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The chimeric soma

Only belatedly did I realize that "chimera" has literary allusions to make-believe that I had not really intended. I might have said "Mosaic self", but that might have been confused with the Book of Exodus -- which it turns out I will be quoting later on. So I will relieve your suspense: by chimerism, I point out that the human (or other body) is not always a unified organism bound by a common origin and purpose. Like the lion and the goat of the mythological chimera, its parts may be at war with one another. The wonder is indeed how well the trillions of our constituent cells abide by an armistice; and you will have guessed that I point to cancer as one of the important indices of breach of that peace on the part of a few rogues looking after their selfish short term interests within the mosaic of the overall organism.

My point of departure is, however, the field of microbiology and infectious disease, the main home base -- as I hardly needed remind the organizers -- of whatever expertise I can claim to bear on this summit. There I have been re-asking some elementary questions: from an evolutionary perspective and with some strain will try to apply a similar Darwinian ideology to our attitudes about cancer. I will have many more questions than answers.

1) Ponder the grossly unequal evolutionary competence of microbial pathogens. Their population numbers and turnover rates give them a pace of adaptive evolutionary change millions or billions as fast as our own. For the animal world, it is hard to point to any fundamental defensive innovations since the invention of adaptive immunity 200 million years ago. Then sporadic tactical maneuvers; shifts in cytokine balance or in specific viral receptors. It is not just that we are so sluggish in our reproduction and evolution -- a year of microbial growth matches the whole 200 million years of vertebrates. We also rapidly splinter off species which are then reproductively isolated from the rest: it does humans no good if rodents or carrion-eating birds have evolved special defensive mechanisms. Well, yes, with the evolution of culture and what optimistically is called social intelligence and technology, we can eventually study what those creatures do and just since the last century get some benefit by emulating what they have evolved.

2) Given the above: how improbable that we should have survived the contest! But this remark belies the Manichean mentality that has dominated germ research for the past 125 years. From an evolutionary perspective, it is no benefit to the pathogen to kill the host. The admonition "Thou Shalt Not Kill" - the Mosaic code from Exodus -- is well taken by an invader whose genetic fitness is governed by its finding new hosts, and lodging there as long as possible. Domestication -- think of us as dairy cows daily feeding the hungry gullets of our staphs and worms and enterics -- is a better strategy than an extermination of the goose making the nutrient gold. That is why we have survived, but not without a burden of commensals, symbionts and typically low grade chronic infections. These hangers on may manipulate our own immune system to fend off superinfection by other related invaders and keep the turf to themselves. Of course there are many exceptions. A limited scale of fatality,

say 1% which is devastating in human affairs would be a minor overshoot for the bug.

3) Why then is there infectious *disease*? Much disease manifestation -- notably inflammation -- is related to the hosts' antiquated defenses. The bugs in turn have to burn their way through to sustain a local beachhead. Severe pathology may be a byproduct of those skirmishes. Symptoms like fever, cough, diarrhea are often designated as host defenses, but if they did not serve the bugs' interests, these would rapidly evolve around them as they are well on the way to doing with antibiotics. The bugs' interests are ambivalent, and they include a) moderating the disease in accord with the host and b) discouraging superinfection by competitors.

Then many of our most severe diseases like HIV are zoonoses, host-pathogen equilibria that are fairly quiescent in their "natural" hosts, where evolution has reached a balanced state. The shift to a host of altered genotype leaves open the odds of disrupted balance. Sometimes this will prohibit an infection, and we then take no notice; at other times the restraints of "Do not Kill" are lost to memory. If the new host -- as say in human plague -- is incidental to the natural history of the bug, these relationships will be irrelevant to the pressures guiding the evolution of virulence.

4) Why is this important? These ideas are hardly novel, but they are almost totally neglected in our basic attitudes, and most importantly in many research and policy paradigms. Particularly worrisome to me is the unfinished crusade of disease eradication, on which we have been embarked the past 2 decades. It is wonderful that smallpox has been eradicated; polio perhaps measles are on the way. But the wake of those conquests will be the abrogation of ongoing prophylactic immunization. With the entire expanded globe one naive herd, there may be hell to pay in the end. This could be mitigated either by an ecological attitude, of seeking to maintain our baseline immunity by providing stimulatory epitopes, or by monitoring and improving the bugs we customarily live with, inhabiting our inner and outer surfaces galore. Or a still higher technology of developing the new antiviral compounds that might leave us some hope when viral infection is initiated.

On the research side, we give very little attention to our indigenous flora, and the mechanisms they have surely evolved, and of which we have meagre substantial hints, to protect the host. For example, they do produce antibiotics against other species that lessen superinfection; albeit, in other settings we may see synergism from concomitant infection. Most invertebrates have adopted pet endosymbionts, and some even have specialized organs -- like the light beacons of some squid -- in which to house them. Barring the ubiquitous mitochondria, we are unaware of these in our own bodies: but remember that all of oxidative metabolism is this legacy of an ancient cellular invasion by bacteria. In higher plants we see the like as well in the chloroplasts.

To dramatize the concept, I propose that we remind ourselves of our chimeric origins and present, and recall that the perambulating person is a "superorganism", comprising

1) Our diploid nuclear genomes, from sperm and egg.
2) Our sometimes heteroplasmic mitochondria, typically inherited matrilineally
3) Possible further intracellular passengers, like the integrated retroviruses in our

chromosomes, and we've not seriously looked for similar plasmids as well

4) Our load of more loosely affiliated partners, the endoflora, which I will extend to embrace also the denizens of our skin and mucous membranes. The majority of these may be seen but hardly ever cultivated. These must play important biological roles, if only as immunogenic stimulants; and I would not exclude both protective and etiological roles vis a vis cancer.

This superorganism is a unit of selection, insofar as there may be heavy costs to breaking the social bonds. As with any other society, we see mixed games of competition, cooperation and alternation of altruism and warfare. But its only intelligence is the directive influence of natural selection perpetuating the fittest complexes. Its "mutations" may also entail encounters with immigrants sometimes better, sometimes worse adapted to the integrity of the whole.

==== Starting from this attitude, let us ask a few questions about cancer.

1) Why do we have neoplasms?

2) Why is there neoplastic disease?

So we have a chimeric soma in another dimension: the diversity of some of our own somatic cells, as well as the shared person-ality of our commensals. We all concur that most cancers are seated in changes in somatic cell genomes, arising either through endogenous gene mutations and chromosome rearrangements, or by oncogenes integrated from external viruses. We have a few examples of unintegrated plasmids, like Epstein-Barr: just how this functions in leukemogesis is not clear. We may then assume that some disorder, some dysregulation in the cellular society merely an imperfection in the clockwork, an inevitable byproduct of the complexity of our physiology. We owe a lot to the flexibility of morphogenesis in the regeneration of the liver and intestinal mucosa; and in the amenability of tissues like breast and gonads to hormonal cycling. Perhaps we made a Faustian bargain in our own evolution when we adopted unremitting somatic diversity as the tool underlying our adaptive immune systems -- this also opened the door to less well regulated proliferation and diversification that we see in leukemias and myelomas. That inference would be fortified if I could go beyond conjecture about the rarity of like tumors in invertebrates.

It is even more difficult to account for disease concomitant with cancer, other than sheer mechanical obstruction: why the pain and suffering which do the tumor cells no benefit? Defensive, though too often ineffectual, reactions by the host; or counter-defenses by the tumor must then be invoked.

I have other serious problems in extending my microbiological attitude to cancer cells. The microbial pathogen is subject to ongoing selection, passing from host to host. Cancer cells have proven to be remarkably ingenious in defying the defenses of the host, including their escape from chemotherapeutic and hormonal control: yet this is a lesson that must be learned de novo by every initiated cancer, and from populations of cells that are measured in mere millions. Severe genetic instability must be a major premonitory enablement: and this may be a byproduct of other physiologies we have not yet plumbed. How much we have yet to learn

about the pathways and implications of apoptosis. With oncoviruses,including hepatitis, it is not obvious how in natural history the generation of a tumor enhances their genetic fitness in any way; that may be a byproduct of more complicated discourse with the immune system or tissue regeneration in the host.

Paradoxically, I could turn the argument around: infectious agents have been constrained by evolutionary history to moderate their lethality, to abide by some rules of engagement. The new cancer cell lacks that evolutionary legacy; its dissemination beyond the one host is foreclosed anyhow.

It troubles me that the evitability of cancer is so variable among species. How do giant whales ever avoid it, when each leviathan is a thousand humans in body mass, cancer in any one of the aggregate being potentially lethal to the whole. If we watch the clock by days rather than lifespan, we could say the same about humans in relation to mice, though these are mainly bred as laboratory artefacts possibly very remote from natural history.

Thinking about whales and mice and men led me to ponder about generic ways in which cancer incidence might be modulated across species, especially long lived ones. One comes to mind from a contemplation of dominant tumor suppressors, of which we know a handful, Rb - retinoblastoma being the prototype. Persons already carrying a deletion of this gene, therefore hemizygous, are marked by a hereditary predisposition to the disease as they are vulnerable to single point failure of the remaining allele in any cell. So all it would take would be a functional duplication of Rb in the genome to eliminate any plausible possibility of retinoblastoma. We do not have to do oncology on whales, we do comparative genomics to seek which tumor suppressors they have duplicated.

And we compare humans and mice likewise. Conversely, tumor genomes should be scrutinized for their burden of gene families in which multiple events have coincided in the full evolutionary progress of the tumor. Many "tumor suppressors", or call them recessive onco-genes, must escape our notice because they have already been duplicated, therefore rarely come to attention in segregating pedigrees.

This discussion also highlights the somatic advantage of diploidy, a buffer against oncogenic somatic mutations. We know few viable haploid animals -- perhaps some frogs -- they might help test the notion. Haploid plants are easier to come by through anther culture -- although they rapidly diploidize -- and they may teach us why the entire plant kingdom is virtually bereft of endogenous neoplasia -- especially as we do see bacterially induced crown galls and cankers.

Such duplications will not be selected for in short-lived species where cancer incidence will have little bearing on reproductive fitness.

We will in any case have been bequeathed a suite of cancer-suppressors that will at least delay cancer lethality past the reproductive prime. That antinomy is stressed further in situations where castration is prescribed as a desperate therapeutic measure. One answer to why we have cancer is our desire that "we should live so long" as to pass into unnatural longevity.

Perhaps there are even more fundamental problems, so that we have strained too hard to analogize the rogue cancer cell with the microbe. What I have read about metastasis and transplantable tumors makes me wonder whether the unit of proliferation is the single cancer cell -- what in microbiology we would call the "colony forming unit". Perhaps following Josh Fidler's writings, this is often a small multicellular organ, entailing continued intercellular, morphogenetic interactions. Otherwise, I could not understand the nonchalance with which diagnostic biopsies of tumors are successfully conducted. And it would help explain how chemotherapy and radiation can be as curative as they are, where there is no hope of total eradication of every cell of the tumor at doses the host will tolerate. That vestige of social interdependence, especially at early stages of tumor progression, may well be a major variable for the integrity of our chimeric soma, and obviously offers prime candidates for research and intervention.