Conclusions

Chapter 21

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„Cancer as a Metabolic Disease: On the Origin, Management, and Prevention of Cancer"

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The journal *Science* recently commemorated the fortieth anniversary of the US National Cancer Act with a series of articles that were thought to encapsulate the state of the field (1). Initiation of this act during the Nixon administration provided a massive stimulus for cancer research. Despite the massive research effort, major questions related to the origin and management of cancer posed in 1971 remain unanswered in 2012. Some of these questions include How do abnormalities in chromosome number arise in tumor cells? Can tissue-specific markers be used to determine the epithelial versus mesenchymal origin of a solid tumor? Can the immune system be manipulated so that it recognizes tumor cells as foreign invaders that must be eliminated from the body? Do viruses play a role in human cancer? The answer is a definite yes to the question of whether viruses play a role in human cancer (Chapter 9). Answers to the other questions have not been forthcoming. On the basis of the information in this treatise, I can provide credible answers to the other outstanding questions. Moreover, my treatise addresses many of the NCI "provocative questions" from the NCI web site (provocativequestions.nci.nih.gov).

I addressed in Chapter 10 the answer to the question of how abnormalities in chromosome number arise in tumor cells. Basically, the stability of chromosome number and the integrity of the genome are dependent on the integrity OxPhos. Spindle assembly and the fidelity of chromosomal segregation during mitosis are dependent on the energy of OxPhos. Injury to cellular respiration with compensatory fermentation will cause genomic instability including aneuploidy and mutations. It is the efficiency of mitochondrial respiration that maintains cellular differentiation and prevents tumorigenesis and dedifferentiation.

The information presented in Chapter 13 addresses the question of how tissue-specific markers can be used to determine the epithelial versus mesenchymal origin of solid tumors. Metastatic tumor cells arise from respiratory damage to myeloid cells, which are already mesenchymal. Many of the biomarkers expressed in metastatic cancer cells are also expressed in macrophages. While epithelial tumor

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cells proliferate rapidly, they do not generally metastasize unless they fuse with a cell of myeloid origin. Tissue biomarkers of myeloid cells are expressed in many metastatic cancer cells.

I present information in Chapters 13 and 17 that addresses the question of whether the immune system can be manipulated so that it recognizes tumor cells as foreign invaders that must be eliminated from the body. According to my view, metastatic cancer cells arise from cells of the immune system (macrophages). While it might be difficult to induce nonneoplastic macrophages to recognize neoplastic macrophages as foreign invaders, it might be easier to eliminate the metastatic cells of immune origin by targeting their energy metabolism and capacity for phagocytosis.

A significant emphasis of the anniversary issue of *Science* was devoted to how targeted drugs could be combined to stop resistant tumors. "Even the most successful targeted therapies lose potency with time. Researchers hope to figure out how tumors escape; they aim to turn months of survival into years" (2). I have real difficulty with these statements. Any successful therapy for advanced metastatic cancer *should* provide long-term management for the disease. That this seldom happens indicates that few successful targeted drug therapies are currently available. It is, therefore, misleading to imply that successful therapies for *advanced* cancers are available.

It is clear to me how tumors escape from the so-called "successful therapies". Cancer cells will escape as long as they can maintain their ability to ferment. Fermentation energy (glycolysis) underlies drug resistance (3). If tumor cells cannot ferment, they will die. How many of the targeted therapies actually shut down glucose and glutamine fermentation? A statement was made indicating that "uncontrolled cell growth is often driven by an aberrant protein in the cell membrane that transmits a spurious signal to the nucleus instructing it to divide" (2). This is nonsense. Proliferation is the default state of cells. Respiration maintains growth regulation and the differentiated state. Fermentation drives unbridled proliferation. Uncontrolled cell growth is not driven by an aberrant protein but by *insufficient respiration with compensatory fermentation*. Rational drug therapies will be realized once this concept becomes more widely recognized.

It is important to recognize that my view of cancer as a metabolic disease is not part of the mainstream view of cancer, which is viewed as an incomprehensively complex genetic disease. Support for my position comes from a perusal of the articles in the *Science* issue commemorating the anniversary of the US National Cancer Act. No aspect of cancer metabolism was mentioned in this issue. As I mentioned in Chapter 10, *the failure to discuss the role of energy metabolism in the origin of cancer would be like failing to discuss the role of the sun in the origin of the solar system.* Should we be surprised that the same questions remain unresolved after 40 years? Should we be surprised that most targeted therapies developed from the cancer genome projects have been a costly waste of time? Should we be surprised that so little progress has been made in managing advanced cancers?

The following is a summary of major conclusions from my treatise. While some of these conclusions are subject to debate and further verification, I believe that they are supported by facts and will be confirmed in time.

MAJOR CONCLUSIONS

1. No real progress has been made in the management of advanced or metastatic cancer for more than 40 years. The number of people dying each year and each day has changed little in more than 10 years.
2. Most of the conceptual advances made in understanding the mechanisms of cancer have more to do with nonmetastatic tumors than with metastatic tumors.
3. Most cancer, regardless of cell or tissue origin, is a singular disease of respiratory insufficiency coupled with compensatory fermentation.
4. Some factors that can cause respiratory insufficiency and cancer include age, viral infections, hypoxia, inflammation, rare inherited mutations, radiation, and carcinogens.
5. The genomic instability seen in tumor cells is a downstream epiphenomenon of respiratory insufficiency and enhanced fermentation.
6. Genomic instability makes cancer cells vulnerable to metabolic stress.
7. Cancer cells do not have a growth advantage over normal cells.
8. Cancer progression is not Darwinian but Lamarckian.
9. The view that most cancer is a genetic disease is no longer credible.
10. Respiratory injury can explain Szent-Gyorgyi's oncogenic paradox.
11. Most metastatic cancers arise from respiratory injury in cells of myeloid origin, possibly involving hybridization events between macrophages and neoplastic epithelial cells.
12. Cancer cells depend largely on glucose and glutamine metabolism for survival, growth, and proliferation.
13. Restricted access to glucose and glutamine will compromise cancer cell growth and survival.
14. Enhanced fermentation is largely responsible for tumor cell drug resistance.
15. Protection of mitochondria from oxidative damage will prevent or reduce risk of cancer.
16. Life style changes will be needed to manage and prevent cancer.
17. Mitochondrial enhancement therapies administered together with drugs that target glucose and glutamine metabolism will go far as a nontoxic, cost-effective solution to the cancer problem.
18. A new era will emerge for cancer management and prevention, once cancer becomes recognized as a metabolic disease.

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