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Preface

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It has almost been a century since the Nobel Laureate, Otto Warburg, first described the phenomenon of *aerobic glycolysis* in cancers that he, at that time, postulated would result in acid-base imbalances. In the 1960s, buoyed by the ability to grow cells in culture for prolonged periods of time, a desire to optimize culture conditions led to the first investigations into the relationship between metabolism, acid-base chemistry, and proliferation. Harry Eagle defined many of the medium and culture conditions for various established cell lines and, from 1969 to 1973, focused almost exclusively in pH optima for growth, with the observation that transformed cells generally had lower pH optima than did their normal counterparts. However, cancer metabolism investigators were soon distracted from metabolism to genomic studies with the advent of new molecular biology tools. In 1976, the famous cancer biologist Sidney Weinhouse was reflecting on this when he said: "Since our perspectives have broadened over the years, the burning issues of glycolysis and respiration in cancer now flicker only dimly". However, despite these scientific headwinds, a number of investigators maintained their interests in cancer metabolism, many using the new tools of molecular biology. Further, in the last few decades, tools have been developed with which to interrogate metabolism and the acid/base balance of tumors *in vivo*.

These tools have shown that the extracellular pH of solid tumors can be profoundly acidic. The proximal **cause** of this acidity is elevated fermentative glycolysis in combination with chaotic and imperfect perfusion. The remaining questions in this arena focus on the evolutionary dynamics that would result in such a dysfunctional tissue architecture: "why and how are cells selected with increased aerobic fermentation?" and "how and why does a chaotic vasculature favor tumors over normal tissue?". These are both important questions that are likely related to acid-base balance. Indeed, cancer cells evolve to become acid-resistant and thus more fit than their normal neighbors.

More broad-reaching and less tractable questions relate to the **consequences** of altered acid-base balance. Changes in steady-state pH will have pleiotropic effects, primarily mediated by the ionization status of histidines. Histidines are overrepresented in the mammalian, and one may speculate, all genomes. Daniel Mazia, the famous sea urchin biologist once said to me: "Biological pH is not hydrogen ion activity, it is simply the ionization state of histidines". Indeed, this is the foundation of the "pH-stat" hypothesis to describe how fish can continue to reproduce at extremely low temperatures, as they are known to alter the quantity and quality of their proteins' histidine content. Because histidines are so abundant in important active or allosteric sites in proteins, it is unequivocal that changes in steady-state pH will have far-reaching and pleiotropic effects. It is the challenge for all of us to categorize these effects into those that are benign and those that are malignant.

A central characteristic of "malignancy" is the ability to metastasize. Hence, Cancer Metastatic Reviews is the best source to collate some of this information and (hopefully) inspire some younger scientists to investigate this field. It is truly a multidisciplinary arena of investigation. The study of cancer acidosis (or biological pH) requires expertise in physiology, transport, metabolism, physical chemistry, biochemistry, cancer biology, and translational oncology. I think you will find that these fields are well represented in the contributions to this volume entitled "Causes and Consequences of Tumor Acidosis."

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