E toxicus unum?

On necessary choices for cells in an unhealthy environment.

The human body is held together by cells, somewhere between 10 to 100 trillion cells. At minimum, 10 trillion cells cooperate for decades. These numbers change as the body changes. The marvel is that our bodies remain intact for more than a few seconds without flying apart, each cell for himself, or herself rather. It is almost unimaginable how so many cells integrate to create a functioning body. In order to maintain our bodies, about 20 billion divisions have to be performed every day. Fault free. Rather, faults must be repaired or a fault-ridden cell needs to be ruthlessly eliminated, so they do not pose a danger to others.

New research in mice shows that damaged cells promote senescence, a theory that has been around for a while, but difficult to test. A brilliant study by Baker et al., published in late 2011, tagged cells with a biomarker for senescence. When cells became senescent within a mouse, they were destroyed by a drug that interacted with the biomarker to kill those aging cells and none others. The disappearance of the aging cells promoted healthier and longer lives in these experimental mice, with significant delays in the onset of cataracts, arterial sclerosis, heart problems, loss of muscle mass and age-related frailty and weight loss.[i]

A more natural way to eliminate damaged cells is to avoid accumulating so many damaged cells in the first place, as a result of living in and creating an unhealthy environment. The problem is that the health damages probably occur decades earlier, precisely through cellular changes that eventually create a domino effect. Prevention is distantly removed from the outcomes of disease.

There are control mechanisms within a cell that cause a cell to self-destruct, that is, commit suicide when it is no longer functional, too old, or too damaged. In other words, the cell sacrifices itself and dies so that our greater body remains whole. Sometimes it is eaten by its neighbors — it is good nutrition, after all, proteins, fats, carbohydrates and more. The upshot of this little death is that another cell must replace it and perform its function, without stopping to learn a new life skill — the integrated on-the-job training to be a kidney cell or lung cell has to have happened before it inserts itself into its final position. The tissue must continually remodel, in the literal sense. There will be, in a real sense, embryonic, young, adult, mature, and old cells in any healthy tissue — a harmonious shifting of position and function, an architectural masterpiece where the young gradually take on the tasks needed by the tissue (becomes "differentiated") while the old or damaged cells fade out.

The circle is endless — but not in reality. Cells can only divide a certain number of times before they, too, must give up the ghost, or rather, their cell body, for good. If we, a coordinated 10 trillion member committee, run out of replacements, the tissues become less and less functional and the body shuts down. If we are lucky, it happens in our sleep. If not, through a gradual attrition that creates all the aches and quirks and vulnerability to disease. Aging. Not necessarily gracefully.

Why do cells only divide a certain number of times? Can that number of times be reset? Back in primordial times, life was represented by single-celled organisms. When a cell had grown to a sufficient size, the cell = the entire animal divided. Alternately, this cell grew quiescent (formed a spore) or died. Divide, differentiate (sporulation), or die. To differentiate is and was to specialize. Cell, tissue, and

organ reach specialized states that are not broken, except by death. Despite three billions years of practice, for individual cells, those three options are still the main forks in the road: divide, differentiate, or die.

Life started as an immortal cell line and only later 'invented' death. The salient point is that single-celled organisms – and very-slow-growing organisms – are effectively immortal, unless they are eaten or irreversibly damaged. The road to immortality is easy and repeatable: just divide and now there are two, then four, and onwards….The default state of the cell, from a historical viewpoint, is immortal. In 1881, the acclaimed developmental biologist, August Weismann, proposed that programmed death was an evolutionary force to counter "useless immortal soma".[ii]

Over time, an incredible number of controls have evolved precisely to rein in this immortal tendency. Why? Immortality seems like a nice state of affairs. However, with community living and division of labor in a multicellular creature, specialization must arise. Cooperation sets restraints on the whole. If some specialized regions divide much faster than others, then unbalance and disproportion ruin the whole. We know what cancer does. Controls must hold cells to a certain division schedule, a compromise between immortal trends and mortal needs. There are an astonishing number of pathways within a cell that keeps it in an “undividing” state, and with luck and cellular repair skills, keeps it in a well-maintained differentiated mature state, and hence, healthy tissues and organs.

Sub-lethal poisons are sneaky poisons, because they tend to have a paradoxical tendency. They 'liberate' controls within the cell, precisely those controls that

prevent a cell from running its own immortal show at the expense of the rest of the organism. When we feed cows growth hormones, we, the milk customers cannot avoid their impact, because the cow does what its body knows what to do: send out secondary signals for cell division, including the secretions from its lactating glands, the nutritious milk. Growth equals cell divisions and more cells. Within specialized cells and tissues, such temptations may lead to disasters. Evolutionarily speaking, organisms take out-of-control division very seriously.

With 20 billion plus daily divisions within a human body, the possibility of some cell taking off at high uncontrolled speed, to become a cancer, is a high risk. The immune system is primed to recognize 'bad ones' and scour the neighborhoods for cancerous cells. They have their inflammatory ways and they cause pain. If environmental insults enhance growth signals, an immune system will also work overtime and it is ruthless. The over-involved cells eat, maim, kill, and torture. We know the congregate cellular responses as autoimmune diseases. Wear-and-tear of coronary artery disease.[iii] The dubious joys of arthritis, diabetes[iv], lupus, and worse. Autoimmune diseases such as diabetes and arthritis affect many millions of people.

It goes almost without saying that the more sublethal damage one exposes oneself to, the more cell repair (and cell suicide or programmed death) and divisions there must be. That, in turn, is accompanied by more cell damage and deaths, because some of those new creations failed.

We can add "x" amount of poison to rat food and watch a rat keel over, but add sub-lethal levels and results can vary widely depending on the species, its environment and other exposures, and most certainly on the length of the study.

With time, statistics, and the advent of cell and molecular biology, these questions have become easier to answer. We are now in the strange position of knowing exactly how sub-lethal poisons affect cell behavior and communication, but still cannot pinpoint how these effects translate into a long-term impact on a human being, a multicellular organism where not all life stages are created equal. Fetuses are a lot more vulnerable than middle-aged men, and older people are resistant in some ways and vulnerable in others.

We are one century behind on the chronic health impact of 80 000 or so chemicals. At the moment, we use about 80 000 synthetic chemical compounds in industry and society that we know little or nothing about (see Web info-sources). We have Materials Hazard Sheets for many chemicals, but each is terse and not up to date at all on chronic impacts to human health. Some 'old' chemicals like formaldehyde, used as a preservative, do have entries on cancer and other long-term disease states. But then, formaldehyde was not exactly invented yesterday — it was made and identified in 1868,[v] yet only definitively proven to be a carcinogen a decade or so ago! Wikipedia has an informative article on formaldehyde -- formaldehyde is found in automobile exhaust, tobacco smoke, forest fires, and numerous human products, even Asian food.

Furthermore, unhealthy and toxic compounds are ceaselessly altered by organisms, from bacteria up the food chain to us. We alter them inside our bodies as well. Unexpected signals interfere with careful body balance, just like uninvited guests do to an already busy household engaged in its own plans before they arrived. Worse still, organisms in all ranks of life seem to have a knack for creating even

more potent compounds from what was already potent enough. For example, injecting any bovine growth hormone into cows, recombinant or otherwise, will increase the levels of insulin growth factor I (IGF I) in milk[vi], a double-edged sword for the body for its promotional effect on cell division and accelerated aging. Growth Hormone and IGF-I can protect against infectious disease, shorten lifespan, promote cancer, 'calm down' acute inflammatory responses, yet maintain the chronic inflammatory states that exist in autoimmune diseases. It is more than a double-edged sword to add even ‘safe’ unknowns to the food supply, much less hormones and their mimics with their potent multi-faceted impacts. It is a multi-faceted ever-shimmering tangent into the future, destination unknown.

Hormone-mimics or endocrine disruptors are particularly pernicious sneaky poisons. Endocrine disruption more than just affect young children and reproductive fitness, whether it is biphenyl A, phthalates, dioxin, or insecticides. Apart from potential developmental disasters in the young (or miscarriages), endocrine disruptors affect the immune system, metabolism, cancer risk, and life span. Moreover, a huge medical problem burgeons, in all senses, with obesity in people and pets. Baillie-Hamilton (2002) hypothesized that lack of exercise and too much eating was only a partial reason for the global obesity epidemic, because chemical toxins and endocrine disruptors had a great deal to do with the way that our bodies react to food — and in other species, too. This proposal has since been verified by many scientific studies. On top of this disturbing fact, early exposure to endocrine disruptors within the womb, or as a newborn, carry long-term impact on bodyweight: "Xenobiotic and dietary compounds with hormone-like activity can disrupt endocrine signaling pathways that play important roles during perinatal

differentiation and result in alterations that are not apparent until later in life." (Newbold et al, 2007). [vii]

Hormones are powerful communicators and complicated. Hormones serve to balance and readjust our bodies on a daily basis. Hormones affect the immune system and vice versa. For a biochemical excursion into the intimate and intricate connections between the body's endocrine/hormonal and immune systems, especially its inflammatory reactions, see the superb review on "Protein hormones and Immunity" written by Kelly et al. (2007) and referenced in the endnotes.

The trouble with hormones and their mimics as toxins is their potency. Hormone-like substances communicate with cells at remarkably low concentrations. Tiny amounts of insect growth regulators, a common pesticide, affect insect eggs so that the embryos within do not hatch. Those embryonic defects are caused by miscues in cell communication highways that we humans happen to share with insects and a lot of the multicellular world, from worms to elephants. This major intersection is called FOXO, a center knot for cell decisions about aging, cell death, or division.[viii]

Cells respond to delicate suggestions so much more readily than blunt instruments. In the latter case, the cells die and do not create long-term mischief. Well, it depends on the food one must eat: owls should refrain from eating poisoned rats.

Herbicides and pesticides straddle the fence between deadliness and insidious effects. Some pesticides are incredibly toxic — after all, they came out of the nerve gases of World War I — and some fall into the category of endocrine disruptors or may affect calcium balance in animals (DDT and bird eggs). Minute amounts of

pesticides should be famous for having estrogenic properties. A twisted call of pesticides to men: the potential to sing falsetto, grow breasts, and stop making sperm. The herbicide, Round-Up, may mimic retinoic acid.[ix] Retinoic acid is a very potent restructuring signal in development, able to help regenerate limbs and able to create weird things in the wrong places in fetuses — and able to augment cancer risk in mature organisms, depending on concentration and delivery and chronic versus acute exposure factors.

What is possibly worse is the recent revelation that chickens in industrial farms were/are fed arsenic in sufficient amounts to change their skin coloration. The Center for Biological Diversity announced recently (2013) that it was a environmental victory that suppliers had to reduce the amount of arsenic in chicken feed by 97% (that leaves 3%). (Why add arsenic? because the chickens gain weight and weight means money). Arsenic affects every single organ system and is an endocrine disruptor,[x] causing an increase in retinoic acid signaling. Retinoic acid is what one calls a potent teratogen. Given that the population of United States seems to be consuming chicken at almost every meal, this means that the entire country, short of vegetarians, receive doses of arsenic. A vast experiment in neurological disturbances is in progress.

With an increased interest in nuclear power and frequent use of air travel, there is exposure to ionizing radiation. Minute, yet constant exposure to radiation undermines the very stuff of life and heredity, its damaging effects showing generations from now. Not one day may be shaved off our lives, but nine generations from now, our descendants will see the mutant recessives that hid in our genomes.

The rich are just as exposed to sneaky poisons as the poor. In today's world, one might argue that an equalizer of the poor and the rich has finally been found, but the poor still face potent deadly toxins more often than the rest of us. To top it off, we still have war, infectious diseases, famine, and enslavement, so one cannot say that one set of ills have been substituted for the other. We tend to forget that pollution was serious in towns and villages in Antiquity and in Medieval times, so that historical records of chronic diseases dating, say, 800-900 years ago, do not give us examples of healthy lives. What 'saved' us from cancer, strokes and arterial sclerosis then, was child mortality, dangers in childbirth, infectious diseases, and accidents with poor medical care.

We demand that our cells should survive a marathon of encounters with sublethal poisons that are everywhere. Resilience and maintenance may keep the cells in the marathon, but odds and 'low toxicity' poisons stack up. Each successful rebound and repair craves energy and carries its own risk. Like gamblers at a casino, cells can and will lose control, at some point. A cell, whether ours or another species', has its limited set of choices. For differentiated cells, we can sub-divide cells into: healthy maintenance with normal repair, senescent, and cancerous. For our sakes, we do better to act prudently, now that it is known that multicellular creatures, from slime molds to human beings, use universal biochemical pathways that are run by the same genetic programs. We are therefore sensitive to the same toxins — with variations for each species and for each individual on earth.

On a planetary scale, we see decay and extinctions within the oceans, in the diminished forests, in industrial wastelands, the agro-industrial diseases, and

pollution within the cities. This litany is not new. We need to tilt our world-wide efforts in the direction of healthy cellular maintenance. We have the requisite and exquisite knowledge to do this, for the entire world, at that. At present, however, I doubt that we have a grip on the quantity of poisons that we surround ourselves with globally. Outright bans need to be set up for the most egregious substances (radioactive materials except for medical use, some agro-chemicals, endocrine disruptors).

We need to put a world limit on the total amount of toxins, in categories such as agro-chemical, heavy metals, oil-and-plastics, and military uses. The alternative is to create a robotics human, partially mechanized and able to survive in a non-natural world. There are researchers working on that eventuality.

Once life became multicellular, another evolutionary invention took place. We carry stem cells within us that have specialized in remaining unspecialized — undifferentiated within each organ system — that is their specialization, until they are needed. A rather nifty trick in a mature multicellular organism to have such cell populations for renewal. Reproduction is a special subset within this category. Multicellular creatures such as sponges, coral reefs, and bristle cone pines can live for thousands of years because they grow so very slowly, yet continuously. They reconstruct themselves with newborn cells and tissue while doing so. Many organisms such as reptiles and fish can regenerate many parts of their bodies, and as it turns out, we can, too, to a point.

If the world is toxic, the constant regeneration will meet the need for constant repairs forced by the surroundings. A standstill, an unnecessary one. We have,

after all, managed to land people on the moon and sequenced the human genome. Can we create a healthy earth with nature as our terrestrial body?

[i] A brilliant study by Baker et al., published in 2012, tagged cells with a biomarker for senescence. When cells became senescent within the mouse, they were eliminated by a drug that interacted with the biomarker to kill those cells and none others. The removal of the ageing cells promoted healthier and longer lives, with significant delays in the onset of cataracts, arterial sclerosis, heart problems, loss of muscle mass and age-related frailty and weight loss.
Baker J.D. T. Wijshake, T. Tchkonia, N.K. LeBrasseur, B.G. Childs, B. van de Sluis, J.L. Kirkland and J. M. van Deursen. 2011. Clearance of $p16^{Ink4a}$-positive senescent cells delays ageing-associated disorders. *Nature* 2011 Nov. 2; 479 (7372): 232-236.

[ii] Thomas B. L. Kirkwood and Thomas Cremer. 1982. Cytogerontology since 1881: A Reappraisal of August Weismann and a Review of Modern Progress. *Hum Genet* (1982) **60**,101-121.

[iii] Behavioral and immunological factors in coronary disease by Willem J Kop. Grant application.

http://www.experts.scival.com/maryland/grantDetail.asp?id=7522954&n=Kop%2C+Willem+J&u_id=762

[iv] Strong evidence that insulin-resistant diabetes is an antoimmune disease: Winer, D.A., Shawn Winer, Lei Shen, Persis P Wadia, Jason Yantha, Geoffrey Paltser, Hubert Tsui, Ping Wu, Matthew G Davidson, Michael N Alonso, Hwei X Leong, Alec Glassford, Maria Caimol, Justin A Kenkel, Thomas F Tedder, Tracey McLaughlin, David B Miklos, H-Michael Dosch & Edgar G Engleman. 2011. B cells promote insulin resistance through modulation of T cells and production of pathogenic IgG antibodies. *Nature Medicine* **17**(2011): 610–617 doi:10.1038/nm.2353 http://www.nature.com/nm/journal/v17/n5/full/nm.2353.html

[2]About formaldehyde and its properties: http://www.chm.bris.ac.uk/webprojects2002/robson/Home%20page.htm

[vi] For general info: http://www.ironmanmagazine.com/site/milk-estrogen-igf-1-and-insulin/ and for more specific data, see review article on the interaction between the endocrine system and the immune system:
Keith W. Kelley, Douglas A. Weigent, and Ron Kooijman. 2007. Protein Hormones and Immunity. *Brain Behav Immun.* 2007 May; **21(4)**: 384-392. can be accessed by this link: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1894894/
For an article about milk and the induction of GH and IGF-1 for the normal onset of puberty, see http://www.nutritionj.com/content/6/1/28.

[vii] Baillie-Hamilton P.F. 2002. Chemical toxins: a hypothesis to explain the global obesity epidemic. *J. Altern Complement Med.* 2002 Apr. **8(2)**: 185-92.

For further reading, please see the review by:
Elobeid M.A. and D.B. Allison. 2008. Putative environmental-endocrine disruptors and obesity: a review. *Curr Opin Endocrinol Diabetes Obes* 2008 Oct. **15(5)**: 403-08.
For evidence of long-term impact of endocrine disruptors, such as from pesticides and plastics, see:
Newbold R.R., Padilla-Banks E., Snyder R. J., T. M. Phillips, and W. N. Jefferson. 2007. Developmental Exposure to Endocrine Disruptors and the Obesity Epidemic. *Reprod Toxicol*. 2007; **23(3)**: 290–296.

[viii] This is also an excellent article:
Eric L. Greer and Anne Brunet. 2005. FOXO transcription factors at the interface between longevity and tumor suppression *Oncogene* (2005) **24,** 7410–7425. http://www.nature.com/onc/journal/v24/n50/full/1209086a.html.

Another article, much more detailed:
Boudewijn M., T. Burgering and R. H. Medema. 2003. Decisions on life and death: FOXO Forkhead transcription factors are in command when PKB/Akt is off duty. *Journal of Leukocyte Biology.* 2003;**73**:689-701.

For insect growth regulators, such as juvenile hormone (JH) mimics, there is a voluminous literature. For instance, the article below reports on the impact of JH

on bee colonies and the central role that FOXO plays. FOXO is a family of transcription factors; they are conserved DNA-binding proteins with a Forkhead box are called FOXO. Honeybees have a different regulatory relationship between JH, vitellogenins, and FOXO than other insect orders, but all tested insect orders have FOXO, insulin, and JH metabolic connections.

Miguel Corona, Rodrigo A. Velarde, Silvia Remolina, Adrienne Moran-Lauter, Ying Wang, Kimberly A. Hughes, and Gene E. Robinson. 2007. Vitellogenin, juvenile hormone, insulin signaling, and queen honey bee longevity. *Proc Natl Acad Sci U S A* 2007 April 24; **104(17)**: 7128–7133.doi: 10.1073/pnas.0701909104. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1852330/

[ix] Paganelli, A., Gnazzo, V., Acosta, H., López, S.L., Carrasco, A.E. 2010. Glyphosate-based herbicides produce teratogenic effects on vertebrates by impairing retinoic acid signalling. Chem. Res. Toxicol., August 9. http://pubs.acs.org/doi/abs/10.1021/tx1001749

[x] Andrés Carrasco. 2013. Teratogenesis by glyphosate based herbicides and other pesticides. Relationship with the retinoic acid pathway. *In* Breckling, B. & Verhoeven, R. (2013) GM-Crop Cultivation – Ecological Effects on a Landscape Scale. Theorie in der Ökologie 17. Frankfurt, Peter Lang.