LEGENDS IN UROLOGY

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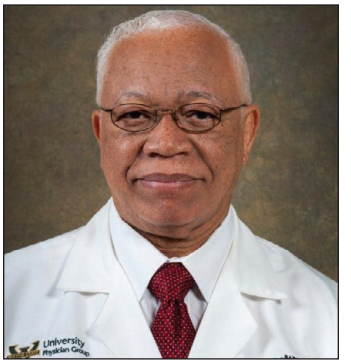

I would like to thank the Legends in the Urology Section of *The Canadian Journal of Urology* for inviting me to tell the story of my challenging journey through uncharted waters to this stage in my medical career. As an African American, there were no paths for me to follow. Nor were there African American mentors to give me direction. In fact early in my life I was directed away from my goal of attending college.

I was born in Cincinnati, Ohio but moved to Gary, Indiana shortly after birth. Gary was a segregated city, but I did not realize the impact of segregation or racism until my early teenage years. Even in northern United States there were schools for "Coloreds" (as we were called at that time) and "Whites". In my second grade, I transferred to a K through 12 school that had just been integrated. The year before I enrolled, which was the first year the school was integrated, the all White teaching staff went on a strike and refused to teach "Coloreds". However, this was quickly resolved. As years passed, it became clear to me that I was not selected to be included in college preparatory classes even though my grades were very good. This impacted negatively on my reading and writing skills. However, I excelled in mathematics and science without any assistance. The greatest insult occurred in my Chemistry class where I achieved one of the highest grade averages in the class and the highest score on the national chemistry examination. When I asked my Chemistry teacher about attending college, he said he didn't think I would succeed in college. He told me to forget about it and get a job in a laboratory of the Gary steel mill. I never forgot about that devastating incident. Today it provides motivation for me to succeed, whereas for others it might have damaged them psychologically and caused poor self-esteem. I attended the University of Michigan and immediately realized that my educational background was inferior to most students there, especially in classes requiring reading and writing. Obviously, this did not allow me to compete at a high level. In the late 50s and early 60s, challenges of racial bigotry in the classroom and off-campus housing in Ann Arbor added to my frustration and stress. This was before the fair housing laws were passed and enacted. Nevertheless, I succeeded enough to graduate but was unable to compete to enter to medical school immediately. I attended graduate school and obtained a Master Degree in Embryology. Finally I was admitted to Indiana University Medical School and I did well. However I still faced the challenge of bigotry in the classroom and in obtaining off-campus housing in Indianapolis. In fact, when moving in with some of my White classmates, I was threaten to be arrested for trespassing and given 1 hour to move out by the landlord. I asked them before moving in to check with the landlord to see if he would rent to "Coloreds". They didn't ask and the rest was history. They were shocked and embarrassed by the incident. I moved to a hotel for a couple weeks before finding a place to live.

In my senior year of medical school, I had difficulty deciding which direction of medicine to pursue. I met Dr. John Donohue who just arrived from Harvard to be the Chairman of the Department of Urology at Indiana University Medical School. I was so impressed with him as a physician, surgeon and gentleman that I immediately decided that Urology was for me. I did my residency at Henry Ford Hospital in Detroit, Michigan expecting to pursue private practice. There were no African Americans in academic Urology known to me. Thus, I thought that to pursue academia would be a challenge I didn't want to engage.

During my residency I met an intelligent and beautiful young lady who was pursuing a PhD in Human Genetics at the University of Michigan. It was love at first sight. After she obtained her PhD, we got married which began an outstanding future. I attended national genetic meetings with her, where there were presentations on chromosomal genetics, including kidney cancer and genetic instability of bladder carcinoma. This got my attention and aroused my interest to study bladder cancer chromosomal abnormalities. My research began while I was in private practice. With tutoring from my wife and other geneticists at Wayne State University (WSU) in Detroit, I was initially successful at publishing our data. However, it became difficult to continue research while in private practice, thus I joined the urology faculty at WSU as an assistant professor.

After a few publications on the loss of chromosome 9 in papillary bladder carcinoma and the difference genetically from CIS (carcinoma in-situ), where re-arrangement of chromosome 1 was more prevalent, I moved on to prostate cancer research. This was in the late 80s and PSA testing for prostate cancer was beginning to identify early prostate cancer. In addition there was significant racial disparity in the diagnosis and mortality rate of prostate cancer amongAfrican American men, (AAM) and European American men, (EAM). The incidence of prostate cancer of AAM was 60% higher and mortality rate was two to three times greater than EAM. Currently, it is unchanged since the reporting of Surveillance Epidemiology and End Result, (SEER) data. The question is why. It became imperative that I pursue prostate cancer research to understand the cause of this racial disparity.

My hypotheses were for the causes in the disparities were health seeking behavior, environmental (diet), and genetics. Initially, I led a team of investigators to study health seeking behavior. Our first funded study included a prostate cancer screening comparison study that investigated men screened with PSA testing at community sites, mostly churches, and compared to men seen in the clinic. We also offered a questionnaire to evaluate health seeking behavior. We identified important barriers to seeking health care, which included fear of the diagnosis of prostate cancer and distrust of the predominately White health care system. Men associated a diagnosis of prostate cancer with death because they were not aware that early diagnosis would most often lead to cure. The distrust was based on the fear of being a "guinea pig" ("experimented on") in a White health care system. Further, some were aware of the Tuskegee experiment where men and women were experimented on without informed consent with very detrimental effects. There was a significant improvement in the stage of disease among men screened for prostate cancer as oppose to those seen in the clinic with symptoms or those seen for general examination. The study was published as the Detroit Education and Early Detection (DEED) study and served as model for others across the nation to follow.[1]

There is a continuing controversy about prostate cancer screening or testing. U.S. Preventive Service recently stated that prostate cancer testing should not be conducted among healthy men. We (our team at Wayne State University) hypothesized that the reduction and elimination of racial survival disparity among AAM (high-risk group) compared to EAM (intermediate-risk group) during the PSA testing era compared with the pre-PSA era would strongly support the use of PSA testing in AAM. We used SEER data to investigate relative survival disparities between AAM and EAM. To evaluate pre-PSA testing era, we selected malignant first primary prostate cancer in AAM and EAM, all stages, diagnosed during 1973-1994. To evaluate relative survival disparities in the current PSA testing era, we selected malignant first primary local, regional, and distant stage prostate cancers diagnosed during 1998-2005 to calculate 5-year relative survival rates. Results demonstrated that age-adjusted 5-year relative survival rates of prostate cancer diagnosed during 1973-1994 in the national SEER data revealed significantly shorter survival for AAM compared with EAM ($p < 0.0001$). The SEER-based survival analysis from 1995 to 2005 indicated no statistical difference in relative survival rates between AAM and EAM by year of diagnosis of local, regional, or distant stage prostate cancer. We concluded that the elimination of prostate cancer racial survival disparity of local, regional, and metastatic prostate cancer relative survival in the current PSA testing era compared with pre-PSA era as an endpoint to test PSA efficacy as a marker for prostate cancer diagnosis is evidence for aggressive testing of AAM.[2] However, the mortality rate continues to be two to three times greater among AAM compared to EAM and has been for 4 decades. Again the obvious question is why!

We proposed that a more rapid prostate cancer growth rate and/or earlier transformation from latent to aggressive prostate cancer in AAM than in EAM contributes to this disparity. To prove this we evaluated entirely embedded prostate glands on autopsy from 1,056 AAM and EAM who died of causes other than prostate cancer. We also reviewed data from our radical prostatectomy database and from the Detroit SEER database. The autopsy data indicated that subclinical prostate cancer in AAM and EAM starts at a similar early age (20 to 29) and clinical characteristics do not differ by race at early ages. Radical prostatectomy specimen data revealed that prostate cancer volume and Gleason grade were greater in AAM than in EAM beginning at age 40. Advanced or metastatic prostate cancer occurred at a 4:1 ratio in AAM and EAM, respectively, in the Detroit SEER registry database. We concluded that these findings support the concept that prostate cancer grows more rapidly in AAM than in EAM and/or earlier transformation from latent to aggressive prostate cancer occurs in AAM than in EAM.[3] Again the question is why! There is growing genetic evidence to support these findings.

The most important fact that I learned from geneticists is that cancer is a genetic disease. A mutation or alteration must happen to a gene before it can code for change in protein phenotypically presenting as a cancer. It may be an environmental, life-style, metabolic or hereditary factor impacting the gene, but something must cause a gene mutation or alteration. This began my translational research of prostate racial disparity. Our (team at WSU) first endeavor included a single gene (CYP3A4) study and a study of how CAG repeats impact on prostate cancer.[4,5] During this time, I was contacted by Dr. Frances Collins at the National Human Genome Research Institute, to help recruit families to study hereditary prostate cancer. I established a national team with a majority of African American clinicians and investigators to accomplish this goal. It was known as African American Hereditary Prostate Cancer (AAHPC) study group. We successfully recruited more than 100 families. Currently the germline genes of these families are being studied as part of our International Consortium of Prostate Cancer Genetic (ICPCG) study group.

However, after considerable discussion with my colleagues at WSU, it was becoming clear that multiple genes and their interactions were responsible for sporadic or somatic prostate cancer. Therefore we studied microarray-based methods to measure expression levels for 517 genes that were previously associated with prostate cancer in archived formalin-fixed paraffin embedded (FFPE) specimens. We tested the hypothesis that gene expression features of functional consequence to cancer distinguish prostate cancer from AAM and EAM. A test was conducted comparing AAM to EAM expression levels for each probe on the array. Results: Analysis of 639 tumor samples (270 AAM, 369 EAM) showed that 95 genes were overexpressed specifically in prostate cancer from AAM relative to EAM and 132 were overexpressed in prostate cancer from EAM relative to AAM. Furthermore, systems-level analyses highlighted the relevant signaling pathways and functions associated with the EAM- or AAM-specific overexpressed gene sets. For example, inflammation was associated with AAM and lipid metabolism with EAM. In conclusion, results bring further understanding to the potential for molecular differences for prostate cancer in AAM versus EAM.[6] We continued our research by using bioinformatics (Computational Biology) to identify functional driver genes among AAM in comparison to EAM. The genes we identified among AAM were reported to be associated with more aggressive prostate cancer than those genes identified among EAM. This was followed by developing a network of interaction of these genes derived from Ingenuity Pathway analysis. Genes do not act alone!

In the future, we plan to validate our above findings in eight other institutions and utilize Next Generation Sequencing. We have submitted a program project grant to carry out this investigation. The specific aims include: Project 1, where we will validate previous gene expression differences for EAM and AAM by high-throughput RNA sequencing and deliver robust and refined gene signatures associated with subsets of patients. Project 2 takes the refined and validated gene signatures and develops gene scores and then tests them in an implementation study to produce clinically viable biomarkers. These biomarkers are combinations of genes specific to each race that can be utilized as predictors of outcomes for men on active surveillance and men who have undergone radical prostatectomy. Project 3 will study specimens from West Africa to address the hypothesis that shared genomic information will clarify why men of African descent, including AAM, have high rates of aggressive prostate cancer. It has recently been reported that Ghana has a higher incidence of prostate cancer than AAM.[7] The comprehensive analysis proposed is essential to understand prostate cancer diversity and will directly influence change in clinical decision making to overcome race disparities. Ultimately the goal will be to develop targeted precise therapy. One size will not fit all!

My professional career has been driven by the word WHY! In order to answer the question "why", requires perseverance, teamwork, the acquisition of knowledge, and of, course funding. My motivation was further driven by being a prostate cancer survivor of 19 years and a muscle invasive bladder cancer survivor of 9 years. Fortunately, the bladder cancer was small but had a 10% to 15% micro-papillary component. I had an aggressive transurethral resection and three courses of chemotherapy and I still have my native bladder with no recurrence. I am blessed. I want to thank my family for supporting me through this challenging adventure and exciting career.

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References

1. Powell IJ, Heilbrun L, Littrup P et al. Outcome of African American men screened for prostate cancer the DEED (Detroit Education and Early Detection) Study. *J Urol* 1997;158(1):146-149.
2. Powell IJ, Vigneau, FD, Bock CH, Ruterbusch J, Heilbrun LK. Reducing prostate cancer racial disparity: evidence for aggressive early prostate cancer PSA testing of African American Men. *Cancer Epidemiol Biomarkers Prev* 2014:23(8):1505-1511.
3. Powell IJ, Bock CH, Ruterbusch JJ, Sakr W. Evidence supports a faster growth rate and/or earlier transformation to clinically significant prostate cancer in black than in white American men and influence racial progression and mortality disparity. *J Urol* 2010;183(5):1792-1796.
4. Powell IJ, Zhou JY, Sun Y et al. CYP3A4 genetic variant and disease free survival among Caucasian and African American men after radical prostatectomy. *J Urol* 2004;172(5, Part 1 of 2):1848-1852.
5. Powell I, Land SJ, Dey, J et al. The impact of CAG repeats in exon 1 of the androgen receptor on disease progression after radical prostatectomy. *Cancer* 2005;103(3):528-537.
6. Powell IJ, Dyson G, Land S et al. Genes associated with prostate cancer are differentially expressed in African American and European American men. *Cancer Epidemiol Biomarkers Prev* 2013;22(5):891-897.
7. Hsing AW, Yeboah E, Biritwum R et al. High prevalence of screen-detected prostate cancer in West Africans: implications for racial disparity of prostate cancer. *J Urol* 2014;192(3):730-735.