Breast Cancer: Targets and Therapy

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PERSPECTIVES

Breast cancer causes and treatment: where are we going wrong?

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Abstract: This discussion paper seeks to provoke thoughts about cancer research in general, and why breast cancer in particular is not yet "curable". It asks the question – are we looking at the disease in the right way? Should we regard cancer as a progressive state, which is part of aging? Should we tailor treatment to "reset" the system or slow progression rather than try using toxic and aggressive therapy to kill every cancer cell (and sometimes also the patient)? The thesis is presented that we need to revisit our fundamental beliefs about the disease and then ask why we cling to beliefs that clearly are no longer valid. The paper also questions the role of ethics boards in hampering research and discusses the concept that breast cancer is an industry with vested interests involving profiteering by preventive, diagnostic, and therapeutic players. Finally, the paper suggests some ways forward based on emerging concepts in system biology and epigenetics.

Keywords: breast cancer, causes, treatment, questioning paradigms

Background

There is a perception that cancer research generally, and breast cancer research specifically, is not progressing as fast as might be hoped from the investment in research. The National Cancer Institute cancer trends progress report for the US for 2011/2012 shows that the incidence of and death rates from breast, colon, and prostate cancers are stable. It calculates that women have a one in eight risk of developing breast cancer, although there is an increased probability of the cancer occurring between their 50th and 70th birthdays. Other reports show slight decreases in mortality (approximately 2% per year) but stable incidence rates.[1–3] However, the worldwide incidence is increasing by approximately 3% per annum and deaths by 1.8% per annum.[4] This suggests that while improved detection and treatment in developed countries may be reducing mortality somewhat, we are perhaps missing something big in how we try to prevent and treat breast cancer in the global context. This paper intends to provide a broad overview of cancer research approaches to determine if there are any particular reasons for this relative lack of progress. We do not claim to be breast cancer experts, and that is why we feel we can contribute an "out of field" perspective.

It could be suggested that because current approaches are not working as well as might be expected, alternative approaches should be considered. Although this might sound reasonable, there are now a large number of organizations heavily invested in the status quo. It has been noted, with irony, that more people benefit from breast cancer than suffer from it. Without impugning in any way the motives of any individual researcher, it could be that

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research structures and funding bodies are stifling innovative research by funding irrelevant but easily publishable work on the minutiae of a gene transcription pathway in a genetically sensitive mouse, rather than human based, but necessarily messier, research. The paper is structured as follows:

1. What are our fundamental beliefs and are they valid?
   - Clonal origin from a mutated gene
   - Aggressive therapy works
   - Screening works
   - Linear hypothesis of dose effect
2. Why do we believe invalid things?
   - Grant system and structure
   - "Easy" mouse models
   - Ethical issues make useful experiments difficult
   - Models assume a linear dose-effect relationship
   - Prevailing paradigms are supported by strong senior people who peer review
3. What can we do?
   - Positive suggestions to move forward.

What are our fundamental beliefs and are they valid?

Causes of breast cancer

If a new "big picture" approach to breast cancer is to emerge, it is necessary to step back from the gene-dominated approaches to causation and examine what might cause this cancer at the gross level and what issues there are in establishing preventative or delaying techniques rather than aggressive treatment approaches. There are well known causes of breast cancer, such as the "Western diet" and the fact that Asian women have a reduced incidence until they come to reside in the West,[5–7] smoking,[8–10] and radiation exposure.[11–13] There is also an ongoing controversy concerning the old idea dating back to 1943 that breast cancer may be caused by a handful of known oncogenic viruses.[14,15] The candidate viruses are mouse mammary tumor virus, human papilloma viruses, Epstein–Barr virus, and bovine leukemia virus. The latter may explain the East–West breast cancer issue via consumption of cow's milk and meat, but the evidence is very limited. It is possible that these viruses may collaborate with each other. The viral breast cancer hypothesis has a long history, with past failure to establish sound evidence of causation. This has dramatically changed because of the availability of new laboratory techniques discussed in the cited reviews. While diet, smoking, and control of oncogenic viruses are the subject of health education and guidance, radiation is not controlled to reduce risk; in fact, medical use of radiation represents the greatest radiation exposure to humans and, in our modern world, the risk of getting breast cancer may increase due to increasing elective or imposed medical radiation exposure. The female breast is, according to the International Commission on Radiation Protection, a very radiosensitive tissue.[16] While "safe" doses are generally determined as those that will not harm the most sensitive tissue, they depend on models using "reference man", ie, an ideal hermaphrodite body shape and epidemiologic data from the atomic bomb survivors of Hiroshima and Nagasaki.[17,18] These approaches estimate safe doses based on old and outdated radiation biology while ignoring modern research, which could mean the "safe" dose is not so safe or even positively beneficial. It is important to know because exposures, particularly in the low-dose exposure region, are increasing. Mammograms (which involve breast irradiation) are offered on an annual basis to women over 50 years in spite of controversy about their effectiveness, the anxiety caused by false positives, and the potential risks of radiation exposure in sensitive individuals.[19–24] Computer axial tomography scans have grown in popularity as elective tests during annual physical examinations. In the US, it is estimated that 90 million scans will be performed this year and a "wellness scan" is a common gift. This is very big business for medical doctors and hospitals as well as for producers of instrumentation. However, members of the public, who intensely fear very small environmental releases of radiation, do not seem aware that the wellness scan involves a whole body radiation dose of 3–20 mGy or more, depending on the specific test and the competence of the technician. In some cases, this is more than the annual dose limit for the general population.[25–27] There has been a lot of publicity about the risks of these scans for children, but there could also be an enhanced risk for females developing breast cancer.[28–31] Another new exposure, which is not so elective, is the use of backscatter X-ray machines as screening devices in airports. Again, they are said to be harmless, but that perception is based on the models referred to above and not on real data. The true risk will only emerge as the big human experiment with these machines progresses. Already there are concerns about skin cancer risk as the X-rays are low energy and do not penetrate far, but the breast is just under the skin and therefore at risk. As security paranoia increases, so may the energy of X-rays used, to enable more and more detail to be seen and to enable body cavities to be "searched". This is already done in diamond mines in parts of Africa.

Clonal origin from a mutated gene

A concept which has probably delayed progress in breast cancer treatment, among others, is the idea that cancer has a

clonal origin, ie, that a mutation occurs in a cell causing it to be initiated and to give rise ultimately to a cancer.[32–34] In the 20th century, this idea dominated to the extent that all other ideas were rubbished and unfundable; the Weinberg model[35,36] and the Knudsen model[37] were beautifully documented and very reductionist, in keeping with the times. In the field of radiation carcinogenesis, the idea that radiation could promote cancer was ignored, as were the concepts of microenvironmental influences, signaling mechanisms, and adaptive or inducible responses. Now there is a more enlightened view of carcinogenesis that admits the importance of these "nontargeted" effects,[38–41] but unfortunately the idea that cancer could be a system level "response" to environmental influences (both at the tissue and organism levels) is still not widely accepted, and the invention of the "cancer stem cell" has merely replaced the older (identical) view of the clonal origin of cancer with all the consequent reductionist approaches to "treatment", ie, eradication of the faulty aberrant culprit.

It is interesting to look at the history of conceptual approaches to the origins of cancer and how these led to the types of treatments used. Back in 1940, Haldane[42] remarked that,

> "When only physical and chemical methods are employed, only physical and chemical facts are forthcoming. The whole is not to be understood by the sum of its parts any more than an architectural masterpiece is to be comprehended by the chemical and physical analysis of the stones of which it is built".

Hyman,[43] a taxonomic zoologist also argued for a system level approach, saying,

> "All recent particulate theories in biology derive from that biological theory called the mechanistic or physicochemical explanation of life and this is in turn developed from the materialistic physics and chemistry of the 19th century according to which the universe consists ultimately of matter moving through space. This means that all vital phenomena can be explained fully in terms of physics and chemistry. Physicochemical investigation has achieved an illusory success by neglecting such matters as correlation, organisation, adaptation, evolution and psychic properties or by inventing special particulate theories for them. However, the synthesis of physicochemical facts about parts of an organism cannot reconstruct the living being".

While these quotes did not address cancer specifically, they do point to the need to adopt a system level approach to the development of a cancer, which takes into consideration the microenvironment, including the very important microvasculature that supports the growth and division of the cells, and the surveillance systems that permit the cancer to develop. The vasculature is a really important target because the tumor cannot survive without an oxygen/nutrient supply.[44–48] Many millions were invested in antiangiogenesis drugs, but these failed to show any beneficial effects in humans.[49–51] However, a new understanding of the processes of vasculogenesis and angiogenesis is emerging, suggesting that "out of field" elements coming from the bone marrow are capable of signaling regeneration of the vasculature in the treated tumor area.[52–55] The fundamental idea that the tumor bed was important in allowing the tumor to develop was first suggested in the early 1900s as a "seed and soil" hypothesis.[56,57] This suggests that this field should be revisited for breast cancer treatment. To quote Denis Noble,

> "Inspecting genome databases alone will not get us very far in addressing these problems. The reason is simple. Genes code for protein sequences. They do not explicitly code for the interactions between proteins […]."[58]

Similarly, inspecting data from genetically predisposed mice or mouse models with abnormal immune function is unlikely to answer questions about human breast cancer in human populations. At the practical level of improving cancer survival rates, possibly the most important new concept is that of Loeb,[59–61] who formulated the concept of the "mutator phenotype". This idea suggests that in a precancer host human, conditions in the microenvironment permit a greater than normal level of random mutations, allowing instability to occur. It is important to focus on the word "phenotype" because this implies change at the level of the tissue and not that an individual gene mutation has started anything. The gene mutations come after not before the system level change. This idea is of course well accepted in evolutionary biology where the concept of stress-induced or environment-induced mutagenesis is well established.[62–64]

Aggressive therapy works

One of the fundamental issues of medicine is that it is an empirical science. It does not have a strong theoretical base. Advances in treatment are usually developments of existing treatment. Clinical trials are between the existing treatment and the proposed new treatment, but there is never a "no treatment" control arm. However, if the existing treatment causes damage that is later attributed to the disease process,

and the proposed new treatment does as well, illusions of an effective treatment are perpetuated. It could be that the "miraculous cures" or "spontaneous remissions" (depending upon your point of view) are attributable not to alternative treatment, but effectively to no treatment.

William Osler, one of the fathers of modern medicine, famously remarked that "One of the first duties of the physician is to educate the masses not to take medicine".[65] It could be argued that this is an explicit recognition of the body as a self-correcting system. He continues "The desire to take medicine is perhaps the greatest feature which distinguishes man from animals". Again, it could be argued that there is recognition that pharmaceuticals can do more harm than good, and by corollary, a wait and see approach might be better. This approach is currently being used in prostate cancer management,[66] where patients are segregated into those with "indolent disease" where active surveillance but no treatment is preferred, those with intermediate disease where standard treatment is given to control local disease, and those with aggressive metastatic disease in whom individualized therapy is being tried. Trials are currently underway at Princess Margaret, Toronto, and at other major hospitals (R Bristow, Princess Margaret Hospital, personal communication, May, 2013). This personalized approach is aimed at identifying the response/nonresponse signatures and identifying those with "noisy" or unstable genomes predisposing to successful tumor evolution, and treating accordingly.[67]

In the breast cancer field, the established idea seems to be that breast cancer is a disease that needs treatment. Perhaps we need to adopt the ideas in the preceding paragraph and think of it instead as a process, like aging. A different conceptual model can then be used. Aging is a natural biological process, and it could be argued that cancer is too. If cancer is a natural process, the question is reformulated, so it is no longer why certain people get cancer, but why the majority of people do not.

The utility of the model is that it is no longer necessary to seek a cure, because there may only be one for symptoms not for cause. Instead, the emphasis would be on control and delay. The advantage of this conceptual framework is that it could avoid many of the treatments that "cure the disease but kill the patient". If cancer is a process, interference with the process could make the situation worse, as happens with many tumors that recur in more aggressive form after treatment. If the Loeb "mutator phenotype" hypothesis is correct, less treatment could equate to more effective treatment.[68] In a relentless, and probably unrealistic, attempt to rid the body of all cancer cells, highly toxic chemicals and immunosuppressives are often used. Apart from the fact that this approach challenges evolutionary and adaptive mechanisms in the host to enable survival of the cancer, the quality of life of the patient plummets, until the disease drops below "detectable levels". If the tumor biomarker level becomes detectable within 5 years, the patient has had a relapse; after 5 years a cure is declared.

One major issue is the confusion between knowledge and belief. Cancer treatment is often based upon belief rather than knowledge. A belief-based system is often unwilling to confront its uncertainty or lack of knowledge. To quote Osler, "The greater the ignorance, the greater the dogmatism".[69] Curing cancer has become in some ways a crusade, a battle of faith not of science. It has become a battle to kill the tumor without killing the patient, without consideration of whether that is the best treatment strategy. Perhaps the patient could survive with the tumor, in the same way we survive with intestinal flora.

In an article appearing in the UK *Daily Telegraph* on May 20, 2013, Lord Saatchi estimated 15,000 deaths occurred every year because of cancer treatment.[70] He told the House of Lords "What we do know is that the cancer drugs do such damage to the immune system that the patient is helpless to resist fatal infections like *E. coli* or MRSA or septicemia". He also said the Office for National Statistics under World Health Organization guidelines only recorded "the single underlying cause of death".

It is therefore very difficult to determine how many patients die during cancer treatment primarily because of the treatment. It is also difficult to have reasoned discussions about this, because of the lack of objective data.

Screening works

There is violent debate about the efficacy of screening (apart from the radiation issue and the problems of false positives and false negatives). Mammography screening is statistically proven to reduce mortality as discussed earlier;[19–24] however, the matter is rather more complex. See, for example, the *New York Times* article by John Allen Paulos published in 2009[71] or the *New York Times* editorial published at about the same time,[72] both of which suggest that there is more controversy than the peer-reviewed medical statistics papers would have one believe. A Norwegian study published in *The New England Journal of Medicine*[24] also suggests that the situation is complex. The idea is simple: if the disease is diagnosed at an early stage, the treatment will be simpler and more effective. Both of these claims need to be analyzed in turn, but first the definition of cancer needs to be examined. Recently, there has been a large increase in the diagnosis and treatment

of ductal carcinoma in situ. It has been treated, with no recurrence, and would seem to validate the screening program. However, there are now calls to re-examine the definition of cancer, and ductal carcinoma in situ would no longer be defined as cancer or warrant treatment. The economic costs of this overtreatment have been calculated to be substantial. Not as readily apparent is the fear engendered in the population, and cancer phobia may be linked to the more documented radiation phobia. Breast cancer is one of the fears of modern women, and some undergo preventive mastectomies and even oophorectomies if they carry the *BRCA 1* or *BRCA 2* gene. This fear is fed by charities encouraging regular screening, which often feature young and attractive models with babies in their advertisements.

Similarly, there is an argument that screening just alters where on the disease progression timeline it is encountered. If the natural history of cancer progression is 15 years, and it is detected early, regardless of whether the tumor is cured or not, the patient will survive 5 years and be "cured". This concept of "5-year survival" has possibly influenced the screening program. Again, it should be noted that screening is a big industry with unproven benefits, like the annual flu vaccine!

Linear hypothesis of dose effect

There is a prevailing wisdom that cause–effect relationships are linear, ie, "increase the dose/activity and you will also increase the effect". However, there is ample evidence that effects are not related to cause in any simple manner. Rather, the system is very complex, allowing for nonlinear, nontargeted, and chaotic elements, including the emergence of unpredictable responses determined by epigenetic influences layered onto an underlying genetic background.[73,74] In relation to the breast, it is part of the reproductive system, and is unique in that it only becomes fully formed in early life after puberty. Breast tissue changes with hormonal fluctuation during the menstrual cycle and during pregnancy. It is therefore one of the tissues where genetics will be secondary to epigenetics. The cancer-susceptible genes are just that, and susceptibility will vary with epigenetics. This can also be used to explain the observed differences between parous and nulliparous women. This could explain the links between smoking and cancers not directly linked to the respiratory tract, but would also indicate there may be links, although not necessarily causative, with birth control pills. Any lifestyle choice could potentially alter cancer risk. Another interesting point is that epigenetics allows hormetic effects to be considered. In the U-shaped hormetic dose–response curves, the same substance can have both stimulatory and inhibitory effects depending upon concentration.[75,76] The menopause then resets the risk, as it were. As Russo and Russo[77,78] remarked, "These changes resulted in a similar appearance of the architecture of the breast of parous and nulliparous women after the fifth decade of life". After menopause temporal changes in all groups remain similar, and only earlier patterns are different.

Why do we believe invalid things?

Background

We all accept that science is the acquisition and organization of knowledge. To quote EO Wilson, "Science is a systematic enterprise that builds and organizes knowledge in the form of testable explanations and predictions about the universe".[79] In an older meaning, "science" also refers to a body of knowledge itself, of the type that can be rationally explained and reliably applied.[80] This implies that science is based on experiments and that "belief" has no place. However, we are human and are all guilty of having pet theories and strong beliefs. The problems arise when powerful people adhere to their beliefs rather than being objective. "Empires" are often built and become sustained by grant or industrial money, meaning that adherence to the sustaining belief becomes critical for survival and vested interest overcomes truth. Data or grant proposals which do not support the dominant paradigm are ignored or not funded. Thomas Kuhn[81] in his classic book, *Nature of Scientific Revolutions*, defined three phases of a revolution: outright disbelief of data that do not fit; grudging acceptance in the face of overwhelming data from many sources; and establishment of a new dominant paradigm, with the contention that the results are obvious and were in the literature since time began (they probably were!). A more cynical commentary is that the ruling scientists need to die before anything will change. The first part of this paper discussed specific issues in relation to breast cancer, which may be fundamentally wrong. In this section, we discuss reasons why things are not really changing. If our contention that breast cancer is now an industry is correct, then it should be possible to "follow the money".

Grant system and structure

To quote Einstein, "If we knew what we were doing it wouldn't be called research". However, like research ethics boards, grant-awarding bodies almost insist that the applicant has the results written before the research takes place, and allow for no deviations. This is a common misconception of the nature of research. The result is that the research funded

is relentlessly prescribed, and of necessity reductionistic, predictable, and largely useless. A more enlightened approach would be to fund productive teams/individuals; ie, assume that good researchers do good research. We tend to confuse the ability to write a good proposal with the ability to deliver good research. A less prescribed approach would allow the researcher to test and develop hypotheses over time. This is an area in which some of the multiple funding research groups could usefully participate; ie, the establishment of an "effective research" policy program.

"Easy" mouse models

In the *Hitchhiker's Guide to the Galaxy*, it is revealed that mice are the real controllers of the universe (and everything!). Certainly this seems to be true in science, where mice can be given, and cured, of any disease. Wildly inappropriate mouse models are used for human disease (presumably because the technology exists), and all kinds of cancer can be cured in mice. For example, the antiangiogenesis drugs which held such promise and did cure mice, did not work in humans.[48–52] Similarly, it is surely a strange approach to curing a systemic disease in a human to knock out a specific gene in a mouse. Normally it is not even possible to have a homozygous knockout, reducing the relevance even more. Since everything in biochemistry is connected, altering one pathway using knockouts will impact everything else. Maybe these approaches might help us to understand the progression of disease, such as in the Vogelstein model,[82] but a cure is not obvious from knowing one level of cause in a complex system. Obviously if the mouse model were either good or relevant it would have resulted in the cure of cancer. Perhaps we did not notice … or perhaps there is a vast support industry involved in mouse research, and it is a branch of science that is now too large to be delegitimized.

Ethical issues make useful experiments difficult

It should also be possible to point a finger at ethical review boards that make it almost impossible to obtain tissue directly from the patient that could form the basis of relevant research. There must be a way of obtaining human tissue for research purposes without having to know the exact nature of the research to be done. If the tissue is to be discarded anyway, there seems to be no compelling reason why it cannot be used for research.

To paraphrase Jane Austen, "It is a truth universally acknowledged that it is virtually impossible to get human tissue for research purposes". Most of this difficulty is due to medical ethics boards that have a basic misunderstanding of ethics and wish to evade responsibility rather than accepting the more difficult challenge of establishing a fair and equitable system that allows unwanted tissue to be used for research purposes. Part of the problem has been caused by the proliferation of patents and the sensationalizing of the Henrietta Lacks case. There is though, in some jurisdictions, a move towards assuming that all deceased persons should be regarded as donors, although there does not seem to be a corresponding move to regard all operatively removed tissue as legitimate for research purposes. Patients have come to sense that any part of them has some commercial value, and would rather see excess tissue discarded rather than risk someone using the tissue and possibly getting rich. This "envy" does not encourage basic research, although presumably it would be permissible if the intention were to individualize treatment, which many hospitals are now advertising. However, it should be stated that usually the individual treatments are prescribed through genetic profiling. As an interesting aside, the proponents of this individualized response are now suggesting that there will never be "one cure" for breast cancer, and that large-scale clinical trials for breast cancer will conceal drugs working in a subset of the population, and that by corollary clinical trials may confuse the issue.

Models assume a linear dose–effect relationship

This is probably one of the most dangerous beliefs because it prevents us from looking at discontinuities in mechanisms. The history leading to the dominance of this paradigm is well documented by Naviaux[75] and Calabrese.[76] Briefly, it goes back to the time of Paracelsus, who in the 16th century said: "Alle Ding' sind Gift, und nichts ohn' Gift; allein die Dosis macht, daß ein Ding kein Gift ist." (All things are poison, and nothing is without poison; only the dose permits something not to be poisonous).[83] However, this idea which is clearly correct, lost favor when homeopathic doctors used it to justify their science,[84] which was clearly an incorrect interpretation of what Paracelsus said. The linear dose–effect relationship became dogma when Hermann Muller, a radiation geneticist and Nobel Laureate, demonstrated in 1926 that radiation could cause mutations.[85,86] His dose–response relationship was linear. This was interpreted to mean that radiation (or other toxins) had no safe dose at which they caused no harm. The idea of beneficial effects of low doses (hormesis or homeostasis) was also excluded. Contrary evidence discussed in Calabrese's paper,[87] which suggested nonlinear responses after low-dose exposure to radiation

and chemicals, was ignored, leading to the current dominant paradigm that all substances have increasingly adverse effects with increasing dose. The protection agencies (both for radiation and environmental chemicals) assume a linear no threshold dose–effect relationship for regulatory purposes. In the cancer treatment field, this leads to the idea that "more is better" and marginalizes creative thinking about adaptive responses, immune stimulation, nonlinear tumor evolution, tissue level emergent responses, or other low-dose effects, which could possibly open up new treatment avenues.

Prevailing paradigms are supported by strong, senior people who peer-review, and multibillion dollar industries selling treatment

Both cynicism and conspiracy theory are, perhaps, features of modern life. As remarked earlier, the cancer industry is a multibillion dollar business, and it remains true that businesses are committed to making money for their shareholders. They are not obliged to act in the best interests of their customers.

Health has to be regarded as any other industry. Pharmaceutical companies have products to sell, and have an advantage over the automotive industry in that the patient (customer) has little choice, is emotionally vulnerable, and is not being sold the product directly, but indirectly through the prescribing physician. The physician is effectively acting as a salesperson for the pharmaceutical industry and using their position of trust. Very few patients query their physicians' choice of drugs. This complex relationship has led to cynicism, and led to links with conspiracy theory, where there is active belief that cancer could be cured if there was not so much money invested in the status quo. To continue the automotive analogy, this is similar to the conspiracy belief that formulae to replace petrol by water were purchased and destroyed by major oil companies. Scientists are equally being sold drugs and research areas. Science into the mechanistic actions of existing drugs and optimizing the effect of existing drugs is encouraged. Drugs are only useful to the pharmaceutical companies as long as they are under patent. Nonpatentable drugs are very rarely given a trial, in part because there is no justification as far as the pharmaceutical companies are concerned as a result of the expense involved in jumping the requisite regulatory hoops.

What can we do?

Positive suggestions to move forward

It is easy to criticize, but necessary to suggest possible solutions. We suggest tackling the thorny issue of determining what we really know about cancer from what we think we know. This involves going back to human data from patient or epidemiologic studies. Nonhuman data should be treated with caution and evaluated critically in the context of what the human data show. As Alexander Pope said, "The proper study of man is mankind." This is partly because nonhuman data derived from inbred tumor-prone, tumor cell-injected, or knockout rodent models are of limited relevance to outbred human populations within which cancers develop in a background microenvironment or system which is currently poorly understood. Also, animal experiments are largely designed to confirm and strengthen the current hypotheses, not to formulate or infer new hypotheses. As Einstein succinctly said, "The intuitive mind is a sacred gift and the rational mind is a faithful servant". We have created a society that honors the servant and has forgotten the gift. This is certainly true in scientific research, but the prevailing dogma is so strong and passions so easily aroused, that it will be difficult to distinguish between that which is known and that which is believed.

The second challenge will be in reformulating the timeframe of disease, and accepting that screening may be of no benefit to the patient. There are arguments made in both sides of this very contentious debate, but again the major difficulty is to assemble the evidence that arises from fact not belief. This probably negates many epidemiologic studies where the data are analyzed to reinforce current models instead of offering competing explanatory narratives. Assuming the fundamental methodology is not flawed, these studies could be reanalyzed.

The third challenge will be to determine whether there is an intervention window between a primary tumor and metastatic growth that is susceptible to epigenetic factors. If the primary tumor could be dissociated from malignant spread, it would be possible to treat these as two independent processes, which might open therapeutic windows. Finally, the idea that aggressive therapy to eradicate every last tumor stem cell, or clonogen, is the only way to treat cancer, needs to be revisited. A more holistic therapeutic approach that works with the body and is mindful of biological principles of evolution and adaptation, is certainly worthy of consideration.

Disclosure

The authors report no conflicts of interest in this work.

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