

## Physician-Scientist Creativity: Challenges to the Three-legged Stool and Paths Forward

Members of the Association of American Physicians, the American Society for Clinical Investigation, the American Physician Scientist Association, and friends; addressing current and future leaders of American medical science on subjects of mutual interest at the 124<sup>rd</sup> AAP and 101st ASCI meeting is a daunting task. I have followed prior presidents in seeking guidance in recent Presidential addresses, which are available online and in the JCI[1-7]. I summarize a few key messages because they afford a sense of our community, recent challenges, and concerns. Lee Goldman artfully used baseball as a metaphor for the collaborative medical research team needed to define the ultimate clinical utility of cardiovascular drugs and devices. Tadataka Yamada described the pharmaceutical and academic collaborations that are critical for creating and testing new therapeutics. More recently, Judith Swain, Jerry Olefsky, and Dennis Ausiello have warned about the anticipated negative impact of the American decline in science, engineering, and mathematics test scores. They discussed the need for enjoining political allies for renewed public education and science initiatives. Elias Zerhouni has also stressed this latter point [8, 9].

Today, the AAP and ASCI have recognized the extraordinary leadership of Senator Arlen Specter in government funding for Education, Maternal and Child Health, and Biomedical Research, awarded him honorary membership in our societies, and invited him to address the Joint Societies. He has articulated a bold view of the importance of biomedical research. He described a newly filed Act, which would increase the NIH budget to 40 billion dollars and set aside an additional 2 billion dollars annually to fund the creation of small companies that would advance basic research discoveries toward development. He also reminded us that we need to extend Sutton's law from the clinic to our Congressmen and Senators, who need to hear from

their constituents about the importance of medical science for health and economic prosperity. We also celebrate the first 100 days of a new administration. President Obama's team is energetically confronting economic problems that threaten employment and long term support for public education and science. The President has consistently espoused enlightened views of the importance of education, science and engineering and will address the National Academy of Sciences, this coming Monday. We may be at the dawn of a new era of national leadership in science and technology.

I am reminded that in 2008, the AAP recognized Tony Fauci's effectiveness in educating our nation's leaders about the need for public investment in HIV, Biodefense, and Global Infectious Disease research, with the Kober Medal Award [10]. Dr. Fauci had recruited me to the AAP Council a decade ago, as Secretary. This past decade of involvement in AAP/ASCI joint meetings has been a wonderful opportunity to befriend and learn from colleagues, whose dedication to science and to the nurturing of young physician scientists is a core *raison d'être*; values, I share. The Secretary is also an important listening post for member concerns. Members were frustrated by the small number of newly elected members. The Council adopted new nomination forms, which enhanced our understanding of each Nominee's scientific accomplishments. Annual calls for nominations stressed the need for the nomination of women, underrepresented minorities, and investigators from underrepresented institutions. The number of new elected members has increased from 55 to 73. Women are now 15% of nominees and of new Members. The AAP and ASCI have welcomed the participation of the American Physician Scientist Association in the Joint Meeting. APSA is a vibrant young organization with members broadly representative of the more than 100 medical schools that have 500 new MD/PhD students per year. The joint meeting trainee poster sessions are well attended and are an

outstanding forum for discussing trainee science and career development. AAP members voluntarily contribute to APSA. Our members are justifiably proud of this progress.

However, more can be done. Our country still struggles with entrenched socio-economic disparities that affect opportunities for our youth. This has implications for the AAP. The single figure is a map of the States with the number of active AAP members and the number of medical schools in each state. Numbers shown in larger print are states with a medical school associated with a historically black University. Unfortunately, these latter institutions are in States that are under represented in AAP active membership. For example, Georgia has 14 active AAP members and four medical schools, including Morehouse. The District of Columbia has 3 active AAP members and 3 medical schools, including Howard. Tennessee has 32 active AAP members and 4 medical schools, including Meharry. In contrast, Massachusetts has 147 AAP members in 4 medical schools. Nominating and electing leading physician scientists from underrepresented and minority medical schools would increase minority physician scientist trainee participation in the Joint Meeting; a goal that we all share.

In looking to my predecessors for inspiration, I have also thought about my own career and what insights I can offer about physician scientist training. I was raised in Philadelphia, attended a predominantly black elementary school through 4<sup>th</sup> grade, benefitted from a tracked educational system, and graduated from Central High in 1960, at age 17. I completed Chemistry at Penn in 1963 and Medicine at Hopkins in 1966. Working in research laboratories from the beginning of college to the middle of my second year at Hopkins enabled me to realize that I could be happy in laboratory research. However, I also developed a deep affection and respect for clinical medicine, having learned physical diagnosis from Victor Mckusick, differential diagnosis from John Harvey, and in-patient care from Osler Interns and Residents.

I maintained that patient focus as I went off to the University of Chicago for Internship. I had chosen Chicago because a Hopkins Laboratory mentor, Bernard Roizman, was establishing a Virology Program and Hans Hecht, Chair of Medicine, allowed fast-tracking to research laboratories after an additional year of Residency. Tools for studying the molecular biology of virus replication in human cells were rapidly evolving. After 3 years on Herpesvirus projects that didn't arouse my colleague's or mentor's interest, I began to study Herpesvirus DNAs, obtained the first intact genomes and compared them to each other and to phage DNAs [11, 12]. In 1971, Hans Hecht and Alvin Tarlov asked me to start an Infectious Disease Division at Chicago. Pharmaceutical companies were producing new antimicrobials that could support patients through abdominal surgery, cancer therapy, or immune suppressive treatments and trainees were keenly interested in learning to use these new drugs. Lectures to medical students and Rounds with a Fellow occupied most of my day. My small laboratory included a technician, a graduate student and a Ph.D. Post-doctoral trainee.

Epstein had discovered the first human cancer virus in African Burkitt Lymphomas [13]. Henle and Pope had found that EBV infection caused perpetual lymphocyte proliferation [14, 15]. A Herpes Virus genome that could drive lymphocyte proliferation demanded attention. Initially, I had to grow 300 liters of tumor cells to get 1ug of intact EBV DNA. To compare genomes from various sources and to identify the virus genes that encoded RNA in tumors and transformed cells, I made DNA polymerase from *E. coli*. and single strand specific endonuclease from *Aspergillus*[16, 17]. I needed help in clinical and classroom Infectious Disease teaching. With Tarlov's support, I recruited Pierce Gardner, an outstanding clinical teacher. As Pierce took the central role in clinical teaching, I had more time for laboratory investigation. With graduate students, and Post-Docs, I made, traded, and bought restriction endonucleases, constructed maps

of EBV genomes, created complete molecular clone libraries, cloned and sequenced cDNAs from transformed cells, and studied the biological and chemical properties of the open reading frames. Together, Pierce and I recruited and nurtured first rate clinical fellows, most of whom became successful clinical teachers or investigators, duplicating the differentiation that served us well. The patient care, teaching, and research legs of our joint stool were in place.

As a result of shortened college, medical school, Residency, and PhD training, by 1978, I was 35, administering an NIH funded Infectious Disease training program, engaged in R01 and ACS funded research in a new NCI funded research building, and working with 6 Ph.D graduate students, 4 MD, Ph.D students, and 4 Post-Ph.D. trainees. Research and training in the molecular biology and genetics of EBV replication, vaccine development, and the pathogenesis of lymphoproliferative diseases was my muse. Our experiments were designed to identify critical genes and peptide sequences necessary for transformation and new pathways in lymphocyte growth and survival [18, 19].

A key component of my story was marriage to my high school girl-friend, Jacqueline. Her extraordinary devotion to our children and home life left me with the time necessary to train and nurture a research team and to plan and execute novel experiments. Flexibility in graduate education enabled her to continue courses and research on a part time basis. Today, many young investigators need a period of flexibility in combining career advancement with family support.

Having achieved mastery of medical skills and knowledge in clinical specialty fellowship, today's physician scientist comes to their mentor's laboratory or research clinic for encouragement and instructive dialectic in how to harness the powerful array of investigative tools for in silico, in vitro, cell-based, model organism-based or human oriented research.

Frequently, experiments that are conceptually and procedurally demanding offer the best chance for major discovery. At the same time, clinical mentors and clinically oriented compatriots urge continued involvement in patient care and teaching. Economic factors also favor retaining some clinical activity. However, a complete break from unrelated clinical activities is critical to an effective transition and subsequent rapid movement to an independent research career.

While most writers on this subject view ages 25-40 as years of maximum creativity, physician scientists are applying for their first R01 in their 40's. Deferral of research independence is most unfortunate and we have let it happen. Can we foster systemic change, shortened training paths, save time and money, and retain youthful creativity? A renewed focus on basic educational principles might help.

First, early engagement in career activities is the best path to a suitable career! We should mentor prospective medical science trainees from the last year of high school onward to engage in scientific research, teaching, or patient care. Trainees with serious scientific or other creative intent should be encouraged to initiate laboratory or other investigations, while they are taking formal courses. The range of creative opportunities in biomedical sciences and medically related engineering, social, cognitive, and psychological sciences, anthropology, ethics, law, and economics is very broad. Trainees should also be encouraged to assess their intrinsic satisfaction and to follow their instincts. They should consider attending a college that offers a robust 3 year curriculum in their area of choice and allows early graduation or early matriculation to Medical School. Medical School can be reduced to a 3 year core curriculum, with the option of a year for creative investigation, perhaps part of a post graduate program. These are not a new concepts. Many European and even some American Colleges and Medical Schools offer 3 year career-oriented curricula. Physician scientist admissions to Medical Schools should be handled by

committee members experienced in the evaluation and recruitment of trainees with focused research or creative interests.

Second, basic statistics and principals of study design need to be taught in the context of reading key scientific articles in college biology and clinical research articles during medical school. All too often, trainees identify this need as they complete clinical fellowship and choose a career in clinical investigation. Since they are more familiar with programmed coursework, they frequently undertake an MPH, thereby accepting further delay and expense, before engaging in research.

Third, basic or clinical laboratory based physician scientist trainees should be allowed to short track in Residency and Fellowship and reduce their direct clinical experience, when that is appropriate for their long term career interest and ability. The current practice of substituting 2 years of outpatient continuity clinics for a year of residency results in patient phone calls, e-mails, and emergency follow up visits, which substantially delay laboratory acculturation. We should work through the APM and the AAMC to request that certifying agencies loosen training requirements. Clinical competence is assessed by Residency and Fellowship clinical trainers and by certification exams. Fellows that are clinically competent and have appropriate exam scores should be allowed to transition to the laboratory. Attendance at relevant weekly clinical conferences can substitute for continued patient care responsibilities.

Fourth, laboratory based physician scientists should not be second class participants in loan repayment, research training, or career development programs relative to “hands on clinical” investigators. Basic cell culture research resulted in the unanticipated growth of Polio Virus in cell culture [20] and immunizations that prevent infection, associated human suffering,

and medical expense. If laboratory based physician scientists are creative and productive they should have appropriate 5-year K08 type support and not engage in clinical teaching activities more than 2 weeks per year, unless that is relevant to their research. Laboratory trainees need 5 years of support to obtain and supplement R01 funding for their laboratories. Mid-career research salary support should be extended to this group. Physician Scientist Career Salary and Grant support programs from the HHMI, Doris Duke, Burroughs Welcome, Pew, Sarnov, Damon Runyon, American Cancer Society, American Heart, Juvenile Diabetes and other private foundations have also had major roles in enabling physician scientists to transition to independence. We must encourage the continuation of these important programs.

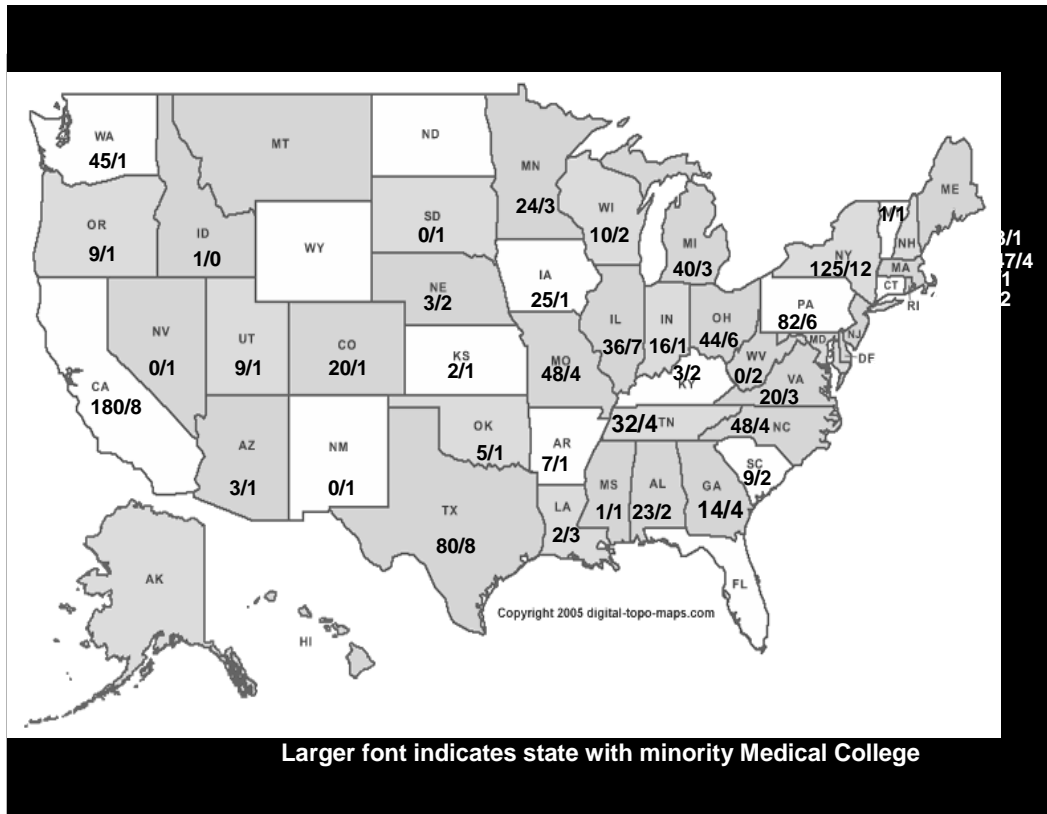
To summarize, building trainee competence and confidence in a chosen area of laboratory or clinical research, patient care, or teaching from high school through college, medical school, and post-graduate medical training will enable earlier career selection and time- and cost- effective education. Loan relief, career development awards, needed changes in education and certification requirements, and acceptance of the importance of differentiation for effective “time-on-task” career advancement can enable physician-scientists to more rapidly become fully independent colleagues. Additionally, the increase in average productive life span over the last 50 years makes it possible to have a flexible period of family social support within careers of major accomplishment in biomedical sciences or other creative areas of medicine.

Thank you for your attention.

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