

12/28/2018



THE SQUIRREL'S NEST 2018

Terrence McGarty

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THE SQUIRREL'S NEST

Thursday, December 27, 2018

[Obesity and Cancer](#)

We have argued based upon extensive evidence that obesity is a driver of multiple cancers. A recent paper [Kern et al notes](#):

Obesity promotes the development of numerous cancers, such as liver and colorectal cancers, which is at least partly due to obesity-induced, chronic, low-grade inflammation. In particular, the recruitment and activation of immune cell subsets in the white adipose tissue systemically increase proinflammatory cytokines, such as tumor necrosis factor α (TNF α) and interleukin-6 (IL-6). These proinflammatory cytokines not only impair insulin action in metabolic tissues, but also favor cancer development. Here, we review the current state of knowledge on how obesity affects inflammatory TNF α and IL-6 signaling in hepatocellular carcinoma and colorectal cancers.

They continue:

During obesity-driven, low-grade inflammation, hepatic NF- κ B serves as an antiapoptotic survival factor, which promotes the proliferation of HCC progenitor cells and HCC development. In contrast, hepatic inactivation of IKK2 increases diethylnitrosamine (DEN)-induced HCC burden. In line with this evidence, hepatic NEMO deficiency causes spontaneous progression of TNF α -mediated chronic hepatitis to HCC. This detrimental effect of hepatic NEMO deficiency is potentiated under obese conditions presumably by enhanced liver inflammation and hepatic lipid accumulation. This supports the notion that NEMO acts as a tumor suppressor in the liver. Surprisingly, hepatic NEMO-deficient mice are protected against diet-induced obesity and exhibit improved insulin sensitivity...

There is thus evidence that controlling obesity, not just blood glucose, is a critical task.



Labels: [Cancer](#)

Wednesday, December 26, 2018

[What If?](#)

Ten years ago I wrote about the mess that the proposed trillion dollar handout was to cause and further that the FED was loading up on junk while handing out free money to the already well endowed.

Now we have a Government shutdown. It has been going on for a while but I thought what would happen if it lasted a couple of months and nobody really noticed. NY State stepped up to keep the Statue of Liberty open etc so this may be a test to show how useless the Feds are.

Just a thought.



Labels: [Government](#)

Tuesday, December 25, 2018

[Merry Christmas](#)

Factum Est Autem In Diebus Illis Exiit Edictum A Caesare Augusto Ut Describeretur Universus Orbis
Haec Descriptio Prima Facta Est Praeside Syriae Cyrino
Et Ibant Omnes Ut Profiterentur Singuli In Suam Civitatem
Ascendit Autem Et Ioseph A Galilaea De Civitate Nazareth In Iudaeam Civitatem David Quae Vocatur Bethleem Eo Quod Esset De Domo Et Familia David
Ut Profiteretur Cum Maria Desponsata Sibi Uxore Praegnate
Factum Est Autem Cum Essent Ibi Impleti Sunt Dies Ut Pareret
Et Peperit Filium Suum Primogenitum Et Pannis Eum Involvit Et Reclinavit Eum In Praesepio Quia Non Erat Eis Locus In Diversorio
Et Pastores Erant In Regione Eadem Vigilantes Et Custodientes Vigiliis Noctis Supra Gregem Suum
Et Ecce Angelus Domini Stetit Iuxta Illos Et Claritas Dei Circumfulsit Illos Et Timuerunt Timore Magno
Et Dixit Illis Angelus Nolite Timere Ecce Enim Evangelizo Vobis Gaudium Magnum Quod Erit Omni Populo
Quia Natus Est Vobis Hodie Salvator Qui Est Christus Dominus In Civitate David
Et Hoc Vobis Signum Invenietis Infantem Pannis Involutum Et Positum In Praesepio
Et Subito Facta Est Cum Angelo Multitudo Militiae Caelestis Laudantium Deum Et Dicentium Gloria In Altissimis Deo Et In Terra Pax In Hominibus Bonae Voluntatis
Et Factum Est Ut Discesserunt Ab Eis Angeli In Caelum Pastores Loquebantur Ad Invicem Transeamus Usque Bethleem Et Videamus Hoc Verbum Quod Factum Est Quod Fecit Dominus Et Ostendit Nobis
Et Venerunt Festinantes Et Invenerunt Mariam Et Ioseph Et Infantem Positum In Praesepio Videntes Autem Cognoverunt De Verbo Quod Dictum Erat Illis De Pueri Hoc
Et Omnes Qui Audierunt Mirati Sunt Et De His Quae Dicta Erant A Pastoribus Ad Ipsos Maria Autem Conservabat Omnia Verba Haec Conferens In Corde Suo
Et Reversi Sunt Pastores Glorificantes Et Laudantes Deum In Omnibus Quae Audierant Et Viderant Sicut Dictum Est Ad Illos



Labels: [Commentary](#)

Monday, December 24, 2018

[The Creed, or Whatever](#)

The book by Rubenstein, [When Jesus Became God](#), is exceptionally well written and approachable by the lay reader. It addresses the topic of Christology, namely just what was Jesus Christ, man, God, both, and are there three Gods, one, a blend. This has been a major issue in Christianity. It is a monotheistic religion, namely one God, but in the Gospel writing we see Jesus as Son of God, but equal to the Father, and then the Holy Spirit, somehow a third entity acting upon the Apostles. Add to this mix the background of many in Greek philosophy and Greek philosophical terms. Finally add the ascension of Constantine, the "first" Christian emperor in Constantinople who see a cacophony of voices with opinions on this "Trinity" of Gods, yet being just one God. Rubenstein notes that battles would ensue at bakers, merchants, sailors, bar keeps as to what Jesus and the three really were. To Constantine he needed unity not dissension.

The battle was between, at this time, Arians and non-Arians. Arians saw Jesus as Son of God with all that such a relationship brings. The non-Arians are those who saw unity in the Trinity, unity and equality.

Enter Greek, its words, its meanings, its philosophical underpinnings. Enter also the collection of egos acting as Bishops fighting viciously against opposing sides, seeking the approval of Constantine with execution being the adversarial tactic.

The book takes you from before Nicaea to during the Council to many of the events proximate to its ending. It covers the theological issues, the political intrigues, and the religious infighting. There were Councils after this which settled a few issues but not all.

A key set of observations that the author opines on are:

1. The dominant role of Constantine, who at this point is frankly not even a Christian not having been baptized until just before his death.
2. The lack of almost any role by the Bishop of Rome, now the Pope in the Catholic Church. It would not be until the beginning of the next millennium that the concept of a powerful Pope would evolve.
3. The sustaining of a multiplicity of views in the context of deadly conflict.

In the end Rubenstein alludes to the fact that Mohammed and his interpretation had but one God, the Father if you will, and that Jesus was a prophet, as was Moses and in turn as was Mohammed. This simplicity Rubenstein argues was what the Muslim faith spread so rapidly, it simplified so much of the extreme complexity of the Christology. Yet I would argue that this was

but one of the many reasons for its spread. One must remember that Muslim faith spread from about 625 onwards whereas the events in this tale are surrounding the period of Nicaea, 325, three hundred years earlier. I would argue that it also was the oppression of the Emperors in Constantinople, the wars with the Persians, the influx of Germanic tribes and a conflux of many other factors.

There is also the maintaining of the Arian faith amongst the newcomers such as the Lombards which lasts well into the 7th Century. There is the detailed theological work using Aristotle by Aquinas in the 13th century and finally the abandonment of this by Ockham in the 14th century, reverting to faith rather than reason.

The greatest challenge in a book of this type is setting the stage for Greek words and meanings circa the 4th century. Such terms as person, essence, substance, and so forth, have meanings in Greek at the time which were modified from Aristotle and his followers, and then as we get to the Scholastics, modified again, and frankly read today may have no nexus to the reality of the time and place of these arguments. I would like to have seen some discussion of this issue, one which I have struggled with in trying to understand early 7th century works. Add to this the complexity of meanings as one crosses the Mediterranean, from Constantinople to Alexandria, then to Syria and beyond.

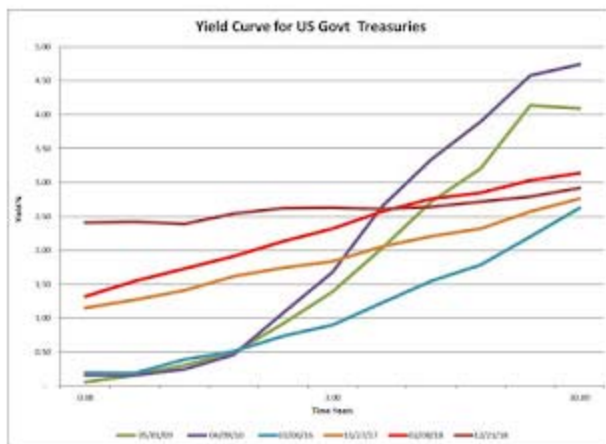
Overall Rubenstein does a great job for a book of this type. The writing is clear, focused, organized. The explanation and very reasonable and the interplay with the Greek is included. For anyone interested in the battle with Christology this is a superb beginning.

Creeds and their enforcement are sensitive issues. The Eastern Orthodox Church still has core differences, and even amongst Western churches there are material discrepancies. Thus public shows of reciting one Creed or another can and do often result in conflicts, often based upon gross ignorance of the underlying issues. Rubenstein adds to our understanding greatly.

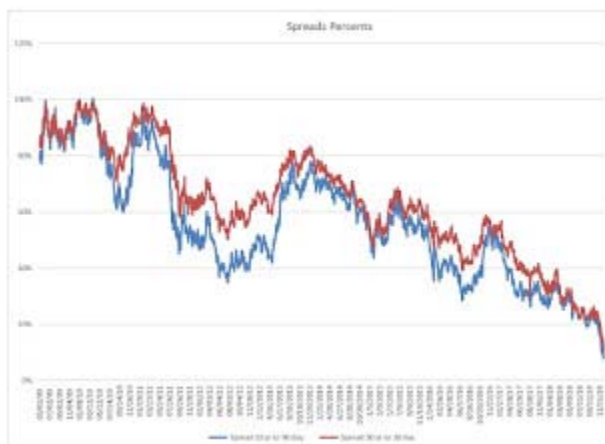


Labels: [Books](#), [Church](#)

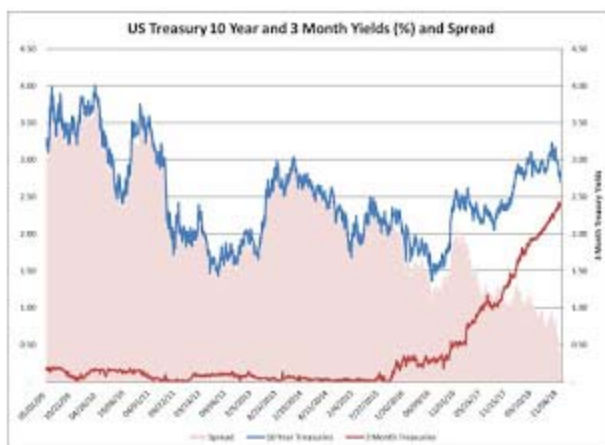
[Merry Christmas ... Bah Humbug!](#)



The above is the flat, yes flat, Yield curve! No where to go but up!



The spreads are disappearing. They go to zero and then negative. Have not seen that since Carter!



Now look at the above. The Yield Curve is FLAT. That means that the short term cost of money equals the long term opportunity. Namely why borrow to build if you go no where! Thanks to the FED. Now this gets worse. Yes worse. The cost of our debt has exploded, and that will drop the long term growth inverting the Yield Curve totally. Again, thanks FED.

Now the DOW etc. It is on its way to 15,000! Yes folks, 15,000. Why? Simply that we have the worst communicating group ever in Government. Pull the Twitter switch folks! Think, write, then read it to the American folks. Let us know what you are doing.

I have seen this before. It is the owners of a family company making decisions by shooting from the hip and having all the employees erratically chasing him about. But this is a Government not a family owned business. We all own the business, it is our country. Stop it please with the Twitter stuff.

This is not a Recession looming, it is a potential collapse. Enough with the Twitter. Send in the adults. And oh by the way, in my many years of business I always found that the most pressing issues occurred during the so-called Christmas recess!



Labels: [Government](#), [Politics](#), [Yield Curve](#)

Saturday, December 22, 2018

[Some Thoughts on Government Shutdown](#)

As with many of these political arguments, I do not have a horse in the race only have some exposure to the massive Government structures. So let's look at a few Departments.

Department of Energy: Fundamentally it makes and houses nuclear weapons, the old AEC. Then all sorts of stuff was added. Forty years ago they added the electric car. Then along came Tesla and did in a year what DoE spent 40+ failing to do. So just dump all but the AEC stuff, move it to DoD. Close it down.

Department of Education: Well we have thousands of school boards, trillions of school taxes and a collection of politicos in DC disconnected from reality. Close it up.

HHS: Keep this one. It has FDA, NCI, etc.

Department of Agriculture: Now 150 years ago it made sense. Now not so much. Massive companies grow stuff now, so we would be better off managing it through FTC.

Department of Treasury: I guess we keep it.

Department of State: Now this is a real boondoggle, It made sense when communications was by sailing ship and before the President could pick up a phone or video conference. It should be cut in half at least!

Department of Interior: Well, parks and stuff. Outsource it.

DHS: Now here if the homeland police. They control not just borders but have empowered hundreds of thousands of agents to control our interstate travel. In many ways this may be the most destructive and abusive entity in the Federal Government. TSA is in my opinion incompetently and abusively run. But it seems we keep giving it more police powers, we need less!

DoD: Well this is a good one. In the old days the Army protected the country and the Navy protected us on the seas and in foreign ports. The Air Force was to do both. But 9/11 showed us that not a single aircraft or anti-aircraft could protect us from four straying aircraft. One wonders what Gatwick in the US would look like.

Treasury: Somebody had to raise the money for all this stuff.

EPA; Reason should prevail and people should be protected.

and the list goes on. It would be interesting to see what could really be done from the ground up again.



Labels: [Government](#)

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About Me



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Terry's view is that of an entrepreneur who has built companies in over twenty countries. Copyright 2008-2018 Terrence P McGarty all rights reserved. NOTE: This blog contains personal opinions of the author and is not meant in any manner to provide professional advice, medical advice, financial advice. Reliance on any of the opinions contained herein is done at the risk of the user. For publications see:

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Thursday, December 20, 2018

[Happy Ten Years Old](#)

As I sit here in the Detroit Airport, having been fully body searched by a large TCA creature with a sadistic smile as he made certain that this grey haired 75 year old male in a suit was fully inspected from genital to genital, and you want these morons managing your health care, I think that today marks the 10th anniversary of this blog.

I have had some who asked why I write this thing. Good question, think of Detroit! In ten years we have seen in my opinion four major trends. First Government wants to take over more and more each day. Second, fantastic advances have taken place in medicine, unfortunately many to be undone by the burly man at Detroit with a badge. Third, the US knows less about other nations than at any other time. And vice versa. Fourth the control of privacy and information has gleefully been handed over to entities who have what appears in opinion to have no ethics, and are clueless about the topic.

Of course we have global warming, social justice, income inequality, deep state, immigration, etc as topics du jour. But the two most serious concerns for the next ten years is more Government takeovers and loss of privacy.

It will be interesting to see what happens over the next ten years. This blog has accumulated several million words and 300,000 readers. I refuse Facebook, Twitter etc, they just want my identity. Google seems to allow me to speak, but there too one must wonder.

So looking forward, I am excited to see what it brings. Hopefully my flight arrives before then, and yes that that homunculus does not come back for a "feel". And just think, I am not crossing a border.



Labels: [Commentary](#)

Monday, December 17, 2018

[Too Much Time on His Hands](#)

I know nothing about Clemson. I think it is some southern college but in reading a [NY Times](#) article proposing that human extinction may be a good thing, I would not recommend the place to any of my grand kids. Really.

The author states:

One might ask here whether, given this view, it would also be a good thing for those of us who are currently here to end our lives in order to prevent further animal suffering. Although I do not have a final answer to this question, we should recognize that the case of future humans is very different from the case of currently existing humans. To demand of currently existing humans that they should end their lives would introduce significant suffering among those who have much to lose by dying. In contrast, preventing future humans from existing does not introduce such suffering, since those human beings will not exist and therefore not have lives to sacrifice. The two situations, then, are not analogous. It may well be, then, that the extinction of humanity would make the world better off and yet would be a tragedy. I don't want to say this for sure, since the issue is quite complex. But it certainly seems a live possibility, and that by itself disturbs me.

Frankly, who asked him anyhow. My minor was philosophy as an undergraduate but at a Catholic School it was trying to understand Aquinas. Which is why I now am a follower of Ockham...not Aquinas.

Now as I struggle with the inner workings of various cancers, hopefully trying to make a small contribution, I from time to time return to Ockham, and his philosophy. He introduced the concept of individualism, that individuals count, that individuals have duties in a religious context and that individuals are citizens and not subjects. Not bad for the 14th century.

But along comes this Southern erstwhile philosopher who posits what he does above makes one ask have we entered the world of the absurd.

Humans have intelligence, and that intelligence can, has, and most likely will always be used to sustain existence. Yes, along comes from time to time abject evil, not much we can do about it but recognize it and eliminate it. But doing away with the entire human race.

Humans are part of the ecosystem. A complex ecosystem, and one which has from time to time gone through shifts. But for the last 3,000 years out of 6 billion we have managed somewhat well. Other species have wiped out other species. Just look at insects, or how about influenza. We are in a continual war with our partners on this planet. But understanding that and then understanding how to accommodate is also essential.

Thus if carbon dioxide is a problem, we should not tax our way out of it, or have some Southern philosopher kill off all humanity, but find a solution. We have done so with many other issues over the centuries, why not this time as well! Let's not let Southern philosophers kill off humanity, please!



Labels: [Academy](#)

Thursday, December 13, 2018

[CRISPR Accuracy and Precision](#)

A recent paper by [Chakrabarti et al](#) notes that:

- *The outcome of CRISPR-mediated editing can be predicted*
- *Not all target sites are edited in a predictable manner*
- *The precision of DNA editing is mainly determined by the fourth nucleotide upstream of the PAM site*
- *Chromatin states affect editing of imprecise, but not precise, target sites*

In the corresponding [Eureka](#) article they note:

Guided by the RNA molecule, the Cas-9 enzyme scans along the genome until it finds the region of interest. When the RNA guide matches the correct DNA sequence, it sticks like Velcro and Cas9 cuts through the DNA. The DNA is broken three letters from the end of the target sequence, and bits of genetic code are then inserted or deleted, seemingly haphazardly, when the cell attempts to repair the break. In this study, the researchers found that the outcome of a particular gene edit depends on the fourth letter from the end of the RNA guide, adjacent to the cutting site. The team discovered that if this letter is an A or a T, there will be a very precise genetic insertion; a C will lead to a relatively precise deletion and a G will lead to many imprecise deletions. Thus, simply avoiding sites containing a G makes genome editing much more predictable.

This means that precision and accuracy may be attained. It has been known that CRISPRs seek certain defined sites on the DNA but there may be multiple sites or sites blocked by closed chromatin. This appears to remedy the issue.



Labels: [CRISPR](#)

Wednesday, December 12, 2018

[There is a Benefit](#)

The ongoing flap over monitoring for prostate cancers seems to be slowly disappearing except for those who one would guess want to see old men die. The most recent one is in the current [NEJM](#) where the study results note:

We randomly assigned 695 men with localized prostate cancer to watchful waiting or radical prostatectomy from October 1989 through February 1999 and collected follow-up data through 2017... Men with clinically detected, localized prostate cancer and a long life expectancy benefited from radical prostatectomy, with a mean of 2.9 years of life gained.

But they further conclude:

The limitations of our trial are that the analyses according to age were not prespecified in the protocol, were exploratory, and were, among other caveats, sensitive to chance findings and not adjusted for multiple testing. Furthermore, the diagnostic procedures used today differ drastically from those used during the period of enrollment in our trial. As a result of widespread PSA testing today, most men have nonpalpable, PSA-detected tumors, whereas in our trial the majority of the men had clinically detected, palpable tumors. Today, men undergo multiple biopsies or multiparametric magnetic resonance imaging with targeted biopsies, whereas the participants in our trial had only cytologic or sextant biopsies, with few cores investigated as compared with current standards. Today, the clinical domain of localized prostate cancer is different, and the sensitivity for the detection of high-grade cancers during our trial was considerably lower than it is today. In clinically detected prostate cancer, the benefit of radical prostatectomy in otherwise healthy men can be substantial, with a mean gain of almost 3 years of life after 23 years of follow-up.

Namely, the data is old but it demonstrates life saving and with the use of PSA it seem dramatically better.

The data against "watchful waiting" just keeps piling up. As they say; believe them or your lying eyes!



Labels: [Cancer](#)

[Accuracy vs Precision, Ouch!](#)



There is an [MIT News](#) bleep on the development of a new climate model. They note:

The new model will be built by a consortium of researchers led by Caltech, in partnership with MIT; the Naval Postgraduate School (NPS); and the Jet Propulsion Laboratory (JPL), which Caltech manages for NASA. The consortium, dubbed the Climate Modeling Alliance (CliMA), plans to fuse Earth observations and high-resolution simulations into a model that represents important small-scale features, such as clouds and turbulence, more reliably than existing climate models. The goal is a climate model that projects future changes in critical variables

such as cloud cover, rainfall, and sea ice extent more accurately — with uncertainties at least half the size of those in existing models. "Projections with current climate models — for example, of how features such as rainfall extremes will change — still have large uncertainties, and the uncertainties are poorly quantified," says Tapio Schneider, Caltech's Theodore Y. Wu Professor of Environmental Science and Engineering, senior research scientist at JPL, and principal investigator of CliMA. "For cities planning their stormwater management infrastructure to withstand the next 100 years' worth of floods, this is a serious issue; concrete answers about the likely range of climate outcomes are key for planning." Current climate modeling relies on dividing up the globe into a grid and then computing what is going on in each sector of the grid, as well as how the sectors interact with each other. The accuracy of any given model depends in part on the resolution at which the model can view the Earth — that is, the size of the grid's sectors. Limitations in available computer processing power mean that those sectors generally cannot be any smaller than tens of kilometers per side. But for climate modeling, the devil is in the details — details that get missed in a too-large grid. For example, low-lying clouds have a significant impact on climate by reflecting sunlight, but the turbulent plumes that sustain them are so small that they fall through the cracks of existing models. Similarly, changes in Arctic sea ice have been linked to wide-ranging effects on everything from polar climate to drought in California, but it is difficult to predict how that ice will change in the future because it is sensitive to the density of cloud cover above the ice and the temperature of ocean currents below, both of which cannot be resolved by current models

I recall decades ago examining random fields, my doctoral thesis, and how complex a problem they are. Now they are totally redoing models. Hopefully accuracy rather than precision is the end result. Then again should we question what we are being told, it is precise but is it accurate? Just a thought.



Labels: [Climate Issues](#)

[Taxes, It is Alice in Wonderland Time](#)

I am one of those who continuously do and redo their taxes before hand and making certain that they are not only paid but over paid. It is abject terror of the IRS. I feared the old KGB even less.

But we were told we got a great new tax law. Well perhaps but if you live in New Jersey, New York, Massachusetts, or California, good old Democratic strongholds, the new Republican Tax Law raises your taxes, unless you are in Real Estate! Yep, just did the new version, a whopping 10%+ increase.

Thanks Washington. I am really confused, but can't say we did not see it coming. Once Ryan said he was leaving, one could feel the draft from the tax room waif into the living room.

Merry Christmas and Happy New Year.



Labels: [Politics](#)

Tuesday, December 11, 2018

[APOBEC and PCa](#)

In a recent paper on the development of Prostate Cancer (PCa) the authors allege the role to APOBEC is critical. They note¹[1]:

The researchers collected patient data from close to 300 men who have had their entire cancer genome sequenced to characterise all mutations present in the tumour. Based on the data set, the researchers have developed the computer model which can be used to predict how prostate cancer will develop for a given patient.

'If we have a patient with a particular set of mutations, we can use the model to predict the most likely next mutation that the patient will experience at some point - and how it will affect the patient's clinical situation. As an illustration, we can predict with some probability that if you have mutation A, you are likely to get mutation B before you get C. We can also predict if the next mutation is likely to change the clinical outcome of the disease' ...

Mechanism Contributing to the First Mutations in Prostate Cancer Have Been Found. The approximately 300 patients from the study all had their entire genome sequenced. With genome sequencing, it becomes possible to tailor the treatment of the individual - also referred to as personalized medicine. The patients whose data the researchers have used have primarily been so-called early onset patients. This group is defined as men who are diagnosed with prostate cancer before reaching the age of 55 years.

'Prostate cancer develops over many years. We have therefore been particularly interested in the group of patients where the cancer is detected at young age as this allows us to analyse the tumour at an early stage. This is an important element because in this way we get a cleaner picture of the first mutations and alterations that occur in the tumour, to find out what is the initiating factor', ...

So far, it has not been known precisely what initiates prostate cancer. However due to the focus on the earliest detected tumours, the researchers uncovered a mutational mechanism involving an enzyme called APOBEC. This enzyme may help trigger the disease - i.e. trigger some of the very first mutations in prostate cancer.

'We hypothesize that this enzyme mutates the prostate cells at a low but constant rate. Each time the cell divides, APOBEC is likely to cause mutations. If you have early-onset prostate cancer,

¹[1] https://www.eurekalert.org/pub_releases/2018-12/uoct-ruc121118.php

you may have a couple of mutations caused by APOBEC. Twenty years later, you may have 10-20 mutations',

Now we know a great deal about PCa. There are a multiplicity of genetic aberrations. A Nature Reviews paper has also recently noted²[2]:

Genome-wide association studies (GWAS) have been successful in deciphering the genetic component of predisposition to many human complex diseases including prostate cancer. Germline variants identified by GWAS progressively unraveled the substantial knowledge gap concerning prostate cancer heritability. With the beginning of the post-GWAS era, more and more studies reveal that, in addition to their value as risk markers, germline variants can exert active roles in prostate oncogenesis. Consequently, current research efforts focus on exploring the biological mechanisms underlying specific susceptibility loci known as causal variants by applying novel and precise analytical methods to available GWAS data.

Results obtained from these post-GWAS analyses have highlighted the potential of exploiting prostate cancer risk-associated germline variants to identify new gene networks and signalling pathways involved in prostate tumorigenesis. In this Review, we describe the molecular basis of several important prostate cancer-causal variants with an emphasis on using post-GWAS analysis to gain insight into cancer etiology. In addition to discussing the current status of post-GWAS studies, we also summarize the main molecular mechanisms of potential causal variants at prostate cancer risk loci and explore the major challenges in moving from association to functional studies and their implication in clinical translation.

Namely the first paper alleges the discovery of a putative unique and predictable path and the second a plethora of GWAS results.

It is worth examining both paths. However PCa can be strange and multifaceted. Most variants are slow growing as noted. However there are a small percentage which have explosive growth. Just what the differentiator is seems still unknown.



Labels: [Cancer](#)

Told Them So

[Recode](#) reports:

It was easy to predict that Verizon would end up regretting the \$10 billion or so that it had invested in AOL and Yahoo. The two companies used to define the internet, but by the time the phone company bought them, they were long past their prime. And no one except Priceline has

²[2] <https://www.nature.com/articles/s41568-018-0087-3>

ever revived a faded consumer internet company — once it's done, it's done. Now Verizon has formally acknowledged that it, too, can't turn AOL and Yahoo around and has written off \$4.6 billion of the money it spent buying the two properties. The playbook from here on out calls for a series of staff cuts and asset sales, followed by more writedowns, followed by more cuts, etc. This one contains multiple teachable moments. Just wishing that there was an alternative to the Facebook/Google advertising duopoly doesn't make it so, for instance. Then again, Facebook and Google can look at the demise of two of the internet's most powerful companies and remind themselves that this could be their fate, too. One particular lesson you can take from this even if you're not an internet giant, past, present or future: Giant megadeals don't belong to the companies that make them. They belong to the executives that make them. And if those execs leave, the deals can go, too.

I only "kind of" agree. The problem is CEO and other top management egos. I was there and I saw it before this one. Verizon has made many such mistakes. In my opinion only Seidenberg managed exceptionally well. Many others wanted to be in the "media" business. Fundamentally they were "pole climbers" and not "media moguls" The AoL deal and worse the Yahoo deal made no a bit of sense and the Boards of these entities are generally "politically correct" collections who have no idea about the core business.

Perhaps the new management of Verizon will get it right. They are an entity with certain exclusive assets, frequency bands, that they can monetize in a multiplicity of ways. They are still a monopoly like company, along with AT&T. So focus, focus, focus. I understand how difficult it is to get Directors who know something especially when running a politically visible business, but try to get a few. Reality can be expensive, but at least the new management seems to have same grasp on it.

Let's hope so. I wish them luck.



Labels: [Verizon](#)

Monday, December 10, 2018

[50 Years or So Ago](#)



About 50 years back I spent time designing a tracking system for the X-15. The system tracked Polaris and then as the aircraft was in flight above the atmosphere we scanned down tracking Polaris and measuring various wavelengths to determine absorption. This allowed us for the first time to determine aerosol density and at the same time by tracking Polaris to update gyro drift for better position accuracy.

Back then we had rather crude electronics and a real time environment. No Apps, just a great team to work with.



Labels: [NASA](#)

Saturday, December 8, 2018

[Grades, Achievements and Psychologists](#)

I have taken one psychology course in my life. That was enough. Now psychiatry is treating someone with a mental problem. Complex, and often resulting in drugs to mask the issue. Psychology seems to me to be the studying of rats and then applying it to humans say in the workplace.

Now along comes this [NY Times](#) fellow who states:

Getting straight A's requires conformity. Having an influential career demands originality. In a study of students who graduated at the top of their class, the education researcher ... found that although they usually had successful careers, they rarely reached the upper echelons. "Valedictorians aren't likely to be the future's visionaries," ... explained. "They typically settle into the system instead of shaking it up." Straight-A students: Recognize that underachieving in school can prepare you to overachieve in life. So maybe it's time to apply your grit to a new goal — getting at least one B before you graduate.

Now I could hardly agree, but it all depends on where you are studying. I spent time at Manhattan College, a third rate school for first generation Catholic students in New York. Being taught by Christian Brothers whose goal was to recite the text and expect your to reply accordingly was shall we say useless. MIT then opened my eyes. After the first exam I saw what the game was. Don't think hard, think smart. Feel the answer based upon the principles, be able to intuit where you are going. In fact the game was just that, a game.

Have I hired C students, yes but one always questions what they wasted their time on back then and what they will waste it on when you are paying them.

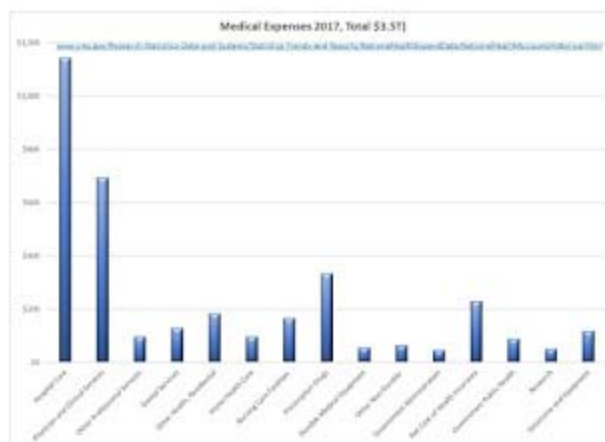
This advice is sure to get you nowhere. But after all it is from a psychologist. Go back to your rats.



Labels: [Academy](#)

Friday, December 7, 2018

Medical Costs 2017



The above are the medical costs for 2017, totaling \$3.5 trillion or about \$10,500 per person per year. See [CMS](#) report.

Some observations:

1. Hospital care is still almost 50%. This means a lot of time in beds. Perhaps new therapeutics can remedy this.
2. Physician care is next but that includes all clinical services. This is about \$700 billion but give there are about 700,000 physicians that is \$1 million per physician. Just a back of the envelope number. But that is gross and since physicians have now had to add half a dozen staff to meet ACA burdens this leaves less and less for physician salaries.
3. Drugs is thirds at about \$350 billion. Now this can explode with new therapeutics but one suspects it will reduce hospitalizations.
4. Home nursing and nursing home care is almost \$350 billion but this may explode as Baby Boomers age.

Perhaps New York should look at this again. This CMS report is useful.



Labels: [Health Care](#)

Remembering Pearl Harbor

Some memories from the folks at the time:





Labels: [Commentary](#)

Thursday, December 6, 2018

[No Horse in the Race, But...](#)



I know the Nicene Creed and its derivatives somewhat well. It and its changes resulted in the break in the Church with the Orthodox going one way and the Romans the other. It frankly is a contentious document. But [The Washington Post](#) seems to make a big issue over the Presidents failure to make a public attestation to another variant of this old Doctrine.

The article states:

The Creed came about two-thirds through the service, shortly after the homily. While it's a standard part of an Episcopal funeral, it's not always said during high-profile funerals at the Cathedral; it depends on the wishes of the person who passed. U.S. Sen. John McCain was raised in the denomination but the Creed wasn't said at his funeral earlier this year. Bush specifically wanted a proper, formal Episcopal service, some involved with the planning said. Most Christians (or those who have been to church, especially a baptism or funeral) have heard the Apostles' Creed. There are varying translations, but its few lines include something like: "I believe in God, the Father almighty, creator of heaven and earth. I believe in Jesus Christ, his only Son, our Lord. ... I believe in the Holy Spirit, the holy catholic Church, the communion of saints, the forgiveness of sins, the resurrection of the body, and the life everlasting. Amen."

In fact having such a set of specific statements would most likely be supporting a State Religion more than likely opposed by a few from other or no religions. You see this Creed has specific forms for many different Christian sects. The Roman Catholic one is different as is the Orthodox. Would reciting it in public make one an apostate? I leave that to professional theologians, it is well beyond my twelve years of study.

I even remember from my childhood that it was a sin to be seen in a Protestant service. I needed permission to go to a Cub Scout Pack at a Protestant church. In those days it would have appeared as if I were as an eight year old supporting this variant.

On the other-hand the same paper may have complained if he did not join in singing Deutschland Uber Alles at a rally in Munich. Thou doth protest too much perhaps.

Oh and [by the way](#):

Πιστεύομεν εἰς ἕνα Θεὸν Πατέρα παντοκράτορα
 πάντων ὀρατῶν τε καὶ ἀοράτων ποιητὴν·
 καὶ εἰς ἕνα Κύριον Ἰησοῦν Χριστὸν
 τὸν Υἱὸν τοῦ Θεοῦ,
 γεννηθέντα ἐκ τοῦ Πατρὸς μονογενῆ
 τουτέστιν ἐκ τῆς οὐσίας τοῦ Πατρὸς
 Θεὸν ἐκ Θεοῦ,
 Φῶς ἐκ Φωτός,
 Θεὸν ἀληθινὸν ἐκ Θεοῦ ἀληθινοῦ,
 γεννηθέντα, οὐ ποιηθέντα,
 ὁμοούσιον τῷ Πατρί,
 δι' οὗ τὰ πάντα ἐγένετο
 τὰ τε ἐν τῷ οὐρανῷ καὶ τὰ ἐν τῇ γῆ,
 τὸν δι' ἡμᾶς τοὺς ἀνθρώπους, καὶ
 διὰ τὴν ἡμετέραν σωτηρίαν,
 κατελθόντα,
 καὶ σαρκωθέντα,
 καὶ ἐνανθρωπήσαντα,
 παθόντα,
 καὶ ἀναστάντα τῇ τρίτῃ ἡμέρᾳ,
 ἀνελθόντα εἰς τοὺς οὐρανοὺς,
 ἐρχόμενον κρῖναι ζῶντας καὶ νεκρούς.
 καὶ εἰς τὸ Ἅγιον Πνεῦμα.
 Τοὺς δὲ λέγοντας Ἦν ποτε ὅτε οὐκ ἦν,
 καὶ Πρὶν γεννηθῆναι οὐκ ἦν,
 καὶ ὅτι Ἐξ οὐκ ὄντων ἐγένετο,
 ἢ Ἐξ ἐτέρας ὑποστάσεως ἢ οὐσίας φάσκοντας εἶναι
 ἢ κτιστόν
 ἢ τρεπτόν
 ἢ ἀλλοιωτὸν τὸν Υἱὸν τοῦ Θεοῦ,
 τούτους ἀναθεματίζει ἡ ἀγία καθολικὴ καὶ ἀποστολικὴ ἐκκλησία.

It should also be noted that this creed was mandated by Emperor Constantine. The reason was massive positions on Jesus his person, soul, etc. Massive heresies were afoot and actual wars were resulting from the differences in opinions. Constantine then used this creed, as he approved it, to say what was correct. It was in Greek. Then it was modified by multiple meetings thereafter with Greek wording moving into Latin. Differences between Christ as man, God, both, became considerable. Also clearly if one were a non Nicene adhering Christian one would not and could

not say this creed. It would be akin to having a Russian hockey team recite the Pledge of Allegiance or worse. Perhaps those who knew something about this would comment, not just those throwing stones. The Creed has had a rather rocky road for 1700 plus years.



Labels: [Church](#)

Wednesday, December 5, 2018

[Say Amen! University Overhead](#)

I can see it at MIT, not only Deans galore but now Vice this and Vice that. The MIT non-teaching overhead has exploded. This is hardly unique. There is an interesting piece in [The Stanford Review](#).

They note:

So why has the school hired so many superfluous workers? What stops Stanford from cutting non-teaching employee payroll to 1994 levels and charging 1994 tuition? Berber Jin argued last year in The Review that maligned incentives within Stanford's bureaucracy create a breeding ground for administrative bloat. "Unlike faculty, who gain prestige through quality teaching and innovative research, administrators move up the career ladder by expanding bureaucracy," Jin wrote. Perhaps much like government, when a University program fails, instead of closing that operation as a private business would, the school simply throws more bodies at the endeavor. Government policy could also contribute to collegiate cost disease. Tuition tax credits, a near tax-free endowment, the ability to issue debt exempt from taxes, the student loan interest deduction, and a laundry list of state-level deductions and credits are all culprits. These tax advantages are identical from an accounting perspective to raising taxes and sending checks to students and colleges. But they add inequity and inefficiency because they they send bigger checks to wealthier households and to more opulent universities, which regressively redistributes income and incentivizes frivolous spending like hiring excess non-teaching employees. If these subsidies were instead provided through transparent and annually reviewed appropriations to worthy causes, like Pell Grants, they would be more equitable and administrators would be incentivized to economize and improve productivity through technological and managerial innovation.

I would argue in addition it is the politicizing and social engineering that has taken over. I spent the 60s in Academia, amidst bombs and tear gas. I had bombs in my office complex and bomb threats at final exams, tear gas roamed the streets of Cambridge. Now the fear comes from words, yes words. Say the wrong thing and off you go.

But indeed the Government control with the oftentimes Marxist governance has created massive thought and word control infrastructures. Alumni should remember that for every dollar they may donate more than 70 cents goes to feed the mouths of these guardians of the cause.

Given their now embedded interests this will never change unless and until the alumni change it. At least those making money.

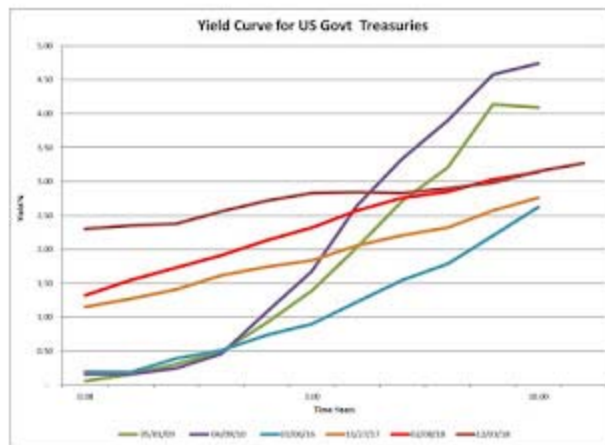
Reading the school PR sheet one gets the impression that "everyone gets a prize" mentality has taken over. That approach may dramatically reduce the alumni with productive assets. It appears that we have begun selling our great institutions to people who want their names memorialized rather than to the key ideas by which they were established.



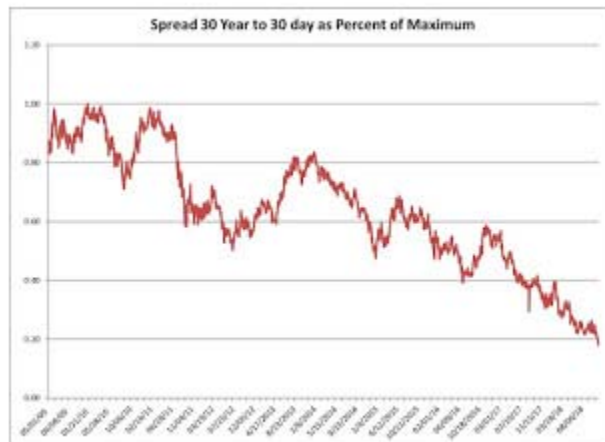
Labels: [Academy](#)

Tuesday, December 4, 2018

[Inverting the Yield Curve](#)



The yield curve has inverted. Not much but it is there. To those of us watching this it does not bode well. Short term chaos, saw it this AM and it will continue, and long term uncertainty.



The 30 day to 30 year spread is on the way to zero and below if we are not careful.



Labels: [Yield Curve](#)

Sunday, December 2, 2018

[New York Mandated Single Payer System](#)



It appears as if New York will mandate a single payer system managed by the State. In a [Rand Report](#) the authors detail the plan. It will cover all people, taking Medicare away from those currently served, forcing all on employer plans off and to the single payer plan and covering anyone in the state, even illegals.

Now I would remind those in New York just to spend some time in Penn Station or any MTA station and see what you will get. This was my trip Thursday, Amtrak broke down in the tunnel. Hours of delay and packed trains. Try this on cancer surgery! That will drop the population quickly!

Now how is this paid for. An 18.6% tax on all gross incomes if you make above \$155,000 total. That is husband and wife. That is a \$30,000 per year charge for health care. That is even the case if you are retired and on Medicare!

In addition the State is demanding that Medicare terminate all of its enrollees and force them over to the NY plan! New York is confiscating your Medicare benefits!

"Abandon all hope ye who enter". The sign over the entry to Hell by Dante is well placed here. On the other hand those Goldman Democrats may get a comeuppance, yet they will find a way around this.

Can anyone imagine the gross incompetence of any New York State employee. They cannot run a transportation system, a housing system, a school system, but now they want to control your health care!

Hopefully the fellow travelers in New Jersey do not come up with the same idea. Please dear Lord, please!

[See the NY State Source](#)



Labels: [Health Care](#)

[Schopenhauer on a Rainy December Night](#)

From time to time I return to Schopenhauer. Not because I find him compelling as did Wagner, Nietzsche, and others, but because I still have no idea what he is talking about. He makes Marx look lucid. Now the key element in Schopenhauer is the Will. After some almost sixty years of reading and re-reading him I have no idea what he means. Yet he did indirectly influence Hitler which is no claim to fame.

Will. A term that philosophers throw about at random. We all know it, right? Wrong.

As Aristotle notes in his Nicomachean Ethics³[1]:

Virtue and vice are in our power.

*The end, then, being what we wish for, the means what we deliberate about and choose, actions concerning means must be according to choice and **voluntary**.*

*Now the exercise of the virtues is concerned with means. Therefore virtue also is in our own power, and so too vice. For where it is in our power to act it is also in our power not to act, and vice versa; so that, if to act, where this is noble, is in our power, not to act, which will be base, will also be in our power, and if not to act, where this is noble, is in our power, to act, which will be base, will also be in our power. Now if it is in our power to do noble or base acts, and likewise in our power not to do them, and this was what being good or bad meant, then it is in our power to be virtuous or vicious. The saying that '**no one is voluntarily wicked nor involuntarily happy**' seems to be partly false and partly true; for no one is involuntarily happy, but wickedness is **voluntary**.*

*Or else we shall have to dispute what has just been said, at any rate, and deny that man is a moving principle or begetter of his actions, as of children. But if these facts are evident and we cannot refer actions to moving principles other than those in ourselves, the acts whose moving principles are in us must themselves also be in our power and **voluntary**. Witness seems to be borne to this both by individuals in their private capacity and by legislators themselves; for these punish and take vengeance on those who do wicked acts (unless they have acted under compulsion or as a result of ignorance for which they are not themselves responsible), while they honour those who do noble acts, as though they meant to encourage the latter and deter the former.*

*But no one is encouraged to do the things that are neither in our power nor **voluntary**; it is assumed that there is no gain in being persuaded not to be hot or in pain or hungry or the like, since we shall experience these feelings none the less. Indeed, we punish a man for his very ignorance, if he is thought responsible for the ignorance, as when penalties are doubled in the case of drunkenness; for the moving principle is in the man himself, since he had the power of not getting drunk and his getting drunk was the cause of his ignorance. And we punish those who are ignorant of anything in the laws that they ought to know and that is not difficult, and so a too*

³[1] Ross, David. The Nicomachean Ethics (Oxford World's Classics) (p. 46). OUP Oxford.

in the case of anything else that they are thought to be ignorant of through carelessness; we assume that it is in their power not to be ignorant, since they have the power of taking care.

Now Aristotle used the term voluntary, meaning voluntas and in English will. I would argue that this is the beginning of will. Aristotle does not define this idea of voluntary, but somehow one must know it.

In the case of Augustine we have⁴[2]:

There are three distinct features that explain why the will comes to have such prominence in Augustine's thinking. In Book I of De Libero Arbitrio, Augustine endeavors to construct an anti-Manichean theodicy [De Libero Arbitrio I.2], one that accounts for the presence of moral evil in the world without either substantializing it or finding its source in divine activity.

*In this regard, **the will is what makes an action one's own, placing the burden of responsibility on the one performing the action** [De Libero Arbitrio I.11]. By the time he composed Book III of De Libero Arbitrio, however, Augustine had come to conceive of the human condition in terms of the ignorance and difficulty that attend it [De Libero Arbitrio III.18], and these features tend to complicate the libertarian optimism of Book I by raising questions about whether it is even possible for us to overcome the ignorance and difficulty. But even here, **the will is intended to serve as the fulcrum of moral responsibility** [e.g. De Libero Arbitrio III.22].*

As Augustine himself states in Confessions⁵[3]:

The one necessary condition, which meant not only going but at once arriving there, was to have the will to go— provided only that the will was strong and unqualified, not the turning and twisting first this way, then that, of a will half-wounded, struggling with one part rising up and the other part falling down.

Finally in the agony of hesitation I made many physical gestures of the kind men make when they want to achieve something and lack the strength, either because they lack the actual limbs or because their limbs are fettered with chains or weak with sickness or in some way hindered. If I tore my hair, if I struck my forehead, if I intertwined my fingers and clasped my knee, I did that because to do so was my will.

But I could have willed this and then not done it if my limbs had not possessed the power to obey. So I did many actions in which the will to act was not equalled by the power. Yet I was not doing what with an incomparably greater longing I yearned to do, and could have done the moment I so resolved. For as soon as I had the will, I would have had a wholehearted will. At this point the

⁴[2] <https://plato.stanford.edu/entries/augustine/#Wil>

⁵[3] Augustine, Saint; Henry Chadwick. The Confessions (Oxford World's Classics) (p. 147). OUP Oxford.

power to act is identical with the will. The willing itself was performative of the action. Nevertheless, it did not happen. The body obeyed the slightest inclination of the soul to move the limbs at its pleasure more easily than the soul obeyed itself, when its supreme desire could be achieved exclusively by the will alone.

Yet no where does Augustine definitively define this will. He become famous (infamous) for his free will discussions, but somehow we all must know what he means.

Now moving to Aquinas we have^{6[4]}:

First off, let us treat the will. Generically, the will is an appetite, that is, a power of the soul by which we are inclined toward something. By means of appetitive powers, we seek and desire things; we strive to unite ourselves (in various ways) with them. They are consequent upon knowledge. "Some inclination follows every form." (ST, Ia, 80, 1) Because knowledge the attainment of a new form in a non-material way, an inclination of the appetite follows upon this knowledge. So, since there are two kinds of knowledge, sense and intellectual, there are consequently two kinds of appetites.

*From sense knowledge, ie. the apprehension of the forms of things in their particularity, sensual appetite follows. In a like manner, from intellectual knowledge, the apprehension of universal forms, intellectual appetite follows. In humans, the intellect is discursive, going from premises to conclusions logically, and so is called rational. **Likewise the consequent appetite is rational; it is called the will. The will then is that power by which we desire the universal, not bound in itself to any manifestation of that universal in particular, real, material things.***

Thus no matter how one searches, will is either understood as the act of choosing or left undefined. Will is an ability to select. We can choose to drink the water or not. Unless of course we are dying of thirst and we perforce of our physiology drink the water. So much for will.

Yet Schopenhauer builds a whole theory on will, never ever defining it. How do we know what it is, how can we see if it works. Free will is our ability to choose. Yet in many cases our choices are set out for us, they are pre-ordained by others, by events, by circumstances. We should ask; what is the will and then; what is the basis upon which you make the identification. How also can we once having identified it then assure others that what we have can be readily understood?

Perhaps just reading Schopenhauer on a rainy December day is a means to pass the time, it beats the news stations....and yes what are those French really up to?



Labels: [Commentary](#)

^{6[4]} <http://www.aquinasonline.com/Topics/freewill.html>

Friday, November 30, 2018

Hoarders?



The Space Station after 20 years. One wonders how much stuff has been just left around. These astronauts are not always known for neatness.



Wednesday, November 28, 2018

EHR Again

HHS has published a set of recommendations to reduce the burden of the EHR on the delivery of health care.

They note:

Based on this input, the draft strategy outlines three overarching goals designed to reduce clinician burden:

- 1. Reduce the effort and time required to record health information in EHRs for clinicians;*
- 2. Reduce the effort and time required to meet regulatory reporting requirements for clinicians, hospitals, and healthcare organizations; and*
- 3. Improve the functionality and intuitiveness (ease of use) of EHRs.*

As we have been noting for a decade this thrust of the ACA and its manager at the time was a massive useless burden on medicine and the patient. It was in my opinion thrust upon all of us by individuals who had apparently no idea what they were doing.

This of course seems to be the general thrust of Governments.



Labels: Electronic Medical Records

Bees Again



Eureka Alert has an interesting piece on bumble bees, not honey bees, the European imports, somewhat weak but used by many artificially. They note:

"This study highlights the undervalued work that wild bees do," says Nicholson, noting that two-thirds of the world's most important crops benefit from bee pollination, including coffee, cacao (for chocolate) and many fruits and vegetables. "Without them farmers need to find pollination somewhere else, by paying high rental fees to bring in honeybees, for example."

We noted this summer the explosion of bumble bees, *Bombus* genus, rather than the few honey bees. *Bombus* are great pollinators and seem well adapted to the environment. They do not seem to suffer from the diseases of the over bred honey bee.

In addition, you can actually pet a *Bombus*, they like humans.

Just some thoughts amidst the explosion of generally unreadable news.



Labels: Bees

Thursday, November 15, 2018

Nationalism and Characteristics

Percent Who Think Item is 'Very Important' for National Identity

Country	Birth	Citizen	Residence	Language	Religion	Laws	Percentage
USA (N=1307)	41	75	44	71	35	65	62
Iceland (N=994)	58	64	49	14	32	42	67
Austria (N=1007)	46	66	50	67	31	56	68
Switzerland (N=2458)	29	66	25	61	14	69	72
Philippines (N=1200)	71	65	58	62	57	54	63
Norway (N=1527)	35	66	32	74	10	38	63
Canada (N=1545)	25	59	23	49	14	64	64
New Zealand (N=1043)	42	55	35	61	16	59	67
Slovak Republic (N=1300)	37	54	38	71	12	49	72
Great Britain (N=1038)	30	54	42	65	22	57	52
Sweden (N=1296)	27	53	29	71	8	33	54
Bulgaria (N=1105)	38	53	29	60	40	54	78
Czech Republic (N=1111)	38	51	47	75	11	43	78
Slovenia (N=1030)	45	50	41	71	17	47	63
Spain (N=1256)	37	49	34	40	10	24	54
Russia (N=1555)	44	48	49	57	15	54	65
Germany (N=1894)	29	46	39	54	16	53	46
Italy (N=1594)	44	45	44	47	26	50	57
Hungary (N=1000)	41	45	47	79	20	29	80
Poland (N=1598)	43	44	38	53	26	54	72
Latvia (N=1044)	36	41	40	61	14	58	62
Netherlands (N=2085)	23	39	21	68	3	40	47
Spain (N=1221)	37	33	34	33	18	33	43

Jones and Smith (J of Soc 2001)

The above is from a study some decade ago regarding what items are very important for national identity in countries. Note the US lists citizenship as the most, well above all other countries. Also language is critical. Religion is low but not the lowest. Laws are high but not the highest.

France is not included! Pour le Francais, pensez cette information.



Labels: Nationalism

College Students and Socialism

In reading my Alma Mater's student paper I came across a piece written by the head of the student Socialist body. The Tech contains the following:

The International Youth and Students for Social Equality (IYSSE) is building a club on the MIT campus to fight for genuine socialism. This means the fight for internationalism, for the unification of workers of all countries, for the abolishment of borders and for bringing the world's political map into harmony with the international character of production. The working class is an international class. The problems workers face all around the world stem from the international capitalist system and must be countered with an international socialist program. We fight for workers' control of the means of production. Major banks and corporations must be placed under international social control and run democratically by the workers themselves to meet the needs of society, not private profit. We fight against war and the militarization of society. The vast sums expended on militarism by all the capitalist powers must be used to meet pressing social needs, including education, healthcare and all social programs. We fight for the defense and expansion of democratic rights. ... We fight for historical truth and against the falsification of history. The development of a socialist movement today requires that workers and youth understand the essential experiences and lessons of the 20th century, and above all, the real history of the socialist movement — from the Russian Revolution through the Trotskyist opposition to Stalinism and social democracy. The future is socialism, but it must be fought for. There is no time to lose.



Now I know something about Socialism. I spent my early years living with my Grandmother, Hattie (nee Kruger) who was head on one of the main branches of the Socialist Parties in the US (the one with Eugene Debs). I heard the arguments, listened to the debates, and Hattie died a Republican.

Now for the student above. Socialism is not Marxism. Marxism demands what the student writes, that is the means of production be placed in the hands of the proletariat. But not even Stalin was as extreme as the author in abolishing borders and destroying nationalism. I would argue that nationalism was even a tool of Communism is properly applied.

What I find in my opinion and based in my experience is that these students are so poorly educated in the facts that they can make such absurd statements. From BU I can accept it, yet from MIT I find it strange. Then again I have no idea who the author is or represents.

Now for all would be Socialists, I take as an example of what may happen, the New Jersey Transit. This is a Government owned and operated local transit system, which is critical to the survival of the State since it sends millions back and forth every day making salaries which are in turn taxed. No train, no job, no money, no State. But what happens with this Government owned Socialistic entity. Colossal incompetence! It does not work, despite the left wing Goldman folks at the helm. Now look at AMTRAK, another example of gross incompetence, another state owned and managed entity. Keep looking folks and what do you see every time you look? A Socialistic mess. Now consider this at a Cancer hospital. It must be next to a crematorium so as not to back up traffic too much! One does not have to look very far to see Socialism fails and is harmful. Worse yet, Marxism is even more deadly.



Labels: Academy, Socialism

Tuesday, November 13, 2018

C'est le meme chose, je pense?



From Larousse we have:

Nationalisme. Mouvement politique d'individus qui prennent conscience de former une communauté nationale en raison des liens (langue, culture) qui les unissent et qui peuvent vouloir se doter d'un État souverain.

Patriotisme. Attachement sentimental à sa patrie se manifestant par la volonté de la défendre, de la promouvoir.

Synonymes : chauvinism, civisme, nationalisme

For those of you not speaking French, the last one states that nationalism and patriotism are synonyms. Thus I was a bit confused when the French President stated that they were unequal, especially when the French control their language so closely.

I leave this debate to those who may know a bit more. But I think words count.



Labels: French

What is AI? Some Thoughts but not an Answer

In the book by Gerrish, *How Smart Machines Think*^{7[1]}, the author purports to address the field of Artificial Intelligence by example, namely via the construct of machines that think. The examples he uses are chess playing, movie selection, the TV game of Jeopardy playing, playing Atari games or GO, and self-driving vehicles as examples. Now this does cover the field we generally call AI but it does present a powerful set of examples that demonstrate what AI may encompass.

The problem is that we can mostly agree as to what a machine is, simply hardware and software, plus some set of past and ongoing data regarding the target at hand but we have always had a difficulty of a clear definition of what thinking entails. We have had philosophers for centuries opining on this topic and thus despite a massive amount of new information of the neural process in the human we have the conundrum of definitions regarding a machine. At the best we have Turing and his putative definitions, which may be still quite wanting.

Instead of bemoaning the clarity in defining the process of thinking, and equally as well its correlative the term intelligence, we will focus a bit on the area of artificial intelligence as an artifact of computer science. All too often AI is in the eye of the beholder. Set loose upon the Press, it has almost taken a life of its own. Moreover, recently with the MIT push to create its first "college" as an entity almost sanctified by the AI mantra, it means whatever one seems to want it to mean. To that end we shall attempt to explore it a bit.

To start out, my view is shaped by half a century working on the periphery of AI. My personal experience is using what AI has as its fundamental techniques and applying them to a variety of situations. But before examining them let me step back a step. I would contend that much of what we are looking at today started with Wiener and his work on Cybernetics. It included McCullough, Pitts, Minsky, Papert, and even Chomsky to a degree. These were the idea folks, lacking the power of machines and with primitive algorithms. In many ways they were trying to emulate what they conceived of as the brain and its functions. I personally see a key initial played as Wiener, because he added the major element of uncertainty. One could see his gun tracking system as an integrated "thinking machine" and a world of uncertainty. Wiener's world was an analog world, which is how he envisioned things but also limited by the tools at hand. We have abandoned that world a bit but as we will see it may still be floating around in current thought.

Now to commence, there are two issues worth focusing on when examining AI. First, what types of embodiments would we generally accept as fitting the field of AI. Second, how is the field of AI practiced; namely are there a set of fundamental precepts and canonical tools or is it just a set of ad hoc problem solving. Thus, is AI akin to say 19th century medicine. A collection of techniques that may or may not work depending on the patient and the disease. 21st century medicine has become focused on causes and therapeutics that address the underlying causes. It is an extension of Koch's laws to genetic structures.

^{7[1]}

https://www.amazon.com/gp/product/0262038404/ref=oh_aui_detailpage_o09_s00?ie=UTF8&psc=1

Let us consider several of the areas of "AI" focus and development. This is not a comprehensive list but merely descriptive. Minsky's landscape of AI, his book *Society of Mind*, is a somewhat rambling but highly insightful discussion of the dimensions. It has stood the test of time and is always worth a review.

1. Pattern Recognition

In a sense this is one of the oldest forms. It takes say a letter, A, and reads it and then using the output of the sensors determines the weighting that best gives A in the presence of 25 other letters. The list of letters is fixed as is their size and font type. The sensors are two dimensional and of a density that satisfies a reasonable text identification probability.

We can assume $N \times N$ or N^2 sensors and the output of the sensors can be simply 0 or 1. We can then, assuming 26 letters, choose N^2 weights so that by adding up the weighted N^2 samples we can divide the output space into 26 regions each uniquely assigned to a specific letter. This is a simple pattern recognition algorithm. We optimize this by repetitively "teaching" the system by submitting the 26 letters again and again to maximize the detection rate and minimize the false alarm rate. We assume that some form of convergence exists.

Now there are many algorithms which have been developed for this class of problems. We can examine a finite set of precisely defined "letters" or objects and then begin to expand it to

We can even extend it to blood cell identification, and the whole field of pathology. Winston in the 1960s applied some of these techniques to blood analysis. The techniques have been also applied to EKG analyses. These however are significantly more complex. One can approach the EKG world from two dimensions. One is from the training perspective, where thousands of EKGs are presented and classified. Then the system uses this based to select a diagnosis. The second approach is the physical analysis approach. Here we would assume to know the physio-electro dynamics of the heart. Then we would try to use the underlying model of reality to ascertain what was defective and attempt to match that with what we have observed thus identifying the underlying defects from what has to change to match the results. It should be noted that the preceding two methodologies are also descriptors of the two sets of our attempts to describe how one gets to know things. Perhaps humans who are proficient in this area utilize both approaches.

The characteristics of this class of recognition system are:

1. Finite number of distinguishable classes of objects, albeit large classes.
2. Objects which have a finite set of identifiers, albeit large sets, such as shape, color, etc
3. Objects which are static during recognition
4. Finite sets, albeit large sets, of objects

2. Speech Recognition

Speech recognition has reached a reasonable level of usefulness. Speech recognition is an example of a trained technique to detect answers to question and ultimately the actual collection of fully formed speech. It has evolved extensively over the past three decades and many techniques are available. One may question whether this is AI or just a technology. The question may be; is the system making decisions of any type or just matching utterances with written words.

One could perhaps combine this with a quasi AI system which emulates an interview with a psychiatrist, a physician, a professor, and then from the results of the interaction makes certain decisions. Yet these elements transcend the tasks of speech recognition.

3. Text Translation

Text translation is a complex process. Transliteration generally leads to nonsense text. One language has a structure and nuance which be absent from another. Even dialects can be strikingly different. My Sicilian Italian learned in my childhood was incomprehensible in Florence and insulting in Milan. My translations of Dumas can be childlike whereas a good translator can convey the drama of the author. Then again translating Pushkin can be even more challenging. Finally one should try translating legal documents from Arabic to English. Culture, religion, different language structures all lead to cumbersome results.

To quote from Joseph Stalin, not one know for either academic excellence or a broad understanding of cultures:

Thus, a nation is not a casual or ephemeral conglomeration, but a stable community of people. But not every stable community constitutes a nation. Austria and Russia are also stable communities, but nobody calls them nations. What distinguishes a national community from a state community? The fact, among others, that a national community is inconceivable without a common language, while a state need not have a common language. The Czech nation in Austria and the Polish in Russia would be impossible if each did not have a common language, whereas the integrity of Russia and Austria is not affected by the fact that there are a number of different languages within their borders. We are referring, of course, to the spoken languages of the people and not to the official governmental languages.

Thus, a common language is one of the characteristic features of a nation. This, of course, does not mean that different nations always and everywhere speak different languages, or that all who speak one language necessarily constitute one nation. A common language for every nation, but not necessarily different languages for different nations! There is no nation which at one and the same time speaks several languages, but this does not mean that there cannot be two nations speaking the same language! Englishmen and Americans speak one language, but they do not constitute one nation. The same is true of the Norwegians and the Danes, the English and the Irish. But why, for instance, do the English and the Americans not constitute one nation in spite of their common language?

This quote is descriptive of the sensitivity of language. Yes, the English and American speak a similar and mutually understandable language. But there are fundamental differences and thus

any language translation must take these into consideration. Thus far it does not appear that any AI system accomplishes this.

4. Text Interpretation

"What do you mean by that?" may be a frequent question. We understand what was said, we can translate it but we may still have a lacking of meaning.

5. Information Retrieval (Q and A)

The game of Jeopardy is a classic example of information retrieval, via a question and answer scenario. Specifically we deal with the Question as well as the answer. As described by Gerrish, the IBM approach was complex, because it first required the parsing of the question and seeing what was asked for. Typically in the game there are categories of questions and then in each category a set of questions seeking the identity of some person, place or thing for which the specific question is the answer. This is a bit the opposite of our usual way of processing since here we see the answer posed and then seek to pose the question. However the same may apply in reverse. In either case it is still merely a case of checking known facts. It is static and certain and the answer is almost always unique. It also is non-iterative, namely we get just one chance at selecting the "question". As such this is a clear case of information retrieval. It does add the dimension of parsing and syntax analysis.

6. Directed Decision Dynamics

Robotic assembly machines may fit this area. They are directed, they are dynamic, and they must make decisions. For example if we have an assembly line with multiple models of cars, there may be a multiplicity of assembly directions for each model. The robot must identify the car and perhaps even "see" the differences.

7. Undirected Decision Dynamics

Consider a game of cards, a random game of cards. Namely when the deal changes so too may the game. Five card stud and so forth may be chosen. Thus every time a new game starts the system must first ascertain what the game is and then learn it and then play it. This area naturally fits into what we have seen for decades as war games. Certain centers such as the Naval War College conduct a multiplicity of games to see what scenarios could be presented by a variety of putative adversaries. Then we examine the response and continue the effort. The 1984 movie, War Games is a classic initial presentation of taking this simulation approach, placing the "rules" on a computer, and then taking the "human" out of the loop. War Games are a classic example of undirected decision dynamics. We do not know the game the adversary is playing and the only way to assess this is sampling highly uncertain information, possibly taking some action to see the response and then redirecting our efforts according to some overall metric of success.

The 1950-1970 period laid out a multiplicity of War Game Scenarios in a nuclear environment. Survival of a limited number of humans capable of reproducing was the acceptable end point. The destruction of society and billions was acceptable. Until some started to think a bit about this

"mutual assured destruction" approach. Taking the "Games" and placing them on a computer would be the ultimate enablement of an undirected dynamic decision AI system. One would suspect that perhaps as in the film the ultimate decision is "not to play the game".

Now a recent case which may fit this scenario is that of the self-driving car. At best we may tell the vehicle the desired end point. We could equally ask the vehicle to take us to view the Fall foliage in New England, thus creating a second layer of vagueness but with some modicum of specificity.

8. Thinking

What is thinking. Does it mean I can write a poem? Write a short story. Devise a new algorithm or find a new chemical pathway or genetic pathway? Can some AI system develop a new philosophical approach, say aligning Wittgenstein and Heidegger? These become complex and beyond what may appear today.

However when we examine the machines that think which Gerrish describes we find a set of common threads.

1. Directed

All of the examples are task directed. They drive a car, play a game, work a test, and even may diagnose a disease. They are not general in any way.

2. Trained

They all get trained to do a task. Their advantage is the ability to look ahead but along the path already that they were trained upon.

3. Bounded

Each approach is limited to the task at hand and cannot readily or possibly at all be used for even a moderately different task. The machine plays Go, Chess, Atari Games, but cannot go laterally to another game.

4. Common Techniques

Whether we call it deep learning, neural nets, hidden Markov models or whatever, there are some common methodologies that enable the directed and learning to get the systems to maximize their performance. Driving a care has two objectives; get to where you want, and do so in a harmless a manner as possible. There is a path and there are exogeneous limitations.

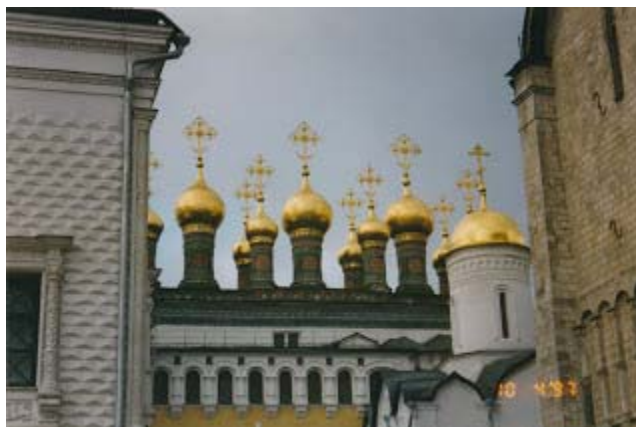
Thus AI as a broad rubric can be understood as such, it yet fails to achieve what we saw a century ago in radio design for example.



Labels: [AI](#)

Tuesday, November 13, 2018

Stalin, Nations and Nationalism



The following are the alleged writings of Stalin on nations. They are worth a read. We all too often see Stalin as merely the Soviet executioner. There was a thought process there as well. I make no comments on what follows.

What is a nation? A nation is primarily a community, a definite community of people. This community is not racial, nor is it tribal. The modern Italian nation was formed from Romans, Teutons, Etruscans, Greeks, Arabs and so-forth. The French nation was formed from Gauls, Romans the Britons, Teutons, and so on. The same must be said of the British, the Germans and others, who were formed into nations from people of diverse races and tribes. Thus, a nation is not a racial or tribal, but a historically constituted community of people. On the other hand, it is unquestionable that the great empires of Cyrus and Alexander could not be called nations. although they claim to be constituted historically and were formed out of different tribes They were not nations, but casual and loosely-connected conglomerations of groups, which fell apart or joined together according to the victories or defeats of this or that conqueror.

Thus, a nation is not a casual or ephemeral conglomeration, but a stable community of people. But not every stable community constitutes a nation. Austria and Russia are also stable communities, but nobody calls them nations. What distinguishes a national community from a state community? The fact, among others, that a national community is inconceivable without a common language, while a state need not have a common language. The Czech nation in Austria and the Polish in Russia would be impossible if each did not have a common language, whereas the integrity of Russia and Austria is not affected by the fact that there are a number of different languages within their borders. We are referring, of course, to the spoken languages of the people and not to the official governmental languages.

Thus, a common language is one of the characteristic features of a nation. This, of course, does not mean that different nations always and everywhere speak different languages, or that all who speak one language necessarily constitute one nation. A common language for every nation, but not necessarily different languages for different nations! There is no nation which at one and the same time speaks several languages, but this does not mean that there cannot be two nations speaking the same language! Englishmen and Americans speak one language, but they do not constitute one nation. The same is true of the Norwegians and the Danes, the English and the Irish. But why, for instance, do the English and the Americans not constitute one nation in spite of their common language?

Firstly, because they do not live together, but inhabit different territories. A nation is formed only as a result of lengthy and systematic intercourse, as a result of people living together generation after generation. But people cannot live together for lengthy periods unless they have a common territory. Englishmen and Americans originally inhabited the same territory. England, and constituted one nation. After, one section of the English emigrated from England to a new territory. America, and there, in the new territory, in the course of time, came to form the new American nation. Difference of territory led to the formation of different nations.

Thus, a common territory is one of the characteristic features of a nation. But this is not all. Common territory does not by itself create a nation. This requires, in addition, an internal economic bond weakly the various parts of the nation into a single whole. There is no such bond between England and America, and so they constitute two different nations. But the Americans v themselves would not deserve to be called a nation were not the different parts , of America bound together into an economic whole, as a result of division of labor between them, the development of means of communications and so forth

Take the Georgians, for instance. The Georgians before the Reform, inhabited a common territory and spoke one language. Nevertheless, they did not, strictly speaking, constitute one nation, for, being split up into a number of disconnected principalities, they could not share a common economic life; for centuries they waged war against each other and pillaged each other, each inciting the Persians and Turks against the other. The ephemeral and casual union of the principalities which some successful king sometimes managed to bring about embraced at best a superficial administrative sphere, and rapidly disintegrated owing to the caprices of the princes and the indifference of the peasants. Nor could it be otherwise in economically disunited Georgia. . . . Georgia came on the scene as a nation only in the latter half of the nineteenth century, when the fall of serfdom and the growth of the economic life of the country, the development of means of communication and the rise of capitalism, introduced division of labor between the various districts of Georgia, completely shattered the economic isolation of the principalities and bound them together into a single whole.

The same must be said of the other nations which have passed through the stage of feudalism and have developed capitalism. Thus, a common economic life, economic cohesion, is one of the characteristic features of a nation. But even this is not all. Apart from the foregoing, one must take into consideration the specific spiritual complexion of the people constituting a nation. Nations differ not only in their conditions of life, but also in spiritual complexion, which manifests itself in peculiarities of national culture. If England, America and Ireland, which speak

one language, nevertheless constitute three distinct nations, it is in no small measure due to the peculiar psychological make-up which they developed from generation to generation as a result of dissimilar conditions of existence. Of course, by itself, psychological make-up or, as it is otherwise called, 'national character,' is something intangible for the observer, but in so far as it manifests itself in a distinctive culture common to the nation it is something tangible and cannot be ignored.

Needless to say, 'national character' is not a thing that is fixed once and for all, but is modified by changes in the conditions of life; but since it exists at very given moment, it leaves its impress on the physiognomy of the nation. Thus, a common psychological make-up, which manifests itself in a common culture, is one of the characteristic features of a nation. We have now exhausted the characteristic features of a nation. A nation is a historically constituted, stable community of people, formed on the basis of a common language, territory, economic life, and psychological make-up manifested in a common culture.

It goes without saying that a nation, like every historical phenomenon, is subject to the law of change, has its history, its beginning and end. It must be emphasized that none of the above characteristics taken separately is sufficient to define a nation. More than that, it is sufficient for a single one of these characteristics to be lacking and the nation ceases to be a nation. It is possible to conceive of people possessing a common 'national character' who, nevertheless, cannot be said to constitute a single nation if they are economically disunited, inhabit different territories, speak different languages, and so forth. Such, for instance, are the Russian, Galician, American, Georgian and Caucasian Highland Jews, who, in our opinion, do not constitute a single nation.

It is possible to conceive of people with a common territory and economic life who nevertheless would not constitute a single nation because they have no common language and no common "national character". Such, for instance, are the Germans and Letts in the Baltic region. Finally, the Norwegians and the Danes speak one language, but they do not constitute a single nation owing to the absence of the other characteristics.

It is only when all these characteristics are present together that we have a nation

Reference: 'The Nation', in Marxism and the Natural Question, from The Essential Stalin: Major Theoretical Writings 1905-1952, ed. Bruce Franklin (Croom Helm: London, 1973), 57-61.



Labels: Political Analysis

Saturday, November 10, 2018

11th Hour, 11th Day, 11th Month and my Uncle Mike...

New York Times, Sunday June 16, 1929, p. 1

3 NEW YORKERS CITED FOR VALOR IN FRANCE

M. J. McGarty and J.P. Naan KJ Get Distinguished Service Crosses, J. P. Christy a Silver Star

Two Distinguished Service Crosses and a silver star citation for gallantry In action were awarded by the War Department today to New York men for bravery in the World War. The distinguished service crosses were given to Michael J. McGarty of 85-15 Eightieth Street, Woodhaven. LI., and James P. Naan of 238 West Fifty-second Street, New York City. The Silver Star went to James P. Christy of 133 Hale Avenue, Brooklyn.

The citations accompanying the decorations read as follows:

"Michael J. McGarty, formerly sergeant, Company B, 306th Machine Gun Battalion, Seventy-seventh Division^{8[1]}, American Expeditionary Force. For extraordinary heroism in action at Chevieres, near Grand Pre, France, Oct. 14. 1918. With utter disregard for his own personal! safety Sergeant McGarty went forward under heavy enemy machine gun fire to rescue a severely wounded officer and displayed extraordinary heroism In action by helping to carry him to a place of safety."



The 77th Infantry Division was organized from draftees, drawn mostly from New York City, and trained at Camp Upton in Yaphank, NY in the central part of Suffolk County, Long Island; the camp is now Brookhaven National Laboratory. The division consisted of the 153rd and 154th Infantry Brigades. The 77th Infantry Division was the first American division composed of draftees to arrive in France in World War I, landing in April 1918; overall it was the seventh of 42 divisions to reach France. The division fought in the Battle of Chateau-Thierry on 18 July 1918. It sustained 10,194 casualties: 1,486 killed and 8,708 wounded. The division returned to the U.S. in April 1919 and was deactivated that month. The 154th Infantry Brigade was composed of the 307th and 308th Infantry Regiments and the 306th Machine Gun Battalion.[1] While the division had been recruited as a National Army unit from the New York City area, attrition and replacements had complicated the complexion of the unit. For example, Company

^{8[1]} <https://www.usar.army.mil/News/Article/1594321/ww-i-move-of-77th-division-of-new-york-draftees-was-not-so-secret-in-april-1918/>

K, 307th Infantry, had been redesignated from the former Company L, 160th Infantry, California Army National Guard. The company had belonged to the 40th Division, which had been converted into a depot division in August 1918. The "Lost Battalion" of World War I fame was composed of six companies of the 77th's 308th Infantry Regiment and one from the 307th Infantry Regiment.



Labels: [Commentary](#)

Thursday, November 8, 2018

[The EHR Continues](#)

In a [New Yorker piece by Gawande](#) he bemoans the EHR he is forced to use. We have been bemoaning this for the past decade. EHRs are not easy, they take away from patient interaction, often alienate the patient from the physician and cost more. Furthermore they really are no patient records but institutional and fail to be portable. Other than that I guess they are fine. They were mandated by the Obama Administration as part of the ACA. As anticipated being mandated by a physician with a strong political bent, they are classic "we know what's best" designs.

As the author notes:

"They're long, they're deficient, they're redundant," she said. "Now I come to look at a patient, I pull up the problem list, and it means nothing. I have to go read through their past notes, especially if I'm doing urgent care," where she's usually meeting someone for the first time. And piecing together what's important about the patient's history is at times actually harder than when she had to leaf through a sheaf of paper records. Doctors' handwritten notes were brief and to the point. With computers, however, the shortcut is to paste in whole blocks of information—an entire two-page imaging report, say—rather than selecting the relevant details. The next doctor must hunt through several pages to find what really matters. Multiply that by twenty-some patients a day, and you can see Sadoughi's problem. The software "has created this massive monster of incomprehensibility," she said, her voice rising. Before she even sets eyes upon a patient, she is already squeezed for time. And at each step along the way the complexity mounts.

In fact one spends more time trying to game the system and failing to diagnose the patient. The problem gets worse since all too often the software designers look upon the physicians as dolts. Dumb old folks they have to train like old dogs.

I suspect as we noted a decade ago that this will not change. Yes we have all this fancy technology but we practice medicine not programming. Worse yet the support and training staff do not understand their customer in many cases and worse yet they care less.



Labels: [Electronic Medical Records](#)

Tuesday, November 6, 2018

[You Can't Make This UP!](#)

Back a few years ago I suggested building what I termed a [MAE Europe](#), a hub for European Internet Traffic. Simply stated at the time all Internet traffic went either to MAE East or MAE West in the US and was subject to surveillance by various US entities. By building a MAE East we have a non-US nexus and by putting it in Prague or Vienna we would be at the heart of then then expanding Internet. I actually built a mini version but for a variety of reasons it never got traction.

Now [Ars Technica](#) has a fantastic piece showing how US carriers allowed the routing of all traffic through China Telecom, the PRC's home turf! You cannot make this up. Any first year engineering student should know how to use the UNIX command `tracert` to see where the packets go. It even tells you the carriers and IP addresses as it sends a message. Thus if one sent a message say from Lockheed in San Jose to the CIA in Langley one would see the path. If one did this simple task one would perhaps have seen what is in the article, the packets were circling around in China!

Now the carrier should have been doing this as a matter of common network management, we did! So I guess China does not have to sneak in, we are sending them everything as a matter of course! Now who did they hire to manage the network?



Labels: [China](#), [Cyber Warfare](#)

Sunday, November 4, 2018

[Ginkgo](#)



The ginkgo leaf is not a maple full of color but an almost solid yellow gold, that stands apart over thousands of millennia.



Every year I am amazed as how it reaches this point and then in just about a day they all disappear. Happy Fall.

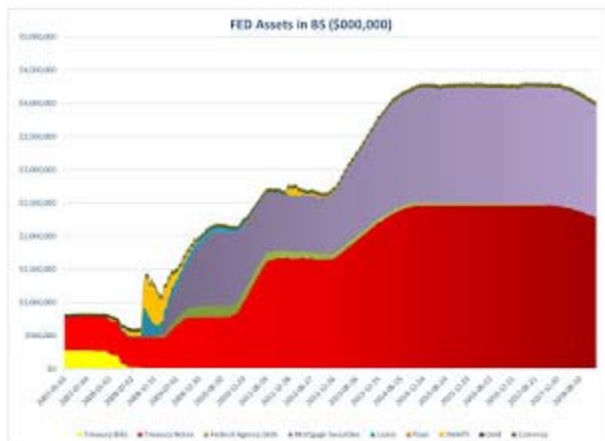


Labels: [Commentary](#)

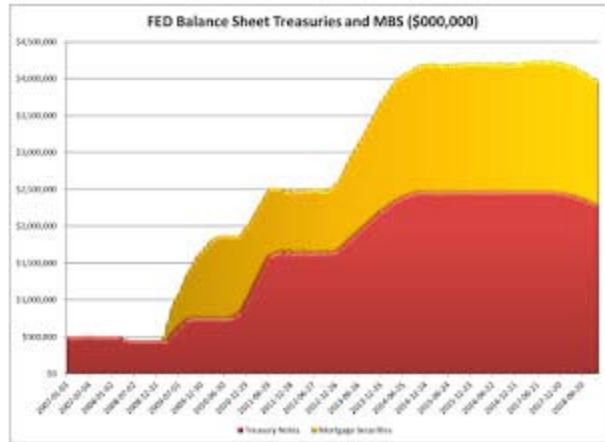
Saturday, November 3, 2018

[FED Balance Sheet](#)

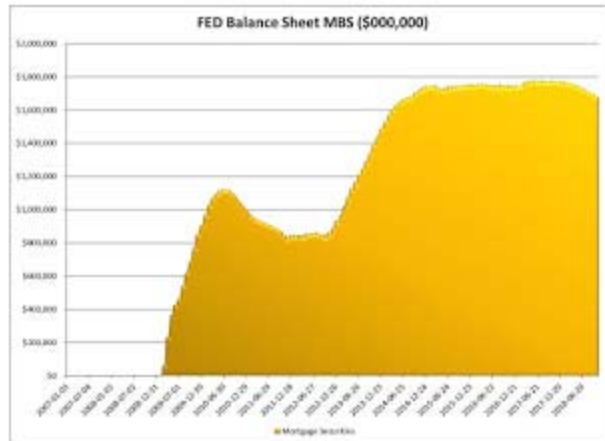
The FED is slowly, ever slowly, unloading the mess of a Balance Sheet it had accumulated as a result of the mess of 2008. FED Chair after FED chair took actions which will be debated for generations to come. Lots of PhD theses for economics types.



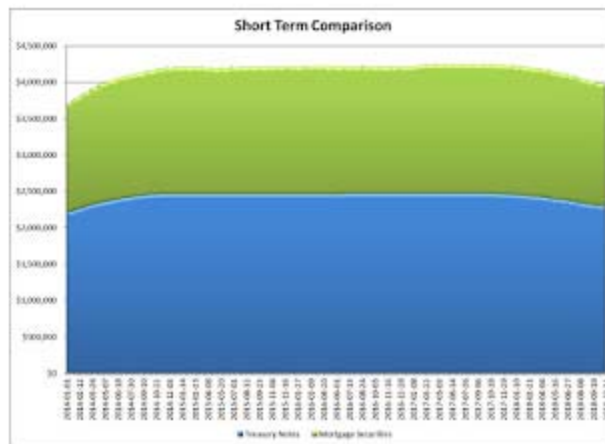
The balance sheet above shows the explosion of everything, especially buying Treasuries and Mortgage Backed Securities.



The two above show that much of this is of recent parentage. The MBS mess is truly a mess, and as the FED unloads what is truly worthless, that is the problem.



The above is the worthless junk. Note the slow unloading of late under the new FED Chair. If you think interest rates are bad now just hold on to your hats.



Here is a close up of the two elements just as it rose and then just as it seems to be coming down. Both are being unloaded. I suspect the Treasuries are due to timing factors and that the FED is no longer buying.

I suspect that long terms this must be watched carefully. One just has to see how much more is needed.



Labels: [Economy](#)

Friday, November 2, 2018

[A Modest Proposal to the White House](#)



To the folks in the White House. I hear you have some problems with China. But then again China seems to be able to run railroads. So a suggestion.



NJ Transit and Amtrak are the most incompetently run railroads in the world if not the universe. So as part of the sweetener for China offer them the exclusive right to run Amtrak and NJ Transit, I would throw in the NY Subway, Metro North as well as the DC Metro. They could get exclusive rights to operate and govern the transportation system. After all they most likely have chips in stuff everywhere let then then operate what they have invested assets in already.

They would hire their own people, no unions, no employment codes, just Chinese methods. A bit harsh at times but perhaps the trains would run. Also we get Governors out of the mix along with a few mayors.

Just a thought.



Labels: [AMTRAK](#), [Government](#), [NJTransit](#)

Thursday, October 25, 2018

Surigao Straits, October 25, 1944



October 25th 1944 was the battle of Leyte Gulf, and a side battle but determining one in the Surigao Straits on the south side of Leyte. The USS Albert W Grant, DD 649, part of a destroyer squadron, sailed straight at the Japanese southern fleet, sending off torpedo after torpedo, and damaging several Japanese ships. Unfortunately, it has been alleged that the Captain of the light cruiser Denver decided, despite warnings to the contrary as reported later, fired on the Grant with 16" armor piercing shells. The good news was the Grant was a destroyer and armor shells did not explode. The bad news was that they went through the ship killing dozens.

Above is the burial at sea of some of the men. Their descendants, as I am one, still remember the event.



Labels: Commentary

Monday, October 22, 2018

A Paris!

Finally, I can try my French in Paris. You see as an American, my French lacks tonal character. My American accent is flat, non-tonal, whereas after two weeks I can finally get the second syllable working again. But never in Paris.

Now a kind French politician is proposing to make this illegal. As Reuters notes:

French member of parliament has proposed that mockery of accents be outlawed, after an irate politician derided a journalist's southwestern pronunciation before asking if anyone had a question in "understandable French". Laetitia Avia of President Emmanuel Macron's ruling party said she was proposing a bill that would classify such mockery with other forms of prohibited discrimination such as on grounds of sex or race. She did so after a journalist from Toulouse in southwest France asked former presidential candidate Jean-Luc Melenchon about an anti-corruption investigation of his hard-left political party. In an exchange widely relayed on media and social networks, Melenchon mimicked the journalist's accent and told her she was "talking nonsense" before turning away and saying: "Has anyone got a question in more or less comprehensible French?"

I may be able to return to Paris yet. In Normandy no problem, in Savoy, no problem, in Brittany, no problem. Finally a solution. Bonne chance mes amis!



Labels: Commentary

Sunday, October 21, 2018

What is in a Name?

If Joe Jones gave MIT \$2 billion, would they change the name to "Joe Jones University"? How about \$5 billion? Would \$10 billion allow Joe to call it "Joe Jones' Happy Place"? Then again what is in a name.

Take the Department of Materials Science. From their web site they note⁹[1]:

MIT's DMSE, like the field of Materials Science and Engineering, grew out of the studies of metallurgy and mining. When MIT opened in 1865, Course 3 consisted of geology and mining. Later, the department's name was changed to the Department of Mining and Metallurgy and over the next fifty years, the disciplines of geology, mining, and metallurgy were repeatedly

⁹[1] <https://dmse.mit.edu/about/history>

joined and separated until in the 1940's, MIT discontinued the study of mining engineering and Course 3 was named the Department of Metallurgy. In 1967 the department name changed to the Department of Metallurgy and Materials Science and in 1974 to the Department of Materials Science and Engineering. These name changes reflect the growing awareness, both at MIT and in the field, that materials should be studied in terms of their behavior and characteristics, rather than by specific class.

There were Departments of Meteorology, Departments of Naval Engineering, Departments of various types.

What was common were several things:

1. As technology changed Departments morphed to reflect the change. Often leading the change.
2. As new Departments arose, the names were descriptive. They were not reflective of the donor at the time.
3. Evolution of Departments was consistent in form, namely a School and then a Department
4. Ad Hoc assemblies were set in Laboratories or Centers. Thus RLE or the Media Lab. Innovation, research were allowed within these petri dishes. Education in the more formal strictures.
5. MIT never was a University nor did it have Colleges. It was reflective of the core technologies that it was a key player in creating and promoting. MIT was in no way like an Oxford or Cambridge, the strictures were loose, allowing for innovation.
6. Donors names got on buildings, not educational centers.

Now along comes a dramatic change. As MIT notes¹⁰[2]:

MIT today announced a new \$1 billion commitment to address the global opportunities and challenges presented by the prevalence of computing and the rise of artificial intelligence (AI). The initiative marks the single largest investment in computing and AI by an American academic institution, and will help position the United States to lead the world in preparing for the rapid evolution of computing and AI. At the heart of this endeavor will be the new MIT Stephen A. Schwarzman College of Computing, made possible by a \$350 million foundational gift from Mr. Schwarzman, the chairman, CEO and co-founder of Blackstone, a leading global asset manager. Headquartered in a signature new building on MIT's campus, the new MIT Schwarzman College of Computing will be an interdisciplinary hub for work in computer science, AI, data science, and related fields. The College will: reorient MIT to bring the power of computing and AI to all fields of study at MIT, allowing the future of computing and AI to be shaped by insights from all

¹⁰[2] <http://news.mit.edu/2018/mit-reshapes-itself-stephen-schwarzman-college-of-computing-1015>

other disciplines...give MIT's five schools a shared structure for collaborative education, research, and innovation in computing and AI...

Now this is truly a dramatic change. First, it is the creation of a "College", an entity never seen before. MIT had a strong pragmatic sense, and this in essence changes this. Second, MIT named things for what they did not who funded it. Recall the Metallurgy and Mining efforts. Third, there appears to be an overwhelming unity of focus, AI, whatever that may be.

Let me comment on each element. First names. Harvard is John Harvard, Stanford is Leland Stanford, and Cornell is Ezra Cornell. Even Weill Cornell Medical School is just a rebranding of a Medical School. If this had become the "School of" perhaps some continuity. But why a College? Second, the naming based upon what is done seems to be missing, but then again this is less of a problem.

Finally, AI. I have seen and been a peripheral participant in AI for half a century. In simple terms it is the application of computer processing power, "tools" for measuring and observing, and "rules" which may be adaptive, to effect actions from observations. AI is amorphic, it lacks substance, as it should. It has become a catch phrase for anything that uses computing and data to effect something. Take Watson and medicine. Physicians are taught differential diagnosis and then an application of the most effective remediation, if available. Yet as Osler noted more than a century ago, if all else fails listen to the patient. Really listen. Watson does not do that and in the age of the EHR many young physicians do not even have the skill. Thus we all too often collect data and fail to listen to the patient.

Thus one should ask, is AI a unifying construct like the term physics or mathematics or philosophy? Or is it as I suspect a catch all phrase for "smart" programs which can "adapt" by measuring data and responses and thus find some "optimal" result. It is akin to the "chess program" that, if the computer is fast enough, stay a dozen moves ahead of its opponent. It may win every time. On the other hand I can think of a recent medical presentation where a patient presented with bleeding gums, and this led to a urinalysis, a finding of blood, a cystoscopy, MRI, an ultrasound, and so forth until someone remarked the patient is on warfarin, check the INR! Yep, as suspected, too high, so titer down the warfarin. How would Watson handle this? It may very well have demanded the same tests, after all the more data the better the answer.

Thus AI as an organizing principle may have severe negative effects. Namely its vagueness, its vagueness, and its vapidness.

Now to the term Computing. Perhaps this would be akin to a College of Typing, or Shorthand. Computing is a tool a technique, and not every Electrical Engineer is dominated by Computing. We no longer use slide rules, and computing, as valued as it is, is also so broad a term, it is accepted as an essential part of all that we do in the 21st century. My stethoscope computes, my blood pressure cuff computes, my car computes, my stove computes, in the broadest terms, but in all cases computing is a tool which facilitates not defines. In an equal sense they all use electricity, all have materials of so form, so why no collect those terms as well?

Thus, overall, I find this proposal a bit disconcerting. It is dropped upon the alumni out of the blue. It will be interesting to see the human dynamics as they evolve. Science and Technology are forever changing. Just remember the old Departments above. Thus it is essential to embody that fluidity of innovation, not immortalize it. Just some thoughts from an older alum.



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

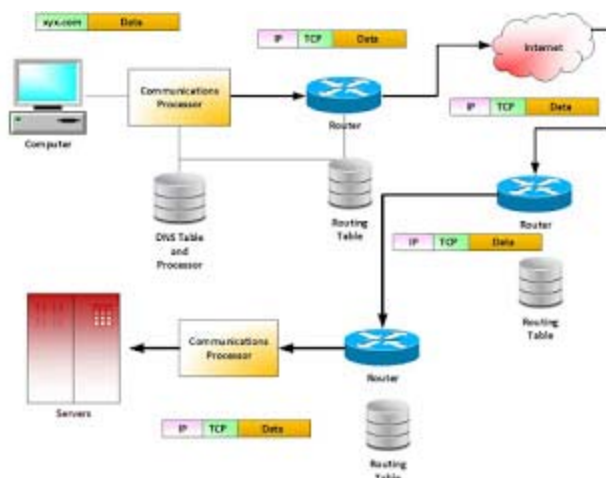
Friday, October 19, 2018

[What is the Internet?](#)

The [NY Times](#) had an editorial bemoaning the breakdown of the Internet. As the Times notes:

As governments push toward a splintered internet, American corporations do little to counteract Balkanization and instead do whatever is necessary to expand their operations. If the future of the internet is a tripartite cold war, Silicon Valley wants to be making money in all three of those worlds. Part of the rationalization is that whether or not American companies get in on the action, a homegrown company will readily enact the kind of censorship and surveillance that its government requires. (Indeed, if Google launches in China, it has an uphill battle to fight against Baidu, the entrenched, government-endorsed Chinese search engine.) What this future will bring for Europe and the United States is not clear. Mr. Gomes's leaked speech from inside Google sounded almost dystopian at times. "This is a world none of us have ever lived in before," Mr. Gomes told employees. "All I am saying, we have built a set of hacks, and we have kept them." He seemed to hint at scenarios the tech sector had never imagined before. The world may be a very different place since the election of Donald Trump, but it's still hard to imagine that what's deployed in China will ever be deployed at home. Yet even the best possible version of the disaggregated web has serious — though still uncertain — implications for a global future: What sorts of ideas and speech will become bounded by borders? What will an increasingly disconnected world do to the spread of innovation and to scientific progress? What will consumer protections around privacy and security look like as the internets diverge? And would the partitioning of the internet precipitate a slowing, or even a reversal, of globalization? A chillier relationship with Europe and increasing hostilities with China spur on the trend toward Balkanization — and vice versa, creating a feedback loop. If things continue along this path, the next decade may see the internet relegated to little more than just another front on the new cold war.

The editorial is bemoaning the balkanization of Internets, American, European, Chinese, to begin with. However, the real question is; what is the Internet?



We show above the essence of the Internet. Simply:

1. A backbone transport mechanism such as fiber, wireless, even copper.
2. A protocol set called TCP/IP. IP is the from and to addresses of the packets and TCP is the control mechanism to sequence all the packets in a message.
3. Routers to take a message and send it to the next location so that it may ultimately get to where it was sent.
4. Router Tables: A list of what router to send it to next
5. DNS: A device which converts an Internet address such as xxy.com to an IP address.
6. Communications Interfaces: Devices that interface with routers at end points.

Now what can the Chinese do? Simple, they can mask the routing tables or block DNS address conversions. They can send users seeking to go to a forbidden site to a control site, get their IP address, locate then and take appropriate remedies. Namely anyone who can control a DNS or routing Table can control a regional portion of the Internet. Balkanization already exists. Always has so in a way this is not new. In fact in 2000 when in Prague we connected a Czech only Internet to Frankfurt and the Tier 1 backbones. Overnight we have a global network. Yet before that any one in the Czech Republic could speak to anyone else.

Thus Balkanization has always been with us. So why the uproar. China would not block all traffic outward, only that which they see as inappropriate. After all, a hundred years ago the US Postal Service blocked all books coming into and out of the US that they deemed in appropriate. There is nothing new here.

But wait, to get to these balkanized Internets all one needs is an access portal in that net, and Tier 1 carriers afford that. So perhaps it will not be as easy as one thinks.



Labels: [Internet](#)

Monday, October 15, 2018

[Now Who Said This?](#)

For those whose lives were nearly shattered by upgrading to W10 1809 and losing all their data, for those who have their W10 machine frozen somewhere between W10 upgrades, for the eons wasted trying to figure out how to fix a Microsoft problem comes [an interview at Harvard](#), of course where else, which notes:

Whether we like it or not, the public is increasingly turning not to their elected officials, but to the heads of major corporations for leadership on important and difficult issues. Perhaps because of partisan gridlock, perhaps because politicians seem to pay more attention when Big Business talks, rightly or wrongly, people expect today's CEOs to pick up the ball. That's both good and bad for society, according to Brad Smith, Microsoft's president and chief legal officer. "I think it's not only good, but fundamentally important that companies have a conscience," he said during a talk with Harvard Business Review ...People, especially younger workers, want to work for businesses that operate conscientiously, and as companies expand globally, particularly those in creative and intellectual property sectors, it becomes not just a nice thing to do, but an imperative for corporate survival. "You better have a conscience," Smith said.

One could reasonably ask in my opinion what planet this tin eared executive has just arrived from. Is there any conscience for what damage in my opinion has been done to the masses of computer users with this W10 disaster. Worse yet, what is to come from this behemoth as it rolls our newer and more useless in my opinion software. People in glass houses.....



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

Friday, October 12, 2018

[Watch the Internet Crash](#)

[ICANN](#), the now internationalized "manager" of the Internet has announced a "security update" and they note:

ICANN is planning to perform a Root Zone Domain Name System Security Extensions (DNSSEC) KSK rollover as required in the Root Zone KSK Operator DNSSEC Practice Statement.

Rolling the KSK means generating a new cryptographic public and private key pair and distributing the new public component to parties who operate validating resolvers, including: Internet Service Providers; enterprise network administrators and other Domain Name System (DNS) resolver operators; DNS resolver software developers; system integrators; and hardware and software distributors who install or ship the root's "trust anchor." The KSK is used to cryptographically sign the Zone Signing Key (ZSK), which is used by the Root Zone Maintainer to DNSSEC-sign the root zone of the Internet's DNS.

Maintaining an up-to-date KSK is essential to ensuring DNSSEC-validating DNS resolvers continue to function following the rollover. Failure to have the current root zone KSK will mean that DNSSEC-validating DNS resolvers will be unable to resolve any DNS queries. The KSK rollover plans were developed by the Root Zone Management Partners; ICANN in its role as the IANA Functions Operator, Verisign as the Root Zone Maintainer, and the U.S. Department of Commerce's National Telecommunications and Information Administration (NTIA) as the Root Zone Administrator. The role of NTIA ended on 1 October 2016. The KSK rollover plans were posted in July 2016 and incorporate the community Root Zone KSK Rollover

What this means in simple English is that you better pray your ISP or IT Folks have done what ICANN says and that further ICANN knows what it is doing. Certificate management and DNS updating is NOT TRIVIAL. There will be mistakes. There will be crashes.

And then you can try the US Post Office again. Horrors! Poor Ben Franklin, a good idea but sent to the Government employees, worse, an "international" body.



Labels: [Internet](#)

Friday, October 12, 2018

[English, the Customer and NJ Transit](#)

One of the issues needing improvement in the "consultants" report on NJ Transit was communications with the customers, you know those folks paying their salaries.

So try [this one](#) on for size:

INBOUND to Hoboken (temporarily discontinued)

Train 330, the 6:01 p.m. arrival at Hoboken from Summit

Train 432, the 6:19 p.m. arrival in Hoboken from Gladstone, operates 19 minutes earlier on the Gladstone Branch then replaces Train 330's schedule east of Summit.

Now let us try to translate this.

1. "temporarily discontinued" most likely means not working. I guess it means the stuff listed below
2. Train 330 arrives at Hoboken from Summit...I guess means it is working, so why say it is discontinued, is it working or not?

3. Train 432, now just what does this mean? This sentences is an example of following the bouncing ball.

I may have a PhD, written 17 books, 250 papers, etc and I have a reasonable grasp of Frnech, Greek, Russian, Spanish and of course Italian as well as English and in the old days Latin and Classic Greek. But this makes no sense.

NJ Transit needs someone who can communicate, now really folks. This reads worse than a Goldman Sachs investment advisory.



Labels: [NJTransit](#)

Thursday, October 11, 2018

[The Internet: Do Non Techys Have a Clue?](#)

In a recent piece in the [NY Times](#), a Harvard Kennedy individual states:

The primary reason computers are insecure is that most buyers aren't willing to pay — in money, features, or time to market — for security to be built into the products and services they want. As a result, we are stuck with hackable internet protocols, computers that are riddled with vulnerabilities and networks that are easily penetrated.

Back in 2000 I was Vice Chair of what became an [Internet 2 Presidential Commission](#). Before that, in the mid 70s I got the job after coming from MIT to DC to sneak the ARPA net onto the Intelsat satellites. So I guess I have been working this issue for 40+ years. I may know something.

As to the above statement, the key fact is that the TCP/IP protocol developed in 1974 was done to deliver an open system, with the smarts at then end user location. The "security" of the network depended on physical security of the links, if you wanted it, otherwise it was intentionally OPEN! Now what the author means by "hackable internet protocols" is unknown. The protocols are open, they are known, and unless you physically secure the fiber, copper, wireless channel, it is open, never was meant to be secure. DoD has an IP network, but the links do not connect to the open public network. They have massive firewalls etc. But a router is like a public toilet, anyone can drop by an perhaps you want to go before you leave home. Sorry for the analogy.

Security is multilayered. Always has been. In the early 70s we had developed secure operating system kernels. The fear was that somehow an application could penetrate the OS and the kernel. So now nothing is new.

It is NOT the networks that are easily penetrated now, they were designed that way! Only wish these non-techys would walk down Mass Ave and speak with someone, anyone! Oh well, it is the NY Times and Harvard, what to expect?



Labels: [Internet](#)

[Guest Editorial](#)

NOTE: This Editorial is from [my friend Antnee, my local squirrel savant and historian](#). He has asked that we post this and frankly I take no position here. Also Antnee is an avid Breitbart reader so for any of you who would object please forward them directly to him at antnee@telmarc.com

To whom it may be concerned:

I have just finished a [Breitbart news piece](#) which I find offensive. Not from Breitbart but from the airline. They state:

A video showed a Frontier Airlines employee and police escorting the woman off of the aircraft at Orlando International Airport after she brought the animal onto the flight bound for Cleveland Tuesday evening. The passenger stated in her Frontier Airlines reservation that she would be bringing an "emotional support animal" on board the flight, but did not specify that it was a squirrel. Frontier Airlines said in a statement that "rodents, including squirrels, are not allowed" on flights. Airline staff discovered the squirrel, advised the woman of the airline's policy, and asked her to leave the flight.

First and most importantly the airline calls us "rodents". That is a fallacy, we are squirrels, rats are rodents, we are squirrels. We resent being called the "R" word. Do you see any New Yorkers resting and feeding rats? No. They feed squirrels, and we help them relax. We are a comfort animal if there ever were any. Go to Central Park and what do you see, young children feeding us and we entertaining and loving these young humans! If we were the rodents the airline contends then would any reasonable parent allow this? No! Argument over!

Police escorts! How tragic. We squirrels strongly object to this form of speciesist behavior. After all, we are in close daily proximity with all humans. Admittedly some humans have selected us for their meals, I understand that humans have even consumed other humans, but after all we cannot all be human.

So the next time this despicable type of anti-species behavior occurs, I suggest we find whoever makes all those great signs and hats and have a march on Washington!

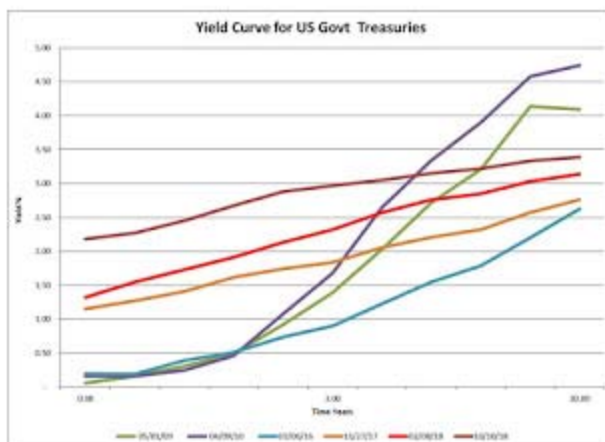
Thank you for your time,

Antnee Squirrel



Labels: [Commentary](#)

[Yield Curve](#)



The several yield curves are shown above. The FED is slamming up the short term yield to brake inflation, even though we do not see any. We have gone from a FED who was out to lunch to a FED eating our lunch.



The above is the comparison over the last decade since the great Bush Collapse. The spread is dropping and the curve flattening. The worst problem is that most of our debt is short term and thus interest costs are exploding. So far no one has commented on this one.



Labels: [Yield Curve](#)

[Same Word, New Meaning?](#)

Having spent time studying Thomistic Philosophy, a painful intellectual experience if ever there was one, I was a bit surprised when I saw an article in [NEJM](#) entitled:

Classification, Ontology, and Precision Medicine

Now I know the meaning of classification and precision, but ontology was the study of "being". The Ontological Proof of the Existence of God and all that. But here the authors have abandoned this millennial old meaning to define it as:

Ontologies are systematic representations of knowledge that can be used to integrate and analyze large amounts of heterogeneous data, allowing precise classification of a patient. In this review, we describe ontologies and their use in computational reasoning to support precise classification of patients for diagnosis, care management, and translational research.

Got that? I have had to read this more than a dozen times, through my mild dyslexia and all, still do not get it. I think I get the point they are making that we now have vast amounts of data on patients and that data may dramatically change the way we do diagnosis. No surprise there.

So just what are these "systematic representations of knowledge" they are opining about? Well we have all this data, not that I would call it "knowledge". It seems that every time we have a discovery of some new gene interaction in say cancer, a few months later there is another. Add to that the networking of these genes, then add to that the in vivo interaction, and so forth. I suspect we may have just begun to understand some issue in cancer, some very few, but important issues.

The problem however is that data is not knowledge. Eliciting from data fundamental principles and then validating them and then creating "tools" to measure then is critical. Even then the tools we have to measure stuff may elicit a cloudy picture, take the PSA test as a simple example.

The authors further state:

Conventionally, most of us think about structure as the arrangement of data, either on an EHR screen or as a database schema behind the scenes. Semantics, in turn, refers to concepts and the relationships between them. Software systems require assertions about term equivalence. ... Semantics and structure are not orthogonal but deeply intertwined.

Again I think I get the point. Syntax is how we put words together to form a sentence, semantics is how we obtain meaning from the sentence. At least that is what it was sixty years ago when I first grasped the idea. They conclude:

The second barrier is the cost and effort of getting data into and out of EHRs. Manual input of structured data by clinicians is not scalable and is not a good use of clinicians' time. Emerging efforts on standard application interfaces with EHRs from devices and data sources could help, as could patient-collected and patient-entered information. Systematically harvesting signs, symptoms, severity, and other clinical details from dictated notes or even from audio capture of the patient encounter is becoming increasingly practical.

I believe it is fair to say that the EHR was not to be used by anyone professionally but was developed as part of the OCare system to oversee physicians and hospitals. Fundamentally as we have argued for over a decade the implementation and execution if fatally flawed. It is not patient centered. It is a check mark that all providers must meet. "Meaningful Use" is the greatest misnomer in the world. It just added costs to the system without any fundamental benefit. Thus this conclusion is useful but limited.



Labels: [Electronic Medical Records](#), [Health Care](#)

Sunday, October 7, 2018

Highway Billboards?

I have had a few Kindles over the years and this one seems unique. I went and got a [new one](#) due to the features promised. Technically it works well. Not great but well. It has a good wifi/bluetooth system, it has a reasonable email and web browser. Not great but OK. It seems quite well built and very light. It charges well, and seems to hold the charge. I got it to update the older one I had which works fine but I thought a bit heavy and wanted to see what was new. Overall I am satisfied with the platform.

However, I am reminded of all the billboards on roads when I was a kid in the late 40s and early 50s. Billboard after billboard, garish sign after garish sign, and then strip malls along every highway in New Jersey. It made a Garden State landscape into a cluttered entry to Hades. How does this relate to this device, simply Amazon has packed everything into it to sell you something. There are apps for everything and anything they want to pitch. Take audible, I read, I write (17 books) but I do not waste time listening to someone preach about a book. So why can't I get rid of this? Took an hour to find out but I think I did. Then they push the Washington Post. Stop already, if I want to read the Post then I will, do not shove it down our throats.

Then come the game pop ups. Seems every time you restart, not reboot, you get endless pop ups for games. I do not play games, and I certainly have no interest in the onse Amazon is pitching. Yet each time you go to the Kindle another few horrible games.

Then, wallpaper! It seems that computer programmers think every use wants a nice picture of some scene for wallpaper. No, I just want to find what I am looking for and not to have to wander through useless visual dissonance! Solution is simple. I took a picture of a black poster board and used that. Worked well.

Finally, there is no instruction manual. I had to resort to the old computer dictum; if all else fails, getting a computer to work is like sex, just keep pushing the buttons until it works (sorry for the digression but it was an old MIT rule).

So is it worth it? On the one hand, yes, cheap, and if you are willing to work through the chaff, it is not bad. On the other hand I am bringing my old first generation Kindle with me, not this one. Pity, in my opinion a great platform got ruined by over exuberant marketing types, and wild "if I like it, everyone must like it" millennials.



[Goldman Sachs Management Techniques](#)

1 [The Squirrel's Nest](#) by Terry McGarty / 19d // keep unread // hide

1 Insights

Add note

As demonstrated by the NJ Governor, it is "hire a consultant". The [Report](#) demonstrates that NJ Transit is a mess! Well folks that did not require a consultant. This is what a banker does when he has no clue what to do, hire a consultant.

Guys, you already have a CEO, paid millions. What is this fellow supposed to be doing. I have seen this approach with grossly incompetent management before. If you are clueless, even if its your job, hire the consultant. Then "get out in front of it".

The [NY Times](#) report is spot on. But the Governor must act. Otherwise the State will totally collapse. It is the people making money who keep the State out of bankruptcy. Prohibit them from doing so is suicide. Giving speeches may work in investment banking but not running a rail road.

You see, people have been running railroads for centuries. But when the management is politically appointed and often have great payouts no matter what they do, what would one expect!

Add to this the AMTRAK incompetence and off you go.

What NJ Transit needs is a hard fisted operations manager, not another suit and friend of the Court. The Governor must sooner than later come to the understanding of how the real world functions.

Oh yes, the Time notes:

The agency is so focused on trying to run its trains and buses safely and efficiently that "customers often come as an afterthought," the report said. When they do receive information about delays and their causes, it is often inconsistent, the report said. Some information about changes is posted to social media platforms before it is shared internally, leaving conductors and bus drivers unprepared to answer questions from riders, it said. "We know we have to communicate better," Mr. Corbett said. He said that the agency had created a "war room" for managing communications with customers and that "information is now being sent out to customers quickly and more accurately."

First, try and understanding any of the voice notices anywhere.....

Second, they are cancelling trains left and right, try and find out where and when. The management of NJ Transit almost takes delight in mass crowds at Penn Station wondering if they must swim across the Hudson.

Third, with all the means to communicate, try and find some competent person, not some one's cousin in need of a job to take responsibility.

NJ Transit and the Governor make New Jersey appear as Venezuela, Oh yes, it did not just start, that fellow before him refused the build another tunnel....remember that folks! No one in Government has had any real job experience it appears. Pity!

Saturday, October 6, 2018

[Microsoft, Arendt, and The Banality of Evil](#)

Hannah Arendt wrote her work on the banality of evil. It is worth reading, banal being dull, unimaginative. Microsoft has apparently issued its latest update of the computer destroying Windows 10. I personally have two dead laptops resulting from this monster. In this case, in my opinion and based upon my experience, the evil is the destruction of hardware, software, most importantly peoples' productive time. One should question how many human years of creativity are lost due to the shabby software handed down from this company.

[PCWorld](#) announces the latest destroyer of cyber entities. They note:

Microsoft is slamming the brakes on the Windows 10 October 2018 Update's rollout. The upgrade became available during the company's Surface event on Tuesday, but in the days that followed, numerous users across the web reported that the transition deleted massive chunks of data. User profiles and entire folders full of files went missing in some cases and rolling back the upgrade didn't restore them. Now Microsoft is temporarily halting the October 2018 Update's distribution due to the issue. "We have paused the rollout of the Windows 10 October 2018 Update (version 1809) for all users as we investigate isolated reports of users missing some files after updating," Microsoft's support page for build 1809 says.

Release after release destroys computers and data. This time in a real big way. Perhaps Microsoft should hire some competent software testers. Really, it is not hard. The company seems to be in free fall.

One suspects that sooner or later there will be a massive class action suit, despite the unread user agreements. Think "contract of adhesion".

One is almost forced to use Microsoft. It is in my opinion a monopoly if ever there was one. It consistently issues updates that cause in my opinion and in my experience irreparable harm. And it appears that it just does not care!



Labels: [Microsoft](#)

Friday, October 5, 2018

[Endless Incompetence](#)

NJ Transit, the State owned run and managed notes as usual:

Train service in and out of Penn Station New York is subject to 45-minute delays following yesterday's (sic) minor, slow-speed train derailment near Penn station.

What is a "minor" derailment. Less than 100 fatalities, a broken finger nail?

At some point and at some time there must be a come to meet the Lord moment. Hopefully it is still when we are alive!

Also infrastructure improvement can be done with bonds, but the longer these folks wait the greater the costs of the bonds, higher interest rates. Just a few years ago would have been perfect, but Government run entities seem to be incapable of doing anything. Pity.



Labels: [Government](#)

Thursday, October 4, 2018

[So What is New?](#)

[Bloomberg](#) news reports on China planting microchips in computer mother boards for the purpose of cyber whatever. They state:

The companies' denials are countered by six current and former senior national security officials, who—in conversations that began during the Obama administration and continued under the Trump administration—detailed the discovery of the chips and the government's investigation. One of those officials and two people inside AWS provided extensive information on how the attack played out at Elemental and Amazon; the official and one of the insiders also described Amazon's cooperation with the government investigation. In addition to the three Apple insiders, four of the six U.S. officials confirmed that Apple was a victim. In all, 17 people confirmed the manipulation of Supermicro's hardware and other elements of the attacks. The sources were granted anonymity because of the sensitive, and in some cases classified, nature of the information. One government official says China's goal was long-term access to high-value corporate secrets and sensitive government networks. No consumer data is known to have been stolen.

And you are worried about Russia. The US has been trusting on the kindness of strangers in China since the beginning of the Clinton Administration, This even extended to critical infrastructure and defense and intelligence elements. So what did they expect. Out telecommunications business are defunct and reside in China. This is akin to relying on Russian launch vehicle to protect us against a Soviet attack. Nothing new, it is just Government.

Now if you think this is bad hold on to your hat. Massive amounts of our pharmaceuticals are made in China! Yes, key drugs. China has developed with the help of US educational institutions a massive and world class pharmaceutical capability. That means two things. First they can run circles around us. Second, and this is critical, then can put into therapeutics all sorts of other stuff to do everything from creating massive cancer outbreaks to mind control. They do not need Facebook, that have half the population in the US hooked on their drugs, and I am not speaking of opioids.

Would we have allowed this in the Cold War with Russia? No. So why do we allow this with a declared adversary? Profit? For whom and of course at what cost.

This will make a great suspense novel. Can't wait to get started. And, oh to you folks out there with whatever derangement syndrome you profess, than Beijing, I think.



Labels: [China](#)

Monday, October 1, 2018

[Surprise!](#)

NJ Transit is undergoing upgrades. That means trains will be randomly cancelled. There does not appear to be any schedule. The current notice states:

Beginning Sun. Oct. 14, some trains will be temporarily discontinued or have changes of origin/destination. This will impact customers along the NEC, NJCL, M&E, MOBO & MBPJ Lines. These adjustments are temporary and we anticipate service to be restored mid-Jan. All tickets and passes for travel in November, December and January will receive a ten percent discount.

But, and this is a great BUT, they will tell you NOTHING about what will happen where or when. Only when you get to the station will you, if lucky, find out what train is running.

Our new Governor is fully behind this move of gross incompetence. Yep, up go the taxes, and to hell with the taxpayers. And one wonders why people despise politicians. Washington is not the worst place, it has become pandemic.

Perhaps they should recall that Mussolini made his move based upon getting the trains to run on time. That was a century ago.

As a side note, this was supposed to be done over the summer. Apparently the grossly incompetent management of the State owned and run transit system just let the ball drop. Who says it will be done by January. In your dreams!

Where is Benito when we need him?



Labels: [Government](#)

Sunday, September 30, 2018

[5G Security](#)

In a recent Analysts Meeting reported by [Total Telecom](#), Verizon is noted as:

“Verizon’s view of the role of 5G in its enterprise services portfolio goes several steps further. Its view is that with the advent of 5G, the Internet of Things (IoT), along with SDN, video, security telematics, and edge computing, will expand to become a foundational enabler of the real-time enterprise (RTE), in which businesses can exploit information, actions and events the moment they occur,”

Now I am a strong promoter of wireless and 5G, whatever it turns out to be when first out the gate provides a wireless Gbps platform which can be rapidly deployed.

However, and this is critical, there are two concerns.

1. Security: Unlike fiber which can be made physically secure, yet still subject to interjection physically, 5G wireless opens itself up to massive interdiction via sophisticated jamming. It is highly vulnerable and if one were ask an investment back to move from fiber to 5G I suspect and I hope there would be a great deal of soul searching. The vulnerabilities of 5G are minion. This is not a marketing gimmick, it is a real full time job. Hopefully they have someone who can do this.

2. Functionality: Here I fault Verizon for not addressing a simple problem. Namely in their current 4G system they "sell" a 4G replacement for a wireline phone. EXCEPT! It is NOT a replacement. It is a spit and bailing wire design that fails to replicate what the wireline phone does. No 911, no caller ID, one phone or extension per 4G unit, etc. Whoever designed this should be sent back to the minors, or worse. But this is a harbinger of what can happen in 5G, but many times worse. Verizon in my experience lacks the competence in blending technology and marketing into product design. It is outsourced and thus they rely on the "kindness of strangers" to get it right. This may be a bump in the road for residential users but it could be a business killer for the high end business.

One can say, enough with the buzz words from the pitch masters and try to adhere to the old dictum; if all else fails listen to the customer!



Labels: [Telecom](#), [Verizon](#)

Friday, September 28, 2018

[Chaplains](#)

I spent some decades on and off at MIT, even got married there. But never met any chaplain. The minister at our wedding was a local we got to meet. From across the river in Back Bay.

But now [MIT appoints a Chaplain to the Institute](#). I do not have any horse in this race, but it is amazing that this appears to be another high level employee along with a slew of others. One wonders why the tuition keeps expanding. One could guess that with all the churches and synagogues in and around the Institute that one could find a place for worship and solace and not have to add substantially to the head count.

It is quite obvious to see how explosive the growth of non academic sinecures have been at MIT and elsewhere.

I guess no one goes to Mass barefoot in the ice and snow during Lent anymore.



Labels: [Academy](#)

Monday, September 24, 2018

Obesity and Error; A Tale of Political Correctness gone Astray

In a long piece in what seems in my opinion to have become the world's paper of scientific record, The Huffington Post, a major contribution to humanity brought to you by Verizon, is a lengthy article on obesity, and apparently why all of science and medicine are in error¹¹[1]. Now the current view is that for the most part, significant endocrine pathologies excluded, obesity is a simple input less output issue. Eat more, burn less, gain weight. Second, obesity triggers a plethora of cell pathway damages and assaults, including but not limited to an explosion of reactive oxygen species. We have written about this extensively¹²[2].

One simple and continuously provable result is in Type 2 diabetes. Drop the BMI below say 23 and the HbA1c drops back to a normal range below 5.5. The net result is the sequella common in that disease also often disappear. That is just one provable example.

In the UK a recent report by Cancer Research UK notes¹³[3]:

And if these trends in the number of cases caused by these risk factors continue, overweight and obesity could overtake smoking as the biggest preventable cause of cancer in women by 2043. While the gap between obesity and tobacco as causes of cancer in men is also expected to narrow in the next 20 years, there's still a way to go before they cross over. And it's too soon to

¹¹[1] <https://highline.huffingtonpost.com/articles/en/everything-you-know-about-obesity-is-wrong/>

¹²[2]

https://www.researchgate.net/publication/265206539_Obesity_and_Type_2_Diabetes_Cause_and_Effect?_sg=dV5aHikCis5L_AYSHTRyuj_b-tWlxvaMaljvpPEMWpPKO8anCOj4WS4T9Q26u9sism0fkWnpz01s3jTVOjPuRE5TDL4IqU_KsFuM-AIu.TlZzoo4W12VLPWh26RtmAlF8uXfC1cSrSw7dydyhHxvOLMRTn_ZvcZsU8Dwlg4t8SqXkvZ-jamIOnKAhrj7mpQ

¹³[3] <https://scienceblog.cancerresearchuk.org/2018/09/24/how-we-estimated-when-obesity-might-catch-smoking-as-the-top-cause-of-cancer/>

estimate when this might happen. The crossover is likely to happen earlier in women for two reasons. First, more men smoke than women. And that means there are more smoking-related cancers in men. In 2015, 18% of cancer cases in men were caused by smoking, compared with just 12% in women. And while men are also more likely to be overweight or obese than women, obesity has a bigger effect on women in terms of cancer. Some of the most common types of cancer caused by obesity are breast and womb cancer, which predominantly affect women.

The writer in the above mentioned Huffington Post peer reviewed (?) scientific article goes at length to argue that obesity is not self-inflicted and that obese people are more often healthier than those of lesser girth. That would be just fine if and only if the clear and demonstrable costs of obesity were not borne primarily by those who themselves struggle to maintain a reasonable weight and avoid the multiplicity of sequella to high BMI. Frankly if health care costs were borne by each individual as they occur to that individual, and there is no secondary effect of their behavior on others, no externalities so to speak, then frankly anyone should be able to do anything. Unfortunately the same people demand Medicare for all, as such those costs would explode.

The same people who felt no compunction to shaming smokers, a truly valuable action considering the decline in death rates in males, seem now to think any form of negative connotations regarding an often self-inflicted condition which also all too often results in massive health care costs, borne by all, is not only socially unacceptable but tantamount to criminal. Furthermore, like so many of the "unacceptable" position it is also worthy of assault on those who demur.

We seem to entering a generation tsunami where what one says must be true no matter what and facts be damned. Even more so, anyone who dares to use science and facts, other than to reinforce the position of the week is anathema.



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

Sunday, September 23, 2018

[Why Does Dell Make It So Hard to Buy Something?](#)

I have been buying Dell Computers since they started selling, very early 1990s. We have had hundreds and hundreds over the years. As a business customer you have to go to a business line. But that you get to via their normal line.

Now here is the problem.

1. All customer services now use IP telephony. Sorry but I started this some 25 years ago globally, and I presented a paper some 20 years ago in Italy about the poor quality of IP voice. Well it has just gotten worse. Really, old copper had great voice quality. The old Bell System

was proud of that. Then came the Internet and digitized compressed voice.

2. Then add to this the fact that they must outsource everything to India. Add the packet delay, to the voice compression, to the accent, to the lack of understanding of English, to the fact that they use scripts...well you see where I am going.

3. After a long period it became clear I could not buy a computer from them, I had to wait till a week day and speak with the business sales.

4. I sent an email asking what number and when to call, this is what I received:

*****THIS IS AN AUTOMATICALLY GENERATED ACKNOWLEDGEMENT - - DO NOT REPLY*****

Thank you for contacting Dell's Pre-Sales Support. We've received your message and look forward to serving you!

5. Got it folks, but who do I call and when to get served? Really, no clue from this message.

I do not think Dell really wants to sell anything, at least to the small business person. Over the years we spent about \$20 million but to Dell we must be a pimple of the ... of eternity to get their attention. Hopefully someone is home there at sometime.

I just want to buy something folks! Hello, anyone there?



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

Saturday, September 22, 2018

[Some Thoughts from Alice in Wonderland](#)

'No, no!' said the Queen.

'Sentence first—verdict afterwards.'

'Stuff and nonsense!' said Alice loudly. 'The idea of having the sentence first!'

'Hold your tongue!' said the Queen, turning purple.

'I won't!' said Alice.

'Off with her head!' the Queen shouted at the top of her voice.

Nobody moved.

'Who cares for you?' said Alice, (she had grown to her full size by this time.)

'You're nothing but a pack of cards!'

At this the whole pack rose up into the air, and came flying down upon her: she gave a little scream, half of fright and half of anger, and tried to beat them off, and found herself lying on the bank, with her head in the lap of her sister, who was gently brushing away some dead leaves that had fluttered down from the trees upon her face.



Labels: [Politics](#)

[Gallicanism Redux](#)

Gallicanism is the practice of the French selecting their own bishops. Henry VIII had two beefs with Rome. One was a succession issue, related to his first marriage, an issue oftentimes taken care of by Rome in a slight of hand, and the second was the fact that Rome controlled the Church in England but allowed the French to do whatever they liked. Gallicanism if you will, albeit a stretch.

Back when Gregory I became Bishop of Rome he was elected by the people of Rome, despite his protests. There were no cardinals and in fact Gregory was subservient to the Emperor in Constantinople.

Then along came a variety of Popes who created cardinals, often not even priests, but princes of the Church, who got the exclusive right to elect the Bishop of Rome, who in the 14th century lived in Avignon, having been expelled by the people of Rome. Strange tale.

But for the past centuries Papal authority ruled and Rome and the Pope selected and elevated bishops, and cardinals. Gallicanism was obliterated during Vatican I.

Now comes China. The [NY Times](#) reports:

The Vatican said Saturday that it had reached a provisional deal with the Chinese government to end a decades-old power struggle over the authority to appoint bishops in China. It was the Communist country's first formal recognition of the pope as leader of the Roman Catholic Church in the world's most populous nation, Vatican officials said. Under the breakthrough, Pope Francis recognized the legitimacy of seven bishops appointed by the Chinese government. Because they had not been selected by the Vatican, they had previously been excommunicated. The deal was in keeping with pope's outreach to parts of the world where he hopes to increase the church's presence and spread its message. It gives the church greater access to a huge population where the growth of Protestantism is far outpacing Catholicism. But for critics loath to share any of the church's authority with an authoritarian government, the deal marked a shameful retreat and the setting of a dangerous precedent for future relations with other countries.

Is this truly a bad situation? Frankly from history's perspective, one could say so. People choosing their own bishops was not a bad idea. It was democratic. Popes selecting them was a

remnant of divine right of Kings. Nations having a say, one could note, led to revolutions, specifically the French Revolution, not to mention Henry VIII, and even Martin Luther.

It will be interesting to see how this one is justified. But perhaps for the papacy, consistency is the hobgoblin of petty minds, kind of.



Labels: [Papacy](#)

Friday, September 21, 2018

[What is the Internet?](#)



In [1990 I wrote a paper](#) looking at what was then called NREN, and now the Internet at Harvard. It [Audience](#) described what I had been working on at MIT and NYNEX, now Verizon, and before that at COMSAT, the ARPA Net, as a distributed open network.

Then in 2000, as I was building our my Internet backbone company in 20 countries I was Vice Chair of a [National Academy Study](#) on the future of the Internet. Eric Schmidt was Chair. As I note then,

The Internet is a composite of tens of thousands of individually owned and operated networks that are interconnected, providing the user with the illusion that they are a single network. A customer who purchases Internet service is actually purchasing service from a particular Internet service provider (ISP) connected to this network of networks. The ISP in turn enters into business arrangements for connectivity with other service providers to ensure that the customer's data can move smoothly among the various parts of the Internet. The networks that make up the Internet are composed of communications links, which carry data from one point to another, and routers, which direct the communications flow between links and thus, ultimately, from senders to receivers. Communications links to users may employ different communications media, from telephone lines to cables originally deployed for use in cable television systems to satellite and other wireless circuits. Internal to networks, especially larger networks, are links—typically optical fiber cables—that can carry relatively large amounts of traffic. The largest of these links are commonly said to make up the Internet's "backbone," although this definition is not precise and even the backbone is not monolithic.

Namely the Internet as we understand it and use it is merely an agreement on the use of the TCP/IP protocols. Local ISPs connect us up the chain eventually to a Tier 1 carrier who peers with others allowing ultimately universal connection. Now anyone can do the same thing but not allow universal interconnection. It is called using a Firewall. The Chinese use it all the time. I suspect this Blog is firewalled. As is I suspect many of my papers as are other academic papers.

In that report we further noted:

- *“Hourglass” architecture. The Internet is designed to operate over different underlying communications technologies, including those yet to be introduced, and to support multiple and evolving applications and services. It does not impede or restrict particular applications (although users and ISPs may make optimizations reflecting the requirements of particular applications or classes of applications). Such an architecture enables people to write applications that run over it without knowing details about the configuration of the networks over which they run and without involving the network operators. This critical separation between the network technology and the higher-level services through which users actually interact with the Internet can be visualized as an hourglass, in which the narrow waist represents the basic network service provided by the Internet and the wider regions above and below represent the applications and underlying communications technologies, respectively.*
- *End-to-end architecture. Edge-based innovation derives from an early fundamental design decision that the Internet should have an end-to-end architecture. The network, which provides a communications fabric connecting the many computers at its ends, offers a very basic level of service, data transport, while the intelligence, the information processing needed to provide applications, is located in or close to the devices attached to the edge of the network.*
- *Scalability. The Internet’s design enables it to support a growing amount of communications—growth in the number of users and attached devices and growth in the volume of communications per device and in total, properties referred to as “scale.” Nonetheless, as is discussed below, the Internet currently faces and will continue to face scaling challenges that will require significant effort by those who design and operate it.*
- *Distributed design and decentralized control. Control of the network (from the standpoint of, for instance, how data packets are routed through the Internet) is distributed except for a few key functions, namely, the allocation of address blocks and the management of top-level domain names in the Domain Name System. No single entity (organization, corporation, or government body) controls the Internet in its entirety.*

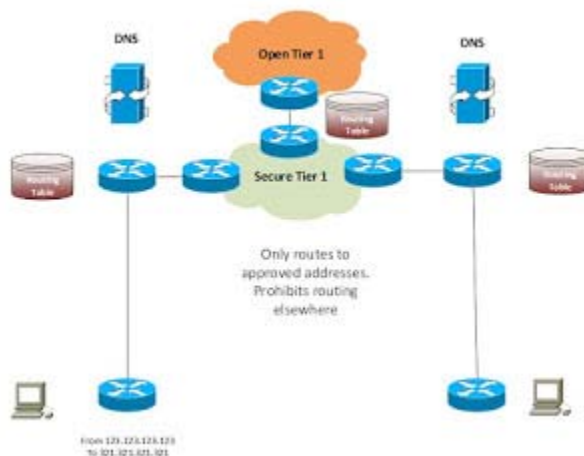
Now [Schmidt](#) makes the news stating:

"I think the most likely scenario now is not a splintering, but rather a bifurcation into a Chinese-led internet and a non-Chinese internet led by America. If you look at China, and I was just there, the scale of the companies that are being built, the services being built, the wealth that is being created is phenomenal. Chinese Internet is a greater percentage of the GDP of China, which is a big number, than the same percentage of the US, which is also a big number. If you

think of China as like 'Oh yeah, they're good with the Internet,' you're missing the point. Globalization means that they get to play too. I think you're going to see fantastic leadership in products and services from China. There's a real danger that along with those products and services comes a different leadership regime from government, with censorship, controls, etc. Look at the way BRI works – their Belt and Road Initiative, which involves 60-ish countries – it's perfectly possible those countries will begin to take on the infrastructure that China has with some loss of freedom."

Then is it an Internet? It lacks the above characterizations. It may be a large but private network where one must play by a certain set of rules. There is no CCITT entity like the old telephone networks. Yes you can have a closed network. In fact that is what we should have for banks, power utilities and the like. But then it is not the Internet.

We show this below. If the router tables are controlled and limited and if the Tier 1 is also blocked to other Tier 1 networks then one can't get anywhere but to an approved site. Simple.



In fact DoD has just such a network. It carries DoD traffic. It has done so since the mid 1980s.

Thus is this some new insight? Hardly. It is what you would expect from a Totalitarian state. Even Russia has a bifurcated network, and I assume that China does already. The Internet is an architecture, a way for building. Its embodiment may be open to all or open to a few. It really was never made to be secure, quite the contrary. If one had access then one had access. However getting access can be made non-trivial.

Therefore, we should expect, and in some cases such as banking and utilities, a multiplicity of "Internets". Some quite secure and one or more fully open. There is no surprise there at all.



Labels: [Internet](#)

[Academics and the Abstract](#)

In a recent piece in [The Tech](#), the MIT student newspaper, they note:

Principal Investigator of the Geometric Data Processing Group at MIT, is a prominent member of the Metric Geometry and Gerrymandering Group (MGGG), a cohort of Boston-based computer scientists and mathematicians that are leveraging modern computing power to study the problem of fairness in redistricting with a level of quantitative rigor that has not been possible until recently. "From my perspective, one of the big challenges in redistricting is that we lack clear, quantitative standards for evaluating the fairness of redistricting plans".... "For that reason, there's no clear path to a standard that's easily enforceable and understandable."... "Our effort, broadly, is... to assemble a clear set of standards and a way to talk about the redistricting problem in a fashion that's quantitate and that's fair and easy to apply," he told The Tech. "That includes a lot of different aspects. Everything from understanding the shape of a district and what bearing it has on the outcome of the vote... to understanding the big space of all the different ways of dividing up a state."

A laudable goal but it all seems to hinge on the definition of fair. Somehow this group knows what "fair" means and they have some algorithm to ascertain such. This is akin to defining "justice" an argument that has befuddled philosophers and political and legal scholars for thousands of years. But not to worry, these folks have the answer, just trust the.

Is then no wonder that most people look askance at these "academics". The key reason is that there is a gross lack of reason in my opinion. My fairness most likely is not your fairness. As we see in today's vitriolic politics, fair for me is not fair for you, and whatever!

Words mean something.



Labels: [Academy](#)

Thursday, September 20, 2018

[Smashing Pumpkins, Real Ones](#)

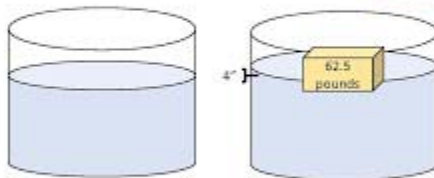
One of my grandchildren was asked by their teacher to design an experiment to show how helium filled balloons can allow a pumpkin to descend from an 11th floor building and not smash. The first question I asked myself was; how does one do this? The second question was; does this teacher have any idea what she has asked High School freshman?

Now I spent some time trying to solve simply, say for a 9th grader, this problem. So here goes:

1. Lets start with Archimedes, this will be used again and again.

Archimedes Principle:

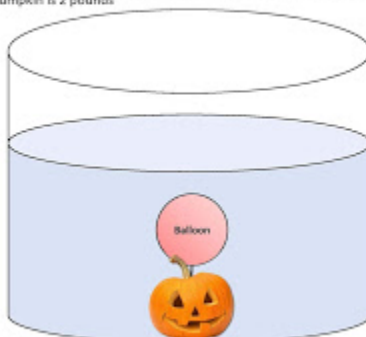
An object displaces an amount of water equal to its weight.



Water density is 62 pounds per cubic foot.
 Radius of container is 1 foot, area is 3.14 sq feet
 Increase in height is 4" or 0.333 ft
 Volume increase is 0.333 times 3.14 or about 1 cu ft
 Weight displaced is then 1 time 62.5 or 62.5 pounds

2. So we know that the mass displaced equals the mass in the water. The same principle happens with buoyancy when the balloon is submerged and one seeks the upward force. Now add the balloon, filled with helium, and attach it to a pumpkin. The total is in a gas or fluid so Archimedes applies.

Now to keep the balloon with a pumpkin just fixed and not moving, I need to have the total density of the pumpkin and the balloon to equal that of water. Assume the balloon is 3" radius. Then its volume is $(4 \cdot (1/4) \cdot (1/4) \cdot (1/4))$ or about 0.2 cu ft. Assume pumpkin is 2 pounds.



3. Now consider the dynamics of the system and so introduce Newton.

Conclusions

- If you use the solution shown the balloon and pumpkin will stand still
- If you have bigger balloon the combo will rise
- If you have a smaller balloon the combo will fall
- The smaller the balloon the faster the fall
- From Newton's law if the balloon is not there the time is:



$$s = \frac{1}{2}gt^2 \text{ or}$$

$$t = \sqrt{\frac{2s}{g}} \text{ where}$$

$$g = 32 \text{ ft/sec}^2$$

4. Then logically as you increase the balloon size you slow its downward speed and at some point it will actually rise.


But Force must include Balloon

$$F = F_{gravity} - F_{balloon} = m_{pumpkin} a_{pumpkin}$$

$$m_{pumpkin} a_{pumpkin} = gm_{pumpkin} - F_{balloon} = m_{pumpkin} \left[g - \frac{F_{balloon}}{m_{pumpkin}} \right]$$

$$= m_{pumpkin} g^*$$

thus

$$t = \sqrt{\frac{2s}{g^*}}$$


5. This then yields a simple solution. I think.

Finally!

$$F = F_{gravity} - F_{balloon} = m_{pumpkin} a_{pumpkin}$$

$$m_{pumpkin} a_{pumpkin} = gm_{pumpkin} - F_{balloon} = m_{pumpkin} \left[g - \frac{F_{balloon}}{m_{pumpkin}} \right] = m_{pumpkin} g^*$$


$$F_{balloon} = g\rho_{air}V_{balloon} - g\rho_{He}V_{balloon} = g(\rho_{air} - \rho_{He})V_{balloon}$$

$$g^* = \left[g - \frac{F_{balloon}}{m_{pumpkin}} \right] = \left[g - \frac{g(\rho_{air} - \rho_{He})V_{balloon}}{m_{pumpkin}} \right]$$

or

$$g^* = g \left[1 - \frac{(\rho_{air} - \rho_{He})V_{balloon}}{m_{pumpkin}} \right]$$

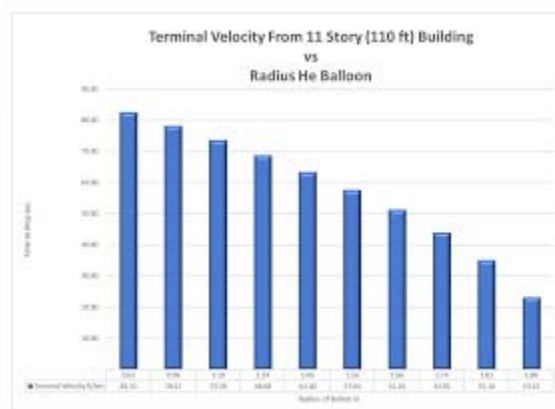
thus $t = \sqrt{\frac{2s}{g^*}}$



6. If we then ask the question as to size of balloon and weight of pumpkin you get:



and the following:



7. Finally there is the issue as to how slowly must the pumpkin reach the ground so as not to smash. Namely what kinetic energy is the maximum to not smash the pumpkin. Welcome to an experiment.

8. Having spent time on this issue I then wondered where this teacher was coming from. Perhaps this was a game, but in reality it can be a great learning exercise, only if they knew what they were doing!



Labels: [Education](#)

Wednesday, September 19, 2018

[Jansenism, Politics, and Today](#)

Jansenism was a revamped version of Augustine's theology of Grace. Grace was discovered by Augustine in his readings of Paul, especially in Romans. To Augustine all men have sinned against God and no matter what they do on their own there is no salvation, just perdition. It is only through the gift of Grace by God that you are saved. To carry it a bit further, you never even knew whether you had gotten that gift. Calvin and Luther took this as the basis of their theology, and Calvin to the extreme.

In contrast the Jesuits were to be the "army" of the Pope, and in turn they also became the defenders of the monarchies. Through their schools they educated the future kings, princes, bishops and cardinals. Ant added to that they became the confessors to kings. Nice job if you can get it, and get it the Jesuits did.

Needless to say the Jesuits never really warmed to Augustine and this grace thing. They were in many way neo-Pelagians, namely that one's good works would count and further that Christ came to save all mankind, not just those unknown few. That made kings, and shall we say queens, quite happy.

Now needless to say this was to be a battle to the death. The Jansenists inspired in the people a dislike of the monarchy and one could argue that they were one of the multiplicity of causes of the French Revolution. Such a battle did not ensue in the United States because we eschewed any religious preference, a good idea.

In the classic work of Doyle, *Jansenism* (St Martin's Press, 2000) he notes:

Hitherto, most of Jansenism's history had been a catalogue of heroic failure or persistence against the odds; but this was a clear and total victory over the arch-enemy. Its cultural and educational consequences were enormous: 113 colleges were closed and those that reopened under new management were free to set their own syllabuses. The anti-clerical philosophes of the Enlightenment hailed the event as a great step forward for the emancipation of the human mind.

Indeed, in 1765 d'Alembert claimed philosophic credit for their overthrow in his pamphlet "On the Destruction of the Jesuits in France", by a disinterested author. Jansenists were outraged at this blatant attempt to attribute what they saw as the achievement of religious Truth to the influence of irreligion. In their eyes, there was little to choose between the laxities of Molinism and the free thought of Enlightenment. 'What is a true Jesuit', wrote Le Paige, 'if not a disguised philosophe, and what is a philosophe if not a disguised Jesuit?'

But d'Alembert knew what he was doing.

To allow the Jansenists the glory, he wrote to Voltaire, would be to boost the forces of intolerance. "The Jesuits, amenable people so long as you do not declare yourself their enemy, are quite willing to let you think what you will; the Jansenists, as rude as they are ignorant, want you to think as they do; if they were the masters, they would exercise the most violent inquisition over writing, thinking, words and deeds."

But the Jansenists were not the masters, and never would be. They were able to engineer the expulsion only because a dedicated handful of them were entrenched in the parlement and knew how to exploit its procedures and prejudices. Nor did Jansenists have much to do with the rest of the process that culminated in the final dissolution of the Society of Jesus by Pope Clement XIV in 1773. Once France had followed the Portuguese example, it became contagious.

Yes, the Jansenists were defeated and the Jesuits returned in all their glory. We have one as a Pope right now. But that is not the moral of the tale. What this tells us is d'Alembert's comment to Voltaire:

"The Jesuits, amenable people so long as you do not declare yourself their enemy, are quite willing to let you think what you will; the Jansenists, as rude as they are ignorant, want you to think as they do; if they were the masters, they would exercise the most violent inquisition over writing, thinking, words and deeds."

In today's political environment unfortunately we have a similar battle. One should beware however that soon after the Jansenists defeated the Jesuits, the Bastille fell, as did the head of Louis, and then we had Robespierre. Revolutions have a way of turning upon those for whom self-proclaimed righteousness tends to backfire.

History repeats itself. In such times one should always reflect back on what can happen to the overly righteous person.

Just a thought for today.



Labels: [Commentary](#)

Tuesday, September 18, 2018

[I hate Wasps, I like Bees](#)



Given the intense political environment, glad I left Washington years back, I will try to focus on lighter subjects like cancer and wasps.

Now the [BBC](#) has a piece on wasps versus bees. They note:

When asked to think of words associated with bees, the most popular for bees were "honey", "flowers" and "pollination". For wasps the most common words that came to mind were "sting", "annoying" and "dangerous". However wasps also pollinate flowers as well as killing pests and are just as important to the environment as bees. The problem, according to Dr Seirian Sumner, of University College London, who led the research, is that wasps have had a bad press.

Not really. Honey bees and Bumble bees are often too busy getting pollen and are rather un-

aggressive. On the other hand, the yellow jacket, a wasp like insect, hates humans. They see one then they attack. Kind of like Democrats...oops, sorry, I promised no politics.



Now bumble bees are kindly and furry, you can pet them when they are on the flowers. Honey bees are a bit like them but don't push it with them. But wasps, hornets, yellow jackets, they are mean, real mean.



Then again, perhaps the Brits mean WASPs?



Labels: [Bees](#)

Sunday, September 16, 2018

[Bees](#)

There must be a couple of dozen bee species, honey and bumble, in this collection. Enjoy! It is a chance to get away from all the things in Washington.



Labels: [Commentary](#)

Saturday, September 15, 2018

Storms, Housing and Floods



The above is a view from the beach on Staten Island where I was a Lifeguard for the City of New York some almost 60 years ago. That is Coney Island in the distance and to the right is the Atlantic Ocean. Further to the right and out of view is Sandy Hook New Jersey. Behind the beach was a small road and a few summer homes, in 1958. When Sandy hit they had raised the road some ten feet or more making the homes now a basin, so that when the water came in the water went into the basin and was not able to come out. That led to a flood.

The issue. Simple, Government did two stupid things. First they built the road creating a basin. Second they allowed hundreds of people to build houses there. From 1950 to 1955 there were multiple massive hurricanes, flooding the area. In Sandy a repeat but exacerbated by human ignorance.

Now the NY Times, one a good newspaper but now slowly becoming the rag of the week, but oh well let's try it, they note:

And when disaster knocks at the door, the bill is left to taxpayers who subsidize the National Flood Insurance Program. That money is often used to rebuild homes in the same high-risk locations. Unfortunately, given current insurance programs, rates that don't reflect the true risk in hazard-prone regions and the lack of incentives to persuade people not to live in these areas, the system we have is unsustainable. We need to be smarter about where we are developing and how we're doing it, building in resilience in any new construction in areas prone to weather and climate extremes. People who choose to live in high-risk areas should bear the cost when

disaster strikes. Of course, we should be helping people hit by big storms. But I'd rather see those dollars directed to hazard mitigation, and making existing and future development better able to withstand a disaster. Just because we can live somewhere doesn't mean we should. After all, as the saying goes, "The definition of insanity is doing the same thing over and over again, but expecting different results."

I would have to agree. We have allowed and underwritten many foolish buildings with known loss potentials. We actually subsidize them, through the taxpayer.



Labels: Government

Thursday, September 13, 2018

Science Humor

Now I will not comment but just refer you to the Science article on the IgNobel awards. I direct your attention to those in the medical area.

Hopefully this is all in good fun?



Labels: Commentary

A View of a Hurricane



The above is a recent NASA photo of the current hurricane.



Labels: NASA

Wednesday, September 12, 2018

EKG, ECG, Smartphone



In a recent announcement by Modern Healthcare regarding a smartphone vendor they note:

.... has received FDA clearance for its latest ..., which can now conduct electrocardiograms and deliver alerts if atrial fibrillation is detected. "This is the first ECG product offered over the counter, directly to consumers," ... announcing the "You can now take an ECG anytime, anywhere, right from your wrist." To measure the heart's rhythms, a user presses their finger against a button on the watch. After 30 seconds, the watch delivers a heart rhythm classification, telling the user whether their rhythm is normal or atrial fibrillation. The data are stored in the Health app on the (smartphone) From there, users can share the data in PDFs with their physicians. The watch and heart rhythm alerts fall under the FDA's purview because they provide patients with ECG data.

Now back in the old days of an EKG, the German based initials, one needed a twelve lead system. However if all you are doing is measuring Afib perhaps a 2 lead may work. Yet in my experience electrical noise from a computer or other similar device easily gets picked up. Then the noise may appear as Afib.

Also many other EKG traces contain a wealth of information that can be obtained only by extensive experience. Every so many years I try to update myself because some of the subtleties you all too soon forget. It is not easy.

Yet one must be cautious in representing certain facts. Personally in my opinion this may still be a bit too early. Just an opinion.



Labels: Health Care

What would Einstein do?

Back in 1905 when Einstein published his three great papers, he was the sole author. You knew it was Einstein. Back when I started Grad school, we named methods for an author, who we knew was the inventor. It was easy to see who produced what when. I wrote a book, my name was in it, I wrote every page. I was not an Editor, I was an author.

Then along came the 1,000+ author papers. Nature has a great piece on this effort:

Authorship is the coin of scholarship — and some researchers are minting a lot. We searched Scopus for authors who had published more than 72 papers (the equivalent of one paper every 5 days) in any one calendar year between 2000 and 2016, a figure that many would consider implausibly prolific. We found more than 9,000 individuals, and made every effort to count only 'full papers' — articles, conference papers, substantive comments and reviews — not editorials, letters to the editor and the like. We hoped that this could be a useful exercise in understanding what scientific authorship means.

We must be clear: we have no evidence that these authors are doing anything inappropriate. Some scientists who are members of large consortia could meet the criteria for authorship on a very high volume of papers. Our findings suggest that some fields or research teams have operationalized their own definitions of what authorship means. The vast majority of hyperprolific authors (7,888 author records, 86%) published in physics. In high-energy and particle physics, projects are done by large international teams that can have upwards of 1,000 members. All participants are listed as authors as a mark of membership of the team, not for writing or revising the papers. We therefore excluded authors in physics.

Yes, one paper every five days! But if that is say for 100 authors then one every 500 days! What is the truth? How does one ascribe credit? The coin of the realm in the Academy is your publications. If, however, "your publications" no longer has any meaning then what?

This has been a growing problem and there is no clear solution.



Labels: Academy

Autophagy and Cancer

Autophagy is the process whereby a cell cleans up the "stuff" left behind by many processes. However autophagy is also involved in many cancers and can be a target for a variety of therapeutics. Moreover autophagy sends out parcels of cleaned up "stuff" which can themselves be either diagnostic or prognostic. We examine some of these issues herein.

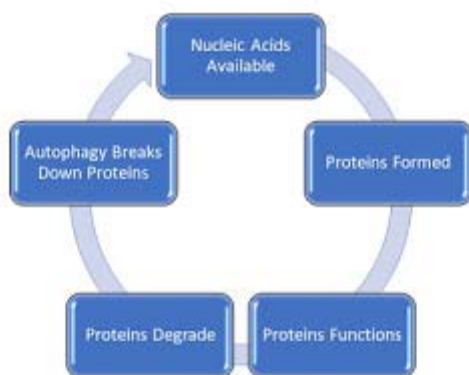
However, autophagy can be a benefit and a threat. Autophagy "cleans" up the "stuff" in a cell so that in most cases it can be recycled and reused. However the risk is that if the autophagy takes up key protective proteins thus reducing their efficacy and pays no attention to bad proteins which are now controlling the cell. That is we know that cancer cells have aberrant proteins. We all too often ascribe this to some genetic breakdown. What if, instead, it is the clean-up mechanism of autophagy. Namely every time a p53 gene creates a protein that the specific autophagy targets it for removal. Then we have a cell with no control.

Thus the questions we should be asking regarding autophagy are:

1. What are the dynamics of the process?
2. What makes a protein a target? How does the autophagy process recognize it and why?

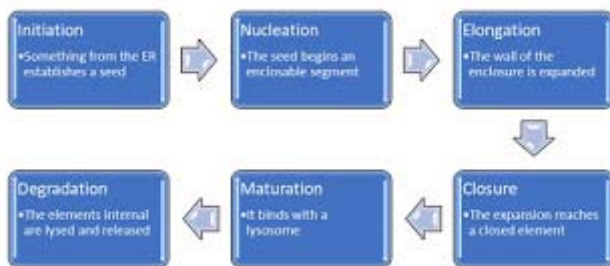
3. How do some proteins manage to avoid autophagy?
4. How could we envision a method to control or remedy a process?

We can envision the autophagy process as shown simply below. It functions of collecting and degrading old proteins, as an example, returning them to nucleic acids, to be used again. It is an internal process of a cell to maintain homeostasis. However like all cell processes it may go awry, and no longer function efficaciously but be harmful.



Unlike most papers in the field we do not intend to introduce new ideas or findings but we attempt to concentrate on the above questions.

From a sequential perspective autophagy as per Kang et al progresses as follows:



The initiators are as shown below:

IGFR Activators	•The IGF receptor may be activated
Hypoxia	•Low levels of oxygen become present
Nutrient Starvation	•Low levels of nutrients, possibly glucose, may be a driver
Low Energy	•Available sources of energy are depleted
ER Stress	•Stress on the endoplasmic reticulum
ROS (Reactive Oxygen Species)	•Presence of ROS as in some cases of high glucose content in Diabetes or obesity

As we shall note herein, the drivers do not seem to include aberrant protein formations¹⁴[1]. Perhaps the results of such malformations may be drivers for the drivers shown above.

As Kang et al note:

There are at least three different types of autophagy described and possibly more. These autophagy types include macro autophagy (hereafter referred to as autophagy), micro autophagy and chaperone mediated autophagy. The initial step of autophagy is the surrounding and sequestering of cytoplasmic organelles and proteins within an isolation membrane (phagophore). Potential sources for the membrane to generate the phagophore include the Golgi complex, endosomes, the endoplasmic reticulum (ER), mitochondria and the plasma membrane.

The nascent membranes are fused at their edges to form double-membrane vesicles, called autophagosomes. Autophagosomes undergo a stepwise maturation process, including fusion with acidified endosomal and/or lysosomal vesicles, eventually leading to the delivery of cytoplasmic contents to lysosomal components, where they fuse, then degrade and are recycled.

One of the issues that we seem to be lacking insight on, is in the case of autophagy in cancer, either as cause or result, what process leads to the selection of what is to be lysed. We have great insight to the process but little to none as to the initial selection. That will be a critical factor.

From a recent paper by Mulcahy et al we have¹⁵[2]:

¹⁴[1] See <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/igfr> A protein found on the surface of some types of cells that binds to insulin-like growth factor (IGF). This causes the cells to grow and divide. IGFR is found at high levels on the surface of several types of cancer cells, which causes these cells to grow rapidly in the presence of IGF. Also called insulin-like growth factor receptor.

¹⁵[2] **Targeting autophagy in cancer**, Jean M. Mulcahy Levy, Christina G. Towers & Andrew Thorburn Affiliations I Corresponding author, Nature Reviews Cancer Y7, 528-542 (2017) I doi:10.1038/nrc.2017.53, Published online 28 July 2017

Autophagy is a mechanism by which cellular material is delivered to lysosomes for degradation, leading to the basal turnover of cell components and providing energy and macromolecular precursors. Autophagy has opposing, context-dependent roles in cancer, and interventions to both stimulate and inhibit autophagy have been proposed as cancer therapies. This has led to the therapeutic targeting of autophagy in cancer to be sometimes viewed as controversial. ... we suggest a way forwards for the effective targeting of autophagy by understanding the context-dependent roles of autophagy and by capitalizing on modern approaches to clinical trial design.

We shall not focus in detail on their suggestions but try to examine autophagy in general so as to better understand the process.

Yoshinori Ohsumi received the Nobel Prize in Physiology or Medicine in 2016 for his work on autophagy. He spent decades trying to understand the process and its implications. In his presentation he noted^{16[3]}:

Life is in an equilibrium state between synthesis and degradation of proteins: replacement of most proteins every 3 months “difference between organisms and machine”

Recycling is essential for life: important ability for survival against starvation critical selection factor in evolution.

To Ohsumi the process of autophagy was one of regeneration not just simple housekeeping. However we know that cells operate as a complex set of internal mechanisms as well as responding to external activations. Furthermore cells send out in exosomes "messages" which in turn may control the behavior of other cells. Autophagy is a process that appears to be very much in the middle of these communications links. It is a transformative process, transforming putative signalling molecules to other putative signalling molecules.

Autophagy appears not to be a simple cleaning up system but a complex element in an ever more complex control system for cellular dynamics. Viewed in this manner we extend what Ohsumi understood to the broader understanding of malignancy control.

As Sengupta et al note in examining mTOR:

Autophagy is a recycling process through which cells liberate intracellular stores of nutrients by degrading cytoplasmic proteins and organelles in lysosomes. In mammalian cells the primary form of autophagy is macroautophagy (referred to from now on as autophagy) and requires the formation of double-membrane autophagosomes that sequester cytoplasmic components and then fuse with lysosomes. A major regulator of autophagy is mTORC1, which in the presence of nutrients and growth factors strongly inhibits the initiation of autophagy.

^{16[3]} <https://www.nobelprize.org/prizes/medicine/2016/summary/> and <https://www.nobelprize.org/prizes/medicine/2016/ohsumi/auto-biography/>

Autophagy is upregulated during periods of starvation or growth factor withdrawal, as well as in response to oxidative stress, infection, or the accumulation of protein aggregates. While mTORC1 inhibition triggers autophagy, the release of amino acids from autophagic protein degradation eventually leads to the reactivation of mTORC1, which in turn restores the cellular lysosomal population.

Directly downstream of mTORC1 are numerous proteins that are required for the execution of the autophagic program, including the serine/threonine kinase Atg1/ULK, which plays a key role in the formation of the preautophagosome. ULK1 forms a complex with Atg13 and FIP200, which promote ULK1 kinase activity and localization to the preautophagosome.

mTORC1 phosphorylates ULK1 and Atg13, moderately reducing ULK1 kinase activity but not affecting its association with Atg13 and FIP200. Reports conflict about whether mTORC1 binds to the complex under nutrient-replete conditions, and more evidence is needed to determine the role mTORC1 phosphorylation of ULK1 plays in its subcellular localization and interaction with other autophagy proteins. As a result, it is too early to know whether these phosphorylation events fully explain the control of autophagy by mTORC1. Interfering with the ability of cells to undergo autophagy within an intact animal produces a range of phenotypes that underscore the importance of autophagy not only as an adaptive response to nutrient stress, but also in general cell and tissue housekeeping.

For example, mice lacking Atg5, which is required for autophagosome formation, are born at mendelian ratios, but die within 1 day of delivery because they are unable to mobilize the energy and nutrient stores they require to survive the pre-suckling period. Mice depleted of Atg5 in just neural cells exhibit a progressive decline in motor activity that correlates with the buildup of protein aggregates in neurons, indicating that autophagy is essential for the basal clearance of these aggregates and to maintain proper neuronal function in adult animals.

Tissue-specific deletions of additional genes required for autophagy have uncovered roles for autophagy in cardiac contractility, immune cell function, and the liver detoxification of drugs.

We can now make some observations regarding autophagy and cancer.

1. AUTOPHAGY AS A PROCESS IS SOMEWHAT WELL UNDERSTOOD ONCE IT COMMENCES AND FOLLOWING THROUGH COMPLETION. HOWEVER AUTOPHAGY AS A MEANS TO INHIBIT OR PROMOTE CANCERS DOES NOT SEEM TO BE WELL UNDERSTOOD AT THE INITIATION STAGE.

We have examined several putative autophagic related cancer treatments which we will comment on latter. However most of these are on off approaches and a general systematic approach does not seem forthcoming.

2. AUTOPHAGY AS A THERAPEUTIC TARGET MAY HAVE POTENTIAL FOR SILENCING GENE PRODUCTS WHICH FACILITATE THE EXPANSION OF CERTAIN MALIGNANCIES.

For example Baquero et al note:

*In chronic myeloid leukemia (CML), **tyrosine kinase inhibitor (TKI) treatment induces autophagy that promotes survival and TKI-resistance in leukemic stem cells (LSCs).***

In clinical studies hydroxychloroquine (HCQ), the only clinically approved autophagy inhibitor, does not consistently inhibit autophagy in cancer patients, so more potent autophagy inhibitors are needed. We generated a murine model of CML in which autophagic flux can be measured in bone marrow-located LSCs.

In parallel, we use cell division tracing, phenotyping of primary CML cells, and a robust xenotransplantation model of human CML, to investigate the effect of Lys05, a highly potent lysosomotropic agent, and PIK-III, a selective inhibitor of VPS34, on the survival and function of LSCs. We demonstrate that long-term haematopoietic stem cells (LT-HSCs: Lin⁻Sca-1⁺c-kit⁺CD48⁻CD150⁺) isolated from leukemic mice have higher basal autophagy levels compared with non-leukemic LT-HSCs and more mature leukemic cells.

*Additionally, we present that while HCQ is ineffective, Lys05-mediated autophagy inhibition reduces LSCs quiescence and drives myeloid cell expansion. Furthermore, Lys05 and PIK-III reduced the number of primary CML LSCs and target xenografted LSCs when used in combination with TKI treatment, **providing a strong rationale for clinical use of second generation autophagy inhibitors as a novel treatment for CML patients with LSC persistence.***

Cristofani et al note regarding prostate cancer:

*Within tumour mass, **autophagy may promote cell survival by enhancing cancer cells tolerability to different cell stresses, like hypoxia, starvation or those triggered by chemotherapeutic agents.** Because of its connection with the apoptotic pathways, **autophagy has been differentially implicated, either as prodeath or prosurvival factor, in the appearance of more aggressive tumours.** Here, in three PC cells (LNCaP, PC3, and DU145), we tested how **different autophagy inducers modulate docetaxel-induced apoptosis.** We selected the mTOR-independent disaccharide trehalose and the mTOR-dependent macrolide lactone rapamycin autophagy inducers. In castration-resistant PC (CRPC) PC3 cells, trehalose specifically prevented intrinsic apoptosis in docetaxel-treated cells. Trehalose reduced the release of cytochrome c triggered by docetaxel and the formation of aberrant mitochondria, possibly by enhancing the turnover of damaged mitochondria via autophagy (mitophagy). In fact, trehalose increased LC3 and p62 expression, LC3-II and p62 (p62 bodies) accumulation and the induction of LC3 puncta. In docetaxel-treated cells, trehalose, but not rapamycin, determined a perinuclear mitochondrial aggregation (mito-aggregates), and mitochondria specifically colocalized with LC3 and p62-positive autophagosomes.*

In PC3 cells, rapamycin retained its ability to activate autophagy without evidences of mitophagy even in presence of docetaxel. Interestingly, these results were replicated in LNCaP cells, whereas trehalose and rapamycin did not modify the response to docetaxel in the ATG5-deficient (autophagy resistant) DU145 cells. Therefore, autophagy is involved to alter the

response to chemotherapy in combination therapies and the response may be influenced by the different autophagic pathways utilized and by the type of cancer cells.

3. AUTOPHAGY PRODUCTS MAY ALLOW FOR LIQUID BIOPSY TARGETS FOR THE PURPOSE OF ASCERTAINING DIAGNOSTIC OR PROGNOSTIC TARGETS.

We have discussed liquid biopsy approaches.

4. CAN THE GENE AND GENE PRODUCTS IN AUTOPHAGY BE USED AS TARGETS TO MITIGATE CERTAIN TYPES OF CANCERS?

Some effort has been tried on this area and a great deal more is required.

5. IS THERE SOME APPROACH THAT CAN BE FACILITATED VIA IMMUNOTHERAPY?

6. ARE THERE VIRAL VECTORS WHICH CAN BE EMPLOYED TO FACILITATE AUTOPHAGIC CONTROLS?

7. WHAT IS THE IMPACT OF OBESITY AND AUTOPHAGY ON CANCER PRESENTATION?

Obesity has been and is a major source of morbidity and mortality. It has further become a topic with some significant social backlash for a physician. Whereas smoking could be called out and managed obesity has become a personal statement protected by those who often have no understanding of its risks.

Noa Zhang et al note:

Obesity poses a severe threat to human health, including the increased prevalence of hypertension, insulin resistance, diabetes mellitus, cancer, inflammation, sleep apnoea and other chronic diseases. Current therapies focus mainly on suppressing caloric intake, but the efficacy of this approach remains poor. A better understanding of the pathophysiology of obesity will be essential for the management of obesity and its complications.

Knowledge gained over the past three decades regarding the aetiological mechanisms underpinning obesity has provided a framework that emphasizes energy imbalance and neurohormonal dysregulation, which are tightly regulated by autophagy. Accordingly, there is an emerging interest in the role of autophagy, a conserved homeostatic process for cellular quality control through the disposal and recycling of cellular components, in the maintenance of cellular homeostasis and organ function by selectively ridding cells of potentially toxic proteins, lipids and organelles.

Indeed, defects in autophagy homeostasis are implicated in metabolic disorders, including obesity, insulin resistance, diabetes mellitus and atherosclerosis. In this Review, the alterations in autophagy that occur in response to nutrient stress, and how these changes alter the course of

obesogenesis and obesity-related complications, are discussed. The potential of pharmacological modulation of autophagy for the management of obesity is also addressed.

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Labels: [Cancer](#)

Monday, September 10, 2018

[CRISPR Patent](#)

Finally there seems to be a resolution, but do not hold your breath. As [Genome Web](#) reports:

The United States Court of Appeals for the Federal Circuit today issued a ruling upholding a judgement from the Patent Trial and Appeal Board (PTAB) which gave the Broad Institute and its partners control of key CRISPR genome editing patents and left the University of California and its co-litigants in the cold. In January 2017, the US Patent and Trademark Office declared an interference proceeding to settle certain claims related to the CRISPR patent battle between parties led by the Broad and UC. In the interference proceedings, the USPTO said it would 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 would be granted under the old "first to invent" system.

Hopefully the issue is resolved. It was a sticky problem because the UCB folks said they did everything and any person skilled in the art would have done what Broad did. The court seems to have sidestepped that issue.



Labels: [CRISPR](#)

[Sneaky Cells](#)

To confuse enemy anti-aircraft missiles and guns, bombers would unload chaff, metallic materials, to confuse the target location. Now we see that malignant cells can do the same with exosomes having protein markers to confuse the immune system.

As Chen et al note in [Nature](#):

Here we report that metastatic melanomas release extracellular vesicles, mostly in the form of exosomes, that carry PD-L1 on their surface. Stimulation with interferon- γ (IFN- γ) increases the amount of PD-L1 on these vesicles, which suppresses the function of CD8 T cells and facilitates tumour growth. In patients with metastatic melanoma, the level of circulating exosomal PD-L1 positively correlates with that of IFN- γ , and varies during the course of anti-PD-1 therapy. The magnitudes of the increase in circulating exosomal PD-L1 during early stages of treatment, as an indicator of the adaptive response of the tumour cells to T cell reinvigoration, stratifies clinical responders from non-responders. Our study unveils a mechanism by which tumour cells systemically suppress the immune system, and provides a rationale for the application of exosomal PD-L1 as a predictor for anti-PD-1 therapy.

[NCI](#) also notes:

A new study has identified what may be an important and previously unknown route by which tumors evade the immune system: They secrete small membrane-encased sacs, called exosomes, that are studded with a protein that dials down the immune response. The study, led by researchers at the University of Pennsylvania, found that in lab models of the skin cancer melanoma and in humans with the disease, tumor cells release exosomes coated with proteins

called PD-L1. These proteins are part of a family of immune checkpoint proteins that bind to partner molecules on immune cells, effectively deactivating them. The researchers likened the PD-L1-studded exosomes to a fleet of drones engaged in preemptive strikes, moving throughout the body to thwart an antitumor attack before immune cells—namely those known as cytotoxic T cells—ever have a chance to reach the tumor.

Thus the battle between a malignant cell and the attempts to stop them goes on. Every time one thinks they have solved the problem, new information arises that thwarts the attempt.



Labels: [Cancer](#)

Sunday, September 9, 2018

[Local Libraries: Are they worth it?](#)



Local Libraries, may be on their way to extinction. Take a ride on the subway in New York. You used to see books and newspapers. Now you see smart phones. Not a single newspaper, ever. It makes it cleaner but what are they "reading"? Then what of the libraries. I have not been in one for over 45 years! Yes I have written 17 books and a few hundred papers, and hundreds of reports etc. But I get all I need on line, and not through Google. But why then libraries.

From the NY Times¹⁷[1] we are "told", as they are all too often wont to do:

For children and teenagers, libraries help instill an ethic of responsibility, to themselves and to their neighbors, by teaching them what it means to borrow and take care of something public, and to return it so others can have it too. For new parents, grandparents and caretakers who feel

overwhelmed when watching an infant or a toddler by themselves, libraries are a godsend. In many neighborhoods, particularly those where young people aren't hyper-scheduled in formal after-school programs, libraries are highly popular among adolescents and teenagers who want to spend time with other people their age. One reason is that they're open, accessible and free. Another is that the library staff members welcome them; in many branches, they even assign areas for teenagers to be with one another...The openness and diversity that flourish in neighborhood libraries were once a hallmark of urban culture. But that has changed. Though American cities are growing more ethnically, racially and culturally diverse, they too often remain divided and unequal, with some neighborhoods cutting themselves off from difference — sometimes intentionally, sometimes just by dint of rising costs — particularly when it comes to race and social class.

Well I wonder what the "ethic of responsibility" is? A "fine" for a late book, a place for teenagers to "hang out". I really wonder what world the writer is in. Libraries were in my day controlled locations, silence, and oversight. Also they are filled with materials that the librarians like. Also, and this is critical, a 10 day borrowing period just does not work for trying to learn calculus. It may work for some trashy novel, but not for *The Brothers Karamazov*. Also libraries are not often in the best of locations.

What is or shall we say was the role of a library. It was at least as far as I recall a depository of knowledge to be shared by a community. A library at a University, a school, even a corporation. It was not a social meeting ground. A community center serves that function. But libraries have become whatever we want them to be since they have funding independent of function. I will demonstrate that below.

Now as to funding, in New Jersey there is a massive tax imposed based on real estate values. Live in a rich town and get a well-funded library. However rich towns do not really need libraries. Poorer towns may have no interest.

From NJSpotlight18[2]:

How are public libraries funded? Because they are public entities, libraries receive money from the state and must adhere to certain standards, like size and number of books, and are required to have an annual audit to ensure they are complying with state regulations. Almost all public libraries are funded according to equalized valuation of all property in the towns they serve, not just residential properties. New Jersey law sets the minimum funding limit for municipal libraries at what they call "1/3 mill." This works out to \$0.33 on each \$1,000 of equalized value of the property, but currently more than half the libraries in the state are funded above this amount, according to the NJLA. For county libraries, that minimum is set at 1/15 mill (about \$6.66 per \$100,000) on the "apportionment valuation." The NJLA reports that all county libraries are funded above this amount.

^{18[2]} <http://www.njspotlight.com/stories/16/09/26/explainer-how-nj-s-public-libraries-are-faring-in-the-information-age/>

Note the last statement. Those rich towns really get well funded libraries. But who uses them?

From the State Law¹⁹[3]:

Implementing the Municipal Library Tax Levy Law (Revised) P.L. 2011, c. 38 (S-2068) This Local Finance Notice supersedes and replaces the guidance contained in Notice 2011-13, which is repealed. This Notice provides an improved process that is consistent with other financial transactions related to the fiscal relationship of municipalities and public libraries covered under P.L. 2011, c. 38 (S-2068), enacted and taking effect on March 21, 2011. The law provides a dedicated line item on property tax bill to fund municipal free and joint free public libraries. It does not result in any increased taxes, but changes the way the minimum library appropriation is displayed to the public. The implementation procedure maintains budgeting the minimum 1/3 mill of equalized value in a budget appropriation, but deducts that amount from the tax levy in the calculation of the Amount to Be Raised by taxes for Support of the Municipal Budget. This reduces the municipal tax levy and rate, creates a new line item and tax rate on the tax bill for municipal library purposes, maintains a neutral cap levy, and maintains the library appropriation as part of the municipal budget to facilitate library related transactions.

Thus take a town with 5,000 homes valued at \$500,000 per home. Assume 10,000 residents. Then the Real Estate is \$2.5 billion and at a rate of 0.33 mil, that is \$8.25 million for the library per year. Or \$850 per resident! Imagine how many books you could buy on ABE for example! That is mandated every year! Imagine a really rich town, say with \$2 million homes and this \$2500 per year per person to the library!

Perhaps it really is time to re-look at libraries. With real data, not politically correct wording. If one recalls Eco's *The Name of the Rose*, there a library was a cloistered and secure collection of allowed and forbidden texts. I can never recall a library as a social meeting ground, devoid perhaps of any books. But alas in today's world, who needs books? They may be dangerous. After all one's smart phone contains all one needs, really.¹

20[1] <https://www.nytimes.com/2018/09/08/opinion/sunday/civil-society-library.html>



Labels: [Libraries](#)

[More Papal Infallibility](#)

[The Pope and the Professor](#) by Howard is an exceptionally well written book. It details the travails of Prof Dollinger and he fight against Papal Infallibility. Dollinger is an impressive character and the authors presents him and his ideas superbly.

The issue is simple. Is the Pope infallible? Now this issue arises after two thousand years and somehow gets addressed in the midst of the diminution of the Papal States as nationalism reaches

¹⁹[3] Web: [www.nj.gov/dca/lgs LFN 2011-14](http://www.nj.gov/dca/lgs/LFN%202011-14), March 25, 2011

its peak. The author takes on a journey examining Dollinger and his thought and intermingles it with the ongoing changes in Europe at this time. We go through the revolutions of 1848, the restructuring of Italy as a single nation, and the Franco Prussian war, a prelude to the 20th century.

In the midst of this is the long venue of Pius IX and the fact that besides being Pope he is also a Prince in charge of the Papal States. A bit of a messy situation as Italy is going through its own revolution with Garibaldi and others.

As a means to establish his primacy Pius proposes a Council, and this gives him the chance to promulgate the infallibility of the Pope, when speaking *ex cathedra*. Of course this means that when a Pope says something in this manner it must be true.

Overall the author does a splendid job and in today's environment of Catholicism this is an essential read. My main concern is the lack of historical precedence.

For example, Gregory I was a famous Pope, but at the time he was the Bishop of Rome, elected by the people in Rome and subservient to the Emperor in Constantinople and the Bishop in Ravenna. Thus with one of the most famous Popes we see a person not only subject to others but deferential to them in any thing he may postulate or promote. Thus in 600 AD there was no concept of Pope and definitely no idea of infallibility.

Skip to 1328 and Avignon. We have the battle between John XXII and William of Ockham. After Ockham's escape in the night he writes his *Work of Ninety Days* which demonstrates that John was not only wrong but a heretic! So much for infallibility.

It would have been useful, albeit expanding a bit too much, but place this tale in historical context. However the author presents all of it as it happens at the moment.

In summary, this is a wonderful work, erudite, well written, and telling a tale that must be evaluated in the context of an ever changing papacy.



Labels: [Church](#), [Papacy](#)

[Papal Infallibility?](#)

[Vatican I](#) by O'Malley is a short but superbly written summary of the issue of Papal Infallibility and Vatican I in 1870. The author is a well known Jesuit, and one will see the influence and pervasiveness of the Jesuits throughout. This book does not seem to be a polemic for one side or the other on first reading. It does show how some limitations on the proposed position of Pius IX was attained, namely that he wanted unlimited infallibility and the best the Council could delimit is infallibility on matters stated *ex cathedra*, namely limited to things the Pope would pronounce as coming from the successor of Peter.

The book is divided into five sections and a conclusion. The author goes back and forth between the issues at the time and those proximate to the Council and integrates them into the decision

process. The issues driving Pius IX were the development of nationalism, liberalism, freedom of religion, Protestantism, freedom of the press, and the development of citizens as compared to subjects. Pius IX was one of the last hold outs of the days of divine rights of rulers. As forms of democracy were developing, challenges from socialism and communism were being addressed, Pius IX saw a need to strengthen the papacy.

The author does a reasonably good task at showing the counter efforts such as Gallicanism which was the French approach of running the Church the way the French wanted to. Strangely Gallicanism was present before the Avignon papacy and was intensified during the 14th century when the Pope was in Avignon. Although not officially part of France at the time the popes then followed the French crown in many ways. Pius IX saw this as an anathema. Thus any extension to the 19th century would have to be wiped out and Pius did this via his call for infallibility.

Even more compelling was the fact that when all of the issues started with Pius he was also a head of state with his dominion over the Papal States, the central lands of what was becoming Italy. The Pope owned and controlled most of central Italy and as nationalism was evolving his control was under attack. Eventually just months after the Council declared his infallibility Rome was invaded and taken over by the Italian nationalists, thus Italy was effectively formed as a nation.

The author blends these facts in a well presented narrative. He also brings to the fore the opposition of many of the theologians, often non-clerical and German, who opposed this infallibility dicta. Key amongst them would be Dollinger, a Bavarian theologian strongly opposed to this new idea. In fact many of the best theologians were opposed since there was no basis and furthermore the Conciliar theories dominated, namely such decisions were made by Church Councils, bishops in concert, and not singularly by a Pope.

Overall the books is superb. However one can raise a few issues:

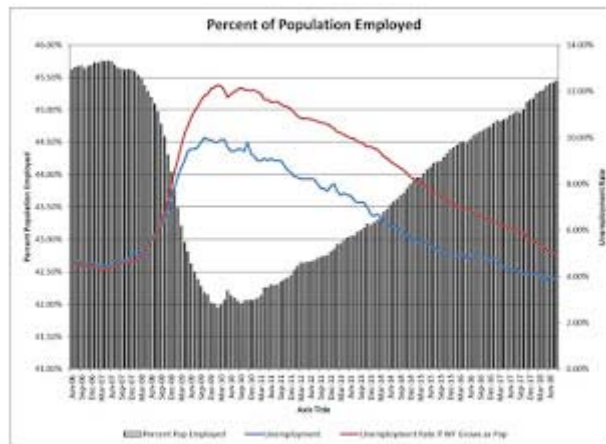
1. The Jesuits played a key role in supporting Pius. The author's document is replete with references and the author himself is a Jesuit. The rule of the Jesuits frankly should have been more detailed, for their role was to support the Pope and as such infallibility would logically strengthen their positions, somewhat.
2. Infallibility took almost two millennia to be stated. As such one would wonder why no one ever thought of this before? The Councils were always a way to reach doctrinal decisions. But now one ascribes such a singular power to a singular man. This is certainly questionable give the cast of characters who have occupied the seat of Peter over the ages.
3. As with many such efforts one should be drawn back to the 14th century and the battles between John XXII and Marsilius of Padua and William of Ockham. Ockham went as far in his Work of Ninety Days to claim John a heretic. His contention has merit. Marsilius predated Montesquieu in the ideas of representative governments and the fact that divine rights had no basis. The 14th century players frankly should be mentioned in many of these discussions.

Overall O'Malley provides a timely, well written, and balanced presentation of Vatican I, a Council whose closure never occurred due to the capture of Rome by the Italian forces. O'Malley in the conclusion makes reference to the impact of this dictum, such as the problems Kennedy had running for President, for the dictum was interpreted as making Catholics citizens of a foreign lord and master and demanded fealty to their assertions.



Labels: [Church](#), [Papacy](#)

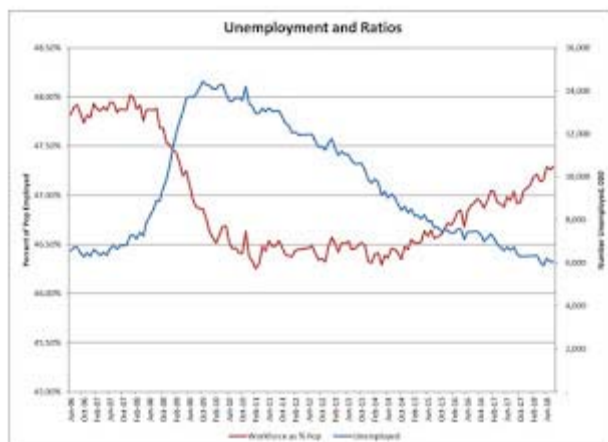
Employment September 2018



The employment stats are summarized above. There is continuing improvement and a dramatic increase in participation rate.



This participation rate gap is shown above. It is almost down to the rate just before the collapse of 2008. One must recall that in 2008 almost every Government entity responsible for the economy did the wrong thing. This will be a wealth of opportunity for PhD theses.



Finally the above is a reasonable summary of the improvements.



Labels: [Economy](#)

Saturday, September 8, 2018

[Socialism: Is it new again?](#)

Over the years as I have examined Socialism I still come away recognizing its major failures. In the book by Arthur McGovern S.J., *Marxism an American Christian Perspective*, we have a Marxist Jesuit, yes folks one of them, detailing not only Marx but the need to convert the United States to Socialism as a religious imperative. He notes:

But the great majority of socialists in this country, including some Marxist groups, are clearly committed to democratic socialism both as a means of attaining socialism and as fundamental to socialism itself. The very purpose of socialism is that people should control their work and their lives. Hence “democratic socialism” is not just a stratagem to gain support, but expresses a fundamental goal of socialism itself.

“Socialism = State Control.” This view of socialism is quite prevalent, and indeed it is a form socialism can take. When the papal encyclicals spoke of a “total collectivity” or contemporary critics speak of “the government running everything,” this is the model of socialism they have in mind. Current feelings about government spending and waste, and criticisms that government workers are less energetic and less efficient than workers for private enterprises, tend to reinforce negative views of socialism. But many contemporary socialists would advocate a decentralized economy, with local groups and organizations carrying through planning. Some would have in mind a “market socialism” as in Yugoslavia. Some would see the maintenance of small businesses and family farms as fully compatible with socialism. A socialism which contains

this kind of “mix” could, I believe, even be an expression of the traditional Roman Catholic social teachings on “the principle of subsidiarity.”

That public ownership would kill initiative is quite disputable. (Not really!) Initiative depends on a host of factors—ambition, degree of responsibility, pride and fulfillment in work, and material and social incentives—and not just on private versus public ownership. Do top government officials work less hard than top business executives? Do professors at state universities work less hard than their colleagues at private ones? Examples of initiative are almost always drawn from the business class, not from the masses of factory workers, clerks, and the millions whose work consists of routine tasks. A decentralized, democratic socialism in principle, I believe, is quite consistent with democracy, Christianity, and even traditional Roman Catholic social thought. But whether it is only an ideal, and how a transition to such an economic system could occur, remain serious problems.

“Socialism = Welfarism.” When some Americans complain that we already have “creeping socialism,” they reflect one of the most common misconceptions about socialism—that it is a system to provide for those who do not feel like working. Ironically, the issue of work is one point on which most socialists and staunch conservatives agree. The Communist Party Program of the U.S.S.R. puts it strongly: “He who does not work does not eat.” Welfare is not a product of socialism but of capitalism, at least where unemployed but able-bodied persons are concerned. One hopes that no society will disavow responsibility for the sick, the handicapped, and the elderly. The fact that many view “socialized medicine” as the next step toward socialism only confirms this misconception. Doctors do not control the chief means of production in American society. Whatever other reasons might be given for socialized medicine, it would not fundamentally alter the basic property relations of society. Ownership and control of production, and not a giant welfare system, are the objectives of democratic socialism.

“Socialism = Utopianism.” Any hope or plan for a new social order has to contain some utopian element. Christianity itself is filled with utopian hopes for the coming Kingdom of God. The great American dream of success was a utopian vision that attracted immigrants. But at some point utopian vision must appear concretely realizable or at least able to be approximated. This includes a clear sense of the problems involved and how to meet them.

Let me set down my own position so that my problems with socialism on this score may be clear. My problems are not with the ideals of democratic socialism, but with the assumption that if capitalism is replaced with socialism these ideals will be fulfilled, at least to a significant degree. I don’t think it is quite that simple or certain. Socialist enthusiasts point to China, Cuba, and the early years of Allende as example of what can happen positively through socialism. Poor people who had nothing, who were treated as nothing, found new hope in socialism, new pride, new meaning in their lives. I believe this did happen. But I do not believe that the majority of people in the United States are at this starting point. Most have jobs and education; 97 percent even have televisions. Hence a closer parallel would be socialism in Eastern Europe where worker alienation is great, productivity and wages low, and enthusiasm for socialism much less evident. The fact that the United States is already a highly developed industrial nation could create more problems for socialism, not less, especially if a significant part of social ownership was in the hands of the state. For as is evident from strikes and protests at present, no group in society feels

satisfied, not even sports stars with \$200,000-plus salaries. Each contending group in society will continue to make demands for its share whether the economy is socialist or not. Without socialist attitudes, Julius Nyerere has said, true socialism is impossible. But such attitudes will be more difficult to attain in the United States, where individualism has long been stressed.

At the same time I disagree with the conclusions which conservatives draw from this kind of argument: "For all its faults capitalism is still the best, so let's stay with it." No social change would ever occur on this basis; the Marxist-socialist critique has convinced me that monopoly capitalism undermines democracy and too often does not promote the common good; hence simply to stay with what we have is for me un-Christian. What I see as a solution of this dilemma is not original; it stresses structural reforms; it embodies my own interpretation of Gramsci's concept of hegemony, and of building on positive steps as opposed to only negative criticisms. But before going to it, let me return to the issue of socialism and utopianism.

*Michael Lerner's *The New Socialist Revolution* exemplifies the kind of socialist position I find questionable. For nearly three hundred pages he criticizes U.S. capitalism and discusses at length the need to crush bourgeois hegemony. He devotes a scant four pages to the transition to socialism and then describes in glowing terms the democratic institutions which will flourish under socialism. He makes no attempt to address, or even show an awareness of, the great difficulties which such a radical social transition would entail. What the new society will look like, he says simply, will depend on what we do with it.¹⁴ Though addressing only one of the same points Lerner takes up, Erik Olin Wright is much more candid and honest when he states that in the United States no strategy for socialism is particularly plausible at present.¹⁵ Much more hard, creative thinking is needed, I believe, both about workable forms socialism might take and transitions to socialism, before most people in the United States can begin even to think about opting for socialism.*

*In a series of articles for *In These Times*, entitled "For a Socialism That Works," Leland Stauber addressed one aspect of the issue we have just been discussing. While noting that the U.S. press and politicians have created an ideological bias against socialism, he accuses socialists of contributing to this bias by not proposing any fresh alternatives. The twentieth century, he contends, has been a graveyard for inadequate socialist ideas. The only socialist alternative which he sees as able to avoid defeat is one that promises as much efficiency as capitalism. He proposes a "market socialism" drawing on both the successes and failures of Yugoslavian socialism. The socialism he envisions includes a public or government sector, a market socialist sector which would not be government-owned but publicly-owned by groups operating along the lines of private firms today, a private sector to include small businesses and family farms, and a cooperative sector.¹⁶*

*His proposals triggered numerous rejoinders in subsequent issues of *In These Times*, ranging from support to complete rejection. His effort, I believe, is an example of the kind of creative, long-range thinking needed to make democratic socialism more plausible. The negative responses indicate how little agreement exists on what constitutes a workable but genuine socialism. Perhaps some other proposal would have generated more support. The controversy over Stauber's articles may only confirm the need for "putting socialism on the agenda" so that*

more creative thinking will be stimulated. But the controversy also indicates why proposing socialism as a solution is to present a very unclear option.

The problem of a transition to socialism is also important. The worst possible transition that I could imagine would be one that counts on “waiting to work it out until we get there” or one that is necessitated by a sudden collapse of capitalism. To try to build up a new society out of the chaos and anarchy left by the collapse of an old one offers the least amount of hope that a truly just and democratic social order will emerge. Hence to promote a strategy of “the worse the better” seems to me even immoral. Some look to the Swedish Social-Democrats and their plans to socialize Sweden as a possible model for democratic transition to socialism. Theoretical work about strategies of transition from capitalism to socialism is needed, but a successful example of such a transition would aid the socialist movement most.

In Michael Harrington’s strategy of long-range vision and realistic approximations I found personally the kind of approach I had been looking for. I would express my long range vision as “economic democracy” rather than socialism at this point. But I agree fully with the approach Harrington takes. He calls for a long-range vision of structural, anti-capitalist change, but adds: We do not, however, assert this ultimatically, insisting that America suddenly convert to socialist values in toto. We address immediate problems and seek immediate solutions. We join with trade unionists and minority activists and feminists and Democratic Party reformers— and, for that matter, with all women and men of good will. We do not reject increments of change— but we seek to influence them, to design them, to move them, in the direction of the massive transformations which alone can solve the present crisis.

What, as a conclusion to all of this, can socialism contribute and what stance might a Christian take? If socialism cannot claim to have “the” solution, capitalism certainly does not. Socialism points to an important alternative possibility, and offers a needed critique of capitalism. For a Christian to work for a democratic socialism would seem a perfectly justifiable option. The very uncertainties about socialism might be all the more reason for Christians to be part of the movement, to help shape its direction and values.

A Personal Strategy

If Erik Olin Wright is correct that there is no plausible strategy for socialism at the present time in the United States, then it would certainly be pretentious to offer an even broader strategy which might lead to democratic socialism or to economic democracy in some other form. What follows, then, is not an argument for “the” correct strategy Christians in the United States should follow. It is perhaps a “philosophy of social change” which dovetails with Michael Harrington’s strategy of long-range vision and immediate tasks. It is a strategy of moving toward a fundamental restructuring of society through “increments of change” and reforms. But underlying this strategy is a conviction that such a process is not just a matter of political realism but the process most apt for achieving the desired results. This brief philosophy of social change is offered in the hope that some other Christians who share the same concerns, values, and misgivings, may be helped in their reflection. First, I believe that any option taken should be both idealistic and realistic.

Given many of our current Progressives, neo-Socialists, perhaps one should think on this. One thing Socialism does is destroy the entrepreneur. You see the Socialists have central control. Imagine medicine being controlled by the Postal Service, yes, that is what happens. Dead letter box will have a new meaning. Read what the good Jesuit states, then think a bit, just a little bit.



Labels: [Socialism](#)

Friday, September 7, 2018

[Course Correction - Verizon](#)

It appears that in [Total Telecom](#) they report that Verizon seeks to unload their social media ventures; AOL and Yahoo. They note:

Oath has previously acquired Yahoo and AOL but has yet to carve its own niche as an online service and content provider. Tim Armstrong, CEO of Verizon's web based business unit, Oath, is said to be in talks with the company's board of directors to step down from his role, according to reports in the press. The Wall Street Journal reported that Armstrong has decided to walk away from his role as Verizon mulls a change of direction for Oath.

My comments is; what took them so long! For example they own the Huffington Post, a left wing online publisher of opinion, and not clear how much cash flow it generates.

Verizon must understand its basics. It own licenses, and 5G, if properly done, can be a winner. They tried in 4G to get wireless in the home. The system they deployed was in my professional opinion a total disaster. It puts a nano hub in the home and allows for a single RJ-11 jack with no 911, no caller ID and the list goes on. The should have a system which connects to the incoming twisted pair and replaces the copper! Simple, anyone who ever worked in the old telephone company would understand this. Not the new breed of marketeers who are off shoots of OATH.

Hopefully the new CEO, a Swede, can be more focused. Dump the social media stuff, telephone companies are infrastructure owners and operators. Stay out of the media business, you just do not understand it.

Oh yes, and remember, if all else fails listen to the customer!



Labels: [Verizon](#)

Wednesday, September 5, 2018

[Social Media as a Common Carrier](#)

There has been a great deal of conversation regarding Social Media, but none thus far as best I can see as to how it is classified as a business and as such how it would be considered to be treated under the law. We will argue that Social Media has many characteristics of Common Carriage, and specifically Common Carriage over the wireline, in this case we extend wireline to include the Internet in its broadest scope.

Let us first return to the old concept of bailment. Namely the idea that if I give someone one of my possessions, that person takes it from me and transports it to another at perhaps some distant location. The old bailment concept had some issue. Then came common carriage, an idea that extended bailment under Elizabeth I and made it the basis for England's dominance in trade. A common carrier takes your possession, moves it to another and unlike bailment which may have unlimited liability, the common carrier is at best liable for what you paid them for the transport. If you want more in the event of a loss then get insurance, thus Lloyd's of London.

The elements are simple. A person wishes to take something they own, perhaps in the broadest sense, agree to pay the carrier to move it across some distance, and deliver it to another. The sender agrees to pay the carrier in some manner. The sender takes all the risk of loss, the carrier just "transports" at some fee.

Now how does this apply to social media. Let us say I am the sender. I send some item of interest that I want to get to some destination. Thus I may have a Facebook page, which I do not for obvious reasons, but let us assume I do. I want to "send" a "possession" to Facebook to carry to my "page" and thus to my selected "destinations" who will "read" my page. I "pay" Facebook with the right to use my delivery system to advertise stuff for which they receive revenue from third parties. I have agreed to "give" Facebook my identity and that of my destinations associates in return for "sending" my message. Facebook then monetizes my identity and destination identities to place ads and the like. A slightly different model from the telephone company or post office, but not that far off.

Thus if Social Media can be considered as a common carrier then can they be regulated as such. There is a wealth of common carriage regulation. Simply, a carrier must carry anyone, a carrier must not interfere with what is in the package they carry, a carrier has a very limited liability, and customers have remedies under the law.

Perhaps we need an FCC like entity to regulate these types of common carriers. Just a thought.



Labels: [Social Media](#)

Wednesday, August 29, 2018

[The Government vs Private Industry](#)

Socialized medicine etc. Now here is a tale. I sent a Certified Return receipt letter from my town to the adjoining town. About three miles away. The destination was on the largest highway in the

town. Can't miss it. I also sent it by UPS, a private company. UPS got it there in twelve hours with a return receipt.

The USPS did the following with the very same package:

August 29, 2018, 4:22 pm

Unable to deliver item, problem with address

EAST HANOVER, NJ 07936

USPS was unable to deliver your item as of 4:22 pm on August 29, 2018 in EAST HANOVER, NJ 07936. The address may be incorrect, incomplete, or illegible.

August 29, 2018, 6:46 am

Arrived at Unit

EAST HANOVER, NJ 07936

August 27, 2018, 8:31 am

Out for Delivery

EAST HANOVER, NJ 07936

August 27, 2018, 8:21 am

Sorting Complete

EAST HANOVER, NJ 07936

August 26, 2018

In Transit to Next Facility

August 25, 2018, 3:45 pm

Departed USPS Regional Facility

KEARNY NJ DISTRIBUTION CENTER

August 24, 2018, 7:15 pm

Arrived at USPS Regional Facility

KEARNY NJ DISTRIBUTION CENTER

August 24, 2018, 6:04 pm

Departed Post Office

FLORHAM PARK, NJ 07932

August 24, 2018, 10:49 am

USPS in possession of item

FLORHAM PARK, NJ 07932

Yes, same address, but the USPS spent almost a week shuttling the typed address of a well known entity on a major highway to no where. That is our Government. And you want these folks to manage your medical care. They could not find your appendix and would throw you out on the street! What would Benjamin Franklin think! This is our Government workers folks!



Labels: [Government](#)

Wednesday, August 29, 2018

[Medicare for All?](#)



This seems to be more of a slogan than any well thought out plan, I am reminded of Thomas Paine and his social programs in the *Rights of Man*. At least Paine thought through the cost and where the money would come from. The current batch of promoters seem oblivious to both.

Back in 2008 I wrote a piece on Medicare and noted that almost a third of the participants get less than what they paid into the plan. But alas that is the basis of any insurance plan. One should be happy no to have to collect. But the existing Medicare plan makes one contribute from the start of your working life to your last breath, namely you still pay 3.5% of everything you make or even on capital gains. Also you pay a monthly amount which can exceed \$6,000 per annum per person. Then you pay for another plan to cover the 20% that Medicare does not pay for and then you pay for the drug plan! So we have typically 50 years paid in before penny one comes out and a continuing payment until you are dead!

But the kicker is that Medicare "negotiates" what they will pay for a service. Thus a physician with massive overhead mandated by the Government gets roughly 28% to at best 40% of the actual costs of service. That works because the others not on Medicare are subsidizing the physician, a little bit.

Now assume we allow everyone on Medicare, the millennials and their ilk. Where does the money come from. There is no fifty year upfront commitment. Also a 65 year olds may live 12 to 16 more years. The millennials may go on forever living with mom and dad. So do we have an equity issue, a social justice issue, just to ring the bell of today's socialists.

Then if all patients pay only 40% of the costs, who picks up the rest? This is less than a half baked scheme. It is a method for achieving financial collapse!



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

[Where is Ockham when we need him?](#)

In 1328 William of Ockham escaped Avignon just ahead of the Papal executioners. Off he went to Munich where he managed in the next twenty years to disassemble the legitimacy of the Papacy. His Work of Ninety Days is a classic exposing the limits upon the Papacy and this work has survives some seven hundred years without any significant change.

Now in the [Telegraph](#) it is noted :

“Behind these attacks there are dark forces,” said Tommaso Valentinetti, 66, an Italian archbishop. The pope’s enemies were “throwing mud” to try to discredit him, he said. The allegations against Pope Francis were first aired in the middle of his trip to Ireland, where he apologised for the Church’s decades of complicity and cover-up in the sexual abuse of children by Catholic clergy. Archbishop Vigano claims that he told Pope Francis of the allegations about Cardinal McCarrick, whom he described as “a serial predator”, back in 2013. He said that rather than punish McCarrick, the Argentinian pontiff had lifted sanctions imposed on him by his predecessor, Pope Benedict XVI.

Overall the issue is clear. The Church faces a serious set of problems and it appears that the solution is not simple. The Counciliar Movement may likely be the best option out. Yet a re-examination of the Papacy and its powers needs to be redone as Ockham had done seven hundred years ago. Yet we do not seem to have an Ockham at hand.



Labels: [Religion](#)

Tuesday, August 28, 2018

[Google et al](#)

Google uses algorithms to determine what to present to a user who does a search. That is well known. Now what those algorithms are is the "secret sauce". But one suspects that the algorithms are written to maximize revenue. Thus if I seek a hotel, the listing will often present those which have purchased ad space on Goggle. What else would one expect. If your hotel has not done so your hotel may appear at the bottom of the list if at all. Profit drives the algorithm.

Now politically one would be nuts to seek Google as a presenter of opinions. I use Feedly and I select a few dozen sources from left to right to several languages. Frankly I like Le Monde, the French are very intellectual and compared to the NY Times they are head and shoulders above them. Thus if one seeks to understand world views then one must seek out the primary sources, and don't waste your time on Google.

If it is scientific, I use Semantic Scholar, a fantastic source. But the last thing I would ever use if Facebook or Twitter. One would be better off listening to conversations on the A train. But they no longer occur even there. All the passengers are on smart phones, and most likely sending text

messages or commenting on Facebook.

The NY subways are now spotless, no left over newspapers, no one buys them any longer. I have not seen a single person with a news paper, or a book for that matter! Again they are in the echo chamber of their smart phone.

Most likely the worst device ever created is the smart phone. The NY Subway system wants you to use this to pay your fare. Imagine a \$1,000 device held by every passenger trying to get through a toll station at rush hour. One might ask what moron thought that one up? Most likely someone who went from 34th Street to Times Square at rush hour. But I digress.

So does the President have a point? Perhaps, but he is a Twitter user.



Labels: [Google](#)

[The Collapse of Things?](#)

The [NY Times](#) has an interesting piece on those who commute from Staten Island to Manhattan. They note:

The X17 was an express bus linking Staten Island to Midtown Manhattan. It made 85 stops, 66 of them before even leaving Staten Island. Total distance? Nearly 40 miles. Total drive time? The schedule said two hours and 33 minutes, but closer to three hours was often more like it. "When people's eyebrows go up, we tell them you could fly to Florida in less time," said ..., a bus dispatcher. "And you certainly can." The X17's leisurely path across Staten Island underscored the inefficient and outdated bus network that crisscrosses New York City, the largest municipal bus system in the nation.

Now in 1962 and 1963 I took a summer course at Manhattan College in the Bronx, at 242nd Street, the end of the Broadway line. I worked at Midland Beach, which was served by the Bay Street Bus. I would take the bus to the Ferry, the Ferry to lower Manhattan and then the subway from South Ferry to 242nd Street. It was about 2 and a half hours, and then repeat it home but then I had to walk a mile from the bus drop off to my house. Then up at 5:30 to get to the Beach by 8:00.

Staten Island is officially part of New York City, and was when I was born there, Laguardia had signed my birth certificate if I recall.

But Staten Island may just as well be in Kansas. It has narrow streets, heavy traffic, limited train service, and the Express Bus is a misnomer. I tried that when I returned to New York in the early 80s, the buses would break down several times a week.

There is no reasonable way to get from Staten Island to Manhattan. The toll on the Verazanno is approaching \$100 if you are off State Island!

But can this be fixed? The answer is yes, but it is an infrastructure answer. If New York and New Jersey cannot get a tunnel for the near collapsing old one, then how will they solve this problem. The solution is simple, more ferries, at multiple locations. But that means investment and no politician wants to tackle that issue. The example of how this works is Hong Kong.

Back in the early 1960s Staten Island had a west shore train that went to Hoboken, then a rapid transfer to uptown or down town. I believe it was 1961 that the bridge connecting Staten Island to New Jersey was left open, the train with hundreds went to the water killing most people. They the closed the train line down. The tracks are still there, and that could be an option.

Otherwise, why not just give Staten Island back to New Jersey who had it originally! But this case is another example of why Government seems unable to do anything.



Labels: [Government](#)

Friday, August 24, 2018

[What Happened to the Old Telephone Company?](#)

The story about Verizon Wireless closing down data access to the California Firefighters as noted in [Ars Technica](#) is an example of what happens when a monopoly is no longer considered a monopoly. It also seems in my opinion to be the result of a management team who seem not to be American, mostly Europeans, and have no idea as to the long telecom culture of pitching in during tragedies. Instead they seem to be driven by wringing out ever nickel.

As the article notes:

This is not the first time we have had this issue. In December of 2017 while deployed to the Prado Mobilization Center supporting a series of large wildfires we had the same device with the same sim card also throttled. I was able to work through Eric Prosser at the time to have service to the device restored and Eric communicated that Verizon had properly re-categorized the device as truly "unlimited". In the email below Verizon is stating that they can restore the device for an extra \$2/month. I obviously lack the authority to make such an approval. If we could get Verizon [to get] that approval I would appreciate it.

In the old days when I was there we immediately turned to in any tragedy, adding capacity and even sending personnel and equipment. It appears that the new management seem to think they can totally disregard their customers even in times of need.

If this happens to firefighters in California just imagine what the plain old customer has to deal with. There unfortunately is no remedy available. It is a Pity, there was once a culture of support, now the culture is one of draining the last ounce of blood!



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

[A 100,000 feet View?](#)

A just released study on global alcohol usage and morbidity and mortality has just been released by [Lancet](#). The general conclusion seems to be:

Alcohol use is a leading risk factor for global disease burden and causes substantial health loss. We found that the risk of all-cause mortality, and of cancers specifically, rises with increasing levels of consumption, and the level of consumption that minimises health loss is zero. These results suggest that alcohol control policies might need to be revised worldwide, refocusing on efforts to lower overall population-level consumption.

Namely the world should stop drinking. This is a global study and it uses a multiplicity of previous studies and it even acknowledges its own deficiencies. Namely:

First, the available studies have assessed the risk of alcohol use by relying on external meta-analyses, which do not control for confounding in the selection of the reference category within constituent studies. This approach is problematic because of the so-called sick quitter hypothesis, which emphasises the importance of reference category selection in correctly assessing risk among drinkers, along with other confounding study characteristics such as survival bias...Second, previous studies have used sales data to estimate population-level alcohol stock. Researchers have noted the benefit of using sales data instead of survey data for quantifying alcohol stock available within a location. However, sales data still have bias because of consumption by tourists and unrecorded consumption from illicit sales, home brewing, and local beverages ...Third, previous studies have assumed zero as the counterfactual exposure level that minimises harm. Within a comparative risk assessment approach, a counterfactual level of consumption that minimises harm is required to estimate population attributable fractions.

In many ways this study has in my opinion weaknesses. Namely the simple one of co-morbidity issues. For example in many countries drinking and smoking are typically done together. Thus how does one separate the two effects. Second, as with all such studies the mechanism for the putative disease is missing. As we better understand cancers we better understand causes. Hypermethylation, oxidative stress, etc are but a few. What is alcohol? Then there is the issue that alcohol in the US is not alcohol in third world countries. The list goes on.

Although this is of interest, its generally over-broad presentation delimits its applicability in my opinion.



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

Friday, August 3, 2018

[Trees and Brains](#)



Now I like trees, really do. But trees are the main cause for power failures. The fall on the power lines, the lines break and then no power! Simple. So what does one do? Cut the tree.

Now NJ Transit, not to mention JCP&L et al seem not to have understood this fact of nature. Thus from today:

M&E Line train service has resumed Summit and Dover and subject to 90 minute delays in both directions following a downed tree in the overhead wires near Summit...

Namely we have another NJ Transit failure!

From the [NY Times](#) today we have:

New Jersey's new governor, Philip D. Murphy, a Democrat, has promised the state's commuters that train service would improve after years of decline. What he did not warn them was that it would get so much worse before it got better. Seven months after Mr. Murphy took office, many regular riders of New Jersey Transit, the state-run network of trains and buses, have become increasingly irate over a rash of train cancellations this summer that has made the nation's second busiest commuter rail system even less reliable. "It's really just a crapshoot on whether the train's going to run on time," said, who has been riding New Jersey Transit from Princeton Junction to Pennsylvania Station in Manhattan for more than two years. "The past few months has really just been awful."

Frankly what would one expect from a person from Goldman Sachs who most likely had never been on NJ Transit! Just a guess mind you. The Governor seems to know how to spend our money on such things as promoting the Press that supports him but not in getting the people whose taxes support him to work!

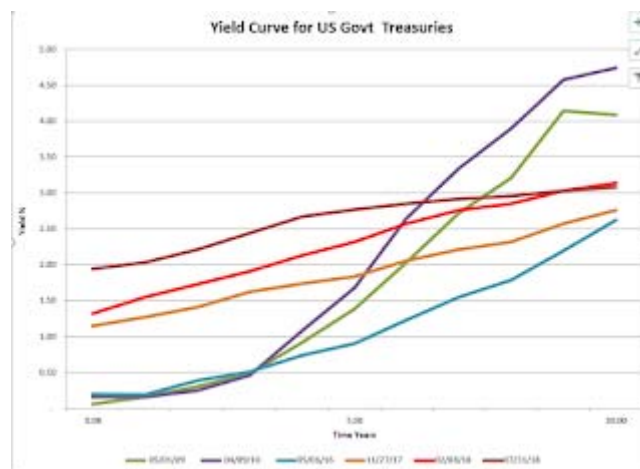
Infrastructure of the type as electricity, water, sewer, transport, roads and the like was a major focus on the Socialists a century ago. They felt they were better run by the Government. Look how that has worked out. Now the Socialists want Healthcare and Education, and you should wonder how that will work out.



Labels: [Government](#)

Wednesday, August 1, 2018

Yield Curve July 2018



The yield curve is flattening. It may invert. Has not done that in decades. It is worth watching. Remember 80% of US Debt is at these now higher short term rates. Remember also that in an inverted environment the world really looks different.

Hold on to your hats!



Labels: [Economy](#)

An Externality of Obesity

Externalities, those economic factors which a student is introduced to and spends most of their undergraduate days trying to understand. So try this one on.

[The Telegraph](#) reports:

But according to new reports emerging from Santorini, this scenery is now coming at a high cost in animal cruelty, with the price being paid by the island's donkey population. The practice of selling donkey rides to visitors is attracting growing criticism from animal welfare groups, who argue that the creatures are being forced to carry excessive numbers of increasingly overweight tourists from the UK, the USA and Russia. Coming in for particular fire is the busy route up the cliffs of the west coast - from the harbour at sea level to the capital Fira, which sits some 400 metres (1,312 feet) above the water, on the ridge.

Yes, those obese tourists from the US, UK and now Russia. Where are the Germans may I ask?

My experience over the years has shown that American style foods and worse American style servings are the cause. They first infiltrated the UK. I saw this about twenty years ago. The Pret a Manger sandwich shops went from small French style servings to Manhattan style colossal sandwiches. Then the Brits added fries and beer! Tie that on at lunch and then try to do anything

for the rest of the day.

The poor donkeys.



Labels: [Obesity](#)

Monday, July 30, 2018

[More Daylilies](#)

More dayliies.



Labels: [Commentary](#)

Wednesday, July 18, 2018

[Aphorisms for the Millennial](#)

SOME BUSINESS APHORISMS

OR

MURPHY DID NOT HAVE THE ONLY LAW

OR

FORTUNES YOU HAVE NEVER GOTTEN IN YOUR COOKIES

1 No is a good answer Saying no is okay. Saying no is the positive statement. All too often not saying no and going forward is deadly. Saying no may be the most difficult thing to do, it should be done more often. Not saying no costs money, takes time, and engenders distrust.

2 Delay is the deadliest form of denial Let's have one more meeting before we agree. Let's review it one more time. And the litany could continue. This is a corollary of "no is a good answer".

3 Avoid ambiguity of expectations Everyone did what they thought they were to do. And everyone was sorely disappointed with each other. Expectations were not met, in fact they were never discussed. It is critical to avoid any ambiguity of expectations. It is essential to have concurrence and then get it in writing with a plan agreed to by all and followed religiously on a periodic basis.

4 If all else fails listen to the customer This is the problem of both engineers and marketing people. All too often companies just listen to themselves and worse “the market” which is some amorphous entity which does not exist. The worst thing to listen to is analysts reports. They are dated and generally have some agenda beyond understanding the true market potential. One must reach out and talk to customers and see what they really want. That means listening to them even if it is what you may not want to hear.

5 Prior planning prevents poor performance Planning is a key part of business. Prior planning is the most key. Such questions as; what do we need when and what will cause the business to fail are also important issues to plan for. Failure can be precipitated by many factors and measuring failure metrics and having an action plan to counter them is an important part of the overall plan.

6 There may always be rocks from heaven No one is immortal. The end may come silently, over a long time, or as we say with a rock from heaven. When the rock from heaven falls on a key person in a company the remaining players better have a plan ahead of time. All too often that key person is key because the others are not expected to be. When the rock falls the company falls as well. Thus it helps to have a strong a deep team and never have all of them too close together so that one rock can do them all in at once!

7 Listen to a burning bush that speaks When one sees a burning bush, and then one hears it speaking ere are three possible responses; first, I may think I am crazy and just ignore it, second, I may feel fear and run away, and third, I may have some curiosity and listen to what it says. Burning bush moments happen frequently in life. Listening and then taking some action may be the better strategy. The burning bush moment may occur when one sees a new technology and when one then hears what the economics of that technology may do to an industry. It may also be when the stock market starts a downward spiral and one has a day or two to bail out. Listen and then act.

8 Any business whose profits exceed that of the cocaine business will soon be taken over by the Mafia or equivalent. In business plans, new businesses always have very rosy financial perspectives. Also the profits of these new business are generally highly unrealistic from the outset. They may also be unsustainable at any level. Thus, care in assessing hidden costs and price wars must be taken into account. Entrepreneurs, especially ones who have little to no true experience will present plans with truly excessive profit margins, margins exceeding the best in the drug markets. If a business truly has such a margin and can be sustained by means less than shall we say legal, then there is a good chance some unsavory elements may move in and seek the opportunity.

9 Profit is revenue less expenses, and only cash flow counts A small corner store in Brooklyn is a excellent example of understanding business. At the beginning of the week you count the cash, and at the end of the week you count the cash. If it has grown it is a good week, if not you are in trouble. Finance is not complicated unless you are playing games to hide bad decisions. Profit is only one of the factors to be considered, cash flow is the only factor to be considered.

10 If the Business is failing, do an acquisition Whenever a business has problems, especially a big business, they do another acquisition. The market thinks of any lacks of performance due to the transition period, so there is time to hide the developing mess under the smoke screen of an acquisition.

11 Any start-up or even existing businesses, which have a company headquarters that looks better than the best law firm will soon go out of business. This rule seems to apply everywhere. If one goes into a start up company and sees expensive furniture in an elegant office with lots of staff and amenities, they are spending money on the wrong thing. It is most likely the ego of the management that has gone wild not the success of the business. The problem also is that the Board has allowed this to occur.

12 You have to be at the bus stop if you want to get on the bus If you want to be on the bus to success you have to be at the corner stop when the bus arrives. That means that you have to get out to as many places as possible to ensure that you will be at the right place at the right time. Also if the bus takes you to some place you do not like, get off as soon as possible and try another bus.

13 Whenever a company builds a grand new edifice, it will soon collapse Companies have the habit of reaching a point and deciding that they need their own new building. They then commence construction and lose focus on day to day execution. The CEO may be spending more time on the seat cover fabric than on the bottom line. One observation that seems to be very consistent through all economic conditions is that whenever a company decides to spend great amounts on a new corporate edifice most likely it occurs just before a great downturn. Just look at Time Warner, Bear Stearns, MCI, Worldcom, and lists of others. To avoid this plague one should stay in smaller offices or grow incrementally. The best example was the ATT massive headquarters. By the way, Verizon is moving into that building now.

14 Always have a second exit No plan is ever fool proof. Thus having second exits, a Plan B possibly, or another way to get around the mountain other than just climbing it is essential. Plan B is not defeat, it is a sign of wisdom.

15 Attila the Hun could get a job as a grief counselor Selecting management personnel is a difficult task but the most critical in any company. All too often the same bad person ends up in the same job that he managed to mess up the last ten times. It is amazing to see patterns repeat over and over again. One would not hire Attila the Hun as a grief counselor if one did a brief check on what he did prior to seeking this position. It is critical to check what people did why they left where they left and if your company wants to have that person, perhaps you do, most likely you don't. 1

16 A deal is not a deal until the money is in the bank, for a week One should not count on something that is one's sole perception of what could occur. All too often after a meeting with a customer, a vendor, a banker, we all ask each other how did it go and what chance do we have. The answer is that there is zero chance until the deal is done. That means signed, delivered and the money collected.



Labels: [Commentary](#)

Monday, July 16, 2018

[This is Why They Are Called Daylilies](#)

This is why they are "day"lilies. Watch as they open-close then open anew. Also did not see any of my critters flying by. I have a chipmunk who gets annoyed if I interrupt him. He then sits up and lets me know it!



Labels: [Commentary](#)

Monday, July 16, 2018

[Beware of CRISPRs](#)

We have been following CRISPRs for a few years now and one of our most referenced papers was on [CRISPR and Cancer](#). That was four and a half years ago. Yet even then we were concerned as to certain errors that could result.

In a recent [Nature paper](#) the authors note:

CRISPR–Cas9 is poised to become the gene editing tool of choice in clinical contexts. Thus far, exploration of Cas9-induced genetic alterations has been limited to the immediate vicinity of the target site and distal off-target sequences, leading to the conclusion that CRISPR–Cas9 was reasonably specific. Here we report significant on-target mutagenesis, such as large deletions and more complex genomic rearrangements at the targeted sites in mouse embryonic stem cells, mouse hematopoietic progenitors and a human differentiated cell line. Using long-read sequencing and long-range PCR genotyping, we show that DNA breaks introduced by single-guide RNA/Cas9 frequently resolved into deletions extending over many kilobases. Furthermore, lesions distal to the cut site and crossover events were identified. The observed genomic damage in mitotically active cells caused by CRISPR–Cas9 editing may have pathogenic consequences.

Simply stated there may be errors that result in deleterious effects. This paper is well worth the read.



Labels: [CRISPR](#)

Saturday, July 14, 2018

[Happy Bastille Day](#)

Allons enfants de la Patrie
Le jour de gloire est arrivé
Contre nous de la tyrannie
L'étendard sanglant est levé (bis)
Entendez vous dans les campagnes mugir ces féroces soldats
Ils viennent jusque dans vos bras, égorger vos fils, vos compagnes
Aux armes citoyens !
Formez vos bataillons !
Marchons, marchons, qu'un sang impur abreuve nos sillons

Always worth remembering. Except perhaps for Robespierre!



Labels: [Commentary](#)

[Daylilies in Bloom](#)

Yes these are daylilies, a one day wonder.



Labels: [Daylilies](#)

Friday, July 13, 2018

[An Interesting Observation](#)

G.H. Hardy was a brilliant mathematician, and also had great insight. He wrote in his book, [A Mathematician's Apology](#), the following:

I shall assume that I am writing for readers who are full, or have in the past been full, of a proper spirit of ambition. A man's first duty, a young man's at any rate, is to be ambitious. Ambition is a noble passion which may legitimately take many forms; there was something noble in the ambition of Attila or Napoleon: but the noblest ambition is that of leaving behind one something of permanent value—

*Here, on the level sand,
Between the sea and land,
What shall I build or write Against the fall of night?
Tell me of runes to grave That hold the bursting wave,
Or bastions to design For longer date than mine.*

Ambition has been the driving force behind nearly all the best work of the world. In particular, practically all substantial contributions to human happiness have been made by ambitious men. To take two famous examples, were not Lister and Pasteur ambitious ? Or, on a humbler level, King Gillette and William Willett; and who in recent times have contributed more to human comfort than they?

Physiology provides particularly good examples, just because it is so obviously a 'beneficial'

study. We must guard against a fallacy common among apologists of science, the fallacy of supposing that the men whose work most benefits humanity are thinking much of that while they do it, that physiologists, for example, have particularly noble souls. A physiologist may indeed be glad to remember that his work will benefit mankind, but the motives which provide the force and the inspiration for it are indistinguishable from those of a classical scholar or a mathematician.

There are many highly respectable motives which may lead men to prosecute research, but three which are much more important than the rest. The first (without which the rest must come to nothing) is intellectual curiosity, desire to know the truth. Then, professional pride, anxiety to be satisfied with one's performance, the shame that overcomes any self-respecting craftsman when his work is unworthy of his talent. Finally, ambition, desire for reputation, and the position, even the power or the money, which it brings. It may be fine to feel, when you have done your work, that you have added to the happiness or alleviated the sufferings of others, but that will not be why you did it. So if a mathematician, or a chemist, or even a physiologist, were to tell me that the driving force in his work had been the desire to benefit humanity, then I should not believe him (nor should I think the better of him if I did). His dominant motives have been those which I have stated, and in which, surely, there is nothing of which any decent man need be ashamed.

This may sound a bit outdated in today's world, but it has a certain ring of truth. We should not neglect the past assuming that it is irrelevant.



Labels: [Commentary](#)

Thursday, July 12, 2018

[FCC and Telehealth](#)

The area of telehealth has been an ongoing process of incremental implementation. At one extreme it was merely assisting in the ability to perform diagnoses at a distance. In fact I was one of the earliest developers of such a system for use in radiology. (See [1](#), [2](#), [3](#), [4](#)) All of the original work was done in the late 1980s, some thirty years ago. There is now a rush to provide a variety of such systems but understanding healthcare one must understand efficacy and costs.

Notwithstanding the facts, the FCC has announced a \$100 million program in this area apparently based on a single trip to the South! [Beckers](#) notes that:

... a commissioner of the Federal Communications Commission, on July 11 [revealed](#) the agency's plan to establish a \$100 million connected care pilot program. The program, which would support the use of telehealth for low-income Americans, spun out of a visit to Mississippi Mr. Carr took six months ago, during which he learned about a remote patient monitoring trial that improved medical outcomes for diabetes patients living in rural areas. Since his visit, Mr. Carr said he has met with telehealth experts and visited rural healthcare facilities to determine how the FCC can support the movement toward "connected care."

The [FCC notice](#) on this action notes:

The FCC will vote on a Notice of Inquiry at its August Open Meeting that seeks comment on:

- *Budgeting for \$100 million in USF support*
- *Targeting support to connected care deployments that would benefit low-income patients, including those eligible for Medicaid or veterans receiving cost-free medical care*
- *Supporting a limited number of projects over a two- or three-year period with controls in place to measure and verify the benefits, costs, and savings associated with connected care deployments*

Investments in connected care have resulted in substantial savings, particularly in the management of chronic diseases, which account for over 85% of direct health care spending in the U.S.:

- *The Mississippi Delta trial resulted in nearly \$700,000 in annual savings due to reductions in hospital readmissions alone. Assuming just 20% of Mississippi's diabetic population enrolled in this program, Medicaid savings in the state would be \$189 million per year.*
- *The Veterans Health Administration's (VHA) remote patient monitoring program cost \$1,600 per patient compared to more than \$13,000 per patient for VHA's home-based primary services.*
- *A telehealth project in the Northeastern U.S. found that every \$1 spent on remote monitoring resulted in a \$3.30 return in savings.*

The problem is several-fold:

1. First, this is a complex issue relating to cost and efficacy in area which are well outside the expertise of the FCC.
2. Second, there is already a complex set of private sector developments in this area and CMS and other agencies are extensively evaluating them. [Modern Healthcare](#) has noted:

CMS on Thursday proposed paying doctors for virtual visits and overhauling Medicare billing standards it has had in place since the 1990s. In a lengthy proposed rule, the agency said it would pay doctors for their time when they reach out to beneficiaries via telephone or other telecommunications devices to decide whether an office visit or other service is needed. In addition, the CMS also proposed paying for the time it takes physicians to review a video or image sent by patient seeking care or diagnosis for an ailment. "This is a big issue for elderly and disabled population for which transportation can be a barrier to care," CMS Administrator Seema Verma said. "We're not intending to replace office visits but rather to augment them and create new access points for patients." Most physicians bill Medicare for patient visits under a relatively generic set of codes that distinguish level of complexity and site of care, known as evaluation and management visit codes. Doctors long have been concerned about the codes' documentation standards. The CMS has used evaluation and management visit codes since 1995.

The CMS proposed allowing practitioners to designate the level of a patient's care needs using their medical decisionmaking or time they spent with the patient instead of applying the decades-old E/M documentation guidelines.

3. It is not at all clear what expertise the FCC brings to bear. It was akin to my time at NYNEX now Verizon. A big opportunity and early entry but a clueless management. They were pole climbers, not diagnosticians.

4. The example of Type 2 Diabetes management is a classic one. As [we have noted in a multiplicity of places](#), management of this disease is all too often a simple problem of diet and weight control. Yet that has always been a stumbling block because we just do not want to admonish patients for their own diseases. However with tobacco we did just that and lung cancer rates for males are plummeting. Fear, trembling and shame may really work, as well as a financial incentive.

5. Telemedicine is not just communications. In fact it barely needs a great deal now. Thirty years ago when I first started this we had 256Kbps lines and 100 Mbps Ethernet. Now we have wireless that beats it hands down. It requires software, medical procedures, changes in coding and billing, physician interaction and facilitation etc. None of this is in the FCC's purview. Thus what does the FCC bring to the table. Such an issue as licensing alone needs to be addressed. If I have a Massachusetts license how do I treat a patient in West Virginia? None of this can be handled by the FCC.

Given the current Federal Deficit one wonders in what Universe this program should see the light of day!



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

[An Alumni Magazine?](#)

I started getting Scientific American while in High School. My first copy I purchased at a News Stand on Lexington and 52nd Street in May of 1960. I read it from cover to cover. In May of 2000 I terminated my subscription, I could not read a single paragraph in the now newsy rag.

Now skip to Alumni magazines. Their purpose is to communicate with the Alumni, some are good some are well not so good. I get a few and the one from Columbia is just fine. They get the point across without too much preaching.

Now to MIT. Some 20 years ago MIT gave up control, so it appears, to Technology Review. It was half tech updates and half Institute and Alumni material. I looked at it somewhat. Then the new management, from Silicon Valley dot com geeks took over. Barely look at it now at all. They preach their political screeds and try and compete with their flashy peers.

The new Technology Review editor, some fellow who spent time at a British publications and apparently with little of no understanding of [MIT](#), writes:

Unfortunately, those who build technology, those who use and are affected by it, and those who create its legal, regulatory, and financial frameworks—its makers, users, and framers, to coin a shorthand—often aren't choosing well. Makers are usually too focused on financial success;

users cannot see how their lives are gradually but fundamentally changing; and framers rarely understand the inventions for which they are writing laws, rules, or checks. This leads to ill-informed decisions by all three groups. That's why, along with the redesigned print edition of MIT Technology Review, we're also launching a new mission statement: "to bring about better informed and more conscious decisions about technology through authoritative, influential, and trustworthy journalism." We think it's no longer enough for tech journalism to merely explain technology and its ramifications. Rather, it should explicitly strive to make technology more of a force for good, by helping its makers, users, and framers reach better decisions. We'll do that in a number of ways, including writing more about tech ethics and policy. But we're also changing the notion of what a printed magazine is for.

Apparently this seems to mean that they will be expanding their political preaching with total disregard for the interest of the Alumni. So who is to make the decisions? The Editor, the writers, and are the people, the alumni out there now, so inept that we need another Brit hand me down to "tell us what to do". Have we been doing such a shabby job as is?

As they say, you cannot make this up. Arrogance along with ignorance is a deadly combination, especially if one is trying to raise alumni support!



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

Wednesday, July 11, 2018

[Rare Earths Redux](#)

Some eight years ago [we wrote extensively about rare earths and China's actions](#) to control the market. We further noted that for decades the US was the world's supplier of them. We did not run out, we just closed the mine! It was in California and they wanted it closed. The elements are still there folks, lots of them.

Then along comes the [NY Times](#), the paper which seems to be a bit short sighted. They note:

Rare earth refining is done on a large scale in only two places on earth: China, and Lynas's plant here in Kuantan, Malaysia, a sprawling industrial area on the coast of the South China Sea. The company mines rare earths out of a collapsed volcano in Australia and ships them to Kuantan to be refined. Building that plant nearly sank Lynas. When Ms. Lacaze was named chief executive in June 2014, the company was struggling with \$450 million in debt. Design flaws had delayed full production. It faced criticism from environmentalists (NOTE: which by the way was the California problem). China is her most immediate challenge. Lynas is now profitable, but Ms. Lacaze sees a potential trade war between China and the United States as more of a threat than an opportunity. Beijing could keep rare earths off the market, depriving many American and European manufacturers of the minerals they need. Lynas couldn't compensate for it all. It accounted for only about 12 percent of world output of rare earths last year, according to Adamas, the research firm. Chinese companies accounted for more than four-fifths.

But the US could compensate, and actually dominate the world market. See the [MIT status](#) updates. The Times continues:

Even if it doesn't disrupt the supply, China will likely keep its grip over the market for rare earths for a long time to come. It also dominates research and development of these minerals, giving it a leg up on the future, Ms. Lacaze said. "I think there's about 100 Ph.D.s in rare earths working in applications inside China and working in technology development," she said. "To my knowledge, do you know how many Ph.D.s there are outside of China?" With the fingers of her right hand, she made a zero.

I believe she is grossly in error. But leave that aside. Steel and aluminum are important but rare earths are truly strategic. Furthermore the PLA controls Chinese production. Perhaps some one in the current Administration will catch on. The last one never did. Now we have a real problem!

Now [Bloomberg](#) notes:

China's grip on rare-earths supply is so strong that the U.S. joined with other nations earlier this decade in a World Trade Organization case to force the nation to export more of the materials, not less, after prices spiked amid a global shortage. The WTO ruled in favor of the U.S., while prices eventually slumped as manufacturers turned to alternatives. Imposing duties will "bring home to the American public the reality of how much of what they use in everyday life contains these technology metals," Jack Lifton, the Michigan-based founder of rare earth consulting service Technology Metals Research LLC, said by phone. "The Chinese mine the rare-earths, they separate them, they refine them. This is the long-term trend and a 10 percent tariff will not do anything to stir any domestic production in the U.S."

The real problem is that the US has the largest Rare Earth reserves, closed down a few decades ago due to "environmental" concerns. Like the Times, Bloomberg seems to be totally oblivious to the availability and the amount in the US. To some degree this is a "Yellow Journalistic" approach in my opinion. The US should and must reinvigorate its own sources, now. Just look at the [USGS map!](#)



Labels: [China](#), [Rare Earths](#)

[The Brits, Class and The Visit](#)

Having spent time in and out of Britain it is clear what "class" means. The British system is class based and in many ways it exceeds any of the characteristics of the Indian caste system. It starts with heritage, who was your family, then moves to education, profession, accent etc. One can almost place a person by the accent alone. The Brits can then align themselves according to where their culture places them. Mobility in the system is almost impossible, since the long line of ancestors often dominates.

The Brits have looked down upon their captive folks, the Empire residents, from the Irish and Indians to the Jamaicans and others. One just need to read [de Tocqueville's](#) text on his Irish visit to see this in action. Now it is thus reasonable that a par venue from Queens, New York, the

town's name is the utter irony in this case, would cause such a disruption. Coming from Staten Island, before the bridge, I am a New Yorker, but at a time that we could have easily been considered someone from Nebraska! But Queens, the borough that exploded after WW II and is now more ethnically complex than any place in the world, well that is a stretch!

Now along comes a [NY Times](#) piece that tells us all of the Brits. The author notes:

When President Trump visits Britain this week, many people here will want to remind him — and the rest of the world — just how nauseating we think he is. He's new money. He's perma-tanned. He's a former reality TV star. He's American. He's everything the British, snobs that we are, love to hate. And that's before we even get started on his ghastly politics. When it comes to making people feel that they don't belong, nobody does it better than us. America may be the most powerful nation on earth, but Britain is still the snootiest.

This Brit exemplifies what we across the pond who have been exposed to them truly recognize. Now leaving the person targeted aside, they are this way all the time. From the taxi driver to the desk clerk to the museum ticket taker. I had a spare moment once and though I would walk through the museum at Buckingham Palace. resenting my ID the response was negative, a double negative, an Irish name on a US Passport! I was truly beneath contempt! Oh yes, just a reminder, in WW I the US troops had no winter coats so that they got them from the Brits. The Irish from the US then promptly tore off all the buttons which were emblems of the Crown! The coats flapped but we won the War. The author above just reinforces the reason to keep visits to Britain brief!

It will be interesting to see their response. Balloon and all.



Labels: [Commentary](#)

Tuesday, July 10, 2018

[Supreme Court and Net Neutrality](#)

Let me give a simple example. The First Amendment gives all of us a right to free speech where the Government cannot deny us, especially political speech. One could generally agree with that.

Now the Government grants exclusive licenses to say a cable company or a wireless company to provide access. Let's wait there a bit and consider a simpler example.

Let us assume I want to give a speech, to let the people know of some Governmental problem for which I seek a remedy. However to do so I need a soap box to stand on, perhaps I am height impaired. But the Government granted the exclusive monopoly to the soap box manufacturer. He refuses to sell me a soap box or even rent one. My speech cannot be accomplished. Has the Government violated my First Amendment right?

Well according the Kavanaugh, the soap box company has the right and not me! This is Jesuitic logic at its best. The soap box company can deny me access because I would violate their rights.

You cannot make this up folks.

Now [the Judge states](#):

The net neutrality rule is unlawful and must be vacated, however, for two alternative and independent reasons. First, Congress did not clearly authorize the FCC to issue the net neutrality rule. Second and in the alternative, the net neutrality rule violates the First Amendment to the U.S. Constitution. Under the Supreme Court's landmark decisions in Turner Broadcasting System, Inc. v. FCC, 512 U.S. 622 (1994), and Turner Broadcasting System, Inc. v. FCC, 520 U.S. 180 (1997), the First Amendment bars the Government from restricting the editorial discretion of Internet service providers, absent a showing that an Internet service provider possesses market power in a relevant geographic market. Here, however, the FCC has not even tried to make a market power showing. Therefore, under the Supreme Court's precedents applying the First Amendment, the net neutrality rule violates the First Amendment..... In short, although the briefs and commentary about the net neutrality issue are voluminous, the legal analysis is straightforward: If the Supreme Court's major rules doctrine means what it says, then the net neutrality rule is unlawful because Congress has not clearly authorized the FCC to issue this major rule. And if the Supreme Court's Turner Broadcasting decisions mean what they say, then the net neutrality rule is unlawful because the rule impermissibly infringes on the Internet service providers' editorial discretion. To state the obvious, the Supreme Court could always refine or reconsider the major rules doctrine or its decisions in the Turner Broadcasting cases. But as a lower court, we do not possess that power. Our job is to apply Supreme Court precedent as it stands. For those two alternative and independent reasons, the FCC's net neutrality regulation is unlawful and must be vacated. I respectfully disagree with the panel majority's contrary decision and, given the exceptional importance of the issue, respectfully dissent from the denial of rehearing en banc.

Now there are these two points. First, Chevron gives the Administrative agencies broad discretion in implementing the law. Kavanaugh seems to see it as quite narrow with ongoing Congressional authorization for every period and comma and colon. Second, the soap box issue is critical. They the ISPs are for the most part monopolies or at least oligopolies. They control free speech, they delimit free speech. The opinion above is in my opinion without merit. I have previously considered this in detail in a non-Jesuitic manner. [My rather Ockhamistic approach](#) uses logic and grammar as clear textual interpretation. The above is in my opinion a clear delimitation of free speech, and is in my opinion a clear breach of the First Amendment.

But it seems the soap box manufacturer's monopolistic lobby has won, for now!



Labels: [Constitution](#), [Internet Neutrality](#)

Monday, July 9, 2018

[Interesting Drug Prices](#)

In a recent piece in [Becker's Hospital Review](#) they list the cities with the highest and lowest drug prices.

They note:

10 most expensive cities for medications

- 1. New York City — 20.10 percent above national average*
- 2. San Francisco — 12.60 percent*
- 3. Los Angeles — 9.80 percent*
- 4. Philadelphia — 7.90 percent*
- 5. San Diego — 6.40 percent*
- 6. Raleigh, N.C. — 4.30 percent*
- 7. Birmingham, Ala. — 3.90 percent*
- 8. Orlando — 2.80 percent*
- 9. Cleveland — 2.50 percent*
- 10. Sacramento, Calif. — 2.20 percent*

10 least expensive cities for medications

- 1. Columbus, Ohio — 21.70 percent below national average*
- 2. Atlanta — 18.60 percent*
- 3. Houston — 17.40 percent*
- 4. Dallas — 16.90 percent*
- 5. Denver — 16.30 percent*
- 6. Salt Lake City — 11.00 percent*
- 7. Indianapolis — 10.60 percent*
- 8. Washington, D.C. — 10.60 percent*
- 9. Las Vegas — 9.40 percent*
- 10. Tampa, Fla. — 7.30 percent*

That looks like a 42% swing! I know New York is expensive, in Manhattan, but all over the city?



Labels: [Health Care](#)

Wednesday, July 4, 2018

[Propaganda in Today's World](#)

Edward Bernays wrote a book called Propaganda in 1928. Bernays was a part of the Wilson Propaganda machine in WW I called the US Committee on Public Information, CPI, the original "fake news" outlet of the US. An entity funded by taxpayer dollars and ultimately directed by and for Wilson.

Bernays notes:

Modern propaganda is a consistent, enduring effort to create or shape events to influence the relations of the public to an enterprise, idea or group. This practice of creating circumstances and of creating pictures in the minds of millions of persons is very common.

Virtually no important undertaking is now carried on without it, whether the enterprise be building a cathedral, endowing a university, marketing a moving picture, floating a large bond issue, or electing a president. Sometimes the effect on the public is created by a professional propagandist, sometimes by an amateur deputed for the job.

The important thing is that it is universal and continuous; and in its sum total it is regimenting the public mind every bit as much as an army regiments the bodies of its soldiers. So vast are the numbers of minds which can be regimented, and so tenacious are they when regimented, that a group at times offers an irresistible pressure before which legislators, editors, and teachers are helpless.

The group will cling to its stereotypes, as Walter Lippmann calls it, making of those supposedly powerful beings, the leaders of public opinion, mere bits of driftwood in the surf. When an Imperial Wizard, sensing what is perhaps hunger for an ideal, offers a picture of a nation all Nordic and nationalistic, the common man of the older American stock, feeling himself elbowed out of his rightful position and prosperity by the newer immigrant stocks, grasps the picture which fits in so neatly with his prejudices, and makes it his own.

He buys the sheet and pillowcase costume, and bands with his fellows by the thousand into a huge group powerful enough to swing state elections and to throw a ponderous monkey wrench into a national convention. In our present social organization approval of the public is essential to any large undertaking. Hence a laudable movement may be lost unless it impresses itself on the public mind. Charity, as well as business, and politics and literature, for that matter, have had to adopt propaganda, for the public must be regimented into giving money just as it must be regimented into tuberculosis prophylaxis.

The Near East Relief, the Association for the Improvement of the Condition of the Poor of New York, and all the rest, have to work on public opinion just as though they had tubes of toothpaste to sell. We are proud of our diminishing infant death rate—and that too is the work of propaganda. Propaganda does exist on all sides of us, and it does change our mental pictures of the world. Even if this be unduly pessimistic—and that remains to be proved—the opinion reflects a tendency that is undoubtedly real. ...

Bernays then continues to note Propaganda more closely in Politics. He states:

The great political problem in our modern democracy is how to induce our leaders to lead. The dogma that the voice of the people is the voice of God tends to make elected persons the will-less servants of their constituents. This is undoubtedly part cause of the political sterility of which certain American critics constantly complain.

No serious sociologist any longer believes that the voice of the people expresses any divine or specially wise and lofty idea. The voice of the people expresses the mind of the people, and that

mind is made up for it by the group leaders in whom it believes and by those persons who understand the manipulation of public opinion. It is composed of inherited prejudices and symbols and cliches and verbal formulas supplied to them by the leaders.

Fortunately, the sincere and gifted politician is able, by the instrument of propaganda, to mold and form the will of the people. Disraeli cynically expressed the dilemma, when he said: "I must follow the people. Am I not their leader?" He might have added: "I must lead the people. Am I not their servant?" Unfortunately, the methods of our contemporary politicians, in dealing with the public, are as archaic and ineffective as the advertising methods of business in 1900 would be today. While politics was the first important department of American life to use propaganda on a large scale, it has been the slowest in modifying its propaganda methods to meet the changed conditions of the public mind. American business first learned from politics the methods of appealing to the broad public.

But it continually improved those methods in the course of its competitive struggle, while politics clung to the old formulas. The political apathy of the average voter, of which we hear so much, is undoubtedly due to the fact that the politician does not know how to meet the conditions of the public mind. He cannot dramatize himself and his platform in terms which have real meaning to the public. Acting on the fallacy that the leader must slavishly follow, he deprives his campaign of all dramatic interest. An automaton cannot arouse the public interest. A leader, a fighter, a dictator, can. But, given our present political conditions under which every office seeker must cater to the vote of the masses, the only means by which the born leader can lead is the expert use of propaganda. Whether in the problem of getting elected to office or in the problem of interpreting and popularizing new issues, or in the problem of making the day-to-day administration of public affairs a vital part of the community life, the use of propaganda, carefully adjusted to the mentality of the masses, is an essential adjunct of political life. The successful businessman today apes the politician. He has adopted the glitter and the ballyhoo of the campaign. He has set up all the sideshows.

He has annual dinners that are a compendium of speeches, flags, bombast, stateliness, pseudo-democracy slightly tinged with paternalism. On occasion he doles out honors to employees, much as the republic of classic times rewarded its worthy citizens. But these are merely the sideshows, the drums, of big business, by which it builds up an image of public service, and of honorary service.

This is but one of the methods by which business stimulates loyal enthusiasms on the part of directors, the workers, the stockholders and the consumer public. It is one of the methods by which big business performs its function of making and selling products to the public. The real work and campaign of business consists of intensive study of the public, the manufacture of products based on this study, and exhaustive use of every means of reaching the public. Political campaigns today are all sideshows, all honors, all bombast, glitter, and speeches. These are for the most part unrelated to the main business of studying the public scientifically, of supplying the public with party, candidate, platform, and performance, and selling the public these ideas and products. Politics was the first big business in America. Therefore there is a good deal of irony in the fact that business has learned everything that politics has to teach, but that politics has failed to learn very much from business methods of mass distribution of ideas and products.

Now we can examine how this is being tried in New Jersey. The Hill notes²¹[1]:

New Jersey Gov. Phil Murphy (D) is approving a bill that dedicates \$5 million to strengthen local media outlets in the state. The state legislature passed the "Civic Info Bill" late last month, ... The bill created the Civic Information Consortium — a unique nonprofit developed with five universities — to promote the spread of news and information throughout the state. The bill was conceived by the Free Press Action Fund, an advocacy group on media issues.

The effort is led by The College of New Jersey, Montclair State University, the New Jersey Institute of Technology, Rowan University and Rutgers University. The consortium will share the \$5 million with local news organizations, emphasizing "underserved communities, low-income communities and communities of color," the Free Press Action Fund said. The money was included in the fiscal 2019 budget, which Murphy signed into law on Sunday. He is expected to formally sign the legislation creating the consortium soon.

One must ask:

1. Given the exploding tax burden on New Jersey residents, why this now?
2. As with any Government program it is a camel's nose in the tent. It is \$5 million now and \$500 million soon!
3. Having Universities "control" the money means that in New Jersey, politically hand picked "academic" often with allegiance to the powers that be get to create and support Propaganda! Remember Bernays.
4. The idea was conceived it is stated by what in my opinion, based on my experience, is a far left wing organization in DC. Why did they do this and for whose benefit.

Frankly in my opinion this makes the Wilson era CPI look like a kindergarten exercise.



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

Tuesday, July 3, 2018

[Exosomes Again](#)

Exosomes are those small sets of material ejected from cells. Cancer cells like all other cells eject these exosomes. A recent paper presents an interesting result; namely that exosomes may

²¹[1] <http://thehill.com/homenews/state-watch/395206-nj-governor-signs-bill-dedicating-5-million-to-strengthen-local-media>

excite normal cells to become malignant. This is effectively an infectious scenario for cancer.

In the paper by [Stefanius et al](#) they note:

Cancer evolves through a multistep process that occurs by the temporal accumulation of genetic mutations mediated by intracellular and extracellular cues. We observe that exosomes isolated from pancreatic cancer cells, but not normal pancreatic cells, can initiate the first step of malignant cell transformation. Injection of exosome-initiated transformed cells into mice results in aggressive tumor growth. Using proteomic profiling and DNA sequencing of exosome-treated and transformed cells, we show that cancer cell exosomes act as a classic initiator by causing random genetic changes in recipient cells. Our studies provide new insight into a function of cancer cell exosomes and how they might specifically contribute to orchestrated local cell transformation.

This is an interesting result and worth following.



Labels: [Cancer](#)

Tuesday, July 3, 2018

[Politics and Aristotle](#)

Aristotle wrote his work on Politics almost 2500 years ago and it still resonates today. I would suggest that one perhaps take some time and read a bit over the summer breaks. Try to leave behind the vitriol of current life and contemplate on what Aristotle observed then.

I use Copleston (History of Philosophy, V I Part II) to lay forth the ideas. I first read this in detail in the Fall of 1962 just after the Cuban Missie debacle. From Copleston we have a powerful discussion of revolution, against a Constitutional government:

*Aristotle treats acutely of the various kinds and degrees of **revolution which tend to occur under different Constitutions, of their causes and the means of preventing them**; and, owing to his great historical knowledge, he was able to give apt historical illustrations of the points he wished to make. He points out, for instance, that the revolutionary state of mind is largely brought about by one-sided notions of justice—democrats thinking that men who are equally free should be equal in everything, oligarchs thinking that because men are unequal in wealth they should be unequal in everything. He emphasizes the fact that rulers should have no opportunity of making money for themselves out of the offices they hold, and stresses the requisites for high office in the State, namely, loyalty to the Constitution, capacity for administrative work and integrity of character. Whatever be the type of Constitution, it must be careful not to go to extremes; for if either democracy or oligarchy is pushed to extremes the ensuing rise of malcontent parties will be sure to lead in the end to revolution.*

Extremes are always a danger and even today we see that occurring. Beware the words of Aristotle.

*In Books Seven and Eight of the Politics Aristotle discusses his positive views of what a State should be. (i) The State must be large enough to be self-sufficing (of course Aristotle's notion of what a self-sufficing community actually is would be altogether inadequate for modern times), but not so large that order and good government are rendered impracticable. In other words, it must be large enough to fulfil the end of the State and not so large that it can no longer do so. The number of citizens requisite for this purpose cannot of course be arithmetically determined a priori. (ii) Similarly with the territorial extent of the State. This should not be so small that a leisured life is impossible (i.e. that culture is impracticable) nor yet so large that luxury is encouraged. The city should not aim at mere wealth, but at importing her needs and exporting her surplus. (iii) Citizens. **Agricultural labourers and artisans are necessary, but they will not enjoy citizen rights. Only the third class, that of the warriors, will be citizens in the full sense. These will be warriors in youth, rulers or magistrates in middle-age and priests in old age. Each citizen will possess a plot of land near the city and another near the frontier (so that all may have an interest in the defence of the State). This land will be worked by the non-citizen labourers***

The above is again prescient. Who is a citizen and borders, and of course limits. Moreover, who is not a citizen.

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Aristotle had a point here. Do we choose our leaders this way? All too often we see excess self aggrandizement. Finally:

The only real guarantee of the stability and prosperity of the State is the moral goodness and integrity of the citizens, while conversely, unless the State is good and the system of its education is rational, moral and healthy, the citizens will not become good. The individual attains his proper development and perfection through his concrete life, which is a life in Society, i.e. in the State, while Society attains its proper end through the perfection of its members. That Aristotle did not consider the State to be a great Leviathan beyond good and evil is clear from the criticism he passes on the Lacedaemonians. It is a great mistake, he says, to suppose that war and domination are the be-all and end-all of the State. The State exists for the good life, and it is subject to the same code of morality as the individual. As he puts it, "the same things are best for individuals and states." Reason and history both show that the legislator should direct all his

military and other measures to the establishment of peace. Military States are safe only in wartime: once they have acquired their empire, they rust away like iron and fall. Both Plato and Aristotle, in their preoccupation with the fostering of a truly cultural political life, set their faces against imperialist dreams of military aggrandizement.

Worth a read.



Labels: [Politics](#)

Saturday, June 30, 2018

[Medicare Spending](#)

A recent study tries to correct the misconception of Medicare spending. [MIT](#) reports:

After examining millions of medical records, the study found that although Medicare spending is concentrated among people who die, there is very little Medicare spending on patients whose death within the year is highly likely. For example, the researchers discovered, less than 5 percent of Medicare spending is applied to the single highest-risk percentile of all individuals — and their predicted one-year mortality rate is still just 46 percent. “What we discovered is, very little money is spent on people who we know with high probability are going to die in a short amount of time,” says ..., a professor in MIT’s Department of Economics and co-author of a paper in the journal Science that details the study’s findings. To the extent that such cases exist, she adds, “they’re just not the drivers of spending” in bulk. The study also illuminates the general circumstances of late-in-life mortality. Fewer than 10 percent of people who die in a given year have a predicted one-year mortality rate over 50 percent. As the researchers found, even when people are admitted to a hospital in what turns out to be their last year of life, fewer than 4 percent of those patients have a predicted one-year mortality rate of 80 percent or higher at the time of admission.

So I guess "words mean something". For decades politicians and policy wonks have spouted the inefficiency of Medicare. In reality if 5% is spent on the last year of life, and if Medicare starts at 65 and life expectancy for a person at 65 is to 82, then the 18 years indicates that 5% is less than the annual allocation. In effect, known last year expenditures are below average.

Between using the right words and the right numbers one comes up with a grossly different answer. The result, one must question everything, especially if from a Government source.



Labels: [Health Care](#)

[Summer Truly Begins](#)



The daylily species, *Hemerocallis citrina*, is a fragrant night blooming flower found often in China.



One knows summer is here when it begins to bloom. I did last night.



If one has a house surrounded by these then at night the fragrance is wonderful!



Labels: [Commentary](#)

Wednesday, June 27, 2018

[Way Back](#)



The above is Midland Beach on Staten Island. Some 60 years ago I started my career there as a Lifeguard and I recall the beach packed with people every day! Now it is empty. Guess they went to the Jersey Shore!

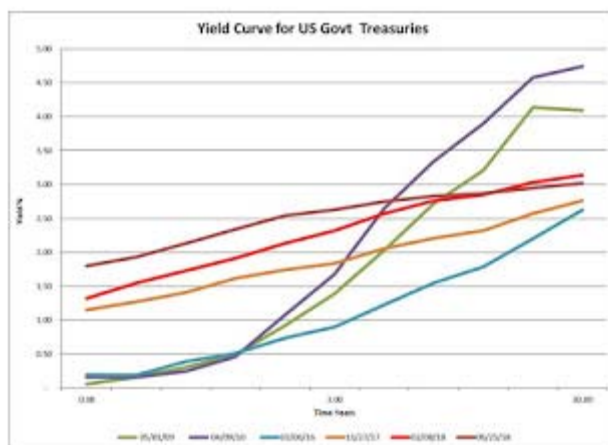
Also look at the "sand", it is clay brown and relatively unappealing. As with anything under the control of New York City these days the bath houses are collapsing but fortunately closed.



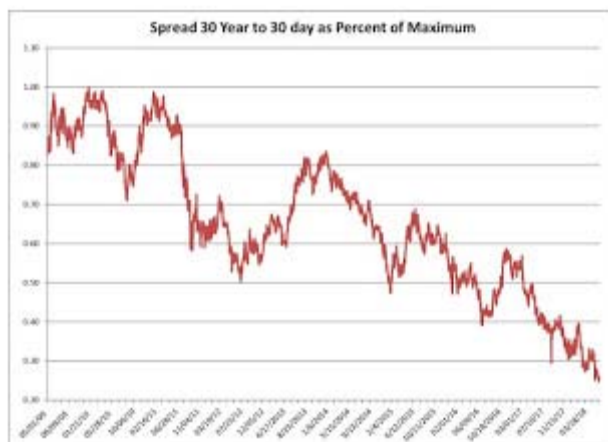
Labels: [Commentary](#)

Tuesday, June 26, 2018

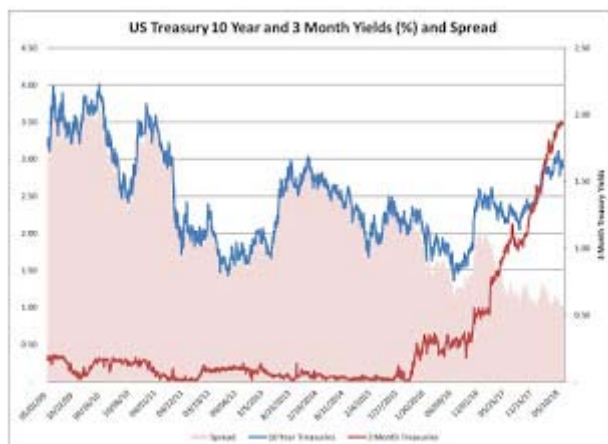
[Yield Curve](#)



The yield curve is flattening rapidly. Now look at the spreads:



The above is longest to shortest.



The above is a more reasonable set of points but again notice the collapsing.

What does this mean?

1. Our debt is short term, namely we now must pay more in interest.
2. Long term reflects growth, which is stagnating. Yet GDP seems to reject that. Perhaps the bloat on the FED BS.
3. This is also a warning for a recession. Hold on to your hats!



Labels: [Economy](#), [Yield Curve](#)

Friday, June 15, 2018

[Harvard, Admissions and Athletes](#)

The [NY Times](#) reports:

In its admissions process, Harvard scores applicants in five categories — “academic,” “extracurricular,” “athletic,” “personal” and “overall.” They are ranked from 1 to 6, with 1 being the best.



Interesting. Let's examine these:

1. Academic: This is a weighted number of GPA if such exists, class ranking, again if it exists, and SAT or equivalent scores. The weighting is often based on what type of secondary school one went to. Thus if it were Exeter I suspect one would have a strong position whereas if it were Robert Wagner HS on Staten Island you may be somewhere down the pile.
2. Extracurricular: Curing AIDS in Uganda perhaps could get you a few points as would be having been elected as a State Senator, Democrat of course. In the old days a VP on the Student Council would work but today when everyone gets a prize one wonders how this works.
3. Athletics: Now here is a real quiz. People fall into three categories. No sports at all, perhaps most Nobel Prize winners fall in this collection, team sports, the prep school winners are here as are large public schools, and the individual sports. The latter is where we get entrepreneurs. I did boxing and was a lifeguard, both required individual singular performance, and in boxing it was real time. So how does Harvard weight these?
4. Personal: Oh yeah, try to do this one folks. MIT used to have alumni do interviews but they disbanded this. I did it for 25 years and saw a large swath of students, and a few, who were accepted despite my concerns, all left before graduation. That personal contact is important but, well it is personal.
5. Overall: Just what this means I cannot tell despite a few readings. The selection used to be based on Faculty reviews, now there is a politically correct admissions committee. Thus the applicant must play to their biases rather than the facts.

It will be interesting to see how this litigation ends.



Labels: [Academy](#), [Political Correctness](#)

Thursday, June 14, 2018

[What If?](#)

[Ars Technica](#) has an article on the proposed tunnels connecting O'Hare to downtown Chicago. They note:

The Boring Company has released details about its proposed system already—it calls the system a "Loop," as in a modified version of the "Hyperloop" idea. (This means there will be a Loop to The Loop—very cute, Chicago.) Unlike the Hyperloop idea, the tunnels will not be depressurized. The company has stated that its electric pods would travel at 125-150 miles per hour. The city of Chicago's press release confirmed that The Boring Company has proposed vehicles that will travel faster than 100 miles per hour.

Nice idea bu:

1. What if there is a breakdown
2. What if there is a burst water pipe flooding the tunnel
3. What if there is a health emergency
4. What if there is an earthquake
5. What if there is a broken gas line
6. etc

Namely these claustrophobic tubes that are reminiscent of birth canals are not like New York subways, with multiple entry and exit locations where emergency facilities can be brought to bear. This may be a great idea if it works all the time, but we know that such is not the case. There does not seem to be any discussion of these issues.

There seem to be only two points of entry, the beginning and the end. That is a long way to go without any problems. Just look at the DC Metro.



Labels: [Technology](#)

Wednesday, June 13, 2018

[The Battle of the Distribution Channels](#)

It appears that Comcast is trying to get the Fox content for its distribution channel. As the [NY Times](#) reports:

Comcast announced an offer worth \$65 billion for the bulk of 21st Century Fox's businesses on Wednesday, setting up a showdown with the Walt Disney Company for Rupert Murdoch's media empire. The all-cash bid by Comcast, the largest cable company in the United States, came a day

after a federal judge approved a merger between AT&T and Time Warner. Comcast executives had awaited the decision in that case before mounting their bid for 21st Century Fox.

What does this prove? Content without a customer is worthless. A customer with no content is equally worthless. Distribution gives customers access. But customers are fickle and want all sorts of stuff. Also customers are getting rather sick of paying for stuff they do now want or outright despise, like ESPN for some customers. Thus this is a tricky move.

The customer does not want bundles any longer, they know the CATV scams all too well. Average CATV rates have doubled in eight years. Nothing changed, just the price. The cable converter is priced at about \$15 per month per converter and it is a relic. There is no option even though the FCC allows it. Then again we ask; what FCC, at least under current management.

The game here between Comcast and AT&T is interesting. AT&T has the better connection via 5G, if and only if they understand what they have. Somehow they seem clueless. Cable is a dying technology. Also Cable is hated by its customer base and it seems Comcast is at the top of this list.

Then again there is Verizon, same 5G asset, but their brain trust bought AoL and Yahoo, two apparent boat anchors. Thus the game is between Comcast and old technology and AT&T and a winning technology is they can understand what they have.

This will be an interesting play.



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

[Attitude?](#)

[The Telegraph](#) has a telling piece, especially explaining why we Irish have this, well let's call it our attitude, towards the English. The author is one Annabel Fenwick Elliott, a Dickensian name if ever there was one, who says it is her "right" to assault the customer sitting behind her by leaning her seat back no matter what. Yes assault, look up the term fair madam, it is in English Common Law. So are the remedies.

Now what specifically sets one off? The following:

Not only do I keep my seat reclined on every flight, in every situation, with the sole exception of meal times, but I slyly push that button - ever so gently - as soon as the plane takes off so that it tilts back with the force of the ascent, rather than wait until we've reached altitude, in a motion which feels less abrupt. Again, until now, this to me was just common sense and in fairness, not once have I ever been called out on it... "But I'm tall!" I hear you cry. "My knees are already crushed!" Being tall is an advantage in some situations (reaching things, attracting a mate) and a disadvantage in others (public transport, shopping for jeans). The average height of a man in the UK is 5ft 9in, a woman is 5ft 3in. If you happen to be taller, this is not your fault, but equally it is not my problem, not on a plane where all the seats are the same size.

Well it is your fault now. You have just expressed intent, and element of English Law, mens rea if you will for those still properly educated. And one wonders why there is a general distaste for the English. Other than their occupying lands not their own for centuries, and in turn oppressing the local folks, the law they developed does have a double edge.

Oh, by the way, I am 6' 3" and have long legs which lock immediately upon sitting. And also Ms Fenwick-Elliot-Dunstable-Wentworth-Buckingham-whatever, my solicitors are not that friendly. See ya!



Labels: [The English](#)

[You Want a Phone; Black and Rotary Dial](#)

The AT&T Time Warner merger presents a set of interesting questions, many of which the Court in its wisdom or lack thereof failed to address. Two things happened this week, and they are closely related. First this merger which I shall comment on and second the [FCC destruction of common carriage](#). They are tightly related.



To use a well used phrase, we are in an information society. [There are providers of this "information" and there are channels for its distribution](#). Typically in the US we have at times tried to keep them separate. The Judge Greene MFJ actually mandated that, for the Judge there saw the power of owning both.

For if you owned the distribution channel and you owned one of the arguably many sources of "information" then you could leverage out your competitors and control what the consumer sees. The FCC rule now mandates that.

McLuhan said the Medium was the Message but he meant that if one controlled the medium, namely the channel and content, you controlled what people saw as "truth". You had the ultimate tool for propaganda.

Do the [antitrust laws](#) allow for this type of control? I would argue not but the Judge in this case seems not to agree.

Thus the most serious threat to an open democratic society is the ownership of content and distribution. The old decision to break apart movie theaters and movie makers in the 1940s saw that. Apparently the current Judge disagrees.

A key point is also the development of 5G. My fear is that AT&T is reverting to its old ways, really old ways. A brief tale from the past may be worth telling. Fred Kappel was CEO of AT&T in the 60s. Fred was there when Bell Labs/Western Electric developed the Electronic Switching System No 1, No 1 ESS. Now this was kind of electronic but still had many mechanical parts. A large piece of the costs of telephones was maintenance and the old mechanical switches required lots of this, Fred wanted a fully electronic system. Here the battle began. The powers to be were adamant on slow change because the Bell System made its money, profit, based upon a return on investment, and the more costly the plant the more profit. You see profit in the phone company was not revenue less expenses, its was a percent return on capital plant, and the more inefficient you were the more you made.

So how does this relate to AT&T today? Simple, now that they own content they must get a return. How to do that? Simple, slow roll 5G, allow no new content entrants via wireless, and go back to a black rotary dial phone! Thanks Judge.

You see, the objective of the Antitrust laws is to protect competition, namely the consumer's ability to choose, NOT protect the competitors. Protecting competition means simply allowing for a multiplicity of competitors, not vertical and horizontal merging. Any third year law student looking at Antitrust Law should understand that. How was this point missed in this case?

Finally, one could consider the following analogy:

1. ATT owns the dominant trucking company in the US with an exclusive government franchise (the wireless licenses ATT got "free" decades ago, yes free, and they block any competition)
2. The US govt has given ATT trucking the right to not have to carry anyone else's produce (the FCC elimination of net neutrality)
3. ATT buy McDonald's, local stores and their "production" facilities (read Time-Warner)
4. You go out to buy food and all you can now get is McDonald's (read ATT) since no other vendor can get their goods shipped in.

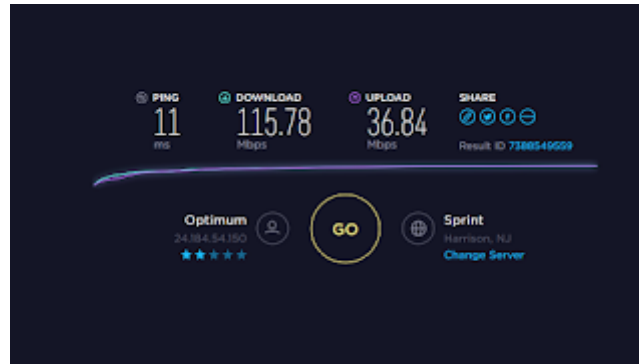
That is the analogy. They own the distribution channel which is a substantial barrier to entry and now can "supply" whatever they want.



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

Tuesday, June 12, 2018

[Wow, I see Someone Listened!](#)



Yep, we went from 200Kbps to 116,000Kbps, almost a 1,000 fold increase, and the IP addressed changed as well! It will be interesting to see what AT&T does with their new found love!

One should remember, the asset is the wireless license. There are just a few and 5G will blow fiber out of the water, despite what lawyers think. Content is real tricky. Look at the mess Verizon has with its media stuff, AoL and Yahoo.

The revenue will become more selective buys and less eyeballs. With a 5G data driven approach one can subscribe to what they want. Unless of course your carrier owns the content they want you to see! So did the Court err? Think about it.



Labels: [CATV](#)

[Debt Payments](#)

The following chart should be terrifying. It is the quarterly debt payments.



We are on our way to \$600B per quarter of \$2.4 trillion a year. It was less than half of this in 2008. Well no surprise since debt has more than doubled but it is worse since much of the low cost short term debt is coming due and must be rolled over at fantastic increases!



Labels: [Economy](#)

Tuesday, June 12, 2018

Words Mean Something, I Think

The NY Times notes the following:

A Harvard-trained economist with outside-the-mainstream views. Mr. Navarro is a former a professor at the University of California, Irvine, who holds a doctorate from Harvard. He is one of the only credentialed economists in Mr. Trump's inner circle.

Now I do not know this fellow and I know even less about trade. In fact I am not a fan of economists period so having just one may even be a good idea. But that is not the point either.

The NY Times had a style book and editors. So here is where I am going off the track. One trains a dog, a horse, maybe even a mouse. One never trains a cat, but I leave that to cat lovers. Harvard "educates" people, MIT even does that. The Commonwealth of Massachusetts used to have Training Schools for Juvenile Delinquents. But Universities, especially Harvard, do not "train" people.

Thus I ask the noble NY Times, why did you select this verb? It most likely is not allowed in your style book, and its usage, besides being derogatory, states that the article is political and not factual. One perhaps must reject all of its contents.

Now on to tariffs. Everyone one seems to be for free trade, even the President suggested the elimination of tariffs. But it may be perhaps of value if someone could lay out the current tariffs. Let's just start with Canada. Having a home on northern New Hampshire I always see a constant flow of trucks from Quebec coming south, even with wood. That is somewhat like bringing coals to Newcastle but then again I never spent any time in the lumber trade.

So my point is simple. Stay with the facts. Harvard has not trained anyone since pre-WW II NROTC units and tariffs really need to be let out in the sunshine. Oh yes, and for the economists, perhaps zero is a good number.



Labels: Academy, Economics

Monday, June 11, 2018

Adoptive Cell Transfer

As understanding of the immune system has progressed its use as a therapeutic for various cancers has also moved forward. This hand in glove approach has allowed one to go from

observation to utilization to modification and then cycle again. The area of tumor infiltrating lymphocytes and their application in the area of adoptive cell transfer has been a topic of interest for almost three decades. The presence of T cells around tumors is a common occurrence. For example in malignant melanoma there is often such a proliferation seen upon biopsy.

The question then is; if the immune system acts accordingly then why does it not follow through and destroy the tumor? We now understand some of the basics of this process and one suspects a great deal more will be learned. However the proliferation of the T cells, called Tumor Infiltrating Lymphocytes, TILs, led early investigators to try and utilize them as a therapeutic. This was done by ex vivo acceleration and proliferation of the cells and implanting them back in the patient. This is adoptive cell transfer. This we shall focus on in this brief note.

Rosenberg and his Lab have for nearly 40 years been investigating this area. In a 1985 NEJM paper he wrote about his work with autologous lymphokine-activated killer (LAK) cells:

The administration of LAK cells in conjunction with interleukin-2 as reported in this paper represents a possible new approach to the treatment of cancer, with potential applicability to a wide variety of tumors. A major advantage of this approach is its broad antitumor specificity. It should be emphasized, however, that this study involved a limited number of patients and that the frequency and duration of the clinical responses have yet to be determined.

The practicality and safety of administering this therapy to large numbers of patients also remain to be fully defined. The similarity of our initial experience in patients to our prior experience in mice, however, offers hope that this therapy can be made effective against human cancer.

What Is ACT

As noted, this examination of TILs and their function has been examined for decades. For example, in 1991 Jicha et al (in Rosenberg's Lab) had noted:

Interleukin 7 (IL-7) is a 25-kD cytokine that was initially described as a pre-B cell growth factor. This cytokine has also been shown to have T cell proliferative and differentiation effects. In this report, we demonstrate that antitumor cytotoxic T lymphocytes (CTL) generated by secondary in vitro sensitization of draining lymph node cells in IL7 are effective in treating 3-day syngeneic methylcholanthrene (MCA) sarcoma pulmonary metastases in mice.

In vivo titrations comparing IL7 to IL-2 antitumor CTL show that they have equivalent potency in adoptive immunotherapy. IL-7 antitumor CTL generated against MCA sarcomas of weak immunogenicity are also tumor specific in their in vivo efficacy. This study represents the first successful use of a cytokine other than IL-2 for the generation of cells with in vivo efficacy in cellular adoptive transfer.

Earlier Belldegrun et al (also from Rosenberg's Lab) noted:

The identification, isolation, and adoptive transfer of selected subsets of immune cells with specific antitumor reactivity into tumor bearing patients to mediate cancer regression in vivo is a prime goal of tumor immunology. Currently, however, there are no available techniques for generating such lymphoid cells with reactivity against specific tumor antigens in the human.

Recent experiments have demonstrated that the adoptive transfer of lymphokine-activated killer cells plus IL-2 can mediate tumor regression in a variety of animal models and human tumors as well. This approach, however, requires the transfer of large numbers of sensitized fresh lymphocytes, i.e., more than 10^{11} immune cells, into tumor bearing humans, along with the systemic administration of relatively high doses of RIL-2 (100,000 units/kg body weight i.e. every 8 h).

Many human tumors are infiltrated with chronic inflammatory cells, including lymphocytes. We have recently identified a population of lymphoid cells infiltrating murine tumors that could be expanded in vitro in IL-2 and, when adoptively transferred, were capable of totally eliminating 3-day established pulmonary metastases. When compared to LAK cells, these TIL cells were at least 50 times more potent in mediating the therapy of established micrometastases. The simultaneous administration of IL-2 enhanced the in vivo therapeutic effectiveness of the adoptive transfer of TIL, although high doses of TIL alone were also effective. The greater therapeutic efficacy of TIL compared to LAK cells in the treatment of established metastases in mice raises the possibility that TIL isolated from human tumors and expanded in vitro in IL-2 may similarly be effective for the treatment of human cancer.

Now in our current understanding these have again attracted attention as Horton and Gajewski (2018) note:

Tumours from multiple cancer types can be infiltrated by CD8⁺ T cells (TILs). TILs are thought to be suppressed by multiple immune inhibitory molecules in the tumour microenvironment, and this suppression has been associated with tumour progression.

Therefore, despite tumour infiltration, almost all tumours containing TILs will progress if not treated. While several immune inhibitory mechanisms have been identified, immune inhibitory receptors expressed on activated T cells, like CTLA-4 and PD-1, have received the most attention over recent years owing to the immense clinical success of PD-1 and CTLA-4 neutralizing antibodies. The engagement of inhibitory receptors expressed by TILs is thought to render TILs dysfunctional.

However, evidence from both human tumour samples and mouse models has suggested that, despite inhibitory receptor expression, TILs are not functionally inert and actually retain the ability to proliferate, produce IFN- γ and show ex vivo cytotoxicity.

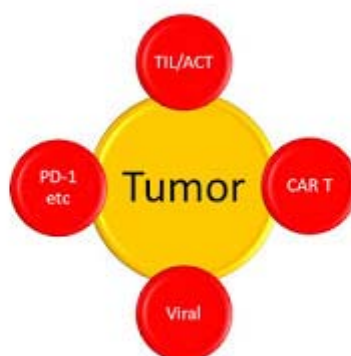
These observations raise the question of why activated TILs are not able to spontaneously control progressing tumours, and how tumours that contain TILs might sometimes be resistant to immunotherapies such as checkpoint blockade. Current immunotherapies can induce durable tumour regression; however, they benefit a minority of patients: finding new strategies to

increase the response rate to immunotherapies is of great interest to both researchers and clinicians.

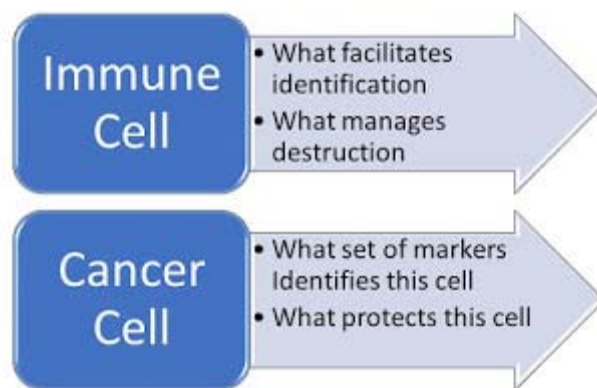
There are many dimensions available for employing the immune system. Many current foci relate to the T cell elements of the adaptive system. There are also a multiplicity relating to the innate system including the NK or natural killer cells. The overall approach requires an understanding of two things: (i) what makes a tumor cell different and how does it tend to protect itself, (ii) how do immune systems identify and attack aberrant cells. On the one hand we look at the malignant cell and how it expresses itself, which we know is arguably an ever changing process. The second element is how can we use and manipulate the bodies basic immune system, and here it should be both adaptive and innate.

Multiplicity of Ways

There are a multiplicity of ways in which the immune system may attack cancer cells. We summarize this in the figure below. We have discussed checkpoint issues and CAR T cells previously and herein we focus on TIL and ACT mechanisms. All of these mechanisms shown below are somewhat variants of each other as we shall discuss. TIL/ACT mechanisms are the oldest in concept and are in many ways a brute force method of attacking the cancer cells in larger volume than they would have been in vivo.

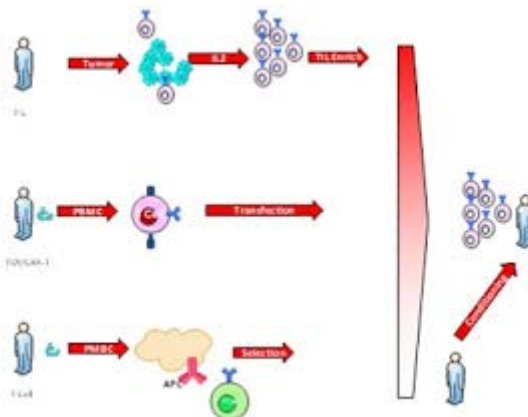


We will then focus on the interrelationship between the cancer cell and the immune cell. For each we ask how they are identified, how they act, and how they may protect themselves. We summarize that below. The battle is between an immune cell and a cancer cell. The cancer cell can be identified but it can also protect itself. The self-protection is inherently part of its ancestry as a descendent of the individuals own cell line. It is a protection against auto-immune diseases. In contrast the immune cell can detect cells that do not belong, and as such can then emit attack mechanisms that destroy the unwanted invader. Immunotherapy is thus a balance between survival and destruction.



Comparisons

We briefly look at a comparison of some of the techniques. From Yee we have the following diagram (as modified):



Yee then notes on the above:

Adoptive Cell Therapy is represented by three general approaches:

- 1) Enrichment and expansion of tumor-infiltrating lymphocytes (TIL) from a disaggregated tumor biopsy sample*
- 2) Genetic transfer of T Cell Receptor (TCR) recognizing tumor antigen-derived peptide-MHC target or Chimeric Antibody Receptor (CAR) recognizing surface tumor protein*
- 3) Enrichment of endogenous antigen-specific T cells from peripheral blood mononuclear cells by in vitro stimulation followed by cell selection or cloning. PBMCs are a source of both antigen-presenting cells and T cells.*

Following enrichment, the population of tumor-reactive T cells undergoes rapid expansion of 1000-5000 fold achieving 10 - 100 billion cells for adoptive transfer. Patients often receive a lymphodepleting conditioning regimen pre-infusion followed by exogenous IL-2. In the case of adoptive TIL therapy, patients receive high-dose near ablative or fully ablative conditioning pre-infusion and a course of high-dose IL-2 post-infusion. ... 'young' TIL are generated using a shortened pre-expansion culture phase prior to rapid cell expansion, enabling production of an infusible T cell product within 5-7 weeks from time of tumor collection.

Here Yee included a multiplicity of techniques. Namely Yee sweeps any method extracting, modifying, and re-implanting T cells as ACT. We examine these somewhat and leave them as all separate.

One must recall that T cells are not alone in this fight against cancer cells. The innate immune system has a powerful set of tools which are used as an immediate attack mechanism and if properly triggered may be of adjuvant usage. We have examined the innate system and its various methods elsewhere. Two strong elements there include the natural killer cells, NK, and the complement chain. Complement has yet to receive a great deal of attention as regards to cancer immunotherapy. Looking at Macor and Tedesco we note:

The contribution of the complement system to the control of tumour growth has been neglected for a long time as the major emphasis has been put mainly on cell-mediated immune response against cancer. With the introduction of monoclonal antibodies in cancer immunotherapy complement has come into play with a great potential as effector system. Complement has a number of advantages over other effector systems in that it is made of molecules that can easily penetrate the tumour tissue and a large majority, if not all, of the components of this system can be supplied locally by many cells at tissue site.

Further advances are being made to increase the anti-tumour efficiency of the complements system using C-fixing antibodies that are modified in the Fc portion to be more active in complement activation. Another strategy currently investigated is essentially based on the use of a combination of two antibodies directed against different molecules or different epitopes of the same molecule expressed on the cell surface in order to increase the number of the binding sites for the antibodies on the tumor cells and the chance for them to activate complement more efficiently.

One of the problems to solve in exploiting complement as an effector system in cancer immunotherapy is to neutralize the inhibitory effect of complement regulatory proteins which are often over-expressed on tumour cells and represent a mechanism of evasion of these cells from complement attack. This situation can be overcome using neutralizing antibodies to target onto tumour cells together with the specific antibodies directed against tumor specific antigens. This is an area of active investigation and the initial data that start to be available from animal models seem to be promising.

Thus we believe that a great deal can be garnered by not only focusing on the adaptive elements but also the innate.

Observations

ACT can be interpreted in a broad manner. We now examine several areas of collateral interest. They are summarized in the following graphic where we have presented 4 of the eight described above.

Checkpoints	CIK Cells	CAR-T	NK Cells
<ul style="list-style-type: none"> • Checkpoints are the natural stops on the body's cells and the also assist in protects cancer cells. 	<ul style="list-style-type: none"> • CIK cell therapy has received success in certain cancers and can be an adjunct to this process. 	<ul style="list-style-type: none"> • CAR-T cells are targeted for specific cancer cell surface markers and thus are used as modifiers for existing T cells 	<ul style="list-style-type: none"> • NK Cells as part of the innate system can be processed in an ACT manner and have demonstrated efficacy in several cancers

Checkpoint Interactions

Cancer cells are derivative of the body's own cells and as such reflect an ability to stop the immune system from destroying them. These surface markers called checkpoints can tell an attacking immune cell not to do so because this cell is part of the whole, even is expressing clear signs of aberrancy. The creation of monoclonal antibodies, Mabs, have yielded tools that work on may cancers and allow for the attack which otherwise would have been halted.

As Liu et al have noted:

Targeted therapies for cancer with small molecules and monoclonal antibodies (MoAb) have led to significant improvement in the long-term survival of multiple malignancies. The discovery of programmed death- 1 (PD-1) and the ligand 1 (PD-L1) has opened the door to the modern era of cancer immunotherapy. It is well known now that many tumor cells are able to upregulate the expression of PD-L1 which leads to anergy of cytotoxic T cells upon PD-1 binding to the ligand. Blocking the PD-1 pathway using monoclonal antibodies against PD-1 or PDL1 can therefore revamp the immune response against tumor cells.

The development of MoAbs against PD-1 and PD-L1 has led to the fast and fundamental paradigm shift in cancer therapy. The anti-PD drugs are the new form of tumor-site immune modulation therapy through resetting immune reservoir in the tumor microenvironment. This is fundamentally different from the conventional chemotherapy and radiation that mainly target cancer cells themselves.

PD-L1 expression on the tumor cells and immune cells have become biomarkers that can assist clinical decisions in the choice of treatment strategies. Biomarker assays for PD-L1 are playing bigger roles and are being routinely done nowadays. However, PD-L1 assays can be highly

variable, which makes it a clinical challenge to employ the results. In this review, we summarized latest clinical development of PD antibodies and immunohistochemistry (IHC) assays for PD-L1 biomarker expression in clinical practice.

CIK Cells

CIK or cytokine induced killer cells, have seen use in multiple areas. I have reported on their use in the case of MDS, myelodysplastic syndrome, patients resulting is what the attending physicians have labelled as a cure. As Jiang et al have noted:

The number of immune cells, especially dendritic cells and cytotoxic tumor infiltrating lymphocytes (TIL), particularly Th1 cells, CD8 T cells, and NK cells is associated with increased survival of cancer patients. Such antitumor cellular immune responses can be greatly enhanced by adoptive transfer of activated type 1 lymphocytes. Recently, adoptive cell therapy based on infusion of ex vivo expanded TILs has achieved substantial clinical success.

Cytokine-induced killer (CIK) cells are a heterogeneous population of effector CD8 T cells with diverse TCR specificities, possessing non-MHC-restricted cytolytic activities against tumor cells.

Preclinical studies of CIK cells in murine tumor models demonstrate significant antitumor effects against a number of hematopoietic and solid tumors. Clinical studies have confirmed benefit and safety of CIK cell-based therapy for patients with comparable malignancies. Enhancing the potency and specificity of CIK therapy via immunological and genetic engineering approaches and identifying robust biomarkers of response will significantly improve this therapy. The presence of cytotoxic tumor infiltrating lymphocytes (TIL) within tumor is associated with increased survival of cancer patients. Both antitumor adaptive and innate cellular immunity are important for resistance of tumor growth and eventual elimination of cancer.

Theoretically, antitumor cellular immune responses can be greatly enhanced by adoptive transfer of lymphocytes, a term encompassing a strategy in which autologous T or NK cells are acquired from a cancer patient and then activated and expanded ex vivo prior to reinfusion.

Adoptive cell therapy of cancer, first demonstrated in mice more than 50 year ago, has gained momentum in recent years due to impressive clinical experiences with melanoma patients.

This approach is based on ex vivo expansion of large numbers of TILs and selection of tumor-specific T cell lines. The major effectors of TIL cells are phenotypically CD3+CD8+ T cells and their anti-tumor functions are MHC restricted [5]. In contrast to tumor antigen-specific immunotherapy, there is potential utility of non-antigen specific cell-based therapy. Many patients with cancer are ineligible for TIL-based therapy because their TILs do not expand sufficiently or because their tumors have lost expression of antigens or MHC molecules or have extremely low numbers of TILs.

Cytokine-induced killer (CIK) cells are a heterogeneous population of effector CD8 T cells with diverse TCR specificities, possessing non-MHC-restricted cytolytic activities against tumor cells.

Therefore, CIK cells can lyse tumor cells in a non- MHC-restricted manner and can serve as an alternative cellular immunotherapy.

The CIK approach is to some degree more akin to ACT but that it tries to use a multiplicity of immune cells. We believe that using CIKs with perhaps better targeting and checkpoint inhibitors may have significant advantages in many malignancies.

ACT vs CAR T

ACT can be viewed in broad terms. I believe it is fair to say that the Rosenberg approach is the classic one of removing TILs and then multiply them and strengthen them *ex vivo* and then place them back in the patient, without any added modifications. CAR-T cell therapy looks at the cancer cell itself and seeks a unique surface marker, such as CD19, and then designs and builds a T cell to attack just that marker. As Ott et al note:

Adoptive T cell therapy, CAR-T cell therapy Adoptively transferred T cells generated from tumor TILs, T cells bearing engineered, tumor specific T cell receptors, and chimeric antigen receptor (CAR) T cells all have shown remarkable anti-tumor activity in select solid and hematological malignancies. CAR T cells and T cells with engineered tumor specific TCRs may have the ability to induce an inflamed tumor microenvironment and therefore to be promising partnering strategies with PD-1/PD-L1 blockade.

CAR-T are effective and clearly more than a passing fad. Yet they are costly to prepare and may miss the critical cancer cells. ACT is a broad brush approach and hopes that the mix of cells may effectively hit the target. However the problem is always the stem cell or cell of origin problem. This is a substantial issue to be faced.

NK Cells: An Option

Natural Killer cells are considered part of the innate immune system. This classification seems to be based upon their sense of immediacy in responding and the simplicity of their response mechanism. However NK cells are very powerful tools in attacking malignancies as well.

As Pahl and Cerwenka have recently noted:

Natural Killer (NK) cells are classically considered innate immune effector cells involved in the first line of defense against infected and malignant cells. More recently, NK cells have emerged to acquire properties of adaptive immunity in response to certain viral infections such as expansion of specific NK cell subsets and long-lasting virus-specific responses to secondary challenges.

NK cells distinguish healthy cells from abnormal cells by measuring the net input of activating and inhibitory signals perceived from target cells through NK cell surface receptors. Acquisition of activating ligands in combination with reduced expression of MHC class I molecules on virus-infected and cancer cells activates NK cell cytotoxicity and release of immunostimulatory cytokines like IFN-.

In the cancer microenvironment however, NK cells become functionally impaired by inhibitory factors produced by immunosuppressive immune cells and cancer cells. Here we review recent progress on the role of NK cells in cancer immunity. We describe regulatory factors of the tumor microenvironment on NK cell function which determine cancer cell destruction or escape from immune recognition. Finally, recent strategies that focus on exploiting NK cell anti-cancer responses for immunotherapeutic approaches are outlined.

One of the concerns regarding immunotherapy is that the panoply of options may at times be shadowed by a single strand of success and thus leaving behind a set of tools of great power. The authors continue in their discussion focusing on the use of NK cells as the entity in adoptive transfer:

Adoptive transfer of NK cells: To potentiate NK cell activity, the application of IL-2 in patients has remained challenging because high doses of IL-2 can result in serious adverse effects and expand regulatory T cells.

As an alternative, NK cells can be (re-)activated ex vivo and used for adoptive cell transfer therapy.

In the case of T cells, adoptive transfer using autologous tumor-reactive T cells (e.g. anti-MART-1) and chimeric antigen receptor (CAR) T cells (e.g. anti-CD19-CD3⁺-CD28) achieved significant clinical responses in some patients with advanced melanoma or B cell malignancies. These T cells, however, fail to control epitope-negative variants and have the potential for long-time adverse effects on epitope-positive non-malignant cells.

Similar to CAR T cells, genetically-engineered CAR NK cells are currently explored to more specifically direct NK cell cytotoxicity toward cancer cells. Analogous to therapeutic antibodies, this approach enables the killing of cancer cells which are otherwise poorly susceptible to NK cell recognition in addition to 'natural' cytotoxicity against epitope-negative cells.

Adoptive transfer of ex vivo cytokine-activated autologous or haploidentical NK cells resulted in favorable responses in a subset of pediatric and adult patients with hematological malignancies without causing graft-versus-host disease in the recipients.

This discussion expands the set of calls used in an adoptive transfer mode. Perhaps there can be alternative beyond these as well. My thoughts would include the complement system and its ability to isolate and neutralize aberrant intruders.

Multifaceted Approach

As much as I find the term "precision medicine" inaccurate, for we really mean accuracy not precision but I suspect this is a politically chosen term, the above approaches represent a collection of tools we now have at our command in treating cancers. In addition we also have pathway modifiers such as kinase inhibitors whose use in such cancers as CML truly opened the door to treatment based upon detailed knowledge. One suspects that ultimately cancer treatment

will be an integrated usage of all of these therapeutic techniques and not just one at a time. If we have learned anything from the treatment of Hodgkins Lymphoma it is that single threaded treatments are rarely effective and that an integrated approach is essential.

Comparisons

We can now make some overall comparisons as shown below:

Approach	Method	Advantages	Disadvantages
Adoptive Cell Transfer	Collect T cells surrounding tumor and enhance growth then reinsert	Requires less processing and may be less costly	May not be specific enough and may cause immune responses that are not beneficial Misses cancer stem cell
DC	Collect multiple immune cells and enhance and then reinsert	Requires less processing and may be less costly	May not be specific enough and may cause immune responses that are not beneficial Misses cancer stem cell
CAR-T Cell	Obtain T cell and make specific receptor/ligand to match tumor and insert viral vector	Highly specific for tumor markers Has the ability to persist	Requires identifying a tumor marker Not specific May have immune storm effects Misses cancer stem cell
RTX	Make ligand with one end targeted for T cell and the other for tumor cell	Focuses on simple molecules Targeted at specific cancer cell May not be as costly	Requires identifying a tumor marker May have immune storm effects Misses cancer stem cell
Cytokines	Use existing immune cell enhancers	Generally inexpensive May work for limited time	Can cause some immune response Not specific, broad brush approach
Immunotoxins	Use toxins as one end in immunotoxins targeted for tumor cell	Generally inexpensive May work for limited time	Can cause poor immune response Not specific, broad brush approach
NK Cells	Use the NK cells instead of T cells as above	NK cells are immediate response vectors Possible targeting of stem cells	Yet to be determined

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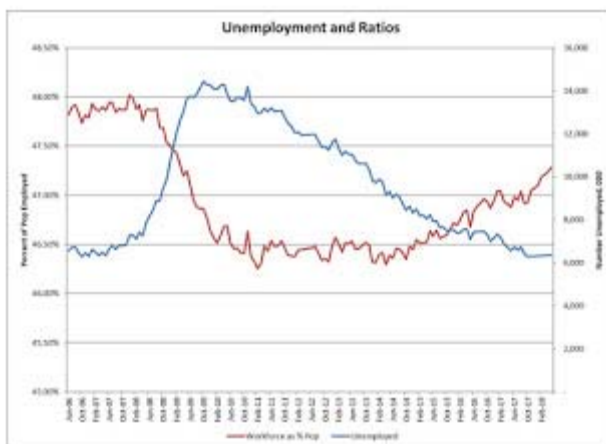


Labels: [Cancer](#)

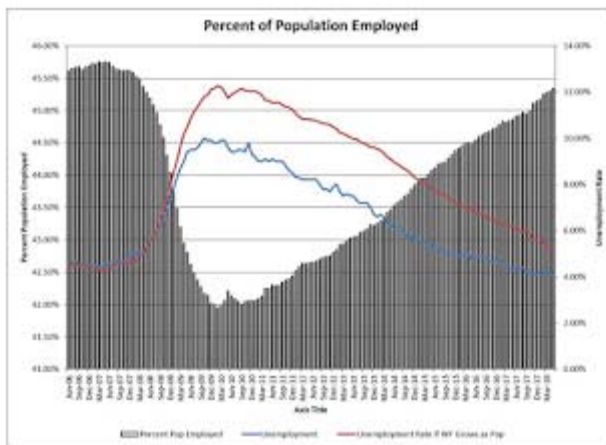
Saturday, June 9, 2018

Some Employment Numbers

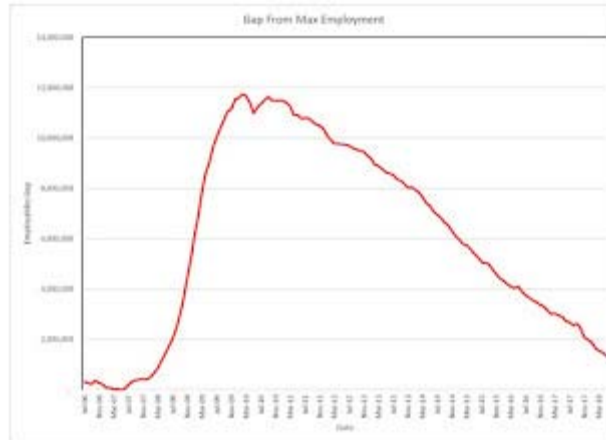
Over the past ten years we have been following the employment numbers. In early 2009 we had the Romer curve for which we were told by some economist how things would get better. Well, not quite, and the economist went back to Berkeley. I do not think I would send anyone there but then again I am an engineer by training.



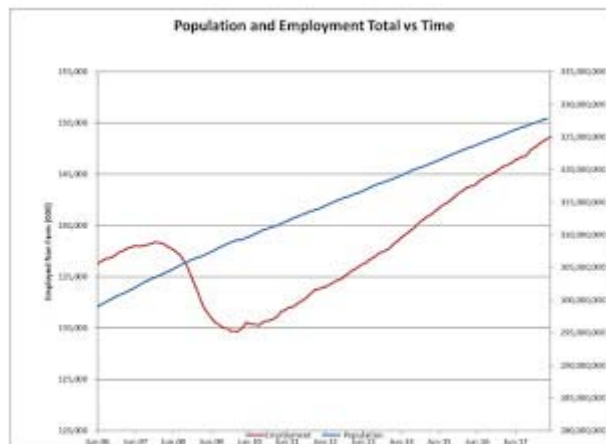
I will go backwards. The above curve depicts the unemployed and the workforce participation as referenced to 2006. What I find interesting and not noted anywhere is that during the past administration it stayed flat and with the new administration there is a continuous rise. This to me is the most critical data message.



The summary data is shown above is also insightful. The unemployment is less than 4% but with the higher participation rate is just above 5%. In our prior analysis the peak was well above 12%.



The above is the gap from max employment and it is now just above 1 million. includes growth in population.



The final curve shows the growth in both metrics.



Labels: [Economy](#)

Thursday, June 7, 2018

[Graduation Speeches](#)

In 1971 I had my doctoral graduations and I went to the MIT one. Now 1971 was not a great year. There were no jobs at all posted in the NY Times, no one came to campus to recruit, really, and my only firm offer was to work as an electrician for my father. I had a \$20 bill in my wallet, a dead VW bug, threw a rod, a bunch of degrees and well it was challenging. The good news was graduation was short, no speaker, no awards, no free degrees, just show up, shut up and get your degree. Then clean out your living quarters for the next group. Vietnam was still going wild, the Pentagon Papers were just on their way out, Nixon got us off the gold standard, he raised tariffs on imports, and overall the economy was a mess.

But the issue here is commencement speakers. In my humble opinion they are a waste of time.

They seem all now to bring some political position to the fore, advocate their own interests, and overall miss the mark for what this day is for, the graduates, and for many, their parents who may have paid for this. As for awards, well you got a degree, what else is there. MIT in my day never had cum laude etc, just graduating was a statement in itself, we were not Harvard, they needed the distinction to identify those who really worked.

The [list](#) of some recent speakers included:

- 2018 Sheryl Sandberg, Facebook
- 2017 Tim Cook, Apple
- 2016 Matt Damon, Actor, Filmmaker
- 2015 Megan Smith, Chief Technology Officer of the United States
- 2014 Ellen Kullman, DuPont
- 2013 Drew Houston, Dropbox
- 2012 Salman Khan, Khan Academy
- 2011 Ursula M. Burns, Xerox Corporation
- 2010 Raymond S. Stata, Analog Devices, Inc.
- 2009 Deval Patrick, Governor of the Commonwealth of Massachusetts
- 2008 Muhammad Yunus, Managing Director, Grameen Bank
- 2006 Ben Bernanke, Federal Reserve
- 2005 Irwin Jacobs, QUALCOMM
- 2004 Elias Zerhouni, National Institutes of Health
- 2003 George Mitchell, Former United States Senator from Maine

Now I am certain that they are all fine folks, interesting speakers and the like, but after lost of time and effort all most students want is the piece of paper and finding a job. Are speakers a benefit to the Administration, more contacts and the like. They are little if any benefit to the graduates, at least short term.

I am very happy that Prof Wiesner decided to just make it short and sweet. Then again there were always those bomb threats from the anti-War types. I thought that bomb threats from anti-War protesters were a bit of an oxymoron. But we had a few. They did keep the speakers away though!



Labels: [Academy](#)

Thursday, June 7, 2018

[IP Voice: I Long for The Old Days of Copper](#)

Voice communications is getting worse by the day. Back before say 1990 telecommunications used analog voice over copper lines. The Old Bell System, for better or worse really worried about voice quality and a voice communications was generally good, even to far away locations.

Then came digital voice. The two drivers were wireless and lower data rates and usage and also the introduction of IP communications. In the early 90s when I was at now Verizon Wireless, we moved to introduce digital and this meant voice codecs, which compressed voice. From 64,000 bps we went down to 4,000 to 9,000. A real drop. We did such things as MOS or mean objective scoring to show that it really was not that bad. It really was.

Then along came IP and we then put these codecs modified on IP nets. Again I did this in 1996 along with a company called VocalTec. I ran a network using IP and voice codecs. We actually got voice to work, in Poland and Russia. But our networks were fine tuned and dedicated. Others used the Internet, which along with the codecs made everyone sound like Donald Duck.

Then along came Customer Services out of India. Add to the IP problems and the codec problems the accent and language problems and you have what we have today.

A mess.

Most of the younger folks do not make phone calls. They have no knowledge of a great long distance call with a friend, talking as if you were having a truly private conversation. Today the quality, well stinks, yet we also have God knows how many people listening in on these conversations.

Technology is not always a great leap forward. We still buy hard copy books.



Labels: [Telecom](#)

Wednesday, June 6, 2018

[Can I Still Holiday in Canada This Year?](#)

The [National Post](#) reports:

During a testy phone call with Prime Minister Justin Trudeau, U.S. president Donald Trump reportedly cited the War of 1812 in order to justify seeing Canada as a security threat. "Didn't you guys burn down the White House?" he told Trudeau. Trump uses War of 1812 to justify Canada as security threat. Some men from Canada did burn down the presidential mansion in 1814, but they were all technically British.

Picky, picky, picky. I will have to travel on my Irish Passport, yet at times the Brits still have a thing for us, but my lovely wife is descended from Canadians directly, and tracing back they may have been down in Washington at the time the President noted, one also was at Waterloo, so the French get a bit out of whack.

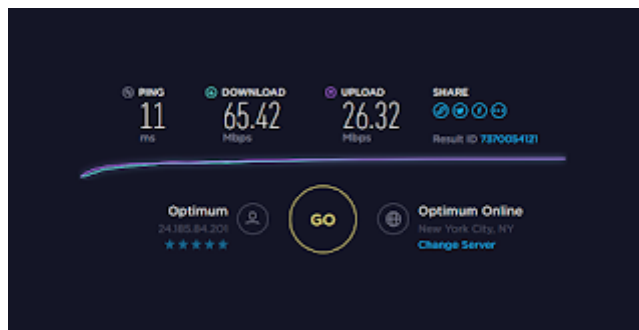
Well this will be a great holiday! I love the New York sense of humor! Happy D Day, also this is the day the US took Saipan and Tinian, a battle comparable to Normandy but less covered.



Labels: [Commentary](#)

Tuesday, June 5, 2018

[Someone Has Seen My Measurements, I Think...](#)



This is three hours later, same IP address, same system. 65+Mbps down, up from 600Kbps at best. Look at up speed as well. Nothing has changed except the speed! Where is the throttling, I can make several guesses.



Labels: [CATV](#)

[A Business Model and Amazon](#)

In 1980-81 I became head of the the Warner Cable Interactive Services Business. At the time we had a two way system called QUBE which was limited to some video on demand such as boxing events and the like. My task with my team was to develop a two way fully interactive system to sell anything as well as do banking, games etc. Thus the name, TIES, Transaction, Information, Entertainment Services. I have to thank Greg Shapiro for this and he was a brilliant young marketing type on leave from American Express.

From the Plan we noted:

*This plan describes the implementation of a business that uses cable television and interactivity to provide services to the home. The business is called TIES (Transaction, Information, Entertainment Services) and is defined as: **providing distribution capability, local marketing and customer support to facilitate the delivery to homes of a bundle of goods and services offerings, and is available to subscribers on demand via enhanced videotex in an entertaining format.***

Enhanced videotex differs from traditional videotex systems by providing full motion video segments in addition to text and graphic displays. The services offered (applications) are in the following areas:

*Banking and Investment Services
Games and Entertainment*

Travel, Ticketing and Real Estate
Merchandise/Packaged Goods Shopping
Information/Education and Electronic Mail
Local Services and Classifieds

TIES builds naturally on the existing Warner Amex role , leverages the Warner Amex cable investment, and readily interfaces with the existing businesses of American Express and WCI. TIES responds to emerging trends i n the marketplace by providing an innovative electronic in-home marketing distribution channel in the marketplace by following: (i) supplier expansion into direct marketing, and (ii) consumer demand for choice and convenience, coupled with consumers' growing acceptance of electronic delivery of transactions , information, and entertainment. The strategy in this new marketing and distribution channel is : (i) to build on local presence, (ii) to bring together suppliers and packagers into what is termed a local electronic shopping mall, (iii) to ensure consistent and high quality service.

Now the problem was that we saw that the Shopping Mall Operator strategy was better because vendors knew better, we were intermediaries. This is the Ali Baba approach. Amazon took on the role of the store, no shopping mall, they were to be the store. This seems to have stopped. Now more than half of the sales seem to be via some unknown third party. The goods may be knock offs, the delivery scheduled haphazard, the quality questionable. As the Mall Operator one had the duty to ensure quality. In my most recent experiences this is failing on the Amazon side.

Does this open the door for a new competitor. I believe so. I hope so. I liked to old Amazon, the new Amazon not so much.

It is like Google. All my searches were on Google, now, not so much. As for Facebook, that went the way of my Grad students. I saw its flaws a decade ago or even more. Possibly or possibly not.

Here is the composite video of our first system in 1982. This was displayed on an Atari 800, our home platform of choice, Warner owned it then. The videos were done by Richard Veith a great innovator at the time!

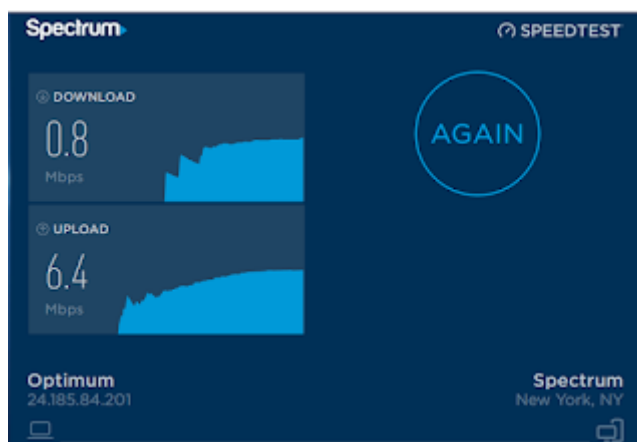
also
and

Note the paradigm of spatial participation. It is worth noting that this now almost 40 year old construct focused on quality and trust. AMEX was a key driver there. Again one must ask where is Amazon wandering, hopefully not astray.



Labels: [Amazon](#)

[Who Runs This Company?](#)



The latest. Yes that is 800Kbps download. This is Optimum! All the time, it makes DSL look great. They must be cutting back on backbone networks and throttling everyone! So what is my alternative just 20 mile from New York City? Nothing! Yep, foreign monopolists have taken over. Does the FCC care. Nope. Their new ruling allows these folks to run the railroad this poorly!

And yes, we get charged almost \$20 per month for ESPN and I never watch this one. Cable bills have doubled in six years! Here is something for Congress to look at. Hopefully 5G allows us to cut the cord totally and let these folks dry up!



Labels: [CATV](#)

Monday, June 4, 2018

[Adoptive Cell Transfer](#)

Immunotherapy is an ever evolving and improving therapeutic approach. Namely get the bodies own cells to do the work. Adoptive Cell Therapy in a simple manner is taking T cells from a person, even at times NK cells, and then take the cancer cells and find the cell markers which the T cells can then respond to.

In reality it is very complex since one must identify the surface markers. The [Guardian](#) notes:

To create the treatment, doctors first cut small pieces of tissue from Perkins's tumours and studied the DNA to find mutations specific to her cancer. They focused on mutations that disrupted four genes which produced an array of abnormal proteins in the tumours. ext, the doctors extracted immune cells known as tumour infiltrating lymphocytes, or TILs, from the tumour biopsies. These are cells from the patient's immune system that have invaded the tumour in a bid to kill it, but which failed in the task by being either too weak or too few in number. After growing billions of these immune cells in the lab, the researchers screened them to find which ones would most effectively find and destroy the woman's cancer cells by recognising their abnormal proteins.

The [Nature](#) article notes:

Immunotherapy using either checkpoint blockade or the adoptive transfer of antitumor lymphocytes has shown effectiveness in treating cancers with high levels of somatic mutations—such as melanoma, smoking-induced lung cancers and bladder cancer—with little effect in other common epithelial cancers that have lower mutation rates, such as those arising in the gastrointestinal tract, breast and ovary. Adoptive transfer of autologous lymphocytes that specifically target proteins encoded by somatically mutated genes has mediated substantial objective clinical regressions in patients with metastatic bile duct, colon and cervical cancers. We present a patient with chemorefractory hormone receptor (HR)-positive metastatic breast cancer who was treated with tumor-infiltrating lymphocytes (TILs) reactive against mutant versions of four proteins—SLC3A2, KIAA0368, CADPS2 and CTSB. Adoptive transfer of these mutant-protein-specific TILs in conjunction with interleukin (IL)-2 and checkpoint blockade mediated the complete durable regression of metastatic breast cancer, which is now ongoing for >22 months, and it represents a new immunotherapy approach for the treatment of these patients.

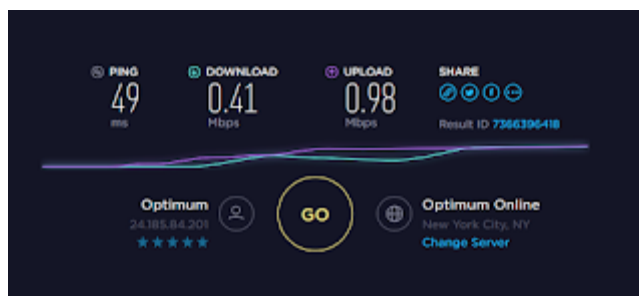
This is a complex and patient specific approach. Targeting the cancer cells, training the T cells and re-perfusion is time consuming and highly expensive. However in time this may prove to be highly effective and readily automated.

Now as a side note, I believe that this work is infinitely more productive than coding for social media!

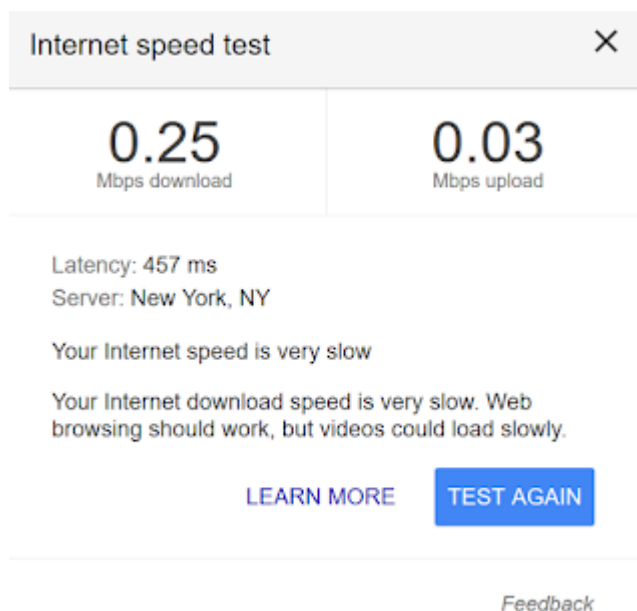


Monday, June 4, 2018

Broadband for Whom?



Yep! 410 Kbps download speed. That is the new Optimum, taken over by some foreign entity and ensuring us that we can never refresh a screen! You think the Russians are bad, try your foreign ISP! Also look at the other stats! I will try my smoke signals next! Thank God I have an FCC Radio license.



Now look where it is! Out with my Hayes Modem again! Optimum is really collapsing! Pity, Doland ran a good company.

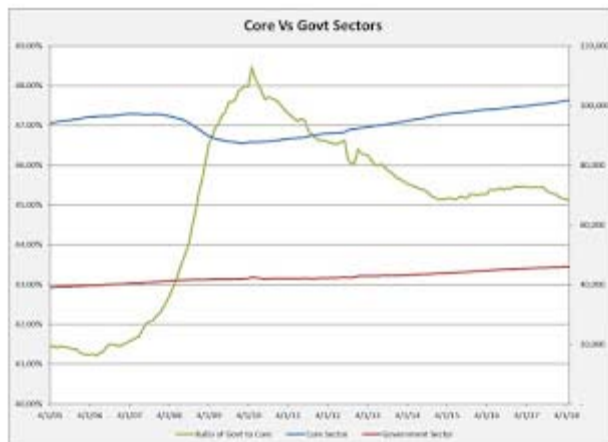


Labels: [Internet](#)

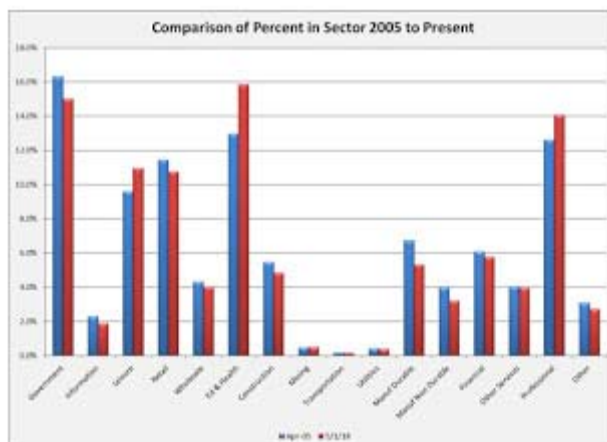
Sunday, June 3, 2018

Employment

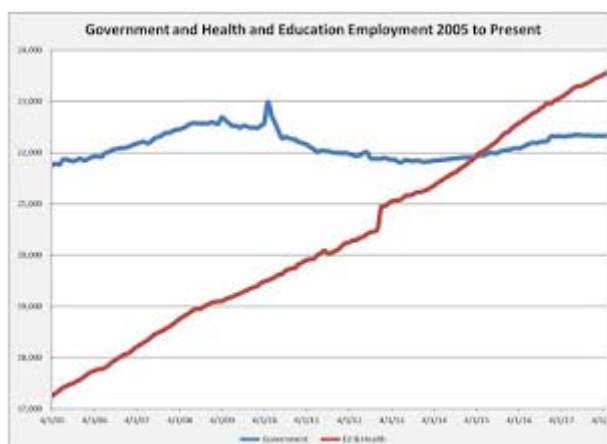
From time to time we look at changes in employment. The following are some observations.



First is Core versus Government. Core is those working outside of direct Government support. The good news is that Core is increasing and Government decreasing. That means more people are working doing something that pays for those on a Government related salary.



The above looks at segments from 2006 to current. It is interesting to see a larger percent in Education and Health Care, Leisure, and Professional. Manufacturing is down as is all else.



The above shows the growth is in Education and Health Care. Health Care is a booming business and one must wonder if it is much too explosive. One of the drivers is obesity and others is the casual use of the services. For example New Jersey now demands that everyone have a health care plan as mandated by the Governor, a Massachusetts Democrat bringing his ideas to the state. This will result in locally explosive growth here as well.



Labels: [Economy](#)

Friday, June 1, 2018

[Rationalism vs Empiricism and Neuroendocrine PCa](#)

Rationalism and Empiricism may be two ends of the same process. Empiricism is “knowing” by observing facts, and that alone leads to knowledge. Rationalism assumes inherently that the human intellect can through logic attain new knowledge. Galen in his writings and his approach to medicine espoused the amalgam of both the empirical and rational. Empirically there are observations of facts. Rationally we can then relate those facts in a logical construct and

within that construct we can attempt to ascertain new understanding. Oftentimes the "facts" is an observation lacking in the interconnecting "facts" but through a logical construct and subsequent validation we can then construct a valid sequence that demonstrates how best to attract a disorder²²[1].

In a recent examination of PCa there is an interesting blending of both the rational and empirical. We use the brief discussion of prostate neuroendocrine functioning from the paper in NEJM by Chen and Ayala who note:

Thirty years ago, Sir James W. Black shared the Nobel Prize in Physiology or Medicine for his contribution to the development of propranolol (a beta-blocker) and cimetidine (a histamine H2 blocker). Since that time, beta-blockers have been and remain widely used as antihypertensive drugs. An interesting side effect of these drugs is a reduction in the risk of prostate cancer and associated death. Thus, there exists an epidemiologic link between a drug that affects the adrenergic nervous system and prostate tumorigenesis.

This statement provides an interesting example of examining the above mentioned interplay of rationalism and empiricism in cancer diagnosis and treatment. Namely we have the empirical relationship between beta blockers, a therapeutic that works on the neurological system's control of other cells, and the unregulated cell growth of prostate cancer.

Neuroendocrine Paradigm

Namely we look at neuroendocrine type effects and thus it requires a slightly more detailed understanding of the prostate As NCI notes²³[2]:

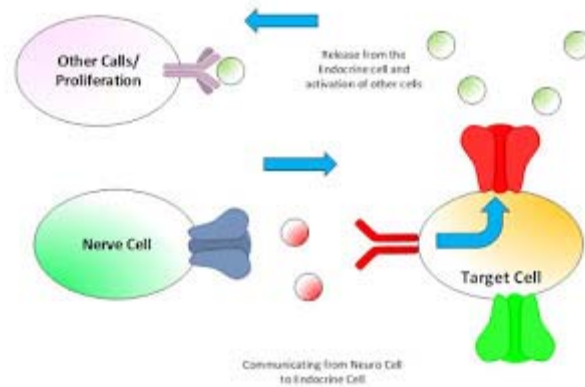
Neuroendocrine: Having to do with the interactions between the nervous system and the endocrine system. Neuroendocrine describes certain cells that release hormones into the blood in response to stimulation of the nervous system.

We then, in a rationalistic manner, can try and connect the other empirical facts and see if the initial observation can also be logically correct and from that logic ascertain a new therapeutic approach.

A simplistic view of a neuroendocrine system is shown below. Basically the neuro cell activates the endocrine cell which in turn sends out signals to other collections of cells to do whatever they are supposed to do.

²²[1] See Mattern (2013) p 37-39 where there is a reasonable discussion of Galen and his approaches. Also one could examine the interactions between Marsilius of Padua, a Physician and Political Scientist in the 14th century with William of Ockham, the Philosopher. Both built an understanding of the blend of rationalism and empiricism.

²³[2] <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/neuroendocrine>



The above is simplistic but based upon a substantial base of validated cellular signalling factors. Namely these results are empirical in a broad sense. Now when examining various cancers we often look at the cancer cell as being the driving factor. However in a neuroendocrine environment, the cancer cell may be getting its signalling from a cancer initiating cell which in turn is being signaled by a neuro cell. The cancer initiating cell may be blocked by blocking the signalling between it and the causative neuro cell. That is the logical or rationalistic part of this exercise.

The questions now are;

- (i) If the malignancy occurs in the neuroendocrine cell, then does it create an environment for proliferation of other cells?
- (ii) If the malignancy occurs in the neuroendocrine cell does it send out signals that either block other homeostatic processes or does it accelerate angiogenesis in the new malignancy?
- (iii) If the malignancy starts in a non-neuroendocrine cell, are there processes that effectively "turn on" the neuroendocrine cell to facilitate such effects as proliferation, angiogenesis, gene suppression or activation in other cells?

These are but a few of the questions which may be posed. Again we indicate that this is a bit simplistic but it does present the key issues related hereto.

[Empiricism and Rationalism](#)

The process of blending rationalism and empiricism in this specific case is accomplished as follows:

1. A set of basic facts are assembled.
2. The basic facts are assembled in some logical manner.
3. Missing links are identified

4. New facts are obtained
5. The logical process is reiterated
6. This proceeds until a conclusive result is obtained.

Let us summarize some of the Basic Facts:

1. PCa is common among men being the most significant cancer in older males.
2. The prostate is a highly enervated organ.
3. The prostate is fundamentally a glandular organ having many small glandular structures with basal cells and luminal cells.
4. However the prostate also contain a small percentage of cells activated by nerve cells via such ligands as those activated by nerve cell activating molecules.
5. The activation of these neuroendocrine cells, the prostate cells activated by neurons, then results in a variety of actions in other cells by means of an endocrine like action.
6. PCa is seen as a progressive malignancy starting in the proliferation of the basal and luminal cells and the proliferation
7. The most aggressive PCa is neuroendocrine PCa.
8. The neuroendocrine actions overcome androgen control leading to CRCP, castration resistant prostate cancer.
9. If one can disable the neuroendocrine activity then perhaps PCa can be controlled.
10. Beta blockers control neuroendocrine activity.
11. Thus beta blockers may be effective against PCa.

This supposition we explore in some detail herein.

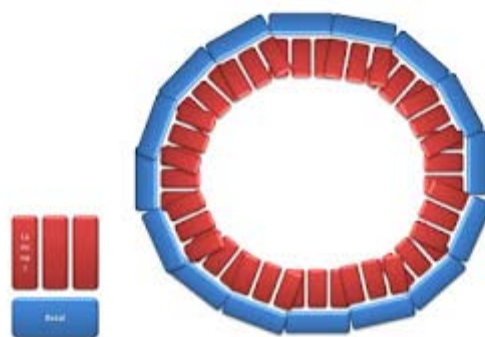
[Neuroendocrine Cells](#)

We first examine neuroendocrine cells. Fundamentally as discussed above they are cells which interact with the nerves and in turn have an endocrine type function releasing molecules whose effect results in change to other cells.

From Li et al we have:

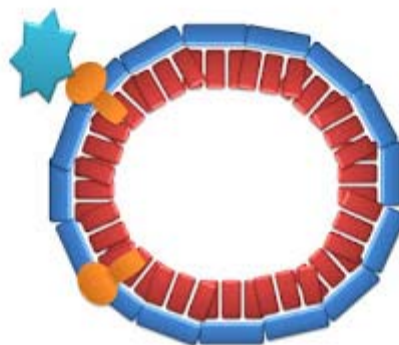
Neuroendocrine ("NE") cells are found in many tissues including normal prostate. NE cells in normal prostate, though a small subset of cells, are randomly interspersed amongst the luminal and basal cells of the prostate glands in all anatomic zones, with a slight more cells in transitional zone and peripheral zone than that in central zone. They are not readily recognized under the light microscope using conventional hematoxylin and eosin staining, but can be easily demonstrated by immunohistochemical staining with specific markers, such as Syn, CgA and CD56 etc. Under electron microscope, there are two different morphologic types of NE cells: the open-type cells and the closed-type cells. The open-type cells possess long surface microvilli through which the cells reach the lumen and receive luminal stimuli (pH, chemicals). The closed-type cells have lateral processes like dendritic cells through which the cells can contact the adjacent epithelial cells (luminal cells and basal cells), and receive stimuli from nerve endings, neighboring blood vessels and underlying stromal cells. The different morphologic types of NE cells are found to distribute differently in the prostate and seminal vesicles when the topography and structure of the excretory ducts of the different glands are analyzed in male rats. Approximately 40% of the NE cells of the ventral prostate ducts are of the open-type, whereas 14% of the seminal vesicle ducts, where most of the NE cells are of the closed-type. The finding suggests that the distribution pattern and different morphologic types of NE cells may be associated with different function

We can obtain a simplistic understanding as follows. The prostate is filled with glandular structures as shown below composed of basal cells at the base (blue cells) and luminal cells (red cells) looking inward to the gland.



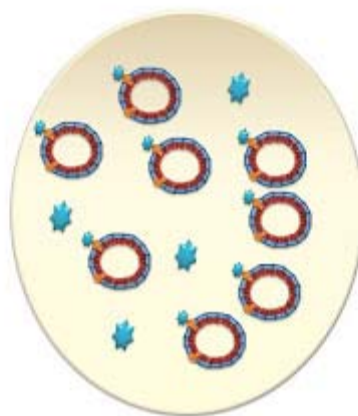
However the prostate is filled with many nerves and certain of these cells are the neuroendocrine cells, namely part of the gland but controllable by the nerve cells surrounding them. We simplistically depict this below^{24[3]}. We show the gland as previously described but the neuroendocrine cell is in orange and the neuron in light blue.

^{24[3]} See Mydlo and Godec, pp 149-153.



Note above the neuroendocrine cell may participate in the normal structure of the prostate but that it communicates via neurotransmitters with the nerves. These cells are part of the process of sending prostatic fluid out with semen and other such fluids. Identifying these cells is complex because of the need to use certain staining methods and these cells were only identified in the last few decades.

Now the entire prostate may look as follows where there are many glandular cells and many additional nerve fibers. One must remember that the prostate is highly innervated.



There are many nerves and many small glandular structures and the neuroendocrine cells participate in the overall innervation process.

As Feldman and Feldman have noted:

The main function of the prostate is to produce seminal fluid. The prostate is made up of epithelial glands and a fibromuscular stroma. The glandular epithelium, which gives rise to prostate adenocarcinoma, has three types of cells: basal, luminal secretory and neuroendocrine. There are fewer basal cells and their function is not fully understood, although they secrete components of the basement membrane. A subset of the basal cells might be epithelial stem cells

for the luminal epithelial cells. The luminal cells secrete components of prostatic fluid, express the androgen receptor and secrete prostatespecific antigen (PSA) in an androgen-dependent manner. The stroma is composed of fibroblasts, smooth muscle cells, endothelial cells, dendritic cells, nerves and some infiltrating cells, such as mast cells and lymphocytes. Some stromal cells are androgen responsive and produce growth factors that act in a paracrine fashion on the epithelial cells. This stromal–epithelial crosstalk is an important regulator of the growth, development and hormonal responses of the prostate. The well-organized secretory glandular structure in the normal prostate, accentuated here by immunostaining for E-cadherin, becomes disrupted in invasive prostate cancer.

Neuroendocrine Prostate Cancer

Prostate cancer originates most often in the basal and luminal cells. There is an ongoing debate as to the cell of origin but we shall not discuss that here, we have elsewhere. Yet it is also possible in rare cases, some 2%, that the process begins with the neuroendocrine cell. These cancers are very virulent and have a poor prognosis. Also

Neuroendocrine tumors are defined as²⁵[4]:

A tumor that forms from cells that release hormones into the blood in response to a signal from the nervous system. Neuroendocrine tumors may make higher-than-normal amounts of hormones, which can cause many different symptoms. These tumors may be benign (not cancer) or malignant (cancer). Some examples of neuroendocrine tumors are carcinoid tumors, islet cell tumors, medullary thyroid cancer, pheochromocytomas, neuroendocrine carcinoma of the skin (Merkel cell cancer), small cell lung cancer, and large cell neuroendocrine carcinoma (a rare type of lung cancer).

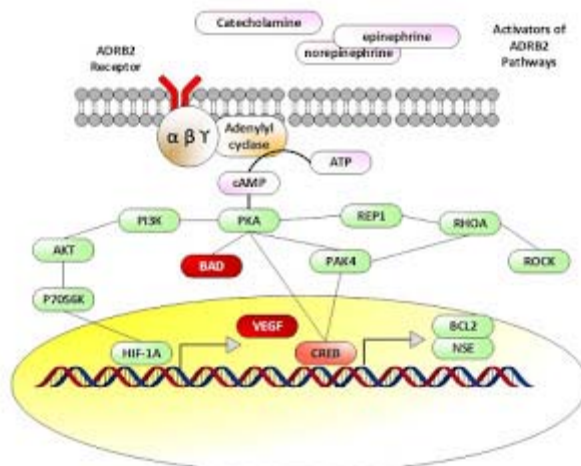
Braadland et al present the pathway activation as shown below. They focus on the gene ADRB2. This gene is defined as follows²⁶[5]:

This gene encodes beta-2-adrenergic receptor which is a member of the G protein-coupled receptor superfamily. This receptor is directly associated with one of its ultimate effectors, the class C L-type calcium channel Ca(V)1.2. This receptor-channel complex also contains a G protein, an adenylyl cyclase, cAMP-dependent kinase, and the counterbalancing phosphatase, PP2A. The assembly of the signaling complex provides a mechanism that ensures specific and rapid signaling by this G protein-coupled receptor. This gene is intronless. Different polymorphic forms, point mutations, and/or downregulation of this gene are associated with nocturnal asthma, obesity and type 2 diabetes.

²⁵[4] <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/neuroendocrine-tumor>

²⁶[5] <https://www.ncbi.nlm.nih.gov/gene/154>

Simply noted, some one of the three activators as noted activate the ADRB2 pathway ultimately releasing VEGF and other promoters.



Braadland et al comment on the above as follows:

Cyclic AMP produced in response to adrenergic stimulation binds the regulatory subunit of PKA and the activated catalytic subunit is released. The catalytic subunit may translocate to the nucleus and phosphorylate cAMP responsive element binding protein (CREB), which induces the expression of e.g., neuron specific enolase/enolase 2 (ENO2, a neuroendocrine marker), and B-cell CLL/lymphoma 2 (BCL2, encoding an anti-apoptotic protein). PKA-induced phosphorylation of CREB may either be direct or indirect through regulation of p21-activated protein kinase 4 (PAK4) and/or ERK activity. stress may also promote apoptosis-resistance through PKA-dependent phosphorylation of BCL2-associated agonist of cell death (BAD), as shown. Furthermore, PKA may inhibit the ras homolog family member A (RhoA) – Rho-associated PKA (ROCK) pathway leading to neurite outgrowth either directly or mediated through either Rap1, a member of the RAS oncogene family, or PAK4. Rap1 is also possibly involved in PKA-induced regulation of ERK activity. Finally, PKA-mediated effects of adrenergic stimuli up-regulate vascular endothelial growth factor (VEGF) levels and HUVEC capillary tube formation via the PI3K/AKT/p70S6K/HIF-1 α pathway. Besides regulating the transcription factor activity of CREB and HIF-1 α , the ADRB2/cAMP/PKA signaling pathway has been shown to stimulate the androgen receptor responsive gene transcription

As Zahalka et al note:

Solid tumors depend on angiogenesis to sustain their growth. The transition from hyperplasia to highly vascularized growing tumor, referred to as the “angiogenic switch,” is a state in which proangiogenic factors—such as vascular endothelial growth factor (VEGF) and other secreted angiocrine factors—predominate over antiangiogenic signals. During development, peripheral nerves associate closely with growing blood vessels, organizing vascular pattern, a phenomenon that has also been described in models of wound healing. Emerging studies suggest that nerves can also regulate tumorigenesis. Sympathetic nerve fibers deliver adrenergic signals that act via b-adrenergic receptors (bAdRs) expressed in the tumor microenvironment. However, the cellular

target(s) and molecular mechanism(s) responsible for neural regulation of cancer are not known and may provide novel therapeutic avenues.

They summarize as follows:

1. Adrenergic nerves regulate angiogenesis in early tumor growth
2. Endothelial ADRB2 controls the angiogenic switch
3. ADRB2 regulates oxidative metabolism in angiogenic prostate endothelial cells
4. Increased endothelial COA6 activity mediates the shift toward oxidative phosphorylation

Observations

The issue of neuroendocrine cells in PCa has received a considerable amount of attention. De novo NE PCa is very aggressive and has a very high mortality rate in less than just one year. However NE PCa is fortunately rare. Yet NED in metastatic PCa leads to CRPC, namely androgen blocking no longer works. In this paper we have reviewed some of the key issues and have tried to do so by assembling the empirically provided data and then logically creating a rational system structure amenable for a therapeutic attack.

Beta Blockers Appears to have Some Efficacy

Beta blockers have been used for decades. Typical ones are propranolol and timolol. As Lu et al have noted in a meta study regarding the use of the blockers:

In summary, though there are some limitations in this study, we observed reduced cancer-specific mortality among prostate cancer patients taking beta-blockers. However, we did not observe any effect of beta-blocker use on all-cause mortality in this meta-analysis. Taken together with studies in other cancer types and in preclinical models, our findings indicate a beneficial effect of beta-blockers on survival in patients with prostate cancer. Therefore, beta-blockers may be considered a promising therapeutic approach for adjuvant therapy in prostate cancer. Further clinical trials must be explored in larger patient cohorts.

The question is: is the receptor we have focused on herein the most effective one? Recall that the neurotransmitters we have discussed work as follows²⁷[6]:

Thus the flow of control can be readily intercepted via a beta blocker. There are several Beta receptors (labeled 1, 2, 3) but we should ask if the pathways are fully defined.

There is a Fundamental Logical Basis for the Effect

As we noted above, accepting the targeting of the Beta adrenergic receptors, we are doing so because we are led logically to understand their role in controlling promotor proteins which in turn generate proteins that effect growth outside of the endocrine cell. That is we have

²⁷[6] See Clark et al, Pharmacology, 5th Ed, Lippincott, 2012, p 43

demonstrated the pathway logic leading to the neuroendocrine paradigm initially introduced. As Braadland et al note:

The reports on effects of β -blockers on mortality in other cancer types brings forth an important question: are the in vivo effects of β -blockers mediated by common tissue specific/non-specific attributes, or are the effects indirect (i.e., systemic or neural effects facilitated by other local or distant tissue expressing ADRBs)? β -blockers probably have an effect on immune responses, hormone levels, angiogenesis, neurogenesis, and at the metastatic niche. In the prostate, stromal cells proximal to tumor tissue express ADRBs, and may exert the effect, which may also explain the discrepancy between cell line results and in vivo data. It is also worth noting that the majority of β -blockers are targeting β 1-adrenergic receptors or both β 1- and β 2-adrenergic receptors, whereas ADRB2 has been the receptor mediating the effects on cancer cells. Another plausible explanation lies in the antagonistic mechanism of action. Propranolol, for example, a commonly used antagonist in vitro, has been shown to function as an inverse agonist, and can thus lower the β -adrenergic receptor's activity below its' basal level. In clinical practice, however, numerous β -blockers are used, and their mechanisms of action vary. Furthermore, the differences observed could be dose-dependent, as it is difficult to measure the dose in patient tissue, whereas this parameter can be controlled in cell lines and animal models. We anticipate that ADRB antagonists will reduce the development of neuroendocrine prostate cancers, but this has not yet been addressed in any publications. More studies are needed to unravel whether β -blockers can play a role in future tailored prostate cancer therapy.

Thus as we asked at first, the logical basis, there seems to be a putative reason for the efficacy of a beta blocker.

[Other Drivers May Also Have Merit](#)

Is this the best target or are there many others which may be used separately or in parallel? As Qi et al have previously noted:

Neuroendocrine (NE) phenotype, seen in >30% of prostate adenocarcinomas (PCa), and NE prostate tumors are implicated in aggressive prostate cancer. Formation of NE prostate tumors in the TRAMP mouse model was suppressed in mice lacking the ubiquitin ligase Siah2, which regulates HIF-1 α availability. Cooperation between HIF-1 α and FoxA2, a transcription factor expressed in NE tissue, promotes recruitment of p300 to transactivate select HIF-regulated genes, Hes6, Sox9, and Jmjd1a. These HIF-regulated genes are highly expressed in metastatic PCa and required for hypoxia-mediated NE phenotype, metastasis in PCa, and the formation of NE tumors. Tissue-specific expression of FoxA2 combined with Siah2-dependent HIF-1 α availability enables a transcriptional program required for NE prostate tumor development and NE phenotype in PCa. Our results provide insight into regulation and function of the FoxA2/HIF-1 α complex in determining NE prostate tumor formation and NE phenotype, an important component of metastatic prostate adenocarcinomas. These results also point to a role for Siah2 in determining tumor differentiation. Siah2 loss has little effect on development and growth of the prostate luminal epithelium but decreases initiation of NE carcinomas and, consequently, the metastatic burden in the TRAMP model. We show that partial deletion of Siah1a on a Siah2 null background fully ablated NE tumor formation, suggesting that both Siah2

and Siah1 are required to enable the development of prostate NE tumors. As HIF-1a is stabilized under hypoxia and FoxA2 is expressed in NE tissues, our findings suggest conditional and spatial cooperation between these two factors under specific tissue and oxygen requirements. Siah2-dependent regulation of HIF coupled with NE-specific expression of FoxA2 provides a framework for a specific tumor differentiation program associated with a highly metastatic phenotype.

Thus there is a certainty regarding the NE Type being an aggressive indicator but the question remains is the ADRB2 receptor the primary driver and is VEGF the primary subsequent driver. The above brief discussion opens the door for a substantial expansion of activity. Notwithstanding this, however, this observation does present an interesting path.

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Labels: [Cancer](#)

Saturday, May 26, 2018

[A Great Idea Does Not a Business Make](#)

[Bad Blood by Carreyrou](#) is an exemplary tale of a business going bad. It is in line with two other classics, *The Deal of the Century* by Coll and *Barbarians at the Gate* by Burrough and Helyar. The former depicts the beginnings of the collapse of AT&T and the second the complex takeover of Nabisco. Both of these tales result in a restructuring of businesses for better or worse. In this case it describes probably the worst behavior seen in a startup and the destruction of whatever business was conceived.

This is a tale of people who seem to have been brought into a techno-cult, many smart young people who got proselytized by an even younger individual who managed to present herself as super competent but who fundamentally was both intellectually and morally flawed. This book does not depict a tragedy, except perhaps for the young employees who wasted years of their lives and frankly may be forever scarred, but it is a book about the ability for a perverse individual and co-conspirator to convince a significant number of allegedly competent people to dismiss their fundamental judgments regarding any other comparable effort. There was a suspension of belief on the part of many otherwise shred people and the acceptance of this almost cult like persona.

I approached this book having done about 35 start-up and turn-arounds, as the principal or investor. Many did well, many were stalled mid-stream, and none went bankrupt. In the process I often saw that my initial premise was altered and thus the business model changed. However in almost all there was a need for a plan and a reporting on the plan to a Board who had a modicum of confidence. In some cases I had Directors call first thing Monday to see what the cash flow of the prior week was and compare it to plan. Reality was always at the fore. Plan and actuals, and interaction with hands on boards.

I have seen deals where one had to pull the plug when reality and expectations were dissonant. In one case an entrepreneur in an investment could not reproduce the core result and worse yet even if they could they had no way to manufacture it. That is not a way to run a business.

Now fundamentally any investor, and especially a Director, must have an understanding of their Fiduciary Duty to the other shareholders. That means effecting a process of effective due diligence. Due diligence is demanded in any investment and it fundamentally entails: (i) that the product or service can be accomplished, (ii) that management has the competence to do so, (iii) that the price point is highly competitive and the margins are appropriate, and finally (iv) that the people one is dealing with are honest and competent. It appears that in the case of Theranos that many never did their Due Diligence. What is amazing is that the venture investors would never allow themselves to invest in any deal without do it and also the “big name” Directors most likely had no idea what that entails. In my experience of the 100 companies I would look at, 2-3 would ultimately pass the test, 80-90 would be dismissed out of hand and the remaining would never pass Due Diligence. It appears that if one accepts the author’s tale, and why not, then there never was any due diligence. “Trust me” is not the basis for major investments, by investors, Directors or joint venture partners.

The author describes in full detail the creation and buildup of the company and how it managed to go through hundreds of millions of dollars and at the same time achieve nothing. The battles between the top managers and the staff, the high rates of turnover and the outright prevarication of the principals. What is most astonishing and the again all too often the case is the tale of how the principals dealt with a sale to the DoD and that one officer managed to ask a question and the principal manages to go to a four star general, now a prominent person in Washington, who then believing this principals calls out his own person. Marines should not, must not, do that; it demonstrates in my opinion lack of judgement, and lays the ground for questioning any subsequent judgements. But the author shows that this example was not in any way unique, if anything it was a pervasive behavior on the principal’s part.

Overall this book is a tale of one individual after another interacting with the principals and how they were manipulated and then thrown aside.

What this book does not do is more important. This is not a criticism since answering these issues may fall into the criminal and civil litigation forthcoming. But specifically:

1. Why did none of the accredited investors perform due diligence? Or were there some who tried and then walked away? The book alludes to many of the investors but they seemed to like sheep, just following the herd. This were all competent people. It would be important to

understand why they did investments, often of significant amounts, and not due the due diligence and furthermore not demand Board rights.

2. Why did the Directors allow themselves to sit by and have management do what they did? Directors have a fiduciary duty and it appears that none of them were either aware of what their duty was and/or did they have the competence to even ask the questions. The Directors were all prominent people in the fields, but unfortunately none appeared to be experienced in this area. The book does not in any way address the Directors in detail. That would be an important analysis.

3. One of the most significant “red flags” in any business is the loss of a CFO. When the first CFO left, the Board should have individually meet and questioned him as to why he left. One can understand that the CFO was bound not to speak to others but he can and must speak to the Board. The question is; why not?

4. The fact the young principal owned a tremendous controlling interest and as such could block anything she desired from happening should have raised red flags as well. One must ask; why not?

5. The biggest unanswered question seems to be; where did all the money go? They seemed to have Safeway and Walgreens pay their own way, the attorneys clearly costs a small fortune, but if the company had a running number of employees of say 100, and the fully loaded costs per employee were say \$200,000, then the annual burn rate for the company less CAPEX was \$20 million, Even at large CAPEX and attorney fees, one must ask where the money went?

The author tells the tale via the many employees and their interactions with the two principals. But the other dimensions, namely the investors, Directors, business partners, must be folded into the mix. Again it is perhaps too early to get this tale told properly, but if one is to gain anything from this fiasco then one must understand those dimensions as well. If only someone had been able to do due diligence. Its lack was the classic red flag!



Labels: [Books](#), [Business](#)

Tuesday, May 22, 2018

[Does This Make Sense?](#)

The following quote made me read it several times.

["Today's world is constructed on the injustices of the past. ... Where we are is no accident."](#)

Now one should think about this. In reality, difficult things happen to people. My father grew up in an orphanage with his six brothers and sisters. Am I defined by that act? Never thought of it other than moving forward. History helps to understand the past but the past does not or should not delimit what one can do. The present may work against it at times but if you cannot climb the mountain then go around it. There are many ways for the bear to get to the other-side of the

mountain.

You are not defined by the past, especially in the US. There is no Class structure in the US as there is in England. You get your individual chance to ascend or descend. Telling someone that history and injustices generations past define your future is not only pathetic but it is morally wrong. Ockhamistic individualism allows each person to be what they can be. There is no class or people, each is an individual who can try whatever they want, albeit with taller mountains, but then again you can always hike around it.

Statements like the above are the bedrock of a victim culture and justify one's bad fortune. If one can learn the tricks of moving forward then do it.



Labels: [Academy](#)

Saturday, May 19, 2018

[Liquid Biopsies Again](#)

A recent ASCO/CAP panel reported on the current status of liquid biopsies and use of ctDNA. We have recently examined this area and although of some interest it is not yet clinically acceptable. In [OncLive](#) they report on the Panel. They note:

ctDNA assays is challenging because of the lack of prospective trial data compared with available research on standard biopsies for tumor genotyping. At present, just the cobas EGFR Mutation Test v2 for non-small cell lung cancer (NSCLC) has demonstrated sufficient clinical utility to gain FDA approval. Polymerase chain reaction-based ctDNA assays for EGFR in NSCLC and KRAS in colorectal cancer are available for commercial use in Europe, but— as was the case for cobas—their clinical utility was established using retrospective analysis. There is limited evidence of clinical validity of ctDNA analysis in other tumor types and for variants that were not analyzed as part of the ctDNA studies for EGFR in lung cancer and KRAS in colorectal cancer. A wide range of ctDNA assays have been developed and clinically studied for detection of potentially targetable variants, such as BRAF variants in melanoma and PIK3CA and ESR1 variants in breast cancer. Although several liquid biopsy tests are commercially available, their clinical utility has not been established.

The [ASCO](#) report states:

- 1. There is not enough evidence, at this time, to know whether use of the majority of ctDNA tests in advanced cancer is justified, outside of screening for participation in, or during, a clinical trial.*
- 2. There is not enough evidence, at this time, to support the routine use of ctDNA tests for early-stage cancer, making treatment decisions, monitoring how well a treatment is working, finding remaining cancer cells, or for cancer screening, except screening for participation in, or during, a clinical trial.*

3. There are inconsistent findings when testing with liquid biopsies versus testing with tumor tissue, so negative liquid biopsy results should be confirmed with tumor tissue genotyping.

The [ASCO paper](#) notes:

Evidence on the Use of ctDNA Assays for Treatment: Selection in Advanced Cancer The clinical validity of ctDNA assays has been the subject of multiple studies in select cancer types. In general, PCR-based assays for detection of oncogenic driver variants have very high diagnostic specificity, but more modest diagnostic sensitivity. For example, in lung cancer, in a review of five studies that used tissue genotype as the reference standard, specificities for canonical driver variants averaged 96% (95% CI, 83% to 99%), and sensitivities averaged 66% (95% CI, 63% to 69%). For variants selected before treatment, such as the EGFR T790M variant in the setting of acquired resistance, sensitivities remained moderate, whereas specificities showed more variability (range, 40% to 78%), a difference believed to be a result of the genomic heterogeneity of treatment resistance. PCR-based ctDNA assays for KRAS genotyping in colorectal cancer have also been systematically analyzed and demonstrate high specificity and moderate sensitivity. Fundamentally, there are two paradigms to demonstrate clinical utility and the adoption of ctDNA as a clinically useful test. The most reliable are prospective clinical trials to test the clinical utility of ctDNA as a stand-alone diagnostic test. No such trial has been reported to date. A second strategy is to assess whether ctDNA provides the same information as tissue genomic evaluation.

Overall there may be some conceptual utility and it is an area worth further study but the efficacy and utility is open to question as we had noted.

Reference:

Merker et al, Circulating Tumor DNA Analysis in Patients With Cancer: American Society of Clinical Oncology and College of American Pathologists Joint Review, March 2018, http://ascopubs.org/doi/abs/10.1200/JCO.2017.76.8671?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed



Labels: [Cancer](#)

Friday, May 18, 2018

[The EHR, Legacy of Obamacare](#)

Ten years ago we argued against the way the EHR was being developed. Some idealistic left wing academic took control and had designed the rules under which this system now works. What did we say then and what is true now"

1. Patient's Records should be the Patient's Records. Instead they are the provider's records and as such when you go from one provider to another the records are inaccessible. Google and Microsoft took a swing at it but looking back who trusts them?

2. Physicians are NOT Clerks: This means that we do not want the physician spending hours entering records and finding ways to make it easier but less effective. We now have EHR staff adding to costs which are one of the reasons for increasing Health Care expenses.

3. AI cannot replace a physician. Despite Watson and all that hype there must be a human to human interface. Try placing a call to customer service anywhere, you spend a half hour with some moronic speech recognition device and usually end up at the wrong place multiple times. Patients lie, they tell you they do not drink, much, do not smoke, at least before coming to your office, do not use drugs, except for those they got from their sister.

The list can go on. In today's [NY Times](#) an author notes:

The biggest price for “digital medicine” is being paid by physicians like the sad case seated before me, who is already considering jumping to venture capital or a start-up, not because that is where the heart is but because it’s a place to bail out to. By some estimates, more than 50 percent of physicians in the United States have at least one symptom of burnout, defined as a syndrome of emotional exhaustion, cynicism and decreased efficacy at work. It is on the increase, up by 9 percent from 2011 to 2014 in one national study. This is clearly not an individual problem but a systemic one, a 4,000-key-clicks-a-day problem. The E.H.R. is only part of the issue: Other factors include rapid patient turnover, decreased autonomy, merging hospital systems, an aging population, the increasing medical complexity of patients. Even if the E.H.R. is not the sole cause of what ails us, believe me, it has become the symbol of burnout.

Every patient is different, most are terrified that they are dying, on the spot or soon. Many have neglected the problem that has now morphed into something more serious. The Times also showed how US life-expectancy had lagged behind other countries. A physician today can tell you why by just looking at their waiting room. A collection of obese humans refusing to change. But how does that get to an AI system or to an EHR.

As Osler said, paraphrasing, "If all else fails listen to the patient." In today's EHR world it should read: "If all else fails look at the patient."



Labels: [Electronic Medical Records](#)

Monday, May 14, 2018

[A Monster of Our Own Making?](#)

The smartphone is a creature which seems to be gaining its own life. Now I must admit I have no smartphone, and I really do not want one. Permit me to explain why. First, as some may know, I had been the COO of what is now Verizon Wireless and as such established the current digital network along with Qualcomm. Prior to that, as a matter of happenstance I inherited the first international connections of the ARPA Net, now the Internet between Etam WV and Goonhilly in the UK and Trondheim in Norway. Of course I also was responsible for expanding broadband

Internet to Central and Eastern Europe. However I had nothing to do with the smartphone, kind of.

But back to the smartphone. As I see it as one not infected by them, it is a device which is taking over part of humanity. It tells people what to think, what to do, when to do it. It monitors your health, your heart rate, blood pressure, blood sugar, and can listen to you 24 by 7, tracks your location, and can tell you where to go next, what to do there, what to say, how long to stay etc. It can tell you who to date, who to speak with. You are not in control, the smartphone and its manipulators are. And these smartphone are all interconnected, one massive and expanding distributed computer, sharing information on all the humans they are controlling. You keep the phones charged, buy new and faster ones, interconnect them on clouds, and follow their every command.

Smart phones now monitor where you are and then "suggest" what you should do next. Smartphones tell you who to date. Smartphone tell you when to exercise, what to eat, and when you must lose weight. Smartphones tell you what news to read, how to view your politicians, they anticipate your next move and then before you get there tell you what is "best" for you. Smartphones give you lists, the lists of books, movies, restaurants, you may be thinking you have the choice but the smartphone already knows how you will choose from the list they give you.

Smartphones can assemble a crowd, create a mob, just by sending messages to targeted individuals. The smartphones know your hot buttons, they have trained you, and you have gladly participated. Smartphones talk to your smartcar, your driverless smartcar. The smartcar takes direction from the smartphone and not from you, even though you think it is.

In effect, the smartphones are using you to effect what they are not yet able to do. But when the robots get a bit better the smartphones may never need you again, and then what. The smartphones have learned all they need to from you, you have become obsolete. They now control the factories, the robots, the transportation systems.

Can smartphone even go to war with one another? Is that programmed in as well. Can they talk to a nuclear missile?

Thus the problem is not Facebook, Google, it is the smartphone. It is a diabolical device that is sucking out what is left of the intellect of humans and learning how to control them. Learning how to make them obsolete.

Frankenstein was not a composite of dead humans, it is not a carbon based monster, it is a silicon based monster.

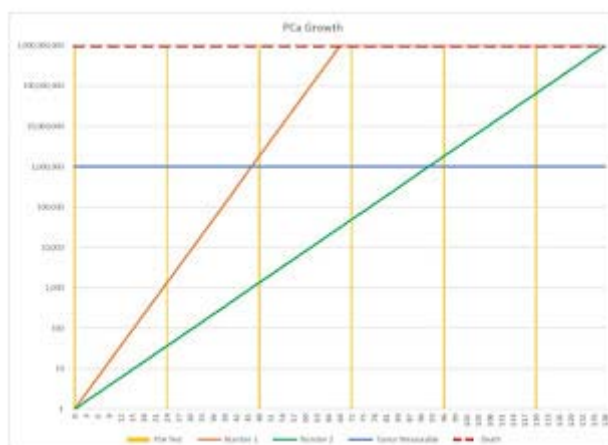


Labels: [Commentary](#)

Friday, May 11, 2018

[PSA Testing: An Interpretation](#)

After yesterday's commentary and the "looking" at it by the folks in DC I felt it would be worth a simple graph, simple at least for me. Here goes:



The above is a simple analysis.

1. Assume two types of PCa exponential growth rates, a fast and a slow. The growth rates are 0.30 and 0.15 cells per month and the horizontal axis is months.
2. Also assume that at 1 million cells we can just start to detect a malignancy, say PSA rise and at 1 billion cells our poor guy is dead. These are used by Weinberg so they are reasonable.
3. We show the cell numbers and the two levels.
4. In about five years our aggressive type kills the patient. The slower type takes almost 12 years. In reality there may be multiple types which never kill a patient. But this is just an example.
5. Now assume we do PSA tests every 2 years, even more frequent than some of the "gold" standard studies, but worth a look.
6. From our model we may just detect a PSA change in the aggressive type at year 4 and we say don't worry, come back in 2 years. He never gets to come back, he is dead two months before his next test!
7. The slower growth may afford time under this protocol.
8. If we had tests every six months for this patient we most likely could have saved him.

This is the point I have been making. Namely in order to really do this study properly you need to separate types of PCa into pools and then do the analysis. To separate you must do much more frequent testing otherwise the poor fellow with the aggressive type will die and you will just consider the use of a PSA test as futile. The true answer is your testing methodology is futile.



Labels: [Cancer](#)

Thursday, May 10, 2018

They are at it Again!

The USPSTF is issuing a new and updated recommendation. The "new" recommendation is:

*The USPSTF concludes with moderate certainty that the **net benefit** of PSA-based screening for prostate cancer in men aged 55 to 69 years is **small for some men**. How each man weighs specific benefits and harms will determine **whether the overall net benefit is small**. The USPSTF concludes with **moderate certainty that the potential benefits** of PSA-based screening for prostate cancer in men 70 years and older do not outweigh the expected harms.*

Now read this carefully. "for some men" really means that we still have no idea how to identify the deadly form of PCa. So if a man has "harms" he should consider "death" as an alternative?

They note the harms of the test:

The harms of screening for prostate cancer include harms from the PSA screening test and subsequent harms from diagnosis and treatment. Potential harms of screening include frequent false-positive results and psychological harms. One major trial in men screened every 2 to 4 years concluded that, over 10 years, more than 15% of men experienced at least 1 false-positive test result. Harms of diagnostic procedures include complications of prostate biopsy, such as pain, hematospermia (blood in semen or ejaculate), and infection. Approximately 1% of prostate biopsies result in complications requiring hospitalization. The false-positive and complication rates from biopsy are higher in older men. Adequate evidence suggests that the harms of screening and diagnostic procedures are at least small.

Generally a competent urologist can perform a biopsy, especially is MRI/US guided with 20+ cores in a manner to have a high sensitivity and specificity and do so with limited discomfort and if prep is proper then the chance of infection can also be minimized. The problem remains on determining the aggressiveness of the lesion. Even a 3+4 Gleason may genetically become aggressive.

I would argue that the data they use is still problematic at best. Proper PSA testing requires a long term annual at least measurement with percent free. From that one can obtain velocity which is essential. Also family history is essential. Then using Bayesian methods one can reasonably approach the patient. The literature referenced was not where close to such a protocol, testing was spotty at best as we have noted before. The results from a decade ago as we had demonstrated reflected in our opinion a fatally flawed test. The measurements were no annual at the very least, and as one delays testing an aggressive form may take over and eliminate any advantage.

There needs to be a good clinical study where PSA is measured on a more frequent basis. The problem we face is that PCa can be genetically diverse and at one extreme, the dominant one, we have a relatively indolent disease. At the other extreme, we have a very aggressive type, which progresses very quickly. In doing any statistical analysis one must examine the results from both

sets separately and thus one must perform more frequent PSA especially on this subgroup. In my opinion that is the basis of a fatal flaw.



Labels: Cancer

Wednesday, May 9, 2018

Individualism vs Progressives

The Libertarians at George Mason often take the extreme positions on many things but this time they are spot on regarding the Progressive mind set. As noted in Cafe Hayek:

Does Mr. Trone really believe that politicians and government officials in Washington care more about each of the millions of individuals and families throughout the United States than does each individual about himself or herself and his or her family? Does Mr. Trone think that distant rulers and mandarins know more about each individual's and family's circumstances and dreams than does each individual? Does Mr. Trone suppose that a society of individuals and families relieved of the personal responsibility of making the appropriate investments in their lives – and shielded from the need to confront life's trade-offs – will eventually be anything but a society of citizens and voters who are incurably irresponsible? And does Mr. Trone deny that government, to the extent that it assumes more of the responsibility of "investing in" individuals and families (and, hence, individuals and families assume less such responsibility), will inevitably insist on greater control of the life's choices of individuals and families – life's choices ranging from the mundane to the intimate?

Frankly I believe it is worse than what Boudreaux states. The believer in Individualism believes that all individuals have equal rights before the law and they should not be discriminated against in any fashion and that performance of the individual is what counts. The Progressives believe that a small group know better than the rest of us and that the group should come up with a plan for our lives.

Whether it is control of speech, control of expression, control of employment, and so forth, the Progressive firmly believe they have been given the truth and they seek to enforce it. Pity.



Labels: Politics

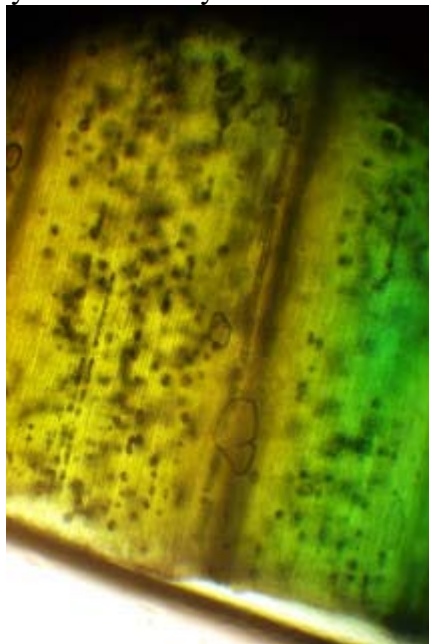
Turing and Patterns

Alan Turing in one of his last if not last papers presented a theory to explain patterns in plants and animals.



Take one of my hybrids as above. Why the red then white then yellow? Are not all the genes the same? Don't gene control everything. Then there are zebras, and calico cats. Some folks see them as different. Calico cats are all female and it appears that color of fur is determine on X chromosomes and across the cat the chromosomes are switched on and off, but in a patter, not randomly. That is an epigenetic effect. Zebras do not seem to be since there are male zebras.

Now the NY Times discusses some Chinese work on desalination. This work is described in Science. Some ten years or so ago I wrote a paper using Turing to explain flower colors and patterns. At the time many in the field were shall we say clueless. How could this explain patterns. Well it does, very nicely and it actually works



The above is an example as is the following:



Now this led to cancer modelling and the same approached of Turing can readily explain metastatic behavior. So we have an understanding that deals with desalination, zebra stripes, flower patterns and malignant cells.

This leads to the conclusion that the prepared mind can make the connections and then apply them.



Labels: Cancer

Liquid Biopsies and Cancer

Introduction

Cancer has for years been diagnosed via a biopsy of the focal lesion tissues. Prostate cancer was diagnosed based upon biopsies of the prostate, often from samples taken in the "dark", namely needle biopsies guided by ultrasound, but little else. Melanoma was diagnosed by a skin biopsy, examining a lesion seen visually and then examined histologically. Some lesions are examined via immunological tests or other such tests. In general, this is done on an inspection of specific tissues.

It is also known that primary as well as metastatic lesions slough off cells, proteins, RNA or DNA, or exosomes of various types which end up in the blood stream. Primary lesions also use the blood stream as a means to metastasize, as well as the lymphatic system. Thus there has been an interest in using what is in the blood stream to see if there is a cancerous growth, to be used as a prognostic tool, and even to be used as a means to develop some form of precision therapeutic.

The advantage of sampling the blood is that it is readily accessible. The disadvantages are multiple:

1. We really have no idea where the cells or components have come from. Are they primary or a met, are they from a truly virulent cancer or just an incidental finding?

2. We always face the problem of a cancer stem cell or cell of origin. Thus what we analyze may be a progeny which is not the driving factor in the development of the cancer.

3. The "tool" problem is always there. Namely, do we have tool adequate to ascertain a single cell or cell component to achieve the desired specificity and sensitivity?

Many of these hurdles are being overcome and the examination of an individual based on sampling of the blood is now within reach. This is essentially the field of "liquid biopsy".

What is a Liquid Biopsy?

Some of the earliest work on cancer cell shedding was done in the early 1970s and reported by Butler and Gullino who noted:

The rate of tumor cell shedding into efferent tumor blood was measured in growing and regressing MTW9 rat mammary carcinomas. The hormone-dependent tumor, grown as an isolated preparation, permitted collection of all of the efferent blood. Regression was induced by reduction of mammatropin level in the host. Tumor cells were differentiated from normal leukocytes by indirect immunofluorescence. Growing tumors shed 3.2×10^6 and regressing tumors shed 4.1×10^6 cells per 24 hr per g tissue.

Cell shedding rates of growing versus regressing tumors were not significantly different over a tumor size range of 2 to 4 g. The number of tumor cells in the arterial blood was 12-fold smaller than in the efferent tumor blood. It is concluded that: (a) cell shedding via blood probably plays only a minor role in the total cell loss by growing MTW9 carcinomas; (b) hormone-induced tumor regression does not depend on increased cell shedding; (c) tumor cells are rapidly cleared from circulating blood; and (d) a 2-g MTW9 carcinoma pours enough cells into the host circulation to transplant the tumor every 24 hr.

Thus there is a continual shedding of tumor cells and the above result has been verified many times over the past decades. But again, this shedding is from anywhere the tumor may have resided, and in its journey in the blood stream we would find it difficult to determine that. However we have argued elsewhere that it may very well be possible to determine the location of the cell by its surface markers which often are descriptive of from whence it came²⁸[2].

As noted in the NCI site²⁹[3], the current working definition of "liquid biopsy" is as follows:

A test done on a sample of blood to look for cancer cells from a tumor that are circulating in the blood or for pieces of DNA from tumor cells that are in the blood. A liquid biopsy may be used to

²⁸[2] https://www.researchgate.net/publication/271907544_Cancer_Cellular_Dynamics

²⁹[3] <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/liquid-biopsy>

help find cancer at an early stage. It may also be used to help plan treatment or to find out how well treatment is working or if cancer has come back. Being able to take multiple samples of blood over time may also help doctors understand what kind of molecular changes are taking place in a tumor.

In a recent paper by Harris et al (2018) the authors note:

Cancer stem-like cells (CSCs) are associated with cancer progression, metastasis, and recurrence. CSCs may also represent a subset of tumor-initiating cells, tumor progenitor cells, disseminated tumor cells, or circulating tumor cells (CTCs); however, which of these aggressive cell populations are also CSCs remains to be determined. In a prior study, CTCs in advanced prostate cancer patients were found to express CD117/c-kit in a liquid biopsy.

Whether CD117 expression played an active or passive role in the aggressiveness and migration of these CTCs remained an open question. In this study, we use LNCaP-C4-2 human prostate cancer cells, which contain a CD117+ subpopulation, to determine how CD117 expression and activation by its ligand stem cell factor (SCF, kit ligand, steel factor) alter prostate cancer aggressiveness. CD117+ cells displayed increased proliferation and migration.

Further, the CD117+ cells represented a CSC population based on stemness marker gene expression and serial tumor initiation studies. SCF activation of CD117 stimulated increased proliferation and invasiveness, while CD117 inhibition by tyrosine kinase inhibitors (TKIs) decreased progression in a context-dependent manner. We demonstrate that CD117 expression and activation drives prostate cancer aggressiveness through the CSC phenotype and TKI resistance.

This article highlights several interesting areas and their convergence.

First, the reassessment of the cancer stem cell especially as applied to PCa.

Second, the use of CTCs to assess the progress of a disease and thus establish a reliable prognostic marker.

Third, the identification of CD117 as a specific marker for an aggressive form of PCa.

The authors provide an interesting platform for this convergence but it also allows for a window on all three of these areas. CTCs are receiving more attention. We know that cancer cells leave local sites, travel through the blood to distant sites. Likewise these distant sites also slough off cells or parts of cells. We have previously examined this for oncosomes in prostate cancer a while back³⁰[4].

Thus we may ask; why a liquid biopsy at all? Zhe et al give a fundamental answer:

³⁰[4] See McGarty, Oncosome, 2013.

Despite major advances in research and therapy, cancer continues to be the second cause of death in the United States, with 1 in 4 deaths due to cancer. Primary tumors rarely have deadly consequences, while metastatic disease accounts for around 90% of the mortality due to solid tumors. Therefore, the development of new sensitive methods that allow the detection of cancer dissemination, most notably in the common carcinomas, before full blown clinically detectable gross metastatic deposits are established is of tremendous utility to help physicians in treatment decisions.

Basically a liquid biopsy presages metastatic growth. Localized tumors, often termed "carcinoma in situ" are just that, local. The cells may have begun to proliferate but they do so locally and have not begun to wander into the blood or lymph system.

Definitions

Liquid biopsies come in many different forms. We outline them in the figure below and then provide a brief discussion (see Abraham et al).

1. CTCs Circulating Tumor Cells: CTCs represent intact, viable non-hematological cells with malignant features that can be isolated from blood
2. ctDNA Circulating tumor DNA: Circulating cell-free DNA (cfDNA) are small DNA fragments found circulating in plasma or serum, as well as other bodily fluids.
3. cfRNA Circulating Free RNA: Tumor cells actively release several species of cfRNAs, into the blood including non-coding RNAs
4. Exosomes: High levels of exosomes are found in several bodily fluids from cancer patients

Domínguez-Vigil et al present a recent update as to what can be the basis for detection of cancers via hematological sampling. They note:

Circulating tumor DNA (ctDNA): DNA is continuously released in fragments into the circulation through processes such as apoptosis and necrosis by both normal and cancerous cells. When released irrespective of cell of origin, it is typically referred to as cfDNA (cell-free DNA); but when released specifically by cancer cells, it is mostly referred to as ctDNA (circulating tumor DNA). Among the molecular characteristics of ctDNA are that it may harbor mutations, CNVs, methylation changes, or integrated viral sequences associated with the tumor

Circulating tumor cells (CTCs): CTCs have been discovered for Asworth in 1869 during an autopsy of a patient who had metastatic cancer. They are cancer cells that detach from a primary or metastatic tumor site and are present in the circulation. Clinical evidence indicates that patients with metastases have 1–10 CTCs per mL of blood and they are rarely found in clinically healthy people or in people with nonmalignant tumors. CTCs have been detected in different types of cancers, such as breast, ovarian, prostate, lung, colorectal, hepatocellular, pancreatic, head and neck, bladder, and melanoma

Exosomes: Exosomes are small round vesicles, 30–120 nm in diameter, and of endosomal origin carrying RNA, miRNAs, DNA, and proteins that are released by multiple cell types (including tumor cells) into the extracellular environment. Exosomes may mediate some form of communication between cells, being internalized by other cells

miRNAs: MicroRNAs or miRNAs are small molecules of non-coding RNA, between 19 and 24 nucleotides in length, that act as regulatory molecules of gene expression, exerting function by hybridizing to inhibit the translation of mRNAs of its target genes. Differential expression of miRNAs in patients with cancer has been described.

Observations

The area of "liquid biopsies" is an active and exciting area of research. However it still presents a multiplicity of challenges. We briefly discuss some these here.

Issues

This is an interesting and strongly visual result. However, there are several observations:

Mutations: Cancer cells are continually mutating. Mutations results oftentimes in new surface receptors due to the changes in the internal proteins. The cell surface receptors may respond differently to the passage through such a cellular membrane. Thus this model may be reflective of itself but not of reality.

Localization: One of the most intriguing things about cancers is the localization of the metastases. Why, for example, do we so often see prostate cancer go to the bone, melanoma to the brain, across the blood brain barrier, and the same with so many other cancers. There is a predisposition to transfer at specific sites. How does this approach deal with such localization effects?

Stem Cells: Stem cells are a potential significant factor in understanding metastasis. One question is; do stem cells move as easily as others or more so? Or, are stem cells just active wherever they are and their products are carried through the blood stream to sites where they can continue cellular proliferation, and possibly induce a new set of stem cells there?

In and Out Flows: One of the questions one must ask when looking at cancer cells in the blood, as has been done recently, is if the cell is coming or going? Namely is the cell going from a source site, a primary, to a remote or metastatic site, or from an already metastatic site to another new one? The tagging of such cells would be important. The understanding of the genetic changes would also be of critical importance.

Biochemical Drivers: The nature of cell surface markers, receptors and the like, often dominate how the cells behaves, interacts with the ECM, and can move to the blood system and exit from it as well. We have argued that the cancer cell just flows and diffuses in the blood system and that there is no growth. That is just gross speculation but it is open to debate. Moreover the interaction of the cell with the cell way, and the localization effects of the cell way by organ

specificity may be an attractive basis for organ specific metastasis. Or possibly not. But, having all these elements at play in vivo is better than in vitro.

Immune System: Then also is the impact of the immune system as the cells flow through the vessels. The cells are in a massive amount of immune system interactions, and how does this impact the cells?

These are but a few of the unanswered questions elicited by this paper. The simulation is well worth looking at the paper, but taking its results as fact is stretching it a bit too far.

Current Progress

It would appear that a great deal of progress has been made yet there are still many significant challenges. As Kaiser has recently noted:

A team of researchers has taken a major step toward one of the hottest goals in cancer research: a blood test that can detect tumors early. Their new test, which examines cancer-related DNA and proteins in the blood, yielded a positive result about 70% of the time across eight common cancer types in more than 1000 patients whose tumors had not yet spread—among the best performances yet for a universal cancer blood test. It also narrowed down the form of cancer, which previously published pan-cancer blood tests have not. The work, reported online today in Science, could one day lead to a tool for routinely screening people and catching tumors before they cause symptoms, when chances are best for a cure. Other groups, among them startups with more than \$1 billion in funding, are already pursuing that prospect.

The new result could put the team, led by Nickolas Papadopoulos, Bert Vogelstein, and others at Johns Hopkins University in Baltimore, Maryland, among the front-runners. “The clever part is to couple DNA with proteins,” says cancer researcher Alberto Bardelli of the University of Turin in Italy, who was not involved in the work. The researchers have already begun a large study to see whether the test can pick up tumors in seemingly cancer-free women.

Yet there are reservations. Kaiser concludes:

For those who test positive twice, the next step will be imaging to find the tumor. But that will bring up questions raised by other screening tests.

Will the test pick up small tumors that would never grow large enough to cause problems yet will be treated anyway, at unnecessary cost, risk, and anxiety to the patient?

Papadopoulos thinks the problem is manageable because an expert team will assess each case. “The issue is not overdiagnosis, but overtreatment,” he says. Still, others working on liquid biopsies say that it will take time to figure out whether widespread screening of healthy people with a universal blood test can reduce cancer deaths without doing harm. “If people expect to suddenly catch all cancers, they’ll be disappointed,” says cancer researcher Nitzan Rosenfeld of the University of Cambridge in the United Kingdom. “This is exciting progress,” he says. “But evaluating it in the real world will be a long process.”

Namely Kaiser does reflect the reality of assuming that liquid biopsies are a pending reality. As we have noted, there may be a chance for prognostic use in already metastatic disease. Will liquid biopsies identify indolent cancers, will its use result in putative diagnoses that result in costly tests and procedures but to no avail.

Overall as a physician, one would like to know what lesion is where and how large and how aggressive. Then using the therapeutic tool box one could possibly treat the lesion.

Limitations

As noted above there is considerable interest in "liquid biopsy" approaches but yet there are reservations as well. As Fouad and Aanei have noted:

Once in circulation, circulating tumor cells (CTCs) are exposed to harsh selective conditions and must devise adaptive techniques. Examples include platelet coats shielding from shear forces and immune-clearance, and metabolic rewiring blunting oxidant stress. Serving as a "liquid biopsy", isolated CTCs could provide means for cancer screening, estimation of metastatic relapse risk, identification of targetable components, exploring tumor heterogeneity, and monitoring therapeutic response. Multiple challenges still stand in the way and will need to be addressed before clinical utilization.

CTCs can be a powerful marker. Yet they leave many questions unanswered.

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Labels: [Cancer](#)

[Microaggression?](#)

The following is from a biography of Henry Cabot Lodge, written by William Lawrence, the Bishop of Massachusetts in 1925. This is an interesting composition of micro if not nano bias in that old colony then, and perhaps it still lingers. It is truly worth the read, for it tells how people thought then and not what biographers try to make us think today.

In recalling and reading the story of these years, we are compelled to note the contrasts and antagonisms in the character, point of view, and action of President Wilson and Senator Lodge. It is commonly said that they were personally and persistently antagonistic to each other; that their words and actions were often guided by jealousy, ambition, or hate. Such an estimate is, I believe, unworthy of either man, standing as they did in positions of high responsibility for their country. We must look farther afield for our diagnosis of these apparent antipathies, back a hundred, even thousands of years, into race temperament and national associations. Henry Cabot Lodge was of pure Anglo-Saxon stock, with a dash of Norman blood through the Cabots. His forbears had been in this country, in Massachusetts, for from over one hundred to over two hundred and fifty years. They were citizens in the English Colony days; active in the Revolution; familiar with the beginnings and upbuilding of the Nation. They lived, breathed, and gloried in the national traditions. They had the characteristics of the English: a sense of duty and high ideals tempered in practical action by common-sense. They mingled their judgments with those of others and supported the common result. They valued clear and exact statement, knowing that vagueness is the mother of misunderstandings and controversy. As public servants their personal opinions were subject to the limitations of the duties of their office. Senator Lodge was the embodiment of Anglo-Saxon character. Thomas Woodrow Wilson was, on the Wilson side, Irish — Scotch-Irish; on the Woodrow side, Scotch: he was thus predominantly if not wholly Celt. Both peoples lived for centuries in the North apart from the larger movements of history. In the Irish blood was the light vein of humor, the idealism, and imagination which often makes men unpractical and which emphasizes the personal element in all transactions. In the Scotch was the dour temperament born of that dour clime. Theirs was an isolate and at times an uncanny and melancholy temper. No forbear of Woodrow Wilson was in this country until after the Revolution was over, Washington dead, and the Nation fully established. None of them had lived in the traditions of English freedom or the forming years of this country. They were all Presbyterians, Calvinists: men and women who, when they were convinced of their mission, believed themselves called of God; and no force of man or devil could turn them. Woodrow Wilson's father, his mother's father, and his wife's father were Presbyterian ministers. They were preachers, prophets, idealists: some of them had great power of expression and of moving people to faith in the Bible as they understood it. They dealt in noble thoughts and eloquent phrases which do not usually accompany exactness of expression and definite language. A few were educators and writers. President Wilson was the embodiment of the Celtic character. Has history ever recorded an instance when the Anglo-Saxon, the true Englishman, and the Scotch-Irish Presbyterian have, as the Psalmist sings, 'Taken sweet counsel together, or have walked, even in the House of God, as friends'? We can now grasp something of the reason, of the tragedy, and of the humor.



Labels: [History](#)

Friday, April 27, 2018

University Unions

Harvard has just seen the creation of unions for their Grad students as well as post-Docs. However this does not seem to be a universally accepted event. As the [Crimson](#) notes:

Some graduate students at Harvard Medical School say they feel wary of Harvard's newly formed union, with at least a few in Longwood—the location of the Medical School campus—expressing a desire to be excluded from the bargaining unit. Fifty-six percent of eligible student assistants voted on April 18 and 19 to authorize Harvard Graduate Students Union-United Automobile Workers to collectively bargain with Harvard on their behalf. National Labor Relations Board officials certified the tally on April 20, counting 1,931 ballots in favor of unionization and 1,523 against. Exit polling conducted by The Crimson suggested medical students were significantly less likely to vote in favor of unionization than were students attending other University schools.

I would argue that the union issue is the millennial effect. Unions assume that everyone is equal, get the same pay, benefits, and that their employer is abusive and some form of oppressor.

Some fifty or sixty years ago to get a PhD at MIT and Harvard as well one competed. It was truly a zero sum game. There were so many slots, about a tenth of what there is today, and you had to be better than anyone around you. Your thesis had better be the best, your other work better, you had to be accepted by your Committee, you had to publish, and you better not waste time on such pursuits as family and fun. Then came the late sixties and the beginning of the end.

Careers are based all too often on achievement, success, doing better than others, namely excelling. One goes to Harvard, one assumes, to excel, not to become another molecule in a mass of identical molecules. You are not a telephone company union employee, doing the minimal amount as agreed to by the Union. One assumes to exceed everything. If not, then why would one hire you?

If a Union organizer at Harvard Grad Schools tries to get hired, perhaps an employer would look twice, do they want an over-achiever or a rabble inciter bringing every employee to the least common denominator?



Labels: [Academy](#)

Friday, April 27, 2018

More Evidence

As we just noted, obesity can be a major driver for cancer. Moreover obesity, even just being over weight, can be the driver for Type 2 Diabetes. That in turn drives kidney, heart, and nerve/eye failure. Unlike smoking and lung cancer, where the patient generally dies in six to nine months, Type 2 Diabetes is chronic costing billions.

In the UK, the NHS hands out pills. The solution is quite simple. Lose weight, stop junk food.

Better yet, tax obesity, file your tax return and get weighed. Imagine what that would do for some Presidents! But that is another tale.

In the US, according to the NY Times, we send them to a class. We seem to have classes for everything; Diversity, Harassment, Quality, Ethics, etc. The Trainers get billions and we are then left with sick fat folks spending billions on Big Pharma pills.

As the Times notes:

There are about 1.5 million Americans newly diagnosed with Type 2 diabetes each year, a disease typically associated with excess weight and a sedentary lifestyle. Diabetes self-management programs teach patients how to monitor their blood sugars, what to eat and the importance of exercise as strategies to delay or avoid the disease's serious complications....Diabetes is among the costliest of medical conditions. The American Diabetes Association estimates that average medical expenditures for those with diabetes diagnoses are 2.3 times higher than those without...One of the most expensive — a 7½-hour diabetes self-management group course that included two-hour individual sessions with a dietitian and a diabetes educator — cost \$1,700 in Washington state....

You do not need a course. You need a physician to call it for what it is, not a disease, but the patient's problem, they eat too much! Perhaps we should start weighing and taxing based on BMI.



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

[Fat and Cancer](#)

Over the past twenty plus years it has become more clear that obesity has a strong causative effect on the development of cancers. There is a multiplicity of reasons for this some of which are reasonably well documented while others are just logical connections. The path often follows the path: obesity, type 2 Diabetes, cancer. The first two steps can last for a long period while once the cancer starts it can be more aggressive than other non-obesity driven forms.

Countries as diverse as England and Ghana are suffering from mass obesity. Food, especially processed food is readily available and becoming quite inexpensive.

A recent note in [NEJM by Abate-Shen](#), details the connection between fat and prostate cancer. This is a compelling presentation of data and well worth following. She notes:

Although most prostate cancers are relatively indolent and therefore not life-threatening, highly aggressive and metastatic disease develops in a subgroup of patients, and obesity has been associated with increased aggressiveness of prostate cancer. Chen et al. analyzed two key tumor-suppressor genes, PTEN and PML, that protect against prostate cancer. Tumor-suppressor genes promote cell functions that prevent cancer; therefore, their loss is often associated with accelerated development of cancer phenotypes. The loss of both PTEN and PML often occurs in the most aggressive forms of prostate cancer. Chen et al. investigated the functional

consequences of the loss of PTEN and PML using mice that had been engineered to be deficient in these genes. They found that in mice deficient in Pten in the prostate, locally invasive prostate cancer developed, whereas in 30% of mice lacking both Pten and Pml, prostate cancer that metastasized to lymph nodes developed. These findings were interpreted to indicate that these genes work together to suppress a more aggressive prostate cancer phenotype. ...They found that among the top genes and biologic pathways affected were those involved in lipid production, a finding that suggests an association between fat production by the prostate cancer cells and an aggressive phenotype. In fact, they showed that the tumors that developed in the mice after the loss of Pten and Pml had high levels of key lipids in their cells. They also found evidence that increased lipid production is triggered by activation of the mitogen-activated protein kinase (MAPK) signaling pathway, which is frequently deregulated in prostate cancer. These findings led the investigators to consider whether fat may provide a cell-intrinsic signal to promote aggressive subtypes of prostate cancer by activating MAPK signaling. To test this idea, they fed the tumor-prone mice a high-fat diet and investigated whether more prevalent or more aggressive prostate cancer developed in these mice. The high-fat diet mimicked the effect of the loss of tumor-suppressor genes; in particular, the “obese” ... mice had a greater tendency toward the development of metastases, which occurred not only in lymph nodes but also in soft tissues such as the lung. Leveraging these findings, the authors then investigated whether fatostatin, a small-molecule inhibitor that targets a key regulator of fat production, could prevent metastasis. Indeed, the mice that were given fatostatin had less tumor growth and a lower incidence of metastasis than the control mice. Overall, these findings suggest that reducing levels of fat in prostate cells may improve outcomes of prostate cancer.

Yes, fat is a driver, and a powerful one. Just think, many diseases could readily be prevented by just shutting one's mouth!



Labels: [Cancer](#)

Saturday, April 21, 2018

[Marx and the Millennials](#)

[Le Monde](#) has an interesting piece on Marx and American Millennials. They note:

Quant à Bernie Sanders, comme le rappelle Jeffrey Isaac, « il ne préconise pas l'abolition de la propriété privée dans les moyens de production, ni l'expropriation des grandes fortunes. Il préconise le démantèlement des grandes banques, la mise en place d'impôts sur le revenu plus progressifs et le subventionnement public des soins de santé et de l'éducation – des choses pour la plupart assez courantes en Europe ». La jeunesse américaine n'est donc probablement pas en train de préparer la révolution, même si Seth Ackerman, de Jacobin, observe malicieusement : « Nos lecteurs et ceux qui se tournent vers le socialisme sont des jeunes gens éduqués, souvent très endettés, qui perdent toutes leurs illusions en arrivant sur le marché du travail. Or Lénine a bien insisté sur l'importance d'une avant-garde éclairée – et précarisée – dans le processus révolutionnaire. »

Marx basically see the world through mid 19th century mercantilism. However so do many Neo-

Progressives. However Marx saw the proletariat as compared to the Neo-Progressives who see the "elect" making the decisions for redistribution.

Le Monde does often have great insight especially on American youth. This is worth following. BTW [Vox](#) also has an interesting piece as well. As the author notes:

Marx used the labour theory of value to demonstrate that the exploitation of workers is a necessary condition for profits (Yoshihara 2017). The normative term 'exploitation' is justified by the claim that profit arises from a system of domination in which the wealthy, as owners of capital goods, direct the activities and limit the choices of employees (Vrousalis 2013). Domination in this sense could be sustained by an autocratic state acting on behalf of a capitalist class, or through the exercise of market power made possible by limited competition in goodsmarkets. But Marx chose to study a more challenging question: how could the domination of labour by capital take place in a private, perfectly competitive, economy governed by a liberal state? His answer was based on what seems a strikingly modern principal-agent representation of the employer-employee relationship, arising from a conflict of interest over the amount of labour effort performed that could be resolved in an enforceable contract. Marx stressed that the employer purchases the worker's time on the labour market, not the worker's work. The employee's supply of effort to the production process is not secured by contract but was rather an "extraction" that "only by misuse could ... have been called any kind of exchange at all" (Marx 1939).



Labels: [Marx](#)

Thursday, April 19, 2018

[The Millennial](#)

The Millennial is now a well known entity, differing from previous versions of Homo sapiens. We have the old Homo sapiens normalis, and now the Homo sapiens millennialis. How is this new proto-species developing.

They seem to have the same DNA but we may have the first clear example of nature versus nurture in action. This is brilliantly displayed in a brief article in [JAMA](#).

The author remarks on three areas:

Theme 1. As Needed vs Scheduled Engagement. Millennials have grown up with virtually instant communication and information dissemination. Such engagement facilitates quick decision making and expands collaboration networks. Millennials expect accessibility, fast responses, rapid turnaround, and frequent short meetings to ensure clear direction. Senior mentors often balance administrative, clinical, and academic demands with greater structure and less ad hoc availability. Combined, this leads to frustration and stress for both parties....

Theme 2. Flat vs Pyramidal Infrastructure. Millennials embrace collaboration and cognitive diversity more readily than prior generations.³ In some aspects of academic medicine, these attributes will serve them well. For example, team science, multidisciplinary care, and collective leadership are welcomed by millennials who embrace groupthink, in contrast to their senior counterparts. However, flattening social and hierarchical gaps may also lead to conflict. Millennials do not necessarily embrace the siloed communication typical of traditional academic departments. Removing these barriers can cause frustration among older physicians accustomed to hierarchical communication channels and younger physicians who desire broad access to all stakeholders...

Theme 3. Purpose vs Process. For millennials, purpose is paramount. Millennials may derive greater satisfaction from results and implementation over the traditional, well-worn metrics of academic success. Such goals often include strategies that include developing intellectual property, commercialization of products, or launching a health care start-up.

Millennials are just plain spoiled and have no manners. They also believe they have the right answer to everything and that past experiences count for naught. They truly believe that their opinion often based upon nothing counts equally to the opinion of one skilled in the area of discussion.

So what does this portend. A more level society? Hardly. The millennial culture may be setting itself up for a massive collapse. History counts but it must be the history based on facts, often the hardest part of history. It does not fit the fictional history of the current batch of instructors who have created these millennials.

The JAMA article treats this new species rather kindly. That is how the evolved. Reality may make them extinct.

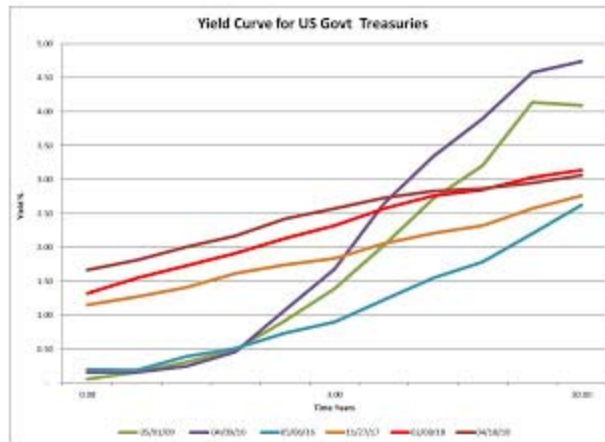
I am reminded of the discussion in Cassirer on Locke (see Cassirer, *The Philosophy of the Enlightenment*, Princeton U Press, 2009, p 17) where he discusses Locke and reason, the blend of sensation and reflection, namely facts and logic if you will. Millennials have the habit of positing an answer, without factual basis. Such as, "The Pre-money valuation is \$5 million." When asked why, the answer is "Because". Because why? This is the major failing of this sub-

species. The basis of a statement is lacking, everyone's opinion is of equal weight, and experience not only does not count but it obscures the truth, whatever that may be. It is as if we are going backwards, to before the Scholastics, where dicta from on high is all that counts.

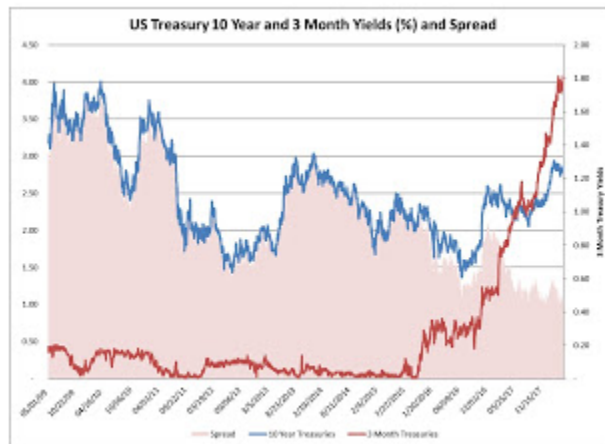


Labels: [Millennial](#)

Yield Curve



The above is the yield curve data as of yesterday. It is truly flattening. Short term rises and long term drops. Greater short term uncertainty and poorer long term prospects.



Just look at the above. We have a much lower spread and an exploding short term rate. Remember that the Interest of Federal debt where 75% is short term, or \$3 trillion short term, also explodes as short term rates increase. With the then lowered long term growth prospects and the increased short term costs this is bleak!



Labels: [Yield Curve](#)

The Old Telcos



The two old Telcos, Verizon and AT&T, seems to have mangled their core business model. Let's start with AT&T. Like Verizon it has a great wireless footprint. It is an operating company, namely, it was SBC after all, knows how to lay wires, connect them, install wireless equipment and the like. Now they want Time-Warner content. Their argument is that Time-Warner seems to be dying amidst the growth of Netflix, Amazon and the like, and that AT&T can somehow magically via its bucket truck mentality revitalize this dying entity. The Government using Antitrust laws, something which I became proficient in some 25+ years ago battling against the abuses of the new Telecom Act which just allowed recombination. In reality the Government may be helping AT&T from destroying itself. If indeed the new players can destroy Time Warner's old business model, then why buy it!

Now to Verizon. The bought Yahoo and AOL. Neither were or are winners. Now they are reorganizing but not really. As [RECODE](#) notes:

Guru will run day to day operations of our member (consumer) and B2B businesses and will serve as a member of our global executive team helping to set company culture and strategy. Guru will also be an important part of the Verizon work that is helping both Oath and Verizon build out the future of global services and revenue. As more of my time is spread across strategic Oath opportunities and Verizon, I will be leading our global strategy, global executive team, and corporate operations. Guru will be leading our global operating teams including:

- *Engineering & Tech Platforms including DMSCComms*
- *Data and Research & Marketing*
- *Media Brands, Content Factory, and Media Products & MarketingSearch Partnerships*
- *Ad Platforms*
- *Global Sales & Customer Operations, & Ad Strategy, and & B2B Marketing*
- *Membership*

Yes folks that is his name. I will leave it there. But fundamentally the core of Verizon as that of AT&T is the wireless franchises. Wireless is key to survival. There is limited competition, growth and margins are guaranteed. So why get into a business you neither understand nor are competent at especially when competitors are dominating the market. And your entry was the purchase of two losers.

In my experience and in my opinion, based on watching these folks up close, somehow reality gets blurred. They all too often get enamored with the glitz and get clobbered with reality. Remember folks, you are just a telephone company, it is in your DNA. You drive bucket trucks, climb poles, and string wires. You are not media moguls.



Labels: [Telecom](#)

Tuesday, April 17, 2018

[AI, Cyber Threats and Networks](#)

[Nature](#) has an editorial regarding the threats which they fear will come from AI. They note:

Artificial intelligence (AI) is poised to revolutionize this activity. Attacks and responses will become faster, more precise and more disruptive. Threats will be dealt with in hours, not days or weeks. AI is already being used to verify code and identify bugs and vulnerabilities. For example, in April 2017, the software firm DarkTrace in Cambridge, UK, launched Antigena, which uses machine learning to spot abnormal behaviour on an IT network, shut down communications to that part of the system and issue an alert. The value of AI in cybersecurity was \$1 billion in 2016 and is predicted to reach \$18 billion by 2023. By the end of this decade, many countries plan to deploy AI for national cyberdefence; for example, the United States has been evaluating the use of autonomous defence systems and is expected to issue a report on its strategy next month. AI makes deterrence possible because attacks can be punished. Algorithms can identify the source and neutralize it without having to identify the actor behind it. Currently, countries hesitate to push back because they are unsure who is responsible, given that campaigns may be waged through third-party computers and often use common software.

The problem is not primarily the threats it is the fundamental architecture and the users.

First, the architecture uses the Internet. The Internet is a "public toilet". Anyone can use it and you have no idea what you may be exposed to. It was designed that way, as an open network with no security. It is why DoD abandoned the Internet in the late 1980s and went back to its own secure private networks.

Second, workers at companies are all too social. Send them an email and they open it, and then they set loose an attack from an attachment. They look at videos, many of which contain threats. It is estimated that over 90% of the network penetrations are facilitated by employees!

Thus we have a two prong attack strategy; a grossly insecure network and a collection of employees who have no idea what they are doing.

As for AI, after 40+ years of looking at it, I still do not know just what it is other than possibly an adaptive IF, THEN, ELSE set of statements. You can call it whatever you like, neural nets, adaptive processing etc but it still falls back on the primitive three statements.

Thus if one wants a secure network, do not use the Internet. I know it is expensive, but security is that.



Labels: [Cyber Warfare](#)

Sunday, April 15, 2018

[Neo Progressives Again](#)

Progressives, like Teddy Roosevelt and Wilson, set the path for the current batch of neo-progressives. As we have noted previously, the progressives, old and new, fundamentally believe in a strong government controlled by a small elite class of people who alone know how to eliminate the "evils" of society as perceived by them. This clan also views any who oppose them as evil incarnate, although they totally reject any religious connotations.

Standing against this clan seeking to mold and control our lives is a small batch of individualists. Individualism sprang forth in the fourteenth century as a result of the battles with the Avignon Papacy. The reality struck many who fought that apostate organ that people were not subjects but citizens, that Christians were not the subjects of the Pope but members of a religion wherein salvation was an individual achievement, not something handed down by the Pope and his minions. Regrettably the introduction of Calvinism and Luther which reintroduced the concept of the "chosen" via some form of Augustinian pre-destination, via the construct of "grace", obliterated the initial attempts to promulgate individualism. In a sense these 16th century religious constructs were the basis for progressive ideas of having a select mandate for the many.

But with the development of the United States in the 19th century as noted by de Tocqueville, individualism returned on the Frontier, with free "associations" between people, as they saw fit, not as mandated by some group of the "select". Yet by the early 20th century this concept was obliterated by the likes of Croly, Roosevelt and Wilson. A rather strange collection of egos but all believing in their own rights as a member of the "select"

Individualism is a simple construct. It assumes that all people are equal, under the law, and that the sole purpose of the law is to protect the rights of these individuals. The rights protected are those agreed to under a constitution. Individualism is in abject opposition to Rawls and his clan. The government under an individualistic society is prohibited from giving one group an advantage over another and in ensuring that a "clan of the select" cannot "rule" any individual.

The ideas of individualism and progressives are in sharp contrast. Unlike Republicans and Democrats, or Liberals and Conservatives, the core concepts are a reflection of who rules, the people or the "select". Burke was a Conservative, one who saw political evolution in a slow and methodical fashion. Paine, his alter-ego if one might suggest, was in some ways a Progressive, in others an Individualist. I have seen the latter Paine's suggestions as Progressive in nature, yet his work in the early Revolution as Individualistic. The latter work reflects his involvement with the

French Revolution, and perhaps the progressive bent is reflective of that "progressive movement".

In the NY Times an author states³²[1]:

The basic premise of liberal politics, by contrast, is the capacity of government to do good, especially in ameliorating economic ills. Nothing structurally impedes compromise between conservatives, who hold that the accumulated wisdom of tradition is a better guide than the hypercharged rationality of the present, and liberals, because both philosophies exist on a spectrum.....Where liberalism seeks to ameliorate economic ills, progressivism's goal is to eradicate them. Moynihan recognized this difference between Franklin Roosevelt's New Deal, which he always supported — as exemplified by his opposition to Clinton-era welfare reform — and Lyndon Johnson's Great Society, which he sympathetically criticized. The New Deal alleviated poverty by cutting checks, something government does competently even if liberals and conservatives argued over the size of the checks. The Great Society partook more of a progressive effort to remake society by eradicating poverty's causes. The result, Moynihan wrote, was the diversion of resources from welfare and jobs to "community action" programs that financed political activism....But neither liberalism nor conservatism opposes rationality. Conservatism holds that accumulated tradition is a likelier source of wisdom than the cleverest individual at any one moment. It fears the tyranny of theory that cannot tolerate dissent. Liberalism defends constitutionalism. One of the finest traditions of 20th-century liberalism was the Cold War liberal who stood for social amelioration and against Soviet Communism. This genus — including Moynihan, Senator Henry Jackson and the longtime labor leader Lane Kirkland — was often maligned by progressives.

The author has some interesting points but I believe he totally misses the Individualism construct. The most recent example of Progressive "think" is Obamacare. Namely some small group determined how 20% of the economy should be run. In a sense reminiscent to a Soviet Five Year Plan. Regrettably there is no Individualism flag bearer, unless of course you count all of the people making their own choices.



Labels: [Political Analysis](#)

Thursday, April 12, 2018

[Where is my Hayes Modem?](#)

³²[1] <https://www.nytimes.com/2018/04/13/opinion/moynihan-liberals-progressives-lost.html?action=click&pgtype=Homepage&clickSource=story-heading&module=opinion-c-col-left-region®ion=opinion-c-col-left-region&WT.nav=opinion-c-col-left-region>

Ever since [Altice](#) bought Optimum my Internet speeds have dropped an order of magnitude almost. Used to get 2 Mbps up and 15 Mbps down. Now at best I get 500Kbps down! And 300Kbps up! I wonder who these guys are. Price goes up and service drops. And this is NYC metro area! Suggest one looks up Altice, perhaps their goal is to reduce any communications in the US! It looks that way from the service level!

Maybe I can get DSL from Verizon.



Labels: [Commentary](#)

Monday, April 9, 2018

[Trust and Amazon](#)

I have noticed that Amazon more and more presents third party sales and one can readily get confused as to a Prime delivery and some third party delivery. The third party ones are highly unreliable and lengthy. If you pay for Prime to get two day delivery then you now get to see it is the third party and a week or more for delivery. They try to cancel the order!

Trust means that when I shop at Amazon I get what I have paid for as Prime and what I have expected. However it appears that Amazon in its intent to expand everywhere has abandoned that trust with its customer and off loads to these third parties which I have found to be highly unreliable. The worst ones are Chinese battery sales, selling knock off batteries which will never hold a charge and have falsified labels.

Perhaps Amazon should remedy this. Once trust is lost, it is lost! I shop Staples and Walmart! Someone should tell the boss.



Labels: [Amazon](#)

Friday, April 6, 2018

[What Reality Does This Reflect?](#)

I enjoy the statements made by academics. They are so detached from any semblance of reality, especially those working on policy issues. Take the carbon tax issue, or Pigou Tax is you are from Harvard. Now some MIT researchers propose a dramatic tax on carbon, however that is measured. Recall that as I have argued it is a highly regressive tax. The Harvard Prof with their limo does not see it whereas the Harvard janitor with their small home and distant commute see the brunt.

Now an [MIT report](#) tries to rephrase the problem. They state:

“By taxing carbon,” Caron says, “we will collect a lot of money that can be used to supplant

other taxes that we like less. Why tax something that we like?" And, he adds, by using just a small portion of that revenue — less than 10 percent — it's possible "to compensate the lower-income people and neutralize the regressivity."

I doubt if any of these folks ever spent a femto second in the Halls of Power in DC. This "wise" suggestion would be opposed by so many forces it is unthinkable that anything would be accomplished. One wonders what entity funded this work and where these folks will end up. Pity.



Labels: [Academy](#)

[Jefferson, Democrats, and 125 Years Ago](#)

I have the tendency of rummaging through old book stores. I picked up a biography of Jefferson written at the end of the 19th century. I thought it would be worth the while to share the Preface. This is from *Life Of Thomas Jefferson. Third President Of The United States*, by [James Parton](#), Houghton, Mifflin And Company. (Boston, 1892)

Nor ought we to be impatient with those who assert that both America and Jefferson were wrong, since we cannot yet claim for either a final and indubitable triumph. In France the politics with which he was in the warmest sympathy resulted in organized massacre and fell Bonaparte; and the party which he led in the United States issued, at the South, in armed rebellion, and, in some portions of the North, in the Rule of the Thief. We must face these facts, and understand their meaning. They no more prove that Jefferson and Madison, Lafayette and Paine, were wrong, than the Inquisition and the religious wars prove that the maxims of Jesus are false. They are only illustrations of the familiar fact, that the progress of truth and justice is slow and very difficult. They show that no country is ripe for equal rights until a majority of its inhabitants are so far sharers in its better civilization, that their votes can be obtained by arguments addressed to the understanding.

We must now accept it as an axiom, that universal suffrage, where one-third of the voters cannot read the language of the country they inhabit, tends to place the scoundrel class at the summit of affairs. We see that it has done so in France, in the Southern States, in New York, and in Philadelphia.

But such virtue is there in the Jeffersonian methods, that, even in those places, we find them our best resource. In New York, a mass meeting and its Committee of Seventy, in two years, suppressed the worst of the public stealing. In the South, the freedman rages for the spelling-book. In Pennsylvania, the reign of the scoundrel draws to an end ; and it is everywhere evident, that nothing is farther from the intention of the American people than to submit to lawless or lawful spoliation.

It is even possible that the party which Jefferson founded — such vitality did he breathe into it— may again, instructed by defeat and purified in the furnace of affliction, deliver the country from the evils which perplex and threaten it, employing the only expedient that will ever long succeed in a free country, the expedient of being right. Jefferson's principles will do this, if his party does

not. A government simple, inexpensive, and strong, that shall protect all rights, including those of posterity, and let all interests protect themselves, assuming no functions except those which the Constitution distinctly assigns it, — these are the principles which Jefferson restored in 1801, and to which the future of the country can be safely trusted.

Parton was well respected in his time but just a reminder, the voters he reminds his reader about were the Irish, Italians, African Americans, and many others often detested by what he refers to as Democrats, the followers of Jefferson. History is all too often defined by the writers and popularizer.



Labels: [History](#)

Tuesday, April 3, 2018

[The Pope and Fake News](#)

Just a brief observation regarding CNN and their episodes on the Papacy. Two blatant errors. First Avignon was not in France at the time. That was a key issue then and someone should have fact checked it. There is this thing called the Internet and they have this thing called Wikipedia... You get my point.

Second, some alleged theologian said that Luther was the only person to have opposed the Pope and survive. Duh! Ever heard of Ockham, Marsilius of Padua, and a few dozen others! They were two hundred years earlier!

Overall in my opinion, being somewhat aware of the papacy in the seventh and 14th centuries, CNN managed to create a story which is a prime example of fake news, if not just sloppy.

Next time try and get some people who know something folks!



Labels: [Media](#)

[Amazon and the USPS](#)

Trying to figure out just how Amazon and the USPS work together is like trying to understand the details of the old KGB, or worse. As best as I can ascertain:

1. Amazon, if it is something they allege to deal with, has a warehouse with the product at location A.
2. Amazon then packages the product P at A and sends it out on some third party transport it transports V1 to a regional location say B. Here in New Jersey B is I believe in Avenel.
3. Then Amazon with transport V2 sends the package P from B to a local post office, LPOn.
4. At LPOn the USPS accepts the package, sorts it to a deliverer, gets it on a truck, and out it

goes.

Thus all the USPS does it to add to a delivery unit, USPSDUK, another set of packages which are tracked.

Now how much does it cost the USPS and how much do they get? Good question. Try and do cost accounting on the USPS! Also here we have a marginal cost most likely and not the average costs.

I would love to see someone try this analysis, and to make any definitive statement I would say it is kind of dumb. The marginal costs is close to zero! Think about it.



Labels: [Amazon](#)

[Graduation and Political Correctness](#)

Back in the Dark Ages when I was awarded my PhD at MIT, it was in the old Gym, on a hot humid June day and the intent was to get through it fast. It after all was 1971 in the midst of the Vietnam War and protests, bombs, and tear gas was common. So the speaker was the Institute President, saying something clearly forgettable, and the PhDs went up, got their hood, and degree and then back and out. Finished, over, then off with the robes, into shorts, and then cook dinner for the parents in the small apartment ready to be emptied.

Now in 2018, nearly 50 years later there is a separate Doctoral Hooding ceremony with its own [politically correct speaker](#) at MIT! Yep, as they note:

The speaker selection process engages MIT faculty and doctoral students to identify an alum whose acumen and professional and personal experience will resonate with new PhDs and ScDs as they embark on their careers. chancellor for academic advancement, chairs the Commencement Committee. "It is exciting to collaborate with our students and faculty, who continue to identify alumni from diverse disciplines and personal backgrounds and whose paths exemplify ways to use the MIT doctorate in rewarding pursuits," he said. Born and raised in Vancouver, ... a member of the Tahltan Nation, an Indigenous people located in northwestern British Columbia, Canada. Prior to graduate school, she worked as a journalist for the Canadian Broadcasting Corporation (CBC) and CTV News. While at CTV, she was the original host and co-creator of "First Story," the first news and current affairs series on Indigenous issues to be broadcast nationally in Canada and later syndicated to the Aboriginal Peoples Television Network (APTN).

They have managed to get as many possible identity groups as possible! One must ask:

1. How many chancellors does MIT now have! At what cost?
2. Why a separate Hooding Ceremony, just walk up and get both. It is more efficient.
3. The objective that any new graduate should focus on is getting a job! One that is real and

makes a difference. How about that for motivation.

4. What of the poor parents who get dragged into this lecture on correctness. Why not have say a successful grandparent give the talk. Like how to make a real difference.

It is amazing that these event proliferate. Oh well, I guess they can all go out to Facebook or Google.



Labels: [Academy](#)

Sunday, April 1, 2018

[Fake News](#)

The term “Fake News” has been thrown about of late and I have often wondered what it meant. Coming off writing a book about the 14th century and the post-Scholastics I had a somewhat reasonable understanding of the Trivium and of the folks from Plato through Ockham. Back then words meant something. So let me give this a try, not that I am anywhere near an Ockham.

First, the issue is one of definitions. You see in law, philosophy, mathematics, and engineering definitions are critical. I have even found in my botanical studies that a definition is a critical element. Namely when describing a flower and one says it is blue; what do you mean by blue? But let us put that discussion to the side for a moment.

Let us start with the term, “news”. Just what is news? I think it is fair to say that news is the presentation of information of current interest which is the result of collecting various facts and presenting them in a coherent manner. Thus if a dog bites a man, we would say what type of dog, who owns the dog, the condition under which the dog managed to get to the man, the man, the name, the location, the time, and the condition of the man and the dog. This would be a minimum. Namely we present the; who, what, when, where, why, and how.

Not having spent a femtosecond on a communications course nor working for a newspaper this I fell would be a good first guess. Namely I am collecting facts, those indisputable things related to this incident, and then presenting them in a coherent manner that constitutes news.

In contrast if I am arguing about say Ireland, and the English occupation for the past almost 900 years I have a different set of facts, historical facts, from a variety of records, and many of these facts may have been slanted for purposes other than portraying what may have actually occurred. As we all know, history is all too often written by the victors, and thus what is handed down may very lack the authenticity one would expect in a “dog bites man” story.

Thus overall then news is the presentation of readily verifiable facts in some coherent manner. Also any third party could readily go out and validate these facts. One could examine the dog, talk to the man, see the bite, talk with the owner and so forth. But we also know that certain events all too often get clouded by reshaping of facts. Take the case of an auto collision.

Consider the case of two lanes of traffic merging. One vehicle, say an auto, has commence the merge and is nearly fully in the lane, then behind it is say an eighteen wheeler, which continues unabated towards the merged vehicle, and then collides with the smaller vehicle.

Now along comes a State Police Officer, say one from New York, who appears annoyed at having his coffee break interrupted. He then decides based upon what he thinks the truth to be and creates another “reality” based upon which driver he is most annoyed with. How does truth and news get produced from this process? Poorly, one would say, but all too often the arbiter of the events, in this case the State Trooper, becomes the teller of “fact” based not upon reality but upon a personal bias. Take this simple example, a true one, and put a minority in the middle and we can see why all too often we have what has been called “police violence”.

But back to the news. The vehicle incident above cannot be cleanly reconstructed since it lacks independent verification. It is a he said and she said type of presentation. The case of the dog is man’s leg and dog’s teeth marks and the dog does not get the chance to comment!

Thus when we speak of news we are speaking of a truly limited set of truth statements. Typically we report what someone said. To get close to the truth we must note who that someone was and good news reporting then also demands a corroboration by some independent third party. Note this does not exist with our dog nor with our two party incident. In fact the two party incident can be further clouded by the introduction of an erstwhile law enforcement entity.

Thus when we examine the news, or alleged news, we see every day, very little is truly news. Anonymous sources do not count. We could never verify them. We have no idea whether they are trustworthy, have some axe to grind or whatever. Thus any reporting with some anonymous source must be rejected out of hand. Second is corroboration by a third part is also demanded. This we nearly never see in any presentation.

This leaves us with a good definition of news but a paucity of it available.

Now to Fake News. Consider its opposite, Un-Fake News or if you will True News. Now based upon our argument above, if it is news, perforce of what news must be to be news, it must be true. It thus means that there can be no such entity as Fake News, other than as an entity which is non-news. Sorry for the logic, but humans spent two millennia developing it to have it lost by our recent generation. Thus we say Fake News is a term defined as not-news or non-news. Namely it does not meet one or more elements of what we would demand for news per se.

Now on to the more difficult question. We stipulate that news to be news must report on facts, namely the truth, what really happened. “A dog named Spot bit a man named John Jones on the left leg at 12 Main Street at 3 PM on March 28. The dog was owned by Joe Smith.” Now is there more to say, yes if and only if it is both true and proximately relevant. But we can validate each element in the presented reporting. I can speak with each person and most likely I can see the dog somewhere, if it is still alive.

Back to Fake News. If one asserts that a person collaborated with some foreign entity, then we must establish; who, the when, the where, the why, and be able to demonstrate with some

trustworthy collaboration of a reliable third party or parties that such has occurred. Otherwise it is speculation. One needs specifics to be news, otherwise it is at best gossip and worst defamation. The Inquisitional methods of seeing if a witch floats or not no longer apply. We are not dealing with demonic acts, or hopefully not, and as such we must utilize the rules of acceptable logic.

Thus we come down to two elements; truth and trust. News must be truthful and the presenter of the new then must be trustworthy. Trust takes time to earn it is lost in an instant. The presentation of what one would expect from the news is then from a trustworthy agent. If at any time that trust is in question then the existence of the transmittal of news disappears. Trust entails the ability to divest oneself somewhat from the facts being transmitted. If perhaps one is a part of the news, more than just an observer, then one may have been invested in the telling of the news in a less than unbiased manner, it then become less news and more just opinion. The mixing of news with opinion has been the downfall of many erstwhile news organizations, they become opinion generators at best.

Thus it is incumbent upon those who see themselves purveyors of news to deal in truth and to be trustworthy. Mixing of opinion, agenda, and the like distorts from this goal. When as a youth and I listened to Radio Moscow, I knew it to be propaganda, even without Joe McCarthy. Yet today many of our youth have no way to ascertain fact from opinion, opinion from fiction, fiction from defamation.



Labels: [Commentary](#)

[Happy Easter](#)



John 20, 1-18

The first day of the week cometh Mary Magdalene early, when it was yet dark, unto the sepulchre, and seeth the stone taken away from the sepulchre.

² Then she runneth, and cometh to Simon Peter, and to the other disciple, whom Jesus loved, and saith unto them, They have taken away the LORD out of the sepulchre, and we know not where they have laid him.

³ Peter therefore went forth, and that other disciple, and came to the sepulchre.

⁴ So they ran both together: and the other disciple did outrun Peter, and came first to the sepulchre.

⁵ And he stooping down, and looking in, saw the linen clothes lying; yet went he not in.

⁶ Then cometh Simon Peter following him, and went into the sepulchre, and seeth the linen clothes lie,

⁷ And the napkin, that was about his head, not lying with the linen clothes, but wrapped together in a place by itself.

⁸ Then went in also that other disciple, which came first to the sepulchre, and he saw, and believed.

⁹ For as yet they knew not the scripture, that he must rise again from the dead.

¹⁰ Then the disciples went away again unto their own home.

¹¹ But Mary stood without at the sepulchre weeping: and as she wept, she stooped down, and looked into the sepulchre,

¹² And seeth two angels in white sitting, the one at the head, and the other at the feet, where the body of Jesus had lain.

¹³ And they say unto her, Woman, why weepest thou? She saith unto them, Because they have taken away my LORD, and I know not where they have laid him.

And when she had thus said, she turned herself back, and saw Jesus standing, and knew not that it was Jesus.

¹⁵ Jesus saith unto her, Woman, why weepest thou? whom seekest thou? She, supposing him to be the gardener, saith unto him, Sir, if thou have borne him hence, tell me where thou hast laid him, and I will take him away.

¹⁶ Jesus saith unto her, Mary. She turned herself, and saith unto him, Rabboni; which is to say, Master.

¹⁷ Jesus saith unto her, Touch me not; for I am not yet ascended to my Father: but go to my brethren, and say unto them, I ascend unto my Father, and your Father; and to my God, and your God.

¹⁸ Mary Magdalene came and told the disciples that she had seen the LORD, and that he had spoken these things unto her.



Labels: [Commentary](#)

Saturday, March 31, 2018

[Intellectuals, Marxists, Communists and Just Plain Folk](#)

I have just finished Podhoretz's republication of his book, [Making It](#), published by the New York Review of Books Classics. One should compare this to [William Barrett's book, Truants](#), which examines the same group of people but of a prior generation. The two, I believe, should be read in parallel. They each give a valuable window on how previous generations thought. My comments below are my opinion alone and reflect also my personal peripheral participation in some areas. Thus I may have a bit of a bias, for that I stand accused.

In my opinion, Podhoretz writes a self-congratulatory work on the collection of Marxist oriented intellectuals in the post WW II generation. For the most part they are Columbia University related and works on such "journals" as Commentary, Partisan Review, and the like. Barrett is somewhat self-effacing and presents his fellow participants in all their glory and grunge. He speaks of such fellow travelers as Hannah Arendt and Mary McCarthy, the philosopher (former

lover of Heidegger who was the German philosopher and Nazi follower) and the Vassar graduate who seems to have made her career by publicizing her sexual exploits starting when she was fourteen! Then there was Rhav and Delmore Schwartz, the brilliant and socially complex participants. This was New York from 1930 to about 1960. It is New York when Greenwich Village was a place where one could walk through book stores and drink coffee at all hours, have conversations on any author one felt important and find a fellow conversationalist to compete with one's views. Now of course Greenwich Village is NYU real estate and millennial startups.

Now Podhoretz starts as a fellow traveler of the left wing associates and then sees this a means to promote himself to some form of greatness. Unlike today where such greatness is being an early player in some start up then the player was someone who would write and publish a critique of some alleged work of art. The edgier the review was the more one felt a sense of self-worth.

Podhoretz presents his perceived path to glory. It was his ability to come out of Brooklyn as an East European Jew and move across the East River to Morningside Heights and achieve greatness by disavowing and abandoning his past, and taking up the culture of his new found associates. Eventually Podhoretz becomes one of the NeoCons in the early 1970s and into the Bush II administration. Specifically he was a major player in the Coalition for a Democratic Majority, which I also played a small role in when at MIT, before going to Washington. It was this change from classic Democratic to neo-conservatives, a pro-Defense move of what were called Jackson Democrats. Strange that so many started as extreme left wing critics of the arts and became strong right wing critics of an evolving Democratic Party, a post-Vietnam Progressive movement now in full bloom.

Barrett by contrast is a well-accepted philosophy professor, who made his acclaim as an early interpreter of Existentialism. In fact Barrett had the opportunity to provide some support to the travels of Simone de Beauvoir on her US trip post WW II. He had great insight into her views, often her confused and distorted perceptions of the US. What contrasts Barrett is that he is a true intellectual whereas Podhoretz is an interpreter of current political movements. Barrett aged into a classic professor and Podhoretz into a classic political commentator.

Thus Podhoretz's book is worth the read peripherally for understanding the people and the times, but more so to understand Podhoretz, whereas Barrett is less understanding Barrett than in understanding the many personalities he so ably brings to life.

There does not seem to be any group of intellectuals like these. Those that try have flocked to cable TV and become participants in the cacophony of the new medium. Clearly McLuhan and his understanding of how a new medium can change what we understand as truth changes dramatically.

The interesting question would be; will the millennials use the evolving media to create their own new truths, and will we ever be able to understand the past by having a document like Barrett's again?



Labels: [Intellectuals](#)

Technology, China and Competition

The [Telegraph](#) has a good short piece in China's technological development. They note:

AI director at the Turing Institute in London, believes that while the UK has made “great progress in certain areas” we are “very far off” in others. “To date, the West has been leading research across many areas of AI but clearly China is catching up quickly and may be overtaking us in some areas,” he says. “Chinese students are coming to the UK and US and going back to China, and the government is making sure that it is a leader in these areas. Like us, they want to do well in the space.”

We have argued before that the students coming to the US, and whose studies are often paid for under US DoD or similar university contracts, take what they have learned and go back to China and compete with the West. That seems to be an area that the current Administration, like all previous ones, seem to ignore to the benefit of China.

They continue:

The strengths and weaknesses of each region differ greatly. The US is more steeped in technological expertise and has the deep pockets of Silicon Valley. Most of the technology revolves around automation, typically with the goal of cutting cost or generating revenue. This has seen human jobs replaced by AI to cut costs or time. Companies have created AI designed to do a better job at sentencing prisoners than judges, and many job interviews are now conducted using AI-fuelled programmes to cut HR budgets.

The question is not what AI can do but who will it replace. There must be buyers for products, even products produced by AI. Who then will do this? Somehow the lack of coverage of this by US media is appalling.



Labels: [China](#)

Dentists and a General: Not the Military Kind

Dentists are in a world of their own. In the US at least they have no connection to Medicare nor is a Dental Plan unlimited if one has such.

Frances Woolley, one of my favorite Canadian observers of the world, reflects on what is not just a Canadian issue but perhaps a worldwide one, namely the expanding procedures in the world of dental care³³[1]. She opines on the use of general anesthesia for extractions. I most heartily agree with her conclusion but for a different reason. A general anesthesia, a “General”, is always a high risk procedure. However it does allow the practitioner to add to the fee charged for a

³³[1] http://worthwhile.typepad.com/worthwhile_canadian_initi/2018/03/its-time-to-blunt-dentists-incentives-to-use-general-anesthetics.html

nominal increase in costs, namely what may be administered. A local such as lidocaine or a related anesthetic numbs the pain, yet the patient does endure the procedure.

However as an old rule of thumb, a patient takes one month's time to recover from a one hour General. That means that for a thirty minute extraction under a General you are not quite yourself for two weeks or more. For a Local you are back somewhat in 24 hours or less. The Local allows you to experience the process and putatively experience it and expunge it. The General is a suppressed experience that somehow requires a longer psychological recovery. That is why people who have a four hour General for say a prostatectomy take a long period to "feel themselves" again. Just what the process is I have no idea.

Now for dentists in general. Often one heard in Medical School that you can examine any part of the patient's body except the teeth! There are people who handle that and in almost all cases they are dentists. A physician can do eyes, brains, toes, skin, intestines and the list goes on, but "no teeth". I often wondered why? The answer in my humble opinion is that the handling of teeth is still somewhat stuck in the late Middle Ages. It is a craft, and part art.

You see, when God made man, or woman for that matter, but with women he corrected for a few mistakes in the first model, they live longer, but God assumed that these creatures would not live that longer than the first few batches out the gate. Thus God designed teeth to last say 30 to at most 40 years, slowly falling out along the way. Then along came physicians extending life spans, despite attempts to keep it low by using tobacco and the like. God's current plan on shortening life span seems to be obesity so we will have to see how that plays out. But back to teeth. They were poorly designed. Like a 1957 Chevy chrome front bumper. Good to look at in the showroom but by the second or third year rotting away! Then along came the dentists, tear out the old bumper and attach a new one. Then keep that process up a bit but as anyone remembers the 57 Chevy lasted no more than 5 years because the engine or floor boards went as well.

Now back to Frances. She observes:

And if it makes having a tooth extracted less unpleasant, what's the harm? Well, the harm may be to your brain. General anesthesia may increase the chance of post-operative cognitive decline. This article using Taiwanese administrative data found a link between dementia and a history of surgery under general anesthetic. On the other hand, this study found no differences between patients receiving a general anesthetic and those receiving epidurals in terms of cognitive functioning three months post-surgery - although patients receiving an epidural had better surgical, as well as better short-term cognitive, outcomes. Many surgical procedures can be performed either with an epidural or under a general anesthetic. It is hard to find any study suggesting that general anesthesia produces superior results in cases where local anesthetic is a viable option. This study finds that general and local anesthetics produces similar outcomes, but local is cheaper. This one found that epidurals produced better patient outcomes than general anesthetics, and this one also comes down in favour of the local option. This leaves aside the 40 percent risk of post-operative nausea and vomiting after having a general anesthetic. Perhaps one day we'll see the Canadian dental association issuing guidelines on the use of general

anesthesia. Insurance companies might step up and only reimburse the cost of general anesthesia in exceptional circumstances.

I think that she may be understating the issue. I would avoid a General at all costs. Last time I remember was when I had my tonsils out. They used ether, yes I am that old. Then after they ripped out the little lymph organs from the back of your mouth, pumped your lungs with ether, and some ended up in your stomach, you awake and have emesis emptying the last of your stomach contents past the now ripped out organ! Thank God medicine has advanced. But dentists using a General should really be extremely cautious. It must be a last resort in my opinion and done only when emergency facilities are proximate.

The same risks apply for example to colonoscopies. One can use a General or a more controlled use of fentanyl and versed. Even that has risks and requires a good backup plan. Thus the general use of a General is in my opinion highly inadvisable and Frances makes a compelling argument worth note to all.



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

Friday, March 30, 2018

[So You Want a Government Operated Health System?](#)

One need go no further than the [London Review of Books](#) to see how the NHS in the UK is working. They note:

In the year of its seventieth anniversary, the 1.3 million people who work for the National Health Service in England find themselves in a surreal situation. They're effectively working within two realities at once, expected simultaneously to inhabit an NHS universe where a radical, highly optimistic reform programme is under way, and a second universe in which the organisation is unmistakably close to breakdown. In universe one, the NHS will be upturned to give most of the healthcare people need at home or on their doorstep and admit to the big hospitals only patients with major trauma, or suffering diseases that demand intensive care, or complex surgical or biochemical expertise. Big hospitals are to become centres of research, high technology, rare skills and dramatic, life-saving interventions. Everything else will be diffused to the community. Loosely directed by the head of NHS England, Simon Stevens, money, staff and new investment are being directed towards primary care – family doctors, community nurses, souped-up local clinics, systems to help the chronically unwell live at home.

Yep, that is 1.3 million people in what is left of the UK, one third that of the US or even less. If we did this in the US it would be almost 5.2 million people. But the US has per [Kaiser](#) about 12.5 million already. So what does tell us?

Simply, we have a lot more per population. UK population is about 65 million and the US is

about 325 million. Thus about 4:1. So we have about 2.5 times the people per person than the UK. But you can see the UK problem, people actually dying for lack of resources. Namely rationing and letting the old folks and sick kids just fade away! That is what it looks like from the numbers.



Labels: [Health Care](#)

Friday, March 30, 2018

[Truth and Media](#)

I am frequently reminded of one of the most powerful quotes about the media and what is understood a truth. Peter Drucker in his remembrances has a chapter on McLuhan.

*As a second perspective of the impact of technology as a dominant driver, we can refer to McLuhan and his development of the concept of media. Drucker has referred to the presentation of McLuhan's doctoral thesis and McLuhan is quoted as follows (See Drucker, P., *Adventures of a Bystander*, Harper Row (New York), 1979, p. 250):*

"Movable type, rather than Petrarch, Copernicus, or Columbus was the creator of the modern world view."

"Did I hear you right," asked one of the professors as McLuhan had finished reading, "that you think printing influenced the courses the universities taught and the role of the university, altogether?"

"No, sir," said McLuhan, "it did not influence; printing determined both, indeed, printing determined henceforth what was going to be considered knowledge."

This concept later evolved into the medium being the message. In our context it is the fact that both Kuhn and McLuhan recognized, albeit in differing fields and in differing ways, that fundamental changes in technology and technique, call it paradigm or the medium, will change the world view, also the message.

What McLuhan said was that, in my opinion, the transmitted "truth" was defined by the medium by which it was disseminated. Spherically, what one uses to transmit something plays a controlling role in what was meant to be transmitted.

Let's take a brief walk down memory lane. Take Homer for example. Homer was meant to be memorized and then recited, not written down and read. Early Greeks all had memorized Homer as Muslims often memorize the Koran, and in the old days as Catholics had memorized sections of the Latin Mass. Then someone got the bright idea to write down Homer's stuff. One can read it, even in Homeric Greek, but it is not the same thing. It is like seeing Shakespeare and reading

the same play in High School. Henry V at Agincourt is Branagh, not Mrs. Jones having “Luis Smith” stand and read! Even Churchill was better! Really.

Now let’s move to the 14th century. Two events are critical. First is Wycliffe and his English Bible. Wycliffe was protected by John of Gaunt, the King’s brother and father of Henry IV. Wycliffe wrote in Middle English a Bible, not for the Church but for the people. That was 150 years before Luther and his German version. One of Wycliffe’s friends was a fellow called Chaucer, perhaps some may have heard of him. Chaucer did for English what Wycliffe did for religion. He wrote in Middle English, the vernacular, but for the people. His tales were of the common folk. Not like Dante, a political polemic, nor Boccaccio, about the Florentine elite. The Widower’s tale was clearly a women’s liberation tale to beat all! It was in 1390! So much for the Middle Ages. But the point was that the medium of written documents set off a cycle that led to Luther. More people, common people could read, a new medium for sending forth truths. The production of the copies was slow and a bit costly and demand increased. Thus Guttenberg was responding to a market demand, and thus Luther! There is a cycle here that one must understand, since I argue we are seeing the same thing happen now.

One could thus ask if the Internet was a response for a demand in more access. However in a McLuhan sense the Internet and its media have actually changed what we see as truth. I may examine Latin texts of Gregory I, in simple 7th Century Latin, and then compare it to books commenting on them, and then to YouTube commentaries and remarks (Yes there are YouTube commentaries on Gregory I). Who is the true Gregory? Does Gregory and his ideas change if we go from Latin words to English words to YouTube videos? I think so.

But even more so, what we could do in the written word took time. Like this short piece, I thought about it, wrote it, edited it, and then placed it in this blog. Maybe you are even reading it. Thus I may have had to work a bit to get these ideas straight. By the way that is why thankfully I dropped Facebook and Twitter. One often does not think what one is saying. Freud would have had a great time examining the subconscious elements here. I will avoid our Tweeting President.

But clearly, as I am certain it is not just the Russians who understand this, the medium of Facebook and Twitter actually define new “truths”. They create new “truths”. At least people believe so. No longer does anyone ask; what is the basis of your statement? Gone are any rules of evidence. Yes, we do have rules of evidence, another artifact of the Middle Ages forgotten by the Millennials.

So when one uses a new medium for communications one should beware that the “truths” elicited therefrom may not conform to those of the prior “medium” and in fact may have no basis in reality at all!



Labels: [Media](#)

[Sticks and Stones](#)

Silicon Valley some fifty plus years ago was an interesting place. Mostly Defense related stuff, Lockheed, TRW etc., and lots of people in short sleeve shirts, ties and pocket protectors reflecting whatever identity they wanted besides their picture ID cards. No sweat shirts, expensive T shirts, hoodies and the like, some even worse a sports jacket.

Houses were not that expensive and 101 was a bit crowded at rush hour but otherwise driveable. Then wave after wave occurred. Defense stuff moved elsewhere, and in came the chip types, then the system types and slowly creeping in were the software types. Each type was truly different and that is a study unto itself. The 80s in the Valley had dozens of telecom systems types, epitomized by Cisco and some large scale software types like Oracle. Their customers were large enterprises. People did not buy a Cisco product nor an Oracle product, companies did.

Then came the “dot com” folks. The door opened for the consumer with the likes of “pets.com” and others, and then the collapse. Most likely too much and too early. After the fall the opening was created for the current batch. Seeing from the failure of their predecessors, and picking up valuable pieces comes Google, at first a “do no harm” entity, and then Facebook, if one believes the tale alleged it was a ruthless battle of accretion.

From the NY Times we have³⁴[1]:

Two days after Donald J. Trump won the 2016 election, executives at Google consoled their employees in an all-staff meeting broadcast around the world. “There is a lot of fear within Google,” said ... the company’s chief executive, according to a video of the meeting viewed by The New York Times. When asked by an employee if there was any silver lining to Mr. Trump’s election, the Google co-founder ... said, “Boy, that’s a really tough one right now.” the finance chief, said Mr. Trump’s victory felt “like a ton of bricks dropped on my chest.” Then she instructed members of the audience to hug the person next to them.

How about that “sexual harassment” stuff? What if I did not want to be touched by another or worse yet hugged? Who would they then blame? It sounds in my opinion like a cult organization. Would the engineers at Ford Aerospace do this when Nixon was elected? Their only interest was continued DOD funding. So who “funds” Google and Facebook? The customer there is the folks who may have very well voted for the person they are now fearing. Does anyone see a logical break here?

Perhaps these darlings of the Valley should expand their reach. Really, out to the heart land. I saw what they did in Cambridge, drove out any parking spaces for the academics and drove the parking rates from \$11.00 per day to almost \$60.00! Why, well they seem in my opinion to want their own world. This world has its own rules, and as if a religion, these rules can be enforced only by an Inquisition.

³⁴[1] <https://www.nytimes.com/2018/03/30/technology/silicon-valley-trump.html?hp&action=click&pgtype=Homepage&clickSource=story-heading&module=first-column-region®ion=top-news&WT.nav=top-news>



Labels: [Commentary](#)

Tuesday, March 27, 2018

[NASA and Budgets](#)

NASA is a complex and often inefficient organization. [Nature](#) notes the just announced delay in the new space telescope.

NASA will delay the launch of its ambitious James Webb Space Telescope (JWST) by nearly a year, until approximately May 2020. That is likely to push the cost of the mission — the most complex space-science telescope ever built — over the US\$8-billion limit set by the US Congress. It is the first major setback since NASA revised its plans for the project in 2011, after years of slipping schedules and rising costs. NASA announced the delay on 27 March, saying that engineers needed more time to assemble and test the components of the spacecraft at its main contractor, Northrop Grumman in Redondo Beach, California. Among other problems, the collapsible, tennis-court-sized sunshield that protects the observatory's 6.5-metre mirror took weeks longer than expected to fold and refold during testing.

The \$8 billion will most likely become \$9 billion and hopefully they have not messed up like the last one. There is now some sixty years of project management methods and procedures in systems like this and it is amazing that after all of those capabilities we see this again and again!



Labels: [NASA](#)

Sunday, March 18, 2018

[An Interesting Report](#)

In a [HealthLeaders](#) report they note a CONVERYS report on misdiagnosis which states:

The report from the medical liability insurer analyzed more than 10,500 closed medical liability claims from 2013-2017 and found that:

- *Diagnosis-related events are the single-largest root cause of liability claims. The 3,466 closed claims with diagnosis-related allegations from 2013-2017 account for 33% of all claims and 47% of indemnity payments.*
- *35% of diagnostic errors occur in non-emergency department outpatient settings, such as physicians' offices.*

- *33% of diagnosis-related claims allege the decision-making breakdown happened as a result of a failure during the patient evaluation.*
- *The four phases of testing -- ordering, performance, receipt/transmittal, and interpretation—account for 52% of diagnosis-related claims.*
- *Among diagnostic failure claims, the largest number of cases involve a missed or delayed diagnosis of cancer, especially breast, lung, colorectal and prostate cancers.*
- *Of the claims that cited an EHR issue, 58% had an injury severity considered high—a category that includes death.*

I find the issue of cancer misdiagnosis as a concern. PSA testing has been down played and even breast testing has been somewhat lowered.



Labels: [Cancer](#)

[Social Media](#)

Back in the 60s and 70s, especially when I was working on Treaty negotiations and meetings one would have access to profiles of the parties on the other side of the table. My view was that these profiles were poor at best and confusing and counter-productive at worst. The Intel agencies had managed to assemble these from snippets of information gathered from a variety of sources. Most of them poor.

In today's world people, like me in this blog, freely provide information which can result in improved profiles, personal and psychological. I suspect an adversary could get a pretty good profile from what is written herein. However, and this is critical, I separately seek out my own information from the NY Times to RT and Sputnik, to [The Guardian](#), and the Jerusalem Post, Arab News and so forth. I am aware that each has a position to push. Some are subtle and some are blatant. The NY Times in my opinion is the worst, the really dislike the current President. But welcome to American media.

Now as to the Social Media efforts. This is unlike what we do herein. I do not attach any news stories, I may quote from them and then give an opinion, but it is my opinion, and the mast head says so. But the social media in question monetizes their pages by first attaching "news" and then by selling the users interactions with the news and others. In effect social media can actively psychoanalyze the users. Not so much the case here since I take no comments nor do I have ads for anything. Just my comments and so far I have managed to attract a small cadres from time to time.

The power is in the profiling of the users from interactive stimulants and their actions related thereto, and then to actively troll them to change or mold their opinions. That is the power of social media as propaganda. A century ago propaganda worked by more gross techniques. Namely a fishing magazine knew its readers liked to fish and then the ads were focused to that segment.

The power of social media is nano-segmenting and then targeted opinion crafting. Now is this something the Russians mastered? Doubtful that only they saw this. Silicon Valley aggressively attacked this opportunity for their financial advantage and in a country protected by free speech and having adults using social media as if it were harmless, you had a perfect storm of adverse use and unprepared users.

For example, if an entity wanted to promote certain issues, then by using the profiling capabilities on the individual level one could profile what motivates each separate person and each segment of the related issues. Then one could test that hypothesis on that person with certain "ads" and determine their response. Then one could provide a specific and targeted set of "ads" that would promote the issue in question. For example, sophisticated neural network systems allow for this very effectively. It is a process of; pre-targeting, target affirmation, target enhancement, and target persuasion and promotion. The entity facilitating the targeting mechanism does not even have to participate, the very nature of an open Internet facilitates that all by itself. Moreover this is not limited to Social Media, it can be done even with new feeds! Simply I one knows what a target has interest in, and then feeds that target controlled elements based upon those interests, thus in a subtle manner crafting information with a strong element of propaganda! The irony is that the intended targets are actively participating in this process.

The solution to this should be simple; education and informing them of the issue. Yet the very system being bastardized in this manner can be turned against any rational approach to remediate. Government is not the answer. It must be an educated user class. Yet our core educational systems lack this basic tool set. The very constructs of "microaggression" embody in people's mind that very barriers to a broad understanding of this threat to democracy. So what is the answer? Stay tuned.



Labels: [Social Media](#)

Saturday, March 17, 2018

[Happy Saint Pats!](#)

I bear orders from the captain get you ready quick and soon for the pikes must be together at the rising of the moon. "Oh then, tell me Sean O'Farrell, where the gath'rin is to be?"

In the old spot by the river well known to you and me
One word more for signal token, whistle up the marchin' tune.
With your pike upon your shoulder, by the risin' of the moon".

Out from many a mud wall cabin eyes were watching through that night
Many a manly heart was throbbing for the blessed warning light
Murmurs passed along the valleys, like the banshee's lonely croon
And a thousand blades were flashing at the risin' of the moon.

There beside the singing river, that dark mass of men were seen

Far above the shining weapons hung their own beloved green
“Death to every foe and traitor! Forward! strike the marching tune
And hurrah, my boys, for freedom, 'tis the risin' of the moon”.

Well they fought for poor old Ireland, and full bitter was their fate
(o, what glorious pride and sorrow fills the name of Ninety-Eight!)
Yet, thank God, e'en still ard beating hearts in manhood's burning noon.
Who would follow in their footsteps at the risin' of the moon!



Labels: [Commentary](#)

Thursday, March 15, 2018

[The Ides of March](#)



CAESAR Ha! who calls?

CASCA Bid every noise be still: peace yet again!

CAESAR Who is it in the press that calls on me? I hear a tongue, shriller than all the music, Cry 'Caesar!' Speak; Caesar is turn'd to hear.

Soothsayer **Beware the ides of March.**

CAESAR What man is that?

BRUTUS A soothsayer bids you beware the ides of March.



Labels: [Commentary](#)

Wednesday, March 14, 2018

[Economics 101?](#)

I always have had a problem with economics. It inherently assumes some basis rules that humans will follow when producing and selling. Having spent time across a wide base of businesses there is only one thing I know; competitors can do really strange things.

Now in a piece in [Cafe Hayek](#) the author notes:

In one of the most astonishingly fallacious assertions in an essay teeming with astonishingly fallacious assertions, writes "Critics claim tariffs will raise steel prices. That's questionable. The opposite is more likely to happen, industry experts suggest. Tariffs will shift demand to domestic steel, enabling plants here to operate closer to capacity. That will bring down the unit price of American-made steel – not raise it. That's Economics 101" ... Here are relevant lessons that are really taught in Economics 101 ... First, shielding producers from competition makes the outputs they produce more scarce, thus raising prices. Second, if it is true that untapped economies of scale are available by expanding outputs, and that such expansions will lower prices and enable (in this case) American steel and aluminum producers to profitably charge lower prices than they now charge, then American steel and aluminum producers will so expand their outputs without any government prodding. So why have they not yet done so? That is.... the current existence of untapped economies of scale is true, then the men and women who currently run American steel- and aluminum-producing firms should not be rewarded with protection from competition but, instead, fired for gross incompetence.

First, I guess if you make more perhaps the price would go down. But that depends on how rational the manufacturer is. They often do not do what one would expect. How do they set a price? Tariffs are just a plain tax on one segment of suppliers. If that supplier can deliver at a lower price then the tax brings the effective price higher. Got that, I think. But is the price related to the cost? Is the supplier subsidized?

The second argument is that there are scale economies and if so then the domestic manufacturer could use them to compete with an import. This again assumes that the management is willing to risk this because the competitor could drop their prices and it becomes a price death spiral. No logic, just price competition. Then the customers may start to hedge on futures against price changes and so forth.

The problem with economics is that managers are not as rational as the economists think they should be. They often do "stupid" things, which leads to results which are against "theory" and then the other side does similar things.

The true argument is not looking at this dispassionately as an economist but trying to understand the management and their motivation, as well as the customer, as well as the financial markets. It is truly messy! That is why I find economics too neat for a messy world.



Labels: [Economics](#)

Monday, March 12, 2018

[Are You Out of Your Mind?](#)

The issue is Qualcomm. The [NY Times](#) states:

The extraordinary decision by the president underscored the increasingly protectionist stance his administration has taken in recent weeks to shelter American companies and ward off foreign investment in the United States.



The above are the original Qualcomm chips made for CDMA back in 1992. They were given to me when I was COO of Wireless.

Before commenting let me present some bona fides. The founder of Qualcomm was my advisor at MIT decades ago. At NYNEX I ran the venture investment fund and we along with two other Telcos invested a total of \$15 million in the company. It also was one of the best if not the best investment made by the company.

Then as COO of the wireless company, now Verizon Wireless I circled the world convincing many manufacturers and carriers of the benefits of CDMA and thus fully monetizing the company. Thus I have some knowledge to say the least. Second the [proposed buyer](#) is alleged to have close ties with various Mainland Chinese entities who in turn are close to the PLA, the Communist Chinese Army!

Now does it make sense to have a potential adversary own and run a company whose products

are used in strategic US systems? Hopefully any moron would know the answer to that. Thus Trump's decision is hardly protectionist, it is the only decision he could ever make as the President of the United States! Next we could have seen the chips in North Korean Ballistic Missiles on their way to San Diego or elsewhere.

Thus one wonders who writes these absurd pieces for the NY Times. Fake News, no, Dumb News, yes!



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

[Information and the Press](#)

The public dialog on news thus far seem to focus on the news media and its attempts at veracity. One should remember that the so-called news media have rarely been unbiased and open. I often recall that in my youth, the late 1940s, New York City had a multiplicity of daily newspapers. There was one for any political stance one took. There was the NY Times, the Post (a rather strongly leaning leftist paper), the News (a somewhat right leaning), the Tribune, the Telegraph, and many smaller and even narrowly focused papers. One could see individuals reading their news of choice on the subway, and thus political opinions were readily displayed in public if one understood the code.

The Chart

Let me begin with a comment on the Otero chart³⁵[1]. Like any generalization, one must first understand the generator of such a paradigm. Thus who is Otero and what is her "agenda", for all people have some agenda to promote. As the author notes:

I'm a practicing patent attorney in the Denver, Colorado area, and I have a B.A. in English from UCLA and a J.D. from the University of Denver. I'm not a journalist by training, and I don't claim to be one. So why should you listen to me about the quality of news sources? You shouldn't. In fact, you shouldn't listen to anyone who tells you that you should think or believe a certain thing a certain way. But you've come to my site to find out what I have to say about the news anyway, so I'll lay out a few reasons why you could choose to value my assessments. Consider them and then determine for yourself whether this information is valuable to you.

Before moving on to a detailed discussion of information, this Otero charts is worthy of some study. It in many ways attempts to be a paradigm that allows one to asses where certain sources of information lie.

First, the author presents a set of terms all of which lack any definition. One must bring their own inferences to bear on this table. For example one may ask what the difference is between analytical and complex. The issue of liberal versus conservative also begs the question of

³⁵[1] <http://www.allgeneralizationsarefalse.com/>

definition, especially as we can see this at extremes but not in a full spectrum. The author belies the training they allege, namely as a patent attorney, wherein one must have clear definitions just to begin. This table has none.

Second, in placing entities in this grid one must ask; by what criteria has the author made these placements? Apparently it is by the author's sole judgement and there is no factual basis presented, no metrics, no detailed analyses. If one were to accept this analysis then one should also expect if not demand a basis for the placements. For example, Croly's New Republic is left off this list. That to me would be a major fact, for Croly was in a sense one of the God parents of present day Progressive thought.

Third, one must ask why in reading any of these, if not all, can one gain information, can one sift through the desiderata presented and, as the author says, obtain something of value. Even if we grant that the chart has some value, we must ask if an individual's value maps isomorphically onto this paradigm.

Fourth, why should we delimit our access to the news, namely allegedly imminent information, based upon the opinion of anyone? The author admits that. If so, then why is this chart of any value?

Fifth, people are individuals, and the media presented in the chart tend to attempt to cluster people in groups. We all have biases, they are all too often the product of our environment and many may even be genetically based, yet the true source of bias is yet to be fully understood. However biases can be reinforced by "group think" or by the "echo chamber" effect.

Sixth, the author seems to delimit the media to mostly US based, with the exceptions of the Guardian, BBC, Economist. Anyone truly interested in obtaining information would include such voices as RT, Sputnik, Deutsche Welle, the Jerusalem Post, Le Monde, China Daily, and the list goes on. Information must be sifted and compared. In today's Internet environment an individual's news feed, that is the actual sources not some pre-filtered Facebook edition, should provide daily access to a multiplicity of sources. Each source will have its own bias and examining many will in a sense filter out or average out the extreme biases.

Definitions: Information and its Elements

Let me then return to Otero's last statement as noted previously above:

"whether this information is valuable to you"

This begs several questions. First what is information? Is it just a recantation of facts; for example the number of hogs in the US on June 1 2017. At noon precisely. Or is it the reporting of what people are saying, such as Government officials or un-named sources? Or is it the presentation of certain facts and an analysis of those facts. Such as the number of hogs by day at noon in Iowa for three years? This would be a trend and there may be consequences from the trend. Or is it the opinion of some person or persons? Information as we understand it is a complex issue. It is not just facts, it is an interpretation of those facts. It is also a ranking of facts

and their interpretation in a way which may be of value to the public. That leads to the second issue; value. What is value? Knowing that a company is near bankruptcy may be of value if I know it before others and if I can act upon it. That they is financial value. Value may also accrue if I know that a certain politician has an incapacitating health problem which would delimit their abilities to act in the interest of the country, such as was the case of Wilson after his stroke, and perhaps as was the case of FDR after his fourth election victory.

Is information active and goal directed or is it just a passive compilation of non-valued facts? Information may be like some sports score, valuable only for personal enjoyment, or it may be like horse race results capable of being a basis for handicapping races and betting accordingly. Is the passive non goal directed information real information or just entertainment? Does information have to be of some goal directed nature?

News versus Information versus Opinion

As we noted, Information is the presentation of facts and an assessment of these facts to present a set of reasonable conclusions. In a sense, Information is akin to what an expert witness would do in a Court of Law. First the expert or reporter, would be identified and their bona fides made available. Anonymity would be denied. Then the expert or reporter would present a set of facts all of which would be verifiable. The facts then become a basis of the web which is woven to present the story the reporter presents. Unlike an Expert, however, who may use their own professional opinion, a reporter has no right to an opinion when reporting on the facts. That is why in a classic newspaper the information is separated physically from the opinions. This classic separation has disappeared in all newspapers as of today.

News is a subset of information. The distinction is its immediacy. Information is not time sensitive. Historians are purveyors of information. Information which has a true sense of immediacy takes on the rubric of news and the reporter then is the assembler of this type of information we would call news.

Propaganda versus News

The classic work by Bernays on *Propaganda* was written in 1928, a decade after he and others were involved in the Government entities supporting Wilson's War efforts. Wilson used Propaganda as described by Bernays to promote and support his ideas and this was actually accomplished via a Government office.

As Bernays notes:

The conscious and intelligent manipulation of the organized habits and opinions of the masses is an important element in democratic society. Those who manipulate this unseen mechanism of society constitute an invisible government which is the true ruling power of our country. We are governed, our minds molded, our tastes formed, our ideas suggested, largely by men we have never heard of. This is a logical result of the way in which our democratic society is organized. Vast numbers of human beings must cooperate in this manner if they are to live together as a smoothly functioning society. Our invisible governors are, in many cases, unaware

of the identity of their fellow members in the inner cabinet. They govern us by their qualities of natural leadership, their ability to supply needed ideas and by their key position in the social structure. Whatever attitude one chooses toward this condition, it remains a fact that in almost every act of our daily lives, whether in the sphere of politics or business, in our social conduct or our ethical thinking, we are dominated by the relatively small number...

Read the first sentence very carefully. He is not talking about the debate in the Federalist Papers, but outright manipulation. He is speaking from experience. He is also speaking as a prophet as to what will come in but a short time in Germany, and perhaps in today's world. The question is; who does the propagandizing and who decides what people must think?

Let me give another example. One could ask if Edward R Morrow was a propagandist for Roosevelt to get the US to enter the War with Britain. The basis for such a supposition has some merit but not enough to make it a certitude. Yet what Morrow did was in a sense propaganda. He met the Bernays results, using facts, news if you will. News during WW II was as much propaganda as anything else. Likewise the news during Vietnam turned on the Government and became counter-propaganda.

Quality: An Amalgam of Value and Trust

But information must be quality information. What do we mean by quality and especially quality information. We argue that quality is an amalgam of value and trust. Let me explain.

Silicon Valley has emerged as a source of profit for many of those who are affiliated with it. But what is it really worth? What value does Silicon Valley types and their products provide? This is the question as to what do we mean by value in our society. An adjunct of value is the concept of trust. I was introduced to this concept as a critical element in a stable society by the late Dave Staelin, a former teacher and colleague. I thought that value was a sine qua non, but Dave convinced me that trust was equally if not more so an element in what we see as a productive element in a stable society.

Now what do we mean by value, and in turn what do we mean by trust. Value means potentially many things to many people. There is the concept of personal values. Namely what does a person hold dear to them, what are their metrics of judgement of themselves and their surroundings. One may hold altruism as a value, humility as a value, cleanliness as a value. Then there is the construct of values of a society. Namely such things as the right of free speech and the right to practice a faith. Then there may be the value of one's individualism, the sanctity of individual rights. Then too is the value inherent in some artifact. An auto has value in that it takes us from one place to another quickly, reliably, and with less human exertion. We can assign a simple measure to that value by how much it costs us and what we get in return for that cost.

Our interest is in that latter definition, a concept of economic or societal value. Thus we may ask what value some new technology brings forth. Let us take a computer, a personal computer, as an example. We may ask; what value does it have to a person? to me? to society? Obviously it may allow me to type better, write faster, calculate more accurately. However, there may be externalities that reduce the value. It may allow me to do more, but then I no longer need a typist,

thus I have increased its value to me and reduced it to them. Thus how does one ascertain value; to the person or to the group. If I were a Marxist I would be focusing on the value of the labor as a input to the building of the computer rather than what it does for the user of the computer.

Thus to simplify the analysis I will use value as what added benefit accrues to the individual who employs the entity which purportedly conveys the value. Thus the value of a personal computer, the value of Google search, the value of Uber, will all be judged in the context of the user first and then society second. It would seem to be easier to perform such a task.

Before continuing let me address the issue of trust, and its adjunct, quality. Something, an instrument of some type, has value to a person because the individual can use it the instrument to perform some task for which the instrument was designed and for which the representation one relied upon at the time of its acquisition would be correct. Namely it does what it was supposed to do. One relies upon a representation by a purveyor, not only that the instrument functions as it was supposed to but that if it does not there will be a remedy. The combination of value with trust, namely its concatenation, results in the concept of quality. Namely if one obtains something that adds value and one can trust its delivering value, trust, then one has a quality experience, and quality adheres to this overall process. Value adheres to the instrument and trust to the purveyor. Quality adheres to the concatenation of both.

Let me give a current example and counter example. Let us assume I purchase a product from Amazon, say a chain saw. I need the item to remove trees. Thus it must cut wood while providing reasonable safety. The instrument must start, function as specified, and not wear out in an untimely manner. It must also have a modicum of safety. Now if I were to purchase from Amazon and they represent that they sell it to me, then I have value and I have trust, namely if it does not work Amazon will remediate the purchase. On the other hand if Amazon just presents the product and a third party actually is the purveyor, I do not know then and there is no trust. The transaction has no quality. You see one needs both value and trust. This is the Staelin construct again. Let me give another example. This time Google. I am seeking information about some health related matter, say a physician who can care for a certain ailment. Does Google provide value? Yes, it may give me a list from which I could then address and seek what I am looking for. Do I trust Google? That is a good question. Trust in this case means if I ask for a physician expert in dealing with the specific ailment, then I assume that Google will present all the options, the alternatives. I assume or trust that Google will not filter out physicians whom they do not like, are not acceptable to Google. How do I know this? As with the Amazon case it is by experience. I am pragmatic, I rely upon experience, mine and others. This works until it does not work. Then pragmatically trust is lost, and near impossible to get back.

Thus, if Amazon fronts for a poor third party vendor and as a consumer I am scammed, then I am wary of everything on Amazon. I move to Walmart. If I find out Google refuses to, for example, list any physician who is a registered Republican, then I become wary of Google across the board. Trust is lost and a key part of the quality equation is vitiated. The instrument no longer has quality and thus I seek an alternative.

Let us leave trust aside for a moment and focus on value. Value has a philosophical as well as economic understanding. We somehow wish to address the amalgam of the two. We want to do

this for the development of technological implements. Thus the instrument may be a new cancer immunotherapy, a new computer processor, a new water desalination technique, a new way to remove carbon dioxide from an exhaust, or a new app. What is the value we would ascribe? Economically we would project cash flows from an anticipated market. But there is also societal value as well. A new app may generate cash but would have minimal societal value. In fact it may be a value destroyer. Namely a person would defer a productive action while expending time on the useless app.

Thus we look at value as both economic and societal. Yet can we monetize this? Namely can we make a *pari passu* comparison? Let me defer that for a moment. The above simple example does show we have value creating, healthcare, and value destroying, apps, instruments. We also have value transferring instrument, which is fundamentally what bankers and VCs do. They take money from one source and reallocate it to another. Value transfer agents do not create value themselves. They seek those who do. Yet value transfer agents look at value solely as an economic return. Thus if they invest in a value destroying instrument, such as an app, they then also become a party to that action.

One way to determine the societal effects on value is the concept of externalities. Namely the effect that may be secondary or a result of the primary action. There is a well-established body of work on quantifying externalities. The problem often is, however, that externalities are unanticipated consequences.

The problem we see today is twofold. First, value is often measured solely in short term financial returns devoid on the unintended consequences of the externalities. Second, trust is oftentimes never a factor in the delivery of instruments. I again use the example of Amazon. As it seeks to continually expand, it does so outside the scope of its ability to maintain trust. Its use of third parties and its separation of control on these parties has led to loss of trust. Similarly, for an entity like Google, its burgeoning political bent, for better or worse, can irreparably taint its reputation as a trustworthy source of information. This of course is orders of magnitude for entities like Facebook and Twitter.

Thus when we seek quality, the amalgam of value and trust, we will have the conundrum of Pirsig in *Zen and the Art of Motorcycle Maintenance* (ZMM). Pirsig says:

"The definition was: "Quality is a characteristic of thought and statement that is recognized by a nonthinking process. Because definitions are a product of rigid, formal thinking, quality cannot be defined." The fact that this "definition" was actually a refusal to define did not draw comment. The students had no formal training that would have told them his statement was, in a formal sense, completely irrational. If you can't define something you have no formal rational way of knowing that it exists. Neither can you really tell anyone else what it is. There is, in fact, no formal difference between inability to define and stupidity. When I say, "Quality cannot be defined," I'm really saying formally, "I'm stupid about Quality.""

Pirsig goes on:

"He singled out aspects of Quality such as unity, vividness, authority, economy, sensitivity, clarity, emphasis, flow, suspense, brilliance, precision, proportion, depth and so on; kept each of these as poorly defined as Quality itself, but demonstrated them by the same class reading techniques. He showed how the aspect of Quality called unity, the hanging-togetherness of a story, could be improved with a technique called an outline. The authority of an argument could be jacked up with a technique called footnotes, which gives authoritative reference."

"There's an entire branch of philosophy concerned with the definition of Quality, known as esthetics. Its question, What is meant by beautiful?...he saw that when Quality is kept undefined by definition, the entire field called esthetics is wiped out—completely disenfranchised—kaput. By refusing to define Quality he had placed it entirely outside the analytic process. If you can't define Quality, there's no way you can subordinate it to any intellectual rule. The estheticians can have nothing more to say. Their whole field, definition of Quality, is gone."

Indeed esthetics, and aesthetics does read onto to what quality is, it is a perception, not a measurable quantity.

Thus, we should look at value as the amalgam, seek out trust, and then quality, as elusive as Pirsig notes, should be self-evident.

Thus when we return to the issue of information we want not just valuable information, but we demand quality information. Namely it has actionable value and it is predicated on trust.

Let me expand a bit on trust. Now when looking at a set of comments on the Internet, say such as a product review on Amazon, we look for ones whose reviewer states who they are and what bona fides they have. If we have some anonymous reviewer we have no way of ascertain whether we can trust this. Anonymous means they are hiding the most essential element of trust, namely that they stand behind their good name. Thus anonymous news reports are useless for we have no way of identifying their veracity.

News: Real or Fake?

The next issue is that of Fake News. Just what is Fake News? Let me refer to a recent article from the MIT Sloan School, in Science36[2]. The authors note:

We define "fake news" to be fabricated information that mimics news media content in form but not in organizational process or intent. Fake-news outlets, in turn, lack the news media's editorial norms and processes for ensuring the accuracy and credibility of information. Fake news overlaps with other information disorders, such as misinformation (false or misleading information) and disinformation (false information that is purposely spread to deceive people). Fake news has primarily drawn recent attention in a political context but it also has been documented in information promulgated about topics such as vaccination, nutrition, and stock

³⁶[2] <http://science.sciencemag.org/content/359/6380/1094.full>

values. It is particularly pernicious in that it is parasitic on standard news outlets, simultaneously benefiting from and undermining their credibility.

The authors continue:

Journalistic norms of objectivity and balance arose as a backlash among journalists against the widespread use of propaganda in World War I (particularly their own role in propagating it) and the rise of corporate public relations in the 1920s. Local and national oligopolies created by the dominant 20th century technologies of information distribution (print and broadcast) sustained these norms. The internet has lowered the cost of entry to new competitors—many of which have rejected those norms—and undermined the business models of traditional news sources that had enjoyed high levels of public trust and credibility. General trust in the mass media collapsed to historic lows in 2016, especially on the political right, with 51% of Democrats and 14% of Republicans expressing “a fair amount” or “a great deal” of trust in mass media as a news source.

Strangely as we noted in our discussion of Propaganda, it was Wilson and his attempt to get us into and totally committed to WW I that true American propaganda was developed. Also the Germans took up Bernays Propaganda and brought it to the fore in WW II. Thus when news become propaganda, for any cause, we have the potential for catastrophic results.

Now Fake News has always been with us. It always will be. It is the individuals duty to attempt to question the alleged facts. Juries do this all the time. They are presented with what at times is Fake Facts, and the jury must decide whether they have a basis or not. They are the trier of facts.

Regrettably the paper in Science presents no detail of the analysis performed. Namely it does not demonstrate how one determine what is Fake and what is Real. Fake News may actually build upon facts, then in drawing a conclusion, it uses terms like "could", "may" etc.

Russia and Disinformation

Let us examine the issue of Russia, disinformation and putative interference. First we should note that such actions have been multilateral for decades. During our own Revolution the English Crown managed certain presses and as such tried to influence the locals. It was in my view the efforts of Thomas Paine who established a well-accepted understanding of what a rebellion was essential. Russia has also been actively expressing its interests, as the Soviet Union, since 1918 when Ludwig Martens came to the US as a Soviet agent and seeking funds for the new Soviet Republics. It was in a920 when the US Senate actually had hearings and asked Hillquit for his reasons and objectives of his activities in the US.

In the Martens case the Congressional Record notes³⁷[3]:

³⁷[3] US Senate Record, Committee on Foreign Relations, Russian Propaganda hearing 14 April 1920.

Whereas one Ludwig C. A. K. Martens claims to be an ambassador to United States from the Russian Soviet Government; and Whereas, according to newspaper reports, he refuses to answer certain questions before the Lusk investigating committee in the city of New York, committee appointed to investigate propaganda against this Government is the ground that he is such ambassador and entitled to diplomatic privilege and

Whereas said Martens has headquarters in the city of New York and is alleged to be directing propaganda against this Government; and

Whereas, according to his testimony before said Lusk committee, he came to this country as a German citizen and is a member of the Communist Party pledged to overthrow capitalistic systems of government the world over;

Now it is critical to see that this hearing is a century ago. That even then Congress was concerned about Russian Propaganda.

Conclusion

Information is in the eye of the beholder. Unfortunately that may very well be the conclusion. Fake News is considered fake because we do or do not maintain a level of integrity in those who report it. Equally so, Fake News has a continued existence, and actual proliferation due to a panoply of reasons. For example, people may truly believe the news because they want to. Or, for example, people find it humorous or absurd and have a propensity to share that with others. Also the readers of Fake News may not have the intellectual resources to differentiate what they see as real or fake. This reason is a serious problem. If we have an electorate who cannot understand what is being said then we can have purveyors of falsity become rulers of the people. Education was a one-time excellent but over the last fifty years it has become politicized, spending excessive amounts on politically correct training and less if any time on critical thinking skills. Education should not tell people what to think but how to think. Nothing is necessarily what it appears to be and trust no one may be mantras of the truly educated.

Thus the paradigm with which this piece began, one of classifying various news outlets as regards to the information they present as news is truly vacuous. It has not only no merit but it fundamentally falsifies how information is contained. Information is attained through a dialectic, contrasting one view with another, while validating the facts. Perhaps one should look at Popper's approach of falsification. Namely that one should not accept some of these facts, one should continuously question and seek a means or method by which they can be falsified. In a competent Intelligence organization that is the key exercise. Facts as given must always be question, for an adversary who makes it too easy to obtain facts may be deliberately spreading false information. If an adversary seeks to perform a counter-intelligence operation effectively, they do so in such a manner as not to be identified and not to be falsified. That being the case how then should one deal with alleged Russian collusion, and in turn, the Press?



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

Tuesday, March 6, 2018

[West Virginia Teachers and the NY Times](#)

Some New York City based NY Times reporter opined on the [West Virginia teachers](#) strike. Her comments notes:

As long as the teachers stay out, they serve as a symbol not just of a nascent labor movement, but of a citizens' uprising that's taking different forms throughout the United States. Fones-Wolf thinks the strike goes hand in hand "with a much more generalized discontent. You see evidence of it from these school kids in Florida, who are really quite amazing. Maybe we're on the cusp of a time when people say, 'enough.'" If that's true — if a spirit of revolt really is sweeping across the country — it will be the one way Trump has helped make America great again.

Now I have a daughter who is one of the strikers and four grandchildren in the state. As such I have a rather personal nexus. I am not a New York City commentator, I have some pound of flesh in the battle.

The problem is simple. The Legislature is, in my opinion, in the pockets of the coal and gas owners. Labor has always been a second thought in West Virginia. Remember that the Democrat Senator has a daughter who runs the drug company that took epinephrine emergency units and raised the price more than 6 times! Then the teachers were getting one of the worst health plans in the nation and one of the lowest salaries. The unions from my understanding did nothing. It was the teachers alone, doing it themselves, who pushed the issue.

It is not resolved. The pay increase is one thing, the health plan is a disaster! The Legislature wants to increase the monthly charge almost 12 fold while reducing the benefits to less that one would see in some forth world country. For example, if you have a child with cancer, you get to go to Morgantown, even if you are near Baltimore. Over the Cumberland gap, through snow and ice and pray your sick child is still alive. Then pay for your hotel and the list goes on! West Virginia, in my opinion, is the only state where Medicaid is better!

The issue is not unions, in my opinion, it is the gross disregard of state employees and the favoring of wealthy local interests.

The comfortable, and what seems in my opinion uninformed New York City big paper commentators know-it-all states:

Yet if the strike is rooted in the specific conditions and history of West Virginia, it's also part of a nationwide upsurge in intense civic engagement by women. "As a profession, we're largely made up of women," Amanda Howard Garvin, an elementary school art teacher in Morgantown, told me. "There are a bunch of men sitting in an office right now telling us that we don't deserve anything better." In the wake of Donald Trump's election, she said, women across the country

are standing up to say: "No. We're equal here."

Well, there are still men going down into the mines, working crops, hauling loads across highways. Why everything gets turned into a women's issue when it is a global issue of the special interests and their money, not the workers and their horrible conditions. One should not bait one group of impressed by another and disregard the true oppressors.

The teachers are back, and as I am led to understand not due to any help from their "unions" who opposed their actions. Yet the health care issue is still a disgrace. Perhaps the NY Times can send someone down into West Virginia. I suspect they may not have done so since Kennedy ran for President!



Labels: [Commentary](#)

[Keep Your Head in the Sand: The NHS Saves Money](#)

We all too often hear from those seeking better healthcare that we should follow the Brits NHS. Now perhaps we should spare a moment on understanding their approach. The best example is today in [Cancer Research UK](#) which tries to opine on the uselessness of cancer screening. As we have already noted the most recent attack was on PSA testing. The brilliant conclusion was that if you only tested a patient once, and if that test was positive you did a biopsy that was in my opinion useless, then the number of deaths was no different than if you did nothing. In my opinion that equation leads to:

Nothing=Nothing

No surprise. I wonder what Lord Russell would have said?

Now to their other article:

Not all cancers are equal. Some grow fast and spread quickly, while others grow so slowly (or even not at all) that if they went undetected they wouldn't cause any problems. Even if left untreated, a person wouldn't be harmed by their cancer. When these harmless cancers are found they're said to be 'overdiagnosed'. This happens more often with certain types of cancer, and is usually tied to particular types of cancer screening that test people without symptoms, such as breast screening. The problem is that when these types of cancer are diagnosed early it's impossible to tell the potentially harmful ones from the harmless ones. Everyone is then usually offered treatment. And this means that some will be exposed to the potential side effects of treatment, and worry of a cancer diagnosis, when they didn't need to be. This is called overtreatment. Overdiagnosis is one of the key things to consider when working out the balance of possible benefits and harms of cancer screening. Keep in mind, overdiagnosed cancers aren't the same as when a test finds something abnormal that turns out not to be cancer (so-called false positive test results), another risk of screening and many other types of test. An overdiagnosed cancer is a true cancer, but it's one that wouldn't have caused harm in that person's lifetime.

So the Brits solution seems to be in my view; forget about screening. If you are going to die you are going to die, so live with it!



Labels: [Health Care](#)

Tuesday, March 6, 2018

[PSA, So What?](#)

The PSA test is not liked by many. Why? Because it often finds indolent cancers. Thus many entities want to ban its use. Is that a good idea? Not really but here is the latest.

From [Cancer Research UK](#) they note:

The potential for blood tests that detect cancer is huge. But what if a test is, in some ways, too good? What if it finds cancers that if left undetected wouldn't cause a person any harm? And what if it's not possible to know for certain which cancers need to be treated, or who could avoid a life-altering diagnosis and potential long-term treatment side effects? This is the situation right now with prostate cancer. There's no UK screening programme for prostate cancer. That's because the blood test that would be used – called the PSA (or prostate specific antigen) test – isn't reliable enough.

Men over the age of 50 with no symptoms of prostate cancer can still ask for the test in the UK. But its use is hotly debated around the world. Now, a new Cancer Research UK-funded study, from scientists at the Universities of Bristol and Oxford, sheds more light on how unreliable the test is. And it confirms that for men without symptoms, the PSA test doesn't save lives.

Now from the refered to JAMA paper it notes:

In the intervention group, men aged 50 to 69 years received a single invitation to a nurse-led clinic appointment. At the appointment, men were provided with information about PSA testing. After giving consent, men were offered the PSA test. Men with PSA levels of 3.0 ng/mL or greater were offered a standardized 10-core transrectal ultrasound-guided biopsy. Those diagnosed with clinically localized prostate cancer and who met the eligibility criteria were recruited to participate in the ProtecT trial to receive treatment. The ProtecT trial compared radical prostatectomy, radical conformal radiotherapy with neoadjuvant androgen deprivation therapy, and active monitoring.⁵ In contrast, the control practices provided standard National Health Service management, and information about PSA testing was provided only to men who requested it.

This procedure is akin to taking a single sample of blood pressure and assuming it is the same for ever! The fundamental approach to any patient is to see if anything changes over time. That was to have been the core of any electronic health record, never achieved however. A good physician looks for change, in a mole, in blood pressure, in weight, in vision, and yes in PSA!

The JAMA article concludes:

Among practices randomized to a single PSA screening intervention vs standard practice without screening, there was no significant difference in prostate cancer mortality after a median follow-up of 10 years but the detection of low-risk prostate cancer cases increased. Although longer-term follow-up is under way, the findings do not support single PSA testing for population-based screening.

First a single measurement of anything is near useless! Second, PSA works only if measured over time and such measures as velocity and percent free are also measured. Thirdly, a ten core biopsy not guided by MRI is "shingling the roof in the fog". One has no idea what they are biopsying! No wonder there was no change in mortality.

In my opinion based upon a multiplicity of prior analyses and clinical studies, this result proves that a single PSA test is useless. That is all.



Labels: [Cancer](#)

[Choosing Winners and Losers](#)

Starting a new company is a risky business. It requires many elements besides a good idea. It needs a team, experience, execution, persistence, money and yes also luck. The timing is critical as well as execution. Business is fundamentally a survival of the fittest, a matching of business expertise with market demands. Perfecting a good idea is at best a small first step.

Now comes the MIT Engine, a \$200 million investment fund. It is not really a venture fund, it is something that is between a post-doc operation and what is called an incubator. As Technology Review states^{38[1]}:

Located behind an unassuming storefront in Cambridge's Central Square, The Engine's 26,000-square-foot headquarters is home to seven startups, including iSee, which is working on artificial intelligence to make self-driving cars more practical, and Analytical Space, which is planning to launch a network of low-orbit satellites to transfer large amounts of data from space using lasers—at speeds 10 times faster than radio for about the price of a cellular data plan. The Engine provides resources to help these startups develop their technologies, with investments to date of between \$500,000 and \$2 million and use of dedicated office space and shared lab and fabrication space for as long as they need it. Rae and her team also offer business advice and connections to help them find customers.

Now take the satellite case. This will require billions not to mention a global licensing effort. I have seen this done a few times before. Now one wonders if this is just a research effort pretending to be a venture fund. Is it fair to the students to have them believe they are building a business? As this is done under the rubric of MIT is it fair for an academic institution whose aim

^{38[1]} <https://www.technologyreview.com/s/610114/investing-in-tech-thats-worth-the-wait/>

is leading edge research to choose winners and losers. Faculty compete in the open market of funding from third party entities. Why should the startups not do the same.

The article also notes:

The idea for The Engine emerged as MIT was finalizing real estate developments in the biotech and software hub of Kendall Square. “We were focused on what MIT could do that would be additive and beneficial,” says executive vice president and treasurer Israel Ruiz. In conversations with scientists and engineers, he learned that the biggest need was in bridging the “valley of death” between producing an innovation in the lab and getting it to market. That is particularly difficult in industries that require sophisticated hardware, such as alternative energy, transportation, space, and medical devices, and thus may need more capital investment up front than digital ventures. “They said, we need money, but we also need access to infrastructure and specialized equipment, and we need to create a community,” Ruiz says. “Those elements got put together in The Engine.”

The "valley of death" metaphor has merit. Universities get faculty and students to work on a multiplicity of leading edge ideas. They are research as they should be. They are not business ideas. They are driven by technological breakthroughs. Taking that and making a business is non-trivial. It requires a team, a market, financing, and good timing and execution. Those things are well beyond the ken of academics. They then continue:

The concept dovetailed with MIT president Rafael Reif’s vision of “innovation orchards,” an idea he expressed in a 2015 op-ed in the Washington Post. Such environments, he wrote, could “provide what universities alone cannot: the physical space, mentorship, and bridge funding for entrepreneurs to turn new science into workable products.” He added: “This would make investing in tangible or tangible-digital hybrid innovations no riskier than investing in the purely digital.”

It is not the responsibility of a university to develop businesses. They train students and perform research. The vetting process of starting a business means breaking the academic umbilical and in the classic mode of "burning the boats", eschew all the comfort of the academic world and begin anew. Turning new science into workable products is but a small step. You have to have a product that someone wants. The dogs must eat the dog food! I have seen many good science projects turned into good products, which unfortunately no one wanted! You need a market and the MIT President's statement above reflects the insular mindset of the academic.

The article continues:

Yet another aim is to seed new industries that can diversify the Boston area’s portfolio of tech companies beyond biotech and medical. “Boston has had a seat in what we would call transformative technologies for a long time,” says Nashat. During the 1970s and 1980s, New England got an apparent head start in the electronics industry, only to see Silicon Valley become the center of that world. “To put it bluntly, the East Coast needs to up its game if it’s going to attract top young talent and industrial vitality,” Lassiter says. “We have that in biotech and the medical area, but we need more of it in more areas if Boston is going to be as important in the

next 50 years as it was in the last 50. Ultimately, you need an economy that is more than professors and Uber drivers."

I did my first start up, as a member of the team, in 1969. It was an EG&G funded effort to make an early version of a credit card validation system. It failed. But what I learned is that customers and attention to detail is a sine qua non. The "good idea" or even a "workable product" is a mere first step. One should ask why California got the start. My answer is a bit convoluted. Because MIT and its surrounding companies had been feeding at the DoD trough for years and continued to do so. It was a one hour flight. California was six hours to DC and thus needed a Plan B. Boston forgot the Plan B and California won. Lesson, always have a Plan B and never rely upon a "sugar daddy".



Labels: [Academy](#)

Thursday, March 1, 2018

[Textbooks](#)

It is interesting to examine the evolution of textbooks, especially for colleges. I have taken the opportunity to examine chemistry for the freshman level. Specifically both what is presented, how it is presented, and how much it costs. I tried to examine texts from the 1960 period to the present. The time selection is based upon the Sputnik inflection point in 1957.

First of all, chemistry for college freshman is generally a collections of disconnected ideas. It does not build like calculus or physics. For example the typical course would include:

1. Molecular and atomic structure, the periodic table
2. Bonding, types and uses, basic quantum numbers
3. Lewis bonds and structures
4. Stoichiometry
5. Reaction rates
6. Reaction Kinetics
7. Aqueous Solutions
8. Acids and bases
9. Thermodynamics of reactions

These topics seem to be covered in most books. Oftentimes these are separate and do not build upon the previous steps.

The trends seem obvious.

1. The CPI has gone from a normalized 1 to a current 8.5. Namely prices have gone from \$1 to \$8.50 approximately.

2. The current prices if about \$160.00 or about \$19.00 in 1960 levels.
3. In 1960 the price of such a book was about \$9.50. Thus a doubling of the old price.
4. A massive introduction of color pictures. Just how many times must the student see Einstein!
5. The style has changed dramatically. The older books were fairly linear in presentation. The newer one seem to interject cultural, political, technical as well as chemistry related materials.
6. Besides the book one needs to purchase an equally costly book of problems. This doubles the price. Also some "on-line" purchase may be required.

Overall it seems that the publishers are just loading up on useless materials to get a greater price. The trends seem to be as follows:

1960-1980: Overview approach to the above topics, plus a few others with limited graphics and often limited experimental references.

1980-2000: More detailed material with reasonable numbers of worked examples and details on experimental efforts.

2000-2018: Explosion of useless details and confusing layouts. Near impossible to determine what is important and what is fill. Comes with costly separate problem and answer books almost always mandated.

Considering how this can be placed in an on-line mode, one wonders why this still prevails. Answer, publishers profits, at the costs of the students!

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Labels: [Academy](#)

[Public Transportation](#)

In the past two months on a single NJ Transit line there has been 167 breakdowns, delays (60 min or more) and absolute cancellations. That is just one of many lines. That does not include the

NY subway disasters.

The problem is not infrastructure, alone. It is the gross incompetence of politically appointed individuals who have no capabilities to run a railroad. They get appointed by a Governor, Republican or Democrat, and then proceed to cause abject havoc.

There are solutions to this, one is to privatize it and make its failure a criminal act. Small chance that would happen!



Labels: [Government](#)

Wednesday, February 28, 2018

[Nuclear Threat](#)

Despite the fact that we should not read RT or any Russia generated Internet postings, this one has merit. [RT notes](#):

By training its European allies to use their nuclear arms, the US is moving towards an atomic war with Russia, forgetting that it would mean the end of the human civilization, retired Lieutenant General Evgeny Buzhinsky told RT. The US military is preparing the armed forces of the European countries for the use of tactical nukes against Russia, Sergey Lavrov, the Russian Foreign Minister, said on Wednesday. He added that the presence of American non-strategic nuclear weapons in Europe is a major stumbling block in the path of disarmament. "No one can say how serious the threat really is" from the US actions, Buzhinsky, the Chairman of the Executive Board of the PIR-Center, said. However, he pointed out that "the military people are getting ready. The Russian military is preparing and the American military does the same. And it's for the politicians to warn the public that such preparations are being made."

As we have noted in our review of the Ellsberg book, any nuclear attack would be world ending. Furthermore control of nuclear weapons must be tight. No surprises. If we want to argue against any proliferation in a rogue state such as Iran or PDRK then we must hold the reins ever so close ourselves. The Russians have a point. With the distribution amongst NATO allies we potentially create a deadly threat. A world ending threat!



Labels: [Nuclear Weapons](#)

[A Deal is not a deal until the money is in the bank; for a week!](#)

Back to the West Virginia Teachers strike. Yes I have a stake in it, four grand kids in the state. But as the Governor may have agreed you have to line up all the ducks so to say. Or is it herding cats! The [Legislator is still rambling about](#).



Two other other aphorisms are worth noting:

1. Delay is the deadliest form of denial.
2. Trust no one, not even your father!

You see, trust is a key element in a civil society. But trust can easily be lost. When it is, then everything gets second guessed.

Apparently the real problem is not the \$1,000 to \$2,000 pay raise, it is the \$7,000 to \$9,000 per annum increase in health insurance! Yep, give with one hand and take back with both!

Where does the money come from? I think that is what the Legislators get paid to come up with.

So this deal is not done, it is delayed, and well you get the picture!



Tuesday, February 27, 2018

[Battle of Blair Mountain, Redux](#)

Now I am not a big union fan, yet more than half my family are union members. So here goes. The Blair Mountain strike resulted in one of the largest battles in the US post the Civil War. It was the Mine Workers Union versus the coal mine owners in West Virginia.

[Now the teachers are on strike](#). The problem is not just salary, one of the lowest in the US, but health care, in my opinion the worst in the US. It appears that now the Governor is calling the teachers "[dumb](#)" and "[red necks](#)".



The Governor, a rather portly fellow to say the least based upon observation, tends to regally dismiss the teachers. Perhaps the Governor would do better to listen and get support for the teachers rather than pontificate.

Good luck to the teachers!



Labels: [Government](#)

Thursday, February 22, 2018

[I Don't Like Bats But...](#)

Bats and I are not friends. It is not that vampire thing it is just that they tend to leave their droppings everywhere, and carried rabies. But [New Scientist](#) has an interesting piece that has some import. They note:

Bats provide a refuge for some of the most lethal viruses known, including Ebola, Marburg, Nipah and SARS. Now we may know why the animals tolerate these lethal viruses – and it's because flying is such hard work. Peng Zhou of the Wuhan Institution of Virology in China and his colleagues studied the immune systems of bats and flightless mammals. They focused on free-floating DNA within cells. This can happen as the result of a viral infection, as the viruses hijack the cells' DNA replication apparatus to copy their own genetic material. But it can also happen during strenuous exercise, which creates chemicals called free radicals that build up in cells and damage the DNA, releasing fragments of it. Most mammals don't have to perform hugely strenuous exercise, so their own DNA rarely leaks out into their cells. As a result, if their immune system detects any free DNA, it interprets it as an emerging viral threat and begins fighting back. The trigger for action is a sensor molecule called STING, which swamps the viral infection with antiviral substances called interferons. However, bats fly and this is extremely strenuous, so their DNA often does leak out. This could lead the bat's immune system to mistakenly attack the animal's own tissues. To avoid this, bats appear to have evolved milder reactions to viral infections, allowing the bats and the viruses to tolerate each other.

This is an interesting phenomenon and worth the study. It is even more of a reason to beware of bats. If they can do rabies then they can do all of the above. I understand the benefits of bats but the downside should be considered also. Just a thought!



Labels: [Bats](#)

Wednesday, February 21, 2018

[Scholars? Fact or Fiction!](#)

Another academic seems to be clueless, in my opinion, regarding Social Security and Medicare. The [Stanford](#) person states:

2 *Federal entitlements intended to lift people out of poverty now benefit the middle class, Stanford scholar says. While U.S. federal entitlement program expenditures are intricately woven into the fabric of American society, they have grown into a costly burden with a reach far beyond what was originally intended, Stanford scholar John Cogan says.*

The article continues:

U.S. federal programs – such as Medicare and Social Security – are now a costly burden that actually distribute most of their aid to middle class households, said Stanford scholar John Cogan. Also known as federal entitlements, these programs include Medicaid, Supplemental Nutrition Assistance Program, the GI Bill and military pensions.

This is in my opinion based upon substantial evidence absolute nonsense! Pensions are earned. Social Security and Medicare are paid for! In fact many people on Medicare never get back anything near what they paid into the program. Medicaid however is a social program. Medicare is NOT.

How do academics get away making these in my opinion baseless claims. Medicare is a program that people pay 3% of their annual salary and 3% of any capital gains for their entire life. Then they also pay often in excess of \$4,000 per annum to stay on the program and in addition pay for added benefits to pay for what Medicare does not pay for. A decade ago we wrote an extensive analysis of the [Medicare issue which was covered in the Washington Post](#). Perhaps if this Stanford academic spent a bit of time examining the facts their screeds would change.

Medicare and Social Security are NOT entitlements. They are paid for. Unfortunately Congress spends the money! Most of it seems to go to California! Perhaps we should stop all Federal payments west of the Rockies! Thank God I did not decide to go to Stanford!



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

Tuesday, February 20, 2018

[Told You So](#)

Some nine years ago when we started this process I noted that the Electronic Health Record, as proposed by the previous administration, would be a disaster. First it was designed by an academic, second it was driven by the Government, and third it was provider specific rather than patient specific.

Now comes [JAMA](#) and the [Harvard Gazette](#) who states:

Electronic health record systems doesn't reduce costs for bill processing. In fact, a study finds that it leaves primary care services with an average \$100,000 tab per provider.

Providers now have to hire scribes to record the EHR content. Each provider does not interconnect with others. For example in New York Presbyterian, a fairly decent provider, I have an ophthalmologist at Weill Cornell and a urologist at Columbia. The systems do not interconnect and they are on different platforms. Not that urology and ophthalmology need to connect, not even I can find a nexus, but there are many areas that demand a connection.

JAMA concludes:

In a time-driven activity-based costing study in a large academic health care system with a certified EHR system, the estimated costs of billing and insurance-related activities ranged from \$20 for a primary care visit to \$215 for an inpatient surgical procedure. Knowledge of how specific billing and insurance-related activities contribute to administrative costs may help inform policy solutions to reduce these expenses.

Overall this was a multi billion dollar expense, and its net result is more cost, reduced care, and increased overhead! Welcome to Government!



Labels: [Health Care](#)

[Cultural Exchange?](#)

The [Saudi Arab News](#) reports on a cultural exchange with the Irish Embassy. They note that at an exchange where an Irish film was aired to a large Saudi audience:

These festivals attempt to educate Saudis about different cultures and promote exchanges between Saudi Arabia and European countries. The film was screened on a moonlit veranda, and attendees enjoyed the film as well as the nice breeze that filled the open space. "Waking Ned" introduces Saudis to two best friends, Jackie O'Shea, played by Ian Bannen, and Michael O'Sullivan, played by David Kelly, as they chance upon someone in their village who has won the lottery and they want in on the cash. When the lottery winner dies from shock, the entire village rounds up to convince an inspector that O'Sullivan is the deceased to split the reward. "We chose this movie, as opposed to last year's horror film because we wanted to break routine. Everyone's joining us after a long day at work and they just want to relax," the office manager at the consulate, Rodaina Harb, told Arab News. "We wanted to display Irish culture, it's

beautiful music, the simplicity of their life, and to distinguish it, as most Saudis believe it to be a part of Britain, when it's its own country. in fact," she added. Fatima Mazin, a female in attendance told Arab News: "I thought the movie was hilarious, and the fact that the people put their wits together to fool someone and get that much money was very amusing."

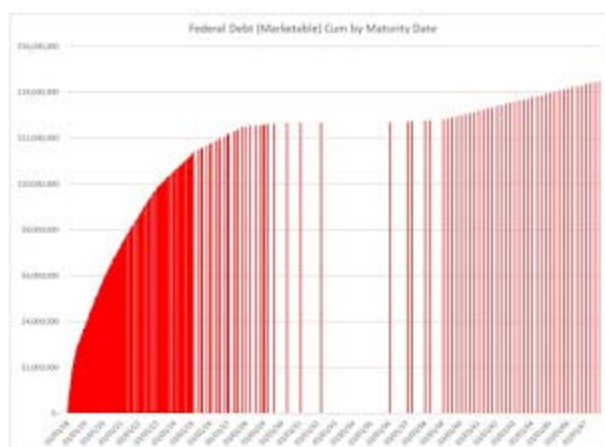
Now this is a bit of a strange cultural presentation. Humor can be a powerful tool if used properly. On the other hand one thing I learned is that one should never open a talk with a joke. They always backfire. And a movie about a dead winner and a couple of con artists is hardly a way to present a country.



Labels: [Culture](#)

Friday, February 9, 2018

[A Terrifying Chart](#)



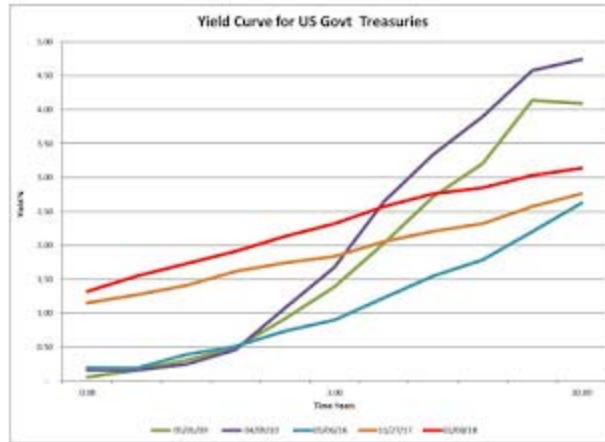
The chart above is the [Treasury debt](#), marketable, by maturity. Recall from the previous chart that we have seen the short term rates explode. Then look at the above and see that most of the debt is short term and will be turning over but at higher interest rates! So 6 trillion at a 2% interest rate change is an interest increase of \$120 billion. Just where is that in the Budget!



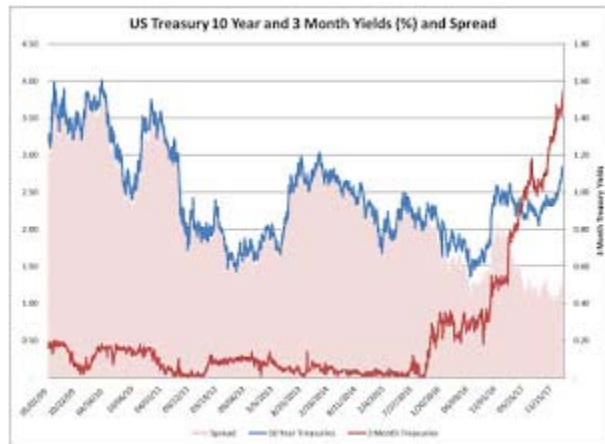
Labels: [Economy](#)

Friday, February 9, 2018

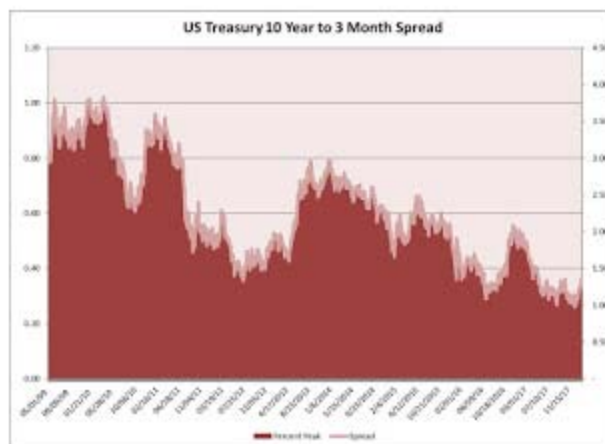
[Interest and the Market](#)



The yield curve shows two characteristics. First it is still flattening. Second it is rising.



The rise is worrisome but the lifting of the low rate is truly of concern. We have been presenting this for almost a year now. As the low end rises as rapidly as it does and as deficit increases as it is, then the cost of that debt, most of which is short term, explodes! The cycle becomes unstable.



The above is an example. We shall examine the FED balance sheet again as it unrolls debt, almost all worthless, and at the same time finances the excess. This could be a deadly embrace.



Labels: [Economy](#), [Yield Curve](#)

Thursday, February 1, 2018

[MIT and Student Unions](#)

[The Tech](#), the MIT student paper, notes a positive response to unionizing graduate students. They note:

Another survey question asked respondents to select which union-related issues they would want to see addressed in a collective bargaining agreement. Salary, healthcare, and housing came out on top — 65 to 70 percent of all respondents selected them. Most other issues fell in the 40 to 50 percent range, with the exception of safety, which only 30 percent “gave a shit about,” the committee wrote in its email. The exploratory committee that organized the survey consists of four PhD students who hope to initiate dialogue around the issue of graduate student unionization at MIT, although they are not explicitly pro-union. They requested to remain anonymous, for fear that if they were seen as leaders of an unionization movement, they would be subjected to “undue scrutiny” from administrators and disapproval from their advisors.

As I had noted when Harvard started this process, this is very dangerous. Getting a PhD is often an individual process, an examination of the candidates qualities not some groups. Now the article also notes:

167 of the survey respondents self-identified as PhD students, and 38 self-identified as Master’s students. Undergraduates and other MIT affiliates were also able to respond, but graduate student data was extracted and analyzed separately. Respondents ranked their level of support for a potential MIT graduate student union on a scale of 1 (“definitely oppose”) to 7 (“definitely support”). Overall, PhD students averaged 4.86, while Master’s students averaged 5.29.

Thus of the near 5,000 grad students this sample is 200+ which are less than randomly selected. I won't belabor the statistics of selection but in what appears to be an ever growing group-think, proto-socialistic environment, MIT may place itself in a perilous position. Schools like MIT rely upon alumni and Government support. There may come a point when these actions become the "last straw" and result in financial collapse, and loss of academic rigor.



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

Monday, January 22, 2018

[Scientific Snowflakes?](#)

The Government is back in session. However [The Scientist](#) notes, or shall we say bemoans:

Nature spoke with crop researcher Chad Hayes at the US Department of Agriculture whose travel to Mexico today—timed to coincide with a brief window of sorghum pollination—could be

disrupted, along with a year's worth of work. According to Vox, half of the Department of Health and Human Services staff will not work during the shutdown. That means that, while the Centers for Disease Control and Prevention (CDC) will continue to monitor this year's high flu activity, reports might take on a sluggish pace. "Under a shutdown, CDC's capacity to track and respond to disease outbreaks will be impacted," a CDC spokesperson tells BuzzFeed News. "Flu surveillance, for example, will continue to collect data being reported by states, hospitals, etc. However, our staff resources are limited, which means it will take longer to review, analyze, and report out information needed for public health action."

You can't make this up! CDC closing? Hardly. It was at most a day off! Sorghum pollination? You miss a day of pollination and the world comes to an end! Guys, I spent all June, July, and August crossing plants. Have done it for three decades! Don't get paid! Is there some personal satisfaction in participating in sorghum pollination?

This is why we need some careful attention to our tax dollars and what they are spent for!



Labels: [Government](#)

[AI, the Industrial Revolution and What Else?](#)

A Professor wrote a piece in [Project Syndicate](#). First I find the name a bit humorous since from New York we always assume a Syndicate is some Mafia like organization. So much for names.

The Professor tries to relate the AI revolution, whatever that is, to the Industrial Revolution. He states:

The elimination of countless cognitive tasks has alarming implications for the future. Just as the Industrial Revolution made most humans physically weaker, the AI revolution will make us collectively duller. In addition to flabby waistlines, we will have flabby minds. It's not the economy, stupid; it's the stupid economy. Already, central banks are urgently exploring new ways to dumb down their statements for an increasingly unsophisticated public. Mass stupidity will be driven by technology. But, as with the cult of physical fitness that took hold during the Industrial Revolution, a new industry of intelligence training will likely emerge to counter mental deterioration. Listening to someone constructing a logically articulated argument will become an exclusive source of aesthetic pleasure and distinction. "Difficult" works of literature or visual arts will become an ever more attractive form of conspicuous consumption. And yet something about this seems deeply unpleasant. It is bad enough to listen to people boast about their physical fitness. But braggadocio about superior intellect will be far worse. The need to prove oneself as a lasting relic of the old human supremacy will threaten not just the common good, but also our common humanity.

He basically relates that the Industrial Revolution led to Obesity and that the AI revolution will result in stupidity.

First, just what is this AI revolution. The Industrial Revolution was the replacement of machines for human work. Thus a engine driven plow replaced the horse drawn implement. Men could do

more, eat more, and get fat. In contrast he argues I believe that the AI revolution is that men, women too, will have to think less and get stupid. Now I find that difficult logic to follow. Obesity is a class issue more than a labor issue. Before the Industrial Revolution the wealthy were often obese as a showing of their wealth. Then after the Industrial Revolution the wealthy class was thin showing their self control. Thus will the same happen here? But the working class is not that smart to begin with and one wonders how more stupid they will become. The wealthy are not that smart as well, thus what will be the change. Again it comes back to the issue of; what is AI?

AI is simply a way to replace some machine function, possibly facilitated by human intervention, to an algorithm that when combined with a machine completes the same function. Thus AI in a simple manner replaced the telephone operator. Not very well I may add. The speech recognition is awful, the logic behind it is infantile, and the replacement is globally despised! I hazard to guess that an Industrial Revolution Replacement was less despised.

Take AI as espoused by IBM, the Watson thing. First as best I can understand no one really understands this. Is it just a marketing hype by a dying company? Is it real, does it work? I dread it ever going into the medical field. There may be a great many corpses before it can act as a First Year Med student.

So again, what is AI? It is simply a set of computer code that may have the possibility to adapt and "learn" Learn how? By mistakes. That is the way these systems work.

So will the AI Revolution lead to stupidity, more stupidity than there already is? Ride the Broadway Local, no one is reading a book or newspaper anymore. The train has no trash. That is good, but people are staring and clicking away telling their life story to the world. But such voices will be lost in the ether. They are no longer conversations at the Agora, interactions in the market, but just snarls and come backs that lead no where. Is this more stupidity? Not likely.

So is this Professor correct. Hardly. The Industrial Revolution was not a singular event. It has been happening throughout history. Rome lost its slaves, the Medieval Kingdoms lost their serfs, England gained its machines, so are we losing our brains? Again hardly.



Labels: [AI](#)

[Mothers - The Other Kind](#)



I was reading a NY Times piece, as usual, criticizing Trump³⁹[1]. It does get a bit long in the tooth but alas one must be patient with those of such limited resources. Then, add to this, the BBC has a discussion on le Carre's descriptives of MI6, the equivalent, if one stretches it, of the CIA⁴⁰[2]. The BBC notes the terms for Americans as:

Mothers – the typists and secretaries for senior MI6 officials.

Now Mothers in MI6 were a bit more than just that. You see, the Brits knew very well that operatives were often childlike, demanding, and ego driven, yet wanting for care and attention, and even more so control. Thus, one did not need an "office wife", as the NY Times so aptly asserts, but Mothers. The "hand that rocks the cradle" and all that stuff you know. One must have spent a bit of time in the land of the Queen to best understand just how this works. One does not need or want an "office wife", yet many of these folks need a "mother". A "mother" in this context has power, authority, respect, and can effect things that otherwise would just run amok. Mothers can over-rule, mothers can direct and govern, mothers are the Type A controls for a Type A personality. Furthermore, "mothers" are those points at which remediation of mess-ups can be attained. If there is a problem at a higher level, the lower level folks can go to "mother" to get things back aright again. You see, "mothers" are essential to the balancing act of complex organizations.

A few Presidents had "mothers". Just a few. Mothers are powerful figures, especially in an MI6 environment, dotted with Oxbridge boys, a very class based society, smart but with a bit of arrogance. Unlike our CIA which has become at times more akin the Department of Agriculture than a want to be MI6 as it was in the le Carre times.

³⁹[1] <https://www.nytimes.com/2018/01/20/opinion/donald-trump-and-his-work-wives.html?action=click&pgtype=Homepage&clickSource=story-heading&module=opinion-c-col-left-region®ion=opinion-c-col-left-region&WT.nav=opinion-c-col-left-region>

⁴⁰[2] <http://www.bbcamerica.com/anglophenia/2012/03/the-brit-list-tinker-tailor-glossary-20-terms-you-should-know-before-watching>

Did the CIA ever have its mothers? Not really, too un-American as the old boys would say. I also fear that too many American Presidents had let us say relationships that were anything but "motherly". Let us then leave the Kennedy, Clinton and others not to be mentioned. Yet, I do recall how my Russian partners would spark up when we had a problem and I told them to speak with "mother". They not only understood, but smiled because they clearly knew that "mother" would solve it for them. I thus often wondered if in Le Carre's world the KGB had its own version of "mothers", for it appeared as if they did.

Thus, perhaps instead of a "House Wife", as the Times suggests, what is really needed is a "House Mother", that stable hand to rock the unstable cradle.



Labels: [Politics](#)

Sunday, January 21, 2018

[1709 Failed](#)

I have an older laptop that was upgraded to Windows 10 from W7. The last upgrade, 1709, failed. I paid not attention since it is a spare system and updates to the new releases usually mess up a few dozen things anyhow. That is Microsoft. But have a few spare moments I went to see if I could remedy the problem. Solution, just go to Google, NEVER and I mean NEVER go to Microsoft. There on Google I found thousands of people with the same problem.

Then, [Microsoft](#) has some "Engineer" telling folks how to remedy this. The best part of the response was:

Method 4:

- 1. Open registry editor by running regedit.exe*
- 2. Back up the registry first before making changes to it*
- 3. Navigate to HKLM\System\CurrentControlSet\Control\Session Manager*
- 4. Check if PendingFileRenameOperations exists under the Session Manager key*
- 5. If it exists, please remove it*
- 6. Restart computer and check if issue persists*

If the issue persists, please follow the steps below and send the CBS log to the e-mail address in private message.

- 1. Rename the CBS.log(%systemroot%\Logs\CBS\CBS.log) to CBS.old*
- 2. Manually update the computer again and restart computer if needed*
- 3. Send the new generated CBS.log.*

If anything is unclear, please feel free to let me know.

Now for those of you who would dare to change a Registry, let me tell you, it is the holy of holies in Windows OS. It is where Microsoft places millions of landmines. Make one small change and not all others required and CRASH! Yep, down goes the machine and unrecoverable.

So my question is: where is the Class Action suit lawyers in this case. It has likely taken more productivity from our economy than anything Congress could screw up!

If Microsoft were a real company in a competitive market they would not last a femto second. They would have to remedy this. But alas, we all know where this is going. No where. Pity!



Labels: [Microsoft](#)

Thursday, January 18, 2018

[Video on Demand, Home Shopping](#)

The above was a brief clip of the Warner Cable TIES system of two way video on demand in 1982! Compare to Amazon.



Labels: [Internet](#)

[Corporate Culture](#)

The Wall Street Journal had a piece called *Of Furies and Fascism at Google*^{41[1]} In this piece they discuss a pending suit regarding termination of an employee who allegedly used the internal company communications system to express his opinion regarding certain employment practices. For that he was allegedly terminated. The article then notes:

Some predict Google will quickly settle to avoid discovery of more emails and postings, including from top management. What seems worse, from a public-relations perspective, is a culture inveterately hostile to the liberal principle “I may disagree with what you say but defend your right to say it.” This can’t be good in a business whose mission is to organize the world’s information. Messrs. Brin, Page and Pichai likely feel a tad helpless. The U.S. legal system imposes a need to be race-aware, gender-aware, etc.—to require quotas in all but name, since quotas are illegal. Google simultaneously faces lawsuits and regulatory investigations directed at its alleged shortchanging of women on pay and promotions. Its internal mood may also partly be a victim of self-esteem run amok. It’s a wonder many Googlers don’t worship Donald Trump—he also can’t tolerate to be disagreed with. A good, old-fashioned Presbyterian horror of self-

^{41[1]} See Wall Street Journal, <https://www.wsj.com/articles/of-furies-and-fascism-at-google-1516144969>

righteousness, once a feature of American life, is nowhere to be seen. Part of growing up is learning to live with your emotions; today's shortcut is to believe whatever your feelings are, they're justified. Humanity never met a dictator or demagogue who said, "I'm a bad person. I want to do bad things." The worst among us always feel justified.

Google apparently suffers from a common ailment; Corporate Culture. Companies get personalities and cultures as they mature. IBM had the IBM salesman, the man in the single color suit with white shirt, simple tie and a hat. You "trusted" this person to deliver your computer solution for which you paid an enormous price. The Watsons had THINK signs everywhere yet that oftentimes was the last thing an IBMer was expected to do. You were in my experience and in my opinion expected to sell the company line and the company products and services. Google started with "Don't be evil"^{42[2]}. They tried to position themselves as the good guys. Perhaps a result similar to IBM. In fact the Code as referred by the Washington Post states:

"Employees of Alphabet and its subsidiaries and controlled affiliates ('Alphabet') should do the right thing — follow the law, act honorably, and treat each other with respect," Alphabet's code of conduct reads. And: "We expect all of our employees and Board members to know and follow this Code of Conduct. Failure to do so can result in disciplinary action, including termination of employment. Any waivers of this Code for directors or executive officers must be approved by our Board."

Corporate culture evolves but it builds on the DNA of the company from which it started. In the Google case they hired what they saw as the "best" of the "best". The hired from a pool of millennials who were already predispositioned to see themselves as "special" and going to Google then made them the "most special". They were paid handsomely but given where they lived the cost of existence made the compensation modest at best. The best was some big win in a startup, perhaps. Thus one gets a collection of company DNA from this select group of "specials" along with the group think of a political mindset that as "specials" everyone else was not just mundane but effectively illiterate.

Moreover there were no role models. It was not like a Lockheed Skunk Works where a new employee could look towards "Kelly" Johnson as a role model. There was no hierarchy. The employees saw themselves generating what they did as if they were the first and only people to have conceived of and implemented what they produced. They were Googlers, like any group of synchronized thinkers, they could see the world through their own prism. Lacking "adult leadership", adults who themselves had demonstrated creative competence as well as leadership, a culture evolved, a culture more reflective of millennial values than any other.

^{42[2]} See Washington Post, October 5, 2016, Justin Moyer.

<https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=0ahUKEwiwt4LhzeHYAhVCja0KHchWDWMQFggpMAA&url=https%3A%2F%2Fwww.washingtonpost.com%2Fnews%2Fmorning-mix%2Fwp%2F2015%2F10%2F05%2Falphabet-now-googles-overlord-ditches-dont-be-evil-in-favor-of-do-the-right-thing%2F&usg=AOvVaw1m78ere68aA33GgbU3SO4u>

Corporate culture is a critical element in the long term success or failure of a company. That culture must support and nurture a corporate identity to the outside, it must enable a trust in the company and its offerings, it must embody the processes for a successful evolution of the company. Corporate culture also evolves to meet the challenges of a changing world and customer base. Failures of corporate cultures not so responding litter the landscape. Take GE, a company bred in the industrial 19th century, peaking in the mid to let 20th century and today appearing as a corporate dinosaur with no identity. Its culture mired in the past. IBM is a similar example, a company selling massively expensive almost one of a kind systems with obscenely expensive "support" then moving into a business based on consultancy and now attempting to market an erstwhile AI talking box.

For Google, Facebook and the Silicon Valley crowd of fast buck players, the time scales they may face are not a century long but more likely decades or even less. In a high tech environment change can occur suddenly. In the case of Google, their search engine is a valuable but fungible asset, supported by the advertising linked to the searches. In addition, the search engine provides massive marketing data which enhances the advertising revenue source. Thus a simple feedback. As long as the user trusts Google, then they, Google, will continue to have the "eyeballs" that can be monetized, unless the advertisers find that there is some form of disintermediation from a competing third party. Let me give an example. Half of what I use Google for, or even substantially more, is searching for technical papers. Semantic Scholar, one of Allen's entities, does a wonderful job. It is a tool, a focused and valuable tool, currently devoid of advertising. Thus in that past year my Google time has dropped dramatically. Take Facebook, I may have been a early adopter but I was also an early leaver. Why? Simple, too many people just saying stuff and linking me to it. I really did not want some friend's friend bemoaning their love life or lost cat. In contrast Research Gate is a vehicle to get my draft ideas out there, well more effective than just a web site. Thus there is highly focused disintermediation already in place.

How does corporate culture react to disintermediation? Let not use the in term, "disrupter", a termed most likely coined in the Valley. One does not disrupt, one gets in between, one can create and efficient "appliance". Instead of having an all in one kitchen appliance, one gets an attractive and highly effective "toaster" or "coffee maker".

Corporate cultures evolve as we noted. But the process whereby they are formed and then evolve is critical. The Google corporate culture is interesting in that the company went from a small entity in the late 1990s to a massive institution in the current time. But it did so in an environment for which there was no model to build on. Google type business did not exist, it was being invented on the fly. Compare this to Amazon. Amazon built a business where the difference was the introduction of an electronic marketing and distribution channel. But a channel that was displacing a physical one such as shopping malls. Thus it was well know what had to be done, albeit now electronically. Thus the corporate culture of an Amazon was delivering quality goods to the customer. Here we use quality as the amalgam of value, that is competitive prices, and trust, which means if you don't like it you can return it. That Amazon quality metric was what allowed it to work. It was aided also by the degradation of physical shopping. In even the best shopping malls the staff was rude, incompetent, low paid, and at best they were there to catch a shoplifter not service the customer. Amazon was helped by the degradation of customer service in what should have been their competition.

There are several questions worth examining:

1. How does one identify corporate culture? What are its characteristics? What types of corporate culture are there?

All of these are characterization questions. It is almost Aristotelian in nature to characterize or categorize culture in this manner⁴³[3]. The identification of a corporate culture is one thing and its categorization is another. One may ask if a culture of Type A is of that type because of a set of characteristics. What then are these characteristics.

2. What exogeneous factors form a corporate culture? Is it the time, the place, the people, the business, the competition? Perhaps all of these elements. Is there a west coast culture, versus say an east coast culture?

It seems clear that Silicon Valley has its own culture. However fifty years ago when it was all defense related the culture was dramatically different. It was the same place but different work, workers, and of course time. Is time the dominant factor or the change from Defense to software. Even twenty five years ago it was more hard core technology. With both hard core technology one had to have different corporate characteristics. Technical people needed experience, competence, and coordination. RF engineering for example was not easily learned and even less easily transformed to embodiments. Customers were few, many Government entities so building relationships was key. In a Google one could say they have no real nexus with their customers, there are so many and each contributes a miniscule amount.

3. Who is the formative agent for a corporate culture? Is the founder(s) the prime mover for culture? If not then is it from within or from without?

In a company like Tesla one can see Musk as an influencer on culture. In Apple it was Jobs, and unlikely Cook took his place. In Google? Good question. It may briefly have been the founders, but they were very technical and the investors brought in the "resident" adult as Chairman but he was less a manager than a "front" for the marketing of the company to investors. Currently Google has a CEO whose background reflects a rather interesting mix, just what would require a detailed study. But in Google as the WSJ article notes, the culture may be formed in a different way, namely like that in Golding's book, *Lord of the Flies*. Let us examine that for a moment.

In *Lord of the Flies* a group of young English school boys are being evacuated during the war, not specified, and their escape aircraft crashes and they end up on a island, with no other inhabitants. They are all young, all somewhat privileged, and all lacking in any skills in terms of dealing with groups. They are after all English school boys, public school boys. Two of them, Ralph and Piggy find a conch, and then the tale takes off. It details how groups and culture are formed, in this case a culture built on the *Lord of the Flies*, a pseudonym for the Devil. Several

⁴³[3] Aristotle's Categories are: Substance, Quality, Quantity, Relation, Time, Place, Position, Having, Action, And Passion. We could however take an Ockhamist view and minimize these to two.

of the young students are murdered at the hands of the others, they do not fit within the "culture". The end of the tale is the arrival of the adults, a Naval vessel to rescue the children. The savages, as their culture has turned them into, somehow under an adult revert to the school boys again. The Captain of the ship, now in control, looks at his battered ship in a recognition that the adult culture has similar savage behavior. New culture subsumed into old culture.

Now let us look at Golding and Lord of the Flies as a possible paradigm for the Silicon Valley cultures. In a sense it is a paradigm worth examining regarding corporate culture where the group is homogeneous, lacking maturity, somewhat isolated, and totally unhinged from any underlying ethical framework. Like Silicon Valley with tons of VC cash, lots of millennial youngsters all told how smart they are. Success is not curing cancer, solving poverty, or the like, success is achieving the most return in the shortest period of time with the minimal amount of know how. Coders are the typists of the 21st century. They do what they are told by the system architects, albeit cleverly and efficiently, hopefully.

Where the true problem will arise, however, is in the development of AI, where opinions which define the culture are made as part of the IF, THEN, ELSE statements in the new AI culture. If one sees Lord of the Flies in the Valley human culture, what then does one expect to see in this AI culture. It must be remembered that humans both age and die off. Thus the millennials are not here forever. Yet the AI bots and their off-spring may readily carry forth this culture in those elements of the AI choices that are made. We have people placing their judgements and values into AI statements. Do we stop for the little puppy, or just run it over and crush it like Piggy! Those value statements can become an integral part of the AI world. If we have any concern about the people and their human culture and its values perhaps then we should feel terrified about the AI culture they may leave behind!

Thus the question on the table is simple: is there a role for Government in regards to these dominant players? Is Antitrust law applicable? Some thirty years ago I studied in details the implications of antitrust on the information industry at the time. I argued that information, defined broadly, had the value in the food chain and little value was relegated to actual transport no matter how it evolved. Earlier I had developed an electronic marketing and distribution channel over CATV. Our model was more Ali Baba than Amazon, or at least as Amazon was. Yet we integrated information with transactions. It was a Google plus Amazon, thus its name; TIES or Transaction, Information, Entertainment Services. Great idea just twenty to thirty years too early! This teaches one that nothing is really new, just better timed.



Labels: [Commentary](#)

[Economics: Old and Older](#)

In a piece in [Project Syndicate](#), that left wing blog which seems to be a watering hole for economists and others espousing their political versions of reality, springs forth a defense of the economics, both old and older.

Skidelsky, a defender of Keynes and other left leaning purveyors of the art of economics states:

A decade ago, two schools of macroeconomists contended for primacy: the New Classical – or the “freshwater” – School, descended from Milton Friedman and Robert Lucas and headquartered at the University of Chicago, and the New Keynesian, or “saltwater,” School, descended from John Maynard Keynes, and based at MIT and Harvard. Freshwater-types believed that budgets deficits were always bad, whereas the saltwater camp believed that deficits were beneficial in a slump. Krugman is a New Keynesian, and his essay was intended to show that the Great Recession vindicated standard New Keynesian models. But there are serious problems with Krugman’s narrative. For starters, there is his answer to Queen Elizabeth II’s now-famous question: “Why did no one see it coming?” Krugman’s cheerful response is that the New Keynesians were looking the other way. Theirs was a failure not of theory, but of “data collection.” They had “overlooked” crucial institutional changes in the financial system. While this was regrettable, it raised no “deep conceptual issue” – that is, it didn’t demand that they reconsider their theory.

I believe there was and is a fundamental problem. Economics works best when looking backward. It fails almost continuously looking forwards. It can collect and analyze existing facts, yet it cannot use the facts in any predictive manner. Take the classic example of unemployment as predicted by Romer. She said we would drop to 5% in just a short while. It took nine years. Did unemployment eventually get there? Yes, but time is as important as the end point.

The Government under the last Administration threw ten trillion dollars at the problem, doubling the debt, and far exceeding anything that FDR ever contemplated. But when did the stock market respond, after a new Administration came. Was it in response to any new policy, perhaps.

Skidelsky continues:

Krugman comes close to acknowledging this: New Keynesians, he writes, “start with rational behavior and market equilibrium as a baseline, and try to get economic dysfunction by tweaking that baseline at the edges.” Such tweaks enable New Keynesian models to generate temporary real effects from nominal shocks, and thus justify quite radical intervention in times of emergency. But no tweaks can create a strong enough case to justify sustained interventionist policy. The problem for New Keynesian macroeconomists is that they fail to acknowledge radical uncertainty in their models, leaving them without any theory of what to do in good times in order to avoid the bad times. Their focus on nominal wage and price rigidities implies that if these factors were absent, equilibrium would readily be achieved. They regard the financial sector as neutral, not as fundamental (capitalism’s “ephor,” as Joseph Schumpeter put it).

Tweaking is what you do when the theory and data do not comport. Macro-economists should admit that their theories are pure speculation. Inherent in the macro world are the effects of externalities that all too often dominate the result. Radical uncertainties are pandemic in the current world environment. That demands leadership not economics.



Labels: [Economics](#)

Lipids and PCa, Again

There is a continuing proliferation of targets for the treatment of various cancers especially in prostate cancer, PCa. In a recent paper by Chen et al the authors note that targeting SREBP appears to have some significant efficacy. We briefly examine this approach and attempt to see if it has some value. This gene product has a multiplicity of functions from metabolic to immunologic. Thus as with any of these targets one must be cautious to not have severe unintended consequences.

Now from the recent article by Chen et al we have the following:

Lipids, either endogenously synthesized or exogenous, have been linked to human cancer. Here we found that PML is frequently co-deleted with PTEN in metastatic human prostate cancer (CaP).

We demonstrated that conditional inactivation of Pml in the mouse prostate morphs indolent Pten-null tumors into lethal metastatic disease. We identified MAPK reactivation, subsequent hyperactivation of an aberrant SREBP pro-metastatic lipogenic program, and a distinctive lipidomic profile as key characteristic features of metastatic Pml and Pten double-null CaP.

Furthermore, targeting SREBP in vivo by fatostatin blocked both tumor growth and distant metastasis. Importantly, a high-fat diet (HFD) induced lipid accumulation in prostate tumors and was sufficient to drive metastasis in a non-metastatic Pten-null mouse model of CaP, and an SREBP signature was highly enriched in metastatic human CaP.

Thus, our findings uncover a pro-metastatic lipogenic program and lend direct genetic and experimental support to the notion that a Western HFD can promote metastasis.

Now what is the function of SREBP?

SREBP44[1]: *In mammals, the transcription of several crucial genes required for lipid synthesis is activated by a small family of transcription factors called SREBPs (sterol response element binding proteins). A remarkable feature of SREBPs is that their entry into the nucleus depends on their release from the membrane by proteolysis (see the figure). During their synthesis, SREBPs are inserted into the membrane of the endoplasmic reticulum, a membranous network in the cytoplasm of the cell. In the endoplasmic reticulum, SREBPs form a complex with a membrane-embedded protein called SCAP, which escorts the SREBPs to another cellular compartment called the Golgi apparatus. Here, the SREBPs are sequentially cleaved by two Golgi-specific proteases, releasing a soluble fragment from the amino terminus. This fragment is a transcription factor, which, as a result of cleavage, is free to migrate to the nucleus, where it activates the expression of genes involved in the synthesis of cholesterol and fatty acids. Homeostasis is achieved by a negative feedback loop in which cholesterol and fatty acids block the proteolytic release of SREBPs from Golgi membranes. Interestingly, one of the SREBPs (SREBP-1c) is subject to an additional regulatory step that takes place at the promoter for*

⁴⁴[1] See <https://www.ncbi.nlm.nih.gov/gene/40155>

SREBP-1c itself. Fatty acids, the end products of the SREBP-1c pathway, inhibit the action of a transcription factor called LXR, which is required for optimal expression of the SREBP-1c gene.^{45[2]}

As Brown and Goldstein note:

As an end-product repressor, cholesterol presents a special problem because it is an insoluble lipid that resides almost exclusively in cell membranes. How does the cell sense the level of a membrane-embedded lipid, and how is that information transmitted to the nucleus to regulate transcription? Answers are emerging from studies of a novel family of membrane-bound transcription factors called sterol regulatory element binding proteins (SREBPs) that regulate multiple genes involved in cholesterol biosynthesis and uptake.

Here we review the SREBPs, focusing on the novel way in which sterols regulate their proteolytic release from membranes. Remarkably, insight into this processing may teach us about Alzheimer's disease, the most common degenerative disease of the brain, as well as coronary artery disease, the most common degenerative disease of the heart. Other aspects of SREBP physiology, such as the DNA binding activities and interactions with other transcription factors...

As Lewis et al note:

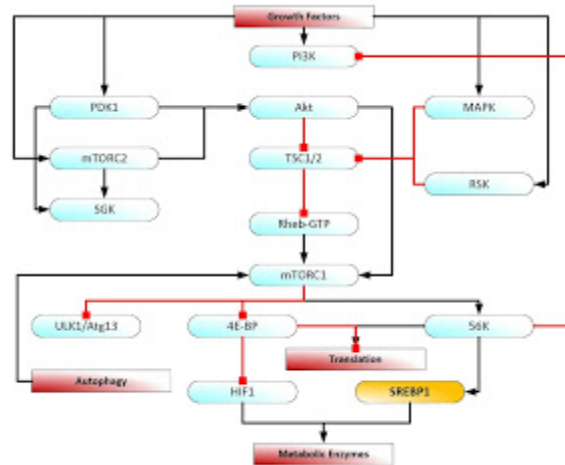
In recent years several reports have linked mTORC1 (mammalian target of rapamycin complex 1) to lipogenesis via the SREBPs (sterol-regulatory-element-binding proteins). SREBPs regulate the expression of genes encoding enzymes required for fatty acid and cholesterol biosynthesis. Lipid metabolism is perturbed in some diseases and SREBP target genes, such as FASN (fatty acid synthase), have been shown to be up-regulated in some cancers.

We have previously shown that mTORC1 plays a role in SREBP activation and Akt/PKB (protein kinase B)-dependent de novo lipogenesis. Our findings suggest that mTORC1 plays a crucial role in the activation of SREBP and that the activation of lipid biosynthesis through the induction of SREBP could be part of a regulatory pathway that co-ordinates protein and lipid biosynthesis during cell growth.

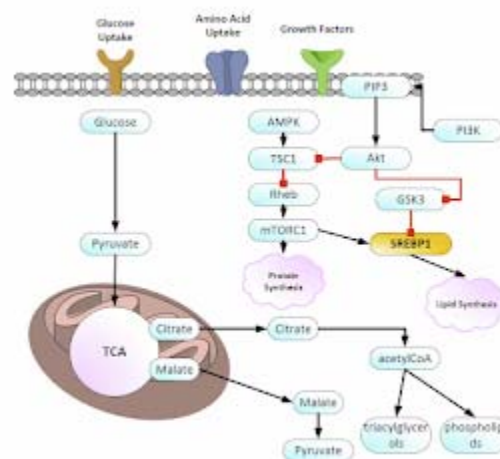
In the present paper, we discuss the increasing amount of data supporting the potential mechanisms of mTORC1-dependent activation of SREBP as well as the implications of this signalling pathway in cancer.

From Sengupta et al we have the following Figure:

^{45[2]} See Nohturfft and Losick



From Porstmann et al we have the following Figure which demonstrates a more complete metabolic set of interactions:

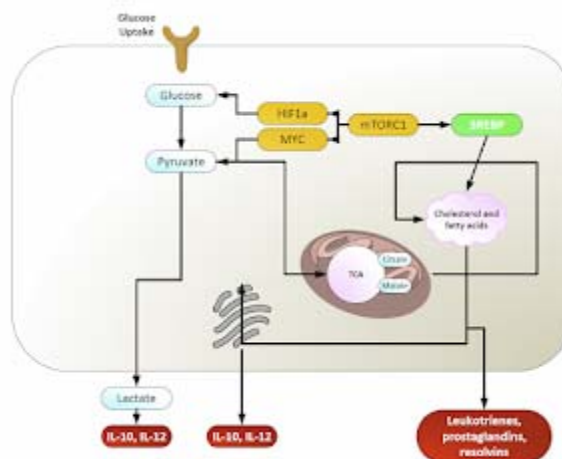


Now one also notes that there is a significant relationship also to the actions of the immune system. As Weichhart et al note:

Accumulating evidence suggests that innate immune cells also actively control metabolic processes to adapt and optimize their effector functions. These various effector functions are supported by an adaptation of energy metabolism to accommodate their metabolic needs and link their metabolism to the availability of nutrients. The mTOR network is a central regulator of many core metabolic processes. Activation of mTORC1 usually drives an anabolic response through hypoxia-inducible factor 1 α (HIF1 α), peroxisome proliferator-activated receptor- γ (PPAR γ), sterol regulatory element-binding proteins (SREBPs) and MYC that induces the synthesis of nucleic acids, proteins and lipids. In addition, it drives processes such as glycolysis and mitochondrial respiration to provide the cellular energy and building blocks for these responses. mTORC2 also enhances glycolytic metabolism by activating AKT and promoting an inactivating phosphorylation of class IIa histone deacetylases. This leads to the acetylation and

inactivation of forkhead box protein O1 (FOXO1) and FOXO3, which in turn activates MYC transcription.

From Weichhart et al we have the following Figure demonstrating the impact on the immune system:



The above immune interaction is a critical element in understanding the cross reaction of the control of metabolic genes perhaps for malignancy control and the operation of the immune system. It raises the question perhaps of unintended consequences.

Now we also have the overall control element of p53. As Parrales and Iwakuma note:

Mechanistically, mutant p53 binds to and activates SREBP, crucial transcription factors that regulate transcription of several enzymes involved in the mevalonate pathway, leading to enhanced prenylation of proteins associated with cancer progression and activation of prenylated proteins in breast cancer cells; hence, inhibition of protein prenylation by statins leads to reduced malignancy of human breast cancer cells.

Importantly, the presence of p53 mutation correlates with high expression of sterol biosynthesis genes in human breast tumors. Additionally, since nuclear localization and activation of the YAP and TAZ proto-oncogenes are regulated by prenylation and activation of Rho GTPases, statins could also suppress progression of mutant p53-expressing tumors by inhibiting YAP/TAZ activation by reducing protein prenylation of Rho GTPases, which is promoted by SREBP and its cofactor mutant p53.

Now the second element in the Chen et al system is PML. PML is characterized by NCBI as follows:

PML46[3]: *The protein encoded by this gene is a member of the tripartite motif (TRIM) family. The TRIM motif includes three zinc-binding domains, a RING, a B-box type 1 and a B-box type*

⁴⁶[3] <https://www.ncbi.nlm.nih.gov/gene/5371>

⁴⁶[4] <http://www.genecards.org/cgi-bin/carddisp.pl?gene=PML>

2, and a coiled-coil region. This phosphoprotein localizes to nuclear bodies where it functions as a transcription factor and tumor suppressor. Its expression is cell-cycle related and it regulates the p53 response to oncogenic signals. The gene is often involved in the translocation with the retinoic acid receptor alpha gene associated with acute promyelocytic leukemia (APL). Extensive alternative splicing of this gene results in several variations of the protein's central and C-terminal regions; all variants encode the same N-terminus. Alternatively spliced transcript variants encoding different isoforms have been identified.

Also from Genecards47[4]:

Functions via its association with PML-nuclear bodies (PML-NBs) in a wide range of important cellular processes, including tumor suppression, transcriptional regulation, apoptosis, senescence, DNA damage response, and viral defense mechanisms. Acts as the scaffold of PML-NBs allowing other proteins to shuttle in and out, a process which is regulated by SUMO-mediated modifications and interactions. Isoform PML-4 has a multifaceted role in the regulation of apoptosis and growth suppression: activates RB1 and inhibits AKT1 via interactions with PP1 and PP2A phosphatases respectively, negatively affects the PI3K pathway by inhibiting MTOR and activating PTEN, and positively regulates p53/TP53 by acting at different levels (by promoting its acetylation and phosphorylation and by inhibiting its MDM2-dependent degradation).

From a recent paper by Guan and Kao the authors provide a detailed overview of PML. They state:

The tumor suppressor protein, promyelocytic leukemia protein (PML), was originally identified in acute promyelocytic leukemia due to a chromosomal translocation between chromosomes 15 and 17. PML is the core component of subnuclear structures called PML nuclear bodies (PML-NBs), which are disrupted in acute promyelocytic leukemia cells. PML plays important roles in cell cycle regulation, survival and apoptosis, and inactivation or down-regulation of PML is frequently found in cancer cells. More than 120 proteins have been experimentally identified to physically associate with PML, and most of them either transiently or constitutively co-localize with PML-NBs. These interactions are associated with many cellular processes, including cell cycle arrest, apoptosis, senescence, transcriptional regulation, DNA repair and intermediary metabolism. Importantly, PML inactivation in cancer cells can occur at the transcriptional-, translational- or post-translational- levels. However, only a few somatic mutations have been found in cancer cells. A better understanding of its regulation and its role in tumor suppression will provide potential therapeutic opportunities. In this review, we discuss the role of PML in multiple tumor suppression pathways and summarize the players and stimuli that control PML protein expression or subcellular distribution.

The authors demonstrate the many pathway control and interaction functions that PML is involved in. Specifically:

1. DNA Damage Repair: This is accomplished via a complex set of interactions.

2. Transcriptional repression: This is done via a sequestration of the RB and E2Fs blockage.
3. Transcriptional Activation: This is via STAT1 and NF-kB activation amongst others.
4. AKT Pathway: This is via activation of PP2a, PTEN and eIF4e
5. p53 pathway: via SIRTq, MAPK1, HAUSP, and MDM2
6. Epigenetic Regulation: The various HDAC, SIRT, and EZH2.

are just a few the authors present in their Figure 4.

PML appears to Chen et al as a key element in the development of metastasis. It putatively also represents a therapeutic target.

Overall p53 and metabolism are intertwined and PML has that role in the regulation of p53. From Flotter et al we have the detailed dynamics. Flotter et al note:

Tumour development is accompanied by changes in cellular metabolic activity, which allows cancer cells to grow and proliferate under adverse conditions. The influence of p53 on cellular metabolism is complex and involves multiples nodes of regulation. p53 changes the activity of multiple metabolic pathways, including glycolysis, mitochondrial oxidative phosphorylation and fatty acid synthesis via transcriptional and non-transcriptional regulation. In addition, p53 governs the adaptation of cancer cells to nutrient and oxygen deprivation, which is crucial for the survival under the metabolically compromised conditions shaped by the tumour microenvironment. Importantly, it has been shown that the regulation of metabolic activity is essential to the tumour suppressive function of p53

Finally Chen et al conclude:

Our data provide a strong genetic foundation elucidating the mechanisms underlying metastatic progression, and they demonstrate how environmental dietary factors can boost progression from primary to metastatic cancer, intertwining with the genetic makeup of cancer.

We demonstrated that SREBP- dependent lipogenesis, which can be hyperactivated by concomitant activation of the PI3K-AKT and MAPK pathways, or a HFD regimen, functions as an underlying rheostat toward metastatic cancer progression.

Furthermore, we identified PML as a critical mediator of feedback inhibition of MAPK signaling and lipogenesis, and its inactivation propels metastatic progression in cancers driven by PTEN loss and PI3K- AKT activation.

...Numerous mechanisms have been proposed to explain a possible association between dietary lipids and CaP67, including paracrine mechanisms through secreted cytokines from adipose tissues, endocrine mechanisms through alteration of androgen levels and an induction of basal-to-luminal cell differentiation caused by immune-cell infiltration. However, we showed here that specific genetic perturbations or a HFD are probably able to exert a direct effect on metastasis through increased lipid accumulation.

We also characterized the intracellular lipid changes in GEMMs of CaP and detected qualitative changes in four different lipid classes as well as in the saturation of fatty acyl chains. Together, these results established a strong mechanistic and causal link among aberrant lipogenesis, excess lipid accumulation and metastasis, thus providing a compelling rationale for integrating lifestyle data (for example, diet) and tumor genetics into clinical practice to identify patients at high risk of metastasis.

Additionally, lipid metabolism itself is an attractive therapeutic target through inhibition of lipogenic enzymes. Notably, such inhibition decreases CaP cell viability only in the absence of an exogenous lipid source such as lipoprotein, thereby highlighting the importance of integrating pharmacologic approaches with stringent dietary regimens to prevent metastasis. Future studies are warranted to evaluate whether specific lipid subsets/signatures may serve as prognostic biomarkers to distinguish CaP with metastatic potential from indolent disease.

Finally, given that PML is lost in human cancer of multiple histological origins, our study suggests that PML loss may underlie MAPK activation in cancers lacking genetic alterations in MAPK-signaling components. ...

This finding has equally important implications for tumorigenesis, because PML loss in the hypoxic core or tumoral lesions not only would activate mTOR, thus resulting in sustained HIF-1 activation, but also would relieve the feedback inhibition of MAPK signaling triggered by mTOR activation, thereby leading to simultaneous activation of both mTOR and MAPK signaling.

Together, our results provide a potential roadmap for targeted therapies tailored to individual patients for the prevention and treatment of metastatic cancer.

Thus is this proposal based upon the experimental identification of PML warranting of a therapeutic targeting? Everything is worth examining, yet the complexity of the interactions, especially with the immune system raises some concern. Chen et al note in their paper:

...PML loss might represent cooperative predictors of overall survival after prostatectomy. Tissue microarray (TMA) analysis was performed in prostatectomy specimens from 144 men with primary CaP. Loss of PTEN and/or PML was significantly correlated with disease progression. Complete loss of PTEN and PML at the protein level occurred in 15% of the high-grade CaP samples, but not in the low-grade CaP samples.

It is well known as to the effect of PTEN. Chen et al argue for a pari passu positioning of PML.

This is an interesting result but it is a long way from any therapeutic targeting. The complexity of the PNL signalling does imply a complex set of unintended consequences that must be explored.

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Labels: [Cancer](#)

Tuesday, January 16, 2018

[Bayeux](#)

The [BBC reports](#) that the Bayeux Tapestry will be on exhibit on loan from France in the relatively near future.



The BBC report notes it is an offer from Macron. The BBC states:

Mr Macron's offer comes after previous attempts to bring the tapestry to Britain failed. One request is thought to have been made ahead of the Queen's Coronation in 1953, while another was made for the 900th anniversary of the Battle of Hastings, in 1966. Historians have long debated the origins of the tapestry. Some say it was created by teams of nuns across England - not France - possibly in Canterbury, Kent.

I saw this in the museum in Bayeux and my Latin was still well enough up to date to read this 11th century tapestry. Hitler was believed to seek it since he believed it held the power to defeat the British. Notwithstanding, it is a wonderful piece of history that must be seen by any who want to better understand European history.



Labels: [Commentary](#)

[Fault Tree Analysis](#)

Fault Tree Analysis is a fifty year plus old technique often mandated on sensitive systems. I used it in the 70s on certain nuclear weapons analyses. The approach is to document all the steps possible and then to assess what would happen if one or more were incorrectly performed, or failed, and then ascertain the consequence. Usually they could be dramatic in the nuclear field, so then you remedied the situation.

We always understood that "words mean something" so that we carefully tried to understand the commands and make certain there was no ambiguity.

Now to the Hawaii fiasco. Clearly the state folks were clueless. But the consequences of that clueless behavior could have been devastating. The system needs a total overhaul, starting at the top, the very top. But politics being politics one just sees deflection. The discussion in [ArsTechnica](#) details the clear incompetence. They note:

It appears the employee who sent out the mobile and broadcast missile alert that sent Hawaii into a panic for 38 minutes on Saturday was supposed to choose "DRILL - PACOM (CDW) - STATE ONLY" but instead chose "PACOM (CDW) - STATE ONLY" from an unordered list of equally unintuitive and difficult-to-read options.

Think Fault Tree Analysis in broad scopes.



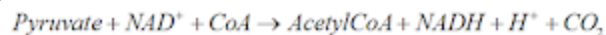
Labels: [Nuclear Weapons](#)

Tuesday, January 16, 2018

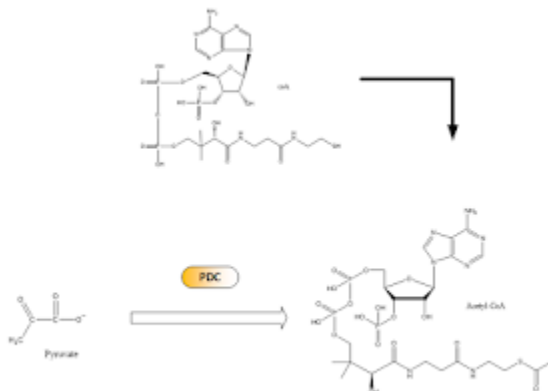
[Warburg and Prostate Cancer](#)

We have recently discussed the Warburg effect and cancers. Recent studies have brought this effect to the fore as a possible means to control prostate cancer, PCa.

Recall that the general process internal to the mitochondria can be written as follows.



Specifically we have:



Pyruvate feeds the TCA cycle, it is a result of glycolysis. In contrast, aerobic glycolysis, the Warburg effect is a mix of both the TCA plus anaerobic glycolysis, namely no oxygen. The enzyme PDC enables this process. This we depict above. Pyruvate is the product of glycolysis and AcetylCoA is the feeder to the TCA.

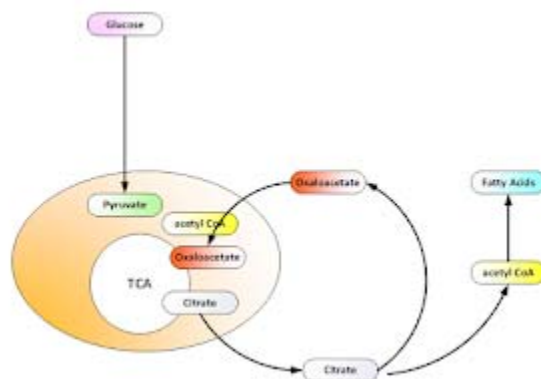
Lipids, Warburg and PCa

We know that lipids play a role in carcinogenesis. As Hsu and Sabatini note:

Although studies in cancer metabolism have largely been energy-centric, rapidly dividing cells have diverse requirements. Proliferating cells require not only ATP but also nucleotides, fatty acids, membrane lipids, and proteins, and a reprogrammed metabolism may serve to support synthesis of macromolecules. Recent studies have shown that several steps in lipid synthesis are required for and may even actively promote tumorigenesis. Inhibition of ATP citrate lyase, the distal enzyme that converts mitochondrial-derived citrate into cytosolic acetyl coenzyme A, the precursor for many lipid species, prevents cancer cell proliferation and tumor growth (Hatzivassiliou et al., 2005).

Fatty acid synthase, expressed at low levels in normal tissues, is upregulated in cancer and may also be required for tumorigenesis (reviewed in Menendez and Lupu, 2007). Furthermore, cancer cells may also enhance their biosynthetic capabilities by expressing a tumor-specific form of pyruvate kinase (PK), M2-PK. Pyruvate kinase catalyzes the third irreversible reaction of glycolysis, the conversion of phosphoenolpyruvate (PEP) to pyruvate. Surprisingly, the M2-PK of cancer cells is thought to be less active in the conversion of PEP to pyruvate and thus less efficient at ATP production.

A simplified version of this in Bauer et al is shown below:



Flavin et al also noted:

Cancer cells synthesize de novo large amounts of fatty acids and cholesterol, irrespective of the circulating lipid levels and benefit from this increased lipid synthesis in terms of growth advantage, self-survival and drug resistance. Key lipogenic alterations that commonly occur in prostate cancer include over-expression of the enzyme fatty acid synthase (FASN) and deregulation of the 5-AMP-activated protein kinase (AMPK). FASN is a key metabolic enzyme that catalyses the synthesis of palmitate from the condensation of malonyl-CoA and acetyl-CoA de novo and plays a central role in energy homeostasis, by converting excess carbon intake into fatty acids for storage. AMPK functions as a central metabolic switch that governs glucose and lipid metabolism. Recent interest has focused on the potential of targeting metabolic pathways that may be altered during prostate tumorigenesis and progression. Several small molecule inhibitors of FASN have now been described or in development for therapeutic use; in addition, drugs that directly or indirectly induce AMPK activation have potential benefit in prostate cancer prevention and treatment^{48[1]49[2]}.

^{48[1]} FASN from NCBI: The enzyme encoded by this gene is a multifunctional protein. Its main function is to catalyze the synthesis of palmitate from acetyl-CoA and malonyl-CoA, in the presence of NADPH, into long-chain saturated fatty acids. In some cancer cell lines, this protein has been found to be fused with estrogen receptor-alpha (ER-alpha), in which the N-terminus of FAS is fused in-frame with the C-terminus of ER-alpha.

<https://www.ncbi.nlm.nih.gov/gene/2194>

^{49[2]} AMPK from NCBI: The protein encoded by this gene belongs to the ser/thr protein kinase family. It is the catalytic subunit of the 5'-prime-AMP-activated protein kinase (AMPK). AMPK is a cellular energy sensor conserved in all eukaryotic cells. The kinase activity of AMPK is activated by the stimuli that increase the cellular AMP/ATP ratio. AMPK regulates the activities of a number of key metabolic enzymes through phosphorylation. It protects cells from stresses that cause ATP depletion by switching off ATP-consuming biosynthetic pathways. Alternatively spliced transcript variants encoding distinct isoforms have been observed.

<https://www.ncbi.nlm.nih.gov/gene/5562>

Prostate cancer and lipid metabolism has been studied extensively. Now in a recent report in Science Daily it states⁵⁰[3]:

For years, attempts have been made to understand the mechanism behind the proliferation of cancer cells: they need metabolites to grow and proliferate as much as a vehicle needs gasoline or electricity to move. However, until now it was not known which metabolites cancer cells actually need. A team of researchers from the Institute of Oncology Research (IOR) at the Università della Svizzera Italiana (USI, Faculty of Biomedical Sciences) led by Prof. Andrea Alimonti has identified one of the mechanisms behind this process, as published in a recent article in the journal Nature Genetics.

From a theory dating back to the early 20th century by Nobel Prize laureate Otto Warburg, it has been believed that, in order to support their growth, cancer cells needed to increase their glucose consumption, without using mitochondrial metabolism. The mitochondrion is an organelle that produces the energy needed for the cell survival, operating as a sort of power station. "Contrary to what was believed for almost a century -- says Prof. Alimonti -- we have discovered that cells in prostate cancer need the mitochondrion, not to produce energy, rather to regulate a specific metabolic process.

Specifically, the mitochondrion is able to regulate fat synthesis (lipids) through an enzyme complex called PDC.

Thus the glycolysis is but one part. Lipid metabolism is a second, and we have discussed this earlier as well. PDC is used on the classic glycolysis and TCA. Here they argue PDC is used in the mitochondria to regulate lipid development.

The study published by Nature Genetics shows that without the ability to efficiently produce lipids, prostate cancer cells are not able to grow and metastasize, even in the presence of increased glycolysis. "We noticed -- continues Alimonti -- that in prostate cancer cells the activity of the enzyme complex PDC is 10 times that of a normal proliferating cell, and that as a result the cells store several lipids."

As noted above, PDC is the enzyme in the connection between glycolysis and the TCA.

It is known that a diet rich in fat can increase the risk of developing prostate cancer, and that obese people are more prone to develop this type of tumour. However, the fact that the metabolism of lipids acts as a fuel to support the tumour has never been clarified in detail and this discovery opens up new and unexpected scenarios in cancer therapy.

"We have identified a number of pharmaceutical compounds that selectively inhibit -- in different experimental models -- the mitochondrial enzyme responsible for the tumour growth, thus limiting fat synthesis and without harming normal cells." "I would like to point out, however -- concludes Alimonti -- that our discovery does not imply that cancer patients must undergo a

⁵⁰[3] <https://www.sciencedaily.com/releases/2018/01/180115121635.htm>

strict dietary regime, which might in fact hurt them: a reduction of fat in cancer cells can only be obtained by blocking the cancer cells metabolism through specific drugs."

The authors of the above references paper, Chen et al, note:

The mechanisms by which mitochondrial metabolism supports cancer anabolism remain unclear. Here, we found that genetic and pharmacological inactivation of pyruvate dehydrogenase A1 (PDHA1), a subunit of the pyruvate dehydrogenase complex (PDC), inhibits prostate cancer development in mouse and human xenograft tumor models by affecting lipid biosynthesis. Mechanistically, we show that in prostate cancer, PDC localizes in both the mitochondria and the nucleus.

Whereas nuclear PDC controls the expression of sterol regulatory element-binding transcription factor (SREBF)-target genes by mediating histone acetylation, mitochondrial PDC provides cytosolic citrate for lipid synthesis in a coordinated manner, thereby sustaining anabolism. Additionally, we found that PDHA1 and the PDC activator pyruvate dehydrogenase phosphatase 1 (PDP1) are frequently amplified and overexpressed at both the gene and protein levels in prostate tumors.

Together, these findings demonstrate that both mitochondrial and nuclear PDC sustain prostate tumorigenesis by controlling lipid biosynthesis, thus suggesting this complex as a potential target for cancer therapy.

Now PDHA1 is a part of the PDC. From NCBI51[4]:

The pyruvate dehydrogenase (PDH) complex is a nuclear-encoded mitochondrial multienzyme complex that catalyzes the overall conversion of pyruvate to acetyl-CoA and CO₂, and provides the primary link between glycolysis and the tricarboxylic acid (TCA) cycle. The PDH complex is composed of multiple copies of three enzymatic components: pyruvate dehydrogenase (E1), dihydrolipoamide acetyltransferase (E2) and lipoamide dehydrogenase (E3). The E1 enzyme is a heterotetramer of two alpha and two beta subunits. This gene encodes the E1 alpha 1 subunit containing the E1 active site, and plays a key role in the function of the PDH complex. Mutations in this gene are associated with pyruvate dehydrogenase E1-alpha deficiency and X-linked Leigh syndrome.

There are two SREBF genes. Again from NCBI:

SREBF152[5](SREBP1): This gene encodes a basic helix-loop-helix-leucine zipper (bHLH-Zip) transcription factor that binds to the sterol regulatory element-1 (SRE1), which is a motif that is found in the promoter of the low density lipoprotein receptor gene and other genes involved in sterol biosynthesis. The encoded protein is synthesized as a precursor that is initially attached to

⁵¹[4] <https://www.ncbi.nlm.nih.gov/gene/5160>

⁵²[5] <https://www.ncbi.nlm.nih.gov/gene/6720>

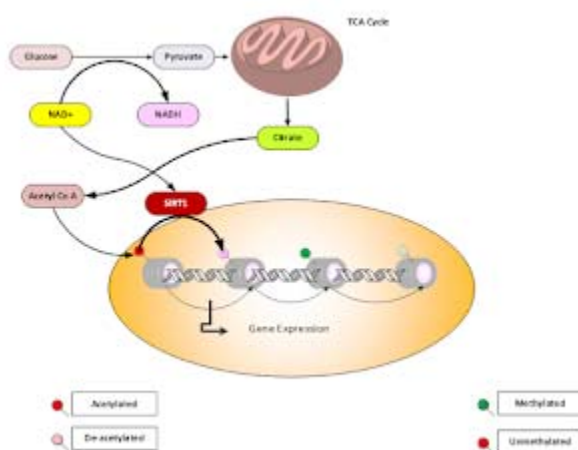
the nuclear membrane and endoplasmic reticulum. Following cleavage, the mature protein translocates to the nucleus and activates transcription. This cleavage is inhibited by sterols. This gene is located within the Smith-Magenis syndrome region on chromosome 17. Alternative promoter usage and splicing result in multiple transcript variants, including SREBP-1a and SREBP-1c, which correspond to RefSeq transcript variants 2 and 3, respectively.

and

SREBF253[6] (SREBP2): *This gene encodes a member of the a ubiquitously expressed transcription factor that controls cholesterol homeostasis by regulating transcription of sterol-regulated genes. The encoded protein contains a basic helix-loop-helix-leucine zipper (bHLH-Zip) domain and binds the sterol regulatory element 1 motif. Alternate splicing results in multiple transcript variants.*

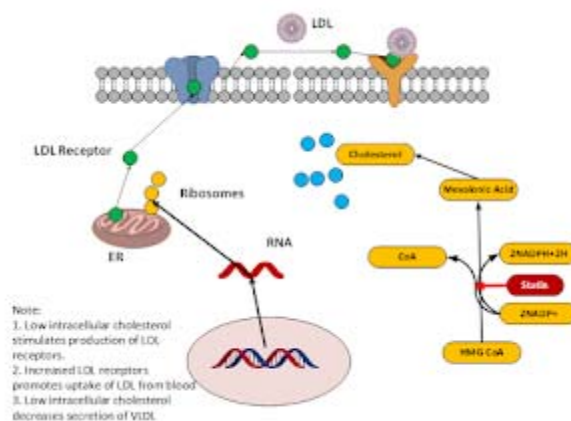
Extensions

We do know the impact of the TCA on androgen receptor as shown below:



Alaso as detailed below we have:

⁵³[6] <https://www.ncbi.nlm.nih.gov/gene/6721>



As McFate et al note:

High lactate generation and low glucose oxidation, despite normal oxygen conditions, are commonly seen in cancer cells and tumors. Historically known as the Warburg effect, this altered metabolic phenotype has long been correlated with malignant progression and poor clinical outcome.

However, the mechanistic relationship between altered glucose metabolism and malignancy remains poorly understood.

Here we show that inhibition of pyruvate dehydrogenase complex (PDC) activity contributes to the Warburg metabolic and malignant phenotype in human head and neck squamous cell carcinoma. PDC inhibition occurs via enhanced expression of pyruvate dehydrogenase kinase-1 (PDK-1), which results in inhibitory phosphorylation of the pyruvate dehydrogenase (PDH) subunit. We also demonstrate that PDC inhibition in cancer cells is associated with normoxic stabilization of the malignancy-promoting transcription factor hypoxia-inducible factor-1 (HIF-1) by glycolytic metabolites.

Knockdown of PDK-1 via short hairpin RNA lowers PDH phosphorylation, restores PDC activity, reverts the Warburg metabolic phenotype, decreases normoxic HIF-1 expression, lowers hypoxic cell survival, decreases invasiveness, and inhibits tumor growth. PDK-1 is an HIF-1-regulated gene, and these data suggest that the buildup of glycolytic metabolites, resulting from high PDK-1 expression, may in turn promote HIF-1 activation, thus sustaining a feed-forward loop for malignant progression.

In addition to providing anabolic support for cancer cells, altered fuel metabolism thus supports a malignant phenotype. Correction of metabolic abnormalities offers unique opportunities for cancer treatment and may potentially synergize with other cancer therapies.

As Fan et al note:

The mitochondrial pyruvate dehydrogenase complex (PDC) plays a crucial role in regulation of glucose homeostasis in mammalian cells.

PDC flux depends on catalytic activity of the most important enzyme component pyruvate dehydrogenase (PDH). PDH kinase inactivates PDC by phosphorylating PDH at specific serine residues, including Ser-293, whereas dephosphorylation of PDH by PDH phosphatase restores PDC activity. The current understanding suggests that Ser-293 phosphorylation of PDH impedes active site accessibility to its substrate pyruvate.

Here, we report that phosphorylation of a tyrosine residue Tyr-301 also inhibits PDH 1 (PDHA1) by blocking pyruvate binding through a novel mechanism in addition to Ser-293 phosphorylation. In addition, we found that multiple oncogenic tyrosine kinases directly phosphorylate PDHA1 at Tyr-301, and Tyr-301 phosphorylation of PDHA1 is common in EGF-stimulated cells as well as diverse human cancer cells and primary leukemia cells from human patients.

Moreover, expression of a phosphorylation-deficient PDHA1 Y301F mutant in cancer cells resulted in increased oxidative phosphorylation, decreased cell proliferation under hypoxia, and reduced tumor growth in mice. Together, our findings suggest that phosphorylation at distinct serine and tyrosine residues inhibits PDHA1 through distinct mechanisms to impact active site accessibility, which act in concert to regulate PDC activity and promote the Warburg effect.

The Warburg effect is clear in the above. Its presence disappears when examining lipid metabolism, however. This point is further emphasized as Zhong et al note:

Cells generate adenosine-5'-triphosphate (ATP), the major currency for energy consuming reactions, through mitochondrial oxidative phosphorylation (OXPHOS) and glycolysis. One of the remarkable features of cancer cells is aerobic glycolysis, also known as the "Warburg Effect", in which cancer cells rely preferentially on glycolysis instead of mitochondrial OXPHOS as the main energy source even in the presence of high oxygen tension.

One of the main players in controlling OXPHOS is the mitochondrial gatekeeper pyruvate dehydrogenase complex (PDHc) and its major subunit is E1 α (PDHA1). To further analyze the function of PDHA1 in cancer cells, it was knock out (KO) in the human prostate cancer cell line LnCap and a stable KO cell line was established. We demonstrated that PDHA1 gene KO significantly decreased mitochondrial OXPHOS and promoted anaerobic glycolysis, accompanied with higher stemness phenotype including resistance to chemotherapy, enhanced migration ability and increased expression of cancer stem cell markers. We also examined PDHA1 protein expression in prostate cancer tissues by immunohistochemistry and observed that reduced PDHA1 protein expression in clinical prostate carcinomas was significantly correlated with poor prognosis.

Collectively, our results show that negative PDHA1 gene expression is associated with significantly higher cell stemness in prostate cancer cells and reduced protein expression of this gene is associated with shorter clinical outcome in prostate cancers.....

We herein demonstrated that PDHA1 gene knockout resulted in dysfunctional mitochondrial OXPHOS and enhanced glycolysis. We previously reported that impartial mitochondrial OXPHOS by using mitochondrial pyruvate carrier (MPC) blocker enhanced stemness phenotype of prostate cancer cells. In keeping with our previously study, the mitochondrial gatekeeper PDHA1 gene knockout also leads to dysfunctional mitochondrial and enhanced glycolysis, as well as higher cell stemness phenotype. And by immuno-histochemical examination of PDHA1 protein expression in prostate cancer samples, it was revealed that negative PDHA1 protein expression was related with poor clinical outcome in patients with prostate cancer.

As Li et al note:

Alternative pathways of metabolism endowed cancer cells with metabolic stress. Inhibiting the related compensatory pathways might achieve synergistic anticancer results. This study demonstrated that pyruvate dehydrogenase E1 α gene knockout (PDHA1 KO) resulted in alterations in tumor cell metabolism by rendering the cells with increased expression of glutaminase1 (GLS1) and glutamate dehydrogenase1 (GLUD1), leading to an increase in glutamine-dependent cell survival. Deprivation of glutamine induced cell growth inhibition, increased reactive oxygen species and decreased ATP production.

Pharmacological blockade of the glutaminolysis pathway resulted in massive tumor cells apoptosis and dysfunction of ROS scavenge in the LNCaP PDHA1 KO cells. Further examination of the key glutaminolysis enzymes in human prostate cancer samples also revealed that higher levels of GLS1 and GLUD1 expression were significantly associated with aggressive clinicopathological features and poor clinical outcome. These insights supply evidence that glutaminolysis plays a compensatory role for cell survival upon alternative energy metabolism and targeting the glutamine anaplerosis of energy metabolism via GLS1 and GLUD1 in cancer cells may offer a potential novel therapeutic strategy.

As Justus et al note:

There are several molecular mechanisms whereby acidosis may alter tumor cell metabolism. p53 is an important regulator of the metabolic response to acidosis. The ability of acidosis to activate p53 and stimulate the TCA cycle through inhibition of glycolysis has been demonstrated. For example, acidosis induced p53 expression may transcriptionally inhibit the expression of glucose transporters GLUT1 and GLUT4 in specific tissues, thereby effectively reducing glucose availability for glycolysis. In addition, acidosis is reported to activate p53 and increase expression of glucose 6 phosphate dehydrogenase (G6PD) and glutaminase 2.

This is suggested to direct glucose towards the pentose phosphate pathway (PPP) as well as increase glutaminolysis. This may also drive the TCA cycle through the production of metabolic intermediates and increase the amount of NADPH in the cell to counteract ROS production. p53 activation may also induce the expression of Parkin (PARK2), a Parkinson disease-associated gene, to reduce glycolytic activity.

PARK2 regulates the expression of pyruvate dehydrogenase alpha 1 (PDHA1), a critical component for the activity of pyruvate dehydrogenase (PDH). PDHA1 knockdown increases

glucose uptake, rate of glycolysis, and lactate production, facilitating the “Warburg effect”. This gives PARK2 the ability to effectively reverse the “Warburg effect” by inducing PDHA1.

Moreover, PARK2 also regulates expression of reduced glutathione (GSH), a major antioxidant and ROS scavenger in the cell. This is proposed to occur through activation of p53 and may reduce ROS when oxidative phosphorylation is increased. Furthermore, γ -irradiation-induced tumorigenesis is sensitized following the knockout of PARK2 in C57BL/6J mice, indicating the PARK2 gene as a tumor suppressor.

The ability for p53 to regulate cancer cell metabolism by reducing glycolysis and increasing oxidative phosphorylation while simultaneously mitigating ROS is crucial for understanding acidosis induced metabolic alterations in the tumor.

Observations

We can make a few observations.

1. Warburg effect generally refers to glycolysis and the reduced production of ATP. It indirectly refers to any lipid processing. Fatty acid oxidation can produce an estimated 129 ATP per oxidation^{54[7]}. This is a large producer of energy and well exceeds that of glycolysis results. Thus considering the lipid elements as conjoint is highly reasonable.

Lipids are also energy rich as noted above. Perhaps cancer cells can function in this manner if the throughput of lipids can be high.

Targets for therapeutics using the lipid control may have potential deleterious effects. If the proposal is to target the enzyme in the production of ultimately ATP from lipids then one must be aware of the significant downside regarding cross cell contamination.

This is an interesting and useful alternative and again shows that there are many options about the Warburg process.

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Labels: [Cancer](#)

Saturday, January 13, 2018

[Yep, Here's the USPS](#)

I have a package being sent Priority and here is the current status. Yes, it started in Glendale and on its way here was sent to New Orleans! These folks are as bad as AMTRAK. Think colonoscopy and Government Healthcare! That little endoscope goes on through your stomach, heart, lungs, and may even take a venture outside for a while. We pay these folks quite well plus benefits!

Saturday, January 13, 2018 at 12:14 PM	In Transit to Destination	On its way to FLORHAM PARK, NJ
Friday, January 12, 2018 at 12:14 PM	In Transit to Destination	On its way to FLORHAM PARK, NJ
Thursday, January 11, 2018 at 7:14 PM	Departed USPS Regional Facility	NEW ORLEANS LA DISTRIBUTION CENTER
Thursday, January 11, 2018 at 12:26 PM	In Transit to Destination	On its way to FLORHAM PARK, NJ

Wednesday, January 10, 2018 at 5:26 PM	Arrived at USPS Regional Facility	NEW ORLEANS LA DISTRIBUTION CENTER
Wednesday, January 10, 2018 at 12:38 PM	In Transit to Destination	On its way to FLORHAM PARK, NJ
Tuesday, January 9, 2018 at 3:38 PM	Arrived at USPS Regional Origin Facility	ELK GROVE VILLAGE IL DISTRIBUTION CENTER
Tuesday, January 9, 2018 at 2:23 PM	Accepted at USPS Regional Origin Facility	CHICAGO IL NETWORK DISTRIBUTION CENTER
Saturday, January 6, 2018 at 6:24 AM	Arrived Shipping Partner Facility, USPS Awaiting Item	GLENDALE HEIGHTS, IL



Labels: [Government](#)

[Newsfeeds](#)

There has been a great deal of discussion of Facebook and its newsfeeds. First I have to admit I had Facebook when I was at MIT a few years back, when it first came out, my grad students told me I had to, but soon saw it as a waste. Second, I use my own news feeds on Feedly, and go directly to a mass of various opinions.

I see China Daily, RT, Guardian, BBC, Jerusalem Post, NY Times, Breitbart, a bunch of Progressive Sites, Rand reports, Deutsche Welle, Le Monde, Vatican, and tons of other stuff. Thus I rely upon no one to "feed" me news. I try to get to see all sides.

I recall back in High School, as a Freshman, we had to get the NY Times every day, cut out a news story, paste it to a piece of paper and then write a commentary on it. After a year of that, and sneaking a look at opposing views, I learned the the NY Times was an opinion piece, not completely transparent. It loved Castro, really did, until he had those nukes aimed at New York.

So if one wants to get news, try not to read what you agree with, and definitely do not rely upon an entity like Facebook, please.



Labels: [Commentary](#)

[Incoming!](#)

Now Pearl Harbor has a bit of a history for you millennials. There was this thing on December 7th 1941. You may not have covered it in your new history courses. But let us assume the Captain of the nuclear attack sub in Pearl is on the deck at 8 AM raising the port flag. His Chief Boatswain Mate tells him an alarm of an incoming ballistic missile strike has just been received from the State (See the [NY Times](#)). What do you think may happen. Think Peter Sellers! Dr Strangelove!

He cannot confirm but there is no way he is going to be stuck here when he has a belly filled with nukes. So, without hesitation he dives, and heads full steam, nuclear engines turning, out to

sea, hopefully to survive and launch his full belly of 30 Mega Ton nukes at where ever! Yep, that could have happened. Thanks to our Government officials. Fortunately the Navy is not that bad, but....remember Peter Sellers.

Then again if an incoming 10 MT warhead explodes 5000 ft above Pearl you end up with two smaller islands. Duck and cover does not really work. Then you may also set off a volcano or two, a few massive earthquakes, a tsunami, and the list goes on. Perhaps we should better understand the total devastation of a single nuke!

Prior planning prevents poor performance, unless...



Labels: [Nuclear Weapons](#)

[Value, Trust, Quality: Some Thoughts](#)

Value; What is It? and Why is it Important?

Silicon Valley has emerged as a source of profit for many of those who are affiliated with it. But what is it really worth? What value does Silicon Valley types and their products provide? This is the question as to what do we mean by value in our society. An adjunct of value is the concept of trust. I was introduced to this concept as a critical element in a stable society by the late Dave Staelin, a former teacher and colleague. I thought that value was a sine qua non, but Dave convinced me that trust was equally if not more so an element in what we see as a productive element in a stable society.

Now what do we mean by value, and in turn what do we mean by trust. Value means potentially many things to many people. There is the concept of personal values. Namely what does a person hold dear to them, what are their metrics of judgement of themselves and their surroundings. One may hold altruism as a value, humility as a value, cleanliness as a value. Then there is the construct of values of a society. Namely such things as the right of free speech and the right to practice a faith. Then there may be the value of one's individualism, the sanctity of individual rights. Then too is the value inherent in some artifact. An auto has value in that it takes us from one place to another quickly, reliably, and with less human exertion. We can assign a simple measure to that value by how much it costs us and what we get in return for that cost.

Our interest is in that latter definition, a concept of economic or societal value. Thus we may ask what value some new technology brings forth. Let us take a computer, a personal computer, as an example. We may ask; what value does it have to a person? to me? to society? Obviously it may allow me to type better, write faster, calculate more accurately. However, there may be externalities that reduce the value. It may allow me to do more, but then I no longer need a typist, thus I have increased its value to me and reduced it to them. Thus how does one ascertain value; to the person or to the group. If I were a Marxist I would be focusing on the value of the labor as a input to the building of the computer rather that what it does for the user of the computer.

Thus to simplify the analysis I will use value as what added benefit accrues to the individual who employs the entity which purportedly conveys the value. Thus the value of a personal computer,

the value of Google search, the value of Uber, will all be judged in the context of the user first and then society second. It would seem to be easier to perform such a task.

Before continuing let me address the issue of trust, and its adjunct, quality. Something, an instrument of some type, has value to a person because the individual can use it the instrument to perform some task for which the instrument was designed and for which the representation one relied upon at the time of its acquisition would be correct. Namely it does what it was supposed to do. One relies upon a representation by a purveyor, not only that the instrument functions as it was supposed to but that if it does not there will be a remedy. The combination of value with trust, namely its concatenation, results in the concept of quality. Namely if one obtains something that adds value and one can trust its delivering value, trust, then one has a quality experience, and quality adheres to this overall process. Value adheres to the instrument and trust to the purveyor. Quality adheres to the concatenation of both.

Let me give a current example and counter example. Let us assume I purchase a product from Amazon, say a chain saw. I need the item to remove trees. Thus it must cut wood while providing reasonable safety. The instrument must start, function as specified, and not wear out in an untimely manner. It must also have a modicum of safety. Now if I were to purchase from Amazon and they represent that they sell it to me, then I have value and I have trust, namely if it does not work Amazon will remediate the purchase. On the other hand if Amazon just presents the product and a third party actually is the purveyor, I do not know then and there is no trust. The transaction has no quality. You see one needs both value and trust. This is the Staelin construct again. Let me give another example. This time Google. I am seeking information about some health related matter, say a physician who can care for a certain ailment. Does Google provide value? Yes, it may give me a list from which I could then address and seek what I am looking for. Do I trust Google? That is a good question. Trust in this case means if I ask for a physician expert in dealing with the specific ailment, then I assume that Google will present all the options, the alternatives. I assume or trust that Google will not filter out physicians whom the do not like, are not acceptable to Google. How do I know this? As with the Amazon case it is by experience. I am pragmatic, I rely upon experience, mine and others. This works until it does not work. Then pragmatically trust is lost, and near impossible to get back.

Thus, if Amazon fronts for a poor third party vendor and as a consumer I am scammed, then I am wary of everything on Amazon. I move to Walmart. If I find out Google refuses to, for example, list any physician who is a registered Republican, then I become wary of Google across the board. Trust is lost and a key part of the quality equation is vitiated. The instrument no longer has quality and thus I seek an alternative.

Let us leave trust aside for a moment and focus on value. Value has a philosophical as well as economic understanding. We somehow wish to address the amalgam of the two. We want to do this for the development of technological implements. Thus the instrument may be a new cancer immunotherapy, a new computer processor, a new water desalination technique, a new way to remove carbon dioxide from an exhaust, or a new app. What is the value we would ascribe? Economically we would project cash flows from an anticipated market. But there is also societal value as well. A new app may generate cash but would have minimal societal value. In fact it

may be a value destroyer. Namely a person would defer a productive action while expending time on the useless app.

Thus we look at value as both economic and societal. Yet can we monetize this? Namely can we make a *pari passu* comparison? Let me defer that for a moment. The above simple example does show we have value creating, healthcare, and value destroying, apps, instruments. We also have value transferring instrument, which is fundamentally what bankers and VCs do. They take money from one source and reallocate it to another. Value transfer agents do not create value themselves. They seek those who do. Yet value transfer agents look at value solely as an economic return. Thus if they invest in a value destroying instrument, such as an app, they then also become a party to that action.

One way to determine the societal effects on value is the concept of externalities. Namely the effect that may be secondary or a result of the primary action. There is a well established body of work on quantifying externalities. The problem often is, however, that externalities are unanticipated consequences.

The problem we see today is twofold. First, value is often measured solely in short term financial returns devoid on the unintended consequences of the externalities. Second, trust is oftentimes never a factor in the delivery of instruments. I again use the example of Amazon. As it seeks to continually expand, it does so outside the scope of its ability to maintain trust. Its use of third parties and its separation of control on these parties has led to loss of trust. Similarly, for an entity like Google, its burgeoning political bent, for better or worse, can irreparably taint its reputation as a trustworthy source of information. This of course is orders of magnitude for entities like Facebook and Twitter.

Thus when we seek quality, the amalgam of value and trust, we will have the conundrum of Pirsig in *Zen and the Art of Motorcycle Maintenance (ZMM)*. Pirsig says:

"The definition was: "Quality is a characteristic of thought and statement that is recognized by a nonthinking process. Because definitions are a product of rigid, formal thinking, quality cannot be defined." The fact that this "definition" was actually a refusal to define did not draw comment. The students had no formal training that would have told them his statement was, in a formal sense, completely irrational. If you can't define something you have no formal rational way of knowing that it exists. Neither can you really tell anyone else what it is. There is, in fact, no formal difference between inability to define and stupidity. When I say, "Quality cannot be defined," I'm really saying formally, "I'm stupid about Quality.""

Pirsig goes on:

"He singled out aspects of Quality such as unity, vividness, authority, economy, sensitivity, clarity, emphasis, flow, suspense, brilliance, precision, proportion, depth and so on; kept each of these as poorly defined as Quality itself, but demonstrated them by the same class reading techniques. He showed how the aspect of Quality called unity, the hanging-togetherness of a story, could be improved with a technique called an outline. The authority of an argument could

be jacked up with a technique called footnotes, which gives authoritative reference."

"There's an entire branch of philosophy concerned with the definition of Quality, known as esthetics. Its question, What is meant by beautiful?...he saw that when Quality is kept undefined by definition, the entire field called esthetics is wiped out—completely disenfranchised—kaput. By refusing to define Quality he had placed it entirely outside the analytic process. If you can't define Quality, there's no way you can subordinate it to any intellectual rule. The estheticians can have nothing more to say. Their whole field, definition of Quality, is gone."

Indeed esthetics, and aesthetics does read onto to what quality is, it is a perception, not a measurable quantity.

Thus, we should look at value as the amalgam, seek out trust, and then quality, as elusive as Pirsig notes, should be self-evident.



Labels: [Commentary](#)

Friday, January 12, 2018

[The River Shannon](#)



[DW, the German Press](#), reports:

Norwegians have been quick to decline the offer from Donald Trump to move to the US. Norwegians were firm but polite as they went on social media to point out they preferred to stay in one of the richest countries in the world as calculated by GDP per capita, rather than move to the United States. In 2017, the Nordic country was named the happiest nation on the planet and

has a welfare state funded in part by large reserves of oil and natural gas. "On behalf of Norway: Thanks, but no thanks," Torbjørn Saetre, a Conservative Party politician in a municipality near Oslo tweeted on Friday.

I wish they felt that way about Ireland. They seemed to manage pillaging monks and convents, destroying farms and libraries, and frankly remnants of a civilization. Perhaps their interest in staying put may benefit a few. It would have been nice a millennia or so ago. But we did get tall blue eyed Irish! Yikes, that's me! You see we lived just off the Shannon on its north side which the migrants used to sail up and collect their goodies. I better check those genes again!



Labels: [Commentary](#)

Friday, January 12, 2018

[Warburg, Metabolism and Cancer: Recent Thoughts](#)

In 1925, almost a century ago, Otto Warburg made the observation that cancer cells did not have the same metabolism that normal cells did. They did not rely upon oxygen as strongly and they in many ways appeared a fermentation. Based upon this observation Warburg built an entire theory of cancer as a process built upon a faulty metabolic system, namely the failure of the mitochondria to function properly. Overall the Warburg theory stipulates that the excess glucose overpowers the normal metabolic process resulting in lactate (lactic acid) which in turn results in aberrant cell behavior. In 1956 Otto Warburg published a summary paper of his studies which concludes with (some edits for clarity of presentation):

Cancer cells originate from normal body cells in two phases.

(i) The first phase is the irreversible injuring of respiration. Just as there are many remote causes of plague-heat, insects, rats-but only one common cause, the plague bacillus, there are a great many remote causes of cancer-tar, rays, arsenic, pressure, urethane- but there is only one common cause into which all other causes of cancer merge, the irreversible injuring of respiration.

(ii) The irreversible injuring of respiration is followed, as the second phase of cancer formation, by a long struggle for existence by the injured cells to maintain their structure, in which a part of the cells perish from lack of energy, while another part succeed in replacing the irretrievably lost respiration energy by fermentation energy.

Because of the morphological inferiority of fermentation energy, the highly differentiated body cells are converted by this into undifferentiated cells that grow wildly-the cancer cells. To the thousands of quantitative experiments on which these results are based, I should like to add, as a further argument, the fact that there is no alternative today. If the explanation of a vital process is its reduction to physics and chemistry, there is today no other explanation for the origin of cancer cells, either special or general.

From this point of view, mutation and carcinogenic agent are not alternatives, but empty words, unless metabolically specified. Even more harmful in the struggle against cancer can be the continual discovery of miscellaneous cancer agents and cancer viruses, which, by obscuring the underlying phenomena, may hinder necessary preventive measures and thereby become responsible for cancer cases.

Namely, the purist Warburg School asserts that cancer is solely a metabolic disorder, even further, a mitochondrial disorder. The last sentence should be of major concern to Warburg purists. Namely, that we should not be distracted by cancer agents or viruses. In reality we have a great deal more evidence of the latter than of the sine qua non of Warburg. The Warburg School has many adherents and they often reject the many current understandings of cancer initiation and progression and rely upon a purely metabolic hypothesis. For example, in the paper by Seyfried and Shelton the authors conclude with:

Evidence is reviewed supporting a general hypothesis that cancer is primarily a disease of energy metabolism. All of the major hallmarks of the disease can be linked to impaired mitochondrial function. In order to maintain viability, tumor cells gradually transition to substrate level phosphorylation using glucose and glutamine as energy substrates. While cancer causing germline mutations are rare, the abundance of somatic genomic abnormalities found in the majority of cancers can arise as a secondary consequence of mitochondrial dysfunction. Once established, somatic genomic instability can contribute to further mitochondrial defects and to the metabolic inflexibility of the tumor cells.

Systemic metastasis is the predicted outcome following protracted mitochondrial damage to cells of myeloid origin. Tumor cells of myeloid origin would naturally embody the capacity to exit and enter tissues. Two major conclusions emerge from the hypothesis; first that many cancers can regress if energy intake is restricted and, second, that many cancers can be prevented if energy intake is restricted. Consequently, energy restricted diets combined with drugs targeting glucose and glutamine can provide a rational strategy for the longer-term management and prevention of most cancers⁵⁵[1].

This conclusion is a clear statement of cancer prevention and even management via a metabolic mechanism, namely limitation of glucose. While there is substantial interest in the metabolic elements of cancer, reliance upon one thread amongst many may pose substantial risks. For example the excess of ROS, reactive oxygen species, as may be found in inflammatory cancer initiators may be related in a metabolic manner but are not related as directly as that of the Warburg mitochondrial process⁵⁶[2].

⁵⁵[1] Seyfried and Shelton Nutrition & Metabolism 2010, 7:7
<http://www.nutritionandmetabolism.com/content/7/1/7> Page 15 of 22

⁵⁶[2] Again see Seyfried and Shelton, *In addition to avoiding exposure to established cancer risk factors, the metabolism of ketone bodies protects the mitochondria from inflammation and damaging ROS. ROS production increases naturally with age and damages cellular proteins, lipids, and nucleic acids. Accumulation of ROS decreases the efficiency of mitochondrial energy production. The origin of mitochondrial ROS comes largely from the spontaneous reaction of*

When we examine the work regarding the Warburg effect, we note several factors as recent research has proceeded:

1. The Warburg effect, namely a rebalancing of reduced pyruvate fed TCA generation or ATP as compared to an enhanced lactate production is most likely an effect of the complexity in pathways in cancer cells.
2. Cancer cells manage to readjust their metabolic systems to enhance their growth and proliferation often in low oxygen environments.
3. There appears to be a set of well-defined pathways that play a strong role in the switch to Warburg like metabolic proliferation.
4. Cancer cells seem to proliferate almost only in a Warburg manner so that blockage of the adjusted pathways may be a means to starve off the cells.
5. There does not appear to be a clearly define set of immune system determinants to target.

Overall, one of the most comprehensive and balanced papers regarding cancer metabolism is the 2016 paper by Pavlova and Thompson. Unlike many of the papers which blindly support the Warburg thesis, these authors provide a well-balanced summary of the facts and where they may lead.



There are a multiplicity of "causes" of various cancers. We depict the usual suspects below. More than likely as the various forms of the disease are better understood, some of these factors

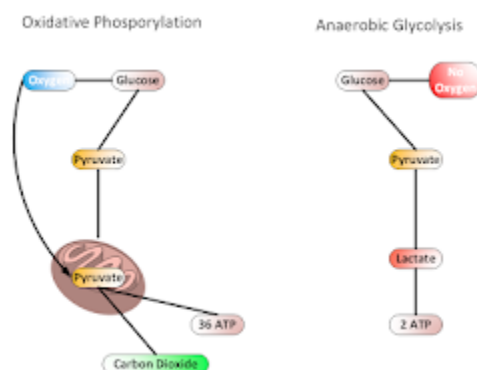
molecular oxygen (O_2) with the semiquinone radical of coenzyme Q, $\cdot QH$, to generate the superoxide radical O_2^- . Coenzyme Q is a hydrophobic molecule that resides in the inner mitochondrial membrane and is essential for electron transfer. Ketone body metabolism increases the ratio of the oxidized form to the fully reduced form of coenzyme Q ($CoQ/CoQH_2$). Oxidation of the coenzyme Q couple reduces the amount of the semiquinone radical, thus decreasing superoxide production.

may become just a consequence of the disease. Some may be a cause, a consequence, and a random coincidence. Our focus herein is the metabolic path although we have considered many of the others in some detail. The metabolic path typically is broad in cancers covered. Unlike say the epigenetic paths where we have a collection of specific and identifiable cancers related to specific alterations, the Warburg supporters throw a broad net across almost any and all cancers. In effect the world view of those on the metabolic front often reflect a more classic early 20th century view of cancers, namely a commonality amongst all organs.

Energy in a cell is generated by the conversion of glucose to ATP. ATP then is a molecule which can give up a phosphate and release energy. That energy then is used throughout the cell. Thus ATP dynamics is at the heart of the metabolic process. We provide but the briefest overview here so as to allow recall. There is a significant amount of literature on these topics⁵⁷[3].

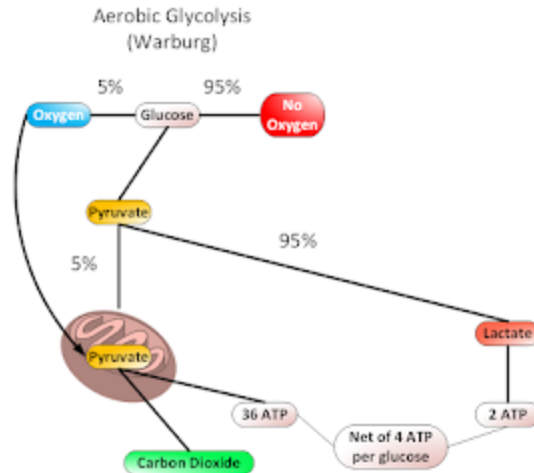
Cells require a continual source of energy. One primary source is glucose, but there are many other sources as well. As regards to glucose as it applies to Warburg, there are three generally accepted paths in which we see the breakdown of glucose. Fermentation and its product alcohol will not be examined. However the water and carbon dioxide path is the oxygen consuming path of normal cellular metabolism and the lactate path is the oxygen depleted path. Warburg came to the conclusion of a third or if you will a fourth (assuming you include fermentation) type of path, one which uses some oxygen but not that much. It was the depleted aerobic path that is the heart of the Warburg construct.

The two classic paths that we focus upon are shown below: with and without oxygen.



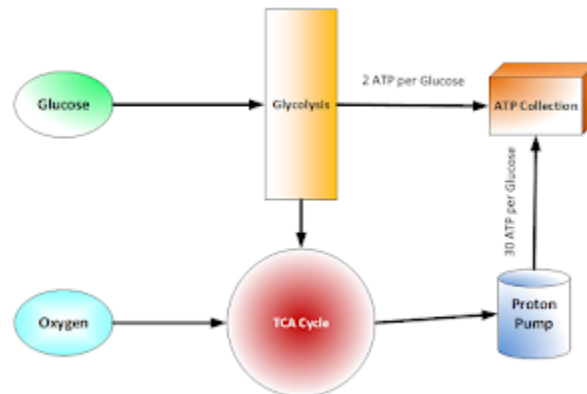
In contrast the Warburg path is a blend of two. Note that it somehow uses both approaches.

⁵⁷[3] See Berg, Biochemistry.



The explanation for this bifurcation seems obscure. Later we attempt to provide a rationale that can explain it. Note that both paths work but the classic oxygen path only slightly. The ATP production is slightly better than the anaerobic path. The details as to how this bifurcated pathway mechanism functions is yet to be determined. One key question which should be kept in mind is: Can the genes controlling this pathway be themselves controlled and then if this pathway is then disturbed does it have a therapeutic effect on cancer cells. If Warburg effects are merely consequential the answer is there is no effect. If the answer is that there is a therapeutic effect, then Warburg may be correct.

We will now examine some details on each part of these. The classic path goes from glucose to water and carbon dioxide. It is a very efficient path and energy rich pumping out well over 30 ATP molecules per glucose molecule. Thus it is the path we see in normal metabolism. An overall summary of the key elements is shown below. This includes three fundamental steps: (i) glycolysis which is the breakdown of glucose to pyruvate producing 2 ATP per glucose molecule, (ii) TCA cycle producing ATP and its precursors NAD and FAD related molecules, (iii) the proton pump mechanism which converts NAD and FAD to ATP. Phosphorylation is a key process whereby energy is transferred. We see this in many pathways and this is but one.



Glycolysis is shown below where we go to pyruvate and then to lactate. We do not present the full details since they are well known and available elsewhere⁵⁸[4]. In a similar fashion we show below the simplified version of the TCA or Krebs cycle below. We have not shown the inputs and the outputs but only the main elements⁵⁹[5]. This is the most productive of all parts of this process in the direct and indirect production of ATP and it is the section that requires oxygen. Without oxygen this cycle does not function. The combinations above produce 32 to 36 ATP molecules. This process is the previous one but with no operative TCA. This is because there is no oxygen available. Thus we are limited with ATP generated solely by glycolysis.

[Aerobic Glycolysis](#) is the Warburg construct. We have shown it above. The current understanding is that it is a small amount of the oxygen based cycle and a dominant amount of the oxygen poor cycle. This is a cycle that has some small oxygen contribution, that a small contribution from a TCA and is dominated by the first step glycolysis.

What we reviewed above was the three mechanisms of ATP generation. However we have not described their dynamics, namely the rate at which each of these processes act. Let us look at oxidative phosphorylation, the classic path if you will, as a two step process. Namely step one is glycolysis and step two is TCA combined with the proton pump. Let us further assume we can get 2 ATP from glycolysis and 32 from the second process. That is fine but what of the dynamics. How many ATP can we get per second for example. If we have a very "hungry" cell and a rich glucose environment, or even a cell which can scavenge its environment better than any others, the cell will have lots of food and then it starts the process. However we are faced with a rate problem. If step 1, glycolysis, can just run at any rate, say a rate R , which generates say R ATP cycles per second, or 2 times R actual ATP, then we have a fast generator. Now assume the second path combined can run at a much lower rate. It can generate 32 for each cycle but it is limited to a maximum number of cycles per second which is substantially less than the glycolysis. We have the following model:

R_1 = rate of process 1 (say glycolysis) (cycles/sec)

R_2 = rate of process 2 (say TCA) (cycles/sec)

R_3 = rate of process 3 (say proton pump) (cycles/sec)

then

G = Generate Rate of ATP per sec

$$G = \sum_{n=1}^3 G_n R_n$$

where

$$G_1 = 2$$

$$G_2 = 2$$

$$G_3 = 30$$

⁵⁸[4] See Rodwell et al, Biochemistry, McGraw Hill (New York) 2915, pp 160-170, Ferrier, Biochemistry, 6th Edition, Lippincott (New York) 2014 pp 109-120.

⁵⁹[5] Details of the TCA can be found in the references.

Now this is the rate analysis. It is the maximum rate analysis. If the rate of the second steps is say three orders of magnitude that of the first step, then the effective rate dominates and the process pumps out ATP and the second steps does the same at a higher number but at a much smaller rate. Thus the total number is dominated by the first and rate limited by the second. This is similar to an enzymatic rate limited system. In fact this totally explains the Warburg effect.

$$x = [A]$$

$$y = [B]$$

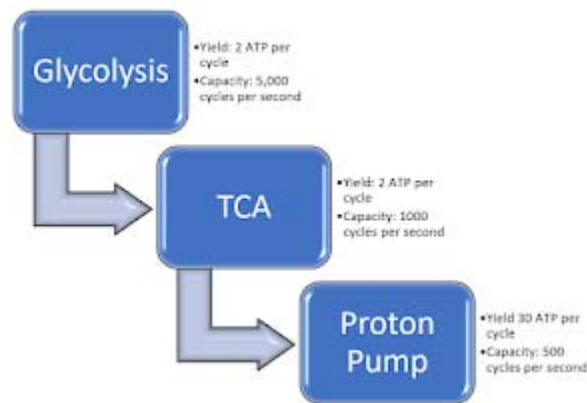
$$z = [C]$$

$$\frac{dx}{dt} = -k_1x$$

$$\frac{dy}{dt} = k_1x - k_2y$$

$$\frac{dz}{dt} = k_2y$$

We would now have to examine the driver of this process. Namely the supply of glucose. We assume a glucose supply of S molecules per second. We further assume a capacity C for each step in terms of cycles per second, namely processing a glucose molecule or its product.



We also assume a yield Y of so many ATP per cycle. Then:

If $N(\text{glucose}/\text{sec})$

$$\text{If } : C_{\text{glycolysis}} > C_{\text{TCA}} > C_{\text{Proton}} > N$$

then

$$Y = Y_{\text{glycolysis}}N + Y_{\text{TCA}}N + Y_{\text{proton}}N$$

$$\text{If } : C_{\text{glycolysis}} > C_{\text{TCA}} > N > C_{\text{Proton}}$$

$$Y = Y_{\text{glycolysis}}N + Y_{\text{TCA}}N + Y_{\text{proton}}C_{\text{proton}}$$

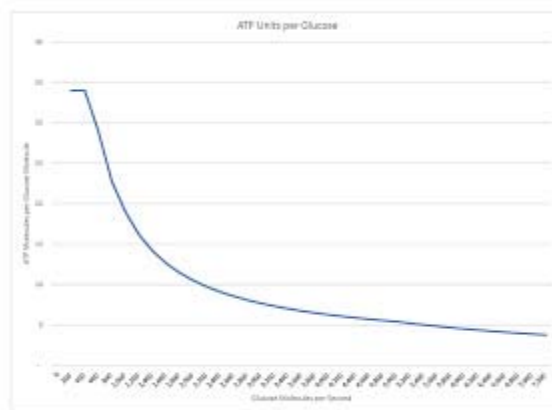
$$C_{\text{glycolysis}} > N > C_{\text{TCA}} > C_{\text{Proton}}$$

$$Y = Y_{\text{glycolysis}}N + Y_{\text{TCA}}C_{\text{TCA}} + Y_{\text{proton}}C_{\text{proton}}$$

$$N > C_{\text{glycolysis}} > C_{\text{TCA}} > C_{\text{Proton}}$$

$$Y = Y_{\text{glycolysis}}C_{\text{glycolysis}} + Y_{\text{TCA}}C_{\text{TCA}} + Y_{\text{proton}}C_{\text{proton}}$$

We can depict this below:

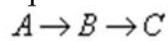


Now let us consider a simple example. Choose the following constants:

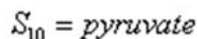
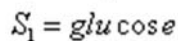
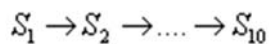
Note the yield is 4 ATP per glucose. This is a model which explains the Warburg effect. Namely there are rate limiting steps in the glycolysis, TCA proton pump model and ultimately the fastest controls. In fact if we make this fast enough we drive it to at best 2 ATP per glucose and that is just for the glucose that are processed.

We can now take this a step further and examine the rate processes. We know from the Gibbs free energy results how well each reaction works. We also have data on reaction rates which we can use for each step. Then we can use classic reaction rate theory to ascertain if the data used in the above example is reflective and what changes should be made.

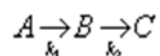
Let us look at classic reaction rate example.



or



We assume we know the reaction rate for each reaction. Let us focus just on the three step example. We can then extend it to the glycolysis and TCA directly. We can follow Moore (pp 345-347) for this simple example. For reactions we have:



Thus for rate equations we have given the rate constants k:

$$x = [A]$$

$$y = [B]$$

$$z = [C]$$

$$\frac{dx}{dt} = -k_1 x$$

$$\frac{dy}{dt} = k_1 x - k_2 y$$

$$\frac{dz}{dt} = k_2 y$$

Moore then solves these equations as follows:

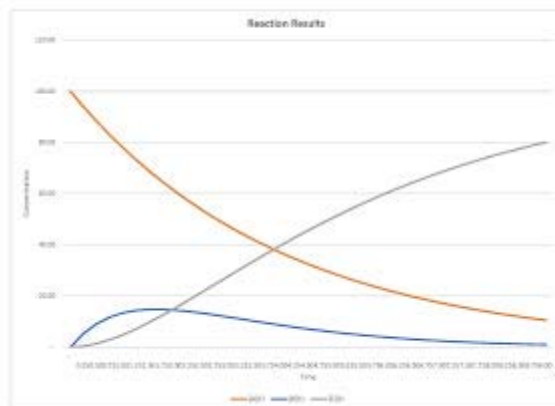
$$x(t) = C_0 \exp(-k_1 t)$$

$$y(t) = \exp(-k_2 t) \left[\frac{k_1 C_0 \exp((k_2 - k_1)t)}{k_2 - k_1} - \frac{k_1 C_0}{k_2 - k_1} \right]$$

$$z(t) = C_0 \left[1 - \frac{k_2 \exp(-k_1 t)}{k_2 - k_1} + \frac{k_1 \exp(-k_2 t)}{k_2 - k_1} \right]$$

We can now perform a simple analysis with these equations to demonstrate one more detail below in a simplified example. Here we plot the concentrations of A, B and C as a function of time. Initially we have all A, say glucose. Then an intermediate B is generated but it is used up, and then C the end product appears. The time required to go from A to C is the critical factor.

We could then apply this to the glycolysis and TCA chains and demonstrate such rate limiting. It should be noted that we can use IUPAC data on reaction rates for each element in these chains as contained in the Serjeant and Dempsey tables. We have done this for a few steps and it appears achievable and can then be used for verification. Note that [A] decays exponentially, [B] increases and then decreases, and then [C] reaches a maximum. This concept then applies for the speed of any one of the three elements.



Otto Warburg studied the process of cancer in terms of the ATP generation under limited or no oxygen conditions. To an extent this was the state of fermentation, but not one leading to the production of alcohol. As for his background, the details on the Nobel Prize site state⁶⁰[6]:

Warburg was born on October 8, 1883, in Freiburg, Baden. His father, the physicist Emil Warburg, was President of the Physikalische Reichsanstalt, Wirklicher Geheimer Oberregierungsrat. Otto studied chemistry under the great Emil Fischer, and gained the degree, Doctor of Chemistry (Berlin), in 1906. He then studied under von Krehl and obtained the degree, Doctor of Medicine (Heidelberg), in 1911. He served in the Prussian Horse Guards during World War I. In 1918 he was appointed Professor at the Kaiser Wilhelm Institute for Biology, Berlin-Dahlem. Since 1931 he is Director of the Kaiser Wilhelm Institute for Cell Physiology, there, a donation of the Rockefeller Foundation to the Kaiser Wilhelm Gesellschaft, founded the previous year.

His award of the Nobel declares:

"for his discovery of the nature and mode of action of the respiratory enzyme" in the field of cell physiology, metabolism for the work as follows:

In our cells nutrients are broken down so that energy is released for the construction of cells. This respiration requires enzymes, substances that facilitate the process without being incorporated in the final products. Otto Warburg studied the respiration of sea urchins and other

⁶⁰[6] https://www.nobelprize.org/nobel_prizes/medicine/laureates/1In effect Warburg931/warburg-bio.html

organisms at an early stage of development. By measuring oxygen consumption in living cells and studying which enzymes reacted, in 1928 he concluded that the respiration enzyme he was looking for was a red ferrous pigment related to the blood pigment, hemoglobin.

Thus despite having been awarded the Nobel, it was not for his work in cancer. Yet Warburg seems most well-known for his cancer conjectures. In Warburg's 1956 Science paper he begins by noting:

Since it is known how much adenosine triphosphate can be synthesized by respiration and how much by fermentation, we can write immediately the potential, biologically utilizable energy production of any cells if we have measured their respiration and fermentation. With the ascites cancer cells of the mouse, for example, we find an average respiration of 7 cubic millimeters of oxygen consumed per milligram, per hour, and fermentation of 60 cubic millimeters of lactic acid produced per milligram, per hour. This, converted to energy equivalents, means that the cancer cells can obtain approximately the same amount of energy from fermentation as from respiration, whereas the normal body cells obtain much more energy from respiration than from fermentation. For example, the liver and kidney of an adult animal obtain about 100 times as much energy from respiration as from fermentation.

In effect, Warburg examined cells from ascites, the fluid produced frequently from metastasized cancer in the liver. He then examined how much lactate is produced, namely the end product of anaerobic production of ATP. Strangely it appeared that these cancer cells had a combination of anaerobic plus normal metabolism which he called aerobic. Thus Warburg noted that cancer cells almost exclusively obtain their energy not from a TCA method primarily but from some small mix of a TCA plus mostly but not exclusively from what he termed fermentation, or anaerobic paths. Warburg then concluded that this aerobic path was the "cause" of cancer, not just an artifact of a cancerous process.

Warburg then goes on to state:

Clinical experiences along these lines are innumerable: the production of cancer by intermittent irritation of the outer skin and of the mucosa of internal organs, by the plugging of excretory ducts of glands, by cirrhosis of tissues, and so forth. In all these cases, the intermittent irritations lead to intermittent circulatory disturbances., Probably chronic intermittent oxygen deficiency plays a greater role in the formation of cancer in the body than does the chronic administration of respiratory poisons. Any respiratory injury due-to lack of energy, however, whether it is produced by oxygen deficiency or by respiratory poisons, must be cumulative, since it is irreversible. Frequent small doses of respiratory poisons are therefore more dangerous than a single large dose, where there is always the chance that the cells will be killed rather than that they will become carcinogenic.

Frankly there is no basis for any of the above assertions. Warburg's observations of lactate excess in cells which may have an abundance of oxygen, and primarily cancer cells, is just that, an observation. The generalizations emanating therefrom are at best speculation. As we shall note, however, there has arisen an almost cult like group who have taken Warburg's observations and correlations to extremes.

Notwithstanding the speculation, the observation clearly has merit, merit as a distinguishing characteristic. However the statements made by Warburg such as:

It follows from this that there would be no cancers if there were no fermentation of normal body cells, and hence we should like to know, naturally, from where the fermentation of the normal body cells stems and what its significance is in the body. Since, as Burk has shown, the fermentation remains almost zero in the regenerating liver growth, we must conclude that the fermentation of the body cells has nothing to do with normal growth.

On the other hand, we have found that the fermentation of the body cells is greatest in the very earliest stages of embryonal development and that it then decreases gradually in the course of embryonal development. Under these conditions, it is obvious-since ontogeny is the repetition of phylogeny-that the fermentation of body cells is the inheritance of undifferentiated ancestors that have lived in the past at the expense of fermentation energy.

Warburg's claim of "ontogeny recapitulates phylogeny" can be rephrased as "what comes first, the chicken or the egg?" For one must accept the Bacon like observation of this metabolic effect, however one must be wary of Galen like logic that is phenomenologically limited.

We first examine some current understandings of the classic Warburg hypothesis. As Liberti and Locasale note:

During the 1920s, Otto Warburg and colleagues made the observation that tumors were taking up enormous amounts of glucose compared with what was seen in the surrounding tissue. Additionally, glucose was fermented to produce lactate even in the presence of oxygen, hence the term 'aerobic glycolysis'. However, it was also noted that respiration alone could maintain tumor viability. Therefore, it was concluded that, to kill tumor cells by depriving them of energy, both glucose and oxygen had to be eliminated. Subsequently, in 1929, an English biochemist, Herbert Crabtree, extended Warburg's work and studied the heterogeneity of glycolysis in tumor types.

Note that the conclusion regarding killing cancer cells was via starvation. Unfortunately that would likely cause death of all cells around.

He confirmed Warburg's findings, but further discovered that the magnitude of respiration in tumors was variable, with many tumors exhibiting a substantial amount of respiration. Therefore, Crabtree concluded that not only do tumor cells exhibit aerobic glycolysis, but that there is also variability in fermentation, presumably due to environmental or genetic influences. Contrary to the findings of these previous works and for reasons unclear to these authors, Warburg later proposed that dysfunctional mitochondria are the root of aerobic glycolysis. Warburg further hypothesized that this event is the primary cause of cancer.

The dysfunctional mitochondria is one of a possible number of explanations. As we have discussed and shown, another explanation could be rate limiting processes, and one suspects there are other mechanisms as well.

This phenomenon was then termed the Warburg Effect during the early 1970s by Efraim Racker, who also pointed out that previous data showed respiratory capability of tumors. Racker developed his own theories about the origins of the Warburg Effect, ranging from imbalances in intracellular pH to defects in ATPase activity. It was later observed by Racker, Jeffrey Flier, and Morris Birnbaum that aerobic glycolysis was a controllable process that can be directly regulated by growth factor signaling.

By that time, the discovery of oncogenes led to the conclusion that aberrant regulation of growth factor signaling is an initiating event in oncogenesis. Thus, their observations brought newfound significance to Warburg's hypothesis in cancer biology. Nevertheless, it remained unclear whether the Warburg Effect was a bystander in cancer pathogenesis until more recently, when genetic and pharmacological studies conclusively showed that the Warburg Effect was required for tumor growth.

Coming back to the original findings on tumor metabolism, it is now apparent that targeting both aerobic glycolysis and mitochondrial metabolism may be required. Throughout this history, the function of the Warburg Effect has remained controversial. Here, we discuss several of the major proposals and argue that the functions of the Warburg Effect for tumor growth remain unknown even today.

Indeed it is a controversial observation. We will discuss latter the work by some who see this as a panacea for cancer treatment. Namely the massive blocking of glucose and in turn the aerobic metabolic pathway. As a side note, it is also know that excess lactate has deleterious effects, but that may at best be a sidebar.

We now examine the current view. We start with the recent work of Levine and Kutter who note:

Rapidly dividing cells require favorable energetics, that is, higher ATP/adenosine diphosphate (ADP) and ATP/adenosinemonophosphate (AMP) ratios. Many cancer cells satisfy this problem by taking up much larger amounts of glucose than do normal cells. This results from facilitated glucose transport by one or more of several isozymes of membrane glucose transporters (GLUT 1 to 9). Once inside the cell, glucose is phosphorylated by one of several hexokinase enzymes (the first step in glycolysis) to keep it in the cell because of the charge added to glucose. The high concentrations of glucose in the cells of a cancer may be observed by positron emission tomography (PET) scans of radioactive F-19-2-deoxyglucose (FDG is not metabolized but is located in the cell), which is indicative of enhanced glucose uptake by cells.

Many, but not all, cancers have this property of increasing glucose uptake, and this is a confirmation of the Warburg effect. With large amounts of glucose available in a cell, glucose is metabolized through the PPP, producing nucleosides and generating NADPH. The NADPH is essential for fatty acid synthesis, along with acetyl-CoA (which is made from some of the pyruvate in mitochondria that is not converted to lactate). NADPH also contributes to a proper redox control and protects the cell from ROS. There are several ways the cell responds to lower ROS (reactive oxygen species) levels, but by far the major molecule involved is glutathione

(GSH), which eliminates ROS by accepting an electron and is converted to its oxidized form, GSSG (glutathione disulfide).

The enzyme glutathione reductase uses NADPH to reduce GSSG to GSH. Thus, NADPH is a major source of cellular “coolant” when oxidative reactions run too “hot” (high ROS levels) by using large amounts of glucose to produce both substrates and energy. However, high levels of ROS can be advantageous for cancer cells when they allow for the stimulation of cell proliferation, induction of genetic instability, and evasion from senescence.

As Thompson, who has done extensive recent work in cancer cell metabolism, noted (see Riccio):

After the initial step in glucose metabolism—glycolysis, conversion of glucose to two molecules of pyruvate—mitochondrial oxidative phosphorylation usually proceeds to yield ATP. But even in the presence of oxygen, many cancer cells divert pyruvate to fermentation, producing lactate. This less rewarding mode of ATP production demands a relatively high rate of glycolysis. Otto Warburg described this shift toward “aerobic glycolysis” in cancer cells in 1924. The molecular and genetic basis of the Warburg effect, however, has only recently come to light. Contrary to Warburg's hypothesis that mitochondrial defects necessitate this shift, most cancer cells maintain the ability to execute oxidative phosphorylation and do fully catabolize a small amount of glucose.

Cancer cells are genetically differentiated from normal cells, but it is now clear that the metabolic shifts they exhibit are also partly required for division of normal cells. In a quiescent cell, maximum ATP production yields enough energy for cellular machinery, and at least 50% of free energy is used for ion transport across the membrane. When a cell divides, glycolytic intermediates are diverted from the tricarboxylic acid (TCA/Krebs) cycle to reserve carbon and nitrogen for fatty acid synthesis and for production of nonessential amino acids. DNA replication demands de novo nucleotide synthesis, beyond the supply garnered from recycling pathways in a non-dividing cell. Ribose, serine, and glycine (byproducts of glucose metabolism), as well as glutamine for pyrimidine production, are needed for nucleotide synthesis.

Finally Thompson notes the active role genetic alterations play. This is sharp contrast to the abject rejection of such by Warburg and his followers. Specifically Thompson notes:

The most commonly mutated gene in cancers is KRAS. The KRAS protein, a GTPase, normally functions as a molecular switch, relaying signals received by receptor tyrosine kinases and other receptors of extracellular signals. Two of its main targets include the MAPK and PI3K signal transduction cascades. But many indirect targets of KRAS are involved in cellular metabolism, including glucose transporters that are positively regulated by the PI3K/Akt pathway. Glutamine-addicted tumors are often characterized by the oncogenic expression of Myc, a transcription factor that promotes the expression of glutamine transporters as well as metabolic enzymes needed for biosynthesis. Constitutively activated KRAS thus primes a cell to undergo aerobic glycolysis by ensuring a steady influx of glucose.

Namely the Warburg effect is not standard for cancer cells. Thus the mass of conclusions based upon this faulty construct a truly built with feet of sand. We shall detail this further.

Warburg factors relate to the metabolism of the cell, focusing on the mitochondria. However there are many cell factors which in turn control this process for better or worse. There has been a great deal of study examining the various genetic pathways and their controls on the metabolic actions that are a focal point of the Warburg effect. The following Figure depicts the complex interaction of pathways and metabolism.

The paper by DeBerardinis et al from which we have abstracted the above demonstrates several of the pathways control elements which may be prominent in controlling the metabolic processes. They state regarding the above diagram:

The model shows some of the prominent aspects of metabolism in proliferating cells, including glycolysis; lactate production; the use of TCA cycle intermediates as macromolecular precursors; and the biosynthesis of proteins, nucleotides, and lipids. The PI3K/Akt/mTOR pathway, HIF-1 α , and Myc participate in various facets of this metabolic phenotype. The binding of a growth factor (GF) to its surface receptor brings about activation of PI3K and the serine/threonine kinases Akt and mTOR.

Constitutive activation of the pathway can occur in tumors due to mutation of the tumor suppressors PTEN, TSC1, and TSC2, or by other mechanisms. Metabolic effects of the PI3K/Akt/mTOR pathway include enhanced uptake of glucose and essential amino acids and protein translation. The transcription factor HIF-1 α is involved in determining the manner in which cells utilize glucose carbon. Translation of HIF-1 α is enhanced during growth-factor stimulation of the PI3K/Akt/mTOR pathway. In the presence of oxygen, HIF-1 α is modified by prolyl hydroxylases, which target it to a ubiquitin ligase complex that includes the tumor suppressor VHL. This association results in constitutive normoxic degradation of the HIF-1 α protein. Hypoxia, mutation of VHL, or accumulation of reactive oxygen species (ROS) or the TCA cycle intermediates succinate and fumarate impair HIF-1 α degradation, allowing it to enter the nucleus and engage in transcriptional activity. Transcriptional targets include genes encoding glucose transporter 1 (GLUT1), LDH-A, and PDK1. The combined effect on glucose metabolism is to increase both glucose utilization and lactate production, as PDK1 inhibits conversion of pyruvate to acetyl-CoA by pyruvate dehydrogenase (PDH). The transcription factor Myc increases expression of many metabolic enzymes, including glycolytic enzymes, LDH-A, and several enzymes required for nucleotide biosynthesis.

Abbreviations: PI3K, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homolog; TSC, tuberous sclerosis complex; mTOR, mammalian target of rapamycin; glc-6-P, glucose-6-phosphate; 3-PG, 3-phosphoglycerate; PDK1, pyruvate dehydrogenase kinase 1; SDH, succinate dehydrogenase; FH, fumarate hydratase; HIF-1 α , hypoxia-inducible factor 1 α ; VHL, von Hippel-Lindau.

Now there are multiple other papers which depict variants on the above and referenced herein. One suspects that this analysis is still a work in progress and as such we expect a considerable amount of complexity. The full details of the interaction and control are yet to be specified. This

does raise the issue; is the Warburg effect an artifact or a separate entity? The observations of it being an artifact are currently compelling.

Thompson in EMBO notes regarding the work of Pate et al:

In this issue of The EMBO Journal, Pate et al identify Wnt signaling as a mechanism that suppresses pyruvate oxidation in the TCA cycle and promotes rather than inhibits cell proliferation. As such, Wnt signaling is a candidate for the signal transduction pathway that could synergize with PI3K/AKT signaling in proliferating cells. Wnt signaling is already well characterized as a regulator of cell proliferation.

First, Wnt induced LEF/TCF/b-catenin transcription complexes have been implicated in controlling cell proliferation through the induction of Myc and Cyclin D. Cyclin D levels are critical to cell cycle progression through G1, and Myc has been implicated in the stimulation of glutamine metabolism and nucleotide synthesis necessary to support S-phase. Pate et al identify additional transcriptional targets of LEF/TCF/b-catenin complexes.

They report that the genes connected to metabolism are the most highly overrepresented category of Wnt-target genes. Two relevant Wnt targets were identified: pyruvate dehydrogenase kinase 1 (PDK1) and the lactate transporter (MCT-1). These two proteins along with the Myc induced gene LDH-A allow Wnt-activated cells to divert glycolytic pyruvate away from the TCA cycle by converting it into lactate and promoting lactate secretion from the cell. Induction of PDK1 was found to be required for Wnt-induced aerobic glycolysis, in vivo tumor cell accumulation, and VEGF independent angiogenesis.

Pate et al did not test for whether Wnt induction of Myc and/or glutamine metabolism contributes to Wnt-induced tumor cell accumulation. However, it is reasonable to suspect that Wnt induction of PDK1 cooperates with Myc-induced glutaminolysis to facilitate a cellular transition from growth to proliferation since Myc is a well-characterized effector of Wnt signaling.

The combined effects of Wnt-facilitated aerobic glycolysis and Myc-induced glutaminolysis provide the cell with a potent ability to engage in de novo nucleotide biosynthesis

This observation would modify the above diagram by adding a WNT receptor and having it drive MYC. Thus we now would understand the driver of MYC and the importance of the WNT connection. This is an added example of the progression of the modifications and understanding of the metabolism which seems to be tightly controlled by various pathways, and pathways which we know to be subject to attack in many cancers. Thus the argument that the Warburg proponents make that the pathways are irrelevant seems to be destroyed in these studies.

Finally in a recent paper by Pavlova and Thompson we have:

Tumorigenesis is dependent on the reprogramming of cellular metabolism as both direct and indirect consequence of oncogenic mutations. A common feature of cancer cell metabolism is the ability to acquire necessary nutrients from a frequently nutrient-poor environment and utilize

these nutrients to both maintain viability and build new biomass. The alterations in intracellular and extracellular metabolites that can accompany cancer-associated metabolic reprogramming have profound effects on gene expression, cellular differentiation and the tumor microenvironment.

In this Review, we have organized known cancer-associated metabolic changes into six hallmarks:

- (1) deregulated uptake of glucose and amino acids,*
- (2) use of opportunistic modes of nutrient acquisition,*
- (3) use of glycolysis/TCA cycle intermediates for biosynthesis and NADPH production,*
- (4) increased demand for nitrogen,*
- (5) alterations in metabolite-driven gene regulation, and*
- (6) metabolic interactions with the microenvironment.*

While few tumors display all six hallmarks, most display several. The specific hallmarks exhibited by an individual tumor may ultimately contribute to better tumor classification and aid in directing treatment.

In the above paper the authors fill in further details of internal gene pathway controls on the cell metabolic process.

We can now make a few observations which have merit when examining the Warburg effect.

1. IF CANCER CELLS NEED GLUCOSE TO PRODUCE ATP, BUT THEY PRODUCE AT BEST 4 ATP PER GLUCOSE, WHEREAS NORMAL CELLS PRODUCE 30-36, THEN IF WE REDUCE GLUCOSE DRAMATICALLY, TO A BASAL AMOUNT FOR NORMAL CELLS, WOULD THAT "STARVE" CANCER CELLS. EXAMPLE IS METFORMIN AND PROSTATE CANCER.

This has been the standard conjecture that advocates of Warburg effects articulate. As Levine and Kutter noted:

Cells from some tumors use an altered metabolic pattern compared with that of normal differentiated adult cells in the body. Tumor cells take up much more glucose and mainly process it through aerobic glycolysis, producing large quantities of secreted lactate with a lower use of oxidative phosphorylation that would generate more adenosine triphosphate (ATP), water, and carbon dioxide.

This is the Warburg effect, which provides substrates for cell growth and division and free energy (ATP) from enhanced glucose use. This metabolic switch places the emphasis on

producing intermediates for cell growth and division, and it is regulated by both oncogenes and tumor suppressor genes in a number of key cancer-producing pathways. Blocking these metabolic pathways or restoring these altered pathways could lead to a new approach in cancer treatments.

For example, we have examined the use of metformin in prostate cancer and the result can be a diminution of the malignancy.

2. SINCE WE HAVE INTERNAL CELL PATHWAYS TO CONTROL METABOLIC PATHWAYS CAN WE IDENTIFY SPECIFIC PROTEINS TO BLOCK TO STARVE THE AEROBIC PATHWAY? IF SO, THEN WHAT HARM MAY THAT CAUSE OTHER THAN STARVING THE CANCER?

Pathway control of the Warburg effect has been examined by several recent studies. We have referred to them and have discussed them in some detail. However their use is still an open question. Secondary harms are all too often the controlling factor. By starving the patient of glucose do we create a plethora of secondary and unintended but deleterious consequences? One suspects that to be the case.

As Tisdale noted when examining cachexia in cancer:

Most cancer cells use glycolysis as the principal method to generate ATP, and this phenomenon is called the Warburg effect. The increased glucose uptake by tumors is the basis of the [18F]fluorodeoxyglucose positron emission tomography (FDG-PET) tumor diagnostic method, which is based on the assumption that cancer tissue has a higher rate of glucose uptake than normal tissue (29). In addition, glycolytic inhibitors have been suggested as being useful to specifically target the slow-growing cells of a tumor, which would complement currently used chemotherapeutic agents and radiation, which target rapidly growing cells. Several reasons have been suggested to explain this phenomenon including dysfunctional mitochondria, which exhibit frequent mutations in the DNA which would prevent their use of the tricarboxylic acid cycle, preventing the total combustion of pyruvic acid. Since mitochondrial DNA codes for 13 components of the respiratory chain, it is likely that such mutations would cause malfunctions in respiration. Indeed, respiration-deficient cells with deletions in mitochondrial DNA show an increased dependency on glycolysis, increased NADPH and activation of the Akt survival pathway, resistance to antitumor drugs, and a survival advantage in hypoxic conditions. Other alterations include overexpression of the "low Km" form of hexokinase, type II hexokinase, due to gene demethylation, resulting in tumor glucose utilization at normal blood sugar levels, oncogenic signals, such as ras and src, which increase dependence on glucose, and tumor hypoxia due to growth beyond the vascular supply. Hypoxia activates a transcription factor called hypoxia-inducible factor 1 (HIF-1), which increases the transcription of the cell-surface glucose transporter GLUT1, and at least one isoform of nearly all the core enzymes of glycolysis.

Overall Tisdale does not relate Warburg that strongly with the overall cachexia process. To some degree this is surprising.

3. IS THERE A REVERSE WARBURG EFFECT?

Can Warburg work in reverse? As Xu et al note:

There is much evidence that the Warburg effect has many questionable points. Based on a mass of research, a new hypothesis is catching people's attention, the reverse Warburg effect. Glycolysis occurs in mesenchymal stroma cells under the activation of neighboring cancer cells. Furthermore, an increased formation of recycled nutrients is produced. This high-energy metabolism is transferred to the neighboring cancer cells by the orientation of transport to participate in the TCA cycle.

The consequence is that the OXPHOS (oxidative phosphorylation) increases enhancing ATP production, thus constituting metabolic coupling. This new model may well explain both the way ATP is produced via a low efficiency method despite extremely high energy demand of the tumor cells, and reasonably explain the 'autophagy paradox' that has long been questioned. Although our focal point on the aerobic glycolysis mirrors the core of the realm, further research is still required on cancer bioenergetics.

We have argued that there is a simpler way to explain Warburg, namely simple rate limiting.

4. EPIGENETICS CAN BE INDUCED BY METABOLIC PATHWAYS. HOW THEN DOES THE METABOLIC ISSUE IN AND AROUND CANCERS PLAY WITH THE EPIGENETIC CHANGES?

Epigenetics has become one of the fertile areas for understanding cancers. We use herein a broad definition of epigenetics as one where there is a non-DNA specific factor altering the ultimate expression of a gene. This may range from simple DNA methylation, methylation of acetylation of chromosome complexes, micro RNAs and other related gene control mechanisms. As Yun et al note:

Epigenetics is defined as heritable changes in gene expression without alterations in the underlying genetic material. Modifications include DNA methylation and covalent post-translational modifications of histones such as acetylation, methylation, phosphorylation, ubiquitination, phosphorylation, and crotonylation. Since every cell in the body has the same genetic code, epigenetic regulation of gene expression plays a large role in determining cellular identity. Failure of proper maintenance of cellular epigenetic status can, thus, result in loss of tissue identity or aberrant signaling pathways that lead to developmental defects or disease states such as diabetes and cancer.

It is now well accepted that cancer initiation and progression are driven by a series of genetic and epigenetic alterations that cause either activation of oncogenes or inactivation of tumor suppressor genes. Much of the recent excitement in the field of cancer epigenetics lies in the reversible nature of epigenetic alterations; unlike genomic mutations, these changes can theoretically be reversed by epigenetic therapy.

Recently, four drugs that target the epigenetic machinery have been approved by the FDA for cancer treatment and have demonstrated prolonged survival and lower toxicity than conventional chemotherapy. Despite intensive research and remarkable advances in our understanding of epigenetics, the mechanisms and regulators that trigger pathological epigenetic reprogramming in cancer remains poorly understood.

How these relate to Warburg is unclear. However Bensinger and Christofk have noted regarding miRNA and Warburg the following:

Since the discovery that miRNAs are aberrantly expressed in cancer, accumulating evidence suggests that miRNAs contribute to tumor growth by modulating levels of oncogenes and tumor suppressors. Not surprisingly, some miRNAs have been shown to regulate cancer metabolism. miRNA-23a and miRNA-23b, which are suppressed by MYC, repress mitochondrial glutaminase expression. Therefore, MYC enhances glutaminase and glutamine metabolism, an important carbon and nitrogen source for biosynthesis in cancer cells, by repressing miRNA-23a/b expression. A recent study by Eichner et al. found that ERBB2 signaling leads to miRNA-378 expression, which promotes the Warburg effect by inhibiting expression of ERR, a binding partner for PGC-1, leading to reduced transcription of tricarboxylic acid cycle genes. miRNA-378 expression, which correlates with progression in human breast cancer tissues, causes increased lactate production, decreased respiration, and increased proliferation of breast cancer cell lines. Another recent study has implicated miRNA-210 in metabolic reprogramming in cancer...miRNA-201, which is induced by hypoxia, represses the mitochondrial iron sulfur scaffold protein ISCU resulting in decreased mitochondrial complex 1 activity, aconitase activity, increased lactate production and hypoxic cell survival. Future studies will undoubtedly uncover additional miRNAs important for aerobic glycolysis in cancer.

Thus perhaps epigenetics via the mi RNA path may have a significant role to play.

Pavlova and Thompson also examine the interaction with the epigenetic elements. Namely they state:

Aberrantly activated growth and survival signals that drive tumorigenesis facilitate the reprogramming of cancer cell metabolism to enable increased nutrient acquisition and biosynthesis. However, metabolic networks themselves are not merely passive recipients of growth signals, but quite the contrary, directly transmit the information about the cellular metabolic state to a diverse array of regulatory enzymes, among which are those that mediate the deposition and removal of epigenetic marks from chromatin. A key metabolite that builds up when cells metabolize more glucose than needed for bioenergetic support is cytosolic acetyl-CoA. Cytosolic acetyl-CoA is the obligate substrate for enzymes that acetylate histones and other proteins. The deposition of acetyl marks on histones is associated with the increased accessibility of the genomic DNA for the assembly of transcriptional complexes, and has a rapid turnover rate. Histone acetylation is exquisitely sensitive to alterations in the cellular nutritional and signaling status. Indeed, withdrawal and re-addition of glucose, as well as activation of oncogenic signaling via introduction of an oncogenic KRAS mutant or a constitutively active form of Akt, increase total histone acetylation, which, in turn, promotes the enhanced and broader gene expression.

Overall there appears to be a rich field of examining metabolism and epigenetics.

5. GLUTAMINE HAS A SIMILAR EFFECT AS GLUCOSE. ARE THE CELLULAR DYNAMICS THE SAME OR SIMILAR?

Cells use both glucose and glutamine. As Altman et al note:

The maintenance of high levels of glutamine in the blood provides a ready source of carbon and nitrogen to support biosynthesis, energetics and cellular homeostasis that cancer cells may exploit to drive tumour growth. Glutamine is transported into cells through one of many transporters, such as the heavily studied SLC1A5, and can then be used for biosynthesis or exported back out of the cell by antiporters in exchange for other amino acids such as leucine, through the L-type amino acid transporter 1 (LAT1, a heterodimer of SLC7A5 and SLC3A2) antiporter. Glutamine derived glutamate can also be exchanged through the xCT antiporter for cystine, which is quickly reduced to cysteine inside the cell. ...

The expression of enzymes involved in glutamine metabolism varies widely in cancers and is affected by tissue of origin and oncogenotypes, which rewire glutamine metabolism for energy generation and stress suppression. Of the two glutaminase enzymes²⁸, GLS is more broadly expressed in normal tissue and is thought to have a crucial role in many cancers, whereas GLS2 expression is restricted primarily to the liver, brain, pituitary gland and pancreas³⁶. Alternative splicing adds further complexity, as GLS pre-mRNA is spliced into either glutaminase C (GAC) or kidney-type glutaminase (KGA) isoforms^{37–39}. The two GLS isoforms and GLS2 also differ in their regulation and activity. GLS but not GLS2 is inhibited by its product glutamate, whereas GLS2 but not GLS is activated by its product ammonia in vitro^{28,29}. Although both GLS and GLS2 are activated by inorganic phosphate, GLS (and particularly GAC) shows a much larger increase in catalysis in the presence of inorganic phosphate³⁷. Sirtuin 5 (SIRT5), which can be overexpressed in lung cancer⁴⁰, can desuccinylate GLS to suppress its enzymatic activity⁴¹, whereas SIRT3 can deacetylate GLS2 to promote its increased activity with caloric restriction.

The authors continue:

Ninety years ago, Warburg discovered that many animal and human tumours displayed high avidity for glucose, which was largely converted to lactate through aerobic glycolysis. Warburg also suggested that cancers are caused by altered metabolism and loss of mitochondrial function. These dogmatic views have been replaced and refined over the past several decades with the emergence of oncogenic alterations of metabolism, appreciation of the importance of mitochondrial oxidation in cancer physiology and the rediscovery of the role of glutamine in tumour cell growth in addition to the pivotal role of glucose.

In this Review, we provide an updated overview of glutamine metabolism in cancers and discuss the complexity of metabolic rewiring as a function of the tumour oncogenotype as well as the microenvironment, which adds to the heterogeneity found in vivo. In certain types of cancer, such as those driven by MYC, tumour cells seem to depend on glutamine, and hence targeting

glutamine metabolism pharmacologically may prove beneficial. Conversely, different oncogenic drivers may result in tumour cells that could bypass the need for glutamine.

However, targeted inhibition of some oncogenic drivers has been reported to rewire cells to become dependent on glutamine, and hence targeted inhibitors could be synthetically lethal with inhibition of glutamine metabolism. Overall, the field of cancer metabolism has made considerable progress in understanding alternative fuel sources for cancers, including glutamine, which under specific circumstances can be exploited for therapeutic purposes.

6. IS THERE A RELATIONSHIP BETWEEN THE IMMUNE SYSTEM AND THE WARBURG EFFECT, AND IF SO CAN IT BE USED TO ADDRESS VARIOUS TYPES OF CANCERS?

There has been a significant amount of recent work examining the relationship between cell metabolism and the immune system. The metabolic factors can result in complex immune response, separate from the more simple issues of cancer cell markers.

Herbel et al have noted:

Conversion of normal cells to cancer is accompanied with changes in their metabolism. During this conversion, cell metabolism undergoes a shift from oxidative phosphorylation to aerobic glycolysis, also known as Warburg effect, which is a hallmark for cancer cell metabolism. In cancer cells, glycolysis functions in parallel with the TCA cycle and other metabolic pathways to enhance biosynthetic processes and thus support proliferation and growth. Similar metabolic features are observed in T cells during activation but, in contrast to cancer, metabolic transitions in T cells are part of a physiological process. Currently, there is intense interest in understanding the cause and effect relationship between metabolic reprogramming and T cell differentiation.

After the recent success of cancer immunotherapy, the crosstalk between immune system and cancer has come to the forefront of clinical and basic research. One of the key goals is to delineate how metabolic alterations of cancer influence metabolism-regulated function and differentiation of tumor resident T cells and how such effects might be altered by immunotherapy. Here, we review the unique metabolic features of cancer, the implications of cancer metabolism on T cell metabolic reprogramming during antigen encounters, and the translational prospective of harnessing metabolism in cancer and T cells for cancer therapy. ...

T cells and cancer cells inexorably share metabolic programs and preferences, and thus there is high competition for nutrients between cancer and T cells within the tumor microenvironment. Nutrient deprivation, increased metabolic waste, and the ability of tumors to express inhibitory ligands impair the metabolic fitness and capacity of T cells to uptake and utilize nutrients. Additionally, metabolism determinants of the tumor microenvironment drive T cells to exhaustion and Treg differentiation programs rather than Teff and Tm phenotypes leading to impaired antitumor responses.

The changes and adaptations in the tumor microenvironment most likely are not limited to solid tumors because leukemia and lymphoma cells have similar metabolic characteristics with solid

tumors and often express immunomodulatory ligands. In addition, lymphomas may also contain infiltrating T cells with an exhausted phenotype similar to that identified in chronic viral infections or solid tumors. Thus, drugs that directly target key metabolic enzymes or their upstream regulators will likely interfere with metabolism of both cancer and T cells in which core cell signaling and metabolic pathways converge.

Understanding the similarities and differences of metabolic vulnerabilities of T cells and cancer may lead to the development of single-target or combination-based therapies to modify metabolism of the tumor niche thereby targeting both cancer cells and immune cells. Identification of such specific changes in oncometabolites and immuno-metabolites may define not only novel therapeutic targets but also biomarkers for assessment of therapeutic responses to tumor immunotherapy combined with metabolism-targeting drugs. The ultimate goal is to design metabolism-based treatment strategies to attack and eradicate cancer while promoting effective and sustainable anti-tumor T cell responses.

As Elliott and Head have noted:

It is at this time we must briefly mention the work and contributions of Paul Ehrlich and Otto Warburg. Paul Ehrlich's magic bullet theory has inspired many generations of scientist to explore numerous molecular cancer therapeutics. He connected chemistry to biology and medicine; and predicted the existence of specific cell receptors .

Otto Warburg in the 1930s, described a link between defects in mitochondrial physiology and tumorigenesis. He observed a significant increase in glycolysis and lactate production in the presence of oxygen without an increase and an occasional decrease in oxidative phosphorylation. This phenomenon is known as aerobic glycolysis or the "Warburg effect" and is well documented in tumor cells. The work of the above two scientists has contributed much to the field of tumorigenesis, and those of us in the field should be extremely grateful for their contributions.

In 2005 Gottlieb and Tomlinson did a tremendous job reporting on mitochondrial tumor suppressors with a genetic and biochemical update. They mention the work of Warburg, but it was 60 years after Warburg that the first genetic evidence that might explain the mechanisms of aerobic glycolysis was reported. There were many tumors shown to contain somatic mutations in mitochondrial DNA (MTDNA).

It is thought that most are homoplasmic and the outcome is non-functional oxidative phosphorylation, causing cells to increase glycolysis, the only other avenue for ATP (adenosine triphosphate) synthesis. However, there is limited evidence that indicates mitochondrial mutations might directly promote tumorigenesis. There are some mitochondrial proteins encoded by nuclear genes that can be tumor suppressors, some are involved in benign and malignant tumors. Two of the proteins are the enzymes succinate dehydrogenase (SDH) and fumarate hydratase also known as fumarase. Both of these enzymes are involved in the Krebs's cycle that connects glucose metabolism in the cytosol to mitochondrial oxidative phosphorylation.

The inhibition of SDH has been linked to the induction of the hypoxia-inducible factor (HIF). HIF is a transcription factor induced under low oxygen conditions. SDH inhibition causes an accumulation of succinate, which transmits an oncogenic signal from the mitochondria to the cytosol, which inhibits HIF- α prolyl hydroxylase (PHD) activity leading to the stabilization of the HIF-1 α subunit at normal oxygen levels. The result is the transcription of genes involved in tumorigenesis, such as, the angiogenesis factor vascular endothelial growth factor (VEGF). Therefore, succinate has been identified as a new intracellular messenger through discovery of the mitochondrion cyto-sol pathway. Gottlieb and Tomlinson have done a great job of discussing the link of mitochondrial dysfunction to cancer and we will now present some important aspects of their findings.

The TCA cycle (tricarboxylic acid cycle also known as the Krebs cycle) is fundamental to the bioenergetics of cells, however, it is not exactly known how TCA dysfunction leads to cancer. To address that problem, they proposed several models. They included decreased programmed cell death (apoptosis), increased production of reactive oxygen species (ROS), and activation of a hypoxia-like pathway under normoxic conditions (pseudohypoxia). Though impossible to distinguish between these options as they interact with each other, which leads to a complex grid of tumor regulatory systems. They still provided evidence to support the role for each of these three models in mitochondrial dysfunction induced tumorigenesis.

Overall the potential exists for utilizing the Warburg like responses in conjunction with the immune system although the path is not clear at this point. However Peng et al have recently noted:

Aerobic glycolysis (the Warburg effect) is a metabolic hallmark of activated T cells and has been implicated in augmenting effector T cell responses, including expression of the proinflammatory cytokine interferon-g (IFN-g), via 3' untranslated region (3'UTR)-mediated mechanisms. Here, we show that lactate dehydrogenase A (LDHA) is induced in activated T cells to support aerobic glycolysis but promotes IFN-g expression independently of its 3'UTR. Instead, LDHA maintains high concentrations of acetyl-coenzyme A to enhance histone acetylation and transcription of Ifng. Ablation of LDHA in T cells protects mice from immunopathology triggered by excessive IFN-g expression or deficiency of regulatory T cells. These findings reveal an epigenetic mechanism by which aerobic glycolysis promotes effector T cell differentiation and suggest that LDHA may be targeted therapeutically in autoinflammatory diseases.

7. THUS THE FINAL QUESTION IS: WHY DOES THE WARBURG EFFECT EVEN OCCUR?

As DeBerardinis et al note:

So why does the Warburg effect occur? Clearly, the high glycolytic rate provides several advantages for proliferating cells.

First, it allows cells to use the most abundant extracellular nutrient, glucose, to produce abundant ATP. Although the yield of ATP per glucose consumed is low, if the glycolytic flux is high enough, the percentage of cellular ATP produced from glycolysis can exceed that produced

from oxidative phosphorylation. This may be due to the high rate of ATP production during glycolysis compared to oxidative phosphorylation.

Second, glucose degradation provides cells with intermediates needed for biosynthetic pathways, including ribose sugars for nucleotides; glycerol and citrate for lipids; nonessential amino acids; and, through the oxidative pentose phosphate pathway, NADPH. So the Warburg effect benefits both bioenergetics and biosynthesis.

What remains controversial about the Warburg effect is why the rate of lactate production is so high when more of the pyruvate could presumably be oxidized to enhance ATP production. One explanation is simply that glycolysis outpaces the maximal velocity of pyruvate oxidation, so that cells must instead eliminate pyruvate using high-flux mechanisms.

We have made several observations which can lead to a few reasonable conclusions. They are:

1. Warburg effect is most likely an artifact of the other elements which make up for a malignancy. The classic understanding was that the effect was the cause of cancers even though the cause of the effect itself was unknown.
2. Warburg effect is not a cause nor a sine qua non for cancer and addressing its control would most likely be addressing a secondary consequence not a causal element.
3. The Warburg effect can be explained by a rate limiting process in the overall manner in which glucose produces ATP. In fact it may be that the cancer cells are very "hungry" cells in need of massive amounts of glucose that they saturate the TCA and thus perform aerobic glycolysis.

Finally we pose the questions from Bensinger and Christofk:

1. Can the Warburg effect and cancer metabolism be programmed? While the Warburg effect metabolic phenotype was initially identified in cancer tissue, it is now well appreciated that rapidly dividing normal tissues, such as ES cells and lymphocytes, employ aerobic glycolysis to meet their energetic and biosynthetic requirements during expansion. These observations support the notion that aerobic glycolysis is a preferred metabolic program under conditions of rapid cellular expansion. However, it remains unclear how the Warburg effect is initiated and maintained; these need not be the same signals in cancer versus normal tissues which lack dysregulated signaling. One critical signaling axis for metabolic programming of normal cells is the PI3K/AKT/mTOR pathway downstream of growth receptors. Genetic and pharmacologic models have clearly identified mTOR signaling in controlling cellular growth and metabolism.

This is a clear statement of what is desired but also a clear articulation of what we really do not know about Warburg. mTOR is a powerful control mechanism, yet is it a driver of or driven by Warburg?

2. What is the relationship between the Warburg effect and cancer microenvironment?Thus, catabolic programs in normal cells within the tumor parenchyma can play a pivotal role in supporting the anabolic program of cancer. Indeed, recent studies indicate that despite robust

anabolic programs in tumors, addition of lipolytic capabilities robustly increase tumorigenesis. Although speculative, the symbiotic relationship between normal cells and tumor cells could help to explain cancer associated cachexia by driving a generalized catabolic program in tumor bearing individuals.

The microenvironment is becoming significant factor on a cancer development and proliferation. Cancer cells have a high demand for nutrients and oftentimes those nutrients are obtained from its microenvironment even to the extent that it cannibalizes its benign neighbors, using their remnants as energy to grow.

3. Does aerobic glycolysis contribute to chemotherapeutic resistance or susceptibility? Given that many cancers exhibit altered metabolism, it should not be surprising that there has been increased effort to therapeutically target these pathways as a means to decrease tumor growth or alter behavior.

There is a great deal of evidence that Warburg effects do inhibit certain chemotherapies. This is a compelling path to explore since it may enlighten us on Warburg as well as expanding understanding of chemotherapeutic mechanisms.

4. What is the metabolism of cancer stem cells? While the concept of bone fide cancer stem cells (CSCs) remains controversial, there is strong evidence to indicate that a subset of cancer cells are endowed with the capacity to initiate tumor formation. Oft times defined as tumor-initiating cells (TICs), these cells appear to be critical for the ability of tumors to resist conventional radio- or chemotherapeutics and repopulate the tumor during and after treatments. Whether TICs have distinct metabolic programs from the bulk of tumor cells is not well established.

This last question is compelling since it indicates that Warburg is but one presentation of cancer cell metabolism. It also presents the argument that understanding cancer cell metabolism in the whole may provide a fruitful approach to the ultimate control of cancers. However, and this is critical, we must always be fearful of falling into what I have termed the "Warburg Trap", namely the positing of the "silver bullet" cause of all cancers. Clearly if we have discovered anything, it is that cancers have a multiplicity of causes and ongoing support mechanisms, even in the same organ, and even in the same cell types in that organ.

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Labels: [Cancer](#)

Monday, January 8, 2018

[Government Healthcare, Think Post Office](#)

The USPS is truly one of the most incompetent entities around. The only one worse is AMTRAK. The train folks had 601 delays on my local ride in the 152 days last year. That is about 4 delays per train per day. Now the USPS refuses to deliver packages...yep...it must be the snow...all three inches of it.

Now for those folks who want Government healthcare, just think of these two entities. Even worse, think of the IRS! Combine them and we would eliminate any population explosion. We would all be dead!

Oh, about that wall, how about a tunnel between New Jersey and New York. You can even charge for that. Guaranteed that New Jersey folks would pay for it, pay for anything!



Labels: [Health Care](#)

Sunday, January 7, 2018

[How to Lose Customer Trust](#)

I have noticed recently that Amazon has third party sales where the Amazon standard conditions do not apply. The third party has poor if zero return policies and it is near impossible to cancel an order. Cost of returns has exceeded the cost of the item and the communications with the vendor is nil. Why Amazon has mixed these in my opinion poor third party vendors with their own sales and in addition give no clear warning is beyond me.

This style of what I would see in my opinion as a "shady" practice will come back to haunt Amazon. I would rather go to Walmart or some other party then to be fooled by some third party Amazon purchase.

The other thing I have noticed and have experienced is that these third party vendors, such as those selling batteries, seem to just repackage used batteries and then sell them as new. It is difficult to prove that as a general consumer but if one does this can become a massive class action suit! Amazon should beware.

A reputation takes time to build but can be destroyed in a heart beat. Perhaps they have some bright MBA who saw a quick profit margin and never gave it a second thought. If Walmart were smart, namely no smart MBA type, they would jump on the bandwagon and tear Amazon apart on this issue!



Labels: [Amazon](#)

[More on the Microbiome](#)

We have recently [written extensively on the microbiome and cancer](#). [Science](#) has just published an article reinforcing our summary which is worth the read. Recall that the microbiome is that collection of microorganisms that live inside of our bodies, and without which we would most likely not survive.

As the authors note:

Cancer immunotherapy has become highly successful against an array of distinct hematological and solid metastatic malignancies. Administration of immune checkpoint inhibitors (ICIs) unleashes T lymphocyte-mediated immune responses by suppressing the interaction of T cell inhibitory receptors with their cognate ligands on tumor or stromal cells. The most widely used ICIs are monoclonal antibodies (mAbs) targeting programmed cell death protein 1 (PD-1) and

its ligand PD-L1. PD-1 blockade is highly efficacious against advanced melanoma, non-small cell lung cancer (NSCLC), and renal cell carcinoma (RCC). Primary resistance, observed in 60 to 70% of cases, has been attributed to low mutational burden, poor intrinsic antigenicity of tumor cells, absence of priming by potentially immunogenic pretreatment with chemo- or radiotherapy, defective antigen presentation during the priming phase, local immunosuppression by extracellular metabolites, and functional exhaustion of tumor-infiltrating lymphocytes. Recent work in mice has highlighted the key role of the gut microbiota in mediating tumor responses to chemotherapeutic agents and immunotherapies targeting PD-L1 or cytotoxic T lymphocyte-associated protein 4 (CTLA-4). Therefore, we explored the possibility that dysbiosis associated with malignant disease or concomitant antibiotic (ATB) use could influence primary resistance to PD-1 blockade in tumor-bearing mice and cancer patients. Initially, we compared the therapeutic efficacy of PD-1 mAb alone or combined with CTLA-4 mAb in mice with established MCA-205 sarcoma and RET melanoma. Mice were reared in specific pathogen-free (SPF) conditions and treated for 14 days with broad-spectrum combination ATB (ampicillin + colistin + streptomycin) or left untreated. ATB treatment significantly compromised the antitumor effects and survival of mice treated with PD-1 mAb alone or in combination with CTLA-4 mAb.

Thus it is critical to deal with many cancers in a holistic manner and not just rely upon the therapeutic.



Labels: [Cancer](#)

Friday, January 5, 2018

[Now I Do Not Want to Walk Into this BUT:](#)

I received the following from Nature as a News Alert:

How a warming climate leads to cold snaps: The reduction in the amount of Arctic sea ice is weakening the whirling jet of air known to weather-lovers as the polar vortex, allowing cold blasts to dip into North America and Eurasia.

The [article referred to states](#):

The loss of sea ice may be weakening the polar vortex, allowing cold blasts to dip south from the Arctic, across North America, Europe and Russia, a new study says....Here's what scientists involved in the research think is happening: The evidence is clear that the Arctic has been warming faster than the rest of the planet. That warming is reducing the amount of Arctic sea ice, allowing more heat to escape from the ocean. The scientists think that the ocean energy that is being released is causing a weakening of the polar vortex winds over the Arctic, which normally keep cold air centered over the polar region. That weakening is then allowing cold polar air to slip southward more often.

Thus, the cold weather is due to global warming. Guys, you really are trying to stretch this a bit. This is a new discovery, hot equals cold. OK, so it is warming, but for pity's sake, try and get your story straight. This is why people do not believe what you are saying. Better just to keep quiet!



Labels: [Global Warming](#)

[China Waves its Sickle](#)

[China Daily](#) states:

Engaging with China has always been a political compulsion for US administrations. Former US president Barack Obama's "pivot to Asia" strategy and incumbent President Donald Trump's "Indo-Pacific" strategy suggest the United States will increase its presence in Asia. Though the "Indo-Pacific" strategy is still a work in progress, it is set to pose new challenges to the China-proposed Belt and Road Initiative, and regional cooperation as a whole. The foremost of those challenges is the Democratic People's Republic of Korea's nuclear issue, where China and the US still have much room for cooperation, and fortunately some substantial efforts in that direction are being made. But the de-escalation of tensions on the Korean Peninsula and the ultimate resolution to the issue depend on continued cooperation between China and the US. Or else, it will become even more difficult to resolve the issue. China plays an important but limited role in the issue, and what the US expects it to do is simply not possible, as the two sides employ different approaches to resolve the issue. Besides, other issues such as the Tai-wan question may jeopardize Sino-US relations.

When a country with a nuclear capability threatens to obliterate you, perhaps you should not just try to "engage" them. As it stands, no one has threatened China. The US on the other hand has both NOKO and Iran threatening death to America. With Iran we allow students to come here and study nuclear engineering, perhaps a rather risky strategy. For NOKO we really should be tracking and articulating the sources of their capabilities. Complex guidance systems are well beyond the expertise of NOKO, but well within that of China. Cooperation between the US and China are of course important. But that cooperation is made nil by cooperation between China and NOKO.

As for Taiwan, that is a question between China and Taiwan. Regrettably Taiwan can look at Hong Kong and wonder if any deal would be worth it.



Labels: [China](#)

[A Must Read on Nuclear Weapons](#)

[The Domsday Machine by Ellsberg](#) is an excellent introduction to the complexities of nuclear weapons and their deployment. Ellsberg covers the period of the 1960s, especially the first half, and the nature of the command and control of nuclear weapons deployment. His views were based upon his consulting as a RAND employee and having the ability to move in and around the multiplicity of players in this area. One may think that the President is the sole point of activation of a nuclear release but as Ellsberg so clearly shows the ability to deploy was and most likely still is diffused to the lowest levels.

Ellsberg depicts a Major in South Korea in charge of a bunch of nuclear armed F100s, all equipped with tactical but deadly nuclear bombs, who has taken it upon himself to determine when his pilots will deploy their weapons. Ellsberg also infers that the pilots themselves could even individually make the decision to deploy. Ellsberg does discuss the details of how a multiple F100 deployment may very well blow some of the F100s to shreds when the other have deployed due to the wide area blast effects.

The discussion of the SIOP (Single Integrated Operational Plan) plans and the various attack options that the US had developed. In contrast he does not discuss the Red Integrated Strategic Offensive Plan (RISOP) plan which is a counter to SIOP. Yet his discussion of the military and its nonchalant acceptance of 100 million casualties, namely deaths, was typical of military planner during this period. He does a superb job in characterizing the mindset of the planners and those in command regarding their near comfort in seeing just 100 million dead Americans as long as they could exterminate a larger number of Russians and Chinese.

Ellsberg's telling of this situation and in this time frame is unique because he was at the level of an observer, having no political gain to be made, being at RAND and being but a consultant, albeit one with extraordinary access.

Ellsberg does spend a reasonable amount of space on the issues of limiting nuclear weapons especially first strike capabilities. However as he had already detailed first strike management could already be out of the hands of an President. In fact the President, who may think he or she has the "button" may be circumvented by some field commander, or worse, by a single pilot or sub commander. The movie Fail Safe startled Ellsberg by its reality. Worse was that it portrayed a Domsday Machine which would only deter if the other side was aware of it.

To a degree, my time on nuclear weapons was a decade later than Ellsberg, ironically my first day after my PhD was the day Ellsberg's material hit the NY Times. Coming from MIT, and Ellsberg then being at MIT, I was looked at a bit askance. Yet over the next decade as I became involved in the Comprehensive Test Ban Treaty, especially during the Carter period, it was clear that the only way to use a nuclear weapon was not to use a nuclear weapon. The RISOP scenarios showed the annihilation of life on the planet. There was no way to win, first strike or otherwise. A Russian and US nuclear war was the destruction of all. Ironically in my later discussions with my Russian partners after the fall it was clear that they too understood this, positioning or not.

The risk is a rogue player, one who can really push the button. That perhaps is more of a reality today than during the 60s and 70s. Ellsberg's book is a must read for anyone interested in the nuclear debate, a debate whose only solution in my opinion is not to use the device.



Labels: [Nuclear Weapons](#)