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Research Philosophy

Understanding the Cancer Biology Universe

Enigmas, Context and Future Prospects

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HISTORICAL PERSPECTIVE

It took me six years to graduate from college with a “C” average and now I hold five professorships at Johns Hopkins. This is a brief story of how this happened and what one might need to know to conquer cancer.

In 1953 at 21 years of age and after much meditation and thought, I dedicated my life to pursuing the riddle of cancer and how this disease might be controlled. I never knew anyone who had cancer, nor did I know any physicians. In fact, this calling was an epiphany to me, and I had to go to the library to look up the meaning of the word cancer. I was born in 1932 in Bristol, Tennessee and Virginia, a twin City. My father had never finished high school and ran a service station, and I had supported myself financially since I was 15 years old by working during my free time. I was troubled by dyslexia, but no one knew of this type of disability then, nor that I had this problem, so they just considered me somewhat different. I had major academic difficulties and did not excel academically; however, outside of school I did well in track, basketball and scouting projects.

At the time of my cancer career revelation, I was working in a bakery on the 3–11 evening shift and commuting by day to East Tennessee State University, 25 miles away. I was married to my college sweetheart, Eula, and we had a baby daughter. With only a “C” average in college, I knew I would have to obtain evening work in some local factory working on science. I took a position as a laboratory technician at the North American Rayon Corporation in Elizabethton, Tennessee and rose up to work in the Research Department where Dr. Lee R. Herndon thought I should attend graduate school and suggested that I attend his alma mater, The Johns Hopkins University in Baltimore, Maryland. I moved to Baltimore in 1957 and assumed a full-time position as a Chemical Engineer at the Westinghouse Corporation. Although I never had a course in engineering, I did well at this position. In the evening I worked a second job as a lab technician in the Department of Urology at The Johns Hopkins Hospital and worked on prostate cancer. In 1953, I took a 50% pay cut and left Westinghouse to take over as the Acting Director of the Urology Research Lab for one year. In 1960, I was interviewed by each member of the faculty of the Department of Biochemistry, headed by Dr. Albert Lehninger and was accepted as a graduate student at Johns Hopkins where I received my Ph.D. in 1964. Dr. Lehninger was then interested in hiring me as a faculty member but not if I wanted to work on cancer, which he considered a “grave yard for Biochemistry.” I declined the Biochemistry appointment and chose instead to join the Department of Pharmacology and was given my first faculty appointment at Hopkins in 1965. I was the Acting Chairman of the Department of Pharmacology in 1974, the Acting Director of the Oncology Center in 1987, and for a year and a half I ran the second largest clinical department at Hopkins without holding an M.D. In 1998, I was elected President of the American Association for Cancer Research, and I was instrumental in helping to double the NIH budget. My greatest contribution has been attracting bright, young students to the field of cancer research such as Bert Vogelstein, Andrew Feinberg, Drew Pardoll, Alan Partin, Leland W.K. Chung, Warren Heston, William G. Nelson, William B. Isaacs, John T. Isaacs, Jonathan Simons, Kenneth Pienta, Robert Getzenberg, Angelo DeMarzo and many others.

My main area of research expertise is tumor cell biology, which contributes to our understanding of the organization of DNA in the nucleus. We discovered that nuclear shape was determined by a nuclear matrix and it possesses the ability to organize DNA loop domains which contain fixed sites for DNA synthesis. I have also spent forty years focusing my research efforts on understanding prostate cancer. Presently, I am the Research Director in the Department of Urology and active in several cancer advocacy groups, such as the National Dialogue on Cancer.
PHILOSOPHICAL VIEWS

How is it possible for a man without any formal training in any of the fields in which he holds five professorships at Hopkins to also become the Acting Chairman of a basic science department and the Acting Director of a cancer center? It’s the same way you become a great chef without having taken any courses in cooking, or a great musician without any formal training. You must love and be totally dedicated to the field, refraining from any form of scientific arrogance which will only blind you. I approach every problem by careful observation, asking “If this is true, what does it imply?” You may have straight A’s from an ivy league college, but still not possess the ability to do this.

First, I assume that everybody’s theory is true and all observations are true, and then conduct the analysis by generating at least five explanations. The second fundamental is to state: “You don’t have to assume anything you can prove.” Your pet theory is not your best friend. I then try to figure out ways to test these theories to determine if they really are true. You can find many experiments performed by others which might shed light in confirming or eliminating one of the mechanisms. I try to spend as much time thinking about the results as I do performing the experiment. Some of these simple thoughts and approaches have been listed in a paper entitled “The Final Exam.”

New insights and critical questions can be hidden within the enigmas and paradoxes of a field and I try to find a new way to look at these questions so that it all might ultimately make some sense. This includes any controversial field in cancer where there are two schools of opposing thought in which I try to find a new mechanism that will make everyone right. One of the best ways to gain biological insight is to study the biology of evolution and determine how that effects what you are studying. There have been 3.5 billion years worth of successful biological experiments conducted by nature, during which the inefficient pathways were eliminated. Therefore, understanding cancer as an evolutionary process is absolutely paramount to this field.

VISIONS OF THE FUTURE

In this section, I outline the series of questions that show how one might apply evolution to resolving these problems.

Critical Questions, Enigmas and Paradoxes. The following list of eight enigmas and paradoxes within the field of cancer research illustrate opportunities for our present thinking. If we can solve these riddles, they might provide new insights into how to unravel the mysteries of cancer. This limited list of enigmas might provide some points of focus for new, young minds to consider as challenges.

(1) The Organ Specificity of Cancer. Why do some organs of the human body never develop cancer? Despite six billion people on the planet and several decades of study, there have been no reported cancers in, for example, the following organs: epididymis, vas deferens, bulbourethral gland. In these organs, cancer is essentially a nonentity in humans. In addition, cancers in the heart, mast cells and seminal vesicle are extremely rare. While one in ten get prostate cancer, less than one in a million have cancer of the seminal vesicles, however they lie in close proximity to each other and are both driven by androgens. The world literature has reported a total of only about 40 seminal vesicle cancers, while there have been many millions of cases of prostate cancer. What could possibly explain this dramatic tissue specificity that varies by more than one hundred thousand fold? This question is particularly perplexing since, in the individual host that contains the seminal vesicles and prostate, the organs share the same genetic and environmental backgrounds and lifestyle. The difference in the bulbourethral cancer and the similar prostate gland is even more difficult to understand. The same blood vessels and nerves that feed the prostate also serve the neighboring bulbourethral gland. The adjacent budding of the urogenital sinus in development that forms the prostate also forms the bulbourethral gland. Both of these glands function together in physiology, endocrinology and growth. At present, we have no insight into the tissue specificities of cancer, and all we can say is that with the same DNA sequence the answer must be within the context of the cell type or by epigenetics. We must explain this at the molecular level. At the moment, we don’t
have a clue except to think that the DNA is organized differently in every cell type. What determined this?

(2) Species Specificity. Of the many thousands of mammalian species, only the human and the dog have any significant risk of dying of prostate cancer. Aging animals who die in the zoo are devoid of prostate cancer, so why don’t the thousands of other mammalian species with prostates, such as cats and dogs develop prostate problems since they age as humans and dogs do? Even though the higher primates, such the chimp, have approximately 98% of the same DNA sequences as humans, the aging primates do not develop full blown cancer, such as prostate cancer that metastasizes to the bone and kills the host. I have addressed this in a recent article in relation to evolution, our diet and how it evolved for 95% of our time without cooking.2 In the past 12,000 years, we dramatically changed our life style and diet and so did our friend, the dog, who shared our diet and prostate cancer. The cat, horse, bull and chimp didn’t make this transition and don’t get prostate cancer.

(3) Geographical Specificity in Acquired Cancers. Approximately 10% of the total number of prostate, breast and colon cancers are directly inherited by what appears to be a Mendelian-like pattern. In contrast, over 90% of the rest of the tumors are acquired through somatic changes. Certainly the genes and environment interact, but the environment is the overwhelming factor. In Asia, the age-adjusted mortality rate of prostate and breast cancer can be more than an order of magnitude less than in the United States and yet when Asian migrate to the United States, the rates increase and in subsequent generations approach the native rate in the United States.2 This would certainly indicate that the environmental factors are paramount in these cancers although there certainly will be some classes of people with increased propensity due to polymorphisms.

We have known this Asian difference for over a half century yet it has not been resolved by any epidemiological studies, indeed, at present I know of no epidemiological factor directly implicated in prostate cancer. Are we missing something here? We need a new approach.

(4) Tissue Specificity of Inherited Defects in Oncogenes and Suppressor Gene Function in Carcinogenesis. Why are inherited cancers so tissue specific, particularly if the genes involved are critically conserved regulatory elements? Inheritance of many defects in suppressors and oncogenes can be shown to cause high penetrance in the development of specific types of cancers, but the same genetic changes have absolutely no carcinogenic effect when inherited in other cell and tissue types within the same host. For example, inheriting gene alterations that cause colon cancer will not at all increase your chances of prostate cancer and vice versa. If many of these are highly conserved cell cycle control genes or DNA repair genes, then how is it possible that the prostate and many other organs are inert to the genes causing colon cancer?

Tissue specificity is always explained as something to do with the context of the cell but what exactly is this? This may be visualized as DNA playing the part of a compact disc and the cell’s context as structure determining the computer part of the system. In biology, cell structure and organization is the hardware equivalent of computers whereas the DNA sequence is like a compact disc and represents the software portion. We are fond of saying cancer is a disease but it is also an epigenetic disease, and our studies may be at times out of balance when emphasizing these two important points. How important is the structural hardwiring of the cell?

(5) Are There Any Common Denominators to the Many Different Types of Cancer? One of the hallmarks of all cancers regardless of where they occur or how they are induced is a cell structure change. The earliest event that occurs in the carcinogenic process, both in vivo and in vitro in both animals and man is a change in cell structure termed morphological transformation. This structural change is seen by the eyes of pathologists, the only one who can diagnose cancer. What the pathologist observes for cancer is termed pleomorphism and indicates a variation in cell shapes. This variation in cell shape extends through the cell, including the nucleus, nucleolus and the chromosome. What determines this shape is a dynamic, interlocking structural scaffolding system termed a tissue matrix.3,4 This highly dynamic nuclear matrix can form self-organizing sites within the cell for fixed sites of replication,5,6 transcription and splicing events, as well as DNA rearrangement.7

(6) Why Can Some Cancers Be Easily Cured While Other Cancers Are Essentially Inert to Therapy. It is hard to believe that some of the most rapidly growing and aggressive cancers, such as acute lymphocytic leukemia, can be cured. Children with this form of leukemia have a 90 day survival time from the point of diagnosis if left untreated. This form of cancer can now be cured in over 80% of patients who live into adulthood. This cure rate is only possible, however, as long as the patient is diagnosed at a young age, and each day the patient ages before diagnosis the less chance there is for curing this cancer. Is this because of the length of the telomeres are shorter with age which causes genetic instability and heterogeneity within the tumor?

Everyone is aware of the fantastically successful therapy that is visualized with testicular cancer. For example, even Lance Armstrong—with multiple large metastatic lesions to the brain and throughout his body—could be cured by chemotherapy and then win the Tour De France. Why is this the case? What is the molecular basis for this type of cure that doesn’t exist in pancreatic cancer and many of our other solid tumors that are so inert to therapy. Who is studying why we succeeded? It is time to resolve why we are so successful with some cancers and why we fail so miserably with other types of tumors. Is this because some tumors are poised to self destruct, because there exist different degrees of genetic instability or is it the state of differentiation?

(7) Cancer Can Become Resistant to Every Form of Therapy while Normal Cells Do Not Become Resistant. Regardless of the type of therapy with any cytotoxic drugs, hormone ablation, radiation or immunological therapy, a clone of resistant tumor cells grows out and can destroy the patient. This is because the cancer cell has reactivated an evolutionary-like process that cause genetic instability and a diversity of tumor cell clones and this heterogeneity in turn produces resistant clones that can be selected to grow out and ignore the therapy. Evolution is the greatest form of assuring biological survival. The cancer cell has captured this evolutionary process and uses it against our therapy. Our normal cells are locked with a stable genome and do not have the ability to develop this cellular diversity so that the toxicity to our therapy does not diminish with time as it does in the cancer cell. Nature not only uses base mutations for evolution but it also uses DNA rearrangements. In fact, immunoglobulin and T-cell receptor rearrangements provides our immune system with the diversity to defend us against any foreign antigen entering our body. Chromosome rearrangements in meiosis are paramount in selecting the genetic traits of our individual children. Chromosome rearrangements are also critical differences in evolution between species. The DNA sequences of chimps and humans are very similar (about 98.3%), while the DNA rearrangements are most marked. Most leukemias and lymphomas that can be cured have balanced reciprocal translocation (T:9-22,
While the solid tumors that are most difficult to treat have unbalanced non-reciprocal translocations. We believe this increased diversity of more unbalanced translocations increases the diversity through chromosome instability and the survival patterns of these cancers. Recently, we reported on a candidate gene that may be implicated in forming illegitimate crossing over in chromosomes, resulting in unbalanced chromosome rearrangements. Transfection of this gene HMG-1 into prostate cancer cells with balanced chromosome rearrangement induced the unbalanced rearrangements.

If these genetic changes of unbalanced DNA rearrangements produce genetic diversity then it may prove very difficult to control any cancer with a single drug treatment. Even leukemias with 9-22 translocations that are treated with gleevec are now developing resistant clones. It may take multiple drugs to defeat cancer, but how many? We believe we must fight tumor evolution with biological drug evolution, i.e., to form a diversity of drugs to match the diversity of tumor cells. This approach is to have the tumor cell select from the diverse drugs of a library that have high affinity for binding to the different tumor cells and to amplify the drug to be specific for binding the tumor cell types. The selected specific binders would then be armed with radionuclides or drug conjugates to destroy the specific tumor cell target. This type of Darwinian therapy may be required to provide diverse drugs to defeat the diversity of tumor cell heterogeneity. We have recently reported the feasibility of this approach by selecting RNA aptamers specific for prostate specific membrane protein on prostate cancer cells from an RNA library.8

(8) Lack of Progress in Translation of Basic Discoveries to the Clinic. In the last two decades, well over 50,000 papers have been published on each major form of cancers, and yet, if you list the clinical changes that have occurred in the treatment of these cancers, they have been extremely rare. For example, in prostate cancer in the past 50 years, you can only point to nine discoveries being translated into clinical use. These include: androgen ablation therapy; the use of serum PSA; the use of the biopsy gun for needles biopsies; ultrasound and MRI imaging; Gleason grade; nerve sparing operation; the insertion of radioactive needles and conformal radiation; and the Partin Tables. These nine discoveries in prostate cancer are the only clinical changes that have occurred in the clinical treatment of this disease in a half century of research and yet there have been many thousands of papers. None of the thousands of R01 grants have yet made a major contribution compared to these clinical contributions that almost all came from the clinical setting. The same situation can also be said for cancer of the lung, colon, bladder, breast and renal cancer. In spite of the fact that we have had 20 years of the oncogene and 10 years of the suppressor gene contributions, we still struggle with how to apply these in the clinical setting. Finding the gene to sickle cell anemia does not guarantee a target clinical application. This is not to downplay the approach of molecular biology but only to stress that we have to broaden our frontiers into the biology and clinical arenas as well. What is esoteric and pleasing to our mind as reductionist doesn’t always translate into rapid clinical applications. Obviously, the frontier to understanding and controlling cancer will reside in combining creative molecular biology, with a better understanding of systems biology and evolution and a clearer view of the disease process. As the Nobel Laureate, Charles Huggins at the University of Chicago said, “I believe in hard work, young people, and the cure of cancer.” Too many of us are jumping on the obvious bandwagons of big science. Some more critical thinking on the issues might help. I hope some of the questions in this paper might spark a young mind. I sincerely hope every dedicated young investigator finds their way through the bureaucracy of grants, government control, bean counters, and naysayers and will follow their bliss to contribute to conquer cancer. Do not give up on yourself—we need you to sail on!

The End

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