Rho Chi Lecture

Stories from a Life of Learning

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Charles O. Rutledge, Ph.D.
Dean
School of Pharmacy
Purdue University
West Lafayette, Indiana 47907-1330
(765) 494-1368
FAX (765) 494-7880
chipr@pharmacy.purdue.edu

In my presentation today, I plan to approach the subject of life-long learning. Learning often takes place as a series of problem solving exercises. In my early days, I would approach all problems in linear fashion. This can have two related formats. One is to proceed slowly through each step of the problem; making sure that all exceptions are addressed and all boundary conditions are met before proceeding to the next step. The other format is iterative meaning that you move quickly through the steps approaching the end and then you return to the beginning, repeating the process, cleaning up the exceptions and boundary conditions as you go. Each time that you go through it, the problem solving is more refined. This is how computer algorithms solve problems. I have been through both processes many times using a To Do list to plan out my daily approach. Each time I complete a step, I receive great satisfaction in checking that step off of my To Do list. In fact, this has been such an important part of my family culture that our family motto is "Check that Sucker Off."

There is another way to solve problems that people in various cultures have used over the centuries. This is called the story-telling approach. That is, one addresses problems by telling stories that illustrate the type of thinking that is necessary to solve the problem. This approach to problem solving is used to solve cultural, value, or attitude type problems. These stories often use metaphors, allegories, or aphorisms to illustrate approaches to the problem. The stories are prominent in all cultures. In Western culture, the stories of Homer, including the Odyssey and the Iliad, are good examples. In Germanic cultures, we have Grimm's Fairy Tales. Native American cultures have many stories of nature featuring rain, wind, sun, moon, and creatures of the forest to illustrate their view of humanity in the physical world. Native African tribes also passed stories from generation to generation to illustrate principles and values to young people as they reached maturity.

I have been an avid reader for many years, reading about 40 books a year in many different styles. Five years ago, I began the task of reading the one hundred greatest books. I am now on book 74, The Wealth of Nations, by Adam Smith. As a result of all of this reading, I have become convinced that storytelling is an effective means of communication. I have had a number of adventures in my years as a student, faculty member, Department Head and Dean that have brought forth important learning concepts. I would, therefore, like to illustrate life-long learning by telling a number of these stories.

The first story is from my early days as a teenager. I spent considerable time outdoors hiking and camping, mostly through the Boy Scout organization, serving as a camp staff member for five summers. I grew up in Kansas, where there are mites, commonly called chiggers. Mites are about the size of the head of a pin. As you walk through grass they crawl up your leg, dig under the skin and cause itching in the ankle and lower leg. Mites exist primarily in the larval stage and as such have six legs, but when they reach the adult stage, they are spiders with eight legs. When I was a junior and senior in high school, I was a member of the Science Field Club that took field trips once a month. Each member worked on his own two-year science project, which should result in a publication upon its completion. My project involved investigating the chiggers in the grass to see if they differed from the chiggers that lived in the ears of field mice. This meant I had to design and build a chigger trap. This was a 3' square metal box, painted black, with a 3" diameter hole in the middle. A petri dish with alcohol was placed beneath the hole and an inverted funnel was placed in the dish. The funnel was lubricated with glycerin. The chiggers would be attracted to the light and slide down the funnel into the alcohol where they would be preserved. I would then compare those chiggers to ones that I found in the ears of several species of field mice that I had trapped in various meadows. In order to identify the

mites, I had to use a mounting medium that would allow me to see the distinguishing features clearly. The Permount medium that I had was not very satisfactory, so I developed a new one consisting of polyvinyl alcohol. I got so involved in the mounting media that I never did complete the mouse ear-grass comparison that I started. My publication was entitled "A comparison of polyvinyl alcohol and a synthetic resin as a mounting media for mites," published in the Transactions of the Kansas Academy of Science in 1954.(1) I thought that I had identified a new species of chigger. I consulted with entomologist Ted Loomis at the University of Kansas. I was going to call it "Chipper's Chigger." It turned out that I had the best preserved species of a rare mite previously identified by someone else.

The lesson to be learned from this story is not only how one can turn curiosity into a scientific experiment, but that exploring one question, namely a comparison of chiggers, led to the unexpected result of identifying a much better mounting media for mites. This occurs over and over in science: searching for one thing leads to something else of value.

I then went to the University of Kansas to complete a pharmacy degree and then to Harvard Medical School for a Ph.D. degree in Pharmacology. There I did a laboratory rotation with a well-known German pharmacologist, Otto Krayer. This story has two parts. The first involves me learning to perform experiments that formed the basis of the discipline of pharmacology from one who witnessed it and was part of its creation.

Otto Krayer was born in 1899 in the village of Kondringen in Germany. He received his M.D. degree at Freiberg, but what he really loved was research. He learned that from Paul Trendelenburg. Krayer soon became an authority in cardiovascular physiology and pharmacology. While I was in Krayer's laboratory, he taught me how to use the Straub Frog Heart preparation exactly as he had learned it from the German masters 35 years previously, with

a specialized glass cannula and lever scratches on a smoked drum to record the contractions. I performed many experiments using this preparation. For example, I compared the effects of two cardiac glycosides, g-strophanthin and gitoxigenin, on heart rate and force of contraction. This preparation was used to investigate the action of many drugs on heart rate, impulse conduction, and contractility. The lesson of this story is that your understanding of drug action is greatly enhanced when you retrace history by repeating legendary experiments upon which whole branches of your field are based.

The story of Otto Krayer continues into a second phase. This story only became known generally after his death in 1982.[2] Early in his career as he was becoming well known for his research, his mentor, Paul Trendelenburg, became seriously ill, in 1930, and died in 1931. In 1933, while Krayer was on leave of absence at Gottingen working with Prof. H. Rein, Krayer was offered the Professorship and Chair of the Department at Düsseldorf. There was only one Chair of Pharmacology at each university, and one usually had to wait until the occupant of the chair passed on before a new Professorship would be approved. So, Otto Krayer, at age 34, was very pleased to have this opportunity for a professorship. But, this was Nazi Germany and the Nazis were beginning their attacks on Germans of Jewish descent. Krayer was not Jewish, but the professorship of Düsseldorf had become open because the previous Professor, Phillipp Ellinger, had just been removed because he was Jewish. Krayer was not a political activist, nor an organizer, nor a preacher for causes. He knew that although this was a dream of a lifetime, which he would probably never have again, he could not accept a position that became open in this way. He wrote the following letter to the Prussian Minister for Science, Art, and National Education.

…"the primary reason for my reluctance is that I feel the exclusion of Jewish scientists to be an injustice, the necessity of which I cannot understand, since it has been justified by reasons that lie outside the domain of science.

This feeling of injustice is an ethical phenomenon. It is innate to the structure of my personality, and not something imposed from the outside. Under these circumstances, assuming such a position as the one in Düsseldorf would impose a great mental burden on me—a burden that would make it difficult to take up my duties as a teacher with joy and a sense of dedication, without which I cannot teach properly.

I place a high value on the role of university teacher, and I myself would want the privilege of engaging in this activity to be given only to men who, apart from their research capabilities, also have special human qualities. Had I not expressed to you the misgivings that made me hesitate to accept your offer immediately, I would have compromised one of these essential human qualities, that of honesty.

…The work to which I have therefore dedicated all my strength, with the goal of applying my scientific knowledge and research expertise to effective university teaching, means so much to me that I could not compromise it with the least bit of dishonesty.

I therefore prefer to forego this appointment, though it is suited to my inclinations and capabilities, rather than having to betray my convictions; or that by remaining silent I would encourage an opinion about me that does not correspond with the facts."

Otto Krayer was the only natural scientist who had the courage to protest openly against the dismissal of Jewish professors. In response, the Prussian Minister for Science, Art and National Education wrote:

> "In your letter of June 15 you state that you feel the barring of Jewish scientists is an injustice, and that your feelings about this injustice prevent you from accepting a position offered to you.
>
> You are of course personally free to feel any way you like about the way the government acts. It is not acceptable, however, for you to make the practice of your teaching profession dependent upon those feelings. You would in that case not be able in the future to hold any chair in a German University.
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> Pending a final decision on the basis of section 4 of the Law on the Restoration of the Professional Civil Service, I herewith forbid you, effective immediately, from entering any government academic institution, and from using any State libraries or scientific facilities."

This was a particular blow to Krayer because he had promised Paul Trendelenburg that he would finish some of Trendelenburg's writings, one of which as Volume II of Die Hormone. Fortunately, Krayer was able to have access to some private libraries in Berlin. He later moved on to American University in Beirut and in 1937 he want to Harvard where he later became Chair of the Department until 1966.

But the story of his being banned from German Universities is not over. He continued to support German scientists during and after the Second World War. He was active in German

Pharmacology Society meetings. In 1965, 32 years later, the Academic Council of Medical Academy of Düsseldorf voted to confer honorary membership on Krayer.

Krayer at first was delighted, but there was difficulty in establishing a date for him to receive the award because of his travel schedule. Krayer finally wrote to the rector of the University of Düsseldorf.

> "In the course of the correspondence with you concerning the time of my visit to Düsseldorf, I have thought more deeply about the honor you are planning for me. I have come to the conclusion that the right thing for me to do is not accept the honorary membership of the Medical academy of Düsseldorf.
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> Despite my happiness at your first letter, which reached me during my trip to Japan, I had certain reservations from the beginning. It is now clear to me that the original ethical position I took in 1933 does not permit of any external reward. I must ask you, therefore, to nullify the decision of the Scientific Council of the Medical Academy. I regret that I took so long to express my convictions clearly."

This story of expression of a personal value system was not known during Krayer's lifetime. It only became known when one of his colleagues at Harvard, Avram Goldstein, went through Krayer's papers in preparation of a biographical memoir published by the National Academy of Sciences (Goldstein, A: Otto Krayer 1988-1982. Biographical Memoirs Volume 57, The National Academy Press, Washington, DC, 1987.)

I think of Otto Krayer whenever there is a case of scientific integrity. His action is a very high standard to follow because it was taken at a personal sacrifice with no intent to receive any credit whatsoever.

Students over the years have expressed concern over the relevance of having so much basic science in our curriculum. I often use a story to illustrate the importance of basic science to the delivery of pharmaceutical care, the story of my adventure in learning to play stride piano. In stride piano, the rhythm and the harmonic structure are maintained with the left hand. That left hand represents the key observations and scientific principles. Then superimposed on that is the clinical skill that it takes to convert those principles into pharmaceutical care. The skill includes asking the right questions, knowing where to go for the answers, and showing dignity and respect for all with whom you interact. The clinical skill then becomes the right hand in stride piano, which forms the variations on a melody line and will be different every time you play. There is considerable improvisation in the right hand, just as there is in application of clinical skills. In order to have a nice composition and great delivery of pharmaceutical care, both the left hand and right hand must fit in well with each other. Clinical skill must fit in with a thorough understanding of the knowledge and principles of science fundamental to the field of pharmacy.

The next story is one of science in which the development of a method allowed us to come up with an explanation of how amphetamine produces its primary pharmacological action: namely, release of biogenic amines from isolated nerve endings. When we began these studies in 1970, it was known that amphetamine inhibited the uptake of norepinephrine and dopamine into the neuron and there was indirect evidence that amphetamine released these amines from nerve ending storage sites. There was no convenient way to study the release of catecholamines from nerve endings. At that time, the methods for measuring release of endogenous amines from the tissue were not sensitive enough. Graduate students and postdoctoral fellows in my lab were able to label the nerve ending stores in isolated brain tissue with ^{3}H-norepinephrine. The excess

^{3}H-norepinephrine was then rinsed out of the nerve ending.[3] This rinsing of the nonspecifically bound catecholamine from the tissue was key because it reduced the background release to very low levels. Then one could add very low concentrations of amphetamine and compare the ^{3}H-norepinephrine in the media with the amount of ^{3}H-norepinephrine remaining in the tissue. With this technique, we were able to characterize the release of catecholamines from the tissue and found that it was temperature dependent and only partially dependent on calcium. There are several possible mechanisms for release, including exocytosis and facilitation of carrier mediated efflux. In a series of about 10 studies, we were able to demonstrate that amphetamine enters the neuron by being transported by the membrane carrier.[4,5] It is co-transported with sodium. Then once amphetamine is inside the neuron it displaces the catecholamine from intraneuronal binding sites, and the newly released catecholamine then binds to the carrier or transporter, thus being protected from metabolism by monoamine oxidase. The transporter then moves in reverse to move the neurotransmitter to the outside of the nerve ending where it can interact with the postsynaptic receptor. It took the development of a sensitive, convenient method for studying release of catecholamines in vitro to allow the design of experiments to generate data supporting a detailed explanation of the mechanism of action of amphetamine.

By 1978, I was heavily involved with the academy of scientists who were studying catecholamines. I was Chairman of the Catecholamine Gordon Conference, and I presented at several international meetings. In 1978, I was elected as President of the Catecholamine Club. This was a group of scientists that met every year in conjunction with a large meeting of the Federation of American Societies of Experimental Biology. When I was President in 1979, I tried to encourage my friends to attend the meeting. The wife of one friend was puzzled as to the nature of the Catecholamine Club. In my enthusiasm to encourage her attendance, I stated in jest

that we even had a song. She said that she would come only if she could hear us sing the song. Now, I was stuck. I had no training in music composition. I had a few piano lessons, but mostly my vocal experience was in leading singing at campfires at Boy Scout Camp. First of all, I needed a tune. I ruled out Row Row Row Your Boat and Three Blind Mice. I settled on the tune of Stout Hearted Men by Sigmund Romberg from the operetta "The New Moon." I sang the first verse of the Catecholamine Club Song in 1979. In 1986, a second verse was added. Charlotte Granholm and Barry Hoffer added a third and fourth verse a few years later. I have been singing this song at every Catecholamine Club dinner since 1979. The song will not die. In 1989, the story of the Club and the song was published in Trends in Pharmacology.[6] I even added a verse in French. Be careful what you promise—you may have to improvise at short notice! Sometimes it works. Sometimes you even find that you can do something you didn't know you could do. And in this case, fun is good! The shared pleasure of singing together is one tie that binds the members of the Catecholamine Club and appears to make the annual meeting a highlight.

The next story I would like to tell is one of administrative perseverance. When I came to Purdue in 1987, one of the strong impressions I had was that neither the student body nor the faculty was very diverse. Most of the students in our professional program came from small towns in Indiana where the entire populations originated from Western European cultures. The few African-American students in our program were all members of SNPhA, the Student National Pharmacists Association, but none were members of the 12 other student organizations. We were also interested in educating pharmacists to provide pharmaceutical care to people from all cultures. In order to do that effectively, I felt that we had to have a more diversified faculty and student body. We, therefore, began a plan of diversification. We now have over 60 under-

represented minority students in our Pharm.D. Program and over 40 students in the Prepharmacy Program. How did we do it? We introduced over 20 different activities to support these students in our program, adding more than one program every year. We have been working on this for 14 years. I first appointed a faculty based Minority Advocacy Committee, of which I have been chair since the beginning. I report our progress at the monthly faculty meeting. This gives the activities of this committee a very high profile in the School. We then formed an Advisory Council from under-represented minority alumni. They were also dedicated to helping us in our diversity efforts. The first thing that this advisory council recommended was to hire a full-time Director of Minority Programs, which I did about ten years ago. Jackie Jimerson is the Director and has been with us since the beginning. We have conducted two surveys assessing the degree of appreciation for diversity among students, faculty, and staff. We have implemented 12 different support programs to assist all students who have come from educationally disadvantaged backgrounds. This was a difficult administrative problem that most programs have struggled with. I have presented this story of perseverance to demonstrate that if you keep at it and work year after year with the same vision, that eventually you will be able to achieve your goal.

The final story I have to tell you is of my newest adventure. I am at an age when most of my contemporaries are entering retirement. I actually thought that I might do that as well. However, the Provost and President at Purdue presented me with an opportunity that I could not refuse. The main reason is that it gives me a chance to continue learning exciting and very important science, which will lead to interesting new products and services. This new opportunity is to be the Director of Discovery Park.

Discovery Park was conceived to enhance interdisciplinary research especially in new fields of nanoscience, bioscience, and e-enterprise. Students will work in interdisciplinary teams with both scientists and engineers. We will also integrate business and management students into these teams to develop a greater sense of entrepreneurship. We also expect to attract financial support leading to enhanced economic development.

Discovery Park has four centers, which have been funded by a 26 million-dollar grant from Lilly Endowment. The four centers are: 1) Nanoscience/Engineering Center, 2) Bioscience/Engineering Center, 3) E-Enterprise Center, and 4) Entrepreneurship Center. These four centers will be housed in four buildings, which will be built as a result of a 100 million-dollar capital campaign that is mostly complete now.

In my new position as Project Director of Discovery Park, I am responsible for implementation of this vision. It will be my responsibility to facilitate the formation of teams of faculty to participate in this new program of interdisciplinary research.

The type of research that will be conducted in Discovery Park is nicely illustrated in a Special Issue of Scientific American called Nanotech (September 2001)[7]. The Nanoscience/Engineering Center will have a clean room with up to a dozen bays to study devices such as small transistors[8]. These are molecules that have well-understood oxidation-reduction reactions within them such that electrons shuffle among the atoms. This reaction puts a twist in the molecule so that clusters of the molecules in one position conduct electricity as much as 1000 times better than when in the off position.

There is a class of artificial molecules called organic dendrimers[9]. A dendrimer branches successively from inside to outside. They are about the size of a typical protein but they do not come apart or fold as easily as proteins because of stronger chemical bonds.

Dendrimers contain voids with an enormous amount of internal surface area. They can be tailored to have a range of cavity sizes that are just perfect for holding drug molecules. They can be engineered to deliver DNA into cells for gene therapy, for example.

Another use of technology is to use DNA molecules to do computing[8]. DNA contains an enormous amount of information. DNA molecules can be attached to a silicon chip encoding all possible values of the variables in a mathematical equation. You can form copies of complementary strands encoding the first clause of the equation, and they attach to any DNA strand that represents a valid solution to the clause. Enzymes then remove all of the single strands. Other proteins melt away the added complementary strands. You then repeat the process for other clauses of the equation. The DNA strand that survives the whole process represents the solution to the whole equation.

Nanotechnology may even bring to reality ideas that thus far have been in the realm of science fiction. One example is to construct small machines[10] that can go to tissues in the body and perform nanosurgery. Another example would be to have a machine that would trap virus particles and remove them from the body.

In summary, from youth onwards, I have learned from reading, hearing, and telling stories. The importance of curiosity, serendipity, lessons from history, ethical values, blending of science and clinical skills, developing model systems for research, collegiality through song, perseverance to solve a difficult administrative problem, and the excitement of continued learning have been important in my saga of learning. I provide this biography of life-long learning to illustrate how varied, and to some degree unpredictable, learning experiences can be. This journey for me has been, and continues to be, exciting and fun.

References

(1) Rutledge, C., A Comparison of Polyvinyl Alcohol and a Synthetic Resin as a Mounting Media for Mites. Transactions of the Kansas Academy of Science 57:133-135, 1954.

(2) Goldstein, A. Otto Krayer, 1899-1982, Biographical Memoirs. National Academy of Sciences 57:151-225, 1987.

(3) Ziance, R.J., Azzaro, A.J., and Rutledge, C.O. Characteristics of Amphetamine-Induced Release of Norepinephrine from Rat Cerebral Cortex *in vitro*. J. Pharmacol. Exp. Ther. 182:284-294, 1972.

(4) Liang, N.Y. and Rutledge, C.O. Evidence of Carrier-Mediated Efflux of Dopamine from Corpus Striatum. Biochem. Pharmacol. 31:2479-2484, 1982.

(5) Rutledge, C.O. Effect of Metabolic Inhibitors and Ouabain on Amphetamine- and Potassium-Induced Release of Biogenic Amines from Isolated Brain Tissue. Biochem. Pharmacol. 27: 511-516, 1978.

(6) Dixon, W.R. and Creveling, C.R. Archives of the Catecholamine Club, Twenty Years On. Trends in Pharmacological Sciences 10: 100-102, 1989.

(7) Stix, G. Litte Big Science: Overview. Sci. Amer. 285: 32-37, 2001.

(8) Lieber, C.M. The Incredible Shrinking Circuit. Sci. Amer. 285: 59-64, 2001.

(9) Alvisatos, A.P. Less is More in Medicine. Sci. Amer. 285: 67-73, 2001.

(10) Collins,G.P. Shamans of Small. Sci. Amer. 285: 86-91, 2001.