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COMMENT

APS Presidential Plenary 2019: the way of science: serendipity and the illusion of linearity

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Looking back in time sometimes creates the illusion of linearity. This is true for an academic career and also not unusual for the advancement of science. Hopefully, you will appreciate this notion even more so on the occasion of my receiving the John Howland Medal and Award as I look back on my way to this point, and then look ahead at the future of pediatric research and the practice of pediatrics.

I am the third holder of the Harold K. Faber Endowed Chair in Pediatrics at Stanford University School of Medicine after Norman Kretchmer, a previous president of the American Pediatric Society (APS) from 1978 to 1979 and previous director of the National Institute of Child Health and Development (NICHD) from 1974 to 1981, and Kretchmer's mentee, Phil Sunshine—still a living legend in neonatology, a previous Apgar Award recipient, and one of my teachers and mentors. Harold K. Faber was also a President of the APS (1946–1947) and received the John Howland Medal and Award in 1956, the fifth recipient.[1] He had come to Stanford in 1915 as head of Pediatrics, a small subdivision in the Department of Medicine. A separate department was established in 1927 under his leadership. I have learned that he was originally planning a literary or journalistic career with an undergraduate background in Latin, Greek, French, and German, and with an interest in English literature. It was a chance chemistry course that ignited his interest in science and ultimately led him to medicine. It was the people whom he met by chance, like L. Emmett Holt at the Babies' Hospital, a part of the Columbia complex, who led him to Pediatrics. Holt was a major figure in the history of Pediatrics, elected as president of the APS twice. Both Edwards A. Park, the first recipient of the John Howland Medal and Award in 1952, and John Howland himself (Fig. 1) trained under him in New York before going to Johns Hopkins University. As the story goes, Holt advised a young Faber, who was conducting studies at the then Rockefeller Institute, not to leave his research there, but Faber did not take his advice and left for Stanford anyway. Although there is more that I can say about Harold K. Faber, the point of telling you a little about his personal history is to acknowledge the importance of serendipity in one's career path and of the people whom we meet by chance. It is only in retrospect that we perceive any linearity in our respective paths. For most of us, our legacies will not be in what we have done—often illusionary linear recounts of the past; they will be reflected in the people whom we have met largely by chance, who have shaped our personal and professional lives, who have contributed to the future of our profession, or who will participate in it.

Much like Harold K. Faber, I did not set out to become a physician and scientist. I studied philosophy and the humanities under the tutelage of a distinguished philosopher, John D. Goheen. My original intent was to become a Professor of Philosophy and to teach philosophy of science, but John advised me that I might serve people better as a physician than as a philosopher. He reassured me that there was little that separated the fields in ancient times, so that I should not think of myself as a failure, if I did not teach philosophy of science, but practiced medicine and science.

In neonatology, I apprenticed with Phil Sunshine, Ron Ariagno (Fig. 2), and other colleagues as they practiced Neonatal–Perinatal Medicine and helped to inform this nascent Pediatric subspecialty through research and empiric observation. I listened to Phil's advice (although I did not always take it)—and I studied the thoughtful and meticulous ways of John Johnson as a clinician and scientist. Over the years, I have relied on the scientific acumen and loyalty of my two colleagues, Henk Vreman and Ron Wong, as well as the advice of many others not at Stanford.

With respect to science, I have been narrowly focused in one regard and more eclectic in another. Newborn jaundice is perhaps the most common phenomenon confronted by pediatricians in practice. Thus, the biology of bilirubin production and its inhibition became a focus of my investigative attention. For that purpose, heme oxygenase (HO), the enzyme that catalyzes the first step in the two-step heme degradation pathway, and its associated biology were most relevant to my projects. We[2] and others[3,4] reasoned that controlling the production of bilirubin in babies who had increased rates of pigment production from a variety of causes would be a logical, preventive strategy for avoiding excessive jaundice. We developed technologies to measure total bilirubin production in living animals by measuring breath carbon monoxide,[5–9] which is produced in equimolar amounts with bilirubin;[10] we proved that it worked in rats (that for every heme molecule degraded to bilirubin, a carbon monoxide (CO) molecule can be recovered in breath)[11] and showed that the same approach also could be undertaken in humans,[12] as others in Sweden had suggested earlier.[13] We simplified these technologies and made them more accessible to clinicians as end-tidal CO detection devices that could automatically correct for ambient CO,[14–17] and we began to observe infants who were high producers of bilirubin even before they would become jaundiced, for example, those with hemolytic conditions like ABO hetero-specificity, thus identifying babies who might benefit from inhibition of bilirubin production. The next task was to identify a compound that would be safe and effective for this purpose, which led us on a several decade-long odyssey of testing various heme analogs (called metalloporphyrins) that would demonstrate

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Fig. 1 John Howland

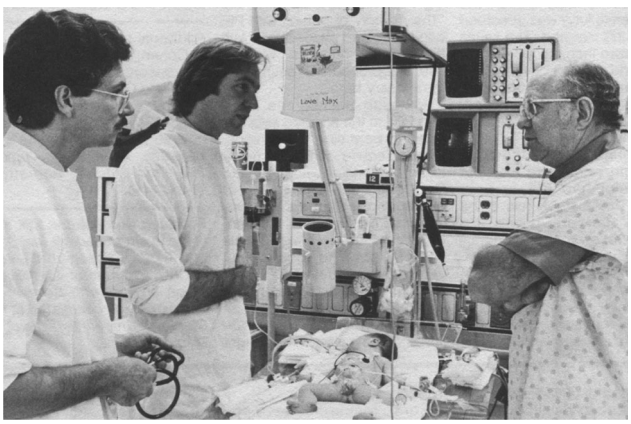

Fig. 2 Ronald L. Ariagno, David K. Stevenson, and Philip Sunshine

all of the desirable properties of a drug to prevent newborn jaundice, with safety being foremost in our minds. In order to ensure that we understood how these compounds were working, we were the first to develop other technologies, such as the optical reporting of gene expression in living mammals reported in 1997,[18] and used this latter and then a novel approach to study the effects of the various inhibitors on HO-1 gene expression. We ultimately identified a naturally occurring compound, zinc protoporphyrin (ZnPP), which is an effective non-photoreactive inhibitor and also meets all of our other safety and efficacy specifications. We have now formulated this compound for oral or intravenous use and it is finally under further development by a company.[19] This work has become even more important since we recognized in a NICHD trial that phototherapy might be dangerous for extremely small translucent babies who have demonstrated what appears to be an increased mortality related to phototherapy exposure.[20] This observation has haunted me because of what Bill Silverman said about "ambitious over-generalization,"[21] as we had never tested phototherapy in newborns as they became smaller and smaller and more translucent. Reducing exposure to phototherapy and still protecting infants from the potential toxic effects of bilirubin have become the two horns of a dilemma in neonatology—with a possible ultimate solution being the introduction of a new safe pharmaceutical product to prevent excessive jaundice altogether. As it turns out, there are many other aspects of HO biology relevant to pediatrics and neonatology, including antioxidant defense and inflammation, immune modulation, and vascular development, which is beyond the scope of this address.

Let me say a few things about some of the changes in the way we are conducting scientific inquiry today. We recently wrote a commentary entitled "Risky Business: Meeting the Structural Needs of Transdisciplinary Science."[22] In this article, we discussed how "convergent" or "transdisciplinary" science might be better suited to solving complex biomedical problems than traditional disciplinary approaches. Stanford was first designated as a prematurity research center by the NIH, one of the original general clinical research centers, in 1963. Ironically, in 2011 we were designated once again as a prematurity research center—this time by the March of Dimes—as the first of six university-based premature research centers. We began this effort with researchers from a variety of disciplines across the University. We initiated both basic and applied research activities and began to focus on creating new technical and computational capabilities to understand and prevent preterm birth. We began to redefine preterm birth and its taxonomy through a process of integrative "omics" profiling. The need to pursue a chance finding or to take advantage of an unanticipated opportunity is characteristic of convergent or transdisciplinary research. Over the past decade, we have welcomed serendipity and the nonlinearity of discovery, while maintaining clarity with respect to our goal—to identify the causes of preterm birth and ultimately prevent it. I can report that many of the most interesting and important scientific opportunities that have emerged through the Center's activities to date have been serendipitous.

For example, two bioengineering students and others of us at the Center recently described a transcriptomic "clock" of pregnancy that could be used to estimate gestational age as well as fetal ultrasound does now and a identified a potential disruption of gestational gene expression, a transcriptomic signature, that could predict preterm birth as much as 2 months before the occurrence.[23] Stimulated by these discoveries, we enjoined other investigators at Stanford to identify an immune "clock" of pregnancy using mass cytometry by time-of-flight mass spectrometry technology to identify unique immune signatures associated with preterm birth.[24] In addition, our computational scientists have been challenged to invent new mathematical algorithms, so that data of different types derived from a variety of sources, such as microbiome data during pregnancy and many of the socio-demographic and psycho-social risk factors that have been historically lumped together as the social determinants of preterm birth, might be integrated with the various "omics" data and analyzed together.[25]

We have learned several things as our Center has evolved over a decade. First, the ability to allocate funds flexibly is highly desirable and often necessary, in order to support new avenues of investigation that become apparent by chance only as investigators from different disciplines begin to work together to solve complex biomedical problems. Moreover, our experience at Stanford has underscored the need for other funding streams, besides the usual extramural grants and contracts, in order to sustain the integrative infrastructure of transdisciplinary research. Such funding sources might involve strategic partnerships with

companies, charitable foundations, or even individual philanthropists. Second, there also has to be a greater tolerance of risk and failure similar to what we see near us at Stanford in the world of start-ups in Silicon Valley. Third, we will need to get better at evaluating scientists, especially young ones, who work on big complex biomedical problems at the interstices of traditional disciplines or as a member of a team, so that they can receive credit for their research contributions, gain recognition by their academic colleagues, and advance in their careers.

If precision health—to predict, to prevent, and cure precisely—is the new kind of medicine that we will practice in the future, then pediatrics is the platform from which the "life-course" approach to human health is launched. In general, the approach is not too different than the one that I took decades ago in the case of neonatal jaundice. I wanted to see where a biologic system was headed, not where it had been. Our practice has been traditionally based upon a paradigm of responding to bilirubin levels representing different categories of risk, when, in fact, knowing the rate at which the pigment is produced and preventing excessive production would be a much safer and appropriate way to address the problem. Throughout my career I have used different scientific tools to answer the questions that I wanted to answer. Questions were always more important than the tools, but building new tools was essential too.

My final example from my own career is our use of light to probe the biochemistry of living mammals and ultimately humans. I noticed that my patients were getting smaller and smaller and more difficult to access. One of our postdoctoral clinical trainees in neonatology began working with me and colleagues in applied physics to develop some of the first applications of magnetic resonance (MR) spectroscopy and functional imaging as a new way to get information about the in vivo biochemistry of babies. When our MR machine broke down, we considered whether we might take advantage of the fact that our ever smaller patients were also more translucent. So we began to consider the use of visible light for the probing of their biology in vivo with minimal perturbation. In 1993 we published in *Science* the first description of time-of-flight absorbance spectroscopy in a living mammal,[26] having demonstrated its efficacy in a model system—a screw in an olive in a tube of blood. This ultimately led to various optical imaging and monitoring technologies that are familiar today.[27–30] Any linearity in the trainee's original research plan had been bent by serendipity.

In the end, I am most proud of what my students, trainees, mentees, and colleagues have accomplished. I thank all of my collaborators who have worked on various projects with me over the years. I look forward to more investigative work at least for a while longer, as younger minds ensure a bright future for pediatric research and the practice of Pediatrics.

ADDITIONAL INFORMATION

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