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Preface: Physics of Cancer

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It has been a real pleasure to have worked with Professor Bernard Gerstman of the Department of Physics at the Florida International University on this special issue of The Physics of Cancer for *AIP Advances*.

Two questions probably spring to mind for the prospective reader of this issue: "why cancer, and why physics?" Let's tackle the "why cancer?" first. If cancer was just another one of the many diseases afflicting mankind it would of course be worthy of study but no more so than other diseases. However, there seems to be something quite special about cancer that makes it of intense scientific interest. That special thing is that we do not understand cancer well enough to have more than the flimsiest means of controlling it, let alone actually decreasing the mortality rate due to cancer. Figure 1 taken from the National Cancer Institute is an example of the rather grim picture in spite of many billions of dollars spent on cancer: the age-adjusted mortality rate is essentially flat over the past 40 years.

There are two basic reasons why the mortality rate is flat: (1) cancer tumors typically evolve resistance to various attempts to kill them, over a period of months to years. Once this resistance has evolved, the procedure designed to kill the growing cancer cells has to be changed and that is often a futile process. The evolution of resistance is basically a Darwinian process of natural selection, but in a very complex environment, and it may not be strictly genomic. (2) Most tumors if they were to stay in one place are survivable. Unfortunately, quite often they metastasize, that is, the cancer cells undergo an phenotype switch and become invasive, spreading to other quite specific parts of the body, depending on the tumor. If the metastasis is connected with the evolution of resistance to chemotherapy it is basically a one-way street to death of the patient. Metastasis can be seen as a change in the strategy of the tumor from being indolent, or slowly growing in one place, to an aggressive invasion of new territory. Thus, the "why cancer" question can be summed up by saying that cancer seems to be an uniquely unsolved problem in biology indicating that there are fundamental aspects of multicellular dynamics which we simply do not understand at present.

"Why physics?" I have been claiming (I am hardly the only one of course) for a few years that physics has to expand its horizons to accept the fact that biology may represent an intellectual challenge every bit as worthy as our attempts to find the Higgs boson, or grasp the emergence of collective phenomena in condensed matter systems, or understand the dynamics of quantum mechanics in atomic systems. It is possible that there remain truly deep mysteries in biology that we have not yet formulated from a physics perspective, but which may yield to the ideas in physics that have been so successful. The fact that we really have been stymied in dealing with cancer means to me that conceptually we really are facing a deep mystery.

Of course, beyond the pure intellectual challenge of cancer there is the technological aspect of physics that can be applied to cancer treatment. Physicists have made extraordinary contributions to biology over the past 100 years that have transformed the field. One need only stroll around the area surrounding Kendall T Station in Cambridge Massachusetts, past the Whitehead Institute and the Broad Institute, to be astonished by how biology has become an extraordinarily high-technology discipline. But we can't stop with genome sequencing; there are far deeper problems in cancer that will hopefully yield to new technologies that are still in the formative stages. Another aspect of

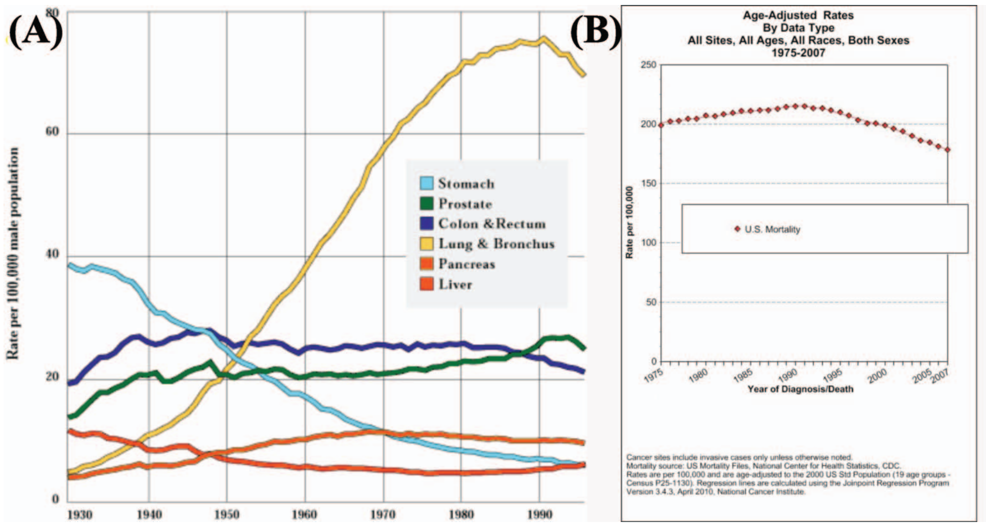

FIG. 1. (A) Rates of cancer diagnosis per 100,000 males versus time. (B) Age-adjusted deaths/100,000 people versus time.

physics which has not fully moved into the cancer world is the highly quantitive and predictive growth of our ability to create sophisticated models to understand the growth and dynamics of mutating cancer cells under stress, both mechanical and metabolic. Although the challenges are great, in principle modeling could be used in the future to do personalized treatment of cancers coupled with the development of high technologies.

I am happy to say that the 16+1 papers Prof. Gerstman and I have selected for this special issue span the challenging range of issues I have discussed above. Let's start at the top: The Big Issues of really rethinking cancer from a physics perspective and asking what new ideas we may need. The furthest one out there is clearly the article by Davies *et al.*,[1] "Implications of quantum metabolism and natural selection for the origin of cancer cells and tumor progression". I may not agree with many of the things posited in this paper, but I would have been very disappointed if we didn't have at least one paper which challenges us at a fundamental level. Another challenging paper that looks at the origins of cancer is the one by Soto-Ortiz and Brody,[2] "A theory of the cancer age-specific incidence data based on extreme value distributions", which questions the usual assumptions that cancer is due to the accumulations of "mistakes" in a random manner.

Less controversial but equally exciting are the papers by Chignola and Milotti[3] ("Bridging the gap between the micro- and the macro-world of tumors") and Jiao and Torquato[4] ("Diversity of dynamics and morphologies of invasive solid tumors") which attempt to understand the dynamics of an invading population of a mutating cells, while Chauviere *et al.*[5] uses the powerful ideas coming out of density functional theory ("Dynamic density functional theory of solid tumor growth: Preliminary models") to see if ideas which really first came out of quantum mechanics can be applied to tumor dynamics. Jia and Torquato[4] in their analysis bridge the gap between the genomic evolution occurring and the physical forces that are exerted on the tumor, a topic taken up in more detail by Gillies[6] ("Some observations on the mechanics and dynamics of tumor heterogeneity") and Pokorný[7] ("Physical aspects of biological activity and cancer"). Our own paper with Chris Cleveland[8] on "Physics of cancer propagation: a game theory perspective" tries to look at cancer invasion from a game theoretic perspective as opposed to a strictly physical one. Our paper brings up the subject of information transfer in cancer, and this is explored by Laise *et al.*[9] ("Modeling TGF-β signaling pathway in epithelial-mesenchymal transition").

In the more applied area of cancer therapeutics there are some very original papers debuting here. For example, there is the time axis: can modulations in the time of dosage alter the way that the tumor responds, and what role does the immune system dynamics play a role in cancer growth and development? These issues are addressed by Portz *et al.*[10] ("A clinical data validated mathematical model of prostate cancer growth under intermittent androgen suppression therapy"), Cerofolini[11] ("Host-guest interaction in cancer and a reason for the poor efficiency of the immune system in its detection and termination") and Wiley and Haraldsen[12] ("The theory of modulated hormone therapy for the treatment of breast cancer in pre- and post-menopausal women"). The development of new technologies, such as laser driven ultra-fast high energy proton therapy by Doria *et al.*[13] ("Biological effectiveness on live cells of laser driven protons at dose rates exceeding 10^9 Gy/s"), Alfano[14] explores using ultra-fast lasers to diagnose metastatic cancer cells ("Advances in ultrafast time resolved fluorescence physics for cancer detection in optical biopsy") while Solano *et al.*[15] explore photo-acoustic imaging ("An experimental and theoretical approach to the study of the photoacoustic signal produced by cancer cells"). I was intrigued by the paper of Frieboes *et al.*[16] which is a combination of sophisticated modeling of drug delivery to tumors coupled with new imaging technologies which will allow us to optimize modeling of drug delivery based upon observations. Bichsel's paper on "Statistics of cell dose and cell survival in C-ion therapy" was a bit late for the special issue but will hopefully appear in a subsequent issue of *AIP Advances*, that is the "+1" of the 16+1 papers we have selected.

This brings up something I hope will change in *AIP Advances*. As I said, I (along with others) feel that physics has to expand its horizons, to accept the fact that biology may represent a fundamental intellectual challenge to "hard" science. I hope that this Special Issue on the Physics of Cancer marks the start of a tradition of excellent biological physics papers in *AIP Advances*.

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