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THE SQUIRREL'S NEST 2016

Terrence McGarty

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THE SQUIRREL'S NEST

THURSDAY, DECEMBER 29, 2016

[CRISPR BLOCKING](#)

Day by day new tools are being found to manage CRISPRs. In [Cell](#) today they announce:

Bacterial CRISPR-Cas systems utilize sequence-specific RNA-guided nucleases to defend against bacteriophage infection. As a countermeasure, numerous phages are known that produce proteins to block the function of class 1 CRISPR-Cas systems. However, currently no proteins are known to inhibit the widely used class 2 CRISPR-Cas9 system. To find these inhibitors, we searched cas9-containing bacterial genomes for the co-existence of a CRISPR spacer and its target, a potential indicator for CRISPR inhibition. This analysis led to the discovery of four unique type II-A CRISPR-Cas9 inhibitor proteins encoded by Listeria monocytogenes prophages. More than half of L. monocytogenes strains with cas9 contain at least one prophage-encoded inhibitor, suggesting widespread CRISPR-Cas9 inactivation. Two of these inhibitors also blocked the widely used Streptococcus pyogenes Cas9 when assayed in Escherichia coli and human cells. These natural Cas9-specific “anti-CRISPRs” present tools that can be used to regulate the genome engineering activities of CRISPR-Cas9.

Likewise in The Scientist they note:

The researchers found these Cas9 blockers by searching bacterial genomes for both a CRISPR sequence and its target, under the assumption that the genome likely contained an inhibitor to prevent CRISPR from cutting that target in the bacterium’s own genome. Indeed, Rauch and colleagues uncovered several anti-CRISPRs in Listeria whose sequences had been left behind in the bacterial genome by prior phage infection. “Just as CRISPR technology was developed from the natural anti-viral defense systems in bacteria, we can also take advantage of the anti-CRISPR proteins that viruses have sculpted to get around those bacterial defenses,” Rauch said in the statement. Two of the inhibitors blocked Cas9 from Streptococcus pyogenes, the form of the DNA-cutting enzyme frequently used in genome editing. In a study published earlier this month in Cell, a different team of researchers reported the discovery of several anti-CRISPRs that block Cas9, but none of them acted against the activity of the Cas9 from S. pyogenes.

It seems we are building up a powerful tool box for cell manipulation. Hopefully the patent war can be settled in 2017.



Labels: [CRISPR](#)

WEDNESDAY, DECEMBER 28, 2016

PREPAREDNESS OF GOVERNMENT

Consider the US Interstate System. It is a mass of disparate roads paid by the taxpayer and under the jurisdiction of the State and Local police. Now consider contingency plans. For example ice, snow, or well let us just consider a car wreck.

Specifically let us look at the state of Pennsylvania and its Interstates. They are for the most part half a century or more in age and almost without exception two lanes. They have no tolls and thus invite the trucks, tons of them, and truck drivers who are in a rush and often less capable of doing what they are.

Now [look at today on I81 in Carlisle](#). An eighteen wheeler going northbound collides apparently with a pickup which cross the divider and both are destroyed and fatalities.

So what does the State have for a contingency plan? Nothing. Zip! Da Nada! One would assume that the State should have a contingency, but do not make that assumption. They are the Government after-all. Traffic is back up for hours, no exits, more than 40 miles sitting and burning fuel.



One would assume there would be a plan, directions, traffic control. The objective should be the care and safety of all, not just a gathering on a closed Interstate. One must ask; who is in charge? I have seen this again and again especially with many different State Police. Some are good, such as here in New Jersey, but if one were to cross state lines then all bets are off. There should be plans for this type of incident. One cannot just close the highway and leave tens of thousands to sit and wait, No Exit Sartre and all!

Then again one should ask; where is the Governor? The people stranded, some with health problems, others effecting commerce, ultimately all assume some modicum of care and attention. But not likely in Pennsylvania!

So how does one drive from New Jersey to Ohio? East through Moscow! Then to Vladivostok. Keep going East! Avoid Pennsylvania at all costs.



Labels: [Government](#)

[SOME HAVE LONG MEMORIES](#)

[China Daily](#) reports:

Japanese Prime Minister Shinzo Abe's visit to Pearl Harbor, criticized by China as lacking in sincerity, was quickly followed by one of his Cabinet ministers visiting a Tokyo war shrine on Wednesday. According to analysts, Abe's visit to Pearl Harbor, the target of the 1941 Japanese surprise attack on Hawaii, had hawkish intentions at heart, not pursuing peace and reconciliation. The purpose, they said, was to broaden Japan's military capabilities and curb the rise of China by strengthening the alliance with the United States. On Tuesday, Abe and US President Barack Obama laid wreaths at the USS Arizona Memorial. Afterward, in a speech, Abe said that Japan would never again wage war. On Dec 7, 1941, the Japanese attack on Pearl Harbor killed more than 2,400 US citizens and drew the US into World War II. Not long after Abe spoke, Masahiro Imamura, the minister in charge of reconstruction of northern Japan after the 2011 tsunami, offered prayers at the Yasukuni Shrine, which honors Japan's war dead, including 14 Class-A war criminals from World War II. Class-A convicts were found guilty of plotting and carrying out the war. Chinese Foreign Ministry spokeswoman Hua Chunying said Japan should reflect upon its war crimes in a sincere manner rather than "make political shows repeatedly". She spoke at a regular news conference on Wednesday.

For almost fifteen years Japan raped and plundered China so it is reasonable to have some lingering recollection. Also from 1941 through 1945 Japan slaughtered Americans and Allied forces as well as their own people.

Perhaps China has a point. For everyone.



Labels: [China](#)

MONDAY, DECEMBER 26, 2016

[COULD NOT AGREE MORE](#)

What is Economics? That question is what was the start of this Blog. Now I am not an economist, nor do I pretend to affect any tenancy thereto. I have studied Economics, I have critiqued Economics, I have even disdained Economics. You see, unlike the real world, and one would think Economics is more real than anything, Economics is in today's world opinion and not science. It is a collection of idea, emboldened by mathematics, that state the way the world should work from the eyes of the presenter.

Now in a recent piece [Skildelsky](#) states:

What unites the great economists, and many other good ones, is a broad education and outlook. This gives them access to many different ways of understanding the economy. The giants of earlier generations knew a lot of things besides economics. Keynes graduated in mathematics, but was steeped in the classics (and studied economics for less than a year before starting to

teach it). Schumpeter got his PhD in law; Hayek's were in law and political science, and he also studied philosophy, psychology, and brain anatomy. Today's professional economists, by contrast, have studied almost nothing but economics. They don't even read the classics of their own discipline. Economic history comes, if at all, from data sets. Philosophy, which could teach them about the limits of the economic method, is a closed book. Mathematics, demanding and seductive, has monopolized their mental horizons. The economists are the idiots savants of our time.

Indeed, if Economists were first engineers, physicians, plumbers, carpenters, or some professions based in reality then perhaps so too would be there prognostications. Remember the employment rate curves sent out eight years ago by the Administrations incoming Economists. Never worked so what did they do? Changed the rules. Eliminated tens of millions from those looking for jobs. If your theory does not work, change the data.

Try that one on a bridge. Gravity is not as kind!



Labels: [Economics](#)

SUNDAY, DECEMBER 25, 2016

GENE DRIVE ISSUES

Gene Drives are an interesting interplay with a set of "tools" available to gene manipulators. The current capabilities of gene manipulation, also we can probably call it gene engineering, is that we have an ever growing collection of "tools". These tools allow bench folks to add this or subtract that from a cell. We can do this with a somatic cell, an existing cell in an existing organ and a germ line cell, a cell from which the organism will eventually be derived. We can add or delete genes and we can in so doing insert a mechanism which will carry on this editing process no matter what the cell becomes as the organism develops. Furthermore if we get this process working in the germ line cell then we can be assured that as the next generation proceeds this inserted tool for manipulating genes within the organism, if not now within the total species, proceeds in a dramatic manner. We lose Mendelian genetics and the tool insertion now produces a single unaltered lineage.

If this gene is of a certain type, say one which produces only a male, then by blocking in all subsequent lines of any females we can effectively wipe out this species when we have just surviving but non-producing males.

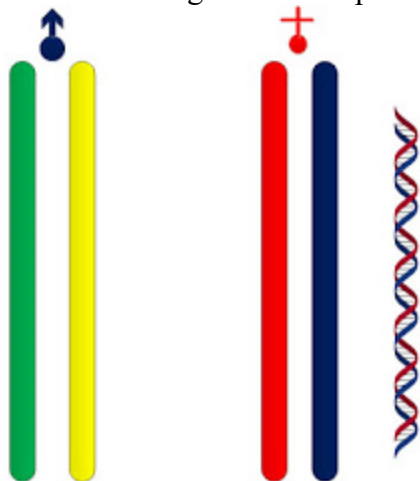
This assembly of tools by the genetic engineer has been called "gene drives". In a sense it "drives" certain genes into all members of a species. At least that is the hope. As the Broad Institute states in its licensing statements^[1]:

Gene drive. This is a way to rapidly spread a new gene throughout an entire species in nature. This approach might be used to block the transmission of malaria by mosquitoes, but has the

^[1] <https://www.broadinstitute.org/news/licensing-crispr-agriculture-policy-considerations>

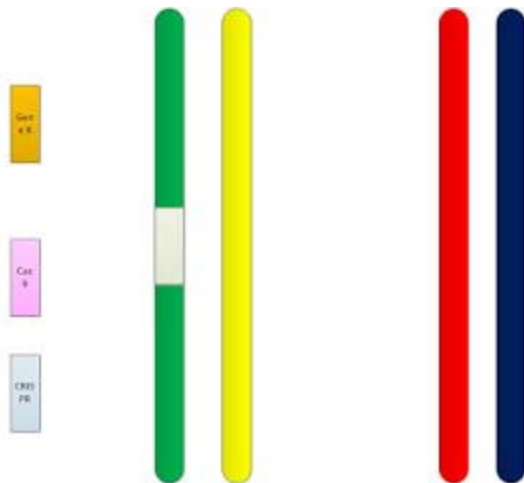
potential to disrupt ecosystems... After consulting with external experts and careful internal consideration, the Broad Institute has decided to make available non-exclusive research and commercial licenses for the use of CRISPR technology in agriculture -- but with important restrictions. These include: Gene drive: We prohibit the use of the licensed technology for gene drive.

Now to repeat a simplified version of the Gene Drive we present the steps simplified below. The basic principle is to insert a gene into a species, yes species, which will alter the entire species, such as making them all males and thus no longer able to reproduce.

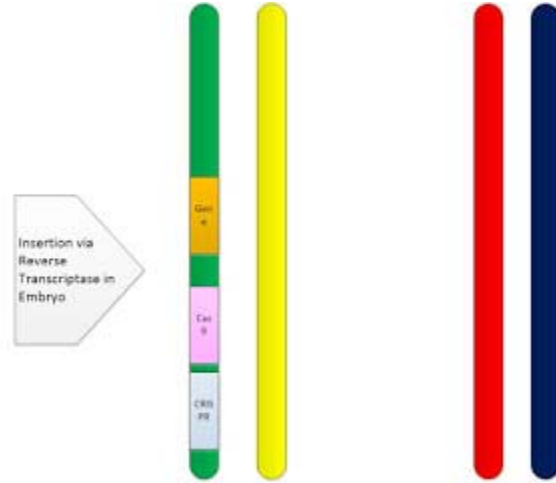


Start with the above, two sets of chromosomes from a wild type in a species. Classic Mendelian genetics would apply. Now we want to introduce some gene to alter then entire species. Usually was can do that say in an embryo but it would remain on one or even both chromosomes but would filter out. Yet if we could somehow also say introduce a CRISPR/Cas9 combo to rewrite this gene over and over then it would spread across all embryos and thus the species.

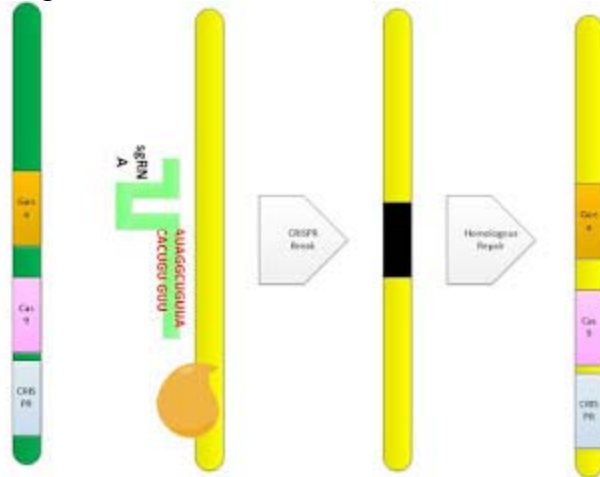
Thus the next step is:



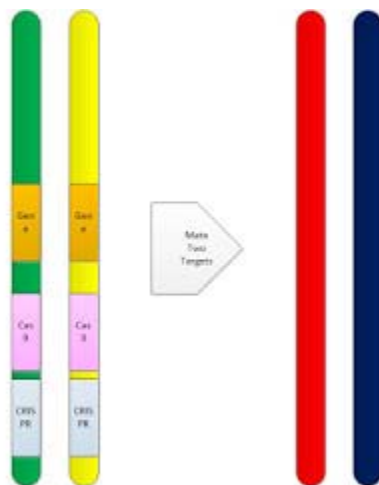
Namely figure out the gene, use say a Cas9 or other similar endonuclease, and a target CRISPR to guide the new gene.



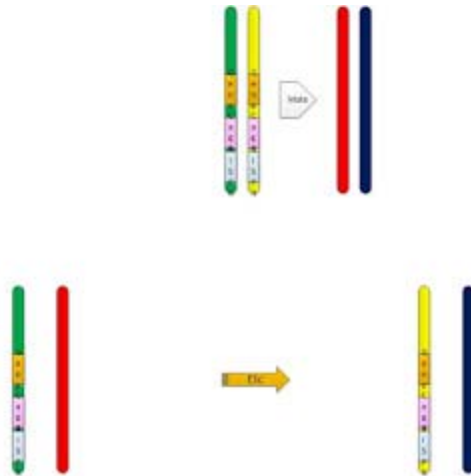
We use some insertion mechanism such as a lentivirus in the embryo with some reverse transcriptase to insert these genes.



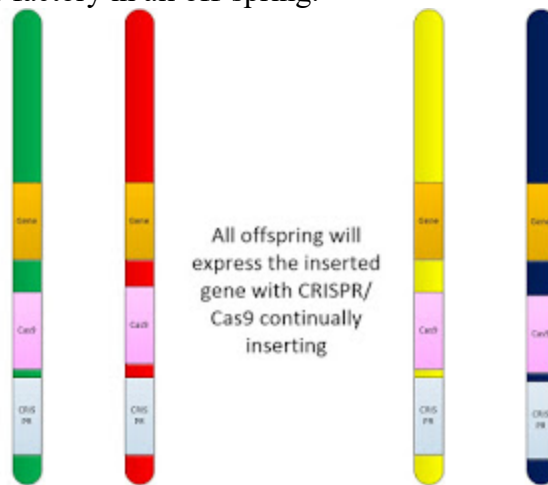
Then in the embryo it duplicates and the entire embryo reflects the gene and duplication mechanism.



Then the mating is between this modified and enabled vector with any wild type.



And we introduce the little factory in all off-spring.



Which perform the same tasks and reproduce the gene throughout the targets. Thus we could get all male insects and drive the species to extinction!

As [The Scientist](#) notes:

The United Nations (UN) biodiversity meeting, held in Mexico this month, could have ended poorly for scientists working on gene drives, genetic elements that can perpetuate specific mutations and may help cull dangerous mosquito populations. But in spite of environmental activists pushing the UN to ban gene drives, citing the risk of accidental release, the UN's final agreement—penned December 16—merely urged caution in testing gene drives, Nature reported. Overall, the organization broadly supported further research in synthetic biology. "I'm very relieved," Andrea Crisanti, a molecular parasitologist at Imperial College

London who works with gene drives, told Nature. “It would have been a disaster for developing the technology.” By engineering mutations that render organisms infertile or less infectious, then perpetuating these mutations with gene drives, scientists may be able to reduce the occurrence of certain mosquito-born illnesses and cull invasive species. Gene drives have already been tested in yeast, fruit flies, and mosquitoes, and may soon be enlisted in the fight against malaria. One team hopes to conduct field trials in Africa as soon as 2024.

In a similar fashion [Nature](#) states:

*When the CBD last met in South Korea in 2014, gene drives were a largely theoretical idea. They are genetic elements that can quickly spread through sexually reproducing populations. In general, an organism's two copies of a gene — known as alleles — each have a 50% chance of being passed on to its offspring. This limits the pace at which a genetic modification can spread through a population. But gene-drive technology tilts the odds, so that a specific change to one allele is inherited by a higher proportion of progeny. In theory, an entire population could quickly carry the same modification. In the past two years, researchers have lab-tested gene drives in yeast, fruit flies and mosquitoes that are based on a gene-editing technology called CRISPR–Cas9. Crisanti’s team, for instance, is working on gene drives in the malaria-carrying mosquito *Anopheles gambiae* that perpetuate mutations causing females to become infertile. Spread of this mutation could mean that mosquito populations plummet to levels that do not support the transmission of malaria. The researchers' project, called Target Malaria, has attracted tens of millions of dollars in funding, and the scientists hope to conduct field trials in Africa as early as 2024. Other groups are developing gene drives to quell island rodents and other pests.*

This development takes the next step and it presents a rather double edged sword. It is essential to be watched as we move forward.

As I have noted again and again. Silicon Valley apps pale to what bio tech is doing. In bio tech, there is a potentially deadly field at play and any country and enter the game. The cost is low, expertise is required, and somehow we seem to be providing it in our Institutions.



Labels: [CRISPR](#), [Gene Drive](#)

LOOK WHO IS TALKING

Having watched technology change over some almost seventy years, one thing you can say if that it is unpredictable.

Silicon Valley back in the early 60s was a Defense haven, filled with technical people focusing on developing new ways to combat the perceived Soviet threat. Salaries were reasonable and living conditions likewise.

My first exposure to a start up was in the late 60s where the result was a great learning experience. Failure results in decapitation and details count. Thus the world of venture investment could be ruthless, it was not a DoD contract of cost plus.

Then the 70s and the Nixon years of Creative Destruction. DoD work disappeared, Congress mandated more and more, and out of the Carter mess came entrepreneurs. My first exposure was a meeting in San Francisco to see if I wanted to join a VC fund, my answer was no, better to create than to try and pick winners and losers.

Then the 90s, and the Clinton I explosion. No more enemies, global markets, and the technology we had used in the military and space efforts was consumerized. Chips got smaller, cheaper, more powerful and "services" became a mantra. The "dot com" boom and bust. Such things as Pets.com came and went to be supplanted by Amazon.

Now dis intermediating classic distribution channels, which is what most of Silicon Valley does, is a business model for a while it does not afford a long term stable plan. Long term is fifty to a hundred years. After every millennial is walking around heads down on a iPhone what else is there.

Now one of the losing Presidential advisers notes that she has a set of recommendations for the winner. These "suggestions" is of course from a lawyer, not anyone who has apparently in my opinion done anything. [She recommends](#):

First, the next Administration must have an aggressive strategy to develop the human capital necessary to power the digital economy in this country. That means educating our people in computer science and STEM education from an early age. ... If talented students from abroad come to American universities and obtain advanced degrees in STEM fields, we should be bringing them into our economy, not pushing them out.

First if all, STEM is really Science and Engineering. Math is a science and technology is a support function. Second, I firmly believe that only a small percent of the population has both intellect and personal drive to prosper in that space. It is not something we just spend billions on educating everyone. It is achieved by supporting winners and, sorry to say, neglecting losers. Sixty years ago Gov. Rockefeller has NY State Regents Scholarships and then Science and Engineering Scholarships. If you demonstrated competence you got free tuition in New York schools. You rewarded the achiever. Second, I agree that keeping people who we educate with our tax dollars is essential. I have seen mass numbers of MIT graduate students get funded on US Tax dollars for PhDs and then go back and compete against us. That frankly is insane. Again the proponent seems to miss this fact. It is a remnant from Clinton I.

Second, the next administration needs a plan for promoting widespread entrepreneurship and inclusion in the digital economy. Tech shouldn't just be a Silicon Valley story; we should see similar innovation clusters emerging across our country, creating millions of jobs as well as products and apps that consumers demand. One policy... proposed in that vein was to support incubators and accelerators for 50,000 new entrepreneurs in underserved areas. Another was to

increase access to capital for small and mediums-sized businesses and startups, especially for minority and female entrepreneurs.

New companies survive and prosper only in a ruthless Darwinian environment. I have spent the last five years wandering around these Millennials warm spots where everything is supplied, and they have whatever they need until reality strikes. Success from these is zero percent! It would be nice if the proposer of this idea had the slightest understanding from a hands on perspective. Lawyers just do not.

Third, there must be a commitment to connectivity. We should settle for nothing less than universal, high-speed broadband for every household. To ensure people can get online through free wifi, we should replicate and extend programs like e-rate, which was successful at hooking up public schools and libraries to the internet, ...

Again she proposes more Government spending. Take a look around. There is lots of WiFi. It is at all libraries, schools, and even public housing. That is NOT a problem.

Finally, helping tech succeed means keeping the internet open, as well as private and secure for users. That begins with embracing the FCC's net neutrality rules, the staple of a free and open internet, rather than seeking to undo them. It means ensuring that users—all of us—continue to trust our internet-based communications platforms.

Internet Neutrality is more than just an Open Internet. It is an issue of privacy, autonomy, individuality, and the right to be informed, a corollary of the First Amendment. We clearly do not want any carrier to throttle our information. Frankly here many Republicans are father to the Left than Joe Stalin and it is shameful.

In conclusion perhaps one should examine these policy and strategy proposals. They reflect an echo chamber and isolated view of reality.

Where is real technology going. Simple. Biotech. Whether it is immune therapy, CRISPR, Gene Drives, and the like, it will be a period of Darwinian development of new ways to manage the world in a way we never anticipated. The Apps folks in my opinion will be left behind. Programming may for the most part become the 1950s Secretary Pool of the future. Understanding the plethora of bio tools in the tool kits and expanding them into what we see today in software will be the basis of a new change.

This environment will not be Theranos like but it will be the explosion about Kendall Square in Cambridge. It will be as a massive a change as we can imagine. Some will be in Silicon Valley, bit much may move East.

The proposals made reflect what the Press sees as technology. Wake up and smell the Cas9.



Labels: [Politics](#), [Technology](#)

SUNDAY, DECEMBER 25, 2016

MERRY CHRISTMAS 2016

1 And it came to pass in those days *that* a decree went out from Caesar Augustus that all the world should be registered.

2 This census first took place while Quirinius was governing Syria.

3 So all went to be registered, everyone to his own city.

4 Joseph also went up from Galilee, out of the city of Nazareth, into Judea, to the city of David, which is called Bethlehem, because he was of the house and lineage of David,

5 to be registered with Mary, his betrothed wife, who was with child.

6 So it was, that while they were there, the days were completed for her to be delivered.

7 And she brought forth her firstborn Son, and wrapped Him in swaddling cloths, and laid Him in a manger, because there was no room for them in the inn.

8 Now there were in the same country shepherds living out in the fields, keeping watch over their flock by night.

9 And behold, an angel of the Lord stood before them, and the glory of the Lord shone around them, and they were greatly afraid.

10 Then the angel said to them, "Do not be afraid, for behold, I bring you good tidings of great joy which will be to all people.

11 For there is born to you this day in the city of David a Savior, who is Christ the Lord.

12 And this *will be* the sign to you: You will find a Babe wrapped in swaddling cloths, lying in a manger."

13 And suddenly there was with the angel a multitude of the heavenly host praising God and saying:

14 "Glory to God in the highest, And on earth peace, goodwill toward men!

15 So it was, when the angels had gone away from them into heaven, that the shepherds said to one another, "Let us now go to Bethlehem and see this thing that has come to pass, which the Lord has made known to us."

16 And they came with haste and found Mary and Joseph, and the Babe lying in a manger.

17 Now when they had seen *Him*, they made widely known the saying which was told them concerning this Child.

18 And all those who heard *it* marveled at those things which were told them by the shepherds.

19 But Mary kept all these things and pondered *them* in her heart.

20 Then the shepherds returned, glorifying and praising God for all the things that they had heard and seen, as it was told them.



Labels: [Commentary](#)

SATURDAY, DECEMBER 24, 2016

[REPLACE THE ROCKETTES](#)

Perhaps the Rockettes and their Union may like to feel what American manufacturing labor has felt over the last decade. Simple, get Vladimir to send over the Bolshoi. We move from Crass to Class, but there would be some tariff involved I think.

As the [NY Times](#) states in its even fully complete coverage of the details of the new President:

The day of statements followed reports that a Rockette was “embarrassed and disappointed” that the decision to perform had been made for her. The dancer’s private Instagram post was published and quoted widely by news outlets. That dancer... did not respond to multiple requests for comment on Friday, nor did several of her fellow performers. Not long after those reports, a statement relayed ...a spokeswoman for the Madison Square Garden Company, said that dancers’ appearances are voluntary.

I suspect that "voluntary" could be transliterated into Russian with a slight change in emphasis.

Frankly this would be a great step forward in multiculturalism.



Labels: [Commentary](#), [Russia](#)

FRIDAY, DECEMBER 23, 2016

[CRISPR AND OTHER ENZYMES](#)

The Scientists reports the identification of new enzymes to effect CRISPR targeting. Recall that CRISPR is a targeting RNA sequence and the enzyme, such as Cas9 is used to cut and then allow splicing of segments. CRISPR targets the gene position and the enzyme does the cutting. Cas9 does DSB or double stranded breaks. Other enzymes allow for sticky ends.

As [The Scientist](#) states:

Banfield’s team searched the genomes for sequences that were both near cas1, which encodes a conserved CRISPR protein, and close to characteristic sequence repeats. The researchers found sequences for Cas9 in two archaeal genomes extracted from the Richmond Mine in Iron Mountain, California. Previously, archaea were known to use class 1 CRISPR systems, but class 2 had only been identified in bacteria. “We don’t really know how it performs, because that has not been achieved in the laboratory yet,” said Banfield. “Archaea have different biology. The fact that [my collaborators] haven’t yet managed to show its function probably means there are components of the system that we don’t yet know about.” The group also uncovered new types of Cas proteins from groundwater and soil bacteria, dubbed CasX and CasY. “They’re really small, especially CasX,” said Banfield. “That means it’s potentially more useful.” CasX is made

up of only 980 amino acids, whereas other Cas enzymes are larger. For instance, the commonly used Cas9 from Staphylococcus pyogenes contains 1,368 amino acids, while a smaller one from S. aureus is made up of 1,053 amino acids (CasY is around 1,200 amino acids). "This is important biotechnologically, because if you look at it from the angle of genome editing, the delivery of small genes into cells is much easier than the delivery of large genes," ... In partnership with UC Berkeley's Jennifer Doudna, Banfield's team demonstrated that CasX and CasY are functional. The researchers introduced CRISPR-CasX and CRISPR-CasY into E. coli, finding that they could block genetic material introduced into the cell.

The article appears in [Nature](#). The article states:

CRISPR-Cas systems provide microbes with adaptive immunity by employing short sequences, termed spacers, that guide Cas proteins to cleave foreign DNA. Class 2 CRISPR-Cas systems are streamlined versions in which a single Cas protein bound to RNA recognizes and cleaves targeted sequences. The programmable nature of these minimal systems has enabled their repurposing as a versatile technology that is broadly revolutionizing biological and clinical research. However, current CRISPR-Cas technologies are based solely on systems from isolated bacteria, leaving untapped the vast majority of enzymes from organisms that have not been cultured. Metagenomics, the sequencing of DNA extracted from natural microbial communities, provides access to the genetic material of a huge array of uncultivated organisms. Here, using genome-resolved metagenomics, we identified novel CRISPR-Cas systems, including the first reported Cas9 in the archaeal domain of life. This divergent Cas9 protein was found in little-studied nanoarchaea as part of an active CRISPR-Cas system. In bacteria, we discovered two previously unknown systems, CRISPR-CasX and CRISPR-CasY, which are among the most compact systems yet identified. Notably, all required functional components were identified by metagenomics, enabling validation of robust in vivo RNA-guided DNA interference activity in E. coli. Interrogation of environmental microbial communities combined with in vivo experiments allows access to an unprecedented diversity of genomes whose content will expand the repertoire of microbe-based biotechnologies.

The targets and capabilities continue to expand. Stay tuned.



Labels: [CRISPR](#)

THURSDAY, DECEMBER 22, 2016

[PROGRESSIVES, STUDENTS AND THE ACADEMY](#)

After this last election members of the Academy have gone public in their need to reduce the fear and uncertainty in the poor students under their care. Frankly, I do not recall any such during the Vietnam War, but then people were getting killed, even fellow classmates. In this case we have "harmful" words. I gather the levels of harm have dramatically changed.

In the [New Republic](#) there is a classic example of this Progressive think that has taken over. Namely the author rebukes one of the NY Times Progressives, a fact in itself which is telling. The author states:

Kristof's portrayal of campus liberals is just another form of elitist stereotyping, the mirror image of assumptions that every Trump supporter is a narrow-minded racist. By burlesquing progressives in academia, Kristof is making a faux-populist gesture of the very sort that drives the Trump-era right in its contempt for teaching and learning. Trump and his supporters have no regard for knowledge or debate, and thrive on petty caricaturing of political opponents. The right has turned the learning process that is student activism, with all of its inevitable triumphs and miscues, into national news fodder that's meant to mock and discredit academia, not to bolster freedom of speech or ideological diversity. In this era of virulent anti-intellectualism, we don't need more caricatures of academic life, especially from the left. We need more public intellectuals, especially progressive ones like Kristof, to stand up for the value of higher education—because without it, our political echo chambers would become that much worse.

One does not need to poke fun at Academia, they do the task so well themselves. It is not the right that turns the student absurdity into what it is, it is the acts themselves. The need to "protect", to deal with such things as micro-aggression, whatever that is. The conversational approach of asking about some students origin is now an overt hostile act. It at one time was a means of starting a friendly conversation. Now it is viewed as real aggression.

Now is it really true that Trump and all his supporters *have no regard for knowledge or debate, and thrive on petty caricaturing of political opponents* as noted above. What is the basis for that statement? If one were to ask such a question then the absurdity of the Left becomes apparent. In fact in a recent set of interactions I found the opposite may have some basis of fact.

This week in two cab rides I had two drivers. One was from Lebanon and the other from Egypt. Just a few hundred miles distance. The Lebanese was a Trump supporter the Egyptian a Trump hater. The Supporter went through his "on the one hand and o the other" which led to a conclusion. I just listened. The Egyptian was a Trump hater, stating each and every point one would hear on MSNBC. Again I just listened. I wondered which one was better off. I guess the Lebanese fellow, he did not spew forth anything.

As we enter our ninth year, I wonder if this issue will become more dominant. Will it be the focus of an ongoing battle with little benefit to the Country. Who benefits from it? That perhaps is the question.



Labels: [Academy](#)

WEDNESDAY, DECEMBER 21, 2016

STUDENT DEBT

Student debt is still exploding. Is it worth the economic risk? Should everyone have a college education, a college degree? Fifty years ago as we entered the Space Age it was still selective. The Government had programs to fund scientists and engineers. They even had programs to learn Russian. The Government spent money on college students via such things as NASA scholarships. Good students would qualify for financial aid in areas which benefited society and its needs at the time. Made sense. It did not fund liberal arts, literature, fine art. It did not even fund finance majors or law students.

Then what happened. I would argue two things.

First, the Government decided that everyone should get a college education. This led to two results. First it allowed massive numbers to major in subjects that allowed reduced standards and no jobs. Just how many fine arts majors do we need or even how many college educated graphics designers. Second, it motivated many to obtain debts that they ultimately had no economic basis to pay off.

Second, the Government backed massive college debt in direct and indirect manners. This meant two things happened. First students bought into the dream and surrendered to massive debt. Second, and this is the most serious problem, as the Government got more involved it drove up University overhead costs and thus tuition costs, with no appreciable increase in quality. In fact the quality I would argue has seriously suffered.

Thus we have a higher education system infiltrated by Government money and demands and universities responding with profligate spending and acquiescence to Government trends, demands, and dictates. University Presidents now talk as if they were managing some recovery center for orphaned and disadvantaged children. They tend to protect them from the fears of what may be happening in the outside.

In the [NY Times](#), a college president states:

Donald J. Trump has made bold and provocative campaign promises on taxes, trade, immigration and infrastructure. These pledges are all in service of bolstering our economic future. While we hope these initiatives will help our economic prospects, there is one important measure missing from the debate. And it could have an even more immediate and direct impact on economic growth: student debt relief. Student debt now stands at \$1.3 trillion. More than half of student borrowers are unable to repay their loans according to the original terms. In a well-intended but poorly executed effort to make college broadly accessible, the government has lent freely to students, with little attention to whether they can repay those loans. The result is millions of young people with debt they cannot afford. As a college president, I frequently hear from students who are anxious about their ability to repay their loans once they graduate. Many let student debt guide their career choices.

I gather that the NY Times mandates some Trump statement, and at least here the author got the demand out of the way in the first sentence. Now back to the facts. More than half the students cannot pay back the \$1.3 trillion. Yes, that is a lot of money. But whose fault is it. I suggest the students. Namely they chose studies for which there is no demand. Further they committed funds to schools which may bring little to the job table. So why burden those making money to pay for those who may most likely never do so?

Then we have the authors policy recommendation. She states:

Mr. Trump should scrap debt financing of higher education and make the transition to true income share arrangements. Borrowers would fulfill their obligations to taxpayers by paying a fixed percentage of their income over an extended period of years. Think of this change as a shift

in the government's role from creditor to equity investor. When you lend to a business, it is obligated to pay you back with interest, but with a stock investment, your returns derive from the success of the company.

Yep! Indentured servitude to the Government. This does not solve or even address the problem. Young people should choose a course of study to get a job. Later on in life they can worry about expanding their horizons if and when they have made enough to do so. This suggestion in my opinion would create a death spiral. Individuals have responsibility to make wise decisions. The young person who enters the military is making a decision to defend their country. A wise and respectable decision. Becoming an engineer, a nurse, a physician, even a banker means contributing to society in an enlightened manner. There is a demand and the investment by the student has a good chance of a return.

One of the big challenges we face is the ever altruistic hand of big Government. It will destroy the entrepreneurial spirit. That spirit is one that takes risks. Government of the ilk of this author wants Government to burden all to minimize or eliminate risks. The result is the death of the entrepreneur.



Labels: [Academy](#), [Politics](#)

[AIR TRAFFIC CONTROL](#)

I had spent a few years working in the Air Traffic Control, ATC, space decades ago. Some at MIT while working at Lincoln Lab and some with FAA while in DC. Back in 1976, yes forty years ago, I was an Advisor on satellite based ATC systems while in DC. Now some forty years later the ESA announces its intent to really really explore it again.

The [ESA](#) states:

ESA recently completed its first flight trials using satellites to help bring Europe closer to its goal of modernising air traffic control. The trials are part of the public-private partnership between ESA and UK satellite operator Inmarsat to deliver high-capacity secure digital data links via satellite for air-ground communications for cockpit crews over European airspace under ESA's Iris Precursor programme. By 2019, Iris Precursor will provide air-ground communications for initial '4D' flight path control, pinpointing an aircraft in four dimensions: latitude, longitude, altitude and time. This will enable precise tracking of flights and more efficient management of traffic.

Unfortunately this time the risks may be much greater. Satellites are vulnerable, networks can be hacked, signals can be spoofed, and not by National adversaries but by some less well intentioned individual with a laptop.

Thus what forty years ago was a great idea, in today's world, could cause havoc. Nice try but it is a bit too late.



Labels: [Technology](#)

TUESDAY, DECEMBER 20, 2016

POPULISM; WHAT IS IT?

Populism as a term has burst forth on the political landscape. In a recent [Nature](#) article, the classic scientific journal turned political commentary sheet for the left, notes:

Right-wing politicians in the crop currently making headlines are populists in that they want the will of the people to be the point of departure for political decision-making. This 'general will' should, according to their populist message, be translated as directly as possible into actual political decisions. All institutions, rules and procedures that stand in the way of such a direct expression of the general will are conceived of as liabilities that should be removed as quickly as possible. Minority rights? They hamper the direct expression of the will of the people. Checks and balances? They delay the decision-making process. Political compromises? They lead to the dilution of policy proposals and therefore to a lack of decisiveness. Free media? It only represents the interests of the 'established order'.

Imagine that, the will of the people is bad. Yes, indeed, when the people vote if the elite think they are wrong then the will should be disregarded.

This is an example of two extremes. Populism is a rule of the majority; Progressivism is a rule of the "elite" or "smart" minority. Frankly neither of them make any sense. [As we have written](#), the concept of Individualism, in the context of de Tocqueville, is in essence what made this country great. Simply Individualism is respect of each person equally, namely there are no special advantages, there are no minorities, because each is equal under the law.

The challenge going forward will be respect the individual. There are no winners or losers, there is only an amalgam of equally persons under the law. There is no Galbraithian group of great thinkers who we look to for guidance. There really is no great wisdom from Harvard, in fact there may just be a collection of disaffected persons.

Thus is one understand Individualism as not being one of isolation but as one of being equal inclusion then we need not fear the tyrants of the Academy nor the Tyranny of the Majority.

The Nature author continues:

More academics must speak out and warn about where we are heading. Part of this is immediate self-interest. There is no reason to expect that academia will be immune to the kind of populist interferences that we are now seeing in Hungary and Poland. Populist attacks on checks and balances and media freedom might well spill over into attacks on academia as well. After all, populists not only attack political and economic elites; they also target 'snobby intellectuals' in academia. In fact, such attacks on academics are happening in Turkey right now. Academics also have a moral obligation to protect liberal democracy. By promoting social and political pluralism, the system produces the circumstances under which researchers can do their jobs and science can flourish. Researchers depend on it.

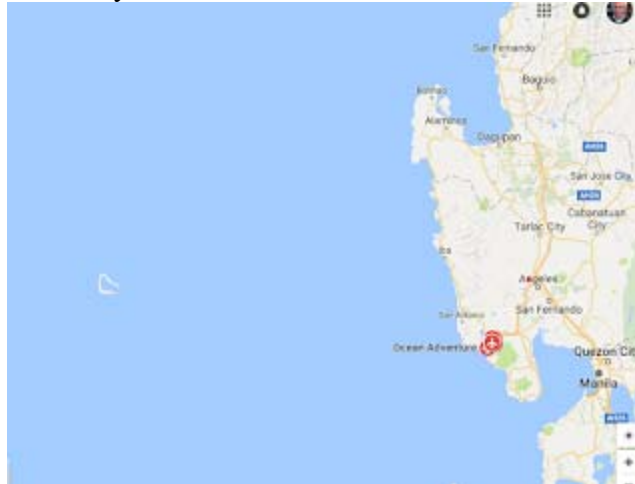
Perhaps Academic should first listen to the people. Academics truly have no idea about the real world. Over fifty years I have seen this phenomenon become greater. They live in an ever diverging echo chamber, leaving behind reality. Unlike Socrates and the Agora, namely teaching in the market where counter ideas flowed from the people, Academics dictate from their positions of power. There is no room for "what ifs" with the Academy. It is the 21st Century version of a religious cult. The Individual is berated, suppressed, so no wonder it emerges as a revolt of the Populace.



Labels: [Political Analysis](#)

[SPIN](#)

The recent events surrounding the taking of the US underwater drone is interesting. It was some 60 miles north west of Subic Bay.



That is about about 60 miles north west of the red dots. About a third the way to the upper left hand corner.

Now as [China Daily](#) states:

The US drone that China seized in the South China Sea has been successfully returned, China's Defense Ministry said. "After friendly negotiation, the drone was transferred to the US at a location in the South China Sea on Tuesday noon," the ministry said in a press release. The drone was discovered and retrieved by Chinese Navy last Thursday to "prevent danger to the safe navigation of passing ships and personnel", the ministry said. It was operating about 93 kilometers northwest of Subic Bay off the Philippines.

Just a friendly removal of a sea lane obstacle or Act of War?



Step back a bit, the location is just a small distance off the coast of the Philippines in International waters, a quite a distance from China.

So what are you to believe. The Chinese or your lying eyes?

[Science](#) makes an interesting statement:

For ocean scientists who have worked with the U.S. military, today's news that Chinese forces seized an oceanographic glider launched by an unarmed U.S. Navy research ship working in the South China Sea has a familiar ring. It's not the first time that Chinese ships have confronted the USNS Bowditch or one of its five sister oceanographic ships, a little-known U.S. Navy fleet operated mostly by civilians that conducts mapping and ocean data collection cruises around the world. In 2001 and 2002, for instance, Chinese Navy frigates dogged the Bowditch as it worked in the Yellow Sea, leading to an exchange of diplomatic complaints. In general, the Chinese object to the U.S. Navy conducting research activities within China's exclusive economic zone (EEZ), which stretches some 320 kilometers off its coastline. But U.S. officials have long held that the United Nations Convention on the Law of the Sea specifically allows military ships to conduct research cruises within a nation's EEZ.

One should also remember for whom this ship is named, the great New England navigation expert.



Labels: [China](#)

[HAPPY 8TH BIRTHDAY](#)

This Blog is eight years old today. Over 200,000 visitors from 152 countries. To remind some readers, in 2008 when we started the focus was the economic collapse. The issue was that the world of economists were clueless. We managed to bumble along to where we are now redefining such metrics as unemployment to yield "good" results while at the same time leaving tens of millions out of the labor pool.

We then moved to Health Care and the then emerging ACA. We demonstrated again and again that what was being proposed had fatal flaws. We argued that Health Care should be universal, mandatory, like auto insurance in that it covers a catastrophic event only. If you want full

comprehensive with no deductibles then you pay. We also argued no pre-existing conditions, no age restraints, and a Government subsidy based on income. Most importantly we argued for individual payment, no Company Plans, and enrollment directly with an Insurer NOT through a Broker. In today's world you can do this on line, why not to some generally ignorant broker.

We then moved to some key observations. People are fat, smoke, do drugs, and for those choices they should and must pay. If you want to be morbidly obese that is your choice but the cost to be incurred should be from your pocket. Same for smoking. Why should those trying to be healthy pay. On the other hand if God forbid you get cancer, then you should not be burdened with the added costs.

Then I moved on to Cancer and the progress of understanding and treating it. We will continue this focus.

Finally, this past election cycle has raised a great number of thoughts. As one who spent almost ten years in and out of Russia I perhaps have a different view. But clearly we need better relations, but better from a position of competence, not one driven by neophytes. The next eight years will present challenges never seen before. How they will be dealt with is anyone's guess. Let's just see.

Oh, and one last thing. Let's try to get out of this fear thing that people are all gaffing about. I have been seeing some of the best Universities turning into homes for over sensitive infants. Thus again, grow up.



Labels: [Commentary](#)

SATURDAY, DECEMBER 10, 2016

[WHEN SCIENCE TRIES TO SHINGLE THE ROOF IN THE FOG](#)

There is an old standard from Cape Cod, "Don't shingle the roof in the fog", you run out of roof real soon. But it seems that Nature and the Intellectuals have seen fit to keep on shingling despite the dense fog about them.

Nature especially has taken to this road. As [Nature](#) has recently touted:

In the United States, the regions hardest hit by globalization have become more politically extreme, according to a working paper published in September by David Autor, an economist at the Massachusetts Institute of Technology in Cambridge, and his colleagues. They found that these areas elected more hard-line candidates of both stripes to Congress between 2002 and 2010 — Republicans in majority-white communities and Democrats in ethnically and racially mixed areas. A separate, as-yet unpublished analysis by the team suggests that the trend towards extreme candidates favoured Republicans in presidential elections from 2000 to 2016 — perhaps enough to win Trump the White House this year.

Thus one must be "extreme" to vote this way. If one does not agree with you then one is extreme. The epithets continue without basis.

The author continues:

The Nazis took advantage of the extreme economic hardship that followed the First World War and a global depression, but today's populist movements are growing powerful in wealthy European countries with strong social programmes. "What brings about a right-wing movement when there are no good reasons for it?" Anheier asks.

Always good to call them Nazis. Especially if you are from across the pond. Try a trip to Munich, I saw that they are still there in places. Not a lot in Iowa.

Then the author continues:

Trump also prevailed in part because the structure of the US electoral college gives outsized influence to Republican-leaning rural areas over Democratic urban centres. And some of his predominantly white supporters voted for President Barack Obama, a Democrat, in past elections.

This is a good one. You see the Founding Fathers were smart. They did not want New York City and LA to elect the President. They wanted some balance. The Electoral College system does balance a bit. The author may want to read the Federalist Papers. Nice explanations. But it appears that these scientists are devoid of facts.

One should ask in a clinical fashion "why" the election turned out the way it did. I have sat through dinners where the battle back and forth never examined the question. Not for want of trying..

Science deals with facts. Facts and causes and results. Science does not deal with name calling as this piece seems in my opinion to reek with.



Labels: [Academy](#)

[PRIVACY AND SECRECY](#)

Some "Novelist" in the [NY Times](#) writes about privacy and encryption. I am always amazed when some "writer" takes it upon themselves to opine on topics for which they seem in my opinion to have little if any understanding, at least so far as their presentation of the topic is concerned. But alas, it is the NY Times which has become the perpetual source of anti putative President paper of record. But let us put that aside. As the writer states:

I've never been able to fit the concepts of privacy, history and encryption together in a satisfying way, though it continues to seem that I should. Each concept has to do with information; each can be considered to concern the public and the private; and each involves aspects of society, and perhaps particularly digital society. But experience has taught me that all I can hope to do with these three concepts is demonstrate the problems that considering them together causes. Privacy confuses me, beyond my simplest understanding, which is that individuals prefer, to different degrees, that information about them not be freely available to others. I desire privacy

myself, and I understand why other individuals want it. But when the entity desiring privacy is a state, a corporation or some other human institution, my understanding of privacy becomes confused.

Let's see. First three concepts; privacy, history, encryption. Kind of like; tomato, jumping, and elasticity. Not a single common thread but somehow he tries to get a nexus. I think I get it. Let us consider the seminal work on American privacy. Namely "THE RIGHT TO PRIVACY" by Warren and Brandeis (Originally published in 4 Harvard Law Review 193 (1890)) which states:

If the invasion of privacy constitutes a legal injuria, the elements for demanding redress exist, since already the value of mental suffering, caused by an act wrongful in itself, is recognized as a basis for compensation. The right of one who has remained a private individual, to prevent his public portraiture, presents the simplest case for such extension; the right to protect one's self from pen portraiture, from a discussion by the press of one's private affairs, would be a more important and far-reaching one. If casual and unimportant statements in a letter, if handiwork, however inartistic and valueless, if possessions of all sorts are protected not only against reproduction, but against description and enumeration, how much more should the acts and sayings of a man in his social and domestic relations be guarded from ruthless publicity. If you may not reproduce a woman's face photographically without her consent, how much less should be tolerated the reproduction of her face, her form, and her actions, by graphic descriptions colored to suit a gross and depraved imagination. The right to privacy, limited as such right must necessarily be, has already found expression in the law of France.

To a degree privacy is a right to be left alone. It goes well beyond the Fourth Amendment. It is a right to live in one's own sphere, not being attacked and examined by others. Now such a concept is extreme and even if such exists then one rejects it once one places oneself on say the Internet!

History is what we try to garner about the past by records available, public and private. For example what did FDR think of Churchill, and did JFK almost get the US nuked because of his dalliances? Good for books, possibly for History. Both gotten from private records.

Then there is encryption. Namely the ability that anyone has to take some record of something which has been reduced to a discoverable entity, and protect its discovery, except by some authorized party by some secure encoding. Thus did JFK send secret love letters to his paramours and if so when and what do they say. If encrypted one may never know and thus the impact on the writer of History could be impaired. I think that is what this fellow is trying to say.

They are three distinct topics, like "Charlie" and "in the water". One is a name and the second is a condition. Perhaps.

But the use of news type to present this is questionable at best. The job of the Historian is to reassemble the past from a puzzle like collection of data. Some may be indecipherable, lost, or just wrong. Privacy is what a person has a right to until such time as they give that right away. The pity is that it is now so easy to relinquish that right before anyone even understands what it is.



Labels: [Commentary](#)

MISSING THE POINT, AS USUAL!

The [Harvard Economist](#) recommends the post by a [CEA member](#) who advocates men take jobs usually performed by women.

The Economist in the article states:

Policy wonks like me have wondered why more lower-skilled men aren't adapting. Why don't they take care of their children when they are out of work? Why don't they take jobs as home health aides? Or sign up for degrees in nursing? One problem is that these occupations conflict with traditional notions of masculinity. They require sitting, caring and communicating, as opposed to working with big machines.

To anyone who has or should have been examining the distribution of labor by segment knows or should have known is that more and more jobs are in Health Care and Education and Government, such as teaching. You see my dear economist friends, all of these jobs are paid from taxes! Yes, surprise, taxes. And these folks want more people to get jobs funded by taxes? Who will pay the taxes? Oh, I forgot, it is the \$10 trillion more debt over the past eight years. I would call that funny money.

Frankly I do not know what the incoming President thinks, but I know the numbers. We need jobs that create value not deplete it. Manufacturing may be the name for the jobs creating value and paying taxes. Nurses are wonderful. But they do not create value in a true economic sense, namely we are taxed to pay for them. Ever heard of the ACA or eve Medicare? Yes, Medicare is a tax that for me I have been paying every years since 1965! Likewise for Social Security, guess it will end when I die, and not really, the Government gets one last grab from inheritance tax.

So folks, jobs that create exogenous value are real jobs. Making a wrench, digging a ditch, writing software, installing an outlet. Not one single Government employee creates value. They live off the dole, the taxes paid or to be paid by those who do create value.

The pity is that we have these economists who I believe have never held a job. A real one at least.



Labels: [Economy](#)

WEDNESDAY, DECEMBER 7, 2016

REMEMBER PEARL HARBOR

Since most Millennials have not a clue of Pearl Harbor or most likely where it even is, I thought for the 75th I may provide a bit of context.







It was an important event. As was 9/11. But it ended much more quickly.



Labels: [Commentary](#)

MONDAY, DECEMBER 5, 2016

[A HEARING TO WATCH](#)

Tomorrow the USPTO will hear the CRISPR patent case. As [The Scientist](#) notes:

CRISPR, the gene-editing technology that has taken the scientific community by storm, will have its day in court tomorrow (December 6) as three judges at the United States Patent and Trademark Office (USPTO) hear oral arguments to decide who owns the valuable intellectual property over its use. “The Broad Institute [of MIT and Harvard] is requesting priority based on its patent application filed on December 12, 2012,” ...The University of California, Berkeley, (UCB)/University of Vienna, on the other hand, is asking for its patent applications—filed on May 25, 2012 as well as in 2013 and 2014—to be prioritized. The first patent for the use of

CRISPR to edit eukaryotic genomes went to Feng Zhang of the Broad Institute of MIT and Harvard University in spring 2014. However, another group—including Jennifer Doudna of UCB and Emmanuelle Charpentier, formerly of the University of Vienna—had filed a provisional patent application for their CRISPR technology six months earlier. In January, at the request of UCB, the US Patent and Trademark Office (USPTO) declared an “interference” between the two, and the agency now seeks to settle once and for all who has intellectual property rights to the gene-editing technology that has taken the scientific community by storm. Although the USPTO recently changed its rules from prioritizing “first to invent” to giving precedence to “first to file,” the CRISPR patent applications in question predate the rule change. The interference proceeding, therefore, will be based on the “first to invent” system.

As we have noted before this will likely be a real Cat Fight. The timing and the rules will be most likely the telling fact.



Labels: [CRISPR](#)

SUNDAY, DECEMBER 4, 2016

[CARPET BOMBING CANCER](#)

The immune system is a powerful attack system. Take the simple example of the common cold. You touch something, or someone coughs and sends particle towards you. The virus enters your nose. Then what? The immune system recognizes this new adversary, the virus, and it sends out warning signals, recruits immediate responders, and at the same time the virus multiplies the immediate immune system releases a volume of cytokines, killer proteins to carpet bomb everything in the path of the virus. The nose starts running, the throat gets sore, the lungs get congested as the battle between the growing virus load is slowly overcome by the ever faster growing immune response. So what makes us feel so bad with a common cold? It may very well be the immune system response rather than the attack.

Now consider working in the garden. Peaceful. Relaxing, at least for some. Then as you dig up weeds, you notice you just unearthed roots that attach to that shiny three leaves plant. Poison Ivy! But no immediate response, you go in and wash your hands, and think all is well. No luck. Slowly you start itching and have wheals all over your hands and arms. Again the near immediate response. Your immune system is after that interloper.

These two examples show how this protector of our lives can make us worse off. It carpet bombs any attacker.

The NY Times notes^{2[1]}:

^{2[1]} <http://www.nytimes.com/2016/12/03/health/immunotherapy-cancer.html?hpw&rref=health&action=click&pgtype=Homepage&module=well-region®ion=bottom-well&WT.nav=bottom-well>

Another recent paper found that 30 percent of patients experienced “interesting, rare or unexpected side effects,” with a quarter of the reactions described as severe, life-threatening or requiring hospitalization. Some patients have died, including five in recent months in clinical trials of a new immunotherapy drug being tested by Juno Therapeutics Inc. The upshot, oncologists and immunologists say, is that the medical field must be more vigilant as these drugs soar in popularity. And they say more research is needed into who is likely to have reactions and how to treat them. “We are playing with fire,” said Dr. John Timmerman, an oncologist and immunotherapy researcher at the University of California, Los Angeles, who recently lost a patient to side effects. The woman’s immunotherapy drugs had successfully “melted away” her cancer, he said, but some weeks later, she got cold and flulike symptoms and died in the emergency room from an inflammatory response that Dr. Timmerman described as “a mass riot, an uprising” of her immune system. “We’ve heard about immunotherapy as God’s gift, the chosen elixir, the cure for cancer,” he said. “We haven’t heard much about the collateral damage.”

Unlike chemotherapy, immunotherapy can be long lasting. For example, the CAR-T cells which we have discussed are the patient's cells genetically engineered to recognize cell surface markers and when seen destroy the cancer cell. That would be fine if and only if the cells destroyed are cancer cells. However, there may be unintended consequences. First, there may be other cells which we do not yet fully understand that express the same or similar surface marker. They then also become targets. Second, and this is an issue, is that the process of destruction may have a lot of surrounding cells getting massacred, due to the released cytokines. This is collateral damage. Third, the collateral damage must be gotten rid of and this is part of the function of the immune system and this may be some positive feedback loop resulting in a set of catastrophic systemic failures.

Unlike chemotherapy, which is some chemical which kills certain types of cells, say rapidly reproducing ones, thus killing cancers as well as say hair. Immunotherapy may be long lasting if not permanent. You just can't stop administering it. Once started it may last forever, or at least until the patient dies. However, some recent work demonstrates that T cells do get "exhausted".^{3[2]} The authors note:

During cancer or chronic infection, T cells become dysfunctional, eventually acquiring an “exhausted” phenotype. Immunotherapies aim to reverse this state. Using a mouse model of chronic infection, two studies now show that the epigenetic profile of exhausted T cells differs substantially from those of effector and memory T cells, suggesting that exhausted T cells are a distinct lineage (see the Perspective by Turner and Russ). Sen et al. defined specific functional modules of enhancers that are also conserved in exhausted human T cells. Pauken et al. examined the epigenetic profile of exhausted T cells after immunotherapy. Although there was transcriptional rewiring, the cells never acquired a memory T cell phenotype. Thus, epigenetic regulation may limit the success of immunotherapies.

^{3[2]} <http://science.sciencemag.org/content/354/6316/1165>

However, there is an explosion of new markers and CAR-T cell targets. Juno Therapeutics lists some of the surface targets which their therapeutics address^{4[3]}. They are:

CD19... a cell surface marker for lymphocytes that is present on most B cell malignancies, including acute lymphoblastic leukemia and various subtypes of non-Hodgkin lymphoma, including diffuse large B-cell lymphoma.

WT-1: ...high-affinity TCR T cell product candidate targets WT-1, an intracellular protein that is overexpressed in a number of cancers, including adult myeloid leukemia, or AML, and non-small cell lung, breast, pancreatic, ovarian, and colorectal cancers.

CD22...Like CD19, CD22 is a cell surface marker for lymphocytes that is present on most B cell malignancies, including acute lymphoblastic leukemia and various subtypes of non-Hodgkin lymphoma, including diffuse large B-cell lymphoma. Importantly, CD22 expression has been shown to be maintained in acute lymphoblastic leukemia that has lost CD19, making anti-CD22 CAR T cells a potential combination or follow on therapy for CD19 CAR T cells.

LI-CAM...also known as CD171, is a cell-surface adhesion molecule that plays an important role in the development of a normal nervous system. It is overexpressed in neuroblastoma, and there is increasing evidence of aberrant expression in a variety of solid organ tumors, including glioblastoma and lung, pancreatic, and ovarian cancers. Our LICAM product candidate was originally developed at SCRI.

MUC-16 / IL-12...a protein overexpressed in the majority of ovarian cancers, but not on the surface of normal ovary cells. CA-125 is a protein found in the blood of ovarian cancer patients that results from the cleavage of MUC-16. CA-125 levels in the blood are a common test for ovarian cancer progression because they correlate with cancer progression. Our MUC-16/IL-12 product candidate, which was originally developed at MSK, has a binding domain that recognizes an extracellular domain of MUC-16 that remains following cleavage of CA-125. Our MUC-16/IL-12 product candidate is our first development candidate that uses our “armored” CAR technology.

ROR-1...a protein expressed in the formation of embryos, but in normal adult cells its surface expression is predominantly found at low levels on adipocytes, or fat cells, and briefly on precursors to B cells, or pre-B cells, during normal B cell maturation. ROR-1 is overexpressed on a wide variety of cancers including a subset of non-small cell lung cancer, triple negative breast cancer, pancreatic cancer, prostate cancer, and ALL. It is expressed universally on B cell chronic lymphocytic leukemia and mantle cell lymphoma. Our ROR-1 product candidate was originally developed at FHCRC.

One major concern is that of targeting the right cell. We assume that we can identify a specific cell by its unique surface marker. We design a specific immune targeting mechanism that goes after that cell. But if we believe in the stem cell theory of cancer, we more than likely have not

^{4[3]} <https://www.junotherapeutics.com/pipeline/clinical/>

targeted the stem cell. We have targeted some of its proliferations but not control elements. In fact, I would be willing to bet we have not targeted the stem cell. Thus, any immunotherapy may just make cancer a chronic illness but would not be curative. One then would be concerned by the continuing mutations.

Immunotherapy is a derived or indirect therapy. It is derived from examining how cancer cells are different, based upon surface markers. It is indirect because it deals with a secondary effect of the failing cell. It does not care what the problem is inside the cell but just that it has a different cell marker. In contrast the pathway methods whereby we know what pathway element is defective addresses a specific direct defect. This is a directed therapy.

Immunotherapy has a wealth of tools. T cells, NK cells, CAR-T cells, Mabs, IL variations and the likes. To a degree, they are all a step up from chemotherapy but do not necessarily represent a panacea. There are two things we must do. First identify the stem cell and its characteristics. Second, eliminate the stem cell or fix the genetic fault. Until then we will always have the unintended consequences.



Labels: [Cancer](#), [CAR-T Cells](#)

SATURDAY, NOVEMBER 19, 2016

[WHAT BUSINESS ARE YOU IN?](#)

I have been following the antics of the current MIT President and his moves into various venues. The last one was setting up a VC fund. Now I noted then that if the Institute chooses winners and losers then it may very likely have a deleterious effect. After all it is the real money folks who do that. I have walked away from dozens of deals before I select one to spend time with.

Now the next venture is Real Estate. As [MIT](#) notes:

On Tuesday, the U.S. General Services Administration (GSA) announced that the federal government has made “the initial selection of Massachusetts Institute of Technology (MIT) as the Exchange Partner for the Volpe Project. The next step of the process will be the joint selection of the Design Team by the federal government and the Exchange Partner for the new federal facility.”

Now the Volpe Center was a consolation prize for Massachusetts after President Johnson moved NASA to Houston. Probably a good idea, last thing Cambridge needed was another Government infrastructure. But now it appears that MIT with the East Campus and now Volpe will get into real estate. Where is Donald Trump when he is needed! Oh, forgot, it is that fear thing.

However real estate is real risk. Real big risk. If you want fear have a \$750,000,000 development fall flat. Or have a 100% over-run. Can a University manage anything like this? Look at Harvard's endowment.

Also perhaps one should look at NYU which bought up old buildings. But with MIT the intent is to totally renovate the area. What about the asbestos in the building folks, Remember Building 20!



Labels: [Academy](#)

TUESDAY, NOVEMBER 15, 2016

[A HEALTH CARE PROPOSAL](#)

Back in 2009 amidst the spinning of Health Care Plans we [proposed an alternative plan](#) that both provided universal coverage and cost less. Of course it did not provide every possible benefit paid by those not getting any and it did not mandate unmanageable overhead increases, and yes it did not have Washington dictate each move. It assume physicians had some understanding of providing Health Care and that Government employees were, shall we say clueless?

Now we have the same folks who thought we were all "stupid", from that school in Cambridge, what is it called? Ah yes, perhaps the Marxist Institute of Technology; close but no cigar. The individual was the one whose credibility was allegedly called into question when caught on camera states in the [Party paper of record](#):

So Mr. Trump would not only continue the insurance discrimination that plagued the country before the Affordable Care Act but even make it worse. In fact, there is simply no Republican replacement for the act that wouldn't leave millions of Americans at serious financial risk. The single most important accomplishment of the Affordable Care Act was to bring the United States into line with the rest of the developed world, as a place where people were not one bad gene or one bad traffic accident away from bankruptcy. Mr. Trump and other Republicans can discuss kind-sounding alternatives as much as they like, but they can't hide the fact that repealing the fundamental insurance protections that are central to the act would be a cruel backward step.

But given this individual's prior record as noted on his statements why should we believe him now? Just a question.

You see the analysis I did some almost eight years ago assumed universal coverage, no per-conditions but it also assumed that the patient would have some part of the process. Namely if one smoked, was obese, drank excessively, or in any other way was involved in a high health risk behavior then they paid more, and they had to pay more.

Physicians would be back in control of providing health care, not Government GS-9s or even MIT economics or business school PhD, and especially not Harvard economists.



Labels: [Health Care](#)

CRISPR AND HUMANS

[Nature](#) discusses the first application of CRISPR technology to humans. It was in China. They state:

On 28 October, a team led by oncologist Lu You at Sichuan University in Chengdu delivered the modified cells into a patient with aggressive lung cancer as part of a clinical trial at the West China Hospital, also in Chengdu. Earlier clinical trials using cells edited with a different technique have excited clinicians. The introduction of CRISPR, which is simpler and more efficient than other techniques, will probably accelerate the race to get gene-edited cells into the clinic across the world, says Carl June, who specializes in immunotherapy at the University of Pennsylvania in Philadelphia and led one of the earlier studies....June is the scientific adviser for a planned US trial that will use CRISPR to target three genes in participants' cells, with the goal of treating various cancers. He expects the trial to start in early 2017. And in March 2017, a group at Peking University in Beijing hopes to start three clinical trials using CRISPR against bladder, prostate and renal-cell cancers. Those trials do not yet have approval or funding.

They note that this may become a race comparable to the space race of the 1960s. We have been following this for about three years now and the potential is significant but CRISPR Cas 9 still has the DSB problem of reassembly as well as the targeting specificity.



Labels: [CRISPR](#)

TUESDAY, NOVEMBER 15, 2016

WHO ARE THESE FOLKS?

What is happening to my old Alma Mater, whoops I used a Latin phrase, perhaps that is now banned in Cambridge. Yet I do not know what the new in word must be. Let it pass.

Well, I get an email from some character who states:

Many of you have reached out to us to express concern about the recent outcome of the United States presidential elections. For us, that your outreach came from all corners of the world is a testament to the potential we have to build a world that is even more connected. Differences in our views do exist, with many of them existentially important, but over the long term we find progress through education and community. They are our ships for the seas of uncertainty.

Then this character includes the letter from the President bemoaning the election. It appears as if this fellow is actually getting paid by the Academy as well. For what? That I cannot figure out.

Not only did I not reach out to him, I did not know he even existed, and worse yet that we are paying for him!

I truly believe that we may have in some cases gone over the cliff in "sensitivity" training and expression. And we wonder why tuition is exploding.



Labels: [Academy](#)

SATURDAY, NOVEMBER 12, 2016

WASNTME

I recall a New Hampshire License plate which said WASNTME. My wife thought that was hilarious. So many people use that excuse. Like the five year old with chocolate frosting all over their face saying it was not them who ate the cake.

Today we get the best of the WASNTME, see the [NY Times](#).

By the way, if you can take a trip to New Hampshire, you will have a wonderful time reading license plates!



Labels: [Politics](#)

HARVARD AND ASSUMPTIONS

As expected a [Harvard Professor](#) believes that those without a proper education led to what occurred this week. He states:

....back in July, I noted that the Brexit vote was strongly correlated with education. The recent presidential election shows the same pattern: "College graduates backed Clinton by a 9-point margin (52%-43%), while those without a college degree backed Trump 52%-44%." The graph below shows that it is unusual for the more educated and less educated to be in such substantial disagreement.

I know a lot of PhDs, Ds, DDS, DMD etc who may disagree. As one somewhat trained in the sciences, engineering is close, we all too often ask, why? Why did this occur. We also note that the polls were totally off. Why? The conclusion reached above may be nothing more than the "echo chamber" effect. Look at the evidence. Then ask, why? If the PhDs, MDs, etc did vote other than how they do at Harvard, why?

Frankly I do not have an answer but after eight years writing the blog I have learned that a lot that comes out of the Yard is oftentimes truly "echo chamber" in character. After all if my next door Professor thinks that way why not all the world?

But what of the folks in West Virginia, where frankly coal has killed a lot of jobs. What do they think? Should all decisions be made by PhDs? I know I have made a few bad judgements and I am not even an economist!

Do I believe the graph alluded to? Not after this past election.

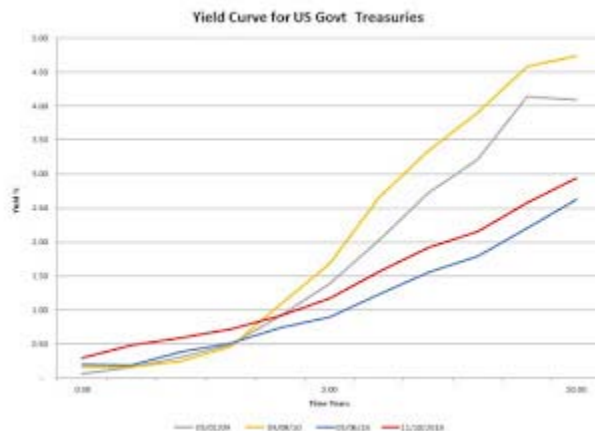


Labels: [Academy](#)

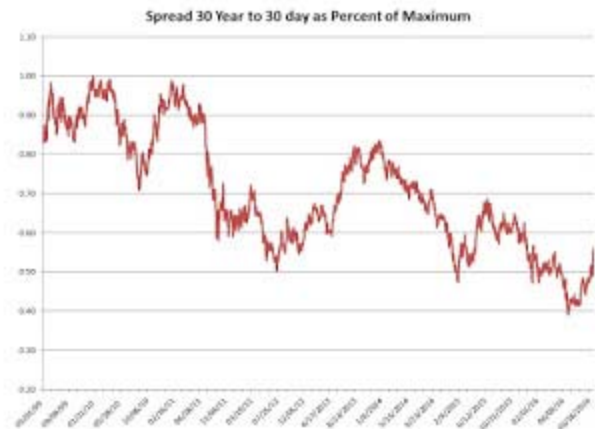
FRIDAY, NOVEMBER 11, 2016

TREASURY SPREADS

From time to time it is worth watching Treasury spreads. The chart below is the yield curve for several dates including yesterday.



Note yesterday has the highest short term rate. The curve is flattening as well.



The above is the spread of 30:30, the maximum spread. It hit a low a few weeks ago, almost 0,40 and now is up again. Remember that a negative yield curve has been seen back in the late Carter days.



The above is the 10 year and 90 day spread. It is quite low but more importantly we see the spike in the short term yields. Remember that the Treasury holds a lot in that category and thus it drives up Government costs.



Labels: [Economy](#)

FEAR, AND TREMBLING?

Fear seems to be a major theme from the left on the new Administration. Fear is a powerful word. I fear the dentist. Why? Simply, pain and cost. Dentists are still 11th century practitioners. They use early medieval instruments to tear, pull, extract, drill, and whatever. So, one can consider fear of a Dentist as real. Now there is also fear of flying. Not the sex type stuff, but the real stuff of being packed in some contraption operated by some low paid pilot whose training was at some school for flying aside some, well what shall we call them?

Now along comes Nature^{5[1]}, a credible journal, entering the fray of US politics and collecting some "scientists" and discussing the "fear" in science about the new Administration. I guess the folks who control "Left Wing Speak", I now believe there are such people, things really don't happen simultaneously, have selected the operative opposition phrase as "fear". Oh, yes, and Nature calls these folks "nine experts". So, I guess we better take their word ex cathedra, got that one folks. But remember, Science is supposed to be all questioning, seeking truth. Yet for Nature and these experts, we should just take their word for it. Not one of them seems in my opinion to present a single fact, but after all they are "experts".

First the comment:

Then there's the US REGROW Act. This seeks to lower standards for cell therapy products — such as stem-cell treatments — and has been stalled in a Senate committee since this spring. Major scientific groups have issued statements opposing the act, including the International Society for Stem Cell Research, the International Society for Cellular Therapy, and the Alliance

^{5[1]} <http://www.nature.com/news/what-scientists-should-focus-on-and-fear-under-trump-1.20974>

for Regenerative Medicine. The bill's prospects had seemed grim. Substantive amendments in recent months had, for instance, removed an alarming call for Congress to prohibit the FDA from requiring phase III clinical trials, typically the final hurdle for therapies to be approved for market for most investigational cell therapy products. Now, under a Republican-dominated government, its dim chances seem to have brightened.

"seem" is the operative phrase. "seem" to whom and based upon what evidence? Oops, I am speaking like a scientist about a scientist. I am only a humble engineer, with a few other areas of expertise, but alas, this is an "expert".

Then we have:

Clean-energy projects generate more jobs than do the coal and natural-gas sectors. With solar and wind projects creating energy prices between 2.5 and 4 ¢ per kilowatt-hour, the economic case is compelling — as is the argument for these technologies being the fastest way to provide energy access to the global poor, boosting their economic opportunities and capacity. The economic benefits of clean energy are even more profound if combined with domestic manufacturing of electric vehicles, which bring new research growth to the high-tech sector. Renewable-energy options, in some cases supported by natural gas, are a faster route out of energy and economic poverty than are coal-energy projects.

Here we have another set of statements that make no sense. 2.5 to 4 cents per KWh? Is that at the wind farm output point? What is the basis for that number? Many of these units are idle all too frequently. They are unreliable and frankly are both environmental hazards, ever seen all the dead birds, and ugly as sin. But the clincher is the above-mentioned cost. It has yet to be proven in on a national basis. One may find an installation here and there but no when looking at a totality.

Now for something I spent time on when in Washington. They state:

I have two concerns about defence policy. First, I'm not optimistic that the White House will understand the negative humanitarian and strategic consequences posed by lethal autonomous weapons systems. The Obama administration took the views of the scientific community seriously in formulating foreign and military policy. Secondly, I fear for the Comprehensive Nuclear-Test-Ban Treaty, one of the pillars of global nuclear non-proliferation policy. Trump has disparaged the Iran nuclear agreement to limit that country's nuclear programme; the deal is widely supported by arms-control experts. He has said that he has no objection to allowing several countries in Asia and the Middle East to have nuclear weapons. He has announced his intention to retaliate with nuclear weapons against a terrorist attack by ISIS (where, exactly, would he detonate them?).

Lethal Autonomous Weapons Systems, LAWP, are drone that target people and then just go and wo whatever. Frankly that is wrong and subject to substantial review. So, put that aside. However, on the nuclear side, nuclear weapons are world ending, period. I spent years on CTBT discussions and years in and out of Russia. We both can agree on that. The problem however is Iran and North Korea, neither a signatory to the aforementioned agreement. So why mention it.

Perhaps a poor rhetorical argument but easily rejected. Iran and its agreement are separate from a CTBT set of agreements. Russia and China know what the consequences. India and Pakistan should but we frankly should be concerned about Pakistan. But the real issue is Iran and North Korea. North Korea should be China's problem. If they want good trade deals, then resolve that issue now. Iran is now our issue. We broke it and now we own it.

Now for the best one:

Trump's success is the crescendo of a long devaluation of the Enlightenment idea that facts are the rightful basis of action. Reason itself is under fire. This mistrust of expertise is a serious threat to the sciences and the humanities. Science is in the business of making knowledge. History is founded on the principle that informed reflection is superior to ignorance. Devaluing evidence and manufacturing doubt can be a powerful strategy — as climate-change deniers and the tobacco industry have shown. Their push for short-term gain threatens our health and environment. The history of science, broadly construed, must shoulder some of the blame. Perhaps the central insight of my field in the past 40 years is that facts are socially constructed. Truth has a social history. But even the most extreme social constructionists still value expertise; they are not the ones trying to destroy the fabric of reality. This subtlety has been lost on the wider public, and to some extent on scientists. The rift between the arts and sciences — the pillars of the university — now threatens all who value reason.

The Enlightenment. A great deal has been written on the subject and our Constitution is based upon the ideas that the movement engendered. Especially the Scottish Enlightenment. "reason itself is under fire". Really? What is the basis for your statement? That is logic and logic precede science. In fact, Galen insisted that physicians be trained in logic before taking on what little science we know about the human body. "truth is a social history" What does that mean? Truth is distinct from falsehood. Is it true that the area of a circle is πr^2 ? Yes, but not just by definition. Truth is more than social history, it is what is done in science. It is true that genes generate RNA and that RNA generates proteins. It is true that proteins can control a lot of things. But so, can methylation, acetylation, and other intermediaries. The simplicity of a Watson and Crick, their "truth" has evolved. Science is ever evolving. Cancer is genetic, it is also epigenetic. Both are true, neither are social history.

So, what should we fear? "Fear itself?" That seemed adequate for FDR. And he was a Democrat.



Labels: [Politics](#)

HAPPY VETERAN'S DAY



The Constitution in Boston. Thanks to all veterans, then and now. Also remember family members like Harold McGarty with DSC in Okinawa in 1945 and Michael McGarty with DSC in France in 1918.



Labels: [Commentary](#)

THURSDAY, NOVEMBER 10, 2016

THE ACADEMY

In the late 1960s I was a Grad student and Instructor at MIT and my office was adjacent to the ROTC offices in the old WW II Rad Lab wooden building, Building 20. Many nights as I worked there were threats of bombs from the students opposing the Vietnam War. For a variety of reasons I also saw it as a nightmare, having lost a few class mates in the process.

Today we have a Presidential election as an event which may or may not change our society, for the better or the worse. And today the current [MIT President](#) sends out a letter saying:

As I saw this afternoon, students have wrapped the six great columns in Lobby 7 with huge sheets of paper. Three ask that you "Share Your Hopes," three to "Share Your Fears." They are covered with handwritten responses. People are lingering to read and add their own. Many say they fear for the future of the country, some for their personal safety, for their civil rights or that "my values no longer matter." Others fear that their peers will never take the time to understand why they voted for the winner. One hope struck me in particular: "I hope to understand the 48 percent of Americans who disagree with me." Nearly all the writers express some kind of pain. Yet together they have created a wonderful example of mutual respect and civil dialogue.

Pain? Pain in 1968 was being blown apart by a War that had no reason. Over 50,000 people died, in a bloody conflict. Those whom we fought are now "allies". Not that it is different. But in 1969 Jerry Wiesner was President, and he let the students express concern but at the same time we had a semblance of order, at least until Kent State, when US Troops executed unarmed students. You want pain, then there was pain as we saw students in pools of blood on a college campus.

Today there is the question of a change. That is the election process we have in our Constitution. Usually almost half like the result and half do not. But saying:

Nearly all the writers express some kind of pain

Begs the question; both the winners and losers had "pain". One must ask; how is their existence to change? Are they to be drafted and sent off to a war? We have a Constitution and a legal system which for better or worse seems to function. Perhaps leaders should lead and not whine with the crowd. Wiesner was a leader, I wonder what we may have at this time?

Now on the [MIT Admission](#) site there is some student blog that list the fears:

I'm afraid for the ENVIRONMENT

I'm afraid for all the people I love

Honestly my fears do not really grow. It is just a new day, and we should be able to go through. The only fear that has been there for a while may be that this country seems separating. But this is not caused by Trump. The US is just as separating as it has been. but Trump may have made it more explicit.

That this will turn people against each other instead of educate them as to WHY we need progress. It's not the time to block or delete people - that won't help us win 2020

I fear that fear will continue to hinder progress.

That persuasion and loving, rational discourse doesn't work in America anymore.

That inequality will grow/deepen, and that we will be a more polarized nation.

I'm afraid of war with Russia.

that we still be stuck playing the blame game

that I don't really have a home, because America clearly doesn't want or love me

I fear because misogyny, sexism, racism and xenophobia are no longer closet feelings.

What do I tell my daughter?

Now I look back a generation or two. Seventy-two years ago my father was in Leyte Gulf, one third of his crew blown to bits by a combination of Japanese and American friendly fire. They fought to keep the destroyer afloat and then in a few months back into battle until August 1945 and then months in Japan on Occupation. Then 100 years ago my Grandmother, who was a leader in Socialist Party in New York, ran for Congress, and petitioned Wilson for the Women's Vote. Talk of fear. Wilson had her and six other women, The Lorton 7, sent to Lorton prison, force fed with hoses, and drenched with cold water every day. Yes, that was the Democrat Wilson.

What is the role of an Academy President? Besides raising money. It is leadership. Wiesner was a leader. I wonder about the current incumbent. Leadership does not play to the crowd. It looks forward, reaches upward, sets positive goals and visions. It appears that many of the current "leaders" seem to respond to the crowd. One must then look at the Governments from whence they came perhaps and ask how well they have done. Leaders set visions, they must look above the chaff of the young voices and understand what American stands for, opportunity equal for each individual. Whether Locke, Montisquieu or Ockham, it was centuries of understanding

equality, the individual, and opportunity. If they can keep that vision then they are doing their job. Fear and pain from privileged youth when there is none palpable based on some physical phenomenon just plays into a theme that we have seen has sent those South American countries into centuries of upheaval.

So pain, fear? Bombs, Vietnam, Leyte, Okinawa, Lorton, Iraq, Syria. So what do I tell my granddaughters? The same as grandsons; that they are individuals, they have the same rights, the same risks, and make sure they accept that and not be intimidated. Don't whine; work, achieve, produce, contribute, respect, help.

Now, let's all get back to work!



Labels: [Academy](#)

[CHANGE](#)

World War II ended over seventy years ago. I do not remember the event but I remember my father's return. Thus for some of us it is a real memory. For those decades the US has been used as the cornerstone of European defense. All the while Europe prospered and used what would have been defense money to pursue their own social goals.

The threat was a Soviet invasion. Now the threat is a Russian invasion, at least that is what they think. But Europe has suffered more deaths from internal "invasions" than Russian troops. Perhaps it is time for them to rethink a great deal.

In the European Socialist site [The Syndicate](#) a Belgian writes:

*Europe has been only too happy to make life easy for itself. For the past century, transatlantic relations have adhered to a perverse, unspoken dynamic, whereby the more active the US has been, the more Europe has dozed off. When the Americans have intervened abroad – as they did in Iraq – Europe has responded with grandstanding lectures about “imperial overstretch.” And when the Americans have failed to intervene, or intervened late or ineffectively – as in Syria and Libya – Europeans have demanded more American leadership. That era is now over. **Trump knows that the EU has the money, technology, and know-how to be a global power equal to the US, and it is not his problem that Europe lacks the political will to harness its full potential.** We Europeans have assumed for too long that it is cheaper and safer to let the US solve our problems, even in our own backyard. With Trump's election (and given America's checkered foreign-policy legacy), we must discard this belief.*

Europe has a duty to defend itself. Frankly it is about time they grew up and decided what they want. The US has its own issues, and in a sense Russia should not be viewed as an enemy but as a counter balance to China. And China is an ever growing economic power that Europe should itself address.

This election in a strange way is truly a realignment of Global concerns. The US is looking inwards to examine how it wants to behave outwardly. The old cliches should and must be re-examined. Russia is still fundamentally an extraction economy. We never see "Made in Russia"

in Walmart. Then again we are seeing less and less of "Made in China" in Walmart and more and more in Defense elements. We rely upon Russia for Space launches and as the Arctic opens we may rely on them for Arctic Circle fiber connections as well.

Germany has the money and capability. Poland has taken steps to defend itself. It remembers the last German advance, and the Russian one before that. So let France, Italy, Germany, Belgium, Denmark, and even the Czech Republic step up to the table and do what the US has been doing for over seventy years.



Labels: [Politics](#)

FRIDAY, NOVEMBER 4, 2016

CBO AND BUDGET

The [CBO](#) has published a report on the Budget and losses going forward.

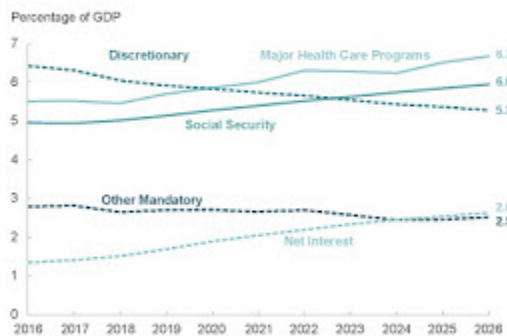
Total Deficits or Surpluses



CONGRESSIONAL BUDGET OFFICE

Going forward we see an ever increasing deficit as a percent of GDP.

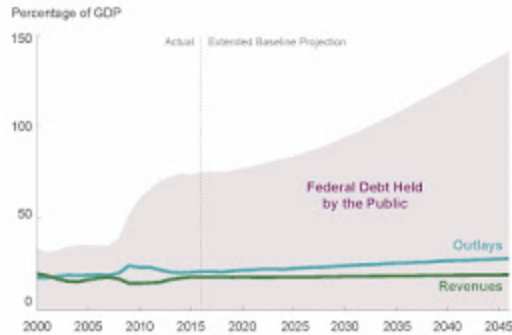
Projected Outlays in Major Budget Categories



CONGRESSIONAL BUDGET OFFICE

The above are the outlays as a percent of GDP. This of course assumes the GDP grows as projected. If it does not, which seems to be the case going forward the numbers explode. Worse look at Net Interest. Now it is just above 1% growing to 2.6%. If we have slower GDP growth and higher interest rates then this could easily double or worse!

Federal Debt, Outlays, and Revenues

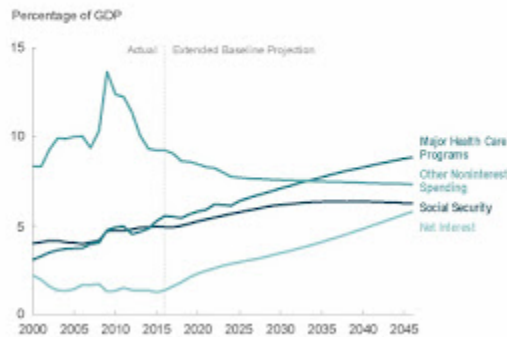


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14

Now the components of Federal Spending are as follows:

Components of Federal Spending



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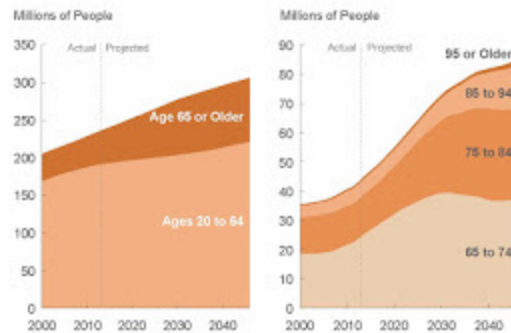
13

These are % Projected GDP which as we have said is very uncertain. The spending amounts are not! In Fact they most likely are more. Note:

1. Net Interest is exploding
2. Social Security is not too bad.
3. Health Programs are going nuclear!
4. All else is dropping, especially Military

Finally look at age groups.

Changes in Population, by Age Group



CONGRESSIONAL BUDGET OFFICE

28

The percent over 65 is growing considerably and the number over 75 is truly explosive. Imagine 60 million people over 75 who have smoked, drank, and were morbidly obese and what their future costs are!



Labels: [Economy](#)

FRIDAY, OCTOBER 28, 2016

[HALLOWEEN AND THE ACADEMY](#)

The Academy has become the extreme distortion of our society. The [NY Times](#) writes:

And when it comes to offensive behavior, one rarely hears students critique or police pop music that is riddled with abusive-sounding insults, mostly about women. Profanity, in general, doesn't seem to be something students worry about. Walk through a crowded cafeteria and curse words pop up gratuitously among students as if vocabulary has failed them. When I say, "Hey, ease up on the language, O.K.?" they look at me with incomprehension, not realizing they've said anything offensive. College officials won't tell students to avoid this kind of horrible stuff, though. Establishing behavioral codes that curtail hookup culture and profanity — those old-fashioned proprieties — are sexist and puritanical, we are told.

Boy am I old! As an Engineer we never had time to cavort at Halloween. I never saw a costume. In 1962 for example we were more concerned about a nuclear strike on New York than about offending some "protected" group.

If one has so much free time as Liberal Arts students seem to have, then this is not an education, it is expensive baby sitting. For \$70,000 per year you get to ship your kid off to some place that teaches them some useless stuff so that when they "graduate" they cannot get a job and move in back home.

Worse they have debt which the parent co-signed for and the parent's retirement goes out the window.



Labels: [Academy](#)

THURSDAY, OCTOBER 27, 2016

[MORE ON THE ACADEMY AND VCS](#)



[MIT](#) sent out a letter to its Community making a statement as to what it is trying to do with its purported VC fund. It states:

Today, innovators in fields like energy, manufacturing, robotics, biotech and medical devices often find it extremely difficult to secure the sustained funding, space, equipment, expertise and networks to fully develop their technologies; this struggle itself can needlessly prolong the development process, stretching it to a decade or more. All too often, "tough-tech" entrepreneurs never find sufficient support, which discourages others from trying, a dynamic that leaves many promising ideas stranded in the lab. MIT's mission statement directs us not only to "advance knowledge" and "educate students," but also to bring "knowledge to bear on the world's great challenges." If we hope to deliver serious technological solutions to urgent global challenges — like clean water, climate change, sustainable energy, cancer, Alzheimer's, infectious disease, and more — we need to make sure the innovators working on those problems see a realistic pathway to the marketplace. The Engine can provide that pathway by prioritizing breakthrough ideas over early profit, helping to shorten the time it takes these ventures to become "VC-ready," providing local space and comprehensive support in the meantime, and creating an enthusiastic community of inventors and supporters focused on delivering new science-based innovation to make a better world.

The essence of Venture Capital is to seek out people with interesting ideas. However it is "people" first. A leader and a team capable of dealing with the uncertainties of an early stage business.

Yes, at a place like MIT, one whose mission is education and research, there is often a gap between the results of research and the reality of a business. I have seen that for fifty years. On the business side we want dedication, complete and absolute dedication, to the execution of the business. Research is allowed if and only if it is essential to supporting the imminent goals of the business. VC firms are making investments. We are not like DARPA or NSF. I have run research groups in the corporate world, yet even there I demanded a nexus to executable reality.

Now the statement above in my opinion shows gross ignorance of the VC world. Yes there often is a gap between the research product and the marketable entity. Oftentimes the gap is the people. Researchers are all too often not those who can execute. They go on to the next unknown

not to delivery of a financially viable product.

Also a University should not, must not, be in the business of selecting winners and losers regarding business options. They know and understand research, not business. So what is "VC ready". To me it means that a team is in place, people who can execute. Those people are dedicated and devoted to the task. They do not want to continue research but want to spend the totality of their existence to execution of a business.

I am still working in this space after fifty years. Ideas from the edge of a University to commercial application. A day to me is eternity. A day to an academic is another Faculty meeting. Grad students oftentimes do not want to go into the real world. Post docs are often worse. They have accepted a position paying a paltry salary to continue research in hopes of some faculty position somewhere in the future. They are often disappointed. Making them entrepreneurs in my experience is both a disservice to them and to any investor.

Medical research is very risky, very costly, and takes many years. Just try and get a new drug through the FDA. The success rates in this area are de minimis. So why encourage researchers to think they can succeed when so many other real business have not.

One must ask why this step was even taken at MIT, an institution surrounded by VCs. It truly is not for want of opportunities or money. It could in my opinion be a poorly envisioned money pit, but worse in my opinion is may take competent researchers and make them think they are entrepreneurs while keep warm in the confines of MIT.



Labels: [Academy](#), [MIT](#)

[ACA AND REALITY](#)

We have been following Health Care Policy for eight years now. It is easier to do cancer genomics than it is to unravel the uncertainties and complexities of Government Health Care Policy.

Along comes the MIT "Professor", one of the authors, who thinks we are all stupid, if memory serves me correctly, in [NEJM](#) and states:

As the country focuses on the 2016 election, we offer several key messages from our findings. State implementation continues to strongly affect the success — or shortcomings — of the ACA. This reality is most obvious in decisions about whether to expand Medicaid under the law, since the lack of expansion in 19 states has left roughly 3 million adults without coverage. But state policies also affect middle-income families' ability to sign up for exchange coverage, which has been impaired in some states by legislative barriers to enrollment and lack of outreach. In essence, some state policymakers who rail against the ACA as a failed policy have created a self-fulfilling prophecy by taking steps to prevent people from signing up and benefiting from new coverage. Such actions may have contributed to the large gap between exchange enrollment rates in states participating in the federal exchange and those in states with their own exchanges. Though undermining coverage expansion may be politically expedient in some places, it is

indefensible from a public health perspective. With one presidential candidate pledging to build on the ACA and the other pledging to repeal it, and with state-level battles over the law ongoing, much is at stake in this year's election. Overall, our results reveal several ACA provisions working effectively to expand health insurance coverage to millions of Americans. Whether the law continues to expand coverage in the future most likely hinges on the outcome of the November election.

The ACA has become a bureaucratic mess. From ICD 10, the EHR, Quality Metrics, ACOs, and the like we now have a system which has massive overhead, dramatic burdens, reduced care etc. One of the major problems is that the Millennials do not get the mandate policies thus making private, or any other plan, excessively costly. We argued eight years ago that it must be universal, it must cover all, like auto insurance. Otherwise there will be arbitrage. Humans, even the Millennials, are economic machines optimizing their own returns. So why pay for something if you don't need it.

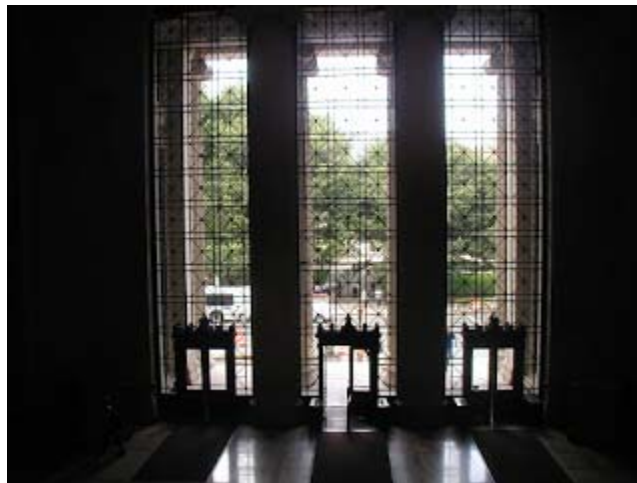
Then again in this article in NEJM we have the author who feels we folks are just fools, I think that is what he implied, and we can be manipulated, again I believe he implied that as well. Thus in my opinion why would one ever listen again? Poor MIT, what is happening? Leadership perhaps?



Labels: [Health Care](#)

THURSDAY, OCTOBER 27, 2016

[THE ACADEMY AND VENTURE INVESTMENTS](#)



In a recent piece by [xconomy](#) they write:

MIT is investing \$25 million in a potentially \$150 million venture capital fund and opening a 26,000-square-foot startup space on the edge of its campus....But MIT hadn't gone that route. A few months before she retired in June, former MIT Technology Licensing Office director Lita Nelsen told Xconomy she felt the Institute simply hasn't needed to form a VC fund on campus because the school has no trouble getting "decent companies" funded. She raised concerns

about conflicts of interest, clearly defining the mission of such a fund, and setting realistic expectations. Nelsen also presented a hypothetical scenario in which MIT spinouts that didn't receive an investment from a university venture fund might have trouble raising money later from outside VC firms. "There's a negative-select bias there for what we don't invest in," she said at the time. "So, better to [create] a level playing field for anybody who wants to play."

[MIT](#) makes the announcement as follows:

The Engine is designed to meet an underserved need. In Kendall Square and Greater Boston, many breakthrough innovations cannot effectively leave the lab because companies pursuing capital- and time-intensive technologies have difficulty finding stable support and access to the resources they need.

They continue:

To fuel The Engine, MIT will seek to attract hundreds of millions of dollars of support and to make available, for entrepreneurs, hundreds of thousands of square feet of space in Kendall Square and nearby communities. The Engine will also introduce startups to their entrepreneurial peers and to established companies, in innovation clusters across the region and around the world: It seeks to power a network of innovation networks.

Frankly the above statement is in my opinion inaccurate on its face. There is a wealth of investment opportunities in the area, as in and around Stanford. It is a well running Darwinian machine. So why change?

Frankly I could not agree more with Lita. She had spend decades managing the MIT IP portfolio. As a result she had first hand experience in how VCs operate. Having done over 35 start ups myself, the investments are "ruthless". Namely the investment works or does not work. If it does then monetize it and if not burn it.

Fundamentally doing a start up is a "burn your boats" scenario. You leave the comfort of MIT, go to some cheap place, tell your story again and again, manage a team, raise money by selling a viable dream. You do not stay at MIT in some incubator.

I firmly believe that this will become a disaster. The amount of \$125 million could be be spent better on MIT's mission, education and research, not high tech investment. It is worse than a telephone company trying to get into the entertainment business. It is a clash of cultures. Lita presented all the correct responses. However it appears that the ever increasing administrative hierarchy wants more and more stuff to control. Investments in and operation of a VC is NOT the way to go.

My first start up involvement was in 1969. An EG&G back company, it made one mistake and it was dean in a heart beat. How do you do this if your people are comfortable in a MIT owned and operated facility? Or is this the Millennial generations approach to high tech, never leave home and have perpetual care and up keep?



Labels: [Academy](#), [MIT](#)

[DON'T HAVE A HORSE IN THE RACE BUT...](#)

This is a messy political year and I am not saying anything new. I don't have any horse in this race, and the race is truly a horse race...however one sees it. But I am surprised, say even shocked, to see [Nature](#) have some PhD candidate from U Penn, that bastion of socialist values comment on the American public.

This writer for example opines:

My own research shows that voters with the largest discrepancies in their affective evaluations of the two candidates, which I refer to as emotional investment in the election, experienced the largest changes in perceptions of electoral integrity following the 2012 presidential election. Among supporters of a losing candidate, the stronger their affective preference for the candidate, the greater are their doubts about the fairness of the process. Regardless of the outcome in 2016, the supporters of the loser are all but guaranteed to have a historically extreme dislike for the winner. Unfortunately, we should expect confidence in the election result to suffer accordingly.

I suspect this young person has never been at a Bingo parlor or a racetrack! Democracy is messy, it always has been, even in Greece, just ask Socrates...

But why, one wonders, does such an esteemed journal, such as Nature, dig up some neophyte to comment on American democracy? Why not just ask people at random waiting for the Times Square Shuttle...after all, they are people!



Labels: [Politics](#)

WEDNESDAY, OCTOBER 26, 2016

[WHAT TOOK SO LONG?](#)

In a report by [Tech Dirt](#) they note:

Back in August a report emerged claiming that Google Fiber executives were having some second thoughts about this whole "building a nationwide fiber network from the ground up" thing. More specifically, the report suggested that some executives were disappointed with the slow pace of digging fiber trenches, and were becoming bullish on the idea of using next-gen wireless to supplement fiber after acquiring fixed wireless provider Webpass. As such, the report said the company was pondering some staff reductions, some executive changes, and a bit of a pivot. Fast forward to this week when Access CEO Craig Barrett posted a cheery but ambiguous blog post not only formally announcing most of these changes, but his own resignation as CEO. According to Barrett, Google will continue to serve and expand Google Fiber's existing markets (Austin, Atlanta, Charlotte, Kansas City, Nashville, Provo, Salt Lake City, and The Triangle in North Carolina), and will also build out previously-announced but not yet started efforts in Huntsville, Alabama; San Antonio, Texas; Louisville, Kentucky; and Irvine, California.

I love the new Valley words; pivot, disrupt, etc. [We have argued for a decade](#) that fiber is too costly and rant with delays and that wireless is the way to go. Yes a decade, ten years, 10% of a century, 1% of a millennium. So much for those bright minds at Google. Perhaps the fact of life has finally hit them in the head.

Now for wireless. You need a license. Lots of them actually. So where do they get them? Acquisitions, but costly one.



Labels: [Broadband](#), [Google](#)

[CAR T CELLS AND CANCER](#)

We have recently published a [Technical Report summarizing CAR T Cells](#) and their application to cancers. We provide a summary here. The immune system is a powerful tool that can be used in a variety of ways. One problem is that it seems that every day we discover another subtlety regarding how this functions. It is a tool, and a very powerful tool, that can be used as a scalpel or a butchering ax. With the advent of CARs, specifically designed killer T cells, CTLs or cytotoxic T cells, one can attack cancer cells, however at times this tool can explode in our hands. This paper is an attempt to examine the CAR T Cells as a tool which can be engineered. The problem we face however is that in engineering the tool we oftentimes do not have a full grasp of its effects.

Our intent herein is not to provide a detailed up to date review of CARs but to provide a summary introduction to the potential they provide. This area is still very much a work in progress and as such is subject to ongoing change.

Steven Rosenberg has been studying how best to use the immune system to fight cancer. His 1992 was a prescient piece that laid out the future opportunities. From then until now, some 25 years, we know a great deal about the immune system which was lacking then and furthermore we have a wealth of tools to manipulate the cells involved.

From Kahilil et al we have an introduction to CARs which provide continuity from the work on monoclonal antibodies, MABs:

In the past decade, advances in the use of monoclonal antibodies (mAbs) and adoptive cellular therapy to treat cancer by modulating the immune response have led to unprecedented responses in patients with advanced-stage tumors that would otherwise have been fatal. To date, three immune-checkpoint-blocking mAbs have been approved in the USA for the treatment of patients with several types of cancer, and more patients will benefit from immunomodulatory mAb therapy in the months and years ahead.

Concurrently, the adoptive transfer of genetically modified lymphocytes to treat patients with hematological malignancies has yielded dramatic results, and we anticipate that this approach will rapidly become the standard of care for an increasing number of patients. In this Review, we highlight the latest advances in immunotherapy and discuss the role that it will have in the future

of cancer treatment, including settings for which testing combination strategies and 'armored' CAR T cells are recommended.

From Batlevi et al we have a discussion on the flow from MABs to CARs with a nexus to checkpoint inhibitors, namely PD-1 inhibitors:

The success of the anti-CD20 monoclonal antibody rituximab in the treatment of lymphoid malignancies provided proof-of-principle for exploiting the immune system therapeutically. Since the FDA approval of rituximab in 1997, several novel strategies that harness the ability of T cells to target cancer cells have emerged.

Reflecting on the promising clinical efficacy of these novel immunotherapy approaches, the FDA has recently granted 'breakthrough' designation to three novel treatments with distinct mechanisms.

First, chimeric antigen receptor (CAR)-T-cell therapy is promising for the treatment of adult and pediatric relapsed and/or refractory acute lymphoblastic leukemia (ALL).

Second, blinatumomab, a bispecific T-cell engager (BiTE®) antibody, is now approved for the treatment of adults with Philadelphia-chromosome-negative relapsed and/or refractory B-precursor ALL.

Finally, the monoclonal antibody nivolumab, which targets the PD-1 immune-checkpoint receptor with high affinity, is used for the treatment of Hodgkin lymphoma following treatment failure with autologous-stem-cell transplantation and brentuximab vedotin.

Herein, we review the background and development of these three distinct immunotherapy platforms, address the scientific advances in understanding the mechanism of action of each therapy, and assess the current clinical knowledge of their efficacy and safety. We also discuss future strategies to improve these immunotherapies through enhanced engineering, biomarker selection, and mechanism-based combination regimens.

One of the observations when dealing with cancer and the immune system is that once when one tries a specific approach one often finds new mechanisms which can either be used or must be thwarted.

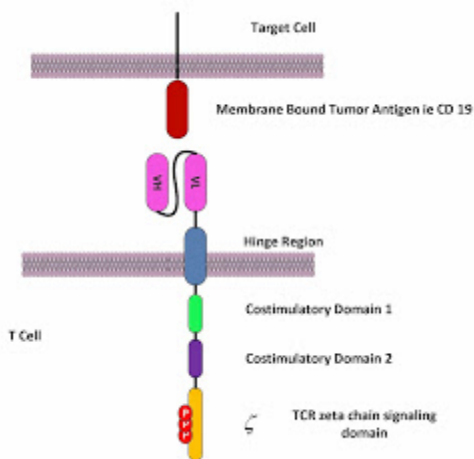
From Jackson et al there is a discussion of the work of CARs using CD-19 targets:

The engineered expression of chimeric antigen receptors (CARs) on the surface of T cells enables the redirection of T-cell specificity. Early clinical trials using CAR T cells for the treatment of patients with cancer showed modest results, but the impressive outcomes of several trials of CD19-targeted CAR T cells in the treatment of patients with B-cell malignancies have generated an increased enthusiasm for this approach. Important lessons have been derived from clinical trials of CD19-specific CAR T cells, and ongoing clinical trials are testing CAR designs directed at novel targets involved in hematological and solid malignancies.

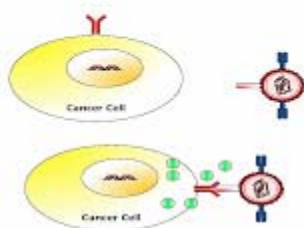
In this Review, we discuss these trials and present strategies that can increase the antitumor efficacy and safety of CAR T-cell therapy. Given the fast-moving nature of this field, we only discuss studies with direct translational application currently or soon-to-be tested in the clinical setting.

CAR T cells are chimeric antigen receptors on T cells. Chimeric because one designs them specifically for the target cells and essentially created a multiheaded receptor that matches the antigen presented by the tumor cell.

We provide a simple example below for a third-generation CAR:

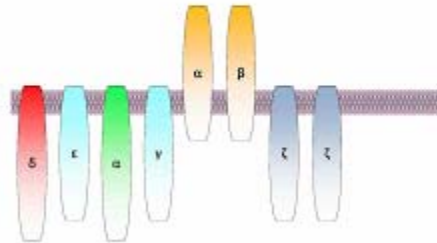


The function of this designed T cell is to allow a normal CTL, killer T cell, attach to a cancer cell with a recognizable antigen, and then to do what CTLs do well, allow the attacked cell to go into apoptosis, and just disappear, its constituents being used elsewhere.



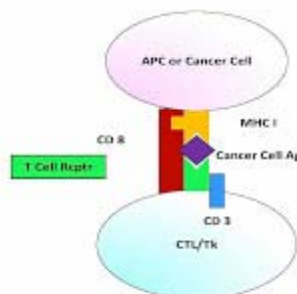
We demonstrate this process graphically above. We now review some of the key functions of T cells. The two types of T cells of interest are T helper and T killer or cytotoxic T cells, CTL. The CTL is the prime target of interest for it is the cell which can attach to a tumor cell and effect apoptosis of the tumor cell by its normal operations. The T helper supports the CTL by expressing IL-2 which allows for proliferation of that specific CTL type.

The CTL has surface receptors as shown below. Two are extending well beyond the cell wall and the remaining four are below the cell wall and provide for intra cellular activation. The complex acts in unison attaching to targeted cells. Now the essence of CARs is to modify this receptor so as to effect targeting of tumor cells and their exposed antigens.

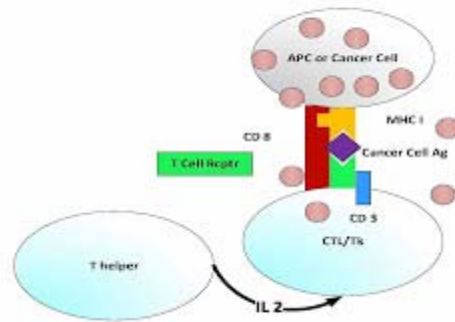


This CTL binding process is shown below. Simply the process is as follows:

1. An antigen presenting cell, APC, in this case a tumor cell, presents an antigen using the MHC I molecule. Also, the tumor cell may have another surface protein that results in the presentation of a tumor specific surface molecule like CD-19 in the case of hematological malignancies. The process starts with the ability to identify this molecule.
2. Then the CTL has a matching or cognate receptor which aligns with the MHC I and Ag combination and it attaches itself, and via CD-8 strongly binds to the cell, also using CD-3.
3. Upon binding the CTL can release cytokines or equivalents that result in the apoptosis of the cell.



We show the apoptosis below. Here the bound CTL recognizes the cancer cell and then releases apoptosis inciting proteins.



Thus, for any cancer cell we should be able to use this process, if we first know the Ag that is presented and second if we can create a receptor on a T killer cell, CTL, that recognizes that ligand and in turn can activate the apoptotic process.

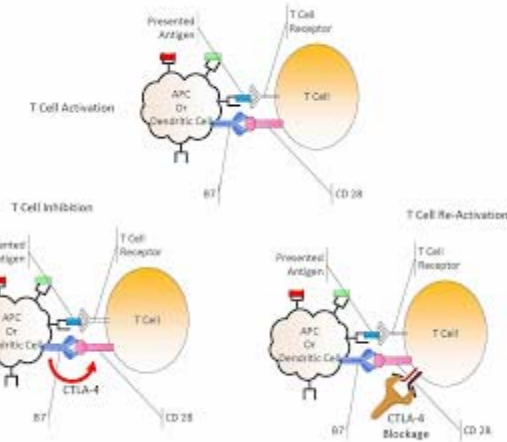
In the simplest terms this is how we might proceed.

1. Extract a tumor cell.
2. Ascertain the surface molecules and determine which one is unique to that type of cell and NOT common in other cells. You don't want the CTLs attacking everything.
3. Create a binding receptor for that ligand.
4. Extract the patient's CTL and insert by some reverse transcription manner, or CRISPR type approach the genes for that designed receptor.
5. Grow these modified cells in vitro using IL-2 or the like.
6. Insert these back in the patient.

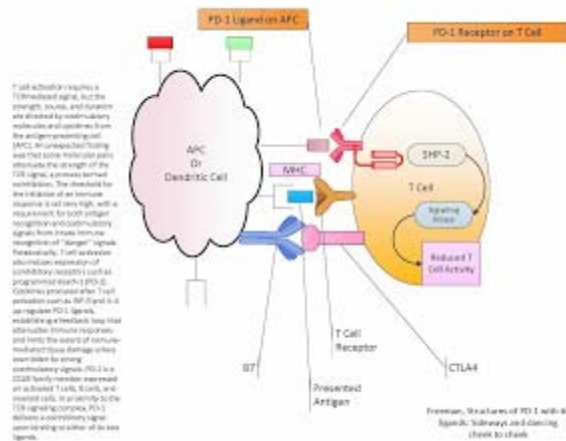
This is the "back of the envelope" approach to CAR therapy. Of course, there are many obstacles and the approach uses tools which may have to be gathered from afar. But as those who have developed CARs have shown it is doable.

Now what we have described above is not that simple. There are what are called a variety of "Checkpoint Inhibitors" that are an integral part of the control mechanisms of the immune system so that it does not go wild and destroy itself.

Let us begin with a brief review of PD-1 pathways. We have previously discussed the CTLA-4 blockage and the current approaches used to inactivate that element of T cell suppression. We summarize that again in the figure below.



Now CTLA-4 is not the only inhibitor of T cell action. PD-1 also can be activated and thus suppress T cell activity. This means that is we can find a way to inactivate or inhibit PD-1 then we have another way to seek possible activation of the T cells. In fact, perhaps we can do both and secure a super active T cell base. That is in essence the Wolchok approach. We depict this in the figure below.



The paper by Okazaki and Honjo in 2007 also details many of the critical elements regarding the PD-1 and its ligands. It details many of the recognized disease states as well. As they state:

Since the discovery of PD-1 in 1992, the biological function of PD-1 remained mystery for many years. Generation of Pcd1 mice and the discovery of its ligands turned around the situation and the function of PD-1 was unveiled thick and fast in these 5 years. Consequently, it became clear that PD-1 plays critical roles in the regulation of autoimmunity, tumor immunity, infectious immunity, transplantation immunity, allergy and immune privilege. The development of autoimmune diseases by Pcd1 mice especially enchanted clinicians and promoted clinical research as well.

Currently, many groups are trying to generate not only PD-1 antagonists for the treatment of cancer and infectious diseases but also PD-1 agonists for the treatment of autoimmune diseases, allergy and transplant rejection. Among these, humanized antibody against human PD-1 was approved by Food and Drug Administration of the United States as an investigational new drug in August 1, 2006. Clinical trials will test its clinical efficacy on cancer and infectious diseases.

Now we can examine the features of PD-1. As Freeman states:

T cell activation requires a TCR mediated signal, but the strength, course, and duration are directed by costimulatory molecules and cytokines from the antigen-presenting cell (APC). An unexpected finding was that some molecular pairs attenuate the strength of the TCR signal, a process termed co-inhibition.

The threshold for the initiation of an immune response is set very high, with a requirement for both antigen recognition and costimulatory signals from innate immune recognition of “danger” signals. Paradoxically, T cell activation also induces expression of co-inhibitory receptors such as programmed death-1 (PD-1).

Cytokines produced after T cell activation such as INF- and IL-4 up-regulate PD-1 ligands, establishing a feedback loop that attenuates immune responses and limits the extent of immune-mediated tissue damage unless overridden by strong costimulatory signals. PD-1 is a CD28 family member expressed on activated T cells, B cells, and myeloid cells. In proximity to the TCR signaling complex, PD-1 delivers a co-inhibitory signal upon binding to either of its two ligands, PD-L1 or PD-L2.

Engagement of ligand results in tyrosine phosphorylation of the PD-1 cytoplasmic domain and recruitment of phosphatases, particularly SHP2

Additional insight can also be provided by examining the regulatory T cells as well. As Francisco et al state:

Regulatory T cells (Tregs) and the PD-1: PD-ligand (PD-L) pathway is both critical to terminating immune responses. Elimination of either can result in the breakdown of tolerance and the development of autoimmunity. The PD-1: PD-L pathway can thwart self-reactive T cells and protect against autoimmunity in many ways. In this review, we highlight how PD-1 and its ligands defend against potentially pathogenic self-reactive effector T cells by simultaneously harnessing two mechanisms of peripheral tolerance: (i) the promotion of Treg development and function and (ii) the direct inhibition of potentially pathogenic self-reactive T cells that have escaped into the periphery.

Treg cells induced by the PD-1 pathway may also assist in maintaining immune homeostasis, keeping the threshold for T-cell activation high enough to safeguard against autoimmunity. PD-L1 expression on non-hematopoietic cells as well as hematopoietic cells endows PD-L1 with the capacity to promote Treg development and enhance Treg function in lymphoid organs and tissues that are targets of autoimmune attack. At sites where transforming growth factor- β is

present (e.g. sites of immune privilege or inflammation), PD-L1 may promote the de novo generation of Tregs.

CAR cells are essentially engineered T cells, specifically cytotoxic T lymphocytes, CTL, engineered to target specific cells such as those in various hematopoietic cell lines. such as leukemias and lymphomas. There is no fundamental reason that they cannot be used for solid tumors but there are certain operational barriers which must be overcome.

As Kershaw et al note:

There are two main types of antigen receptors used in genetic redirection.

The first utilizes the native alpha and beta chains of a TCR specific for tumor antigen.

The second is termed a chimeric antigen receptor (CAR), which is composed of an extracellular domain derived from tumor-specific antibody, linked to an intracellular signaling domain. Genes encoding these receptors are inserted into patient's T cells using viral vectors to generate tumor reactive T cells....

The specificity of CARs is derived from tumor-specific antibodies, which are relatively simple to generate through immunization of mice. Recombinant techniques can be used to humanize antibodies, or mice expressing human immunoglobulin genes can be used to generate fully human antibodies. Single-chain variable fragments of antibodies are used in the extracellular domain of CARs, which are joined through hinge and transmembrane regions to intracellular signaling domains.

As Miller and Sadelain note:

The advent of gene transfer technologies, in particular those enabling the transduction of human T lymphocytes using gibbon ape leukemia virus envelope-pseudotyped g-retroviral vectors, created new opportunities for immune intervention based on T cell engineering. Patients' T cells, easily accessible in peripheral blood, can be genetically instructed to target tumors by transduction of receptors for antigen, utilizing either the physiological TCR or synthetic receptors now known as CARs.

Both approaches have shown clinical successes, particularly in melanoma, targeting NYESO1, and in acute lymphoblastic leukemia, CARs are artificial, composite receptors for antigen that integrate principles of B cell and T cell antigen recognition. They are particularly attractive in that they elude human leucocyte antigen (HLA) restriction and are thus applicable to all patients irrespective of their HLA haplotypes, unlike TCRs. CARs may also overcome HLA downregulation by tumors, which deprives T cells of a ligand for their endogenous TCR.

The critical function of CARs is, however, not to merely target the T cells to a tumor antigen, but to enhance T cell function. Thus, effective CARs further integrate principles of T cell costimulation and provide a broad spectrum of functional enhancements acquired by directly soliciting selected costimulatory pathways

Juillerat et al note:

Adoptive immunotherapy using engineered T-cells has emerged as a powerful approach to treat cancer. The potential of this approach relies on the ability to redirect the specificity of T cells through genetic engineering and transfer of chimeric antigen receptors (CARs) or engineered TCRs. Numerous clinical studies have demonstrated the potential of adoptive transfer of CAR T cells for cancer therapy but also raised the risks associated with the cytokine-release syndrome (CRS) and the “on-target off-tumor” effect.

To date, few strategies have been developed to pharmacologically control CAR engineered T-cells and may rely on suicide mechanisms. Such suicide strategies leading to a complete eradication of the engineered T-cells will result in the premature end of the treatment. Consequently, implementing non-lethal control of engineered CAR T-cells represents an important advancement to improve the CAR T-cell technology and its safety.

Small molecule based approaches that rely on dimerizing partner proteins have already been used to study, inter alia, the mechanism of T-cell receptor triggering. Very recently, Lim and colleagues have adapted this approach to control engineered T-cells through the use of a multichain receptor.

Here, we describe a strategy to create a switchable engineered CAR T-cells. Our approach is based on engineering a system that is directly integrated in the hinge domain that separate the scFv from the cell membrane. In addition, we chose to implement this strategy in a novel CAR architecture that relies on the FcεRI receptor scaffold.

The particularity of this design resides in the possibility to split or combine different key functions of a CAR such as activation and costimulation within different chains of a receptor complex, mimicking the complexity of the TCR native architecture. In this report, we showed that the hinge engineering approaches allowed to turn a T-cell endowed with an engineered CAR from an off-state to an on-state.

By controlling the scFv presentation at the cell surface upon addition of the small molecule, our system allowed to further induce the cytolytic properties of the engineered T-cell. Overall, this non-lethal system offers the advantage of a “transient CAR T-cell” for safety while letting open the possibility of multiple specific cytotoxicity cycles using a small molecule drug.

Principles of T Cell Engineering and CAR Design

(A) Integration of B cell and T cell antigen recognition principles in the design of CARs. The heavy and light chain chains, which are components of the B cell receptor and Igs, are fused to the T-cell-activating α chain of the TCR-associated CD3 complex to generate non-MHC restricted, activating receptors capable of redirecting T cell antigen recognition and cytotoxicity.

(B and C) Integration of T cell activation and costimulation principles in dual signaling CARs designed to enhance T cell function and persistence in addition to retargeting T cell specificity. In

(B), the physiological abTCR associated with the CD3 signaling complex is flanked by the CD28 costimulatory receptor.

(C) shows a prototypic second-generation CAR, which comprises three canonical components: an scFv for antigen recognition, the cytoplasmic domain of the CD3 ζ chain for T cell activation, and a costimulatory domain to enhance T cell function and persistence. Unlike the abTCR/CD3 complex, which comprises γ , δ , ϵ , and ζ signaling chains and is modulated by a multitude of costimulatory receptors, CARs possess in a single molecule the ability to trigger and modulate antigen-specific T cell functions.

There are currently three generations of CAR T cell design. We examine each here. As Cartellieri et al note:

In an attempt to extend the recognition specificity of T lymphocytes beyond their classical MHC-peptide complexes, a gene-therapeutic strategy has been developed that allows redirecting T cells to defined tumor cell surface antigens. This strategy uses both the cellular and humoral arm of the immune response by assembling an antigen-binding moiety, most commonly a single chain variable fragment (scFv) derived from a monoclonal antibody, together with an activating immune receptor.

Once this artificial immune receptor is expressed at the surface of a modified T lymphocyte, upon binding of the scFv to its antigen an activating signal is transmitted into the lymphocyte, which in turn triggers its effector functions against the target cell (Figure 2). In the first attempts to reconfigure T cells with antibody specificity the variable parts of the TCR α and β chains were replaced with scFv fragments derived from monoclonal antibodies. These hybrid T-cell receptors were functionally expressed and recognized the corresponding antigens in a non-MHC-restricted manner. As a consequence of the finding, that CD3 ζ chain signaling on its own is sufficient for T-cell activation, the first “true” chimeric single-chain receptors were created by fusing a scFv directly to the CD3 ζ chain. At that time this concept was called the “T body approach”.

Nowadays these types of artificial lymphocyte signaling receptors are commonly referred to as chimeric immune receptors (CIRs) or chimeric antigen receptors (CARs).

The use of CARs to redirect T cells specifically against TAA-expressing tumor cells has a number of theoretical advantages over classical T-cell-based immunotherapies. In contrast to the long-lasting procedure of in vitro selection, characterization, and expansion of T-cell clones with native specificity for MHC tumor peptide complexes, genetic modification of polyclonal T-cell populations allows to generate TAA-specific T cells in one to two weeks. Engraftment with CARs enables T cells to MHC-independent antigen recognition; thus, major immune escape mechanisms of tumors such as downregulation of MHC molecules are efficiently bypassed.

Furthermore, proliferation and survival of modified T cells can be improved by the implementation of a multitude of signaling domains from different immune receptors in a single CAR

First Generation

Following Cartellieri et al we note regarding all three generations that:

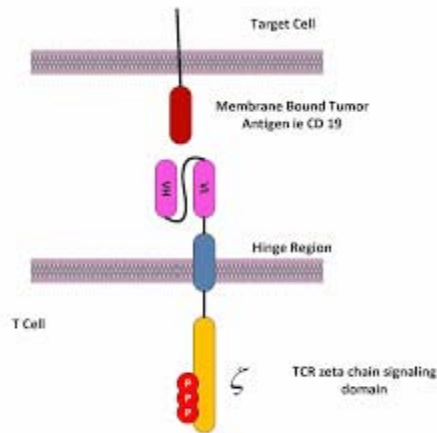
Evolution of CAR signaling capacities.

First generation CARs transmitted activating signals only via ITAM-bearing signaling chains like CD3ζ or FcεRIγ, licensing the engrafted T cells to eliminate tumor cells.

Second generation CARs contain an additional costimulatory domain (CM I), predominantly the CD28 domain. Signaling through these costimulatory domain leads to enhanced proliferation, cytokine secretion, and renders engrafted T cells resistant to immunosuppression and induction of AICD.

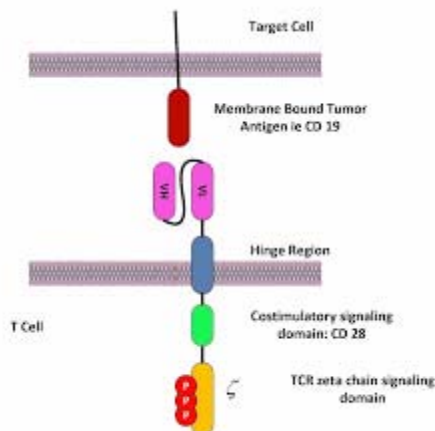
(Third Generation) Recent developments fused the intracellular part of a second costimulatory molecule (CM II) in addition to CD28 and ITAM-bearing signaling chains, thus generating tripartite signaling CARs. T cells engrafted with third generation CARs seem to have superior qualities regarding effector functions and in vivo persistence.

The first generation shown below is the simplest.



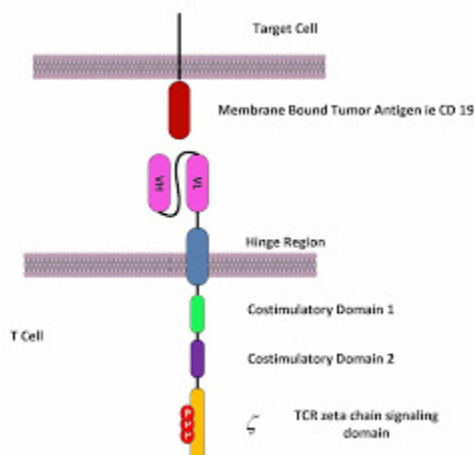
Second Generation

The second generation is as per below with the added element.

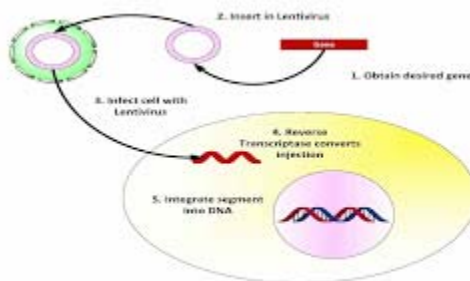


Third Generation

The third generation has added flexibility as shown below and described above.



Now the insertion of the genes to create the previously described receptors uses a reverse transcription process. It is akin to what we see in HIV reverse transcription and specifically uses lentiviruses as the delivery mechanism.



As Naldini notes regarding lentiviruses:

Major hurdles for hematopoietic-stem-cell (HSC) gene therapy include achieving efficient ex vivo gene transfer into long-term repopulating HSCs, preventing activation of oncogenes by the nearby integration of a vector and controlling transgene expression to avoid ectopic or constitutive expression that leads to toxicity.

As compared to early generation gammaretroviral vectors (γ -RVs), HIV-derived lentiviral vectors result in more efficient gene transfer and stable, robust transgene expression in HSCs and their multilineage progeny. Extensive preclinical work indicated important features in vector biology and design that affect genotoxicity and highlighted strategies to alleviate it. The self-inactivating long terminal repeats (LTRs) and integration-site preferences of lentiviral vectors were shown to substantially alleviate insertional genotoxicity.

When tested in γ -RVs, the self-inactivating LTR design was shown to improve the safety of this platform as well. Retrospective analysis of several earlier trials suggests that disease background, transgene function, ex vivo culture and the efficiency of host repopulation can all influence the likelihood that insertional genotoxicity will manifest in a trial.

These data helped to shape the ideas that not all integrating vectors have the same effects and that genome-wide integration of improved vector designs, although still a mutagenic event, can be tolerated in the absence of aggravating circumstances. Self-inactivating lentiviral vectors are also being used to engineer T cells with chimeric antigen receptors (CARs) or T-cell antigen receptors for use in adoptive immunotherapy for the treatment of cancer. The advantages of this new platform in comparison to earlier-generation γ -RVs, which perform satisfactorily in this cell target, are yet to be fully established. Lentiviral vectors are thought to give rise to more robust and stable transgene expression in T cells in vivo, and could facilitate more efficient and versatile ex vivo gene transfer while supporting coordinated expression of multiple transgenes.

These advantages will become more relevant as the gene-therapy field implements refined strategies, such as improved T-cell manipulation to preserve T memory stem cells, or more demanding cell-engineering tasks, such as the co-expression of multiple CARs (to improve specificity) or a conditional safety switch/suicide gene (to improve safety).

We now review the process below. We have initially presented a logical approach, then we explained how it could be accomplished and now we return and demonstrate how this could be accomplished. We explain in detail in the Appendix a multiplicity of such protocols in use today.



Now the mechanism above may lose some elements of control and switch mechanisms to turn it on or off have been considered.

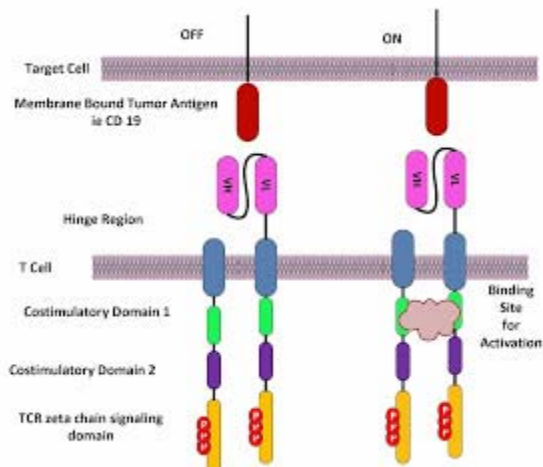
From Wu et al a specific mechanism is presented with its advantages and possible concerns. They state:

Cell-based therapies have emerged as a promising treatment modality for diseases such as cancer and autoimmunity. T cells engineered with synthetic receptors known as chimeric antigen receptors (CARs) have proven effective in eliminating chemotherapy resistant forms of B cell cancers. Such CAR T cells recognize antigens on the surface of tumor cells and eliminate them. However, CAR T cells also have adverse effects, including life threatening inflammatory side effects associated with their potent immune activity.

Risks for severe toxicity present a key challenge to the effective administration of such cell-based therapies on a routine basis.

The ON-switch CAR exemplifies a simple and effective strategy to integrate cell-autonomous decision-making (e.g., detection of disease signals) with exogenous, reversible user control. The rearrangement and splitting of key modular components provides a simple strategy for achieving integrated multi-input regulation. This work also highlights the importance of developing optimized bio-inert, orthogonal control agents such as small molecules and light, together with their cellular cognate response components, in order to advance precision-controlled cellular therapeutics.

We graphically demonstrate this mechanism below.



The authors continue:

Titrateable control of engineered therapeutic T cells through an ON-switch chimeric antigen receptor. A conventional CAR design activates T cells upon target cell engagement but can yield severe toxicity due to excessive immune response.

The ON-switch CAR design, which has a split architecture, requires a priming small molecule, in addition to the cognate antigen, to trigger therapeutic functions. The magnitude of responses such as target cell killing can be titrated by varying the dosage of small molecule to mitigate toxicity. scFv, single-chain variable fragment; ITAM, immune receptor tyrosine-based activation motif.

CAR T cell therapy has had successes and failures. It seems to be appropriate for hematological cancers and some related ones where immunodeficiency is an element. However, it often has some several unintended consequences. The immune system is a very powerful system in the body. Setting CTLs loose to do what they do best can be at times very overpowering. In addition, the use of these systems without a means to throttle them back can present a danger to a wide selection of patients. We examine some of these issues as follows.

As Brudno1 and Kochenderfer have noted:

CAR T cells could damage tissues that express the antigen recognized by the CAR. This mechanism of toxicity can be minimized but not eliminated by an exhaustive search for expression of a targeted antigen on normal tissues during preclinical development of a CAR.

Examples of this mechanism of toxicity have been reported in the literature. In one study, 3 patients with metastatic renal cell carcinoma who received infusions of autologous T cells transduced with aCAR targeting carboxyanhydrase- IX experienced grade increases in alanine aminotransferase, aspartate aminotransferase, or total bilirubin.

Liver biopsies of affected patients revealed a cholangitis with a T-cell infiltration surrounding the bile ducts, and bile duct epithelial cells were unexpectedly found to express carboxyanhydrase-IX.

A patient with metastatic colorectal cancer who received an infusion of autologous CAR T cells directed against the antigen ERBB2 (Her-2/neu) experienced acute respiratory distress and pulmonary edema requiring mechanical ventilation. The patient subsequently died.

As Pegram et al note:

CD19-targeted chimeric antigen receptor (CAR) T cells are currently being tested in the clinic with very promising outcomes. However, limitations to CAR T cell therapy exist. These include lack of efficacy against some tumors, specific targeting of tumor cells without affecting normal tissue and retaining activity within the suppressive tumor microenvironment. Whilst promising clinical trials are in progress, preclinical development is focused on optimizing CAR design, to generate “armored CAR T cells” which are protected from the inhibitory tumor microenvironment. Studies investigating the expression of cytokine transgenes, combination therapy with small molecule inhibitors or monoclonal antibodies are aimed at improving the anti-tumor efficacy of CAR T cell therapy. Other strategies aimed at improving CAR T cell therapy include utilizing dual CARs and chemokine receptors to more specifically target tumor cells. This review will describe the current clinical data and some novel “armored CAR T cell” approaches for improving anti-tumor efficacy therapy.

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Labels: [Cancer](#)

WEDNESDAY, OCTOBER 26, 2016

HARVARD AND UNIONS

Harvard Grad students, some of them, are moving towards unionizing all Grad student assistants. There are surprises to the Grad students as they progress as noted in [The Crimson](#). There is a fundamental assumption in unions that what is compensated is the job, the position, not the person. In fact unions by their very nature deny the existence of an individual and base their very existence on the group. There are assembly line workers, packagers, maintenance staff, clerical staff. Each position has an agreed to salary or salary range, and there shall be no deviation from them.

Unions were made for the world of mass production, thousands of people doing the same job, day after day.

Unless something has changed, Graduate Teaching Assistants, having been one half a century ago, do something different hour after hour. Some are good, some great, some poor. It is a test that many do not pass. It is not the research test, that is a different path. It is the test to see if you can do a part of some future job.

One critical item however is that some people are great and some are horrible. In a meritocracy, one is recognized and rewarded for excellence. In a union world one is rewarded equally for the position and not for the product.

Perhaps these students do not recognize this fact, or perhaps quality of one's work no longer matters. Especially at Harvard.



Labels: [Academy](#)

TUESDAY, OCTOBER 25, 2016

ASHES TO ASHES, DUST TO DUST

Now if anyone has ventured to some European church one will find bones, skin, vials of blood, and various body parts from Saints. They are relics. Even parts of these things hang around necks, in scapulas, etc.

Today the Vatican ruled that ashes cannot be scattered about or kept say on you bedside. As the [Guardian](#) reports:

Catholics are forbidden from keeping the ashes of cremated loved ones at home, scattering them, dividing them between family members or turning them into mementoes, the Vatican has ruled. Ashes must be stored in a sacred place, such as a cemetery, according to instructions disclosed at a press conference in Rome on Tuesday.

So what does one do with all those loose body parts floating around? If one is turned into basic

chemicals why no fertilize the lilies in the field? What of say Joan of Arc, ashes scattered by the English.



Labels: [Vatican](#)

MONDAY, OCTOBER 24, 2016

CLASH OF CULTURES

The AT&T and Time Warner merger is a complicated deal. Complicated because it tries to tie up vertically the media/content and distribution business. I will leave that to the political types since mergers of this sort bring out all sorts of strange characters. The Law and Economics have little to play here and it is the Lobbyists and big money that rule the day.

The other issue is; how risky is this deal. The intent is to merge two dramatically different cultures; creative and operations. Telephone types are fundamentally order takers and order executioners. To be successful in a Telco first never make a mistake, have other people do that, and then fit the mold. Also do not try to be smart or creative. You are dealing with the most uncreative business in the world. Keep the stuff running, that's it. In wireless it is an asset business where the asset is the license. It is at worst a duopoly, AT&T vs Verizon, and a bunch of also rans. Keep the circuits running and send out the bills.

On the other hand Time Warner is creative, other than CNN that is. The creative business has a totally different group of people, risk takers, dreamers, deal makers, and LA types.

One wonders how in God's name these two cultures will ever work together. They are each 5,000 pound elephants, and they done even have the same DNA. The are different genera, not just species.

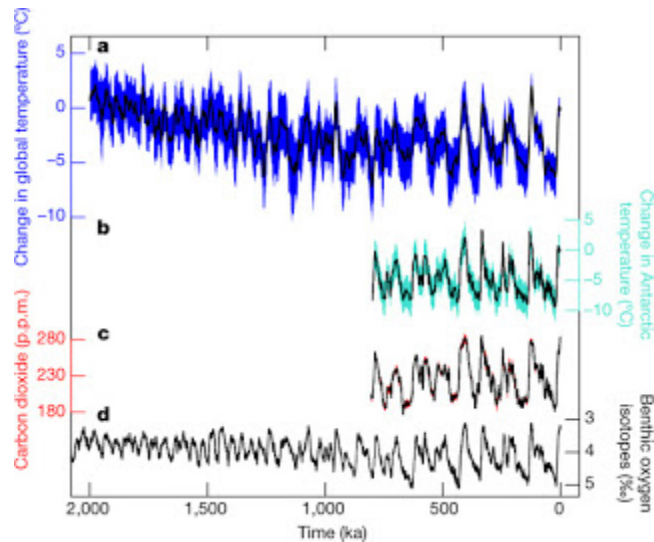
I saw this having first been at Bell Labs and then Verizon/NYNEX. I was at Warner in between. I loved Warner and the genius of a Steve Ross. On the other hand Verizon folks took a while to understand that profit had become revenue less expenses. They were fundamentally knuckle draggers, pole climbers, coin collectors, and followers of the Executive Instruction Manual.

Thus the real challenge is how a Texas operating company will blend with a New York/LA media company. And yes, somehow get a CNN stuck in there, whatever they do.



Labels: [CATV](#), [Media](#), [Telecom](#)

SUNDAY, OCTOBER 16, 2016

GLOBAL WHATEVER

In a recent [Nature](#) article there is a presentation of the cycling of global temperatures as shown above.

They note:

Here I present a spatially weighted proxy reconstruction of global temperature over the past 2 million years estimated from a multi-proxy database of over 20,000 sea surface temperature point reconstructions. Global temperature gradually cooled until roughly 1.2 million years ago and cooling then stalled until the present. The cooling trend probably stalled before the beginning of the mid-Pleistocene transition, and pre-dated the increase in the maximum size of ice sheets around 0.9 million years ago. Thus, global cooling may have been a pre-condition for, but probably is not the sole causal mechanism of, the shift to quasi-100,000-year glacial cycles at the mid-Pleistocene transition. Over the past 800,000 years, polar amplification (the amplification of temperature change at the poles relative to global temperature change) has been stable over time, and global temperature and atmospheric greenhouse gas concentrations have been closely coupled across glacial cycles. A comparison of the new temperature reconstruction with radiative forcing from greenhouse gases estimates an Earth system sensitivity of 9 degrees Celsius...

Not really clear what this data/simulation leads us to conclude. Other than cycles and noise.



Labels: [Global Warming](#)

HOW GOOD IS CRISPR?

We have been following CRISPR technology for the past three years. Logically it makes sense. The CRISPR guide RNA targets a sequence and the Cas 9 or equivalent cuts it. There are few issues however. One is it creates a double stranded break which often creates a worse situation

than before. Second, the RNA target may not find the sport we sought but some other identical but wrong sequence.

As noted in STAT:

As always, what worked in mice might not in patients. A constant concern with CRISPR is that it edits genes it isn't supposed to, because the guide RNA mistakes a healthy region of DNA for the mutation. Testing the most likely of these "off-target" sites, the scientists found that the one that was mistakenly CRISPR'd the most often wasn't a gene at all, or even near any genes. Other off-target sites were CRISPR'd in fewer than 0.10 percent of cells. But even that low level of error might be dangerous, perhaps triggering a cancer-causing gene, so Corn and his team are running more animal studies of whether their CRISPR approach will be safe.

In a recent [Science Translational Medicine](#) they note in applying this to blood disorders:

Genetic diseases of blood cells are prime candidates for treatment through ex vivo gene editing of CD34⁺ hematopoietic stem/progenitor cells (HSPCs), and a variety of technologies have been proposed to treat these disorders. Sickle cell disease (SCD) is a recessive genetic disorder caused by a single-nucleotide polymorphism in the β -globin gene (HBB). Sickle hemoglobin damages erythrocytes, causing vasoocclusion, severe pain, progressive organ damage, and premature death. We optimize design and delivery parameters of a ribonucleoprotein (RNP) complex comprising Cas9 protein and unmodified single guide RNA, together with a single-stranded DNA oligonucleotide donor (ssODN), to enable efficient replacement of the SCD mutation in human HSPCs. Corrected HSPCs from SCD patients produced less sickle hemoglobin RNA and protein and correspondingly increased wild-type hemoglobin when differentiated into erythroblasts. When engrafted into immunocompromised mice, ex vivo treated human HSPCs maintain SCD gene edits throughout 16 weeks at a level likely to have clinical benefit. These results demonstrate that an accessible approach combining Cas9 RNP with an ssODN can mediate efficient HSPC genome editing, enables investigator-led exploration of gene editing reagents in primary hematopoietic stem cells, and suggests a path toward the development of new gene editing treatments for SCD and other hematopoietic diseases.

Thus there is potential but also a concomitant risk.



Labels: [CRISPR](#)

THURSDAY, OCTOBER 13, 2016

[BOB DYLAN, CONGRATULATIONS](#)

Being of a certain age I can appreciate Dylan differently than others. In the summer of 1962, I was a Lifeguard in New York City and somehow, I really don't recall how, I got this blind date with a girl from Brooklyn, at Nostrand and Newkirk. So off I go, from Staten Island, across the Ferry, then into the bowels of Brooklyn. I am then told by the young lad, I don't recall her name of looks, but I remember Nostrand and Newkirk, that she wanted to go into the Village and see some guy in some coffee house. So back on the subway and off the Village to some place you walked down stairs to the basement and drank dark coffee in small cups amongst a few dozen

people all of whom smoked except for me. Subway fare at \$0.15 each way for each person was equal to half a pack and I wanted to spend my money on transport.

So up come this guy with a guitar, frizzy hair, and a harmonica hanging off his neck. He started to sing, the sound was like a cat dragged by the tail, but the words, well the words had meaning. He was not the Kingston Trio or Buddy Holley; he definitely was not Elvis. He was Bob Dylan. The memory festered in my head after I dropped the young lady back in Nostrand and Newkirk, and then back to the Ferry and then straight to work, for you see New York was not an easy place to get around. I would find it easier to get to Moscow by plane than Brooklyn by train, and yes Ferry.

About a year later my roommate Bob Glasser had become a Dylan fan. He had a guitar and that stupid harmonica, and song after song he imitated the dead cat howling, but the words, they were the same, and that was the power. He would sing Dylan and then listen to Jean Shepherd, or Shep, on the radio. It was a time when words meant something. Dylan stirred the soul, and Shep the imagination. You did not need an iPad, an iPhone, or an iWhatever. You heard words and used your mind.

Then in the summer of 1966 I went to a Dylan concert in New York, after the Dylan transmogrification into a rock personality. It meant less, but then I had changed as well.

So where does this lead? To a Nobel prize, and one I feel as a minor observer, well deserved. Dylan made many of us think, not wiggle with Elvis, sing along with the Beatles, or blend in with Peter Paul and Mary.

To my surprise some you person who appears to have a view of their own greatness feels the opposite. It appears in the [NY Times](#), where else? After all it is the NYT, that rag of record, which has dragged its front page down the level of current day politics. One does wonder what else is going on in the world. But alas, one gets more from China Daily or RT, or even The Guardian and Le Monde. But from this lost lass we are told:

The committee probably did not mean to slight fiction or poetry with its choice. By honoring a musical icon, the committee members may have wanted to bring new cultural currency to the prize and make it feel relevant to a younger generation. But there are many ways they could have accomplished this while still honoring a writer. They could have chosen a writer who has made significant innovations in the form, like Jennifer Egan, Teju Cole or Anne Carson. They could have selected a writer from the developing world, which remains woefully underrepresented among Nobel laureates. They could have picked a writer who has built an audience primarily online, like Warsan Shire, who became the first Young Poet Laureate of London in 2014. Instead, the committee gave the prize to a man who is internationally famous in another field, one with plenty of honors of its own. Bob Dylan does not need a Nobel Prize in Literature, but literature needs a Nobel Prize. This year, it won't get one.

My first response was; just who are you? My second was; oh well it is just the NY Times. Communicating ideas, complex thoughts, emotions, are literature, and doing so as did Dylan, especially at that time, was world changing. He started a process that lasted but a short while but

which had great and lasting consequences. My question would be; what let's this young lass make such baseless a set of comments. The answer, the New York Times. Pity.



Labels: [Commentary](#)

WEDNESDAY, OCTOBER 12, 2016

WHAT'S OLD IS NEW AGAIN

The debate on the use of PSA in Pca continues. In a response to a recent [NEJM](#) article, a [renowned researcher concludes](#):

For today, we can conclude on the basis of level 1 evidence² that PSA monitoring, as compared with treatment of early prostate cancer, leads to increased metastasis. Therefore, if a man wishes to avoid metastatic prostate cancer and the side effects of its treatment,³ monitoring should be considered only if he has life-shortening coexisting disease such that his life expectancy is less than the 10-year median follow-up of the current study.² In addition, given no significant difference in death due to prostate cancer with surgery versus radiation and short-course androgen-deprivation therapy, men with low-risk or intermediate-risk¹ prostate cancer should feel free to select a treatment approach using the data on health-related quality of life³ and without fear of possibly selecting a less effective cancer therapy.

Yes, if one has a diagnosed PCa, or a PSA that is indicative of such, with subsequent positive biopsy, chances of not going with mets is not "watchful waiting" but acting.

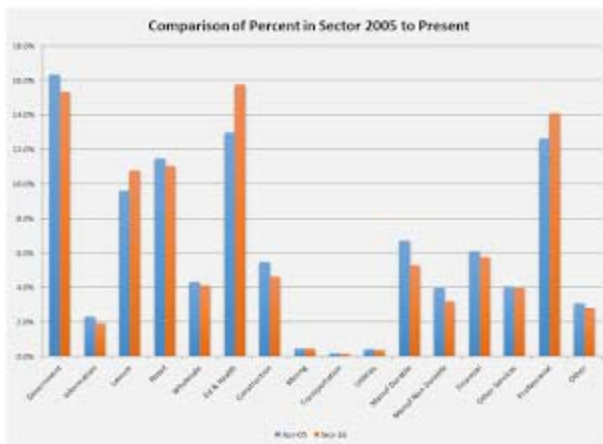


Labels: [Cancer](#)

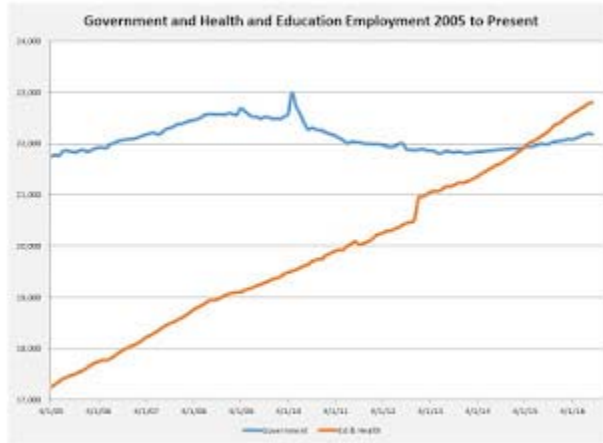
MONDAY, OCTOBER 10, 2016

EMPLOYMENT OCTOBER 2016

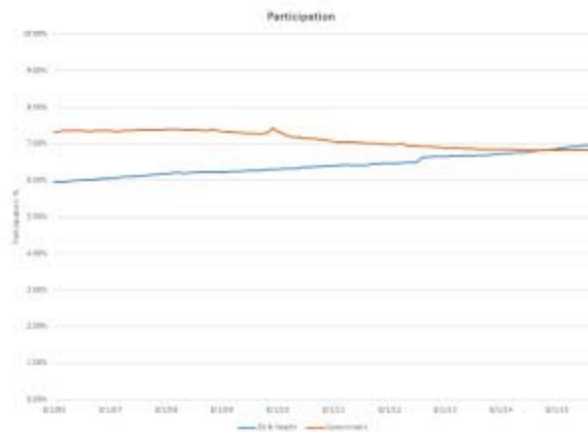
We have been tracking the employment situation after the eight years since the collapse. It frankly is not as good as one suspects. Let's examine some numbers.



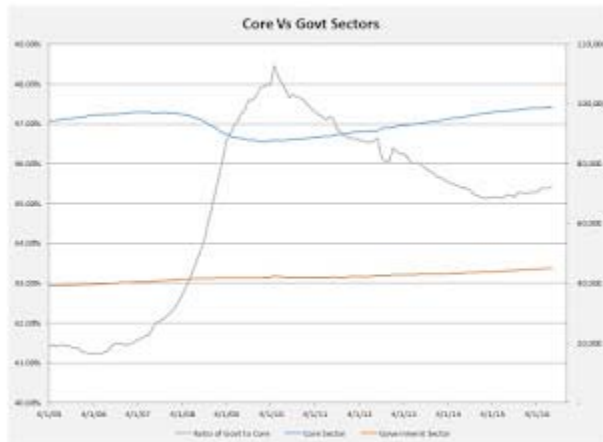
The above is a comparison by sector between 2005 and last month. As we have been noting the higher paying jobs are down and the service and lower paying jobs are up.



The growth in Government supported jobs continues. Government employment is starting a rebound and Health and Education is advancing ever more quickly. Since both sectors are effectively tax payer supported they become a true weight on growth.



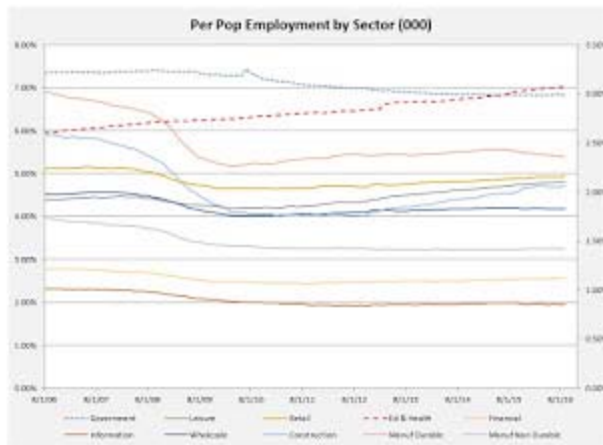
The above is a metric for participation rate which still is decaying. Thus the putative employment numbers are highly skewed.



The Core versus Government sectors are rebounding so that as we noted earlier more people are being supported by fewer.



Sector changes are shown above with Mining taking a massive hit.



The same is shown above.

Overall things really are not getting better despite the verbiage.



Labels: [Economy](#)

TUESDAY, OCTOBER 4, 2016

WHAT BUSINESS IS GOOGLE IN? REDUX

Over the last eight years we have seen Google wander into businesses with great fanfare that frankly they had no core competence in. Google is in the software business, search and OS. Now they tried Nexus, and I was a buyer, early. The unit died promptly and when calling the customer service line you got Valley Speak, Silicon Valley speak. They "shared" my concern but alas

when I sent the unit to the Executive I had worked with on a Presidential Panel, well, never got a reply. Google, you see, does not like people, in my opinion. It likes computers and getting them to do stuff and then getting commercial entities to ride on that stuff and pay them money.

There is a fantastic summary of "Google's Follies" in [ArsTechnica](#) which states:

Google is definitely pushing itself as a hardware company like it never has before, but this is hardly the company's first effort to get into the smartphone hardware business. The first was the Nexus One, which drew iPhone comparisons when it was launched. But low sales almost killed the brand—Eric Schmidt said in 2010 that the Nexus One “was so successful [in helping Android along], we didn’t have to do a second one”—before it was resurrected and pointed at the developer-and-enthusiast niche. The second and more serious effort began in 2011, when Google bought Motorola for \$12.5 billion. After clearing out the old Motorola’s product pipeline, in 2013 and 2014 the company introduced a series of high-end and midrange Moto phones that were critical darlings for their price tags, their focus on fundamentals, and their fast Android updates. These were three non-broken things that Lenovo promptly “fixed” after it bought Motorola from Google for just \$2.9 billion three years later. Google made no mention of its Motorola experiment onstage today, even though the same guy who ran Motorola is now running Google’s hardware efforts. But the sense that all of this has happened before is just one of the contradictions of Google’s new mobile strategy. More importantly, the company’s actions and stated goals contradict one another, to the extent that I wonder just how committed Google is to its hardware plans and, on a related note, just how good its chances of success are.

The author however has forgotten Google Fiber, the ongoing stumble that could clearly have been avoided by a simple conversation with folks who had done this before. Instead they follow a pure tech and then a pure sales led strategy. Unfortunately even if you can build it, and can sell it, for nothing it is a political and operational problem, expertise which seems anathema at Google.



Labels: [Google](#)

MONDAY, OCTOBER 3, 2016

[FIBER, WIRELESS AND GOOGLE](#)

Some decade ago I mentioned to some top folks at Google that fiber to the home was a long and unfruitful hill to climb. Wireless would be the game of the future and those with a license will have a head start. Google bought into Meraki, a mesh WiFi system, and then proceeded to plow ahead with fiber just as we got out. And yes, let Cisco buy Meraki. Between the Franchise and pole attachments, and the massive delays of build outs we have no way we can see that an overbuild of fiber will work. Add to that the new advantages of wireless and well, only big egos with no insight would go forward.

Now it appears as if Google is heading towards wireless but at the 70-80 GHz band. Ooops, another mistake. As [Wired](#) notes:

The spectrum in question—the 70/80 Ghz band—is used by Webpass, the San Francisco

broadband company now owned by Google Fiber (the acquisition closed today). Webpass uses this band to beam an Internet signal to the roofs of apartment buildings and condos, before stringing cables into living rooms. Google wants FCC rules that would allow it to use such technology on a much larger scale. Google Fiber is as a separate company under the umbrella operation called Alphabet, and according to some reports it is under pressure to cut costs—even as it expands its high-speed Internet service and pushes entrenched companies like Verizon and AT&T toward similar services. A faster Internet is good for Google.

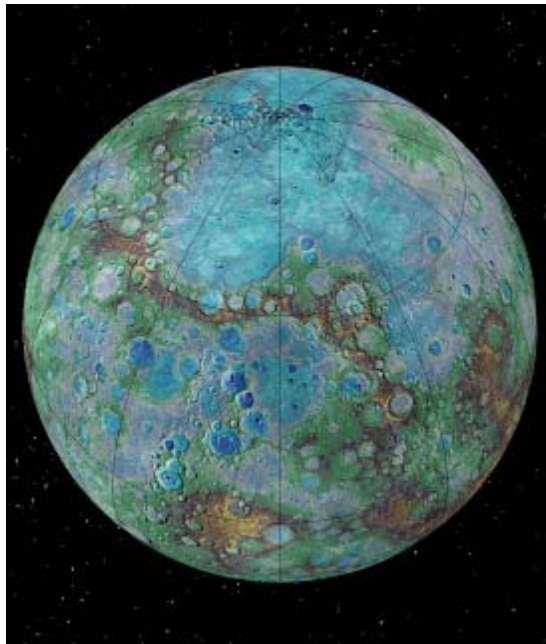
What should be good for Google is growing positive cash flow. This adventure may not be one.



Labels: [Broadband](#), [Google](#)

THURSDAY, SEPTEMBER 29, 2016

[MERCURY](#)



Another pic from [NASA](#). It is always interesting to see what our tax dollars are doing. It is a compelling photo.



Labels: [NASA](#)

WEDNESDAY, SEPTEMBER 21, 2016

[THE VALUE OF PATENTS](#)

Some sixty years ago when I first started some semblance of academic pursuit, I got involved in my first patent discussion. A friend's mother was a telephone receptionist. In those days when you called Mr Smith or Mrs Jones at a company the call went to the switchboard and then to a telephone receptionist, the person who placed the call. Back then these people, all women as far

as I could tell, wore official Bell System issued head gear. It was heavier than a sonar operators ear phones during WW II. After all it was Bell System. These women wanted something lighter and not as destructive to their expensive hair styling. I suspect Bell System engineers were all male and most likely never even noticed their spouses.

Thus one of these women suggested a new head set. I wrote a patent application and then it was suggested we send it to AT&T. Yes, not my idea, but we "trusted" them. We naturally got a letter back saying "thanks but no thanks". Five years latter that very same head set came out from, you guessed it, the Bell System. Coincidence? You guess.

Now what did this teach me? That patents may very well be useless unless you have a large pool of money for lawyers, since any good idea can be copied and unless you can sue and win, if and if, you are wasting time. Might just as well tell the world, get visceral credit and block the big guys patents.

Now why all this old stuff? CRISPRS!

In [Nature](#) they discuss the current battle which we had anticipated. They state:

Much of the focus is on the teams centred at Berkeley and the Broad Institute, whose 'foundational' patents cover a wide swathe of CRISPR–Cas9 applications. Although Berkeley's team filed for a patent first, the Broad opted for an expedited review process, and its patents were granted earlier. The Berkeley team then asked the USPTO to declare a 'patent interference', launching a complicated process to establish who first came up with the invention. Since January, the two sides have been making their case in filings to USPTO patent judges. The Broad asserts that Berkeley's initial patent filing described using CRISPR–Cas9 in prokaryotes such as bacteria, but did not sufficiently describe the procedure in eukaryotes such as mice and human cells. That distinction is important: CRISPR's most lucrative applications are likely to be in medicine, and several biotechnology companies have already licensed patents from either Berkeley or the Broad. Berkeley argues that the application of CRISPR–Cas9 to eukaryotic cells was obvious and that "persons of ordinary skill", such as a postdoc with relevant expertise, could have made the leap. Berkeley points to the swift success of several teams — led by Doudna; Zhang; Church (at Harvard Medical School in Boston, Massachusetts); and genome engineer Jin-Soo Kim at the Institute for Basic Science in Seoul — that applied CRISPR to human cells. The Broad countered that these scientists are all leaders in their field and could hardly be considered 'ordinary'.

Yes this is a proverbial "p.....g" contest. Broad (MIT and Harvard) versus Berkeley (California). And in the middle the USPTO. Now the PTO is not the brightest set of bulbs on the rack, especially when it comes to litigation. This is Administrative law and we don't have a bunch of Harvard and Stanford lawyers. They are patent types. That means GS-11 thru 13s.

How this will end is uncertain. What will be of interest is how the Nobel Committee handles this.



Labels: [Academy](#), [Patents](#)

TUESDAY, SEPTEMBER 20, 2016

MICROSOFT AND CANCER

From the folks who brought Windows 10 upgrade we now have it that they want to cure cancer. From [Microsoft](#) they say:

Microsoft's research labs around the world, computer scientists, programmers, engineers and other experts are trying to crack some of the computer industry's toughest problems, from system design and security to quantum computing and data visualization. A subset of those scientists, engineers and programmers have a different goal: They're trying to use computer science to solve one of the most complex and deadly challenges humans face: Cancer. And, for the most part, they are doing so with algorithms and computers instead of test tubes and beakers.

They continue:

One approach is rooted in the idea that cancer and other biological processes are information processing systems. Using that approach the tools that are used to model and reason about computational processes – such as programming languages, compilers and model checkers – are used to model and reason about biological processes. The other approach is more data-driven. It's based on the idea that researchers can apply techniques such as machine learning to the plethora of biological data that has suddenly become available, and use those sophisticated analysis tools to better understand and treat cancer. Both approaches share some common ground – including the core philosophy that success depends on both biologists and computer scientists bringing their expertise to the problem.

Trusting these folks to cure anything is highly unrealistic. Just try seeking help on a Microsoft site. No way. It was not until Google came along that people could wend their way through the horrific complexity of Microsoft. Customer friendly? Not. So guess how they would treat patients!

Just a simple example. Almost 2 months after the Anniversary W10 release, one cannot use their H.264 cameras, a global standard. Would Microsoft perhaps blind the world! How could anyone realistically trust these people to do anything in medicine!



Labels: [Cancer](#), [Microsoft](#)

MONDAY, SEPTEMBER 12, 2016

TRIGGER WARNINGS



The [NY Times](#) has give space to some student at U Chicago to protest the letter from some Dean there about not paying deference to "trigger warnings".

As this poor young thing states:

A safe space is an area on campus where students — especially but not limited to those who have endured trauma or feel marginalized — can feel comfortable talking about their experiences. This might be the Office of Multicultural Student Affairs or it could be Hillel House, but in essence, it's a place for support and community. This spring, I was in a seminar that dealt with gender, sexuality and disability. Some of the course reading touched on disturbing subjects, including sexual violence and child abuse. The instructor told us that we could reach out to her if we had difficulty with the class materials, and that she'd do everything she could to make it easier for us to participate. She included a statement to this effect on the syllabus and repeated it briefly at the beginning of each class. Nobody sought to "retreat from ideas and perspectives at odds with their own," as Dean Ellison put it in the letter, nor did these measures hinder discussion or disagreement, both of which were abundant.

Now back in the late 50s and early 60s most of us who went to College went to get a job. Thus I spent time on Advanced Calculus, Thermodynamics, Organic Chemistry, Electromagnetic Theory and Applications. I even too Philosophy and Logic. I managed to go through tend years of various studies without a single trigger warning. Then I got a job!

Perhaps the issue is that if these young folks took say Accounting, Finance, Biochem, then there would be no need for such trigger warnings and they would be more terrified of making the grade. You see your opinion has zero value in analyzing a Banach Space or a Wiener Process, not that guy in New York who spells his name differently any how.

Trigger Warnings are a result perhaps of wasting your time on things that you would be better off just watching on your iPhone.



Labels: [Academy](#)

THURSDAY, SEPTEMBER 1, 2016

[FCC 600 MHZ SPECTRUM AUCTION](#)

Watching the Kentucky Derby is worth the time. Nice clothes, good horses, and the outcome is generally uncertain. The race is a simple thing. A bunch of fast horses, good riders, and round track. The first across wins. Simple.

In contrast the FCC auctions are now one of the most bizzare systems ever. Let those academics loose and you get backward and forwards low and high and so forth. Imagine a Kentucky Derby where you run backwards the first time around, then the top ten horses run forward, but only after three months. Oh yes and the riders may change mid stream and even the horse may be replaced by a camel if it is Thursday.

The current [FCC 600 MHz auction](#) is worth a watch. The players are the big guys are their surrogates. You see, we condemn the Russian oligarchs but we have our own, the incumbents. Thus even Google does really play here. This is despite their long awakening to the problems with fiber.

It is worth watching this facade, a tax collection process of tens of billions into the Government coffers spent even before it is collected, many times over.



Labels: [Broadband](#), [FCC](#)

[YIKES, ANOTHER POOR ISP](#)

I have been a customer of Verio for well over fifteen years. They got bought by some conglomerate (see this [Site](#)) and some moron decided to switch all servers the day before the Labor Day weekend. Guess what? Crash....

Then you try to get some support....well it is 12 hours off in India and they keep telling me what a wonderful day it is...it is 3AM in Delhi! What day?

So off we go for a ten day set of business meetings trying every configuration under the sun to get and hopelessly try to send emails.

There is a fantastic market here for some company willing to render service. All I wanted was mail in and mail out. Then they also deleted all my history. And not a single warning...and we have had dozens of sites hosted on them and hundreds if not thousands of emails.

Have this folks no shame? In fact try and find out who they even are! Thank God for Google....

There used to be a time when quality was not just some abstract concept but a way of doing business. Not any longer.

No wonder one of the Candidates had their own server...who would trust the Government to secure anything...and the commercial folks are now even worse! It was probably a wise move after all.

I gather that the new parent is [Endurance](#) in Burlington Mass. A massive collection of poorly inter-managed ISPs with what appears to be an ever growing collection of disgruntled customers.



Labels: [Commentary](#)

[UNINTENDED CONSEQUENCES](#)

It is always amazing to see how our Government has no idea what unintended, I hope, consequences are of the massive sets of rules and regulations.

Medicare under CMS has the Social Security number of the individual on the card. It is your ID number once you fall under their control. It is also a source of consumer fraud. Especially in Healthcare, when staff who are not background checked, under paid and not bonded rip off the patients.

So along comes Government and says "turn on a dime" and change everything. Like SSA who decided every 6%+ person had a smart phone with text messaging and the costs for that were zero, after all the Government gives free ones away to the "underprivileged" and to Government employees, so why not the taxpayers as well, and this change blocked access to SSI data sites.

Now with this "security" change it will cost billions to change data in physician offices, insurers, third party processors, pharmacies and the list goes on. It is the OCD 10 for Medicare payments.

As [Modern Healthcare](#) notes:

The CMS is getting to work on replacing Social Security numbers as identifiers for 150 million Medicare recipients, both living and dead. By the end of 2019 the agency intends to use randomly generated identifiers instead of the health insurance claim number, composed of a Social Security number plus one or two letters. The proposed new ID will have seven numeric and four alphabetical characters. This is happening because Congress, in the 2015 Medicare Access and CHIP Reauthorization Act, gave the CMS four years to issue cards to Medicare beneficiaries that don't have Social Security numbers printed on them. The provision is intended to make seniors less vulnerable to identity theft. Some industry stakeholders, however, are already griping that the way the Obama administration is carrying out the mandate will further stratify the flow of healthcare data. The planned conversion requires reprogramming 75 complex legacy information technology systems that the CMS and its contractors use to process Medicare claims, according to the agency. It would also mean updating hundreds of thousands of private-sector computers that handle healthcare claims. The users will include hospitals, physician practices, claims clearinghouses, billing companies, post-acute providers and Medicare Advantage carriers. A CMS spokesman said the agency would solicit input from the industry "at various points throughout the project to ensure a smooth transition that maintains beneficiaries'

access to care while avoiding disruptions to the payment process.”

First this applies to the 50 million alive plus 100 million dead. Yes dead! The cost would be astronomical.



Labels: [Government](#), [Health Care](#)

WEDNESDAY, AUGUST 31, 2016

[UNIONS AT THE ACADEMY](#)

Let's totally destroy the University in the United States! How? Make all Grad students join a Union! Take away any merit based rewards, make every student the same...they are not. As the [Harvard Crimson](#) states:

Overturning precedent, the National Labor Relations Board ruled that student assistants at private universities are considered employees with collective bargaining rights, a move that would force Harvard to legally recognize an elected graduate student union. The 3-1 decision handed down Tuesday marks a significant milestone for the unionization effort at Harvard, which began in April 2015 and has since grown in size and sophistication despite opposition from University administrators. However, the ruling has implications far beyond Harvard and comes as debate over the issue of graduate student unionization has roiled campuses across the country. The decision does not only affect Ph.D. students or graduate students; the NLRB ruled that employees under a collective bargaining unit could include undergraduate teaching assistants and research assistants as well. Harvard's unionization movement, the Harvard Graduate Students Union-United Auto Workers, ramped up efforts over the last year to push Harvard to recognize a graduate student union and has already gained more than enough support among graduate students to call for a union election.

The Academy is based on merit and performance. It is not a Ford assembly line. Now the useless grad student gets the same rights as a Nobel Prize winner. Next we will see Washington forcing unions on brain surgeons! Talk about dumbing down!



Labels: [Academy](#)

WEDNESDAY, AUGUST 31, 2016

[IT'S AMAZING TO SEE PEOPLE LEARN THINGS](#)



As a follower of the CATV and Telco critic on [Backchannel](#) I was amazed to see that she has finally grasped an element of reality, namely pole attachments. There are lots of hidden costs in building fiber and competing with the incumbents. Franchise is one, and a costly one. Pole attachments is another. To get that fiber from point A to point B you have to get some right of way. Been that way for centuries, it relates to property law, an old English concept that one would assume a lawyer would have some understanding of.

You see you have no right to the poles, you have to negotiate, with the Telco or Power company. You have to do pole counts, rights of way negotiations etc.

Our young newcomer to reality notes:

*But many cities don't control their own poles. In some areas, poles are controlled by utilities, or even telecom companies. Anyone hoping to string fiber in those places faces two nightmarish, indefinite periods of delay and uncontrolled costs: first getting an agreement in place with the pole owners, and then getting the poles physically ready for a new wire. We'll call these steps **Swamp One and Swamp Two**.*

Well that really is NOT new. Towns make money from the poles, however they are owned by third parties. So how can they "control" something they have no property right to? First year law school anyone?

She continues:

***Swamp One: Attachment.** At the moment, the FCC gives regulatory assistance ("pole attachment rights") in negotiations with utility pole owners only to cable TV providers, companies selling internet access, and phone companies. The FCC's assistance comes in the form of mandatory deadlines and set formulas for calculating fees to be paid to the pole owner.*

For anyone in the real world who had done this the process is rife with delays. And as an old colleague once said to me; "*Delay is the deadliest form of denial!*" They do not say no, they just kick the can down the street! And Google thought they would change this world? Told them no fifteen years ago, but I guess if you have a big ego and lots of money then Newton's law do not apply to you!

She continues:

Swamp Two: Make-Ready. Even if a city wrestles into place an agreement with pole-owners that allows it to string fiber on their poles, or uses a company that has pole attachment help from the FCC, there's still a gruesome, unpredictable process left to get the pole ready for a new attachment.

This is just a corollary to the first problem. First get a pole attachment agreement and second wait.

This is a prime example of why wireless is the way to go. But this person seems to just want to attack the mountain hoping somehow that it will collapse and she can get herself and all her minions to the promised land. Fat chance!



Labels: [Broadband](#)

SATURDAY, AUGUST 27, 2016

[IF ALL ELSE FAILS LISTEN TO THE CUSTOMER](#)

Government works well, right? Well just look at the Social Security Admins new Internet Security scheme. They call it "multifactor authentication". Simply when you logged in with your ever changing password you must also have a mobile phone with text messaging. Not an email connection, but a decade old text system which costs you about \$0.25 per message at least. Then they, SSA, sends you an additional authentication key, which you then enter into your SSA web site.

Now there is the Mini Mental Exam, that wonderful test we use to test old folks for mental acuity. This 80 year old comes in while under a dozen mind altering meds and we ask them to count backwards from 100 by sevens! No child currently in a Public School with no meds could do this, but we want Grand Ma to do it. Now we want grandma to use a multi transactional random key entry system, like arming a nuclear warhead, to get on their SSA site!

As [SSA has stated](#):

On July 30, 2016, we began requiring you to sign into your my Social Security account using a one-time code sent via text message. We implemented this new layer of security, known as "multifactor authentication," in compliance with a Presidential executive order to improve the security of consumer financial transactions. SSA implemented the improvements aggressively because we have a fundamental responsibility to protect the public's personal information. However, multifactor authentication inconvenienced or restricted access to some of our account

holders. We're listening to your concerns and are responding by temporarily rolling back this mandate. As before July 30, you can now access your secure account using only your username and password. We highly recommend the extra security text message option, but it is not required. We're developing an alternative authentication option, besides text messaging, that we'll begin implementing within the next six months. We strive to balance security and customer service option...

Frankly one should ask what moron came up with this approach. Most SSI recipients are on limited incomes, many have limited mental faculties to deal with this, and then we get a procedure that is not even used for launch codes! Why? Because they can't keep their own system secure. So what do they do? Put the burden on the customer. No business would survive with this type action.

One wonders where they get the people who run these organizations? Take a look and you would be shocked, or perhaps not. If you think the Presidential race is an issue you really should look behind the curtains at the million or so Federal employees.

Let's see what SSA comes up with next!

But one should read the comments on the SSA site referenced above. The individual in charge of this fiasco was Jim Borland, Assistant Deputy Commissioner, Communications. [People said such things as:](#)

Evidently you're committed to making it impossible to use My Social Security. Extra burdens do NOT make things more secure. Thanks for nothing.

There are many simpler and more effective schemes. However security starts with the team that operates the servers and comm interfaces. That means the SSA. Specifically the above named person. Pushing it off to the "customers" is just reckless and abusive. But alas, it is our Government. Could it be worse? Try the EU.



Labels: [Government](#)

FRIDAY, AUGUST 26, 2016

[THE GANG WHO CAN'T CODE STRAIGHT!](#)

Microsoft is at it again with W10. As [Ars Technica](#) reports:

As if that weren't bad enough, Microsoft has pushed out a bad update that breaks important PowerShell functionality. The update, KB3176934, is the latest cumulative update for the Anniversary Update and was released on August 23. It breaks two key PowerShell features: Desired State Configuration (DSC), which is used to deploy configurations to systems, and implicit remoting, a feature that makes it easier to use PowerShell commands that are installed on remote systems. The reason that these things have broken is remarkable. The Cumulative

Update doesn't include all the files it needed to. One missing file breaks DSC; a second missing file breaks implicit remoting. A revised package that includes these missing files will be released on August 30; although Microsoft recognizes that the problem exists, it isn't apparently important enough to rush out a fix, so it'll have to wait for the next Tuesday.

Yep, a bad and broken update causing billions of dollars of down time!

[Microsoft](#) notes:

Known issues in this update

Issue 1

After you apply this update and then start a remote Windows PowerShell session, the functionality to import a module (implicit remoting) no longer works.

Issue 2

After you apply this update, PowerShell Desired State Configuration no longer works. Users will receive an "Invalid Property" error message when they run any DSC operation.

And then follow this to [Microsoft](#):

On August 23, Windows update KB3176934 released for Windows Client. Due to a missing .MOF file in the build package, the update breaks DSC. All DSC operations will result in an "Invalid Property" error. In addition, due to a missing binary in the build package the update breaks PowerShell implicit remoting. Implicit remoting is a PowerShell feature where PowerShell commands work on a remote session instead of locally. Specifically, importing a remote session no longer works.

One has to ask if there are any adults in Seattle. Perhaps it is some form of massive substance excess. The solution starts with a new CEO who has the customer in mind! Where is the Board, that is the problem. There will be massive class action suits sooner or later!



Labels: [Microsoft](#)

THURSDAY, AUGUST 25, 2016

ROCKPORT 2016

Just for those who want a moment of serene quiet. The wave lapping on the sand and the sun setting to the west behind the harbor in Rockport, MA.



Labels: [Commentary](#)

WEDNESDAY, AUGUST 24, 2016

MICROSOFT AND THE WORLD

The gross disrespect of their customers continues. As [Tech Republic](#) reports:

The Windows 10 Anniversary Update, which began rolling out on August 2, came with some unfortunate side effects for some users—it killed their webcam. A Windows employee has addressed the issue, but it looks no fix will be available until September. The problem was initially noted by several users a few days after the update went live. Basically, this issue renders USB webcams and network-connected webcams inoperable in programs like Skype or Open Broadcaster Software (OBS), among others. The update also caused some devices to unintentionally freeze up. The reason for this behavior seems to rest in the changes that were made to how the OS access the camera in the Anniversary update. Before the update, only one application could access the camera at a time. With the Anniversary update, also known as version 1607, a new service called the Windows Camera Frame Server allows for multiple connections at once, and that's causing some problems.

Yep! September, but don't count on that! All those billions of dead web cams, watch Skype just die on the vine. The will do nothing till September, most likely December. This is in my opinion abject evil. Where are the tort lawyers. This could become the world's largest class action suit!

It would serve Microsoft right to just disappear! Could you imagine what would happen if this were a drug company! Is there a Board somewhere at this useless company!



Labels: [Microsoft](#)

FRIDAY, AUGUST 19, 2016

[THE MORONS AT MICROSOFT!](#)

For those who may have noticed, Logitech and other cameras have stopped working on the 1607 W10 release. Why? Now [ArsTechnica](#) gives a great rendition.

The version 1607 frame server, however, only supports uncompressed data. Microsoft's rationale for this is that most applications receiving compressed data will have to immediately uncompress that data in order to actually manipulate it. With the new camera-sharing capability, this means that multiple applications could be performing the MJPEG-to-YUV or H.264-to-YUV conversion simultaneously. It's more efficient in this situation to simply read YUV data from the camera in the first place and skip those extra conversions. H.264 adds additional complexity: applications can negotiate specific compression parameters with the camera to alter the compression quality on the fly. This isn't an issue when an application has exclusive control of the camera but becomes a problem when two different applications try to use different parameters with the same camera.

They continue:

By preventing the use of the compressed formats, Microsoft avoided these issues. But it came at a great cost. Applications demanding or expecting support for MJPEG or H.264 data have stopped working. This could manifest in strange ways. I have a Logitech C920 camera, and I use it with Skype. Skype progressively enhances video quality; a connection may start out using a lower quality, and it'll then be upgraded as bandwidth and processor usage settle down. What I found was that an initial video call would connect, with the application using something like 640×480 YUV data. After a few seconds, however, Skype would try to upgrade the call to 720p or 1080p video. This should work, and in old versions of Windows, was seamless. But with the Anniversary Update it means switching from an uncompressed data stream to a compressed stream—and so it fails. The video just freezes after a few seconds of correct operation.

Yes indeed, the folks in Seattle are totally clueless. H.264 is a compression technique used, you guess it, everywhere! For years! You think it would have made its way to Seattle. These folks are doomed! Doomed! If this keeps up we can all switch back to Windows 95, watch for the hourly reboot, and then load a Linux OS.

If there people worked for me they would be history! Along with the CEO who apparently does not give a damn about the customers!

We need a Harvard Business School Case Study on this one, now!



Labels: [Microsoft](#)

FRIDAY, AUGUST 19, 2016

USPSTF AND WHAT HAPPENS NOW?

The USPSTF or U.S. Preventive Services Task Force back in 2011 made the problematic determination based on what is in my and many others' professional opinions flawed data the recommendation that men no longer get PSA tests. The result? Apparently a massive drop in the detection of early stage prostate cancer. What does that mean? Has for some strange reason the incidence of PCa just stopped, slowed down, disappeared Or are we awaiting a time bomb of massive proportions of men having metastatic cancers. One need just read a 1950s version of Harrison or Cecil to see. Men will just show up with terminal bone mets.

[Science Daily](#) reports on a [JAMA](#) study:

From 2012 to 2013, the localized/regional-stage prostate cancer incidence rates per 100,000 men declined from 356.5 to 335.4 in men 50 to 74 and from 379.2 to 353.6 in men 75 and older, according to the study. The authors note the decrease from 2012 to 2013 was smaller than that from 2011 to 2012 (6 percent vs. 19 percent). Previously reported findings indicate PSA testing rates decreased significantly between 2010 and 2013. Other factors that could contribute to the decline in incidence rates for early stage prostate cancer include changes in the prevalence of unknown risk factors and preventive measures. "In conclusion, the decrease in early-stage prostate cancer incidence rates from 2011 to 2012 in men 50 years and older persisted through 2013 in SEER registries, albeit at a slower pace. Whether this pattern will lead to a future increase in the diagnosis of distant-stage disease and prostate cancer mortality requires long-term monitoring because of the slow-growing nature of this malignant neoplasm," the research letter concludes.

As the JAMA report concludes:

In conclusion, the decrease in early-stage prostate cancer incidence rates from 2011 to 2012 in men 50 years and older persisted through 2013 in SEER registries, albeit at a slower pace. Whether this pattern will lead to a future increase in the diagnosis of distant-stage disease and prostate cancer mortality requires long-term monitoring because of the slow-growing nature of this malignant neoplasm.

I think we may already know the answer. As part of our "new" health care system we may very well be just letting the "old men die". Pity!



Labels: [Cancer](#), [Health Care](#)

SPECTRUM

The FCC is auctioning off 126 MHz in the 600 MHz band. As noted in my recent critique to that attorney who seems to be technically clueless in my opinion, 600 MHz bends around corners! And 126 MHz at 100 bps/Hz and a reuse factor of 10-50 in a multibeam environment one gets a phenomenal capacity, in basements!

As noted in [Telegeography](#):

According to the Federal Communications Commission (FCC), the 600MHz Broadcast Television Spectrum Incentive Auction ('Auction 1002'), which commenced on 16 August, has generated bids worth USD10.588 billion after five rounds of bidding. Round six is scheduled to commence today (Friday 19 August). As expected, spectrum allocations covering New York and Los Angeles have attracted the highest bids thus far, followed by the likes of Chicago, San Francisco, Baltimore-Washington, DC and Philadelphia. Interest in smaller markets has already began to wane, however, sources have noted. The current Auction 1002 'Forward Auction' was preceded by a 'Reverse Auction' between the FCC and the TV broadcasters that held the 600MHz spectrum. This process saw the 'clearing cost' for 126MHz of spectrum established at USD86.423 billion, seriously exceeding analyst expectations. If that figure is not met in the Forward Auction, the FCC will reduce the amount of spectrum it will free up and resume bidding with TV broadcasters in a second stage of the Reverse Auction.

The FCC has a rather obscure auction process, backward and forward, but as of now it has topped \$11 billion.

[Fierce Wireless](#) states:

The generic license blocks offered in the initial stage during the forward auction under this band plan will consist of a total of 4030 "Category 1" blocks (zero to 15 percent impairment) and a total of 18 "Category 2" blocks (greater than 15 percent and up to 50 percent impairment). The FCC said approximately 97 percent of the blocks offered for the forward auction will be "Category 1" blocks, and 99 percent of the "Category 1" blocks will be zero percent impaired. These figures likely will cheer wireless carriers and other auction bidders since unimpaired spectrum can be used more quickly.

This can be a game changing play. Watch the process.



Labels: [Broadband](#), [FCC](#)

THURSDAY, AUGUST 18, 2016

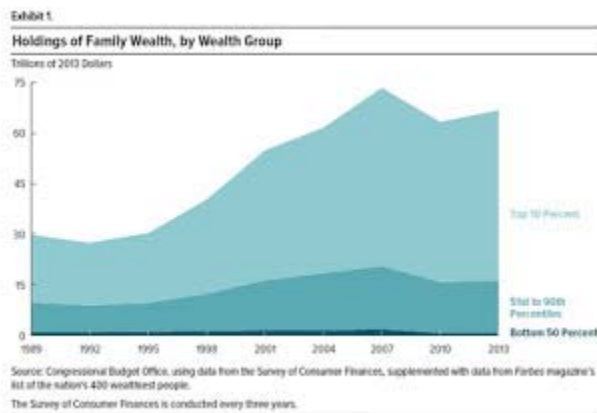
[WEALTH DISTRIBUTION](#)

The [CBO](#) has an interesting report on wealth distribution. They note:

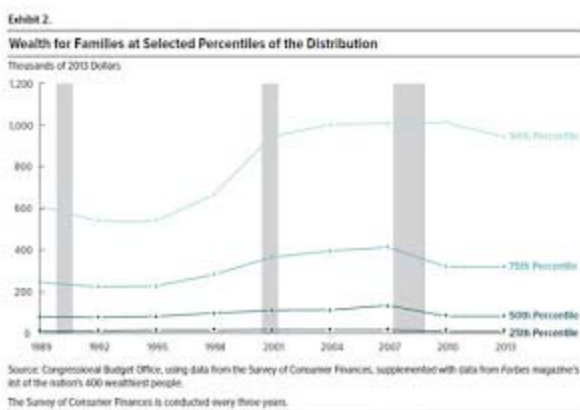
In 2013, aggregate family wealth in the United States was \$67 trillion (or about four times the nation's gross domestic product) and the median family (the one at the midpoint of the wealth distribution) held approximately \$81,000, CBO estimates. For this analysis, CBO calculated that measure of wealth as a family's assets minus its debt. CBO measured wealth as marketable wealth, which consists of assets that are easily tradable and that have value even after the death of their owner. Those assets include home equity, other real estate (net of real estate loans), financial securities, bank deposits, defined contribution pension accounts, and business equity. Debt is nonmortgage debt, including credit card debt, auto loans, and student loans, for example. In 2013, families in the top 10 percent of the wealth distribution held 76 percent of all

family wealth, families in the 51st to the 90th percentiles held 23 percent, and those in the bottom half of the distribution held 1 percent. Average wealth was about \$4 million for families in the top 10 percent of the wealth distribution, \$316,000 for families in the 51st to 90th percentiles, and \$36,000 for families in the 26th to 50th percentiles. On average, families at or below the 25th percentile were \$13,000 in debt.

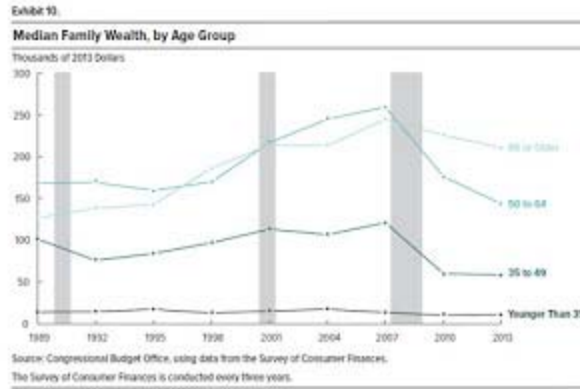
They present the following Figures:



The above is the relative distribution by percentile. It appears that the 90s sent many sky high.



The above is a more selective view.



And the above by age. So guess who is supporting whom?



Labels: [Economy](#)

WEDNESDAY, AUGUST 17, 2016

ALMOST TWENTY FIVE YEARS AGO

From a filing for Pioneer Preference in May 1992 I wrote the following:

From FCC Pioneer Preference May 3 1992

Telmarc Telecommunications

KEY TECHNOLOGICAL ELEMENTS

5. The following technological approaches will be deployed, integrated, tested, and optimized to determine their effectiveness in providing the specified service quality goals.

(1) Adaptive Network Management: Adaptive Network Management, ANM, is a system that uses in-situ sensors to monitor the power and signal quality throughout the network. The number of sensors will greatly exceed the number of cell locations. This set of dynamic measurements will then be used in a feedback schemes to adaptive change the characteristics of the cell transmit power and other characteristics to maximize the service quality. Specifically, the Petitioners have individually designed a proprietary network management system that uses the in-situ sensors that monitor all key signal elements. These elements are power, frequency, interference, noise, and other significant signal parameters. The system then transmits these signals back to a central processor which then generates an optimal signal to control the cell site transmission characteristics, such as power, frequency and other factors. The overall objective is to optimize the system performance from the users perspective.

(2) Gateway RF Digital Front Ends: A broadband, digital front end will be used to act as a

gateway to interface the air interfaces of CDMA, TDMA and other access methods through the same cell and in the same frequency band. This system will permit multiple air interfaces to be gatewayed into the same network access point thus reducing the need for a single standard, and increasing the ability to provide a national network. This front end has been developed by Steinbrecher Assoc, of Woburn, MA. The system element allows, through its use of large gain bandwidth product front end and fully digital RF processing, the ability to handles many different and simultaneous multiple access methods, such as TDMA and CDMA. This ability goes to the heart of interoperability and standards.

(3) CDMA Backbone Network: The Petitioner will use a CDMA air interface and access methodology. The Petitioner fully supports the efforts of QUALCOMM in their development and implementation of CDMA in the 800 MHz band and their recent movement of this to the 1.85-1.90 GHz bands. Although there is no uniqueness in the use of CDMA, the Petitioners argue that this technology has specific characteristics that allow for the delivery a maximum benefit to the public.

(4) Co-Located Distributed Switch Access: Unlike other proposed schemes which use redundant MTSO accesses, this trial will focus on Central Office Co-Location methods that reduce capital and operating cost redundancies. The co-location approach, will minimize access line costs and eliminate the need for a MTSO. The adjunct processors at the Central Offices will be interconnected by a high speed bus to allow for adequate control and call hand-off. Co-Location is achieved via the intelligence that is contained in the CDMA cell sites and the adjunct processor distribute communications and processing capabilities. The fundamental existence of this capability was demonstrated by QUALCOMM in their CDMA trial, albeit not in the Co-Location context. The QUALCOMM QTSO was in effect a no Co-Located adjunct. The Petitioners propose to request access from the PUC in the Commonwealth of Massachusetts to access New England Telephone on a Co-Locations basis. The public good achieved is through the reduction in costs and the ability to use existing capital assets provided by the LECs. The uniqueness of the Petitioners proposals are the fact that extensive use of adjuncts will be made in the system operation.

(5) Adaptive Beam Forming Phased Array Technology: One of the current problems with a cellular systems will be the use of broad beam antennas and the inability to provide additional antenna gain on both transmit and receive to the individual portables. With the use of adaptive beam forming antennas, the service to lower power portables may be improved. The Petitioners approach will include such capabilities. Time dynamic control of these multiple bean antennas will permit higher localized gain on portables, which will in turn allow for lower transmit power and thus longer portable battery life. The Petitioners have been discussing the use of the technology developed at the Massachusetts Institute of Technology's Lincoln Laboratory in this area.

All of the above are now becoming a reality in wireless. Timing is everything, so is living long enough!



Labels: [Biodiversity](#)

[MICROSOFT, WINDOWS 10 AND PRIVACY](#)

The [EFF](#) has a great piece on the lack of privacy in W10 and more importantly the loss of any form of control.

They note:

The trouble with Windows 10 doesn't end with forcing users to download the operating system. By default, Windows 10 sends an unprecedented amount of usage data back to Microsoft, and the company claims most of it is to "personalize" the software by feeding it to the OS assistant called Cortana. Here's a non-exhaustive list of data sent back: location data, text input, voice input, touch input, webpages you visit, and telemetry data regarding your general usage of your computer, including which programs you run and for how long. While we understand that many users find features like Cortana useful, and that such features would be difficult (though not necessarily impossible) to implement in a way that doesn't send data back to the cloud, the fact remains that many users would much prefer to opt out of these features in exchange for maintaining their privacy.

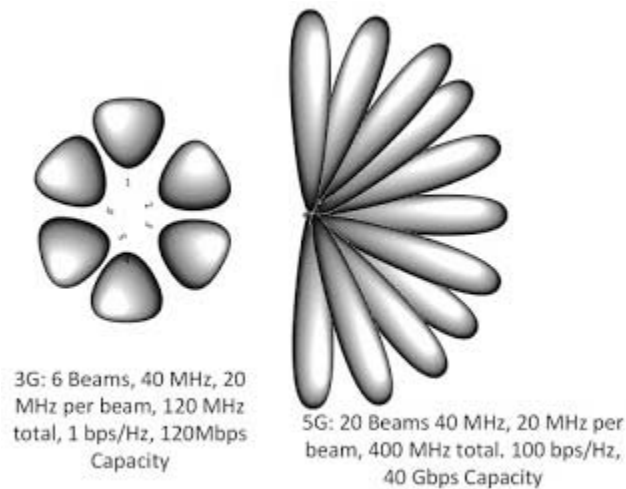
And while users can opt-out of some of these settings, it is not a guarantee that your computer will stop talking to Microsoft's servers. A significant issue is the telemetry data the company receives. While Microsoft insists that it aggregates and anonymizes this data, it hasn't explained just how it does so. Microsoft also won't say how long this data is retained, instead providing only general timeframes. Worse yet, unless you're an enterprise user, no matter what, you have to share at least some of this telemetry data with Microsoft and there's no way to opt-out of it.

Thus Microsoft can track your every move. Worse however is that Microsoft single-handedly can block you emails to those who use MS emails such as hotmail. Thus not only do they have potential access to any and all of your emails they also decide who you may communicate with. And you will never know this. Namely if MS decides for reasons only known to them that the sender's email is unacceptable they then block it. The MS email user will never know that it was blocked. The blocked email sender must go through multiple hoops to the extent of threatening litigation to free up the connection.

Overall in my opinion and based upon my experience the world would be a lot better with an alternative, soon!



Labels: [Microsoft](#)

MORE THOUGHTS ON WIRELESS

Wireless can work in amazing ways. Just consider the above. In classic cellular world we would have say 6 beams, over 360 degrees, or six 60 degree beams. Each beam would be say 20 MHz of a 40 MHz spectrum available, and each adjacent beam would have a different 20 MHz, alternating. Thus using a classic QPSK system say for even 3G we have 1 bps/Hz and in 40 MHz we have say 120 Mbps capacity. Now for 5G, we have OFDM and we have multi beam antennas. Here we have 20 beams, and 100 bps/Hz. due to OFDM and higher EIRP per beam, and we get 40 Bbps per 40 MHz!

That is only half the tale. The other half is that the data, say video, is being compressed at higher and higher amounts.

Thus as we expand capacity we are compressing content! There are of course even more ways to manipulate this process.

In a [Nature](#) article the author makes the following statement:

The most advanced commercial networks are now on 4G, which was introduced in the late 2000s to provide smartphones with broadband speeds of up to 100 megabits per second, and is now spreading fast. But to meet demand expected by the 2020s, say industry experts, wireless providers will have to start deploying fifth-generation (5G) technology that is at least 100 times faster, with top speeds measured in tens of billions of bits per second. The 5G signals will also need to be shared much more widely than is currently feasible, says Rahim Tafazolli, head of the Institute for Communication Systems at the University of Surrey in Guildford, UK. "The target is how can we support a million devices per square kilometre," he says — enough to accommodate a burgeoning 'Internet of Things' that will range from networked household appliances to energy-control and medical-monitoring systems, and autonomous vehicles (see 'Bottleneck engineering').

Well given the simplistic example above the tools to do this are readily available. They have been known for several decades already, only now can silicon do this. The author continues:

MIMO is already used in Wi-Fi and 4G networks. But the small size of smartphones currently limits them to no more than four antennas each, and the same number on base stations. So a key goal of 5G research is to squeeze more antennas onto both. Big wireless companies have demonstrated MIMO with very high antenna counts in the lab and at trade shows. At the Mobile World Congress in Barcelona, Spain, in February, equipment-maker Ericsson ran live indoor demonstrations of a multiuser massive MIMO system, using a 512-element antenna to transmit 25 gigabits per second between a pair of terminals, one stationary and the other moving on rails. The system is one-quarter of the way to the 100-gigabit 5G target, and it transmits at 15 gigahertz, part of the high-frequency band planned for 5G. Japanese wireless operator NTT DoCoMo is working with Ericsson to test the equipment outdoors, and Korea Telecom is planning to demonstrate 5G services when South Korea hosts the next Winter Olympics, in 2018.

As noted above the MIMO function can be at the cell site not at the end user device. Thus the above argument is a straw man at best. At worst it may be a gross misrepresentation.

On comment on this article states:

Unfortunately, this article is unsound and should be withdrawn. Currently and for many years, congestion on the Internet backbone and most local broadband in the developed world is extremely rare. They are almost never a bottleneck, especially the backbone. While traffic has gone up, as noted, Moore's Law has brought down the cost of carrying bits at about the same rate. This has been established by, among others, As ... notes, the only evidence of congestion in the article (except local like a convention center) is a failure of HBO to meet demand. This is almost certainly because HBO didn't buy enough capacity, not that the Internet couldn't handle the volume. I hate denigrating the work of another writer in these tough times, but this one is so misleading it should be retracted to get errors out of the public discussion

The above is in my opinion spot on. Perhaps Nature should stick to genes and molecules and leave the engineering to those who do or have done it for a living.



Labels: [Broadband](#)

SATURDAY, AUGUST 13, 2016

[WIRELESS V FIBER](#)



There have been some recent moves in expanding wireless. Fiber is still fiber. Let us examine the differences and try to explain to some people what the facts are.

Recently in Backchannel^[6] one of the writers, a lawyer I believe by calling, has made statements which in my opinion and my experience are not just wrong, they a truly outright apparent fabrications based on nothing that is in my opinion acceptable to those with even a modicum of competence.

Let me first restate some bona fides. Besides a PhD in EECS from MIT in communications, I then added some fifty years of design and deployment experience in wireless and fiber. One need look no further than a list of hundreds of papers on the topic. I have built out fiber in about twenty countries and frankly found the US the most difficult due to Franchise rules and pole attachment regulations. The incumbents in the US have a permanent barrier to entry for any new entrant. Put that aside for the moment.

Let us first compare fiber and wireless.

I. Fiber

Fiber has substantial capacity. Yet it requires many hurdles and costs an excessive amount per subscriber in capital. Let me list the hurdles:

1. Franchises: In every town and state there are Franchise requirements. You just can't build out a fiber system. You must get permission. The problem; twofold. First towns have Selectmen or the like who generally are clueless, often supported by Cable Companies, and willing to spends months if not years negotiating a Franchise. This adds thousands of dollars to the cost per subscriber and is all too often not realized.

^[6] <https://backchannel.com/the-next-generation-of-wireless-5g-is-all-hype-1790239b8ca8#huar3weoz>

2. Pole attachments: If you get a Franchise, then you have to get pole rights or other rights of way. You cannot start the negotiations until you have a franchise so it is sequential and the incumbents who owns the poles is in no hurry to get to the end.

3. Build Out: The laying of fiber has negative economies of scale. Even assuming the fiber is free, which it is not, the labor costs are always increasing and the delays are ever expanding. What may have cost \$50,000 per mile five years ago is now \$75,000.

4. Drops: Assuming you have achieved the above then you must get to the subscriber. That is the drop. It generally must be buried and if say you are in New England the rocks etc. will drive the costs to extreme levels.

5. Capital: The Capital per Sub can readily exceed \$5,000 which is quite excessive. If the above were non-existent then one could do it for almost a tenth but the above are real. Our lawyer friend seems to be ignorant of these facts.

II. Wireless

Wireless is a totally different tale. First the key difference is the lack of infrastructure. You do not need a Franchise; you need a license but if you already have it so be it. Here are the advantages of wireless:

1. Ever Scalable Technology: The introduction of 4G with OFDM allowed the bits per second per Hz to go from 1 to 10. For 5G we see that using multiple beam antennas we can go from 10 times to 100 times! That means each user can get well in excess of 10 Gbps.

2. Capital is Incremental: Unlike fiber and even more so unlike a satellite system, wireless capital per subscriber can be deployed incrementally. I demonstrated that twenty-five years ago! Again we did it. Fiber requires a build of infrastructure. Wireless builds as we follow the customers.

3. Technology Changes in Short Time Periods: Cable TV converters are an average of 10-15 years old. They seem never to be replaced or upgraded. A wireless device is upgraded every 18 to 24 months! Thus the customer can follow the technology curve. As one upgrades cell sites using software defined modems and the like, then technology is always at the leading edge and the capital to the infrastructure provider is low.

4. Distributed Systems Can Evolve: As we build out systems we can do so in a distributed manner. WiFi can be integrated with backbone wireless and mesh networks are readily available.

We have argued again and again that the Google fiber builds were fruitless. Now we see they want to build out wireless. Is Google seeing the light? Not really, they needed licenses. If there is however a sharable band then perhaps they can execute this strategy.

Now for what in my opinion are the falsehoods of this lawyer:

Statement 1 is:

One way to increase the information-carrying capacity of a wireless network is to encode data on those wobbling frequencies more efficiently. The standards you've heard about—CDMA, 3G, LTE—they're all about jamming more data into each unit (hertz) of spectrum. A new 5G set of standards will do the same thing, in an even fancier way: the antennas for very, very high frequencies can be so tiny that you can put 8 or 16 of them into a handset or base station and then have them all work together in an array to create a beam of data. Tons and tons of data can be carried on those aggregated beams. Transmission beams in an array can be steered in milliseconds to point to an individual user. You couldn't do this kind of thing at lower frequencies, because many antennas would need, say, three feet of space—and you can't fit that into a handset.

Yes, you can use small antennas at the lower frequencies. Ever hear of Ham radio? I have a 140 MHz hand held set, I can create a beam from a set of small antenna. Ever hear of WiFi, even 802.11n uses MIMO, many antennae. The above statement is just wrong. But even more so, the real antennas are beam-formers at the base station! I did this in 1992, and filed it with the FCC for my Pioneer Preference. We developed it jointly with MIT Lincoln Lab. The military has done this for decades. The statement as presented is just wrong, totally wrong!

She continues:

Until there's a standard, carriers that want to be able to reach global markets won't be anxious to make devices that will work in just a few places. They want to be able to use the same frequencies everywhere. Current phones and other widely-used private-sector communications devices have radios that transmit and receive only frequencies below 6 GHz, and the very, very high frequency spectrum that the FCC recently said it would open up for 5G purposes is all above 24 GHz. So we have a huge legacy replacement problem that will take a while to overcome and requires a standard to fix. All of this takes years.

Now back in 1990-92 I was COO of what is now Verizon Wireless. I worked with Qualcomm to introduce CDMA. We worried about turning the ship, from analog to digital, but it worked, seamlessly. Frankly I would suggest that the customer never noticed. Why? Simply because the replacement time for handsets is about 2 years! Thus with such a short replacement time the turnaround is painless. It did not and does not "take years". I did it! Good Lord, look at the facts!

She continues:

Again, wireless and fiber are complementary. Carriers know this. People call the cables between cell towers and central network offices "backhaul," and when Verizon launched its 4G LTE network in the US covering 93% of the population it needed about 30,000 towers, each one of which had to have a fiber connection. But for a high-frequency 5G spectrum to cover that same population, you'd need to reach many millions of towers and base stations with fiber. Remember, you need to be very close to base stations to pick up and transmit these ginormous amounts of data across high-frequency airwaves. We're going to have to have fiber interconnection points right next to houses and office buildings, and in many places fiber running inside those

buildings. And to reach indoor areas with reliable high capacity, you'll need multiple antennas inside rooms that can beam signals towards you from multiple angles (to avoid the "people as bags of water" problem).

The back-haul has always been with us. We actually used wireless for many of them but alas fiber can work as well and it can be shared with multiple carriers as are the cell towers. I agree that with the ultra-high bands proposed for the new releases they are of short distance. Worse they do not work in humid environments, tried that one folks. So using the higher bands may not be really good to use and why then does one assume millions of towers! That is just in my opinion a stupid idea! One may then have an evolving multi-tiered network, with micro and nano cell nodes at customer premises as we have WiFi today.

Also 5G is a technological change, and evolution. One can use the old bands but with the new technology. One can get 100 bps/Hz and with a few hundred MHz and adaptive beam formed antennas one gets Gbps links to local users on demand.

It is my opinion that this lawyer has put forth a straw man that does not in any manner reflect reality. Indeed, no one is proposing building millions of towers. Engineers just are not that, shall we say, stupid. I cannot perhaps say the same for those technologically impaired.



Labels: [Broadband](#)

[DOG DAYS OF AUGUST](#)

In one of the [left wing blurbs](#) the author writes:

Heat waves are a growing trend across the globe. This summer, the Middle East has experienced record temperatures. July saw the heat index in Iran and the U.A.E. hit an almost unimaginable 140°F. Actual temperature in the region hit hemispheric records of 129°F. According to Live Science, most people will experience hyperthermia after 10 minutes in 140°F. While we are not seeing temperatures go quite that high—yet—it is the unrelenting heat that kills. High temperatures combined with high humidity mean no relief. Even at night, temperatures do not fall sufficiently for the human body to adequately cool itself. In 2010, 55,000 people in Russia died in a heat wave. In 2003, 70,000 people across Europe were killed by heat. For decades, scientists have been warning that climate change...

Well it just is August. For those of us who work outside, especially protecting ourselves from the rays of the sun, it is a challenge. But it is August. I have daily records for the past thirty years of hybridizing and frankly there is no substantial change.

I recall the summer of 1964 at NY Tel, my summer job, with no air conditioning at 140 West Street. When the temps exceeded 90 for more than 4 days we got out at 2:30. That did happen frequently. Then I took the Broadway Line to 242nd Street, from 95F to 120F in the subway! With a half million or more people at rush hour! Try that one on.

So have things changed much? Slightly but not warranting the hysteria. Data and facts are strange things. Just watch the dogs. BTW it is 64F in Moscow right now!



Labels: [Climate Issues](#)

SUNDAY, AUGUST 7, 2016

[WINDOWS 10 NEW RELEASE](#)

Some how the folks at Microsoft must really hate their customers. Really, really, really!

Windows 10 new update takes 5-10 hours to process! Really. Then you find that your Logitech interfaces no longer function, no video. Then you also find you must re-register some expensive software and hope it takes. It goes on and on. If the developers worked for me it would have been their last day on the job! But after all that seems not to be the case with Microsoft management.

For what? Well the changed the format so you now have to get used to a new layout. Yes folks, you spent a year learning the old one and now you have a new one.

They seem to be the spawn of Satan! Google works the same now as it did fifteen years ago. It just works, although we know a great deal has changed. Yet Microsoft seems to continuously annoy and aggravate its customers.

Stop it guys! Really! We paid for this piece of junk so stop messing around with it. Perhaps it is Seattle. Too much coffee?

Oh yes and one more thing. In the previous incarnation W10 booted very quickly. Now it take 5-8 minutes! On several machines, even a simple laptop! What have these morons done. It is faster to boot an XP machine.



Labels: [Microsoft](#)

WEDNESDAY, AUGUST 3, 2016

[CABLE AND PRIVACY](#)

Privacy is a difficult issue. Especially in the world of the Internet. Back in the telephone days the customer records were sacrosanct. One need a Court Order to tap a line, to see customer records and the like. In today's world we are all too eager to assume that such is still the case and the FCC seems to be trying to make it so. Yet the CATV companies not only want unfettered access to our records but they also want to monetize them.

[ArsTechnica](#) reports on the Comcast proposal to the FCC. They note:

Comcast executives met with FCC officials last week, and "urged that the Commission allow

business models offering discounts or other value to consumers in exchange for allowing ISPs to use their data," Comcast wrote in an [ex parte filing](#) that describes the meeting.

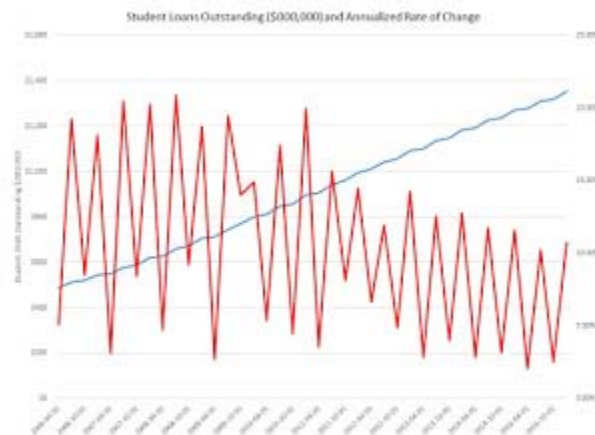
Now one can view this another way. Namely the customer must pay more to keep their privacy, not get a discount. There is no price in CATV, it is totally unregulated. Frankly if one desires to allow the CATV to see and monetize their information, fine, but that should be an "opt in" approach not an "opt out".



Labels: [CATV](#)

TUESDAY, AUGUST 2, 2016

[STUDENT LOANS AND THE NEXT BUBBLE](#)



The above is the summary of outstanding student loans. As of January 2016 they were in excess of \$1.4 trillion, yes "trillion". Unlike the housing bubble, there really is no asset behind it. Unless the student is a Chemical or Electrical Engineer, we really don't need any more Progressive Political Scientists. We need people to create, not to talk. In fact we most likely don't need any more MBAs or Lawyers.

What we really do not need is to continue this explosion. It is three times the Medicare load. And for that people paid in and continue to pay in.

Frankly this is truly terrifying. It is all unsecured and one Party is saying they will just wipe it out. Really!



Labels: [Academy](#), [Government](#)

MONDAY, AUGUST 1, 2016

HERE IS ANOTHER REASON FOR HEALTHCARE STRESS

In a recent [Healio](#) article they discuss the duty of physicians to identify CMS over-payment mistakes and to then contact CMS and make restitution all within 60 days. They state:

Have you ever heard someone in your office say, “I think Medicare may not have paid these claims correctly?” After that statement, did the relevant documents get buried in a pile on a desk — never to be reviewed again? Be careful. Earlier this year, CMS issued a final rule governing the responsibility of providers to report and return Medicare overpayments. The rule makes clear that providers are responsible for identifying and repaying overpayments that may have occurred within a 6-year lookback period, and repayment must be made to Medicare within 60 days of identifying the overpayment. Failure to take action could trigger liability under the “reverse” false claims provisions of the federal False Claims Act, which punish the retention of federal dollars paid in excess of the actual amount to which the provider was entitled....The rule applies to overpayments arising within Medicare Parts A and B, and it requires any Medicare provider or supplier that has identified an overpayment to report and return the overpayment within 60 days after the date on which the overpayment was identified. Somewhat helpfully, the final rule recognizes that providers cannot meaningfully “identify” an overpayment without also confirming and quantifying the overpayment; consequently, under the rule, “a person has identified an overpayment when the person has, or should have through the exercise of reasonable diligence, determined that the person has received an overpayment and quantified the amount of the overpayment.”

Now on top of EHR management, paperwork, the new CMS payment scheme, you have to become the auditor for CMS as well as their working capital manager.

One should wonder how many such traps there are out there today. Physicians will all end up as employees and getting salaries, working 40 hour weeks, and ultimately getting paid accordingly. There will be no more Oslers, Cushings, Kaplans and the like.



Labels: [Government](#), [Health Care](#)

MONDAY, AUGUST 1, 2016

THE RETURN OF THE HMO?

In a recent new piece in [Modern Healthcare](#) they state:

The CMS will launch an ambitious primary care quality improvement initiative in four regions and 10 states that include Arkansas, Colorado, Hawaii, Michigan, Montana, New Jersey, Oklahoma, Oregon, Rhode Island and Tennessee. The markets for the Comprehensive Primary Care Plus (CPC+) initiative were selected based on density and interest shown by practices and payers. Fifty-seven not-yet-named payers will participate. The regions include Kansas City, the North Hudson valley in New York, Philadelphia and Northern Kentucky. Under CPC+, the CMS

and other insurers would pay physicians a monthly fee for patient primary-care visits. The new model aims to improve health outcomes and lower cost not only for Medicare beneficiaries, but also consumers enrolled in commercial plans and other coverage options such as insurer-managed Medicaid plans.

This appears to be a revamping of the HMO model of the 90s. We knew how that played out. But now it is for Medicare where the patients have no second exit.

As [CMS](#) states:

The Centers for Medicare & Medicaid Services (CMS) today announced its largest-ever initiative to transform and improve how primary care is delivered and paid for in America. The effort, the Comprehensive Primary Care Plus (CPC+) model, will be implemented in up to 20 regions and can accommodate up to 5,000 practices, which would encompass more than 20,000 doctors and clinicians and the 25 million people they serve. The initiative is designed to provide doctors the freedom to care for their patients the way they think will deliver the best outcomes and to pay them for achieving results and improving care....Building on the [Comprehensive Primary Care initiative](#) launched in late 2012, the five-year CPC+ model will benefit patients by helping primary care practices:

- *Support patients with serious or chronic diseases to achieve their health goals*
- *Give patients 24-hour access to care and health information*
- *Deliver preventive care*
- *Engage patients and their families in their own care*
- *Work together with hospitals and other clinicians, including specialists, to provide better coordinated care*

Primary care practices will participate in one of two tracks. Both tracks will require practices to perform the functions and meet the criteria listed above, but practices in Track 2 will also provide more comprehensive services for patients with complex medical and behavioral health needs, including, as appropriate, a systematic assessment of their psychosocial needs and an inventory of resources and supports to meet those needs.

This may dramatically curtail any Medicare services and it considered a dramatic means to ration care by putting the burden on the primary care physician.

As of today [CMS](#) notes:

Comprehensive Primary Care Plus (CPC+) is a national advanced primary care medical home model that aims to strengthen primary care through a regionally-based multi-payer payment reform and care delivery transformation. CPC+ will include two primary care practice tracks with incrementally advanced care delivery requirements and payment options to meet the diverse needs of primary care practices in the United States (U.S.). The care delivery redesign ensures practices in each track have the infrastructure to deliver better care to result in a healthier patient population. The multi-payer payment redesign will give practices greater financial resources and flexibility to make appropriate investments to improve the quality and efficiency of

care, and reduce unnecessary health care utilization. CPC+ will provide practices with a robust learning system, as well as actionable patient-level cost and utilization data feedback, to guide their decision making.



Labels: [Health Care](#)

[STUPID IS AS STUPID DOES](#)

In a recent editorial piece in the [NY Times](#) states:

*Stupidity is not an accusation that could be hurled against such prominent early Republicans as Abraham Lincoln, Theodore Roosevelt, Elihu Root and Charles Evans Hughes. But by the 1950s, it had become an established shibboleth that the “eggheads” were for Adlai Stevenson and the “boobs” for Dwight D. Eisenhower — a view endorsed by Richard Hofstadter’s 1963 book “Anti-Intellectualism in American Life,” which contrasted Stevenson, “a politician of uncommon mind and style, whose appeal to intellectuals overshadowed anything in recent history,” with Eisenhower — “conventional in mind, relatively inarticulate.” The John F. Kennedy presidency, with its glittering court of Camelot, cemented the impression that it was the Democrats who represented the thinking men and women of America. Rather than run away from the anti-intellectual label, Republicans embraced it for their own political purposes. In his “time for choosing” speech, Ronald Reagan said that the issue in the 1964 election was **“whether we believe in our capacity for self-government or whether we abandon the American Revolution and confess that a little intellectual elite in a far-distant Capitol can plan our lives for us better than we can plan them ourselves.”** Richard M. Nixon appealed to the “silent majority” and the “hard hats,” while his vice president, Spiro T. Agnew, issued slashing attacks on an “effete core of impudent snobs who characterize themselves as intellectuals.”*

Now Hofstadter is a well know left wing Communi9st supporting Catholic hating pseudo intellectual from Columbia University, and I will let you know how I really feel later. But Regan had a point. It is the very distinction between Individualism versus Progressivism. Progressivism is fundamentally a belief that there is a small select group, often the Public Intellectuals, who single-highhandedly have insight and that the people are clueless sheep and need to be guided. Individualism is a belief that we are all equal, with equal rights under the law and can participate in our political life equally.

The Progressives seem to have the singular belief that they are the High Priests of our Government, and that their insight must be accepted as if it were ex-catherdra.

Hofstadter's book Anti-Intellectualism is a rant against anyone who does not accept his almost dive view of how people should live. From high upon Morningstar Heights he condemned all Catholics, as well as any and all Republicans, and those not agreeing with him. Frankly anyone who examines the facts of Eisenhower and his contribution to the survival of this Country during both the 40s and 50s and then compare it to Stevenson, there is no comparison. The irony of course was when Hofstadter was screaming Eisenhower was President of Columbia!

The left, as exemplified by the Russian author of this article, seem to have a total and in a sense malignant detachment from what has made the US a formidable bastion of individual liberty. Perhaps a scan of Toynbee. Or better look back to Aristotle and his three types of good Government and three types of bad.

For Good Aristotle states:

1. Monarchy
2. Aristocracy
3. Polity, namely a representative Government of the people

For Bad Aristotle said:

1. Tyrant
2. Oligarch
3. Democracy

We left the top two of Good for the third. We should abandon all the bad, for the top two there is what appears to be the case in Russia. Thus one should ask; is a Progressive elite Intellectualism an Aristocracy or Oligarchy, or just another form of Tyranny?

Well I guess it is election time again.

For those intellectuals, I provide *Aristotle's Politics Book 3 Chapter 10*:

There is also a doubt as to what is to be the supreme power in the state:—Is it the multitude? Or the wealthy? Or the good? Or the one best man? Or a tyrant? Any of these alternatives seems to involve disagreeable consequences. If the poor, for example, because they are more in number, divide among themselves the property of the rich—is not this unjust? No, by heaven (will be the reply), for the supreme authority justly willed it. But if this is not injustice, pray what is? Again, when in the first division all has been taken, and the majority divide anew the property of the minority, is it not evident, if this goes on, that they will ruin the state? Yet surely, virtue is not the ruin of those who possess her, nor is justice destructive of a state; and therefore this law of confiscation clearly cannot be just. If it were, all the acts of a tyrant must of necessity be just; for he only coerces other men by superior power, just as the multitude coerce the rich. But is it just then that the few and the wealthy should be the rulers? And what if they, in like manner, rob and plunder the people—is this just? If so, the other case will likewise be just. But there can be no doubt that all these things are wrong and unjust. Then ought the good to rule and have supreme power? But in that case everybody else, being excluded from power, will be dishonoured. For the offices of a state are posts of honour; and if one set of men always hold them, the rest must be deprived of them. Then will it be well that the one best man should rule? Nay, that is still more oligarchical, for the number of those who are dishonoured is thereby increased. Some one may say that it is bad in any case for a man, subject as he is to all the accidents of human passion, to have the supreme power, rather than the law. But what if the law itself be democratical or oligarchical, how will that help us out of our difficulties? Not at all; the same consequences will follow.

Perhaps my Russian emigre may want to reconsider his intellectualism.



Labels: [Government](#)

SUNDAY, JULY 31, 2016

FROM THE PEOPLE WHO BROUGHT YOU GREECE! THE CURRENT MESS THAT IS.

One of the former Greek politicians complains and conflates a combination of elements in what appears to be a self defense attempt. In the left wing [Project Syndicate](#) he bemoans:

One bloc represents the old troika of liberalization, globalization, and financialization. It may still be in power, but its stock is falling fast, as David Cameron, Europe's social democrats, Hillary Clinton, the European Commission, and even Greece's post-capitulation Syriza government can attest. Trump, Le Pen, Britain's right-wing Brexiteers, Poland's and Hungary's illiberal governments, and Russian President Vladimir Putin are forming the second bloc. Theirs is a nationalist international – a classic creature of a deflationary period – united by contempt for liberal democracy and the ability to mobilize those who would crush it. The clash between these two blocs is both real and misleading. Clinton vs. Trump constitutes a genuine battle, for example, as does the European Union vs. the Brexiteers; but the two combatants are accomplices, not foes, in perpetuating an endless loop of mutual reinforcement, with each side defined by – and mobilizing its supporters on the basis of – what it opposes. The only way out of this political trap is progressive internationalism, based on solidarity among large majorities around the world who are prepared to rekindle democratic politics on a planetary scale. If this sounds Utopian, it is worth emphasizing that the raw materials are already available.

One can agree that neither bloc leads forward, but neither does the Neo Progressives. Individual equality, rights, responsibility are more critical than societal agglomeration under the control and direction of those who believe they have found the way and all we must do is follow them, However comparing people to the Nazis is always a dangerous path, for on the one hand it simplifies the evils of that regime and on the other hand dilutes true evil by making claims against anyone that the claimant dislikes.

Progressive internationalism is an abandonment of any and all individual rights and the submission of the individual to some elite set of often self chosen managers. Cultures are different and what may work in the US may not work in Greece. How Americans react to change is not the way Germans do. Utopian realizations of group think never work.



Labels: [Government](#)

SATURDAY, JULY 30, 2016

[ANOTHER COOL NASA PHOTO](#)

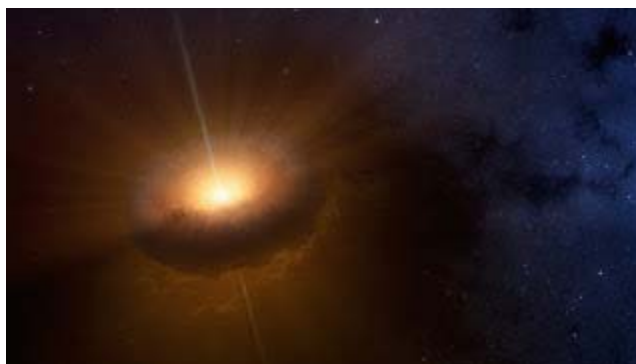


One should ask how much these cost. Just to check.



Labels: [NASA](#)

[GETTING YOUR MONEY'S WORTH](#)



[NASA](#) has a wealth of photos. The one above is worth considering.



Labels: [NASA](#)

FRIDAY, JULY 29, 2016

[DO YOU TRUST AN ECONOMIST?](#)

Over the past eight years I have examined economists and the economy. Now in many ways economists are akin to the Scholastics in the 13th Century. They follow a set of rules for the

debate and adherence to the rules often surpasses the facts. We have gotten a mass of confusing and conflicting tales from some of the best. I had followed Romer's employment projections just before the change in Administration and we all know how they turned out.

Now another Ivy league savant basically states that is is we uneducated, that is PhD engineers from MIT, who are misguided. In the [NY Times](#) the savant states:

Voters clearly aren't listening to economists. In a recent poll, an overwhelming number of leading economists agreed that Brexit would most likely lower incomes both in Britain and in the rest of the European Union. Similarly, in the United States, most top economists agree that "past major trade deals have benefited most Americans" and that "trade with China makes most Americans better off." But those aren't sentiments we will be hearing anytime soon from Mr. Trump or Mrs. Clinton. In one respect, it is easy to understand why. According to a CBS News/New York Times poll conducted last month, only 35 percent of registered voters thought the United States gained from globalization, while 55 percent thought it lost. On issues of international trade, the current crop of candidates is following public opinion.

The real problem is not that we are not listening but that we are and it is all too often a cacaphony of conflicting ideas devoid of any factual base. They are politically oriented opinions. There are no laws of nature in economics. We know more about cancer genetic dynamics than we know about trade. We feel trade as a good or bad thing, yet it is complex and its benefits are often lacking. We see everything as made in China, Vietnam, Philippines, Malaysia, Cambodia, but then again we see nothing made in Russia or even Argentina.

Leadership can focus the populace on the benefits and make them see what works, Lack of leadership results in lack of trust, lack of trust then in suspicion, especially of all things.

Thus it is not the white non-college educated males that are the economists problem. It is the PhDs who work in the real world that do not tolerate the mystical machinations of these soothsayers. Sorry folks, we just don't trust you.



Labels: [Economics](#)

FRIDAY, JULY 29, 2016

[EISENHOWER AND THE BUDGET](#)

There is a wonderful book by Fred Kaplan, *The Wizards of Armageddon*, where he states:

Although a former Army general—and, therefore, a man might be expected to support extravagant defense budgets—Eisenhower was a penny pincher, perhaps especially when it earns? to overseeing the military establishment that he knew so well early as 1946, he frequently lectured fellow officers on the need to pay close attention to what "the economy can stand." During the 1952 Presidential campaign, he declared that "the foundation of military strength is economic strength" and that a "bankrupt America is more the Soviet goal than an America conquered on the field of battle."

Eisenhower had an almost mystical attachment to the unfettered free market and a loathing toward any tampering with it. Like most Republicans, he despised taxation, debt and inflation, feeling that if they were allowed to spiral out of control, the free economy, and with it, the free society, would collapse.

*On May 4, not quite four months after taking office, Eisenhower wrote a confidential letter to his good friend General Alfred Gruenther, Chief of Staff of SHAPE, the Supreme Headquarters Allied Powers Europe. "As you know," he began, "we are trying * bring the total expenditures of the American Government within reasonable limits. This is not because of any belief that we can afford relaxation of the combined effort to combat Soviet communism. On the contrary, it grows out of a belief that our organizer effective resistance must be maintained over a long period of years and that this is possible only with a healthy American economy. If we should proceed recklessly and habitually to create budget deficits year after year, we have with us an inflationary influence that can scarcely be successfully combated. Our particular form of economy could not endure."*

Two and a half months earlier, Eisenhower's Budget Director, Joe Dodge, had produced a report that must have disturbed Eisenhower greatly. The size of the federal debt, Dodge noted, was \$267.5 billion, more than five and a half times the debt held just before World War II. If the spending policies of the Truman Administration were continued, the debt would reach \$307 billion by 1958, \$33 billion beyond the statutory limit. Thirty percent of national income was currently being snatched by government; more than two-thirds of that revenue was being taken by the federal government, and two-thirds of that went toward foreign aid and military spending. Foreign aid had the full support of Eisenhower; he considered it the program in which "the United States is getting more for its money than in any other." Therefore, given the statistics and given Eisenhower's economic philosophy, holding the line on military spending seemed mandatory. And since a huge conventional force of troops, tanks, ships, fighter planes, artillery and so forth needed for large-scale combat was most expensive of all, Eisenhower was determined to cut back on this nonnuclear side of the military.

There was something else besides economic concerns that drove Eisenhower to this position, however, and that was Korea. The Korean War had been trudging along for nearly two and a half years when Eisenhower took office, and it seemed to be heading nowhere, toward neither victory nor defeat. By the following July, when an armistice would finally be signed, more than 33,000 Americans would have died in the war, and for a purpose that few back home could figure out. "No More Koreas" became a popular slogan, especially among politicians who liked to boost the Air Force, whose philosophy of Air Power saw no need to slug things out in a messy ground conflict, at the expense of the Army, whose mission involved precisely that. Retired Army General Eisenhower certainly had no favoritism toward the Air Force, but, perhaps with convictions more sincere than most, he joined in with the "No More Koreas" cry.

Eisenhower's hesitation to get involved in small, distant battles, especially battles fought in Asia, antedated Korea by many years. In the early-to-mid-1920s, Eisenhower was an Army major assigned as chief aide to General Fox Conner, commander of U.S. forces in Panama. Conner

taught him how to think about military decisions systematically, according to the logic of the standard five-paragraph field order—assessing Mission, Situation, Enemy Troops, Our Troops, Plans, Logistic Support and Communications, in that order.

It is worth reading this again in the context of today.



Labels: [Commentary](#)

THURSDAY, JULY 28, 2016

[EATING ONE'S YOUNG](#)

There is an interesting tale in [Fast Company](#) about Yahoo. They note:

According to John Sullivan, a talent management consultant who advises firms on recruiting strategies, this strategy failure shouldn't come as a huge shock. "Most mergers don't work," he says. Only a few big companies acquire smaller organizations successfully, and it's a very thoughtful process. "It's like divorced families joining," he adds. The big issue with Yahoo was that it simply did not have the system in place to cultivate the new talent and make them feel part of the new company. "Yahoo has a bad habit of killing the products [it buys]," Sullivan says. "It doesn't make you feel welcome." A few examples of the dozens of startup products Yahoo bought and then shut down include MessageMe, Vizify, and EvntLive. Many companies are simply not good at acquiring. Sullivan used to work at Hewlett-Packard, and he noted the stifling culture that often led to unhappy new entrants. To get talent to work well under new management, they have to be enthusiastic. The new company should look exciting—a place where they can continue to do their work. By appearances, Yahoo is likely not that place. Sullivan points to Facebook, whose campus is filled with perks like "a free ice cream store." Just the space itself, he believes, could likely energize new additions. Sullivan adds that Facebook's ethos is designed to build and innovate new products. In contrast, Yahoo's office and internal culture, says Sullivan, doesn't appear (from his outsider's perspective) to have that kind of startup excitement.

So why does Verizon think it can do what Yahoo did not accomplish? Having watched Verizon since my NY Tel days in 1964, that is some 52 years, both within and without, one thing is clear. The "immune system" of Verizon rejects anything new. So the above mentioned problem with Yahoo will certainly not be remedied by Verizon. If anything it will be accelerated.

All one has to do is look at those whom Verizon brought in from the outside, the average tenure was less than four years. Their replacements were long time company stalwarts. Not that they really were any better, in fact they were often worse, look at Genuity, but the system will not accept new folks. Even those who started there and then returned!

Can a company change this cycle. I have yet to see it happen. It is often not the CEO who does it but the corporate culture. The resentment of the old times, the pole climbers, the Community College grads who resent the Harvard and Stanford grads. It just does not seem to work. Period!



Labels: [Verizon](#)

WEDNESDAY, JULY 27, 2016

[HERE WE GO AGAIN!](#)

Melanoma is one of the deadliest forms of cancer. It is a skin cancer and it multiplies and metastasizes at a phenomenal rate. Back when I first started to study this in the 1960s it presented as an already metastasized lesion. I saw mothers and young people die in a most horrific fashion.

Then along came skin exams. By a dermatologist using a dermatoscope one can get a fairly good assessment of the malignant potential while still in early and curable stages. namely skin exams really do save lives. They are cheap, and skin biopsies are also somewhat inexpensive.

Now along come our friends at the USPSTF, the same crew that has been opining on prostate cancer. In [JAMA](#) they state:

The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of visual skin examination by a clinician to screen for skin cancer in adults...

That's right folks, don't do those skin screenings, just wait till there is a spreading bleeding lesion that stains your shirts and then perhaps you should see someone! But, wait, there is nothing we can do then, so just go home and die.

Don't we just love these folks!

Now read this one on the harms:

Evidence is adequate that visual skin examination by a clinician to screen for skin cancer leads to harms that are at least small, but current data are insufficient to precisely bound the upper magnitude of these harms. Potential harms of skin cancer screening include misdiagnosis, overdiagnosis, and the resulting cosmetic and—more rarely—functional adverse effects resulting from biopsy and overtreatment.

The harms are negligible. You want patients to be aware and to see someone before it gets to where it was in 1964! Back then we just about wrote people off.

They state:

Melanoma mortality rates for men and women in the Schleswig-Holstein region of Germany, which participated in the Skin Cancer Research to Provide Evidence for Effectiveness of Screening in Northern Germany (SCREEN) study, as compared with the whole of Germany. The original SCREEN study reported a relative 48% reduction in melanoma mortality (or 1 fewer death per 100 000 screened) resulting from a program of 1-time clinical visual skin cancer screening combined with a disease awareness campaign.

I have heard the author speak several time. The problem with the result is several fold. First is is northern Germany, not Miami! Second, Germany has limited the number of Dermatologists so

that screening is at best problematic due to access. The payment by German Health Authorities is de minimus.

Thus if the data is not there then go get it folks. Instead this group just like stopping all Health Care!

One wonders when one looks towards the [NCI and their recent warning](#) to people:

In the trial, patients and their skin-check partners who received training in how to find and track suspicious moles over time found substantially more early-stage melanomas than pairs who only received reminders from their doctors to perform regular skin self-examinations. The training also reduced the worry often felt by patients who are told to keep an eye on their skin but not offered detailed guidance, explained June Robinson, M.D., of the Northwestern University Feinberg School of Medicine and lead author of the study.

Here we have not physicians but family members! Apparently the NCI relies on clinical studies. Perhaps the USPSTF could learn something from this as well! They should check it out, there is this thing called the Internet and it has this thing called Google, try it folks!

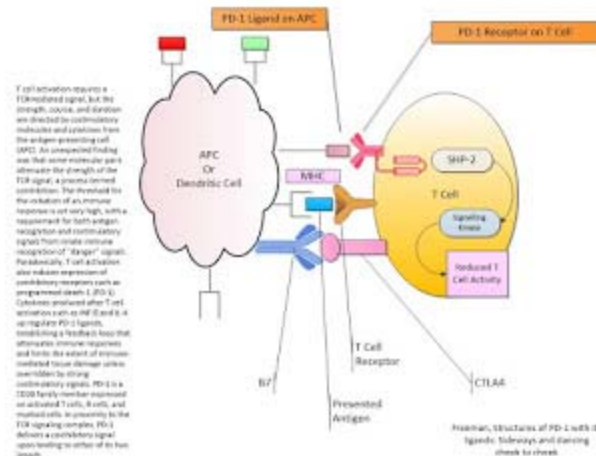


Labels: [Cancer](#)

[CRISPR TRIAL IN CHINA](#)

We have been watching CRISPR technology for about three years now with a combination of expectation and concern.

Nature reports a CRISPR trial in non small cell lung cancer by blocking the mediating effects of PD-1.



The [Nature](#) article states:

The Chinese trial will enrol patients who have metastatic non-small cell lung cancer and for whom chemotherapy, radiation therapy and other treatments have failed. "Treatment options are very limited," says Lu. "This technique is of great promise in bringing benefits to patients, especially the cancer patients whom we treat every day." Lu's team will extract immune cells called T cells from the blood of the enrolled patients, and then use CRISPR–Cas9 technology — which pairs a molecular guide able to identify specific genetic sequences on a chromosome with an enzyme that can snip the chromosome at that spot — to knock out a gene in the cells. The gene encodes a protein called PD-1 that normally acts as a check on the cell's capacity to launch an immune response, to prevent it from attacking healthy cells.

Now the PD-1 blockade helps the body to reject self immune attack. It also blocks targeted immunotherapeutiucs. The risk is that by placing this gene in certain cells it may proliferate and cause catastrophic immune breakdown. There does not as of yet appear to have been adequate research along these lines. We know that many MAB therapies require this blockage but there are two way elements at work. Here we are inserting a gene to block, well just possibly everything!



Labels: [CRISPR](#)

SUNDAY, JULY 24, 2016

[WATCH THE STOCK](#)

Verizon it seems has decided to buy Yahoo for some \$5 billion per the [BBC](#). They state:

US internet firm Yahoo announced in February that it was looking at "strategic alternatives" for its core internet business. Verizon declined to comment on the reports. A formal announcement is expected on Monday before US markets open for trading. Over the last few years Yahoo has struggled to keep up with the changing internet advertising landscape, with some analysts arguing that it has failed to remain relevant in many of its core markets.

The key question the shareholders should ask is what is the basis of this valuation. Verizon has value because it owns licenses to spectrum. That is an asset and one can value that. Really.

However what does Yahoo own? Customers? No, they can disappear in a heart beat. Then what is the basis for this valuation? Good question. Let's see how they spin this one.

Now look at the Balance Sheet.

In Millions of USD (except for per share items)	As of 2016- 06-30
Cash & Equivalents	1,325.40
Short Term Investments	5,055.68
Cash and Short Term Investments	6,381.09

Accounts Receivable - Trade, Net	991.18
Receivables - Other	-
Total Receivables, Net	991.18
Total Inventory	-
Prepaid Expenses	224.73
Other Current Assets, Total	-
Total Current Assets	7,597.00
Property/Plant/Equipment, Total - Gross	-
Accumulated Depreciation, Total	-
Goodwill, Net	431.37
Intangibles, Net	202.12
Long Term Investments	34,412.45
Other Long Term Assets, Total	245.12
Total Assets	44,214.29
Accounts Payable	171.62
Accrued Expenses	982.86
Notes Payable/Short Term Debt - Current Port. of LT Debt/Capital Leases	-
Other Current liabilities, Total	122.03
Total Current Liabilities	1,276.51
Long Term Debt	1,266.28
Capital Lease Obligations	-
Total Long Term Debt	1,266.28
Total Debt	1,266.28
Deferred Income Tax	13,115.82
Minority Interest	32.41
Other Liabilities, Total	159.38
Total Liabilities & Shareholders' Equity	15,850.40
Redeemable Preferred Stock, Total	-
Preferred Stock - Non Redeemable, Net	-
Common Stock, Total	-
Additional Paid-In Capital	-
Retained Earnings (Accumulated Deficit)	-
Treasury Stock - Common	-
Other Equity, Total	28,363.89
Total Equity	28,363.89

Total Liabilities & Shareholders' Equity	44,214.29
Shares Outs - Common Stock	-
Primary Issue	
Total Common Shares Outstanding	948.25



Labels: [Verizon](#)

FRIDAY, JULY 22, 2016

ASSIGNING CREDIT

Back in the early 50s with Watson and Crick, one could argue over perhaps a dozen people at best who were in the fray. The paper had two authors.

Today we have papers with in excess of a thousand authors. The recent CRISPR debate provides focus on this issue.

In the recent [Nature article](#) there is an excellent discussion of how best to attribute what to whom.

They note:

The history of CRISPR–Cas9 gene editing has become a subject of fierce debate and a bitter, high-stakes patent battle. Researchers and institutes have been jostling aggressively to make sure that they are credited for their share of the work in everything from academic papers to news stories.

They continue:

In January, Eric Lander, president of the Broad Institute of MIT and Harvard in Cambridge, Massachusetts, tossed into this minefield a historical portrait called 'The Heroes of CRISPR'². It was instantly controversial. Some said that it marginalized the contributions of certain researchers, and they questioned the decision to publish the article without a conflict-of-interest statement noting that the Broad Institute is embroiled in a patent dispute that hinges on determining who invented CRISPR–Cas9 gene editing.

Lander may very well have stepped into a hornets nest. One suspects he was just trying to lay out the best understanding of what occurred. That is always useful. But in today's world we have a proliferation if not explosion of post docs and junior faculty. How does one best account for all the conversations, insights, bench work, and the like.

It continues:

Outside that community, however, the accolades continue to be heaped on senior investigators.

“We need to invent ways to expand the medals podium,” says Lander. “The idea that scientific discovery involves just one, two or three people is so nineteenth-century.”

Science is no the Oscars. There is no Best Director or Best Film. It is an incremental process of incremental contributions until that one moment that some it comes together. The biological sciences especially is a team effort, and for better or worse the team may be what gets recognition. The recent Silicon Valley attempt to make this Hollywood just intensifies the star issue, a politically correct stardom at that.



Labels: [CRISPR](#), [Genetics](#)

FRIDAY, JULY 22, 2016

[GREATER FOOL THEORY](#)

The "greater fool theory" is a basic principle in the financial markets and real estate. If one buys something it is a good deal only if someone else at a later time will pay you more.

Now in business reasonable people examine revenue potential, look at cash flows on a projected basis, consider contingencies.

In the mid 90s I taught a finance course at Columbia Business School and one case was AOL. I saw it as a total zero. My students saw it differently. Warner bought it and it almost destroyed the company.

Now Verizon wants Yahoo. Why? What "value" does it have? Verizon has assets in licenses, exclusive rights to ever increasing assets. Yahoo has nothing. As a shareholder and former executive, I really wonder who came up with this idea.

As the [NY Times](#) reports:

The end of Yahoo as an independent company may be near, and Verizon — long considered the leading contender to buy the aging web pioneer — is the most likely acquirer. The two companies are in advanced talks over a takeover of Yahoo that could be worth close to \$5 billion, a person briefed on the matter said on Friday. Any transaction would be for Yahoo’s core internet business, although it is unclear whether a deal would also include other assets like real estate or patents. Both companies are hoping to announce a deal as early as next week, this person said. Verizon is scheduled to report earnings on Tuesday. Still, no final deal has been reached and the talks could still falter, the person cautioned. One of the other finalists could also re-emerge with a higher bid. A spokesman for Verizon declined to comment, while a Yahoo spokeswoman said the company would not comment “until we have a definitive agreement to announce” because it wanted to maintain “the integrity of the process.”

How does one monetize this company. It has not for wont of trying, yet they are still a dead pig. Verizon is in the infrastructure business. It has never, and I mean never, demonstrated its ability

in content. Look at AOL. Now egos may drive the deal but from a fiduciary duty perspective it should be cash flow. That is currently elusive.



Labels: [Verizon](#)

THURSDAY, JULY 21, 2016

[JULY 21, 1969](#)

Some 47 years ago today a couple of men landed on the moon. I had the opportunity having worked at MIT Instrumentation Lab to had done a small part in the on board star tracker used for navigation. But instead of sitting down in our offices watching the event I was at the hospital with one of my children and a salmonella infection. It was an interesting lesson. We managed to get a man, actually two, on the moon, but deadly infections were still running loose in the world.

So what was more important that day; moon landing or a broad spectrum antibiotic? I will let you determine! Just a thought to put things in perspective.



Labels: [Commentary](#)

[HE DOTH PROTEST TOO MUCH](#)

We commented on the recent article indicating the almost 80% increase in metastatic prostate cancer and the correlation, not yet a causation, with the ACA and the Government's attempt to control health care costs. Now a representative of one of the institutions which have focused on cancers comes out stating what seem obvious, correlation is not causation, but if it talks like a duck, looks like a duck and walks like a duck, well you get the idea.

The [blog piece](#) states:

“This study makes a dramatic claim about an issue all of us have been watching eagerly: namely, whether less PSA screening might lead to more advanced cancers. But the current analysis is far from adequate to answer that question sufficiently”

Well not quite. The article just reported the fact and made no causal claim. Why the extreme protest? Political ties, funding? Should we follow the money? The [author stated](#):

“We looked at a trend and we reported an observation, but we do not claim to have a causative link.”

Yep, that's all folks. No claim. The blog continues:

In addition, in this study, the rise they detected began before USPSTF guidelines for screening changed. There may or may not be a rise in the rates of metastatic disease; but because of a flawed analysis, this study does not answer that important question. “So why was this unusual study leading to calls? It’s a safe guess that a press release sent to reporters nationwide with a somewhat alarming headline was the reason.

Causative or correlative? The same question can be asked about the above conjecture.

What are the facts. First the USPSTF came out with a recommendation based upon flawed studies, the American and European, which indicated that PSA testing did not impact mortality. Second the Task Force then stated that PSA testing had no value and should not be done. Third, many Internists, most of whom do not spend their days reading and understanding the literature here, just went along with the recommendation. After all, many of their patients would have to pay out of pocket. Fourth, multiple other recent studies have indicated the flaws in the prime studies as well as having demonstrated a rise in metastatic PCa.

So what should believe? Our own lying eyes or the government experts?

In today's environment, trust in Government experts has dwindled to near zero. All one has to do is look at the current political campaigns.



Labels: [Cancer](#), [Government](#)

TUESDAY, JULY 19, 2016

[WHAT'S OLD IS NEW AGAIN](#)

I remember playing with lasers in the late 60s, we were using them in a laser scanning gyro, an exceptionally accurate and precise mechanism to be used in navigation systems. Mechanical gyros had significant drift and required resetting. The result was in my first paper, co-authored with some pretty bright folks, I was just a tag along as the engineer. Then in the 70s we considered optical inter-satellite links, the 80s we did point to multi-point links, in the 90s I was Chairman of an Israeli company, JOLT, Jerusalem Optical Light Transmission, where we used IR and visible.

Yet whenever you put this stuff in the air with any form of moisture you suffered significant loss.

[PCWorld](#) announces another try:

Facebook says it has developed a laser detector that could open the airwaves to new high-speed data communications systems that don't require dedicated spectrum or licenses. The component, disclosed on Tuesday in a scientific journal, comes from the company's Connectivity Lab, which is involved in developing technology that can help spread high-speed Internet to places it currently doesn't reach. Getting Internet signals to new areas is typically done using wireless, because it's much more cost-efficient than running cables to communities outside of urban areas. But traditional wireless comes with speed limitations and requires radio spectrum that often needs to be purchased from the government. Faced with these limitations, engineers have increasingly eyed sending data from point-to-point over laser beams. They don't need any special spectrum or permission, and multiple systems can work in the same area without interfering with each other.

Yep! No license. Never was required. However watch out for water loss and eye damage. Never want one of those pointers poking in your eye. Most of the above is well known and obvious. It appears however the "new" part is the nature of a distributed receiver. Optical receivers were always a problem. You needed to track a narrow beam, and that was complex. Often we had pigeons sitting on the receiver, just enough stress and strain to off set the beam.

So, all too often the real world comes slamming down on you. One of our biggest problems was the swaying of the old World Trade Center, just enough to lose connections.



Labels: [Technology](#)

[PROSTATE CANCER AND THE ACA](#)

As we have been writing for the past seven years the ACA and the [USPSTF](#) have stated that PSA tests and prostate exams have no merit. In [Science Daily](#) they report:

The number of new cases of metastatic prostate cancer climbed 72 percent in the past decade from 2004 to 2013, reports a new Northwestern Medicine study. The report considers whether a recent trend of fewer men being screened may be contributing to the rise, or whether the disease has become more aggressive -- or both. The largest increase in new cases was among men 55 to 69 years old, which rose 92 percent in the past decade. This rise is particularly troubling, the authors said, because men in this age group are believed to benefit most from prostate cancer screening and early treatment. In addition, the average PSA (prostate-specific antigen) of men who were diagnosed with metastatic prostate cancer in 2013 was 49, nearly double that for men diagnosed in 2004 with an average PSA of 25, indicating a greater extent of disease at diagnosis.

In the the article by [Weiner et al](#) they note:

Beginning in 2007, the incidence of metastatic prostate cancer has increased especially among men in the age group thought most likely to benefit from definitive treatment for prostate cancer. These data highlight the continued need for nationwide refinements in prostate cancer screening and treatment.....Although the social and biologic factors underlying these PSA escapes and rising metastatic prostate cancer cases are unknown, the implications of these recent trends highlight the continued need for nationwide refinements in prostate cancer screening and treatment to prevent the morbidity and mortality associated with metastatic prostate cancer. This will be particularly critical for population health economics in the United States considering the added cost of care for metastatic prostate cancer and an aging constituency whose population over the age 65 years will double to over a projected 80 million by the year 2050. In addition, our findings and forthcoming changes in the number of elderly individuals should provide impetus to improve treatments for men with metastatic prostate cancer whose cancer-specific survival has not changed significantly in the past two decades.

Thanks to the ACA and their minions we have managed to see the excruciating increase in death from a manageable disease.



Labels: [Cancer](#), [Health Care](#)

[BRIDGE VS TRUMP](#)

The [BBC](#) was the first to report the collapse and closure of the Tappan Zee Bridge, a part of the NY State Thruway and one of the four major connectors to New York. In fact a major US Interstate, I87/I287. Millions of cars at a time.

What of the NY Times? Nothing! But there must be two dozen Trump stories. Now perhaps the Times missed Brexit, the BBC did not, but those folks in London caught a major infrastructure calamity in the US largest city. Now perhaps the Times thinks Trump is a bigger calamity, one would think so given their coverage. Or perhaps those who follow the Times all live in a small cluster in Manhattan and may not even know what a bridge is. Could be possible.

Then there is the issue of Civil Engineering 101. The center of gravity of a crane if placed in the incorrect spot can result in a crane collapse. They even have instruments for this. The law suits on this will be fantastic. Then there is the issue that the State just left the old bridge alone because in two years they will have a new one. But when a crane slices the old one in half, try getting to work, to Boston to New York, etc.

Oh yes, [RT, the Russian News Outlet](#) also carried a piece. But still no NY Times.



Labels: [Government](#)

SUNDAY, JULY 17, 2016

[BREXIT, HARVARD AND MARSILIUS](#)

History is worth examining. For millennia humanity has created, endured, suffered under, prospered with, survived as a result of political structures. Brexit is a change in such a structure which has evolved over the past few decades.

Why Brexit? I keep thinking of [Marsilius of Padua](#) and his rejection of papal control over governments. By 1320 under John XXII the papacy in Avignon was attempting to control all the Government in what was then Christian countries. Kings could make some local laws but if the folks back in Avignon did not like them, overthrown! The Church was to Edward II and III in the 14th century what the EU was to England in the 21st. Of course then came Luther, albeit it took the printing press, but now we have the Internet.

Some [Harvard person writes](#):

It may be too difficult to determine the exact relationship between Trump and Farage's harmful scare tactics, but observers in both countries should pay close attention. It is evident now with the Brexit vote that racist rhetoric and discriminatory policies are not just limited to the United States. They are, in an age of globalization and rapid change, quickly taking hold in international politics, and becoming an influential determinant of policy. Aggressive anti-immigrant rhetoric and the scapegoating of minorities and immigrants must be taken seriously. Britain's vote to exit the European Union, a decision highly influenced by the xenophobic

rationale of UKIP, is just another indicator that there is a serious wave of nativism ascendant in both British and American politics. With international focus on Britain's recent decision, there is great potential for conversation and change to take place. However, there is also the possibility that rising anti-immigrant sentiment and xenophobia will worsen. With the risk of increased hostility and prejudice on the horizon, the world's eyes are fixed on American elections as a key indicator of things to come.

Somewhat like the NY Times, blaming everything on the current contender for the Republican party but totally failing to ask why? And moreover; what are the historical precedents and where did that lead. Somehow there is that statement of those neglecting to understand the past mistakes are doomed to repeat them, or whatever.

We have been through this process before. Marsilius in 1324 wrote his now famous work on the heretical views of the papacy in Avignon, namely baseless and moreover fraudulent claims of political supremacy, and then failing to understand the development of self rule and regulation.

Revolutions result oftentimes from oppressive rule. They also result from just nonsensical rules as well. Remember the Tea Party! No, Harvard, not those folks walking around today, those folks in Boston back in the 18th century, it must be in some High School text somewhere in a old book store.



Labels: [Government](#)

[MORE ON W10](#)

These guys must be in a panic for some reason, possibly not a good one.

[PCWorld](#) reports:

As July 29 gets closer and the free Windows 10 upgrade offer reaches its final days, Microsoft is pulling out all the stops in order to convince users to upgrade. It's even willing to give you a new laptop. ... Microsoft retail stores are offering to install Windows 10 on any compatible machine for free. If the store's technicians don't complete the upgrade by the end of that business day, they'll give you a free 15-inch Dell Inspiron notebook. The offer runs between now and July 29.

Now as we have reported earlier, W10 knocked out some older software, especially my Chem Draw, not cheap, as well as a half a dozen drivers. We now have 6 W10 machines, all the on line ones, 2 XPs which are old desk hold overs, limited use, and one W7 lab interface. The W7 is blocked from any updates, never goes on line, and connects to all lab equipment. If that crashes the old XPs will work. The W10 systems will not.

So why upgrade? Been there and done that but the driver problem and SW incompatibility is a nightmare. Sorry Redmond, I know you want customers to do it your way but we have a life too. Good thing they do not run the IRS/ Yet!



Labels: [Microsoft](#)

SATURDAY, JULY 16, 2016

CORIOLANUS

Coriolanus is one of Shakespeare's last plays and frankly one of the more complex. It was based upon one of the Plutarch tales^{7[1]} and as such is consistent with the many uses Shakespeare made of classic events. As Plutarch observed:

It may be observed, in general, that when young men arrive early at fame and repute, if they are of a nature but slightly touched with emulation, this early attainment is apt to extinguish their thirst and satiate their appetite; whereas the first distinctions of more and solid and weighty characters do but stimulate and quicken them and take them away like a wind in the pursuit of honour; they look upon these marks and testimonies to their virtue not as a recompense received for what they have already done, but as a pledge given by themselves of what they will perform hereafter, ashamed now to forsake or underlive the credit they have won, or, rather, not to exceed and obscure all that is gone before by the lustre of their following actions. Marcius, having a spirit of this noble make, was ambitious always to surpass himself, and did nothing how extraordinary soever, but he thought he was bound to outdo it at the next occasion; and ever desiring to give continual fresh instances of prowess, he added one exploit to another, and heaped up trophies upon trophies, so as to make it matter of contest also among his commanders, the latter still vying with the earlier, which should pay him the greatest honour and speak highest in his commendation. Of all the numerous wars and conflicts in those days there was not one from which he returned without laurels and rewards. ... But Marcius, believing himself bound to pay his mother Volumnia all that gratitude and duty which would have belonged to his father, had he also been alive, could never satiate himself in his tenderness and respect to her.

From this did Shakespeare develop his character. The more recent version by Ralph Fiennes^{8[2]} presents Coriolanus in a contemporary setting and presents him as an awkward savior of Rome which then through a manipulation of the masses turn on him which leads to his destruction. Coriolanus is a warrior, not a politician. The politicians manipulate the mob, yet within the mob there are other layers of manipulators. There are what I have called from time to time the "professional back stabbers". This is a group of what may be genetically oriented persons whose sole goal in life is to destroy others. Nothing personal, nothing for a desired end, just the process of personal destruction. Washington is a current day example of where they most congregate. Thus this class attacks Coriolanus who appears both clueless and disinterested. Fiennes does a splendid job at depicting this.

^{7[1]} <http://classics.mit.edu/Plutarch/coriolan.html>

^{8[2]} <https://www.amazon.com/Coriolanus-Ralph-Fiennes/dp/B0059XTUR2> It is interesting to read the one star reviews of this film. It truly tells one about the masses! The resonance of the reviewers with Shakespeare is amazing. The reviewers of course have no idea what they are reflecting upon.

Now comes a version at the Shakespeare Theatre of New Jersey. In this presentation the Fiennes role is displaced by an actor who I would have seen growing up on Staten Island. A big brutal thug, whose demeanor is not that of a lost Fiennes but of some muscle in the local mob. Perhaps appropriate for New Jersey but I fell totally missing the point. The presentation was mediocre at best and the mob complexity was totally missing its thrust.

Yet come the NY Times and its review^{9[3]}. They conclude:

If several among the other performances are wanting, the combined effectiveness of the 25-member company is greater than the sum of its lesser parts. The director's decision to have the actors frequently throng the theater's aisles lends immediacy and a sense of speed to this resonant production, which sprints along at a fast-paced two hours and 35 minutes, including the intermission.

Frankly this presentation was cacophonous. It lacked any cohesion, it spent too much time on the rabble, and the undercurrent against the current political scene is sophomoric. As expected the Times cannot seem to even give a recipe without making a comment on the current election. The NY Times reviewer states:

Shakespeare's political drama, of a candidate for high office unsuccessfully coping with seesawing public opinion, assumes fresh resonance in our own interesting times that witness Brexit regret overseas even as so many American voters are voicing their own discontent over their presumptive presidential nominees.

Yes, the mob is a key element of Coriolanus. Yes, the mob can be manipulated. Yes, the results are tragic for all. But that is not why Shakespeare wrote this play. At the time James I was King, and it was the James from whence we get the so named Bible.

Shakespeare seems not to like the populous. As note by Prescott his use of the term popular, as understood to me in relation to the masses seemed always to end in some disaster^{10[4]}. The masses can and could be manipulated. The manipulators often do so just for the process itself without any end in mind. The tragedy here is that Coriolanus was a good soldier who was thrown out of his ken, and at first accepted and then destroyed by the masses, to no benefit to them.

But what most seem to miss about Coriolanus as a play and political metaphor is in the play the Tribunes manipulate the masses. In the current election cycle on the Republican side, this seems not to be the case. In fact the masses are rejecting the Tribunes. It is thus an interesting and telling drama. Can the masses be manipulated? All the time. We see it in every strategy. As one

^{9[3]} <http://www.nytimes.com/2016/07/17/nyregion/review-coriolanus-in-madison-has-20th-century-costumes-and-21st-century-conflict.html>

^{10[4]} See Shakespeare, Grazia and Wells, Cambridge, 2011, pp 271-272. Language was key and the reference usage in time is essential.

of the Democrat Tribunes states; never let a tragedy do to waste. As immoral as such a statement may be, it is echoed so many times.

Thus I would rate the Fiennes presentation as a five star one and the NJ Shakespeare team as at best a one star! To do Shakespeare well, one must understand the underlying human tragedy, not try to make it some anti-politician statement. Done that way it becomes just an echo from the very mob itself, it is popular to paraphrase Shakespeare.



Labels: [Politics](#), [Shakespeare](#)

FRIDAY, JULY 15, 2016

PEACE

In the opening portion of Marsilius of Padua's magnificent work, *Defensor Pacis*, he states:

Every realm must desire tranquility, under which peoples prosper and the profit of the nations is safeguarded. For she is the seemly mother of good arts. She it is who, multiplying the human race in unending succession, extends its resources and refines its manners. And if a man is perceived not to have sought her, he is marked for ignorant of such great concerns...

In the first of his letters, in the passage just set down, Cassiodorus gave expression to the advantages and fruits of the tranquility or peace of civil regimes, in order that he might - by using these, as the best fruits, to explain the greatest of all human goods, viz. the sufficiency of this life, which none can achieve without peace and tranquility - inspire the wills of men to be at peace with each other, and hence tranquility. His pronouncement was in harmony with the view of the blessed Job, when he said in chapter 22: "be at peace: thereby the best fruits shall come unto Thee."

That was in 1328, it applies equally today.



Labels: [Commentary](#)

IRIDIUM, THE BOOK

The book by Bloom on Iridium, *Eccentric Orbits*, is an amazing tale of persistence and corporate bumbling. This review is somewhat personal because I had direct contact with Motorola over this period and specifically with many of the principals noted. As to the author's characterization of many of those I knew personally, they were in my opinion "spot on".

My first dealing with Motorola was in the Fall of 1976. I was at Comsat and just finished the architecture for Intelsat V. I was asked to think about domestic mobile satellite communications. I got one helper, a summer employee, my first, and it was also her first job as well. Her name was Anne Holton, the daughter of the former Governor of Virginia, now the wife of the current

Senator, also a former Governor. Thus Anne and I set out to design a system to provide domestic mobile service. Anne got the job of market research and her first task was get from the Virginian State Police their requirements and what we would need to get them as a customer. Note that we started with revenue first, real revenue, and as Bloom notes again and again that was not the Motorola way. Our competition was Marisat, the Comsat predecessor to Inmarsat. It was a satellite system for ships. We wanted it for cars. The system became MobSat, a horrible name but back then we thought it appropriate.

In the Fall of 1977 I took a trip to Schaumburg to meet some now forgotten Motorola VP to see if we could get them interested. I managed to spill my coffee all over his desk so I believe we were viewed as a bunch of bumlbers. My main point was first a customer base and then a simple design. I also presented an Intersatellite link plan we had considered in Intelsat V, a microwave plan, because we had an MIT study that let us understand that lasers were just not yet up to it. We did not get any interest.

Then in 1985 I got a call from Bob Galvin's office. Please come out to Schaumburg. I went, and I did not know Galvin. I met him in his office and he said let's have lunch. Down we went to the cafeteria, me and the Chairman/CEO. He got a peanut butter sandwich and I was clueless as to what I should have. Here I was with Galvin and he wanted me to help him get into the service business. Why? Simply, Bob said, paraphrasing:

"We sell pagers, and for the revenue per pager, the paging company gets that every year. We sell cell phones, and for the revenue we get for a phone the cellular company gets that every year several fold. We have a data radio product, I would like you to see how we could be not just the manufacturer but the service company, so that we get to keep the recurring revenue."

My task, should I accept it was simple, use this product to see if Motorola could get itself in the service business. I had spent the last five years in Cable and was well versed on service businesses. But at Warner we made nothing, we had vendors.

I spent the next five months trying to see if Motorola could do this. It was my introduction to a mid-West manufacturing culture. I was assigned handlers, namely people to "help" me who reported back to the VPs who saw this as a threat. I started out to see if there was revenue. That I was told was not the Motorola way, I should focus on technology. I told them, "If all else fails, listen to the customer." So I went to find customers for mobile data. Three months of talking to customers, one on one, listening and asking questions to listen some more. What was clear was that what Motorola had could work but it was a technology in search of a market. The food chain necessary for its success was absent. Customers such as distributors needed software and what we now call "apps" to get this to be useful. Many saw the vision, but the steps to be filled in were considerable. I managed to complete the business plan but met with one Motorola obstacle after another. The "Comm Sector" sales team tried its best to intimidate me with their way of selling. You don't sell a service the way you sell a piece of hardware. Their problem fundamentally was how did they get paid? What was the commission plan? If they did not have a clear path to getting paid they had no interest.

The most important observation I made was when I went to Kraft. They were in the food distribution business. They had trucks, distributed food, took orders, and the like. A great target for the use of data; managing trucks, inventory and the like. I could see a rationale. I spend a half day with a manager there, nice person, willing to listen. At the end of the meeting he asked me; now just how do I use this? I told him that he just has to connect his software to the terminal. His response was; what software? Metaphorically I realized that there was a gap in the food chain. They made cheeses, managed factories, Motorola made data terminals and even networks. There was a massive gap in connecting the two. Whose job was that? I told Motorola that if they wanted to be in the service business then they had to provide a full end to end solution; thus the software was their problem. But Motorola did not do software. The sales force wanted to know why the customer could not get their own software. I decided not to pursue that discussion. When having presented the plan and noting that perhaps it was both a bit too early and that Motorola had a hardware culture not a service business culture I got a job offer. I was smart enough to politely turn it down.

Now in 1990 I took over as COO of the cellular company at NYNEX. One of my main tasks was to move to digital. Since I knew Irwin Jacobs from MIT, he was my Faculty Adviser, I naturally went to Qualcomm. I fought against the TDMA parties such as Southwest Bell and McCaw and managed to move CDMA up to the US option. I managed to get AT&T, subsequently Lucent, to move in that direction, but had a difficult time with Motorola. They somehow did not get it. I even went to Chris Galvin in Florida for a pitch.

Then when I went to do PCS, I used MIT Lincoln Labs as my technical support. Hearing of Iridium and knowing the principals, I thought what we knew at Lincoln, may be of help to Motorola. After all, Lincoln had built a few satellites and had demonstrated inter-satellite links as well and a few mobile terminals. The meeting was with the top folks at Motorola, just read Bloom, and we told them that perhaps they should consider taking some smaller steps, this was a massive jump with lots of uncertainties. We were politely escorted out. Never heard from them again.

Then in 1997 when I started my international fiber and IP company, I needed VOIP nodes and Motorola had one. At least that is what I thought. Actually they just OEMed one from a former colleague which I did not know about. But after a year they suggested investing, and somewhat foolishly I agreed. As usual the agreement required almost instantaneous repayment via hardware and system service contracts. The subsequent dealing with Motorola was filled with excruciating pain. I had investors over ten time zones and I continually had major issues with Motorola, a five-minute issue would take weeks! We finally sold the company in 2005, and the problem disappeared.

Overall my view of Motorola was simply:

1. A hardware manufacturer with a strong sales force and dominance in their classic markets.
2. A company which did not understand the service business.
3. A company where many managers dealt with issues by confrontation not by collaboration.

4. A company where getting customers first was not the way to do things. Selling a box, a technology, was the key. Get the customer to buy a box, not solve the customer's problem and become an ongoing part of the solution. They did not understand IBM and the "service" culture.

Thus with almost thirty years of dealing with Motorola, they had some great technology folks, great political infighting skills, fantastic hardware sales, but it was a culture in my opinion of survival of the fittest, not necessarily pursuit of the best.

To preface my review of Bloom's book it is worthwhile to briefly lay out my experience in this area with satellites, mobile systems and Motorola. I had a thirty-year relationship with Motorola, as a joint venture partner, as a consultant to the Chairman, as a customer when COO of NYNEX Mobile now Verizon, and as the CEO of a company in which they had invested. The relationship allowed me to see most of the principals in the book first hand and further to see the company in a broad context. I also spent time in the satellite world, actually architecting one of the first mobile systems in the 70s. I also had a parallel experience to Colussy, albeit an order of magnitude smaller.

Thus I approach Bloom's book with a somewhat jaded experience set. I also approach it with a firsthand knowledge of the principals and moreover of the technical and business facts as I was exposed to. Bloom tells a fantastic story. I have no knowledge of his principal, his Odysseus, and his sailing through Scylla and Charybdis. But I can commiserate with him and his frustrations. I dealt with only 20 countries and an order of magnitude less in scale of the financing. But the trials and tribulations all ring true. It is told with a sense of being there and having to deal with the many characters thrown in the way. One wonders how anything gets accomplished given what the entrepreneur goes through in today's world. There are very few who set out and continue to the completion. Bloom takes the reader on that journey, and his inclusion of the steps are essential to appreciate the success.

Bloom presents a fast paced tale of the birth and near death of the Iridium satellite system. This is really a story of three "characters" First of Iridium, the satellite system developed by Motorola to provide global telecommunications coverage. Second, Motorola and its management and how they mis-managed the whole process. Third, it is about Colussy, the man who sought to revive Iridium just at its death's doorstep, and managed to working through the problems of financing, bankruptcy, Motorola, the US Government, and some 200 plus countries. The book then is the interplay of all three of these characters, animate and inanimate.

First, Colussy, ostensibly a successful businessman, in retirement, sees an opportunity in resurrecting Iridium just as Motorola is ready to push a self-destruct switch. Just what he sees is often problematic because each time he takes a hill, there are several more in front of him. But he manages to persevere. His interactions are all too familiar to any person who has tried to start a business, especially one spanning many countries and involving the US Government.

Second is the Iridium project. Here Bloom touches on some of the details but this is not a book for anyone who wants to understand Iridium. It is clear again and again that Bloom is not technical and that he does not want to venture down that path. However, understanding Iridium is essential to understanding the overall problem.

During the 1990s, mobile communications was expanding. It moved from analog in the late 80s to digital systems in the 90s with CDMA and TDMA in the US and GSM (a TDMA variant) throughout the world. With digital one had ever improving voice compression systems but the need to expand coverage was ever increasing. Cell sites had at best a 1-mile radius of coverage and that meant about 3 sq mi of coverage per site. The large cities were being covered at a rapid rate but major portions of the world had none. To achieve that would be very costly. Thus Motorola, and some others, came up with what could be called cell sites in the sky, lots of satellites. In addition to work properly they had to be low, to reduce the delay in the voice signal. Classic satellites like those of Intelsat were at 23,000 miles and the voice delay was about 0.25 sec, which was unacceptable. Thus Motorola came up with a constellation of dozens of small satellites that were close to the earth and allowed low power and minimal delay. However, they had to "hand-off" calls, like cell sites did on the earth, but to do so in space, thus using a complicate dynamic inter-satellite link. Then of course they needed bandwidth and agreements with 200 countries, no mean task.

Third, we have Motorola. This book is as much about Motorola as about anything. Motorola was a Chicago based company with a great record in radio communications for the public and government entities. They made boxes, transmitters, receivers, processing units. They sold boxes to customers who then did something with them. Mobile companies integrated them into cellular systems, paging companies integrated them into paging services, and police and fire departments integrated them into their operations. Thus Motorola was a manufacturer with great quality and a sales force that sold the boxes better than anyone else.

However, Motorola was not a service company. It was a product company. What is the difference between a product business and a service business? It is best characterized by the metaphorical statement: The dogs have to eat the dog food. Product business sells to the owner of the dog. Nice label, good price, great placement, fantastic advertising and promotion. The service business requires that the dog food be consumed, again and again. The dog does not care about the label, about the sales person. The dog sniffs it and eats it, or not. Service means that one must understand their end customer.

Iridium was to be a service company. The structure became Byzantine however, in an attempt for Motorola to still execute its role as a product company. Motorola just did not understand the service business. It thus created a monster in the way it structured Iridium, protecting its underlying product business construct.

Also Motorola management was often times blunt and aggressive. It grew up dealing with truckers, police departments, local governments, and never really dealt with customers. They knew how to "push" a sale through a difficult channel, and yet did not understand end user customers. The dogs at the end of the dog food.

Bloom lays out each of these elements on a step by step basis giving examples so that by the time the reader completes the book they all fall elegantly in place.

Now the problem was, as Bloom notes, Motorola had a brilliant team on the design of the system. The built off of the Star Wars technology of Brilliant Pebbles and related designs. What is clear from Bloom, but perhaps should have been more emphasized, is that no one seems to have thought of revenue or costs. Who was to buy this system and what price? The team never seems to have signed up users ahead of time, they relied on weak third party inferences that there were customers.

The second problem was that the system design, albeit elegant was very technically challenging and the overall system was complex. Bloom lays this out in detail.

The third problem was just time. It took longer but at the same time the world was changing. GSM penetration exploded, digital was pervasive, and the Internet was the stalking horse of the future. Voice was becoming a tertiary service at best. Data, namely Internet access, was becoming the critical element. I was at the time this was occurring switching from a IP voice business to a fiber Internet backbone system. The irony was that Motorola was one of my investors and they should have seen this happening as it did in literally a few months! Namely the world was changing under their plan.

Thus Bloom starts out with Chris Galvin commencing the deorbiting of about 80 satellites, namely allowing them to just drop from orbit and hopefully burn up before hitting anyone. Then the tale takes Colussy through the never ending impediments thrown in his path by Motorola, as Motorola itself is starting its own downward spiral, which will take a bit longer.

Bloom then takes Colussy from the near death of the system to his final snatching victory from the jaws of defeat. It reads superbly and should be viewed as how not to do something in the corporate world and how a real entrepreneur works.

Bloom on the other hand from time to time makes statements which do not necessarily reflect the facts. It seems clear he got them from somewhere but reality may have had an alternative.

On p67 Bloom makes the statement that Comsat was not interested in voice communications. Having done the architecture for Intelsat V at Comsat in 1975 I remember, and still have the documents, that were mostly voice. This is a typical statement I see again and again in Bloom and it detracts, and was unnecessary for his exposition.

On p69 he talks of inter-satellite links. Lincoln Lab had designed and launched several satellites for the Air Force, the LES series. I was at Lincoln before Comsat. I was in that Group and interfaces with DoD. When I did Intelsat V we looked at inter-satellite links and the design actually had them. It would be microwave because the problem of pointing a laser were too complex. In 1993 my colleagues from Lincoln and I met with the Motorola Iridium management to discuss these factors. It was then known that laser pointing still had a bit to advance.

On p 90 there is a discussion of the antenna. The Marisat satellites of the 70s had such antenna for the same reasons.

On p 111 there is a discussion of the Galvin discussions. Here as elsewhere the question keeps coming up; where is the revenue coming from. I recall one of the senior management saying they were targeting executives on elephant hunts in Kenya. I did not know any of these folks but somehow the source of revenue should have been a bit stronger than that.

On p 122 was the balloon discussion. I had seen at least a dozen balloon proposals over the years and I still see a few. Needless to say they never materialized for a variety of reasons, most obvious from just an operational perspective.

On p 150 the discussion of Motorola and the Russians is classic. I never had any problems with the Russians, but then I did not act so arrogantly.

On p 180 there is a discussion regarding the fact that the system was not interoperable with mobile and it had poor propagation characteristics inside buildings. By the late 90s GSM could work inside a beer house in Prague. Thus user expectations were changing. The system required a complex interoperability capacity and that just added costs and complexity.

On p 183 there is the discussion of the FBI and CALEA. Any telecom operator would know of CALEA, namely we had to have access for Government agencies using a CALEA warrant. This was something they should have known, especially given their government businesses. Also their cellular systems we often carrying more wiretaps than the fixed line businesses.

On p 198 is the most telling part. "How to get the million subscribers/" One would have thought they had this laid out before spending penny one, but alas this was classic if you had never been in the service business.

On p 330 it relates the crash of a Soviet satellite and the concern. The reason for concern was twofold. First the Russian made indestructible satellites. They just did not burn up. Second this satellite if I remember had a nuclear power source, I believe plutonium. It landed somewhere in western Canada. The concern was radiation as well as the indestructible Russian design.

Overall the book is superbly well organized and does a great job in presenting each of the characters. It also presents a near tragic tale of over management and under estimation. To recall my father's warning; prior planning prevents poor performance. My corollary was; always make sure there is a second exit.



Labels: [Books](#)

[THE VALUE OF A PHD](#)

The [NY Times](#) has a piece on the apparent oversupply of PhDs. They note:

The United States is producing more research scientists than academia can handle. We have been told time and again that the United States needs more scientists, but when it comes to some of the most desirable science jobs — tenure-track professorships at universities, where much of the exciting work is done — there is such a surplus of Ph.D.s that in the most popular fields, like biomedicine, fewer than one in six has a chance of joining the club in the foreseeable future.

While they try to get a foot in the door, many spend years after getting their Ph.D. as poorly paid foot soldiers in a system that can afford to exploit them.

Now this article does a disservice. A PhD is not necessarily a path to some academic position. It is a tool, like that of its lowly cousin, the MD, to pursue a career. How one uses that tool is up to the individual. Pharmaceutical companies, bio tech entities and the like seek these capabilities all the time. In fact one would be hard pressed to accept an academic career given the oppressive environments in the Academy where political correctness overshadows everything.

The article continues:

The engineering school at M.I.T., for example, often gets 400 applicants for every open assistant professor job, says Richard Larson, an operations research professor there. Many, he adds, are “superstellar.” One way to see what is happening is to look at a measure, called R0, used in demography to show how a population is growing. If every baby girl in a population grows up to have one baby girl on average, R0 is one, and the population size will remain constant. If R0 is significantly greater than one, the population can explode. Dr. Larson and his colleagues calculated R0s for various science fields in academia. There, R0 is the average number of Ph.D.s that a tenure-track professor will graduate over the course of his or her career, with an R0 of one meaning each professor is replaced by one new Ph.D. The highest R0 is in environmental engineering, at 19.0. It is lower — 6.3 — in biological and medical sciences combined, but that still means that for every new Ph.D. who gets a tenure-track academic job, 5.3 will be shut out. In other words, Dr. Larson said, 84 percent of new Ph.D.s in biomedicine “should be pursuing other opportunities” — jobs in industry or elsewhere, for example, that are not meant to lead to a professorship.

Back in my day, yes it was fifty years or more ago, one sought a job after the PhD. Except when I got out in 71' and Nixon had managed to totally collapse the economy and there were no jobs, really, no jobs. Then one settled for a teaching job eventually looking for a real job. What came of that process, however, was that if you want a real job, go create your own. The PhD develops skills. The Post Doc is really nearly free labor for some faculty person. It is not necessarily a path to academia.

Thus the PhD is only a waste if you do not know how to monetize it. One should pursue the goal but avoid the path of indentured servitude, the Post Doc.



Labels: [Academy](#)

THURSDAY, JULY 14, 2016

[RAIN, RAIN, GO AWAY!](#)

The [FCC](#) today assigned new bandwidth for alleged 5G and shared usage.

They state:

The new rules open up almost 11 GHz of spectrum for flexible use wireless broadband – 3.85 GHz of licensed spectrum and 7 GHz of unlicensed spectrum. With the adoption of these rules, the U.S. is be the first country in the world to open high-band spectrum for 5G networks and technologies, creating a runway for U.S. companies to launch the technologies that will harness 5G's fiber-fast capabilities.

Then the details are:

1. Licensed use in the 28 GHz, 37 GHz and 39 GHz bands: Makes available 3.85 GHz of licensed, flexible use spectrum, which is more than four times the amount of flexible use spectrum the FCC has licensed to date.

- Provides consistent block sizes (200 MHz), license areas (Partial Economic Areas), technical rules, and operability across the exclusively licensed portion of the 37 GHz band and the 39 GHz band to make 2.4 GHz of spectrum available.*
- Provides two 425 MHz blocks for the 28 GHz band on a county basis and operability across the band.*

2. Unlicensed use in the 64-71 GHz band: Makes available 7 GHz of unlicensed spectrum which, when combined with the existing high-band unlicensed spectrum (57-64 GHz), doubles the amount of high-band unlicensed spectrum to 14 GHz of contiguous unlicensed spectrum (57-71 GHz). These 14 GHz will be 15 times as much as all unlicensed Wi-Fi spectrum in lower bands.

3. Shared access in the 37-37.6 GHz band: Makes available 600 MHz of spectrum for dynamic shared access between different commercial users, and commercial and federal users.

Anyone who has ever worked these bands should know that moisture is a real killer! Especially at the 64-71 GHz bands. This is point to point only and absorption is severe. There is no diffraction and no multi-path survives.

Why not just move to IR? I did that twenty plus years ago. But that worked well in the desert, not too well in New York and not at all in Bangkok.



Labels: [Broadband](#), [FCC](#)

MONDAY, JULY 11, 2016

JAMA ON THE ACA

In the current issue of [JAMA](#) for the first time in its history there is an article by the current President, or at least it has the individual's name attributed to it. One wonders if it were written solely by the alleged author, since there is no reference of any other contributor. I will let history deal with that fact.

The article summarizes as follows:

Policy makers should build on progress made by the Affordable Care Act by continuing to implement the Health Insurance Marketplaces and delivery system reform, increasing federal financial assistance for Marketplace enrollees, introducing a public plan option in areas lacking individual market competition, and taking actions to reduce prescription drug costs. Although partisanship and special interest opposition remain, experience with the Affordable Care Act demonstrates that positive change is achievable on some of the nation's most complex challenges.

Has the ACA made a difference? In some ways yes, but generally not for the better. Has it extended health care to many via Medicaid? Yes, and at a very low cost but at a likewise low access. So where does the money come from? One source is increases to Medicare payments, especially from those over 65. A full time working 70 year old is paying a total of well over \$20,000 per year for a husband and wife, including Medicare Excess, Medicare, and Medicare Plus! The average per person expenditure for Medicare is about \$16,000. That is \$32,000 per husband and wife. Yet they are paying well about two thirds of that on an ongoing basis! Some deal, wait till you are 75!

It then states several conclusions:

First, many of the reforms introduced in recent years are still some years from reaching their maximum effect...

Yes, many reforms are still in process. Reforms like denying surgery for prostate cancer, and other potentially costly procedures for Medicare patients. Then just look at teachers in West Virginia, the state teachers plan is worse than Medicaid, and costs orders more!

Second, while the ACA has greatly improved the affordability of health insurance coverage, surveys indicate that many of the remaining uninsured individuals want coverage but still report being unable to afford it...

Affordability? Frankly it is allowing Millennials to now live with their parents and get their grand parents to pay for the deal of a health care plan. Grandma pays \$10,000 after paying in for 50 years and the millennial get by with \$29 per month while exploring life!

Third, more can and should be done to enhance competition in the Marketplaces. For most Americans in most places, the Marketplaces are working. The ACA supports competition and has encouraged the entry of hospital-based plans, Medicaid managed care plans, and other plans

into new areas...

Yes, the marketplace is a mess. Trying to get a bid on a health care plan is more complex than setting up multiple crude oil contracts across seven currencies. Try it! [Prof Herzlinger](#) at HBS has a great piece in the same issue on this point.

Fourth, although the ACA included policies to help address prescription drug costs, like more substantial Medicaid rebates and the creation of a pathway for approval of biosimilar drugs, those costs remain a concern for Americans, employers, and taxpayers alike

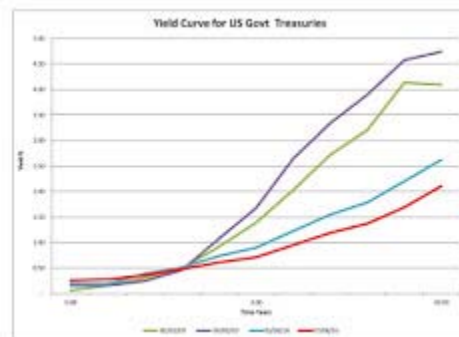
Drugs are a mess. Yes a total mess. Why, for several reasons. One, the FDA, in its attempt to be safe may have increased costs dramatically. Second, we are subsidizing drug costs for other countries. Third, Medicare should be able to negotiate. Fourth, the new drugs mabs and nibs are very costly to deal with cancers and other diseases. The costs is due to the need for complex and long lasting trials. Is there a solution to the trial issue? I cannot see an easy one.

Overall one has to ask why JAMA has done this? Policy is important, but a debate is essential. Taking sides may very well be regretted in the long run.



Labels: [Health Care](#)

[YIELD CURVE JULY 2016](#)



The above is the yield curve for last Friday and previous dates. The yield curve is flattening out at a rapid rate. The short term has increased and the long term dropped. Below is the details by date. Note the sudden rise in short term and the continuing drop in long term. This is a sign for a stalled economy despite the stock market.



The above clearly shows the short term bump up early in 2016 and it is volatile but retaining the bump.



Labels: [Economy](#)

THURSDAY, JULY 7, 2016

[THE PHD THESIS](#)

There is an interesting article in [Nature](#) recounting three scientists who had looked back upon their PhD theses.

It comments:

Francis Collins shakes his head in bewilderment as he flicks through the pages of his thesis. “At this point it looks very much like another language,” he says, looking with puzzlement at page 71, which contains far more equations than text. The PhD was on theoretical quantum chemistry, and had “absolutely no practical application”, Collins says. Looking at it now, “it does feel a little bit like this was another person”.

Now I have from time to time looked back on my thesis. I have asked what was the purpose of a thesis? Clearly in my mind it was:

1. How well could you convince some small group of faculty that you were capable of eventually doing real research and not embarrass the institution.
2. In some cases it was your advertisement for a job. This was not the case in engineering.
3. It was a tests to see how much pain you could go through and still persevere.
4. In the old days, before say 1970, you were not tied as a research assistant and thus cheap labor. You were funded by other means, I was junior faculty. So the game was to continue the turnover to get new funding of such positions. Today they are all extinct.

But I was a bit different having spent time in industry, having written a book, having published, and thus having already demonstrated some of the steps that the thesis would prove. Thus my thesis was chosen to get me out as soon as possible, it took eighteen months. Not bad

considering. Yet the thesis was what the faculty advisor wanted, not what I would have considered important. My first book has more legs than my thesis, but the thesis was what gets the degree, not your accomplishments.

Fifty years later I still use my book, never used my thesis. However what is shocking is that on [Research Gate](#) some 44 people in one year downloaded a 50 year old thesis. Maybe they saw something there. I for some strange reason keep thinking I could go back to it again, perhaps when I turn eighty!



Labels: [Academy](#)

TUESDAY, JUNE 28, 2016

[MORE ON W10](#)

The [BBC](#) has an interesting piece on the W10 litigation.

...her Windows 7 computer had automatically tried to update itself to Windows 10 without her permission. She said the update had made her machine unstable, leaving her unable to use it to run her business. Microsoft said it had dropped its appeal to save on legal costs. Microsoft has been aggressively pushing the latest version of its widely used operating system, which is currently available as a free download for computers running Windows 7 and 8. However, many people have chosen not to upgrade, because they are running old hardware, have software that does not run on Windows 10, are concerned over the software's tracking features, or simply do not want it.

In February, the company bundled Windows 10 in with its security updates and made it a "recommended update", which meant it was automatically downloaded and installed unless blocked by the user. Some people accused the company of trying to "trick" customers into installing the update.

Indeed, W10 in my experience has several negatives:

1. It clobbers existing activations on certain products. I had an expensive Chem Draw system and it wiped out my registration.
2. It wipes out drivers. Several of my systems were disabled.
3. It disables older SW. Again this was the case with even old Microsoft SW.

I have one machine left used on a lab bench for imaging and running W7. I have disabled all updates for fear of the above because Dell says it is not compatible with W10. Microsoft has the arrogance in my opinion that no matter what they do to the users who have paid for the systems they rely upon that they can do whatever!

This should some FTC issue. But then again it is an election year and perhaps they are looking for lobbying jobs.



Labels: [Microsoft](#)

MONDAY, JUNE 27, 2016

[MICROSOFT, W10, AND LITIGATION](#)

[PC World](#) has an interesting piece on Microsoft and W10.

A travel agent in California recently took Microsoft to court over the company's Windows 10 upgrade tactics, and she won. After an unauthorized Windows 10 upgrade borked her small business PC, Teri Goldstein from Sausalito, California sued Microsoft over the issue, as first reported by The Seattle Times. In the end, the judge sided with Goldstein and Microsoft had to pay \$10,000 to compensate her for her troubles. Microsoft told the Times it opted not to appeal the matter in order to avoid further legal expenses.

Good for them!



Labels: [Microsoft](#)

MONDAY, JUNE 27, 2016

[ANOTHER SLANT ON BREXIT](#)

[Greg Mankiw](#) has a pictorial presentation of Brexit in the form of food. I think it is spot on. Anyone who had been in London say in the mid 60s would even appreciate the can of beans. I recall how horrible almost everything was. Faulty Towers was the Four Seasons then. I recall staying at a hotel near Buckingham Palace and had lunch with a colleague since it was down the street from Victoria Station. There must have been 20 people bustling around the dining area and we were the only two customers. Never got served!

Went to a local place and cardboard was better! The only reason England went to war with France was for the food! The only place worse was Ireland, my family knew how to take the green out of any vegetable! Boil it for a few hours or more!

Oh yes, one more thought. To France, get rid of those foreigners, return it to the Neanderthals!



Labels: [Commentary](#)

SUNDAY, JUNE 26, 2016

[THE IGNORANCE OF SOME ACADEMICS](#)

In a recent review of the book *Life's Greatest Secret: The Race to Crack the Genetic Code* by Matthew Cobb, a book I admit I have neither read nor do I have any intent to waste my time thereupon, there is however a letter to the editor of the New York Review of Books, NYRB, a generally leftist oriented opinion publication, which stated some rather revealing opinions.

In the above mentioned letter to the NYRB the author states regarding the original review^{11[1]}:

He notes that developments in mathematical information theory and cybernetics soon after World War II had a strong influence on the way biologists began to talk about life and heredity —specifically the idea that DNA contains a “genetic code” replete with “information.” Much the same point can be made about psychology and neuroscience: they too were influenced by these developments in the mathematical theory of information, introducing this notion into the heart of theories of the mind and the brain. But Orr goes on to remark:

“In the end, the information sciences provided biologists with loose but useful metaphors and analogies, a language that allowed scientists to think and speak in new ways. But the high-powered mathematics of these fields proved mostly impotent in biology [I would add in psychology and neuroscience too]. No one, for instance, used Shannon’s equations to say anything especially interesting about organisms...”

This raises a troubling question: If these recent ways of talking in biology, psychology, and neuroscience are really just loose but useful metaphors, now deeply ingrained in these sciences, what is the literally true way of speaking for which they substitute? How can we reformulate these sciences in such a way that the information metaphors are replaced by sober statement of fact? And do scientists now agree that the borrowed way of talking really is just loose metaphor, or have they come to take it for literal truth? This question seems to me not sufficiently addressed, though very important.

Now the original Reviewer notes^{12[2]}:

A second theme concerns the respective roles of theory (of any sort) versus experiment in biology. In the early 1960s, mathematicians confidently declared that “it will be interesting to see how much of the final solution [to the coding problem] will be proposed by mathematicians before the experimentalists find it.” As Cobb concludes, the “answer. . . was simple: not one single part of it.” The interesting question is why theory failed here. Part of the answer, as Cobb emphasizes, is related to Crick’s idea of the frozen accident. The genetic code seems at least partly arbitrary. It represents a half-decent arrangement arrived at by the imperfect, tinkering process of evolution by natural selection and, once settled on, it couldn’t be “improved,” or made somehow more systematic. In such a situation theory is likely useless.

Let me examine these statement a bit in detail.

First:

Let me reiterate Wiener and Cybernetics. He made basically the following observations:

^{11[1]} <http://www.nybooks.com/articles/2016/07/14/dna-a-metaphor/?pagination=false&printpage=true>

^{12[2]} <http://www.nybooks.com/articles/2016/06/09/dna-power-beautiful-experiment/>

1. The world is filled with uncertainty. Things are random, and we have to acknowledge and accept that.
2. Many organic entities are systems. Namely they have actuators and effectors. They have cause and effect. They are in effect a system which means we can model cause and effect, albeit under condition 1 above it may very well be random.
3. Systems have feedback elements, namely inputs yield outputs which in turn can effect inputs. That means we have systems whose dynamics are uncertain systems with dynamic effects.

In simple terms the Cybernetic world is a stochastic dynamic system. Now what about cells, DNA and their functions? They are stochastic dynamic systems. Ligands attached to receptors which activate pathways which start DNA reading via a promoter and conversion which produces RNA and then produce proteins which then become ligands. Some proteins actually modulate the pathways and receptors. Thus the dynamics of cells is a stochastic dynamic system. Almost all studies in cancer pathways revolve about that fact. Cybernetics from a Wienerian mindset is fully accepted in systems biology. It is the very heart of systems biology.

The letter writer is thus in error. The Cybernetic model is hardly a loose model. It is at the very heart of understanding cancer dynamics. It is necessary. The Reviewer, the Author and the Letter Writer are in gross error in their understanding and articulation of cybernetics.

Furthermore, as we have shown in repeated malignancies, one can view cancer as a separate dynamic stochastic organism, growing apart from the human host. Yet if one accepts such a model, then it is possible using systems approaches to use systems identification theory to identify the system and systems control theory to mitigate the threat from this organism. One misses the point in examining single cells, one must view the amalgam, albeit a heterogeneous organism genetically.

Second:

Now for Shannon. Frankly his approach is quite limited. I started teaching Information Theory at MIT more than fifty years ago, and even earlier with a Wienerian view. Shannon and Information work on communications. Frankly the very term information is a misnomer, mainly since we do not know what we mean by information from an epistemological basis so by applying this terms to data bits was cute and catchy but does it a disservice because people who fail to have any understanding of it will err in its application. Shannon was interested in signals sent over a noisy channel where there were limits in transmission capacity, say bandwidth.

He has two main theorems. The Channel Coding Theorem which says how fast or at what rate you can transmit a signal over a channel at a rate where the channel has a capacity in say bandwidth and an interference in terms of noise. There frankly is no real "information" here. Secondly is the Source Coding Theorem which says how much you can compress some signal with excess stuff, called information. For example, we can compress voice to a few hundreds of bits, 0 and 1, per second or we can likewise do the same with video at so many thousand bits per

second. The Source and Channel Coding Theorems of Shannon describe dealing with redundancy and dealing with limited capacity and noise respectively. That's it folks! It does not tell you about "information", whatever that means to someone. To Shannon it was changing a sine wave to a bunch of on and off signals. That's all folks.

So when one sees articles, letters, books like this one shudders and understands why we have so many poorly educated students. It's the teachers stupid!

Now; do biologists use any of these approaches? Think Eric Lander and the human genome. How do you think he got to match all the broken pieces of DNA into a genome; mathematics? After all he was a trained engineer in coding, that Shannon stuff. So he may not have used the two Theorems but he did employ the ideas resulting therefrom.

Pity we have people who make these statements. But alas this is all too common.



Labels: [Academy](#), [Genetics](#)

SATURDAY, JUNE 25, 2016

[ILLEGAL ALIENS AND ENGLAND](#)



Just a thought about 1066. That William fellow did not have a passport when he decided to cross the Channel. I wonder if the Brits want them out as well. DNA analysis for everyone I guess.



Labels: [Commentary](#)

[A THOUGHT ON BREXIT](#)

To understand Brexit one must understand Edward I and his progeny. Frankly, they started this process off. We Americans have little understanding of history; ours is but some two hundred and forty years. Edward I brutally attacked and hacked his way through Scotland, Wales and Ireland while having occupation rights on most of what we now know as France. His son, Edward II, was most likely the worst King ever, and that include John I and Richard III. His bumbling started the Hundred Years War, yes folks, it was a hundred plus years. Then Edward III managed to intensify this war, and despite the small period with Henry V, the English hacked and slaughtered their way through the Fourteenth and Fifteenth centuries.

So perhaps the roster, well you get the point. Also for almost all Americans who have never lived in Europe, that includes any diplomat or corporate type since they are just ex-Pats, they have no idea how a few thousand years of history still has a day by day impact. I recall the terror in my Czech partners in visiting the Austrians, and the Austrians dislike of the Italians and the French dislike of everyone, and the fact that everyone dislike Germans. Welcome to Europe.

The final issue is that Democracy has a strange effect. People vote and unless you are listening to the people you can get surprised. Will the French be next?

Then there is Russia. Having spent time there and looking at Russian from a non-Kennan like perspective, namely looking at Russia in a long term historical context, one sees the Russians having a point. Between Napoleon and Hitler they have a concern as to threats on their borders. I also believe that includes China and frankly should include North Korea. Eastern Russia, Vladivostok and environs has at its borders an unstable nuclear enabled state. That may be a balance for China but it is an unstabilizing factor for Russia.

The challenge for the next US President will be to understand these complexities. All the way back to Edward I and even before! One should remember why the Metropolitan of Moscow will not convene with the Bishop of Rome. Think about it.



Labels: [Commentary](#)

MONDAY, JUNE 20, 2016

[CAKES AND BAKES BY KELLER](#)

At the other end of grandsons is Keller and his baking business; [Cakes and Bakes by Keller](#), try it out!



Go try them out! He has mastered the art of fine eating!



Labels: [Commentary](#)

[ANOTHER EAGLE SCOUT](#)



Terrence IV received his Eagle Scout award Saturday, having spent a total on nine years in the process. Congratulations!



Labels: [Commentary](#)

TUESDAY, JUNE 14, 2016

[IS AI HELPFUL OR IS IT MERELY THE OPINION OF MILLENNIALS IN CALIFORNIA](#)

McCarthy defines AI, Artificial Intelligence, thus:

Q. What is artificial intelligence?

A. It is the science and engineering of making intelligent machines, especially intelligent computer programs. It is related to the similar task of using computers to understand human intelligence, but AI does not have to confine itself to methods that are biologically observable.

Q. Yes, but what is intelligence?

A. Intelligence is the computational part of the ability to achieve goals in the world. Varying kinds and degrees of intelligence occur in people, many animals and some machines.

Q. Isn't there a solid definition of intelligence that doesn't depend on relating it to human intelligence?

A. Not yet. The problem is that we cannot yet characterize in general what kinds of computational procedures we want to call intelligent. We understand some of the mechanisms of intelligence and not others.

Now in contrast my definition of AI is as follows:

If A=B

Then C

Else D

End

That's is, no more no less. But the key question is; what is A, B, C, D? You see we are dealing with computers and we must use numbers, namely bits. Therefore, ultimately each is some binary number in a memory location. They are to reflect some reality. Thus the issue is:

1. Who selects the reality?
2. What measures of the reality are used?
3. What weights on the measures are employed?
4. How does one relate the measure of one's perceived reality with the actual reality, whatever that is?

One can see from the above that a great deal of human judgement is used. That is even the case if we "adaptively" change weights and measures. For example, one can use a first level system, namely one where the programmer assigns weights and measures. Namely we measure x and we weight it by y to generate z which we call A. Or we could use an adaptive system. We all like

adaptive systems because they allegedly adapt to reality. But they are ultimately just the first level system pushed down one level. The adaptive system adapts its variable but by another selected measure called w . That is, we look at x and y over some data space and weight it adaptively by w to get z which we now call A . This of course can be carried on forever but we still have some human making some value judgement somewhere. Thus that human value judgement stays with us forever! It can become immortal.

Consider a case from NEJM a few years ago. The answer was "rabies". From a Bayesian perspective, its probability of ever occurring would have been zero, and the diagnosis is not definitive until autopsy with the identification of Negri bodies in the brain. The question of how does one develop an algorithm, an AI procedure if you will, to identify something that would generally have zero probability until after death is problematic. Obviously there are many A, B, C, D, and they may operate sequentially or in parallel. Furthermore, they may also adapt, namely the weights that map diagnostic variables into some binary number may change.

Consider the initial presentation in the NEJM article:

The patient had been well until 4 days before admission, when aching developed in the left elbow, which improved with ibuprofen. The next day, right-elbow discomfort occurred, and he had decreased appetite. Two days before admission, he noted difficulty forming words, mild light-headedness, and mild recurrent pain in both elbows. An attempt to drink a glass of water precipitated a gagging sensation. He had difficulty breathing and could not swallow the water. The choking sensation resolved when he spat out the water, but it recurred with subsequent attempts. He stopped drinking liquids and became increasingly anxious. One day before admission, he was unable to shower because of increased anxiety and noted intermittent decreased fluency in his speech and pruritus at the nape of his neck. He was concerned that he was having a stroke, and he drove to the emergency department at a local hospital.

Now if one were in a region where rabies was pandemic one would immediately think of rabies. But in Massachusetts where there had not been a case for 80 or more years that would be the last thought. Thus how would one "program" this decision.

The added results were as follows:

On examination, the patient appeared anxious, with dry mucous membranes. The blood pressure was 171/80 mm Hg, the pulse 86 beats per minute, the temperature 36.4°C, the respiratory rate 16 breaths per minute, and the oxygen saturation 98% while he was breathing ambient air. Other findings included ptosis of the right eyelid, mild facial twitching, postural hand tremors, and dysmetria on finger–nose–finger and heel-to-shin testing, without truncal ataxia. Deep tendon reflexes were symmetrically hyperactive throughout; plantar reflexes were flexor. There was mild difficulty with tandem walking. The patient's speech was rushed and fluent, except for occasional slurred words and pauses for word finding; the remainder of the general and neurologic examination was normal. The hematocrit, platelet count, erythrocyte sedimentation rate, and levels of hemoglobin, C-reactive protein, and troponin T were normal, as were tests of renal and liver function

Each result has to be added to some metric and some decision point.

One of the biggest problems in any AI is the judgements made when developing the primal metrics. The recent discussion regarding the alleged Facebook new bias is a prime example. AI is not politically neutral. It can be and remain as such highly biased by the very means by which selection bias is made. This is the case even if adaptive learning is utilized because even then the learning algorithms are also elements of bias perforce of their developers input.

To quote Drucker, who paraphrased McLuhan;

"Did I hear you right," asked one of the professors in the audience, "that you think that printing influenced the courses that the university taught and the role of university all together." "No sir," said McLuhan, "it did not influence; printing determined both, indeed printing determined what henceforth was going to be considered knowledge."

Thus this led to McLuhan's famous phrase that the medium is the message. Specifically, as we developed a new medium for human communications, we dramatically altered the nature of the information that was transferred and the way in which the human perceived what was "truth" and what was not. The television generation of the 1960's was a clear example of the impact of television versus film in portraying the war in Vietnam as compared to the Second World War. The perception of these two events was determined by the difference of the two media that displayed them to the public masses. Television allowed for a portrayal that molded more closely to the individual human's impact of the events as compared to films overview of the groups involvement's. Both media deal with the same senses but they are different enough to have determined two different outcomes of the wars. This conclusion is a McLuhanesque conclusion but is consistent with the changes that McLuhan was recounting in the 1960's in his publications.

But a corollary to McLuhan and the medium, is the use of putative AI techniques to present to humans certain facts. The AI becomes the new medium, it is the filter between the facts, whatever they are, and the perceived reality. For example, if one were to be tracking News on politics, then perhaps the AI presenter, the new medium if you will, may present you negative only facts on say Trump and positive only on Clinton. The result is strong medium reinforcement. We know that is the case in print, we clearly can see this say in The New York Times, hardly a Trump fan, but we know the sources and can weight it accordingly. However, if there is some AI engine in the background, hidden behind some curtain, written and architected by the feelings of some unknown person or persons, then how do we interpret that.

For example, we are now all told that Silicon Valley is the hub of the new entrepreneurial gestalt. However, this reality is a reality of apps, and software manipulations and social networking. In contrast we have a massive entrepreneurial present in Cambridge, here we have genomic engineering and lifesaving technology. We seem to weight a new app or social network well above a new pathway inhibitor or monoclonal antibody. Why? Perhaps because the social networks are self-reinforcing.

Thus our concern is that when we have humans developing AI algorithms say for medical diagnosis or news presentation the algorithms are inherently biased. Again in medical diagnosis, does a machine respond as a human when by misdiagnosing the patient dies. For the machine it is just another data point. For the human it can be mind altering.

Machines do not make data mistakes, humans do. Yet machines do not weight their mistakes in such a drastic fashion as humans do. Also humans are always inserting their value judgements. The result may then, as Drucker noted, be perceived as the new truth. Thus if we have some group of Millennials in California writing algorithms called AI, it really must be understood as nothing more than complex multi-layer opinion pieces, and pieces which may have long lives. Do we really want their value judgements telling us what is reality? One would hardly think so. Thus AI poses a significant danger as nothing more than propaganda from privileged protagonists.

Reference

Greer et al, Case 1-2013: A 63-Year-Old Man with Paresthesias and Difficulty Swallowing, NEJM, 2013;368:172-80.

Drucker, Peter F., Adventures of a Bystander, Harper Row (New York), 1979.



Labels: [Commentary](#)

MONDAY, JUNE 13, 2016

[WHAT IS THE VALUE OF THE SATS?](#)

The [Admissions Office of UVA](#) notes:

3. Scores from different exams aren't combined. We don't mix sections from different exams together. So we wouldn't put a math score from the ACT together with a reading/writing score from the SAT. Similarly, we won't mix sections from the old SAT and the new SAT. The College Board directed colleges on this last summer. They said it isn't appropriate to mix old and new because the exams are different.

Thus read that last sentence again. Well then what is the purpose of the SAT. It is to measure just what again? I gathered that some of the senior folks there came from the current Administration. That ought to pan out well, just look at their overall record.

SATs are like any other multiple choice exam. Drill Drill Drill. It is the low end equivalent of say the Chinese National Exams. You could have sequences several genomes, modeled successfully cancer pathway dynamics, or solved a few of Hilbert's challenges, but if you do not conform you are in my experience and in my opinion going to do poorly.

I truly feel sorry for some smart kids. If their profile does not meet the new world order then...but after all the Facebooks need some programmers...



Labels: [Academy](#)

[CANCER STEM CELLS: A PHILOSOPHICAL LOOK](#)

The recent book by [LaPlane on Cancer Stem Cells](#) is a brilliantly well-crafted introduction to the field from a philosophical perspective. Such an approach is significant since it was Galen who promoted the use of logic, and in fact the full trivium, as an integral part of the practice of medicine. Words do mean something and the term "cancer stem cell", the CSC, has been used by many over the last decade and a half oftentimes for multiple and possibly conflicting purposes.

As LaPlane initially notes the somewhat accepted definition of a CSC is (p. 2):

"Cancer stem cells are, as their name suggests, cells that combine two identities; they are both cancer cells and stem cells."

Thus starts the debate. For one must then ask what is a cancer cell and what is a stem cell. There is also a somewhat adjunct issue of the Cancer Cell of Origin. This construct is one that states that the initial change occurs in some cell. Then the CSC states that there may very well be another cell which carries on the proliferation. The questions then are: what are the characteristics of that cell, how can it be identified, how can it be targeted, and what are the therapeutic strategies that should be pursued? This is what the author examines.

The author's approach is philosophical in that she is concerned about definitions and the words that are applied. It is a bit of a return to the Trivium and even to Boethius. Words have meaning and what do we really mean by them. Furthermore, the author examines the meanings in terms of the phenomenological basis of each. As such this is a unique and frankly brilliant approach to a complex area.

It is not clear if this is an exclusive coverage but it logically appears to be. It does assume that the CSCness is defined and immutable. On p. 4 the author raises the concern:

"Stem cells and CSCs raise philosophical questions regarding their identity because we still do not know exactly what they are."

Thus we are beginning to read an analysis of things for which we have a great deal of uncertainty as to their very nature.

On pp 28-31 the author starts to provide some structure to the definition of a CSC. She initially uses the definition by Reya from 2001 and she appears to give a definition (p. 29) as follows:

"If a cell is capable of self-renewal (a) and differentiation (b) then it is a stem cell."

The above describes stemness. Yet there are two other requirements. One requires that it is a CSC is a tiny amount of the total cancer growth and that, this is critical, that (p. 30):

"...cancers are initiated and maintained by cancer stem cells."

Just what and how the terms initiated and maintained are to be interpreted is yet to be determined. Now this word study albeit being philosophical is essential. Somehow to study something we must be able to define it in a universally accepted manner so that phenomenologically it is consistent. The author keeps driving this critical point.

The author, in summary, thus divides CSC into several categories. First is:

1. Intrinsic: CSCs are CSCs and that is all. Once a CSC always a CSC. Once a cell has CSCness it always retains that character, and thus is intrinsic to the cell.

2. Extrinsic: CSCness may be dependent on where and when the cell resides. A CSC may become a CSC and then change back to something else depending on some yet to be defined extrinsic factors.

Then for Intrinsic we have (Chapter 7):

1.1 Categorical: It is in its very essence. It is what it is.

1.2 Dispositional: It depends on some extrinsic factor. It has a potentiality but it must be activated by some externality.

and for Extrinsic we have (Chapter 8):

2.1 Systemic: It can be determined from any niche. As the author states on p. 169:

"...at least two kinds of processes can induce stemness: stochastic events affecting gene expression and cell population level regulations. In both cases stemness appears to be regulated at the population/system level suggesting stemness would be a "systemic property""

2.2 Relational: This is purportedly analogous to Dispositional but it is for the extrinsic mode. Namely some extrinsic niche element.

Thus there are four models of the CSC and each has some element of plausibility. Frankly perhaps all exist. The author then proceeds to examine each with both phenomenological analyses as well as logical. She further posits possible therapeutic mechanisms for each. This is exceptionally well done and understandable.

Overall this is a unique and highly valuable contribution to the literature as well as to the discussions on the field of CSCs. Phenomenologically we seem to be obtaining new insights each day and having a framework to consider them is essential.

There are several areas where the author should have explored more. Let me name a few.

Mitosis: We know that cells divide by a process of mitosis. Generally, the cell divides and the resultant two cells are identical to the parent. Unless of course if some aberrant change occurs in copying the DNA as it splits. Thus it would be useful to demonstrate phenomenologically how this process would work so smoothly in CSCs. How does mitosis occur with a CSC so as to enable this bifurcation into a duplicate and an aberrant albeit non-CSC cell? What are the phenomenological steps that allow this? Thus far it appears to be some magical process which is just skipped over.

Dynamics of CSCs: In the classic CSC model each CSC divides creating a single copy of itself and a copy of some type of non-CSC cancer cell. Then somehow this collection of non-CSC cancer cells increases. If they do not divide, then growth rates are dominated by the CSC. For example, in the simplistic clonal theory where a single cell mutates and thence this cell just multiplies the resultant population grows exponentially. This may be modified by some form of apoptosis or lack of cell progression but it states that it is just a clonal explosion. We now know however that cancer cells as they go through the body are highly heterogeneous. Thus cancer is not purely clonal.

Epigenetics: We now understand that epigenetics plays a key role. However, their cellular dynamics is relatively little understood. Certain cancers such as MDS are really methylation disorders, that is epigenetic, and yet they often progress to AML.

Ensemble Models: In physics such as in statistical dynamics and in engineering in large scale stochastic adaptive control systems one develops ensemble models. Namely one could consider cancer as ensemble of cell states with transitions occurring between these states. A cell state would be the expression state of the genes, namely what genes are functioning and which are not. This of course is suggestive. Then one could consider a model for a space time spread of this new organism, the cancer states, and instead of looking for a CSC one could look to identify the "control elements" of this new quasi organism. This would be an adaptive system approach based upon a totally different view of the cancer. Thus is the CSC a transient artifact or a fundamental target for cancer?

Coverage: Are the epistemological models posited by the author complete? Do they cover all possible options in which a putative CSC can take? The four seem to be so: internal with internal control, internal with external control, external with internal control, and external with external control. It appears that these cover all options. Yet is it too all encompassing? Or as an Ockhamist is each CSC just another representation of how cancer can develop. Is the attempt by the author to categorize to be defeated by nominalism?

Overall this is a superb book and should be read and consumed by those in the field. The debates still continue but having such an approach brings new insight and discipline that is of great value.



Labels: [Cancer](#)

THURSDAY, JUNE 2, 2016

[MORE ON BATS](#)

The [CDC](#) reports a troubling case of a death from rabies. They state:

Rabies is a nearly universally fatal zoonotic disease, but is preventable if exposed persons receive postexposure prophylaxis (PEP). During recent decades, most domestically acquired human rabies cases in the United States have been associated with bat exposures; however, in the majority of these cases, no bite was reported. In 2015, a Wyoming woman aged 77 years died from infection with a rabies virus variant enzootic to the silver-haired bat. The patient had contact with a bat while sleeping, but she and her husband, her primary caregiver, were unaware of the risk for rabies in the absence of a visible bite wound; they did not seek medical evaluation or receive PEP after the incident. The patient's family had reportedly contacted several local agencies about bats near their home over multiple years, but had not been informed about the risk for rabies.

Rabies and bats are always paired. Bats are invasive and seek home for their settings. Bats also are as noted the most significant carrier and transmitter of rabies. How any physician missed this is unthinkable. Prophylactic treatment is essential even is a minimal exposure is considered.

The problem is that the vaccine is expensive and often not covered by insurance and further most Health Authorities are not attuned to the risk.

Hopefully the CDC can address this issue. Death from rabies is preventable if only one were to act.



Labels: [Health Care](#)

SUNDAY, MAY 29, 2016

[AND WHO PAYS FOR THIS?](#)

In a recent [Nature](#) article they indicate that the most recent recommendation for treating Type 2 Diabetes is surgical.

They state:

Clinical guidelines published this week announce what may be the most radical change in the treatment of type 2 diabetes for almost a century. Appearing in Diabetes Care, a journal of the American Diabetes Association, and endorsed by 45 professional societies around the world, the guidelines propose that surgery involving the manipulation of the stomach or intestine be considered as a standard treatment option for appropriate candidates. This development follows multiple clinical trials showing that gastrointestinal surgery can improve blood-sugar levels more effectively than any lifestyle or pharmaceutical intervention, and even lead to long-term remission of the disease

Let us examine some basic facts:

1. Type 2 Diabetes is a glucose metabolism malfunction. It is essentially an overpowering of the pancreas and its ability to maintain insulin secretion at levels to maintain safe glucose levels.
2. Glucose is byproduct of carbohydrate intake and its breakdown. More carbs in the more glucose produced and the more stress on the pancreas and its ability to handle the load.
3. Excess carb intake leads to obesity. Obesity is thus a measure of this overload.
4. A BMI of 25 or less is generally a metric for good glucose control and it generally is reflective of HbA1c, the 60 day average glucose load.
5. Excess glucose also creates an excess free radical problem which in turn can result in a plethora of disorders including cancers.
6. To keep the glucose low one need only keep the carbs down and in turn the weight down.
7. A pound of added weight is an excess of 3500 Kcal of food intake. If one consumes 2,000 Kcal per day and has a BMR of 2,000 then the net is zero. If however the BMR is less then one starts gaining weight, usually reflective of a carb overload.
8. The zero costs solution is intake control and proper weight balance. It is really cheap, at zero.

Now the suggestion for significant invasive surgery are say a cost of \$75,000 or more is insane. On the other-hand if the fattys get us old folks to pay for it then one guesses it is the ultimate gift of the ACA. And some candidates want free universal health care. Nothing is free folks!



Labels: [Diabetes](#), [Health Care](#)

WEDNESDAY, MAY 25, 2016

[THE NY TIMES AND PROSTATE CANCER](#)

The [Times](#) has a propensity of having women write on prostate cancer and result in telling men they should just forget it.

The latest writer, who it appears spent a short time at MIT *sans degree*, is pushing the "watchful waiting" approach, or why spend money on a lot of old useless men argument.

She states:

Without the word "cancer," Dr. Epstein said, men may not take seriously the need for regular biopsies and other tests. He and his colleagues at Johns Hopkins proposed a grading system to make it clear that Gleason 6 cells are less frightening than higher-grade tumors, but not necessarily benign. In the Gleason system, which involves a pathologist's assessment of how ominous the prostate cells look, 6 is actually pretty much the lowest score for cells that are

cancer, despite the Gleason scale officially starting at 2. The highest is a 10. But many men, hearing that their cancer is a 6, assume the worst.

The problem with prostate cancer it is real sneaky. Some are indolent, some are real killers. How does one tell the difference. No good answer. There are tests now that use the biopsied material to give better prognostic values but this write up totally ignores this. One wonders why? Ignorance or deliberate.

One also wonders why almost every other day we have another female reporter, no males yet, telling men not to worry! Perhaps they have run out of Trump stories.



Labels: [Cancer](#)

MONDAY, MAY 23, 2016

[PROSTATE CANCER AND OLDER MEN](#)

If any man had the nerve to say that only a few women die of breast cancer after 65 so why test any more there would be an uproar. Furthermore if a man wrote this in the NY Times he would be hanged in effigy. However it is OK for a woman to write in the [NY Times](#):

Because most prostate cancer develops slowly, it doesn't typically threaten survival or cause troubling symptoms for eight to 10 years. Even medical associations that disagree with some of the 2012 conclusions, like the American Urological Association, therefore discourage PSA testing for men with limited life expectancy.

One should at least see that she uses the word "typically". What if it is NOT typical, then it is OK for the man to die?

Perhaps we could try to get this covered as part of the NY Mayor's speech control, we could fine her say a few million for even thinking such a thought! By the way, what is a limited life expectancy, it all too often is in the eye of the beholder. It should not be some columnist in the NY Times.



Labels: [Cancer](#), [Commentary](#)

SATURDAY, MAY 21, 2016

[LANGUAGE AND GENDER](#)

[The Washington Post](#) has a reasonable take on language and the recent dictum on how to use it in New York City. It concludes:

Feel uncomfortable about being forced to use terms that express social status views ("Milord")

or religious views (“Your Holiness”) that you may not endorse? Well, you should feel uncomfortable about people being forced to use “ze,” which expresses a view about gender that they might not endorse. And, more broadly, I think we should all feel uncomfortable about government regulators forcing people to say things that convey and support the government’s ideology about gender.

But there is a bigger problem. You see the Romance Languages, such as Spanish, have gender specific nouns, verbs, etc. So if this applies to English does that mean we must change all of our Spanish, and the list goes on, to gender non specific. I remember my first Latin word when I was still quite young, agricola. Farmer. It is feminine. It was not until now that I wonder why it is feminine, I assume most farmers were men or at most fifty fifty back in 100 BC.

Perhaps when I look at my Italian, French. Greek, Russian as well I am going to have a problem. It is not discriminatory to change one language, why not all 235 spoken in New York. We are discriminating against English. Think of all those subway signs.

I have been using they, theirs and them just to avoid sex discrimination. Yes I know it is grammatically incorrect but it got me out of a few sensitive discussions. But this perhaps is a step too far. Then again there is that pesky First Amendment, but well who cares about those first Ten Amendments anyhow!



Labels: [Political Correctness](#)

FRIDAY, MAY 20, 2016

[THE EXECUTIVE ASSISTANT](#)

The last time I had a Secretary, aka Executive Assistant, who was really just that was sometime in 1986 or 1987. I managed a 20 country corporation with travel, expenses, scheduling, etc with something call Email and the Internet. It really worked, even back when I used Delphi as an Internet Service Provider with an early release of Eudora thanks to Irwin Jacobs. I also had a mobile phone so that if there were any questions over some 11 time zones I could address them.

Now I see that Theranos CEO is looking for both an Executive and Personal Assistant, two people. Perhaps that is why things are such a mess. You do not need assistants you need focus and leadership and you really must know something. Really. If I had a delay problem on the Internet backbone I had to analyze the delay characteristics on a piece of paper at at worst use Excel for a quick analysis of a solution.

As [Entrepreneur](#) reports:

After voiding thousands of faulty diagnostic tests and saying goodbye to its company president, Theranos is looking for some new blood, including an executive assistant as well as a personal assistant to CEO Elizabeth Holmes. With each passing week, the list of controversies and challenges Theranos faces grows longer. Since October, the biotech company has confronted scrutiny for deception regarding its technology, the accuracy of its blood tests and its failure to adhere to scientific standards. The government has threatened sanctions against its lab

operations and top executives, and president Sunny Balwani has entered early retirement in an obvious “you can’t fire me, I quit” move. At the same time, Theranos is adding new executives and board members to bolster its credibility, the company is sending out tens of thousands of notices regarding the invalidity of its tests.

Perhaps good leadership is better than more employees, especially as the walls are on fire.

One could see the problem back in 2014. In a [New Yorker](#) puff piece:

Holmes was driven from Palo Alto to the San Francisco airport, where she boarded a seven-seat Gulfstream 150 for a flight to Chicago. She would be speaking at a panel; from there she would fly to Cleveland to attend meetings at the She was travelling alone. Members of the Theranos board sometimes worry about Holmes. “My wife and I feel that one of our jobs is to bring her out,” told me. They invite her to the theatre, and this year threw her a thirtieth-birthday party at their home, which was attended by her parents, her brother,, and several members of the board and their spouses. and his wife, have tried, without success, to fix her up on dates. Her mother told me, “As a parent, I do hope that at some point she will have time for herself.” This concern is lost on Holmes. The plane had reached cruising altitude, far above a bank of clouds, and another green vegetable drink had materialized in her hand. “I have done something, and we have done something, that has changed people’s lives,” she told me. “I would much rather live a life of purpose than one in which I might have other things but not that.” Also, she said, with a smile, “I think I’m very young. Still.”

Now I have from time to time been snookered but this was just too obvious even then. Remember, always look behind the wizards curtain, there may be a great deal of just smoke and mirrors. Or as some of these well known politicians had advocated; "trust but verify". If you cannot verify then you better find someone who can!



Labels: [Commentary](#)

THURSDAY, MAY 19, 2016

THE TRIVIUM AND OCKHAM



In the 14th Century at Oxford and in Paris scholars studied first the Trivium; grammar, logic and rhetoric. For Grammar the ultimate question was; what does this word mean? Likewise for Logic; does this syllogism ring true? Finally in rhetoric: can I make an argument based upon facts using logic to convince my audience? Disputation was the forum of discussion. Namely opposing parties and inquisitors were allowed to engage the party presenting the argument in challenging the position. Debate was open.

Along comes William of Ockham and his adversary John XXII, the alleged Bishop of Rome whose intent was to remain in luxury at Avignon. Ockham challenged the Grammar and Logic of John, and the result was the beginning of what we now recognize as individualism; namely the fact that each individual is equal before God and the Law and that further it is the responsibility of the individual to act to secure their salvation. Collectivism, socialism, is the counter to Christian thought, it is not the group which seeks salvation, it is the individual.

In a [speech today the current Bishop of Rome opines](#):

The day's first reading, taken from the Letter of Saint James, is a forceful warning to the rich who accumulate wealth by exploiting the people. "Riches in themselves are good," the Pope explained, but they are "relative, not absolute" goods. He criticized the so-called "theology of prosperity"— according to which "God shows you that you are just if He give you great riches," saying those who follow it are mistaken. The problem lies in being attached to wealth, because, as the Pope recalled, "You cannot serve both God and riches." These become "chains" that "take away the freedom to follow Jesus." In the reading, St James writes, "Behold, the wages you withheld from the workers who harvested your fields are crying aloud; and the cries of the harvesters have reached the ears of the Lord Almighty."

When riches are created by exploiting the people, by those rich people who exploit [others], they take advantage of the work of the people, and those poor people become slaves. We think of the here and now, the same thing happens all over the world. "I want to work." "Good, they'll make you a contract, from September to June." Without a pension, without health care... Then they suspend it, and in July and August they have to eat air. And in September, they laugh at you about it. Those who do that are true bloodsuckers, and they live by spilling the blood of the people who they make slaves of labour. The exploitation of labour is a mortal sin.

Now let us begin with grammar. What do we mean by exploiting? Let us take a simple economic example in a capitalist society. Let us assume that the alleged exploiter owns a coffee shop. In order to sell coffee he must: (i) make good quality coffee, (ii) provide good service, and (iii) sell it at a competitive price. Now how does this capitalist accomplish this? Simply. First; revenue less expense equals profit. If the "profit" is negative then he goes out of business, unless of course the Bishop of Rome somehow underwrites his expenses. Now how does the Revenue get set? Well it is the market, namely the prices set by the competition. Lots of suppliers drive prices down. Lots of suppliers creates demand for labor and drives costs up. At some point the market clears. Happens all the time especially in a commodity bushiness. Thus the Expenses are dictated by the market not by the Bishop of Rome. Exploitation does not exist as an act of the owner but as a consequence of the dynamics of a market. Price settles to a level and salaries meet the level for survivable businesses. Simple. Economics 101.

Thus we return to Grammar. What does "exploitation" mean? There is no exploitation in a capitalist market, it is just the meeting of supply and demand on both the revenue and the expense side. The paragraph about the months and the contract appear confused. Must one supply pension, health care and the like, Perhaps, but that must be included in the total cost. It is not a gift, it is not charity, at least in an economically viable environment. If we were in some Marxist environment, then perhaps.

The the statement that exploitation, apparently defined as not providing a pension, is a mortal sin. Looking at the Old Testament, and then to the New, I saw nothing; perhaps this was written on the third stone Moses left on the mountain. Exploitation means no health care and no pension. But if the salary is at market then why not buy your own health care, why is it a moral imperative?

I suspect we need more Grammar, more Logic, more Rhetoric and a little disputation. Words mean something, so do the realities of the market.

Yet perhaps we should examine some recent comments by the [NY Times](#) on the Jesuits. As they noted:

The human cargo was loaded on ships at a bustling wharf in the nation's capital, destined for the plantations of the Deep South. Some slaves pleaded for rosaries as they were rounded up, praying for deliverance. But on this day, in the fall of 1838, no one was spared: not the 2-month-old baby and her mother, not the field hands, not the shoemaker and not Cornelius Hawkins, who was about 13 years old when he was forced onboard. Their panic and desperation would be mostly forgotten for more than a century. But this was no ordinary slave sale. The enslaved African-Americans had belonged to the nation's most prominent Jesuit priests. And they were

sold, along with scores of others, to help secure the future of the premier Catholic institution of higher learning at the time, known today as Georgetown University.

Yes the Washington based home of Presidents, Diplomats and CIA Heads was also the home of slaves and sold these slaves to preserve itself. This was done well withing the movement in the North to abolish slavery as a morally reprehensible act. Yet to these Jesuits it was a business transaction. Thus if one follows the Logic of the Bishop of Rome these people, the Jesuits, should be guilty to mortal sins, thus anathema, since clearly they were in chains and their freedom was taken away, again and again. Then perhaps we should rip these sinners from their graves on the Washington cemeteries and declare them anathema.

One should always be certain that their house is clean before complaining of others.



Labels: [Commentary](#)

GARBAGE IN GARBAGE OUT?

In an article today in the [NY Times](#) the author comments on the Facebook debacle with its search algorithms. First of all I had Facebook shortly after it came out and forced by my students at MIT to joining the future. Then after seeing it as a total distraction left several years ago, as I suspect did the students. Today, I, at almost 75, and my granddaughter just 13, see Facebook used only by "old folks", those 50 year olds who insist on telling everyone about their most intimate thoughts.

The Times author does bemoan the neutrality of the algorithm. She states:

The first step forward is for Facebook, and anyone who uses algorithms in subjective decision making, to drop the pretense that they are neutral. Even Google, whose powerful ranking algorithm can decide the fate of companies, or politicians, by changing search results, defines its search algorithms as "computer programs that look for clues to give you back exactly what you want." But this is not just about what we want. What we are shown is shaped by these algorithms, which are shaped by what the companies want from us, and there is nothing neutral about that.

Indeed, algorithms are anything but neutral. I recall doing clustering algorithms back in the day to discriminate Soviet subs from whales. No matter, whenever I changed a weighting constant I could change everything.

You see the "algorithm" may itself be neutral, or at least as neutral as possible but the constants and weights or how they are derived are not. That is where opinion comes in. And sadly we now know the West Coast bias, a true bias to the left, controls the world view.

What Facebook hope to achieve in a meeting like this is uncertain. One suspects that not one of the "conservatives" would have a clue about an algorithm, no less understand how bias is inserted.



Labels: [Internet](#), [Media](#)

WEDNESDAY, MAY 18, 2016

[SOME THOUGHTS ON KENDALL SQUARE](#)

Kendall Square was a dilapidated location when I first went to MIT over fifty years ago. A dying location with a small bar with great free pickles. A desolated T Station and dark at night. Behind the old buildings were small strip mall like edifices housing electronics start ups. Back then the entrepreneurs actually made things that pushed society ahead, unlike many of the newer Apps companies.

[MIT has finally gotten approval](#) for a new Kendall Square.



But take a look, it will have massive glass sided buildings with acres of concrete. For those of us who understand micro environments this will create a massive heat source and will distort the environment even more than it already is.



The current buildings are a bit better because they have more balanced facades. All glass is a well know contributor at least to local warming, just look at the Gehry building in LA. It almost fries people in its grasp.

The intent of this design is to be open and invite people. The real question is how do people get there? The parking has become either extortionary, \$50 per work day or more, or no-existent. The T has some access but it too is limited. What this is creating is a dense multi usage area where it appears that no usage will be optimized.

Residential use most likely be very upper income, akin to Battery City and its environs. Buildings like this are really not appropriate for raw start ups, despite the claims of the local incubators.

Cambridge housing is already going through the roof and soon this whole section of Cambridge will be gentrified. The final step will be the removal of the asbestos infested Court House, another example of Government sophistication.

This area has consequences, it will now be interesting to see what the unintended ones are.



Labels: [Academy](#)

MONDAY, MAY 16, 2016

THE ATTACK OF THE HACKERS?

Just a brief note. I tried to install Adobe Flash and down came Intel TrueKey some unwanted and un-removeable software that appears to hack into my passwords. I think! Just try and get rid of it...no way. Beware, I guess we just block Adobe and Intel (which owns McAfee) You would think they would ask...one wonders who owns TrueKey, NSA? I am truly amazed by the total lack of informing and getting some form of agreement to proceed....just a warning to you folks!



Labels: [Commentary](#)

SUNDAY, MAY 15, 2016

IS THIS GLOBAL WARMING?

The flower measured above is pictured below taken this AM.



For thirty years we have been recording the date of first bloom on a selected set of species plants and Hemerocallis is excellent. H minor is an early bloomer and we have about 25 years worth of data. The chart shows the days from the first of the year that the plant bloomed. Now blooming is driven by two factors; number of daylight hours and average temperature. Clearly there has been no change in daylight hours but a change in ambient temperature.

Thus is this data suggestive, conclusive, just noise? There appears to be a trend but it is a bit too scattered. I cannot explain the differences even though there may be micro-environmental issues. The latter are such things as trees there blocking sun and then removed. Nature is always changing conditions. We also have the total precipitation as well albeit considered small in the case.

Just some thoughts and more to come.



Labels: [Global Warming](#)

SATURDAY, MAY 14, 2016

[TIME CHANGES: BOLOGNA 1316 AND MIT 2016](#)

Seven hundred years and one expects a change, of some type. As [MIT announces](#):

MIT is honored to welcome actor, filmmaker, co-founder of Water.org, and native Cantabrigian Matt Damon as the guest speaker for the 2016 Commencement Exercises.

Yes it is a movie actor whose role as a South Boston vagabond who managed to show that without any education he could out smart any MIT Math post doc.

Then in 1316 at Bologna we have this description (from a Ciba Symposium document in 1945^{13[1]}):

^{13[1]} THE ORIGIN OF THE UNIVERSITY OF BOLOGNA, ARTURO CASTIGLIONI, M.D., Yale University, School of Medicine, Ciba Symposium, VOLUME 7, NUMBERS 5 AND 6 , AUGUST-SEPTEMBER 1945.

The graduation ceremony at Bologna was presided over by the Archdeacon. Graduation consisted of two parts, the private examination and the public examination called conventus, or conventatio. The private examination was the real test of competence, the so-called public examination being, in practice, a mere ceremony. The candidate who had passed the private examination and was admitted to the public one, was called a licentiate. Generally, the licentiate proceeded to the ceremony which made him a full doctor after a very short interval. On the day of the public examination, the love of pageantry characteristic of the medieval, and especially of the Italian mind was allowed ample gratification. Before the appointed day, the candidate, preceded by the beadles of the Archdeacon, rode around the city inviting public officials or private friends to the ceremony or to the ensuing banquet. On the day of the conventus the candidate was accompanied to the cathedral by the presenting doctors and by fellow students lodging in the same house with him. The idea of the ceremony was essentially the same as that of the "commencement" of American universities. It derived from the principle of Roman law according to which a man was invested with office by a solemn performance of its functions.

By this act a new doctor was recognized by his colleagues, and received among the doctors, he., into the teaching guild or brotherhood. Arriving at the cathedral, the licentiate delivered a speech and read a thesis which he defended against opponents who were selected from among the students. He was then presented by his sponsor or promoter to the Archdeacon who delivered a complimentary oration and concluded by solemnly conferring the degree of doctor by the authority of the Pope and in the name of the Holy Trinity." A gold ring was placed upon his finger, either in token of his espousal to science or as a symbol of the doctor's claim to equality with knights, the magisterial cap was placed upon his head, and the sponsor left him with a paternal embrace, the kiss of peace, and a benediction. The ceremony concluded, all present were required to escort him in triumph through the town, surrounded by a mounted cavalcade of personal friends and wealthier students and preceded by three university pipers and four university trumpeters. It appears that in the case of poorer students these expensive ceremonies were dispensed with.

Proof of the great importance attached to the graduation is the fact that Charles V granted to the college the right of conferring knighthood upon doctors; and that the doctors of the college were themselves knights and counts of the Lateran. One of the most interesting differences between the University of Bologna and the other universities lies in the relationship between the various faculties. In Paris and in other European universities, the doctors and students of all faculties were united in a single body. In ancient Bologna there was no connection between the faculty of law and that of the arts, i.e., liberal arts and medicine, other than that the students of both received their degrees from the same chancellor, the Archdeacon of Bologna. The organization of law students attained a high development earlier than that of the students of medicine.

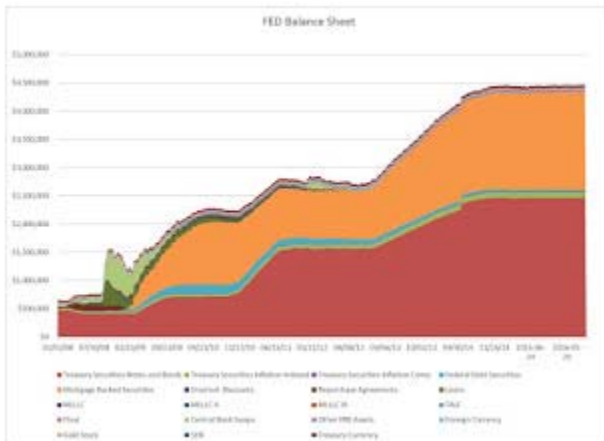
At that time the focus was on the new Doctor, and recognized now as a Knight, pari passu with the equivalent in society. The work of the student now a Doctor was the focus on the event.

It appears that we now "Hood" the new Doctors off stage and bring to the fore the characters who portray what the new Doctors were incapable of doing. Things have changed in 700 years, perhaps not really for the better. Are we honoring the right people?

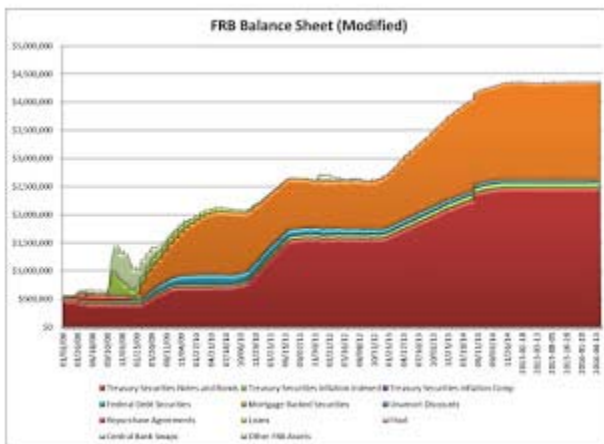


Labels: [Academy](#), [MIT](#)

FED BALANCE SHEET MAY 2016



The above is the total FED Balance Sheet. It appears to be stable for the past two years.



A little closer and no change.



Finally the key two items. The problem is; how do they unwind the old mortgage stuff? That will be the painful step. Also they have ratcheted up additional currency and that may also need unwinding. The above shows the Easings over time, stability now is there but it is a very unstable stability.



Labels: [Economy](#)

SATURDAY, MAY 7, 2016

[SOME OBSERVATIONS ON THE WORKFORCE](#)



The above is an analysis by element of the workforce as a percent of the total population comparing August 2006 to the current. It is interesting to see what is happening.

1. Professional is increasing. Just what that represents is questionable.
2. Education and Health is the largest increase. We understand that one.
3. Construction takes a big hit. Now you really cannot outsource construction so this is a serious number.

4. Government contracted and this is due mainly to the Recession.
5. Leisure is up but one suspects that is minimum wage jobs and has displaced other higher income jobs.
6. Manufacturing has taken a big hit. This is both demand and outsourcing.
7. Information is down but not clear if this may also be outsourcing.

Overall this is not a pretty picture.



Labels: [Economy](#)

WHAT IF ROSALIND FRANKLIN USED A LAPTOP WITH POWERPOINT?

I have been watching a Broad Institute set of talks on CRISPR. For the most part they are superb but there was a thought that arose.

Back in the early 50's and thru probably;y the early 90's at least we used transparencies or 35 mm slides in presentations. They were both time consuming to produce, expensive, and were cumbersome. Half the time people put the 35 mm backwards/up side down or mixed them up.

Now with your laptop and PowerPoint you can make real time changes and you can click through hundreds of content dense slides in a femto second.

Then I thought of Rosalind Franklin and Jim Watson and the famous X Ray diffraction pattern. What if she had this on a PowerPoint slide presentation and just flipped through it at the speed of light while walking about as if in some TED Talk! Would "Jim" have taken poorer notes, would they have forever messed up the double helix, would Pauling had seen his mistake and published?

Sometimes technology may not be beneficial. Talks with infinite data packed on uncountable slides and spoken as if one is in some evangelical group meeting may not get the point across. Oftentimes great ideas occur in a pause, a new idea presented, then a slight respite, and connections occur.

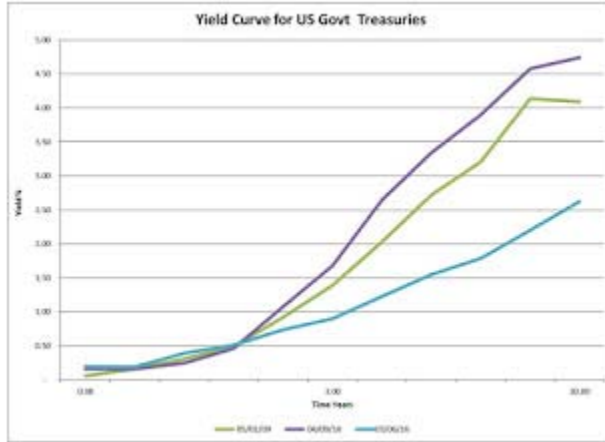
Not that I am against PowerPoint slides, I am a big abuser of them, always have been, but simplicity and clarity are critical. One does not have to tell the audience every fact you gathered, just the important ones. And also, keep the preaching to the Church! Oh yes, and take the mike off before you start commenting.....



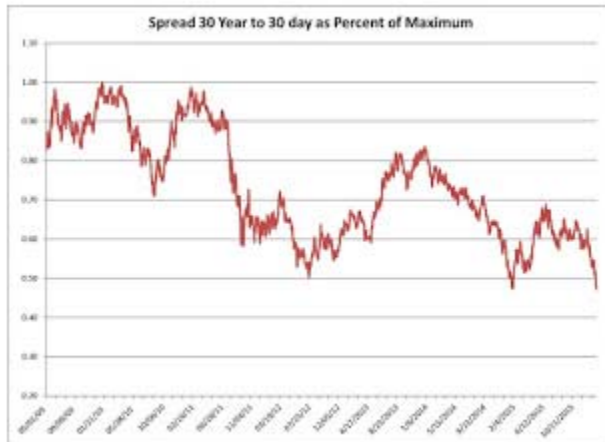
Labels: [Academy](#)

SATURDAY, MAY 7, 2016

YIELD CURVE MAY 2016



The yield curve as of yesterday is nearly flat. This is one of the lowest and flattest yields ever and driven by FED policy. It may be good for the Stock Market and may reflect the abysmal growth in the economy but it lacks reality. Money should have value.



The above is the 30:30 spread, the shortest to longest. It has reached a record LOW! That should be a concern, no faith in growth.



The 90:10 spread is shown above and it too is at all time low.

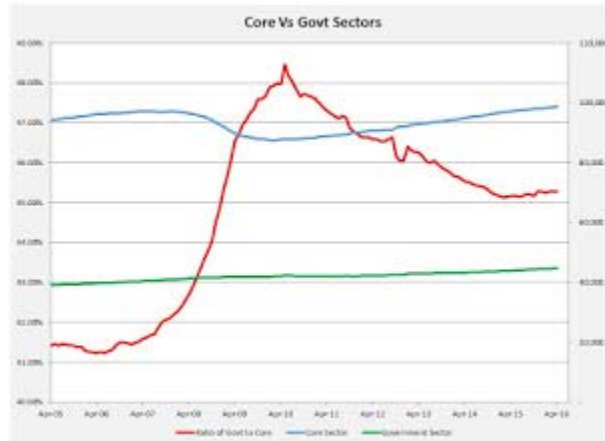
One suspects that things will not be getting any better at this level.



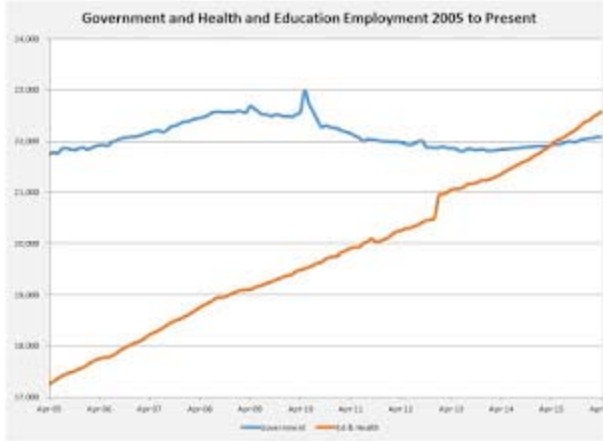
Labels: [Economy](#)

[MORE ON EMPLOYMENT](#)

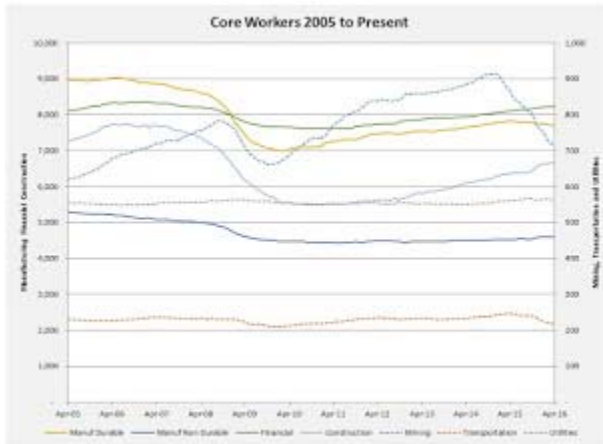
We have not been examining the details here as we had during the Crash of 08'. But perhaps a re-look as we approach election year is worth it.



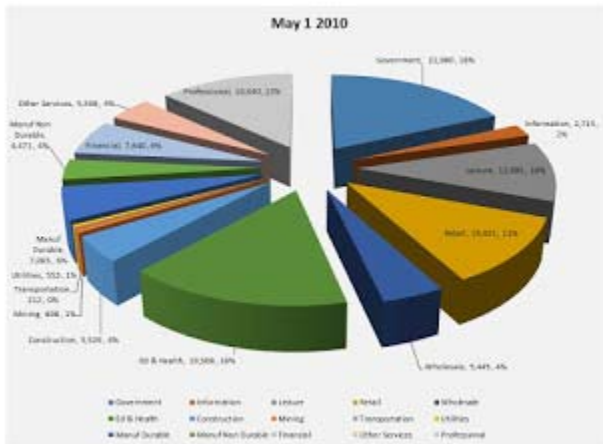
First one of my favorite charts is what is Core versus Government. Government here is Government plus Education plus Health Care. You see the ACA, Medicare, Medicaid make them one as well. The ratio was about 41% in 05' Now it is 45% and rising again. That means that almost one person works in doing something productive for every person being supported doing Government related things. This means two things. More Government and less real value production.



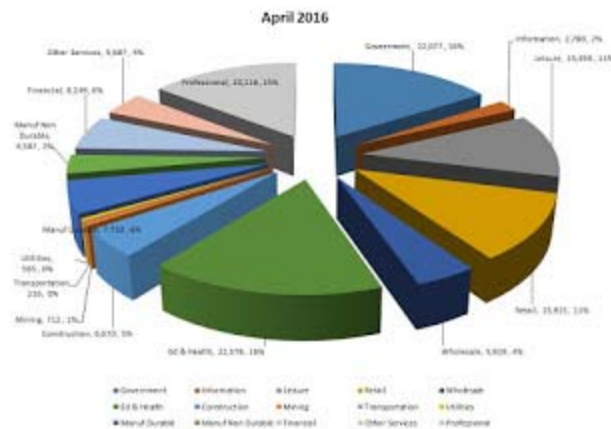
Looking in more detail we see Ed and Health on a steady climb! It is nu-relentless. Government is now climbing again as well.



The above shows all other sectors. It appears better than it looks because it does not reflect a significant population growth.



The above was the split in 2010 and below is today.



It is worth examining the differences.



Labels: [Economy](#)

FRIDAY, MAY 6, 2016

[SOME THOUGHTS ON RUSSIAN NETWORKS](#)

During the period from 1960 thru 1990 Russia developed a variety of networks, many for military use and many for central command and control. Based upon my own personal first hand experience working with them they clear were ate the same level as the west. Thus in rethinking the book by [Peters](#) which I reviewed I thought that his title was most likely totally out of place.

Using the title [How Not to Network a Nation: The Uneasy History of the Soviet Internet](#) was in my opinion out of place. The Internet was a construct that grew out of the arrogance of AT&T more than any uniqueness on the part of US technology. If AT&T had agreed to work with ARPA then this would have just been an extension of the monopoly network. Instead the arrogance of the monopolist, the entity that saw itself above everything else, created the creative destruction that led to its collapse.

Thus there is a real story of a set of brilliant technologists in Russia that may very well go untold. It was not a question of "How Not to" but the advantage the early ARPA team had in facing an adversary, not Russia but AT&T, and having the resources to overcome it.

Perhaps some day there will be a work on Soviet networks, a works which commends the efforts of many brilliant men and women in Russia who created a parallel universe and who when the borders fell allowed in a seamless manner the full expansion of the global IP network.

If one further looks at the time one also sees the IBM SNA network, akin to many of the centralized schemes we may see in Russia and Europe. But as a backdoor way to get around AT&T we had TCP/IP.

Thus understanding the reality of what occurred, it is not, "How not to" but ask ourselves the question; what really happened. Also one hopes there is a tale of Russia's advances to tell the

complete story. From that we can learn that our then adversaries were as bright as we think we were.



Labels: [Academy](#), [Russia](#)

[THE USPSTF IS AT IT AGAIN](#)

The USPSTF had previously made a recommendation that PSA testing did not have any positive effect in mortality. So frankly they said "stop it". Then various studies indicated they were wrong. The two NEJM studies in 2009 that the USPSTF relied upon were fatally flawed for a variety of reasons, many of which we discussed here at the time (See recent [NEJM](#) comments).

The folks at the USPSTF are now back at it again. This time to try and put a stake through the hear of PSAs. It seems they just want to get rid of old men. That's one way to cut Medicare.

The [USPSTF](#) has proposed a study whose goals are:

1. *Is there direct evidence that prostate cancer-specific antigen (PSA)-based screening for prostate cancer reduces short- or long-term prostate cancer morbidity and mortality and all-cause mortality?*
 - a. *Does the effectiveness of PSA-based screening vary by subpopulation/risk factor (e.g., age, race/ethnicity, family history, and clinical risk assessment)?*
2. *What are the harms of PSA-based screening for prostate cancer and diagnostic followup?*
 - a. *Do the harms of PSA-based screening for prostate cancer and diagnostic followup vary by subpopulation/risk factor (e.g., age, race/ethnicity, family history, and clinical risk assessment)?*

Frankly they already seem biased. But that is not just my view. As [Medscape](#) notes:

"Finding high-quality data to answer this will be challenging," Dr Hoffman told Medscape Medical News. None of the major screening trials enrolled men younger than 50 years, most subjects were white, and investigators did not routinely assess clinical risk. "While some studies are now recruiting patients to address screening in higher-risk populations, it will likely take at least a decade to determine the effects of screening on morbidity and mortality," he summarized. In the meantime, Dr Hoffman is concerned that "abandoning PSA screening" is proving harmful. The rate of distant-stage prostate cancers in the United States is increasing, according to a population-based study for which he was lead author. However, "it's too early to tell whether this will lead to an increase in prostate cancer mortality," he said. The USPSTF research plan separates the review of evidence about the potential harms of PSA testing, biopsy, and treatment.

Indeed to validate these questions takes time, and a decade is not bad. The issues of "harms" is so individual and personal it appears that only the Government can make the decision for all of us. Why not, but perhaps they did not notice the recent elections!

[I have noted the complexity of the PSA test](#). It is far from perfect. The Bayesian analysis is also far from perfect. Namely increasing PSA, or PSA velocity is not a clear indicator, family history is not a clear indicator, a prior biopsy with HGPIN is not a clear indicator, and a contrast MRI using diffusion weighting is not a clear indicator! So what is? Ultimately it is a biopsy, but even that samples some 1-2% of the tissue.

So what is the solution. For those who recall the Hippocratic Oath, "Do no Harm!"



Labels: [Cancer](#), [Health Care](#)

[I DON'T THINK SO](#)

The [NY Times](#) discusses the weight gain/loss issue and blames the brain rather than will power. They state:

The root of the problem is not willpower but neuroscience. Metabolic suppression is one of several powerful tools that the brain uses to keep the body within a certain weight range, called the set point. The range, which varies from person to person, is determined by genes and life experience. When dieters' weight drops below it, they not only burn fewer calories but also produce more hunger-inducing hormones and find eating more rewarding.

No the root problem is that 3500 Kcal equals one pound. And if you only burn 1200 Kcal per day you have a problem if you consume 2400 Kcal per day, you gain 1 pound every 3 days! Now the problem is burn rate. Genetic control has allowed certain peoples to live on fewer calories. Native Americans in certain areas were living off of very few calories and when introduced to a European diet one saw massive levels of obesity and Type 2 Diabetes. When they had fewer calories they did well and survived, it was the diet change that did it.

The problem in my opinion is what we allow ourselves to consume as food. Often also it is the spouse or family that is non-supportive and almost antagonistic to the dieter. The environment during the weight loss period is focused but then after it returns to an excess caloric one where all too often family members reinforce the eating misalignment.

Thus it may very well be will power, but the will power of the family and friends to change.



Labels: [Health Care](#), [Obesity](#)

[THE CABLE BOX](#)

As [TechDirt](#) notes:

Congress is simply fed up with the FCC's pesky new habit of standing up to giant cable and broadband companies. Congress was outraged when the FCC announced it wanted to stop states from letting large ISPs write horrible, protectionist state laws. Congress was outraged when the FCC announced it wanted to pass actual, functioning net neutrality rules. Congress was even

outraged when the FCC decided to raise the standard definition of broadband to 25 Mbps, since it only served to highlight a lack of competition for next-generation broadband service.

They continue:

A [new letter from sixty Congressmen and women](#) (pdf) reads as if it was written by a cable industry lobbyist (because it probably was), deriding the FCC for daring to interrupt the cable industry's glorious history of innovation with a pesky quest for better, cheaper, consumer-facing hardware:

"The Federal Communications Commission's recently proposed rules on the Competitive Availability of Navigation Devices, if adopted, will jeopardize the incredible evolution of video distribution services enabled by generally reasonable regulation. Imposing new, onerous regulations on pay-TV providers would produce very few benefits for consumers, while potentially harming the viability of these providers. The particular obligations being considered by the FCC are all the more troubling because they would mandate compliance with technical standards that do not yet exist, injecting even greater uncertainty into the marketplace. How horrible! Except it's not true. The [FCC's proposal as it currently stands](#) (pdf) says that cable providers can use any technology they see fit, and any copy protection they'd like, to ensure their content can be delivered to third-party hardware under the FCC's rules.

The Cable Box and Cable modems are antiquated boat anchors that the consumer pays extortionist rates for in my opinion! Most homes have vacuum cleaners that are newer than cable boxes. One wonders if Congress is truly on payrolls. Perhaps the Trump backlash is reflective of the electorate becoming aware of these folks and their persistent attempts to pay service to those lobbyists and companies that fund their campaigns while these people extract money from the poor taxpayer. Often the arrogance of the "elected" officials is amazing. The cable box issue is one of the most powerful symptoms of this in practise. I could buy a cable model from [Amazon](#) for just a bit more than \$50 retail. But I am paying \$10 per month for the past fifteen years! That is a total of \$1,800 for a \$50 box! Do these Congress folks have the slightest clue.

Then go to the cable box itself. It uses 1980s technology to operate. I know because I was in Cable then. It is truly a boat anchor. My Amazon unit has voice control etc and costs peanuts and does infinitely more.

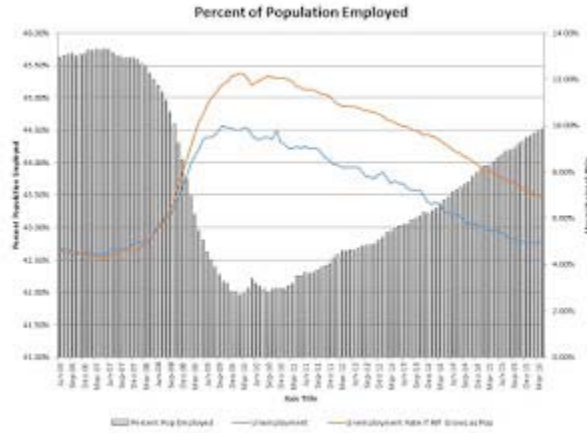
One should read the letter from Congress. In fact one should be seriously concerned if your Congress person signed it, you should ask just what they are doing. The system should be open, namely open to vendors, like even wireless! Yikes, Verizon is more open than the Cable folks!



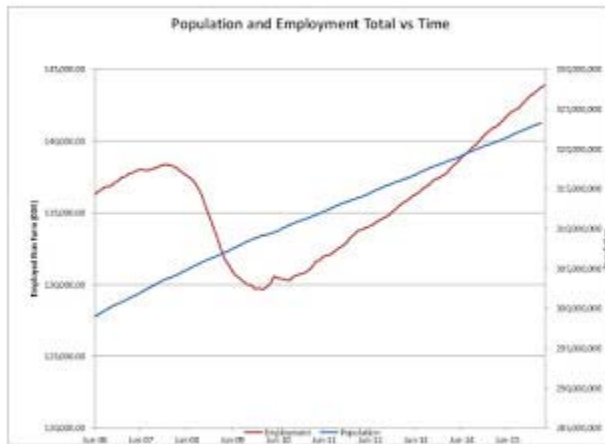
Labels: [CATV](#), [FCC](#)

FRIDAY, MAY 6, 2016

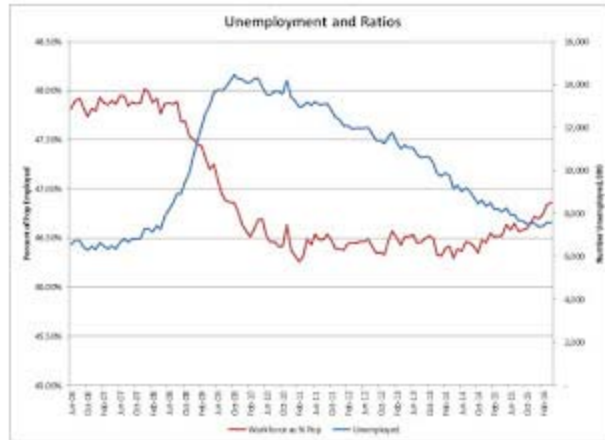
EMPLOYMENT



Overall employment is still weak. The participation is still very low and this impacts Government revenue dramatically.



The above shows this fact that as the population continues to increase employment also does but barely at the rate necessary to provide jobs to those in need.



There may be some hope given the slight increase in participation but one always questions the numbers.



Labels: [Economy](#)

THURSDAY, MAY 5, 2016

[IF ALL ELSE FAILS LISTEN TO THE CUSTOMER](#)

I used that phrase many times to explain why things did not turn out the way they should have. The analog in Medicine is a paraphrase of Osler which is *"If all else fails listen to the patient!"* I have seen that one many times.

The [NY Times](#) states regarding the Trump win:

But in the end, you have to point the finger at national political journalism, which has too often lost sight of its primary directives in this election season: to help readers and viewers make sense of the presidential chaos; to reduce the confusion, not add to it; to resist the urge to put ratings, clicks and ad sales above the imperative of getting it right.

Now I try to avoid Presidential politics but this paragraph just stands out. The Times appears to despise Trump and day after day they have been slamming him mercilessly. Ok that's their prerogative. But then to say that their job is to help us poor voters to make sense, it is their very slamming that educates the voters!

Perhaps one should regain composure and ask why this has occurred, a business man who never spent a femtosecond in Government now becoming the putative candidate. Whether you are trying to sell a product or heal a patient you cannot insist that they adhere to your way of dealing with things. The new media has created a distortion field. Yes as the Times notes telephone polls are useless. The young do not answer and the older folks have call blocking. That leaves the middle ground who will most likely say anything! Garbage in etc.

This will be an interesting campaign. It appears that even the establishment does not seem to get it. The alleged "principles" are actually dictated by the public, and apparently they are on the prowl.



Labels: [Politics](#)

[RUSSIA, NETWORKS, INNOVATION](#)

Peters' book on [Networking the Soviet Union](#) is less a tale of the technology developed in the then Soviet Union than a tale about the structure of the centralized bureaucracy that managed to nearly bankrupt the entity. As regards to the actual technology I would go back to the mid-1970s when I was in Washington. At the time I was at Comsat and was "befriended" by the Technical Attaché at the Czechoslovakian Embassy. Also the home of the Cuban delegation as less than an idle point of interest. As part of my tasks at the time I followed my new friend around as he tried from one occasion to another to collect data on US telecommunications and network systems. At the same time, I had the task of connecting what was then the early stage of the ARPA Net to the Intelsat system connecting Etam West Virginia to Goonhilly in the UK and Trondheim in Norway. In the U*S we basically placed all of this in the public domain so I would guess my "friends" job was fairly easy.

I saw him I believe in the Fall of 1977 at a Conference at Cornell at which time the Diffie Hellman encryption algorithm was discussed. I guess that half the attendees were not necessarily who they may have said they were.

Then some twenty plus years later I now had partners in Russia running my Russian network and the former head of the Czech PTT was now my Czech partner. My former "friend" used to work for him. Small world. Since I had worked on the Comprehensive Test Ban Treaty Negotiations in the late 1970s, doing the networking for the seismometers, my Russian friends clearly knew me. During one of my conversations I was told by my Czech partner, a senior figure both in Czech as well as Soviet circles that they used the Bell System Technical Journals to design their telecom systems and the IEEE journals for data systems.

In fact, one of my Russian partners was one of the first to introduce the Internet to Russia and we completed the task in the late 90s. As such I have a different view than the author, one based on technical facts of the network and its operations.

This book is NOT about the Internet or its Soviet clone from a technical or operational perspective. Rather it is about the Soviet bureaucratic system and the need to make some sense out of its overwhelming administrative overhead using networks on both the economic administrative side and the military side.

Chapter 1 is a discussion of Wiener and Cybernetics. The author presents one of the best discussions regarding the acceptance of Cybernetics in the Soviet Union I have seen. Wiener was a brilliant mathematician and in addition could think in large scale systems. His book on Cybernetics was warmly received in the US but its theme was understanding large scale systems and the US was no longer, at that time, interested in that. It was moving from a War footing and

into a capitalist industrial footing in the 50s. The Soviet Union on the other hand was further consolidating a centralized command and control economy and Wiener's ideas rang bells. Thus they adopted his view of the world. Chapter 2 presents a good overview of how the Soviet Union then took these ideas and tried to integrate them into this centralized world.

Chapter 3 is allegedly an attempt to present the networks used. It really is a discussion of the people and the politics and not the technical issues. Although interesting I really wanted to see some discussion of what the Russian had implemented and how their designs differed from ours. There were a mass of varying data protocols and data speeds and network transport mechanisms that were developed in the US and I wondered what did the Soviets do in parallel. The author depicts the Soviet's response as a response to SAGE and then I wondered what the response was to the packet ideas of Baran. In fact, the work of Roberts and in turn Kahn at ARPA were almost all in the open literature and the goal was a survivable network, apparently perceived by the Soviets as a threat. If so I wondered just what they did. I am certain that there must now be a great deal of unclassified CIA and DIA reports that would clarify that but the discussion is missing.

Chapters 4 and 5 go through the 60s and then 70-80s respectively and the author presents the principals who tried to accomplish something in this realm. The politics seemed to be always creating roadblocks and the innovation that ARPA allowed seemed to foster what we have today.

The author has an interesting discussion on the Mansfield Amendment, that in 1969 put an end to DoD funding anything but specific program supported work. Until that time DoD funded what has become the foundation of our information based economy, and with Mansfield we saw a total collapse of that development. I often wondered if the Soviets saw that for what it did.

Overall the book is an excellent presentation of the people and politics of what would become some of the infrastructure in the Soviet Union. I wondered what the role of a RosTelecom would be in that mix, an element not discussed. In addition, the Soviets had satellites the Molyniya System which were not equatorial but polar, and thus their communications ground stations were expensive and subject to failing. Their cable connections were also mixed with spotty interconnections across the wide expanses. The author provides some maps but it would have been more useful to have some detail.

This is a well-organized and presentation of the system, as politics, not the system as technology. Given how closely the Soviets monitored US technology and how open we were then and now, I have often wondered what the Russian created from whole cloth and what was reproduced. The Russians were and are technologically on a par with the West in terms of human capital but it was often the weight of the system that slowed them down. That burden was lifted after the fall but I wonder how much may have returned.



Labels: [Internet](#), [Russia](#)

SOCIALIZED MEDICINE

What is Socialized Medicine? Simply it is Medicine which is controlled by the Government. It is the NHS in the UK. Physicians are employees and they get a salary from the Government. They work 40 hours a week, they get a vacation, health benefits, pension etc. They are like the postal service, the subway conductors, the Ferry Boat operators. Yes they are like IRS agents and frankly like all other Government employees. You are sick, well if it is 5 PM and they are off duty hope the replacement is on time and has some clue what they are doing. If you die then like the VA they get a bonus and your family gets the ashes, at best. That way no one can check to see if they lost your body.

Now along comes a group of docs who want to do that in the US. They are Progressives but in reality they are Socialists. I know because my grandmother was head of a Socialist Party in New York. I grew up in a Socialist group and we went to Public Health clinics with white porcelain metal chairs.

Now [Eureka](#) reports:

In a dramatic show of physician support for deeper health reform - and for making a decisive break with the private insurance model of financing medical care - 2,231 physicians called today for the creation of a publicly financed, single-payer national health program that would cover all Americans for all medically necessary care. Single-payer health reform, often called "Medicare for All," has been a hotly debated topic in the presidential primaries, thanks in part to it being a prominent plank in the platform of Sen. Bernie Sanders. The new physicians' proposal is strictly nonpartisan, however. The proposal, which was drafted by a blue-ribbon panel of 39 leading physicians, is announced today in an editorial titled "Moving Forward from the Affordable Care Act to a Single-Payer System" published in the American Journal of Public Health. The editorial links to the full proposal titled "Beyond the Affordable Care Act: A Physicians' Proposal for Single-Payer Health Care Reform" and the names of all the signers, and it appeals for additional physicians to add their names as endorsers. The proposal currently has signers from 48 states and the District of Columbia. "Our nation is at a crossroads," said Dr. Adam Gaffney, a Boston-based pulmonary disease and critical care specialist, lead author of the editorial and co-chair of the Working Group that produced the proposal. "Despite the passage of the Affordable Care Act six years ago, 30 million Americans remain uninsured, an even greater number are underinsured, financial barriers to care like co-pays and deductibles are rising, bureaucracy is growing, provider networks are narrowing, and medical costs are continuing to climb. "Caring relationships are increasingly taking a back seat to the financial prerogatives of insurance firms, corporate providers, and Big Pharma," Gaffney said. "Our patients are suffering and our profession is being degraded and disfigured by these mercenary interests."

Now how much will this cost? We know that under the ACA we are running at about \$12,000 per person per year. Then simply 30 million yields \$360 billion! No problem, just up Medicare monthly amounts as the Baby Boomers enter.

I am always amazed by Socialists. Somehow there will always be someone to foot the bill, not them. Perhaps they just want a 9 to 5 job. They should have gone to the Post Office.



Labels: [Health Care](#)

[A TELEPHONE COMPANY?](#)



Verizon has an asset, a very valuable asset. It is the spectrum. It is not the copper plant, given union costs the copper has become a liability. So sell the copper, they have done a great deal already. A second asset is the property. They have billions in off balance sheet real estate, in New York City and elsewhere. They have monetized some of this via selling off part of 140 West Street, my first place of real employment.

Back to the wireless. With 5G systems they can provide Gbps service to anyone. They are mobile but they are wireless, no copper and no union, and most importantly little competition, it's that asset again.

So what is management doing; they bought AOL and now are looking at Yahoo. AOL was dead in 1996! Time Warner bought a corpse. It has not risen from the dead. And Yahoo, the blood has stopped flowing there ages ago. Somehow corporate management gets infatuated with glitz. I saw this at Verizon before when they tried to get into content, hundreds of millions down the drain!

So what should Verizon do? Well we tried answering that several times a decade ago. Expand wireless. It is an oligopoly with oligopoly rents. Content is a hits business. I saw this at Warner, it only works when you are (1) really smart, and (2) you have a large portfolio. Steve Ross and his group were really smart. They could really pick winners. They also had a large portfolio. Telephone folks are not really smart. They run a utility, albeit a semi regulated one.

The rule there should be; leverage assets. Content does not leverage assets. It tries to compete with other content providers and some are really smart.

So what does the current strike do. It presents an opportunity to Verizon. Sell off the rest of copper, sell it to anyone, but first sell off the buildings with a sale lease back clause, for some period, not forever! Monetize the old stuff and focus on the new.



Labels: [Telecom](#)

BIOFILMS AND DRINKING WATER

Clean drinking water is an essential in any modern society. As has been well known, even the well managed drinking water may be contaminated as a result of the presence of biofilms^{14[1]}. External contaminants are carefully restricted but the growth of biofilms is almost inevitable. The growth is often fostered by the pipes themselves with iron based pipes providing a fertile ground for the biofilm^{15[2]}. Biofilms are the development of an integrated bio mass resulting from the growth of bacteria and other microorganisms. The biofilm aggregates and builds into a large mass which can degrade pipes, inhibit flow, and initiate bio hazards if the fluid such as water is to be used in a potable manner. Biofilms are a significant cost in the operations and maintenance of various water flow mechanisms in residential and commercial facilities.

[We have prepared an analysis of biofilms](#) and their inhibition in remodified drinking water systems.

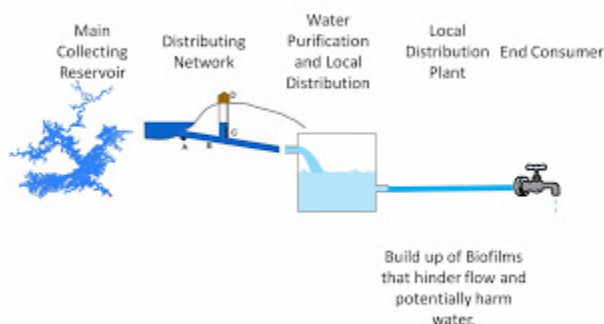
There are many nano bacteriostatic mechanisms for surface treatment have been demonstrated to inhibit bacteria and the resultant biofilm growth. The application of additive nano-Se appliqués or other extractive nano-surfacing have been shown to inhibit biofilm growth via the bacteriostatic actions. The nano technology can be applied to the repair and maintenance of existing distribution systems.

This analysis focuses specifically on the use of the nano technology to public water supply systems. Specifically, it addresses the issue of system remediation and the need for a low cost and fast method to purge the biofilm contaminants as well as shielding other contaminants such as lead from public water supply systems. The proposal focuses on the use of PVC treated with the nano surfacing technology as well and the development of the insertion and installation methodologies to achieve a very low cost remediation system.

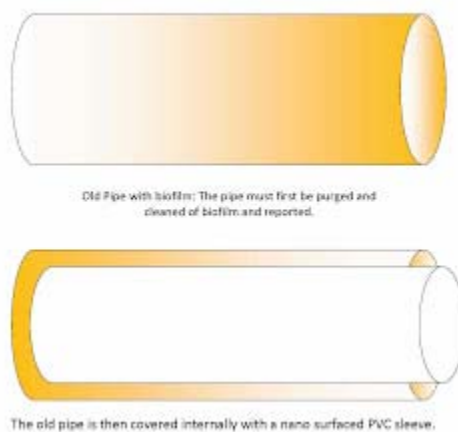
The problem being proposed for study here is the mitigation and inhibition of biofilms in the transport and distribution of water in public water distribution systems. We demonstrate the typical system below.

^{14[1]} See EPA Report 1992.

^{14[2]} See NRC 1998 report in detail.



As the above demonstrates water is generally collected from aquifers, or other storage areas, and at times directly from flowing bodies. It is then treated and purified and perhaps stored in local facilities. Then as demand occurs it is distributed across a local network. It is that local network which is extensive and in many cases aged that biofilms occur. It in this network that seeks to examine the efficacy and cost efficiency of deploying PVC nano-treated insertions. The proposed installation is demonstrated below:



The process is simple: 1. Purge old pipe and clean with a standard "pigging" device and then repurge for all removed biofilm. 2. Insert nano treated PVC sleeve for a new pipe.

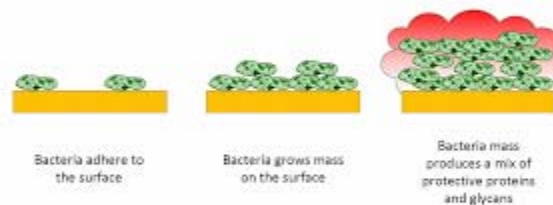
Preliminary analysis indicates that this nano treatment will inhibit regrowth of biofilms for extended periods and further the PVC sleeve will inhibit outflow of such elements as lead from the old pipe. The primary purpose of this study therefore is to validate this approach using the existing nano technology based upon data and sample obtained from actual systems in situ.

Biofilms are created by the adhesion of bacterial aggregates on the surfaces of various fluid processing, transport and containment mechanisms. The basic physics surrounding this phenomenon was presented by van Loosdrecht et al and it is based upon the construct of surface energy. The small biological particles can adhere to surfaces and one attaching can create via

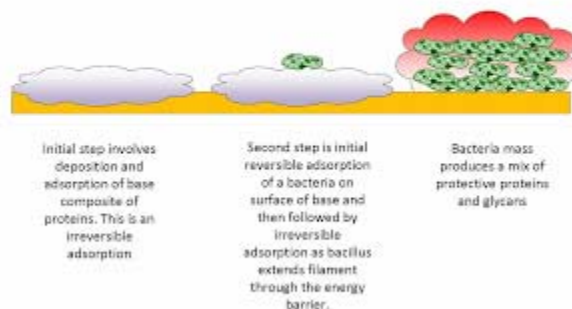
extracellular membrane extension the foundation for a developing biofilm. The problems with this biofilm are significant in a variety of areas such as oil pipelines as discussed by AlAbbas et al and in desalination as discussed by Elimechem et al in desalination plants. Srey et al provide an excellent survey of the impact of biofilms in the food industry. A typical biofilm encrustation is shown below:



Note the significant growth of biofilm. In the reference by Pervical et al they have extensive discussions regarding the development process in potable water. The effect of chlorine in the water does diminish the growth slightly but it is a common factor not only in loss of flow but in contamination. Fundamentally the process is some three steps as shown below:



The details on the above are also in Kanematsu and Barry. The first step is the development of a protein film on the surface. Then the bacteria reversibly attach and finally the bacteria irreversibly attach and additional biofilm mass grows to cover the bacteria. Another more detailed view will incorporate a combine reversible and then irreversible process initiated by the coating of the surface by a protein like substance shown below.



Note in the above we must have the layer irreversibly adsorbed to allow an initial reversible bacterium to attach. We will explain this later when examining the issues regarding forces. From Fleming and Ridgeway, we have:

The term “biofouling” is referred to as the undesired development of microbial layers on surfaces. This operationally defined term has been adapted from heat exchanger technology where “fouling” is defined generally as the undesired deposition of material on surfaces, including:

- *Scaling, mineral fouling: deposition of inorganic material precipitating on a surface*
- *Organic fouling: deposition of organic substances (e.g. oil, proteins, humic substances)*
- *Particle fouling: deposition of, e.g., silica, clay, humic substances and other particles*
- *Biofouling: adhesion of microorganisms to surfaces and biofilm development*

The conditioning film shown above is essential. It is a laying down of proteins and water which adhere to the surface via an adsorption process. We generally suspect that such an adsorption is due to the van der Waals forces from the surface to the structure of the specific proteins. We will expand this discussion later. Upon completion of the surfacing then the proteins extending from the bacillus manage to penetrate this barrier and also become attached via van der Waals forces. Darouiche discusses the impact of biofilms on medical implants as well. He notes:

The essential factor in the evolution and persistence of infection is the formation of biofilm around implanted devices. Soon after insertion, a conditioning layer composed of host-derived adhesins (including fibrinogen, fibronectin, and collagen) forms on the surface of the implant and invites the adherence of free-floating (planktonic) organisms. Bacterial cell division, recruitment of additional planktonic organisms, and secretion of bacterial products (such as the glycocalyx) follow.

As Batte et al note:

Most of the pipes used in drinking water distribution systems are made of plastic (PVC, PE, etc.) or metal (copper, cast iron) which can become highly corroded (Figure 11). A recent survey of

public distribution system pipes in France showed that a large proportion of them are PVC (40%), while the rest are grey iron (22%) or ductile iron (20%) (Cador 2002).

They continue:

The effects of the organic nutrients released by plastic pipes on bacterial growth in drinking water have long been questioned. Organic additives which leach out of plastic have a measurable impact on biofilm accumulation, and are known to promote the multiplication of opportunistic, pathogenic bacteria in laboratory tests. However, no field studies have looked at these events...The lack of information on biofilm dynamics is a limiting factor in managing the quality of water in distribution system and conducting drinking water surveys. In spite of the difficulty of gaining access to the inner surfaces of distribution pipes, biofilm measurement on pipe walls is indispensable if more information on the water contamination risks is to be obtained. New methods need to be developed, adapted, evaluated and optimized. Such methods will create important advantages: continuous, non-destructive, simple, in situ, online information on biofilm location and development.

From Preedy et al we have:

Biofilms are defined as a layer or layers of cells adhered to a substratum which are generally embedded in an organic biological matrix, i.e., extracellular polymeric substances (EPS). It is due to biofilm formation that many bacteria survive in highly diverse and adverse environments as a result of the polymicrobial ecosystem....Not surprisingly, biofilms have formed on a variety of surfaces and are not only restricted to attachment at a solid—liquid interface but have been observed at solid—air and liquid—liquid interfaces, with some having beneficial results as well as detrimental; for example, in industry biofilms are used successfully to separate coal particles from mineral matter. On the other hand, biofilms have been known to cause biofouling reducing mass and heat transfer and effectively increasing corrosion; also from a medical point of view, biofilm colonized implanted medical devices often lead to implant failure.

Current technological areas focus on several areas. The areas are:

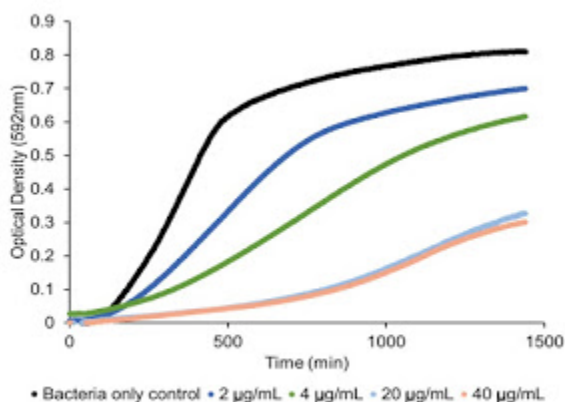
Nano Surface Enhancements: These are nanotechnology enhanced titanium surfaces which demonstrate reduction in bacterial infection potential and also demonstrate enhanced tissue and bone growth ensuring improved human acceptance.

Surface Bactericidals for Intracorporeal Applications: These are nanotechnologies for surface coatings of various catheters and the like that result in dramatically reduced risks of infection by inhibiting bacterial growth.

Selenium Enhanced Bactericidals: This is a selenium based product which enables the control of bacterial growth. It appears to function as a bacteriostatic agent. Combined with a bactericidal agent the combination may affect dramatic control for long periods of bacteria on surfaces. This area of product development appears to have several areas of application: (1) Those applications which can be seen to be applied directly to the skin (cosmetics, wound dressing, etc.), and (2)

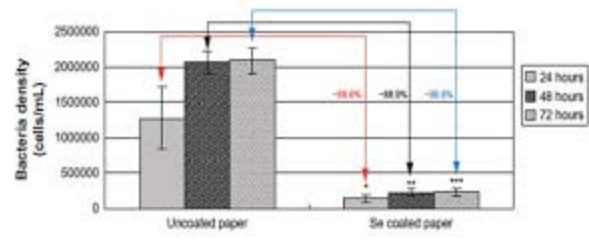
Those applications which can be used in clinical and consumer applications to treat surfaces for anti-bacterial purposes, (3) The control of growth on various surfaces of harmful flora or fauna.

Treatments have developed an approach to mitigate the growth of biofilm. This is via the treatment of the surface by nano processing. The treatments may be either by addition of materials such as nano Se or by the selective deletion of surfaces to create a similar nano surfacing effect by the use of lipase and other similar surface treatments. For example, nano Se has been demonstrated to slow down *S. aureus* proliferation at a dose-dependent rate. Increased lag time (in 40 and 20 $\mu\text{g}/\text{mL}$ doses) would allow for the body's immune system to attack bacteria before exponential growth. We demonstrate some of these results below:



In the above we note that the regrowth of bacteria is dramatically reduced by the application of a Se surface at concentrations of 20-40 micrograms/milliliter. It has also been observed that surface coatings of a density of 100 ng/sq cm of 20-70 nm diameter nano Se on the surface are also adequate. The question we pose herein is; what is the physical process that causes this to occur? Bacterial efficacy has been demonstrated as shown below:

- Gram positive *Staphylococcus epidermidis* was decreased by several logs on SeNP-coated paper towels
- SeNP coatings have also reduced gram negative *Pseudomonas aeruginosa*, *E. coli*, MRSA, and ampicillin resistant *E. coli*



We now examine the physical processes which may account for this twofold process. Namely:

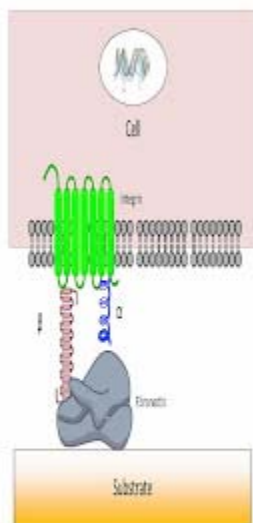
1. Nano Se coatings and lipase nano processing of surfaces tend to create a bacteriostatic environment.
2. Nano Se coatings and nano surface processing tend to create an environment that enhances tissue adhesion.

These appear to be contradictory results. It would appear that both processes are controlled by the same physical mechanism. Yet the outcomes are dramatically different. We attempt to explain some of these effects. However, it should be noted that in our analysis the explanation is yet far from clear.

The following is a brief discussion of some of the basic principles and specific technologies. Details are contained in the papers by Webster and his team at Northeastern and Brown University. We have also examined the literature in general and provides a summary regarding that as well.

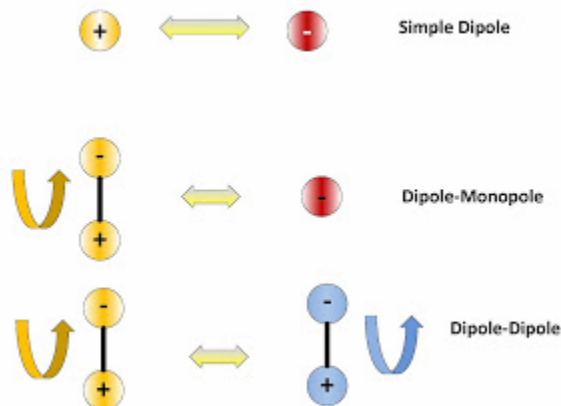
[Surface Energy](#)

The principal basis for the technology is understanding surface energy as relates to bacterial adhesion and subsequent biofilm growth. We demonstrate the basic principle below for a eukaryotic cell using the approach by Webster. On a smooth surface we have with cells a fibronectin, a glycoprotein, which binds integrins. This allows the pathogen cell to attach to the surface and commence biofilm growth.



The issue then is to create a surface which is not conducive to the binding. This can be accomplished by manipulating the surface energy by mechanical means. We can show that the

protein absorption is proportional to the surface energy. We can briefly examine van der Waals forces as discussed by Butt and Kappl. Let us first consider simple Coulomb forces. We can consider three types of surface to external adhesion for vdW. They are shown below:



Later we shall see that many argue for the simple connection of inverse square where one surface is positive and the other is negative. This is a simple vdW approach. However, the other two can be equally valid depending on the nature of the molecules connecting. Namely in the case of proteins the protein structure can be quite complex depending on the specific amino acid construction. Note that for proteins the bonds generally are inverse fourth power strength due to the dipole-monopole configuration. There may even be cases in certain protein structures where the bonds are inverse sixth power^{16[3]}.

The adhesion of bacteria to surfaces is a complicated and yet to be satisfactorily answered phenomenon. There are several theories and we will examine one herein. We use the DLVO approach which is a force or energy approach. Alternative approaches using thermodynamically defined terms and Gibbs Free Energy, G , have also been proposed but they do not seem to provide adequate answers. Let us first review some general principles.

The DLVO (Derjaguin, Landau, Verwey, Overbeek) approach uses the two forces; van der Waals and Ionic. The paper by Trefaly and Borkovec is an excellent summary of this and we shall follow its approach.

Now the surface may be seen as below with these two forces:

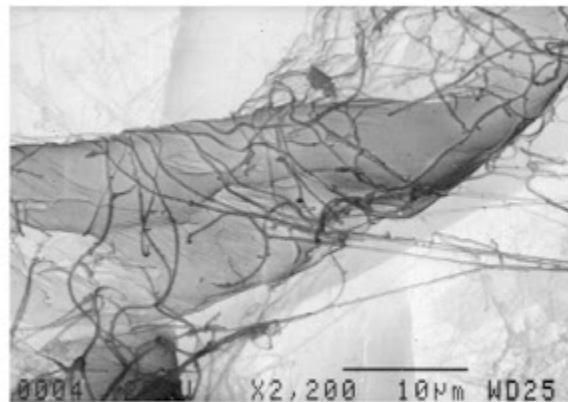
^{16[3]} See Petsko and Ringe, Protein Structure and Function, Sinauer (Sunderland, MA) 2004. Pp 8-11.

^{16[4]} See Butt et al, pp161-180.



Note that in close we have an attraction due to van der Waals and then at a distance we have the double layer effect. The scales are not precise but just descriptive. The vdW force is much stronger but there is a positive "barrier" between it and the outer layer. Brownian motion can get a bacterium close to the surface and catch it reversibly in the ionic or DL area. However, to have an irreversible bond something must get to the vdW section, a much stronger section.

Now the bacterium sends out a filament to try to bond to the surface via the vdW forces. It must penetrate the barrier and then bond. In the Boland et al paper we have an example of such bonding showing the extending filaments:



They discuss what they term cellulose binding domains, CBD, areas of the protein which do the binding in this case to cellulose. They state:

These CBDs have been classified into 10 families (I-X) on the basis of amino acid sequence homology. The amino acid sequences of CBDs in C. cellulovorans and C. josui show high homology with those from other cellulolytic genera such as Bacillus. CBDs in this family contain several highly conserved amino acid sequences:

1. Tryptophane-aspartate-phenylalanine-asparagine-aspartate-glycine-threonine
2. Isoleucine-alanine-alanine-isoleucine-proline-glutamine

3. Isoleucine-leucine-phenylalanine-valine-glycine

We can then ask; what if we roughen the surface, what will that do? The specific answer is not known and even less understood conceptually. A logical conclusion is that by roughing the surface we increase the positive side by moving the inner vdW in and out and thus make it more difficult to adhere. The Thermodynamic argument is a hand waving discussion of surface energy. But we tried that argument above without success on adhesion of human tissue cells.

As Bok noted in his Thesis:

The forces that govern microbial deposition, adhesion and detachment are still not fully understood, and difficult to relate with each other. In a previous study we successfully investigated the characteristic shear force to prevent adhesion of microbial strains. In the current research we used a more systematic approach by including not only the shear forces to prevent adhesion, but also those that stimulate detachment of adhering bacteria, as well as theoretical adhesion forces calculated using the extended DLVO theory. ...

1) A strong hydrodynamic shear force to prevent adhesion relates to a strong hydrodynamic shear force to detach an adhering organism. ...

2) A weak hydrodynamic shear force to detach adhering bacteria implies that more bacteria will be stimulated to detach by a passing air-liquid interface through the flow chamber....

3) DLVO interactions determine the characteristic hydrodynamic shear forces to prevent adhesion and to detach adhering micro-organisms as well as the detachment induced by a passing air-liquid interface. ...

Thus from the above experimental analyses the DLVO has some merit but it clearly does not describe the entire process. There are significant issues still outstanding to be explained theoretically. Bacterial adhesion and the formation of biofilms is still in the process of being fully understood. Kanematsu and Barry provide an exceptionally strong discussion here but we must resort to experimental data for phenomenological insight. Boland et al also provide a substantial discussion on this but fail to provide a strong analytical basis. Their analysis is useful to better understand some of the phenomenology.

[The Thermodynamic Paradigm](#)

The thermodynamic paradigm is based upon certain principles that aggregate large collections of common particles like gas, steam, or a fluid. Thermodynamic principles work in the large like those used in reactors or distillation columns or heat exchangers. We shall review some of these principles and then demonstrate their lack of efficacy in this model.

For example, when considering the process of wetting, one can generally use thermodynamic and surface tension methods. There is a homogeneity on the surface and on the wetting materials. Tran and Webster (2013) have provided an interesting analysis for nano scale wetting. They

explain it via the Wenzel and also the Cassie-Baxter models. They all involve surface tension as is done in the core Young's analysis^{17[4]}.

van Loosdrecht et al were one of the first to explain the adhesion via thermodynamic principles. Then they state:

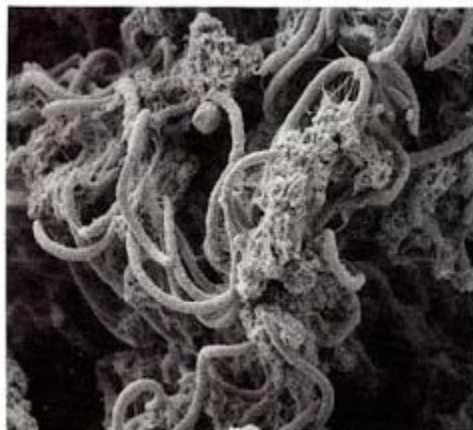
The Concept of Short-Range Interactions

If adhesion is performed at constant pressure and temperature, and if the molecular composition of the surface does not change, all G 's can be replaced by the corresponding interfacial tensions. This concept is restricted to those cases where bacteria and the solid surface are in direct contact and the original phase boundaries are replaced by a new one, namely, the bacterium solid interface. When this new interface is formed, interfacial tensions may be used for a direct estimation of the adhesion Gibbs energy. ...

The Concept of Long-Range Interactions

The DLVO theory for colloidal stability can be used to calculate the interaction Gibbs energy between a particle and a surface as a function of the separation distance (H). The balance of interracial Gibbs energies ... is the basic premise of this theory. The net interaction Gibbs energy is interpreted in terms of Van der Waals interactions (which are usually attractive) and an electric interaction due to the overlap of the electrical double layers at the charged surfaces. The most important parameters determining the van der Waals interaction are the Hamaker constant, which is a material property, the distance (H) between bacterium and substratum, and the geometry of the system. ...

alAbas et al demonstrate oil pipeline biofilm as below:



Now in contrast alAbas et al note:

Thermodynamic approach

The thermodynamic approach assumes the system is in equilibrium and the bacterial attachment is a reversible process. The interfacial free energies between the interacting surfaces are compared and calculated, This comparison is expressed in the so-called free energy of adhesion. ...The microbial adhesion will be favorable when the change in G, is negative (< 0) and will not be energetically favorable if ... positive.

They then continue:

DLVO Approach: The drawback of the thermodynamics approach is that it ignores the electrical double-layer interaction with the bacteria... This assumption is invalid as the bacterial cells have a surface-negative or-positive charge. In contrast, the DLVO approach displays a balance between attractive Lifshitz- van der Waals... and repulsive or attractive electrostatic forces ... These two forces are function of the distance (d) between the bacteria and surface. In order to calculate the adhesion free energy ... the electrostatic interactions between surfaces should be included. The inclusion of electrostatic interactions requires that the zeta potentials of the interacting surfaces be measured, in addition to measuring contact angles...Extended DLVO approach: The extended DLVO theory relates the origin of hydrophobic interactions in microbial adhesion and includes four fundamental interaction energies: Lifshitz-van der Waals, electrostatic, Lewis acid-base, and Brownian motion forces ...

The above approach makes semi-macro thermodynamic assumptions. Specifically, a large mass of surface, liquid and biofilm concentrate. In fact, the dynamics of the process are totally overlooked. This is the general failing of thermodynamic approach; they assume some form of steady state along with homogeneity. In reality we have a dynamic process in a highly heterogeneous environment. We briefly discuss the technology to be employed. The details are contained in the references by Webster discussed herein.

[Nano Technology](#)

Nano surface treatments can be accomplished by treating the surface itself or adding nano materials to the surface. The result is a stable nano surface that inhibits bacterial growth and ensuing biofilm development. The Gecko has nano fibrils on its feet that allow it to climb any surface by means of van der Waals attraction as we see in nano material surfaces. The production of nano Se is performed via a proprietary process but fundamentally is the following:

Glutathione +NaOH + Se --→ Nano Se

As Mendonca et al note, using reference to Webster's work, the details of surface energy effects and adhesion or lack thereof:

The changes in initial protein–surface interaction are believed to control osteoblast adhesion. This is a critical aspect of the osseointegration process. When implants come into contact with a biological environment, protein adsorption (e.g. plasma fibronectin) that occurs immediately will mediate subsequent cell attachment and proliferation. Cell binding to protein domains of

adhesive extracellular matrix proteins involves receptors termed integrin receptors that transmit signals through a collection of proteins on the cytoplasmic face of the contact, termed focal contacts. ... Webster and colleagues observed an increased vitronectin adsorption on nanostructured surfaces when compared to conventional surfaces. They also found an increased osteoblast adhesion when compared to other cell types, such as fibroblasts, on the nanosurfaces. ... Surface roughness at the nanoscale is an important determinant of protein interactions that ultimately direct cell activity in control of tissue formation at implant surfaces.

Material Processing

To obtain a proper nano surface there are two methods. The additive method uses nano Se which can be made at specific nano size and in a very well controlled and defined distribution so as to assure the proper surface energy. The second approach is the deletive approach whereby a nano surfacing has a process that removes materials in such a controlled manner so as to achieve the same desired surface energy.

Additive

Nano Selenium has been demonstrated as highly effective. In addition, as we demonstrate below it is also safe and sustains the effect on the surface for an extended period of time.

Why Se? The reasons are as follows:

- Essential micronutrient metalloid, and component of several key antioxidants, detoxifying and metabolic enzymes, in form of selenocysteine, selenomethionine
- Two allotropes: red (bioactive) and grey (crystalline) and Strong associations with reduction of Reactive Oxygen Species^{1,2,3} (ROS) as well as Cofactor of glutathione peroxidase
- Antibacterial activity to a broad range of pathogenic strains
- Νανο Σε χαν βε προδυχεδ ατ σπεχιφιχ νανο διαμετερσ ωιτη μινιμαλ δισπερσιον,
□ Spherical in shape
- Monodisperse—size distribution fits within one bell curve and negatively charged (uncoated)

Deletive

The deletive approach used extraction mechanisms which produce similar effects to the additive mechanism of nano Se. The advantage of such an approach is that it does not add anything to the material. The disadvantage in certain active biological surfaces such as human skin is that it causes immunological effects. However, its used in stable media such as PEEK, Titanium, steel, and other materials used for water flow and containment is that it can be readily effected and at low cost. There are numerous processes to implement nanoscale surface features on metallic or polymeric surfaces. We then utilize one of our processes to create such nanoscale features: Anodization or Chemical etching. The deletive approach provides comparable results to that for Se coatings.

Biofilm Inhibition Results

There have been a variety of biofilm inhibition methods. As Garrett et al note:

Bacterial adhesion has become a significant problem in industry and in the domicile, and much research has been done for deeper understanding of the processes involved. A generic biological model of bacterial adhesion and population growth called the bacterial biofilm growth cycle, has been described and modified many times.

The biofilm growth cycle encompasses bacterial adhesion at all levels, starting with the initial physical attraction of bacteria to a substrate, and ending with the eventual liberation of cell clusters from the biofilm matrix. When describing bacterial adhesion one is simply describing one or more stages of biofilm development, neglecting the fact that the population may not reach maturity. This article provides an overview of bacterial adhesion, cites examples of how bacterial adhesion affects industry and summarizes methods and instrumentation used to improve our understanding of the adhesive properties of bacteria.

The NRC report states^{18[5]}:

The pipe surface itself can influence the composition and activity of biofilm populations. Studies have shown that biofilms developed more quickly on iron pipe surfaces than on plastic PVC pipes, despite the fact that adequate corrosion control was applied, the water was biologically treated to reduce AOC levels, and chlorine residuals were consistently maintained...In addition to influencing the development of biofilms, the pipe surface has also been shown to affect the composition of the microbial communities presents in the biofilm. Iron pipes supported a more diverse microbial population than did PVC pipes. The purpose of these studies is not to indicate that certain pipe materials are preferred over another but to demonstrate the importance of considering the type of materials that come into contact with potable water.

We examined several issues. Specifically:

1. What is a Biofilm? This we have answered by reference to various studies.
2. How do biofilms form? The answer to this may often depend but it is clearly a dynamic process.
3. What is the physical phenomenon that allows biofilms to adhere and have strong adsorption? This is a work in progress. We believe the thermodynamic approach is problematic at best. It is necessary to consider more detailed dynamic physical phenomenon. We make some suggestions here.

^{18[5]} See p 230-234.

4. What is the effect of nano-surfacing on biofilms? This appears to be uncertain at best. There are contrasting phenomenological results.
5. Why does nano-surfacing enhance adsorption of certain eukaryotic cells such as bone and ligaments while inhibiting the adsorption of prokaryotic cells such as bacteria? This appears not to have been examined.
6. How can nano-surfacing be optimized to minimize biofilms? Argument from surface energy have been proposed but are problematic.

These questions can and have been answered in part but there remains a set of uncertainties that challenge the effective utilization of nano technologies.

We can possibly argue the following explanation from what we have developed herein.

1. The first coating of a surface is by the protein layer. Generally, this is done by some local van der Waals forces since the proteins are close to the surface and are well known to exhibit such forces. Also the protein layer seems to be a prerequisite for adhesion. However, the type of protein layer may very well depend on the surface structure. Their structure of proteins vary widely and perhaps if we adjust the nanostructure we selectively change the type of protein adhering to the surface.
2. We know that bacteria seem phenomenologically to require proteins to adhere for them in turn to reversibly adhere to the proteins. Thus the proteins must be electrostatically and vdW wise strongly attracted to the surface and the cell.
3. After a reversible adhesion then we seem to have the appearance of protein filaments extruding from the bacteria and down through the protein layer, most likely using the protein to overcome the barrier wall normally between van der Waals and electronic forces. Once the filament hits the surface then it adheres irreversibly and the biofilm commences growth.
4. The supposition is that by changing the roughness of the surface we change the types of proteins or the nature of their adhesions on the surface. There does not appear to be any research determining this one way or the other at this time.

The challenge of this analysis is shown below. On the one hand certain biologicals adhere on roughness and others are repelled. *One of the* continuing questions is why, and what is the fundamental physical reason.

Nano Surfacing: A Contradiction?



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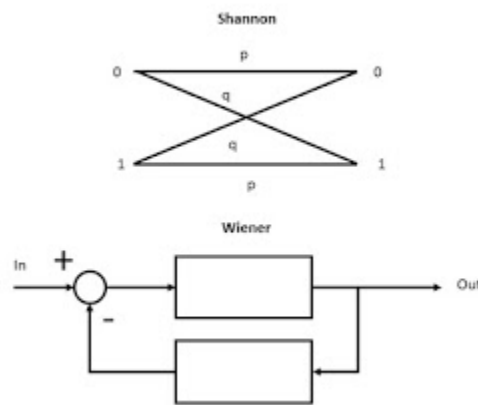
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Labels: [Biofilms](#)

THURSDAY, MAY 5, 2016

PARADIGMS: SHANNON AND WIENER



The [IEEE](#) is honoring the 100th anniversary of the birth of Claude Shannon. In contrast Norbert Wiener seems to slowly go into the history books and not as well praised as Shannon. I had the opportunity to see both at a distance and to have studied under their students. Each introduced a new paradigm, a simple example as how to see things.

For Shannon it was the binary symmetric channel, BSC as shown above. Bits, probabilities, information, coding. For Wiener it was the feedback loop, cybernetics, least square estimation, and the Wiener process. Both are paradigms of uncertainty. For Shannon it was p as the probability of sending a bit correctly and q for not. For Wiener it was noise introduced into the system at various points.

As they IEEE article states:

Bell Labs, now part of Nokia, organized the Claude Shannon Centennial Conference to reflect on the immense legacy of one of its most legendary alumni and look at the future of the information age he helped launch. Invited speakers discussed how Shannon's work transformed their research fields and their own careers, and what lessons his life offers to today's innovators.

Now Murray Hill is a long stones thrown from my computer. It is now owned by Nokia, formerly Alcatel, formerly Lucent, formerly AT&T. The parking lot is now filled with solar arrays, that seems to be it most profitable output. Thus one wonders why the fuss?

Was Shannon as important as Wiener or the reverse. Wiener thought in the large. He saw the world as massive feedback loops driven by uncertainty. Shannon saw BSCs and codes. Wiener worried about the automation of manufacturing and the impact on workers, kind of like the current political campaign. Shannon did games.

Yet this was a gathering to honor Shannon. His impact was that his writing was simple, clear, and spawned careers that were in turn Shannonesque. Wiener wrote and thought, yet he like Shannon was a bit of a loner, yet Cybernetics took hold in Russia and not the US, yet Black-Scholes the option trading formula is merely an artifact of Wiener and his theory. One changed communications the other finance. One played games the other worried about the world. You choose.

Paradigm changes are critical. Yet what one does with them is also important.



Labels: [Academy](#)

[LYSENKO AND THE SOVIET ACADEMY](#)

[Graham](#) has written a wonderful book on Lysenko and the Russian School of Genetics during the Stalin era. Lysenko viewed inheritance in the sense that certain characteristics could be handed down in generations based upon environmental factors experienced by parents. That is the change in a genetic makeup was not solely due to genetic changes per se. He could turn summer wheat to winter wheat by getting it used to a change in weather. Thus he did not need a genetic alteration but an environmental alteration was sufficient. In a sense the concept did play into the hands of the Marxist reasoning.

Graham blends the understanding of epigenetic changes that are currently being understood with the ideas of Lysenko and asks if this new understand then justifies Lysenko's ideas. On the other hand, Graham details Lysenko's way of dealing with his academic adversaries often resulting in their imprisonment and demise. The current understanding of gene expression and thus phenotype is that genes can be turned on and off by such epigenetic factors as methylation. Methyl groups bind to the nucleotides and also suppress expression directly by blocking the gene or indirectly by blocking transcription factors.

This is somatic epigenetics. Germ line epigenetics, parent to child has also been observed. Namely effects on the parent causing epigenetic changes can be handed down to the child, where it was assumed that the methylation of certain bases was eliminate but somehow they can be preserved. Thus, in a simplistic sense, an environmental change imprinting the parent can imprint the offspring. This may or may not be consistent in a broad sense with Lysenko but the author discusses it in some detail. Graham's discussion is limited as one would expect in a short book of this type but he does explain some of the issues well including the event of the "Dutch Winter", an epigenetic benchmark.

Graham has a wonderful discussion of his opportunistic meeting with Lysenko at a lunch table in the Russian Academy, and the brief attempt to elicit some explanation from Lysenko. Lysenko was as one would expect defensive since this occurred after he was taken down from his perch yet retained his academic credentials. This discussion is quintessential east meets west based upon my personal experiences in Russia when first meeting some notable. It was clear from Graham's description that Lysenko was still wary especially since Graham had been critical of him in Graham's prior writings.

Graham also presents a clear and coherent discussion of the players in this tragedy, the geneticists following the true path and how Lysenko and his actions resulted in their fall.

The only point that would have been useful to explore would be the need by the Marxist theorists to have a Lysenko position versus a Darwinian one. I had seen this battle with the probabilists. Marxist theory is deterministic and probability is its enemy. Yet many probabilists managed to work and prosper. Individuals like Gnedenko, Kolmogorov, Stratonovich, Markov and others developed the basis for stochastic processes that we see used in fields as broad as finance with the Black-Scholes theorem in options trading, a thought anathema to the Marxists. Graham does provide some insight but it would be worthwhile to have a more in depth discussion of this potential conflict.

Overall the book is an excellent addition to understanding both the Russian Academy and its functioning, the Stalinist management of the overall society, and a petri dish model of Academic infighting. It is very worthwhile for those seeking to understand both Russia as well as the politics of Science, albeit in a different vein.



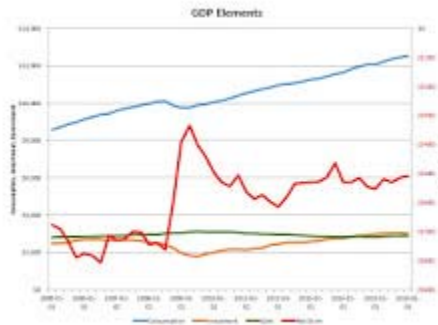
Labels: [Academy](#), [Epigenetics](#), [Genetics](#), [Russia](#)

MONDAY, MAY 2, 2016

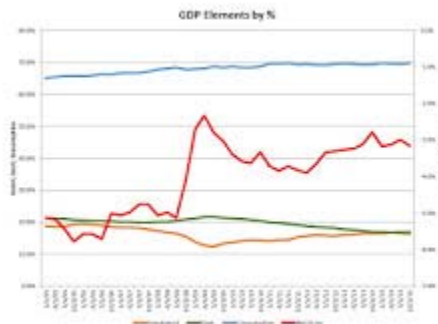
[GDP AND THE GREAT ECONOMY](#)



So how is the economy doing? As we see above the GDP is dragging at best. A growth rate of 3-4% would be necessary to stay ahead of the debt bow wave but at just above 1% we are treading on a recession again. Since 2008 we have been periodically dropping to 1% or below.



The above shows the GDP elements. Some growth but anemic.



The above shows the relative percent as well. No big change here either.

Overall we are weak and getting weaker. Costs of doing business are increasing and more and more employees are being supported by fewer workers.



Labels: [Economy](#)

TECH ANCHOR?

What is a Tech Anchor? Some writer in the [NY Times](#) argues that Tech anchors are companies. Sorry folks but they are Universities. The writer argues:

Silicon Valley and the surrounding region have had these companies for decades, from Hewlett-Packard and Intel to Facebook and Google. The Seattle area has its giants in Microsoft and Amazon. Even Austin has had its own tech powerhouse in Dell, though that company has seen better days. But New York? The biggest city in the country has plenty of tech companies and plenty of tech workers and it is second — though a distant second — among regional tech investment. A giant that can compete with behemoths of Silicon Valley, however, remains elusive.

First did the writer ever hear of Boston? Route 128? Try taking a trip to Kendall Square! The Tech anchor is a place called MIT. Then Silicon Valley, ever heard of Stanford? Then Austin, how about UT.

Now for New York. There is an effort to put a high tech entity on the abandoned tip of an island in the East River. Land was available but every time I go by I wonder how one gets there. I can take a T train to MIT, and possibly even a car, although Google has apparently bought up all parking spaces, not environmentally friendly but this is not California.

New York has no real high tech institution. Columbia struggles, it is really a Liberal Arts shop, they try to do engineering but not really. NYU, well they got Brooklyn Poly, let's see how that works. Not really that much else.

So one needs a Tech Anchor, the anchor is academic not some start up and the anchor takes a while to mellow. So don't expect this for a few decades at best.



Labels: [Academy](#)

THURSDAY, APRIL 28, 2016

DEPARTMENT OF ENERGY

Most people do not know that the largest portion of DoE's business is nuclear weapons. Somehow over the decades from Carter thru the current administration we have had Secretaries who at times were clueless as to their domain. Perhaps that has been planned, after all you can get a lot more done if your boss has no idea that you may even exist. But generally we do not appoint Secretary of Defense individuals who cannot distinguish a tank from an aircraft carrier. But well all too often have Sec DoE who would not know a MIRVed warhead from an electric car!

I just noted, perhaps with some humor, but also with possible abject terror, the [Hill](#) stating a potential DoE head. As The Hill states:

Trump said early in his campaign that he'd welcome the GOP's 2008 vice presidential nominee into his administration — "I'd love that," he said in July — and Palin wasted little time specifying the post she'd want. The former Alaska governor said she'd like to head the Energy Department — for the opportunity to dismantle it. "I think a lot about the Department of Energy, because energy is my baby — oil and gas and minerals, those things that God has dumped on this part of the Earth for mankind's use instead of us relying on unfriendly foreign nations," Palin told CNN last fall. "I'd get rid of [the DOE], and I'd let the states start having more control."

This is concerning. You could get rid of the electric car project at DoE but what of those nukes! It is not as if the understanding of DoE is unknown by all, the Russians and the Chinese are very familiar with DoE weapons programs. Perhaps for once we could get a DoE head who knows something about its core business, the potential destruction of all life on the planet!



Labels: [Nuclear Weapons](#)

SUNDAY, APRIL 24, 2016

[GINKGO NUTS, BIODIVERSITY AND CLIMATE CHANGE](#)

Some twenty five or so years ago I got some ginkgo nuts from the New York Botanical Garden. I planted them and last year one of the trees, a female, was filled with nuts. Fantastic. The squirrels did not seem to have any interest, smelly seed coats, but well that was not the end. Come Spring, the coat had gone and the squirrels managed to consume every one! The ginkgo has managed to survive some 100 million plus years but it had not faced the squirrel.

Now as we go further north we see the grey squirrel also going there as the warming occurs and thus many flora that were dependent on small consumption by red squirrels will be under siege by grey ones. The issue of changing and complex biodiversity means that there will be challenges to flora and fauna.

I make this comment because I have read a paper by [Dr. Victoria Karchenko](#) at The Botanical Garden Institute in Vladivostok where she states:

Now the climate changes become more pronounced. This affects to biodiversity and distribution of plants. Therefore, we need to study of the biodiversity and trends distribution of plants in specific environments. In this connection is necessary to clarify real composition of species in the of regional floras potential of their variability of and disseminating. A pressing problem remains the creation of a unified database of the flora of Russia, which takes into account the data of regional studies. Research program allows executing posed problems if it would coordinate with other botanical gardens. This program will allow revealing structural and functional adaptation of species to various environmental conditions. This will help create a basis for design ways to regulation the development of plants and biotops.

As I had indicated, the paper by Dr. Kharchenko presents a very compelling argument for the development of a detailed flora for Russia especially the Eastern parts. We have been using

certain sentinel plants such as Hemerocallis which are native to this part of Russia to measure long term climate changes. It is essential to have a detailed data base not only of the flora per se but more importantly an understanding of their propagation status based upon the balance with pollinators as well as fauna which may consume the plants before they can complete their re population cycle. We have seen not only a shift in bloom time and divergence with pollinators but more importantly animal predators on plants growing in numbers. This is a critical study especially in this highly bio-diverse area.

Eastern Russia is an relatively unexplored treasure trove of biological species. Many of my Hemerocallis are from there and there are still new species of that genus being discovered. However there may have been a balance in biodiversity for millennium but as we see warming we would expect drastic changes. To understand the changes we need a baseline and the proposal to establish such a well defined baseline is essential. There clearly should be substantial support for this effort, since one would expect the time scale for change to be quite short.



Labels: [Biodiversity](#), [Botany](#), [Russia](#)

SUNDAY, APRIL 24, 2016

[TRUSTING THE KINDNESS OF STRANGERS](#)

Silicon Valley gets stranger by the day. I recall my first start-up in the Fall of 1969. It was funded by EG&G whose main business at the time was photographing nuclear explosions. The company had a great idea, as many start ups do. In 1969 stores had credit cards but no computers and the printed every week a phone book size document containing all the bad cards in numerical order. When you wanted to charge something the cashier would first take your card and read through the book to see if it was a bad card. If not then you could charge.

Well these folks came up with the following idea. They could take the bad card numbers and put them on a 45 RPM record, and then when you came to the cashier they would type in the credit card number and if it was not bad the green light came on and if it were bad the red light lit. Now the 45 RPM was coded so that N grooves in were numbers n(N) which were in some range. This the unit knew if you entered a number it would be N grooves in so it dragged the record needle some N-M grooves and started reading the data until it went past your number. It was one of the first disk drives, but with a 45RPM record and dragging across grooves. Now the grooves would wear out but the solution was to coat the disk with some coating which allowed it to work for a couple of weeks. Great idea before any internet.

Well it worked for about a week. Then someone forgot to coat the records and Voila they all scratched out and so did the company. Details count. Lesson one.

Now in [Scientific American](#) there is a great piece on Theranos. The author notes:

Just a few weeks before regulators proposed banning Holmes and Theranos President Sunny Balwani from the blood-testing industry, the company tried to remedy this by bulking up its medical advisor board with well-qualified experts in chemistry, pathology and clinical

chemistry. It's hard to imagine these experts would have signed on amid all the bad publicity and allegations without demanding proof that the technology works, but who knows? It still remains possible that Theranos has discovered a breakthrough technology that can do hundreds of lab tests on a drop of fluid from a patient's finger. But even if this increasingly unlikely prospect is a reality, Holmes' erstwhile acolytes need to remember the lessons learned from the pantheon of past pied pipers and summed up by statistician W. Edwards Deming: In God we trust; all others must bring data.

Now the lesson is that due diligence is essential, it means that you did enough work to determine if there are any fatal flaws. I have been through the process dozens of times. Often we find things. People have done it on my companies and I have done it on others. The first thing you must do is understand the validity of the offering. You must understand it. Second you must examine the team. In Silicon Valley having no experience is valued. I would not climb Mt Everest with a Guide who had never been outside of Florida! I want experience and I would due due diligence. Somehow major investors and major corporations just blew it. That may not be good for some careers but it is also not good for the industry. However it may be great for the lawyers!



Labels: [Health Care](#), [Innovation](#)

WEDNESDAY, APRIL 20, 2016

[CRISPR MUSHROOMS!](#)

As I watch my Hemerocallis slowly emerge from the ground and wonder what I could do if I let CRISPR techniques go wild I read today in [Nature](#) about the CRISPR mushroom.

They note:

*The US Department of Agriculture (USDA) will not regulate a mushroom genetically modified with the gene-editing tool CRISPR-Cas9. The long-awaited decision means that the mushroom can be cultivated and sold without passing through the agency's regulatory process — making it the first CRISPR-edited organism to receive a green light from the US government. “The research community will be very happy with the news,” says Caixia Gao, a plant biologist at the Chinese Academy of Sciences’s Institute of Genetics and Developmental Biology in Beijing, who was not involved in developing the mushroom. “I am confident we’ll see more gene-edited crops falling outside of regulatory authority.” Yinong Yang, a plant pathologist at Pennsylvania State University (Penn State) in University Park, engineered the common white button (*Agaricus bisporus*) mushroom to resist browning. The effect is achieved by targeting the family of genes that encodes polyphenol oxidase (PPO) — an enzyme that causes browning. By deleting just a handful of base pairs in the mushroom’s genome, Yang knocked out one of six PPO genes — reducing the enzyme’s activity by 30%.*

I wonder what I could do with flower colors!



Labels: [CRISPR](#)

SUNDAY, APRIL 17, 2016

CANCER STEM CELLS

I have been spending some time on examining the issue of the cancer stem cell concept again. The literature is expanding yet there seems to be no convergence or consensus. This brief set of quotes is from more than a dozen major sources and at best one may become further confused. Just thought this would be an interesting exercise.

1 The Challenge

Definitions are important. In mathematics and law, the definition will determine the outcome. In engineering we define certain parameters and we design accordingly. If there is a concern, we spend a great deal of time on the definition. In cancer studies the term "cancer stem cell" has been introduced.

Definitions should be clear and they should be actionable. Namely the definition should present a way to ascertain through objective measures readily understood by someone trained in the science or art to determine if what is presented satisfies the definition. Namely we should with a good definition know if what we have is a cancer stem cell.

The results below are a sample of what seems to be definitions from the literature. Reading these one can readily see what the complexity is in understanding this topic. The descriptions are each from the source noted.

2 Definitions

Ailles, and Weissman: Cancer stem cells (CSCs) are cells that drive tumorigenesis, as well as giving rise to a large population of differentiated progeny that make up the bulk of the tumor, but that lack tumorigenic potential. CSCs have been identified in a variety of human tumors, as assayed by their ability to initiate tumor growth in immuno-compromised mice... In addition, specific signaling pathways play a functional role in CSC self-renewal and/or differentiation, and early studies indicate that CSCs are associated with a micro environmental niche... several important biological properties of CSCs: first, what is the cell of origin for a given tumor? Second, what are the signaling pathways that drive self-renewal and/or differentiation of CSCs? Third, are there molecules uniquely expressed on CSCs, regardless of whether they are functional, that will allow targeted therapies to be developed? Fourth, what are the mechanisms by which CSCs escape conventional therapies and can we defeat these mechanisms?

Burgess: Should stem mitotic activity become unregulated or uncontrolled, a tumorigenic and perhaps malignant phenotype may result hence the term cancer stem cell... tumor initiating sells that have malignant properties have been referred to as CSCs...

Dalerba et al: Stem cells are defined by three main properties:

1. differentiation—the ability to give rise to a heterogeneous progeny of cells, which progressively diversify and specialize according to a hierarchical process, constantly replenishing the tissue of short-lived, mature elements;
2. self-renewal—the ability to form new stem cells with identical, intact potential for proliferation, expansion, and differentiation, thus maintaining the stem cell pool;
3. homeostatic control—the ability to modulate and balance differentiation and self-renewal according to environmental stimuli and genetic constraints

Like their normal tissue counterparts, tumors are composed of heterogeneous populations of cells that differ in their apparent state of differentiation. Indeed, the differentiation features of a tumor, morphological and architectural, are the key parameter used in routine clinical practice by surgical pathologists to define a tumor's primary anatomical origin.

This simple observation suggests that tumors are not mere monoclonal expansions of cells but might actually be akin to “abnormal organs,” sustained by a diseased “cancer stem cell” (CSC) population, which is endowed with the ability to self-renew and undergo aberrant differentiation. This hypothesis is further reinforced by the fact that cancer is known to result from the accumulation of multiple genetic mutations in a single target cell, sometimes over a period of many years (3). Because stem cells are the only long-lived cells in many tissues, they are the natural candidates in which early transforming mutations may accumulate.

Dubrovskaja, A., et al: One possible explanation for the initial positive response to therapy followed by androgen-refractory disease is that although current therapies eliminate the bulk of the tumor, they fail to eliminate cancer stem cells (CSCs) or tumor-initiating cells (TICs). In fact, it has been argued that many cancers are maintained in a hierarchical organization of rare CSCs, rapidly dividing cells, and differentiated tumor cells; the CSCs are not only a renewable source of tumor cells but are also a source of tumor resistance leading to tumor recurrence, metastasis, and tumor progression. Support for this hypothesis came with the identification of TICs in leukemia in 1994 and, subsequently, in a variety of cancers, including solid tumors. In addition, cancer cell lines have been shown to harbor cancer stem-like cells and are a promising model for CSC research because these progenitors can be readily expanded under anchorage independent (sphere formation) serum-free conditions

Fang et al: Recent studies suggest that cancer can arise from a cancer stem cell (CSC), a tumor-initiating cell that has properties similar to those of stem cells. CSCs have been identified in several malignancies, including those of blood, brain, and breast.

Hurt et al: The cancer stem cell hypothesis suggests the existence of a small subpopulation of cells within the tumour that give rise to differentiated tumour cells. It is thought that the cancer stem cells survive conventional treatment to later re-emerge more resistant to therapy. To date, putative cancer stem cells have been identified in blood, brain, breast, lung, skin, pancreas, colon, and prostate....

Jordan et al: Stem cells have three distinctive properties: self renewal (i.e., at cell division, one or both daughter cells retain the same biologic properties as the parent cell), the capability to develop into multiple lineages, and the potential to proliferate extensively. The combination of these three properties makes stem cells unique. The attribute of self-renewal is especially notable, because its subversion is highly relevant to oncogenesis and malignancy. Aberrantly increased self-renewal, in combination with the intrinsic growth potential of stem cells, may account for much of what is considered a malignant phenotype. Biologically distinct and relatively rare populations of “tumor-initiating” cells have been identified in cancers of the hematopoietic system, brain, and breast. Cells of this type have the capacity for self-renewal, the potential to develop into any cell in the overall tumor population, and the proliferative ability to drive continued expansion of the population of malignant cells. Accordingly, the properties of tumor-initiating cells closely parallel the three features that define normal stem cells. Malignant cells with these functional properties have been termed “cancer stem cells”

Lawson and Witte: Two theories were proposed to explain this paradox. The stochastic theory suggested that all cancer cells are equally malignant but only clones that randomly possess favorable biological properties will grow upon transplantation. An alternative theory predicted that tumors are hierarchical like normal tissues and only the rare subpopulation of cells at the pinnacle of that hierarchy have the unique biological properties necessary for tumor initiation. Studies by John Dick and colleagues provided evidence for the hierarchy model. This group demonstrated that only the small subpopulation (0.1%–1.0%) of Lin[–]CD34⁺CD38[–] cells within human acute myelogenous leukemia samples were capable of initiating disease when transplanted into immune-deficient mice (10). These cells possessed the same antigenic profile as normal human HSCs, which are at the pinnacle of the normal hematopoietic hierarchy. This population also had the unique capacity to self-renew to propagate the disease as well as differentiate to produce the many leukemic cell types represented in the original leukemia. Since these cancer cells possess properties unique to normal tissue stem cells, they have been termed “cancer stem cells” (CSCs).

Lobo et al: Stem cell: a primitive cell defined by its capacity to self-renew and differentiate into at least one mature cell type
Cancer stem cell: a self-renewing cell within a tumor that has the capacity to regenerate the phenotypic diversity of the original tumor

NCI: The theory of the cancer stem cell (CSC) has generated as much excitement and optimism as perhaps any area of cancer research over the last decade. Biologically, the theory goes, these cells are distinct from the other cells that form the bulk of a tumor in that they can self-perpetuate and produce progenitor cells, the way that traditional stem cells do. The progenitors’ job is then to repopulate tumor cells eradicated by treatments such as chemotherapy or radiation. But for all the attention and fanfare CSC research has received, the findings reported to date are far from clear-cut, investigators acknowledge. For example, most of the studies that have identified human CSCs have used mouse xenograft assays and cells from only a small number of human tumor samples, making it difficult to draw firm conclusions. In addition, other researchers haven’t always been able to replicate initially reported findings. And while these tumor-initiating cells, as they are also called, have been described as being a rare class, several studies have found that the number of cells that can form tumors in these mouse experiments is actually quite large, suggesting that perhaps CSCs aren’t such a privileged breed.

Pavlovic and Balint: As the stem cells that created the tumor to begin with are so few in number, scans following treatment usually fail to identify populations of CSCs in this limited population....^{19[1]}

Perego et al: Although there is no definitive consensus on the phenotype and frequency of CSCs in the majority of human tumors, much experimental evidence supports the contentions that many tumors of both epithelial and nonepithelial origin have operationally defined CSCs (cells able to propagate tumors in immunodeficient mice) and that the presence of these CSCs affects tumor biology.

Rajasekhar: The "cancer stem cell model" CSC ...envisions tumors as "pathological organs" sustained in their aberrant growth by a mutated population of stem cells, in which normal homeostatic controls on tissue expansion have been lost.

Roesch et al: The CSC concept postulates a unidirectional hierarchy of tumor cells...According to the traditional CSC concept, tumor initiation is regarded as an exclusive characteristic of CSCs

Rosen and Jordan: Thus, the CSC paradigm refers to the ability of a subpopulation of cancer cells to initiate tumorigenesis by undergoing self-renewal and -differentiation, like normal stem cells, whereas the remaining majority of the cells are more "differentiated" and lack these properties.

Soltysova, et al: Normal stem cells in the adult organism are responsible for tissue renewal and repair of aged or damaged tissue. A substantial characteristic of stem cells is their ability for self-renewal without loss of proliferation capacity with each cell division. The stem cells are immortal, and rather resistant to action of drugs. They are able to differentiate and form specific types of tissue due to the influence of microenvironmental and some other factors. Stem cells divide asymmetrically producing two daughter cells – one is a new stem cell and the second is progenitor cell, which has the ability for differentiation and proliferation, but not the capability for self-renewal. Cancer stem cells are in many aspects similar to the stem cells. It has been proven that tumor cells are heterogeneous comprising rare tumor initiating cells and abundant non-tumor initiating cells. Tumor initiating cells – cancer stem cells have the ability of self-renewal and proliferation, are resistant to drugs, and express typical markers of stem cells. It is not clear whether cancer stem cells originate from normal stem cells in consequence of genetic and epigenetic changes and/or by redifferentiation from somatic tumor cells to the stem-like cells. Probably both mechanisms are involved in the origin of cancer stem cells. Dysregulation of stem cell self-renewal is a likely requirement for the development of cancer. Isolation and identification of cancer stem cells in human tumors and in tumor cell lines has been successful.

^{19[1]} This book is near incomprehensible in my opinion. It appears impossible to find a definition, only secondary referral characteristics at best!

Visvader: It is important to note that the cell of origin, the normal cell that acquires the first cancer-promoting mutation(s), is not necessarily related to the cancer stem cell (CSC), the cellular subset within the tumour that uniquely sustains malignant growth. That is, the cell-of-origin and CSC concepts refer to cancer-initiating cells and cancer-propagating cells, respectively. Although the tumour-initiating cell and the CSC have been used interchangeably, the tumour-initiating cell more aptly denotes the cell of origin. There is considerable evidence that several diverse cancers, both leukaemias and solid tumours, are hierarchically organized and sustained by a subpopulation of self-renewing cells that can generate the full repertoire of tumour cells (both tumorigenic and non-tumorigenic cells). The cell of origin, the nature of the mutations acquired, and/ or the differentiation potential of the cancer cells are likely to determine whether a cancer follows a CSC model. In most instances, the phenotype of the cell of origin may differ substantially from that of the CSC. Normal cellular hierarchy comprising stem cells that progressively generate common and more restricted progenitor cells, yielding all the mature cell types that constitute a particular tissue. Although the cell of origin for a particular tumour could be an early precursor cell such as a common progenitor, the accumulation of further epigenetic mutations by a cell within the aberrant population (in this case expanded) during neoplastic progression may result in the emergence of a CSC. In this model, only the CSCs (and not other tumour cells) are capable of sustaining tumorigenesis. Thus, the cell of origin, in which tumorigenesis is initiated, may be distinct from the CSC, which propagates the tumour.

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Labels: [Cancer](#)

THURSDAY, APRIL 14, 2016

[THE CRISPR WARS](#)

Back in the 60s when I first started in Academia we did not focus on Patents. The laws had not yet made it a potential profit center for Universities and Start Ups had been few and far between. We published everything, usually with one or at most two authors. Now Academics patent everything and papers have thousands of authors.

The CRISPR wars are just heating up. As [Nature notes](#):

Last month, in an extraordinary dispute before the US Patent and Trademark Office (USPTO), university lawyers laid out their clients' legal strategies for claiming patents that cover the celebrated gene-editing technology CRISPR–Cas9. Over the next year, the USPTO will receive volumes of evidence centred on who first invented the technology. Battles over scientific priority are as old as science itself. But the CRISPR–Cas9 patent dispute is unusual because it pits two leading research institutions against one another for the control and industrial development of a foundational technology: the University of California, Berkeley (UC Berkeley), and the Broad Institute of MIT and Harvard in Cambridge, Massachusetts. As scientific institutions increase their involvement in the commercialization of research, it is worth considering the potential consequences for science if more institutions follow the path of UC Berkeley and the Broad Institute.

The battle is costly. Litigation can cost millions and result in outcomes that are counter productive. We remarked when the CRISPR patent was issued that it was a first for the PTO. Less than six months from filing to issuance.

Perhaps when stones are overturned in the litigation one may find things that would have best been hidden. Also it puts one of the game changing technologies in Limbo for a while.



Labels: [Academy](#), [CRISPR](#)

[OF MICE AND MEN](#)

Obesity is a growing threat to overall health. It is not just the development of Type 2 Diabetes and its sequellae but the other sequellae that arise directly. Strangely many studies focus on mice and genetic aberrations that lead to obesity. In [NEJM](#) they discuss such a case.

They note:

A recent study by Dalgaard and colleagues forces us to rethink aspects of the heritable component of obesity. Dalgaard et al. characterized mice carrying a mutation in the gene encoding tripartite motif-containing 28 (Trim28). Trim28 is a zinc-finger transcription factor that enhances transcriptional repression — in other words, a mutation in one copy of Trim28 causes an unexpected heritable bimodal (on–off) obesity distribution that seems to depend on certain environmental factors to “flip the switch.” The average weight gain (approximately 7 g) in the obese (“on”) mouse with the Trim28 mutation was largely due to an increased mass of adipose tissue distributed uniformly across all adipose depots and a very slight increase in length (1 to 2%), whereas the weight in the “off” phenotype did not differ from that in wild-type animals. The approximate doubling of the adipose-tissue mass in the “on” phenotype was accompanied by a doubling in the number of adipocytes in the tissue.

Well first off, they are mice. Give a mouse food and they will eat it. Some more than others. I look at our bird feeder and there is one squirrel that is just stuffing herself all day. Perhaps she has a gene but also perhaps she is just a deliberate over eater. Perhaps a lot of things. Humans however have scales, they should have will power, they should see the damage caused. We humans do not exercise as much as squirrels. Thus the comparison has many faults.

Regarding humans they note:

Are these findings relevant to obesity in humans? The bimodal obesity phenotype was obvious in the inbred Trim28 mice, and the authors obtained suggestive data that polyphenism is also manifested in human populations. They observed that TRIM28 expression levels in human adipose tissue sorts samples into one of two subsets. Persons with low levels of TRIM28 expression have IGNI dysregulation and are more likely to be obese than are persons with high levels of TRIM28 expression, a finding that is in line with the observations in mice. In addition, they report that the distributions of body-mass index within a homogeneous pediatric cohort (4000 children of European ancestry) as well as within a heterogeneous cohort (persons of black American, Mexican-American, and Han Chinese ancestries) fit two distinct gaussian distributions rather than a single gaussian distribution. However, we note that there could be other explanations (e.g., skewed social and environmental stratification) for a bimodal distribution. The regulation of TRIM28 expression in humans remains unknown.

What does all of this mean? Good question. Humans with their will power can refrain from heavy caloric intake. There is a movement to portray obesity as a disease akin to say breast cancer. It is not, it can be controlled at no cost. Thus the search is in my opinion just another way to offset blame to some third party entity.



Labels: [Health Care](#)

MONDAY, APRIL 11, 2016

[THE MOOC FALLACY](#)

The MOOC fallacy is that "students" can grade other students; honestly, fairly, and competently. I bemoaned a course I took a year ago where some 10-20% of one's grade was via "peer review"

grading.

Namely the concept is to take students, often not having English as a first language, or even second, and let them grade other students. Now besides the language barrier this means people who have no knowledge grade those with some knowledge. Furthermore what I also observed was gaming of the system by ganging up on those grades of what was clearly say Americans by those from other countries to suppress the American grades.

This year the course has raised the percent of the grade subject to this less than ethical practice to a level of some 36%. That means collections of students can target others and suppress grades for their benefit.

Anyone who has ever taught knows gaming. This system however verges in my opinion on the immoral. One subjects themselves to the rigor of the material only to have it grades by some one having no understanding of the material along with an interest in them succeeding and you failing. This is a wonderful example of a rigged game. It also in my opinion is an example why no one really trusts these systems.



Labels: [MOOCs](#)

MONDAY, APRIL 11, 2016

[FACTS STILL COUNT, AS WELL AS DETAILS](#)

In an [MIT study](#) they claim that the lower income groups have almost a 15 years shorter life span than the high income groups. They state:

Poverty in the U.S. is often associated with deprivation, in areas including housing, employment, and education. Now a study co-authored by two MIT researchers has shown, in unprecedented geographic detail, another stark reality: Poor people live shorter lives, too. More precisely, the study shows that in the U.S., the richest 1 percent of men lives 14.6 years longer on average than the poorest 1 percent of men, while among women in those wealth percentiles, the difference is 10.1 years on average. This eye-opening gap is also growing rapidly: Over roughly the last 15 years, life expectancy increased by 2.34 years for men and 2.91 years for women who are among the top 5 percent of income earners in America, but by just 0.32 and 0.04 years for men and women in the bottom 5 percent of the income tables.

Now what of this fact. We have examined this in detail back in 2009 when looking at the proposed Health Care Plans. The real problem is that the lower income have the worst health habits. Obesity is rampant in lower incomes. Their diet is atrocious. They are smokers and are drinkers. They also do get poorer medical care but for reasons often less related to availability and economics than to mindset and attitude.

The upper income are more readily inclined to visit a physician and to address lifestyle issues. The lower income individuals often live neglectful lives regarding their health due to fear of doctors.

Thus the fact in the study may be correct the reasons are far to complex than just the income differences. It is a shame in my opinion that such research get so biased a coverage. Details count, not just the facts.



Labels: [Health Care](#)

FRIDAY, APRIL 8, 2016

[INDENTURED SERVITUDE?](#)



The problem of the high price of the university education is due to the unnecessary explosive investments in "pyramids" built on campuses which result in voracious appetites for maintenance. Build a \$200M new research center from wealth alumni and be strapped with a 10% pa maintenance bill growing at inflation plus. No sensible business person would take on that liability unless of course you have an ever ending ability to tax the "consumer".

So as the [NY Times](#) notes the next way to get money is to monetize the economic lives of your graduates. One can envision multiple hedge fund type strategies to make profit off of this process. As the Times notes:

At Purdue University, some undergraduates will have a new option to help finance their degrees: pledging to pay a percentage of their future incomes in return for funds today. Starting this fall, juniors and seniors will have access to the school's Back a Boiler program, an alternative financing arrangement known as an income-share agreement. Such programs are not loans. Instead, students get funds to cover current education expenses, and, in return, they agree to pay a percentage of their future income over an agreed-upon period of time. When that repayment term ends, so does the student's obligation, even if their total payments are less than the amount they received. Though an emerging corner of the educational finance industry, such programs help ease the often crushing debt many American college students face after graduation, proponents say. A small number of lenders have tested the model in recent years, but Purdue is the first American university to officially embrace the concept.

This is in my opinion an indentured servitude, and servitude to whomever holds the note. Hopefully students can be more astute but in today's world the helicopter generation has no competence in determining the impact. They will walk freely like lambs to the slaughter.



Labels: [Academy](#)

[GOOD JOB SPACE-X](#)

Space-X just launched a package to the space station and then landed the first stage back on a seaborne platform. [Ars Technica](#) has a great video. It is amazing what private industry can do. The Government spent tens of billions and decades, since 1966 is when I first recall, on electric cars and space vehicles.

Great job folks!



Labels: [Commentary](#)

MONDAY, APRIL 4, 2016

[ANOTHER DIAGNOSTIC TOOL](#)

The ongoing debate about PSA and PCa in men continues and the search for an improved diagnostic tool has also progressed. Three years ago [we wrote a piece on Oncosomes](#). Recently in a [JAMA Oncology Editorial](#) the authors speak of this technique as if it has now been accepted. The Editorial concludes:

Currently, we do not have a single population-based screening test to supplant PSA-based stewardship in screening for prostate cancer. However, McKiernan and colleagues have introduced a novel urinary gene expression signature that may be the least invasive of available options by not requiring a digital rectal examination or phlebotomy as a reflex test in men for whom PSA testing raises the suspicion of prostate cancer.⁷ In the near future, a panel of markers associated with the risk of high-grade prostate cancer may decrease the rate of overdiagnosis and overtreatment of prostate cancer that prompted the US Preventive Services Task Force to issue a grade D recommendation for prostate cancer screening.

The paper by [McKiernan et al](#) presents a several year definitive study of this oncosome approach. They conclude:

This urine exosome gene expression assay is a noninvasive, urinary 3-gene expression assay that discriminates high-grade (\geq GS7) from low-grade (GS6) cancer and benign disease. In this study, the urine exosome gene expression assay was associated with improved identification of patients with higher-grade prostate cancer among men with elevated PSA levels and could reduce the total number of unnecessary biopsies.

The question is; how effective will this be in saving lives at the cost of saving on unnecessary prostate biopsies. [We have commented on this conundrum lately](#). It is a complex issue. In light

of the "Moonshot" approach of the Vice President, this is still somewhat in the pre Galileo period of celestial dynamics.



Labels: [Health Care](#)

[ANOTHER WAR ON CANCER](#)

Preparing charts, developing strategies, allocating expenditures, all flow from any new initiative. Cancer is a highly complex disease. As we have been noting for a decade in just a few cancers, a "simple" and significant cancer such as that of the prostate has hundreds if not thousands of genetic complex profiles. Thus diagnosis and prognosis not to mention treatment must and will be tailored personally. It is not one size fits all.

In an article in [NEJM](#) the NIH authors announce the key elements of their program:

Cancer vaccines: Produce Epstein–Barr virus (EBV) vaccine for human safety testing; explore development of other vaccines for high-risk persons.

Early cancer detection : Develop tools and techniques to improve sensitivity, specificity, and utility of molecular-detection assays.

Single-cell genomic analysis: Conduct single-cell analyses to uncover the -omic spectrum of malignant and nonmalignant cells in the tumor microenvironment.

Cancer immunotherapy: Support basic research to further elucidate cancer immunology and extend the reach of immunotherapy to all kinds of cancer.

Pediatric cancer: Prepare and screen new libraries of compounds chosen for their potential to interfere with these transcription factors; intensify the collection and analysis of very rare childhood cancers.

Data sharing: Expand capacity of the National Cancer Institute Genomic Data Commons to handle and analyze genomic and clinical data from patients and health care providers.

Exceptional Opportunities in Cancer Research Fund : Pursue previously unanticipated and novel scientific opportunities to improve basic and applied cancer research.

It is worth examining the above.

Vaccines have some value on well known virus that can be directly linked to cancers. There are few at this stage and of course we always want to identify others and prevent them. However this may be far from number 1. Early detection is a complex issue due to several factors, First we really do not know what to look for. Second it is expensive. Third most people just will not seek the opportunity until too late. The smoker, the alcoholic, the obese person all present risks far in excess of viruses. Single cell analysis is another door that is just opening. As we have indicated

elsewhere in PCa the expression is massively different in almost ever presentation and in every part of the body. Furthermore we do not understand the dynamics of the stem cell. Immunotherapy with MABs is moving along. But the more we learn the more we can fine tune the approach. Pediatric cancers are devastating and always worth a try. Data sharing can and is being done already so what is new here? Doing something new; of course.

NIH also announces the [Blue Ribbon Panel](#) to work this Program. They state:

“This Blue Ribbon Panel will ensure that, as NIH allocates new resources through the Moonshot, decisions will be grounded in the best science,” said the Vice President. “I look forward to working with this panel and many others involved with the Moonshot to make unprecedented improvements in prevention, diagnosis, and treatment of cancer.”

The Moonshot metaphor has always been misplaced. Having spent a few years in the 60s on Apollo Program I know something about it. We had Kepler and Newton, we had Kalman and Battin, we had computers and Gyros. We even had improved German rockets. It was a matter of scale and not new knowledge. Cancer still has many unknowns. We want accuracy and NOT precision. It is akin to saying that we will land on the planet at exactly noon, and it will be Mars or Jupiter. Very precise but not very accurate.

They conclude:

Fueled by an additional \$680 million in the proposed fiscal year 2017 budget for the National Institutes of Health (NIH), plus additional resources for the Food and Drug Administration, the initiative will aim to accelerate progress toward the next generation of interventions that we hope will substantially reduce cancer incidence and dramatically improve patient outcomes. The NIH’s most compelling opportunities for progress will be set forth by late summer 2016 in a research plan informed by the deliberations of a blue-ribbon panel of experts, which will provide scientific input to the National Cancer Advisory Board.

Regrettably Boards are managed by Government Staff and we don't have the Feynmans to participate and add reality. Hopefully they accomplish something other than just assuage the grieving.



Labels: [Health Care](#)

[THE TOP TEN](#)

I am always amazed about the top ten choices of anything. Back in 1999 the [NY Times](#) opined on their view of the top 10 of the 20th Century in Non Fiction.They stated:

1. "THE EDUCATION OF HENRY ADAMS," Henry Adams
2. "THE VARIETIES OF RELIGIOUS EXPERIENCE," William James
3. "UP FROM SLAVERY," Booker T. Washington
4. "A ROOM OF ONE'S OWN," Virginia Woolf
5. "SILENT SPRING," Rachel Carson

6. "SELECTED ESSAYS, 1917-1932," T. S. Eliot
7. "THE DOUBLE HELIX," James D. Watson
8. "SPEAK, MEMORY," Vladimir Nabokov
9. "THE AMERICAN LANGUAGE," H. L. Mencken
10. "THE GENERAL THEORY OF EMPLOYMENT, INTEREST AND MONEY," John Maynard Keynes

Now [The Guardian](#) has somehow gotten into the act. The state:

1. The Sixth Extinction
2. The Year of Magical Thinking
3. No Logo
4. Birthday Letters
5. Dreams from my Father
6. Brief History of Time
7. The Right Stuff
8. Orientalism
9. Dispatches
10. The Selfish Gene

This is an interesting comparison. Two on the first list are women, three on this list are. One on the Times is about science and two on the Guardian. Personal recollections there are many. One could make up lists that have had impact. In the Guardian list one could ask; who has read more than three at best.

The key question is; did any of the books have a lasting impact and which ones. Clearly Keynes did. Silent Spring eliminated DDT yet tens of million of humans died of malaria while the same number of birds survived. Good trade off? Watson records a tale of human intellectual competition. Brilliant and highly readable. Mencken ages too quickly in a caustic culture. Adams is too New England. Sixth Extinction is a trendy catastrophe book, and suppose it will fall in the genre of all the others so one wonders why it was Number 1. Dawkins does stimulate and writes well. I guess the President's alleged recollections is compulsory for The Guardian. The Time book was a great seller but I doubt many truly grasped it or even more so if any of it makes a difference in daily existence.

Marx and his writings made a difference as did Locke, Mill, Montesquieu and others. People read them and it changed their lives. I doubt than any of the Guardian list did any of that.



Labels: [Books](#)

FRIDAY, APRIL 1, 2016

ADULT SUPERVISION

[The Guardian](#) tells of the Google April Fool joke. Now really, you suspect that the kids at Google would ever consider consequences, after all they are Masters of the Game, King of the

Hill, Gods of the Universe. So people got fired, lost jobs, had other personal disasters.

As The Guardian notes:

The first of April is normally a day of frothy fun, where newspapers and brands compete to produce the best jokes and the worst puns to fool their readers. But this year some of the more complex pranks did not go quite to plan. Google's April Fools' Day prank had to be pulled within hours after some users complained a new feature installed in their email service, Gmail, might have cost them their jobs or reputations. The stunt was the "Gmail Mic Drop", an augmented send button which attached a gif animation clip of a crown-wearing Minion character from the film Despicable Me dropping a microphone like a brash rap star, which instantly ended an email exchange.

Well welcome to the world of real privilege. They can watch your email, scan your searches, time your day, monitor your likes and dislikes.

Perhaps there should be an "Adult Supervision" branch located in Topeka to approve of any of the brainchildren.



Labels: [Google](#)

SUNDAY, MARCH 27, 2016

[AN ANALYSIS ABOUT WHAT?](#)

In a recent article in [JAMA Oncology](#) there is a study about the alleged usefulness of PSA tests. Simply stated they did the following:

1. Examined 18 variations on a theme, namely PSA levels and duration between tests.
2. Costs associated with procedures resulting from the tests.
3. Determined the cost of each life year saved compared to not testing.

The result if the QALY measure, that generally useless, essentially banned by the ACA from use in any medical care. But alas, here it comes.

Their conclusion is simple:

For PSA screening to be cost-effective, it needs to be used conservatively and ideally in combination with a conservative management approach for low-risk disease.

We know that PSA is problematic. But we also know:

1. That PSA testing makes sense if and only if we examine it over time, specifically over a 5 year window of annual data at the very least. It goes up and down and it changes as the prostate grows. So like fasting blood sugar it all too often just tells us what happened last night.

2. Family history is also a significant factor. If you have no relatives with PCa then you have a good chance that you will not have it. Bayes to the rescue. But the corollary is not really true. Namely if you have a first degree relative you may have an increased risk. To be determined.

4. PCa is not simple. It is a complex genetic disease and it is highly heterogeneous in its spread.

5. PCa is all too often not that serious but when it is it really is. Yet we do not know that boundary.

6. Calculating QALYs without taking the above into account is really really bad in my opinion.

Thus the more of these results that get published the more we confuse the patient. We just do not really know. Remember, if all else fails, listen to the patient. Let them be part of the informed decision process and please keep the QALYs in the UK where they belong!



Labels: [Cancer](#)

[FORCES ON THE NANO SCALE](#)

The book by [Butt and Kappl](#) is a must have for anyone working in the field of surface interactions, especially the developments of nano technologies. The classic work was done to understand colloidal solutions and their dynamics, often lasting many decades, and also the issue related to van der Waals forces. The development of the quantum understanding expressed in London forces as well as the various varieties developed over the past few decades are both highlighted and detailed in this work.

The first major Chapter is on van der Waals forces and its derivatives. The authors have a wonderful style combining simple explanations along with detailed but readily understandable derivations. The clarity of the work is truly exceptional. One can almost see the Gecko feet adhering to the walls as they climb!

The Third Chapter details measurement techniques. Again the authors present the principles employed in a clear and readily understandable manner and then progress to explain the actual implementation.

They then move through electrostatic forces, capillary forces, hydrodynamic forces, and interfacial forces. All are explained simply and then in detail. They continue with such topics as friction and polymers surface energies.

Although this is presented as a text book it is truly an exceptional reference work because of both its breadth and depth.

My only issue is that perhaps they could have discussed some of the specific applications to nano materials. Specific materials such as nano Selenium where one tries to best understand the surface stickiness on the one hand and the bacteriostatic behavior on the other.

Overall this book is a necessity for anyone working in the area of intermolecular forces and their impact on adhesion and interaction.



Labels: [Books](#)

[UNDERSTANDING CANCER SIGNALLING](#)

The book by Robert, the [Textbook of cancer signaling](#), is one of the best works on cell signaling available as an introduction. As the author indicates in the preface the intent is for oncologists to obtain a better perspective of the issues associated with the wealth of new therapeutics as well as some of the key issues behind their introduction. For the most part the work is a high level, but not simplistic, organization and presentation of the key signaling paths. The general approach is to detail one class of paths after another and describe in excellent detail the elements of those pathways and how they function. Then there is a brief exposition of how aberrations in the pathways lead to oncogenic effects and then a discussion on pharmacological possibilities. This is done chapter by chapter.

The author's collection and organization is superb and it presents the reader with an organization that they can come back to time and time again. He covers kinases, including MAP and other elements, cytokines, TGF, G protein, Wnt, Notch, and Hedgehog. He also discusses integrins and a collection of adhesion molecules. There is a discussion of B and T cell issues including Toll Like receptors and lymphocytic receptors. He ends with excellent discussions on cell cycle control as well as apoptosis.

The Appendices are superb summaries of DNA control, gene expression and protein activity. Overall this is a book that should be on the desk of almost every oncologist and it is an excellent summary for those involved in pathway analysis and their implications.

The most important elements of the book are the author's organization and integration. It is simple, straightforward and touches on all the current elements under consideration.

This is not a book for the specialist but it is worth reading by those deeply involved in that work to see how one person who truly understands the depth and breadth sees it structured.

On the side of a critique, and this is hard given the superb effort displayed, issue such as epigenetic factors should have gotten some bit of discussion. Specifically the issue of methylation and miRNA silencing need to be integrated into the overall signaling fabric. However that would clearly have extended and expanded the work

Also the reader should not look at this as a reference book, it was not intended as such.

Finally my only one negative is the lack of an Index. That most likely is a publisher problem and not the author's problem. The lack of an index is not that serious since the author has organized the book so well it is almost not necessary.

I would strongly recommend this book for anyone seeking to learn pathway issues in cancer and those who are deeply involved already. The logical wholeness of the work is worth understanding by all.



Labels: [Books](#), [Cancer](#)

FRIDAY, MARCH 25, 2016

[THE THREE HORSEMEN](#)

In a set of recent JAMA Viewpoints three of the key players in the delivery of the ACA are giving their updates on the progress of the bill.

First is the assessment from the one who seeks to just pass on when he turns 75 I believe^{20[1]}. His assessment is mixed but full of praise. What is most telling is his last set of comments. He states:

Even though the ACA is not a perfect bill, it has improved the US health care system. If venture investing is a trustworthy indicator and if additional reforms enabled by the ACA, such as more payment change and drug cost controls, are implemented, Americans can be optimistic about the future of the US health care system.

This single paragraph is in my opinion the most telling. First he admits the ACA is not perfect. Far from it. As we have already noted it has added some 15 million new participants costing the taxpayers about \$15,000 per year per participant. This is more than Medicare participants who being older should have been costlier albeit having paid some 50 years' worth into the system. The conclusion of efficacy is not justified. Second the grab to venture investing as a proof of success is truly mind blowing! There is no basis for this assertion. Why not indicate the rise of ISIS as well? Coincidence is not correlation is not a proof!

The second horseman is the fellow who brought us Meaningful Use and the EHR^{21[2]}. As we have seen since its inception the CMS mandated HER has in my opinion led to higher costs, less patient interaction, and less inter physician communications. The design in my opinion is fatally flawed by setting up islands of non-interconnected data elements with the patient nowhere to be found. As he states as a key step in his proposal^{22[3]}:

^{20[1]} <http://jama.jamanetwork.com/article.aspx?articleid=2499847&resultClick=3>

^{21[2]} <http://www.fiercehealthcare.com/story/cms-berwick-gets-work-selling-meaningful-use-ehr-rule/2010-07-13>

^{22[3]} <http://jama.jamanetwork.com/article.aspx?articleid=2499845&resultClick=3>

Third, Shift the Business Strategy From Revenue to Quality: Maximizing revenue continues too much to dominate the business models of health care organizations. That reflects short-term thinking. A better, more sustainable route to financial success is improving quality. This requires mastering the theory and methods of improvement as a core competence for health care leaders. It also requires that the CMS and other payers continue to unlink incomes from input metrics, such as “relative value units” for specialists’ incomes, which are not associated with quality and drive volume constantly upward.

Now as we have noted frequently the term Quality is in the “eye of the beholder”. Quality means what and to whom? The CMS has also promulgated mandatory “quality” measures. If one looks at them there is nothing more than a useless list of check marks adding costs and detracting from the delivery of services!

Now the third horseman. He was the strategists again on health care information. As he stated just after the ACA^{23[4]}:

The widespread use of electronic health records (EHRs) in the United States is inevitable. EHRs will improve caregivers' decisions and patients' outcomes. Once patients experience the benefits of this technology, they will demand nothing less from their providers. Hundreds of thousands of physicians have already seen these benefits in their clinical practice.

And how did that work out for us. More cost and less care. We have physicians becoming typists or if they can't type hiring a third party to sit in the examining room typing away and interfering with patient-physician contact. The result, better patient care and lower costs, it does not seem so.

In his most recent paper he states^{24[5]}:

Given some Americans’ skepticism of foreign experience, home-grown examples may be more compelling. The Commonwealth Fund State Scorecard suggests that

(1) if US health spending per person averaged the same nationally as among the 5 lowest-cost states (Utah, Arizona, Georgia, Idaho, and Nevada), an estimated \$535 billion (approximately 20%) less would have been spent on personal health services in 2014;

(2) if rates of health insurance coverage averaged the same nationally as among the 5 areas with the highest rates (Massachusetts; Vermont; Hawaii; Washington, DC; and Iowa), an estimated 20 million more Americans would have been insured in 2014; and

^{23[4]} <http://www.nejm.org/doi/full/10.1056/NEJMp1006114>

^{24[5]} <http://jama.jamanetwork.com/article.aspx?articleid=2499844&resultClick=3>

(3) if the national levels of mortality amenable to health care averaged the same as among the 5 states with the lowest rates (Minnesota, Vermont, New Hampshire, Utah, and Colorado), an estimated 77 000 fewer deaths would have occurred in 2014.

Let's look at the above and examine it for facts. First the states of Utah, Nevada, and Arizona have high Mormon populations. Mormons live health life styles. So perhaps it would cost less. Georgia just has less access.

Second, Massachusetts has world class hospitals that do leading edge care. Idaho does not. Vermont is a socialist state in many ways and people pay for that. Hawaii always has high costs, buy a gallon of milk!

Third, look at the demographics of the states with lowest mortality. I reside part time in New Hampshire. It soon will see a rise as obesity takes its toll but for the most part it is rural and of modest income.

Frankly in my opinion this type of sweeping ad hoc propiter hoc argument is baseless. One must ask why. But that does not seem to be in the vocabulary.

It is worth reading the comments of these three who played so much of a role in what has happened. This is the left wing of medicine, yet they managed in my opinion to set the agenda for the next generation, and the cost may be overwhelming.

Then of course one asks who is the Pale Horse?



Labels: [Health Care](#)

THURSDAY, MARCH 24, 2016

[DOING WHAT YOU WERE NOT TO DO](#)

In a recent [Healio](#) piece they describe a study evaluating QALY on PCa. This was frankly expressly prohibited by the ACA for any service provided thereunder. But the cat is out of the bag. The study states:

Under selective therapy, men with lower Gleason scores (< 7) and clinical stage cancer (T2a) would only receive treatment after clinical progression. All other cases underwent contemporary treatment practices. Key study endpoints included life-years (LY), quality-adjusted life-years (QALY), direct medical expenditures, and cost per LY and QALY gained. Researchers evaluated cost-effectiveness as willingness-to-pay thresholds ranging from \$50,000 to \$150,000 per QALY. When compared with no screening, all screening strategies increased LYs (range, 0.03-0.06) and costs (range, \$263-\$1,371). Costs ranged from \$7,335 to \$21,649 per LY gained.

Not really clear what was concluded. Was the cost low compared to the benefit? They conclude:

“Our work adds to the growing consensus that highly conservative use of the PSA test and biopsy referral is necessary if PSA screening is to be cost-effective,” Roth and colleagues wrote. “Among the strategies considered, less frequent screening and more restrictive criteria for biopsy resulted in greater chances of PSA screening being cost-effective — particularly when combined with selective treatment strategies that do not immediately treat low-risk, screen-detected cases.”

This of course is studying on the basis of past practises and having not a clue what causes or differentiates the disease.

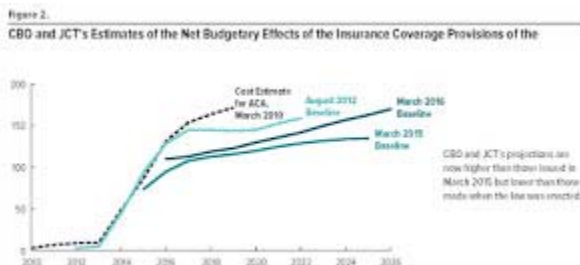


Labels: [Health Care](#)

THURSDAY, MARCH 24, 2016

[THE COST OF THE ACA](#)

The [CBO](#) has a report describing the anticipated costs of the ACA, exclusive of Medicare for those who have paid in and are over 65.



We depict this above. It will soon exceed \$200B annually and that is for an increase of some 14-15 million people. That amounts to an insurance premium of some \$15,000 per person enrolled! Now the Medicare participant over 65 has paid in some 50+ years worth at 3% of their gross income plus some \$2,400 per year plus a Medigap plan and a Part D plan costing an additional \$4,500, plus a deductible, at a total in excess of well above \$7,500. That is in addition to what they paid for 50 years!

So who are these people. Read the report and moan!



Labels: [Health Care](#)

TUESDAY, MARCH 22, 2016

[WHY PEOPLE BUY APPLE COMPUTERS](#)

For the past few weeks, yes weeks, I have been struggling with a dying W7 computer. Each death is different. In this case it was a result of what we think is registryoma, a malignant condition in the Microsoft Registry. We all know that Microsoft has designed this devilish system to control its world but one small base pair mismatch and if you think melanoma is bad

try this on for size. There is no immune therapy available and there is not way to block the pathways.

The first symptoms are insidious. Google desktop stops. It just disappears. It was akin to a small mole, just a small change, just a little sensitive. So you do a work around. Then Quick Books fails. The mole starts to bleed. Maybe I scratched it, denial. Another work around. I will do my books on another machine. No problem. Put another bandage on it, how bad can it be.

Then the web systems fail to connect. No problem I can use Filezilla, another work around. It is another mole popping up where there was none before. I do not see lungs becoming engorged with metastatic patches.

Then I try Skype. Dead. It will not even load. It has spread to the brain. The patient does not know it yet. But Office is not loading properly, it freezes up all the time. Firefox has to be loaded 2 or 3 times before it starts. The patient has a seizure.

At this point I would say the patient is a goner! Well I got another machine. Started all over again. New patient, left the old one in the basement. Not totally dead but it is hospice care for the dying!

Microsoft has with its Registry invented a malignancy that makes cancer seen benign. It starts slowly and then spreads and infirm the "patient" and the user. There is no cure, just put the old guy in a hospice and let him die. Kind of like the ACA approach. Thanks Microsoft, you make cancer research looks trivial!



Labels: [Commentary](#), [Microsoft](#)

MONDAY, MARCH 7, 2016

[SPY VS SPY](#)

Ad Blockers have become a common thing. I use Badger on Firefox. One can see masses of white space where the ads were before being blocked. I now see that Wired senses the ad blockers and then blocks the page. Cute game, but I just switch to somethi9ng else.

The worst of these techniques is the pop up video, silently I work, check out a headline on Feedly and then WHAM! Blasting video. Now stopped by Badger.

Do these people really think that if I accept the ads I will in any way be persuaded. Rather to the contrary.

How do I find things? Well look at Lookeen, I had an indexing problem. Most likely some Microsoft update on W7. Killed Google Desktop. So I searched Google for an alternative and got a better result. Did I ever see them in an ad? No. Would I have responded to an ad? No.

Marketing folks really do not understand the consumer dynamic. Pity!



Labels: [Commentary](#)

WEDNESDAY, MARCH 2, 2016

[GREAT PRODUCT!](#)

I have never endorsed any products before but when my Google Desktop crashed and would not reboot I panicked since my life depends on indexing my some 300,000 files! So after a few tries I stumbled on [Lookeen](#), a German company, and for about \$50 you get a fantastic indexing system. It is one of those simple things that you find a better part each time you use it. It is what Google Desktop could have become.

Moreover their customer support is fantastic! Real people answering real questions to make the experience better. So for any of you who want a great indexing system for a PC I would strongly suggest you try them out! No disclosures to make here, just that when one relies on a good indexing system and the only one you had is no more it is a God send to get this one! Hope they do well.



Labels: [Commentary](#)

TUESDAY, MARCH 1, 2016

[HOW STUPID IS THE USPTF?](#)

First they did away with mammograms. Women went ballistic. Then they did away with PSA tests. Men were silent. Now they are doing away with vision testing for the elderly. At least the JAMA folks complained.

The [USPTF](#) states as of today:

The U.S. Preventive Services Task Force released today a final recommendation statement on screening for impaired visual acuity in older adults. The Task Force concludes that the evidence is insufficient to make a recommendation for or against screening in older adults without reported vision problems within a primary care setting.

In contrast [JAMA](#) states:

In 2009, the US Preventive Services Task Force (USPSTF) concluded that there was insufficient evidence to warrant recommending visual acuity screening of older adults. A recent update, published in JAMA,¹ reaches the same conclusion. How (one might ask) can that be, especially as the USPSTF also concluded that impaired vision is common among elderly adults and that the major causes of impaired vision that the recommendation targets—refractive error, cataract, and age-related macular degeneration—are prevalent among elderly individuals and responsive (often dramatically) to clinical intervention?

It appears that these medical wizards always come up with recommendations that impair health and reduce costs. Remember we said seven years ago that this would happen!

Have any of these brains heard of ARMD, dry or wet, it leads to blindness! Any second year medical student should recognize drusen on a retinal exam. Did these folks ever do one in their life?



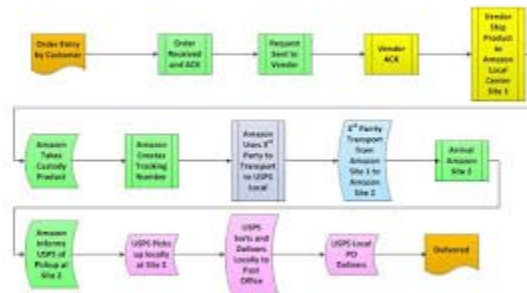
Labels: [Health Care](#)

MONDAY, FEBRUARY 22, 2016

WILL AMAZON SURVIVE?

Amazon has created a level of customer expectation that seems hard for them to meet. They charge Prime customers a fee and then promise 2 day delivery but seem almost always to fall short. At least here in the Greater NYC area. I have spent some time trying to unravel their process using the USPS and think I have some detail.

The following is my best guess based upon a few hundreds of samples.

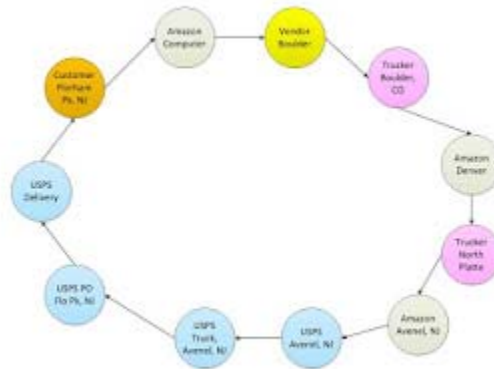


The above is a flow example. This is a case where they get a product from a third party vendor, they do not have it on hand. Often there is a delay here. The vendor connection and transport is subject to poor execution and thus begins the collapse of the two day promise.

Once Amazon "takes" possession they assign a shipping number from USPS. But apparently it is still a long time before USPS takes custody of the product. Amazon moves it to a local shipping point, one of theirs, then assigns it to some other third party transport to take it to a local Amazon site near the delivery. For us it is in Avenel in NJ.

At that point they contact the USPS for local transport. Up till that point one tracks Amazon NOT USPS apparently. I believe that USPS picks up and distributes the package to the local USPS where sometimes tracking data may be recorded. After all this is NOT UPS, it is the Government so don't expect people to follow through as expected.

Then the USPS delivers the package, hopefully, to the right address and not left in the rain, snow, or the wrong address.



This may be a low cost solution but it is highly prone to faults and failures. No longer is 2 day 2 days nor especially is next day ever next day, despite the extra fee charged.

My personal opinion is that this whole system must be redesigned. It is a mess and will soon cost Amazon customers. In addition one may initially assume delays are due to the USPS but it appears that they do not take custody until delivered locally and that the tracking is just to keep the customer happy, albeit delayed.

There may have to be some shakeup at Amazon. Customers will not tolerate extra payments for poor service. At least I believe so.



Labels: [Amazon](#)

THURSDAY, FEBRUARY 18, 2016

WHERE IS OCKHAM WHEN NEEDED?

It has not been since 1328 that we have seen Papal injunctions of this kind. Perhaps we should make Ockham's "Ninety Days", [Opus nonaginta dierum](#), mandatory reading in the Vatican.

As the [NY Times](#) reports:

Inserting himself into the Republican presidential race, Pope Francis on Wednesday suggested that Donald J. Trump "is not Christian" because of the harshness of his campaign promises to deport more immigrants and force Mexico to pay for a wall along the border. "A person who thinks only about building walls, wherever they may be, and not building bridges, is not Christian," Francis said when a reporter asked him about Mr. Trump on the papal airliner as he returned to Rome after his six-day visit to Mexico.

As this Bishop of Rome had previously said about those with a different orientation that he could not see into their souls, so should he say about any person. This statement is a clear interference into the politics of a country and sets a dangerous precedent. It is for this reason that John Paul II was almost at the point of disbanding the Jesuits.

There is a long and not very praiseworthy history of the Bishop of Rome wandering into politics. This may very well be another such path. Whatever a candidates views, they should be considered by the public voting, those of all religions, at least in a democracy. Papal interference is a double edged sword.

There is an excellent review by [Reid at the Cornell site](#) on the book by [Tierney](#) and Ockham. It is truly worth the read. He notes:

Tierney's treatment of Ockham on political rights is similarly original and provocative. He shows that Ockham argued that both the emperor and the pope were obliged to respect the rights of their subjects. Ockham maintained that the emperor derived his power from the people, who "could not confer more power than it actually possessed." A provision of the canon law of corporations, Ockham continued, limited this power, holding that a governing majority and, by extension, the emperor-could infringe on the rights of the other members only in the case of "necessary actions. The pope, furthermore, was limited by the canonistic maxim that no one was to be deprived of rights "without fault" (sine culpa), and the fundamental principle of evangelical liberty...

Definitely worth the read. Now Reid quotes Tierney in the same page:

Ockham's favorite way of proving [the restraints on papal power] was to argue that the evangelical liberty proclaimed in scripture limited papal power by safeguarding the natural and civil rights of the pope's subjects.... Christian law was a law of liberty, indeed, "a law of perfect liberty" according to the Epistle of James. Paul too wrote of "the freedom that we have in Christ Jesus" and declared that "Where the spirit of the Lord is, there is liberty." But, if the pope could command anything not contrary to divine and natural law, then Christian law would be a law of most horrid servitude. All Christians would be made slaves of the supreme pontiff, for to command anything not forbidden by divine and natural law was precisely the kind of power that a master held over his slaves.... The proper limits to papal power were set by the liberties and temporal rights of emperors, kings, princes and other persons, rights that came to them from natural law or the law of nations or civil law.

Thus there was indeed a well understood separation of Church and State. Ockham battled John XXII who as a Canon Lawyer by training was now dealing the the Theologian. But clearly the almost century spent in Avignon was a turning point for what was formerly the Bishop of Rome. In a sense, one can agree with Tierney and see in Ockham the foundations of modern day political theory and understanding. I would further argue that the Nominalism of Ockham is also key but Tierney may not. Notwithstanding this battle spans centuries.



Labels: [Politics](#), [Vatican](#)

[THE END OF THE SET TOP BOX?](#)

The FCC voted an NPRM regarding the set top box. Advocacy groups such as [Public Knowledge](#) state:

Today, the Federal Communications Commission approved a Notice of Proposed Rulemaking, requesting comment on a proposal to allow pay TV customers to access programming on the devices and apps of their choice without having to rent a set-top box from their cable provider. Public Knowledge applauds the FCC for taking such a significant step toward breaking open the stranglehold pay TV giants have over consumers.

We have been following this for well over a decade. One Commissioner, [Ajit Pai](#), made some interesting remarks that are worth following. He simply said; why not just get rid of the box totally? Good question. Most TV sets if not all have their own tuners, and manual controls. Almost all sets today have Internet connections. So why use a set top box if you already connect to the Internet and could have a simple APP?

That would open the system up totally. Then if you opened the CATV system, just a thought, and made it a common carrier...well you know where that goes!

Just a thought. Frankly there really is no need for the box any longer. We can manage our sets over the Internet already. So why not cable? And Pai is a lawyer at that.



Labels: [CATV](#), [FCC](#)

MONDAY, FEBRUARY 15, 2016

[5G AND A CHANGE OF PARADIGM](#)

As we have been arguing for a few years now, the evolution from 4G to 5G will be significant. 5G will allow 100X the speed of 4G. But that is not the half of it. If the carriers are smart, a big if however, they can see this in a distributed mesh network, using intelligent customer based mesh routers so that coverage can be seamless and costs reduced.

In [ArsTechnica](#) there and article on the work at ATT. They state:

AT&T is collaborating with Ericsson and Intel on outdoor trials. "We expect field trials of 5G technologies to provide wireless connectivity to fixed locations in Austin before the end of this year," AT&T said. "The trials will help guide our 5G standards contributions and set the stage for widespread commercial and mobile availability once technology standards for 5G are established." LTE could remain AT&T's primary mobile network technology for a few years. AT&T said it wants to be ready to switch to 5G once the technology standards are set by 3GPP, the international standards body. 3GPP "will likely complete the first phase of that process in 2018," AT&T said.

Besides smartphone data, AT&T says 5G will be used for virtual reality, self-driving cars,

robotics, smart cities, and massive sensor networks. On the back end, AT&T said it is relying heavily on network function virtualization and software-defined networking to reduce the cost of delivering data and to support new applications more quickly. AT&T is trying to ditch the "traditional model [that] relied on complex and cumbersome hardware" in favor of one that "turn[s] routers, firewalls and other network equipment into virtual functions running on commodity hardware," the company said.

The cost can be minimized by having the customer become part of the network at their cost.

The only barrier will be the carrier's greed in delimiting access to what they feel is of value. A smart carrier will see the ever expanding value in distributed access and not try to follow the CATV carriers down the road to perdition.



Labels: [Wireless](#)

[THEOLOGIAN AND CANON LAWYERS](#)

From 1324 to 1328, William of Ockham battled John XXII the ersatz Pope and factual Bishop of Avignon, not Rome just to make a point. John was the second Avignon "Pope" and he had been trained as a Canon Lawyer. This was a critical skill at the time because the Church had taken over more than just mankind's souls. The had land, managed kings, and their empires. Canon Law was, and still is, a remnant of Roman Law and the Code of Justinian. On the other hand Ockham was a Theologian. Theology was the Queen of such studies and it was Theology that could get you called a heretic, not a nice thing to happen at the time.

Ockham reviews John's writing and behold he considers John a heretic! The result is that John declares him a heretic. From that point on Ockham becomes the first real modern political science writer. He gave up Theology and started writing about mankind and who we were and how we should be ruled. He was the first in the path to Locke, Mill, and the like.

But the point is that Ockham was a Theologian and John a Canon Lawyer. Their trades at the time were not only orthogonal but dissonant. Now reading a blog of, I guess, one of the libertarian folks at [George Mason](#) I see in it the the battle between businessman and economists. The author opines:

Such a claim is illogical, even if we assume – falsely – that Trump earned every cent of his monetary fortune honestly rather than at least some of it through government-orchestrated theft. Knowing how to run a business is not the same thing as knowing economics. To assume that the two domains of knowledge and expertise are the same is an error equivalent to assuming that a successful NASCAR driver is thereby an expert automotive engineer. Of course, it's possible for a successful NASCAR driver to know something about automotive engineering, just as it's possible for a successful business person to know something about economics. But success at each of the former tasks (driving a race car and managing a business) is not the same thing as, and requires very little familiarity with, the latter domains of knowledge (automotive engineering and economics).

I get it, the author does not like Trump. Well I have no horse in this race but the point is; economists are not entrepreneurs. Economists deal with theories. Economics is not a science. You cannot do an experiment. They fling around curves and equations sine any basis. Theologies at least had the Bible to work off of. There were God's word. Try and get two economists to agree on any word.

Business and entrepreneurs deal with facts. You make money or you lose money. Entrepreneurs can create value in society, economists have no chance of doing so. So unlike John and Ockham, the lawyer and the theologian, the entrepreneur and the economist really have no point of commonality. One lives in the world of personal consequences the other on preaching to people who often with due cause have no idea what they are shouting about.



Labels: [Economics](#)

[TAX, TAX, TAX](#)

Over the past seven plus years we have examined multiple proposals to "tax carbon". The academic's idea appears to be that by taxing something one uses less of it and thus since "carbon" is bad, hopefully not in the cells of our body but alas these are economists after all who most likely never took a biology course, then by taxing it there will be less of it.

Take a simple example. We tax liquor and gambling. Yep, we sure do. Have we seen its consumption decrease, no. It worked on cigarettes but there we had to tax it to oblivion, but one could also argue that it was social pressure more so.

Take the left leaning web site [Project Syndicate](#). These folks from the left leaning policy house in DC suggest:

If, since then, each \$5 increase in the oil price brought a \$30 per ton decrease in the carbon tax, and each \$5 decline brought a \$45-per-ton increase, the result would be a \$0.91 difference between the standard market price and the actual tax-inclusive consumer price last month. That increase would have raised the carbon price substantially, providing governments with revenue – reaching \$375 per ton of carbon today – to apply to meeting fiscal priorities, all while cushioning the fall in gasoline prices caused by the steep decline in the price of crude. While \$375 per ton is a very high price, reflecting the particularly low price of oil today, even a lower carbon price – in the range of \$150-250 per ton – would be sufficient to meet international climate goals over the next decade.

No this is not a paragraph from the new SAT. It is from two fellows who are arguing for a tax on carbon.

The question should be; what is the problem?

Let us for the sake of brevity assume the problem is carbon emissions. Frankly I like warm weather but I guess my likes are irrelevant. Now the question should then be; how do we reduce carbon? There are two ways to answer this:

1. Economics: Tax the hell out of it.
2. Technology: Develop extraction and emission reduction mechanisms as well as non carbon emitting sources.

Now the first is easy to do if you control the economy and have no idea what else to do.

The second way is the way that took mankind out of the state of nature and into what we now call civilization. We invent things! New idea. So perhaps by not wasting time on a new App we could devote the efforts to carbon extraction. It is not really that hard, just takes focus.

So why the economics's approach. Does it solve the problem? Only at extortionary rates and only by placing the burden on those at the lower income levels. Why not for once consider the technological and stop raising taxes. And yes, the Government will just waste the money the raise any way.



Labels: [Economics](#)

SATURDAY, FEBRUARY 13, 2016

[ONLY PART OF THE STORY](#)

Some five or six years ago we wrote a piece on benefits of Medicare. We showed that the fallacy issued by the Right that the Taxpayer is funding all benefits is utter nonsense, at least for a significant portion of the recipients. Recently we further showed that a significant portion, 10-15%, actually are underwriting the ACA recipients under the new programs.

So along comes what appears to be baseless assertions from the alleged Right Wing folks at [Heritage](#).

They state:

Have senior citizens really “paid for” the Medicare and Social Security benefits they enjoy in retirement? Many believe so. But for the vast majority, the answer is – unequivocally- No. Federal entitlement payroll taxes and general revenues finance Medicare and Social Security benefits on a “pay-as-you-go” basis, meaning today’s workers’ taxes fund today’s retirees. Workers’ taxes are not deposited in anything like a private sector “trust fund” today and “saved” for tomorrow’s benefits.

Now one must remember that for Medicare:

1. One pays 3% of the Gross Income for say 45 years.
2. If one continues to be productive one not only pays an additional 3% for the rest of ones life then:
3. One pays an excess premium on Medicare. Say your salary is \$200,000 then Medicare triples

your monthly payment to \$360 per month.

4. Then if you sell anything you get 3% tax on any capital sale

5. Then you also have to buy a Medigap and Medicare Part D plan, most of which are useless anyhow, for about \$4,000 pa.

Now just what is the deal here? Well it is that Medicare negotiates the rates for reimbursement. It pays what we have calculated as about 40% of the actual cost.

So when I see comments like this, comments which in my opinion are both unbalanced and lacking in factual analysis, I can say that both Left and Right are purveyors of what is less than factual. Pity!



Labels: [Health Care](#)

SATURDAY, FEBRUARY 13, 2016

[THE NEW BELL SYSTEM IS THE OLD BELL SYSTEM](#)

In a [NY Times](#) piece today there is a long discussion on how ATT is trying to adjust its workforce to meet the challenge from Amazon, Google, Netflix. Well good luck guys!

I had spent, on and off, about ten years in the System before and after Divestiture. Early on in NY Tel and Bell Labs. Frankly it was the most rigid environment ever. Only after doing a few dozen start up and even Corporate America the old Bell System was designed for drones.

For example, when I went to NYNEX at a dinner one night the head of HR said that the rule was that "The A students went to ATT and the Labs, the B students to Western Electric, and the C students to the Operating Companies" Furthermore in the Operating Companies you had grads from fourth rate schools like Manhattan College, I spent time there, and few if any from say Harvard or MIT (again went there too). Schools like Manhattan educated great swarms of followers, for NYC jobs, Con Ed, the Telephone Company, the Government. You learned how to separate green papers from pink ones.

Now along comes a world of competition. The Old Bell System approach is to set the walls up higher. Remember that the new ATT is really South West Bell, an Operating Company filled deliberately with all those C students.

But wait! Their competition such as Google, has A+ students from MIT and Stanford. The world is now technical, and how do we see the paper sorters competing? Not well.

So according to the Times the ATT CEO is trying to retool. Good luck. It is a 40 year task. First they cannot attract the great students. For when they do these people will report to the old C students and the smart one do not tolerate fools very well, so they will leave, and the old guard will say to themselves that the new ones were bad to begin with.

The CEO is now trying to revamp the company. The Times states:

In an ambitious corporate education program that started about two years ago, he is offering to pay for classes (at least some of them) to help employees modernize their skills. But there's a catch: They have to take these classes on their own time and sometimes pay for them with their own money. To Mr. Stephenson, it should be an easy choice for most workers: Learn new skills or find your career choices are very limited.

Now that really makes sense. You want to educate C students on their own dime to become A+ students. Well fish without wings will have trouble flying.

The article continues:

By 2020, Mr. Stephenson hopes AT&T will be well into its transformation into a computing company that manages all sorts of digital things: phones, satellite television and huge volumes of data, all sorted through software managed in the cloud. That can't happen unless at least some of his work force is retrained to deal with the technology. It's not a young group: The average tenure at AT&T is 12 years, or 22 years if you don't count the people working in call centers. And many employees don't have experience writing open-source software or casually analyzing terabytes of customer data.

Yes, 22 years, you have to remove the call centers. Is there a way to "train" someone to be a high techy? Not really. Never works. These people have been enculturated to be followers, paper sorters, understanding the GEI, the General Executive Instructions. Yes there is or was a "book" that you followed. For the most part he has a workforce of 220,000 chosen to do what they are told, by the book. The world has changed however.

Then there is this statement:

But Randall said his brother was not necessarily like the rest of the work force because there will always be hard, outdoor tasks for people like him. "There will be people turning screws and digging trenches. I'll be long gone before that is over. But other guys I know in Oklahoma will do a skills pivot" with additional training, he said.

The problem is that technology will make this outdoor workforce obsolete. Strange the lack of discussion on wireless here. It is wireless that will replace lines, be they copper or fiber. 5G will be Gbps to each users from towers that can be set up in a day or actually purchased and facilitated by the customers themselves! As Tom Sawyer go the others to white wash the fence so too can a carrier get customers to create and operate their own network. That is thinking outside the box. ATT is still justifying copper lines on poles in Oklahoma. That is why Google may win, if it gets rid of that fiber business. But alas most likely it will be some other new Creative Destruction entity which will do that.

And the key risk is that if one tries to bring in better people, like Google, the existing culture will generate "antibodies" and attack and eliminate the new. Happens all the time. It is a Gresham's law applied to competence, bad employees chase out the good. Right now ATT has a somewhat

monopoly in wireless along with Verizon. That is the survival hook for a while. The barrier to entry is the license. The risk there, however, is that when unlicensed bands can become more effective then the value of the license deteriorates. Things always change.



Labels: [Telecom](#)

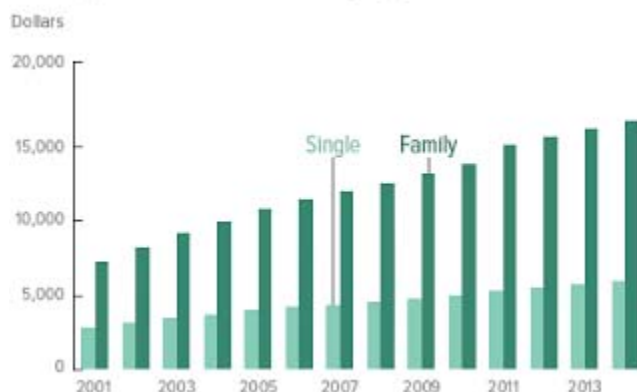
FRIDAY, FEBRUARY 12, 2016

HEALTHCARE IS GETTING BETTER?

The [CBO](#) has a report on the projections of Healthcare costs. It is worth the read. For all the "good news" from our Government, somehow CBO manages to state the obvious. Things are really not that good.

They state:

Average Premiums for Employment-Based Plans



Most Americans are covered by private health insurance, which they either obtain through employment or purchase individually. Insurance premiums—the payments made to buy that coverage by enrollees or by other parties on their behalf—are high and rising. CBO and the staff of the Joint Committee on Taxation (JCT) project that in 2016, the average premium for an employment-based insurance plan will be about \$6,400 for single coverage and about \$15,500 for family coverage. Average premiums for coverage purchased individually (in what is called the nongroup market) are also high—but not quite as high as average employment-based premiums, mostly because nongroup coverage is less extensive and thus requires enrollees to make higher out-of-pocket payments when they receive care. Although premiums for private insurance have grown relatively slowly in recent years, they have usually grown faster than the economy as a whole and thus faster than average income. Over the period from 2005 to 2014, premiums for employment-based insurance grew by 48 percent for single coverage and by 55 percent for family coverage. CBO and JCT expect them to grow at similar rates over the next decade—by about 5 percent per year, on average, or about 2 percentage points faster than income per capita. As a result of that growth, average premiums for employment-based coverage are projected to be about \$10,000 for single coverage and about \$24,500 for family coverage in 2025, nearly 60 percent higher than they were in 2016.

Now combine that with the Yield Curve data we presented and we can see that with any bump of

inflation the 5% can readily go to 10% again and compounded inflation is a disaster. Furthermore we have not really insured the 20 million stated we have insured the sicker 10 million. Furthermore the insured are not paying any premiums of any consequence, they get a free ride while increased Medicare fees are somewhat making up for the difference.

But wait! The real problem is the added costs to providing Healthcare; the EHR, the EHR audits, the Quality metrics, the Quality metric audits. Not only do we have added overhead but we have added Government overseers. We will soon have fewer physicians, of a poorer quality, after all we do not want to make prior academic performance a decision metric any longer, and we will ultimately end up looking like the NHS, single payer or not.



Labels: [Health Care](#)

[COMMON CARRIAGE, ELIZABETH I, AND THE FCC](#)

Common Carriage has been around now for over 500 years in English and in turn American Law. What this means simply is that there exists an entity called the carrier and you enter into a de facto agreement with them to transport your packet from point A to point B for a certain publicly published price. In return for that service as a common carrier the entity has liability only for the cost of carriage if the packet is somehow lost.

Thus if you ship a pound of gold, 16oz is you will, and at \$1,200 per oz you have almost \$20,000 worth of gold and the carrier charges you \$5 a pound, then if it is lost you get \$5 back. That is all. If however you are not a common carrier and you loose it you may be sued for both the \$20K plus and consequential damages resulting therefrom.

Now in today's debate on Internet Neutrality there are three issues:

1. Wireless: Is wireless somehow protected perforce of their bought and paid for licenses? We have answered No. First the old RBOC go their free as did many of those who "won" license lotteries. Second, there is an issue of ownership versus right to use. What did the carrier get when the auction occurred, ownership or a right to use. We argue the latter.
2. Interconnection: Interconnection is the process of having one carrier deal with another. We have also argued for well over 25 years that interconnection should be mandated at zero price. The factotum of externalities is nonsense. The French economist Tirole has argued its existence and has tried to justify the incumbents right to compensation. For anyone with a femto second of experience that is utter nonsense. Sock companies cannot charge shoe companies for interconnection!
3. Last Mile: This is the Net Neutrality argument. Namely should each entity connecting to the last mile pay the same rate for carriage as any other? Or can the carrier discriminate? I think when it comes to people we have finally agreed that its is both immoral and illegal to discriminate against anyone. If not we should start now a full policy and legal structure against any form of discrimination. When I buy a loaf of bread it should be the same as anyone else. But the ATTs, Verizon's, Comcasts see the world differently. If they do not like me for some reason

they can charge more or even prevent me from buying access at any price. They want to determine what I can get. I don't want to carry the analogy too far but well one can see where this would go. They all have take advantages of Governmental, read from the people, advantages to render their services and make profits. They are or should be common carriers. They should not discriminate.

This is the issue before the FCC. The big guns and deep pockets of the incumbents are out in force. We should watch how this evolves. If it goes the wrong way they we may suffer the consequences.

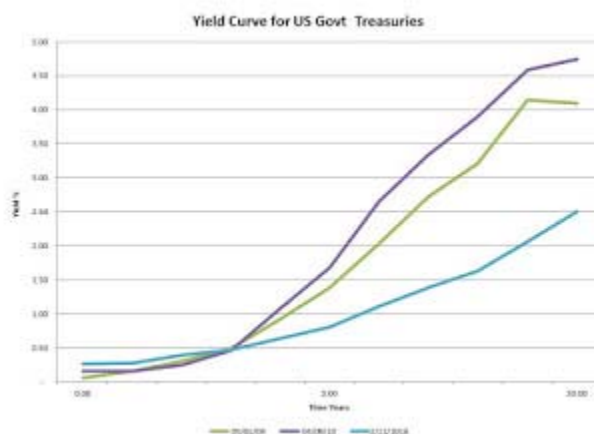


Labels: [FCC](#), [Internet Neutrality](#)

THURSDAY, FEBRUARY 11, 2016

[THE NEXT ECONOMIC COLLAPSE](#)

The FED and our wonderful Government is taking on another collapse. Let us look at the yield curves.



We have this soon to be inverted curve. Watch the short term rates.



The above shows the spread between 10 year and 90 days. It is dropping very quickly. That is always a problem. But it is due to short term increasing while long term decreases!



The above is even more inspiring. The red line on the left is short term exploding. Watch the DOW, it is directly related. In my view Yellen is clueless, as are all economists, the Witch Doctors of the 21st Century!

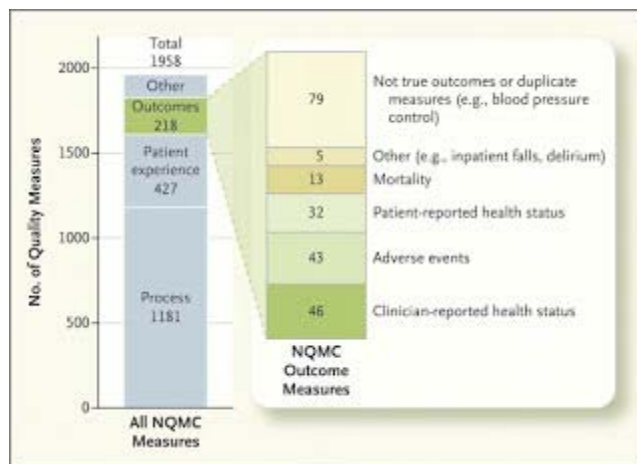


The above shows the spread a bit better. What this process is doing is making those who can leverage richer and the poor schlubs who are trying to save for the future indentured servants.

This is what Sanders should focus on. It is his actions leading this train wreck!



Labels: [Economy](#)

THE ILLUSION OF QUALITY

The above is from [NEJM](#) and is discussed in a recent article on Quality in Health Care. As they note:

Why has arriving at the essential measures of performance been so difficult in health care, when it seems to occur naturally in other fields? First, in health care we've allowed "quality" to be defined as compliance with evidence-based practice guidelines rather than as improvement in outcomes. Of the 1958 quality indicators in the National Quality Measures Clearinghouse, for example, only 139 are actual outcomes and only 32 are patient-reported outcomes. Defaulting to measurement of discrete processes is understandable, given the historical organization of health care delivery around specialty services and fee-for-service payments.

What this is referring to is that under the new ACA, besides everything else, physicians must report on "Quality Measures", almost the totality of which are fabrications of metrics which have nothing to do with the patient's health. They are getting messier all the time. The Government process is creating an overhead that is unsustainable, it matches Czarist Russia, with half the population working for the Czar checking on checkers etc. For example I recently was told that a certain Government agency now had statement of work reviews to check proper use of pronouns! Yes, pronouns.

The NEJM article continues:

Second, the limited outcomes measurement that has occurred has been led overwhelmingly by specialty societies. But outcomes are not strictly related to individual specialties or procedures; they reflect the overall care for a patient's medical condition, in which multiple specialties are usually involved. What generally matters to patients are outcomes that encompass the whole cycle of care — including health status achieved (e.g., survival, functional status, quality of life); the time, complications, and suffering involved in getting care; and the sustainability of benefits achieved (e.g., time until recurrence). Specialty societies naturally focus on their constituents, often choosing measures that physicians can reliably control. The perspective expressed, for example, in a cardiology society's statement that "outcome measures are highly desirable but often difficult to incorporate into performance measure sets because of vulnerability to influences outside the provider's control" distances providers from the work of improving

patients' actual results and contributes to outcomes-measurement paralysis.

The Societies try come up with metrics to meet the Government demands and game the system as well. In today's new ACA world we have physicians using useless EHR systems, they cannot communicate with each other, then they must re-certify, a process which just adds to the cost without adding to quality, creating artefactual "quality" metrics, and somewhere trying to treat a patient.

The process of medicine will soon come to a standstill. It is well above \$3 trillion a year and rapidly approaching \$4 trillion. These artificial measurements will not only add to the costs but detract from the care.



Labels: [Health Care](#)

WEDNESDAY, FEBRUARY 10, 2016

[HARVARD AND HELL?](#)



As the [Crimson](#) notes:

Ninety-one percent of contributions to current presidential candidates made by Harvard faculty, instructors, and researchers in 2015 went to former Secretary of State Hillary R. Clinton, according to a Crimson analysis of Federal Election Commission filings.

I guess they fear the fires of everlasting perdition?



Labels: [Academy](#)

TUESDAY, FEBRUARY 9, 2016

[PERHAPS THIS IS WHY MOOCS HAVE PROBLEMS?](#)

I just read a note on the [edX](#) blog extolling the benefits of a MOOC in place of in person lectures. Sometimes the words can also be interpreted to demonstrate the problems more so than extol the thought of benefits.

Let me explain. First they state:

The course attracted over 7,500 students from 147 countries in its first run and was a prized specimen for researchers, data analysts and online course developers alike. By studying the dataset, correlations among different student demographics, learning patterns (e.g., clicking and seeking) and performance can be examined. An interesting finding was that students who performed best in assignments did not have high engagement in forums, probably meaning that they did not require much peer assistance in understanding the contents.

The problem is that the background and interest of the students bias the results greatly. In addition the data set is most likely in error. People report what they want to report and the reliability of anything in a MOOC is highly suspect.

They continue:

Although producing a MOOC takes more effort than face-to-face (F2F) lecturing, in Dr. Kajimoto's point of view, the benefits outweigh the costs. As every single word in the videos has to be scripted, having a solid script helped Dr. Kajimoto realize how repetitive on-campus lectures are and how time in class can be better spent. Flipping the lectures also resulted in better activities engagement and quality of discussion, as students had much more time and motivation to prepare for tutorials. Peer pressure was also a factor as students fear lagging behind their classmates.

There is a key point in the above, namely that *having a solid script helped Dr. Kajimoto realize how repetitive on-campus lectures are and how time in class can be better spent..*

Repetitive is often what is needed in class. Saying or presenting a new concept once in one way often does not work. I recall again my first MOOC, if you will, a College Chemistry course on Television in 1959. 6AM and every day for 45 min. Somewhere along the way I missed the definition of a mole, not the ones on skin, but a chemical metric. So for a few weeks, not having access to anyone who knew, I wandered until I found it out. Then, back on track. The same problem befalls MOOCs today. For example a recent MOOC told you to open R, a statistical package, with 4 screens. Well try and find the other 2! It is that type of brick wall that redundant teaching, inefficient teaching if you will, eliminates.

Redundancy allows, enables, conversation and thought. If all you want to do is transfer your facts then the MOOC works, but remember that the other side may not get them.

Thus this Blog note states a long list of problems, much more so than any benefits.

Labels: [MOOCs](#)

[ANOTHER SET OF BIOMARKERS](#)

Introduction

As we have noted there seems to be a never ending progression of biomarkers for PCa as well as other cancers. In this most recent one a Spanish research group (see Mengual et al) makes the following proposition:

Seven of the 42 genes evaluated (PCA3, ELF3, HIST1H2BG, MYO6, GALNT3, PHF12 and GDF15) were found to be independent predictors for discriminating patients with PCa from controls. We developed a four-gene expression signature (HIST1H2BG, SPP1, ELF3 and PCA3) with a sensitivity of 77 % and a specificity of 67 % (AUC = 0.763) for discriminating between tumor and control urines. The accuracy of PCA3 and previously reported panels of biomarkers is roughly maintained in our cohort. Our four-gene expression signature outperforms PCA3 as well as previously reported panels of biomarkers to predict PCa risk. This study suggests that a urinary biomarker panel could improve PCa detection. However, the accuracy of the panels of urinary transcripts developed to date, including our signature, is not high enough to warrant using them routinely in a clinical setting.

Admittedly we have a set of such non-invasive markers, including the 4K, which have been approved for use to ascertain patients who may have PCa versus those who do not. Let us consider the four proposed as an interesting case.

mRNA Specifics

The following Table and details discuss the four genes which they use.

<i>Gene</i>	<i>Description (NCBI)</i>
HIST1H2BG ^{25[1]} (also H2B/a; H2BFA; H2B.1A)	Histones are basic nuclear proteins that are responsible for the nucleosome structure of the chromosomal fiber in eukaryotes. Nucleosomes consist of approximately 146 bp of DNA wrapped around a histone octamer composed of pairs of each of the four core histones (H2A, H2B, H3, and H4). The chromatin fiber is further compacted through the interaction of a linker histone, H1, with the DNA between the nucleosomes to form higher order chromatin structures. The protein has antibacterial and antifungal antimicrobial activity. This gene is intronless and encodes a replication-dependent histone that is a member of the histone H2B family. Transcripts from this gene lack polyA tails; instead, they contain a palindromic termination element. This gene is found in the large histone gene cluster on chromosome 6p22-p21.3

^{25[1]} <http://www.ncbi.nlm.nih.gov/gene/8339>

^{25[2]} <http://www.ncbi.nlm.nih.gov/gene/6696>

<i>Gene</i>	<i>Description (NCBI)</i>
SPP1 ^{26[2]}	The protein encoded by this gene is involved in the attachment of osteoclasts to the mineralized bone matrix. The encoded protein is secreted and binds hydroxyapatite with high affinity. The osteoclast vitronectin receptor is found in the cell membrane and may be involved in the binding to this protein. This protein is also a cytokine that upregulates expression of interferon-gamma and interleukin-12.
ELF3 ^{27[3]} (also see Wang et al)	Aberrant regulation of the Wnt/ β -catenin pathway plays important roles in colorectal carcinogenesis, with over 90% of cases of sporadic colon cancer featuring β -catenin accumulation. While ubiquitination-mediated degradation is widely accepted as a major route for β -catenin protein turnover, little is known about the regulation of β -catenin in transcriptional level. ...Elf3, a member of the E-twenty-six family of transcription factors, drives β -catenin transactivation and associates with poor survival of colorectal cancer (CRC) patients. ... first found recurrent amplification and upregulation of Elf3 in CRC tissues, and further Gene Set Enrichment Analysis identified significant association between Elf3 expression and activity of WNT/ β -catenin pathway. Chromatin immunoprecipitation and electrophoretic mobility shift assay consistently revealed that Elf3 binds to and transactivates β -catenin promoter. Ectopic expression of Elf3 induces accumulation of β -catenin in both nucleus and cytoplasm, causing subsequent upregulation of several effector genes including c-Myc, VEGF, CCND1, MMP-7 and c-Jun. Suppressing Elf3 in CRC cells attenuates β -catenin signaling and decreases cell proliferation, migration and survival. Targeting Elf3 in xenograft tumors suppressed tumor progression in vivo. Taken together, our data identify Elf3 as a pivotal driver for β -catenin signaling in CRC, and highlight potential prognostic and therapeutic significance of Elf3 in CRC.
PCA3 ^{28[4]}	This gene produces a spliced, long non-coding RNA that is highly overexpressed in most types of prostate cancer cells and is used as a specific biomarker for this type of cancer. This gene is embedded in an intronic region of the prune2 gene on the opposite DNA strand. The transcript regulates prune2 levels through formation of a double-stranded RNA that undergoes adenosine deaminase actin on RNA-dependent adenosine-to-inosine RNA editing. In prostate cancer derived cells, overexpression of PCA induced downregulation of prune2, leading to decreased cell proliferation. Conversely, silencing in prostate cancer cells resulted in increased proliferation. Regulation of this gene appears to be sensitive to androgen-receptor activation, a molecular signature of prostate cancer. Alternative splicing results in multiple transcript variants.

Some additional comments are worth note.

HIST12BG

Histones are proteins that assist the structuring of the DNA into nucleosomes. As noted by Stankiewicz et al:

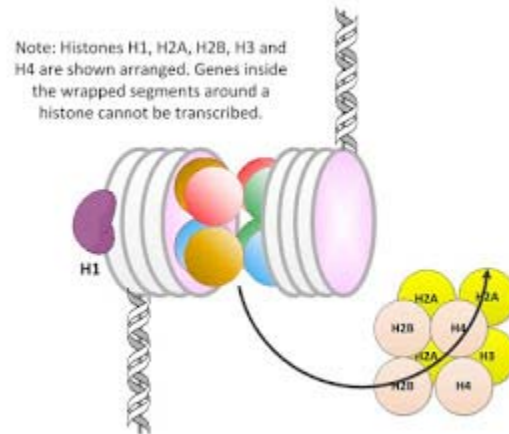
Results.... argue for the significance of epigenetic mechanisms in the regulation of chronic stress. Microarray studies have revealed alterations in mRNA expression levels of seven factors involved in chromatin modification in adult male Swiss-Webster mice subjected to various stressors for five weeks.

^{27[3]} <http://www.ncbi.nlm.nih.gov/gene/1999>

^{28[4]} <http://www.ncbi.nlm.nih.gov/gene/50652>

Three transcripts that encode histones were found to be upregulated (*H2afj*, *Hist1h2bm*, and *Hist1h2bg*), and four were down-regulated. These four down-regulated genes encoded histones (*Hist1h2bn*, *Hist1h2bh*), a silencing factor known to recruit histone methyltransferases and deacetylases (*Satb1*, and a protein involved in histone acetylation (*Hmgn2*).

We show the relationship of H2B to the histone and nucleosome structure below:



SPP1

As we have noted previously, SPP1 is secreted phosphoprotein 1, also commonly known as Osteopontin (OPN), also known as bone sialoprotein I (BSP-1 or BNSP), early T-lymphocyte activation (ETA-1), 2ar and Rickettsia resistance (Ric), is a human gene product which is also conserved in other species^{29[5]}.

From Hendig et al, they state that it is a secreted, highly acidic phosphoprotein that is involved in immune cell activation, wound healing, and bone morphogenesis and plays a major role in regulating mineralization processes in various tissues. Increased expression is often associated with pathological calcification. Furthermore, is a constitutive component of human skin and aorta, where it is localized to the elastic fiber and hypothesized to prevent calcification in the fibers?

SPP1 is a predominantly transcriptional regulated gene, and the promoter is highly conserved among different species (22). Several polymorphisms in the gene affect expression and have been associated with various disorders, e.g., systemic lupus erythematosus and arteriosclerosis.

SPP1 is a SIBLING glycoprotein that was first identified in osteoblasts. OPN is an important anti-apoptotic factor in many circumstances. OPN blocks the activation-induced cell death of macrophages and T cells as well as fibroblasts and endothelial cells exposed to harmful stimuli.

^{29[5]} Also see <http://www.ncbi.nlm.nih.gov/gene/6696> also see <http://www.wikigenes.org/e/gene/e/6696.html>

OPN prevents non-programmed cell death in inflammatory colitis. It has been shown that OPN drives IL-17 production; OPN is overexpressed in a variety of cancers, including lung cancer, breast cancer, colorectal cancer, stomach cancer, ovarian cancer, melanoma and mesothelioma; OPN contributes both glomerulonephritis and tubulointerstitial nephritis; and OPN is found in atheromatous plaques within arteries. Thus, manipulation of plasma OPN levels may be useful in the treatment of autoimmune diseases, cancer metastasis, osteoporosis and some forms of stress. Research has implicated osteopontin in excessive scar-forming and a gel has been developed to inhibit its effect.

ELF3

ELF3 is part of the ETS family. The ETS family of genes is positive or negative regulators of gene expression. They can up or down regulate expression. They are named for the initial gene discovered, the E26 Transforming Sequence, where E26 was the oncogene v-ets characterized in 1986 of an avian transforming virus called E26. It is also called the erythroblast transforming specific family, as discussed by Zong et al. As Watson et al note regarding this gene:

Four genes, ESE3 (EHF), ESE1 (ELF3), ESE2 (ELF5) and PDEF, were expressed at higher levels in breast cancer cells than normal epithelial cells. The expression of ELK3, ETS1 and FLII were reported to be reduced in breast cancer cells [114]. This pattern defined in cell lines does not absolutely correlate to that observed in tissue specimens. As noted above, ETS1 is overexpressed and PDEF protein is often reduced or lost in human breast cancer. While further studies are needed, ESE3 protein was absent in one breast cancer sample examined by IHC.

PCA3

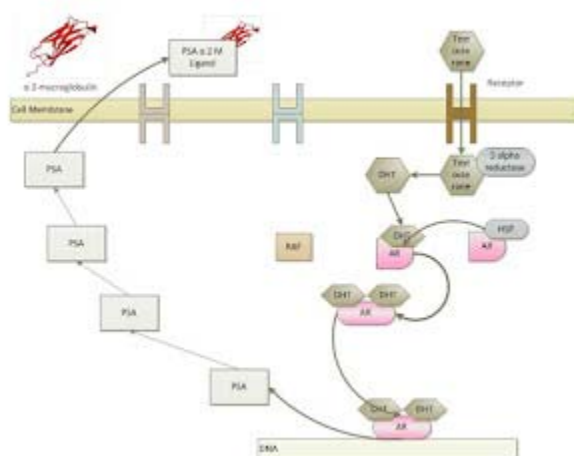
PCA3 has received a great deal of attention of late. It is a non-coding RNA and the controlling gene is located at 9q21-q22^{30[6]}. It is also called prostate cancer antigen 3 (non-protein coding). The presence of PCA3 is generally now believed to be a marker for PCa. Testing is now underway on many patients to determine if they have PCa using the PCA3 assay. Thus there is a great deal of interest in better understanding what the full networks are for PCA3 generation as well as looking at those pathways as a possible means to control PCa. We examine two recent studies in this area.

In the recent paper by Ferreira et al, they state:

Our findings suggest that the ncRNA PCA3 is involved in the control of PCa cell survival, in part through modulating AR signaling, which may raise new possibilities of using PCA3 knockdown as an additional therapeutic strategy for PCa control.

^{30[6]} <http://www.ncbi.nlm.nih.gov/gene/50652>

This may be of significant merit as a new potentially useful therapeutic. Now it should be recalled that the AR pathway and the PSA generation is known as shown below^{31[7]}.



Now Ferreira et al continue:

Due to the increased PCA3 expression in androgen-responsive cells compared with androgen-insensitive cells, and because AR signaling is an important pathway controlling PCa survival, we tested whether PCA3 expression was modulated by the androgen-active metabolite DHT and whether this expression pattern involved the activated AR.

Upregulation of PCA3 expression in response to LNCaP stimulation with DHT was significantly counteracted by the AR antagonist flutamide, indicating that PCA3 expression was induced by the activated AR. AR activation was further confirmed by the observation that LNCaP cells stimulated with DHT also showed AR transcriptional activity. Consistently, the entire AR target genes tested that contains canonical AR response elements (AREs) in their promoter sequences was upregulated upon DHT treatment. Although eight of the genes showed at least a 1.5-fold increase after AR activation, only two of them showed a significant increase in their expression levels. Interestingly, PCA3 upregulation upon DHT treatment has been observed previously, but no study has demonstrated the involvement of activated AR in PCA3 expression by using AR antagonists. Although our data also suggest that PCA3 is an androgen-responsive gene, the precise molecular mechanism by which PCA3 expression responds to this activation is still unknown.

One hypothesis is that activated AR can directly activate the PCA3 promoter, as has been demonstrated for the miR-101 and miR-21 regulatory regions, which are also modulated by the activated AR. However, no consensus AREs has been identified in the 500-bp PCA3 promoter

^{31[7]} Note we use the reference, Prostate Cancer Genomics, McGarty (2012, DRAFT, <http://www.telmarc.com/Documents/Books/Prostate%20Cancer%20Systems%20Approach%203.pdf>) as the source for some of this information. From this source one may obtain the initial sources.

region. We further screened for consensus ARE elements in the entire PCA3 genomic region at the 5 Kb region upstream from the PCA3 transcription start site, and have so far identified no canonical element (data not shown). Nevertheless, we cannot exclude the possibility that other, noncanonical ARE elements could also promote AR binding and directly activate PCA3 expression, as has been previously described for other genes modulated by the AR activation. PCA3-upregulated expression in response to DHT treatment could also be a result of activated AR binding to the regulatory regions of other AR-responsive genes, which in turn could induce PCA3 expression. Further experiments should investigate direct AR binding to different PCA3 genomic regions, in order to answer these open questions.

Now they examined genes which are known pathway controllers of PCa. The CDKs especially control cell cycle flow.

As an approach to investigate the signal by which PCA3 controls PCa cell survival, we analyzed the transcript expression of PSA, AR, TMPRSS2, NDRG1, GREB1, FGF8, CDK1, CDK2, and PMEPA1 genes, all of which have key roles in PCa growth and progression, and are classical AR target genes.

Also highly regulated by androgens, fibroblast growth factor 8 (FGF8), cyclin-dependent kinase 1 (CDK1), cyclin-dependent kinase 2 (CDK2), and the gene regulated in breast cancer 1 (GREB1) gene products have classical stimulating roles in prostate growth and proliferation. Conversely, the PMEPA1 gene, although a direct transcriptional target of the AR, has been described as a negative regulator of cell growth in the prostate epithelium, as well as negatively regulating AR protein levels in different cell-culture models. We also observed that the AR transcription level was downregulated after PCA3 knockdown. These results accord with previously published data, which demonstrated that the AR gene is transcriptionally regulated by AR through binding to AR regulatory elements (autoregulation). However, differently from the other AR-responsive genes tested here, the ARE elements required for this process have not been found in the AR promoter or in the 5'-flanking region, but rather in AR coding sequences.

The observation that PCA3 is involved in the control by modulation of the AR target genes is a key observation. As we have shown, based upon various prior works, the change in AR is critical to the loss of any control over the PCa cells. They state:

Here we demonstrate for the first time that PCA3 is involved in the control of PCa cell survival, at least in part by modulating the transcriptional activity of AR target genes. To our knowledge, this is the first characterization of the functional role of PCA3 in PCa cells, and will not only improve the understanding of key roles of this transcript in prostate carcinogenesis, but also suggests an alternative strategy to use PCA3 as a putative specific target for PCa treatment approaches. Because PCA3 seems to be a regulator of the expression of AR target genes and PCa cell survival, treatment options aiming to downregulate PCA3, in combination with other androgen-depletion-based strategies, could potentially circumvent androgen-ablation resistance mechanisms.

In an earlier paper by Ferreira et al, they state:

The prostate cancer antigen 3 (DD3/PCA3) is a non-coding RNA (ncRNA) specifically expressed in prostate tissues and overexpressed in prostate cancer (PCa) tumors. Although widely applied as a diagnostic marker for PCa, to date nothing has described about its role in PCa biology. We used herein small interfering RNA (siRNA) in order to knockdown DD3 mRNA message as an approach to elucidate DD3 functional roles in PCa cells.

LNCaP cell line was been used herein as an in vitro model for DD3 functional assays. siRNA sequences were specifically designed for DD3 exon 4 mRNA sequences (siDD3), as well as scrambled siRNA (siScr), as negative control. LNCaP cells were transiently transfected with siDD3 or siScr and DD3 expression was analysed by real time PCR (qRT-PCR) using DD3 specific oligonucleotides. LNCaP cells transfected with siDD3 demonstrated a marked decrease in cell proliferation and viability, as compared to siScr transfected cells.

Further, LNCaP cells in which DD3 was knocked-down presented a significant increase in proportion of cells in SubG0/G1 phase of cell cycle and presenting pyknotic nuclei, indicative of cells undergoing apoptosis. In order to investigate the putative mechanisms underlying the decrease of LNCaP cell survival as a result of DD3 knockdown, we then evaluated the involvement of DD3 on androgen receptor (AR) pro-survival signaling. DD3 expression was significantly upregulated as a result of LNCaP treatment with dihydrotestosterone (DHT), the active androgen metabolite. This effect was reverted by the addition of the AR antagonist, flutamide.

Consistent to an AR activation by DHT treatment, LNCaP cells presented a significant upregulation of AR target genes. Notably, siDD3/LNCaP transfected cells significantly inhibited the expression of tested AR responsive genes. Besides, DD3 knockdown was able to counteract DHT stimulatory effects over AR target gene expression. Despite negatively modulating the transcription of AR target genes, DD3 knockdown did not alter Akt and ERK phosphorylation, suggesting that DD3 is mainly controlling the expression of signaling pathways downstream to AR activation.

In summary, our findings indicate that DD3 is a ncRNA whose expression is AR regulated and is involved on the control of PCa cell survival and proliferation, in part by modulating the AR signaling pathway and its target genes.

These findings correspond to the first description of DD3 roles on PCa cells and could provide new insights into understanding prostate carcinogenesis, besides opening new prospects to use DD3 not only as a biomarker for PCa, but also as an specific target for therapeutic approaches aiming to inhibit PCa growth by negatively modulating AR pro-survival signal and their target genes.

In this slightly earlier paper the authors focus on the PCA3 as a target and examine its pathway significance.

Other researchers have examined PCA3 as well as other markers. It is well known that the TMPRSS2:ERG fusion is often seen in PCA. As Salagierski and Schalken conclude:

In recent years advances in genetics and biotechnology have stimulated the development of noninvasive tests to detect prostate cancer. Serum and urine molecular biomarkers have been identified, of which PCA3 has already been introduced clinically. The identification of prostate cancer specific genomic aberrations, ie TMPRSS2:ERG gene fusion, might improve diagnosis and affect prostate cancer treatment. Although several recently developed markers are promising, often showing increased specificity for prostate cancer detection compared to that of prostate specific antigen, their clinical application is limited. The only 2 true prostate cancer specific biomarkers identified to date remain PCA3 and TMPRSS2:ERG gene fusion.

Observations

As with so many of these other putative markers we have here four mRNAs that seem diverse yet somehow are reflective of a diagnostic malignancy test. Clearly PCA3 is already a marker with some merit. ELF3 is also arguably as part of the ETS family in the same neighborhood as PCA3. The H2B mRNA fragment may or may not be reflective of a process. Finally SPP1 seems to be an outlier. Clearly causative linkages should be drawn here. But this is an interesting find.

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Labels: [Cancer](#)

MONDAY, FEBRUARY 8, 2016

[ABANDON ALL HOPE YE WHO ENTER](#)

Dante had this sign hanging on the gates of Hell. Then inside he had level after level of evil doers. I guess he missed one. As the [BBC](#) reports:

"There's a special place in hell for women who don't help each other," says former Secretary of State Madeleine Albright. The comment was supposed to help Hillary Clinton but it has also exposed her problem appealing to women voters.

She must be the Czech version of Dante. Now I like Prague a great deal. It has one of the oldest Universities, founded in 1348, it was the home of Kafka, its people managed to knock off the number 2 in the SS, they make great beer, fantastic cars, brilliant minds. But this accusation of eternal damnation for voter's choice may be even a bit too much for even Dante.

The response from the international press was quite interesting. It is worth the read.

Oh yes, and Cerberus, perhaps for this candidate it was the Investment Bank and not the dog at the gate!



Labels: [Politics](#)

SATURDAY, FEBRUARY 6, 2016

[MOOCS AND THE DISCONNECT](#)

I figured I would try another MOOC, this time R, since I have been doing statistics for fifty years and would like to see what they are proposing.

Well like so many of these things, you download R, then see the video, which does not in any way tell you how to load the R windows. The woman giving the lesson just proceeds assuming you know how to work the software!

If you cannot load the required 4 windows how in God's name do you follow the instructions? Well this is a U Texas program so why expect any more. I guess these folks do not do any programming. Remember, avoid ambiguity of expectations folks!

What does some poor person in Romania do here....spend hours flicking keys! Well it is Texas after all. Back to the Alamo!



Labels: [MOOCs](#)

[SO THIS IS GETTING BETTER?](#)

The [CBO](#) reports:

The federal budget deficit was \$165 billion for the first four months of fiscal year 2016, CBO estimates—\$29 billion less than the shortfall recorded in the same span last year. Receipts were 3 percent higher than they were at this time a year ago, and outlays were about the same. If not for shifts in the timing of certain payments (which otherwise would have fallen on a weekend), the deficit for the first four months of fiscal year 2016 would have been \$10 billion larger than it was last year. If lawmakers enact no further legislation affecting spending or revenues this year, the federal government will end fiscal year 2016 with a deficit of \$544 billion, or 2.9 percent of gross domestic product (GDP), CBO estimates, up from \$439 billion, or 2.5 percent of GDP, in 2015. An estimated \$43 billion of this year's projected increase in the deficit will result from a shift in the timing of some payments that the government would ordinarily have made in fiscal year 2017 but that will instead be made in fiscal year 2016, because October 1, 2016—the first day of fiscal year 2017—falls on a weekend. If not for that shift, the projected deficit in 2016 would be \$500 billion, or 2.7 percent of GDP.

Not really an improving situation. Perhaps this is a driver of the current market.



Labels: [Economy](#)

[NET NEUTRALITY OR ANTITRUST](#)

As [ArsTechnica](#) reports:

Verizon Wireless is testing the limits of the Federal Communications Commission's net neutrality rules after announcing that it will exempt its own video service from mobile data caps—while counting data from competitors such as YouTube and Netflix against customers' caps. The only way for companies to deliver data to Verizon customers without counting against their data caps is to pay the carrier, something no major rival video service has chosen to do. While data cap exemptions are not specifically outlawed by the FCC's net neutrality rules, the FCC is examining

these arrangements to determine whether they should be stopped under the commission's so-called "general conduct standard." The FCC is already looking into data cap exemptions—also known as zero-rating—implemented by Comcast, AT&T, and T-Mobile USA.

This is less of a Net Neutrality issue than possibly an Antitrust issue. The wireless channel is a distribution channel. It was "bought" at an auction but still is using a public airwaves. More importantly they are bundling or tying a purchase at the disadvantage of a competitor.

One wonders where the DoJ Antitrust Division is on this one. Some [20 years ago I addressed](#) this specific point. But somehow the Government has spent 20 years in some alternate universe. My specific concern then was Verizon and access and it is essentially the same argument.

In addition some decade ago [I also discussed Internet Neutrality](#) in similar terms. The combination of the 1996 paper and the 2006 paper are ever so more relevant today.



Labels: [Antitrust](#), [FCC](#), [Internet Neutrality](#)

SATURDAY, FEBRUARY 6, 2016

[WHO IS UNDERWRITING WHOM?](#)

The ACA and Medicare may very well have created a tremendous distortion in the payment for Health Care. In a Pro ACA puff piece in [Modern Healthcare](#) the author writes:

Here's what Manhattan freelance writer feared when she went to an Affordable Care Act enrollment counselor for 2016 health insurance: a "terrible premium with a terrible deductible for a plan that covered nothing." Instead, she says she was "absolutely surprised" by an option she knew nothing about. ... signed up herself, her husband, who's a freelance artist, and their young son for New York State's new Essential Plan. Her family will pay \$49 a month for a plan through Empire Blue Cross and Blue Shield that has no deductible and covers most of their regular providers. They were previously paying \$500 a month for an exchange plan with a \$3,500 deductible. "I can't tell you how relieved we were," she said. On Jan. 1, New York became the second state to launch a version of the Basic Health Program (BHP) option authorized by the ACA, serving people with incomes between 138% and 200% of the federal poverty level, plus legal immigrants who don't immediately qualify for Medicaid. Consistent with experience, the state's advertising slogan for the Essential Plan is "You'd be surprised."

Yes indeed, a young family in New York City with a child is paying just \$49 per month. While a Medicare family with no medical bills pays \$500 per month additional to Medicare, \$8,000 per year to a Medicare gap Plan, then another \$2,000 per year for a Medicare Part D, and then if they are lucky to work or have other income an added 3% tax on that plus 3% on any capital gains. That is on top of having paid into Medicare since 1965! And yes, we have not included the deductible.

So we now have a system where those who have contributed are underwriting and financing those who are NOT contributing.

This is not Socialism, it is "Let's let the old folks die off!" not realizing that it is still the old folks who are footing the bill!

So why no discussion about this inequity? Imagine, \$49 per month and no deductible! Try and get that on Medicare!



Labels: [Health Care](#), [Politics](#)

THURSDAY, FEBRUARY 4, 2016

[OCKHAM AND THE PRESENT](#)

[Ockham Explained](#) by Keele is an excellent work describing Ockham and his philosophical thought. It is worth reading for those who want an introduction to Ockham and also for those who have spent time reading and trying to understand Ockham.

The book is arranged chronologically with Ockham's life and it presents a well-orchestrated flow of the development of his philosophical ideas, especially the development of his view of nominalism. What is important to understand is that Ockham came from the culture of Scholasticism and form of argument was often as important as content. The Scholastic was initially trained in the Trivium (Grammar, Logic, and Rhetoric) which placed significant emphasis on forms of usage and methods of argumentation. Breaking through that cultural-temporal mask can oftentimes be difficult if not impossible but Keele does a brilliant job in making is accessible to the present day audience.

The book is arranged by chronological segments in his life. Chapter 2 is an excellent presentation of the education of a young Friar in the Franciscans in England. pp 17-18 is one of the better presentations of the ten Categories of Aristotle, as learned in the Trivium by all students in the day. It would become one of the pillars that Ockham would chip away at. Aristotle, the Philosopher, was regarded as a near divinity in understanding by many of the Scholastics but it was Ockham who using the tools of Scholastic analysis started to chip away at this then 1600 century façade. pp 21-22 discusses the construct of Universals and its importance to the Church. This is acritical factor to understand. Whereas much of Aquinas had been rejected shortly after his death he was soon resurrected and canonized a Saint and his "logic" became a bulwark for the Church. This is a problem for Ockham.

Chapter 3 takes the student as Ockham a bit further from the basics of Grammar to the intricacies of logic. The author does a wonderful presentation on terms and also on the basics of logic as engaged by Ockham at the time. This is a critical chapter for the reader to understand the transition of Ockham from a student who learns the tools to Ockham the philosopher who starts to break them down. The summary on p 59 is excellent in setting the stage for the development of what would be the rebel phases.

Chapter 4 discusses Ockham as a teacher. It is not clear from the record as to whether Ockham was at Oxford or in London and what time he may have been at each. In the records of Merton at Oxford there is even ambiguity and uncertainty. However he did manage to go back and forth. This Chapter does a brilliant job in explaining how Ockham took apart Aristotle's Categories and in the process sets the stage for nominalism. Starting on pp 63-64 he uses Porphyrian trees to demonstrate the categories and in turn the individuals which we recognize. A good example of the problem is the statement that "Roses are red". We understand the universal species of a rose and the predicate red. But what do we mean by red? Today we can use a spectrophotometer and present a detailed spectrum of a red rose. The problem is that each red rose may very well have a slightly different spectrophotometer reading. So what are we to believe; the facts of our "lying" eyes? That is a challenge for Ockham. This Chapter ends on p 84 with a discussion of the connotation theory which is essential to much of the further insight.

Chapter 5 starts the discussion of the attacks on Ockham. One would have suspected attacks by the Dominicans but his attacks came from Franciscans. Chapter 5 is an excellent discussion of those attacks and especially the articulation of the "razor" principle and its explanation. The author has a superb talent in explaining the razor with various twists and turns and all in very readable style. Frankly this is one of the best I have read over the years.

Chapter 6 discusses Ockham's response. But what I found most enlightening was the discussion on Ockham and motion. I have read some of Ockham's writings on motion and unless one truly understands the Scholastics mind one can get quite confused. Motion to Ockham was not motion as we understand it. pp 122-131 is a superb discussion of this issue and the author presents the understanding of motion by the Scholastic as something much different than what we do today. It does raise the question, however, of what influence the work of Roger Bacon may have had since Bacon "measured" things whereas Ockham remains in the world of Scholastic abstraction. The reader less attuned to Scholastic thought and technique may wonder what the fuss is all about; but read the material and it will easily explain.

Chapter 7 takes Ockham to Avignon and in a sense this is the beginning of the Renaissance and the end of the Middle Ages. Ockham is ordered to report to Pope John XXII, the Avignon French Pope, no longer and the Bishop of Rome. The initial demand to appear is over possible heretical implications in his writings. Frankly this was not all that uncommon; many writings were purged with no serious consequence to the author, Aquinas being one at times. But Ockham was then drawn into the battle of poverty, the Spirituals in the Franciscan order and the examination of the writings of John XXII. John XXII was a regal pope and educated as a Canon Lawyer. Canon Lawyers and Theologians were like plumbers versus vascular surgeons. No criticism on plumbers, but they knew the code often as they wrote it. Theologians were few and far between whereas Canon Lawyers ran rampant in Papal hallways. Thus the battle was joined. Ockham read the writings on John XXII and to his surprise found them heretical. Thus he saw the Pope as a heretic, since after he explained them the Pope did not recant but attacked. One suspects that Ockham lacked some basic Palace social skills!

In Chapter 8 the author briefly takes Ockham on his midnight escape from Avignon to Munich. The chapter is brief and of all the writing in the book I had hope for an equal amount of attention, at least on the Work of Ninety Days, his political thesis. It was from 1328 through

1348 when he dies that there was a mass of writings on political thought. In fact it was some of the most powerful political writings and the beginning of what we now understand as democratic liberalism (I use liberalism in the classic English political sense). Thus the one thing I would have really like would be the author's writings on this period.

As noted, the book is not all of Ockham. To some degree that is regrettable but understandable. What the author presents of Ockham and his philosophical insight as explained above. What is missing are the other two parts of Ockham's writings; his theological works and most importantly his political works. Theologically Ockham was in stark contradistinction to Aquinas. As Aquinas saw logic and reason as a means to understand God we see Ockham reintroducing faith. On the political front there is a significant amount of Ockham introducing the concepts of individualism, the separation of Church and State, and the limited powers of the ruling class. The author has no mention of Marsilius of Padua who played a parallel role to Ockham in the political area.

But why is Ockham so important today? His philosophy or theology is just fine. However his political philosophy is critical. He was the first true philosopher of individualism. He saw in a Pope a heretic and said so. Strange that John XXIII took a name to follow John XXII. But Ockham stated that Popes have at best some limited spiritual authority but no temporal. He also noted the essential nature of the individual and that the power of the ruler came from the people and not God. This is an excellent work and worthy of some thought.



Labels: [Books](#), [Political Analysis](#)

WEDNESDAY, FEBRUARY 3, 2016

[PRO-NPY AND PCA](#)

We continue to find new markers for the detection of and prognostication of prostate cancer. We herein examine one of the somewhat newer one the pro-NPY protein. There are always two questions that arise. The first is diagnostic; namely, does this patient have PCa? We have examined several of the recent methodologies in this area^{32[1]}. The second is prognostic tests, where we are looking for markers of aggressive PCa. Just because a patient is diagnosed with PCa it is well known that very few will die of the disease. Thus the issue of identifying that group and using aggressive treatments is an imperative.

This search for the markers has been going on for several decades. For example from Walker et al (1999) we have the following:

We wish to identify genes associated with disease. To do so, we look for novel genes whose expression patterns mimic those of known disease-associated genes, using a method we call Guilt-by-Association (GBA), on the basis of a combinatoric measure of association. Using GBA, we have examined the expression of 40,000 human genes in 522 cDNA libraries, and have

^{32[1]} See the list of White Papers attached for details. They are part of and an addition to the Draft book, Prostate Cancer

discovered several hundred previously unidentified genes associated with cancer, inflammation, steroid-synthesis, insulin-synthesis, neurotransmitter processing, matrix remodeling, and other disease processes.

The majority of the genes, thus discovered, show no sequence similarity to known genes, and thus could not have been identified by homology searches. We present here an example of the discovery of eight genes associated with prostate cancer. Of the 40,000 most-abundant human genes, these 8 are the most closely linked to the known diagnostic genes, and thus are prime targets for pharmaceutical research.... PSA, the most closely coexpressed genes are glandular kallikrein, three novel genes, prostate seminal protein, PAP, a fourth novel gene, prostate transglutaminase, a fifth novel gene, and neuropeptide Y. (IPCA-9, IPCA-10 and IPCA-11 are coexpressed with PSA but appear to be 38 untranslated sequences.)Neuropeptide Y is coexpressed with PSA. It has been reported to be associated with prostate cancer

The neuropeptide Y, NPY, has thus been on the list as a putative marker for almost two decades. This specific one, namely pro-NPY, the predecessor of NPY, is the target of recent interest. A recent paper purports to establish a basis for pro-NPY. Namely from MedicalNews^{33[2]} we have the following:

Researchers at the University of Copenhagen have identified a new prognostic biomarker: the neuropeptide pro-NPY, which may help determine the risk of dying from prostate cancer. This particular type of protein is very specific to prostate cancer cells and could help identify whether newly diagnosed patients require radical prostatectomy surgery or if it is safe to delay surgery. The research has been published in the journal, European Urology^{34[3]}.

Using mass spectrometry, the researchers measured concentration changes in thousands of proteins in both normal and tumour tissue from prostate cancer. They discovered that in comparison to normal tissue, the prostate tumors exhibit numerous metabolic alterations including exacerbated activity of mitochondria.

Among the 9000 proteins identified, one protein, the neuropeptide, pro-NPY, was demonstrated to exhibit high levels in a subgroup of prostate cancer samples. Pro-NPY was analyzed in 750 patients with prostate cancer to show that pro-NPY levels correlate with increased risk of prostate cancer death.

"Our research shows that high pro-NPY levels are very specific to prostate cancer and can serve to predict prostate cancer related death among diagnosed patients who have not received surgical treatment," says Professor Amilcar Flores-Morales from the Department of Veterinary Disease Biology, University of Copenhagen.

^{33[2]} <http://www.medicalnewstoday.com/releases/305722.php>

^{34[3]} See References Inglesias-Gato et al.

"So identifying the biomarker pro-NPY could help us identify patients who would benefit from early active treatment, whereby we would also reduce unnecessary treatment of patients who undergo surgery when they have low-grade tumors that for the most part do not put their lives at risk. In the end, due to side effects, this could prove more harmful than beneficial to patients," adds Amilcar Flores-Morales.

Proteins are key effectors of cellular functions. Therefore, a better understanding of the protein signaling pathways deregulated in prostate cancer could lead to better preventive and therapeutic strategies for the treatment of this disease. Specifically, it is possible that metabolic alterations such as the increase in mitochondria activity could be targeted in the treatment of prostate cancer.

"We hope to contribute to the advance of translational cancer research and the implementation of precision medicine in the field of prostate cancer by providing a unique insight into the protein level alterations associated with tumor tissue in clinical samples," adds Flores-Morales.

This specific gene product pro-NPY has been studied by many, either directly or as its product NPY.

From Shay and Mangian we have a history of the identification and understanding of the function of NPY. Specifically they state:

In the 1970s, it was determined by Wurtman, Fernstrom and colleagues that dietary concentrations of tyrosine and tryptophan could affect the synthesis and concentrations of the neurotransmitters norepinephrine and serotonin. In turn, the diet-affected central concentrations of these neurotransmitters could affect the relative appetite/satiety state of an individual. These findings spurred nutrition researchers to connect zinc deficiency, dietary amino acid intake and anorexia. In 1980 it was reported that norepinephrine had a profound influence on feeding behavior within specific sites in the hypothalamus. Leibowitz and Brown (1980) reported that the predominantly inhibitory neurotransmitter norepinephrine had a strong stimulatory effect on food intake. When exogenous norepinephrine was delivered to the paraventricular nucleus (PVN) of the hypothalamus, short-term food intake increased. Later in the 1980s, neuropeptides were also discovered to have a profound impact on feeding behavior.

In 1982, neuropeptide Y (NPY) was first isolated from neural tissue within the porcine intestine. Soon after, NPY was found to have significant stimulatory effect on food intake (Clark et al. 1984). Although NPY may be synthesized by all neurons within the body, it is synthesized at very high levels within cell bodies derived in the arcuate nucleus of the hypothalamus. A high percentage of these neurons project to the PVN of the hypothalamus. Within the PVN, exogenously administered NPY has been demonstrated to stimulate appetite to a greater degree than any other agent yet tested, when considered on a molar basis. Interestingly, it was also found that the administration of NPY to the PVN specifically stimulated carbohydrate intake when rats were allowed to freely select from a three-choice macronutrient diet system.

Some investigators have also suggested that the results demonstrating an effect of NPY on macronutrient preference may be influenced by the past history or dietary preferences of rats

chosen for study (Welch et al. 1994). Even specifics of the diet ingredients used in macronutrient choice studies may influence the results obtained (Glass et al. 1997). Because of its very potent effect on food intake, NPY has been investigated very vigorously at many laboratories. Targets of research have included the effects of NPY, the development of agonists and antagonists of NPY and the identification and study of NPY receptors. The development of an NPY antagonist with an appetite-modulating activity is of interest to pharmaceutical concerns.

Consistent with the complex nature of the appetite regulation system, NPY has proved to be a difficult target to study.

First, it has been found that there are a family of NPY receptors, and it is still unclear whether a single NPY receptor or a subset of a few receptors mediate the appetite-generating effect of NPY.

Second, the NPY knockout mouse regulates food intake in a relatively normal fashion.

This has led some to suggest that the large set of physiological studies investigating the effect of NPY on food intake may need to be reconsidered. A possible explanation for normal appetite in the NPY knockout mouse is that NPY action may be accommodated for by other neuropeptides during development. The paradox between physiological data and the NPY knockout results is of great interest and is likely to be further investigated.

Finally in the current Inglesias-Gato et al paper they conclude:

The evaluation of pro-NPY as a biomarker of disease progression in historic TURP-detected watchful-waiting cohorts has some limitations as PSA levels are not available and also as tumor tissue obtained through TURP could be different from small cancers located in the peripheral zone. However, it also has some strength. Watchful-waiting cohorts are superior for identifying patients with an excellent outcome also in the absence of treatment and for identifying tumors that will progress when left in situ.

Markers for long-term indolent tumors, or tumors that will eventually progress when left in situ are difficult to identify in cohorts where patients are treated at an early stage. However, in order to implement pro-NPY measurements into current practice, the prognostic potential of pro-NPY should be addressed in modern, PSA tested cohorts, to evaluate its performance relative to current standard of care.

Furthermore, pro-NPY's nature as a secreted peptide and its high specificity for PCa would support additional studies to validate pro-NPY as a prognostic blood biomarker for disease progression in PSA screened patients and patients on active surveillance.

Neuropeptides are a class of molecules that have the capability of establishing communications between neurons. They are most common therefore amongst the nerve cells. Thus their presence in the prostate and especially their over-expression is of some interest. One of the key questions one may ask is; why do we see such an overexpression of neuropeptides in aggressive PCa? We will examine also the presence of neuroendocrine cells in the prostate as well. Neuroendocrine cells are a special class of cells that receive signals from nerve cells in the form of

neurotransmitters, such as the neuropeptides, and then release various hormones^{35[4]}. Neuroendocrine PCa is a highly aggressive and androgen receptive negative form of PCa with associated fatal results^{36[5]}. We shall focus on this collection of relationships to interpret some of the results of the paper in discussion.

Specifically we focus on pro-NPY and not its successor NPY. As Wulff et al noted the following about NPY, a successor to pro-NPY:

Peptide hormones, neuropeptides, and most other biologically active peptides are generated from larger precursors through proteolytic processing at dibasic or monobasic sites . In recent years a series of enzymes have been characterized that appear to be involved in this maturation process.

The two so-called precursor convertases, PC2, cloned from a human insulinoma and from mouse pituitary, and PC3, cloned from mouse pituitary and from AtT-20 cells , both have the expected specificity for certain pairs of basic residues. These enzymes are also expressed exclusively in peptide producing neuronal and endocrine cells . Coexpression of proopiomelanocortin and the two precursor convertases indicate that the balance between the expression of PC2 and PC3 probably can explain certain cases of tissue specific processing of precursors .

Furthermore, the processing of proopiomelanocortin in AtT-20 cells has been suppressed by antisense constructs of PC3 . Thus PC2 and PC3 appear to constitute key enzymes of the precursor processing machinery in the neuroendocrine system.

PP and NPY belong to the so-called PP-fold family of peptides, which have relatively simple precursors with a single dibasic processing site, plus, in pro-PP, an additional mono basic processing site.

The overall homology of the secreted products, PP and NPY, is 45%, and this homology is mainly restricted to residues that are important in the stabilization of the PP-fold structure and to the C-terminal part of the molecules, which is involved in receptor recognition.

From NCBI they discuss the NPY gene and its product:^{37[6]}

This gene encodes a neuropeptide that is widely expressed in the central nervous system and influences many physiological processes, including cortical excitability, stress response, food intake, circadian rhythms, and cardiovascular function. The neuropeptide functions through G protein-coupled receptors to inhibit adenylyl cyclase, activate mitogen-activated protein kinase (MAPK), regulate intracellular calcium levels, and activate potassium channels. A

^{35[4]} See Mydlo & Godec, pp 149-155.

^{36[5]} See Staibano, pp 87-109.

^{37[6]} <http://www.ncbi.nlm.nih.gov/gene/4852>

polymorphism in this gene resulting in a change of leucine 7 to proline in the signal peptide is associated with elevated cholesterol levels, higher alcohol consumption, and may be a risk factor for various metabolic and cardiovascular diseases. The protein also exhibits antimicrobial activity against bacteria and fungi.

First we examine NPY, a 36 amino acid molecule derived from pro-NPY which as we will discuss is 69 amino acids in size. From Silva et al we have the following discussion on NPY:

NPY (neuropeptide Y) is a 36-amino-acid peptide involved in the regulation of the cardiovascular system. It has vasopressor effects and potentiates the effect of other vasoconstrictor molecules such as noradrenaline or histamine. When used at low, non-vasoconstrictive doses on cultured vascular SMCs (smooth muscle cells), NPY stimulates SMC proliferation, an effect potentiated by noradrenaline.

NPY also acts on vascular ECs (endothelial cells). The potentiating effect of NPY on noradrenaline-induced vasoconstriction has been shown to be endothelium dependent on human saphenous veins.

NPY is capable of promoting EC proliferation, migration and adhesion on the extracellular matrix. It also stimulates capillary tube formation in vitro and angiogenesis in vivo. Similar to other secreted peptides, NPY is produced as a pre-pro-peptide. After removal of the signal peptide in the endoplasmic reticulum, pro-NPY is further cleaved by successive enzymes to generate the biologically active amidated NPY.

In neuroendocrine cells, mature NPY is localized in secretory granules, e.g. in neurons, chromaffin cells or in the pituitary. Immunoreactive NPY has been detected in HUVEC (human umbilical-vein endothelial cells), but NPY synthesis, storage and secretion have not been studied.

The potential for NPY to promote endothelial cell proliferation may be one of the factors in its excess and the growth of PCa beyond AR inhibition. It may facilitate angiogenesis via its endothelial action. Again this is speculative. The identification in neuroendocrine cells may also be significant in view of the aggressiveness of neuroendocrine based PCa. Again we are speculating here as well.

But pro-NPY is a more complex molecule as described by Egelkraut-Gottanka:

Similar to many other hormones and neurotransmitters, neuropeptide Y (NPY) is derived from a larger precursor molecule, the 69 amino acid pro-neuropeptide Y (pro-NPY). Precursor proteins undergo a highly specific conversion process to yield their biologically active products. As part of a finely tuned regulation network, the biosynthesis of hormones and neuropeptides plays a major role in many physiological and pathophysiological processes.

Diseases such as diabetes, obesity and diverse sorts of cancer could be associated with dysfunctions in the biosynthetic pathways.

From Silva et al who connect pro-NPY and NPY as follows:

The present study shows the expression of NPY and its precursor pro-NPY in HUVEC at the mRNA and protein levels as demonstrated by RT-PCR and ELISA. NPY expression has previously been determined in HUVEC only in a small number of HUVEC cultures. In the present study, NPY expression was evidenced in all cell preparations tested, independent of the medium used for cell culture ...The difference between the results of these two studies may be due to a different initial amount of RNA used for RT-PCR and the number of passages, since we used cells at passage 1, whereas ...The presence of NPY and pro-NPY in HUVEC was also assessed by immunofluorescence. NPY immunoreactivity appeared as small punctate granular structures disseminated in the cytoplasm...The antibody NPY02 used in our study is directed against an epitope borne by both NPY and pro-NPY, thus leading to the labelling of both NPY and its precursor. The small punctate granular appearance of endocytic vesicles However, it is unlikely that intracellular NPY derives from cell-culture medium since NPY staining is not lost or altered in HUVEC incubated in the absence of serum. Furthermore, labelling of EEAI, an early endosome marker, showed a staining completely different from the immunolabelling of NPY.

From the work of Magni and Motta (2001) we know that:

By showing that NPY receptors are expressed in the androgen-independent cell line PC-3 and that their activation results in cell proliferation, the present data suggest that NPY-related mechanisms might be relevant in certain stages of CaP, such as the progression of the disease during the androgen-independent stage.

They continue to state:

Prostate cancer (CaP) is initially often androgen dependent, and it may progress to androgen independence in later stages. In this condition, hormonal therapy is no longer useful and the prognosis becomes worse. It is believed that the molecular basis underlying this transition includes a host of factors, some of which are now being identified as peptidic molecules, such as growth factors and neurohormones. Several studies suggest that neuroendocrine mechanisms play an important role in the control of the development and the function of the normal prostate, as well as of the progression of CaP to androgen independence.

Few data, however, are presently available about one of these neuroendocrine modulators, neuropeptide Y (NPY), and on the related receptors in the normal as well as in the tumoral prostate. NPY, a peptide of 36 aminoacids, is abundantly distributed through the nervous system, and activates specific membrane receptors that exist in at least five different isoforms .

NPY participates to the regulation of a variety of physiological functions, including regulation of neuroendocrine mechanisms, cognitive functions, eating behavior and cardiovascular activity, and has also been shown to stimulate cell proliferation . In the context of the normal human prostate, NPY is mainly localized in the nerve fibers, and in the neuroendocrine (NE) cells .

In conclusion, the present study, together with other data present in the literature, suggests that the prostatic NPY neuroendocrine system might participate in the modulation of the proliferation of CaP cells. Moreover, the presence and the activation of NPY receptors might represent a marker of CaP progression toward a stage sensitive to non-androgenic trophic and proliferative agents. Further studies in this field might also give indications about possible novel future lines for the treatment of CaP, especially when this disease has progressed to the androgen-independent stage.

The regulation of neuroendocrine regulation may be a significant factor in the presence of pro-NPY in PCa and its aggressive forms. Again we have examined also the neuroendocrine types and these are driven by neuropeptides and are AR independent. From the recent paper (2015) which we are examining by Inglesias et al^{38[7]}:

Clinical management of the prostate needs improved prognostic tests and treatment strategies. Because proteins are the ultimate effectors of most cellular reactions, are targets for drug actions and constitute potential biomarkers; a quantitative systemic overview of the proteome changes occurring during prostate cancer (PCa) initiation and progression can result in clinically relevant discoveries. To study cellular processes altered in PCa using system-wide quantitative analysis of changes in protein expression in clinical samples and to identify prognostic biomarkers for disease aggressiveness. Over 9000 proteins were identified as expressed in the human prostate. Tumor tissue exhibited elevated expression of proteins involved in multiple anabolic processes including fatty acid and protein synthesis, ribosomal biogenesis and protein secretion but no overt evidence of increased proliferation was observed. Tumors also showed increased levels of mitochondrial proteins, which was associated with elevated oxidative phosphorylation capacity measured in situ. This study represents the first system-wide quantitative analysis of proteome changes associated to localized prostate cancer and as such constitutes a valuable resource for understanding the complex metabolic changes occurring in this disease. We also demonstrated that pro-NPY, a protein that showed differential expression between high and low risk tumors in our proteomic analysis, is also a PCa specific prognostic biomarker associated with increased risk for disease specific death in patients carrying low risk tumors.

The identification of proteins whose expression change in prostate cancer provides novel mechanistic information related to the disease etiology. We hope that future studies will prove the value of this proteome dataset for development of novel therapies and biomarkers. Deep and quantitative proteomic profiling was obtained from formalin-fixed paraffin-embedded prostate cancer specimens and revealed that: prostate cancer cells preferably use oxidative phosphorylation for energy production; and proneuropeptide-Y expression defines a subgroup of prostate cancer patients with worsened prognosis, who might benefit from active intervention.

^{38[7]} <http://www.europeanurology.com/article/S0302-2838%2815%2901087-8/abstract/the-proteome-of-primary-prostate-cancer>

As with many such markers this results is not a causative result but a fortuitous result from observation. It appears to provide a prognostic marker. From Science Daily^{39[8]}:

A new prognostic biomarker has been identified by researchers: the neuropeptide pro-NPY, which may help determine the risk of dying from prostate cancer. This particular type of protein is very specific to prostate cancer cells and could help identify whether newly diagnosed patients require radical prostatectomy surgery or if it is safe to delay surgery.

Researchers at the University of Copenhagen have identified a new prognostic biomarker: the neuropeptide pro-NPY, which may help determine the risk of dying from prostate cancer. This particular type of protein is very specific to prostate cancer cells and could help identify whether newly diagnosed patients require radical prostatectomy surgery or if it is safe to delay surgery.

Using mass spectrometry, the researchers measured concentration changes in thousands of proteins in both normal and tumour tissue from prostate cancer. They discovered that in comparison to normal tissue, the prostate tumors exhibit numerous metabolic alterations including exacerbated activity of mitochondria. Among the 9000 proteins identified, one protein, the neuropeptide, pro-NPY, was demonstrated to exhibit high levels in a subgroup of prostate cancer samples. Pro-NPY was analyzed in 750 patients with prostate cancer to show that pro-NPY levels correlate with increased risk of prostate cancer death.

"Our research shows that high pro-NPY levels are very specific to prostate cancer and can serve to predict prostate cancer related death among diagnosed patients who have not received surgical treatment," says Professor Amilcar Flores-Morales from the Department of Veterinary Disease Biology, University of Copenhagen.

"So identifying the biomarker pro-NPY could help us identify patients who would benefit from early active treatment, whereby we would also reduce unnecessary treatment of patients who undergo surgery when they have low-grade tumors that for the most part do not put their lives at risk. In the end, due to side effects, this could prove more harmful than beneficial to patients," adds Amilcar Flores-Morales.

Proteins are key effectors of cellular functions. Therefore, a better understanding of the protein signaling pathways deregulated in prostate cancer could lead to better preventive and therapeutic strategies for the treatment of this disease. Specifically, it is possible that metabolic alterations such as the increase in mitochondria activity could be targeted in the treatment of prostate cancer.

"We hope to contribute to the advance of translational cancer research and the implementation of precision medicine in the field of prostate cancer by providing a unique insight into the protein level alterations associated with tumor tissue in clinical samples," adds Flores-Morales.

^{39[8]} <http://www.sciencedaily.com/releases/2016/01/160127115510.htm>

This work is the result of collaborations between the research groups of Professor Flores-Morales at IVS, Professor Matthias Mann at Novo Nordisk Foundation Center for Protein Research both from the Faculty of Health and Medical Sciences together with the Danish Cancer Society Research Center and Associate Professor Pernilla Wikström from the Umeå University, Sweden. The validation of pro-NPY as a biomarker was possible due to the contribution of patients and clinical researchers from several institutions in Sweden.

The creation of NPY from pro-NPY is discussed in Brakch et al as noted below:

Proneuropeptide Y (ProNPY) undergoes cleavage at a single dibasic site Lys38-Arg39 resulting in the formation of 1-39 amino acid NPY which is further processed successively by carboxypeptidase-like and peptidylglycine alpha-amidating monooxygenase enzymes.

To investigate whether prohormone convertases are involved in ProNPY processing, a vaccinia virus derived expression system was used to coexpress recombinant ProNPY with each of the prohormone convertases PC1/3, PC2, furin, and PACE4 in Neuro2A and NIH 3T3 cell lines as regulated neuroendocrine and constitutive prototype cell lines, respectively. The analysis of processed products shows that only PC1/3 generates NPY in NIH 3T3 cells while both PC1/3 and PC2 are able to generate NPY in Neuro2A cells.

The convertases furin and PACE4 are unable to process Pro-NPY in either cell line.

Moreover, comparative in vitro cleavage of recombinant NPY precursor by the enzymes PC1/3, PC2 and furin shows that only PC1/3 and PC2 are involved in specific cleavage of the dibasic site.

Kinetic studies demonstrate that PC1/3 cleaves ProNPY more efficiently than PC2. The main difference between the cleavage efficiency is observed in the V_{max} values whereas no major difference is observed in K_m values.

In addition the cleavage by PC1/3 and PC2 of two peptides reproducing the dibasic cleavage site with different amino acid sequence lengths namely (20-49)-Pro-NPY and (28-43)-Pro-NPY was studied. These shortened Pro-NPY substrates, when recognized by the enzymes, are more efficiently cleaved than Pro-NPY itself.

The shortest peptide is not cleaved by PC2 while it is by PC1/3.

On the basis of these observations it is proposed,

first, that the constitutive secreted NPY does not result from the cleavage carried out by ubiquitously expressed enzymes furin and PACE4;

second, that PC1/3 and PC2 are not equipotent in the cleavage of Pro-NPY; and

third, substrate peptide length might discriminate PC1/3 and PC2 processing activity.

From Khan et al:

A total of 80 proteins was found to be elevated in PCA compared with Benign. Included among these were previously known alterations for prostate cancer, namely GOLM1 , transcription elongation factor B (SIII), polypeptide 1 (15 kDa; elongin C or TCEB1) , neuropeptide Y , Parkinson disease (autosomal recessive, early onset) 7 (PARK7 or DJ-1) , anterior gradient homolog-2 (AGR2) , growth differentiation factor 15 (GDF15, MIC-1, or NAG-1) , ferritin heavy chain (FTH1) , tumor necrosis factor, -induced protein 9 (STAMP2 or STEAP4) , fatty acid-binding protein (FABP5) , and VIM .

A similar analysis for down-regulated proteins revealed 81 proteins whose expression was decreased in PCA compared with Benign. Prominent among these were lactotransferrin , 2-glycoprotein (AZGP1) , microseminoprotein (prostatic secretory protein of 94 amino acids, PSP94, or MSMB) , isoforms of glutathione transferase (GSTP1 and GSTM3) (58–60), lactate dehydrogenase B , and N-myc downstream regulated gene (NDRG1) , all of which have been reported earlier to be down-regulated in organ-confined disease.

From Inglesias-Gato et al:

Over 9000 proteins were identified as expressed in the human prostate. Tumor tissue exhibited elevated expression of proteins involved in multiple anabolic processes including fatty acid and protein synthesis, ribosomal biogenesis and protein secretion but no overt evidence of increased proliferation was observed. Tumors also showed increased levels of mitochondrial proteins, which was associated with elevated oxidative phosphorylation capacity measured in situ. ...Pro-NPY expression, alone or in combination with the ERG status of the tumor, was associated with an increased risk of PCa specific mortality, especially in patients with Gleason score 7 tumors.

They continue at length:

Pro-NPY as a novel biomarker of disease progression Patients with primary Gleason grade at diagnosis have a more aggressive disease courseIn order to further select candidate biomarkers for clinical validation, we also employed a supervised learning approach, support vector machines, and combined it with feature selection...The pro-NPY derived tryptic peptide most commonly identified by MS corresponded to a portion of the protein C terminal end, which is normally proteolytically removed to generate mature NPY. This specificity for PCa was further confirmed in a panel of tumors available from the human protein atlas database.

PCa has several modes or presentation, the most common is the adenocarcinoma type of the gland, basal and luminal, and also a neuroendocrine variety, less well known but highly aggressive. Both Staibano and Mydlo and Godec provide an extensive discussion of this form. We briefly examine it here since it relates to neuropeptide presence. Neuroendocrine Differentiation, NED, is considered a normal and ultimately lethal step in PCa progression. The neuroendocrine, NE, are a small part of the prostate cell mass. They tend to infiltrate the basal layers and at times may even penetrate into the lumen. They get signals from nerve cells and in

turn emit stimulants to the surrounding cells. The set of surrounding cells impacted by this signalling also includes the blood network and their endothelial structures^{40[9]}.

The NE have some specific characteristics of note here:

1. They are AR negative. Namely they androgen receptors are non-functional
2. They are PSA negative
3. They emit NPY to the surrounding cells. This is the nexus we have been examining. Perhaps it is the NE PCa via the NED that is the reason we have the nexus between lethal PCa and the presence of pro-NPY

From PCF we have a brief description of neuroendocrine PCa^{41[10]}:

Over 90 % of malignant prostate cancers occur in the form of adenocarcinoma, which is characterized by uncontrolled growth of the prostate cells that secrete the prostate specific antigen (PSA). This is why many men with malignant adenocarcinoma of the prostate have elevated PSA levels. Generally adenocarcinoma is highly treatable with excellent cure rates, even though every prostate cancer of this type has the subtype neuroendocrine cancer cells scattered throughout the tumor. (Even benign, normal prostate glands have a tiny population, roughly about 0.1 %, of neuroendocrine cells, nested throughout the gland. See Figure One. It is thought these neuroendocrine cells normally play a role in early prostate development or perhaps function.)...

The neuroendocrine cells scattered throughout adenocarcinoma of the prostate generally make up about 1% or less of the total tumor. Neuroendocrine prostate cancer (NEPC) is diagnosed when vast numbers of neuroendocrine cells are found in a tumor. "Neuroendocrine prostate cancer cells look small under the microscope," ... "And they tend to metastasize not just to bone, as is common in adenocarcinoma, but to liver or other abdominal visceral organs." There are also a number of biochemical markers for NEPC that can be detected by tissue-staining lab tests, which aids in diagnosis of this disease.

Very rarely are men newly diagnosed with prostate cancer that is the neuroendocrine subtype. When this does occur it is called de novo NEPC, referring to the thought that this subtype of cancer has been there de novo, or from the beginning. Far more commonly, NEPC is a result of treatment with hormone therapy, and is known as treatment-related NEPC, or t-NEPC.

From Aggarwal et al:

^{40[9]} See Mydlo and Godec p 150.

^{41[10]}

http://www.pcf.org/site/c.leJRIROrEpH/b.8747629/k.F201/Subtype_of_Highly_Aggressive_Prostate_Cancer_Increasing_Tied_to_Drug_Resistance_to_Hormone_Therapy.htm

Neuroendocrine prostate cancer (NEPC) encompasses various clinical contexts, ranging from the de novo presentation of small cell prostatic carcinoma to a treatment-emergent transformed phenotype that arises from typical adenocarcinoma of the prostate. The development of resistance to potent androgen receptor signaling inhibition may be associated with the emergence of aggressive phenotype, advanced castration-resistant NEPC.

Clinically, small cell prostate cancer and NEPC are often manifested by the presence of visceral or large soft tissue metastatic disease, a disproportionately low serum prostate-specific antigen level relative to the overall burden of disease, and a limited response to targeting of the androgen signaling axis. These tumors are often characterized by loss of androgen receptor expression, loss of retinoblastoma tumor suppressor copy number or expression, amplification of Aurora kinase A and N-Myc, and activation of the PI3K pathway.

As Parimi et al state:

Neuroendocrine cells are one of the epithelial populations in the prostate. Neuroendocrine differentiation (NED) has been observed in prostate cancer. In addition to small cell neuroendocrine carcinomas and carcinoid tumors of the prostate, prostatic adenocarcinomas may have NED. The incidence and clinical relevance of NED in prostatic adenocarcinoma is not clearly understood because of conflicting results in the reported studies, and evaluation of NED is not routinely performed in clinical practice. ...we are stratifying these lesions into separate subtypes based on histologic parameters such as tumor morphology, neuroendocrine cell density and distribution and clinical parameters.

They continue to describe NE as follows and then details some of the specifics in type:

Even though the definition of neuroendocrine prostatic carcinomas is still emerging, in this review from a morphologic standpoint, neuroendocrine prostatic carcinomas is considered as a special type of neuroendocrine differentiation of prostatic epithelial neoplasms (Table 2). Neuroendocrine carcinoma of the prostate may represent a subset of prostate cancer phenotypes which may be linked to resistance to androgen receptor (AR) signaling inhibition with aggressive tumor characteristics and a largely dismal prognosis. Neuroendocrine prostatic carcinomas (NEPC) are often diagnosed on primary prostate needle biopsy or on biopsies of metastatic lesions with negative or low PSA levels.

Thus the existence of NED and the relationship to NPY and pro-NPY is worthy of further examination. As noted we continue to see the reporting of many new markers for both detection of and prognosis of PCa. However in many cases these markers are not always causative but adventitious. They just happen to be there and may or may not reflect a process, one which may allow for a therapeutic approach. As we have noted in Inglesias-Gato et al where they conclude:

The combined assessment of pro-NPY levels and ERG status improves prediction of PCa related death High NPY protein expression was recently demonstrated in prostate tumors harboring the TMPRSS2-ERG fusion gene .

Previous evaluation of ERG expression in the ... cohort showed it to be related to increased risk of disease-related mortality. Therefore we analyzed whether pro-NPY expression correlated with ERG expression in our sample cohort. Forty-four percent of the tumors included in the analysis were positive for ERG expression and of these, 52% showed high pro-NPY levels.

Patients with tumors expressing high levels of pro-NPY with positive ERG protein expression have a significant increase in the relative risk of PCa related death, especially within the low GS group. Accordingly, multivariate regression analysis shows that high expression of both ERG and NPY increases the risk for PCa mortality independently of GS

We use this to examine a few issues.

Causative Results: The above indicate the ERG expression which we know has causative effect, especially when we see the ERG: TMPRSS merge. However the relationship and systemic details on the pro-NPY effect are missing. One would like to see this in some detail.

Therapeutic Targets: It is not clear if NPY or pro-NPY can be therapeutic targets or even more so the underlying gene. Since the causative effect does not seem apparent one wonders if having a prognostic marker is of substantial value. Metastasis is most likely an existing fact, albeit on a micro scale. Thus the question can be stated: of what clinical value do we have measuring pro-NPY?

Process Control: What are the pathways, receptors, ligand, and the like that are involved in pro-NPY and NPY generation, communication, and activation? The details appear to be missing in this overall analysis.

Neuroendocrine Differentiation: When we examined the NED type of progression we saw the presence of NPY as a secretion from the NE cells to the remainder of the prostate. We also understand the evolution of NED in most PCas and the question posed would be; what is the driver for NED? Also does the NE communications somehow relate to stress activation via the nerve cells communicating with the NE cells. Also is it the endothelial enhancement of the NE cells that facilitate the metastatic growth.

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Labels: [Cancer](#)

TUESDAY, FEBRUARY 2, 2016

[WHERE HAVE THE ADVERBS GONE?](#)

From the [Hill](#) we have:

Sen. Tim Kaine (D-Va.) speculated that Carter's decision will mean future generations of women will be more equipped to meet standards without them being lowered. "Daughters raised today are going to be raised different than daughters 30 years ago," he said. "When there's a social cap or ceiling or limitation, that sort of gets absorbed by people and they don't even focus on what they might be able to do.

Now I can hear Sister Rosita telling us to mind our adjectives and adverbs. The Trivium, Grammar, Logic and Rhetoric. But what has happened to grammar? The good Senator should

have said "raised differently"; how were they raised?, adverb, differently.

Strange in this case since his wife worked form me some 40 years ago, Anne Holton, and her grammar was perfect.

Where is Sister Rosita when we need her now?

Oh and by the way; it is "on" State Island and not "in". Only worms are "in" Staten Island, and some ground hogs, Happy Ground Hog Day.



Labels: [Commentary](#)

[THE ACA AND ECONOMIC GROWTH](#)

Has the ACA helped or hurt. If you listen to [The Commonwealth Fund](#) you would think it is the greatest thing since sliced bread. Well, perhaps the Whopper. Or the Big Gulp.

They state:

- *The U.S. economy has gained nearly 14 million private sector jobs over five years. All of the net gain in employment has been in full-time work.*
- *There are 5 million more people working now than during the peak level prior to the recession, and the unemployment rate has plummeted. Recent annual gains in jobs have been faster than gains in any year since the 1990s.*
- *Still, labor force participation rates have yet to return to their pre-recession peak.*
- *Inflation-adjusted economic growth in the United States in recent years has rivaled or exceeded that of many other high-income nations.*
- *Health care spending growth per person—both public and private—has slowed for five years.*
- *A number of ACA reforms, particularly related to Medicare, have likely contributed to the slowdown in health care spending growth by tightening provider payment rates and introducing incentives to reduce excess costs.*
- *Faster-than-expected economic growth and slower-than-expected health care spending have led to multiple downward revisions of the federal deficit and projected deficits.*
- *These trends have also been a boon to state and local government budgets, as job growth has improved state tax revenues while cost growth in health care programs has slowed. At the same time, expanding insurance to millions of people who were previously uninsured has supported local health systems and enhanced families' ability to pay for necessities, including health care.*

Well not so fast Swiftly.

The jobs gained fail to account for the dramatically lower Participation Rate, a factor we have been focusing on since the early days of the Romer Curve. You see Romer presented her now infamous curve seven years ago in January 2009 saying that unemployment would be at 5%. But 5% of what. If you take tens of millions out of the workforce than you eventually get to 5% but if

you were to normalize to prior Participation Rates you would be back at 9%!

Economic growth is horrible. Do these folks ever look at the GDP growth rates, in fractional digits! That is less than 1% pa.

Now to Health Care. The biggest burden on Health Care is the EHR created by the now head of this entity. It is the worst creation ever. It should have been cloud based and patient centered. Instead it is physician based and incompatible. One physician cannot get the records of another unless they go through the patient! Duh! Told you so folks.

You see we have the ability to do a good EHR. Simple:

1. Patient based. Single cloud based HIPAA compliant where for each patient the practitioner can ask and add. It is portable.
2. Digitally readable info is uploaded, parsed, collated, and portable. That is a biopsy may be added and the results parsed and added to a hypertext readable and accessible system.
3. Image enhances and readable. All images are stored and indexed and accessible. Want an MRI, here it is.
4. Accessible via simple interfaces.
5. Cheap. Yes, one system and no complex learning. Let the system do the learning.

Well did this happen.No. Thank the folks at Commonwealth!

Oh about those job growth comments. We have just added more to manage a health care practice with negative value. Thanks guys!



Labels: [Health Care](#)

TUESDAY, FEBRUARY 2, 2016

HAPPY GROUNDHOG DAY



Out there somewhere is a groundhog looking for their shadow.



Labels: [Commentary](#)

SUNDAY, JANUARY 31, 2016

WHY IS GOOGLE BUILDING FIBER?

In a article [ArsTechnica](#) discusses Google's expanding fiber footprint. They seem to have targeted 20 major US cities. Having been down this road a bit I wonder what they are doing.

1. Franchises: You must have a Franchise in every location, unless your political "pull" allows you somehow to avoid it. [I have been there for 36 years](#), and I never found a way. Franchises are costly and a delay. Getting 20 Franchises in face of companies like Comcast can be overwhelming.
2. The costs of fiber are extraordinary. Verizon has walked away and they really know what they are doing. [It was just not worth it.](#)
3. [Wireless can do better](#) are an order of magnitude or less per customer.
4. All of this has been know for a decade or more. What does Google know that everyone else does not?

They cannot build it cheaper, cannot get fewer Franchises, cannot get cheaper pole attachment fees, cannot dig cheaper. So what is it? Just a way to get PR or is Google just wasting shareholders money? I suspect it is the latter but it is just my guess. After all, what do I know, I have only done this for 40 years! They just did a part of one friendly town, they must be smarter, they are Google.....



Labels: [Google](#)

THURSDAY, JANUARY 28, 2016

[FLINT, WATER PIPES, SELENIUM AND COSTS](#)



I heard one reporter ask why they did not replace all the water pipes in Flint. Since the reporter had no idea what she was saying and apparently the Government leader was also clueless we got what we can expect from the media; nonsense.

But some thoughts may be worthwhile.

1. Most old cities have no idea where all these pipes are. Records are not that great nor are they accurate and things move. So trying to find them is tough.
2. The cost to even dig and install new pipes is fantastic. My guess is about \$5 million per mile of pipe, maybe even more.
3. However the old pipes can be used, somewhat.
4. In the oil industry they face the same problems. Oil pipeline get what is called a biofilm growth. Like arteries in old folks. What they do is use a device called a "pig" that has razor sharp blades that rotate and cut off all the old biofilm. Let's assume you can do that in the old lead pipes. The tools exist and they work. Much less that the replacement costs. And the pigs collect the biofilm masses and expel them as it move forward.
5. But you still have lead. So what you do is install a PVC or equivalent pipe sheath inside the lead. This keeps the lead out.
6. The you coat the PVC with [nano Selenium](#) to inhibit future biofilm growth. Real cheap.
7. This replaces 95% of the lead pipe and provides a stable bacteriostatic flow path.

8. It may leave some residual lead local pipes in homes but they were there anyway. You will reduce the lead burden by well over 99.9%, well within EPA limits.
9. When using the pigs you also use modified GPS to fully map the system for future reference.
10. Estimates are about \$250,000 per mile of pipe.

Let's see what the Government comes up with!



Labels: [Government](#)

WEDNESDAY, JANUARY 27, 2016

[AMAZON AND THE US POST OFFICE](#)

The USPS is the worst delivery entity in the world. They score lost packages at 1 out of every 10! Why Amazon uses them is absurd. You have one effective entity relying on the most incompetent, result; total incompetence. And we want the Government to handle Health Care. Just look at the EHR nightmare. We have docs typing on screens and never look up at patients; that is meaningful use! You get some pediatrician to head up the group to define what should be done; please. Perhaps we really do need a Washington shakeup. Never been in a Trump hotel though, so no comments there. Well back to the USPS. Ben Franklin would be so unhappy!



Labels: [Government](#)

[SET TOP BOXES AND THE FCC](#)

The [FCC](#) today noted:

Ninety-nine percent of pay-TV subscribers are chained to their set-top boxes because cable and satellite operators have locked up the market. Lack of competition has meant few choices and high prices for consumers – on average, \$231 in rental fees annually for the average American household. Altogether, U.S. consumers spend \$20 billion a year to lease these devices. Since 1994, according to a recent analysis, the cost of cable set-top boxes has risen 185 percent while the cost of computers, televisions and mobile phones has dropped by 90 percent. Congress recognized the importance of a competitive marketplace and directed the Commission to adopt rules that will ensure consumers will be able to use the device they prefer for accessing programming they've paid for. Today, FCC Chairman Wheeler is circulating for a vote a Notice of Proposed Rulemaking (NPRM) that would tear down anti-competitive barriers and pave the way for software, devices and other innovative solutions to compete with the set-top boxes that a majority of consumers must lease today. The proposal will be voted by the full Commission on February 18, 2016. This proposal is about one thing: consumer choice. Consumers should have options created by competition. The Chairman's proposal will let innovators create and then let consumers choose.

This could allow homes to get their own cable box at the cost of a wifi router and save \$250 per box per year. It may also eliminate a great deal of dust which these boxes seem to accumulate!

Just don't hold your breath, it is the Government after all. Just watch Comcast, they will be seen kicking and screaming all the way!

We should remember the Carter Phone decision, better yet the Hush a Phone ruling. See my [1989 Harvard paper](#).



Labels: [CATV](#), [FCC](#)

[HOW MANY INNOVATORS](#)

One of the main functions of a University is to demonstrate reality. Giving a student the tools and then presenting a realistic path to achieve something with those tools. Not every Physicist will obtain a Nobel Prize. In fact by the nature of the prize it is limited to 3 per year. Assuming a productive lifetime of a Physicist of at most 40 years, say 20 to 60, one has at most 120 opportunities to be in that tier. Now the odds are quite low. That does not mean one's life is meaningless, but that a balance of expectations is reasonable.

Now entrepreneurs fall somewhat in the same category. Almost all fail, and do so the first, second, or third time. The major rule of an entrepreneur, however, is to "burn the boats", meaning to give up all else except achievement of the goal. That is what often makes entrepreneurs appear ruthless, they are of a single focus. The goal. That is also why so few who set out can succeed. Any of us who have been down that path know what that means. It is seven days a week, fifty two weeks a year. It is total dedication, no distractions.

So how does this work out in Academia? MIT has had many entrepreneurs. But they like almost all others had "burned their boats" to get there. One cannot be an active academic and be an entrepreneurial leader. You can be an advisor, a Board member, but not the change agent, not the leader.

So where is this going? Well [MIT](#) has announced the Sandbox, the very name being a bit insulting. Sandboxes are for kids, and pets, yes dogs seem to like them, and not for adults. But this Sandbox alleges:

MIT Sandbox invites 11,000 students to innovate. Offering funding up to \$25,000, mentoring, and tailored educational experiences, the program will open up new pathways for student entrepreneurs and innovators.

What does this mean? Does this mean that every MIT Grad and Undergrad can start a company while doing their day jobs. It seems so. They continue:

MIT Sandbox Innovation Fund Program (Sandbox), an Institute-wide program that will support student-initiated ideas, launched today. The endeavor opens more pathways for all types of student innovators — whether they have a seed of an idea, a nascent technology, a specific startup in mind, or are planning the next moonshot. Sandbox will connect students with tailored educational experiences, mentoring, and up to \$25,000 to help qualified students and teams nurture their creative brainstorm. "The primary aim of Sandbox is to develop people, not necessarily startups or products, but the learning will be in the context of advancing an

entrepreneurial venture or innovative idea — one that serves an important market or social need,” says Ian A. Waitz, dean of MIT’s School of Engineering and the originator of the program. “It is designed to help students develop the knowledge, skills, and attitudes to be more effective when they go off in the world and practice MIT’s brand of deep scientific and technological innovation.”

The problem is that to be an entrepreneur means to dedicate oneself to a single focus; the success of the business. This may be a gross distraction from what the Institute is supposed to do as its prime mission; educate and innovate. Entrepreneurs must fight for market position, fight for funding, fight for survival. Those are not the talents one builds as an academic; not that there is not a lot of infighting but that type is less than productive in a start up.

In my experience the Academy is not the place for startups. The skill set is not there. The dreams and ideas may be there, but the details of building a team, leadership of a team, selling an idea, raising funding, dealing with contracts and corporate structure, and the day to day issues of running a business, even a candy store, just do not come across anywhere but in the process of doing it. If you want to be an entrepreneur, then leave academia and start.



Labels: [Academy](#)

TUESDAY, JANUARY 26, 2016

[JOHN HARVARD ROLLS OVER IN HIS GRAVE!](#)

In a report by [StatNews](#) they indicate that Harvard Medical is considering the rendering of naming rights to the School for a substantial donation. They note:

That’s the value of Harvard Medical School’s name: A billion dollars, or more? That question is swirling around the school’s historic quad. After Harvard broke with tradition last year and renamed its public health school in return for a billionaire’s record-setting \$350 million gift, faculty members have been discussing whether Harvard Medical School should be next, according to Dr. John Rowe, chair of the Board of Fellows that advises the medical school. The suggestion has been met with enthusiasm — and some trepidation — from the Harvard community. Some call it a good way to catapult medical research forward and dig out of annual deficits at the medical school. Others balk at the suggestion of corrupting the world-famous Harvard Med brand by selling it to the highest bidder.

Well there is already a name, namely Harvard, there is a Hopkins, a Weill Cornell, a Duke, and the list goes on. But wait, they further state:

“If they named it the Trump School of Medicine, half of the faculty would resign,” Jones said.

So one guesses that you could name it anything but Trump! Well let's see where that would go....not yet. There is an academic political correctness that is in Boston. What ever happened to anonymous gifts? You still get a tax benefit but no recognition. Imagine Longwood Avenue becoming Trump Lane, the old Peter Bent Brigham, the ice cream guy, becoming Trump and

Women's, isn't that a kick in the whatever.

Just following this internal cat fight will be interesting. It would have been interesting if they kept and renamed the old Lying In Hospital as well....

Talk of gasoline and a match, academics and politics....



Labels: [Academy](#)

MONDAY, JANUARY 25, 2016

[HOW NOT TO LEARN A LANGUAGE!](#)

I just tried out a MOOC from that college west of Boston famed for a Presidential Candidate. It was Italian. Now being raised on Staten Island, Italian was a second language, Spanish a third. You see Italian was very important. The best priests to go to for Confession were the Italian ones down the street, not the old Irish guys at the local parish. But you had to speak Italian. At least enough.

Then I for some reason had to take Italian with a US State Department group. Then I took Italian from a woman from Trieste; try that accent on after Sicilian. Then I was in Italy. Fact, there is no one Italian and on Staten Island it is like Sicily. So do not try it in Florence.

Now how does this relate to the Italian MOOC. Well, it was the worst possible course ever to try and teach any language. It was literally all over the place. It was high Italian, Milan most likely, and in my picking up five other languages the key is simple:

1. Get the 100 most important words; here, there, numbers, please, thank you, my name is, where is the bathroom, how much is it, etc. You can survive a little,
2. Learn the present tense of about 30 key verbs including to have and to be.
3. Learn 20-50 new words each day. Get index cards and walk around memorizing them.
4. Read the newspaper each day.
5. Watch 2 hours of television each day in the language. Watching the Sopranos in Greek or Sex in the City in German really adds to your insight. On the other hand French TV is all intellectual stuff, like Sartre on steroids.
6. Speak to cab drivers. You can even do this in New York.
7. Try it out on waiters. This may work sometimes.
8. Shop, shop, shop. Read the signs. Find a restroom. It was amazing in Greece, Anthropos, Gynekon, yes anthropology and Gynecologist. Limbic valence on the spot.

9. Never waste time on a MOOC!

The course was almost cartoon like. The exams forced you to answer in a specific way. No one speaks that way. You learn to use phrases to express ideas, requests etc. My favorite experience is that French uses subjunctive, *je voudrais*, English uses I want. You never say I want in French, unless you do not want it. Language is culture, culture is expression, that is what a language is. Not what this MOOC does.



Labels: [Academy](#), [MOOCs](#)

THURSDAY, JANUARY 21, 2016

THE CABLE BOX

Almost all homes have these antiques. They are the cable box. Apple introduces a new phone at least annually, software is updated monthly, lap tops are replaced about ever 2 years. The cable box has not changed in almost two decades! It is older than my furnace, my water heater and even my roof on my house. I have had 4 cars in the period in which the cable box has sat there collecting dust and thousands of dollars for the cable company. They will never appear on Antique Road Show since they will never be replaced.

[ArsTechnica](#) has an interesting piece on the attempt to change this. You see legally even now you should be able to buy your own box, just over \$100. Instead you pay \$250 per year in fees! Why, well just try to buy your own and install it!

As ArsTechnica states:

What if, instead of renting a set-top box from your cable company, you could get all your TV channels and online video services delivered to a single device that you only pay for once? The Federal Communications Commission could make it happen, consumer advocacy groups say. "An open set-top box market is a key component of freeing consumers from unnecessary monthly rental fees, and it would enable them to more easily access online video content right alongside their subscription TV programming," the groups said in a letter to FCC Chairman Tom Wheeler yesterday. The letter was written by Common Cause, Demand Progress, Free Press, Fight for the Future, the National Hispanic Media Coalition, New America's Open Technology Institute, and Public Knowledge....The CableCard standard created nearly 20 years ago was supposed to make the set-top box industry competitive. And it has succeeded to an extent, letting cable subscribers use TiVo boxes and other devices. But the FCC long ago admitted that CableCard had only limited success. About 99 percent of customers still rent set-top boxes directly from their providers and pay an average of \$231.82 a year in rental fees, US senators found in a survey of TV providers last year.

What is the chance of this happening. Zero! Why? The Cable Lobby. They want to keep those mastodons in place. At some point the FCC ought to consider the customer! For over 40 years we have been able to select our own telephones, what few are left in the home. The cable box is another issue.

Oh and the cable modem is another one of these issues.

It is not that the Cable companies cannot do this. They have massive Deep Packet Inspections operations to check out every customer. They can make the NSA look like tyros. But they are allowed by the FCC to tie-in their boxes and delimit customer choice! Whether it is ESPN or cable boxes, some how the FCC ought to do something. But alas it is Washington after all!



Labels: [CATV](#), [FCC](#)

WEDNESDAY, JANUARY 20, 2016

[BLUE FLOWERS](#)



I have been focusing on CRISPRs for several years now, ever since I heard about them from Lander at Broad. I also hybridize flowers, using details genetic analysis, but not CRISPRs. You see, CRISPRs are like handling nuclear materials. If they get into a cell they can cause havoc. I limit my selections of chemicals to methanol for pigment separation.

In the [WSJ](#) is an article about some person moving to that edge. The article states:

After his parents go to bed,usually retires to the third bedroom of the family apartment, where he has built a laboratory. There, amid the whirl of climate-controlling fans and equipment harvested from eBay, he is working on what he hopes will one day become a lucrative career., 25 years old, is a plant hacker. "I want to make flowers no one has ever seen," he says, wearing shorts and a T-shirt on a recent day at his home in "What would happen if you combined features of a pine tree with an eggplant?" He also wants to turn a rose blue.

Now I have also sought the [blue flower](#), and have written extensively on it. It is not simple. You need the DNA structure of the plant, namely the Cas9 target, it must be the gene that controls blue, and you better know what you mean by blue. And that is just the beginning.

The article concludes with:

....., of, is also the founder of a company that raised \$484,000 on the crowdfunding website Kickstarter for its glowing plant in 2013, but hasn't delivered yet. He said delivery of glowing

plant seeds to backers will start this year. Next in production is a new kind of moss that smells like patchouli that could be a replacement for air fresheners one day. After that, he too will make a go at the blue rose, he says.

Plants are tricky. They have many more genes than humans and many more base pairs. You see plants have been around a lot longer than we mammals. Humans have been manipulating plants for tens of thousands of years and we have corn and a variety of other results. What we do not really know is how plants are colored. [I have taken a swipe](#) at it for the past ten years. I am still trying to understand the process. Yet it takes an understanding of plants and genetics as well as a well controlled lab. One must be careful, especially with CRISPR technology, especially in a poorly controlled environment.

So if you worry about Iran and nukes you should be terrified by CRISPRs and labs in the "homes" of what may be less than educated 25 year olds.



Labels: [CRISPR](#)

[FREE COLLEGE?](#)

The [NY Times](#) has a piece on Free College. Now this is not really a new idea. Back in the 50s or so, when I went through this mill, if you were in New York City you did have several options. One was to go to CCNY, City College. It was free, but it was highly competitive. The best of the best went there. Stuyvesant, Brooklyn Poly, Bronx HS of Science, and a few Catholic Schools, but a very few. Back then Catholic High Schools educated cops and firemen, not scientists or engineers. A second option was Regents Scholarships and even better Regents Science and Math Scholarships. The latter were full tuition if you majored in Science, Math, Engineering and they were give out to only a few hundred students in the State, based on academic performance and a competitive test. That was my ticket to college.

Now the game is to give free tuition to those who cannot afford college, independent of any academic performance. If you are from the correct group you would get a free ride. If you were academically highly proficient then that would not apply.

Several observation can be made:

1. Performance seems to have disappeared from student support.
2. Tuition has exploded so fast that the modest amount supplied in say 1960, it was \$1,000 I believe, would not buy books.
3. Room and board could add significant burdens.
4. What does the nation want for its investment? That perhaps is the key question. It should NOT be just to give everyone a college degree that has no value. How many communications, fine arts, political science majors do we really need? Probably very few. So if we d this then perhaps we focus on productivity and accomplishment.

This is a difficult issue. As of now the better institutions have found was to accomplish this. But they do so selectively and generally have some success. Making this another tax grab for everyone is not the solution.

There are many highly qualified students that fall through the cracks. That should be the target we focus on.



Labels: [Academy](#)

[PSATS STILL NOT OUT](#)



Almost six weeks of delay at this point! The [WaPo](#) reports:

The College Board's new online system to deliver test scores has, to be charitable, not gone as well as planned, with delays and other complications with PSAT/NMSQT results angering counselors and students and raising questions about how well it will work when the new SAT is soon unveiled.

The PSAT/NMSQT is the Preliminary SAT, the test that mostly sophomores and juniors take as a practice for the SAT and that provides scores used to qualify students for the National Merit Scholarship program. In October, more than 4 million students took the PSAT. Scores were expected by the end of the year, but the College Board released them only a week ago, about a month late. Sandra Riley, vice president for communications at the College Board, said the delay was caused by a new online system created to accommodate scoring reports for the newly designed SAT debuting in March.

Yep, 4 million kids took the test. No results yet for almost all of them. The examiner.com ([See here](#)) reports:

The PSAT is primarily a practice run for the SAT exam to determine where to study more but it also functions as the National Merit Scholarship Qualifying Test NMSQT. Only those with an NMSQT score in the 99th percentile have the chance to receive scholarship money. Still even those students that receive recognition, Letters of Commendation or are named semi-finalists

have an extra prestige in their race for college admissions into the school of their choice. Instead of admitting they are wrong the College Board is blaming guidance counselors and students for not being able to access PSAT scores. The College Board is insisting that all the scores are available to access but schools and students are not using the "new protocols for accessing" the scores correctly. Some schools, however, are insisting the scores are not there. Many are agreeing the scores are there but the instructions the College Board gave are "confusing." There have been other problems with the College Board's system; there have been two outages. The College Board's website crashed last week and this on Tuesday, Jan. 12 into Wednesday, Jan. 13 according to the Washington Post's report. There are also very long waits if counselors, students, or parents want to contact the College Board by phone.

Yes College Board, blame your customers, those folks who pay you for your poorly done job! These folks must all have come from some Government job! It appears that the same crew that may have done the ACA web site may be involved here, just a guess. This is a clear sign of the gross incompetence of the Educational administrative community. These folks are being paid very big dollars to control the lives of our future societal contributors.

Solution? Abandon any and all use of the College Board NOW. I have said this for 55 plus years. As a writer for the [NY Times](#) notes:

"Turning the Tide" follows other reexaminations of the admissions process. A growing number of colleges have made the SAT or ACT optional. And late last year, more than 80 colleges, including all eight in the Ivy League, announced the formation of the Coalition for Access, Affordability and Success, which is developing a website and application process intended in part to diversify student bodies.

Abandon them now. Imagine the grief these poor young folks are going through. Perhaps a class action suit will work? Gross negligence and irreparable harm, try those words on for size College Board! Have you no shame, College Board, have you no shame!



Labels: [Academy](#)

SUNDAY, JANUARY 17, 2016

[THE EHR DISASTER: MEANINGFUL USE](#)

The EHR has been a disaster. We said this seven years ago. It did not take much insight to see that having physicians become typists and disregarding their patients was a dumb idea. It took, in my opinion, one of those Harvard Professors to promulgate a system that has cost billions and needlessly encumbered health care.

As [MedPageToday](#) reports:

For the first time, the leader of the Centers for Medicare & Medicaid Services has said publicly that the agency "has the opportunity" to sunset the meaningful use program in 2016. Andy Slavitt, acting administrator of CMS, made his remarks Tuesday at the J.P. Morgan Healthcare

Conference in San Francisco. Slavitt's full remarks were then posted on the CMS blog, and summarized in a series of tweets. "As any physician will tell you, physician burden and frustration levels are real," Slavitt said. "Programs designed to improve often distract. Done poorly, measures are divorced from how physicians practice and add to the cynicism that people who build these programs just don't get it. "The Meaningful Use program as it has existed, will now be effectively over and replaced with something better."

Hospitals such as New York Presbyterian have two dissonant systems, one on the Columbia side and one on the Cornell side. They do not talk to one another.

Moreover the systems are input and measurement directed and do nothing to help the physician. They are not connected. If there is an order for Lab work, it must be faxed! Yes team, fax machines proliferate health care!

The next issue will be quality. Try and define it, try and measure it. It is in the eye of the beholder.

Washington and the ACA have raised the costs of health care with absurd programs such as meaningful use. Some one must put an end to all of this.



Labels: [Health Care](#)

TUESDAY, JANUARY 12, 2016

OBESITY AND PCA

In a paper in [Nature](#) the authors provide a compelling analysis for the impact of fat cells via obesity and the development of aggressive PCa.

They state:

Obesity favours the occurrence of locally disseminated prostate cancer in the periprostatic adipose tissue (PPAT) surrounding the prostate gland. Here we show that adipocytes from PPAT support the directed migration of prostate cancer cells and that this event is strongly promoted by obesity. This process is dependent on the secretion of the chemokine CCL7 by adipocytes, which diffuses from PPAT to the peripheral zone of the prostate, stimulating the migration of CCR3 expressing tumour cells. In obesity, higher secretion of CCL7 by adipocytes facilitates extraprostatic extension. The observed increase in migration associated with obesity is totally abrogated when the CCR3/CCL7 axis is inhibited. In human prostate cancer tumours, expression of the CCR3 receptor is associated with the occurrence of aggressive disease with extended local dissemination and a higher risk of biochemical recurrence, highlighting the potential benefit of CCR3 antagonists in the treatment of prostate cancer.

This is not at all unanticipated. The work does give a basis for the genomic characteristics of the process as well as describing a therapeutic target. Clinically this has often been observed. In addition obese patients also often have progression on a more aggressive manner. Clearly the fat cell mechanism as discussed is a viable and credible path. The aggressive oxidation effects may

also play a role especially via methylation.

This is a strong and prescient paper and well worth following.



Labels: [Cancer](#)

[A CAT FIGHT TO WATCH](#)

CRISPR technology is moving forward with great speed, so too now are the lawyers. As [GenomeWeb](#) states:

The US Patent and Trademark Office yesterday declared an interference proceeding to settle certain claims related to the CRISPR patent battle between parties led by the Broad Institute and the University of California, respectively. In the interference proceedings, the USPTO will collect, consider, and compare historical documentary evidence to establish invention dates. Because the applications were filed before the US moved to a "first to file" patent system in 2013, the patent rights will be granted under the old "first to invent" system. In a document declaring the interference, the USPTO named the University of California as the senior party, effectively placing the burden on the Broad Institute to establish that it invented the technology first, even though the USPTO granted it the first CRISPR-related patent in April 2014.

We have been following this since the beginning. I was amazed at how the PTO turned around the first patent in less than 6 months. Now comes the reality of the PTO, it is a Government entity after all.

There will be a East vs West battle afoot. This should be watched because it will play out across many landscapes. In a sense it will be the Valley vs 128, and the winner will provide definition and direction for a generation. The Valley has ready take a PR shot with their Oscar like award to the California team, Hollywood like awards. The MIT/Broad team seem to be just cranking out start ups. I suspect result will better galas but who knows when the lawyers enter the fray?



Labels: [CRISPR](#)

[KEEP MAKING THOSE BUGGY WHIPS](#)

There is some lawyer who I had critiqued a while back for her lack of technical acumen. Lawyers often have that problem, even some who have technical backgrounds. After all they are lawyers.

As she states in [Backchannel](#):

Fiber is the best—the only —alternative, and it could win subscribers in areas where cable exists. But we're not building these networks. Verizon sold its FiOS lines in California, Texas, and Florida, and AT&T's GigaPower fiber plans are (with small exceptions, where the company feels the pressure of genuine competition) mostly "fiber to the press release." AT&T is most likely to continue playing defense by further squeezing the capacity of its existing copper lines,

which means that only densely packed apartment buildings that are very close to AT&T's central offices will see the advantage of the company's work on its copper connections, as signals can't travel very far over copper. (By contrast, signals can go for dozens of miles over fiber without being boosted.) And despite all the hype, Google Fiber is predicted to reach no more than 10 million homes over the next few years—although Google's recently announced plans to consider Chicago and Los Angeles may change that part of the picture. Some of the problem with building fiber networks is that the needs of these profit-grabbing companies diverge from the public good, which requires long-term investments where the gains accrue to the economy in general.

Now to the facts.

1. No, fiber is not the only alternative. In fact it is the last.
2. 4G allows 10 bps/Hz and with hundreds of KHz available that is lots of Gbps deliverable by wireless.
3. Data rates for video are dropping like bricks so the demand for bandwidth per user is dropping.
4. 5G adds adaptive antennas and increases the bps/Hz another factor of ten.
5. Wireless is relative cheap and the infrastructure is already there.
6. Mobile is taking over. You cannot drag a fiber around with you! I have tried.

The list goes on. She totally misses the point. The problem with fiber is not greedy companies, it is that is NOT the technical solution. But then again she has apparently never examined this issue.

What I find with her followers, read the comments, is a religious fervor of the socialist, devoid of facts and replete with belief. I remember well, my grandmother headed the Socialist Party in New York.

How long will we have to hear these specious arguments? Why is Verizon delaying an aggressive move in wireless? Well, the answer, it is still the phone company!

And oh by the way, CATV companies do not use copper pairs.



Labels: [Broadband](#)

THE COLLEGE BOARD: OR HOW TO MESS WITH MILLIONS OF MINDS

I took the PSATs some almost 60 years ago. Going to a Christian Brothers High School, a classic education for boys who were destined to be cogs in the wheel of civilization, not necessarily leaders, we took this test with zero preparation. We just came in one day and were told to take this test. Needless to say I paid little attention since it was a way to avoid Cicero in Latin 3 and I

had not prepared my translation. Thus my score was dismal.

Then I found out what it meant. I was told by this body of the elite, the College Board, that my life was now determined, indeed I should prepare for Con Ed or possibly the NY Sanitation Department. Perhaps a Bus Driver.

Well I decided to study for the SAT, something the College Board said was not useful. Now the following Fall, early December, I took the SATs. Results, I recall it was almost 800 in Math and over 700 in English, somewhat over 1500 if I recall. More than double the PSAT equivalent. And I found two errors on the exam which I promptly wrote the College Board about and I also finished in half the time. Amazing what a little prep will do. And yes, NOT listening to that collection of educational "experts" at the College Board. Even since I have given NO credit to any College Board score.

Now comes the latest set of characters to destroy the minds of young Americans, the Common Core money makers. This time it is the PSAT, that old exam I remember, given in October with scores issued in December, but now with the present management. They did not come out until just a couple of days ago. In the age of computers one would have thought otherwise, but alas, these highly paid "educators" managed to show students just what not to do if they want to succeed in a highly competitive world.

As the [Washington Post](#) notes:

The College Board has just released PSAT scores — months after the tests were actually taken in high schools. About one-quarter of the students who took the test have accessed their scores online, though some have experienced trouble getting them, and many counselors who were supposed to get them have also had trouble doing so. Problems with score delivery has also plagued the SAT this past fall, frustrating students and counselors...vice president for communications at the College Board, said a new online scoring system created to accommodate scoring reports for the newly designed SAT, which is launching this coming spring, is to blame. She said that initial testing did not reveal "large-scale issues" but a series of "small issues" that are being fixed as they present themselves.

One cannot "blame" the "system", one must blame the management. The WaPo concludes:

Yes, College Board is in the business of selling SATs and ACT in the business of selling ACTs, and you may hate to fill their coffers. But, as most universities require standardized tests for admissions, your focus is just in doing well and then getting back to normal life. Or, if these tests simply aren't your thing or you simply refuse to partake, mosey over to FairTest to check out hundreds of score-optional colleges and universities.

Namely the time to end the SATs is NOW. It will only get worse. You have what in my opinion is a collection of overly paid political job holders establishing norms for American students and the result is that we have managed in my opinion to destroy the lives of our future contributors. The SAT does NOT work in my experience and in my opinion. It can be gamed. It fills the pockets of folks rather than the minds of students.

The Academy should abandon it this year!

To better understand the problem one should read the [Huffington Post](#). Their write states:

David Coleman was at the center of Common Core State Standards (CCSS) development, a position about which he publicly declared post-CCSS that he and others in his Student Achievement Partners (SAP) nonprofit were "unqualified." One year later, in 2012, Coleman became president of the College Board, where he thought he would tinker with the SAT "so that it better meets the needs of students, schools, and colleges at all levels." Coleman's tinkering isn't going so well. In fact, he could well drive the College Board into the ground as his bumbling efforts for an SAT redesign (one that makes the SAT look more like the ACT) results in "updated" messages to test takers and their parents as scores are delayed. Such was the case for students who took the October 14, 2015, SAT and counted upon the College Board to deliver timely scores for early admissions. Their scores-which were supposed to be delivered using the College Board's new score reporting system-were delayed for more than three weeks beyond the common November 1st deadline. And now, students who took the mid-October PSAT are also facing score reporting delays.

This appears as if it is another version of the current White House staff. Namely people who have nor extensive career experience. The NSC leadership in the White House is someone with an MFA from NYU. Understanding Picasso and DaVinci may not be the best skills for dealing with Putin and Iran! Why the College Board is not staffed with competent carrer folks in my opinion is amazing. But it appears to be devastating for students, and I have two grandchildren in the middle of this mess now!

So to repeat, abandon the College Board, now!



Labels: [Academy](#)

[NOW I HAVE SEEN EVERYTHING!](#)

In a recent [Nature \(Prostate Cancer\)](#) paper the authors state:

Digit ratio (2D:4D) has been suggested as a proxy biomarker for prenatal androgen activity and has been linked to prostate cancer, as the genes that regulate the formation and differentiation of the fingers are also related to the carcinogenesis of prostate cancer. To investigate the possible correlation between right hand, left hand and right hand minus left hand (DR-L) 2D:4D and prostate cancer of Brazilian subjects by comparing 2D:4D ratios of individuals diagnosed with prostate cancer and individuals without the disease. Also, to inquire the relationship between 2D:4D and severity of prostate cancer through Gleason scores....2D:4D seems to be a marker for screening patients for prostate cancer in an admixed population, as males with prostate cancer present lower 2D:4D than healthy subjects. On the other hand, 2D:4D does not appear to be associated with the severity of prostate cancer.

Yes, your ring finger length less your index finger length will be prognostic on PCa. I have to

try this one out with the folks at the bench! Forget the Illumina stuff, clean the tables, just use a ruler. Wait till the USPTF is told of this one, no mre PSA period! Forget the biopsies.

There is even a better one regarding this metric at [Mayhew et al](#) who relate this difference to a variety of complex physiological issues.

The Nature results states:

The PCA group presented significantly lower right and left 2D:4D ($P=0.001$ and $P=0.002$, respectively) in comparison to healthy controls, but DR-L were not significantly different between groups ($P=0.589$). In addition, digit ratios were not correlated to Gleason score for either hand or in DR-L.

I think what they are saying is that if your ring fingers are much longer than your index fingers then you are less likely to be susceptible to PCa. I think. Why, no one knows. It would help to have some causation. But, hey, it is just one more test. Wait till the FDA gets this one.



Labels: [Cancer](#)

TUESDAY, JANUARY 12, 2016

[CAN THINGS GET WORSE? IT APPEARS SO!](#)

With slaughter in the US and France and now bombs and slaughter in Turkey, not to mention the daily menu in the Middle East, the [Guardian](#) notes an RBS report for 2016 that the financial markets will drop by another 20%! This is without a housing bubble.

The Guardian states:

In a note to its clients the bank (ie RBS) said: "Sell everything except high quality bonds. This is about return of capital, not return on capital. In a crowded hall, exit doors are small." It said the current situation was reminiscent of 2008, when the collapse of the Lehman Brothers investment bank led to the global financial crisis. This time China could be the crisis point.

They also state:

Morgan Stanley has said oil could fall to \$20 a barrel, while Standard Chartered has predicted an even bigger slide, to as low as \$10. Standard said: "Given that no fundamental relationship is currently driving the oil market towards any equilibrium, prices are being moved almost entirely by financial flows caused by fluctuations in other asset prices, including the US dollar and equity markets. "We think prices could fall as low as \$10 a barrel before most of the money managers in the market conceded that matters had gone too far."

This may very well have more impact on the US elections than anything else. In the US the Government has exploded Medicare costs to those with a modicum of a pension while promising the young unemployed, and due to our educational system, unemployable, near free health care.

Tonight we will again hear about the State of the Union. Doubtful we will hear anything factual. It is reminiscent of a Five Year Plan in Russia in the 1930s. And how well did that go for them?

Fear is both contagious and a driver of mass economic instability. Fear comes from lack of reality and leadership. Pretending does not work, political world views which deny reality does not work.



Labels: [Economy](#)

MONDAY, JANUARY 11, 2016

BEING RICH DOES NOT MAKE YOU SMART, IN EVERYTHING

Biotech is a challenging and complicated field. Cancer detection and prognosis is even harder. As we have tried to demonstrate over the past seven plus years many new "markers" for cancer have been proposed. But frankly we are still at a standstill.

Here is the problem as I observe it:

1. What causes cancer? Is it a mutation, an epigenetic change such as methylation, or something else.
2. What about that cancer stem cell thing? We know there are CSC. We also know they can be the conductor in the complex orchestra of metastases. But how do we identify it, collect it, and isolate it?
3. Germline cells do present tendencies towards certain cancers. Frankly there are just a few of these. Most cancers are still unknown. So what cells do we examine?
4. Using blood cells we are collecting a lot of "stuff". We get core DNA, but we may not know what is silenced in cells. We get blood DNA and NOT cell DNA, at least from blood cells. Put that DNA in a cell in say a melanocyte or basal prostate cell, or bone stem cell and we get a totally different formation of histones and expression. So what does that mean?

And the list goes on. Now Bezos and Gates have thrown some money in a pot with Illumina to create a company, called Grail, I guess they are looking for a King Arthur, not the flour guy I suspect.

From a [Business Day](#) article they state:

On Sunday, San Diego-based Illumina said it would form a new company, called Grail, with more than \$100m in Series A financing. Illumina will be the majority owner. Key investors include technology giants Bill Gates — founder of Microsoft — and Jeff Bezos, founder of Amazon.com, as well as backing from ARCH Venture Partners and Sutter Hill Ventures. Grail's test will use Illumina's DNA sequencing technology to scan for bits of cancer genes originating in tumours and circulating in the bloodstream. The hope is to detect many types of newly forming

cancers, which could be treated at an earlier stage to increase the chances of survival. Cowen & Co estimates that use of DNA blood tests for cancer screening will exceed \$10bn a year by the end of the decade. Several companies are developing liquid biopsies, mostly for use with patients already diagnosed with cancer. Experts say it will take huge clinical trials to provide the kind of evidence necessary to make DNA blood tests part of routine cancer screening. Direct-to-consumer testing company Pathway Genomics last year launched a DNA blood test for healthy people without having conducted such trials. Illumina, a much bigger player, intends to provide that evidence.

Now Illumina makes sequencing machines. A great company with great skills and products for sequencing. That is a far cry for cancer genomics. We all know what the other two guys do. But I have not seen a word from either of them about their understanding of what they are doing. One should always remember Theranos, and beware of wild dreams and black turtle necks. Dream Merchants can be dangerous if not grounded.

The problem here is that we have a massive ambiguity of expectations. The process of cancer detection is still a science, not a technology amenable to engineering skills. It is a scientific arena of unanswered and worse un-posed questions.

Add to this mess is the FDA. They are not known for rapid acceptance and Silicon Valley mentalities do not like being told "NO". This may very well mean that we can see a massive set back as a result of colossal failures. Microsoft is software and sales, Amazon is Retail and software, neither is new. Cancer genomics is still a work in progress and the challenge is to not thinking out side the box but figuring out what a box even is!



Labels: [Amazon](#), [Cancer](#), [Microsoft](#)

FRIDAY, JANUARY 8, 2016

[MORE ON THE DEBATE](#)

In a [Science Daily](#) piece the authors state regarding PSA testing:

The researchers measured whether four areas were communicated with patients. Below are the areas and results.

- 17 percent of patients were told that some experts disagree about whether men should have PSA tests;*
- 23 percent were told that some types of prostate cancer are slow-growing and need no treatment;*
- 25 percent were told that the PSA test isn't always accurate in diagnosing prostate cancer; and*
- 31 percent of patients were told that treating any type of prostate cancer can lead to serious side effects such as urinary incontinence and erectile dysfunction.*

Now let us examine the 4 points above.

1. Yes "experts" disagree. Frankly it is the very definition of an "expert". I see this all the time.

One need look no further than Expert Witnesses. They range from real experts who do the work they are opinion on as a day job to the full time "expert" who just make a living by opining without ever doing.

2. Yes some is slow growing and others fast. The problem is that we cannot identify which is which. And fast is fast! So do you want to take the chance?

3. PSA is not at all accurate. It is suggestive at best. But it provides a relatively inexpensive way to watch. It is not the one PSA test, it is a pattern. And as we have shown even the pattern, say PSA velocity, may not be the sine qua non.

4. Side effects, what about death?

So the debate continues. In my experience getting advice from your GP or Internist is of little value. Not because of any lack of competence but due to the complexity of the issue.



Labels: [Cancer](#)

THURSDAY, JANUARY 7, 2016

[THE DEBATE CONTINUES](#)

There is an endless debate on PCa and the use of PSA. A month ago [we wrote a paper](#) on the confusion about PSA testing. We entitled it "[Trust but Verify](#)", trying to symbolize the complexity of PSA testing.

In the [NY Times](#) some upcountry physicians opine:

Nevertheless, screening is a choice. Medicare should not penalize doctors for ordering PSA tests, but it should make sure it is not giving the test away free. Requiring men to bear the small cost of the test is not a punishment, it's a motivation for them to consider the screening decision more carefully. Not only does the test have important implications for adverse health outcomes in the near future, but it also has near-term implications for some serious out-of-pocket costs from potential follow-up care. Support the process by rewarding doctors for taking the time to discuss the trade-offs patients face. Medicare already requires, and reimburses for, shared decision making for lung cancer screening; it should do the same for prostate cancer screening.

PCa is a major killer or men in the US. Also is can be a significantly indolent disease, it just goes no where in almost all inflicted. Yet we do not know which men will be indolent and which will die a horrible death with collapsing spinal cords and the like. So the best course is to assume the worst and hope for the best. Not many other cancers are this way, although some DCIS may be of the same ilk, yet women would never allow that conversation. Men on the other hand just seem to let them be told whatever some "expert" deems appropriate.

So what should be done? The above suggestion is place a financial burden on the test. That is not at all unreasonable. But men should get a balanced discussion of the risks. Namely, we really do

not have a great grasp on this disease. It is complicated and it defies many of the Bayesian rules we are told to follow.

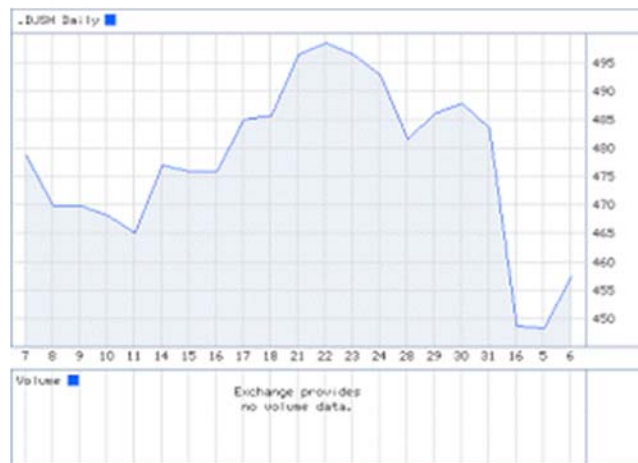
But "Trust but Verify" may be the best path.



Labels: [Cancer](#)

WEDNESDAY, JANUARY 6, 2016

2016 MAY BE A TOTAL MESS



As we have watched the last seven plus years we again come back to the >7% drop tonight in China. Let's see:

1. China is now down 15% this week alone.
2. The US Markets may likely collapse another 400 points Thursday
3. Iran and Saudi may start swapping God knows what.
4. North Korea is exploding test bombs targeted for California.
5. California is now being flooded after a well you know.
6. Guns will be restricted by fiat, or something like that.
7. Heroin is becoming the drug of choice
8. We have rampant terror rings in Asia, Africa, Europe, and yes a few here.
9. Health care costs are going through the roof, while payments under Medicare a dropping below the basement.
10. The FED will now raise interest rates significantly.

11. The percent of the population considered employable is the lowest since the early 60s, namely there are millions doing nothing and getting a free ride on the backs of the working old folks.

Yep, things are just really great!

Welcome to an election year.....



Labels: [Commentary](#)

MONDAY, JANUARY 4, 2016

[WHAT HAS HAPPENED TO ANTITRUST?](#)

The [Washington Post](#) reports:

ESPN is Disney's biggest single business and its most profitable cable channel, and the Big Mouse once regarded it as a virtually unstoppable media force. The traditional cable bundle, in which channels are offered only in bulk, made it an especially sweet deal: The largest chunk of the cable bill goes to ESPN — about \$7 a month — whether a subscriber watches it or not. To maintain that stronghold, and to ward off rivals like Fox Sports 1 and NBC Sports, ESPN has spent aggressively on massive multi-year contracts for the sports broadcasting rights. In 2011, ESPN agreed to pay more than \$15 billion for 10 years of rights to air NFL games — nearly four times what Disney would pay for Lucasfilm, owner of the "Star Wars" and "Indiana Jones" mega-franchises, a year later.

Actually it is more like in excess of \$10 per month and it then funds football teams etc. It then is these high paid athletes that end up abusing women and the like. Thus we have a bundle, or in Antitrust terms, a tying arrangement, an act that could be controlled by the [Antitrust laws](#) (also [See 1996](#)). But it seems we never get there!



Labels: [CATV](#)

SUNDAY, JANUARY 3, 2016

[IT'S GREEK TO ME](#)

As usual the [NY Times](#) has a personal tale about one's dissatisfaction with humanity. This time it is some Classic Greek instructor bemoaning his students lack of ability in declension and conjugation, nouns and verbs.

The author states:

Reading Greek (or Latin) depends, first and foremost, on recognition of case endings. A student must develop an instinct for seeing the word "anthrōpou" as "of a man," "anthrōpois" as "for

men," and similarly with eight other forms of the same word. To look for meaning rather than case, to see only "man" in either word, is what readers of English are programmed to do. My task, as a teacher, is to defeat this impulse. The experience of reading without reference to word order, once students "get it," can be exhilarating, like being freed from a kind of gravity. But for reasons I don't understand, some take far longer than others to "get it," and a few never will. Lack of intelligence isn't the problem; it's more about adaptability, acceptance of change. How long should such students go on in the language, hoping for an epiphany? Should I encourage them to continue? And if I do, is it only to assuage my own sense of failure?

Now anyone who has had an early classics education will understand the problem. They do not even understand English grammar! It is not taught anymore so how is a student to understand anything else. To conjugate the verb "to be" or "to have", the two essential verbs in any Western tongue. The student is clueless. Then the difference between adverbs and adjectives, and the abuse of prepositions.

Now when I was in secondary school I studied Latin, French, and even a year of classic Greek. Each had their own rules, and classic Greek was near impossible. So some forty years later I am at a Bar in Athens, and to show my colleague my expertise I proceeded to ask the waitress using my Greek, yes Homeric Greek! I thought I would try. Her response was, "I am from Queens, I work for my uncle here and frankly I have no idea what you said." It was perfect Queens accent. So I replied in my perfect Staten Island accent that I understood, and we got free drinks, first round. Then I became curious, how quickly could I learn current Greek? The basic verbs were the same, really, and as anyone educated to the minimal amount will know, almost every word has a Greek root. In three months I could negotiate my way in Greek in Athens. I knew declensions, and conjugations, and 1,000 words! I was fluent, and off I went.

Yet I could not translate Sophocles, Homer, or any of the classics. I could read the newspaper and understand the Greek on reruns of the Sopranos on American TV. One must remember that the Greeks ran Sicily for centuries, so they are all a bit Greek!

The question then is what does the good instructor want? Current day Greek has all the elements of classic Greek, one can learn declensions and conjugations. One can read Kazantzakis, and that alone is a reason for learning Greek. Maybe Sophocles can come later? After all the Scholastics managed Aristotle in Latin translation.

Back to the purpose of a language. Learning French can mean understanding the French. The language is filled with subjunctives. Learning Russian brings the same. Arabic is depleted of a solid future tense. Languages tell how a people think. English can be assembled in some understandable form with the worst combinations of grammar. Listen to any Television commentator or news reader. Not only do they use the wrong grammar but all too often the wrong words! And for spelling, my dyslexia is an excuse, what is their?

Classic Greek is complex, a language that contains the subtlety of Greek thought, and the beginnings of our civilization. To begin to understand it one needs English, then perhaps Latin, and another language, and then try Greek. One reads Sophocles and understands that only with

the tools of a civilization we are losing by the day. That I believe is the problem. Don't be critical of the students, the mere fact that they tried is credit alone!



Labels: [Academy](#)

FRIDAY, JANUARY 1, 2016

[THE POST OFFICE?](#)

Now I have been to Turkey. Of all the strange places I travelled, and meals I have consumed, Turkey was the only place in this wide world I ever got food poisoning, and I mean real food poisoning. And so did everyone else in my team. But the good news was that Turkey has Drug Stores where no prescription is required and in addition by choosing well you can buy a pharmaceutical from Germany. Thus the risk of further food poisoning and their effects was hopefully reduced at that time. Just to be clear my food consumption also included street vendors in jungle hamlets in Thailand, never a problem there.

So when I saw the [NY Times](#) piece on our wonderful US Post Office I was a bit taken aback. The author states:

My first year in the United States was full of surprises. I remember trying to figure out if the 24-ounce glass of ice water the waitress placed in front of me was a pitcher, to be shared by the whole table. But where was the spout? I had expected some of what I encountered — I had seen enough movies, and came to this country expecting big cars and big houses and wide open spaces. I got used to gigantic glasses. But I didn't expect the post office. The first time I needed to mail something, I trekked over to my campus's post office, looking for the line to get my envelope weighed. The staff was used to befuddled international students like me, I suppose, and one clerk took my envelope without fuss, said "first class letter," and took my change. ... Yes, I was told, in the United States, mail gets picked up from your house, six days a week, free of charge.... Over the years, I've come to appreciate the link between infrastructure, innovation — and even ruthless competition. Much of our modern economy thrives here because you can order things online and expect them to be delivered. There are major private delivery services, too, but the United States Postal Service is often better equipped to make it to certain destinations. In fact, Internet sellers, and even private carriers, often use the U.S.P.S. as their delivery mechanism to addresses outside densely populated cities.

Now I would take fault with the above. At least my USPS. They leave packages in the rain, snow, under bushes, or not at all. Then talk of friendly, the KGB was more friendly than any USPS agent. As to their competition....well 1 out of 10 Amazon packages are lost, delayed, sent to Guam....Imaging a USPS for Health Care, kidneys removed rather than small basal cell carcinomas, both kidneys! Ooops! That is the USPS and that could be the ACA in action....remember we had to pass it to see what it did!

UPS is profitable, and it would not be if it did not perform. USPS is never profitable. Try and complain. I can track any UPS package, try that with the USPS web site. Packages go from Nashville, to Kearney, to Rochester, to Palm Beach and then to some alien spacecraft!

So perhaps my perception is based upon a comparison between a for profit and a Government entity, and over decades of observation. Amazon has switched to the USPS here in the Greater New York City area. Since then two day delivery has moved to a week, one of ten packages are kidnapped by those aliens, those that do make it are placed in jeopardy since the package sits there in rain or snow, and their computer tracking system is based on "Where's Waldo?".

So perhaps the USPS is better than that in Turkey. So is street food in Thailand!



Labels: [Commentary](#)