Figure 5. *Elsa and Floyd on the occasion of Floyd's 90th birthday gathering in Tucson, AZ.*

As a distinguished Fellow of the ASA, Floyd was recognized with its highest awards: the Silver Medal in Bioresponse to Vibration (1989), of which he was the first recipient, and the Gold Medal (1998).

Floyd received many prestigious awards and honors in recognition of his distinguished career and the research he and his graduate students conducted. He was a member of both the National Academy of Sciences and the National Academy of Engineering.

A list of his honors and achievements does not come close to recognizing Floyd for the giant he was in the field of ultrasonic biophysics. But, nonetheless, we are left with these imaginative, creative giants: Elsa and Floyd, who, as Aunt Minnie observed, were "both crazy." We have been blessed with such craziness, and we are better for it.

Acknowledgments

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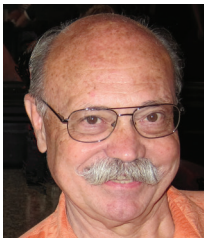
BioSketch



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