

## MASTER'S PERSPECTIVE

# Principles on the Path to a Hepatologist's Enlightenment

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I was thrilled to receive an invitation from the editors to contribute to this Master's Perspective series and only hope this piece reflects a mid-career perspective, not a final chapter! Rather than focus on a simple chronology of my career or advances in my area of investigation, hepatic fibrosis, I've used this opportunity to crystallize 10 key principles that have underpinned my career, and in doing so, I hope it provides a useful framework that may resonate with others.

**1. Imprint the Young.** My interest in hepatology was sparked by second-year medical school lectures at Mount Sinai given by Fenton Schaffner and Hans Popper. Dr. Popper's and Dr. Schaffner's lectures conveyed the beauty of the liver and led me to wonder whether pursuing its mysteries would be stimulating. I sought Dr. Schaffner's guidance as my advisor, and he arranged for me to spend 3 months after my second year of medical school at London's Royal Free Hospital in 1977. That period was a golden era at the Royal Free, ruled by the brilliant and demanding Professor Sheila Sherlock. The Royal Free was *the* mecca for liver study and treatment, with patients, physicians, and pathology slides converging from around the world to define new paths of inquiry and clinical care. Little did we know how little we knew, and in retrospect, our knowledge was remarkably fragmentary. Still, my lifelong passion for understanding hepatic disease started at this formative and impressionable stage, which is why, as a Liver Division chief, I have insisted that our faculty share their passion and knowledge with those at the earliest stages of their training. This philosophy, in turn, has yielded a new generation of enthusiasts here at Mount Sinai who con-

tinue to pursue hepatology with the passion and intellect that trace their origins to the foundational days of Popper, Schaffner, and Sherlock.

**2. Get the Best Training You Can.** As a lifelong New Yorker, I was reluctant to leave the region after medical school, but I was encouraged by Dr. Schaffner to seek the very best training, wherever it led me. To my surprise, I matched at Beth Israel Hospital (Boston, MA), where I learned how to care for sick patients with compassion and rigor while finding joy through friendship and shared sacrifice in the days before work-hour restrictions for trainees. Seeking the best training served me well when interviewing for a gastroenterology fellowship. While I had assumed that Boston would remain my home, it became clear when interviewing at University of California San Francisco (UCSF) that its program and environment had no equal. It was a veritable New York Yankees of liver disease, with major textbook authors, journal editors, and academic leaders populating three major teaching hospitals, led by the charismatic and incisive Rudi Schmid. Of course, I had to convince Dr. Schmid of my genuine interest in pursuing bench research, despite my lack of experience. Though he initially offered me only clinical training, he reconsidered when I insisted on trying research, and he later became one of my most passionate supporters. My peer group of trainees was impressive, and several remain lifelong friends and leaders of our discipline.

A corollary to the principle of seeking the best training is to embrace advanced training opportunities whenever possible. Today, this conundrum faces many gastroenterology trainees who are hesitant to spend a fourth year in clinical hepatology training or extended

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Abbreviations: ECM, extracellular matrix; HSCs, hepatic stellate cells; LT, liver transplantation; HSCs, hepatic stellate cells; UCSF, University of California San Francisco.

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Fig. 1. Members of the San Francisco Liver Center Laboratory, 1992. In addition to Monty Bissell, top left, others include yours truly (top row, black sweater), Jackie Maher (bottom row, second from left), Joe Roll (bottom row, fourth from left), and Bill Jarnagin (bottom row, fifth from left).

time in the laboratory. I remind them that training is not a prison sentence; apart from the lower pay, being a trainee offers the clear advantage of having education as an ingrained part of their job description. Moreover, once they pass through the portal of a faculty job, it is rarely possible to go back and obtain the training they could once readily access.

Seeking an environment that brings out one's best and pursuing every opportunity for advanced training are critically important to achieving one's potential, given that the training environment will invariably mold us in a way that is enduring.

**3. Mentoring: A Lifetime Contract.** More than anyone else, Monty Bissell is most responsible for introducing me to a career path that continues to yield enormous satisfaction. I was gratified to see that his HEPATOLOGY Master's Perspective piece in 2009 focused on mentoring, because it was his example in creating a collaborative and creative scientific environment that has now been transmitted to dozens of investigators throughout the world through his values and those of his trainees (Figs. 1 and 2). A tangible legacy of that mentorship is a framed list of Fuller Albright's *Ten Rules for the Clinician Investigator*, which he presented to each departing member of the laboratory (see Bissell DM. Of mentors, mentoring, and extracellular matrix. HEPATOLOGY 2009;50:1330-1338 for details). Once I established my own lab at Mount Sinai in 1998, I expanded that tradition by not only distributing a framed certificate containing these same ten rules to my trainees, but also by posting a second personalized copy above the scientific bench where each trainee

worked, creating a legacy of the lab's history. Knowing that their work is linked to generations before them through this certificate not only here at Mount Sinai, but also to Monty Bissell and others in the field (Fig. 2) offers them a gratifying recognition that they are part of a long and vibrant legacy.

My experience as a mentee deeply imprinted the importance of mentoring to my career success, as well as my responsibility to mentor effectively to my trainees. While space does not permit me to enumerate all the critical elements that I think make mentoring successful, there are a few especially important ones worth highlighting. First, trainees should be among mentors' highest professional priorities. Furthermore, mentors have a responsibility to make this value explicit to their trainees. Monty always made this clear through his actions, such as rapidly reviewing manuscripts and meeting with us on short notice when asked. Reviewing a draft manuscript or abstract within 24 hours lets the trainee know that they are important, and that addressing their needs trumps other professional obligations under most circumstances. Second, I emphasize that my trainees get a "lifetime contract," and there are few interactions more gratifying than receiving requests for advice by former trainees who are now highly accomplished in their own right. Third, it's the little things, the daily interactions and the off-hand comments that resonate with trainees. I was reminded of this when my trainees created a lab T-shirt replete with many of my casual comments, which they called "Scottisms," that I had uttered during our weekly lab group meetings.



Fig. 2. The Founding Generation of Hepatic Fibrosis Investigators from San Francisco—Trainees of D. Montgomery Bissell, reunited in 2011. Surrounding Monty (seated) are: Jacob George, M.D., Ph.D., Director, Storr Liver Center, University of Sydney; Michael Arthur, M.D., President and Provost of University College London; Don Rockey, M.D., Chairman of Medicine, Medical University of South Carolina; Jacquelyn Maher, M.D., Director, UCSF Liver Center and Chief of Gastroenterology, San Francisco General Hospital; Rolf Hultcrantz M.D., former Chief of GI at Karolinska, Stockholm; Chantal Housset, M.D., Ph.D., INSERM Professor, Director of IFR65 Health Research Institute, University of Paris; Scott Friedman, M.D., Dean for Therapeutic Discovery and Chief of Liver Diseases, Icahn School of Medicine at Mount Sinai; and Dominique Roulot, M.D., Universitaires Paris-Seine-Saint-Denis-APHP, Hôpitaux Universitaires Avicenne.

#### 4. *Physician-Scientists Will Never Be Obsolete.*

Because I had no laboratory experience preceding my gastroenterology fellowship, I was willing to invest 2 years to see whether this path was worth pursuing, but realized that my choice of laboratory would greatly influence whether I would succeed in, and enjoy, bench research. In addition to being drawn to Monty Bissell because of his values and style, the focus of his research was especially attractive to a clinician like me who had not worked in a lab before. Monty had recently established a new laboratory at San Francisco General Hospital focused on extracellular matrix (ECM) biology (Fig. 1). Although the topic of collagen metabolism brought back memories of the most boring lectures in medical school, I could look beyond that to understand that advancing our knowledge of fibrosis could ultimately yield clinical benefit, although we were naïve about how long it would take, as only now are antifibrotics in widespread clinical trials. Still, I focused on the cellular basis of fibrosis, and after 6 months of frustration in trying to tease cultured hepatocytes into making collagen, it became clear we were studying the wrong cell type. Thanks to the mentorship of Joseph Roll, we attempted to isolate hepatic stellate cells (HSCs; then called lipocytes or fat-storing

cells) from rat liver by using *in situ* perfusion methods that Monty had pioneered, then exploiting their buoyancy in employing a density gradient to separate them from other nonparenchymal cells. My early success in isolating HSCs ignited an emotion that only research can provide—the intoxication of creating new knowledge, providing an insight, however small, that has not been unearthed before. The search for that moment is what makes research a unique and endlessly stimulating experience.

Those were incredibly exciting days in the San Francisco General Liver Center Laboratory, filled with a real sense of fun and teamwork, and, as a group, we laid a foundation for the fibrosis field, attracting some of the brightest young physician-scientists in this emerging discipline from around the world (Fig. 2).

My scientific journey has steadily taken me deeper into an exploration of cell and molecular biology, cell signaling, and ECM metabolism, while always remaining true to my passion: HSCs and hepatic fibrogenesis. In pursuing this path, I have often felt handicapped by the lack of a Ph.D., but, in reality, my training as a physician more than compensated for this deficiency. Because patient care requires decisions to be made without all the data one would like, clinical training

conditioned me to tolerate uncertainty, attacking new challenges by immersion in a topic and seeking collaboration from the best experts I could find. These instincts honed by clinical training serve physician-scientists well and underscore the unique perspective we bring to laboratory work. Despite the fact that success in a laboratory-based research career has become progressively more difficult, the need for physician-scientists in our discipline could not be more acute, given that we increasingly are called upon to translate new principles of molecular biology into novel diagnostics, devices, and therapies.

**5. Communication Is Everything.** Effective oral and written presentation of one's ideas is an absolute requirement for success in academic medicine and requires constant practice and feedback. Physicians are notorious for making simple concepts sound complicated, when the exact opposite is needed. My writing style as a trainee was, frankly, embarrassing. Only by focusing on the effective writing styles of others and engaging in honest self-criticism have I reached an acceptable level of competence, yet I believe I can still do much better. Similarly, I've invested a great deal of effort into refining my oral presentation skills, to the point where I now regularly give lectures to groups at Mount Sinai about how to lecture effectively. Compiling a lecture represents a moment of truth: If I can't explain and illustrate a concept clearly to others, then I do not understand it sufficiently myself. Effective speaking and dissemination of my knowledge about fibrosis have paid off handsomely by allowing me to travel for lectures around the world, meeting and learning from colleagues who share a common passion. My personal and professional lives have been immeasurably enriched by these travel opportunities, which have also allowed me to indulge a lifelong passion for photography that fosters respect for other cultures. The Depression-era photographer Dorothea Lange once said, "A camera is a tool for learning how to see without a camera." This principle has been my guidepost in learning to really see the world beyond the postcard vistas and stereotypes of other cultures.

Strong communication skills are also essential in our professional interactions, and the same principles that apply to effectively interacting with patients and their families likewise apply to the research environment. Always telling the truth, tempering bad news or criticism with positive comments, and not letting unspoken tensions linger are tenets of good patient care, but they are equally valuable in working with peers, subordinates, and superiors.

**6. There Are No Solo Artists in This Business.** From my clinical training, through my years in Monty Bissell's

lab, and then during my sabbatical at the Weizmann Institute in the laboratory of Professor Moshe Oren in 1995-1996, I have learned about the absolute interdependence of scientists on one another. Whereas science is a competitive world, teamwork always trumps individualism in creating synergies and yielding breakthroughs. Throughout my career as a principal investigator, I have focused on understanding each individual's motivations in order to extract their best work and highest satisfaction in creating a shared sense of accomplishment. At the same time, people with different personal styles and work habits typically populate a laboratory, and it is a perpetual challenge to identify the right project for the right person who has the appropriate technical and social skill sets, and then to adjust my and their expectations when necessary. Among the most valuable experiences of my career was a full-day workshop at the 1993 American Society for Cell Biology meeting focusing on "motivational work needs assessment" in building an effective scientific team. This ongoing interest in team building has been further enlightened by reading great books on leadership, including *Organizing Genius*, by Patricia Ward Biederman and Warren Bennis.

**7. Savor Success and Use Rejection and Criticism as Opportunities to Improve.** The academic life is replete with rejection of many stripes: rejection of manuscripts, grants, and abstract submissions, to name a few. There is no shortage of opportunities to feel diminished and to question one's abilities and potential. Amidst all the ingredients that augur success, however, tenacity is one that is rarely acknowledged, yet without it, success is rare. My most significant professional rejection came in response to the submission of first my junior faculty National Institutes of Health KO8 grant in 1986, after we had published a paper in *PNAS* characterizing the HSC as the principal fibrogenic cell in the liver. The critique of this grant noted, "The major weaknesses of this application. . . cast doubt on the validity of any data obtained and may impair Dr. Friedman's ability to compete for research funding as an independent investigator." Fortunately, I had a mentor who simply advised resubmission without emotion or hand wringing. Taking umbrage at rejection must be channeled into insistence on overcoming obstacles and proving the value of one's ideas, not into self-doubt. At the same time, peer review can offer a perspective that may be more clear-eyed than our own perceptions and should be viewed constructively, not defiantly.

Rejection and criticism have often provoked in me a festering fear of inadequacy. Few of us publicly acknowledge the insecurity that inevitably accompanies medical and scientific training, even though we are a

highly self-critical cohort. Though my achievements in later years have mitigated some of my insecurities, I've learned to acknowledge this insecurity as an immutable feature of my temperament, but one that can be channeled into the drive for self-improvement. In other words, anxiety and insecurity only make sense if they provide a pretext for heightened focus and greater determination to succeed, but not to question one's fundamental competence. I suspect that I am not alone in this mindset.

Although the sting of rejection can linger for a long time, we rarely stop to savor success when it does arrive, yet this, too, should be imbued to trainees. What are my successes? My most important scientific contribution is the description and characterization of HSC activation, first through the observation that freshly isolated rat HSCs spread and became proliferative in primary culture on plastic in the presence of serum, then by the recognition that this response occurs during liver injury *in vivo*. Through these observations, we proposed a paradigm wherein HSC activation occurs through "initiation" then "perpetuation" phases. Initiation represents early changes that render the cells responsive to many extra- and intracellular signals, whereas perpetuation reflects the downstream consequences elicited by each of the signals. The model has proven remarkably durable and continues to provide a useful context in which to position newer findings; for example, the clearance of HSCs through either apoptosis, senescence, or reversion, as well as the interplay of inflammatory signals and HSC responses. More recently, it has also provided a useful template for classifying the targets of antifibrotic therapies. Thus, our description of HSC activation has followed a remarkably gratifying arc, beginning with a method to isolate, culture, and characterize HSCs, then extending over 25 years to yield novel treatments that promise to improve patients' lives.

**8. Embrace Change.** Although the fundamental principles of great clinical care and rigorous scientific investigation have not changed in the 30 years since I entered the field, the tools and social constructs that now support these pursuits would have been unthinkable in the 1980s. Hepatology has evolved from a specialty that could only offer Lasix, lactulose, and prednisone within the confines of a provider's practice office, to a discipline that relies on advanced diagnostics and multiple therapeutics, including liver transplantation (LT), which are provided within a team environment populated by multiple specialists with a range of advanced degrees and skills. Now that we are on the cusp of an era driven by big data solutions to personalize medicine by exploiting individual genomic variation,

change is likely to accelerate. This will require nimble thinking, flexibility, and lifelong learning. In basic research, fields that did not exist 30 years ago now dominate liver biology, including epigenetics, the microbiome, and stem cells. The more one is conditioned to jump into the unknown, the easier it gets. Throughout my career, I have tried to embrace new approaches while remaining true to the key clinical challenges that affect our patients: hepatic fibrosis, cirrhosis and its complications, and, more recently, liver cancer.

**9. Hepatologists Are a Nice Group of People.** The privilege of working with so many terrific colleagues as American Association for the Study of Liver Diseases president in 2009 solidified a concept I had appreciated subconsciously, but never explicitly; namely, that individuals who choose a career in hepatology are a wonderful lot. The traits required of our specialty include an ability to work well in teams, a nonjudgmental perspective toward patients, and a probing intellect tempered by curiosity and humility. We have not become as financially secure as our gastroenterology colleagues, but this has been amply offset by the richness of our community and the gratitude of our patients. With so many recent successes in treating viral liver disease, and restoring lives through LT, it is easy to forget how much we relied on our instincts for compassion and comfort, rather than cures, in the early years. I have been especially privileged to be among the last generation of hepatologists who knew and worked with the founders of this discipline, who embodied these values.

**10. Be a Mensch.** Loosely translated from Yiddish to mean a good person, someone who always tries to do the right thing, this parting advice is hardly unique to hepatology or medicine. Yet, the simple acts of kindness, friendship, and generosity bestowed upon me by my mentors, colleagues, and trainees have reinforced how much respect and kindness shown toward others comes back to reward each of us in multiples of what we give. Remembering how awed I was to meet the authors of key articles I had read as a young trainee, I try to return the favor with genuine interest in those who request my attention, promptly answering e-mails from others seeking advice, and remembering the challenges of seeking success and validation as a young physician scientist just trying to make a contribution. This all boils down to having integrity in defining and practicing one's core values, and acting upon them even when inconvenient, painful, or frustrating. I have had many role models and colleagues who have illuminated my path in this way and only hope that I can continue to light the way of those who follow.