



Parallel Causation in Oncogenic and Anthropogenic Degradation and Extinction

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Abstract

We propose that the onset and progressive destructive action of cancer within an individual bears a profound and striking similarity to the onset and progressive human-engendered destruction of global ecosystems and the extinction of entire species. Cancer in the human body and our human role in planetary, especially biotic, degradation are uncannily similar systems. For starters, they are the only two known complex systems where a discrete component changes its normal ecological role and function—turning on and potentially killing its host, and in so doing, itself. Both are “hostile takeovers.” Clearly, humans are integral to both systems. With cancer we are the host and victims of the rogue behavior of what starts out as a normal, healthy, and functionally important part of our bodies. With the biodiversity crisis, we are the part of the system that has changed, expanded, and proven so destructive to the system in which we live. We argue that given that these threats to our bodies and Earth are both essentially ecological diseases, understanding the critical role of ecological interdependencies for avoiding both cancer’s and humankind’s destruction of their respective homes should hopefully promote better stewardship of both by the only animal capable of recognizing the problems—us.

Keywords Agricultural revolution · Biodiversity crisis · Oncogenesis · Sixth extinction · Tissue ecology

Introductory Statement

Cancer results from tissue-level (somatic) evolution within an individual, requiring both cancer-causing (oncogenic) mutations as well as altered tissue environments that engender selection for these mutations. It is important to pursue the rather new ecological and evolutionary aspects of modern cancer theory (Greaves 2001; Gatenby and Gillies 2008; Maley et al. 2017; Ujvari et al. 2017; DeGregori 2018), which seek to understand how aging, carcinogenic exposures, and the growth of the tumor itself can alter tissue environments so as to promote selection for tumor-promoting genetic changes adaptive to these new environments.

This perspective mirrors the ecological and human cultural evolutionary causality entailed in analyses of current anthropogenic theories of the origin and progression of the “sixth extinction” (Barnosky et al. 2011), also known as the “biodiversity crisis” (Eldredge 1998). The agent that profoundly took humans out of their functional roles in local ecosystems was the invention of agriculture. The first Agricultural Revolution, occurring in several places ~ 10,000 years ago, explosively transformed a global human population of an estimated five million people to the current seven billion plus (Eldredge 1998). Ten thousand years is a brief interval compared with the ~ 200,000 years of the existence of *Homo sapiens*.

Thus, in both systems, the ecological change-in-state lifts the normal Malthusian cap on population sizes, as the nascent tumor and human populations gain active control of nutrient supply, increasing carrying capacity and supporting abnormally high rates of population growth. In both systems, the rogue component tends to degrade the local environments, and either attacks and destroys neighboring populations of different cells or species, or co-opts them for its own use, as in the neutralization and even selfish use of immune cells in cancers, and the domestication of wild plants and

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animals as a hallmark of agriculture, and the banning of others not useful or even harmful (Table 1). There were no “weeds” before agriculture was invented, and we co-opted wolves for our own purposes, thus in part mitigating their threat to ourselves and our domesticated animal species.

In short, both tumors and anthropogenic extinction of other species begin with an event that takes a cellular clone, or a human population, both initially small, outside of the normal sustainable ecological niche each occupies in its own systems. They go rogue and run amok.

The parallels run still deeper, and include the increase in mutation rates in cancer, comparable to the logarithmically accruing technological innovations in human society. Through the generation of new traits, both can lead to the enhancement of fitness—essentially the relative ability to reproduce. In cancer, a tumor’s cellular fitness is enhanced, typically at the expense of its host. In the case of the biodiversity crisis, cultural innovations continue to develop, enhancing our own fitness, often inimical to the welfare of the by-now planetary system in which we humans live.

And both systems have metastatic propensities: they spread. What starts locally ends up dominating the entire host system—even eventually going so far as to take that system down.

We see the potential for reciprocal illumination between the study of cancer, on the one hand, and still-growing attempts to grapple with the destruction of life on planet Earth. Thus, there may be hints of treatments—if not cures, then at least stabilization—that knowledge of one system may suggest for the other. Our general approach is to explore specific applications of ecological/evolutionary theory that have already shown promise in one system and ask whether that theory might be relevant to the other. Here, we have chosen, as just one example, to focus on niche-width theory, both as a potentially fruitful application to cancer and biotic degradation, and as an exemplar of the kind of resonance that comes from considering one aspect of the theory in one system, the light it can shed on the other system, and reciprocally, the further light it can shed on the initial system. Our hope is that our demonstration of the causative parallels between the two systems may stimulate thought amongst our fellow humans to explore the nature of, and solutions to, the problems of oncogenic disease and anthropogenic ecosystem and species degradation and destruction.

It is not lost on us that humans are integral to both systems. With cancer we are the host and victims of the rogue behavior of what starts out as a normal, healthy, and functionally important part of our bodies. With the biodiversity crisis, we are the part of the system that has changed, expanded, and proven so destructive to the system in which we live.

Tissues, healthy or not, are parts of our human bodies. Human bodies are still parts of our species *Homo sapiens*,

though no longer parts of small bands integrated into local ecosystems in the manner of our pre-agricultural hunter-gathering forebears. So think of it this way: cancer does not realize that death awaits it as it invades and wreaks havoc on our tissues. And biotic Earth does not know that it is being attacked—even though ecosystem repair, even under attack, is as common as tissue repair. But we the people are the only ones in these games that can see and understand what is going on. We are the only entity of life on Earth that sees and understands at our level of sophistication; who knows, maybe in the entire universe. Nearly all of us are deathly afraid of cancer. We should be equally afraid of our cancer-like destructive attack on the host in which we were born as a species. Unlike cancer, we *know* that our own future as a species is as imperiled by our behavior as we ourselves are by any cancer lurking within us. We can use that foresight and our intelligence to limit the destructive impact of both scourges.

Fundamental Aspects of Economics, Genealogy, and Evolution

Before we embark on a more detailed discussion of the causal resemblances between the two systems—cancer and human environmental destruction—we need to clarify basic issues of the use of the term “evolution” in what are actually three distinct systems: traditionally construed evolutionary systems, evolution of cancer, and evolution of the human capacity to secure nutritional resources that has led to the sixth extinction and worsening conditions on the globe that threaten our own continued existence.

“Evolution” and “evolutionary theory” are terms traditionally applied to understanding the dynamics of stasis and change in organizational elements in the natural world—chiefly populations (demes), seen as individuated subsets of entire species. Largely developed for sexually reproducing species, among the more prominent causal elements are (1) mutation as the ultimate cause of (2) within-population genetic variation expressed in the phenotypes (seen for the most part as adaptations), on which (3) natural selection acts to stabilize or further modify genetically based phenotypic properties which can be further crystalized, developed, and conserved in (4) the speciation process. There is, of course, more to biological evolution than these four elements (e.g., genetic drift), but these are the core basics of our understanding how life evolves.

To speak of the “evolution” of cancer (aka “somatic evolution”), or, likewise, of “cultural evolution,” can initially prompt a mild form of cognitive dissonance—given the common understanding of what “evolution” actually is in the history of biology over the past 200+ years. Both of us are steeped in the tradition of biological evolutionary theory,

Table 1 Partial list of formal equivalencies between oncogenic disease and anthropogenic ecosystem disruption and species extinction

Common feature	Cancer cells	Humans
Individuated parts abandon usual role in local ecosystem, triggering explosive population growth	Lose usual functions in tissues	Invent agriculture and “step outside” universal role of within-ecosystem living
Individuated parts ensure own nutrient system	Co-opt blood supplies, increase uptake of sugars, amino acids, and other nutrients	Produce energy resources rather than living off the natural fruits of the land
Normal Malthusian caps lifted	Selection and population expansion depend on altered/controlled physical and biotic environments	Reproductive success and population expansion depend on altered/controlled physical and biotic environments
Degradation of their environments	Depletion of competing normal stem cells; tissue acidification and extracellular matrix perturbations; impairment of normal tissue/organ function	Driving non-agricultural human populations and other species extinct through resource overconsumption, habitat destruction, pollution, and directed killing
Co-opt neighboring non-conspecific “species,” previously in competition or at odds with, for their own purposes	Tumors evolve to manipulate T-cells, macrophages, and vascular cells to their benefit	Domestication of dogs, and plants and animals in general—plus efforts to eradicate pests and weeds
Migration to new territories	Invasion and metastasis with adaptation to new environments (genetic and epigenetic)	Migration around globe with adaptation to new environments (genetic and cultural)
Increased rate of acquiring novel innovations	Increased mutation rates provide fuel for somatic selection of phenotypes that are adaptive to the changing tissue and tumor landscape	Cultural evolutionary innovations have increased logarithmically over the past ~ 10,000 years
Both have the very real potential to cause the demise/death of the system of which they were once a functioning synergistic part	About half of all cancers lead to the death of the host	Extinction of many component species of biotic Earth; damage to abiotic Earth. If not, ultimately, death of <i>Homo sapiens</i> , at least the extinction of advanced culture is a real possibility

This table summarizes the main points of what we see as analogous processes between oncogenic and anthropogenic systems that are destructive to other entities of their respective host systems—and ultimately to their entire host system. We note that the analogies are general, not highly specific: in general, the ecological/evolutionary biological processes of oncogenesis (e.g., somatic mutations) are analogous here to ecological innovations in a cultural evolutionary context (e.g., invention of spear points). Likewise, higher reproductive success rates engendered by co-option of nutrient supplies in both systems are measured against earlier, “normal” rates in non-disturbed systems, recognizing of course that reproduction is asexual/somatic in cancer and sexual in humans. In general, post-agricultural humans have developed primarily cultural (i.e., nonbiological) environmental adaptations—the supplementation, or downright supplanting of earlier genetically based morphological, physiological, and behavioral ecological adaptations

and have contributed to its further development. But it is important to the two systems we confront and compare in this article to recognize explicitly that each departs conceptually from the basic biological evolutionary syllogism as outlined just above.

In a cancer system, we are dealing with the origin, growth, and change of aberrant cell types within tissues and organs within the body (soma) of a single organism. The “evolution of cancer,” in this context, does not mean “the development of cancer generally across the history of life.” That, with cancer, we are in fact discussing somatic evolution initially proved confusing to one of us, a paleontologist, when first confronted with somatic evolution by the other, a cancer biologist, in 2010. Auguste Weismann, the nowadays unsung hero of understanding the nature and transmission of what we now call genetic information, taught in the 1880s that what happens to the soma stays with the soma. Transmission of genetic information to descendant organisms is effected solely through the germ line. With notable exceptions (Ujvari et al. 2016), that distinction has held up

as an essentially true description of multicellular forms of life. It was extended downwards as the Central Dogma of the emerging field of molecular genetics half a century ago (Crick 1970). And it lives on as the fundamental distinction, in higher levels of organization, in the recognition of the dichotomy between (1) functional, economic (“ecological”) activities of organisms in the day-to-day “struggle for existence,” where the somatic component of organisms is engaged, perpetually, in the ongoing second-by-second processes of matter-energy transfer. At higher levels, this economic aspect of life is expressed in local avatars (species populations) integrated into local cross-genealogical ecosystems—with matter-energy interchange processes occurring at appropriately slower rates in these spatiotemporally larger-scaled systems.

In contrast to the economic side of life, there is the (2) “genealogical” side of life—amounting to the origin, transmission, and fate of genetic information within a system, ranging from the molecular up through species and the genealogical skeins of species we recognize as higher taxa.

Species and higher taxa are the prime focus historically of the vast bulk of evolutionary theory. Organisms (including humans) are components of both systems, leading their daily economic lives and occasionally diverting their attention to reproductive matters. Higher up, species are genealogical systems, profoundly different from the nature and internal functioning of cross-genealogical ecosystems.

The interaction between the realms of genealogical and economic/ecological systems is critical to understanding the evolutionary process in general: genealogical systems (demes, species), as larger-scale repositories of genetic information, have no function other than to continually provide the “players” in the somatically run economic game of life. Because more organisms are produced each generation than can possibly survive and reproduce due to the constraints of environmental carrying capacity (Darwin 1859); and because organisms within populations vary genetically, how well they fare economically statistically governs how well they fare reproductively: Darwin’s original conceptualization of natural selection developed in the late 1830s (see Kohn 1987; Darwin 1859). Economics and genealogy are indeed connected—but first we must understand how they are ontologically different before those connections become apparent. This is our intellectual inheritance from Auguste Weismann.

Nowhere in modern biology is Weismann’s distinction between the germ line and soma, between the economic and genealogical, better remembered than in cancer biology and medicine. On the macroscopic scale, one of us used it as the conceptual framework to organize the Hall of Biodiversity at the American Museum of Natural History—where the phylogenetically arranged “Wall of Life” stands opposite presentations (in dioramas and other media) of global ecosystems.

And now we speak of cancer evolution within the soma, a logical extension distinct in important details from “biological evolution.” Somatic cells reproduce, passing on their genetic information to descendant cells. Mutations occur, and are passed on, unless chance or selection eliminates them. Cells differentiate, and develop into the functioning cellular components of normal tissues. Selection is always winnowing, conserving some cell variants, discarding others. And though nothing like “speciation” has yet been described within the soma of individual organisms, cell types (within tissues and organ systems) clearly have differentiated in phylogenetic history [the evolution of immune systems has been particularly well-studied (Hirano et al. 2011)]. An analogue to “speciation”—fissioning of reproductive communities into two or more descendant forms—might one day prove useful as well to understanding somatic evolutionary processes. And thus, though the soma functions as an economic entity, embedded within is a reproductive component, where descendant cells of like kind are continually produced.

We also rely on concepts of “material cultural evolution” in our characterization of the human ecological/evolutionary journey that has led to our resemblance to a cancer, with each human being a component cell, currently conjointly wreaking havoc, not only within the biosphere, but by now expanded to unmistakable changes in the atmosphere, hydrosphere, and even the lithosphere (Eldredge 1999).

Here the evolution—the stasis and change of transmissible cultural information—is the core process. Humans have, of course, evolved according to the basic core rules of biological evolutionary processes. We are still evolving through the usual processes of mutation-based genetic variation and selection—although it must be said that the opportunities for speciation (fairly rampant in the past four million years or so of hominid history) are dampened given our interconnectedness in reproductive and economic functions.

In human cultural systems, information is spread laterally as well as vertically. Information transfer is primarily about economic concerns (as it is in organismic biology: instructions on how to build a functioning soma predominate over instructions on how to transmit the underlying information reproductively). Lateral information transfer in human cultural systems is ubiquitous and dominates cultural systems (reminiscent of some prokaryotic systems). And lateral information transfer has been accelerating. Such evolution of technology has been evident in the last century of computer innovations, with improvements (such as in information storage) often accumulating logarithmically. This very technology, and associated advancements such as the Internet, has itself dramatically accelerated lateral information transfer. The information changes—through random error, or deliberate intentional design. These are the point origin discrete changes that are analogous to actual genetic mutations. Variation accrues and is subject to a winnowing process of selection.

It is material cultural evolution that concerns us most here: the origin and development of what has recently come to be called the “technosphere” (Tëmkin pers. comm.). Material cultural evolution is similar to, but not the same as or reducible to, traditionally conceived evolutionary biological theory—much in the same way oncogenic evolution is similar to, but actually importantly distinct from, biological evolution conventionally conceived.

If both evolution in cancer and evolution of human material cultural attributes are informed by, but distinct from, the traditional domain of organic evolution, is it valid to perceive all three general sorts of systems as “evolution”? We believe it is indeed valid. All we need do is reenvision evolution as “the fate of transmissible information.” Or, perhaps better, “the fate of transmissible information in an economic context”—realizing that phenomena such as sexual selection appertain, mostly if not wholly, to reproduction, sometimes even at the risk of the somatic life of the reproducer.

For more on our views on the three evolutionary systems discussed here, see Eldredge (1985, 1986) on the Weismannian distinction between germ line and soma and its expression at higher levels; DeGregori (2018) on cancer/somatic evolution; and Eldredge (2009) on the fundamentals of material cultural evolution.

We structure our discussion of the parallel elements of causation outlined in Table 1 by presenting first a basic description of each of the two systems viewed in an evolutionary/ecological context, occasionally cross-referencing to the other system. We follow this by a section on prevention and remediation in each system—again noting points in common. We conclude with a back-and-forth discussion of a possible example of how a specific subset of biological evolutionary theory as applied to one system might be usefully applied to the other.

An Ecological and Evolutionary Perspective on Cancer

About 40% of people living in developed nations will develop cancer in their lifetime, and about half of these will die from their disease. Cancer afflicts other animals across the tree of life (Aktipis et al. 2015), and thus appears to be a ubiquitous consequence of multicellularity. But why do we and other animals develop cancer? The conventional view is that cancers result from mutagenic exposures that we experience throughout our lives, together with mutations that occur during the many cell divisions required to make and maintain a human body (Peto et al. 1975; Serrano and Blasco 2007; Hoeijmakers 2009; Tomasetti et al. 2017). Whether from external or internal causes, some of these mutations are thought to either activate genes that promote inappropriate cell growth (oncogenes) or inactivate genes that limit cell growth (tumor suppressor genes). As such, cancer is thought to arise through the progressive accumulation of oncogenic mutations that promote inappropriate cellular growth. However, this common view of cancer genesis is akin to explaining the current spectrum of species on Earth as the progressive result of mutation accumulation without considering the environmental changes that dictated evolutionary trajectories.

Just as for organismal evolution, an appreciation of the somatic evolution that can lead to cancer requires understanding the tissue (micro) environmental influences on evolutionary trajectories, and how contexts associated with cancer (including exposures like cigarette smoking or old age) impact microenvironments that thus increase the odds of cancer evolution. The evolution of cancer follows most of the same rules as established in classical evolutionary theory. One such rule is that mutations do not have defined effects on fitness, with fitness determined by the relative contributions of a given genotype to future generations (whether

of seals or cells) (Rozhok and DeGregori 2015). For example, we know that genetic variants that changed the color of peppered moths from white with black speckles to solid black were only advantageous (increasing fitness) when trees in England were covered in soot, but the black moth populations declined again when pollution controls led to normal bark coloration (Clarke et al. 1985). Similarly, studies have shown how oncogenic mutations that decrease somatic cell fitness in young animals can increase cell fitness in older animals, and that selection for these oncogenic mutations in the old animals was due to age-dependent changes in the tissue environment (Henry et al. 2015). Additional studies have substantiated context-dependent selection for oncogenic mutations, being *selectively* adaptive in the damaged microenvironment (whether by old age, radiation exposure, inflammation, or other causes) (Jonason et al. 1996; Bondar and Medzhitov 2010; Fleischman et al. 2011; Marusyk et al. 2010; Vas et al. 2012; Vermeulen et al. 2013; Parikh et al. 2017). Changes in tissue adaptive landscapes thus lead to the expansion of the oncogenically initiated clone, starting the cells down the path towards cancer. The evolutionary reason for this age-dependent change in tumor suppression is that, like all animals, we did not evolve to live forever, but only long enough to maximize reproductive success (but see Greaves 2018; Rozhok and DeGregori 2019) for potential explanations for exceptions to the late-life pattern of cancers, such as those in childhood). So aging in general, and increased cancer incidence in particular, represent the waning of the force of natural selection to maintain our fitness at ages where we would likely be dead from other causes, at least for most of our evolutionary histories.

An Ecological and Evolutionary Perspective on Human History

We have come to the point in human history where we can no longer ignore the destructive side effects of the dramatic human cultural evolutionary successes as measured by the sheer numbers of people on the planet (some 7.5 billion and counting).

Mass extinctions have, at least five times prior to human existence (Bambach 2006; MacLeod 2013), eliminated many species globally in a geologically short period of time. The most extensive so far has been the end-Permian Period event, either through volcanic or extraterrestrial bolide collisions, or a combination of both—an event that took away over 90% of all marine and terrestrial multicellular plants, animals, and fungi (Benton 2005).

After each such event (end-Ordovician, Late Devonian, end-Permian, end-Triassic, end-Cretaceous—the latter most notorious for wiping out the remnants of the non-bird dinosaurs), after a lag of up to ten million years, new species, derived from surviving stock, evolved and rebuilt new,

localized terrestrial and aquatic ecosystems. Evolution has been the long-term biotic component of the analogue of “tissue repair” for larger-scale biotic systems throughout the history of life on Earth.

But it is important to see that such drastic global extinction events, “repaired” in the long-term by the evolutionary generation of adaptive novelties within new species (which in genealogical skeins equates with new higher taxa), are the largest-scale end-member of a spectrum of such destructive/recovery-through-repair events. At the lowest end lies ecological recovery through recruitment of survivors persisting outside a localized disaster area (after forest fires, earthquakes, tsunamis, hurricanes, etc.). The tipping-point events—those that trigger speciation and adaptive change at the species level, are the intermediate-scale “turnovers” (Vrba 1993), where regional environmental change drives entire species extinct, and triggers speciation events from the remaining gene pool. Hominid biological evolution over the past five million years or so is an excellent example of the role of turnovers in the continued generation of new species (Vrba 2013).

Virtually all ecological destructive events, from local ecosystem downgrades and extinctions up through the roughly five truly global mass extinctions, have been engendered by physical events impinging on the biotic realm. Until now. The current “sixth extinction” (Barnosky et al. 2011) also known as the “biodiversity crisis,” where according to recent estimates Earth is losing ~ 10,000–20,000 of its estimated 10,000,000 species each year, is almost entirely due to human activity and population growth, and especially though not solely through the development, growth, spread, and ever-increasing technological improvements in agriculture. Human-caused destruction of habitat is the main cause of species loss, followed closely by overharvesting, pollution, and the introduction of alien species. These problems have morphed within recent centuries to embrace the side effects of the industrialized world, transcending agriculture and causing the problems of global climate change.

As we write, the media have become increasingly focused on the terrifying question: are we quickly approaching the brink—the point of no return in our largely inadvertent destructive modification of terrestrial, atmospheric, and oceanic components of the global physical/biotic systems? Indeed, the recent United Nations report on climate change warns that we have less than 11 years to reverse course, requiring unprecedented action, before the ultimate catastrophic consequences become irreversible (IPCC 2018). And, even should we be sufficiently determined, and fortunate enough, to curb carbon emissions to some level of mitigation, there would remain the underlying problems of human-engendered habitat destruction and species loss—the original source of concern of the environmental movement only a few decades ago. The problem was then, and remains,

a matter of out-of-control population growth triggered by key events in human ecological history.

Living Within Ecosystems

Over the roughly 200,000 year evolutionary/ecological history of *Homo sapiens*, it is manifestly clear that both genetic factors (the traditional bailiwick of evolutionary, not to mention medical, discourse) and especially cultural evolutionary factors have been at play in the transformation of the hominid primordial ecological state. It is human behavior, especially sentient materially imbued cultural behavior—the “technosphere”—that underlies most of the recent “evolution” within *Homo sapiens*. Indeed, most of the conspicuous adaptive evolution that has occurred over the last 10,000 years of human existence has been in the technosphere, rather than within our bodies.

Prior to the advent of agriculture a mere ~ 10,000 years ago, members of our species lived as every other metazoan species has done since the dawn of time (for metazoans, at least a half billion years): humans lived in local ecosystems, generally in resource-limited small bands usually ranging between 30 and 50 people. Malthusian caps, population by population, were firmly held in place by the capacity to get whatever nutritional resources were needed and available—by hunting (and perhaps scavenging) animals and otherwise collecting edibles, generally plants. For an informative portrait of the lives of the Mbuti peoples (so-called “pygmies”) of the Ituri Forest of what was then the Belgian Congo, see anthropologist Colin Turnbull’s account (Turnbull 1961) as well as Eldredge (1995) for a suggestive guide to how life was lived prior to the Agricultural Revolution.

Early hominids, enabled by a developing technosphere, started expanding out of Africa long before the advent of *Homo sapiens*, in successive migratory waves out of Africa and into the New World (an early-on shade of metastasis) (Tattersall 2015). Stones, naturally enough, preserve very well in the geo-archeological record; the earliest no-doubt human-fashioned tools are approximately three million years old, found in east Africa, crafted perhaps by *Homo habilis* (the aptly named “handy man”). Part of the diversifying stone (and less-well-preserved bone/tooth/horn/wood) early kit bag was of course devoted to hunting, and perhaps warfare. The upshot: there is a stunning correlation between the arrival of modern humans (and to a lesser extent, earlier species in our clade) and the extinction of large Pleistocene mammalian species: e.g., ~ 12,000 years ago in the Americas, ~ 5000 years ago in the Antilles, and only ~ 2000 years ago, oddly enough, in Madagascar (though this long-accepted date is currently under challenge; see Lawler (2018), for a review of evidence that Madagascar might have been home to hunting parties as early as 10,000 years ago).

It is not unreasonable to think that the so-far greatest survival of large-bodied mammalian species, in Africa, reflects the fact that they were already there as modern humans evolved, and experienced humans as they invented and passed down, slowly at first, but with increasing sophistication, hunting skills and tools. The African mammals evolved to cope. The lesser survival of large-bodied mammalian species in Eurasia (and much later, the Americas) probably reflects the shocking arrival of humans, with their unparalleled, culturally imbued hunting efficiency. Nowhere is this more evident than in the relatively sudden demise of so many species shortly after 12,000 years ago in the Americas. The parallel trackways of a human being and a single giant ground sloth (*Megatherium*) along the shores of Bahia Blanca in Argentina stands as ineffable evidence of this species-level encounter (Fig. 1) (Bayón et al. 2011). Humans survived in droves in the Americas (through successive waves of immigration). *Megatherium*, along with other ground sloths, glyptodonts, and many others, are recently, but irrevocably, gone. But through all of that, the human “niche” was still very much a matter of living off nature’s unvarnished bounty: technically, we were still living within the confines of local ecosystems. Humans, through cultural evolutionary innovations, were getting very good at making a living the old-fashioned way, within local ecosystems.

The Agricultural Revolution and Human Exit from Local Ecosystems

According to biologist Joel Cohen (Cohen 1995), the median informed estimate of the global human population size before the Agricultural Revolution is between one and ten million people. The Agricultural Revolution came ~ 10,000 years ago—in several far-flung places, but perhaps most notably in what is now the Middle East. That was when humans took life into their own hands and quite literally stepped outside local ecosystems: With the invention of agriculture, humans stopped relying, wholly, at least, on seasonal, renewable energy resources and productivity. Humans learned, seemingly in a flash, how to control plant life cycles—in so doing engaging in the rudiments of selective breeding, which after all is the primitive version of genetic engineering.

Other species have expanded their niches in their evolutionary histories. And many have expanded their ranges and/or population sizes. But, until *Homo sapiens*, no other species is known to have abandoned life in a local ecosystem for some other mode of subsistence. Nascent cancer tumors, abandoning their normal economic functions within their tissues, commonly co-opt blood, hence nutrient, supplies by inducing angiogenesis. This is in effect what humans achieved with the invention of agriculture.

And this efficient way of life, of ensuring nutritional needs—a technospheric cultural evolutionary innovation that greatly enhanced the fitness of those who adopted it—quickly spread. It metastasized, taking root elsewhere, as it was good for the people who possessed it.

In so taking charge of energy needs, humans co-opted lands—allowing only a few cultivars to grow; the rest became “weeds.” Animals, fungi, and microbes that ate, or competed with, farmed crops became vermin and pests and were dealt with accordingly. Animals were domesticated for food and ultimately labor—and some were brought into homes for protection and companionship. Humans effected a revolutionary, pretty much utterly different relationship to the biotic world than they had started out with (though people still rely on resources such as fisheries, most of the dozen or so most important of which are in a chronic state of depletion because humans just keep on getting better and better at improving technologies to harvest those fish). And humans still utilize an estimated 40,000 native plant, animal, fungal, and microbiotic taxa globally per year.

Hence, the Agricultural Revolution-engendered mass extinction, adumbrated by increasingly successful hunting/gathering and its initial spread over the globe, quickly



Fig. 1 Trackways of *Megatherium* and a human (a presumed hunter). Image is from Bayón et al. (2011), with permission from Dr. Teresa Manera, Universidad Nacional del Sur, Bahia Blanca, Argentina

became a reality. Clearance of vast tracts of lands became the norm, and cities, as the concentrated locus, grew as partners with the core need to feed ourselves, supplying the necessary finance, technology, political control—and eventually research, education, and media—all components of today’s human-centered, human-obsessed world (see Eldredge and Horenstein (2014)). We have forgotten who we were and where we came from.

And much of this seems good, *is good—for people*. But we are not spending nearly enough time considering the dangers of driving our fellow species extinct, and the destruction, as well, of the physical systems of the planet that support, envelop, and sustain life on Earth. This could turn out very badly—for us, along with the rest of the components of the biosphere. Just as is already happening in the realm of cancer medicine, it’s time to redouble our efforts to combat the ills we humans are visiting on our own earthly body.

Implications of the Ecological Perspective for Cancer Prevention

Just as our destructive impacts on Earth endanger constituent species, we need to consider how damage to our tissues, both avoidable and unavoidable, during life affect the relative dominance of normal and malignant cell clones. Just as investments in neighborhoods, such as through schools and infrastructure, can reduce crime, we can appreciate that strategies to promote healthy tissues should limit cancer. Thus, while we cannot avoid many if not most of the mutations that accumulate in our bodies throughout life, we can potentially limit the odds that cells with oncogenic mutations will become cancers. To do so, we need to change tissue environments so that these mutations are no longer adaptive. Since we know that these oncogenic mutations are much less adaptive in young tissues (as we evolved to *not* get cancer through youth), the simple solution would be to rejuvenate our tissues. Of course, this is easier said than done, and science is a long way from learning how to prevent aging or restore youth. Still, we have learned that reversing certain features of old age, such as increased inflammation, can abrogate the aging-dependent selective advantage conferred by oncogenic mutations (Henry et al. 2015). Since inflammation is an important program needed for pathogen defense and tissue repair, any strategy to reverse aging-dependent inflammation will need to be carefully developed, in order to maintain normal protective functions.

In this regard, we need to be very cautious when attempting to manipulate ecosystems, whether on Earth or in our tissues, as club-handed approaches can end badly. Just as the introduction of cane toads and rabbits into Australia wreaked havoc on ecosystems there, studies which have inhibited inflammation in people, while effectively reducing cancer

risk, have resulted in undesirable side effects like increased bleeding, gastrointestinal symptoms, or increased risk of death from bacterial infections (Todoric et al. 2016; Ridker et al. 2017). Ecosystems at both macro and micro levels are complicated, and we have to recognize our inability to fully predict outcomes from manipulations, given the many complicated relationships between players. Millions of years of evolution have sculpted ecosystems and interdependencies (whether of species or cell types), largely in ways that we do not appreciate.

So how do we take care of our bodies so as to limit cancer risk? Once we realize that our cells are not working in isolation, but that their fate is dependent on their environments, we can then ask—how do we best maintain these tissue environments? While a pill to ward off aging might be desirable, in some ways we already know how to best maintain our tissues: eat a balanced diet, exercise regularly, and don’t expose yourself to carcinogens like cigarette smoke. The common perception of being fit aligns well with the lifestyle choices that maintain our tissues so as to maximize cellular fitness. Taking care of the whole (the body) can limit the destructive behavior of the constituents (our cells), just as properly managing Earthly ecosystems can help mitigate the destructive tendencies of constituent humans. In this sense, it is notable that cancer rates in humans (and other animals removed from nature, such as pets and laboratory animals) are much higher than in “wild” animals, which, together with living much longer, has resulted from modern environmental exposures and lifestyles that diverge from the ancestral conditions under which our genes largely evolved (Hochberg and Noble 2017; Giraudeau et al. 2018).

It comes down to maintaining the status quo. Essentially, we should promote behaviors or policies that favor “the evolved type,” whether we are referring to an ecosystem in the absence of human impacts or the tissues of an ideal healthy youngster. Such macro and micro ecosystems will be under strong stabilizing selection, essentially a self-reinforcing stasis. Regarding the soma, we, and all other animals, evolved stem cells to be well adapted to their tissue environments, leading to strong stabilizing selection (meaning that mutations that change the traits of stem cells will be selected against) (DeGregori 2018). As the cells responsible for maintaining tissues for a lifetime, stem cells are also typically where cancers initiate. So at least through our reproductive years, where the action of natural selection has been strongest, oncogenic mutations will be typically selected against in these youthful tissues. If we could figure out how to maintain the youthfulness of tissues, beyond eating well, exercising, and not smoking, we should be able to limit cancer incidence. As mentioned above, rejuvenation of our tissues is a tall order, and thus we need to learn what are the key parameters that change with age or exposures like smoking that are responsible for altered oncogenic selection.

And then we need to figure out how to safely manipulate these factors to limit cancer evolution.

Implications of the Ecological Perspective for Cancer Treatment

As a cancer grows within us, it creates its own microenvironment, which can diverge substantially from the tissue environment in which it arose (Gatenby and Gillies 2008; Maley et al. 2017). While the many evolved hurdles to cancer development, from the stabilizing selection discussed above to immune-mediated elimination of cancer cells, frequently nip a cancer in the bud, the rare successful cancerous clone evolves to manipulate its environment for its own purposes. Cancers render immune cells (like T-cells and macrophages) suppressive rather than tumor-reactive, recruit other cells to build blood vessels to feed the tumor, and remodel the surrounding matrix to favor their aberrant lifestyle (Table 1). Likewise, humans have forged environments that protect us and feed us, even while these extrinsic alterations have come with a significant cost to ecosystems on Earth. Recent studies have shown how cancers can be tamed—their evolution can be directed to less aggressive and less invasive lifestyles, allowing patients to live with their cancers (Ibrahim-Hashim et al. 2017; Zhang et al. 2017). Since elimination of humans from Earth is not our goal, can we be similarly “tamed” to allow for a more peaceful coexistence with our planet?

Dominant therapies for cancer today have the implicit goal of eliminating as much of the cancer as possible without killing the patient. As such, these therapies, largely based on cytotoxic chemotherapies and radiation treatments, destroy not only cancer cells but also much of noncancerous tissues. For example, the destruction of blood-producing cells and immune cells often leads to deficiencies in neutrophils (critical for eliminating bacteria), T-cells (essential immune cells), and platelets (effectors of coagulation and wound healing). This is the ecological equivalent of trying to eliminate brown snakes on Guam by torching the island. Perhaps not surprisingly, most patients with advanced cancers that are treated with cytotoxic chemo and radiation therapies relapse, and the cancer at relapse is more aggressive than the original disease—damaged landscapes favor the evolution of nasty cancer cells (DeGregori 2018). Instead, we could develop strategies for cancer that consider the vulnerabilities of the cancer cells, but also the ecological context that dictates the fitness value of these cancer cells. Even if we cannot manipulate the tissue environment to disfavor cancer per se, evidence suggests that changes in the microenvironment can direct the cancer along a less aggressive, less invasive evolutionary trajectory (Gillies et al. 2012).

The lesson here is that we cannot just target the cancer cells, whether pre-malignant or full-blown cancer, any more

than we can act as if humans should be the sole focus of action on Earth.

Global Environmental Mitigation and Restitution

Ecological and evolutionary “repair” does not kick in until the vector of devastation—extraterrestrial bolide impacts, regional climatic events, local volcanic eruptions—has run its course. This suggests that, if our species is the causal vector in this case, only our own extinction would fully stop the current sixth extinction. No one thinks that is a good idea. So, as in the case of cancer within our own bodies, we must turn instead to mitigation, seeking a dynamic stabilization in which humanity can coexist in a mutually beneficial way with at least a semblance of the biosphere in which we arose and initially lived, when we were playing by the ancestral rules of within-local ecosystem existence.

The environmental movement is by no means as old as medicine. But the founders of modern biological theory were well aware of the dangers humans pose to the Earth’s biota at least as far back as the early to mid-19th century (Eldredge 2015). Serious measures, undertaken with increasing ingenuity, and vigor, intensified during the latter half of the 20th century and have met with palpable, if limited, success. We no longer look away as rainforests and other ecosystems are destroyed at an alarming rate—and through the designation of protected conservation areas the world over, all manner of ecosystems are increasingly conserved, albeit in partial, piecemeal fashion.

There are efforts to conserve the genomes of everything from landraces of localized adapted crop species to Madagascar’s highly endangered lemurs. Pollution is not nearly as tolerated as it was in the mid-20th century. Steps to guard against invasive species have come a long way since it was considered a good idea to bring back exotic plants and animals and release them into backyards and parks. All is not yet lost.

Yet all is still far from well. As recently as the late 20th century, it seemed sufficient to identify the root cause of human-engendered destruction of planetary systems as the out-of-control population growth triggered by the Agricultural Revolution. Currently population growth appears to be slowing down, arguably through reaching limits of global distribution, as predicted by such early savants as von Leeuwenhoek (Cohen 1995), abetted by purposive programs of education, promotion of literacy, and other socioeconomic initiatives (Eldredge and Horenstein 2014). Focus has shifted to runaway climate change, driven in largest measure by atmospheric carbon release, itself driven by the technosphere.

Yet, since at least 1987 (Newell and Marcus 1987), scholars have been reporting a correlation in excess of 99% between measured CO₂ levels and estimates of the global human population size. To estimate how many people are on Earth, obtain CO₂ data from sites around the world; to estimate the amount of CO₂ in the atmosphere, get the latest estimates of global population. To know one value is to know the other.

So the problem is, after all, global human population size. Cohen, in the final section of his book (Cohen 1995) asks the question, “How many people can the Earth support?” He then says it depends on what you mean by support. For everyone to live at the level of, say, middle-class Americans in the 1990s (when he was writing), that would be a global population of around three to four billion. The number as it stands in 2019 is twice that. But, just as a matter of base-level sustenance, some estimates are as high as 40 billion. That would be truly apocalyptic.

The devastation, not only of the planetary biota, but of the fundamental physicochemical state of the atmosphere and oceans (the latter not long ago assumed to be inviolate), continues if anything at an ever-more rapid pace of intensification. Clearly, cultural evolution, manifestly decoupled from human population numbers, is speeding up at a mind-boggling clip. Technology lies behind our ever-more-efficient ways to extract the “resources” of our earthly home. It also inadvertently imperils the planet ever more as the machinery of war becomes ever more sophisticated.

We need to modulate and mitigate our very use of this growing armamentarium of technology. As in medicine, most certainly including cancer, technology provides the ultimate hope that we can tame the scourge. Let us apply this thinking to solving—not exacerbating—the problems human life poses for the rest of the components of our own host.

Reciprocal Illumination and Implications for Understanding Both Systems

How, then, does the conceptual juxtaposition of the nature of cancer within our bodies with human-driven extinction within the biosphere lead us to new insights into the management and abatement of both of these scourges? Do any of these points-in-common suggest the application of ecological/evolutionary theoretical concepts that might be brought to bear in some manner on both? Are there existing theory-based strategies already employed in one domain that might usefully be applied to the other?

Invasive species are a prime cause of the currently intensifying wave of extinction engulfing species the world over (Blackburn et al. 2019). And though it is true that species can expand their territorial ranges entirely on their own steam, the accelerated uptick in the rate of alien species’

invasion into unfamiliar ecosystems correlates well with the logarithmic increase in human population and our concomitant global spread. We ourselves are the prime example of an invasive species. All the others—and there are very many of them—are for the most part collateral invasions, aided and abetted by our own spread and ecological disruption of the world’s ecosystems.

Humans come from a long evolutionary lineage of ecological generalists (“eurytopes”)—able to eat a wide range of foodstuffs and live in an impressive array of habitats. Having done away with our traditional niche within local ecosystems, and with the incredible expansion of our knowledge and technology, we have not so much expanded our resultant niche but redefined it. We are the kings of eurytopy.

Most successful invasive species are themselves broad-niche eurytopes, literally able to live in many places. And eurytopes are notoriously difficult to dislodge: native horseshoe crabs, true ecological generalists, were among the last to disappear from New Jersey’s heavily polluted Raritan River a few decades ago. But disappear they eventually did—until that river was finally cleaned up to the point of again being capable of sustaining the normal estuarine biota. Aquatic “tissue repair” was able to save the day, as a semblance of the normal ecosystem was restored as species—generalists and specialists—were able to recolonize. Just as the microenvironmental mitigation efforts described above can limit cancer development, ecosystem management and restoration plans may be able to limit species loss.

But it is the non-native eurytopic invasive species that are the extinction culprits. And they are profoundly difficult to dislodge. Consider “Norway” rats, European starlings, and house sparrows. Or North American gray squirrels in Europe. Kudzu and lantana (which tigers in India love to sleep under and ambush prey from). The list of alien plant, animal, fungal, and microbial species is virtually endless, and growing day-to-day (Blackburn et al. 2019). They kill off native species by variously eating them, stealing their food, or infecting them. They can destabilize local ecosystems. They flourish all the more by often having no predators on hand to exploit them. They have already driven thousands of species to extinction in recent memory. Occasionally clever directed agents can be devised to dampen alien species without threatening the natives: a poison derived from native Australian plants, a substance to which native predators have long since developed resistance, has recently made the news (Aguirre 2019) as being used at least locally to kill off invasive cats that in their great numbers have been playing hob with the smaller marsupial fauna. But such success stories are relatively rare.

Add invasive species to the list of other potent factors: rampant habitat destruction, overexploitation of resources (fisheries are on the verge of depletion), pollution—and now, the explosive effects of global climate change, which were

only a distant worry when confronting the issues of the sixth extinction as recently as the 1990s. There is no doubt, as the rising chorus of scientific and humanitarian voices is now shouting daily, that man-made disaster to the biosphere, of which we ourselves are still very much a part, is upon us.

The current condition of the biosphere is really stage IV metastatic disease, where “early detection” is no longer possible, and stabilization strategies rather pie-in-the-sky. A recent *New York Times* editorial promotes the dual concepts of intensification and improved efficiency of farming techniques plus greatly expanding the acreage of conserved spaces as the main strategies open to us to at least slow down the destruction of the world’s species and ecosystems (Editorial Board 2019). But the elephant in this particular room is not mentioned in that editorial: the response to increased nutritional efficiency will inevitably be still further increases in global population. Our unchecked success at the game of reproduction is the root cause of all these ills, and the real underlying threat to our own survival. We still haven’t come to grips with this issue. And no one wants to leave it to famine, warfare, and disease—which, so far, have failed to slow human population growth for more than a generation or two. Self-control is not an especially notable attribute of the human condition.

What, then, of the possible relevance of niche-width theory to understanding the dynamics of tumor growth? And are there any attendant implications for the treatment of cancer? As one example, a primary tumor rarely kills you. It is cancer’s invasion and metastases to other tissues that rob us of life, by disrupting essential organ functions (and rendering the cancer impossible to surgically remove) (Hanahan and Weinberg 2011). A metastatic cancer is almost by definition more eurytopic, as it has evolved the ability to grow (and outcompete) in a very different tissue. And a cancer from one tissue, such as the breast or lung, that has metastasized to the bone or some other tissue is much harder to eliminate. Essentially, the cancer has mastered diverse environments. What’s bad for us with cancer (eurytopy) is good for a species facing habitat destruction or climate change.

How can we leverage this understanding to better manage cancers? First, we can put more efforts into developing early detection methods and therapies for cancers *before* they spread—when the cancers are more stenotopic and thus more easily pushed to extinction. Currently, spending on research to develop therapies for advanced cancers far exceeds investment in developing early detection and preventative interventions (Cialdella-Kam et al. 2012). Second, for metastatic cancers that escape early detection, we can learn how to better manage these cancers. Complete elimination of a cancer is rarely an option as this requires poisoning *everything*. Hence, the still dominant chemo and radiation therapies rarely engender cures for most people with advanced cancers (the exceptions being for some cancers

that are highly sensitive to such therapies, such as testicular cancer). Destruction of the entire ecosystem is not the wise course. More recently, Bob Gatenby and colleagues at the Moffitt Cancer Center have developed a new ecological approach to advanced cancers that leverages competition *within* a cancer (Zhang et al. 2017). The approach uses only as much drug as is needed to manage the cancer burden, without eliminating it. By doing so, drug sensitive cancer cells rebound between treatments, keeping the cancer cells treatable. Moreover, this “adaptive therapy” reduces damage to normal cells and the tissue in general, helping to favor more normal cellular lifestyles. Obviously, a eurytopic species can coexist in balance with other species, which all keep each other in check. Similarly, maintaining the health of more normal “species” (nonmalignant cell types) during therapy can keep a cancer in check, by providing competition for resources (niche space) and by even acting as “predators” (immune cells). Supporting the “normal” (e.g., native species), such as through habitat restoration, should also help reduce the impact of invasive species. Finally, we can explore whether leaving a more specialized lifestyle for a more eurytopic one upon metastatic spread engenders novel vulnerabilities for the metastatic cancer—is there a cost of a more generalized lifestyle? Does the same hold true for eurytopic species, and can this cost be exploited, such as to eliminate an invasive species? Research, guided by evolutionary and ecological theory, is necessary to better target and control metastatic cancers, and to better manage earthly ecosystems.

Closing Thoughts

Our agricultural-based settled condition, and its ramifications such as the division of labor, made necessary because not everyone whose lives can be supported through agriculture can possibly actually *be* a farmer, has also led to wonderful things—if not for the rest of the world, certainly for our species. Human history is not just a story of famine, warfare, and disease, or rampant reckless destruction of the biomes in which we used to live, and on which we once depended for our own survival. It is also the story of the growth of knowledge.

Our newly invented approach, with its of-necessity settled existence, growing populations, and inevitable divisions of labor, gave us all the truly wonderful things about sentient human existence. Sentience was preexisting, but in its post-Agricultural Revolution coddled, comfortable state it has blossomed, and so has given us poetry, science, music, the visual arts, and so on. And above all else, it has enhanced our ability to witness and try to understand our own existence. It has allowed us to build upon the deeply honed sentience, the

beautiful gift, inherited from our hunter-gatherer forebears, of knowing that we are alive, and can observe and try to figure out what it means to be alive. Along, of course, with the hard-to-metabolize corollary realization that we are all going to die.

Thus, if it is so that if cancer “knew” that its behavior would ultimately lead to its own death—and presumably, with that imagined knowledge, would at least throttle down its own rampantly destructive behavior, should we not take that thought experiment and apply it, as sentient beings, to our own behavior before pushing things too far? While we may have ourselves left local ecosystems, we are no more independent of the natural world than cancer is from our bodies.

But cancer does not know its own demise lies in the cards with the destruction of the life of its host system. Earth does not know that she is under attack, even as her tissues are repaired by recruitment of survivors—and, in extremis, by the evolution of new species that replace those exterminated. There is a simple hierarchy here: cancer is rogue cells abandoning their usual, genetically determined roles in the tissue ecosystem. Such events can and often do kill individual sentient human beings.

Likewise, human beings, in turn, have abandoned their primordial ecological roles, and like each individual case of cancer, have been wildly reproductively successful. Things go well for the *tumor(s)* for a while in most cancer cases (unless the immune system can step in—or, in some cases, the medical armamentarium is successfully brought to bear and tumor growth is arrested if not eradicated). Likewise, things have gone well for humans (though the horrors of human life for the disadvantaged have only grown as human population numbers have exploded). And, like an advanced cancer, we are at the brink of destroying the very system upon which we still depend—if not in the way in which evolution originally shaped our ecological adaptations.

So here we are in the middle. Hosts and victims to non-seeing, non-sentient marauding cancerous growths within us—growths that do not understand that they will go down with the ship as they take human lives. And, as the equivalent cancer-like growth on Earth, we ourselves are threatening the very life of our own species. Except we are sentient. We have medical and ecological/evolutionary knowledge and understanding, incomplete as both are.

We have two hypnotically similar problems to solve—and only we can do it. Understanding the critical role of ecological interdependencies for avoiding both cancer’s and humankind’s destruction of their respective homes, our bodies and our Earth, should hopefully promote better stewardship of both by the only animal capable of recognizing the problems.

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