Cancer arises from stress-induced breakdown of tissue homeostasis[1]

Is it time to abandon mutation-centric metastasis as the dominant paradigm? Does 'seed and soil' do more harm than good?

By Denis G. Rancourt [2], PhD

Abstract

Part-I: I critically review the context of cancer research, where it has been advanced that most published research findings are false, that medicine itself is the third leading cause of death in the Western world, and that experienced stress arising from an individual's position in society's dominance hierarchy is the primary determinant of individual health.

Part-II: I critically review the randomized trials for treatments and screening, especially for breast cancer. It has been advanced that screening does more harm than good, and that treatment protocols have little effect on net population mortality from cancer. There is no robust demonstration that the treatment protocols for the common cancers do more good than harm to individual patients.

Part-III: I critically review the mutation-centric metastasis dominant paradigm of cancer, and various efforts to somewhat or definitively challenge the dominant paradigm, with an eye to answering the question "What is cancer?"

Final section: I propose a conceptual model of cancer, which incorporates the leading criticisms of the dominant paradigm, and which is testable. In my model, cancer is an age-dependent and tissue-specific stress-induced breakdown of tissue-shape homeostasis. My model is aided by a graphical picture depicting age-specific and tissue-specific curves of steady-state nodule size (D_T) versus experienced stress level (S). A given curve has a critical stress (S_C) beyond which there is runaway tumour growth due to tissue-response feedback. Here, "metastasis" is the simple consequence of the individual's tissue susceptibility to loss of shape homeostasis having gone supercritical for a cluster of tissue-specific D_T v. S curves. The model provides treatment strategies on three branches: Psychological, tissue-surface-shape homeostasis, and tumour growth feedback attenuation.

Introduction

This paper was presented in the uOttawa Cinema Academica series at the University of Ottawa on November 21, 2005.[3] It will be "peer reviewed" if peers and others review it.

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[1] This article was open-source published at archive.org on November 30, 2015, where comments and reviews are invited: https://archive.org/details/DGRArticleOnNewCancerModel2

[2] Email: denis.rancourt@alumni.utoronto.ca

[3] Video of the presentation is on the film maker's YouTube channel: https://www.youtube.com/user/docupeter

I am not a medical doctor. I am an interdisciplinary scientist with a *PhD* in physics. I have published over 100 articles in scientific journals, in a broad array of disciplines.[4]

My starting outlook in researching cancer is best represented by these three non-journal-article publications:

- "A Theory of Chronic Pain: A social and evolutionary theory of human disease and chronic pain" (2011)[5]
- "Self-Image-Incongruence Theory of Individual Health" (2014), and references therein[6]
- Chapter: "Human Biology id Such that People Make and Inhabit Dominance Hierarchies", in my 2013 book[7]

The paper is organized in three main parts, followed by my proposal for a unifying model of cancer.

PART-I: Context of Cancer Research

Approximately 30% of us who are fortunate enough to live in the Western countries will be diagnosed to have died of cancer. Breast cancer is the main life-threatening disease affecting women, when tumours are present on several organs.

Prior to starting this review to find out what establishment science actually knows about cancer, it is important to admit the possibility that medicine is largely a pack of lies, the usual kinds of lies that provide the mental environment substrate that is created and maintained by any professional group that claims high status in society. In that sense, medicine should be viewed as no different than law, or even basic science itself.[8]

Some prominent critics have made this observation from within the medical establishment, in different ways. For example, the "Gold Effect" was described by Professor T. Gold in 1979 and is the phenomenon in which a scientific (often medical) idea is developed to the status of an accepted position within a professional body or association by the social process itself of

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Facebook event page: "The Science of Cancer and Cancer Treatments — A talk and discussion with Denis Rancourt" https://www.facebook.com/events/1650084238603401/

[4] Google Scholar profile: https://scholar.google.ca/citations?user=1ChsRsQAAAAJ

[5] Denis Rancourt, in *Dissident Voice*, December 26, 2011, http://dissidentvoice.org/2011/12/a-theory-of-chronic-pain/

[6] Denis Rancourt, in *Dissident Voice*, October 26, 2014, http://dissidentvoice.org/2014/10/self-image-incongruence-theory-of-individual-health/

[7] Denis G. Rancourt. *Hierarchy and Free Expression in the Fight against Racism*. Stairway Press, 2013, http://www.stairwaypress.com/bookstore/hierarchy-and-free-expression-in-the-fight-against-racism/

[8] Denis G. Rancourt. On the False Science of a Fundamental Basis for Progress. *Activist Teacher*, January 5, 2011, http://activistteacher.blogspot.ca/2011/01/on-false-science-of-fundamental-basis.html

scientific conferences, committees, and consensus building, despite not being supported by conclusive evidence.[9]

The Gold Effect was reviewed by Drs. Petr Skrabanek and James McCormick in their book *Follies and Fallacies in Medicine*,[10] and it is used to analyze errors in public health policy and practice, such as the widespread use of cholesterol screening in the prevention of cardiovascular disease.[11]

Most published research findings are false

From a different perspective, renowned medical researcher John P.A. Ioannidis applied Bayesian statistical modelling to prove that it is likely that "most published research findings are false".[12] I know something about Bayesian inference theory.[13] I found Dr. Ioannidis' argument to be entirely rigorous. Other Bayesian practitioners were critical of the work,[14] but Ioannidis ably put them in their place.[15]

Ioannidis showed that published medical claims of net benefits of a treatment (such as a regiment of one or more drugs) or of policy implementation (such as cancer screening or vaccination), based on statistical evaluation of large randomized trials, are most often false. In his words:

> "Simulations show that for most study designs and settings, it is more likely for a research claim to be false than true. Moreover, for many current scientific fields, claimed research findings may often be simply accurate measures of the prevailing bias."

He also points out what is essentially an alternative statement of the Gold Effect:

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[9] R.A. Lyttleton. The Gold Effect. In: *Lying Truths. A critical scrutiny of current beliefs and conventions*. Duncan R., Weston-Smith M., Eds. Pergamon Press, Oxford, 1979, pp. 182-198.

[10] P. Skrabanek and J. McCormick. *Follies and Fallacies in Medicine*. Third Edition. Tarragon Press, Whithorn. 1998. pp. 54-55.

[11] A. Hann and S. Peckham. Cholesterol screening and the Gold Effect. *Health, Risk & Society*, vol. 12, 2010, pp. 33-50. DOI: 10.1080/13698570903499608

[12] J.P.A. Ioannidis. Why Most Published Research Findings Are False. *PLoS Medicine*, August 2005, vol. 2, issue 8, e124, pages 696-701.

[13] For example: L. Dou, R.J.W. Hodgson and D.G. Rancourt. Bayesian Inference Theory Applied to Hyperfine Parameter Distribution Extraction in Mössbauer Spectroscopy. *Nuclear Instruments and Methods in Physics Research B* (NIMB), 1995, vol. 100, pages 511-518.

[14] S. Goodman and S. Greenland. Why Most Published Research Findings Are False: Ploblems in the Analysis. *PLoS Medicine*, April 2007, vol. 4, issue 4, e165 e168, page 773.

[15] J.P.A. Ioannidis. Why Most Published Research Findings Are False: Author's Reply to Goodman and Greenland. *PLoS Medicine*, June 2007, vol. 4, issue 6, e224 e214 e215, pages 1132-1133.

> "… when more teams are involved in a scientific field in chase of statistical significance … The hotter a scientific field (with more scientific teams involved), the less likely the research findings are to be true."

And he clearly describes main sources of researcher bias:

> "Prejudice may not necessarily have financial roots. Scientists in a given field may be prejudiced purely because of their belief in a scientific theory or commitment to their own findings. Many otherwise seemingly independent, university-based studies may be conducted for no other reason than to give physicians and researchers qualifications for promotion or tenure. Such nonfinancial conflicts may also lead to distorted reported results and interpretations. Prestigious investigators may suppress via the peer review process the appearance and dissemination of findings that refute their findings, thus condemning their field to perpetuate false dogma. Empirical evidence on expert opinion shows that it is extremely unreliable [28]."

In his most recent critical overview, Ioannidis is merciless in his assessment of the medical research enterprise, even questioning whether fundamental lab-bench science is of any use in advancing medicine for patient benefit.[16] In his words:

> "… a novel model is needed in funding research to avoid the creation of narrow, isolated specialties that only self-perpetuate … For example, human genetics research has received tremendous funding. This money has not been wasted because other activities and high-tech industry have emerged to support the needs of the genetics community. However, few lives have been saved because of accumulated human genetics knowledge to date, and future prospects (eg, extensions to personalized and precision medicine) also are not promising. Similarly, intellectual fascination in neuroscience for many decades has led to few new practical applications …"

Medicine is itself a leading cause of death

Part of the context of medical research is not only that most positive findings of benefits of drug regimes are probably false but also that the drugs themselves, in the hands of clinical practitioners, are lethal. Let us explore this lethality.

Prior to 1999, the mainstream medical establishment did not acknowledge that it is itself a leading cause of death in Western countries. For example, typically the best that the profession could maybe muster was to admit that operative mortality depends on hospital patient volume.[17] This is worrisome enough: Patients are more likely to be killed by surgery in hospitals

[16] J.P.A. Ioannidis. Is It Possible to Recognize a Major Scientific Discovery? *Journal of the American Medical Association* (JAMA), 2015, vol.314, pages 1135-1137.
[17] C.B. Begg *et al*. Impact of Hospital Volume on Operative Mortality for Major Cancer Surgery. *Journal of the American Medical Association* (JAMA), 1998, vol. 280, no. 20, pages 1747-1751.

where the surgical teams get relatively less practice. This, in itself, depreciates the myth of meaningful professional certification and safety accreditations, but it is nothing compared to the tectonic release that was about to occur.

In 1999, the Institute of Medicine, a division of the National Academies of Sciences, Engineering, and Medicine (a US non-profit organization), published its Committee on Quality of Health Care in America's report entitled "To Err Is Human: Building a Safer Health System".[18] For the first time, an authoritative body put it to the medical professions that they were themselves responsible for staggering numbers of patient deaths.

In the words of Dr. Barbara Starfield, and many others, it is therefore incontrovertible that establishment medicine is the third leading cause of death in industrialized countries, after deaths from heart disease and cancer,[19] which in turn are causes that medicine can do very little about. The next and fourth leading cause of death is cerebrovascular disease and its rate is far below that from medical-induced (iatrogenic) deaths, such that "medical manslaughter" is not about to give up its rank of third leading cause.

Using Dr. Starfield's best estimates for 2000, between 6% and 8% of US citizens die from medicine rather than any other cause, including both medical-error deaths and non-error medical deaths.[20] One can only conclude that, in addition, the statistics for debilitating iatrogenic harm that does not cause death and has no net benefit would be staggering if they were tabulated.

The medical professions have reacted with the classic cover-up scenario. There is now a vibrant industry of research about "patient safety", which "studies" the problem and makes all kinds of policy evaluations and recommendations, without any substantive changes in actual clinical training and practice, and without any resulting measurable improvements. The professional associations are strong at lobbying for ineffective lifestyle recommendations but are virtually silent on asking government to pass laws to require the reporting and investigation of medical errors, never mind iatrogenic non-error deaths and injury.

One might have expected that "To Err is Human" would have jolted medical practitioners into rigorously taking professional responsibility for their actions. But that was not the case. In just one example of a recent study, Li *et al.* studied all the English-language syndicated media reports about medical errors in cancer "care" published between 2000 (after "To Err is Human") to 2011.[21] They found 64 media reports of egregious errors, with news titles such as:

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[18] L. Kohn, J. Corrigan and M. Donaldson (Eds.). *To Err Is Human: Building a Safer Health System*. National Academy Press, DC, 1999.

[19] B. Starfield. Is US Health Really the Best in the World? *Journal of the American Medical Association* (JAMA), 2000, vol. 284, no. 4, pages 483-485.

[20] Using 230,000 to 284,000 deaths per year, a 2000 US population of 282 million, and the average US longevity of 79 years.

[21] J.W. Li *et al*. Perceptions of Medical Errors in cancer Care: An Analysis of How the News Media Describe Sentinel Events. *Journal of Patient Safety*, vol. 11, no. 1, March 2015, pages 42-51.

"Montclair surgeon hit with lawsuit; allegedly left gauze in cancer patient"
"Surgeon faces discipline for removing wrong breast"
"Hospital kept breast cancer surgery blunder secret from me for nine years"
"Missing Instruments"
"Officer compensated for misdiagnosis: Told she had cancer, she had operations, cashed in savings"
"Police arrest doctors who gave teenager fatal injection"
"Medical errors killing thousands in Canada"
"Tears of the wife who lost a breast by mistake; Mother sues a hospital over its cancer test blunders"
"Neglect verdict over hospital overdose: Inquest on cancer victim told of drug error"
"Surgeon laughed as he told memy breast had been removed in error"
"Doctor admits manslaughter in cancer case"
"Clinic overly irradiated 111 patients"
"W'chester Hosp Cuts Out Wrong Kidney"
"Cancer patient has the wrong kidney taken out by surgeon"
"Removal of healthy kidney focus of Tennessee lawsuit"
"The women sentenced to die by arrogance; Breast cancer patients failed by health chiefs who ignored warnings over blundering doctor"
"Man died after lung removed by mistake"
"MD suspended for surgery on the wrong lung. Error, cover-up came in 2000"
"LA hospital: Error caused 206 radiation overdoses"
"20 People a year incorrectly given chemotherapy, N.L. Health group says"

These are solely the cases that made it into the media. The authors complained that "Four in 10 articles failed to present medical errors as 'systems' problems". The study found four reported types of medical errors: errors implicating medications (34%), diagnoses (25%), radiation (22%), and surgery (19%). However, the study also found that none of the US articles reported medication or diagnosis errors, whereas these were common elsewhere. These differences give an indication of the incompleteness and bias of such media reports.

Despite the medical establishment's inertia in addressing the small problem that it is the third leading cause of death and that it can't help with the other leading causes of death, more and more prominent researchers are making the said small problem painfully apparent. One eminent example is the tireless work of Professor Dr. Peter C. Gøtzsche, Nordic Cochrane Centre, Denmark. He has come to the point of flatly concluding that long term use of psychiatric drugs cause more harm than good. In his words, based on a decade of research:[22]

[22] P.C. Gøtzsche, A.H. Young, J. Crace. Does long term use of psychiatric drugs cause more harm than good? *British Medical Journal* (BMJ), 12 May 2015, vol. 350, h2435, pages 1-3. doi: 10.1136/bmj.h2435; and see P.C. Gøtzsche. Author's reply to Tovey and colleagues. *British Medical Journal* (BMJ), 2 June 2015, vol. 350, h2955, page 1. doi: 10.1136/bmj.h2955

> "Psychiatric drugs are responsible for the deaths of more than half a million people aged 65 and older each year in the Western world, as I show below. Their benefits would need to be colossal to justify this, but they are minimal. ... Overstated benefits and understated deaths ..."

The American psychiatrist Dr. Peter Breggin is also an outspoken critic of his field of medicine. His legal successes, books and public lectures should give even the most hardened careerist pause.[23]

It's the brain stupid

I end Part-I with another important fact that is overlooked or wilfully ignored by the medical establishment. In addition to most published medical research being false, and to medicine being itself the third leading cause of death in the Western world, now this: Stress, as mediated by the brain, is the dominant determinant of individual health, far outweighing any other factor.

The dominant determinant of individual health in primates (including humans) and other mammals is the individual's rank in the social hierarchy, because rank determines the stress level to which the individual is generally subjected. This is the result of a large body of work, which was reviewed by Robert M. Sapolsky in 2005.[24]

Medical students are superficially given lip service about the importance of psychological factors in health, but are trained to ignore anything but lab results, and measurable symptoms.

Nonetheless, stress (both excessive stress and deleterious absence of stress or stimulation) is the overriding determinant of health, via its massive impact on the entire organism. Sapolsky's most recent commentary is a brilliant overview of the situation.[25] In his words:

> "It is a truism that the brain influences the body and that peripheral physiology influences the brain. Never is this clearer than during stress, where the subtlest emotions or the most abstract thoughts can initiate stress responses, with consequences throughout the body, and the endocrine transducers of stress alter cognition, affect and behavior. … the brain is an endocrine gland, secreting releasing and inhibiting hormones into the hypothalamic-pituitary portal system … the stress response, conceptualized in the context of acute physical crisis, can be robustly activated by purely psychological states, such as loss of control, predictability and social support … prolonged stress increases the odds of being sick. This has facilitated the birth

[23] http://www.breggin.com/

[24] R.M. Sapolsky. The Influence of Social Hierarchy on Primate Health. *Science*, 29 April 2005, vol. 308, pages 648-652.

[25] R.M. Sapolsky. Stress and the brain: individual variability and the inverted-U. *Nature Neuroscience*, October 2015, vol. 18, no. 10, pages 1344-1346.

> of other subfields (for example, psychoneuroimmunology), and is now an area of tremendous amounts of reductive research. As a result, we have a fairly good idea as to how, say, a fleeting, stressful thought changes transcriptional events relevant to oxidative metabolism in your big toe. … when we are stressed, we learn more readily to be afraid when there is no need to and less readily detect when we are safe. The road to a crippling anxiety disorder is paved with perky amygdaloid synapses. … These linkages both take the form of early life stress predisposing toward adult illness and periods of acute stress during adulthood triggering episodes of disease. … stress is the poster child for the environment part of gene × environment interactions … Is stress more about the unpleasantry in the outside world (that is, the stressor) or the resulting changes in the body (that is, the stress response)? Or is it mostly about the neurobiological and psychological space floating between the two? … the word encompasses all of the above … The far more interesting version of this question addresses the fact that in any species you'd care to study, different individuals respond to stress differently; there are typically dramatic individual differences as to whether a particular event or internal state is even perceived to be stressful. In other words, what is stress…for this individual? Of course, individual variability is not always the case; a severe injury, a major burn or a sprint from a predator will reliably activate the stress response and evoke an aversive subjective sense in virtually any organism. But these are not the circumstances of stress that are most pertinent to understanding health and disease in contemporary life. Instead, individual differences are most notable as we navigate life's social exigencies. … the response to stress depends on
> the nature, intensity and duration of a stressor (which at least partially translates into a dependence on the pattern of activation of the sympathetic nervous system, the adrenocortical axis and the other mediators of the stress response)."

Sapolsky goes on to describe the unifying concept of the "inverted-U" of stress response:

> "Enormous unifying clarity came with the recognition that, to a large extent, the effects of stress in the brain form a nonlinear 'inverted-U' dose-response curve as a function of stressor severity … with profoundly adverse effects seen in impoverished environments ranging from childhood … to old age, from humans to zoo animals in sterile cages. … And the downswing of the inverted-U is, of course, the universe of "stress is bad for you"."

The physiological and biochemical responses to intense external and perception-mediated stress are massive and involve releases of large arrays of metabolically active agents, on several time scales, and affecting virtually every major body function and body system.[26]

Finally, as part of examining the context of cancer research, we should also be open to even "crazy" ideas from broad areas of social-animal evolution. For example, it is not harmful to

[26] For example, see: R.M. Sapolsky *et al*. How Do Glucocorticoids Influence Stress Responses? Integrating Permissive, Suppressive, Stimulatory, and Preparative Actions. *Endocrine Reviews*, vol. 21, no. 1, pages 55-89.

consider provocative questions such as: “Does cancer serve a species-survival purpose?” or “Is cancer sometimes an escape strategy for the individual?”.

Just as there is evolutionary adjustment to the systematic use of antibiotics in the medical response to common infections, is cancer adapting as part of an evolutionary response to cancer “treatment”? Are there common circumstances of net advantage for an individual to develop cancer, and be treated for cancer, in terms of escaping a toxic work or family environment? Does stress-induced disease serve the human species?[27]

PART-II: Review of the randomized trials for treatments and screening

This very month I received a personal letter to my home from a vice-president at “Cancer Care Ontario” inviting me to “get checked for colon cancer”. The Canadian province of Ontario has state-funded screening programs for breast, cervical, and colorectal cancers. The program logo says: “Screen *for* Life. Cancer screening sees what you can’t.” (italics in the original). The colour-flyer supplement directs me to “Get informed about this important health initiative”, but it does not contain any information or provide a link to information that would allow me to judge “this important health initiative”. What is the science that justifies these government programs, and how reliable is that science?

There is a relation between screening and treatments (surgery, chemo, radiation, and various adjuvant therapies) because screening is only beneficial if treatments are sufficiently effective. To be critical of screening programs is somewhat to pooh-pooh the treatments. As a result, the insider policy debates have been intense (see below).

I have chosen to concentrate on breast cancer, which is classified as the leading life-threatening disease in women, when tumours are also present in other organs. As I did the reading, I was continually amazed at the plethora of false logic and researchers’ trust in dubious methods and tenuous statistics. Here are some examples.

For a start, I was not able to find even a reference to a study that established that surgery was of any value in treating breast cancer. Quite simply, practitioners are so convinced that to remove a breast tumour *must be* beneficial that a rigorous scientific evaluation of this point is never entertained; so much for “evidence-based medicine”.

For example, in 1961, Goldenberg *et al*. put it this way:[28]

[27] For example, see: D.G. Rancourt. A Theory of Chronic Pain: A social and evolutionary theory of human disease and chronic pain. *Dissident Voice*, December 26, 2011, http://dissidentvoice.org/2011/12/a-theory-of-chronic-pain/

[28] I.S. Goldenberg et al. Female Breast Cancer: A Re-evaluation. Annals of Surgery, September 1961, vol. 154, no. 3, pages 397-404.

> "… the first recorded description [of breast cancer] was in an Egyptian papyrus written about 1500 B.C. Operative therapy was not recognized then; rather, it was left to the internist to apply caustic ointments locally. A great deal of progress was made during succeeding centuries so that by 1600, standard therapy was elevation of the diseased breast by large pincers, amputation with a knife and application of a poker heated to red intensity to the massive wound for hemostasis. In 1746, Angelo Nannoni published his *Surgical Treatise on Diseases of the Breast* in which he advocated, for the first time, removal of the breast, underlying fascia, pectoralis major muscle and "hardened axillary glands" as soon as the surgeon recognized a possible malignant process. The basis was thereby established for operative treatment of breast cancer. … but it was not until the 1890's that Halsted and Willy Meyer almost simultaneously described radical mastectomy as the operation of choice. Little has been added to the operative procedure since that time." [p. 397] "… Radical mastectomy has been standard therapy, not so much because patients are always cured by this operation, but rather because surgeons do not know what else to do." [p. 402]

These authors went on to describe their study of 1,458 breast cancer patients. They concluded that surgery improved survival (i.e., avoiding death in the years following the first diagnostic). However, this conclusion is unreliable since, in their own words: "…there are always some patients who receive no treatment at all. This latter group is, fortunately, small and consists mainly of those who refuse recommended therapy." [p. 402]. Thus, this study, which became a cited source claiming that surgery is beneficial, used a small *unspecified* number of untreated patients, which were not selected by randomization. No double-blind, no comparative study, not even randomization, on a "small" sample.

Fisher *et al*. cited Goldenberg *et al*. in 1969 in exclaiming:[29] "That earlier diagnosis, i.e., the discovery of smaller tumors, will result in improved survival has been categorically accepted, and evidence from the literature tends to support this consideration. Indeed, the concept upon which all neoplastic surgery is predicated is that time—considered synonymous with tumor size—is the important factor between localized and disseminated disease, and that operations performed at the earliest possible time give the best chance of cure." —All without evidence, of course.

Fisher *et al*. went on to explain: "Surgery for cancer has been and is predicated on the concept that, a. a growing tumor remains localized for a period of time, b. at some instant during its growth, depending upon the tumor type, tumor cell dissemination to regional nodes begins to take place, c. after a further time interval associated with continued increase in tumor size, systemic dissemination ensues, and d. adequate surgery performed prior to the latter event ensures cure."

[29] B. Fisher *et al*. Cancer of the breast: Size of neoplasm and prognosis. *Cancer*, November 1969, vol. 24, no. 5, pages 1071-1080.

In other words, the dominant paradigm of the disease (i.e., metastasis, see Part-III below) is so psychologically compelling that researchers, let alone clinicians, don't need evidence.

Thus, surgery alone, as a treatment, is never evaluated and its supposed benefits have never been demonstrated. Only so-called adjuvant ("preventative") therapies are considered, in combination with tumour removal or ablation. Again in 1969, the prominent researcher Fisher wrote:[30]

> "The concept of administering a chemo-therapeutic agent systemically in conjunction with radical mastectomy to decrease the recurrence rate and enhance survival of patients with breast cancer is an appealing one." [Really?]
>
> "As a result of publicity accorded these studies at their onset - before their worth or danger was remotely established - adjuvant chemotherapy was widely employed by many in the treatment of breast cancer. Only recently have definitive results of this project become known." [Emphasis added.]
>
> "At the end of 5 years, there was no significant difference in recurrence rate between patients receiving TSPA or placebo … Fifty-two percent of patients who received 5-FU suffered local complications, and significantly more patients receiving that drug demonstrated systemic complications. Moreover, 42 percent of patients administered 5-FU became leukopenic and almost half of those had counts < 2,500. Of the 16 deaths occurring within 60 days following surgery in the 1,725 patients of this second study, 8 were recipients of 5-FU and all demonstrated toxic manifestations of the drug."

It is a wonder that lawsuits did not cause the science to become more rigorous, and that highly toxic substances would continue to be prescribed to this day, without any robust demonstrations of net benefits.

A massive government survey published in 1981 made the following common sense conclusion about cancer treatments:[31]

> "Consequently, as we are not convinced that changes in treatment have materially affected the outcome of most of the major types of potentially fatal cancer, it seems to us wiser for most types of cancer to estimate the real trends in disease onset rates chiefly from the recorded trends in mortality since 1950 among people under the age of 65."

[30] B. Fisher. Systematic chemotherapy as an adjuvant to surgery in the treatment of breast cancer. *Cancer*, December 1969, vol. 24, no. 6, pages 1286-1289.

[31] R. Doll and R. Peto. The Causes of cancer: Quantitative estimates of avoidable risks of cancer in the United States today. *Journal of the National Cancer Institute*, June 1981, vol. 66, no. 6, pages 1192-1308.

In other words, forget all the claims of treatment benefits and look at hard numbers of deaths from cancer, if you want an objective measure.

Following this criterion, I have looked for robust demonstrations of benefits, based on actual comparative studies without bias (not simple "randomization" without proper controls; with double-blind treatment dispensation and reporting; using arms-length evaluations of diagnoses and outcomes)—there are none.

Next, I have tried to identify the most cited papers, and those cited in the most prestigious reviews. I consistently found that the data interpretations are dubious, that the conclusions of statistical significance are overly optimistic, and that the study methods and designs are susceptible to large bias. (References[32],[33],[34],[35],[36],[37],[38],[39],[40] are a sample.)

In one case, I followed a large randomization-trial study about alleged benefits of screening, throughout its published history.[41],[42],[43],[44] Such trials have a large potential for bias, and require difficult determinations of the cause of death, where the numbers of deaths from all other causes are approximately ten times greater than the numbers of deaths from cancer. This study reported a staggering 30% difference in mortality at 7 years following "randomization" (i.e., 7

[32] D.M. Parkin. Cancer of the Breast, Endometrium and Ovary: Geographic Correlations. *European Journal of cancer and Clinical Oncology*, 1989, vol. 25, no. 12, pages 1917-1925.
[33] C.L. Carter. Relation of Tumor Size, Lymph Node Status, and Survival in 24,740 breast Cancer Cases. *Cancer*, 1 January 1989, vol. 63, no. 1, pages 181-187.
[34] Early Breast Cancer Trialist's Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy: 133 randomized trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. *Lancet*, 4 January 1992, vol. 339, no. 8784, pages 1-15.
[35] R. Peto. Five Years of Tamoxifen—or More? (Editorial). *Journal of the National Cancer Institute*, 18 December 1996, vol. 88, no. 24, pages 1791-1793.
[36] R.G. Blanks et al. Effect of NHS breast screening programme on mortality from breast cancer in England and Wales, 1990-8: comparison of observed with predicted mortality. *British Medical Journal* (BMJ), 16 September 2000, vol. 321, no. 7262, pages 665-669.
[37] J. McCann et al. Predicted long-term mortality reduction associated with the second round of breast screening in East Anglia. *British Journal of Cancer*, 2001, vol. 84, no. 3, pages 423-428.
[38] Early Breast Cancer Trialist's Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomized trials. *Lancet*, 14 may 2005, vol. 365, pages 1687-1717.
[39] D.A. Berry *et al*. Effect of Screening and Adjuvant Therapy on Mortality from Breast Cancer. *New England Journal of Medicine* (NEJM), 27 October 2005, vol. 353, no. 17, pages 1784-1792.
[40] M. Dowsett *et al*. Meta-Analysis of Breast Cancer Outcomes in Adjuvant Trials of Aromatase Inhibitors Versus Tamoxifen. *Journal of Clinical Oncology*, 20 January 2010, vol. 28, no. 3, pages 509-518.
[41] L. Tabar *et al*. Reduction in mortality from breast cancer after mass screening with mammography: Randomized trial from the breast cancer screening working group of the Swedish National Board of health and Welfare. *Lancet*, 13 April 1985, pages 829-832.
[42] L. Tabar *et al*. The Swedish two county trial of the mammographic screening for breast cancer: recent results and calculation of benefit. *Journal of Epidemiology and Community Health*, June 1989, vol. 43, no. 2, pages 107-114.
[43] L. Tabar *et al*. The Natural History of Breast Carcinoma: What Have We Learned from Screening? *Cancer*, 1 August 1999, vol. 86, no. 3, pages 449-462.
[44] L. Tabar *et al*. Swedish Two-County Trial: Impact of Mammographic Screening on Breast Cancer Mortality during 3 Decades. Radiology, September 2011, vol. 260, pages 658-663.

years following invitation to be screened). I found inconsistencies in the articles and asked the lead author for explanations. The answers from him and a co-author did not alleviate my concerns, and suggested that, at best, important methodological features had not been specified in the published articles.

As the latter randomization-trial study was coming to completion, Jørgensen and Gøtzsche found that mammography screening programmes have an overdiagnosis rate of 52%.[45] "Overdiagnosis" is "the detection of cancers that will not cause death or symptoms". This means that 46% to 58% (95% confidence interval) of the patients unnecessarily suffer all the inconveniences, stresses, and health harms directly resulting from diagnoses and treatments.

Recently, the renowned expert Peter Gøtzsche has firmly concluded "mammography screening is harmful and should be abandoned", and a nationally appointed body in Switzerland has recommended that the country stop its breast cancer screening program because it is harmful.[46] In the end, all those "randomized" trials supposedly proving that there are benefits to screening for breast cancer are probably a lot of hogwash. This is not surprizing in the light of the studies reviewed in Part-I, above.

This does not mean that those patients that did have symptoms and died benefitted from the treatments. It only means that half of the screened patients were aggressed by the medical system, at great cost, for no valid reason. The question of whether there is ever any benefit from the accepted treatments, which does not arise purely from the psychological context of the treatments, is an open question that cannot be answered in the affirmative.

An objective and robust measure of treatment benefit lies in the death rates from breast cancer. Even given the system bias in wanting these reported rates to decrease as treatments are "improved" (and as Big Pharma profits soar), the death rates cannot be related to changes in treatments.[47]

In conclusion, breast cancer oncologists prescribe poison, radiation, and invasive surgery with little regard for the harm caused by their diagnoses and "treatments". The history of the "treatments" is gruesome and the professional culture is antithetical to evidence-based science, despite the lip service.

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[45] K.J. Jørgensen and P.C. Gøtzsche. Overdiagnosis in publicly organized mammography screening programmes: systematic review of incidence trends. *British Medical Journal* (BMJ), 2009, vol. 339:b2587 doi:10.1136/bmj.b2587 - 8 pages.

[46] P.C. Gøtzsche. Mammography screening is harmful and should be abandoned. *Journal of the Royal Society of Medicine*, 2015, vol. 108, no. 9, pages 341-345. doi: 10.1177/0141076815602452

[47] *Ibid.*, Figure 2; and see J.L. Botha *et al*. Breast cancer incidence and mortality trends in 16 European countries. *European Journal of Cancer*, 2003, vol. 39, pages 1718-1729.

Furthermore, there is a large inertia against self-examination and self-criticism, as can be seen from any lofty professional association statement:[48]

> "Quality of life needs to be evaluated in selected randomized clinical trials to examine the impact of the major acute and long-term side effects of adjuvant treatments, particularly premature menopause, weight gain, mild memory loss, and fatigue. Methods to support shared decision-making between patients and their physicians have been successful in trials; they need to be tailored for diverse populations and should be tested for broader dissemination."

This is where we have ended up: "We need clinical trials to evaluate the "side" effects of toxic substances that have not been shown to be of net benefit…" (my words).

PART-III: What is cancer?

Dominant paradigm "metastasis"

Part-III should make it clear that one reason that treatments are so "off" is that the medical profession has an incorrect model of what cancer actually is. I review the scientific literature about what cancer actually is and is not. There is no observational basis for the medical establishment's dominant paradigm of cancer known as "metastasis", as we shall see.

Ninety percent of patients who die from solid-tumour cancers die from a multitude of tumours on many organs in the body.[49] The first diagnosis typically involves detection of a single tumour that is most evident because it is palpable near the outside of the body, such as in a breast. But those patients that die are found to be burdened with many tumours, which are detected by autopsy after death. As a result, since the surgeon sounded the alarm on the basis of the first-discovered single tumour, and since the surgeon has been focussed on removing that first-discovered tumour, the surgeon saves face by proposing and believing that the other tumours are "secondary growths", that the cancer is a "disseminated cancer", and that the first-discovered tumour must have "spread" to internal organs. This temporal illusion of disease development has plagued oncology for well over one hundred years,[50] and appears to be irresistible to virtually the entire medical profession.

Since the cancer must have "spread", then the question becomes "How did it spread?" The overwhelmingly dominant model of cancer initiation and spread is mutation-centric (see below)

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[48] National Institutes of Health Consensus Development Panel. National Institutes of Health Consensus Development Conference Statement: Adjuvant Therapy for Breast Cancer, November 1-3, 2000. *Journal of the National Cancer Institute*, 4 July 2001, vol. 93, no. 13, pages 979-989.

[49] G.P. Gupta and J. Massagué. Cancer metastasis: Building a framework (Review). *Cell*, 17 November 2006, pages 679-695. doi: 10.1016/j.cell.2006.11.001

[50] S. Paget. Distribution of secondary growths in cancer of the breast. *Lancet*, 23 march 1889, pages 571-573, and references therein.

and is called “metastasis”. It is also called the “seed and soil” model of cancer. In this model, a first tumour (the “primary tumour”) is postulated to be initiated by one or more cells that become genetically mutated into cells that have the ability to command tumour growth in their host organ or tissue. Then, supposedly, the primary tumour eventually releases genetically mutated cells (seeds) that spread to distant organs and tissues (soil) and that manage to initiate tumour growth in the new locations. The next question, since the “seeds” are spread throughout the entire body, is “Why do some organs develop “secondary” tumours more frequently than other organs?” The relative inferred capacity to grow tumours is taken to be a property of the host organ (soil).[51]

There is no proof that these steps actually occur. The idea was proposed by analogy with the population spread of infectious diseases:[52] “The eruptions of the specific fevers and of syphilis, the inflammations after typhoid, the lesions of tuberculosis, all show the dependence of the seed upon the soil.” And the idea itself was infectious. Now, a century later, we are at the same place:

> “In spite of the importance of this phenomenon, little is known about the pathogenesis of metastatic foci or their relationship to the primary tumor.” (1977)[53]
>
> “Surprisingly though, in spite of the clinical importance of metastasis, much remains to be learned about the biology of the metastatic process. In part, knowledge is limited because metastasis is a ‘hidden’ process, which occurs inside the body and so is inherently difficult to observe.” (2002)[54]
>
> “How tumors spread and kill their host organism remains an enigma, but not for lack of attention. For more than a century, cancer biologists have postulated that metastasis results from the interplay of wandering tumor cells with permissive target tissues.” (2006)[55]
>
> “However, despite its clinical importance, little is known about the principles governing the dissemination of cancer cells to distant organs.” (2015)[56]

There is no conclusive evidence to corroborate the dominant paradigm

(i) that cancer arises from genetic mutation,

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[51] *Ibid.*
[52] *Ibid.*
[53] I.J. Fidler and M.L. Kripke. Metastasis results from pre-existing variant cells within a malignant tumor. *Science*, 26 August 1977, vol.197, pages 893-895.
[54] A.F. Chambers *et al*. Dissemination and growth of cancer cells in metastatic sites. *Nature Reviews Cancer*, August 2002, vol.2, pages 563-572. doi: 10.1038/nrc865
[55] G.P. Gupta and J. Massagué. Cancer metastasis: Building a framework (Review). *Cell*, 17 November 2006, pages 679-695. doi: 10.1016/j.cell.2006.11.001
[56] G. Gundem *et al*. The evolutionary history of lethal metastatic prostate cancer. *Nature*, 16 April 2015, vol.520, pages 353-357. doi: 10.1038/nature14347

(ii) that tumour growth is directed by mutated cells, and
(iii) that tumours spread by "seed and soil" metastasis;

despite technology to isolate and characterize "circulating tumor cells",[57] and despite all the genetic analysis work on tumours, circulating tumour cells, and tissues.

Bloated paradigm "metastasis"

The problem with a dominant paradigm that is incorrect is that as more and more observations emerge that are contradictory or somewhat inconsistent, the model must complexify to accommodate the observations, without the new complexity being of any predictive value. This is seen repeatedly with cancer.[58] Is there a single seed per tumour or several seeds per tumour? Both. Do genetically identical virulent seeds always give rise to tumours in the same tissues of genetically identical mice? It depends. Can seeds survive and be dormant for decades? Sure. Why would cells genetically evolve abilities to induce tumour growth while further evolution would confer the opposite ability to proliferate? "Striking conceptual inconsistency", indeed.[59] Why are the most virulent cells in a primary tumour not the selected originators of the distant tumours?[60] Because it's random.[61] How do relatively few genetic deviant cells recruit the majority of non-deviant cells in a tumour to grow a complex tumour and its supporting structural and vascular network, in what is otherwise healthy tissue of a healthy organ? Whatever.[62]

OK, let's start again. What do we know for certain about cancer? And what have recognized medical researchers said outside of the dominant paradigm?

There are two fundamental and undeniable facts about cancer. First, cancer death rates, for all but rare cancers, increase exponentially with age, as a high power of age.[63] Second, there is a large variation (some five orders of magnitude) in the rates of cancerous tumour occurrences in different organs or tissues.

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[57] S.L. Stott *et al*. Isolation and characterization of circulating tumor cells from patients with localized and metastatic prostate cancer. *Science Translational Medicine*, 31 March 2010, vol. 2, no. 25 25ra23, pages 1-10. doi: 10.1126/scitranslmed.3000403

[58] See this review (that is biased towards genetic interpretations): B. Weigelt *et al*. Breast cancer metastasis: markers and models. *Nature Reviews Cancer*, August 2005, vol. 5, pages 591-602. doi: 10.1038/nrc1670

[59] R. Bernards and R.A. Weinberg. A progression puzzle: Metastasis genes - The prevailing model of tumour progression carries with it a striking conceptual inconsistency. *Nature*, 22 August 2002, vol. 418, page 823.

[60] O. Schmidt-Kittler *et al*. From latent disseminated cells to overt metastasis: Genetic analysis of systemic breast cancer progression. *Proceedings of the National Academy of Sciences* (PNAS), 24 June 2003, vol. 100, no.13, pages 7737-7742. doi: 10.1073/pnas.1331931100

[61] L. Milas *et al*. Spontaneous metastasis: random or selective? *Clin. Expl. Metastasis*, 1983, vol. 1, no. 4, pages 309-315.

[62] J.A. Joyce and J.W. Pollard. Microenvironmental regulation of metastasis. *Nature Reviews Cancer*, April 2009, vol. 9, pages 239-252. doi: 10.1038/nrc2618

[63] See, for example, these modelling attempts of the measured death rates: P. Armitage and R. Doll. The age distribution of cancer and a multi-stage theory of carcinogenesis. *British Journal of Cancer*, March 1954, vol. VIII, no. 1, pages 1-12; and June 1957, vol. XI, no. 2, pages 161-169.

The second fact relates to Paget's hypothesis about propensity of cancer to form in specific "soils", and to Ewing's idea that such propensity is due to differences in the extents of the circulatory patterns in different organs.[64] In contrast, seminal work in this regard was done this year. Tomasetti and Vogelstein showed that the 5-order of magnitude variation in lifetime cancer risk in different tissues varies systematically (log-log) with the 7-order of magnitude variation in lifetime stem cell divisions in those tissues, for 31 tissue types.[65] Stem cells are "generic" or "undifferentiated" cells that get assigned to a specific role or identity in a tissue, which are used to construct or renew the tissue.

The latter recent observation somewhat contradicts classic metastasis because the "soil" is seen as playing a determinative role, whereas the "seed" is nowhere to be seen.

One might be tempted to draw the conclusion that the age-dependence of cancer incidence and its stem-cell-division tissue-dependence both arise from cancer being caused, in most circumstances, by accumulated random genetic mutations occurring through normal cell division over an individual's lifetime. This would accord with a dominant but substantively challenged theory of aging wherein aging itself arises from the accumulation of random genetic mutations that degrade tissue quality.[66],[67]

On the other hand, some rather sobering studies suggest that genetics itself is not directly implicated in cancer via mutations acting on an existing code. For example, in one study of 44,788 pairs of twins the authors concluded: "Inherited genetic factors make a minor contribution to susceptibility to most types of neoplasms. … The relatively large effect of heritability in cancer at a few sites (such as prostate and colorectal cancer) suggests major gaps in our knowledge of the genetics of cancer."[68]

Of course genetics is important. But the question here is whether we should believe the hypothetical theory that cancer is caused by accumulating genetic mutations in individual cells, which confer abilities onto those cells themselves to: resist growth-inhibiting signals, avoid programmed cell death, direct tumour-structure development, and (later) disseminate into the body fluids in order to "seed" entirely different distant organs.

This dominant paradigm has such a life of its own that it is difficult for medical researchers to see the house of cards that it has become. But let us try.

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[64] See the Chambers *et al*. review of 2002; and Milas *et al*., 1983.
[65] C. Tomasetti and B. Vogelstein. Variation in cancer risk among tissues can be explained by the number of stem cell divisions. *Science*, January 2015, vol. 347, no. 6217, pages 78-81. doi: 10.1126/science.1260825
[66] K. Jin. Modern biological theories of aging. *Aging and Disease*, October 2010, vol. 1, no. 2, pages 72-74.
[67] M.V. Blagosklonny. Answering the ultimate question "What is the proximal cause of aging?" Aging, December 2012, vol. 4, no. 12, pages 861-877. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3615154/
[68] P. Lichtenstein *et al*. Environmental and heritable factors in the causation of cancer: Analysis of cohorts of twins from Sweden, Denmark, and Finland. *New England Journal of Medicine* (NEJM), 13 July 2000, vol. 343, no. 2, pages 78-85.

Paradigm critics

Not all medical professionals have agreed to sing the same tune. One important departure from orthodoxy is represented in the seminal 1986 paper by Harold Dvorak.[69] Dvorak reminds his colleagues that a tumour is a complex organ that could not grow and survive without a suitable intrinsic mechanistic-response of the host tissue, and concludes that tumour growth proceeds as does the process of wound healing, except that in a "successful" tumour the wound never heals and the healing sequence is continuously activated or re-activated. He also points to early classic studies (Trousseau's sign of malignancy: 1860s) that found that aggressive cancer is associated with abnormal hemostasis (blood clotting).

This sustained-wound-healing idea, in my view, is supported by many studies that find that Aspirin (and non-steroidal anti-inflammatory drugs, NSAIDs, in general) acts as an effective tumour-growth inhibitor in colorectal cancers — because Aspirin is a powerful anti-coagulant, which prevents the clotting feature of wound healing.[70] In contrast, medical researchers consider solely the potential molecular mechanisms for the antineoplastic (anti-cancer) activity of NSAIDs, rather than considering a tissue-scale tumour-formation sustained-wound-healing mechanism.[71]

The significance of Dvorak's proposal is that tumour growth would primarily be dependent on the intrinsic tissue response or process of wound healing, rather than being primarily directed by mutated cells within the tissue. I extrapolate that this would imply that tumours cannot easily grow in a tissue or organ that has a strong and healthy ability to control its healing process, and to maintain itself (homeostasis), whereas tumours could easily develop in tissues or organs that are made susceptible to going out of whack, or that are physiologically stressed (see below).

Fortunately, a few major players have been injecting realism into cancer research ideas, possibly inspired by Dvorak's foray. In her work, Mina Bissell has stressed the fact that a tumour is a growing organ, and that the "micro- and macroenvironment [of cancer cells] create a context that promotes tumour growth", while downplaying the overemphasized genetic controls. In her words:[72]

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[69] H.F. Dvorak. Tumors: Wounds that do not heal. Similarities between tumor stroma generation and wound healing. *New England Journal of Medicine* (NEJM), 25 December 1986, vol. 315, no. 26, pages 1650-1659.
[70] A.I. Schafer. Effects of nonsteroidal anti-inflammatory drugs on platelet function and systemic hemostasis. *Journal of Clinical Pharmacology*, 1995, vol. 35, pages 209-219.
[71] For example: S.J. Shiff and B. Rigas. Nonsteroidal anti-inflammatory drugs and colorectal cancer: Evolving concepts of their chemopreventative actions. *Gastroenterology*, 1997, vol. 113, pages 1992-1998; and Editorial — Aspirin, NSAIDs, and colon cancer prevention: Mechanisms? *Gastroenterology*, 1998, vol. 114, pages 1095-1100.
[72] M.J. Bissell and D. Radisky. Putting tumours in context. *Nature Reviews Cancer*, October 2001, vol. 1, pages 46-54.

> "Occasionally, the intercellular signals that define the normal context become disrupted. Alterations in epithelial tissues can lead to movement of epithelial sheets and proliferation — for example, after activation of mesenchymal fibroblasts due to wounding. Normally, these conditions are temporary and reversible, but when inflammation is sustained, an escalating feedback loop ensues. Under persistent inflammatory conditions, continual upregulation of enzymes such as matrix metalloproteinases (MMPs) by stromal fibroblasts can disrupt the [extracellular matrix], and invading immune cells can overproduce factors that promote abnormal proliferation."

Others are following suit, while not abandoning the mutation-centric paradigm component of cancer initiation:[73]

> "It is widely accepted that the development of carcinoma — the most common form of human cancer — is due to the accumulation of somatic mutations in epithelial cells. The behaviour of carcinomas is also influenced by the tumour microenvironment, which includes extracellular matrix, blood vasculature, inflammatory cells and fibroblasts. Recent studies reveal that fibroblasts have a more profound influence on the development and progression of carcinomas than was previously appreciated."

Bissell is also including stem-cell-preeminence results into her picture of the importance of the tissue "context",[74] and is pursuing her educational mission with her colleagues:

> "Lest we forget, within every higher organism, there are literally billions of cells with identical genetic information that serve as constituents of the different tissues and organs. Given that genetic information is the same in all cells, including the stem cells, by definition, cells in higher organisms do not possess a sense of place or purpose by themselves. Therefore, in order for each organ to operate successfully within the context of the organism, all cells must be integrated into an architectural and signaling framework such that each cell knows exactly which commands to execute at any given time. Success at this daunting task leads to homeostasis, while failure results in a spectrum of dysfunctions, including cancer. How do organisms achieve this remarkable feat, and how does each cell in return know what to do within the tissues? … If cancer were exclusively due to genetic mutations, then we should expect every organ to eventually become cancerous. Moreover, heritable cancer syndromes almost exclusively affect just a single tissue type, even though every cell contains the mutation. Therefore, in addition to known defense mechanisms such as DNA repair, factors from the tissue microenvironment must play key roles in cellular decision making and maintenance of homeostasis."

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[73] N.A. Bhowmick *et al*. Stromal fibroblasts in cancer initiation and progression (Review). *Nature*, 18 November 2004, vol. 432, pages 332-337.

[74] M.J. Bissell and M.A. LaBarge. Context, tissue plasticity, and cancer: Are tumor stem cells also regulated by the microenvironment? *Cancer Cell*, January 2005, vol. 7, pages 17-23. doi: 10.1016/j.ccr.2004.12.013

Paradigm-shift terrorists

All of this has finally led a few researchers to boldly suggest that cancer research is on the verge of a paradigm overhaul: "Research on early-stage carcinogenesis: Are we approaching paradigm instability?"[75] Baker *et al*. point out that the somatic mutation theory of cancer has had its day, has been extensively studied, has not provided a testable mechanistic understanding, has not resolved outstanding contradictions, and has not led to any treatment breakthroughs. They claim that cancer research is in a rut and that this might encourage a paradigm shift:

> "The more resources expended to try to uncover the exact nature of somatic mutation theory, the more you think that you are nearing a breakthrough in understanding somatic mutation theory and the more you think that a competing theory such as tissue organization field theory is correct, especially in light of observations that are paradoxical under somatic mutation theory. … The current paradigm also tends to be reinforced, because the experimental tools used to investigate it may be increasingly excellent for investigating somatic mutations but suboptimal for investigating a new paradigm, which adds another hurdle to exploring new paradigms. Just as there is no such thing as theory-free investigation, there are no such things as theory-free tools of investigation."

Baker *et al*. go on to suggest the alternative paradigm of "tissue organization field theory" (TOFT) as a promising progenitor theory. TOFT is a field theory — akin to the field theories of physics — in which the "field" (or fields) represent the spatiotemporal evolution of properties (mass, density, concentrations of bio-active substances, concentration of tissue-structure components, physical stress fields, chemical potentials, and so on) of the tissue or organ, on the scale of the tissue or organ rather than on the scale of an individual cell. In this way, general rules governing the field(s) can be postulated and tested, even if one does not know all of the tissue properties that are represented by the "field(s)" and does not know all the molecular-level mechanisms. As such, TOFT is a systems view of the tissue on which a tumour can develop, and the tumour is a manifestation of the field and appears as a local field distortion. In TOFT one largely admits ignorance at the cellular and molecular levels and looks for system-level organizational and time-evolutionary rules. It's like looking for a theory of gravitation even if one does not yet understand the thermonuclear details of star creation and death or all the processes that can occur on the surfaces of planets (including life itself). The approach has had some success in physics.

Rozhok *et al*. have taken on the challenge of considering a paradigm shift and recently (2014) showed by stochastic modelling of "real data on age-dependent dynamics of [hematopoietic stem cell] division rates, pool size, and accumulation of genetic changes" that the somatic

[75] S.G. Baker *et al*. Research on early-stage carcinogenesis: Are we approaching paradigm instability? *Journal of Clinical Oncology*, 10 July 2010, vol. 28, no. 20, pages 3215-3218. doi: 10.1200/jco.2010.28.5460

mutation-centric theories of both aging and cancer are not tenable. In their words (their abstract):[76]

> "Age-dependent tissue decline and increased cancer incidence are widely accepted to be rate-limited by the accumulation of somatic mutations over time. Current models of carcinogenesis are dominated by the assumption that oncogenic mutations have defined advantageous fitness effects on recipient stem and progenitor cells, promoting and rate-limiting somatic evolution. However, this assumption is markedly discrepant with evolutionary theory, whereby fitness is a dynamic property of a phenotype imposed upon and widely modulated by environment. We computationally modeled dynamic microenvironment-dependent fitness alterations in hematopoietic stem cells (HSC) within the Sprengel-Liebig system known to govern evolution at the population level. Our model for the first time integrates real data on age-dependent dynamics of HSC division rates, pool size, and accumulation of genetic changes and demonstrates that somatic evolution is not rate-limited by the occurrence of mutations, but instead results from aged microenvironment-driven alterations in the selective/fitness value of previously accumulated genetic changes. Our results are also consistent with evolutionary models of aging and thus oppose both somatic mutation-centric paradigms of carcinogenesis and tissue functional decline. In total, we demonstrate that aging directly promotes HSC fitness decline and somatic evolution via non-cell-autonomous mechanisms."

This means that the somatic (differentiated cell) mutations are driven or constrained by limitations in the environment or tissue-context, as is believed to occur in evolution, rather than tumours being caused by the accumulation of random mutations in cells that somehow direct aberrations in tissue form and function, and that the tissue-context "quality" is itself determined by whole-system (body) circumstances (aging). Rozhok *et al*. suggest that the dominant paradigm has the cart before the horse. They cite current theories of aging,[77],[78] in which mutation-centric models have been discredited with reason, and in which system-views are prominent.

In conclusion to Part-III, it does appear that the medical establishment may be on the cusp of a discontinuous paradigm shift in the theory of cancer. If such a shift occurs honestly and without cover up, then it will be a painful transformation because many careers and an economic enterprise are committed to both genetic-centric thinking and the war against metastasis.

In my view, as an outsider, the mutation-centric metastasis paradigm of cancer is a Gold-Effect edifice on steroids (see Part-I), which is used to justify the unjustifiable. The medical professional's ability to invent ever more elaborate imaginary and untestable molecular-and-

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[76] A.I. Rozhok *et al*. Stochastic modelling indicates that aging and somatic evolution in the hematopoietic system are driven by non-cell-autonomous processes. *Aging*, December 2014, vol. 6, no. 12, pages 1033-1048.
[77] K. Jin. Modern biological theories of aging. *Aging and Disease*, October 2010, vol. 1, no. 2, pages 72-74.
[78] M.V. Blagosklonny. Answering the ultimate question "What is the proximal cause of aging?" Aging, December 2012, vol. 4, no. 12, pages 861-877. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3615154/

cell mechanisms with erudite-sounding names in order to construct a self-serving "scientific" narrative is astounding, especially considering the deadly interventions that are performed as a matter of clinical protocol.

Cancer as age-dependent stress-induced breakdown of tissue homeostasis

Allow me now to describe my tentative picture of cancer, which is consistent with the observations about the nature of common cancers, while being as conceptually simple as possible. The model is predictive and therefore testable, and if it is correct, then it should be a guide for prevention and treatment, and for new experimental designs of lab models for use in research.

In essence, tissue homeostasis, that is, the dynamic preservation of organ shape, structure, and associated function, is a daunting task. The organ, like the body, must preserve its shape and internal structure, in the face of continued cell replacement, cell assignment, attack, repair, and a changing and fluctuating biochemical environment of the organ imposed by the whole body in interaction with its outside world (such as the office cubicle environment, the lunch counter, etc.).

On a given tissue, especially a surface tissue of the organ where there is direct contact with the extra-organ world, things go momentarily and locally wrong all the time. These localized mishaps spill over and grow until corrected, within a certain response and repair time. As such, we can postulate that for a given tissue in a given mean extra-organ environment, there will be a mean steady-state[79] nodule or "tumour" size (diameter or volume). Call it the mean steady-state "tumour" diameter, D_T.

Next, given the discussion provided above in Part-I, I postulate that in most circumstances the dominant control parameter relevantly affecting the extra-organ environment (the tissue's environment, in all its possible biochemical complexity) is stress experienced by the whole organism (body), S.

In low experienced stress S, D_T is small (1 mm or less, say) and the corresponding nodules are just the random fluctuations of organ-surface shape or roughness or density, and there are no symptoms — there is no cancer. On the other hand, beyond some critical stress, S_C, the tumour itself, as a wound, induces additional growth that cannot be completely countered by the stressed tissue and a runaway growth occurs, corresponding to an infinite D_T (in steady-state).

This means that the particular tissue or organ, in the particular mean extra-organ environment induced by a super-critical stress, will continuously grow one of more large tumours that will

[79] A "steady-state" condition is a condition that does not change with time or in which change in one direction is continually balanced by change in another. The steady-state condition occurs after some response time following a change in causal factors (here, following a significant change in the tissue's biochemical environment).

disrupt organ function and may physically cause body-system interferences (e.g., a large brain tumour physically compressing the cranium-encased brain).

I draw a graph of D_T (y-axis) versus S (x-axis), for a given tissue in a given individual experiencing various degrees of stress, and I draw different curves for the different tissues, each tissue-specific D_T v. S curve having its own S_C for that individual (of a given age):

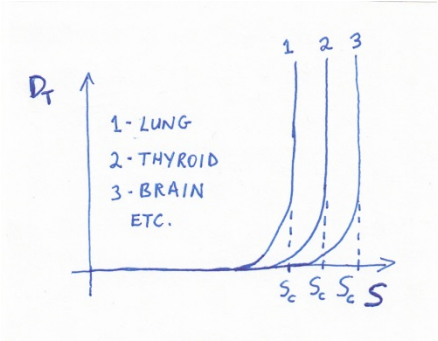

Figure 1: Steady-state nodule or tumour diameter versus stress experienced by the individual, for three different tissues or organs, each tissue having its own critical stress for that individual.

It is natural that different tissue types (organs) have different intrinsic stabilities, or capacities to maintain homeostasis. Slow-growth scantly irrigated tissue, with little environmental contact with outside elements and with low rates of stem-cell division, such as bone and cartilage will be relatively stable in shape, whereas high-turnover well irrigated tissues, with surfaces having significant environmental contact with outside elements and with high rates of stem-cell division, such as lung, mammary organs, and intestinal tract, will have high susceptibility to surface-shape instability. Thus, I imagine a sequence of tissue-specific critical stress values that follow the lifetime-stem-cell-division sequence introduced by Tomasetti and Vogelstein.

Next, I propose that the cluster of tissue-specific D_T v. S curves moves to the left, towards lower experienced-stress tolerance, as the individual ages. Like this, where only the most unstable tissue is represented, for the sake of clarity:

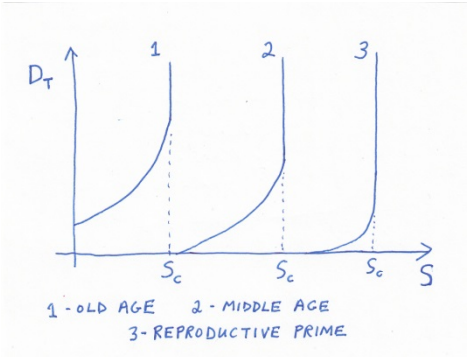

Figure 2: Steady-state nodule or tumour diameter versus stress experienced by the individual, for one tissue type or organ, and for three different ages of the individual. As the individual ages, the organs become more susceptible to a runaway loss of homeostasis.

In this model, the cancer outcome arises from reciprocation between the tissue's susceptibility to loss of shape-homeostasis (TSLH) and the level of stress experienced by the individual. Stress is subjective but its effect on the tissue's complex biochemical environment is objective, in that it can in-principle be measured.

The TSLH will depend not only on stress-induced changes of the tissue's environment but also on:

- the intrinsic tissue-type properties (as measured by lifetime stem cell divisions) (Fig. 1),
- the tissue's background environment in the specific individual,
- the tissue surface's continued contact with homeostasis-process-mediating environmental substances (smoking in the lungs, diet in the digestive tract, sunlight on the skin),
- regular intake of drugs and medications (such as Aspirin, see above), and
- the changes with age of both intrinsic tissue quality and the tissue's background environment (Fig. 2).

Likewise, sustained stress may change tissue quality itself, not just the tissue's biochemical environment.

Thus, for a given individual at a given period in his/her life, there will be a unique D_T v. S curve for the tissue of most concern, with a corresponding critical stress S_C. The individual's persistently experienced stress level will either be lower or higher than S_C, thereby determining whether or not the individual is developing a malignant cancer in the said tissue. If several tissues have critical stress levels below the individual's persistently experienced stress, then the said several organs will form malignant tumours.

In this way, we understand "metastasis" as the simple consequence of the individual's TSLH having gone supercritical for a cluster of tissue-specific D_T v. S curves. There is no "spread". The tumours develop simultaneously, each at their own tissue-specific rates, and there are also subcritical nodules everywhere… Carving out one or several tumours will not help. Radiation will not decrease TSLH, nor will toxic chemotherapy.

The resulting focus on prevention and treatment appears as three-fold:

(i) One branch addresses the societal and psychological factors causing the stress experienced by the individual,

(ii) A second branch considers how TSLH might be altered towards lower susceptibility, and

(iii) The third branch considers how one might interfere with the feedback process that causes the runaway tumour growth, in a wound-healing-like process.

Branch-(i) probably is not aided by current treatment protocols, but the clinical attention given to certain patients even in administrating poison and radiation may sometimes have a net benefit?

Branch-(ii) might be affected by drugs that interfere with cellular capacity to acquire energy, such as dichloroacetate (DCA)?[80]

Branch-(iii) is probably affected by non-steroidal anti-inflammatory drugs (NSAIDs), which interfere with blood clotting.

The stress-induced TSLH model, or D_T v. S model, allows conceptual room for "soft" (and "low-tech") chemotherapy treatments because TSLH and feedback processes in tumour growth may be relatively easy to affect with small molecules that cause general biochemical changes in the tissue or tumour environment, related to coagulation, viscosity, pH, oxidative potential (pE), unknown chemical potentials, etc., without necessarily having a high-degree of metabolic target specificity.

Likewise, tackling the human stress side of the equation could have important "spin-off" benefits for society at large. The science of stress could use a boost.

Let's end the "war on cancer" and start the peace process.

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[80] E.D. Michelakis *et al*. Dichloroacetate (DCA) as a potential metabolic-targeting therapy for cancer (Minireview). British Journal of Cancer (BJC), 2008, vol. 99, no. 7, pages 989-994.