A Serendipitous Spiral Path to a Career in Hearing

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A Package in the Mail

The package weighed about 25 pounds. I knew it was coming, and it was like so many that I received or sent in the following decades, but this was the first. Far bigger than I expected, the size doubled the excitement. Opening the box, I found an intimidatingly large, heavy cube of bone, quite solid, ivory colored, and with an odor that was not repellent but with a mustiness that made clear it was the real thing, a chunk of a mammalian skull that promised to hold an "ear." The specimen had been sent by William (Bill) Watkins, who had been gracious enough to obtain it during his examination of a dead sperm whale. Bill was a colleague of my doctoral thesis advisor, Douglas Wartzok, and knew that I needed whale ears for my recent research project, but whale ears were not items one could trivially obtain. Indeed, access to any marine mammal ear was literally a matter of serendipity; would a whale or dolphin regrettably strand and die and if so, was there a chance to extract the tissue needed to explore how they hear in water.

Why would anyone pick a project dependent on chance, lucky, or serendipitous events. One answer could be naïveté or perhaps plain foolishness. Little did I realize at the start how much of my future work would depend on numerous instances of repeated, sometimes infrequent, fortuitous events. Serendipity was not the term that came to mind when this package arrived. In fact, the main reason I was now looking for whale ears and hoisting a package containing one of the largest ears on earth, was the result of a string of unpredictable events that at the time did not appear to be fortuitous.

The Concept of Serendipity

The term "serendipity" is widely acknowledged to have originated in the writings of Horace Walpole in a letter he wrote to Horace Mann in 1754 (Serendipity, Wikipedia) in which he described his novel word to mean a happenstance that leads, unexpectedly, to a discovery or insight. However, the concept of discovery by a fortunate, chance event has a far older provenance. In 1747, Voltaire published *Zadiq*, a philosophical work on the effect of fate. Both Voltaire and Walpole noted their inspiration came from a Persian tale, "The Three Princes of Serendip," that tells the story of three banished brothers who deduce from a series of tracks and marks left in the dirt that they were made by a camel that was lame and blind in one eye, ridden by a pregnant woman and carrying sacks of grain and wine. On reporting that they know where this camel may be, they are first accused of theft of the camel and sentenced to death, but after explaining their reasoning, are rewarded. There are even earlier versions of this parable of deductive reasoning from serendipitous chance clues dating back to sixteenth-century Venice and even in the writings of Rabbi Johanan bar Nafcha (180-279 CE) in the Talmud.

Later writers, including Huxley, Edgar Allen Poe, and Arthur Conan Doyle (Shades of Sherlock!) certainly made use of the same idea that there is power in observation of

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potentially relevant traces of events, if the eyes, ears, and brains of the individual are open to the unexpected. In science, examples of serendipity are even more frequent, such as the discovery of penicillin by Fleming from a contaminated bacterial culture, the discovery of Rh factors by Landsteiner and Weiner, and the nearly simultaneous discoveries of radioactivity by Becqueral and X-rays by Roentgen.

Some discoveries are not so evident nor quickly accepted, like the competing theories of how neurons work by Golgi (reticular theory that neurons are a fixed network) versus Ramon y Cajal (neuron theory of dynamic individual neurons producing a variable system). Both theories were based on observations on the same tissues using the same silver staining technique invented by Golgi. Despite their contradictory conclusions, the work of both was acknowledged in a shared Nobel Prize (Grant, 2007). The controversy between "neuronists" and "reticularists" continued well into the twentieth and twenty-first centuries, with translations of relevant publications by Cajal published in 1954 with commentaries and reviews by others published as recently as 2005 (Guillery, 2005).

Similarly, there can be unintended, adverse consequences to a serendipitous discovery. The eponymous Nobel Prizes were created by Alfred Nobel, who invented dynamite as an alternative to nitroglycerin to provide a more controllable explosive that would benefit mankind. The uses of explosives, of course, went fearfully far beyond those Nobel envisioned.

Chance Encounters and Positives from Negatives

The box described in **A Package in the Mail** was the start of a "project" to examine whale ears on which I was embarking as a new graduate student. It had sprung from a string of what I considered bad luck tinged with what proved to be invaluable chance encounters that continue to shape my research. My applications to doctoral programs had gone well, with several acceptances to prestigious and respected laboratories. First among them was an opportunity to work with Arthur (Art) Popper. By a quirk of fate, the arrangements for admission to his laboratory fell through when his departmental chair died unexpectedly. The delays that reapplication would have entailed resulted in my accepting another opportunity but meeting him was consequential to not just my intended graduate work but also to my growth as a scientist. I am continually grateful that Art has continued to be an extraordinary and invaluable mentor to me even though I was not able to formally join his laboratory. That disappointment, though, resulted in another opportunity.

The next step was hopeful but also a bit quirky. I was accepted into the laboratory of Douglas Wartzok, to whom I am equally grateful for his guidance and friendship but also his extreme patience with my quixotic path as a student. I had applied to work with Doug because of his excellent reputation as a marine mammal scientist. My goal was to work on neural processing of underwater sound in dolphins. I had trepidations about how things would go because Doug was a faculty member in the Johns Hopkins School of Hygiene and Public Health (JHSPH), Baltimore, Maryland, now known as the Bloomberg School of Public Health. The combination seemed odd, but it turned out that his appointment was related to animals as vectors, and he actually did have live seals in the building!

Another good sign was that the National Aquarium in Baltimore, Maryland, had just acquired several dolphins for its new tanks, and discussions began on access to them that would have entailed noninvasive recordings of brain activity. Shortly after I completed preliminary exams, expecting to start work with these dolphins, there was an unexpected event; the dolphins at the aquarium disappeared. In fact, they were removed to a facility in Florida to recover from multiple potential stressors, including sounds resulting from throngs of visitors and intermittent vibrations of their tank walls from adjacent maintenance equipment.

This was a setback, but the animals were expected to return within a few months. I opted to use the time to learn as much as I could about auditory systems, particularly those of aquatic mammals. It shortly became apparent that a wide variety of literature on whale and dolphin hearing did exist, but there were several opposing theories, not only about how but also what they could hear. In part, this was due to limitations on what forms of experiments and measurements could be made, not to mention the practicalities of adapting any recording gear to operate in water on animals of such exceptional size. Atop that, images in the literature on the anatomy of whale ears suggested there was great variability in ear structures but little on whether these variations resulted in differences in hearing across species.

A wise person might have said, "Back to models and measures of hearing in mice." Then the package arrived. Several elements converged that day. First, the received specimen was a large and dense block of bone with no hint of where within it there was anything resembling an ear. Second, the Johns Hopkins Department of Radiology was just across the street from our laboratory. Third, the head of the Neuroradiology group was Arthur Rosenbaum, who was amazingly welcoming to investigations that would explore the limits of radiographic imaging that he shared with the head of Experimental Radiology, James Anderson and his assistant Frank (Rusty) Starr. When I blithely showed up asking if they could X-ray this whale bone block to locate the ear inside, there was no hesitation. Not only did they locate the ear, they suggested we try their new Siemens computerized tomographic (CT) scanner that would not just locate the ear with greater precision but also provide sectional images of the inner and middle ear. That first set of scans opened my eyes to new avenues of research.

This whale ear was exceptionally dense compared to any bone the radiologists conventionally examined. In fact, it appeared to approximate the X-ray attenuation characteristics of soft metals. Because the Hopkins Hospital Radiology facility was relatively new, it was also a site at which Siemens was beta testing new imaging software. I was shortly introduced to their engineers who were interested in testing their ability to remove artifacts from scans of dense objects, like metal prostheses implanted in tissues.

I found myself in a perfect storm of equipment, ideas, and data that were totally unexpected, and because the dolphins were not back yet, the anatomical work continued. More packages arrived, and the more ears I was able to image, the clearer it became that there were multiple anatomical species-related variations in size and shape of whale and dolphin ears. Very few of these variations had been documented because of the difficulty of dissection of these extraordinary bones.

Some variations I found in these ears had been explored in land mammal ears, particularly dimensions of the cochlear canal and basilar membrane. The scanner, of course, had limitations of resolution compared with histology, but it allowed not just the measurements but also the reconstructing, viewing, and imaging of cochlear structures in three dimensions. This noninvasive imaging was a major breakthrough that substantially increased the accuracy of inner ear measurements and analyses without the time and potential distortions of decalcification normally required to investigate inner ear morphology. It soon became apparent that there were correlations between cochlear length and body size, but, more important, was that the shape and dimensions of the cochlear canal spirals correlated with differences in frequency ranges and peak spectra of vocalizations produced by different species. In particular, there were striking differences in the cochlear spiral curvatures that physically affected what frequencies of sounds penetrated the cochlea.

A year passed with still no live dolphins to test, but a larger focus than just describing the ears of a few species was emerging. A thesis project developed that would assess the biomechanical implications of anatomical variants of the inner ears of odontocetes, the toothed whales, that are known to hear and analyze ultrasonic signals in water and to use echolocation to image their aquatic environment. To accomplish this project required cooperation and guidance from multiple departments and individuals with a range of unique specializations, all of whom were available at Hopkins. In addition to those in Radiology, the Division of Computer Sciences and Alan Walker and Patricia Shipman of the Comparative Anatomy Department were especially valuable advisors.

Without the fortunate coincidence of all these individuals and resources, the project simply would not have happened and no functional insights on these ears would have been found. Nor would I have pursued my future parallel studies into the hearing of even larger, low-frequency specialized ears of elephants, baleen whales, and their fossil ancestors (**Figure 1**).

Another Twist to Inner Ear Spirals

Another completely unexpected chapter of research grew out of this experience. I was quite fortunate to be offered a postdoctoral position in the Eaton-Peabody Laboratory (EPL) that is located within the Massachusetts Eye and Ear Infirmary (MEEI) in Boston, Massachusetts. The EPL was the brainchild of Nelson Kiang. It is an amalgam of engineers, researchers, and clinicians, and,

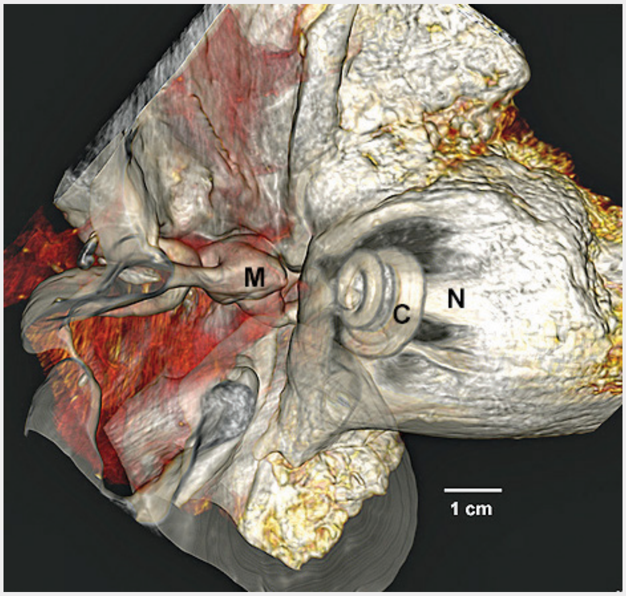

Figure 1. *Three-dimensional reconstruction from computerized tomographic (CT) scans of the middle and inner ears of a blue whale* (Balaenoptera musculus). *The bones surrounding the ear have been rendered translucent digitally to reveal the spiral fluid and membranous inner ear labyrinth of the cochlea (C), the auditory nerve (N), and the malleus (M), one of the three middle ear bones. A video of this reconstruction is available at acousticstoday.org/ketten-media. Images and multimedia used with permission, copyright © 2018 D. R. Ketten, all rights reserved.*

consequently, is a rich environment for blending basic and applied auditory research. Although I was ostensibly there to learn more about in vivo measurements of hearing, one day, in the hall, I overheard the chief of the Otolaryngology Department, Joseph Nadol, Jr., speaking with Donald Eddington, an engineer whose research group worked on cochlear implant design and measurements of implant patient postoperative auditory function. They were discussing the inability to determine the intracochlear positions of cochlear implant electrode arrays in individual patients and knowing whether any differences may affect patient results. The problem was that metal artifacts from the electrodes on postoperative CT scans obliterated visualization of much of the cochlear anatomy.

Admittedly, it was brash, but also irresistible, to volunteer that there were options to "fix" that. In the most courteous manner, despite understandable skepticism, Nadol suggested it may be possible for me to view postoperative scans for some patients and demonstrate whether the image processing I was suggesting could help. Because the scanners at the MEEI were Siemens machines, we were able to obtain the metal artifact reduction software that had been developed and tested on the Hopkins Hospital machines.

That accidental conversation led to my shifting my work at the EPL to over a decade of CT scan-based research on the imaging and individualized mapping of cochlear implants of patients at the MEEI as well as other implant centers, especially Margaret Skinner's group at Washington University in St. Louis, Missouri, and Mario Svirsky's at the New York University Langone Health, New York, New York. We did discover significant differences in implant distributions and, in many cases, developed a better understanding of how both implant array construction and surgical approaches may affect patient outcomes. Working on these practical issues that potentially improved patient outcomes was a radically different and rewarding experience compared with my then-limited experience of discovery in basic research.

The common thread to all of this was being open to recurring serendipitous opportunities to explore new ideas and use developing technologies that happened to be available to me. Even more important was learning from the wealth of mentors and colleagues who shared their ideas and knowledge at every step. The richness of collaboration should never be underestimated and seizing such opportunities should not be missed.

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