2019 Life Achievement Award

Edwin W Rubel, PhD

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Background

Edwin W Rubel (Ed) was born in Chicago IL, and grew up in a suburb of Chicago. His father was a graphic designer who developed a small graphic design company. His mother did the accounting for the company. Academics were not a major focus of the Rubel family, and did not occupy a central part of Ed's life until late in college. Most of the time, he played sports with the other neighborhood kids. Ed's sister was an artist from early childhood and that continued throughout her life. Ed attended Michigan State University, with the short-term goal of becoming an intercollegiate wrestler. That didn't work out, but he met Wendy Knutson, now his wife of 55 years. They married during his senior year at MSU and he immediately started Graduate Studies in Psychology, with an intended emphasis on Industrial Psychology and modeling. During his second year, Ed enrolled in a Physiological Psychology Methods course taught by Glen Hatton and John I. Johnson, and he found a home. Ed's interests change to the fledgling field of neurobiology which sought to explain how brain mechanisms can explain animal behaviors. He completed a Masters Degree with a study of imprinting in fledgeling quail and then joined the sensory physiology laboratory of John I. Johnson. There, Ed first participated in, and then led, neurophysiological studies of somatic sensory pathways of a variety of mammals, including neonatal cats. His doctorate was awarded during the tumultuous year of 1969, and he began a brief postdoctoral fellowship at UC Irvine at year's end. His first child, Trevor, was born in Laguna Beach in June of 1970. In January of 1971, Ed joined the Psychology and Biology Departments at Yale University as an Assistant Professor, and child number two, Lisa Ann, was born the next year. Ed's lifelong passion, the study of auditory system development and plasticity, began when he started his own lab at Yale. In 1978, Ed took accepted a Full Professorship at the University of Virginia, and the family moved to Charlottesville. In 1986, Ed accepted an appointment as Professor of Otolaryngology-HNS and Physiology & Biophysics at the University of Washington, and the family moved to Seattle. Over this period, Wendy skyrocketed from Special Education Teacher to receptionist at a hippie Laguna Beach restaurant, and then to pursue her professional interests as a then a Substance Abuse Councilor in Charlottesville and Seattle. Trevor and his family live near Seattle; Lisa and her family live near San Diego, in Leucadia. Ed's four grandchildren range in age from 13 to18.

Scientific Contributions of Edwin W Rubel

Ed has made significant contributions to science at four levels. First, he has carried out careful and complete experimental studies that significantly add to our understanding of nature. Second, he has solved a significant problem posed in the scientific literature. Third, he has initiate new fields of inquiry.

Fourth, and perhaps most importantly, Ed has mentored and launched the independent career of dozens of students and postdocs, thereby ensuring the continuity of scientific discovery.

Most of the work of the Rubelab academic family focuses on development of hearing and the cellular components comprising the auditory system. This work has impacted our current understanding of the auditory system at several levels, from behavioral development to subcellular mechanisms that regulate development of cells in the brain and inner ear. The work from his laboratory has advanced our general understanding of nervous system development and has had clear impact on the future of clinical medicine. Listed below are seven important and specific areas to which Ed has contributed.

Providing a scholarly foundation for the field.
In 1978 Ed Rubel published the first comprehensive review on the development of the auditory system. He compiled and organized an exhaustive review of the literature on development of the inner ear and auditory nervous system since the discovery of the organ of Corti. This highly cited review provided a comprehensive background for most people who would later join this field, and continues to serve as the most inclusive summary of the literature prior to 1978.

The avian auditory system.
Rita Levi-Montalcini, winner of the 1986 Nobel Prize in Physiology or Medicine, performed a very influential study on the avian auditory system development in the 1940's. However, it was not until the 1970's that the importance of this system for understanding sensory system development was appreciated, largely through the research from Ed's lab and work of Jim Saunders. These studies provided an in-depth structural, functional, and cellular analysis of this system, ranging from quantitative descriptions of the physiological characteristics, organization, and connections that support binaural processing of sound. Most importantly, each of these studies provided detailed quantitative descriptions of the development of cellular and system-level phenotypes. These foundational investigations provided the bases for all current experimental work that uses the avian model to address neurobiological questions about hearing.

Cellular mechanisms underlying experiential influences on brain development.
Since 1974, Ed and his colleagues have used the brainstem auditory pathways of birds and mammals as a model with which to systematically examine the role of activity in development and maintenance of neurons in the brain. His findings in this area have been particularly influential because they quantify both the rate and magnitude of cellular changes that accompany manipulations of neural activity during development. For example, Ed's studies of dendrite structure in the brainstem nucleus called nucleus laminaris provide the most direct evidence that localized input to a neuron membrane surface independently regulates the structural integrity of its subcellular elements. His ongoing investigations of the avian and mammalian cochlear nuclei have elucidated the intercellular and intracellular pathways underlying activity-dependent regulation of the molecular pathways that promote cell death or support cell survival. The clinical importance of this information emerged with the recognition that sensory prostheses can maintain the structural integrity of the CNS following injury.

Development of the Place Code.
Ed and his colleagues answered to longstanding paradox of auditory development: Why does high frequency hearing appear later in development, when the cochlea develops from its high frequency, basal region, to its low frequency apex? A theoretical explanation was advanced in 1978, and the empirical studies published in 1983 demonstrated profound developmental changes in the functional organization of the inner ear. Specifically, Ed's group showed that the coding of frequency along the basilar membrane changes during development such that a given basal position gradually comes to respond to higher

frequencies. This was the first evidence for significant modulation of the fundamental organization of the inner ear, and pioneered a new area of investigation in auditory neuroscience.

Hair Cell Regeneration.
Beginning in 1987, Ed Rubel and his colleagues discovered that birds can regenerate damaged and destroyed hair cells in the inner ear. This observation, along with parallel observations by Dr. Douglas Cotanche's, were the first examples of inner ear hair cell regeneration. They have led to an entirely new field of investigation, the goal of which is to restore hearing and balance in people suffering sensorineural hearing loss. Prior to 1987, it was assumed that hair cell loss caused permanent and irreversible hearing and balance disorders. Ed and colleagues have gone on to identify hair cell progenitors, to show that regenerated hair cells mediate hearing and balance recovery, to develop *in vitro* preparation of mature avian and mammalian inner ear sensory epithelium, to demonstrate that potential progenitor cells reside in the mature mammalian inner ear sensory epithelium, to begin investigating cellular/molecular mechanisms underlying hair cell regeneration in birds, and to initiate the discovery of molecular methods that trigger hair cell regeneration in mature mammalian inner ear. These and other pioneering studies from the UW group played a key role the establishment of a new area of molecular neuroscience with the potential for dramatic clinical impact.

Hearing Research Center.
Ed Rubel founded, and served as the original leader, of a major new center for hearing research at the University of Washington. The Virginia Merrill Bloedel Hearing Research Center uniquely combines fundamental and clinical investigations of hearing and hearing disorders. Since its inception in 1989, this center has grown to over 50 faculty affiliates with research ranging from human genetics and perceptual development to molecular biology of hearing disorders and to medical and surgical treatments of hearing loss. Ed served for 5 years as the Founding Director, and was succeeded by Drs. George Gates, and then Jay Rubinstein.

Preventing Hearing Loss.
Since joining the faculty of the University of Washington, Ed and his colleagues have studied the cellular pathways underlying the loss of mechanosensitive hair cells used for hearing and balance. These studies took an unexpected and unique direction when the Rubel lab and the lab of Dr. David Raible began a collaboration that resulted in a new approach to the discovery of drugs for hearing protection. In 2001 they began using the hair cells of the lateral line organs in zebrafish larvae as a platform for discovering genes and drugs that could protect hair cells from degeneration due to ototoxic drugs. This led to a high throughput small molecule screen that yielded sarong candidate molecule that provided robust protection of zebrafish hair cells exposed to aminoglycoside antibiotics and protection of hearing in mammals. After further development and testing, this drug ORC-13661, has been approved by the FDA for testing in humans to prevent antibiotic-induced hearing loss. As a new chemical entity, ORC-13661 is patented by the University of WA, and licensed to Oricula Therapeutics. Clinical trials are underway and it may be the first drug to effectively prevent hearing loss due to ototoxic therapeutic drug treatment. This seemingly successful translational research achievement caps off nearly a half century career devoted to hearing science, from cells to patients.

Epilogue
By far the most rewarding, and what is responsible for all the success of the Rubel lab, is the wonderfully smart, wonderfully enthusiastic and wonderfully dedicated students, postdocs, professional staff, and faculty research colleagues that have worked together over the past 40 years. The scientific traditions and areas of inquiry started by this group continue today in labs widely scattered around the world and will live on indefinitely, while all the specific findings of the science are surpassed by those that follow in our footsteps.