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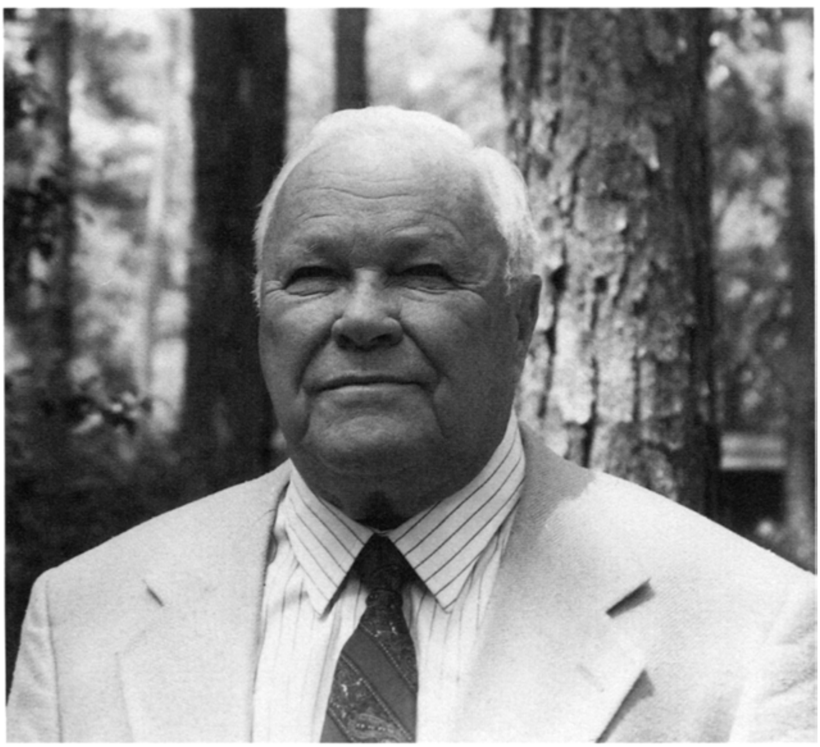

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Allentown, Pennsylvania
January 17, 1922

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Muhlenburg College, B.S. (1943)
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HONORS AND AWARDS:

National Academy of Sciences U.S.A. (1974)
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Lloyd Beidler carried out pioneering physiological studies of chemoreception working with a variety of species and sensory systems. He carried out psychophysical studies with sensory nerves, and he demonstrated turnover in sensory cells. He is an authority on the sensory physiology of taste.

The History of Neuroscience in Autobiography, Volume 2

Lloyd M. Beidler

My Early Life

My interest in science as a possible career started when I was a senior in college. Most of the attitudes, skills, and philosophy utilized in my scientific career, however, were developed long before. The effects of growing up with family stability, in a semirural environment, and with great personal freedom were reflected throughout my life.

My father's family were Mennonites whose origin can be traced to 1736 in Pennsylvania. My mother's family emigrated from Germany more recently. My father left school after eighth grade and became a railroad clerk in Bethlehem, where my mother also worked after she graduated from high school.

I was born in 1922 in Allentown, Pennsylvania. My two sisters Rose and Doris were born a few years earlier. When I was about 6 months old, my father purchased half of a two-home dwelling in a newly formed rural development north of Allentown. The house was 20 feet wide and two and half stories high. We were on the edge of the development and faced a large farm. About 300 feet from our house was a large abandoned iron ore pit which was used as a trash dump by the city. The church was our only social center. It contained a large worship area, a small, one-room library on the first floor, and a basement where the Boy Scouts and other social groups met. The village had only one store, located in the large front room of a house. We children had no playground or any other gathering place. As a result, my chief entertainment as a boy was at home and at the trash pit, which became the source of parts for any toy I desired, including my first and only bicycle. Later the pit became the source of parts for electrical devices and components for radios. Thus the pit contributed greatly to my interest in the physical sciences.

My father worked hard and followed a rigorous schedule from the time I was born until after I graduated from college. He assigned jobs of cutting the grass, weeding the garden, and taking the coal ashes outside, and they had to be accomplished on time. Serious offenses were followed by spankings but I soon learned to avoid them. When my chores were finished I had almost complete freedom but I had to be home when my father returned from work. Home rules were strict and clear, but because my sisters and I obeyed them, we had an unusual amount of independence.

My father was an avid reader and we three children again followed his example.

The depression greatly impacted my life as it did most people of the time. We collected rainwater from the roof of the house and stored it in an underground cistern. A hand pump in the kitchen brought the water up from the tank. My mother heated water on a wood stove for our baths every Saturday night. Our toilet was an outhouse about 20 feet from our dwelling. We converted the house to indoor plumbing when I was in high school. Today this type of living seems primitive but then it was the norm and most families were considered neither poor nor wealthy. My life, and those of my friends, was greatly influenced by the immense social and economic upheaval produced by the great depression and World War II. Simultaneously, though, the rewards of science were noticeable. Electrification was spreading rapidly to rural areas. Electric-powered delivery trucks were being replaced by noisier but faster gasoline-powered trucks and roads were being constructed. As a boy, I ran outside if I heard a small plane. Radio was introduced and television came later. The practice of medicine was still primitive and we waited until shortly before the war before antibiotics were available. These were tough but exciting times for a future scientist.

My formal education started in a two-room, six-grade schoolhouse. Mrs. Kistler, a motherly teacher with 2 years of normal school education, taught the first three grades. I then moved across the hall to Mr. Kistler's class for the next three grades. I still remember doing my arithmetic assignment in Mrs. Kistler's class while others were either singing or reading in the same room. In winter the classes would be interrupted by students who had to get dressed to go to the outhouse. The mental discipline needed to study at school was also useful at home because neither of my parents could help with homework. My father, however, carefully scrutinized our monthly school grades.

Middle school and high school were quite different. We were bussed several miles to the middle school, but walked only about a mile to the high school. The buildings were modern and the teachers quite accomplished and well educated. The high school curriculum was broad and included arts, music, and industrial training every year. My experience in wood working and metal lathe operation was helpful years later when I had to make much of my own research equipment. The most interesting courses for me were chemistry and physics. I obtained permission to do experiments in both laboratories instead of attending a study period. My experiment in the physics lab was to build a Tesla spark producer. Another student and I used a high-voltage transformer from an old neon sign. We fed the high voltage into a coil made from ¼-inch-diameter copper tubing which served as the primary winding of the Tesla device. The secondary winding consisted of No. 22 wire wound on a 6-inch-diameter and 30-inch-high cardboard cylinder that we obtained in a dress shop. Our Tesla device produced a very high-voltage but low-current spark about 10 inches long. Our teacher never came into that part of the laboratory while we were experimenting! We demonstrated the coil to the class with dramatic results. During my senior year I did a series of chemistry experiments on making dyes and applying them to different types of cloth. The principal often came into the lab and showed his interest by asking questions.

My father and I never discussed future plans and I had little idea of what I might do after graduation. However, when I was a senior, my high school principal took me to see the dean of a local liberal arts college, Muhlenberg College. The meeting resulted in a scholarship and a change in my life.

Muhlenberg College in Allentown

The depression was still being felt when I entered college in 1939. Fortunately the cost of a college education was not high. I bicycled to college and carried a packed lunch. I dusted library books 10 hours a week and was paid 40 cents an hour. That federal program helped the college and allowed me to graduate without owing a debt to the government. I also worked in a grocery store every Saturday and as a laborer in the Bethlehem steel plant during the summers. Thus, my father had only to contribute 100 dollars for each year of my undergraduate experience. This seemingly small amount, however, was approximately what my mother was given to feed the family for 5 months.

As a boy I built a radio with a triode vacuum tube, a variable capacitor, a resistor, and a self-wound inductance, all from components found at the trash pit. To this day I still remember the thrill of hearing my first successful radio receptions. Such experiences influenced my decision to major in physics in college.

The chairman of the physics department, Dr. Ira Zartman, received his doctorate from the University of California and was one of the first researchers to measure molecular velocities. He left Muhlenberg when I was a sophomore and went to Johns Hopkins University to organize a research and development group for the Navy. This left a rather young faculty to teach physics to about six physics majors as well as general physics to the science majors. We physics majors had a close relationship with the professors; one of them took us on a hiking trip through the mountains of Vermont during our junior year. The attack on Pearl Harbor was announced on radio while I was a junior studying for an exam in atomic physics. The government responded quickly by organizing new research groups to design and build weapons. Our physics curriculum at Muhlenberg changed rapidly as a result. We physics majors wanted to respond to the need of the military for scientists in electronics and for physicists both to work in the new government laboratories and to help train newly inducted men.

Johns Hopkins in Baltimore

A few months before I graduated from Muhlenberg College in December 1942, I received a phone call from Dr. Zartman. He had learned that I had received offers to join a research group in Oak Ridge, Tennessee, and to teach at a University in New York. He asked me to consider the physics department at Johns Hopkins University in Baltimore. Two months later I accepted a junior instructorship as a graduate student in physics at Johns Hopkins.

I received an M.S. in physics after a year of graduate work and I was again approached by Dr. Zartman. He was desperately searching for more researchers for the naval laboratory located just one floor beneath the physics department! The mission of this group was to develop proximity fuses that could not be jammed. The antiaircraft shells had small radio transmitters which were energized when the shells were shot toward a flying aircraft and the transmitted beam was reflected by the aircraft back to the shell. When the signal was large enough, the shell exploded. These new antiaircraft shells were very effective; more than 90% of the Japanese attack planes were being destroyed in the Pacific in a single encounter. However, the shells could be harmlessly exploded on the way to their target if a radio transmitter at the same frequency as the shell was operating in the vicinity of the planes. The new research mission was to design electronic fuses that would not respond to the enemy's attempt at jamming. I joined this group and developed new electronic designs. The fuses were then tested for their radiation patterns by four women in the laboratory. One of these women, Mary Lou, became my wife. She had recently graduated from Goucher College in Baltimore, majoring in physics. Her interest in science had led her to join the Civilian Pilot Training program, which was supported by the government to form a group of women that might be called on later to learn to fly larger planes that could be shuttled to England. It was in this program that she obtained her pilot license.

Johnson Foundation for Medical Physics, University of Pennsylvania

I believed that most biological processes could be explained by a series of physical and chemical events and that someone with my training could contribute to advances in biology and medicine. I discussed my interests with Dr. Samuel Talbot of the Wilmer Institute of Ophthalmology and this led to the opportunity to work in his laboratories in the evenings and hear his views of the future of biophysics. He encouraged me to enter the new field of biophysics when the war was over in 1945 and I applied to the Johnson Foundation for Medical Biophysics at the University Pennsylvania.

The director, Professor Detlev Bronk, had performed the first recording from a single nerve fiber in Lord Adrian's laboratory in Cambridge, England, while he was a postdoctoral fellow. (This research led to the establishment of the famous sensory law relating the frequency of nerve firing and the number of nerve fibers responding to the intensity of sensory response, an important contribution to the total research for which Adrian received the Nobel Prize.) The Johnson Foundation had previously trained many postdoctoral fellows but few predoctoral students.

The faculty included Drs. Frank Brink, Martin Larrabee, and Phil Davies in neurophysiology, Keffer Hartline in vision, and Tom Anderson in electron microscopy. There was no defined curriculum except that everyone had to take human physiology in the medical school. I also studied general physiology with Lewis V. Heilbrunn, chemical embryology with Jean Brachet, and x-ray diffraction with A. L. Patterson. We were required to take three of the five exams required of the doctoral students in the department of physics and show competence in German and French. The program was more like a research apprenticeship. All of the students were very close to the faculty.

We arrived in the laboratory at about 9:00 AM, ate lunch together in the library room, and left the laboratory at about 10:00 P.M. Each student was assigned to a professor and worked in his office–laboratory. I worked with Frank Brink but he never assigned me a research project. Thus, I made my own decision and chose to study frog embryonic development. After my first year at the Johnson Foundation I married Mary Lou who then became a graduate student and assistant in physics at Bryn Mawr College. Her major professor was A. L. Patterson, who had developed a mathematical method for analyzing x-ray diffraction patterns of crystals and determining their three-dimensional atomic structure. This he did while also serving as a lecturer for several years at the Johnson Foundation where he was attempting to determine the atomic structure of proteins. My marriage caused a stir among the graduate students because, unknown to me, Dr. Bronk had an unwritten rule that Johnson Foundation students should not marry until after they had obtained their Ph.D.

Professor Bronk was very active in the National Research Council of the National Academy of Sciences as well as many other scientific organizations, and seldom was in his office in the daytime. However, he was often at the Foundation in the evening. One evening he asked me about my dissertation plans. As a graduate student I had been independent and had chosen my own dissertation topic without first talking with Dr. Bronk. I had taken graduate courses in quantum mechanics, theory of molecular structure, valence theory of organic chemistry, and statistical mechanics, and thought I would study the interaction of ions and molecules in a biological system; specifically the interactions of ions and molecules with taste and olfactory receptors. Dr. Bronk was not pleased with my choice of research and suggested instead that I study under Adrian in Cambridge, England, who already had written several papers on olfaction. This suggestion came as a shock to me because Mary Lou, who was now working in x-ray diffraction at the Franklin Institute, and I had no resources to move to England.

Within a few weeks my problem was unexpectedly solved. Dr. Hartline announced that Dr. Bronk was to become president of Johns Hopkins University and that he was to become chairman of a new department of biophysics that was to be located next to a building that housed the departments of biology and psychology. He said that he would like to form good relationships with both departments and that I could help him if I would consider selecting a dissertation in the field of either taste or olfaction because both Vincent Dethier of biology and Elliot Stellar of psychology were interested in the chemical senses! I was ecstatic. Both Mary Lou and I loved Johns Hopkins and we still had friends there. It became apparent to me later that Keffer Hartline knew of my previous conversation with Dr. Bronk about my interest in the chemical senses, but neither Keffer Hartline nor I knew that I would form a lifetime relationship with both Vince Dethier and Elliot Stellar and that Curt Richter would later ask me to do research in his laboratory after I received my Ph.D.

Back to Johns Hopkins

Several months later, all the students and the neuroscience component of the faculty moved to Johns Hopkins. I started my research with the blowfly by investigating the neural response of the peripheral nerve to chemical stimulation of the leg. After several months of failures I switched to studying the taste responses of the rat by recording from the chorda tympani nerve. The magnitudes of the responses were disappointing and after several months of failures, Hartline suggested I contact Professor Carl Pfaffmann at Brown University. Pfaffmann was most helpful and suggested I visit his laboratory. Several weeks later Mary Lou and I journeyed by bus to Providence, Rhode Island. This proved to be an excellent and helpful trip. I soon learned that Carl had been a postdoctoral fellow with Bronk at the Johnson Foundation for a year after Carl received his Ph.D. in physiology with Adrian in Cambridge! Thus, we had many common friends. Carl spent an entire day showing me the tricks of taste nerve recording. Not only did we become lifetime friends, but he taught me the importance of behavioral science in the study of the senses. Although I was a student and he a professor, he always treated me as an equal. At no time did this relationship ever change. In later years he sent me many of his newly granted Ph.D. students for additional postdoctoral experience.

After returning from Dr. Pfaffmann's laboratory, I used his methods to record from the chorda tympani of the rat. My first recording equipment was primitive. I pushed a 6-foot-long table against another one and suspended a black cloth from the ceiling to separate the two. Alongside my table was a Cambridge camera which contained a string galvanometer, a carbon arc, and a container for photographic paper 6 inches wide and many meters in length. The electrical activity fed into an electronic amplifier that was connected to the string galvanometer. The spark of the carbon arc was focused on the mirror of the galvanometer and the image reflected on to the photosensitive paper in the box. When the experiments were complete, I took the box into the dark room and developed the paper.

One evening I applied a high concentration of sodium chloride to the surface of the rat tongue and turned the amplifier to high. A tremendous volume reverberated throughout the room! Unfortunately, it was late at night and no one else heard the response. Because I had spent such a long time in taste research with no response as a reward, I wanted to share that night's experience with some of the other students. I measured the voltages across the speaker coils and then plotted them as a function of time as I placed various concentrations of stimuli over the surface of the rat tongue. The results were magnificent.

The next morning the first student in the lab was Ted MacNichol, a graduate student of Hartline's who was very experienced in electronics. He appeared impressed with the results and suggested I use a method to plot the results electronically rather than use the tedious method of manual plotting. I gave this some thought and decided to average electronically by using an RC network and a half-wave rectifier vacuum tube much as was used in AC power supplies. Thus, I had a running average of the magnitude of the neural activity in response to taste stimulation. This worked well, but the laboratory's electrical engineer, John Hervey, later designed a much improved instrument. I thought of using this method of measuring taste response to determine appropriate concentrations of taste stimuli to use when recording from single taste nerve fibers. This method was so well received by others who studied taste that it was quickly and widely adopted. It was particularly useful to researchers who studied the taste behavior of animals.

I researched many taste substances and accumulated many data, and now I needed to find a job. Dr. Hartline offered to help and I discussed my predicament with Mary Lou, who was now working in color vision at Wilmer Institute of Ophthalmology at Johns Hopkins Medical School. I remembered a short ad by Bernice Larson in Science magazine indicating that she was in the business of matching employer with employee. I answered her ad which resulted in a phone call from the dean of Arts and Sciences at Florida State University. Two weeks later, Mary Lou and I visited the university, toured Tallahassee, met other researchers who were recruited the year before, accepted an offer to begin September 1, 1950, and returned to Baltimore.

Planning for the Future

Shortly before we left for Tallahassee, Mary Lou and I had to plan for our future. What kind of a life did we want and how should we proceed? I already knew I wanted to teach and initiate a research program. What did Mary Lou envision? Her father was a very energetic engineer who had designed automobiles at a time when there were dozens of small companies competing for dominance in the industry. After the auto industry matured and only a few companies remained, he entered aeronautical engineering and designed the first variable pitch propeller for small planes. Thus, Mary Lou was raised in a family where the father was consumed by his profession.

Mary Lou chose physics as a career opportunity and obtained her M.S. from Johns Hopkins. She had experience as a scientist in a research institute, a university, and two industries before we arrived in Tallahassee. Now she was expecting a child within a few months. She decided that she would like to have several children and raise a family rather than continue a professional career in science. An integrated family was envisioned where the father as well as the mother undertook home chores and raised the children together. Mary Lou also wanted to continue to have some social contacts with scientists and share much of my travel to meetings. We agreed that we would take our children with us when traveling, either in the United States or abroad. This was accomplished even though by the time we first visited Europe and attended meetings in Stockholm, six young children accompanied us, the youngest being four years of age. Fortunately, all of her views of a family unit were similar to mine, but now we had to plan ahead or else we would never reach our goals.

First, we needed to live in Tallahassee within 10–15 minutes of the university so that I could eat lunch with the family every day and also return to the lab in the evening if needed. Furthermore, it would be very helpful if our home could be in a rural setting, with plenty of space and with construction codes that allowed me complete freedom to build whatever structures I needed.

Adjusting to Florida State University

We decided to move to Tallahassee by car. This presented a problem because my father had never owned a car, and none of my high school or college friends drove one. I had been in a car only a few times before graduate school! I knew little about how a car worked and nothing of how to drive one. I decided to employ a driving instructor for a week but first I needed a car. I soon purchased a used Kaiser sedan for $400. At the end of the week my trainer said I was ready for the exam but it would help if I gave the examiner 15 dollars for an incentive! That turned out to be good advice and the following morning, license in hand, we left for Tallahassee, not going over 40 miles per hour for the first 2 days.

Florida State University was completing its transition from a women's college to a coeducational university with a graduate program. I was assigned to the department of physiology, which consisted of five faculty, a large undergraduate program, and a new graduate program with about seven students. I was assigned to a 10 by 12-foot room which was to serve as an office and laboratory. A long hallway connected the office with the main corridor and I immediately moved my office door to the end of the twenty-foot hallway in order to gain more laboratory space. The Dean gave me $750 in research money which I used to buy a drill press, a table saw, an oscilloscope, and an audio amplifier kit that could be assembled easily. This left about $500 for animals and supplies for the remainder of the year. I wrote a letter to the director of the Bell Telephone Labs in New Jersey and requested any surplus electronic equipment that they might be able to send to me. Several weeks later I received a large wooden box full of such helpful items.

My first research grant was from the U.S. Army Quartermaster Laboratory and the following year I was also funded by the Office of Naval Research (ONR). The latter was important because ONR supported a large number of scientists who studied the senses. Within a few months, but before equipment arrived for the grant research, I received a letter stating that I would have to submit quarterly research reports. I was disturbed and phoned Dr. Hartline for suggestions. In his rather amusing manner he suggested that I should by no means send reports to Washington, saying there would be no one there who would understand them, someone would be obligated to file them, and I would be making work for many people. I sent no reports for 5 years but then one day received a letter of apology. ONR had lost all my reports! Would I please send a one-page report of my research findings that would cover the past 5 years! I never forgot this lesson and it saved me huge amounts of time in later years.

Teaching–Research Interactions

During my early years at Florida State I had to concentrate on teaching several courses, including one on human physiology for undergraduate nonscience majors and another on sensory physiology for graduate students. I soon learned that the graduate students had no knowledge of electronics and little of shop practice so I devised a course that included both. I purchased kits of parts for audio amplifiers, oscilloscopes, audio generators, and electronic voltmeters, which the students then assembled. All the equipment used vacuum tubes.

The sensory physiology laboratory included experiments in all the sensory areas. Each student had to learn to record cat cochlear microphonics, Limulus single optic nerve fiber activity, rat taste nerve integrated responses, frog skin tactile responses, cat Pacinian corpuscle responses to tactile stimulation, and several others from a selection of another six that included the infrared receptors of the rattlesnake! Each student had to collect all his own animals except the rat. Often a student attempted to do two of the laboratory experiments on the same animal to save both time and an animal. One of the students recorded the cat cochlear microphonics and then recorded the taste response from the chorda tympani nerve on the same animal. As a result, a whole new avenue of taste research was born! We soon learned that the cat responded to taste stimuli quite differently than a rat or rabbit. This was one of the most exciting discoveries for our laboratory in 1954, since it was commonly assumed that most animals were similar in their responses to simple taste stimuli.

Irving Fishman, Clarence Hardiman, Mohessen Nejad, and Henry Tamar (students who indicated an interest in working in the sensory area), and I decided to study the taste responses of other animals such as the guinea pig, hamster, cow, pig, sheep, raccoon, and dog. All the rodents responded to sodium more than to potassium, whereas the reverse was true for the carnivores.

I was excited with our findings and immediately phoned my friend Carl Pfaffmann. I was astonished to learn that he also was studying species differences in taste, so we agreed to publish at the same time and cross reference each other.

A Colleague's Offhand Comment Spurs Me On

The biochemistry and physiology faculty held joint seminars. In 1953 I was asked to present a seminar and decided to talk about a mathematical expression of the magnitude of taste response as a function of stimulus concentration based on the law of mass action. This mathematical expression allows one to calculate the magnitude of taste response as a function of concentration, magnitude of maximum response, and equilibrium constant of the reaction. The equation fitted the experimental data well. With some assumptions the binding energy could be calculated to be just a few kcal/mol, a very weak bond. I had never expected to publish this but one of the biochemists, Earl Frieden, thought the story was both interesting and important and urged me to publish. I reconsidered, obtained more data, and published my theory in 1954. This stimulated others to consider weak van der Waal forces instead of covalent chemical bonding in the stimulus–receptor interaction.

The Japanese Relationship

The majority of my early graduate students were World War II veterans who were receiving benefits under the GI bill. Some, such as Don Tucker, served in the marines and fought the Japanese on many Pacific islands. It was with some trepidation that I accepted my first Japanese post doc, Katsumi Kimura. He and his wife arrived in 1955. Not only did he come to the country of his former enemy, but he was introduced to our separate but equal process as soon as he stepped off the train in Tallahassee. There were two entrance doors to the station. One said 'colored' and the other 'white'. Which should he chose? Was he considered white or colored? Similar differences in culture confronted the Japanese daily but they never mentioned them to me until many years later.

Dr. Kimura used microelectrodes to record from single cells of the taste buds of the rat and hamster in response to stimuli representing the four basic taste qualities; salty, sour, sweet, and bitter. Their concentration–response curves were similar to those obtained from neural recordings.

Our excellent experience with Dr. Kimura led me to accept another dozen Japanese scientists to come to our laboratory at FSU during the next decade. Almost half of these researched the olfactory system with the late Don Tucker. About eight are now professors in Japanese universities.

Pensacola Meetings

The Office of Naval Research held the first of a number of symposia in 1955 at the Naval Air Station in Pensacola where much of their in-house research on naval aviation medicine was conducted. All the scientists (about 40) supported by ONR in the field of sensory systems were invited to attend by Captain Ashton Graybiel, of the U.S. Naval School of Aviation Medicine. These included many of the leaders of sensory areas such as Keffer Hartline, George Wald, Clarence Graham, Georg von Bekesy, Hallowell Davis, Glen Wever, Frank Geldard, Paul Nafe, Smitty Stevens, Carl Pfaffmann, and about 25 others, including juniors in the field such as Howard Baker, Dan Kenshalo, and me from Florida State University. We gave a short summary of our research and there was plenty of time for interaction. The lectures, figures, and discussion were all published by ONR. Three of this group would later receive the Nobel Prize! Those meetings were excellent for those of us who were still in the infancy of our careers. We were exposed to the newest in all the sensory fields and became personal friends with a number of leaders. They became acquainted with us and could judge the merits of our research. Tallahassee is not far from Pensacola, and we often invited individuals to visit us and talk to our students. Many years later I gave a lecture to the psychology department at the Massachusetts Institute of Technology and met a graduate student named Ann Graybiel. I was surprised and pleased to learn she was Capt. Graybiel's daughter. Dr. Ann Graybiel is now professor of Brain and Cognitive Sciences at MIT.

Dr. von Bekesy visited Florida State after the Pensacola meetings on several occasions. We often talked about research in taste and olfaction. He mentioned that he thought research in olfaction was not quantitative enough and also pointed out similarities between the tongue, the skin, and the basilar membrane. I was surprised to learn that he was working on a problem involving taste; he later sent me a paper where there was confusing terminology on stimulating a single papilla versus a single taste bud. He had read many of my papers and had examined pictures of single fungiform papillae from the rat, which contain only one taste bud. Human fungiform papillae, however, contain several taste buds. He thanked me for "extensive remarks on my paper on electrical taste," and then wrote:

> You may be interested in the history of this confusion. When I first described activities in the inner ear, I used the term "stimulation of the basilar membrane." I was told that the term was wrong, since the basilar membrane is a ligament, and one cannot stimulate that. It was this experience that made me reluctant to use the term "stimulation of the papilla," since the papilla again is supporting tissue mainly. Therefore I used the term "stimulation of the taste buds in the papilla." The experiments submitted for publication have already been going on for a year, so I got tired of this long term, and my subjects and I used the word bud.

Don Tucker's Unexpected Entry into Olfactory Research

One of the faculty at Florida State worked on thermal control processes in animals and used the opossum as his research animal. He was going to discard one of them and asked if I wanted to use it. I accepted the animal and asked a graduate student to look at the olfactory epithelium in the nose. The graduate student spent several days on the project and each day Don Tucker, an electrical engineer by training who was employed to build and repair our electronic equipment, made negative remarks about the student's skill. I found Tucker's remarks distasteful and thought I would teach Tucker a well deserved lesson. I told him to take over the project I had given to the student. Contrary to what I expected, Don did an excellent job and proved to be an outstanding researcher. I terminated his work as a technician and placed him in a research position to study the opossum olfactory tissue.

The sheet of olfactory tissue that Tucker first removed from the opossum was rich in fine olfactory and trigeminal nerve fibers. Odors from cloves, cajeput, eucalyptus, oranges, coffee, etc., excited the recorded single fibers but no two fibers responded in the same way. Were they olfactory or trigeminal responses? The action potential size and type of odor stimulus could not define the nerve source and we had to devise another preparation.

We decided to leave the olfactory tissue intact. (Opossums are plentiful in the Tallahassee vicinity, are easily handled, and have a large area of olfactory epithelium in the snout.) We used small strands of both olfactory and trigeminal nerve bundles for recording. The olfactory system responded sooner and the neural firing was more regular than that of the trigeminal.

We found that autonomic activity greatly affected the magnitudes of olfactory and trigeminal neural activity. Usually, increased sympathetic stimulation resulted in increased olfactory and trigeminal activity, whereas parasympathetic responses were more complex. Because many events can affect these responses, it was interesting to see the olfactory response increase when the experimenter clapped his hands or when he touched the naris with his forceps. The reverse is also true: the response to an odor can affect respiratory and cardiac activities. The results of these chemosensory experiments emphasized how integrated are the body's functions and demonstrated the importance of requiring the study of mammalian physiology for all of our students.

The possibility of recording olfactory action potentials was questioned, particularly in Europe. The olfactory nerve diameter is about 0.2 μm. When I had difficulty recording from chemosensory nerves of insects when I was a student, I was often told that the message was perhaps transmitted by the spread of small local potentials rather than by action potentials. In addition, it was known that the olfactory epithelium in vertebrates is usually near the olfactory bulb. However, we knew that in many fish the two tissues were separated by a large distance, sometimes more than 10 inches, and that local potentials could not spread over such large distances.

One day I received a phone call from Lord Adrian who was visiting Rockefeller University. He asked if I would come to New York and talk with him and with Professor Herbert Gasser who had studied the anatomical and electrical properties of the olfactory nerve. I was delighted and went to New York to spend an afternoon talking about the olfactory system. I believe they became convinced that one can, indeed, record electrical activity from olfactory nerve strands that contain but one active fiber.

Recording from Human Taste Nerves

As a student I had read about the discovery by Galvani (1737–1798) that the human chorda tympani nerve passes through the middle ear on its travel from the tongue to the higher nervous system. Some time later others demonstrated that if the human ear canal were filled with salt water and electrically stimulated, the subject perceived a taste. Quite accidentally in 1954 I also came across a paper by Dr. Samuel Rosen, an otolaryngologist who showed that he could cure certain deafness (otosclerosis) by mobilizing the footplate of the stapes in the middle ear while the patient was under local anaesthesia. During this operation he often cut the chorda tympani nerve to get a better view of the foot of the stapes. Because much of the chorda tympani nerve is not embedded in tissue as it traverses through the middle ear, I wondered why not try to record the neural activity while the tongue is chemically stimulated? When I returned to Tallahassee I wrote to Dr. Rosen and suggested we try recording from his patients. In August he replied, noting that he would be willing to cooperate. I was excited because the patients might also tell us something about their taste sensation while we record from their taste nerve.

Clarence Hardiman, an FSU graduate student, and I spent several weeks with Dr. Rosen at two different hospitals in New York City trying to record suitable neural activity without success. We realized finally that we had two major obstacles. First, the injection of a local anesthetic often impaired the function of the chorda tympani taste nerve from which we were trying to record the electrical activity. Second, Dr. Rosen, as surgeon, was the only person allowed to manipulate the nerve before recording. Both Clarence and I had much experience with chorda tympani nerve recording, but it was difficult to explain our knowledge to Dr. Rosen without actually touching the patient. We spent about 3 weeks in the operating room without success.

The success of Dr. Rosen's new method of stapes mobilization spread quickly throughout the world. Two or 3 years after our unsuccessful attempts at taste nerve recording, Professor Yngve Zotterman and Dr. Herman Diamant tried the same experiments in Umeå, Sweden with some success. In 1959, they published beautiful recordings of human neural responses to various tastants. I later visited Umeå where Zotterman and Diamant showed me recordings in the operating rooms. The reasons for their great achievement—the use of general anesthetics and careful handling of the chorda tymani.

Building Our Home

My monthly salary in 1950–1951 was $400. Although the economy was much improved by the end of World War II, my concern for the future remained. In the meantime our family size was increasing. Somehow I had to protect my family from any downturn in the economy. We therefore purchased 10 acres of farm land about 6 minutes from the university and I started to lay a house foundation in January 1955. In Tallahassee, almost every day can be an outside workday, so building progressed well. By May of the same year I had finished the roof. The house was about 35 feet wide by 50 feet long.

When a problem occurred that I did not know how to solve, I visited other houses being constructed to learn the answer. I finished the electricity and plumbing by the end of 1956 and we moved in July 1957. I had not yet finished the inside walls but each month we lived in the house was a month for which I paid no rent. As the family grew to six children (five boys and one girl), we added another room. As my boys grew, their participation in home affairs also increased. To each we assigned daily chores of planting the garden or feeding the chickens, turkeys, cows, pigs, and a horse.

Life Span of Sensory Cells

The library is a good place to broaden ones approach to science. Since the library at Florida State did not have much of the older science literature, I decided in 1959 to use the excellent library at Woods Hole. I obtained a key to the library and the use of a desk for two weeks. Among the articles I read were several on cell life span and cell replacement in epithelial tissue. I also learned that in 1914 M. Heidenhain, the great histologist, thought taste cells may have a short life as do skin cells. Other histologists did not agree because few mitotic figures were found in taste buds when compared with basal cells in the tongue epithelium. However, I often wondered how taste cells can be surrounded by hundreds of different chemicals at various concentrations and not be injured. Perhaps Heidenhain was right, and new methods would prove or disprove the concept. Many students of skin replacement used the mitotic inhibitor, colchicine, to study cell replacement. Our initial studies with colchicine indicated that cells surrounding the taste bud underwent division and that the daughter cells could enter the taste buds. However, a chance engagement with Dr. H. Quastler of the Brookhaven Labs resulted in an offer to visit his laboratories and learn how to study cell turnover more quantitatively with tritiated thymidine.

A graduate student, Ron Smallman, and I accepted his offer to learn quantitative methods for measuring cell turnover and replacement. We then learned, as a result of quantitative techniques, that rat taste cells are indeed replaced and that half of them are replaced within 9–10 days. Because the tagged population declines exponentially, one-quarter of the labeled population is still present after 18–20 days and one-eighth after 36–40 days.

Since all the rat cells that undergo cell division within the period of our taste cell labeling are also labeled, several other tissues were also studied in our laboratory by various students, visiting scientists, and fellow faculty members.

We also labeled other animals, such as fish, that possess electroreceptors. They appeared to be replaced much as taste cells are. Another student, Janet Wise, studied the turnover of the cells at the center of the rat eardrum and their migration to the periphery of the eardrum.

We thought that there were similarities between auditory receptors and taste receptors, but we studied rat auditory receptors without success. When Hallowell Davis visited our lab, he made it known that this was not a very good idea. He said that histologists had never seen mitotic figures in auditory cells. I replied that perhaps the auditory cells were replaced only after auditory damage; however, we had little experience in cutting and preparing bone-embedded tissue, and did not proceed with the project.

We examined many tissues after rats were injected with tritiated thymidine for our taste studies. One of them was the olfactory epithelium that contains many millions of olfactory receptors. Unlike taste cells which have an epithelial origin, olfactory cells are of neural origin. We observed cells in the olfactory epithelium that were radioactive. Closer scrutiny indicated that these may be olfactory receptors.

Pasquali Graziadei, who later joined our Psychobiology group, was a professional neuroanatomist with very broad experience. Our previous experience with the study of auditory cells suggested to me that someone much more familiar with anatomical studies should study the olfactory system. Time determined that this was a wise decision. Furthermore, Dr. Graziadei published a number of excellent papers on the olfactory epithelium as well as on the olfactory bulb. These studies should be of interest not only to those studying sensory systems but also to those interested in spinal cord and brain repair processes.

Expanding the Research Opportunities

One Thursday afternoon in 1958, I received a phone call from someone at the National Institutes of Health (NIH). The caller wanted to know if I would be interested in applying for a training grant to expand my research. I replied no, saying that I already had enough work to do. The caller persisted and asked if he could visit me the following Monday.

After my visitor left, I reconsidered my initial reaction and outlined a plan and budget. The next month a five-man committee came to see me. My tentative budget included salaries for a secretary, histologist, electronic technician, a half-time machinist, and five postdoctoral stipends. One member of the committee, in particular, did not think I needed so much support staff. My reply was that Florida State was just forming a graduate program and that the facilities were not adequate. If I trained postdoctoral fellows, I would need the same facilities as my competitors at the major research universities up north. To my surprise the committee was convinced and NIH funded the grant which later was extended several times until its termination in 1980.

International Symposium on Olfaction and Taste

Graduate students flooded the universities in the 1950s due to the GI bill. By the end of the decade chemical senses were no longer being studied by only a small group of physiologists and psychologists. In 1959, Walter Rosenblith sponsored a symposium on sensory communication at MIT. Carl

Pfaffmann asked Yngve Zotterman from Stockholm and me to visit his laboratory at Brown University and meet his students during late afternoon. This we did, and the three of us then talked about taste as we sat around a small table. I said that it would be nice if my students and Carl's could get together every few years as they had much in common. Yngve thought this would be good and wondered if there was some way that his students could also meet our students. I jokingly replied that my students certainly would like to visit Sweden! Immediately, Yngve said that his position as Secretary of the Wenner–Gren foundation in Stockholm might allow him to invite all of us. Carl and I laughed and did not take Yngve seriously; however, Yngve did organize an excellent meeting in Stockholm and this in 1962 became the first of a series entitled International Symposium on Olfaction and Taste (ISOT), held every 3 years since then.

ISOT was a jewel for many of us. However, all the speakers were invited, and the cost of international travel limited the number of students who could attend. Furthermore, whereas most of our research monies were coming from the medical and industrial communities, we decided that a new society (ACHEMS) should be formed with annual meetings in the United States with adequate attention given to industrial and health needs. The group meets in Sarasota, Florida once a year, but this meeting focuses on basic research with little attention to medical or industrial needs.

Seattle World's Fair

After the Soviets launched Sputnik to orbit in 1957, President Kennedy and the American military became concerned about the adequacy of science and technology in the United States. Their concern included how science and mathematics were taught in the schools and how well the public was informed about science. An international World's Fair was soon to be held in Seattle in 1962, and the President's science advisors (including Detlev Bronk, Harry Harlow, and Paul Weiss) suggested that the U.S. exhibition should center on science and technology. A budget of about $10 million was allocated to the Department of Commerce for this purpose. Five modern buildings were designed and constructed. Professional science writers were contracted to develop scripts that could be used by industrial designers for posterboard exhibits on various science themes. It soon became apparent that a professional scientist was needed to oversee the design process, develop new exhibits that used material other than posterboards, expand the exhibits on biology and animal behavior, and coordinate the many small but important interfaces with the scientific community. For these objectives, Athelstan Spilhaus, Dean of Technology at the University of Minnesota, was appointed Commissioner. Spilhaus was a trained oceanographer, a writer of popular books on science, and author of a syndicated comic strip on science. I was appointed Science Coordinator of the U.S. Science Exhibits in Spring 1961.

After working in Washington, DC for several months, it became apparent that I needed to be in closer daily contact with the exhibit designers. I moved my office to Madison Avenue in New York to one of the offices of the industrial design firm, Teague Associates. I felt strongly that the exhibits must contain more than posterboards. We designed a real laboratory and made it ready for operation, so that the public would get a better idea of what science was all about. It contained much of the equipment found in a typical university laboratory. In addition, each morning one of the demonstrators would dissect the optic nerve of *Limulus* (horseshoe crab), and record the electrical neural activity in response to light stimulation, and display it on a large overhead oscilloscope and play it on an audio amplifier. The demonstration was impressive and the audience asked questions about both the animal itself and the electrical activity within their own bodies.

My previous experience with animal behaviorists also became very useful in planning the exhibits. For example, I had read an article by B. F. Skinner at Harvard University about pigeons playing ping pong. I thought that experiment could be a center attraction for our exhibits on animal behavior. I phoned Professor Skinner but he informed me that such an exhibit would be too difficult to put together. He suggested that I visit one of his former students, Dr. Donald Blough at Brown University and our visit culminated in the best exhibit of the Fair! We had a continuous show of working pigeons displaying color discrimination. Similar personal contacts with Professor Eckard Hess at the University of Chicago, Professor Harry Harlow at the University of Wisconsin, Professor Paul Fields at the University of Washington, and many others resulted in an excellent series of animal exhibits.

It soon became obvious that we needed someone to be available to the public to answer questions about the exhibits. I suggested that we employ 40 college women. We had more than 120 applicants, and I interviewed each one. Most had no college science courses, and we therefore had to employ someone as a trainer and an overall coordinator. I needed someone I knew and could trust to get the job done and who would interact well with the young students. We employed Ron Smallman, a former graduate student of mine, who did an excellent job.

My family and I moved to Seattle in Fall 1961, although I kept my office in New York for several months more and visited Seattle every weekend. The fair opened officially in Spring 1962. Because Dr. Spilhaus had many other commitments, I was assigned the additional task of being on hand when honored dignitaries arrived or when television appearances were needed. As a result, I met many interesting visitors such as Jonas Salk, Walter Cronkite, and the Shah of Iran and his wife, and appeared on many

TV programs, including a 15-minute talk about cell turnover on a morning show. The latter produced an embarrassing incident when the host asked what the relation was between cell turnover and reincarnation!

We returned home to Tallahassee in Fall 1962. When I first visited Florida State for an interview, the dean had made it very clear to me that each faculty member had three duties, namely, teaching, research, and service. I now felt that I had amply fulfilled my service commitment and needed to concentrate on my graduate students whom I had left behind. While working on the exhibits I visited my laboratory only four days a month but several postdoctoral fellows, including David Moulton, had been available to help the graduate students. I also needed time at a good library.

Formalizing Our Psychobiology Program

In 1964 the National Science Foundation initiated its Centers of Excellence throughout the nation. The Florida State University vice president appointed a seven-member committee, including Dan Kenshalo and me to represent psychobiology. The committee concluded that Dan and I should present a budget of about one million dollars. The psychobiology budget included many technical positions and 14 new faculty to be shared by the departments of psychology and biological sciences. The State of Florida was obligated to keep the faculty intact after the grant period expired five years later. The Center was awarded, the State of Florida kept its word, and as this chapter is being written the number of faculty and staff positions remains the same as it was after the grant was awarded.

Nature's Taste Modifiers

Can one modify a taste? Can one change a sour taste to a sweet taste? Can a sweet taste be completely inhibited? Can bitterness be completely suppressed? The highest authority says yes. According to the Bible:

> When they came to Marah, they could not drink the water of Marah because it was bitter; therefore it was named Marah. And the people murmured against Moses, saying, "What shall we drink?" And he cried to the Lord; and the Lord showed him a tree, and he threw it into the water, and the water became sweet. (Exodus 15:22)

In 1964 I decided to search for possible taste modifiers. I learned about a red fruit about the size of an olive that grew in West Africa. It was supposed to produce sweetness when eaten before eating sour food. I located some specimens, called miracle fruit, in a nursery in south Florida. I purchased several small plants and planted them in the greenhouse at Florida

State. When I had about two dozen mature plants with berries, I tasted them. They were excellent in taste and when eaten before sour lemons, the lemons then tasted very sweet. The sweet taste was natural in character, unlike that of saccharin.

Upon producing a good crop after three years of propagation, I decided to determine the chemical nature of miracle fruit. I followed the usual procedures of organic chemistry by trying to extract the active principle with chloroform, acetone, benzene, and other reagents, but without success. Either it did not have the properties of an organic substance, or else we were degrading it. After many months of extractions, I wondered if there was something in saliva that was important that I was overlooking. We tried extraction with saliva and we were successful! We made an artificial saliva without the organic constituents and hit the jackpot! We knew how to extract the ingredient with only inorganic substances.

In 1967 Dr. Kenzo Kurihara, a protein chemist, joined our laboratory and I turned the problem over to him. This was serendipity because the active ingredient in the berry was a protein! No one expected this because all known tastants at that time were small molecules. When Kenzo determined the molecular weight to be about 44,000, I felt uncomfortable and hesitated to consider publishing the results. After more experiments he convinced me that the ingredient was indeed a protein and we sent a paper to *Science.* We waited for almost 5 months before it was published in 1968. In recent years Dr. Yoshie Kurihara in Japan has determined the amino acid composition and sequence, but we still do not have a complete understanding of how this protein stimulates the taste cell to modify its response.

Protein Synthesis and Transport in Olfactory Nerve

As a student at Hopkins I had learned of the possibility that the polio virus could travel from the nose to the brain by using the olfactory pathway. I also knew that taste buds disappear if the nerve connection is cut and that taste buds regenerate when the taste nerve again innervates the buds. Thus, I was interested in chemical transport by the nerve axons. Paul Weiss told me that he used the frog olfactory nerve to study axonal flow. This nerve has a large and homogeneous population of C fibers. In 1970 my colleague at Florida State, Dr. Dexter Easton, informed me that the garfish, which is plentiful near Tallahassee, has an accessible olfactory nerve bundle more than 10 inches long. Furthermore, the bundle contains a homogeneous population of millions of small C fibers. This encouraged me to use a row boat at a local lake and fish for gar at least 3 feet in length.

I used this preparation to study colchicine blocks of the olfactory nerve. Guenter Gross, then a new graduate student trained in engineering, became interested in this preparation for a dissertation. He did a series of excellent studies of axonal flow in C fibers and determined a velocity of 222 mm/day in olfactory fibers with a 0.244-mm diameter. These highly quantitative methods are excellent for the study of transport of proteins with radioactive labels. The labeled amino acid is placed into the nostril where the olfactory epithelium is both visible and easily accessible. Dr. Cancalon, a postdoct in my laboratory, studied the various subcellular fractions of molecules that are synthesized in the olfactory nerve cell bodies and rapidly transported in the olfactory nerve as well as those slowly transported.

Because there is a direct route from the nose to the brain, one wonders whether other substances placed into the nose, such as medicines or pollutants, can enter the olfactory nerve bundle and also pass directly to the brain.

Gustatory Nerve Synthesis and Transport

I decided to use axoplasmic flow to determine what fraction of the cells of the taste bud are innervated. The nodose ganglia of the rat which contain the cell bodies of the nerves that innervate the taste buds of the epiglottis, were injected with labeled amino acids. If the nerve innervates a taste cell, I thought, labeled molecules may pass from the nerve ending into the innervated cell. Six hours after nodose injection of labeled amino acids, cells of the taste buds were heavily labeled. Thus, there appeared to be an axonal route for molecules that are synthesized and labeled in the axon's cell body to cells of the taste bud. (These experiments also demonstrated a method whereby the neural pathways can be labeled.)

Determinants of Taste Cell Characteristics

One of the most important questions in the area of chemoreception is, what determines the response characteristics of taste cells? Is it the nerve that innervates them or properties at the location of the taste buds? We know in humans that we taste sweet things better in the front of the tongue and bitter tastes are more pronounced in the back. However, not all animals exhibit this same taste pattern. Irving Fishman showed that the taste buds on the front of the tongue of the fox are sensitive to bitter substances, and this finding was recently verified in my laboratory.

In 1987, Mohssen Nejad, a postdoc in my laboratory, cross-regenerated the greater superficial petrosal nerve of the rat, which normally innervates the palatal taste buds, with the chorda tympani nerve, which normally innervates the anterior two-thirds of the tongue. The taste response characteristics followed the area in which the taste buds were located—not the innervating nerve. These findings were similar to those of Dr. Bruce Oakley's laboratory. The effects of bilateral sectioning of both of these nerves on the sweet taste in the rat were studied by Krimm and others in 1987.

Looking Back

Many years ago I was having dinner with a group of food industralists in England. During our conversation the elderly man next to me asked what was my profession. I replied that I was a professor. He said he was president of one of the largest food companies in England and would trade his job for mine any day. He was so busy he had no time to travel, to visit other people, or to interact with the youth of the day! I traveled all over the world and interacted with many different kinds of people without any cost to me. Usually my wife traveled with me and we took the children with us when they were young. Later, only one or two of them accompanied me: Steve and Allan to Japan; David to Iran, Turkey, England, and Spain; John to the mountains of Venezuela to hunt special sweet plants; Dianne to Russia.

I remember the comment of Vernon Mountcastle a number of years ago. He said, "Lloyd, we were born at the right time. We started our research careers when research money was becoming plentiful. As research money becomes scarce, we look forward to retirement." The change that affects me most, however, is not only money but the fact that now there is less freedom to get up in the morning with an interesting research idea and go into the lab and pursue it without first getting approvals from everyone concerned followed by making a report to someone in Washington who files it where it forever remains, unread. However, the race was worth running.

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